Paper No. 10

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS V LLC, HAYMAN CREDES MASTER FUND, L.P., HAYMAN ORANGE FUND SPC – PORTFOLIO A, HAYMAN CAPITAL MASTER FUND, L.P., HAYMAN CAPITAL MANAGEMENT, L.P., HAYMAN OFFSHORE MANAGEMENT, INC., HAYMAN INVESTMENTS, L.L.C., nXn PARTNERS, LLC, IP NAVIGATION GROUP, LLC, KYLE BASS, and ERICH SPANGENBERG,
Petitioner and Real Parties in Interest,

v.

HOFFMANN-LA ROCHE INC., IMMUNEX CORPORATION, and AMGEN INC.,
Patent Owner and Real Parties in Interest.

CASE IPR2015-01792
Patent 8,163,522

PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107 OF PATENT OWNER AND REAL PARTIES IN INTEREST

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TABLE OF EXHIBITS

Patent Owner's Exhibit No.	Description
2001	Enbrel® Prescribing Information
2002	U.S. Patent No. 8,063,182 Patent to Brockhaus et al.
2003	Kohno et al., Presentation 1495, poster 271 presented at American College of Rheumatology Annual Meeting, Nov. 13-17, 2005, San Diego, CA
2004	Khare et al., Poster 715 presented at the Annual Meeting of the Society for Investigative Dermatology (SID), May 3-5, 2006, Philadelphia, PA
2005	Barone et al., Arthritis Rheum., v42(9) supplement, Sept. 1999 (S90)
2006	Mohler et al., *J. Immunol.*, 151:1548-61 (1993)
2007	Dembic et al., *Cytokine* 2(4):231-7 (1990).
2008	Hohmann, et al., *J. Bioi. Chem.* (1989)
2009	Janeway et al., *Immunobiology* (6th ed. 2005)
2010	Bryn et al., *Nature*, 344:667-670 (Apr. 1990)
2011	Kelley et al., Textbook of Rheumatology (3rd ed. 1989)
2012	Suitters et al., *J. Exp. Med.* 179:849-56 (1994)
2013	Kingsley et al., *Immunology Today* 12(6):177-79 (1991)
2014	Asherson et al., *Postgrad Med J.* 67:114-39 (1991)
2015	EP 0 325 262 to Seed
2016	Declaration of Taruna Arora, Ph.D. Under 37 C.F.R. 1.132 dated December 16, 2010
2017	Declaration Under 37 C.F.R. §1.132 of Dr. Werner Lesslauer dated Dec. 3, 2004
2018	'522 File History, IDS considered March 1, 2007
2019	'522 File History, Non-Final Rejection dated Oct. 15, 2010
2020	'522 File History, Notice of Appeal dated Dec. 22, 2011
2021	'182 File History, Final Rejection dated Feb. 23, 2007

Patent Owner's Exhibit No.	**Description**
2022	'182 File History, Appeal Brief (Appeal No. 2009-014889) dated Feb. 28, 2008
2023	'182 File History, Examiner's Replacement Answer (Appeal No. 2009-014889) dated Mar. 24, 2009
2024	'182 File History, Reply Brief (Appeal No. 2009-014889) dated May 26, 2009
2025	'182 File History, Decision on Appeal (Appeal No. 2009-014889) dated Nov. 22, 2010
2026	'182 File History, Office Action dated Mar. 7, 2011
2027	'182 File History, Response dated Mar. 29, 2011
2028	'182 File History, Notice of Allowance dated Aug. 31, 2011
2029	'279 File History, Examiner's Action dated April 14, 1994
2030	Morgenson, "Working to Lower Drug Costs by Challenging Questionable Patents," N.Y. *Times* (Nov. 27, 2015)
2031	WO 89/09622 to Queen
2032	Vane et al., "Inflammation and the mechanism of action of anti-inflammatory drugs," *FASEB* 1:89-96 (1987)

I. INTRODUCTION

The Petition levels a single-issue challenge to U.S. Patent No. 8,163,522 ("the '522 Patent"), which claims nucleic acids, host cells, and methods used to produce Enbrel® (etanercept), the first fusion protein approved by the United States Food and Drug Administration. The Petition argues—despite no prior disclosure of the etanercept fusion protein, a teaching away from such structure in the references relied upon, and mounds of objective evidence showing unexpected and non-obvious results from such structure—that the DNA, host cells and methods for making etanercept were obvious to a skilled person at the time of the invention. Not only are the Petition's arguments without merit, but the same arguments, based on the same or nearly identical references, were considered and rejected by the Board and the Office during examination of the '522 Patent and the related etanercept product patent. Those arguments should meet the same fate here and the Petition should be denied.

Etanercept is a homodimeric protein resulting from expression of a recombinant construct joining DNA coding for the soluble portion of the human 75-kilodalton TNF receptor ("p75 TNFR") with DNA coding for the "Fc" portion[1]

[1] The "Fc" (fragment crystallizable) portion of an antibody appears at the opposite end from its antigen-binding portion, is responsible for dimerization of the antibody's heavy chains, and often interacts with "Fc receptors" and proteins of the complement system to activate an immune response. Ex. 2009 at 3-4, 6. The etanercept fusion

of the human IgG antibody heavy chain. By capturing free, excess TNF ("tumor necrosis factor"), etanercept can reduce signs and symptoms of a number of TNF-mediated inflammatory conditions, including moderately to severely active rheumatoid arthritis, chronic moderate to severe plaque psoriasis, and psoriatic arthritis.

This Petition is one of a series that hedge-fund billionaire Kyle Bass has filed in the name of the Coalition for Affordable Drugs ("Petitioner") against blockbuster therapeutics as part of his reported business model of filing IPR petitions and then shorting the target company's stock.[2] While this does not preclude consideration of Bass' Petition, it does explain its less-than-rigorous approach.

The claimed methods and materials in the '522 Patent are directed to making the fusion protein that is claimed in U.S. Patent No. 8,063,182 ("the '182 Patent") (Ex. 2002).[3] The '522 and '182 Patents are related, they share identical disclosures, and

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protein incorporates the polypeptide sequence encoded by the "genetic" IgG Fc (*i.e.*, all the exons of the constant region of the human IgG_1 immunoglobulin heavy chain gene except those coding for the first domain of the constant region). Ex. 2001 § 11.

[2] *See, e.g.,* Ex. 2030 (N.Y. *Times* article) at 2 ("Mr. Bass and Mr. Spangenberg are short-sellers of shares in companies whose patents they consider vulnerable.").

[3] The '522 Patent issued from an application filed in response to a restriction requirement in its parent application, No. 08/095,640. The claims issuing in the '522 Patent were found patentably distinct from the protein claims later issued in the '182

they issued from applications claiming priority to the same priority filings. During '182 Patent prosecution, this Board's predecessor (the Board of Patent Appeals and Interferences) reversed the Examiner's obviousness rejection based on the arguments and references in that record. And the Office recognized later, during examination of the '522 Patent, that the Board's earlier rejection of this obviousness theory for the protein was a compelling reason to withdraw rejections based on that same theory of the corresponding claims to methods and materials for producing that same protein.

Thus, there are three reasons why the Petition failed to establish a reasonable likelihood that any of the challenged claims is unpatentable. *First*, the Petition presented nothing new when assessed against the examination records of the '522 and '182 Patents and the favorable Board decision decisive for both. *Second*, the Petition failed to establish that a skilled artisan, objectively following "guidance" in the prior art, would have arrived at the claimed invention.[4] *Third*, the Petition avoided tackling

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Patent. Ex. 2029 at 2. Consequently, the '522 Patent claims are shielded under 35 U.S.C. § 121 from a finding of double patenting over the claims of the '182 Patent.

[4] Two of the references (Smith and Capon) were expressly considered—and rejected. The third (Seed) is nothing new. Though cast as "not of record," the same disclosure was actually before the Examiner in the form of Seed's European application (Ex. 2015), and does not differ substantively from Capon, which was fully considered by the Board and Office. *See* Ex. 2018 (IDS noting Seed was considered) at 2.

the merits of Patent Owner's considerable evidence of objective indicia, including unexpected results that the Board found independently persuasive of non-obviousness, and which precludes any contrary determination now.

In sum, Petitioner disregarded the dispositive Board decision, substituted hindsight for insight in what a person of skill would actually confront at the relevant time, and failed to address the substantial body of objective indicia of non-obviousness. The Petition should be denied.

II. SUMMARY OF ARGUMENT

The Petition asserted just one theory: that because techniques for making certain types of cell receptor-Ig fusion proteins were known in the art (specifically as taught by Capon and Seed) and because the p75 TNFR sequence was also known in the art (as taught by Smith), a person of ordinary skill in the art would have found it obvious, with a reasonable expectation of success, to devise methods and materials for producing the "p75 TNFR-Fc" fusion proteins according to the '522 Patent claims. This argument has three major defects. Each one is separately dispositive.

The Board and the Office previously rejected the same obviousness theory.

The Petition ignored the Board's conclusions and reasoning in the intertwined examination of the '522 and '182 Patents. In the prior Board appeal involving the '182 Patent, the Examiner argued (as Petitioner did here) that disclosure of the p75 TNFR protein, in combination with teachings that show production of certain cell receptor-immunoglobulin/Fc fusion proteins, would have rendered the claimed p75 TNFR-Fc

fusion proteins of the '182 Patent obvious.[5] Ex. 2023 (Examiner's Answer) at 18-20. Patent Owner refuted this, explaining that, even within the four corners of those references, that argument was wrong. Ex. 2022 (Appeal Brief) at 39-46; Ex. 2024 (Reply Brief) at 23-27. Further, Patent Owner also provided extensive objective evidence of non-obviousness, including:

- unexpectedly superior properties, such as a 50-fold increase in binding affinity for TNF and a 1000-fold increase in TNF neutralizing potency in *in vitro* biological activity assays, compared to soluble p75 TNFR alone;
- unexpectedly different properties, such as that the claimed p75 TNFR-Fc fusion proteins did not form aggregated complexes, which thereby provided important therapeutic benefits in its intended application in treating inflammatory disorders; and
- absence of expected properties such as antibody effector function; the reduction in such function seen in the claimed p75 TNFR-Fc fusion

[5] For disclosure of p75 TNFR, the Examiner relied on Dembic (Ex. 2007). Ex. 2023 at 18-20. Later, he relied on Smith (Ex. 1003). Ex. 2026 at 5-13. For disclosure of cell receptor-immunoglobulin/Fc fusions, the Examiner relied on Capon (Ex. 1002). Ex. 2023 at 18-20. Petitioner cited Smith and Capon, adding Seed (Ex. 1006).

proteins was contrary to what would have been predicted, *e.g.*, by Capon and Seed, for a fusion protein incorporating the Fc portion of an IgG molecule. Ex. 2022 (Appeal Brief) at 48-55.

The Board agreed with Patent Owner, specifically finding that the substantial evidence of unexpected results for the p75 TNFR-Fc, even when standing alone, was sufficient to rebut the '182 Patent Examiner's obviousness rejection. Ex. 2025 (Board Decision) at 7.

