Trials@uspto.gov
Tel: 571-272-7822

Paper 14
Entered: March 11, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS V LLC,
Petitioner,

v.

HOFFMAN-LaROCHE INC.,
Patent Owner.

Case IPR2015-01792
Patent 8,163,522 B1

Before SUSAN L. C. MITCHELL, BRIAN P. MURPHY, and TINA E. HULSE, *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 Coalition for Affordable Drugs V LLC ("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. and Real Parties-in-Interest, Immunex Corporation and Amgen Inc. (collectively, "Patent Owner"), filed a Preliminary Response. Paper 10 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314. 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 a court proceeding involving the '522 patent, which has been terminated. *See Sandoz Inc. v. Amgen Inc.*, 773 F.3d 1274 (Fed. Cir. 2014); Pet. 2; Paper 8, 2. Patent Owner also states that a complaint asserting infringement of the '522 patent was filed on February 26, 2016 in the United States District Court of New Jersey. *See Immunex Corp. v. Sandoz Inc.*, Case No. 2:16-cv-01118-CCC-JBC (D.N.J.). Paper 13, 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.

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.

E. Prior Art References Applied by Petitioner

Petitioner challenges the patentability of claims 1–10 on the basis of the following references:

Capon et al. ("Capon")	5,116,964	May 26, 1992	Ex. 1002
Smith et al. ("Smith")	5,395,760	Mar. 7, 1995	Ex. 1003
Seed ("Seed")	6,004,781	Dec. 21, 1999	Ex. 1006

F. The Asserted Ground of Unpatentability

Petitioner contends that the challenged claims 1–10 are unpatentable under 35 U.S.C. § 103(a) based on Seed, Smith, and Capon (Pet. 22–60).

II. ANALYSIS

A. 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). 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).

Petitioner proposes constructions for the terms "TNF receptor," "all of the domains of the constant region of a human IgG [or human IgG_1] immunoglobulin heavy chain other than the first domain of said constant region," and "about." Pet. 13–14. Patent Owner also addresses the appropriate construction for these terms. Prelim. Resp. 20–22.

1. "TNF receptor"

Petitioner offers that "TNF receptor" should be interpreted to mean "soluble or non-soluble proteins, or fragments thereof which bind TNF, in homogenous form." Pet. 13 (citing Ex. 1004 ¶ 21 (citing Ex. 1001, 4:14–18)). Patent Owner responds that the passage from the Specification of the '522 patent cited by Petitioner's Declarant, Dr. James J. Greene, *see* Ex. 1001, 4:14–18, refers to "proteins of the present invention," or TNF fusion proteins and not to TNF receptors. Prelim. Resp. 20–21. Patent Owner offers that "TNF receptor" should be given its plain and ordinary meaning of a receptor that binds TNF. *Id*. at 21. We agree that "TNF receptor" should be given its ordinary meaning, but we are not persuaded that this claim limitation needs an express construction at this stage of the proceeding.

2. "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 "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"

Petitioner asserts that the claim phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the

first domain of said constant region" should be interpreted as "'-hinge-CH2-CH3' region of an IgG (or IgG_1) immunoglobulin heavy chain." Pet. 14 (citing Ex. 1004 ¶ 22 (citing Ex. 1001, 2:37–43)). Patent Owner agrees with the construction with two caveats: (1) that the reference to IgG should refer to claims 1 and 7, and the reference to IgG_1 should refer to claim 4; and (2) that IgG and IgG_1 be limited to human origin. Prelim. Resp. 21–22.

