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Paper 13
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES, INC.,
Petitioner,

v.

HOFFMAN-LaROCHE INC.,
Patent Owner.

Case IPR2017-01916
Patent 8,163,522 B1

Before SUSAN L. C. MITCHELL, TINA E. HULSE, and WESLEY B. DERRICK, *Administrative Patent Judges.*

MITCHELL, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

A. Background

Petitioner Coherus Biosciences, Inc. ("Petitioner") filed a petition (Paper 1, "Pet.") to institute an *inter partes* review of claims 1–10 (the "challenged claims") of U.S. Patent No. 8,163,522 B1 (Exhibit 1001, "the '522 patent"). *See* 35 U.S.C. §§ 311–319. Patent Owner Hoffman-LaRoche Inc. ("Patent Owner"), filed a Preliminary Response. Paper 9 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. *See* 35 U.S.C. § 314(b); 37 C.F.R. 42.4(a). To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). For the reasons set forth below, we conclude that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of any challenged claim of the '522 patent. Therefore, we do not institute an *inter partes* review for any challenged claim of the '522 patent.

B. Related Proceedings

The parties identify two court proceedings involving the '522 patent, one of which has been terminated and one that is ongoing: *Sandoz Inc. v. Amgen Inc.*, 773 F.3d 1274 (Fed. Cir. 2014) (terminated) and *Immunex Corp. v. Sandoz Inc.*, Case No. 2:16-cv-01118-CCC-JBC (D.N.J.) (pending). Pet. 7; Paper 8, 2.

The parties also identify a previously filed request for *inter partes* review of the '522 patent that was not instituted: *Coalition for Affordable*

Drugs V LLC v. Hoffman-LaRoche Inc., Case IPR2015-01792 (PTAB) ("the 1792 IPR"). Pet. 7, Paper 8, 2; Ex. 1010. Petitioner has also filed a request for *inter partes* review of related U.S. Patent No. 8,063,182 B1 ("the '182 patent"), Case IPR2017-02066. Paper 8, 2.

C. The '522 Patent (Ex. 1001)

The '522 patent is directed, in part, to polynucleotides encoding the extracellular region of an insoluble human TNF receptor (also, "TNF-R") described by an apparent molecular weight and as containing particular amino acid sequences in addition to all domains of the constant region of a human IgG_1 immunoglobulin heavy chain except the first domain of the heavy chain constant region. Ex. 1001, Abs., 2:26–49. The '522 patent also addresses methods for culturing a host cell comprising the polynucleotide and purifying the expression product of the polynucleotide from the cell. *Id.*

D. Illustrative Claims

Claims 1 and 4 are illustrative of the claimed subject matter. Claims 1 and 4 are reproduced below.

1. A method comprising the steps of:

(a) culturing a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein consisting of:

(i) the extracellular region of an insoluble human TNF receptor, wherein the insoluble human TNF receptor has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel and comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), and

(ii) all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region, and

(b) purifying an expression product of the polynucleotide from the cell mass or the culture medium.

Ex. 1001, 45:45–62.

4. A polynucleotide encoding a protein consisting of:

(a) the extracellular region of an insoluble human TNF receptor,

wherein the insoluble human TNF receptor (i) has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel and (ii) comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), and

(b) all of the domains of the constant region of a human IgG_1 immunoglobulin heavy chain other than the first domain of said constant region.

Id. at 46:44–55.

E. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims 1–10 are unpatentable under 35 U.S.C. § 103(a) based on the following grounds. Pet. 9.

References	Statutory Basis	Claims Challenged
Watson[1] and Smith[2]	§ 103	1–10
Smith, Watson, and Zettlmeissl[3]	§ 103	1–10

[1] Watson et al., *A Homing Receptor–IgG Chimera as a Probe for Adhesive Ligands of Lymph Node High Endothelial Venules*, 110 J. CELL BIOL. 2221–29 (June 1990) (Ex. 1003).
[2] Smith et al., U.S. Patent No. 5,395,760, issued March 7, 1995 (Ex. 1004).
[3] Zettlmeissl et al., *Expression and Characterization of Human CD4: Immunoglobulin Fusion Proteins*, 9 DNA & CELL BIOLOGY 347–53 (June 1990) (Ex. 1005).

Petitioner supports the Petition with the testimony of Dennis R. Burton, Ph.D. (Ex. 1002).

II. ANALYSIS

A. Application of 35 U.S.C. § 325(d) or 35 U.S.C. § 314(a)

Patent Owner asks that we use our discretion under 35 U.S.C. §§ 325(d) or 314(a) to deny *inter partes* review in this case. Prelim. Resp. 21–31. Specifically, Patent Owner asserts that we should exercise such discretion because Smith, used in both grounds in this case, was considered in the 1792 IPR and during examination of the '522 patent, Watson describes the same fusion protein as described in references used in the 1792 IPR challenge and by the Examiner during prosecution, and Zettlmeissl discloses the same fusion protein constructs described in a reference considered in the 1792 IPR. *Id*. at 27–28.