Notwithstanding the Board's conclusion that the claimed p75 TNFR-Fc fusion protein was not obvious, the Examiner attempted one last time to reject the protein claims by substituting the original reference used to teach the availability of the TNFR sequence, Dembic (Ex. 2007), with Smith (Ex. 1003). Ex. 2026 (Office Action) at 5-13. Patent Owner disputed this rejection as well, citing, *inter alia*, the Board's findings concerning the objective indicia of non-obviousness of the claimed fusion protein, and further noted that whereas the fusion proteins produced by the claimed methods all required *modified* constant region domains, Smith instead taught proteins that combined p75 TNFR sequences with "either or both of the immunoglobulin heavy and light chains and having *unmodified* constant region domains." Ex. 2027 at 10-26. In response, the Office withdrew the rejections. Ex. 2028 (Notice of Allowance) at 7.

The examination record of the '522 Patent tracked the '182 Patent record. In the former, the Office imposed would-be rejections based on the same set of prior art references, and employed essentially the same argument of obviousness advanced

during the '182 Patent's examination. *E.g.*, Ex. 1019 (Office Action) at 6-12 [5-11].[6] However, after the Board reversed the original obviousness rejections in the '182 Patent, and the Office withdrew the subsequent rejections of the '182 Patent claims based on Smith and Capon, the Office withdrew the corresponding rejections to the '522 Patent claims as well. Ex. 1026 at 6 [2]. Thus, the Petition offers nothing in terms of art or arguments not already considered during the prosecution of the '522 Patent.

The Petition's cited art does not establish a case of obviousness.

Even setting aside the prior findings of the Office and Board, the Petition itself failed to establish the requisite showings to warrant institution of trial. The Petition failed to advance an articulated rationale for why the skilled person, without the benefit of hindsight and ignoring the admittedly unpredictable features of the p75 TNFR-Fc fusion proteins that result from use of the '522 Patent's claimed methods and materials, would have nevertheless modified the teachings of the prior art to arrive at the claimed invention. *See infra*, Section VI.B. Thus, combining the three relied-upon references does not come close to establishing a *prima facie* case of obviousness.

The Petition tried to avoid the effects of this record evidence and past actions

[6] Petitioner's page numbers on certain exhibits do not always match the original pagination. This Response uses Petitioner's page numbers, but where possible also includes the actual page numbers of the document in brackets.

of the Board and Office by asserting that the "unconsidered" Seed reference provides materially different insights and teachings than those previously considered. Specifically, the Petition contends that Seed provides a more specific suggestion than Capon about desired features of fusion proteins, and that this supposedly more probative insight differs from the obviousness question that the Office and Board considered. *E.g.*, Pet. at 15-16, 29-32. That contention is both misleading and baseless.

The Petition's contention is misleading because the Office did consider Seed's substantive teachings by considering a related Seed patent application, EP 0 325 262 (Ex. 2015). *See* Ex. 2018 at 2. That related Seed application shares the same disclosure as the Seed reference cited by Petitioner. The Petition failed to mention this fact.

The Petition's contention is also baseless. As explained below, Capon, like Seed, expressly describes fusion proteins that retain the hinge, CH2, and CH3 domains of the constant region of an immunoglobulin heavy chain. *See infra*, Section V.B-V.E; *see also, e.g.*, Ex. 1006 at 6:8-21; Ex. 1002 at 10:10-12. Capon, like Seed is directed primarily to production of fusion proteins to be used in ways entirely unrelated to those that concern the claimed p75 TNFR-Fc fusion proteins; namely, to target and destroy unwanted cells. *See, e.g.*, Ex. 1002 at 4:30-47; Ex. 1006 at 5:13-17. And, critically, for both the '182 and '522 Patent claims, the Office advanced, but ultimately abandoned, the *same argument* that the Petition presented: that based on Capon's guidance, the ordinary artisan would somehow have had the insights to make, and thus would have made, the various choices needed to yield the claimed p75

TNFR-Fc fusion proteins. Ex. 2028 at 7; Ex. 1026 at 6 [2]. Capon (like Seed) makes no mention of p75 TNFR as a fusion partner candidate, and its discussion of more than 250 ligand-binding-partner/Ig fusion proteins would not have provided any direction to the skilled person to pursue the counterintuitive inclusion of a pro-inflammatory Ig constant region within a p75 TNFR fusion protein designed to reduce inflammation. *See id.* Indeed, Seed adds nothing—its disclosure is more limited than Capon, and is focused on production of a single CD4-Ig fusion protein that was designed, like the proteins in Capon, to target and destroy cells using the body's immune system. *See, e.g.*, Ex. 1006 at 9:11-19. Indeed, the common message in both Seed 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. *See infra*, Section V.D.

The Petition then, without any rational basis, simply assumes the skilled person would ignore these instructions in Seed (and Capon), and combine those teachings with Smith. But adding Smith does nothing to cure the deficiencies in Seed and Capon; Smith proposes chimeric antibody molecules that incorporate *unmodified* constant region domains rather than *modified* constant region domains as required by the claims. *See* Ex. 1003 at 10:53-57. Capon, Seed, and Smith, individually and collectively, thus would have led the skilled person away from, not towards, the claimed methods. Indeed, the Petition identifies nothing in any of those references

that might even foreshadow, much less establish, any scientifically reasonable basis for believing that such p75 TNFR-Fc fusion proteins could be successfully used to treat a variety of autoimmune conditions such as rheumatoid arthritis. For these and other reasons, discussed below, combining the three references does not establish a *prima facie* case of obviousness.

Petitioner failed to address the objective evidence of non-obviousness.

The Petition also, remarkably, failed to address the probative value of the objective evidence of non-obviousness in the examination record of the '522 Patent. Separate and apart from the fact that the Board found it to be so, this objective evidence of non-obviousness is dispositive.

As explained above, the novel p75 TNFR-Fc fusion proteins, made using the claimed methods and materials, possesses surprising properties. Ex. 2022 at 48-55; Ex. 1022 at 25-39. They exhibit a 50-fold increase in TNF binding affinity and a 1000-fold increase in TNF neutralizing potency in *in vitro* activity assays, compared to unfused, soluble p75 TNFR alone. *Id.* They do not form aggregated complexes, which could thereby provide important therapeutic benefits in its intended application in treating inflammatory conditions. *Id.* They also provide an observed reduction of antibody effector function, which was ***contrary*** to what Capon (or Seed) would have predicted for a fusion protein incorporating an IgG Fc. *Id.*

Instead of addressing the merits of the substantial evidence of objective indicia the Board found probative to non-obviousness, the Petition asked the Board to

simply ignore it because it concerns p75 TNFR-Fc *proteins* while the claims of the '522 Patent are directed to *nucleic acids*, *host cells*, and *methods* of making these same novel p75 TNFR-Fc fusion proteins. Pet. at 10-11. But to contend that the *nucleic acids*, *host cells*, and *methods* claimed in the '522 Patent are obvious, Petitioner relied exclusively on the putatively "obvious" features of *fusion proteins* – it pointed to teachings in Capon and Seed of features of fusion *proteins*, and likewise points to the putative teachings in Smith regarding the p75 TNFR receptor *protein* to make its case for obviousness. *E.g.*, Pet. at 15-22. Petitioner cannot have it both ways.

The Petition's argument is a paradigmatic example of what obviousness law forbids: substituting hindsight for insight. No ordinary artisan had ever conceived of—let alone achieved—the fusion proteins yielded by the claims of the '522 Patent. Because the Petition failed to demonstrate that it is more likely than not that any claim of the '522 Patent is unpatentable, the Board, pursuant to 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(c), should not institute trial. Separately, this case warrants the exercise of the Board's discretion under 35 U.S.C. § 325(d) to decline to institute trial.

III. BACKGROUND

A. Prosecution of the '522 Patent (Method Claims to Fusion Proteins) and the '182 Patent (the Resulting Proteins) Were Intertwined

The examination of the '522 and the '182 Patents was intertwined, for reasons beyond the facts that the two patents share a common disclosure and derive from a common set of parents. During the '182 Patent's prosecution, the Board determined

the claimed fusion proteins were not obvious over references that disclose p75 TNFR and methods to make receptor-IgG fusion proteins. Ex. 2025 at 7. In the '522 Patent's prosecution, that decision persuaded the Office, which concluded that the claimed nucleic acids, host cells, and methods (all directed to the production of those fusion proteins) were not obvious. Ex. 1026 at 6 [2].

B. The Board Effectively Rejected Petitioner's Obviousness Theory Back in the Prosecution of the '182 Patent

The '182 Patent claims are directed to proteins that fuse a soluble fragment of p75 TNF receptor to the hinge, CH2, and CH3 domains of human immunoglobulin. During examination, the Examiner rejected the claims of the '182 Patent for lack of written description, for the alleged introduction of new matter, and for obviousness. Ex. 2021 (Final Rejection) at 5-24. The Examiner contended that a disclosure of the p75 TNFR polypeptide in Dembic, when considered in view of the certain cell receptor-Fc fusion proteins taught by Capon, would have rendered the claimed p75 TNFR-Fc fusion proteins obvious. *Id.* at 13-19. Patent Owner ultimately appealed that conclusion to the Board. *See* Ex. 2022 (Appeal Brief) at 39-62.

In the appeal, Patent Owner proffered extensive record evidence of objective indicia of non-obviousness. *See id.* at 47-55. Patent Owner explained, for example, that the claimed p75 TNFR-Fc fusion proteins possessed a number of unexpected properties, including (i) a drastic reduction in effector function; (ii) an inability to form aggregated complexes; (iii) a surprisingly large (*i.e.*, 1000x) increase in TNF

neutralizing potency, and (iv) an improved binding affinity for TNF-α and kinetic stability of the bound complexes. *See id.* at 48-54. Each of these properties was shown by testimonial and non-testimonial evidence.

Increased neutralization of TNF. Patent owner presented evidence during examination showing that, when compared to unfused, soluble p75 TNFR alone, the claimed p75 TNFR-Fc fusion proteins exhibited an unexpected 50-fold increase in binding affinity for TNF and a dramatic 1000-fold increase in TNF neutralizing potency in *in vitro* biological activity assays. *See id.* at 53. This was unexpected because no such increase in potency had been observed for CD4-Fc fusion proteins, and there was no basis in the literature for predicting this marked increase in binding affinity and potency. *See id.*; Ex. 1040 (Capon paper) at 5 [529] & Fig. 5 (reporting that CD4-IgG fusion proteins had the same neutralizing potency as soluble CD4).

