

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BICARA THERAPEUTICS, INC.,

Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,

Patent Owner.

PGR2026-00025

U.S. Patent No. 12,295,968

DECLARATION OF JONATHAN DAVIS, PH.D.

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I. INTRODUCTION

1. I have been engaged as an expert witness to respond to the opinions of Dr. Geoffrey Hale (EX1003) concerning U.S. Patent No. 12,295,968 (“the ’968 patent”) and to offer opinions in support of Patent Owner’s Response to the Petition for Post-Grant Review.

2. My assignment includes analyzing, from the perspective of a person of ordinary skill in the art (“POSITA”), whether challenged claims 1 and 9 of the ’968 patent satisfy the written description and enablement requirements of 35 U.S.C. § 112.¹ I also address the technical bases for Dr. Hale’s opinions and the arguments advanced in the Petition.

II. BACKGROUND AND QUALIFICATIONS

3. I received a Ph.D. in biophysics from the University of California, San Francisco (UCSF) in 1996, where my work focused on the structural biology of enzymes and toxins. I then joined Prof. Jack Szostak’s lab at Harvard Medical School (jointly with Gerhard Wagner) where I studied selection, *in vitro* evolution, and structure of RNA aptamers and ribozymes.

¹ I understand that Patent Owner is filing a motion to amend the claims of the ’968 patent, requesting that claims 2-8 of the patent be cancelled. I therefore limit the opinions in this declaration to responding to Dr. Hale’s assertions about the patentability of claims 1 and 9 of the ’968 patent.

4. I have approximately 25 years of hands-on experience in protein engineering and antibody engineering. During the period relevant to the earliest claimed priority dates, I was a Senior Scientist II in New Technologies and Protein Engineering at EMD (later EMD Serono, known also as Merck KGaA and Merck Serono) (2001-2008), and a Principal Scientist in Protein Design at Adnexus, owned by Bristol-Myers Squibb (BMS, 2008-2019).

5. The Boston-area EMD site I worked at from 2001 to 2007 had originally been a biotechnology company called Lexigen, started and led by Dr. Steve Gillies, who is well known as one of the early experts and innovators in Fc and antibody fusion proteins, particularly involving cytokines. At EMD, I built out a phage display lab for antibody discovery, designed numerous fusion proteins, invented a novel scaffold binder based on an *in silico*-designed protein, and invented the SEEDbody heterodimeric Fc platform, including work associated with U.S. Patent No. 8,871,912 (EX2051). At BMS, starting in 2008, I developed new libraries for discovery of Adnectin binders and antibodies, designed novel IL-2/IL-2 receptor fusion proteins, and co-invented Combinectin, a multi-component trispecific fusion biologic targeting HIV-entry. From 2019-2024, I was Head / VP of Innovation and Strategy at Invenra, a biotechnology company located in Madison, WI, where I led the development of a novel bispecific antibody platform and the design and construction of naïve human-like antibody libraries. I have

published or patented work concerning Fc-fusion proteins, linker design, and antibody-fragment engineering. Since leaving Invenra in 2024, I have been self-employed as a consultant to biotech and pharma companies, law firms, and investment groups.

6. Through much of my professional and industry career, I have actively participated in dozens of international conferences and symposia as an invited speaker or chairperson. I am currently an active member of the communications committee for The Antibody Society.

7. My curriculum vitae is attached as EX2041. The curriculum vitae includes a list of publications and patents of which I am an author or inventor, as well as a discussion of my educational and professional background. I have been involved with two confidential prior engagements with law firms in patent matters, neither of which is related to the subject matter of this proceeding, and I have not offered expert testimony or testified in either matter.

III. COMPENSATION AND RELATIONSHIP WITH PARTIES

8. I am being compensated for my time at a rate of \$700 per hour. This compensation is not contingent upon my performance, the conclusions I reach in my analysis, the outcome of this matter, or any issues involved in or related to this matter.

9. I have no financial interest in Patent Owner or any related parties.

IV. MATERIALS CONSIDERED

10. In preparing this declaration, I have reviewed and considered the '968 patent (EX1001), its prosecution history (EX1002), the PCT application to which the '968 patent claims priority (PCT/US2011/027317, "the '317 application") (EX1017), the Expert Declaration of Geoffrey Hale, Ph.D. (EX1003), including Appendices A-C, and the Patent Owner's Response and the exhibits on which it relies.

11. I have also considered the materials cited in this declaration, including the cited literature and exhibits concerning antibody fragments, Fc-fusion formats, linker design, recombinant expression, and epidermal growth factor receptor ("EGFR") binding. I have considered these materials in light of the knowledge that would have been available to a POSITA at the relevant time.

12. Should new information be disclosed or discovered during this proceeding, I may supplement and further elaborate on the opinions I express in this declaration as necessary.

V. LEGAL STANDARDS

13. My opinions in this declaration require an understanding of various legal principles. I am not an attorney, and I offer no legal opinions. Counsel has informed me of the legal principles relevant to my analysis, and I summarize below the principles as I understand them. I apply them from the perspective of a

POSITA, and where a question is ultimately a legal one, I confine my testimony to the underlying technical matters.

A. Burden

14. I understand that Petitioner Bicara Therapeutics, Inc. (“Petitioner”) bears the burden of proving unpatentability in this proceeding by a preponderance of the evidence, and that this burden remains with Petitioner throughout the proceeding. I understand that the burden never shifts to Patent Owner to prove that the challenged claims are patentable.

15. I understand that the preponderance-of-the-evidence standard requires Petitioner to show that unpatentability is more probable than not. I understand that it is not enough for Petitioner to identify a theoretical possibility of a defect, to raise a question, or to assert a conclusion; Petitioner must prove the facts on which its theory depends.

16. Consistent with that allocation, I have not assumed the correctness of any factual premise advanced in the Petition or in the declaration of Dr. Geoffrey Hale (EX1003).

B. Level of Ordinary Skill in the Art

17. I understand that my analysis is to be conducted from the perspective of a POSITA as of the time of the invention. For the challenged claims, I understand the relevant period to be the 2010-2011 priority period. I understand that the analysis is not performed from the perspective of a POSITA today.

18. I understand that a POSITA is presumed to possess ordinary creativity and the ordinary knowledge and skills of the art, including familiarity with routine laboratory techniques then in general use. I understand that a patent specification is written for a POSITA rather than for the general public.

19. I understand that a POSITA is presumed to bring to the patent the knowledge of what came before it, and that the disclosures of a patent are therefore read against the state of the art as it existed at the relevant time. I understand that hindsight is not permitted, and that neither the written description nor the enablement analysis may be conducted by working backward from the issued claims.

C. Claim Construction

20. I understand that, in Post Grant Review (“PGR”) proceedings, a claim of a patent shall be construed using the same claim construction standard that would be used to construe the claim in a civil action filed in a U.S. District Court (which I understand is called the “*Phillips*” claim construction standard), including construing the claim in accordance with the plain-and-ordinary meaning of such claim as understood by one of ordinary skill in the art in view of the specification and the prosecution history pertaining to the patent.

21. I understand that claim terms carry their plain and ordinary meaning unless the patentee acted as its own lexicographer or clearly disavowed claim

scope in the specification or during prosecution, and that these are the only two exceptions to that rule. I understand that both exceptions are exacting, and that neither is satisfied by a specification's mere use of a term in a particular example.

22. I understand that "comprising," when used as a transitional phrase, is inclusive and open-ended. It requires the recited elements but does not exclude additional, unrecited elements. Accordingly, I understand that a claim reciting a particular structural component does not thereby exclude a molecule that also contains additional structure not recited in the claim.

23. I understand that where a claim is genuinely ambiguous and amenable to more than one reasonable construction, claims should, where possible, be construed so as to sustain their validity rather than to invalidate them.

24. I understand that claim terms need be construed only to the extent necessary to resolve the disputes presented, and that a construction proposed for the purpose of manufacturing an internal inconsistency in the claims is not a proper application of the standard.

D. Written Description

25. I understand that written description does not require the specification to recite the claims verbatim. It may be satisfied by a combination of words, structures, figures, diagrams, and formulas, and it need not describe every detail that was already known to skilled artisans.

26. I understand that written description is assessed from the perspective of a POSITA and asks whether the specification reasonably conveys that the inventors possessed the claimed subject matter as of the filing date of the application. The inquiry is based on the specification as a whole and the knowledge of a POSITA.

27. I understand this to be an objective inquiry into the four corners of the specification, from the perspective of a POSITA who comes to the patent with knowledge of what has come before.

28. I understand that the inquiry is based on the specification as a whole, together with the knowledge of a POSITA, and that the specification need not recite the claims verbatim. I understand that the requirement may be satisfied by any combination of words, structures, figures, diagrams, and formulas contained in the specification and may also include the claims.

29. I understand that written description does not require an actual reduction to practice, and does not require a working example of every claimed embodiment. I understand that it likewise does not require that the claimed construct have been previously made, separately named in the literature, or reported by others.

30. I understand that where the specification does not expressly recite a claimed subgenus or species in the words of the claim, the requirement may be

satisfied by sufficient “blaze marks” in other words, guidance, direction, or other suggestions directing a POSITA to the claimed subgenus or species. I understand that blaze marks may take structural and typographic form, including annotations within a disclosed sequence that identify its component domains, and that a figure disclosing a single, specific combination of components may itself serve as a blaze mark to that combination.

31. I understand that the claim limitations must be considered together as an integrated whole. I also understand that the limitations need not all appear in a single sentence, and that the requirement is satisfied where the claimed combination is disclosed in a single embodiment or in figures and passages that the specification evidently and clearly links together.

32. I understand that, in evaluating written description, relevant considerations include the nature and scope of the claims and the complexity, predictability, and maturity of the technology at issue.

E. Enablement

33. I understand that the specification, read together with the knowledge of a POSITA, must teach how to make and use the full scope of the claimed invention without undue experimentation, measured as of the effective filing date.

34. I understand that the relevant question is whether the experimentation required would be undue, not whether any experimentation would be required. I

understand that undue experimentation is a matter of degree, that a reasonable amount of experimentation is permissible, and that routine experimentation including the ordinary design, construction, expression, purification, and testing cycles used in recombinant protein work is not undue merely because it takes effort or time.

35. I understand that whether experimentation is undue is context-specific and may be informed by the factors commonly called the “Wands” factors that include but are not limited to the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Accordingly, I understand that no single factor is dispositive, that not every factor need be met, and that the factors are weighed together.

36. I understand that an enabling specification need not describe every detail of the invention, need not repeat information already known to a POSITA, and need not exemplify every potential embodiment.

37. I understand that enablement is measured against what the claims actually require, and that the number of theoretical arrangements a claim might be said to encompass is not the same as the number of independent experiments a

POSITA would need to perform. I understand that a POSITA applies ordinary judgment and does not pursue constructions that a skilled artisan would recognize as structurally unreasonable or without prospect of working.

38. I understand that claims reciting specific structural limitations, such as defined amino acid sequences, are materially different from claims defined solely by function that would require a POSITA to screen an undisclosed universe of candidate molecules by trial and error.

VI. OVERVIEW OF U.S. PATENT NO. 12,295,968

A. Technical Background

39. An immunoglobulin G (IgG) antibody is a common type of antibody that includes heavy and light chains. Each heavy chain includes a variable domain and constant domains, and each light chain includes a variable domain and a constant domain. Pairing of the variable heavy and variable light domains forms the antigen-binding site, while constant regions and Fc domains contribute other structural and functional properties.

40. Antibody fragments are portions of an antibody that can retain antigen-binding or other activity. As of 2010, a POSITA would have understood that the field included, for example, Fab, F(ab')₂, scFv, single-chain Fab, single domain antibodies, Fc fragments and Fc-fusion products, and fragments including a VL or VH domain. The precise structure of a fragment depends on the intended format and the antibody sequence. EX2042, Hale Dep. Tr. at 33:17-34:6.

41. Fusion proteins join domains derived from different proteins, often using flexible peptide linkers to preserve folding and biological activity. By 2010, recombinant antibody engineering and fusion-protein formats were established areas of research and development. Common formats included, on the antibody side, monoclonal antibodies (mAbs), Fabs, scFvs, Fc, and single domain antibodies, and on the fusion partner side, cytokines and chemokines, enzymes, soluble fragments of receptors and ligands, soluble ligands, peptides, scaffold binders, and other proteins.

42. When designing a fusion protein, one design decision is to choose which free termini to genetically connect, and a second decision is to choose what kind of linker, if any, to insert between the fusion partners. In the absence of insights derived from previous work or structure/function knowledge, it has been common practice to design two or more constructs with different orientations (*e.g.*, $A \rightarrow B$, $B \rightarrow A$) and/or linkers, in order to determine empirically which one works best for the desired application.

43. EGFR was a well-characterized antibody target by 2010. Cetuximab is a chimeric anti-EGFR antibody comprising mouse variable regions linked to human constant regions and had received FDA approval in 2004 for colorectal cancer and later for head and neck cancer. The '968 patent uses anti-EGFR

sequences shown in Figure 3, which are cetuximab-derived/based but are not identical to the complete cetuximab chains.

44. Transforming growth factor-beta receptor type II (“TGFβRII” or “TGFB2”) also was a well-studied receptor as of 2010. According to PubMed, there are 3259 papers between 1985 and 2009 mentioning “TGFB2.” A structure of the extracellular domain of TGFβRII bound to TGFβ was published in 2002 (P. John Hart et al., *Crystal structure of the human TβR2 ectodomain–TGF-β3 complex*, 9 Nature Structural & Molecular Biology 203-208 (2002) (EX2046)) and the extracellular domain of TGFβRII was available for purchase by 2006 at the latest, consisting of a 137 amino acid portion of the extracellular domain (“ECD”) (Thr23 - Asp159) fused to human Fc. This 137 amino acid fragment is the same as that found in the ’968 patent (Seq ID NO: 87).

B. Patent Description

45. U.S. Patent No. 12,295,968, titled “Compositions and Methods for Targeted Immunomodulatory Antibodies and Fusion Proteins,” lists Atul Bedi and Rajani Ravi as the inventors, and was filed on September 12, 2024, and issued on May 13, 2025. EX1001.