Petitioner asserts that its Petition differs from the petition in the 1792 IPR because "Watson and Zettlmeissl both provide a clear and compelling reason why a POSA would have specifically selected a fusion protein incorporating the hinge-CH2-CH3 region of an IgG." Pet. 17–18. Specifically, Petitioner argues that Zettlmeissl reports poor expression for fusion proteins with CH1 domains and excellent expression for a receptor protein that is joined to the hinge-CH2-CH3 region of human IgG1. *Id*. at 18. Likewise, Petitioner asserts that "Watson identifies *only one* location as optimal for fusion of a receptor protein to the immunoglobulin." *Id*.

Instead of analyzing whether there are differences between the art asserted in this Petition and that discussed during prosecution of the '522 patent or the previous Petition in the 1792 IPR, we find it more efficient to resolve our decision on institution on the merits presented in the Petition.

Because we find that Petitioner has no reasonable likelihood of prevailing on either ground presented in the Petition and, therefore, deny institution, we decline to exercise our discretion under either 35 U.S.C. § 314(a) or 35 U.S.C. § 325(d) to deny the Petition.

B. Level of Skill in the Art

Petitioner states that one of ordinary skill in the art in the relevant field of recombinant DNA processes for the production, isolation, and use of chimeric proteins "would have held an advanced degree, such as a Ph.D., in molecular biology, biochemistry, cell biology, molecular genetics, or a related field, and would have experience using recombinant DNA processes to construct chimeric proteins, as well as experience using techniques for the expression, isolation, and purification of proteins." Pet. 19–20 (citing Ex. 1002 ¶ 30). Patent Owner's declarant essentially agrees with this definition, but states that he "disagree[s] that the Ordinary Artisan would have had much experience constructing chimeric proteins, as this was a relatively new development in August 1990." Ex. 2001 ¶ 31.

We do not discern an appreciable difference in the parties' respective definitions of the level of ordinary skill. Moreover, we note that Patent Owner does not contest the level of skill in the art in its Preliminary Response. Accordingly, we adopt Petitioner's uncontested definition of the level of ordinary skill mindful that the experience using recombinant DNA processes to construct chimeric proteins may have been somewhat limited. Ex. 2001 ¶ 31. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention including the level of experience using recombinant DNA techniques to construct chimeric proteins. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001)

(explaining that "specific findings on the level of skill in the art . . . [are not required] 'where the prior art itself reflects an appropriate level and a need for testimony is not shown'") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Claim terms are given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). An inventor may rebut that presumption by providing a definition of the term in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). In the absence of such a definition, limitations are not to be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993).

Each independent claim of the '522 patent requires that the protein encoded includes "*all of the domains* of the constant region of a human IgG [or IgG1] immunoglobulin heavy chain other than the first domain of said constant region." *See* Ex. 1001, 45:58–60, 46: 53–55, 47:1–3 (claims 1, 4, and 7) (emphasis added). Petitioner relies on the Board's previous interpretation in the 1792 IPR of this claim term. Pet. 20–21. The Board had previously interpreted this claim phrase to mean "-hinge-CH2-CH3

region of a human IgG (or IgG_1 as appropriate to the requirements of a particular claim) immunoglobulin heavy chain." *Id.*; Ex. 1010, 7.[4] As Patent Owner notes, Petitioner relies on these previous constructions without further comment. *See* Prelim. Resp. 13 (citing Pet. 20–21; Ex. 1002 ¶¶ 33–34).[5]

The Petition does not otherwise elaborate on the meaning of the phrase, or the import of our earlier determination in the 1792 IPR, as to what is, in fact, required by the claims. *See* Ex. 1010, 7; *see generally*, Pet. The Petition does, however, contend that Watson and Zettlmeissl "both reported optimal results by employing the ***identical*** portion of the IgG heavy chain as claimed in the '522 patent." Pet. at 5 (citing Ex. 1002 ¶¶ 76–78, 84–86, 132). The Petition explains that both references "report[] that receptor:IgG hinge fusion proteins are most 'efficiently synthesized' when the light chain and CH1 domain are deleted, so that the receptor is attached directly to the hinge-CH2-CH3 region of an IgG antibody's heavy chain." *Id.* at 4–5 (citing Ex. 1002 ¶¶ 151–158; Ex. 1003, 2224; Ex. 1005, 347).