Reduced effector function. Also unexpected was an observed reduction of antibody effector function. Ex. 2022 at 49-51. This property is contrary to what Capon (and Seed) would have predicted for fusion proteins retaining the Fc portion of an IgG. *See, e.g.*, Ex. 1002 at 15:4-17. During examination, Patent Owner submitted evidence that etanercept only weakly binds to FcγR or C1q, the proteins that mediate the initiation of antibody-dependent cellular cytotoxicity ("ADCC") and complement dependent cytotoxicity ("CDC"), respectively. *See* Ex. 2022 at 49-50. Indeed, the claimed p75 TNFR-Fc fusion proteins exhibited little or no detectable ADCC and

very markedly reduced CDC. *See id.* Patent Owner explained that this unexpected result provided significant clinical benefits in treating inflammatory disorders, such as rheumatoid arthritis, in which a pro-inflammatory response is undesirable. *Id.*

Lack of aggregation. The Patent Owner also provided evidence showing that, unexpectedly, the claimed p75 TNFR-Fc fusion proteins did not form aggregated complexes. As Patent Owner explained to the Board, "[o]ne would have predicted that a divalent TNF binding molecule would form aggregated complexes with trimeric TNF ligand." *See id.* at 52. Because aggregation enhances effector functions such as ADCC and CDC, this unexpected property of the claimed p75 TNFR-Fc fusion proteins provided important therapeutic benefits in the intended application of treating inflammatory conditions. *Id.*

Increased binding affinity and kinetic stability. Finally, Patent Owner presented evidence during examination showing the claimed p75 TNFR-Fc fusion proteins demonstrated increased binding affinity and increased kinetic stability of the bound complexes, resulting in improved inhibition of TNF. *See id.* at 54. This too was contrary to the result that would have been predicted based on experiences seen with other fusion proteins. *See id*; Ex. 2016 (Arora Decl.) ¶¶ 2-6; Ex. 1041 at 1 [68] ("We describe here the generation of molecules which combine the specificity of CD4 and the effector functions of different immunoglobulin subclasses.").

Significantly, the Examiner did not dispute these surprising results, unexpected properties, or absence of expected properties. *See* Ex. 2023 (Examiner's Answer) at

62-65. In its November 22, 2010 decision, the Board reversed the Examiner's obviousness rejection. Ex. 2025 at 7. The Board cited Patent Owner's expert declaration, noted that the Examiner did not dispute the unexpected results, and concluded that the evidence of unexpected results "supports a conclusion of nonobviousness." *Id.*

Despite the Board's reversal, the Examiner advanced a new non-final rejection. Ex. 2026 at 5-13. The Examiner substituted Smith for Dembic, but otherwise attempted to revive the same theory of obviousness in combination with Capon. *Id.* Patent Owner contested the new § 103 rejections, arguing that the evidence of unexpected results previously accepted by the Board compelled a finding of non-obviousness, and noting, in light of Smith having taught the use of *unmodified* constant domains, that the "new, weaker rejection" actually "leads one of ordinary skill even further away from the claimed invention." Ex. 2027 at 12. The Examiner agreed, allowing the '182 Patent claims. Ex. 2028 at 7.

C. Adopting the Board's Analysis and Applicant's Arguments, the '522 Patent Examiner Ultimately Rejected the Same Obviousness Theory Petitioner Attempted to Repackage

The '522 Patent issued from U.S. Patent Application No. 08/444,791 ("the '791 application"), filed May 19, 1995. The '791 application is a divisional of U.S. Patent Application No. 08/095,640 ("the '640 application"), filed July 21, 1993, which is a continuation of U.S. Patent Application No. 07/580,013, filed September 10, 1990. The '522 Patent claims priority to several foreign patent applications, including

EP 90116707, filed August 31, 1990. The Petition acknowledged that the claims of the '522 Patent are entitled to at least this priority date. Pet. at 12. Patent Owner and Real Parties in Interest ("RPIs") rely on this date solely for this Preliminary Response.

During examination of the '791 application, two of the three references on which the Petition relied—Smith (Ex. 1003) and Capon (Ex. 1002)—were discussed at length. In a June 8, 2010 Office Action, the Examiner issued a series of rejections under § 103(a) based on Capon (Ex. 1002) in view of several references related to TNF receptors, including Smith (Ex. 1003).[7] *See* Ex. 1019 at 7-12 [6-11].

Patent Owner responded, explaining that (a) the skilled person would not have combined either Smith or Smith 1990 with Capon, as Capon discloses over 100 species of Ig fusions, all of which require the entire heavy and light chain constant regions and yield multimeric and monomeric proteins (versus Patent Owner's homodimer); (b) the skilled person would not have considered it desirable to join an ***anti***-inflammatory TNF-binding protein with a ***pro***-inflammatory immunoglobulin; and (c) the Examiner had failed to consider the submitted evidence of unexpected results, including unexpectedly superior properties, unexpectedly different properties,

[7] The Examiner also rejected certain claims as obvious over Capon in view of Smith et al., *Science* 1990 (Ex. 1038); over Capon in view of Hohmann et al., *J. Biol. Chem.* 1989 (Ex. 2008); or over Dembic et al., *Cytokine* 2:231-237 1990 (Ex. 2007) in view of Capon. Ex. 1019 at 7-12 [6-11].

and absence of expected properties. Ex. 1020 at 24-45.

The Examiner maintained rejections of then-pending claims 233-237, 239-243, 246-253, 255-261, and 274-283 as obvious over several sets of references, including Smith in view of Capon, Dembic in view of Capon, and Smith in view of Hohmann and Capon.[8] Ex. 2019 at 7-14. Nonetheless, the Examiner withdrew the rejections based on Smith 1990 in view of Capon because Smith 1990 did not teach any p75 TNFR/IgG fusion proteins.[9] *Id.* at 10-11.

In its response, Patent Owner amended the claims and argued the claims, as

[8] Prosecution claims 274 through 283 were ultimately allowed. *See* Ex. 1026 at 5.

[9] Petitioner contends the order in which the references were cited in the rejections has some consequence. Pet. at 6-7. It plainly does not. The skilled person is not an automaton, but considers the *substance* of the teachings of the prior art references together, not the form or sequence in which they are presented to that person. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360-61 (Fed. Cir. 2011); *In re Mouttet*, 686 F.3d 1322, 1333 (Fed. Cir. 2012) ("where the relevant factual inquiries underlying an obviousness determination are otherwise clear, characterization by the examiner of prior art as 'primary' and 'secondary' is merely a matter of presentation with no legal significance."). And there is no question the *substantive* teachings of the three references were exhaustively considered during examination of the '522 and '182 Patents.

amended, were patentable over the prior art. In particular, it argued the Board's decision in the prosecution of the '182 Patent warranted reversal of the comparable obviousness rejections based on Dembic and Capon. Ex. 1022 at 11-12, 17-18.[10]

In a subsequent Final Rejection, the Examiner maintained its obviousness rejection based on Smith in light of Capon. Ex. 1023 at 9-20 [7-18]. The Examiner contended that Smith taught a nucleic acid encoding an IgG_1 fused to the soluble portion of a 75 kilodalton TNF receptor wherein the fusion protein is bivalent for the p75 TNF receptor, and that Capon taught that the claimed form of the fusion protein is commonly made in the art. *Id.* The Examiner also stated that other obviousness rejections based on Dembic, Smith, Capon, and Hohmann were being maintained for the reasons already of record. *Id.* at 20-23 [18-21]. And the Examiner asserted the evidence of unexpected results was irrelevant because "the claimed inventions are drawn to nucleic acids, cells containing said nucleic acids and a method of use, not proteins."[11] *Id.* at 13 [11].

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[10] Petitioner's Ex. 1022 differs from the official file history record. Specifically, pages 17 and 20 contain red notations, and page 18 contains comments. These alterations are inappropriate, and Patent Owner and the RPIs object to them.

[11] Petitioner made the same argument—that "the properties of a protein (even if unexpected)" cannot overcome the obviousness of the '522 claims, none of which are

In response, Patent Owner emphasized that (a) one of ordinary skill would be deterred from removing the CH1 domains and light chains from the protein because Smith explicitly states that one should use *unmodified* constant domains; (b) unexpected results evidence is not required to compare the claimed invention to subject matter that does not exist in the prior art; and (c) the Examiner had improperly focused only on evidence of superior results, rather than results that are *different* than expected or results that indicate an *absence* of an expected result. Ex. 1024 at 6-13.

Patent Owner also again cited the Board's decision during the prosecution of the '182 Patent, arguing that the Board found the unexpected results of the particular p75 TNFR fusion proteins encoded by the claimed nucleic acids of the '522 Patent application to be persuasive evidence of non-obviousness. *Id.* at 6. As Patent Owner explained, "the prior holding by the Board applies with even more force to this present, weaker rejection." *Id.* Patent Owner then filed a Notice of Appeal to the Board, intending to secure reversal of the Examiner's improper rejections. Ex. 2020.

In response, in the next Office action, the Examiner withdrew the rejections and allowed the claims, explaining that "[t]he previously pending rejections are withdrawn in view of the cancellation of claims that have been cancelled ***and applicants[']*** ***arguments***." Ex. 1026 at 6 [2] (emphasis added). The '522 Patent

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directed to a protein *per se*; they are instead directed at the methods that will yield those proteins. Pet. at 10-11.

subsequently issued on April 24, 2012.

IV. CLAIM CONSTRUCTION

The Petition proposed constructions for only three claim terms, stating that "[o]ther claim terms should be given their plain and ordinary meaning." Pet. at 13-14. The proposed construction of "TNF receptor" is substantively wrong and would lead to nonsensical results; in any event, construction of this term is not necessary. The proposed construction of "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region" is essentially correct, but requires clarification, as it contains unintended oversights. The proposed construction of "about" to mean "approximately" is unneeded, and Petitioner provided no reason for having offered it.

A. The Petition's Construction of "TNF Receptor" is Nonsensical

Petitioner proposed that "TNF receptor" be construed as "soluble or non-soluble proteins, or fragments thereof, which bind TNF, in homogenous form." Pet. at 13. That proposal is imprecise and substantively wrong. Petitioner argued that the patent's passage that "proteins of the present invention that are non-soluble proteins, *i.e.* for example membrane proteins or so-called receptors, and soluble or non-soluble fragments thereof, which bind TNF (TNF-BP), in homogenous form" is an express definition. *Id.* (citing Ex. 1001 at 4:14-18). But the cited passage refers to "the *proteins of* ***the present invention***" (*i.e.*, TNF ***fusion*** proteins), not to TNF receptors. The cited statement is not a definition of "TNF receptor"—the term does not even appear

in the sentence—but simply a characterization of the invention as broadly described in the specification. The claims, of course, define the invention.

More importantly, Petitioner's imprecise proposed construction would lead to nonsensical results. It would rewrite claim 1 to require "the extracellular region of an insoluble human ~~TNF receptor,~~ soluble or non-soluble proteins, or fragments thereof, which bind TNF, in homogenous form wherein the insoluble human ~~TNF receptor~~ soluble or non-soluble proteins, or fragments thereof, which bind TNF, in homogenous form has an apparent molecular weight . . . ." Or, in other words, a claim to "the extracellular region of an insoluble human soluble or non-soluble proteins[.]"

The term "TNF receptor" should be given its plain and ordinary meaning of a receptor that binds TNF. *See* Office Patent Trial Practice Guide, 77 F.R. 48756, 48764 (Aug. 14, 2012) ("[I]t may be sufficient for a party to provide a simple statement that the claim terms are to be given their broadest reasonable interpretation, as understood by one of ordinary skill in the art and consistent with the disclosure."). The claims further narrow the recited TNF receptor to the known p75 TNF receptor.

B. The Petition's Construction of "All of the Domains of the Constant Region of a Human IgG . . ." Is Acceptable with Two Small Clarifications to Correct for Petitioner's Inadvertent Imprecision

Petitioner proposed that the 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" be construed as "'-hinge-CH2-CH3' region of an IgG (or IgG_1)

immunoglobulin heavy chain." Pet. at 14. With two clarifications, Patent Owner does not object to this construction for purposes of these proceedings.