As all of the claims refer to *human* IgG or IgG_1 immunoglobulin heavy chain, *see* Ex. 1001, 45:58–60, 46:53–55, 47:1–3 and Petitioner acknowledges this fact in its discussion concerning claim construction, Pet. 14 (referring to claim phrase denominating "*human* IgG immunoglobulin"), the parties do not appear to disagree that the required IgG or IgG_1 immunoglobulin heavy chain recited in the claims refers to *human* IgG or IgG_1 immunoglobulin heavy chain. Also, claims 1–3 and 7–10 of the '522 patent refer to human IgG, *see* Ex. 1001, 45:58–60, 47:1–3, and claims 4–6 of the '522 patent refer to human IgG_1, *see id.* at 46:53–55. We agree with Patent Owner that the construction for the claims should reflect this distinction.

Dr. Greene provides a schematic for immunoglobulin structure showing a heavy chain with a variable region followed by a constant region, denominated C_H1, a hinge region, and two other constant regions, denominated C_H2 and C_H3. Ex. 1004 ¶ 24; *see also* Ex. 2009, 1, Fig. 3.1 (showing same structure for IgG). Dr. Greene also relies on a statement in the '522 Specification that states that "[t]his invention comprises DNA sequences which combine two partial DNA sequences, one sequence encoding soluble fragments of TNF binding proteins and the other partial sequence encoding all domains except the first domain of the constant region

of the heavy chain of human immunoglobulin IgG, IgA, IgM, or IgE, and the recombinant proteins encoded by these sequences." Ex. 1004 ¶ 22 (citing Ex. 1001, 2:37–43).

Both parties appear to agree that all the domains of the constant region of either human IgG or IgG_1 other than the first domain of said constant region includes a hinge region, and C_H2 and C_H3 constant regions. *See* Pet. 14; Prelim. Resp. 21–22, 12 (stating claims in related U.S. Patent 8,063,182 B1 ("the '182 patent") that includes similar claim language "are directed to proteins that fuse a soluble fragment of p75 TNF receptor to the hinge, CH2, and CH3 domains of human immunoglobulin"). Based on the record before us, we construe "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region" to mean "'-hinge-C_H2-C_H3' region of a human IgG immunoglobulin heavy chain," and "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" to mean "'-hinge-C_H2-C_H3' region of a human IgG_1 immunoglobulin heavy chain."

3. "about"

Petitioner offers an interpretation of "about" as used in the claims to mean "approximately." Pet. 14. Although Patent Owner does not disagree with the construction, it questions whether such construction is necessary. Prelim. Resp. 22. We agree with Patent Owner that we do not need an express construction of "about" at this stage of the proceeding.

B. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that

the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see Translogic*, 504 F.3d at 1259. A prima facie case of obviousness is established when the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Rinehart*, 531 F.2d 1048, 1051 (CCPA 1976). We are mindful that the level of ordinary skill in the art also is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc*., 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

We analyze the asserted ground of unpatentability in accordance with the above-stated principles.

C. Obviousness over Smith, Capon, and Seed

Petitioner contends that claims 1–10 are unpatentable under 35 U.S.C. § 103 as obvious over Seed, Smith, and Capon. Pet. 4. Petitioner asserts that Smith teaches IgG fusions containing the soluble derivatives of the full-

length, human TNF receptor. *Id.* at 17 (citing Ex. 1003, 4:12–16). Petitioner also asserts that both Seed and Capon teach fusions using the hinge-C_H2-C_H3 regions of the constant region of the human immunoglobulin heavy chain. *Id.* at 15–17 (citing Ex. 1006, 4:47–5:29, 6:13–14, 14:6–9; Ex. 1002, 4:38–47, 10:10–12, 40:65–69; Ex. 1004 ¶¶ 25, 26). Petitioner asserts that "*Smith's* soluble TNF receptor would be suitable as a ligand-binding partner in the hybrids of *Seed* and *Capon*. The need for 'practical yields' would have motivated one to use *Seed* or *Capon* to express the TNF-R gene of *Smith*." *Id.* at 18 (citing Ex. 1004 ¶ 28). Petitioner also asserts that enhanced TNF binding affinity as taught by Smith for dimeric assemblies, *see Id.* (citing Ex. 1003, 10:61–66; Ex. 1004 ¶ 29), would also have motivated a person of ordinary skill to use Seed or Capon to provide dimeric TNF-R-Fc assemblies. *Id.*

1. Smith

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_κ) 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.