46. The specification uses terms that reflect the nomenclature and structural concepts familiar to a POSITA working in antibody engineering and fusion-protein design. For example, the specification states that a targeting moiety

can be an antibody, antibody fragment, scFv, Fc-containing polypeptide, fusion antibody, polypeptide, peptide, aptamer, ligand, nucleic acid, or combination. It also explains that an antibody fragment can include variable regions alone or in combination with portions of the hinge, CH1, CH2, or CH3 domains.

47. Figure 3 and the related disclosures of the immunomodulatory and linker sequences are technically meaningful to a POSITA because the figure identifies the variable-region, linker, and TGF β RII portions within a single fusion sequence. The specification also expressly describes an immunomodulatory polypeptide fused to the C-terminus of a targeting antibody's light chain (EX1001 at 35:48-50; EX1017 ¶ [0182]).

48. Figure 3 provides an anti-EGFR1 heavy-chain plus TGF β RII extracellular-domain fusion sequence, SEQ ID NO: 2, and an anti-EGFR1 light-chain sequence, SEQ ID NO: 71. Its key identifies underlining as the anti-EGFR antibody variable region, plain text as the antibody constant region, italics as the linker, SEQ ID NO: 104, and bold text as the TGF β RII extracellular domain (SEQ ID NO: 87).

49. Claims 1 and 9 recite portions of the anti-EGFR targeting sequences and the entire TGF β RII sequence identified, for example, in Figure 3. Claim 9 further specifies an antibody fragment, the light-chain and variable-heavy-chain

domains, linker SEQ ID NO: 104, and the orientation in which the light chain and TGF β RII moiety are fused to the linker. Claims 1 and 9 are reproduced below:

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.

50. The specification identifies recombinant-DNA methods for making fusion proteins: coding sequences for the relevant portions can be linked at the nucleic-acid level and the resulting proteins can be produced using a host cell well known in the art. EX1001 at 43:40-52. I address below how that guidance, the working TGF β RII:Fc example (EX1001 at 40:41-41:7), and the state of the art bear on the issues of written description and enablement.

C. Level of Ordinary Skill in the Art

51. Petitioner proposes that a POSITA for the challenged claims, as of 2010 or 2011, would have held a Ph.D. or equivalent (for example, four to five years of work experience) in biochemistry, molecular biology, immunology, or a closely related field; experience with antibody-domain and sequence manipulation, construction, expression, and purification of recombinant antibodies and/or fusion proteins; experience with assays for expression levels and activity; and experience collaborating as part of a medicinal, pharmaceutical, or biotechnology research team (Pet. at 16-17; EX1003, Hale Decl. ¶ 111).

52. I apply Petitioner's proposed definition for purposes of this declaration. As of 2010, I held a Ph.D. in biophysics, had about a decade of hands-on experience with protein and antibody engineering, and held senior scientist and principal scientist roles in the relevant field. I therefore qualified as a POSITA, and I offer my opinions from the perspective of a POSITA in 2010-2011.

53. Petitioner's definition also assumes work in a team or collaboration. My contemporaneous industry work was performed in that setting and involved protein design, structural biology, antibody engineering, and fusion-protein platforms. The SEEDbody, IL-2/IL-2 receptor, and Combinectin work identified above provides a direct factual basis for my opinions about recombinant expression, linker design, domain engineering, and protein characterization.

54. The subject matter of my contemporaneous positions was directly aligned with the proposed POSITA definition. From 2001-2008, I held senior scientist roles in structural biology and protein engineering at EMD Serono, and beginning in 2008 I was a Principal Scientist in Protein Design at BMS. The particular site of EMD Serono at which I worked (a former biotech originally called Lexigen) specialized in Fc and antibody fusions, with numerous papers and patents in the field. I therefore am familiar with the state of the art in 2010-2011.

55. The technical practices discussed below—including recombinant DNA construction, host-cell expression, purification, linker selection, antibody-fragment engineering, and antigen-binding assays—were part of the relevant field and known to a POSITA by at least 2010.

56. In applying Petitioner's proposed POSITA definition, I understand that a person with the stated Ph.D. or approximately four to five years of relevant experience, including experience constructing, expressing, and purifying

recombinant antibodies and/or fusion proteins, would ordinarily exercise independent technical judgment. In my experience, such a person would design, troubleshoot, and optimize recombinant-antibody and fusion-protein constructs as part of routine work, rather than merely follow another person's instructions.

57. Dr. Hale's deposition characterization of a POSITA as someone who would "just . . . follow instructions and carry out experiments diligently," like technicians he supervised, and who might have difficulty designing experiments understates the capabilities of the POSITA described in his declaration. EX2042, Hale Dep. Tr. at 27:11-22.

58. The specific choices that Dr. Hale alleges were above an "ordinary" skill level for a POSITA—selecting and incorporating a flexible (GGGGS)_n linker, including SEQ ID NO: 104; choosing domain orientation and the fusion terminus; selecting a suitable expression vector and host cell, such as CHO or HEK293, and appropriate codons; and conducting antigen-binding assays—were routine, bounded technical choices for this POSITA by 2010. A POSITA would make those choices based on the known properties of antibody formats, established mammalian expression systems, standard recombinant-DNA methods, and available binding assays, and would adjust them through ordinary design-test cycles. A typical company, research group, or team would have in-house protocols for all these techniques, and would possess validated production cell lines and

transfection protocols for transient or stable expression. Thus, a POSITA would not need explicit instructions from the patent specification, as they would apply their own set of techniques and materials to produce the final molecules, which is typical practice in the field. Dr. Hale acknowledges that recombinant IgG manufacture was “comparatively predictable and routine” and that GGGGS linkers were well known by 2010. EX1003, Hale Decl. ¶¶ 61-62; EX2042, Hale Dep. Tr. at 50:2-20, 56:16-57:25.

59. In my opinion, and as discussed in more detail below, Dr. Hale’s undue-experimentation conclusion depends on treating the POSITA as unable to make these routine design choices. Applying the POSITA definition in EX1003 ¶ 111, the design-and-test work for the sequence-defined constructs of claims 1 and 9 is routine and bounded, consistent with my approximately 20- and 2-construct analyses discussed below. Dr. Hale has not identified literature showing that a POSITA would have difficulty making the fusion proteins of claims 1 or 9, and I understand he testified that he never performed his nine-step plan for a molecule within those claims. EX2042, Hale Dep. Tr. at 150:3-13, 153:21-154:3.

VII. WRITTEN DESCRIPTION (GROUND 1)

A. Claim 1: Figure 3 and the Targeting Moiety

60. Dr. Hale asserts that claim 1 of the ’968 patent lacks adequate written description support. I disagree with Dr. Hale’s opinion that the specification fails

to adequately describe the targeting moiety of claim 1. EX1003, Hale Decl. ¶¶ 117-122.

61. For example, Figure 3 identifies an anti-EGFR1 heavy-chain plus TGFβRII extracellular-domain fusion sequence (SEQ ID NO: 2) and the corresponding anti-EGFR1 light-chain sequence (SEQ ID NO: 71). The figure's key identifies the underlined sequence as the anti-EGFR antibody variable region, the italicized sequence as the linker (SEQ ID NO: 104), and the bold sequence as the TGFβRII extracellular domain (SEQ ID NO: 87). Those markings convey the relevant structural components to a POSITA. Figure 3 is reproduced below:

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):

QVQLKQSGPGLVQPSSQLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPTTSR
LSINKDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEFAYWGQGLVTVSAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVSMHEALHNHYTQKSLSLSPGK
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):

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQRTNGSPRLIKYASESISGIPSRFSGSG
SGTDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-EGFR antibody variable region

Plain: Anti-EGFR antibody constant region

Italic: Linker

Bold: TGF β RII ectodomain

FIG. 3

62. A POSITA would recognize the first 119 residues underlined in SEQ ID NO: 2 as a discrete structural unit, the variable heavy-chain domain. The underlining identifies the variable region, and the sequence length is within the

range of common lengths of human or mouse immunoglobulin variable heavy domain. The final 11 amino acids of a VH domain are quite conserved, even across species, particularly in length. A POSITA would be able to compare or align the first 119 residues of SEQ ID NO: 2 with any other representative VH domain, and would see that WGQGTLVTVSA aligns with the last 11 residues of the other VH, thus confirming the identification of the domain and providing the “blaze mark” for where to fuse the variable domain to any other desired protein.

63. As I explained above, I understand that written description does not require the specification to include a verbatim recitation of the claim language. Dr. Hale himself recognizes that the requirement may be satisfied by “any combination of words, structures, figures, diagrams, formulas, etc.” in the specification (EX1003, Hale Decl. ¶ 114). Here, the figure supplies a sequence, an identified antibody, and typographic marks that distinguish the variable region, linker, and TGFβRII portion. A POSITA would read those linked disclosures together, rather than disregard the structural information conveyed by the figure, and would understand that the inventors possessed the claimed subject matter as of the effective filing date.

64. The fact that the exact phrase “amino acids 1-119 of SEQ ID NO: 2” does not appear elsewhere in the specification does not change the technical disclosure in the specification (EX1003, Hale Decl. ¶¶ 118-19, 121). The first 119