First, the phrase the Petition sought to construe appears in independent claims 1 and 7 of the '522 Patent. The Petition failed to mention that there is an almost identical phrase in independent claim 4; the only difference being that claim 4 recites IgG_1, rather than IgG. If Petitioner's proposed construction ("…IgG (or IgG_1)…") is meant to suggest that the phrase in claim 4 should be construed in a similar fashion as the phrase in claims 1 and 7, but using "IgG_1" in that claim, Patent Owner agrees.

Second, Petitioner's proposed construction omitted the term "human." The Petition did not explain why "human" was omitted from its proposed construction. As the claim language expressly requires that the antibody fragment be of human origin, it would be improper to exclude it from the definition. Patent Owner suggests this clarified construction: "'-hinge-CH2-CH3' region of a human IgG [IgG_1 in claim 4] immunoglobulin heavy chain."

C. The Petition's Proposal to Construe "About" as "Approximately" Is Not Objectionable, But Does Not Seem to be Necessary

The Petition proposed to construe "about" to mean "approximately." Pet. at 14. The Petition did not explain why this construction is necessary. It appears not to be, which is a reason not to construe it. *See* Trial Practice Guide, 77 F.R. at 48764. But if construction is required, Patent Owner does not object to it for purposes of these proceedings.

V. THE PRIOR ART'S TEACHINGS

An obviousness inquiry requires, as an initial factual determination, an accurate description of the teachings of the prior art. In this proceeding, three references have been advanced; namely, Smith (Ex. 1003), Capon (Ex. 1002), and Seed (Ex. 1006). These references fall into two categories: Smith is directed to TNF receptor proteins (and the p75 TNFR protein in particular); while each of Capon and Seed is directed to specific fusion proteins that combine portions of certain cell surface receptor proteins with portions of immunoglobulins. Their relevant teachings appear below.

A. Smith Disclosed the p75 TNFR, but Taught Use of Unmodified Constant Regions of the IgG in TNFR Fusion Proteins

Smith teaches the known sequence of the p75 TNF receptor and describes soluble forms of p75 TNFR as well as a number of derivatives and variants. *See generally* Ex. 1003 at 7:9-10:68. While Smith teaches some types of p75 TNFR fusion proteins, it does not teach fusion proteins anything like the p75 TNFR-Fc fusion proteins recited in the claims at issue.

Smith suggests 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 immunoglobulin molecule heavy and light chains and having unmodified constant region domains." *Id.* at 10:53-57. This hypothetical "chimeric antibody molecule" comprises two heavy and two light chains, in which only the ***variable*** regions of the heavy and light chains are replaced with a TNFR. *Id.* at 10:57-68.

Notably, Smith does not teach or suggest p75 TNFR fusion proteins that omit the first domain of the heavy chain constant region or that, consequently, omit the light chain altogether. To the contrary, Smith teaches use of fusion proteins that include ***unmodified*** constant region domains of an immunoglobulin. *Id.* at 10:53-57. An antibody with unmodified constant domains will contain ***both*** heavy and light chains and will naturally assemble into a tetramer. *See id.* at 10:66-68 (citing WO 89/09622 and EP 315062 for "additional details relating to the construction of such chimeric antibody molecules"); Ex. 2031 (WO 89/09622) at 3:24-33, 6:15-22, 7:30-8:5 (describing construction of chimeric antibody molecules in which the native variable regions have been replaced with other antigen-binding regions, to produce proteins that contain two heavy and two light chains); *see also* Ex. 1002 (Capon) at 5:35-39, 11:10-20, 11:31-35, 11:59-66, 15:19-26. This type of construct also yields fusion proteins with four p75 TNFR components—one at the end of each of the heavy and light chains in the tetramer. *Id.* Thus, the ordinary artisan reading Smith would have been led away from the '522 Patent's claimed approach of producing p75 TNFR-Fc fusion proteins, which lack the first domain of the heavy chain constant region and, consequently, assemble into dimers that lack IgG light chains. *See, e.g.*, Ex. 2022 at 13.

Further, Smith discloses no working examples of these "chimeric antibody molecules" and provides no disclosure from which a skilled person could begin to guess what the properties of any particular p75 TNFR fusion protein might be. Smith

thus plainly does not direct the skilled person to the particular choices reflected in the p75 TNFR-Fc fusion proteins that are the object of the '522 Patent claims.

B. Capon Taught Many Ligand-Binding-Protein/Ig Fusions, But Did Not Mention TNFR or Similar Receptors as Possibilities

Capon teaches a large number of fusion proteins comprising a ligand-binding portion of a receptor combined with a portion of an immunoglobulin or other type of "plasma" protein. Ex. 1002 at 5:13-47. Capon notes that it was known to be possible to substitute the variable domain of an immunoglobulin with certain immunoglobulin variable-like domains from two members of the immunoglobulin gene superfamily—CD4 and the T cell receptor (TCR)—thereby yielding CD4 or TCR fusion proteins. *Id.* at 2:1-5. Capon focuses on fusion proteins that incorporate CD4 and LHR ligand binding regions. *E.g.*, *id.* at 5:1-8, 5:48-55. And despite disclosing over 100 different general formats for ligand-binding-protein/Ig fusions, it fails to even mention the possible use of TNF or TNF receptors as the ligand-binding-protein component of a fusion product.[12] *Id.* at 11:1-14:52. Capon also discloses that the Ig portion may be

[12] As addressed further below, the lack of any reference to TNFR is understandable, as the Capon reference characterized the therapeutic benefits of its fusion proteins as being achieved through inclusion of pro-inflammatory Ig constant region sequences, alone or with other agents that would function to kill cells being targeted by the cell receptor component. *E.g.*, Ex. 1002 at 4:30-47.

selected from among "IgG-1, -2, -3, or -4 subtypes, IgA, IgE, IgD or IgM, but preferably IgG-1." *Id.* at 14:65-67. In total, Capon discloses numerous types of potential binding-protein/ immunoglobulin combinations that typically "retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain." *Id.* at 10:10-12.

Significantly, Capon does not express any preference for a particular structure or formula to be used for creating fusion proteins. To the contrary, Capon states that "[t]he 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" but "[t]he optimal site will be determined by routine experimentation." *Id.* at 10:21-26 (emphasis added). Capon further describes hybrid immunoglobulins assembled as "monomers or hetero- or homo-multimers, and particularly as dimers or tetramers." *Id.* at 10:27-29.

C. Seed's Disclosures Were Even More Limited than Capon's, and Similarly Omitted Mention of TNFR as a Fusion Component

Seed provides an even more limited disclosure than Capon. Seed is directed to fusion proteins in which the variable region of the light or heavy chain in IgM, IgG_1 or IgG_3 immunoglobulin has been replaced with the extracellular ligand-binding region of a single receptor, the CD4 receptor (*i.e.*, one of the species of candidate ligand binding partners identified in Capon). *See* Ex. 1006 at 4:48-53 ("The invention relates to a gene comprising a DNA sequence which encodes a fusion protein

comprising 1) CD4, or a fragment thereof which binds to HIV gp120, and 2) an immunoglobulin light or heavy chain; wherein said CD4 or HIV gp120-binding fragment thereof replaces the variable region of the light or heavy immunoglobulin chain."). Like Capon, Seed nowhere mentions TNF, much less any TNFR, as a ligand-binding portion of a possible fusion protein. Also like Capon, Seed teaches that while any portion of the immunoglobulin may be replaced, the resulting fusion proteins will preferably include the CH2 and CH3 domains as well as the hinge. *Id.* at 6:15-21. As Seed emphasizes, other deletions are acceptable "***as long as the remaining fragment has antibody effector function***." *Id.* at 6:15-18 (emphasis added). In other words, Seed envisioned fusion proteins including varying degrees of incorporation of the Ig constant region, provided that the incorporated antibody fragment ***retained*** the ability to trigger an inflammatory immune response—the key feature that would enable these fusion proteins to kill HIV-infected cells expressing the GP120 protein. *Id.* at 9:11-19.

The Petition misleadingly implied that Seed is significant because its teachings were never presented to or considered by the Office during examination of the '522 Patent. Pet. at 4 ("Seed was not of record in the 08/444,791 application."). That is simply wrong. During the '522 Patent's prosecution, the Office considered a related Seed application—a published EP application having a virtually identical disclosure (*i.e.*, Seed EP 0 325 262 (Ex. 2015)). *See* Ex. 2018 (IDS considered Mar. 1, 2007) at 2. And given that Seed adds no guidance or insights beyond those which are fully

conveyed by Capon, it is not surprising it was never employed in a rejection of the claims of the '522 or '182 Patents.

D. Seed and Capon Both Emphasize as a Benefit the Pro-Inflammatory Properties of Ig Fragments When Included Within Cell Receptor Fusion Proteins

Both Seed and Capon contain zero guidance on production of TNFR fusion proteins. Indeed, neither reference mentions any TNFR receptor, despite Petitioner's suggestion that each provides expansive and detailed guidance on production of a wide variety of types of receptor/Fc fusion proteins.

This omission is significant for a different reason. Both Seed and Capon envision creating therapeutic ligand-binding/Fc fusion proteins that include an immunoglobulin constant region (or portions thereof). Each reference then clearly explains that doing this—including Ig constant region sequences within a fusion protein—will enable the fusion proteins to trigger *in vivo* responses characteristic of antibodies, and that this is what gives these fusion proteins their therapeutic utility. For example, as Capon explains:

> Additionally, even truncated or soluble ligand binding partners may not be optimally effective as therapeutics since they possess a relatively short in vivo plasma half-life, may not cross the placental or other biological barriers, and since merely sequestering their ligand recognition site *without delivering an effector function may be inadequate for therapeutic purposes*.

> Accordingly, it is an object of this invention to produce ligand binding partners fused to moieties which serve to prolong the in vivo plasma half-life of the ligand binding partner, such as immunoglobulin domains or plasma proteins, and facilitate its purification by protein A. *It is a further object to provide novel hybrid immunoglobulin molecules which combine the adhesive and targeting characteristics of a ligand binding partner with immunoglobulin effector functions such as complement binding, cell receptor binding and the like.*

Ex. 1002 at 4:30-47 (emphases added); *see also id.* at 10:1-26; 15:4-18; 15:55-62; 40:48-59; Ex. 1006 (Seed) at 5:13-17 ("The IgG1 fusion proteins and immunoglobulin-like molecules may be useful for both complement-mediated and cell-mediated (ADCC) immunity, while the IgM fusion proteins are useful principally through complement-mediated immunity."); 6:15-21 ("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."); *see also* Ex. 1006 at 6:61-7:2; 9:7-19.

