UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES, INC.,
Petitioner,

v.

HOFFMANN-LAROCHE INC.,
Patent Owner.

Patent No. 8,163,522

PETITION
to Institute an *Inter Partes* Review of U.S. Patent No. 8,163,522
under 37 C.F.R. § 42.100 et seq.

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Patent Trial and Appeal Board
United States Patent and Trademark Office
PO Box 1450
Alexandria, Virginia 22313–1450
Submitted Electronically via the PTAB E2E

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EXHIBIT LIST

Petitioner Exhibit No.	Document
1001	U.S. Patent No. 8,163,522, Brockhaus et al.
1002	Declaration of Dennis R. Burton, Ph.D.
1003	Watson et al., "A Homing Receptor-IgG Chimera as a Probe for Adhesive Ligands of Lymph Node High Endothelial Venules," J. Cell Biology, 110:2221-2229 (June 1990)
1004	U.S. Patent No. 5,395,760, Smith et al.
1005	Zettlmeissl et al., "Expression and Characterization of Human CD4: Immunoglobulin Fusion Proteins," DNA and Cell Biology, 9(5):347-353 (June 1990)
1006	Applicants' Appeal Brief for U.S. Patent App. No. 08/444,790 (filed Feb. 28, 2008)
1007	Smith et al., "A Receptor for Tumor Necrosis Factor Defines an Unusual Family of Cellular and Viral Proteins," Science, 248:1019-1023 (May 25, 1990)
1008	"Preliminary Response Under 37 C.F.R. §42.107 of Patent Owner and Real Parties In Interest" filed in *Coalition for Affordable Drugs V LLC v. Hoffmann-La Roche Inc.*, IPR2015-01792, Paper No. 10 (PTAB Dec. 14, 2015)
1009	Physicians' Desk Reference, entry for ENBREL®, pp. 1752-1755 (56th ed. 2002)
1010	"Decision Denying Institution of Inter Partes Review" filed in *Coalition for Affordable Drugs V LLC v. Hoffmann-La Roche Inc.*, IPR2015-01792, Paper No. 14 (PTAB March 11, 2016)
1011	European Patent App. No. 90107393.2, Karjalainen et al. (filed April 19, 1990)
1012	Declaration of Joseph B. Tamblyn, with English Translation of European Application Ser. No. 90116707.2, filed August 31, 1990, attached as Exhibit A, and original application attached as Exhibit B

1013	Declaration of Joseph B. Tamblyn, with English Translation of CH Application Ser. No. 1347/90, filed April 20, 1990, attached as Exhibit A, and original application attached as Exhibit B
1014	Declaration of Joseph B. Tamblyn, with English Translation of CH Application Ser. No. 746/90, filed March 8, 1990, attached as Exhibit A, and original application attached as Exhibit B
1015	Declaration of Joseph B. Tamblyn, with English Translation of CH Application Ser. No. 3319/89, filed September 12, 1989, attached as Exhibit A, and original application attached as Exhibit B
1016	Applicants' Amendment and Request for Reconsideration in Response to Non-final Office Action for U.S. Patent App. No. 08/444,790 (filed Sept. 8, 2010)
1017	Applicants' Amendment and Response to June 24, 2011 Office Action for U.S. Patent App. No. 08/444,790 (filed Nov. 23, 2011)
1018	Dembic et al., "Two Human TNF Receptors Have Similar Extracellular, But Distinct Intracellular, Domain Sequences," *Cytokine*, 2(4):231-237 (July 1990)
1019	U.S. Patent No. 5,116,964, Capon et al.
1020	Declaration Under 37 C.F.R. 1.132 of Dr. Werner Lesslauer for U.S. Patent App. No. 08/444,790 (filed Dec. 13, 2004)
1021	Decision on Appeal for U.S. Patent App. 08/444,790, *Ex parte* Brockhaus, No. 2009-014889 (BPAI Nov. 22, 2010)
1022	U.S. Pat. No. 5,428,130, Capon et al.
1023	Final Office Action for U.S. Patent App. 08/444,791 (filed June 24, 2011)
1024	Declaration of Taruna Arora, Ph.D. Under 37 C.F.R. 1.132 for U.S. Patent App. No. 08/444,790 (filed Dec. 16, 2010)
1025	Notice of Allowance of U.S. Patent App. No. 08/444,790 (filed Feb. 15, 2012)
1026	"Petition" filed in *Coalition for Affordable Drugs V LLC v. Hoffmann-La Roche Inc.*, IPR2015-01792, Paper No. 1 (PTAB Aug. 22, 2015)
1027	U.S. Patent No. 6,004,781, Seed
1028	Affidavit of Spencer J. Johnson with Exhibits A-D