residues are identified graphically as the anti-EGFR heavy chain variable region, and the sequence listing is numbered, allowing a POSITA to perform the routine task of mapping the numbers from the claim to the sequence, to ensure a match to the underlined segment in Figure 3 (EX1001 at SEQ ID NO: 2, Fig. 3). The SEQ ID NO: 2 sequence listing is reproduced below:

```

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

SEQUENCE: 2
QVQLKQSGPG LVQPSQSLSI TCTVSGFSLT NYGVHWRQS PGKGLEWLGV IWSGGNTDYN 60
TPFTSRLSIN KDNSKSQVFP KMNSLQSDNT AIYYCARALT YYDYEPAWYG QGTLVTVSAA 120
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTWSW NSGALTSGVH TFPAVLQSSG 180
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVPEK SCDKTHTCPP CPAPELLGGP 240
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL 360
TKNQVSLTCL VKGFPYSDIA VEWESNGQPE MNYKTTTPVL DSDGSFFLYS KLTVDKSRWQ 420
QQNVFSCSVM HEALHNHYTQ KSLSLSPPGK GGGSGGGSG GGGSTIPPHV QKSVNNDMIV 480
TDNNGAVKFP QLCKPCDVRP STCDNQKSCM SNCSITSICE KPQEVCAVAV RKNDENITLE 540
TVCHDPKLPY HDFILEDAA S PKCIMKEKKK PGETFFMCSC SSDECNDNII FSEEYNTSNP 600
D                                                                601

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65. A POSITA would neither expect nor require the specification to restate a residue range in claim-style words when the figure identifies the same structural unit; the appearance of that phrase in the issued claims therefore is not evidence that the underlying structure was not adequately disclosed in the rest of the specification. Recitation of “amino acids 1-119 of SEQ ID NO: 2” is just a precise numerical way of expressing “The VH domain from the antibody that binds EGFR,” or “The underlined sequence in the heavy chain in Figure 3,” both of which are clearly disclosed, for example, in Figure 3.

66. Dr. Hale’s Appendix C tabulates 35 exemplary fusion proteins containing antibody targeting moieties and states that each uses a full-length antibody (EX1003, Hale Decl. ¶¶ 80-81, App’x C). That tabulation does not negate the express disclosures that targeting moieties may include antibody fragments, scFv formats, Fc-containing polypeptides, and fragments containing variable domains (EX1001 at 27:38-43, 29:24-35, 34:40-52, 35:56-62). A sequence listing of a complete expressed chain can provide the full sequence context, while a figure separately identifies a functional fragment or domain within that chain. A POSITA would not infer from the format of the sequence list that the expressly identified fragment formats were excluded.

67. Dr. Hale notes that the term EGFR appears three times, while CD4 and CD20 appear five times and CD25 appears ten times, and that “[i]n another aspect” appears more than 115 times and “[i]n one aspect” more than 90 times (EX1003, Hale Decl. ¶¶ 93, 154). But the frequency with which an antigen appears in a set of figures is not, by itself, a reliable measure of what a POSITA would understand from a particular figure, and those counts do not diminish Figure 3’s disclosure. Figure 3 discloses an anti-EGFR antibody coupled to a TGFβRII domain, as Dr. Hale admits. EX1003, Hale Decl. ¶ 94.

68. Petitioner relies on Dr. Bedi’s April 17, 2025 declaration from the file history of U.S. Application No. 18/811,627, arguing that Dr. Bedi agreed in a

different prosecution that broad, optional disclosures in a common specification did not disclose an anti-PD-1 antibody, and contending by analogy that the broad targeting-moiety disclosures here likewise do not support the claimed anti-EGFR targeting moiety. Pet. at 37-39; EX1044 at 1-2. Dr. Bedi's declaration concerning an anti-PD-1 antibody—a different antibody and a different target—does not change my opinion about the anti-EGFR construct in Figure 3. That declaration did not address the specific anti-EGFR sequences, the Figure 3 annotations, or the TGF β R2 fusion shown here. The fact that a different target was discussed in that prosecution record does not show that a POSITA would disregard the specific anti-EGFR disclosures at issue here.

69. Dr. Hale argues that the minimal construct of claim 1 includes an unpaired cysteine (Cys214) free thiol at position 214 in the light chain, which he contends would lead to instability, aggregation, or failure of expression (EX1003, Hale Decl. ¶¶ 101, 119, 169). I disagree. An unpaired cysteine would be a problem, at most, only if it is not subsequently paired with another cysteine, and the word “comprising” allows this to happen.² A POSITA looking at the elements in figure

² Dr. Hale also states that “The actual subgenus of molecules covered by claim 1 is far more varied than those examples shown, since it may include any of the linker peptides and *any number of unspecified components or chains*.” EX1003, Hale Decl. ¶ 162 (emphasis added). Accepting Dr. Hale's argument would mean that any patent claim using the word “comprising” would be invalid, as it could include any number of components or chains in addition to those expressly recited in the claim. But as I discuss in this declaration, a POSITA would use their experience

D of Dr. Hale's declaration (EX1003) would know to do two things based on the specification and their ordinary knowledge of antibodies. First, they would recognize that 3/4 of a Fab is already there, and for stability and expression purposes, it would be clear that adding a CH1 domain would be the favorable next step, and this domain would have a cysteine in the proper place to pair with Cys214 of the light chain. (The location of that Cys would depend on which class or subclass of heavy chain constant domain was chosen, but regardless of the choice, Cys214 would not be unpaired). Second, they would see that the claim is for "An isolated molecule," not a complex or pair of molecules, so SEQ ID NO: 87 would be fused genetically to one of the termini, either directly or after the insertion of a linker or additional constant domains. This is straightforward antibody construction, not requiring extraordinary creativity or skill in the art.

70. A POSITA familiar with the antibody literature would readily understand that a claim reciting, for example, "a VH domain with sequence X and a VL domain with sequence Y"—without any mention of any other domain, linker, or component—does not mean that the two domains would be expressed as two independent proteins. A POSITA would know to link them somehow, likely by adding either a linker to make a scFv, or adding constant domains to make a Fab or

and common sense and would not be left to guess at an unbounded universe of potential molecules.

a full-length antibody. This would be common and understood by a POSITA.

Claims 1 and 9 in '968 are no different in this regard.

71. Dr. Hale states that, so far as he is aware, “an isolated molecule having just a heavy chain variable region combined with a complete immunoglobulin light chain has not been described in the scientific literature” (EX1003, Hale Decl. ¶ 119). Even if Dr. Hale is not aware of this exact fragment having been made or described in the literature, that observation does not answer the written-description question. I understand that written description asks whether the specification conveys possession to a POSITA; it does not require that the claimed construct already be known, previously made, or separately named in the literature. Figure 3 supplies the relevant sequence and structural signposts, and the specification expressly identifies fragment formats that a POSITA would have understood.

72. The specification’s disclosures therefore show that the inventors possessed the subject matter in claim 1.

B. Claim 9: Light-Chain Linkage and Dr. Hale’s Statements About the “Integrated Whole” in the Claims

73. I disagree with Dr. Hale’s opinions in paragraphs 152-154 of his declaration that the specification provides no disclosure or blaze marks for attaching a linker to the light chain. The specification states at column 35, lines 48-50, for example, that in another aspect, an immunomodulatory polypeptide is

fused to the C-terminus of the light chain of a targeting antibody. Read with Figure 3's anti-EGFR sequence, linker, and TGF β RII markings, a POSITA would understand from that disclosure that light-chain-side fusion was an intended configuration, not an impermissible reconstruction. EX2042, Hale Dep. Tr. at 98:15-99:6, 103:13-21.

74. I respond to Dr. Hale's opinions at paragraphs 147-154 that claim 9 must be assessed as an "integrated whole" and that the common specification does not describe that whole. While I agree that claim 9 should be assessed as a whole, that is precisely what Figure 3, read together with the passage at column 35, lines 48-50 (describing fusion of an immunomodulatory polypeptide to the C-terminus of the light chain of a targeting antibody and the recited linker of SEQ ID NO: 104) supplies. Claim 9's integrated whole is not an arbitrary collection of unrelated options. It specifies four structural components: the light-chain sequence of SEQ ID NO: 71, the variable heavy-chain sequence comprising amino acids 1-119 of SEQ ID NO: 2, the TGF β RII sequence of SEQ ID NO: 87, and the linker of SEQ ID NO: 104. It then fixes the spatial arrangement by requiring the light chain at the linker's N-terminus and the immunomodulatory moiety at its C-terminus. Figure 3 thus supplies the sequence context and typographic signposts, while column 35, lines 48-50 supplies the light-chain-side orientation. EX2042, Hale Dep. Tr. at 125:18-126:19.

75. Furthermore, viewed another way, Figure 3 and the disclosure at column 35, lines 48-50 provide a complete molecule with no additional design necessary. Figure 3 (and the rest of the figures depicting sequences of antibodies with fusions on the C-terminus of the Fc) are examples of embodiments, but not an exhaustive list of all embodiments. The passage at column 35, lines 48-50 gives a simple instruction to attach the fusion protein to the C-terminus of the light chain. In other words, a POSITA simply cuts the sequence at the end of the Fc, and moves the entire fusion protein (linker plus TGF β RII) to the C-terminus of the light chain—a bit of antibody design that would be well within the capabilities of a POSITA in 2010. This one operation creates a molecule that is both reasonable to make and that satisfies both claims 1 and 9.

76. I understand that, in his deposition, Dr. Hale suggested that the language of the statement “. . . the immunomodulatory moiety is a polypeptide that is fused to the C-terminus of the light chain of a targeting antibody” (EX1001 at 35:48-50) only allows direct fusions with no linker, and that the word “linked” would be used when a linker is present. I further understand that the purported basis for this argument is that the phrase from earlier in the same paragraph (EX1001 at 35:33-36) referring to a targeting moiety being “linked or fused to an immunomodulatory moiety consisting of a polypeptide, with a linker or without a linker” essentially defines the word “linked” to be used when joining two

sequences via a linker, and “fused” used when there is a direct connection with no linker. I disagree. In fact, this cannot be correct, because (a) there is no indication of a parallel phrase (such as the word “respectively”); the term “linked or fused” simply acknowledges two different terms for attaching two polypeptide chains, and includes both for completeness, and (b) in the ’968 patent col. 43, lines 53-61, the word “fused” is used without the word “linked,” yet the illustrative sequence (SEQ ID NO: 1) includes an identified linker. I identified six instances of the word “linked” in the ’968 patent, and none of the other five are used when referring specifically to fusions including an intervening linker sequence. This contrasts with the 27 uses of the word “fused,” many of which describe a construct that does include a linker. Thus, Dr. Hale’s new and unsupported argument that “. . . it seems to be that it uses the language linked when there’s a linker, fusion when they’re directly joined” (EX2042, Hale Dep. Tr. at 102:25-103:2) has no basis, and a POSITA would not agree with it.

77. Light-chain-side engineering was also technically feasible and known before the relevant date. Müller (EX2031 at 259-260), for example, describes an scFv-CL construct in which the kappa light-chain constant domain is fused to an anti-CD2 scFv, as well as an scFv-CH1 construct involving an anti-EGFR scFv. EX2034 describes an scFv-CH1-CL format retaining the constant domains of a natural Fab, and EX2035 discusses the domain interactions of engineered scFv and

Fab formats. These references provide concrete evidence that a POSITA understood how to incorporate light-chain constant-domain material into fragment-based constructs. My antibody-fragment and Fc-fusion design work provides an additional practical basis for the same conclusion. EX2042, Hale Dep. Tr. at 51:25-53:7, 125:18-126:19.

78. A POSITA would be expected to be aware of advances in the field, particularly those published in widely read protein and antibody engineering journals. In the 2000s, Protein Engineering, Design & Selection (PEDS) was one of the leading journals for reporting engineering advances. Orcutt et al. (EX2038) published a paper describing fusions of several different modules to the C-terminus of an antibody light chain: Orcutt et al., A modular IgG-scFv bispecific antibody topology, 23 Protein Engineering, Design & Selection 4, 221-228 (2010) (published online Dec. 17, 2009). For example, Orcutt at 221 describes that disulfide-stabilized scFv fused to the C-terminus of an IgG light chain retains parental affinities, IgG-like stability, and in vivo targeting. Orcutt at 223 and Figure 1 describes a light chain constructed as VL-C κ -(Gly4Ser)₂-scFv—*i.e.*, C-terminal fusion to the kappa light-chain constant domain via a (G4S)₂ linker. The paper was published online on December 17, 2009, and thus a POSITA would have been aware of it. In addition, Xencor in U.S. Patent Application Publication No. 2006/0222653 A1 (filed Nov. 14, 2005; published Oct. 5, 2006) (EX2045)

describes antibodies with non-antibody proteins fused (via a Gly-Ser type linker) to the C-terminus of the light chain. These disclosures, combined with the “blaze marks” in the patent specification, support my conclusion that a POSITA would have understood that the inventors possessed the design of claim 9 and would have been able to generate it.

79. From a technical standpoint, I consider fusing a moiety to the C-terminus of an antibody light chain—typically through a flexible Gly-Ser linker, such as (G4S)_n—to have been an established and workable protein-engineering technique before 2010-2011. Müller (EX2031 at 259-260) describes functional constructs in which an scFv is fused to the C-terminal CL domain and an scFv is fused to the C-terminal CH1 domain. Orcutt (EX2038) describes a disulfide-stabilized scFv fused to the C-terminus of an IgG light chain through a (G4S)₂ linker, with retained parental binding affinities and IgG-like stability in vitro and in vivo. Notably, Orcutt specifically notes the lack of difficulty in making these constructs, and the fact that linker length is not critical: “To date, we have synthesized several versions of the construct with various IgG and scFv domains, and all molecules bind simultaneously to their respective targets and retain parental affinities within 2-fold. No linker-length optimization is required for expression and retention of scFv and IgG binding.” EX2038 at 226. In addition, Xencor (EX2045) depicts in Fig. 4A an intact IgG1 with C5a fused to the C-terminus of

the light chain through a Gly-Ser linker and describes Gly-Ser/(GGGGS)_n linkers of approximately 1-20 amino acids. Taken together, these disclosures show, as a technical matter, that a POSITA would have understood the claim 9 architecture—a complete light chain (SEQ ID NO: 71) fused through the (GGGGS)₃ linker (SEQ ID NO: 104) to the TGFβRII ectodomain (SEQ ID NO: 87) at the light chain's C-terminus—and understood that the inventors possessed it.

80. In addition, Schanzer et al. (2011) (EX2043) analyzed scFv fusions at the N- and C-termini of the heavy or light chain of a master IgG using (G4S)₂ and (G4S)₃ linkers. Xencor (EX2045), WO 2012/178137 A1 (December 27, 2012) (EX2044), likewise describes light-chain C-terminal immunoglobulin fusion proteins using (Gly₄-Ser)_x linkers. These disclosures confirm that the technique continued to be used and recognized even after the earliest claimed priority date of the '968 patent.