Those well-known immune responses—including attraction of complement, induction of CDC, and ADCC—are each *pro-inflammatory* in nature. In other words, these responses all involve the recruitment and upregulation of the body's immune response—a response expected to occur when the cells that make up that immune

system encounter the fusion proteins that Capon and Seed teach. Ex. 2010 (Bryn) at 667-70; Ex. 1041 (Traunecker) at 1-3 [68-70]. Administering an agent that induces a *pro-inflammatory* response to a patient afflicted with rheumatoid arthritis or another form of an autoimmune disease would make no sense to the ordinary artisan. *See, e.g.*, Ex. 2011 (Kelley) at 906. That person would recognize that such diseases can be *worsened* by administering agents that might amplify the effects of the patient's already overactive immune system. *See id.*; Ex. 2012 (Suitters) at 854.

Petitioner and its expert[13] simply ignored this logical and scientific disconnect. They instead advanced the hindsight-driven rationale that the ordinary artisan would

[13] Petitioner's expert declaration added nothing and in most places merely parrots the conclusory language of the Petition. *Compare* Pet. at 7 ("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 or 'LHR'") (citations omitted; brackets in original) *with* Ex. 1004 ¶ 36 (similar); *compare* Pet. at 26 ("So, the POSITA would have understood that deleting the transmembrane region of *Smith's* TNF-R would create an extracellular region compatible with the expression methods of *Seed* and *Capon* that specifically employ inactivation or deletion of transmembrane regions.") *with* Ex. 1004 ¶ 45 (same). It is well-established that naked,

have somehow had the insight (and reasonable expectation of success) to stretch the examples in Capon and Seed and incorporate any TNFR sequence into a TNFR/Ig fusion protein. They did so without recognizing that such a therapeutic agent would have been expected to do precisely the opposite of what is needed for patients—it would have been expected to activate the patient's immune system according to Capon and Seed's explicit teachings. *See, e.g.*, Ex. 1002 at 4:30-47; Ex. 1006 at 5:13-17.

E. Seed's Teachings Are Cumulative to Capon's Teachings

Although the Petition portrayed Seed as providing insights beyond Capon, in reality Seed is entirely cumulative to teachings within Capon. One need only compare the corresponding disclosures in each of the two references to appreciate this fact. Making that comparison shows the Petition for what it actually was: an attempt to simply rehash and reargue the obviousness theory that was advanced, fully considered, and ultimately rejected by both the Board and the Office.

1. Seed Provides No Additional Guidance Over Capon on the Potential Ligand-Binding Candidates to Use in the Fusions

Neither Seed nor Capon make any mention of any TNFR as a candidate for fusion proteins. And while Capon envisions a broader range of possible ligand-binding/Ig fusions (albeit a range encompassing only ligand-binding candidates

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conclusory declarations are entitled to no weight. *See, e.g.*, *Tate & Lyle Americas LLC v. Cargill, Inc.*, IPR2014-00084, Paper 12 at 17 (April 1, 2014).

intended to provoke an immune response), Seed is narrowly focused on only one of those—namely, CD4. This is evident from a simple inspection the corresponding passages of each reference, reproduced below:

Capon (Ex. 1002) at 5:13-20: The objects of this invention are accomplished by providing novel polypeptides comprising a ligand binding partner fused to a stable plasma protein which is capable of extending the in vivo plasma half-life of the ligand binding partner when present as a fusion with the ligand binding partner, in particular wherein such a stable plasma protein is an immunoglobulin constant domain. Capon (Ex. 1002) at 5:48-55: A particular multichain fusion of this sort is one in which the variable region of one immunoglobulin chain has been substituted by the ligand binding region of a first receptor such as CD4 while the variable region of another immunoglobulin chain has been substituted by a binding functionality of the LHR, both immunoglobulin chains being associated with one another in substantially normal fashion. Capon (Ex. 1002) at 2:1-5: It has also been shown that it is possible to substitute immunoglobulin variable-like domains from two members of the immunoglobulin gene superfamily—CD4 and the T cell receptor–for a variable domain in an immunoglobulin….	Seed (Ex. 1006) at 4:47-53: The invention relates to a gene comprising a DNA sequence which encodes a fusion protein comprising 1) CD4, or a fragment thereof which binds to HIV gp120, and 2) an immunoglobulin light or heavy chain; wherein said CD4 or HIV gp120-binding fragment thereof replaces the variable region of the light or heavy immunoglobulin chain.

2. Seed Provides No Additional Guidance Over Capon on What Portion(s) of a Ligand Binding Candidate Must be Omitted

Seed and Capon both explain that the fusion proteins they teach need not include only the extracellular domain of that protein, but also may include the intact ligand binding protein. They do not specify the omission of any specific portions. Again, this is evident from simply inspecting the relevant passages in each reference:

Capon (Ex. 1002) at 10:1-9:	Seed (Ex. 1006) at 6:22-27:
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. The transmembrane regions or lipid or phospholipid anchor recognition sequences of ligand binding partners comprising such regions or sequences are preferably inactivated or deleted prior to fusion.	The CD4 portion of the fusion protein may comprise the complete CD4 sequence, the 370 amino acid extracellular region and the membrane spanning domain, or the extracellular region. The fusion protein may comprise fragments of the extracellular region obtained by cutting the DNA sequence which encodes CD4.

3. Seed Provides No Additional Guidance Over Capon on What Immunoglobulin Ig or Portion(s) of the Ig Must Be Used

Contrary to the assertions in the Petition, Seed provides no additional guidance relative to that in Capon as to either the isotype or which particular portions of the immunoglobulin constant region sequences that must be used in its fusion proteins.

Immunoglobulin isotype

Capon (Ex. 1002) at 14:65-67:	Seed (Ex. 1006) at 9:7-10:
IgG-1, -2, -3, or -4 subtypes, IgA, IgE, IgD or IgM, but preferably IgG-1.	…the constant region of an IgM, IgG1 or IgG3 antibody which binds complement at the Fc region.

Immunoglobulin portions

Capon (Ex. 1002) at 5:35-43: …the ligand binding partner will be substituted into at least one chain, and ordinarily for the variable region of the immunoglobulin or suitable fragment thereof. However, it will be understood that this invention also comprises those fusions where the same or different ligand binding partners are substituted into more than one chain of the immunoglobulin. Capon (Ex. 1002) at 10:10-12: Typically, such fusions retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain. Capon (Ex. 1002) at 15:55-64: The LHR extracellular domain generally is fused at its C-terminus to the immunoglobulin constant region. The ***precise site at which the fusion is made is not critical***, other sites neighboring or within the extracellular region may be selected in order to optimize the secretion or binding characteristics of the soluble LHR-Ig fusion. The optimal site will be determined by routine experimentation. The fusion may typically take the place of either or both the transmembrane and cytoplasmic domains. *See also* Ex. 1002 at 10:12-16; 10:21-25.	Seed (Ex. 1006) at 6:4-21: …a fused protein comprising CD4, or fragment thereof … 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 Just [sic] 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. Seed (Ex. 1006) at 6:41-46: Where the fusion protein comprises an immunoglobulin light chain, it is necessary that no more of the Ig chain be deleted than is necessary to form a stable complex with a heavy chain Ig. In particular, the cysteine residues necessary for disulfide bond formation must be preserved on both the heavy and light chain moieties. *See also* Ex. 1006 at 13:45-14:1, 14:6-9, 14:13-16, 14:20-23, 14:27-30, 14:31-34.

4. Seed Provides No Other Useful Guidance Relative to Capon

Seed also provides no unique insights beyond those in Capon regarding general techniques and parameters for recombinantly producing certain types of fusion proteins. For example, Seed adds nothing to Capon regarding host cell choices that may be used, construction or use of vectors, purification techniques, or the like.

VI. PETITIONER HAS SHOWN NO REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM IS UNPATENTABLE

The Petition presented a single ground for challenge, exhuming old arguments to try to show that the claims of the '522 Patent would have been obvious. It failed.

A. The Board Rejected the Petitioner's Repackaged Obviousness Theory During Examination of the '182 Patent, a Determination Ultimately Persuasive to the '522 Patent Examiner As Well

The initial, and wholly dispositive, reason to reject the obviousness grounds presented in the Petition is that the Board and the Office have already rejected that exact theory of obviousness.[14]

First, the Board rejected the same theory of obviousness when it reversed rejections imposed during examination of the '182 Patent claims that were premised on the belief that a skilled person would have found obvious the particular p75 TNFR-Fc fusion proteins that are produced by use of the methods, nucleic acids and

[14] Earlier factual and legal determinations of the Board are entitled to deference and, in this instance, compel denial of the Petition.

host cells claimed in the '522 Patent based on prior art teaching cell receptor-Fc fusion proteins and the p75 TNFR protein. *See* Ex. 2025 at 3, 7.

Second, different Examiners handling examination of the '182 and the '522 Patents rejected that theory of obviousness. Most directly, during examination of the '522 Patent, which claims the nucleic acids encoding and host cells and methods for producing the very same fusion proteins that the '182 Patent claims, the Examiner withdrew the same type of obviousness rejections based on Smith and Capon in the face of Patent Owner's arguments. Those arguments pointed not only to the Board's earlier decision of non-obviousness, but to the underlying evidence showing unexpected results of the particular p75 TNFR fusion protein—the object of the application's claimed nucleic acids, host cells, and methods. As Patent Owner stated then, that evidence "applies equally, if not with greater force, to the obviousness rejection in the present case." Ex. 1022 at 18. The Examiner agreed. Ex. 1026 at 6 [2].

The Petition tried to avoid those facts with what amounted to a sleight of hand: it led its challenge with Seed, contending that this reference provides a more probative teaching on production of fusion proteins than Capon. *See* Pet. at 15-16, 28-32. That is demonstrably wrong.

Both Seed and Capon describe production of fusion proteins that consist of cell receptors fused to immunoglobulin fragments, and, if anything, Capon provides the more comprehensive discussion of that topic. *See supra*, Sections V.B-V.E. Both Seed and Capon describe production of fusion proteins that retain the hinge, CH2,

and CH3 domains of the constant region of an immunoglobulin heavy chain. *E.g.*, Ex. 1002 at 10:10-12; Ex. 1006 at 6:4-21. And, critically, the Petition does not cite to the Seed reference as the source of guidance for the selection of which portions of the immunoglobulin molecule to use; it instead relies on ***Capon***, contending Capon (not Seed) teaches the idea of using a "functional" (incomplete) hinge region that would yield the TNFR-fusion proteins having a dimeric structure. *See* Pet. at 16-17, 30-31.

In reality, neither Seed nor Capon provides any guidance regarding production of TNFR fusion proteins. Before the Board appeal, the Examiner sought to fill that gap using Dembic (Ex. 2007), which showed the p75 TNFR protein was known to be a ligand-binding receptor. *See* Ex. 2021 at 13-14. After the Board's reversal of the rejections based on Dembic (but before the Examiner ultimately admitted that the Patent Owner was correct all along), the Examiner switched gears, citing Smith instead as the source of teachings for use of p75 TNFR as the ligand-binding component of a fusion protein.[15] Ex. 2026 at 5-13.

Notwithstanding the Office's subsequent abandonment of this obviousness rationale in both of the '182 and'522 Patents, the Petition embraces and advances this same reference for the identical purpose in its repackaged obviousness challenge. But the Board and the Office exhaustively considered the same substantive disclosures in

[15] The Examiner used this same combination of references and reasoning to reject the '522 Patent claims. *See* Ex. 1023 at 9-20 [7-18].