2. Capon

Capon teaches polypeptides comprising a ligand binding partner fused to a stable plasma protein, such as an immunoglobulin constant domain, which is capable of extending the in vivo plasma half-life of the ligand binding partner when present as such a fusion. Ex. 1002, 5:13–21. Capon states that

> Ordinarily, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of immunoglobulins in place of the variable region(s) thereof, however, N-terminal fusions of the binding partner are also desirable. . . .
>
> Typically, such fusions retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain. Fusions are also made to the C-terminus of the Fc portion of a constant domain, or immediately N-terminal to the CH1 of the heavy chain or the corresponding region of the light chain. . . .
>
> The precise site at which the fusion is made is not critical: particular sites are well known and may be selected in order to optimize the biological activity, secretion or binding characteristics of the binding partner. The optimal site will be determined by routine experimentation.
>
> In some embodiments the hybrid immunoglobulins are assembled as monomers or hetero- or homo-multimers, and particularly as dimers or tetramers.

Ex. 1002, 10:1–29.

In describing a particularly preferred embodiment, Capon states that this embodiment

> is a fusion of an N-terminal portion of a LHR, which contains the binding site for the endothelium of lymphoid tissue, to the

> C-terminal Fc portion of an antibody, containing the effector functions of immunoglobulin G_1. There are two preferred embodiments of this sort: in one, the entire heavy chain constant region is fused to a portion of the LHR; in another, a sequence beginning in the hinge region just upstream of the papain cleavage site which defines IgG Fc chemically . . . is fused to a portion of the LHR. The latter embodiment is described in the Example 4.

Id. at 15:4–18. The murine LHR-IgG chimeras of Example 4 describe truncated proteins of murine LHR that

> are all joined to a human heavy chain gamma 1 region just upstream of the hinge domain (H) such that these chimeras contain the two cysteine residues (C) of the hinge responsible for immunoglobulin dimerization as well as the CH2 and CH3 constant regions. . . . Junctional sites between the LHR and human IgG sequences was chosen such that the joining of the molecules near the hinge region resulted in chimeric molecules that were efficiently synthesized and dimerized in the absence of any light chain production.

Id. at 40:43–55.

3. Seed

Seed describes a DNA sequence encoding a fusion protein of CD4, or a fragment of CD4, which binds to HIV gp120, and an immunoglobulin light or heavy chain where the CD4 or fragment thereof replaces the variable region of the light or heavy immunoglobulin chain. Ex. 1006, 4:48–53. Seed specifically defined "fusion protein" as

> a fused protein comprising CD4, or fragment thereof which is capable of binding to gh120, linked at its C-terminus to an immunoglobulin chain wherein a portion of the N-terminus of the immunoglobulin is replaced with CD4. In general, that portion of immunoglobulin which is deleted is the variable region. The fusion proteins of the invention may also comprise immunoglobulins where more than [j]ust the variable region has been deleted and replaced with CD4 or HIV gp120 binding

> fragment thereof. For example, the V_H and CH1 regions of an immunoglobulin chain may be deleted. Preferably, any amount of the N-terminus of the immunoglobulin heavy chain can be deleted as long as the remaining fragment has antibody effector function. The minimum sequence required for binding complement encompasses domains CH2 and CH3. Joining of Fc portions by the hinge region is advantageous for increasing the efficiency of complement binding.

Id. at 6:4–21. Seed also defines "antibody effector function" as the ability to fix, complement, or to activate antibody-dependent cellular toxicity. *Id.* at 5:56–57.