81. In fact, Dr. Hale characterizes claim 9 as narrower than claim 1 because it covers only antibody fragments and specifies the light-chain fusion orientation (EX1003, Hale Decl. ¶ 166), and claim 9 further fixes linker SEQ ID NO: 104 (EX1001 at claim 9). Those arguments and the claim language itself undermine Dr. Hale's reliance on the random-orientation hypotheticals used against claim 1. The specification's light-chain fusion disclosure, Figure 3, and the

known fragment formats therefore provide a focused technical path to the claimed architecture.

82. The specification's disclosures therefore show that the inventors possessed the subject matter in claim 9.

VIII. ENABLEMENT (GROUND 2)

A. Claim Scope, Architecture, and Experimental Burden

83. Dr. Hale constructs a scope calculation to argue that the specification discloses an unwieldy number of candidate molecules, from which a POSITA would have had no blaze marks to arrive at the claimed combination. He first offers a lower bound of 6,720 candidates based on 24 named targets $\times$ 10 immunomodulators $\times$ 14 linkers $\times$ 2 orientations (EX1003, Hale Decl. ¶ 88), and then advances a substantially larger figure of 227,332, using 269 possible targets plus 84 named antibodies $\times$ 23 immunomodulators $\times$ 14 linkers $\times$ 2 orientations (EX1003, Hale Decl. ¶ 89 & n.7). The apparent purpose of both calculations is to portray the specification as a vast, undifferentiated forest in which the claimed combination cannot be found without impermissible hindsight.

84. That framing fails because it ignores the specification's narrowing. Dr. Hale counts 24 or 269 targets because his theory assumes the specification provides no "blaze marks" favoring EGFR over any other target (EX1003, Hale Decl. ¶¶ 89-90). But the specification does narrow. First, EGFR is expressly named as a target in the Summary of the Invention (EX1001 at 2:43-54). Second, the

Detailed Description identifies EGFR as a target for the targeting moiety alongside a short list of named antigens, and expressly pairs an anti-EGFR antibody with TGF β RII (EX1001 at 3:49-55). Third, Figure 3 provides the only exemplary fusion protein that combines an anti-EGFR antibody with a TGF β RII extracellular domain, identifying the specific sequences (SEQ ID NO: 2 and SEQ ID NO: 71), the specific immunomodulatory domain (the bold TGF β RII portion, which is SEQ ID NO: 87), and a (GGGGS)₃ linker (EX1001 at Fig. 3, Sheet 6/75, col. 7:65-8:4). Fourth, the brief description of the drawings expressly names the linker (GGGGS)₃, which corresponds to SEQ ID NO: 104 (EX1001 at 8:27-30). Each of those steps narrows the field: from hundreds of targets to EGFR; from EGFR to a specific anti-EGFR antibody sequence; from the genus of immunomodulatory moieties to TGF β RII; and from 14 possible linkers to SEQ ID NO: 104.

85. Dr. Hale's calculations suffer from several logical and practical errors.

86. First, in his second calculation, he sums the targets and antibodies.

This would be reasonable if the set of antibodies in the antibody count did not bind any of the targets in the target count. But for any target with an antibody in the list, adding them both is double counting. Because of that, a more accurate way to phrase even Dr. Hale's calculation would be to say, "185 possible new targets plus 84 named antibodies," where the "new targets" are targets for which there is not an antibody in the list.

87. Second, Dr. Hale proposes that a POSITA would have to test every individual length of linker in the range of 1-8 repeats of GGGGS and every one of the linkers suggested in SEQ ID NOs: 104-111. This is unreasonable and a POSITA would not expect or require that this be done. When testing linkers of different lengths, a POSITA would understand that it is sufficient to sample representatives examples. This is consistent with my experience involving numerous instances of linker optimization, where I never saw a situation where the length was so critical that fine sampling was necessary to identify an active molecule. It is also consistent with Dr. Hale's own work. In the patent application GB2535753A (EX2037) on which Dr. Hale is a named inventor, table 11 describes a number of constructs the inventors designed and tested, with different length linkers. In this case, one of the core polypeptides, identified as *E. coli* ferritin, was tested with linkers ranging from 10 to 50 copies of the 5-amino acid sequence EAAAK. The inventors did not systematically test every one of the 41 possible linkers; they only tested 5 linkers, with lengths of 10, 20, 30, 40, and 50 EAAAK units. This is consistent with the way a POSITA would have approach such a task as well. In my opinion, a POSITA would sample approximately 2 different GGGGS linker lengths, as well as no linker at all. To that we can add 2 of the other defined linkers, as several of them are extremely similar, so by the same logic there is no reason to test them all up front.

88. With these adjustments applied, when claim 1's sequence limitations are applied to Dr. Hale's formula, there is 1 antibody VH/VL pair (that binds EGFR) + 0 new targets that have no antibody already counted, 1 immunomodulatory moiety (TGFβRII), 5 different linkers, 2 different chains to fuse (heavy and light), and 2 orientations for each chain (N- or C-terminus). Multiplying these options together, $(1 + 0) \times 1 \times 5 \times 2 \times 2$ yields 20 combinations.

89. Claim 9 narrows further still: it specifies the antibody-fragment format, fixes linker SEQ ID NO: 104, and fixes both fusion orientations, reducing the combination count to approximately 2 candidate architectures (Fab or full-length antibody, each with TGFβRII fused to the light-chain C-terminus via the linker of SEQ ID NO: 104). The claim-limited result is the same under either of Dr. Hale's starting figures because the reduction comes from claim 1's sequence limitations, not from the size of Dr. Hale's starting universe, and his starting universe is inflated because it ignores the narrowing the specification provides.

90. Although I believe the adjustments described above reflect what a POSITA would actually do, I have also applied Dr. Hale's formula at its outermost boundary, without any of those adjustments, in order to identify the maximum number of combinations that could be said to fall within the scope of claims 1 and 9. Dr. Hale's formula multiplies (targets + antibodies) $\times$ immunomodulators $\times$ linkers $\times$ orientations (EX1003, Hale Decl. ¶¶ 88-89 & nn.5-7). Claims 1 and 9

recite a single EGFR-targeting antibody, supplied by the cetuximab-derived sequences of amino acids 1-119 of SEQ ID NO: 2 and SEQ ID NO: 71, and a single immunomodulatory moiety, the TGFβRII extracellular domain of SEQ ID NO: 87 (EX1001 at claims 1, 9). Retaining Dr. Hale's own convention of summing the target and the antibody, retaining the full set of 14 linkers disclosed in the specification rather than the representative subset a POSITA would select (SEQ ID NOs: 104-110 and 123; EX1001 at 10:56-58, 11:28-31, 35:37-42; EX1003, Hale Decl., App'x B § 5), and retaining his 2 fusion orientations—fusion at the C-terminus of the heavy chain, as exemplified in Figure 3, and fusion at the C-terminus of the light chain, as described at EX1001 at 35:48-50—the calculation is $(1 \text{ target} + 1 \text{ antibody}) \times 1 \text{ immunomodulatory moiety} \times 14 \text{ linkers} \times 2$ orientations, which yields 56 combinations. In my opinion, 56 is therefore the outer ceiling of the claim-limited design space under Petitioner's own methodology. I emphasize that 56 is a ceiling rather than a prediction of the experimental work a POSITA would actually perform. It is the number obtained by applying Petitioner's methodology, unmodified, to the actual sequence limitations of claims 1 and 9, and it is useful principally because it demonstrates that even on Petitioner's own approach the claimed design space is small and bounded—not the universe of 6,720 or 227,332 candidates Dr. Hale derives from the specification as a whole (EX1003, Hale Decl. ¶¶ 88-89). The realistic figure is substantially smaller

for two independent reasons that I have described above. First, summing the target and the antibody double counts the same molecule, because the single antibody recited in claims 1 and 9 is an antibody to the single recited target; correcting that error alone reduces the figure to approximately 28 combinations. Second, a POSITA would not design and test all 14 disclosed linkers before learning anything from the first constructs; sampling approximately 2 GGGGS linker lengths together with a no-linker construct, plus 2 of the remaining defined linkers, gives the 5 representative linkers I describe above and yields the figure of approximately 20 combinations. The 56-, 28-, and 20-combination figures are therefore complementary rather than inconsistent: 56 is the outer ceiling under Dr. Hale's unmodified assumptions, approximately 28 corrects his double counting of targets and antibodies, and approximately 20 reflects the representative linker sampling a POSITA would actually employ. In my opinion, every one of these figures falls well within the range of routine design, expression, and testing work for a protein-engineering or drug-discovery program in the 2010-2011 timeframe, and none of them approaches undue experimentation.

91. That calculation should be understood in context. Dr. Hale's formula $(\text{targets} + \text{antibodies}) \times \text{immunomodulators} \times \text{linkers} \times \text{orientations}$ uses 14 linker choices and 2 orientations as multipliers (EX1003, Hale Decl. ¶¶ 88-89 & nn.5-7). Applying the claim-specific values to the target, antibody, and immunomodulatory

variables, and including the reasonable sampling decisions a POSITA would know, as I did above, yields approximately 20 combinations for claim 1. That figure represents the *fusion-protein* set of molecules a POSITA would actually design and produce using the specification's disclosures.

92. The 20-combination figure assumes every claim 1 molecule contains a fusion protein, in most cases with a linker, in one of two orientations. As a textual matter, claim 1 does not expressly recite a linker or a fusion between the targeting and immunomodulatory moieties, and Dr. Hale reads the claim as reaching molecules that are not fusion proteins (EX1003, Hale Decl. ¶ 92). But I understand the question for enablement is not what the claim might theoretically encompass at its outermost boundary; it is whether the specification enables a POSITA to make and use the claimed invention. In my opinion, a POSITA reading the '968 patent—a patent titled “Compositions and Methods for Targeted Immunomodulatory Antibodies and Fusion Proteins” (EX1001 at Title)—would understand the specification as directed to fusion proteins and would pursue fusion-protein architectures using the specification's disclosures. The specification teaches recombinant-DNA construction of fusion proteins (EX1001 at 43:40-52), identifies (GGGS)_n linkers (EX1001 at 35:33-42), and discloses light-chain fusion orientation (EX1001 at 35:48-50). Every exemplary construct containing an antibody targeting moiety is a fusion protein, and all 35 such constructs in Dr.

Hale's Appendix C are full-length antibody heavy-chain fusions (EX1003, Hale Decl. ¶ 81, App'x C). The specification does not teach unlinked, non-fused molecular arrangements, and a POSITA would not interpret it as directing such work.

93. A POSITA also would not be concerned by the scope of claim 9. Claim 9 requires a polypeptide linker of SEQ ID NO: 104 and specifies that SEQ ID NO: 71 is fused to the linker's N-terminus and SEQ ID NO: 87 is fused to its C-terminus (EX1001 at claim 9). Those limitations fix both the linker and the fusion orientation, reducing the scope to 2 candidate architectures under Dr. Hale's counting method, a Fab-format construct and a full-length-antibody-format construct, each with the TGF β RII domain fused to the C-terminus of the light chain via the (GGGGS)₃ linker. Both architectures are straightforward for a POSITA to design and produce using the specification's disclosures and established recombinant methods.

94. Dr. Hale's Figure K and paragraphs 162-163 describe molecules in which VH, light chain, and immunomodulatory moiety are separate chains; chains are covalently associated; two components are genetically fused in six possible pairings; or all three are genetically fused in six possible orders (EX1003, Hale Decl. ¶ 162). Those are theoretical architecture categories, not a showing that every permutation falls within the scope of claim 1. Claim 1 still requires the specified

sequences, a targeting moiety that specifically binds EGFR, an immunomodulatory moiety comprising SEQ ID NO: 87, and an isolated molecule. A POSITA would readily understand that claim 1 does not encompass every molecule identified by Dr. Hale. A POSITA would apply ordinary protein-engineering judgment to identify structurally reasonable constructs worth making and to exclude configurations that are incomplete, chemically conjugated rather than recombinantly expressed, or inconsistent with the claim's "isolated molecule" requirement. So in the case of Figure K from Dr. Hale's statement, all the group (a) designs would be eliminated because they do not produce an isolated molecule, those in group (b) would be eliminated because they require a complex and difficult chemical conjugation that is not the way a POSITA would attempt to generate fusions of these proteins, and group (d) would be eliminated because they are not well formed designs for this context, and are all missing a CH1 domain.

95. I identified the following eight structures as both satisfying claim 1 and, in my opinion, making logical sense from the perspective of a POSITA. The "sense test" I performed simply eliminates those that are 1) incomplete (*e.g.*, a CL with no CH1, such as the first construct in Dr. Hale's Figure K, group (c)) and that therefore would have a high chance of instability, aggregation, or other liability; 2) fused using a synthetic mechanism (*e.g.*, covalently linked by a chemical linker, such as those shown in Figure K, group (b)), and that would therefore be

unnecessarily difficult to produce; and 3) not an isolated molecule (*e.g.*, that have multiple chains that are not linked covalently, such as those in Figure K, group (a)), and that therefore fall outside the bounds of claims 1 and 9, both of which require “an isolated molecule.” These diagrams (taken from Dr. Hale’s Figure K) do not show linkers, but linkers could be inserted. However, contrary to Dr. Hale’s suggestions that linkers could be put anywhere, any POSITA knows that linkers are there to link domains, and in particular, to link domains that do not already have a natural linkage. Thus, the only place a POSITA would put linkers is between an antibody domain and the TGF β RII domain. Thus, the eight possible constructs could be 16 (with or without linker), or 24 (no linker, short linker, longer linker), but any POSITA would know that a small number of linkers is sufficient to provide guidance as to what would work best. Thus, the amount of experimentation required would fall well within the normal, expected amount of experimentation for a therapeutics program.

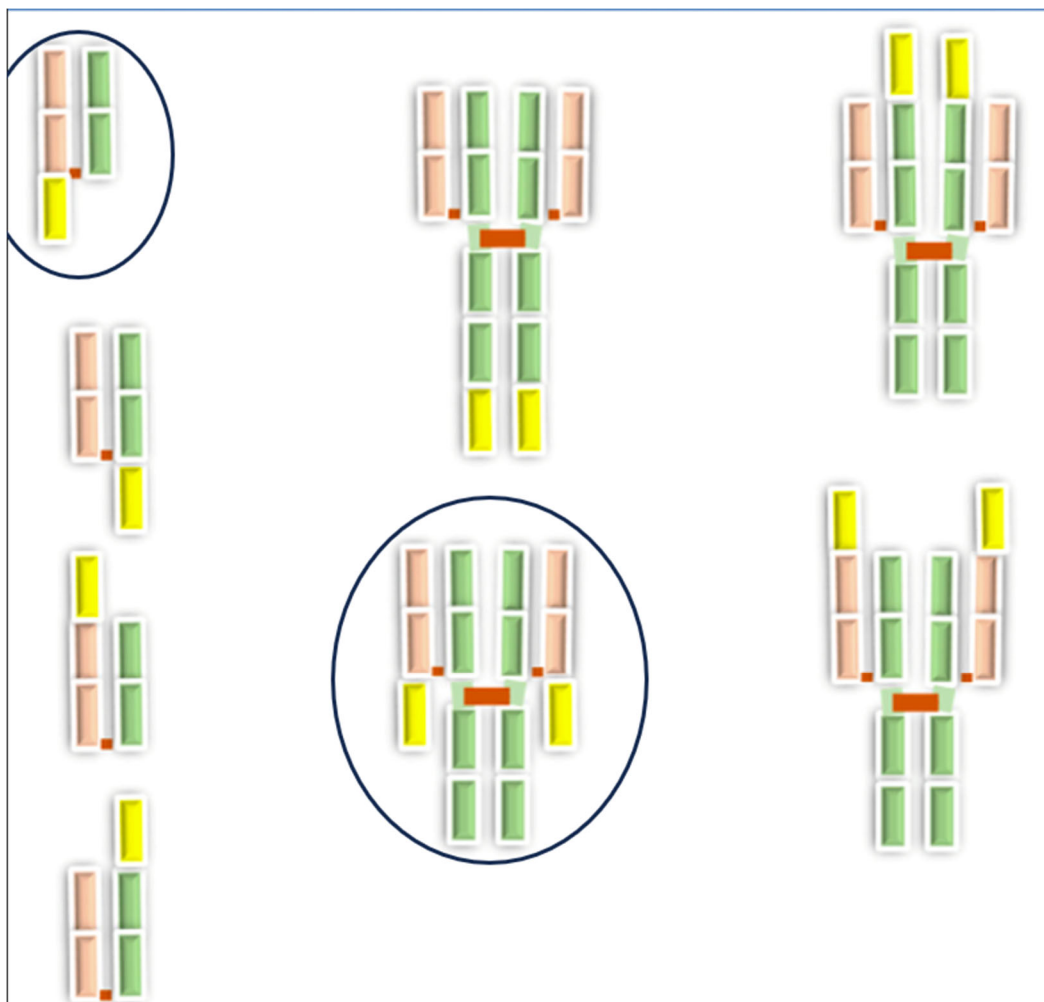


Figure 1: eight constructs that satisfy claim 1. Circled constructs satisfy claim 9 if they contain the specified linker.

96. Dr. Hale states that a POSITA “would have to design a research plan and experimentally validate” each molecule within claim 1’s scope (EX1003, Hale Decl. ¶ 171), and the Petition asserts that “a POSA would have to do the same amount of experimentation for each molecule covered by claim 1” (Pet. at 75). His “research plan” in paragraphs 172-173 is hypothetical (EX1003, Hale Decl. ¶ 173). In my opinion, the listed steps describe an ordinary workflow for constructing and testing a recombinant protein, not a research assignment unique to these claims.