Patent Owner contends that the claims require the proteins to include the complete hinge-CH2-CH3 region of the heavy chain, that is, "all of the domains of the constant region . . . other than the first domain [CH1] of said

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[4] In the 1792 IPR we found that two other claim terms, "TNF receptor" and "about," did not require express construction. Ex. 1010, 5, 7. Petitioner offered no express construction of either term in this proceeding and asserted that each term should be given its ordinary meaning. Pet. 20.

[5] Petitioner requested authorization to file a reply brief to address whether the Board's prior construction of "all of the domains of the constant region . . . other than the first domain of said constant region," to which, Petitioner contends, Patent Owner agreed, includes a functional as well as a genetic hinge. Paper 12, 10:17–12:3. After extensive discussion by both parties, we declined to allow Petitioner an additional brief. *Id.* at 49.

constant region." Prelim. Resp. 7. Patent Owner further contends that the Board's prior construction is wholly consistent with "the claims requir[ing] use of the entire hinge-C_H2-C_H3 region of the IgG/IgG1 heavy chain, not a truncated portion of that region." *Id.* at 15. Patent Owner notes that the claims were distinguished during prosecution "from other fusion proteins having 'only a portion of a hinge domain'" and adds, with emphasis, that as "noted during the CFAD-IPR [1792 IPR] . . . the claims 'were drafted to exclude other p75 TNFR/IgG fusion proteins (such as Delta 57 and Protein 3.5D) that contained only a portion of the hinge domain and did not display the unexpected properties." *Id.* at 18–19 (citing Ex. 2110, 35; Ex. 1008, 40, 47).

Patent Owner also provides evidence supporting the contention that "the plain and ordinary meaning" of the CH1, hinge, CH2, and CH3 domains of human IgG heavy chains set forth in our prior decision is the respective amino acid sequence "encoded by the C_H1, hinge, C_H2 and C_H3 exons." Prelim. Resp. 15–17 (citing Ex. 2012, xix; Ex. 2014, Fig. 4; Ex. 1050, 4072; Ex. 2001 ¶¶ 62–64).

We determine that the broadest reasonable interpretation of the phrase "*all* of the domains of the constant region . . . other than the first domain of said constant region" means "*all* of the hinge, CH2, and CH3 domains." That is, all of the constant region forming domains, *i.e.*, CH1, hinge, CH2, and CH3 domains, is included except for the first domain. Thus, any protein with less than all of the amino acid sequence of the hinge domain of a human IgG (or IgG1) immunoglobulin heavy chain, even if functional, falls outside the scope of the claims as properly construed, because it omits a portion of the constant region forming domains other than the first domain.

This construction is consistent with statements the applicant made during prosecution that a fusion protein that includes only a portion of a hinge domain "are missing the first several amino acids of this domain, and thus do not comprise 'all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain.'" Ex. 2110, 35. Also, there is evidence in the record that the Specification of the '522 patent is consistent with this interpretation on the basis that the described fusion proteins include all of the amino acid sequence of the heavy chain constant region except the first domain. Ex. 2001 ¶¶ 59, 42–45, 46–47 (describing Example 11 TNFR-based fusion protein); *see also* Prelim. Resp. 18–19, 18 n.35 (discussing vectors used in examples in the '522 patent contained exons encoding the full hinge, CH2, and CH3 domains).

The question remains, however, where in the constant region the divide lies between the first domain of the constant region and the hinge domain. Because Petitioner fails to answer this question in a consistent manner, we determine on this record that Petitioner has not shown sufficiently that the claims are unpatentable as obvious.

D. Asserted References

1. Watson (Ex. 1003)

Watson reports the "develop[ment] [of] a chimeric protein containing the murine [pln homing receptor] and the hinge and constant regions of the human immunoglobulin heavy chains . . . thus, converting the pln HR into a monoclonal antibody-like molecule." Ex. 1003, 2222. Watson describes a "truncated [murine homing receptor] protein [] joined to a human heavy chain gamma-1 region immediately NH_2-terminal to the hinge domain (*H*) such that this chimera contains the two cysteine residues (*C*) of the hinge

responsible for immunoglobulin dimerization as well as the CH2 and CH3 constant regions." *Id.* at 2223, Fig. 1. Watson describes data "indicating that the hinge region was fully functional in this chimera." *Id.* at 2224. Watson does not otherwise define the hinge domain, its bounds, or sequence, but refers to published work by Capon et al. (Ex. 1032) as guiding "[t]he choice of junctional sites between the mHR and human IgG sequences"; Capon's work is described as "demonstrat[ing] that the joining of the molecules near the hinge region resulted in chimeric molecules that were both efficiently synthesized and dimerized in the absence of any light chain production." *Id.* at 2224.