1029	Declaration of Lynne Weaver with copy of Watson et al. "A Homing Receptor-IgG Chimera as a Probe for Adhesive Ligands of Lymph Node Endothelial Venules," J. Cell Biology., 110:2221-2229 (June 1990) stamped by Lipscomb Library on June 14, 1990 attached as Exhibit A
1030	Declaration of Carmen Debord with copy of Zettlmeissl et al., "Expression and Characterization of Human CD4: Immunoglobulin Fusion Proteins," DNA and Cell Biology, 9(5):347-353 (June 1990), stamped by the Library of Congress on July 10, 1990, attached as Exhibit A
1031	U.S. Patent No. 8,063,182, Brockhaus, et al.
1032	Capon et al., "Designing CD4 immunoadhesins for AIDS therapy," Nature, 337:525-531 (Feb. 9, 1989)
1033	Byrn et al., "Biological properties of a CD4 immunoadhesin," Nature, 344:667–670 (Apr. 12, 1990)
1034	Brennan et al., "Inhibitory Effect of TNFα Antibodies on Synovial Cell Interleukin-1 Production in Rheumatoid Arthritis," The Lancet, 334:244-247 (July 29, 1989).
1035	Traunecker et al., "Highly efficient neutralization of HIV with recombinant CD4-immunoglobulin molecules," Nature, 339:68-70 (May 4, 1989)
1036	Smith and Baglioni, "The Active Form of Tumor Necrosis Factor is a Trimer," J. Biol. Chem., 262(15):6951-6954 (May 25, 1987)
1037	Smith and Baglioni, "Multimeric Structure of the Tumor Necrosis Factor Receptor of HeLa Cells", J. Biol. Chem., 264(25): 14646-14652 (Sept. 5, 1989)
1038	Karush, "Multivalent Binding and Functional Affinity," Contemporary Topics in Molecular Immunology, 217-228 (1976)
1039	Greenbury et al., "The Reaction with Red Cells of 7S Rabbit Antibody, its Sub-units and their Recombinants," Immunology, 8:420-431 (1965)