Smith, Seed and Capon when it assessed—and rejected—the theory upon which the Petition grounded its challenge.

The Petition also urged that the substantial and compelling evidence of objective indicia of non-obviousness considered by the Board and Office during examination of both the '182 and '522 Patents cannot be used here because that evidence concerns the p75 TNFR fusion proteins *per se*, rather than nucleic acids that encode these proteins or methods of producing them. Pet. at 10-11. That is a strange argument, given that the Petition rests its obviousness theory on the properties of the fusion proteins taught in the prior art to contend the claimed nucleic acids, host cells and methods are obvious. Pet. at 15-22. It is hardly appropriate for Petitioner to argue for obviousness based on expectations or beliefs about features of fusion proteins in the prior art, and then protest that objective evidence of surprising features of those same fusion proteins—the ultimate object of the challenged claims—is irrelevant.

The cases cited for Petitioner's contention that this evidence can be disregarded actually stand for something much different; namely, the unsurprising legal principle that unexpected properties shown for one or a narrow range of embodiments of an invention may be insufficient to establish objective indicia of non-obviousness for a claim embracing a much broader range of embodiments of the invention. *See In re Clemens*, 622 F.2d 1029, 1035-36 (CCPA 1980) (holding that unexpected results for tests conducted at 110ºC and 130ºC could not prove the non-obviousness of claimed VBC-based resin condensate polishing "at elevated temperatures," including

temperatures below 60ºC); *In re Peterson*, 315 F.3d 1325, 1330-31 (Fed. Cir. 2003) (holding that unexpected increase in stress rupture life shown for 2% rhenium did not support conclusion of non-obviousness for claimed range of "about 1 to 3 percent" rhenium as distinct from prior art range of "0-7%", when data for 1% rhenium only showed mild increase and data for 3% rhenium showed decrease in stress rupture life); *see also In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (finding unexpected results "limited to sodium only" were not commensurate in scope with claims to catalyst having "an alkali metal"); *In re Greenfield*, 571 F.2d 1185, 1189 (CCPA 1978) (concluding that unexpected results for "only one" compound did not render non-obvious claim that covered "several hundred compounds").

More recently, the Federal Circuit has clarified that this question is evidentiary, explaining that those prior cases only precluded findings of objective indicia of non-obviousness "where the evidence was plainly disproportionate to the scope of the claim." *Genetics Institute LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308 (Fed. Cir. 2011) (no error in district court's non-obviousness decision based on unexpected improved stability through binding with von Willebrand Factor ("vWF") that resulted from retaining the a3 region of a truncated Factor VIII protein, notwithstanding that "one particular amino acid substitution at one particular position eliminates vWF binding" such that unexpected result was not observed for that claimed variant).

Here, there is no discrepancy in the breadth of the claims of the '182 and '522 Patents relative to embodiments that have the unexpected properties. Both sets of claims define the invention through the lens of the p75 TNFR fusion proteins that possesses the unexpected properties and benefits; the nucleic acids, host cells and methods defined by the claims of the '522 Patent each are limited in their scope to these particular p75 TNFR fusion proteins. This is not a case, thus, where the subject matter encompassed by the claims only tangentially overlaps with the subject matter having the unexpected or surprising properties—the '522 Patent claims each are limited in their scope to subject matter that encodes or is used to produce the very p75 TNFR fusion proteins that even Petitioner does not dispute has numerous unexpected properties and benefits. Indeed, the record shows that the '522 Patent 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. Ex. 1022 at 34-35; Ex. 2016 at §§ 2-6.

The evidence provided in the '522 Patent's prosecution history conclusively establishes that the unexpected results are directly associated with the claimed invention of the '522 Patent. During examination of the '182 and '522 Patents, both the Board and Office found this evidence to support the conclusion that the '182 and '522 Patent claims were not obvious. Ex. 1022 at 25-39; Ex. 1024 at 6, 18; Ex. 1026 at 6 [2]; Ex. 2025 at 7; Ex. 2027 at 22-26; Ex. 2028 at 7. Those conclusions were correct then, and they are correct now.

Critically, the Petition nowhere suggests the Board or Office erred in reaching their conclusions based on the substance of the evidence, much less explains why this Board should reach a different conclusion now. The Petition also does not dispute that p75 TNFR-Fc fusion proteins at issue actually possess the aforementioned unexpected properties; it only half-heartedly argued that this evidence of unexpected results is irrelevant because none of the '522 claims are directed to proteins, *per se*.[16] Pet. at 10-11. The exact form of the claims here is irrelevant—each of the claimed embodiments (whether nucleic acid, host cell or method) is directly and inextricably linked to the same p75 TNFR-Fc fusion proteins that have been proven to possess unexpected properties, either because the claim defines a nucleic acid encoding that exact protein, or because it specifies a method or host cell which when practiced or used will yield that protein. The Petition elected to not address the substance of Board's prior decision regarding the evidence of unexpected results, and there is no basis for the Board to revisit that decision. This is so regardless of whether the Petition presented a *prima facie* case of obviousness (it did not, as explained below).

[16] The Examiner made a similar argument during prosecution of the '522 Patent, Ex. 1023 at 13 [11], but the claims were ultimately allowed without further discussion of whether the unexpected results were commensurate with the claims of the '522 Patent after the Patent Owner argued for adoption of the Board's earlier conclusion of non-obviousness from the appeal for the '182 Patent. Ex. 1024 at 6; Ex. 1026 at 6 [2].

B. The Petition Failed to Establish Any *Prima Facie* Obviousness with Regard to Any of the Challenged Claims of the '522 Patent

While the Petition quoted liberally, albeit selectively, from each of the cited references, it failed to articulate a reasoned basis why a person of ordinary skill, by following the actual teachings found in Seed, Smith, and Capon, would have arrived at the claimed inventions. Instead, Petitioner engaged in a classic hindsight analysis: it simply assumed that the skilled artisan would have had the same insights as the inventors and would have made the same choices the inventors did when they conceived of fusing the soluble portion of a p75 TNF receptor to the hinge, CH2, and CH3 domains of an IgG. It then engaged in a prior art scavenger hunt in an attempt to cobble together each element of the claimed invention or some combination of teachings that it contends would yield the same result. In other words, the Petitioner simply assumed the particular combination required by the claims was obvious and then built its case by trying to find in the prior art the constituent elements of the invention to support that pre-determined conclusion.

This hindsight-driven rationale is flatly prohibited by the law of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007). And to advance it, the Petition presents a skewed characterization of what the prior art it cites actually teaches and where it would have led the skilled artisan. It is also revealed by the manner in which the Petition presents its obviousness challenge. Instead of objectively describing the teachings of the prior art references and then identifying

differences between what those references teach and the claimed invention, the Petition simply catalogs what it perceives as the relevant portions of these references (*i.e.*, those matching particular claim elements) and contends that since these elements are putatively found in the prior art, the claimed invention must be obvious. *E.g.*, Pet. at 15-22, 22-34. The Board has repeatedly found that type of showing insufficient to establish a reasonable likelihood that a claim would have been obvious. *See*, *e.g.*, *Nautique Boat Co. v. Malibu Boats LLC*, IPR 2014-01045, Paper 13 at 14-15 (Nov. 26, 2014) (rejecting obviousness grounds because "[w]ithout having identified specifically the differences between the claimed invention and the prior art, the Petition failed to make a meaningful obviousness analysis under 35 U.S.C. § 103, and thus failed to make a threshold showing of [unpatentability]"); *see also Graham v. John Deere Co.*, 383 U.S. 1 (1966).

When the teachings of the prior art are objectively and accurately considered, particularly from the required perspective of the skilled person at the time of the invention, they plainly fall short of establishing a reasonable likelihood that any of the claims of the '522 Patent would have been unpatentable as obvious.

1. The Petition Failed to Establish a *Prima Facie* Case of Obviousness with Regard to Claims 1, 2 and 3

Accurately reading the prior art references establishes that there is no objective rationale in them that would have led the person of ordinary skill to perform the steps recited in independent claim 1, or dependent claims 2 and 3, to make p75 TNFR-Fc

fusion proteins that could be used as therapeutic agents in treating inflammatory conditions. The Petition simply fails to establish a *prima facie* showing of obviousness of these claims.

a. **Neither Seed Nor Capon Suggests Making Any Anti-Inflammatory Therapeutic Fusion Proteins, Much Less by Practicing the Methods of Claims 1, 2 and 3**

An initial, and fundamental, flaw of the Petition is that it ignores what both Seed and Capon explain to be a key feature of the therapeutic fusion proteins they teach; namely, the retention of Ig constant region sequences in order to induce *pro-inflammatory* responses in a patient. *See supra*, Sections V.D-V.E. Indeed, each of Seed and Capon is focused on production of fusion proteins that will target and destroy cells. *See, e.g.*, Ex. 1002 at 30:54-58, 4:43-47; Ex. 1006 at 9:11-19. For example, the CD4 targeting fusion proteins of Seed are described to be a useful approach for fighting HIV infection, as HIV attacks those cells of a host's immune system that present the CD4 antigen, thereby destroying the very cells that would ordinarily fight a viral infection. *See* Ex. 1006 at 2:3-10. The body's natural inflammatory response is appropriately triggered in response to a viral infection, and there would be little reason to be concerned with an antibody-based therapeutic approach causing more inflammation when fighting HIV. *See id.* at 2:20-31. In fact, destroying HIV-infected cells through ADCC would be a reasonable goal of HIV therapy. *E.g.*, *id.* at 9:11-19.

TNF, however, is different. TNF levels are often elevated in inflammatory conditions such as rheumatoid arthritis. Ex. 2013 (Kingsley) at 177. Before the

invention, the skilled person would have known it to be counter-productive to cause additional inflammation in a rheumatoid arthritis patient. Ex. 2011 (Kelley) at 906; Ex. 2012 (Suitters) at 854. In fact, at the time of the invention, standard therapy for rheumatoid arthritis used agents known to generally dampen inflammation in patients, which was believed to thereby reduce the symptoms, such as swollen joints. Ex. 2032 (Vane) at 89-90. There was no therapy that could arrest the progression of the disease. *Id.* at 95; Ex. 2014 (Asherson) at 117 ("we are unable to influence the long term outcome of radiological progression, diminished earning capacity and increased mortality in our patients with RA in 1991.").

Seed and Capon, correctly read, actually demonstrate why one of skill in the art would not have believed a fusion of p75 TNF receptor and the hinge, CH2, and CH3 domains of IgG would be an effective therapeutic approach for inflammatory disease. Seed explains that one purpose of making IgG fusion proteins is to ***promote*** ADCC and CDC, and any fusion protein should ***retain*** "antibody effector function." Ex. 1006 at 5:13-17, 6:15-17. Capon teaches likewise. Ex. 1002 at 4:43-47. A skilled person reading Seed alone or with Capon, would not have been led by that teaching to seek to create p75 TNFR fusion proteins that would be expected to exacerbate, rather than alleviate, inflammatory symptoms.