2. Smith (Ex. 1004)

Smith teaches DNA sequences encoding human tumor necrosis factor receptors (TNF-R), *see* Ex. 1003, 2:38–41, recombinant expression vectors comprising these DNA sequences, and also isolated or purified protein compositions comprising soluble forms of TNF-R. *Id.* at 2:59–61. Smith also states that

> A recombinant chimeric antibody molecule may also be produced having TNF-R sequences substituted for the variable domains of either or both of the immunogl[o]bulin molecule heavy and light chains and having unmodified constant region domains. For example, chimeric TNF-R/IgG$_1$ may be produced from two chimeric genes—a TNF-R/human κ light chain chimera (TNF-R/C$_\kappa$) and a TNF-R/human γ$_1$ heavy chain chimera (TNF-R/C$_{\gamma\text{-}1}$). Following transcription and translation of the two chimeric genes, the gene products assemble into a single chimeric antibody molecule having TNF-R displayed bivalently. Such polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand.

Id. at 10:53–66.

3. Zettlmeissl (Ex. 1005)

Zettlmeissl reports the development of chimeric antibody-like molecules consisting of human CD4 extracellular domains fused to different portions of human IgG1 heavy chain constant regions. Ex. 1005, 347, Abstract. Five different fusion genes, for expressing the different fusion proteins, included a "portion encoding the extracellular domain of CD4 . . . and [a] 5-amino-acid linker . . . upstream from the CH1, hinge, or CH2 exons of the human IgG1 gene, or upstream from the CH1 or CH2 exons of the IgM gene." *Id.* at 348. Zettlmeissl observed poor expression "for fusion proteins bearing CH1 domains." *Id.*

E. Obviousness of the Challenged Claims

Petitioner contends that each of the challenged claims is unpatentable as obvious over (1) Watson in view of Smith, and (2) Smith in view of Zettlmeissl and Watson. Pet. 1, 9. In the first ground, Petitioner sets forth a combination in which the portion of the IgG heavy chain used in Watson is fused to the 75-kDa extracellular sequence of the 75-kDa TNFR from Smith. *Id.* at 5 (citing Ex. 1002 ¶¶ 132–144); *see also id.* at 28–43. In the second ground, Smith's TNFR:IgG fusion protein is modified by deleting the light chain and CH1 region of the heavy chain so that only a portion of the IgG heavy chain is used in light of the teaching in Zettlmeissl and Watson that doing so results in optimum expression. *Id.* at 5 (citing Ex. 1002 ¶¶ 145–161); *see also id.* at 43–64.

Petitioner relies on Zettlmeissl and Watson as teaching the use of the same, identical portion of the IgG heavy chain as that taught in the '522 patent, and relies on that portion for use in the claimed fusion protein. *Id.* at 5 (citing Ex. 1002 ¶¶ 76–78, 84–86, 132). As explained below, however, the

portions of the IgG heavy chain used in Zettlmeissl and Watson—and in particular the hinge regions—are not identical to each other or what is taught in the '522 patent. Thus, by asserting that the fusion protein of Watson could be modified by adding the 75-kDa extracellular sequence of the TNFR from Smith or that Smith could be modified with either the heavy chain portion of Zettlmeissl or Watson, Petitioner is unclear what it considers to be "all of the hinge . . . domain[]," for either construct under our interpretation of this phrase as "all of the hinge, CH2, and CH3 domains."

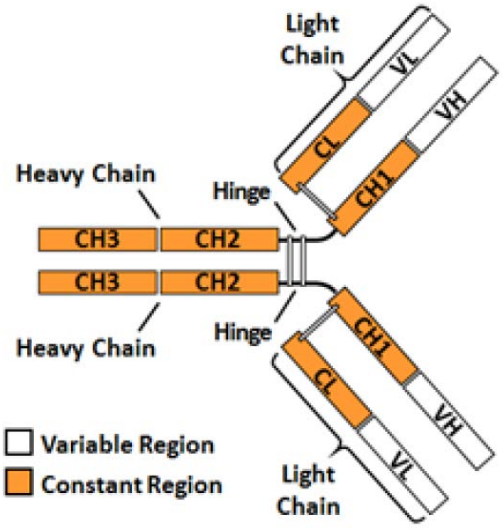
1. Obviousness over Watson and Smith

Petitioner contends that claims 1–10 are unpatentable as obvious over Watson in view of Smith. Pet. 28–43. Petitioner further contends that the case of obviousness cannot be overcome by objective indicia of nonobviousness. *Id.* at 51–64. Patent Owner opposes Petitioner's contention of obviousness (Prelim. Resp. 31–56) and contends proffered objective indicia of nonobviousness confirm the patentability of the invention (*id.* at 65–82).