One common thread is that while there are choices at many of the steps, a POSITA—including a POSITA that is part of a research organization or lab—would typically have a set of protocols and standards for many or all of the steps laid out as part of their standard practice.

- Step A: deciding whether chains should be expressed separately or from the same cell—does not reflect a uniquely difficult research problem for the constructs a POSITA would actually make. A POSITA would begin with the selected antibody or antibody-fragment architecture and would choose a single-plasmid or dual-plasmid expression format based on standard laboratory practice and the construct design. I have worked with teams that prefer single plasmid designs and others that prefer dual plasmid designs, and they both work fine.
- Step B: selecting an expression vector and host cell while considering secretion, glycosylation, codon usage, and related factors is also standard protein-engineering practice. These choices were part of the routine team-based work reflected in my 2001-2019 structural-biology and protein-design positions, not decisions requiring an undisclosed scientific breakthrough. The decision would likely be in part driven by the specific lab's practices and available expression cell lines.

- Step C: designing the vector with promoter, enhancer, signal peptide, and related expression elements—would involve ordinary recombinant-DNA design choices available to a POSITA by 2010. These choices require technical judgment, but they do not require an undisclosed scientific breakthrough. And as before, any lab would have one or two go-to vectors for antibody constructs that already contain all those elements, and with which the POSITA would be familiar. So the reality is that the POSITA would pick from the short menu, rather than doing any designing.
- Step D: producing the vector, this is routine work for any POSITA, and would not need to be spelled out in a specification at the time of filing.
- Step E: transfecting or infecting the selected host, and step F, checking whether the desired polypeptides are produced, were standard expression and characterization steps. A POSITA would use their lab's standard transfection protocol, followed by ordinary expression analyses to determine whether the construct was produced and, if expression was suboptimal, would troubleshoot the vector, construct, host, or culture conditions. That iterative optimization is ordinary experimentation in recombinant protein development; it is not a random discovery process as you might find in situations involving functionally defined candidates with no structural identity, contrary to what Dr. Hale asserts in his declaration.

- Step G: purifying the desired polypeptide would use purification methods selected for the chosen format, including methods already familiar for recombinant antibodies and fusion proteins.
- Step H: chemical crosslinking—would not be the approach a POSITA would select for the sequence-defined fusion constructs at issue. The specification expressly teaches recombinant-DNA construction of fusion proteins, and a POSITA would use that route for these constructs (EX1001 at 43:40-52).
- Step I: characterizing the product would include assessing identity, assembly, purity, and stability, all of which were readily performed by POSITAs in 2010. Testing EGFR binding would use the standard binding-assay tools available for a well-characterized antibody target. By 2010, cetuximab had been on the market for years and was known in the literature, so a POSITA could simply compare the binding results with literature results, using whatever method is available.

97. Each step is a conventional part of making and using a recombinant antibody or fusion protein.

98. Dr. Hale’s nine steps map onto the four-step “routine” process he describes in elsewhere in his declaration (EX1003, Hale Decl. ¶ 62). Steps A-D are design and construct preparation; steps E-F correspond to transfection, selection, and expression; steps G-H correspond to purification and characterization; and step

I is functional binding assessment. Dr. Hale acknowledges that the plan is “merely hypothetical” and offered in the *absence* of guidance or working examples (EX2042, Hale Dep. Tr. at 150:3-13, 153:21-25). That matters here because the specification supplies the sequences, Figure 3 markings, linker information, and recombinant-production direction as I explain in this declaration. Nothing about Dr. Hale’s hypothetical nine-step process suggests that undue experimentation would be needed to make and use the claimed invention.

B. State of the Art, Predictability, and Retained Binding

99. The state of the art by 2010 was sufficiently mature that recombinant fusion-protein production was a known engineering discipline rather than an unbounded research problem. In fact, my own contemporaneous work included the SEEDbody heterodimeric Fc platform, IL-2/IL-2 receptor fusion proteins, and Combnectin, a multi-component fusion biologic. Those platforms required the same core activities at issue here—designing domains and linkers, constructing nucleic-acid fusions, expressing recombinant proteins, and characterizing their structure and function.

100. Dr. Hale’s description of the field confirms that numerous fusion proteins had been described by 2010, that several had been approved and marketed, and that most included one or more immunoglobulin domains (EX1003, Hale Decl. ¶ 59). Peptide linkers were known; a flexible linker consisting of one or

more copies of GGGGS was commonly used (EX1003, Hale Decl. ¶ 61; EX2042, Hale Dep. Tr. at 56:16-57:25). Multiple Fc-fusion proteins had received International Nonproprietary Names (“INNs”) by March 2010, including abatacept, aflibercept, alefacept, atacicept, baminercept, belatacept, briobacept, eftrenonacog, and rilonacept (EX1003, Hale Decl. ¶ 59). Dr. Hale also identifies antibody-active protein fusions such as Zemab (anti-HER2 scFv linked to pseudomonas exotoxin), MFECP1 (anti-CEA scFv linked to carboxypeptidase), and EMD 273066 (anti-EpCAM IgG linked to interleukin 2) (EX1003, Hale Decl. ¶ 60). These examples, drawn from Dr. Hale’s own survey of the field, show that by 2010 the field had established formats, methods, and expectations, and that a POSITA would not be starting from an undefined and blank slate in attempting to practice the claims.

101. For example, flexible (GGGGS)_n linkers were standard tools by 2010. Dr. Hale states that the different protein domains making up fusion proteins “are commonly linked by a short peptide, the sequence of which is optimised to ensure that the fusion protein can be manufactured efficiently and the biological activity of each component is maintained,” and that “[o]ften a flexible linker consisting of one or more copies of four glycine residues and one serine residue (GGGGS) is used” (EX1003, Hale Decl. ¶ 61; EX2042, Hale Dep. Tr. at 56:16-57:25). Dr. Hale also observes that a fusion protein oriented A-linker-B may be functional while B-

linker-A is not (EX1003, Hale Decl. ¶ 64). That observation does not show undue experimentation. A POSITA would construct the orientations required by the design, test them, and select the functional format; a routine exercise in protein engineering, not an unpredictable research program. That issue is especially manageable for claim 9, which fixes the linker as SEQ ID NO: 104 and specifies that the light chain is fused to the linker's N-terminus and the immunomodulatory moiety to its C-terminus (EX1001 at claim 9). But even for claim 1, the linker issue is bounded: the specification discloses a concrete set of linkers (SEQ ID NOs: 104-110 and 123), and Dr. Hale's own combinatorial formula uses those 14 linkers as one of its multipliers (EX1003, Hale Decl. ¶ 88), and realistically, a subset of these linkers would be selected for testing. Figure 3 further provides a starting architecture showing C-terminal heavy-chain-side fusion with a (GGGGS)₃ linker (EX1001 at Fig. 3, Sheet 6/75). A POSITA would treat linker selection for claim 1 as a finite design exercise informed by the specification's disclosures and the established state of the art, not as an open-ended research problem.

102. Dr. Hale asserts that a POSITA would not know whether molecules falling within the scope of claim 1 would specifically bind EGFR, reasoning that "incorrectly folded, aggregated, or insoluble fragments are unlikely to specifically bind to their target" (EX1003, Hale Decl. ¶ 170; see also EX1003, Hale Decl. ¶¶ 167-169). That framing treats binding loss as the expected outcome of adding a

second functional domain. A POSITA would not share that assumption. Antigen binding depends primarily on the variable domains, and a C-terminal fusion—where the added domain is physically distant from the antigen-binding interface—is the least likely architecture to disrupt binding. Dr. Hale’s own survey of the field confirms the point: the antibody-cytokine fusions he identifies, including Zemab, MFECp1, and EMD 273066, all retained targeting-moiety function with the non-immunoglobulin protein linked at the C-terminus (EX1003, Hale Decl. ¶ 60). Even the IL-2/ch14.18 example Dr. Hale uses to illustrate fusion-protein difficulties shows that the full-antibody-format fusion retained function; it was a specific CH2-domain fusion that failed to assemble, not a C-terminal fusion to the intact heavy chain (EX1003, Hale Decl. ¶ 63). And a careful reading of the paper describing this work shows that the authors were just systematically testing the fusion at each domain, regardless of chance of success (SD Gillies et al., 1992 PNAS <https://doi.org/10.1073/pnas.89.4.1428> (EX2047)). A POSITA would have known that CH3 domain interaction was the driving force behind heavy chain assembly, so a construct missing the CH3 domain would be expected to fail to assemble. Thus, this failure had nothing to do with the fusion partner and everything to do with the removal of the CH3 domain. A POSITA would expect retained antigen binding to be evaluated across the relevant fusion formats, not assumed lost merely because a second domain is present. My experience across antibody-fragment and

fusion-protein platforms supports the use of domain boundaries and flexible linkers to preserve the antigen-binding structure while adding another functional domain. A POSITA would readily understand that while not every construct is guaranteed to bind, binding can be expected from a known antibody sequence in a C-terminal fusion architecture and confirmed with routine assays (EX1003, Hale Decl. ¶ 172(I)), rather than discovered through an open-ended search for new antibodies.

103. The enablement question follows the same technical point. Constructing a light-chain-side fusion did not present a category of difficulty distinct from the heavy-chain-side fusion disclosed in Figure 3. The C-terminus of C κ and the C-terminus of CH3 share two features relevant to fusion-protein design: both are solvent-exposed and both are physically distant from the antigen-binding CDR loops at the N-terminal tips of the V H and V L domains. In a standard IgG, the C κ C-terminus is oriented away from the Fab's antigen-binding interface, and separated from the binding domains by length of the CL domain (EX1003, Hale Decl. ¶ 42, Fig. A (depicting light-chain constant domain opposite the variable-region binding site)). Petitioner may contend that the C κ C-terminus sits adjacent to the interchain disulfide bond that connects the light chain to the heavy chain CH1 domain. That disulfide is a single covalent bond between defined cysteine residues; it does not create a steric barrier to appending a flexible linker at the C κ C-terminus. A (GGGGS)₃ linker of the type specified in the patent provides

approximately 45 Å of reach, which is more than sufficient to project the TGFβRII domain away from the interchain disulfide and the Fab core. Orcutt et al. (EX2038 at 221, 223 and Fig. 1) demonstrated precisely this kind of C-terminal light-chain fusion before the relevant date, appending functional modules to the Cκ C-terminus with retained binding. My own experience designing Fc and antibody fusions at EMD Serono, where the laboratory specialized in cytokine-fusion formats, and at BMS, where I co-invented Combinectin, a trispecific fusion biologic, confirms that a POSITA in 2010-2011 would have treated the choice of fusion terminus—Cκ or CH3—as a routine design variable to be evaluated empirically, not as a qualitatively different engineering challenge (EX1003, Hale Decl. ¶ 62 (acknowledging that recombinant IgG manufacture was “a comparatively predictable and routine process” by 2010); EX2042, Hale Dep. Tr. at 50:2-20). In either orientation, a POSITA would select the coding sequences and linker, express the construct in a suitable host, characterize the product, and test its binding and activity. The need to evaluate a construct empirically does not mean the configuration was beyond the understanding or capability of one skilled in the art.

104. The cetuximab-derived anti-EGFR sequences recited in claims 1 and 9 provide a particularly strong example of the fact that retained antigen binding can be expected from a known antibody sequence in a C-terminal fusion architecture

and confirmed with routine assays, rather than discovered through an open-ended search for new antibodies. Dr. Hale describes M225, a mouse monoclonal antibody recognizing the extracellular domain of human EGFR, and the chimeric C225, which combined the mouse heavy- and light-chain variable regions with human immunoglobulin constant regions (EX1003, Hale Decl. ¶¶ 55-56; Goldstein 1995 (EX1055) at 1311). Cetuximab was approved by the FDA in 2004 for treatment of colorectal cancer and later for head and neck cancer (EX1003, Hale Decl. ¶ 57; Prescribing Information 2004 (EX1073) at 6; Prescribing Information 2007 (EX1074) at 1). The claimed anti-EGFR sequences in claims 1 and 9 derive from that well-characterized binding framework; their variable regions correspond to the cetuximab variable regions that had already demonstrated clinical-grade EGFR binding in cetuximab. Standard assays for EGFR binding, including cell-based receptor-binding assays and ADCC assays, were available and routine by 2010 (EX1003, Hale Decl. ¶ 57), although Dr. Hale's hypothetical research plan treats assay development as if it were an open question requiring the POSITA to "devise assay method(s)" from scratch (EX1003, Hale Decl. ¶ 172(I)).

105. A POSITA would not face that problem here: the anti-EGFR variable regions are sequence-defined, cetuximab's binding properties were thoroughly characterized, the extracellular domain of EGFR was available for purchase, and confirming retained EGFR binding after C-terminal fusion would require

established assay formats, not new assay development. For these reasons, the cetuximab-derived sequences give a POSITA a well-characterized starting point for which retained EGFR binding after C-terminal fusion, including light-chain-side fusion, could be expected and readily confirmed.

C. Eight-Factor Wands Analysis

106. Below I address the eight “Wands” factors that I understand are relevant to the enablement question.

107. **Wands factor 1—Quantity of Experimentation.** Dr. Hale states that “[d]ue to the potential difficulties in producing many of the species, it is unpredictable exactly how much work might be required but it would certainly require a substantial team of highly skilled scientists working for many months or years, without any certainty of success.” EX1003, Hale Decl. ¶ 186. I disagree. Dr. Hale’s prediction is not tied to a particular molecule as recited in the claims, or to a project plan using the disclosed sequences. But a POSITA would have the patent’s disclosures and would not need to start from nothing, as Dr. Hale seems to assume. For example, a POSITA would begin with the defined anti-EGFR and TGFβRII sequences in the specification and claims, select a conventional recombinant format, and make and test the resulting construct. I have first-hand experience with this kind of routine experimentation many times in my career.