Remarkably, the Petition offers no explanation, much less persuasive evidence, that attempts to reconcile the conflict between these teachings in Seed and Capon and the beliefs of the skilled person that it would be illogical to put a pro-inflammatory

agent at the very location within an rheumatoid arthritis patient's body where inflammation is causing problems—the site of action of TNF. In reality, those teachings in Seed and Capon would have led the skilled person away from the idea of incorporating functional Ig constant regions into a p75 TNFR fusion protein designed to reduce inflammation in a patient. At a minimum, these teachings in Seed and Capon would have raised significant questions in the mind of the skilled person regarding whether the p75 TNFR fusion proteins retaining active Ig constant region sequences would prove viable as therapeutic agents for treating patients with rheumatoid arthritis and similar inflammatory conditions. The failure of the Petition to even recognize this conflict, much less provide a reasoned basis supported by persuasive evidence to resolve it, dooms the Petition. Simply put, there is no explanation or evidence in the Petition that explains *why* one of ordinary skill in the art would have fused p75 TNFR to any portion of IgG, much less the hinge, CH2, and CH3 domains of IgG to create a therapeutic agent to treat patients suffering from inflammatory diseases.

The generalized guidance found in Seed and Capon also would not have otherwise provided any specific insight or rationale that would have led the skilled person to focus on production of p75 TNFR-based fusion proteins having structures corresponding to those which are the object of the '522 Patent claims. Instead, both Capon and Seed teach that a wide variety of approaches can be taken as to the particular design of a fusion protein, with flexibility as the portions of the

immunoglobulin constant domain one might include or exclude. *See supra*, Sections V.B-V.E; *see also* Ex. 1002 at 5:35-43, 10:10-26, 15:55-64; Ex. 1006 at 6:4-21. In fact, the particularly preferred embodiments of Capon indicate that "the entire heavy chain constant region" (including CH1), *see* Ex. 1002 at 15:9-11, or part but not all of the hinge domain, *see id.* at 15:11-17 ("a sequence beginning in the hinge region"). Capon also contemplates fusion proteins having a wide range of valencies of the ligand receptor protein component of the fusion protein relative to its ligand, ranging from monomeric fusion proteins to heterotetrameric fusion proteins and everything in between. *Id.* at 10:40-11:29. It would not, thus, point the skilled person in any way to selecting choices to yield a divalent form of a p75 TNFR/Ig fusion protein.

To account for this lack of any suggestion from the prior art teachings, Petitioner actually asked the Board to invert the legal test for evaluating obviousness and to find obviousness because ***nothing*** in the three references specifically ***teaches away*** from doing what the claims require. *See* Pet. at 31 ("[n]othing in *Seed* or *Capon* ***discourages*** a POSITA from selecting the TNF receptor of *Smith*, and nothing in *Smith* ***discourages*** one from using *Seed* or *Capon's* methods for expressing TNF-R. This shows that neither *Seed*, nor *Capon* nor *Smith* ***teach away*** from the claimed fifth element of claim 1.") (emphases added). But Petitioner cannot establish obviousness by arguing, or even proving, that there was ***an absence of discouragement*** in the prior art references from pursuing the invention. It is not Patent Owner's burden to prove that the prior art teaches away from the claimed invention, even though it

clearly does. It is Petitioner's burden to establish the opposite, that the skilled artisan, following the prior art without the benefit of hindsight, would have had some objective reason to make the changes to the prior art teachings to arrive at the claimed invention, and would have had a reasonable expectation of success in doing so. It has not met this burden.

Further, as explained in the section below, the Petition simply ignores teachings in the prior art contrary to its hypothesis: Smith would indeed have discouraged the skilled person from seeking to produce p75 TNFR-Fc fusion proteins that lack a light chain constant domain and a heavy chain constant domain CH1 using the claimed methods, nucleic acids and host cells.

b. **Smith Teaches Away From Making p75 TNFR/Ig Fusions with Less Than the Entire Constant Domain**

In setting forth its inverted "absence-of-discouragement" standard, Petitioner disregarded the actual guidance in Smith, including its specific guidance 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 immunoglobulin molecule heavy and light chains <u>and</u> having unmodified constant region domains***." Ex. 1003 at 10:53-57 (emphasis added). In other words, when discussing a possible p75 TNFR fusion protein, Smith specifically teaches that: (i) the fusion proteins should contain ***both*** heavy and light chain components (*i.e.*, having both a p75 TNFR-light chain fusion and a p75 TNFR-heavy chain fusion) and

(ii) the fusion proteins should use ***unmodified*** constant region domains of immunoglobulin (*i.e.*, those which do not omit domains or portions of the immunoglobulin constant region sequence). *See also id.* at 10:57-68.

The Petition additionally mischaracterized Smith's teachings by suggesting it specifically teaches "bivalent" p75 TNFR fusion proteins. *See* Pet. at 32 ("Smith taught the importance of 'bivalent' (*i.e.*, dimeric) structures to enhance TNF binding affinity…."). Smith does no such thing. First, Smith did not produce the hypothetical fusion protein it discusses, and thus could not "teach" what properties any such hypothetical protein might or might not have. Second, the hypothetical heavy/light fusion protein it describes would not be "bivalent" as is the claimed invention—it would be ***tetravalent***, with each "arm" of the chimeric antibody having two p75 TNFR proteins in place of corresponding variable region sequences of the heavy and light Ig chains. This is why Smith uses the term "polyvalent" to describe the assembled p75 TNFR fusion protein rather than "bivalent." Ex. 1003 at 10:61-66 ("Following transcription and translation of ***the two chimeric genes***, [*i.e.*, the chimeric p75 TNFR-heavy and p75 TNFR-light sequences] 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."). Elsewhere, Smith indiscriminately identifies monovalent and polyvalent forms of p75 TNFR, nowhere suggesting a preference for a ***bivalent*** p75 TNFR

binding molecule, and never suggesting a molecule in which the Ig constant domains would be modified. *Id.* at 10:33-52.

When the prior art is considered objectively and using the required perspective of a skilled person prior to the invention date, Petitioner's assertions of obviousness based on the combined teachings of Seed, Smith and Capon are unsupported. As the evidence in the record of the '522 Patent makes plain, the skilled person at the time of the invention would not have had any objective reason for choosing to specifically fuse the extracellular, soluble portion of the p75 TNF receptor to the hinge, CH2, and CH3 domains of an IgG protein. For example, the skilled person would have not known of the necessary spatial geometry of the p75 TNF receptor binding site at the time of the invention, and would not have been able to reasonably predict whether a p75 TNFR/IgG-Fc fusion protein would bind TNFα. *See* Ex. 2017 (Lesslauer Decl.) at 8-9. Scientific questions such as these were not answered by the prior art.

Moreover, as explained above, Smith's guidance would have led the skilled person away from, rather than toward, the particular structures required by the claims. In particular, the skilled person, following Smith, would not have arrived at a p75 TNFR fusion protein that omits from the protein any portion of the CH1 region of the immunoglobulin, much less one that, in completely deleting the Ig CH1 region, precludes altogether the incorporation of a corresponding Ig light chain. Ex. 1003 at 10:53-57 ("A recombinant chimeric antibody molecule may also be produced having TNF-R sequences substituted for the variable domains of either or both of the

immunoglubulin molecule heavy and light chains and having **unmodified constant region domains**.") (emphasis added). Instead, the skilled person following Smith would have been primarily led to do what Smith actually says to do; produce a homotetrameric fusion protein in which the TNF-binding region of p75 TNFR replaced each of the four variable regions in the IgG. *Id.* at 10:53-66. Smith provides no other guidance regarding the preferred structure of a p75 TNFR fusion protein, including any desired valency of the TNFR component relative to TNF. Only by using improper hindsight could a skilled person be "led" to the precise combination of TNFR and IgG-Fc sequences that comprise the fusion proteins claimed in the '182 Patent and that are the ultimate object of the '522 Patent claims.

2. The Petition Failed to Establish a *Prima Facie* Case of Obviousness with Regard to Claims 4, 5, and 6

The Petition's arguments with respect to independent claim 4 were largely duplicative of its arguments for claim 1 and deficient for the same reasons. Pet. at 36-48. Specifically, the Petition failed to explain why a person of skill in the art would have had an objective reason to combine the references to generate a p75 TNFR/IgG-Fc fusion protein when neither Seed nor Capon even contemplates the combination of a pro-inflammatory Ig fragment with an anti-inflammatory receptor like p75 TNFR. *See supra*, Sections V.B-V.E. And while Petitioner points to additional disclosures from Seed and Capon teaching the use of IgG_1 (or portions thereof) as components of their preferred embodiments, it failed to explain why a person of skill

in the art, even if seeking to create a p75 TNFR/IgG_1 fusion, would have ignored Smith's requirement to use "unmodified constant region domains" in preparing such fusion proteins. *See* Ex. 1003 at 10:57-58.

3. The Petition Failed to Establish a *Prima Facie* Case of Obviousness with Regard to Claims 7, 8, 9, and 10

The Petition's arguments with respect to independent claim 7 were largely duplicative of its arguments for claim 1 and deficient for the same reasons. Pet. at 48-58. Claim 7 is identical to claim 1 except it recites a different amino acid sequence for the p75 TNF receptor portion of the fusion protein. As it did for claims 1 and 4, the Petition failed for claims 7-10 to explain why a person of skill in the art would have had an objective reason to combine the references to generate a p75 TNFR/IgG-Fc fusion protein when neither Seed nor Capon even mentions the fusion of a pro-inflammatory Ig with an anti-inflammatory receptor like p75 TNFR. *See supra*, Sections V.B-V.E. The Petition similarly failed to explain why a person of skill in the art, even if seeking to create a p75 TNFR/IgG fusion protein, would have ignored Smith's requirement to use "unmodified constant region domains" when preparing such proteins. Ex. 1003 at 10:57-58.

Thus, the Petition should be denied under § 314(a).

C. The Petition Failed to Substantively Address Any of the Objective Evidence Additionally Demonstrating Non-obviousness

The Petition entirely failed to address the substance of the comprehensive and compelling evidence in the prosecution history of the '522 Patent of objective indicia

attributable to the claimed invention. The Federal Circuit has "repeatedly held that . . . objective evidence ... must be considered before determining whether the claimed invention would have been obvious." *Apple Inc. v. ITC*, 725 F.3d 1356, 1365 (Fed. Cir. 2013). "[O]bjective indicia of nonobviousness are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements." *Leo Pharm. Products, Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Such objective indicia include unexpected results. *Apple*, 725 F.3d at 1375.

First, the evidence shows there was no reasonable expectation of success; namely, that dimeric p75 TNFR fusion proteins that are the subject of the '522 Patent claims would effectively bind TNFα, which was known to be a trimer. As Dr. Lesslauer explained in his declaration submitted during examination of the '522 and '182 Patents, "the spatial geometry of the receptor binding site was unknown. Thus, it could have been possible that the fusion with IgG fragments created a spatial structure that would have contained TNF receptor sequences but which, due to its spatial structure, was completely unable to bind TNFα." *See* Ex. 2017 at 8-9. Dr. Lesslauer went on to describe the excellent binding activity, the higher kinetic stability, and unexpectedly superior neutralization of TNF activity by p75 TNFR/IgG-Fc as compared to soluble p75 TNFR alone. *Id.* at 9-11.