Petitioner contends that "Watson's fusion protein is identical to the fusion protein of the '522 patent claims, except that the receptor protein is different." Pet. 30. Petitioner argues that "[t]he straightforward application of Watson's method to the 75-kDa TNFR disclosed by Smith (*i.e.*, joining the extracellular receptor to the hinge-CH2-CH3 region of IgG1) results in exactly the same polynucleotides and methods claimed in the '522 patent." *Id.* at 31 (citing Ex. 1002 ¶¶ 141–142, 158). Petitioner further offers reasoning for the combination stating that "Watson . . . indicates that it has *optimized* the location for attaching a receptor to an IgG to make a fusion protein," and that a person of ordinary skill in the art "would have readily

applied Watson's optimized technique of attaching the soluble receptor to the hinge-CH2-CH3 portion of an IgG1 . . . to improve on Smith's recommendation to prepare a TNFR:IgG1 fusion protein." Pet. 38–39 (citing Ex. 1002 ¶¶ 129, 142, 145, 156–158; Ex. 1003, 2224; Ex. 1004, 10:53–66).

The problem with Petitioner's argument as a whole is that it is unclear what Petitioner considers to be the complete hinge. That is, Petitioner is inconsistent as to where the boundary lies between the first constant domain and the hinge. As background, Dr. Burton sets forth the structure of IgG (Ex. 1002 ¶¶ 35–39) that is identified as "[a] schematic depiction of an IgG immunoglobulin" (Ex. 1006, 12), reproduced below:



Ex. 1002 ¶ 36 (stating the schematic is "[a]dapted from Ex. 1006, p. 12"). In defining the structure and function of IgG, Dr. Burton states:

> The hinge region is located between the CH1 and CH2 domains of the heavy chain. The hinge region contains all of the interchain disulfide bonds that link the heavy chains together. I note that *in the human IgG$_1$ molecule there is a third disulfide bond* (shown above) *that links the CH1 domain* to the constant region of the light chain.

Ex. 1002 ¶ 39 (emphasis added).

Dr. Burton further states that amino acid sequences were known in the prior art, citing Ellison.[6] Ex. 1002 ¶ 129 (citing Ex. 1050). Patent Owner agrees and also relies on Ellison to teach the hinge domain. *See* Prelim. Resp. 15–17, 36. Ellison discloses that the hinge segment is encoded by a single exon providing the following amino acid sequence, which includes *three* cysteine (C) residues as opposed to the two set forth in Dr. Burton's schematic of IgG immunoglobulin set forth above:

E P K S C D K T H T C P P C P

Ex. 1050, 4072, Fig. 2. Dr. Burton also discusses Capon (Ex. 1032)[7] as teaching fusion proteins comprising a soluble fragment of a receptor protein and portions of an IgG heavy chain. *See, e.g.*, Ex. 1002 ¶¶ 63–68. Like Ellison, Capon (Ex. 1032) discloses the hinge region of IgG1 as including *three* cysteine (C) residues (Ex. 1032, 526, Fig. 1) and that "[t]he hinge region of each immunoadhesin [Capon's fusion protein] contains three cysteine residues, one normally involved in disulphide bonding to light chain, the other two in the intermolecular disulphide bonds between the two heavy chains in IgG" (*id.* at 526).

Notwithstanding this conflicting evidence and testimony as to what constitutes the complete hinge, Dr. Burton asserts that a person of ordinary skill in the art would have understood both Watson's construct and Zettlmeissl's construct, although using different receptors in their respective fusion proteins, to achieve "optimal results by employing the ***identical*** portion of the IgG heavy chain as claimed in the '522 patent," thus,

[6] Ellison et al., 10 NUCLEIC ACIDS RES. 4017–79 (1982) (Ex. 1050)
[7] Capon et al., 337 NATURE 525–31 (1989) (Ex. 1032) ("Capon (Ex. 1032)").

containing "all of the domains of the human IgG heavy chain except for the first constant region." Pet. 5 (citing Ex. 1002 ¶¶ 76–78, 84–86, 132); *see* Ex. 1002 ¶ 106 (citing Ex. 1003, 2223, Fig. 1), ¶ 105 (citing Ex. 1005, 348, Figs. 1–2).