108. For example, claim 1 describes a molecule comprising three different polypeptide sequences, which are diagrammed in cartoon form by Dr. Hale in Figure H (EX1003, Hale Decl. ¶ 126, Fig. H). These three sequence elements are well-defined by the claim in combination with the figures describing the sequences; there is a VH domain, a complete light chain (VL + Ckappa), and a fragment of TGFβRII that is known to bind to TGF. In addition, the claim instructs that these three elements are all part of a single molecule. Note that while a canonical antibody is expressed as 2 separate sequences, the final molecule contains two copies of each chain, linked together by various inter-chain covalent disulfide bonds, so is thus considered a single molecule. This demonstrates that a single protein can include not only genetically linked domains but also disulfide-linked domains. The word “comprising” means that these three elements must be included but does not restrict the inclusion of other elements as well. So the question is whether reasonable or excessive experimentation would be required to generate an effective molecule of the invention, given the specification. In my opinion, it would not be required.

109. Dr. Hale reads the “comprising” language broadly. He states that claim 1 “does not require these moieties to be linked in any way, so it includes molecules which are not fusion proteins” (EX1003, Hale Decl. ¶ 92), and he lists a wide range of theoretical molecular architectures in his Figure K, extending to

“molecules which comprise additional components not enumerated in the claim, such as heavy chain constant domain(s), which would further expand the subgenus” (EX1003, Hale Decl. ¶¶ 162-163, Fig. K). Much of Dr. Hale’s enablement argument is directed at that expanded universe of theoretical molecules—constructs with arbitrary additional domains, unusual chain permutations, and architectures the specification does not teach and a POSITA would not pursue. But claim 1 does not instruct a POSITA to append arbitrary or unrelated proteins to the claimed construct. The three recited sequence elements—amino acids 1-119 of SEQ ID NO: 2, SEQ ID NO: 71, and SEQ ID NO: 87—define the molecule as having an anti-EGFR targeting moiety and a TGFβRII extracellular domain (EX1003, Hale Decl. ¶ 126, Fig. H). A POSITA in 2010-2011 would understand that each additional arbitrarily chosen domain beyond those recited elements would add expression, folding, stability, and purification risk without advancing the molecule's stated function of delivering TGFβRII to an EGFR-expressing target. Dr. Hale’s discussion of the field confirms that linking together two unrelated polypeptides could be unpredictable and lead to instability (EX1003, Hale Decl. ¶¶ 63, 167).

110. A POSITA exercising ordinary engineering judgment would therefore confine the work to structurally reasonable constructs informed by the specification's disclosures—Figure 3’s architecture, the disclosed linkers, and the

recombinant-DNA production instruction—rather than attempt to make every theoretical permutation Dr. Hale catalogs. That exercise of engineering judgment—identifying which constructs are worth building and which are not—is the ordinary work of an antibody engineer and is precisely what Petitioner's proposed POSITA, with a Ph.D. or equivalent experience in the relevant disciplines (EX1003, Hale Decl. ¶ 111), would have been expected to do.

111. From a technical perspective, the combination reflected in claims 1 and 9 is (i) EGFR binding supplied by the specific CDRs in the targeting moiety's variable regions and (ii) the immunomodulatory action of the TGF β RII extracellular domain. The heavy-chain constant region is not what supplies EGFR binding and does not define that technical combination, but it does bind to the open interface of the CL domain, and completes the disulfide bond with the C-terminal cysteine of the light chain, thus in two ways stabilizing the binding domains. A POSITA would certainly know to fuse the CH1 domain to the C-terminus of the VH domain (amino acid 119 in SEQUENCE ID NO: 2). Claims 1 and 9 require structural elements—the specified amino acid sequences (amino acids 1-119 of SEQ ID NO: 2, SEQ ID NO: 71, and SEQ ID NO: 87, and, for claim 9, SEQ ID NO: 104)—together with a functional element, specific EGFR binding. The functional binding requirement is determined by the variable regions, not the heavy-chain constant region. Neither claim requires a specific heavy-chain

constant-region sequence. Dr. Hale acknowledged in his deposition that a POSITA would understand Figure 3's markings to identify the variable regions, linker, and TGF β RII ectodomain, and would understand the plain portion as the heavy-chain constant region. EX2042, Hale Dep. Tr. at 74:6-15.

112. A POSITA would also know that therapeutic antibodies were ordinarily built on IgG backbones. The four IgG subtypes—IgG1, IgG2, IgG3, and IgG4—were defined by well-known sequences and were not ordinarily modified except for objectives such as changing half-life or effector function.

113. Thus, the relevant heavy-chain constant-region field is a small, defined set and not an unlimited set of arbitrary sequences. The specification supports an IgG1 embodiment. Its antibody definition states that an immunoglobulin may be of any type or class, including IgG1 (EX1001 at 34:35-41), and Figure 3 provides the anti-EGFR1 heavy-chain constant-region sequence. Consequently, only a limited number of heavy-chain constant-region sequences could realistically form the basis of a molecule within claims 1 and 9. The “blaze mark” provided by the IgG1 heavy chain constant domain in Figure 3 adds confidence for a POSITA to use IgG1. And further restriction is supplied in the specification, where there are many example sequences described in the figures and sequence listing that contain a full-length IgG1 heavy chain sequence. Any POSITA would understand this teaching and use the sequence in the patent,

particularly the one found in SEQ ID NO: 2, which is part of the anti-EGFR antibody. This bounded constant-region field is consistent with, and does not expand beyond, the approximately 20 claim 1 combinations and approximately 2 claim 9 architectures described above; it does not support treating the constant region as essentially unconstrained.

114. Additionally, in my opinion, a POSITA would further understand that the immunoglobulin subclasses are not interchangeable and have distinct, well-understood use-cases, and that this knowledge informs the selection of a heavy-chain constant region even where the figures and claims do not expressly specify one. As of the 2010-2011 period, a POSITA would have understood that IgG1 is the subclass ordinarily selected for antibodies targeting tumor-associated antigens (TAAs) and directly killing cells, because IgG1 efficiently engages Fc γ receptors and complement to mediate effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), whereas IgG2 and IgG4 exhibit substantially lower effector activity and are ordinarily reserved for niche or non-oncology applications in which effector function is not desired—for example, certain anti-inflammatory, allergy-related, or receptor-blocking contexts, or when the antibody is delivering an exogenous cytotoxic payload such as a drug or radionuclide—and IgG3 is rarely used therapeutically, in part because of its comparatively short serum half-life. Liu 2008

(EX1066). Because the claimed fusion proteins are directed to oncology, and the closest related antibody, cetuximab, was built on an IgG1 backbone, a POSITA designing a molecule within claims 1 and 9 would select an IgG1 heavy-chain constant region as a matter of routine. Accordingly, the absence of an express heavy-chain constant-region specification in the figures and claims—does not make claims 1 or 9 unsupported or non-enabled, because a POSITA would have known to use IgG1 for the relevant oncology context from the ordinary knowledge in the art, and the specification's antibody definition expressly contemplates IgG1 (EX1001 at 34:35-41). And ultimately, there are many examples of full IgG1 sequences in the figures and sequence listing, which can serve as blaze marks. This understanding is consistent with my opinion above that the relevant heavy-chain constant-region field is a small, defined set rather than an unbounded universe of arbitrary sequences.

115. In my opinion, the likely experiments a POSITA would use to explore the structurally reasonable sequence space around claim 1, guided by the information in the specification and figures of the '968 patent, and not adding in superfluous fusion partners or unusual structures, would look something like this:

- a. Complete the antibody or antibody fragment structure. It would be known to a POSITA that a VH plus a complete light chain requires some additional elements to be a useful sequence. This

would be at a minimum the addition of a CH1 domain to the C-term of the VH (defined as amino acids 1-119 of SEQ ID NO: 2), forming a complete Fab domain, the minimal antibody fragment that can be reasonably made with the limitations in claim 1. A POSITA would know that the CH1 domain needs to include a cysteine that is located in one of two positions (depending on the sub-type used), in order to properly form a covalent disulfide bond with the light chain. They would further know that the CH1 domain would be terminated somewhere before the cysteines that reside in the hinge region and form interchain disulfides between the two heavy chains. These are basic Fab design features, well-known to any POSITA. Dr. Hale appears to ignore this knowledge of a POSITA.

- b. Dr. Hale describes claim 1's minimal targeting moiety as an unusual antibody fragment consisting of only amino acids 1-119 of SEQ ID NO: 2 and the full light chain of SEQ ID NO: 71, and he identifies an unpaired cysteine at the C-terminus of the light-chain constant domain as a source of unpredictability (EX1003, Hale Decl. ¶¶ 101, 119, 169, Fig. D). That concern is specific to the minimal fragment, and fails to take advantage of

the word ‘comprising’, which allows the POSITA to fill out the design in advantageous ways, based on general knowledge of antibody design. Claim 1 does not preclude additional heavy-chain structure, and a POSITA would recognize that a Fab format—which includes a CH1 domain to pair with the light-chain C_κ domain and resolve the free cysteine—is a standard and well-understood antibody-fragment architecture (EX1003, Hale Decl. ¶ 48, Fig. B). While a Fab is a useful and acceptable antibody fragment, it is also reasonable to make a full-length antibody. Dr. Hale acknowledges that Figure 3 discloses a full-length antibody targeting moiety and that all 35 exemplary fusion proteins in the specification containing an antibody targeting moiety use full-length antibodies (EX1003, Hale Decl. ¶¶ 81, 121-122, App’x C). For a full-length antibody, the POSITA would simply continue the heavy chain from the Fab through the hinge, CH2, and CH3 domains. Human IgG1 CH3 terminates with a lysine that is generally removed post-translationally, leaving a terminal glycine. The POSITA may choose to omit the lysine from the construct or to let the cell

perform the removal; the two approaches yield functionally equivalent and essentially identical products.

- c. The next step is to fuse the sequence encoding the TGF β RII extracellular domain (SEQ ID NO: 87) to the antibody or antibody-fragment construct described above. Although the specification references chemical cross-linking as a known method (EX1001 at 43:40-44; EX1003, Hale Decl. ¶ 172(H) n.12), a POSITA designing the sequence-defined constructs at issue here would not select chemical conjugation as a first-line approach. As is the case for the antibody-toxin fusions (Zemab), antibody-cytokine fusions (EMD 273066), antibody-enzyme fusions (MFECP1), and Fc-receptor fusions (etanercept, abatacept, and others) that Dr. Hale describes, the TGF β RII domain would be genetically fused—that is, encoded in a single open reading frame and expressed as a contiguous polypeptide—to one of the termini of the antibody or antibody fragment (EX1003, Hale Decl. ¶¶ 59-60). Chemical conjugation would introduce site-selectivity and heterogeneity issues that recombinant expression avoids; a POSITA would reach for it only if the recombinant approach failed for a particular

construct. Since there are two chains in each construct (heavy and light) and each chain has two termini (amino and carboxy), there are four candidate fusion sites. Dr. Hale recognizes this range of permutations in his Figure K, where he catalogs molecules with the immunomodulatory moiety genetically fused at different positions on the heavy or light chain (EX1003, Hale Decl. ¶ 162, Fig. K). With two antibody formats (Fab and full-length antibody) and four terminus choices, this yields eight candidate fusion constructs to evaluate.

- d. Potential linkers: While claim 1 does not require a linker, a POSITA would routinely consider whether to include one. It is standard practice in fusion-protein design to insert a flexible linker between genetically fused domains to allow each domain to fold and function independently. Dr. Hale confirms that “a flexible linker consisting of one or more copies of four glycine residues and one serine residue (GGGGS) is used” and that the linker sequence “is optimised to ensure that the fusion protein can be manufactured efficiently and the biological activity of each component is maintained” (EX1003, Hale Decl. ¶ 61; EX2042, Hale Dep. Tr. at 56:16-57:25). Although the

specification references chemical cross-linking as a known coupling method (EX1001 at 43:40-44), a POSITA designing the sequence-defined constructs at issue here would not select chemical conjugation as a first-line approach for the reasons I described above. The specification provides direct guidance on linker choice: Figure 3 depicts the anti-EGFR/TGF β RII fusion with a (GGGGS)₃ linker (SEQ ID NO: 104) connecting the heavy-chain constant region to the TGF β RII extracellular domain (EX1001, Fig. 3, Sheet 6/75), and the specification identifies a family of related linkers including (GGGGS)_n repeats from n=1 through n=8 (EX1001 at 10:56-58, 11:28-31, 35:37-42; EX1003, Hale Decl., App'x B § 5). A POSITA would likely make each construct with and without a linker, using an intermediate-length (GGGGS)_n linker (n=2 or 3), consistent with the specification's Figure 3 example. This doubles the eight candidate constructs from the previous step to 16 total constructs.³ Sixteen constructs was a completely

³ An argument could be made that linker length can sometimes have a significant effect on fusion-protein expression or function. In that case, in my experience, making the construct with a longer and a shorter version of the linker is sufficient to accommodate any length bias. This would bring the total number of constructs

routine number to design, express, and test in the 2010-2011 timeframe in the context of a drug-discovery or protein-engineering project. This would in no way amount to undue experimentation.

116. Claim 9 is narrower than claim 1. A POSITA evaluating how to make a useful molecule satisfying claim 9 would identify two primary construct formats. Both start from the same expression unit: claim 9 specifies the (GGGGS)₃ linker of SEQ ID NO: 104, with the complete light chain (SEQ ID NO: 71) fused to the linker's N-terminus and the TGFβRII extracellular domain (SEQ ID NO: 87) fused to the linker's C-terminus (EX1001, claim 9). This creates a single-chain expression construct consisting of VL-Cκ-(GGGGS)₃-TGFβRII ECD. Because the final molecule must also include the VH domain from amino acids 1-119 of SEQ ID NO: 2, and because that domain alone would not complete a stable antigen-binding unit, a POSITA would add at least a CH1 domain to the heavy chain to generate a Fab-like structure. That is the first format: a Fab with the TGFβRII domain fused to the C-terminus of the light chain via the (GGGGS)₃ linker. The second format adds the hinge, CH2, and CH3 domains to the C-terminus of the heavy chain, creating a complete antibody with TGFβRII fused to the C-terminus

to 2 formats × 4 termini × (2 linker lengths + 1 no linker) = 24 total constructs—still a routine number for a POSITA to prepare and test.