1040	Mohler et al., "Soluble Tumor Necrosis Factor (TNF) Receptors Are Effective Therapeutic Agents in Lethal Endotoxemia and Function Simultaneously as Both TNF Carriers and TNF Antagonists," J. Immunology, 151(3):1548-1561 (Aug. 1, 1993)
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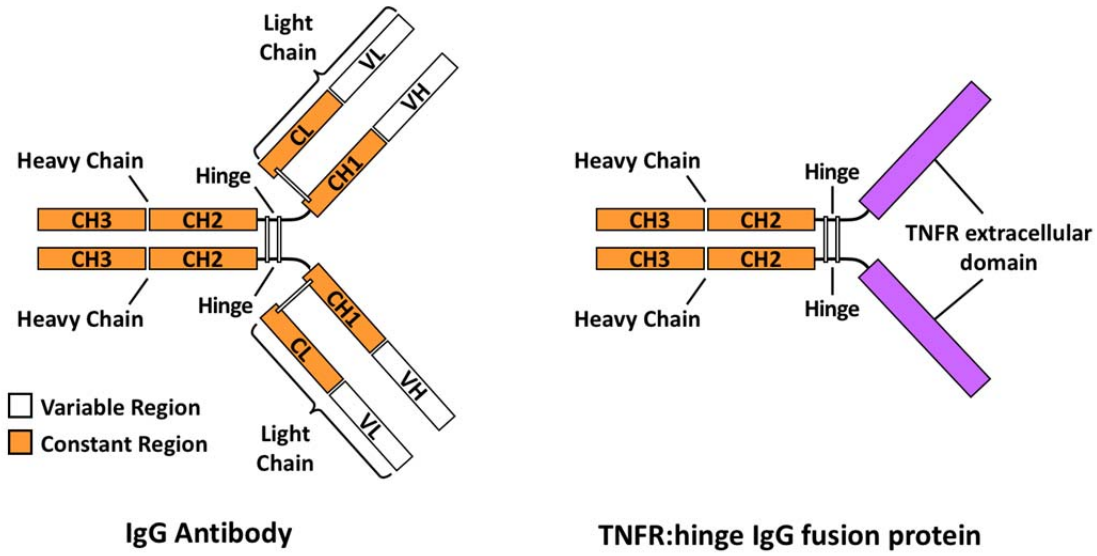
1042	Schneider et al., "Genetically engineered immunoglobulins reveal structural features controlling segmental flexibility," Proc. Natl. Acad. Sci. USA, 85:2509-2513 (Apr. 1988)
1043	Oi et al., "Correlation between segmental flexibility and effector function of antibodies," Nature, 307:136-140 (Jan. 12, 1984)
1044	Gregory et al., "The Solution Conformations of the Subclasses if Human IgG Deduced from Sedimentation and Small Angle X-ray Scattering Studies," Molecular Immunology, 24(8):821-829 (1987)
1045	Lachmann and Hughes-Jones, "Initiation of Complement Activation," Springer Seminars in Immunopathology 7:143-162 (1984)
1046	Kohno et al., "Adalimumab and Infliximab Bind to Fc-Receptor and C1q and Generate Immunoprecipitation: A Different Mechanism From Etanercept," Amgen Inc., 1495 (2005)
1047	Khare et al., "Mechanisms of Cell Death Induced by Tumor Necrosis Factor Antagonists," Amgen Inc. (2005)
1048	Mitoma et al., "Mechanisms for Cytotoxic Effects of Anti-Tumor Necrosis Factor Agents on Transmembrane Tumor Necrosis Factor α-Expressing Cells," Arthritis & Rheumatism, 58(5):1248-1257 (May 2008).
1049	FDA Drug Safety Communication: Drug labels for the Tumor Necrosis Factor-alpha (TNFα) blockers no include warnings about infection with Legionelle and Listeria bacteria (Sept. 7, 2011)
1050	Ellison et al., "The nucleotide sequence of a human immunoglobulin Cγ1 gene," NAR, 10(13):4071-4079 (1982).
1051	Jayapal et al., "Recombinant Protein Therapeutics from CHO Cells - 20 Years and Counting," Chemical Engineering Progress 103(10):40-47 (2007)

1052	Klinman et al. “The Role of Antibody Bivalence in the Neutralization of Bacteriophage,” 99(6):1128-1133 (1967)
1053	Loumaye et al., “Binding Affinity and Biological Activity of Gonadotropin-Releasing Hormone Agonists in Isolated Pituitary Cells,” Endocrinology, 111(3):730-736 (1982)
1054	Gliemann and Gammeltoft, “The Biological Activity and the Binding Affinity of Modified Insulins Determined on Isolated Rat Fat Cells,” Diabetologia, 10:105-113 (1974)
1055	Parekh et al., “Development and validation of an antibody-dependent cell-mediated cytotoxicity-reporter gene assay,” Landes Biosci., 4(3):310-318 (2012)
1056	Beutler and Cerami, “Tumor Necrosis, Cachexia, Shock, and Inflammation: A Common Mediator,” Ann. Rev. Biochem. 57:505-18 (1988)
1057	Arend and Dayer, “Cytokines and Cytokine Inhibitors or Antagonists in Rheumatoid Arthritis,” Arthritis & Rheumatism, 33(3):305-315 (March 1990)
1058	Engelmann et al., “Two Tumor Necrosis Factor-binding Proteins Purified from Human Urine,” J. Bio. Chem., 265(3):1531-1536 (January 1990)