The problem with Petitioner's argument that is evident from the respective disclosures of Zettlmeissl and Watson is that they do not, as contended, employ the identical portion of the IgG heavy chain. *See* Prelim. Resp. 24–38 (explaining Watson's fusion protein does not use the complete hinge-CH2-CH3 portion of the IgG1 heavy chain because it lacks the first five amino acid sequences of the hinge including the first cysteine residue), 64 (explaining Zettlmeissl includes an artificial linker between the receptor and immunoglobulin sequences). In Zettlmeissl, the sequence "encoding the extracellular domain of CD4 . . . and the 5 amino-acid linker sequence were placed upstream from the . . . hinge . . . exon[] of the human IgG_1 gene." Ex. 1005, 348. The expressed fusion protein, accordingly, would include all of the amino acid sequence encoded by the hinge exon of the human IgG1 gene, but also include a 5 amino-acid linker, which is not identical to Watson's disclosed portion of the IgG heavy chain. Because of the transitional phrase "consisting of" that is used to describe the protein encoded by the claimed polynucleotide for all claims of the '522 patent, the addition of the 5 amino-acid linker would result in a protein encoded by a polynucleotide that is not encompassed by any challenged claim. *See AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239, 1244–45 (Fed. Cir. 2001) (holding the phrase "consisting of" is a "closed" transition phrase that is "understood to exclude any elements, steps, or ingredients not specified in

the claim"). Zettlmeissl does not further define the amino acid sequence of the hinge region of IgG1.

Watson's fusion protein, in contrast, and as contended by Petitioner, includes only the two cysteine residues involved in joining the heavy chains, i.e., the cysteine residues separated by two proline (P) residues as shown in the sequence set forth above as disclosed by Ellison. Pet. 29–33; Ex. 1002 ¶¶ 76–82. The other cysteine, normally involved in intermolecular bonding to light chain, is, according to Dr. Burton, part of the CH1 domain. Ex. 1002 ¶ 39 ("[I]n the human IgG_1 molecule there is a third disulfide bond . . . that links the CH1 domain to the constant region of the light chain."). As Patent Owner points out with regard to the Watson and Smith combination, "Petitioner repeatedly emphasizes the supposed criticality of using the ***same*** IgG portion as the Watson protein to achieve its supposed benefits" to achieve the claimed fusion protein. *See* Prelim. Resp. 38.

Also, with regard to the Smith, Watson, and Zettlmeissl combination, we agree with Patent Owner that Petitioner "incorrectly contends that 'modifying Smith's TNFR:IgG fusion proteins as taught by Zettlmeissl and Watson results in the exact fusion proteins recited in the '522 Patent." Prelim. Resp. 38, 63, respectively; *see also* Pet. 18 ("Both Watson and Zettlmeissl expressly directed the POSA to choose exactly the immunoglobulin fragment claimed in the '522 patent—the 'hinge-CH2-CH3' region of a human IgG heavy chain."). We agree with Patent Owner that "[f]ollowing Petitioner's rationale of replacing only the 'receptor' in its proposed combination of Smith with both Zettlmeissl and Watson would thus yield fusion proteins that include a third component (*i.e.*, an artificial

'linker') between the receptor and IgG components [with Zettlmeissl] and omit part of the hinge [with Watson]." Prelim. Resp. 64.

Thus, with respect to Zettlmeissl, Petitioner appears to assert that "all of the hinge domain" requires the hinge segment encoded by the hinge exon, including three cysteine residues, but with respect to Watson, Petitioner appears to assert that "all of the hinge domain" simply requires a portion of sequence that includes the two cysteine residues involved in joining the heavy chains. Petitioner cannot have it both ways, particularly without an explanation why.

Petitioner fails to provide sufficient explanation why a person of ordinary skill in the art reading Watson, which cites to Capon as to the sequences and methods used (Ex. 1003, 2222), would understand the hinge region of human IgG1 to be any less than that identified by Capon, which includes three cysteine residues (Ex. 1032, 526), one of which Dr. Burton states is part of the CH1 domain (Ex. 1002 ¶ 39). Watson depicts the structure of its mHRLEC fusion protein in Figure 1A and describes what is depicted, thusly: "This truncated protein is joined to a human heavy chain gamma-1 region immediately NH_2-terminal to the hinge domain (*H*) such that this chimera contains the two cysteine residues (*C*) of the hinge responsible for immunoglobulin dimerization as well as the CH2 and CH3 constant regions." Ex. 1002, 2223, Fig.1. The cited figure legend further identifies other elements included in the figure using other like notation, e.g., (*mHR*), (*SS*), (*CBD*), and (*TMD*). *Id.* Thus, the description reasonably identifies where the included hinge domain sequence is in the construct, but does not convey that the hinge portion included in the construct was complete.

Other prior art of record similarly refers to the hinge region as including all three cysteine residues. Byrn (Ex. 1033), cited in the Petition as prior art "[i]n addition to the prior art relied upon in Coherus's grounds of unpatentability" (Pet. 26), has many authors in common with Capon (Ex. 1032), and likewise identifies the hinge region as including three cysteine residues (Ex. 1033, 668, Fig. 1). Byrn also teaches that the use of the label "Hinge" does not necessarily convey the presence of three cysteine residues. For example, Byrn depicts a fusion protein (labeled "CD4 Immunoadhesin") with a hinge (labeled "Hinge") having only the two cysteine residues and describes the fusion as joining the CD4 protein element to "the first residue *in the IgG1 hinge after the cysteine residue involved in heavy-light chain bonding*." *Id.* (emphasis added).