of the light chain. Dr. Hale himself recognizes that claim 9 is narrower than claim 1 because it covers only antibody fragments and specifies the light-chain fusion orientation (EX1003, Hale Decl. ¶ 166). These two constructs are the only ones that both clearly satisfy the structural limitations of claim 9 and represent formats that a POSITA would consider worth designing and testing.⁴

117. For the reasons stated above, the quantity of experimentation required to make and use the claimed subject matter of claims 1 and 9 is not undue. This factor supports enablement.

118. **Wands factor 2—Direction or Guidance.** Dr. Hale argues that the specification provides no meaningful guidance for making the claimed fusion proteins, pointing to the hybridoma statement and the reference to solid-phase Merrifield-type synthesis as affirmatively misleading (EX1003, Hale Decl. ¶¶ 157-159, 184). I disagree. The specification provides more than a generic invitation to experiment. It supplies the relevant sequences, Figure 3's domain-identifying typography (underlining for the variable region, plain text for the constant region,

⁴ A third format—F(ab')₂—could also be considered. The usual way to make an F(ab')₂ is to produce a full-length antibody (the second format above) and enzymatically cleave the Fc portion at a site in the hinge region below the inter-heavy-chain disulfide bonds. This does not require a separate construct design; it requires only an additional processing step applied to the full-length antibody construct. Accordingly, the total number of constructs a POSITA would need to design and express under claim 9 remains two, even if three final formats may be tested.

italics for the linker, and bold for the TGF β RII extracellular domain), the (GGGGS)_n linker family, the light-chain fusion passage (EX1001 at 35:48-50), and the recombinant-DNA production instruction (EX1001 at 43:40-52). A POSITA would use those disclosures together with established expression and purification methods to design the constructs I have described above. That Dr. Hale identifies a Merrifield-synthesis reference and a hybridoma statement in the specification does not erase the express recombinant-DNA route, and a POSITA would not treat those passages as the operative instructions for making a long, multi-domain fusion protein when the specification separately provides a directly applicable recombinant method. Dr. Hale's analysis assumes that a POSITA would be unable to distinguish useful guidance from inapplicable alternatives. A POSITA with the qualifications Petitioner proposes—a Ph.D. or equivalent experience in the relevant disciplines (EX1003, Hale Decl. ¶ 111)—would exercise technical judgment to identify the most productive construct designs from the specification's disclosures and the state of the art. That exercise of judgment is precisely what “ordinary skill” entails in this field.

119. For the reasons stated above, the specification provides sufficient direction and guidance for a POSITA to make and use the claimed subject matter of claims 1 and 9. This factor supports enablement.

120. **Wands factor 3—Working Examples.** Dr. Hale identifies the TGF β RII:Fc construct in Example 1 as “just one example of a fusion protein [that] appears to have been actually used by the inventors,” but dismisses it because the construct has no targeting moiety comprising an antibody or antibody fragment and therefore “does not fall within any of the claims of the ’968 patent” (EX1003, Hale Decl. ¶¶ 160-161). But Example 1 demonstrates that the TGF β RII extracellular domain can be incorporated into an immunoglobulin-fusion format and retain TGF β -antagonist function (EX1001 at 40:41-41:7). That is relevant because TGF β RII is the immunomodulatory moiety recited in both claims 1 and 9. A POSITA would understand that once the immunomodulatory domain has been shown to fold and function in one immunoglobulin-fusion context, the remaining work—substituting the anti-EGFR antibody or antibody-fragment targeting moiety using the sequence disclosures and recombinant methods described in the specification—involves components and methods that were established in the field by 2010. A POSITA would not require a separate working example for every sequence-defined embodiment under those circumstances.

121. For the reasons stated above, the working example and specification disclosures provide sufficient technical guidance to support a POSITA in making and using the claimed subject matter of claims 1 and 9. This factor supports enablement.

122. **Wands factor 4—Nature of the Invention.** The claims are not defined only by a desired function across unknown proteins. They identify specific amino acid sequences for the targeting and immunomodulatory components, and claim 9 additionally directs that the final molecule contains an antibody-fragment, and identifies the linker sequence and fusion orientation. Those are sequence-defined engineering tasks using known protein domains. Although the claims permit more than one molecular arrangement in claim 1, that breadth does not convert the claimed subject matter into an undefined class of newly discovered proteins.

123. For the reasons stated above, the nature of the claimed invention—sequence-defined fusion proteins using known antibody-engineering formats—does not present obstacles that would require undue experimentation. This factor supports enablement.

124. **Wands factor 5—State of the Art.** Dr. Hale concedes that “general methods of producing recombinant monoclonal antibodies were known, including methods for producing chimeric or humanized antibodies” and that “numerous fusion proteins had been described and a number of different peptide linkers were known” (EX1003, Hale Decl. ¶ 178). He then argues that “there were important gaps in the prior art relating to fusion proteins” and that “[t]hese unnatural molecules were far more complex than antibodies and the consequences of linking

together two unrelated polypeptides was unpredictable” (EX1003, Hale Decl. ¶ 179). I disagree with the characterization that the prior art contained gaps material to the claimed constructs.

125. Dr. Hale’s discussion of the field confirms the opposite. He identifies multiple Fc fusion proteins that had been assigned an International Nonproprietary Name (“INN”)—a designation administered by the World Health Organization to track approved or designated names for biologic drugs, including fusion proteins—by March 2010, including abatacept, aflibercept, alefacept, atacicept, baminercept, belatacept, briobacept, eftrenonacog, and rilonacept (EX1003, Hale Decl. ¶ 59; Wilkinson 2022 (EX1086); Wilkinson 2022 Supplementary Materials (EX1087)). He further identifies antibody-protein fusions that had been described and in several cases assigned INNs by that date, including Zemab (anti-HER2 scFv linked to pseudomonas exotoxin), MFECP1 (anti-CEA scFv linked to carboxypeptidase), and EMD 273066 (anti-EpCAM linked to interleukin 2, also known as tucotuzumab celmoleukin) (EX1003, Hale Decl. ¶ 60; Ko 2004 (EX1062); Mayer 2006 (EX1068); Schmidt 2009 (EX1079)). He also acknowledges that flexible (GGGS)_n linkers were commonly used to connect fusion-protein domains (EX1003, Hale Decl. ¶ 61) and that, by 2010, the manufacture of conventional recombinant IgG antibodies was “a comparatively predictable and routine process” involving transfection, selection, culture, and purification (EX1003, Hale Decl. ¶

62). These concessions establish that the foundational components of the claimed constructs—recombinant antibodies, antibody fragments, Fc fusions, antibody-protein fusions, flexible linkers, and the relevant expression and purification methods—were established in the art by 2010.

126. My contemporaneous industry experience independently confirms this conclusion. From 2001 to 2008, I was a Senior Scientist II at EMD Serono (the former Lexigen site, which specialized in Fc and antibody fusion proteins under Dr. Steve Gillies), where I designed numerous fusion proteins, built out a phage display laboratory for antibody discovery, and invented the SEEDbody heterodimeric Fc platform (U.S. Patent No. 8,871,912 (EX2051)). The SEEDbody work required designing Fc-domain variants with engineered strand-exchange interfaces, expressing the resulting heterodimeric Fc constructs in mammalian host cells, purifying them by Protein A chromatography and size-exclusion chromatography, and characterizing their assembly, stability, and effector function—the same core recombinant-expression, purification, and characterization methods at issue in this proceeding. I then designed fusion proteins using the SEEDbody Fc and fusion partners such as IL-2, which expressed and behaved very well. Beginning in 2008, as a Principal Scientist in Protein Design at BMS, I designed novel IL-2/IL-2 receptor fusion proteins, which required cytokine-domain fusion construction, linker optimization, and functional

characterization of receptor-binding activity, and I co-invented Combinectin, a multi-component trispecific fusion biologic targeting HIV entry, which required assembling three distinct binding domains (an Adnectin, a second Adnectin, and a binding peptide) into a single recombinant polypeptide chain using flexible peptide linkers, expressing the construct, and confirming that each domain retained its target-binding function in the multi-domain context. This construct was then fused to Human Serum Albumin (HSA) to confer a long half-life.

127. Each of these platforms required the same activities that a POSITA would perform to practice claims 1 and 9: selecting domains, designing linkers, constructing nucleic-acid fusions, expressing recombinant proteins in mammalian host cells, and characterizing the resulting products for structure and function. The fact that I and my colleagues performed this work in a collaborative industry setting during the 2001-2011 period demonstrates that the relevant methods were not only known but practiced at scale.

128. For the reasons stated above, the state of the prior art as of 2010-2011 provided a POSITA with established methods for designing, expressing, purifying, and testing the types of constructs claimed in claims 1 and 9. This factor supports enablement.

129. **Wands factor 6—Relative Skill of Those in the Art.** Dr. Hale opines that “the relative level of those in the art would be insufficient to tackle the

considerable challenges posed by the full scope of the claims” (EX1003, Hale Decl. ¶ 180). I disagree.

130. Petitioner’s proposed POSITA definition contemplates a person with a Ph.D. or equivalent (four to five years of work experience) in biochemistry, molecular biology, immunology, or a closely related field, with experience constructing, expressing, and purifying recombinant antibodies and fusion proteins, experience with assays for expression levels and activity, and experience collaborating as part of a research team (See Pet. at 16-17; EX1003, Hale Decl. ¶ 111). I apply that definition for purposes of this declaration, and I qualify under it as I have described throughout this declaration.

131. A POSITA with the qualifications described above, working as part of a collaborative research team, would possess the skills necessary to design, express, purify, and test the constructs claimed in claims 1 and 9 using the specification's disclosures and established methods.

132. Dr. Hale refers to his own experience, stating that “even with thirty years of experience and a full team of postdoctoral scientists at my disposal, I was unsuccessful in reducing to practice an invention relating to fusion proteins.” EX1003, Hale Decl. ¶ 181. I understand he is referring to work at the Native Antigen Company, where he filed patent application GB2535753 (EX2037), entitled “Particles comprising fusion proteins,” and later withdrew it “due to lack

of success in actually making the proposed fusion proteins” (EX1003, Hale Decl. ¶ 65). Dr. Hale also describes his experience at Absolute Antibody, where two CD52-Fc fusion proteins were made in opposite orientations (the CD52 antigen, a small peptide, fused to the C-terminus or N-terminus of a mouse Fc region) and only one orientation was active, with activity defined as binding a particular antibody. EX1003, Hale Decl. ¶¶ 66-67. Neither experience is probative of what a POSITA could accomplish with the claimed constructs, for the following reasons.

133. First, the GB2535753 project concerned “Particles comprising fusion proteins”—a structurally distinct class of molecules in which fusion proteins are incorporated into particle architectures (EX2037). Dr. Hale does not disclose the specific fusion-protein sequences, domain structures, or expression systems used in that project, and he acknowledges only that some constructs proved “extremely difficult for reasons which were never obvious” (EX1003, Hale Decl. ¶ 65). According to the patent application, the goal was to develop a way to express transmembrane proteins by fusing them to self-assembling polypeptides and expressing them embedded into the membrane of a virus-like particle (VLP). The challenge of expressing such integral membrane proteins is still with us, as no one has yet devised an ideal solution. The important point for the topic at hand is that while this work included making a fusion between two proteins, that was the end of the similarity to any of the fusion proteins contemplated by the ’968 patent.

Failure to create a system that expresses well folded transmembrane proteins in VLPs has nothing to do with antibody-protein fusions where both fusion partners are soluble. The claimed constructs here present a fundamentally different engineering task. Claims 1 and 9 specify well-characterized, sequence-defined components: the cetuximab-derived/based anti-EGFR sequences (amino acids 1-119 of SEQ ID NO: 2 and the full amino acid sequence of SEQ ID NO: 71), the TGF β RII extracellular domain (SEQ ID NO: 87), and—for claim 9—the (GGGGS)₃ linker (SEQ ID NO: 104) in a defined orientation. The antibody component derives from cetuximab, a clinically validated, FDA-approved antibody with an extensive characterization record (EX1003, Hale Decl. ¶¶ 56-57; Prescribing Information 2004 (EX1073)). The TGF β RII extracellular domain had been expressed as a functional Fc fusion (TGF β RII:Fc) with retained TGF β -antagonist activity in the specification's own Example 1 (EX1001 at 40:41-41:7). And the antibody formats at issue (Fab, full-length IgG) are standard recombinant antibody formats that Dr. Hale himself concedes were “comparatively predictable and routine” to manufacture by 2010 (EX1003, Hale Decl. ¶ 62). A POSITA working with these defined sequences in established formats would not face the same undefined challenges that Dr. Hale encountered in a particle-based fusion-protein project with undisclosed components and no specification guidance.

134. Second, the CD52-Fc orientation result at Absolute Antibody demonstrates that orientation can matter in fusion-protein design—a well-understood principle—not that a POSITA would be unable to construct and test the claimed constructs. CD52 is a small glycopeptide with properties unlike the 137-amino-acid TGF β RII extracellular domain or the multi-domain antibody structures in the claimed constructs. That one CD52-Fc orientation was unable to bind a particular antibody while the other was able to bind is the kind of empirical result a POSITA expects and resolves by screening a limited number of defined candidates—precisely the approach I describe elsewhere in this declaration for claims 1 and 9.

135. For the reasons stated above, the relative skill of those in the art was sufficient for a POSITA to design, express, purify, and test the constructs claimed in claims 1 and 9 using the specification's disclosures and established methods. This factor supports enablement.

136. **Wands factor 7—Predictability.** Dr. Hale asserts that “although there was a degree of predictability in the field of recombinant antibodies, the same was not true for fusion proteins,” that “[s]ome fusion proteins were comparatively straightforward to produce; others were difficult or impossible,” and that “[t]here were few, if any, general rules by which a POSA could tell a priori which was which.” EX1003, Hale Decl. ¶ 183. He further states that “the functionality and