4. Analysis

Petitioner presents an explanation demonstrating where the limitations of the challenged claims may be found in the cited references. Pet. 15–60. Petitioner also relies on the Declaration of James J. Green, Ph.D. Petitioner's argument focuses on how the combination of cited references teach a polynucleotide consisting of the extracellular region of an insoluble human TNF receptor and all of the domains of the constant region of a human IgG or IgG_1 immunoglobulin heavy chain other than the first domain of said constant region.

For instance, Petitioner states that Smith discloses a TNF receptor, and Seed and Capon each discloses receptors linked to IgG_1 upstream from the hinge region, with Capon defining the hinge region functionally. *Id.* at 4. Petitioner concludes that

> Once *Smith* had disclosed the TNF-R gene, a POSITA would have used *Capon's* method to make TNF-R-Fc with a reasonable expectation of success:
>
> [X receptor]-Fc (dimer) → [TNF receptor]-Fc (dimer)

> wherein [X receptor] is CD4 (**Ex. 1002**, 44:60–62; 45:6–12, Example 5 of *Capon*), or cell surface glycoprotein lymphocyte homing receptor of "LHR" (**Ex. 1002**, 15:4–8; 40:30–32, Example 4 of *Capon*). **Ex. 1004,** ¶36.

Id. at 7. Petitioner also asserts that Capon discloses a "typical" approach, set forth in examples 4 and 5 and Figure 8 of the Specification of the '522 patent, of omitting the C_H1 domain from the constant region of IgG. *See id.* at 8–9. Petitioner concludes that "[m]odifying such chimeras by replacing their receptors with *Smith's* TNF-R required no selection from among multitudes. (It merely required using *Capon's* method for its intended purpose.[)] [(]**Ex. 1004,** ¶36[)]." *Id.* at 8.

Petitioner addresses a teaching away argument concerning Smith made by Patent Owner during prosecution of the '522 patent. Petitioner asserts that, although Smith teaches unmodified IgG heavy chains, Smith teaches this structure as just one embodiment, "giving no reason why any other structure should be avoided." *Id.* at 10 (citing Ex. 1020, 40:2–6; Ex. 1022, 24:16–20; Ex. 1024, 9:16–18). Petitioner's Declarant, Dr. Greene testifies that neither Smith nor Capon "discourages the POSITA from using *Capon's* method to make *Smith's* TNF-R." *Id.* at 11 (citing Ex. 1004 ¶¶ 53, 76, 98).

Finally, Petitioner noted the unexpected properties of p75 TNFR fusions as compared to properties of soluble, recombinant forms of p75 TNFR, but did not address the unexpected properties substantively. *Id.* at 10–11; *see also* Ex. 1020, 33–36; Ex. 1024, 9–13. Petitioner asserts that the evidence of unexpected results is

unavailing because the claims are not commensurate in scope.

Pet. 10. Petitioner states:

> Claims 1–10 are not commensurate in scope with any protein because: (1) they are directed to either polynucleotides, host cells, vectors, or methods of protein expression, but not to proteins *per se*, and (2) all of the claimed subject matter has alternative uses that were obvious over *Seed*, *Smith*, and *Capon*.

Id. at 11.

Patent Owner responds that institution of an *inter partes* review should be denied because Petitioner has failed to demonstrate a reasonable likelihood that it would prevail in demonstrating that the challenged claims are rendered obvious over the combination of Smith, Capon, and Seed[1] for the following three reasons: (1) the Petition presents no new art that was not considered previously by the Office; (2) the Petition did not explain adequately why one of skill in the art would combine teachings of the references to arrive at the claimed invention; and (3) the Petitioner failed to address Patent Owner's evidence of unexpected results presented in the prosecution history of the '522 patent. Prelim. Resp. 3–4.