Watson's guidance is further insufficient as to what is included from "the domains of the constant region of a human immunoglobulin IgG heavy chain." Specifically, even assuming that a person of ordinary skill would have understood from Watson that the first domain and hinge domain do not correspond to the encoded CH1 region and hinge region, respectively, Petitioner has not explained adequately how Watson provides sufficient guidance as to the sequence of the disclosed hinge region included to provide a fusion protein including all of the heavy chain constant region other than the first domain. *See generally* Pet. Petitioner cites Watson for "explain[ing] that '[t]he choice of junctional sites between the mHR and human IgG sequences was guided by work with human CD4-IgG chimeras that demonstrated that the ***joining of the molecules near the hinge region resulted in chimeric molecules that were both efficiently synthesized and dimerized*** in the absence of any light chain production'" (Pet. 24 (citing Ex.

1003, 2224)), 18. This, however, does not identify the junction site used in Watson. The further discussion in the Petition, cited portions of Watson, and cited portions of Dr. Burton's Declaration do not identify the particular sequence used in Watson. Pet. 23–24 (citing Ex. 1002 ¶¶ 76–82, 132–134, 140 ; Ex. 1003, 2223–2224, 2228, Fig. 1A); Pet. 29–31 (citing Ex. 1002 ¶¶ 76–79, 132, 141–142, 148, 157–158; Ex. 1003, 2222–25, Figs. 1A, 3; Ex. 1032, 526, Fig. 1).

Even if Watson *arguendo* teaches including all of the constant region other than the first domain, its failure to define the boundary between the two is not remedied by Dr. Burton's description of IgG structure (Ex. 1002 ¶ 39) because it also fails to identify what must be included in a construct containing all domains of the constant region except for the first domain. In particular, Dr. Burton's statements that the "[t]he hinge region contains all of the interchain disulfide bonds that link the heavy chains together . . . [and] that in the human IgG_1 molecule there is a third disulfide bond . . . that links the CH1 domain to the constant region of the light chain" (Ex. 1002 ¶ 39) fail to define this boundary because they fail to identify the character of the amino acid residues lying between the pair of cysteine residues involved in linking the heavy chains together and the cysteine residue involved in linking the heavy chain to the light chain (Ex. 1050).

In sum, we find that Petitioner has failed to show a reasonable likelihood of prevailing in its assertion that claims 1–10 are unpatentable over Watson and Smith because Petitioner has failed to show that Watson describes "all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain of said constant region" as required by all claims.

2. Obviousness over Smith, Zettlmeissl, and Watson

Petitioner contends that claims 1–10 are unpatentable as obvious over Smith in view of Zettlmeissl and Watson. Pet. 43–51. Petitioner further contends the case of obviousness cannot be overcome by objective indicia of nonobviousness. *Id.* at 52–64. Patent Owner opposes Petitioner's contention of obviousness (Prelim. Resp. 56–65) and contends proffered objective indicia of nonobviousness confirm the patentability of the invention (*id.* at 65–82).

Petitioner contends that "it was obvious to modify the TNFR:IgG fusion proteins expressly taught by Smith to arrive at the claimed subject matter, because Zettlmeissl and Watson taught that removing the CH1 region and the light chain of the IgG immunoglobulin would optimize expression of the fusion protein." Pet. 43 (citing Ex. 1002 ¶¶ 145–161; Ex. 1003, 2224; Ex. 1005, 347 (Abstract)). Petitioner further contends that "[m]odifying Smith's fusion proteins to attach the extracellular receptor at the hinge region of the IgG heavy chain, which both Zettlmeissl and Watson teach as a means to optimize expression of the resulting fusion protein, results in the *exact* fusion proteins recited in every claim of the '522 patent." *Id.* at 45 (citing Ex. 1002 ¶ 158) (emphasis added).