The p75 TNFR fusion proteins that are the ultimate object of the claims also unexpectedly resulted in decreased or no effector function, despite including the portion of an IgG that would have been expected to retain effector function. Ex. 2022

at 49-50; Ex. 2003 at Figs. 8 & 9 (showing only weak binding to FcγR and C1q, the proteins that mediate the initiation of ADCC and CDC); Ex. 2004 at Figs. 3 & 4 (showing little or no detectable ADCC and markedly less CDC compared to an anti-TNF antibody); Ex. 2005 at 1 (showing that etanercept was completely unable to mediate complement-dependent killing of TNF-expressing cells: 0% lysis compared to 60% lysis for an anti-TNF antibody). This result would not have been predicted by one of ordinary skill in the art, who would have expected the claimed fusion proteins to retain the pro-inflammatory effector activities. Ex. 2010 at 668 (showing that a CD4/IgG fusion protein mediates ADCC); Ex. 1041 at 2 [69] (reporting that a CD4/IgG fusion protein retained the ability to bind both FcγR and C1q); Ex. 1040 at 4-5 [528-29] (reporting that their CD4/IgG fusion protein retained the ability to bind FcγR).

The p75 TNFR fusion proteins that are the object of the '522 Patent claims also unexpectedly exhibit a lack of aggregation of large complexes of TNF, which typically results from the homodimeric binding activity of unmodified antibodies and enhances effector functions such as ADCC and CDC. Ex. 2022 at 52; Ex. 2003 at Fig. 6 (showing no TNF-etanercept aggregates were detected in Ouchterlony test). One of ordinary skill in the art would have predicted the opposite because, like antibodies, etanercept is divalent and was expected to form aggregated complexes with TNF trimers. Ex. 2022 at 52. Yet, etanercept binds only one TNF trimer, not two. *Id.*; Ex. 2003 at Figs. 2 & 5 (showing that when etanercept and TNF are mixed at varying

molar ratios, etanercept will bind only one TNF trimer and that complexes in which one molecule of etanercept bound two TNF trimers were never observed).

The record evidence also shows that the p75 TNFR fusion proteins that are the object of the contested claims unexpectedly had a dramatic increased ability to neutralize TNF, increased binding affinity, and increased kinetic stability. Ex. 2022 at 53-54; Ex. 2006 at 1550-51 (reporting an unexpected 50-fold improvement in binding affinity for TNF and a 1000-fold improvement in neutralizing TNF-induced cytotoxicity by the TNFR/IgG fusion as compared to the soluble TNFR fragment alone); Ex. 2017 at 9-11 (demonstrating that p75sTNFR/IgG exhibited "excellent binding activity", "unexpectedly higher kinetic stability", and "a surprisingly improved inhibition of the effect of TNF in biological cell culture tests"). No such increase in potency would have been predicted based on what was known with respect to CD4/IgG fusion proteins. Ex. 1040 at 2 [526] (showing that both CD4/IgG fusion proteins had the same kinetic stability as soluble rCD4); *id.* at Fig. 5 and 5 [529] (showing both CD4/IgG fusion proteins had the same potency as soluble rCD4). Indeed, the dramatic increase in TNF-neutralizing potency was even higher than would have been predicted from the degree of increased binding affinity for TNF. Ex. 2022 at 53.

The references the Petition cited in support of its obviousness theory confirm that these results were unexpected. Capon states a preference for including in a fusion protein the Fc portion of IgG_1 because ***it retains effector function***. Ex. 1002 at 15:4-

8; *see also id.* at 4:43-47 (noting as an object of the invention "to provide novel hybrid immunoglobulin molecules which combine the adhesive and targeting characteristics of a ligand binding partner with *immunoglobulin effector functions such as complement binding, cell receptor binding and the like*") (emphasis added). Likewise, Seed describes one advantage of immunoglobulin fusion proteins is that they can provide effector functions of ADCC and CDC, Ex. 1006 at 5:13-15, and that fusion proteins according to its disclosure should include sufficient Ig protein to retain such effector function, *id.* at 6:15-21.

The increased neutralization of TNF by the p75 TNFR fusion proteins at issue was also unexpected in view of, *inter alia*, another article by Capon. *See* Ex. 1040. In that Capon reference, CD4-IgG fusion proteins reportedly had the *same* neutralization potency as soluble CD4. Ex. 1040 at 5 [529] & Fig. 5. The increased binding affinity and increased kinetic stability of the bound complexes of Patent Owner's p75 TNFR fusion proteins thus would have been an unexpected result to the skilled person considering other of Capon's teachings.

In the Board appeal involving the related '182 Patent, the Examiner acknowledged these results associated with the TNFR fusion proteins of the contested claims were unexpected. Ex. 2023 at 62-65. The Board also determined that this substantial evidence of unexpected results supported "a conclusion of non-obviousness" that was sufficient to rebut the Examiner's rejection based on the

disclosures of fusion proteins in Capon and of the p75 TNFR sequence in Dembic. Ex. 2025 at 7.

Nonetheless, Patent Owner submitted even more evidence of unexpected results after the Board Appeal, including a Declaration from Dr. Arora, showing unexpected properties of etanercept when compared to two different anti-TNF antibodies and two different p75 TNF/IgG fusion proteins (Delta 57 and Protein 3.5D), proteins that fall outside the scope of the claims because they contain only a portion of the hinge domain. Ex. 2016 at §§ 2-6. And when the Examiner later rejected the claims, notwithstanding the Board's decision, as obvious in light of Smith in view of Capon, Patent Owner aptly responded that "the current rejection leads one of ordinary skill even further away from the claimed invention and, therefore, the prior holding by the Board applies with even more force to the new, weaker rejection." Ex. 2027 at 12. The Examiner subsequently allowed the claims, noting in particular "the evidence of unexpected results" provided by Dr. Arora's declaration. Ex. 2028 at 7. The Office similarly agreed the unexpected results previously communicated by Patent Owner rendered the '522 Patent claims non-obvious, issuing a Notice of Allowance after Patent Owner argued that the objective indicia evidence relied upon by the Board with respect to the '182 Patent "applies equally, if not with greater force, to the obviousness rejection in the present case." Ex. 1022 at 18; Ex. 1026 at 6 [2].

The same conclusion is compelled here. The combination of art the Petition proffered—Capon, Seed, and Smith—adds nothing to the combined teachings of Capon and Dembic that the Board considered and rejected.[17] The Petition's obviousness theory here is also entirely cumulative to that based on Capon and Smith. *See, e.g.*, Ex. 2026 at 5-13; Ex. 1023 at 9-20 [7-18].

As explained in Section VI.A above, the unexpected results established by the evidence in the prosecution history has a clear nexus to the '522 Patent claims. The lack of effector function, lack of aggregation of TNF complexes, increased TNF-neutralizing potency, increased binding affinity, and increased kinetic stability were all properties uniquely observed with the p75 TNFR/IgG Fc fusion proteins that result from practicing the claimed methods and using the claimed nucleic constructs, vectors and host cells. Ex. 2022 at 48-54; Ex. 1022 at 25-39. The nexus between the unexpected results and the claimed inventions is further cemented by Dr. Arora's declaration, which compared etanercept to two different p75 TNFR/IgG fusion proteins that fall outside the scope of the claims and did not exhibit the unexpected properties. Ex. 2016 at §§ 2-6.

[17] Smith was also before the Board on appeal. Ex. 2025 at 2.

D. The Petition Could Also Be Denied Under § 325(d) Because the Board Already Effectively Heard and Rejected the Same Theory

"In determining whether to institute or order a proceeding," including an IPR, the Board "may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). The Board should exercise that discretion here.

As noted above, Petitioner's obviousness theory was indistinguishable from that considered during examination, and relied on prior art teachings entirely cumulative to those considered and rejected during examination of both the '522 Patent and the '182 Patent. *See supra*, Section VI.A. Obviousness based on the combined teachings of Capon and Smith was one of the primary combinations that the Examiner relied on throughout the prosecution of the '522 Patent. *See* Ex. 1023 at 9-20 [7-18]. Seed adds nothing to the teachings of Capon; it is entirely cumulative. *See supra*, Section V.E. In other words, the obviousness theory and evidence supporting it that was presented in the Petition was front and center during the examination and was ultimately rejected. Ex. 1023 at 9-20 [7-18]; Ex. 1026 at 6 [2].

The cumulative nature of the proposed grounds relative to those exhaustively addressed during examination, weighs strongly against the institution of trial. *See Nora Lighting v. Juno Mfg.*, IPR2015-00601, Paper 13 at 11-12 (Aug. 12, 2015) (declining to institute where reference was "duplicative of" one in request for *ex parte* reexamination); *see also Excelsior Medical Corp. v. Lake*, IPR2013-00494, Paper 10 at 19-

20 (Feb. 6, 2014) (declining to institute because asserted references and arguments previously considered notwithstanding later change in law). Because the Petition presents no new theories of unpatentability, but instead has simply rehashed arguments previously considered and rejected, the Board should exercise its discretion and deny the Petition under § 325(d).

VII. CONCLUSION

The Board has already rejected Petitioner's obviousness theory. The Examiner has rejected it, too. Even considered independently, the ground presented in the Petition fails to establish that any claim of the '522 Patent is obvious. Instead, it sets forth a paradigmatic example of why the obviousness law so firmly guards against hindsight. Separately, the evidence of objective indicia of non-obviousness in the '522 Patent examination record conclusively refutes the assertion of obviousness made in the Petition—the only theory of unpatentability advanced. Because the Petition fails to establish a reasonable likelihood that any claim of the '522 Patent would have been obvious to the person of ordinary skill in the art, the Board should deny the Petition and not institute trial. Finally, the Board should exercise its discretion under 35 U.S.C. § 325(d) and decline to institute trial because the Petition presents a ground the Office, and indeed the Board, has already found insufficient to show the claims of the '522 Patent and its sibling '182 Patent were obvious.

Dated: December 14, 2015

Respectfully submitted,

/Jeffrey P. Kushan/

Jeffrey P. Kushan (Lead)
Reg. No. 43,401
Sidley Austin LLP
1501 K Street, N.W.
Washington, DC 20005
Telephone: (202) 736-8914

Jill J. Schmidt
Reg. No. 54,172
Sidley Austin LLP
1001 Page Mill Road, Building 1
Palo Alto, CA 94304
Telephone: (650) 656-7050

Attorneys for the Patent Owner Hoffmann-LaRoche Inc. and Real Parties in Interest Immunex Corporation, and Amgen Inc.

CERTIFICATE OF SERVICE

I hereby certify that on this 14th day of December, 2015, a copy of **PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107 OF PATENT OWNER AND REAL PARTIES IN INTEREST** has been served in its entirety via e-mail on counsel of record for Petitioner at the following addresses:

rhahl@neifeld.com

rmihail@neifeld.com

general@neifeld.com

jkpike@neifeld.com

Dated: December 14, 2015

Respectfully Submitted,

/Jeffrey P. Kushan/

Jeffrey P. Kushan
Registration No. 43,401
Sidley Austin LLP
1501 K Street NW
Washington, DC 20005
Attorney for the Patent Owner Hoffmann-LaRoche Inc. and Real Parties in Interest Immunex Corporation, and Amgen Inc.