Patent Owner asserts that both Capon and Seed teach fusion proteins that retain the hinge, C_H2, and C_H3 domains of the constant region of an immunoglobulin heavy chain to target and destroy unwanted cells. *Id.* at 8. Patent Owner concludes that "[i]ndeed, the common message in both Seed

[1] Petitioner acknowledges that Smith and Capon were before the Office during prosecution of the '522 patent, but asserts that Seed was not, *see* Pet. 4. Patent Owner asserts, however, that the substantive teachings of Seed were before the Office because a related Seed patent application, EP 0 325 262, which shares the same disclosure as the Seed reference asserted by Petitioner, was before the Office during the prosecution of the '522 patent. Prelim. Resp. 8 (citing Ex. 2015; Ex. 2018, 2).

and Capon is to create therapeutic fusion proteins by combining *pro*-inflammatory receptors with *pro*-inflammatory IgG components, not therapeutic fusion proteins that combine an *anti*-inflammatory receptor with a *pro*-inflammatory Fc fragment." *Id.* at 9. Smith provides no further guidance to combine the teachings of the references, Patent Owner asserts, because Smith teaches chimeric antibody molecules that incorporate unmodified constant region domains. *Id*. Patent Owner concludes that the combination of references would have led the skilled person away from the claimed methods. *Id*.

We agree with Patent Owner that Petitioner has not shown a reasonable likelihood to prevail on any challenged claim. Petitioner has failed to show an articulated reason with a rational underpinning why one of skill in the art would have combined the teachings of Smith, Capon, and Seed to arrive at the claimed invention.

We agree with Patent Owner that the generalized guidance in Seed and Capon would not have led one of ordinary skill in the art to produce a p75 TNFR-based fusion protein having a structure that corresponds to the expression products of the challenged claims or the protein encoded by the polynucleotides described in the challenged claims. *See* Ex. 1001, 45:45–48:4. For instance, Capon describes utilizing all of the heavy chain constant region of an immunoglobulin or deleting the C_H1 portion, but does not distinguish the hinge-C_H2-C_H3 construct as offering any advantage that would lead one of skill in the art to choose it in making a p75 TNFR-based fusion protein. *See* Ex. 1002, 10:1–26. In fact, Capon specifically states that the precise site at which the fusion protein is made is not critical, but can be determined by routine experimentation. *Id.*

Seed offers no better guidance for one of skill in the art in arriving at the claimed invention. For instance, Seed also teaches that, in general, the entire heavy chain constant region of the immunoglobulin may be used. *See* Ex. 1006, 6:4–21. As an alternative, Seed states that more than the variable region may be deleted and replaced, such as the C_H1 portion of the constant region, so long as the remaining fragment has antibody effector function. *Id*.

Petitioner's offer of a rationale to combine the references is unavailing. Petitioner offers that one of skill in the art would have been motivated to use the teachings of Seed or Capon to express the TNF-R gene of Smith, *see* Pet. 18 and Ex. 1004 ¶ 28, but fails to offer persuasive evidence to explain why one of skill in the art would choose the Fc portion of the immunoglobulin heavy chain from the choices taught in Seed or Capon.

Petitioner offers only generalized teachings from the references to show a rationale to combine. For instance, Smith states that practical yields of its fusion protein may be obtained "only by cloning and expressing genes encoding the receptors using recombinant DNA technology." Pet. 17–18 (citing Ex. 1003, 2:22–25). From this statement, Petitioner concludes that "[t]he need for 'practical yields' would have motivated one to use Seed or Capon to express the TNF-R gene of *Smith*," *see id.* at 18 (citing Ex. 1004 ¶ 28), but such motivation does not provide a reason for one of skill in the art to select the hinge-C_H2-C_H3 constant region of the immunoglobulin from the teachings of Seed or Capon to combine with Smith's TNF-R gene.