I. INTRODUCTION

Coherus BioSciences, Inc. ("Coherus") petitions for *inter partes* review ("IPR") of claims 1-10 of U.S. Patent No. 8,163,522 ("the '522 patent," Ex. 1001), assigned to Hoffmann-LaRoche Inc. ("Patent Owner"). This petition and the accompanying declaration of Dennis R. Burton, Ph.D. (Ex. 1002) demonstrate that each of the claims is unpatentable as obvious over (1) Watson (Ex. 1003) in view of U.S. Patent No. 5,395,760 ("Smith," Ex. 1004), and (2) Smith in view of Zettlmeissl (Ex. 1005) and Watson.

The '522 patent claims polynucleotides and host cell expression methods for producing "fusion proteins" that combine: (1) the extracellular region of the 75 kilodalton human tissue necrosis factor receptor ("TNFR"); with (2) the hinge-CH2-CH3 region of the heavy chain of a human IgG antibody. Ex. 1002 ¶40. The resulting fusion protein replaces the variable region of an IgG antibody's heavy chain with the 75-kDa TNFR, and eliminates the unnecessary light chain and CH1 domain:



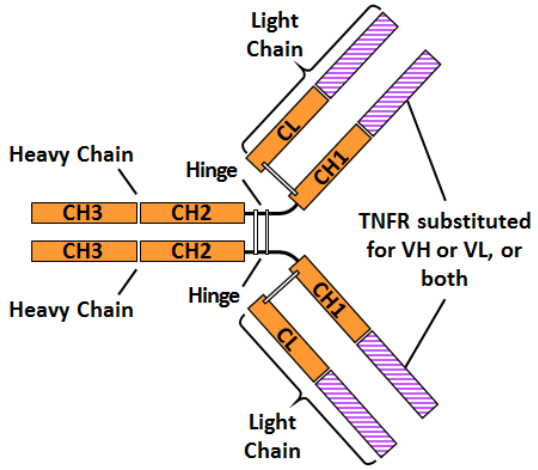
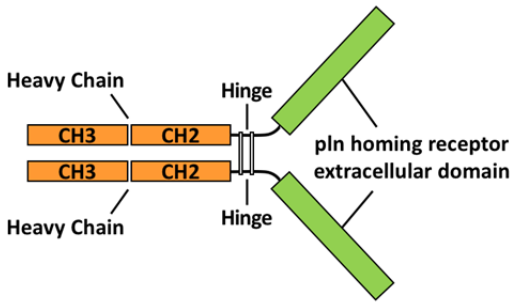
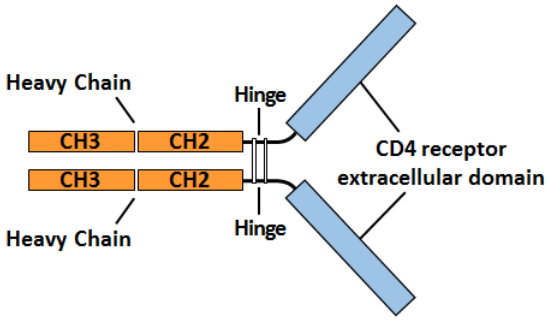
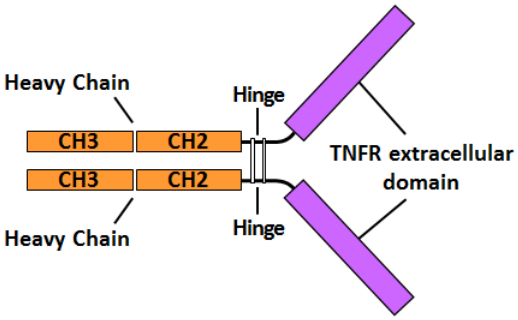
Id. ¶¶36, 40 (figures adapted from Ex. 1006, 12-13).[1]

The Patent Owner was not the first to isolate and sequence the 75-kDa TNFR, nor was it the first to develop a fusion protein combining the extracellular region of a receptor protein with the hinge-CH2-CH3 region of a human IgG heavy chain ("receptor:hinge IgG"). Multiple prior art publications recognized the promising therapeutic potential of such fusion proteins, and reported their advantageous properties such as specific binding to the receptor's target ligand, bivalent display of the receptor, increased neutralization, ease of production and purification, and long serum half-life. Ex. 1002 ¶¶63-89, 126-127; Ex. 1003, 2224-25; Ex. 1005, 350-51.