Petitioner argues that there is "no tangible benefit to including the light chain." Ex. 1002 ¶ 149; *see also* Pet. 43–48. Petitioner, in contending that "Smith . . . teaches a fusion protein" in which TNFR "is attached directly to the CH1 domains of the IgG molecule," sets forth a figure including both heavy chains and light chains of a human IgG fusion depicting "TNFR substituted for VH or VL, or both." Pet. 44 (citing Ex. 1004, 10:53–61; Ex. 1002 ¶¶ 57–58, 146; Ex. 1032, 526). Petitioner

further argues that because "Smith clearly contemplates bivalent TNFR:IgG fusions . . . it was no leap for the [person of ordinary skill in the art] to modify Smith's fusion proteins by employing only the IgG heavy chain, as taught by Zettlmeissl, Watson, and others before them." *Id.* at 45–46 (citing Ex. 1002 ¶¶ 146–149; Ex. 1003, 2224; Ex. 1005, 347 (Abstract); Ex. 1032, 526). Petitioner relies on Capon (Ex. 1032), in particular, as "demonstrat[ing] that expression of the immunoglobulin light chain was unnecessary in fusion proteins based on human IgG." Pet. 46 (citing Ex. 1002 ¶¶ 64, 150–152; Ex. 1005, 347 (citing Ex. 1032); Ex. 1032, 526). Capon (Ex. 1032) reports that its "CD4-heavy-chain hybrids . . . constructed using the constant region of human IgG1 heavy chain . . . were secreted in the absence of wild-type or hybrid light chains." Ex. 1032, 526.

Petitioner also argues that a person of ordinary skill in the art would have been motivated to remove the CH1 region because its presence in the absence of the light chain results in poor expression. Pet. 46–48. Petitioner relies on Zettlmeissl for "report[ing] that '[i]n general, ***poor expression was observed for fusion proteins bearing CH1 domains*** from either murine or human immunoglobulins.'" *Id.* at 46–47 (citing Ex. 1005, 347 (Abstract), 348). Further, paragraph 150 of Dr. Burton's Declaration, relied on as supporting that "expression of the immunoglobulin light chain was unnecessary" (*id.* at 46), states that "the portions of the CH1 domain that interact with the light chain are hydrophobic, and without a binding partner (i.e., the light chain) the CH1 region would have been expected to interfere with secretion of the protein" (Ex. 1002 ¶ 150 (citing Ex. 1005, 352; Ex. 1035, 70)).

Petitioner fails to adequately reconcile how one of ordinary skill in the art would view the contradiction that the light chain is unnecessary and that problems arising due to its absence require significant modification, namely, the removal of the CH1 domain in applying the teachings of the prior art.

Dr. Burton's further statements that "[n]othing in Smith would have led a [person of ordinary skill in the art] away from optimizing Smith's fusion proteins to delete the CH1 and light chains" (Ex. 1002 ¶ 146) and that "[t]here is a general motivation in the field to simplify things whenever possible, and that is particularly true if the more complex approach would not have conveyed any benefit" (*id.* at 149), also fall short of reasonably providing the necessary rationale to modify Smith as proposed. *See* Pet. 46–48. There is, in particular, no sufficient showing that one of ordinary skill in the art would undertake the effort required to modify Smith's TNFR:IgG fusion on the basis that the modified fusion would be simpler than Smith's extant fusion. "[O]bviousness concerns whether a skilled artisan *not only could have made* but *would have been motivated to make* the combinations or modifications of the prior art to arrive at the claimed invention." *Belden v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015).

Petitioner's contended ground of unpatentability over Smith in view of Zettlmeissl and Watson is also undercut by the inconsistencies in the evidence and in the arguments relating to where the boundary lies between the first constant domain and the hinge region, as discussed above in regard to the ground of unpatentability over Watson in view of Smith.

On this record, we determine that Petitioner has failed to show a reasonable likelihood of prevailing on its assertion that claims 1–10 of the

’522 patent are unpatentable as obvious over Smith (Ex. 1004) in view of Zettlmeissl (Ex. 1005) and Watson (Ex. 1003).

III. PATENT OWNER’S MOTION TO SEAL

Patent Owner filed a motion to seal Exhibits 2083 and 2097, which Patent Owner alleges contains confidential proprietary information. Paper 10. Petitioner did not file an opposition to Patent Owner’s motion. We did not rely on Exhibits 2083 and 2097 in rendering this decision. Accordingly, we dismiss as moot the Motion to Seal.

Patent Owner is authorized to file a motion to expunge Exhibits 2083 and 2097 within thirty days of the date of this decision, or within thirty days of a decision on rehearing, if rehearing is requested.

IV. CONCLUSION

In the instant proceeding, Petitioner has not established a reasonable likelihood of prevailing on its assertion that claims 1–10 of the ’522 patent are unpatentable.

V. ORDER

For the reasons given, it is:

ORDERED that the Petition is *denied* as to all challenged claims of the ’522 patent and no trial is instituted.

FURTHER ORDERED that Patent Owner’s motion to seal is *dismissed as moot*; and

FURTHER ORDERED that Patent Owner is authorized to file a motion to expunge Exhibits 2083 and 2097 within thirty days of the date of this decision, or within thirty days of a decision on rehearing, if rehearing is requested.

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