Petitioner also offers Smith's teaching that polyvalent forms of TNF-R may have enhanced binding affinity for a TNF ligand as a motivation to combine the teaching of the references to arrive at the claimed

invention, *see* Pet. 18 (citing Ex. 1006, 6:53–56), but Smith teaches use of the entire constant region of the immunoglobulin to achieve such binding affinity. This teaching would not point to selective deletion of the C_H1 domain to achieve any enhanced binding affinity, and as we discussed above, neither Capon nor Seed point to why one of skill in the art would choose to use the -hinge-C_H2-C_H3 portion of the constant region of the immunoglobulin over other constructs. Capon's teaching of a prolonged in vivo plasma half-life of the ligand binding partner is not linked to the use of the -hinge-CH2-CH3 portion of the constant region of the immunoglobulin over other constructs. *See id.* at 16 (quoting Ex. 1002, 4:38–47), 20. Therefore, this would not provide a sufficient reason to combine the references to achieve the claimed invention. Petitioner has not shown that it is reasonably likely to prevail with respect to any challenged claim in the Petition.

Petitioner also does not address adequately the objective indicia of nonobviousness presented to the Office during the prosecution of the '522 patent, merely asserting that such evidence was not commensurate in scope with the claims. *Id.* at 10–11.[2] Petitioner states that the claims are directed to polynucleotides, host cells, vectors, and methods of protein expression, while the unexpected results evidence addresses fusion proteins. *Id*. at 11.

[2] Petitioner does assert that the claimed subject matter of the '522 patent "has alternative uses that were obvious over *Seed*, *Smith*, and *Capon*." Pet. 11. Petitioner, however, does not provide any explanation as to what these alternative uses are. As this statement is mere attorney argument, we give it little weight. *See Meitzner v. Mindick*, 549 F.2d 775, 782 (CCPA 1977) (stating "[a]rgument of counsel cannot take the place of evidence lacking in the record").

The challenged method claims, however, address purifying a fusion protein "expression product" encoded by the polynucleotide set forth in the claim, *see* Ex. 1001, 45:45–67, 46:59–48:4, and the remaining challenged claims address the polynucleotides encoding the fusion proteins. *See id*. at 46:44–58; *see also* Ex. 1023, 13–14[3] (addressing presented unexpected results after noting that the claimed inventions were "drawn to nucleic acids, not proteins" (emphasis omitted)). The evidence of unexpected results is commensurate in scope with the claims.

During the prosecution of the '522 patent, Patent Owner offered expert testimony concerning the unexpected results of improved TNF binding affinity, potency, kinetic stability, and reduced antibody effector function and aggregation ability. *See* Ex. 1020, 27–36; Ex. 1022, 25–39; Ex. 1024, 9–13; Ex. 2017. We agree with Patent Owner that the unrebutted objective indicia of nonobviousness presented in the prosecution history of the '522 patent, and apparently relied upon by the Examiner, at least in part, in allowing the claims of the '522 patent, *see* Ex. 1026, 6, supports the non-obviousness of the challenged claims. The Petition, moreover, should have addressed the evidence of unexpected results as part of Petitioner's showing of a reasonable likelihood of success on the merits.[4] *See Praxair Distrib., Inc. v. INO Therapeutics, Inc*., Case Nos. IPR2015-00522, -00524, -00525, -00526, slip op. at 16–17 (PTAB July 29, 2015).

[3] The cited pages refer to Petitioner's pagination of the exhibit as opposed to the original page numbers for the exhibit.

[4] Because we have addressed the Petition on its merits, we need not address whether to exercise our discretion under 35 U.S.C. § 325(d).

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing any of claims 1–10 of the '522 patent are unpatentable under 35 U.S.C. § 103(a).

IV. ORDER

Accordingly, it is

ORDERED that the Petition is *denied* at to all challenged claims of the '522 patent.

PETITIONER:

Robert W. Hahl
Robert Mihail
John K. Pike
NEIFELD IP LAW, PC
rhahl@neifeld.com
rmihail@neifeld.com
jkpike@neifeld.com

PATENT OWNER:

Jeffrey P. Kushan
James A. High
Jill J. Schmidt
Peter S. Choi
SIDLEY AUSTIN LLP
IPRNotices@sidley.com
jhigh@sidley.com
jschmidt@sidley.com
peter.choi@sidley.com