Conventional recombinant DNA techniques and host cell expression

[1] All citations refer to the Exhibits' native page numbers, except that IPR Page numbers are used for Exhibits 1012-1015 and 1020.

methods made it a routine matter for a person of ordinary skill in the art ("POSA") to create fusion proteins, or to replace one receptor with another in such a fusion. Ex. 1002 ¶¶44-46, 107-108. The '522 patent simply claims an obvious combination of the known 75-kDa TNFR with optimized fusion proteins taught in the prior art, as summarized in the following table:

 Smith (Ex. 1004), May 1990	 Watson (Ex. 1003), June 1990
 Zettlmeissl (Ex. 1005), June 1990	 '522 patent, *no earlier than* 8/31/1990

The Patent Owner also was not the first to suggest incorporating the 75-kDa TNFR into a fusion protein. Smith and co-workers at Immunex Corporation published and patented the complete sequence of the 75-kDa TNFR in May

1990—beating the Patent Owner in the race to do so. Ex. 1004; Ex. 1007. Smith identified the soluble, extracellular sequence of the 75-kDa TNFR, and described its therapeutic administration "for suppressing TNF-dependent inflammatory responses in humans." Ex. 1004, 16:60-66, 4:12-21. Smith suggested making TNFR:IgG fusion proteins because their bivalent display of the TNFR could result in "enhanced binding affinity for TNF ligand." *Id.* at 10:53-66; Ex. 1002 ¶¶57-58, 139.[2]

After Smith was filed—but before the effective priority date of the '522 patent—several research groups conducted extensive studies to optimize the location at which the receptor protein is linked to the IgG antibody fragment. This work culminated in publications by Watson and Zettlmeissl, which independently reported that receptor:IgG hinge fusion proteins are most "efficiently synthesized" when the light chain and CH1 domain are deleted, so that the receptor is attached directly to the hinge-CH2-CH3 region of an IgG antibody's heavy chain. Ex.

[2] Patent Owner asserts that the '522 patent "claims nucleic acids, host cells, and methods used to produce Enbrel® (etanercept)." Ex. 1008, 1. Etanercept is a fusion protein developed by Immunex Corporation that combines the extracellular portion of the 75-kDa TNFR with the hinge-CH2-CH3 region of a human IgG1 heavy chain. *Id.* at 1-2, n.1. Immunex's Smith patent (Ex. 1004) covered etanercept until its expiration in 2012. Ex. 1009, 1755.

1003, 2224; Ex. 1005, 347 (reporting the "best expression" was observed for heavy chain fusion proteins lacking the CH1 domain); Ex. 1002 ¶¶151-158.

Watson and Zettlmeissl used different receptors in their fusion proteins, but both reported optimal results by employing the ***identical*** portion of the IgG heavy chain as claimed in the '522 patent. Ex. 1002 ¶¶76-78, 84-86, 132. Watson also taught that, based on success using different types of receptor proteins, the methods it reports could be "of general applicability" for making receptor:hinge IgG fusions. Ex. 1003, 2228; Ex. 1002 ¶¶82, 140.