properties of any produced fusion proteins were equally unpredictable.” EX1003, Hale Decl. ¶ 183. I disagree with the implication that the unpredictability Dr. Hale describes applies to the claimed constructs.

137. Dr. Hale’s unpredictability concerns are directed at fusion proteins as a general class, including constructs with novel domain architectures, uncharacterized binding partners, or functionally undefined fusion combinations. He points to difficulties such as “scrambled disulphide bonds,” “inappropriate glycosylation,” “insolubility, instability, or aggregation caused by unnatural combinations of hydrophobic or ionic regions,” and “proteolytic degradation, particularly of the linker peptide.” EX1003, Hale Decl. ¶¶ 63-64. Those are challenges in some fusion-protein projects, but they do not describe the engineering task presented by claims 1 and 9. The claims specify defined, well-characterized components: the cetuximab-derived/based anti-EGFR sequences, the TGFβRII extracellular domain (SEQ ID NO: 87), and—for claim 9—the (GGGGS)₃ linker (SEQ ID NO: 104) in a fixed orientation. The antibody component derives from a clinically validated binding framework with an extensive manufacturing and characterization record (EX1003, Hale Decl. ¶¶ 56-57). The TGFβRII extracellular domain had been expressed as a functional Fc fusion with retained biological activity (EX1001 at 40:41-41:7). Dr. Hale concedes that by 2010, the manufacture of conventional recombinant IgG antibodies was “a

comparatively predictable and routine process” involving transfection, selection, culture, and purification (EX1003, Hale Decl. ¶ 62).

138. Fusion-protein design necessarily involves empirical confirmation, but empirical confirmation is not the same as unpredictability in the sense relevant to enablement. By 2010, a POSITA could predict the basic behavior of recombinant antibody domains, use standard flexible (GGGGS)_n linkers (EX1003, Hale Decl. ¶ 61), select established mammalian host-cell systems, and test expression, assembly, stability, and binding using routine assays. Format-specific issues—such as whether an A-linker-B or B-linker-A orientation functions better, or whether a particular construct aggregates—were routine engineering questions addressed by constructing and screening a limited set of defined formats, not by embarking on open-ended discovery. My contemporaneous work at EMD Serono and BMS on the SEEDbody, IL-2/IL-2 receptor, and Combinectin platforms confirms that such empirical screening was standard practice and routinely yielded functional products within the expected timelines of an industry drug-discovery program.

139. For the reasons stated above, the relevant experimentation for the sequence-defined constructs of claims 1 and 9 falls within the predictable range of protein-engineering work a POSITA would undertake. This factor supports enablement.

140. **Wands factor 8—Breadth of the Claims.** Dr. Hale asserts that “the patentee intended the claims of the ’968 patent to be broad in scope, covering antibodies and a range of antibody fragments, molecules with multiple polypeptide chains, molecules with polypeptide chains that are covalently attached, as well as fusion proteins which could include a variety of possible peptide linkers or no linker” (EX1003, Hale Decl. ¶ 175). He calculates a lower bound of 6,720 candidate molecules ($24 \text{ targets} \times 10 \text{ immunomodulators} \times 14 \text{ linkers} \times 2 \text{ orientations}$) (EX1003, Hale Decl. ¶ 88) and an upper figure of 227,332 candidates ($((269 \text{ targets} + 84 \text{ antibodies}) \times 23 \text{ immunomodulators} \times 14 \text{ linkers} \times 2 \text{ orientations})$) (EX1003, Hale Decl. ¶ 89 & n.7). He states that “[r]emarkably, it appears that not a single one of these putative candidates was actually made or tested by the inventors” (EX1003, Hale Decl. ¶ 89). I disagree with the characterization of breadth that those figures imply, because they count the full universe of targets, antibodies, immunomodulators, linkers, and orientations disclosed in the specification rather than the claim-limited choices.

141. Claims 1 and 9 are constrained by the specified anti-EGFR sequences (amino acids 1-119 of SEQ ID NO: 2, SEQ ID NO: 71), the TGF β RII extracellular domain (SEQ ID NO: 87), and the requirement that the targeting moiety specifically bind EGFR. As I explain above, applying those claim-specific sequence limitations to Dr. Hale’s formula modified by me as described in

paragraphs 86-88—substituting no new target (EGFR), one antibody sequence (the cetuximab-derived/based anti-EGFR), and one immunomodulatory moiety (TGF β RII)—yields $(0 \text{ target} + 1 \text{ antibody}) \times 1 \text{ immunomodulator} \times 14 \text{ linkers} \times 2 \text{ orientations}$, or approximately 28 combinations for claim 1 under either of Dr. Hale's starting universes. That figure is itself an outer ceiling because it retains Dr. Hale's full 14-linker and 2-orientation multipliers even though the specification identifies the (GGGGS)_n family and Figure 3 fixes the heavy-chain-side orientation.

142. Claim 9 is narrower still. It specifies an antibody-fragment format, fixes linker SEQ ID NO: 104, and fixes the spatial arrangement (light chain fused to the linker's N-terminus, immunomodulatory moiety fused to the linker's C-terminus), reducing the scope to approximately 2 candidate architectures (a Fab-format construct and a full-length-antibody-format construct, each with TGF β RII fused to the C-terminus of the light chain via the (GGGGS)₃ linker). Dr. Hale himself acknowledges that claim 9 is narrower than claim 1 (EX1003, Hale Decl. ¶ 166). Both architectures are straightforward for a POSITA to design and produce using the specification's disclosures and established recombinant methods.

143. The relevant breadth of the claims is therefore materially less than Petitioner suggests. Dr. Hale's starting universe is inflated precisely because it ignores the successive narrowing the specification provides—from hundreds of

targets to EGFR, from EGFR to a specific anti-EGFR antibody sequence, from the genus of immunomodulatory moieties to TGF β RII, and from 14 possible linkers to the (GGGGS)₃ family and ultimately SEQ ID NO: 104.

144. For the reasons stated above, the effective scope of claims 1 and 9—when limited to the constructs a POSITA would actually pursue—does not require undue experimentation. This factor supports enablement.

145. Dr. Hale concludes that practicing the claims “would certainly require a substantial team of highly skilled scientists working for many months or years, without any certainty of success” (EX1003, Hale Decl. ¶ 186). I disagree.

Considering the eight factors together, the record does not support that conclusion.

The claims identify the specific sequences and, for claim 9, the precise architecture. The specification supplies Figure 3’s sequence and structural signposts, the (GGGGS)_n linker family, the light-chain fusion orientation passage at column 35, lines 48-50, recombinant-DNA production guidance at column 43, lines 40-52, and a working immunoglobulin-fusion example (TGF β RII:Fc) that demonstrates the immunomodulatory domain can be expressed and function in a fusion context. The state of the prior art and my contemporaneous industry work confirm that the foundational methods—recombinant antibody expression, Fc and antibody-fusion design, flexible-linker engineering, and standard purification and characterization—were established by 2010. A POSITA would need to perform

ordinary construction, optimization, and testing of a defined and limited set of candidate constructs, but that work falls within the range of routine experimentation in a protein-engineering program. For these reasons, in my opinion, all eight Wands factors support the conclusion that claims 1 and 9 of the '968 patent are enabled.

IX. TECHNICAL DISCLOSURE AND EXAMPLE 1

A. “Misleading” Disclosure

146. Dr. Hale contends that the specification’s statement that “a hybridoma can produce the polypeptides corresponding to SEQ. ID NO: 1-69” (EX1001 at 35:54-55) would be misleading to a POSITA (EX1003, Hale Decl. ¶ 157). He explains that “[a] hybridoma is normally created by fusing a myeloma cell line with a spleen cell from a rodent and it secretes the intact antibody encoded by the spleen cell,” and that SEQ ID NOs: 1-69 “represent fusion proteins which are single polypeptides consisting of immunoglobulin heavy chains linked to another protein or combinations of other proteins” that are “not normally produced by hybridoma cells” (EX1003, Hale Decl. ¶ 158). The Petition echoes this point, stating that “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” (Pet. at 67; *see* EX1003, Hale Decl. ¶¶ 157-58).

147. I disagree. A POSITA would understand a hybridoma as an antibody-producing cell context and would not read this single sentence in isolation. The specification separately provides an express recombinant-DNA production instruction at column 43, lines 40-52, directing that a targeting moiety, including an antibody, “can be coupled to an immunomodulatory moiety” and that fusion-protein coding sequences can be linked at the nucleic-acid level and expressed in a host cell (EX1001 at 43:40-52). A POSITA would read those two disclosures together. The hybridoma reference at column 35, lines 54-55, identifies a cell type capable of producing the individual antibody chains; the recombinant-DNA instruction at column 43, lines 40-52, provides the technically applicable route for constructing and expressing the fusion proteins. The specification does not present hybridoma production as the exclusive method for making fusion constructs, and a POSITA—with the qualifications Petitioner proposes, including experience with recombinant antibody construction and expression (See Pet. at 16-17; EX1003, Hale Decl. ¶ 111)—would not be misled into attempting hybridoma production as the sole approach to making multi-domain fusion proteins. The recombinant-DNA instruction supplies the method a POSITA would use for the sequence-defined fusions at issue.

148. For these reasons, the hybridoma statement does not render the specification misleading as to the methods for making the claimed constructs, and

this disclosure does not establish that undue experimentation would be required to practice claims 1 and 9.

149. Dr. Hale further contends that the specification's reference to solid-phase Merrifield-type synthesis would mislead a POSITA (EX1003, Hale Decl. ¶ 159). He quotes the passage at column 37, lines 4-10: "A peptide of the present invention can be synthesized by any of the techniques that are known to those skilled in the polypeptide art, including recombinant DNA techniques. Synthetic chemistry techniques, such as solid-phase Merrifield-type synthesis, are preferred for reasons of purity, antigenic specificity, freedom from undesired side products, ease of production and the like." EX1001 at 37:4-10. Dr. Hale states that "such complex polypeptides have never been made by solid-phase Merrifield-type synthesis, and even if this were attempted, the products would not be pure, free from side products, or easy to produce." EX1003, Hale Decl. ¶ 150. The Petition similarly asserts that "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" and that "[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." Pet. at 68; EX1003, Hale Decl. ¶ 159.

150. I disagree. A POSITA reading the passage at column 37, lines 4-10, would understand the reference to Merrifield-type synthesis as a general disclosure of peptide-synthesis techniques, not as the sole or even primary route for producing the multi-domain fusion proteins at issue. The same passage begins by identifying “recombinant DNA techniques” as one of the available methods. More important, the specification separately provides a direct recombinant-DNA instruction at column 43, lines 40-52, explaining that a targeting moiety can be coupled to an immunomodulatory moiety and that fusion-protein coding sequences can be linked at the nucleic-acid level and expressed in a host cell (EX1001 at 43:40-52). A POSITA would recognize that the column 43 instruction is the technically applicable route for constructing the antibody-TGF β RII fusion proteins claimed here, which are multi-domain constructs requiring post-translational modification, disulfide-bond formation, and correct folding—processes that solid-phase chemical synthesis does not provide. Even if the word “preferred” was overbroad in the column 37 passage, it would not erase the separate, technically appropriate recombinant-DNA instruction. A POSITA would rely on the recombinant route for the claimed constructs and would not be misled into attempting solid-phase synthesis as the primary production method for a multi-domain antibody-fusion protein.

151. For these reasons, the Merrifield synthesis reference does not render the specification misleading as to the methods for making the claimed constructs, and this disclosure does not establish that undue experimentation would be required to practice claims 1 and 9.

152. The Petition points to the specification's citation of U.S. Patent No. 5,736,167 as further evidence of the specification's purported lack of clarity. 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 at 30:10-12). The Petition notes that U.S. Patent No. 5,736,167 is titled "Mold Device for Making Safety Shoe" and that "the term antibody is not found once in this patent," characterizing the reference as a "miscite" (Pet. at 68-69; EX1045, cover).

153. The citation to U.S. Patent No. 5,736,167 in the sentence at column 30, lines 10-12, is an evident clerical error in a prosecution list of antibody references. A patent titled "Mold Device for Making Safety Shoe" has no connection to antibodies, fusion proteins, or any of the subject matter of the '968 patent. A POSITA encountering this reference in a list of three patents would recognize the mismatch immediately and would rely on the surrounding technical disclosure—including the correctly identified antibody-engineering methods and the other two cited patents (U.S. Pat. Nos. 7,060,808 and 5,821,337)—for any relevant antibody examples. Nor would a POSITA believe that one miscited patent

number in a list erases the specification's express sequence disclosures, its Figure 3 structural signposts, its linker and orientation guidance, or its recombinant-DNA production instruction.

154. For these reasons, the mis-citation of U.S. Patent No. 5,736,167 does not undermine the specification's enablement of claims 1 and 9, and it would not cause a POSITA to undertake undue experimentation to make and use the claimed constructs.

B. Example 1

155. Example 1 concerns a soluble TGF β RII:Fc construct: the extracellular domain of TGF β RII is fused to the Fc portion of murine IgG1, and the construct functions as a stable TGF β antagonist. I do not characterize this molecule as a fusion protein with an antibody fragment of claim 1 or 9. It does not contain the anti-EGFR targeting moiety required by claims 1 or 9, consistent with Dr. Hale's observation that it is outside those claims.

156. Although Example 1 is not itself a claimed anti-EGFR antibody-fragment molecule, it is probative of enablement. As I explained above, it is a working example of linker-mediated fusion of the claimed TGF β RII immunomodulatory moiety to an immunoglobulin domain with retained TGF β -antagonist function. It demonstrates that the immunomodulatory domain can be incorporated into a stable fusion format and retain its biological activity. Together

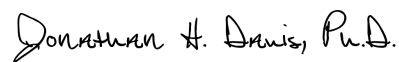
with Figure 3, the recombinant-DNA instruction, and the known antibody-engineering methods, Example 1 provides relevant technical guidance without being misdescribed as the claimed targeting construct.

X. CONCLUSION

157. For the reasons set forth above, it is my opinion that claims 1 and 9 of the '968 patent are adequately described and enabled from the perspective of a POSITA including as of the relevant 2010-2011 period.

158. I hereby declare that statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I reserve the right to revise or supplement my opinions as additional information becomes available. I declare under penalty of perjury that the foregoing Declaration is true and correct.

Dated: October 6, 2026



Jonathan Davis, Ph.D.