It was obvious to apply Watson's general method for preparing receptor:hinge IgG fusion proteins—which Watson taught could be used as "therapeutic reagents against inflammatory diseases"—to prepare a fusion protein incorporating the anti-inflammatory soluble TNFR taught by Smith. Ex. 1003, 2228; Ex. 1002 ¶¶132-144. In the alternative, it was obvious to modify Smith's TNFR:IgG fusion proteins by deleting the light chain and CH1 region of the heavy chain, because Zettlmeissl and Watson taught that doing so results in optimum expression of the fusion protein. Ex. 1002 ¶¶145-161. Regardless of the approach chosen, the prior art taught that the ***expected*** result is a fusion protein having a long half-life that binds to and scavenges TNF to reduce inflammation, with increased binding affinity for TNF compared to the monomeric receptor. Ex. 1002 ¶¶126-131; Ex. 1004, 3:3-6, 10:61-66; Ex. 1005, 350-51.

This strong case of obviousness is not overcome by the purported evidence of unexpected results relied on by Patent Owner during prior proceedings. Dr. Burton, a renowned expert in antibody engineering, thoroughly rebuts Patent Owner's claims. *First*, the fusion proteins' apparent enhanced affinity for TNF, and the associated increase in neutralization potency, as compared to the soluble TNFR were entirely expected—indeed, these were express reasons identified in the prior art for making receptor:IgG fusions. Ex. 1002 ¶¶165-179. *Second*, Patent Owner's claims of a surprising reduction in alleged "pro-inflammatory" functions (complement-dependent cytotoxicity ("CDC"), antibody-dependent cell-mediated cytotoxicity ("ADCC"), and aggregation) compared to monoclonal antibodies are unsupported by the prior art and/or based on unreliable data. *Id.* ¶¶182-207. *Third*, the Patent Owner has not compared the claimed fusion proteins to the closest prior art, and its comparisons to FDA-approved monoclonal antibody treatments demonstrate no practical benefit that could support a finding of nonobviousness. *Id.* ¶¶180-181, 208-211.

This petition establishes that each and every feature recited by claims 1-10 of the '522 patent was disclosed by the prior art, and that claims 1-10 are unpatentable as obvious. Therefore, there is at least a "reasonable likelihood that the petitioners would prevail with respect to at least 1 of the claims challenged," 35

U.S.C. § 314(a), and Coherus respectfully requests that its Petition for IPR be granted.

II. MANDATORY NOTICES

A. Real Party-in-Interest (37 C.F.R. § 42.8 (b)(1))

Coherus BioSciences, Inc. is the real party-in-interest.

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

The ’522 patent is the subject of the following judicial or administrative matters, which may affect, or be affected by, a decision in this proceeding:

The ’522 patent is involved in the pending litigation *Immunex Corp. v. Sandoz Inc.*, No. 16-cv-01118 (D.N.J. Feb. 26, 2016). Additionally, the ’522 patent was involved in a litigation that is no longer pending: *Sandoz Inc. v. Amgen Inc.*, 773 F.3d 1274 (Fed. Cir. 2014). The Board also has issued a Written Decision denying a Petition for *inter partes* review of the ’522 patent filed by Coalition for Affordable Drugs V LLC (IPR 2015-01792) (Ex. 1010).

Coherus identifies the following U.S. patent applications and patents that claim the benefit of priority of the filing of the ’522 patent or from which the ’522 patent claims priority: U.S. Patent No. 8,063,182 (“the ’182 patent”) (Ex. 1031); U.S. Patent No. 5,610,279; U.S. Application Nos. 07/580,013 (now abandoned); and 10/715,609 (now abandoned).

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

Coherus provides the following designation of counsel:

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

Please address all correspondence and service to counsel at the address provided in Section II.C. Coherus consents to electronic service at the email addresses above, in addition to litigationparalegals@rothwellfigg.com.

III. PAYMENT OF FEES (37 C.F.R. § 42.103)

Coherus authorizes the Patent and Trademark Office to charge Deposit Account 02-2135 for the fee set in 37 C.F.R. § 42.15(a) for this petition, and further authorizes any additional fees to be charged to this Deposit Account.

IV. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

A. Grounds for Standing Under 37 C.F.R. § 42.104(a)

Coherus certifies that the ’522 patent is available for IPR and that Coherus is not barred or estopped from requesting an IPR. Coherus is a biopharmaceutical company that is developing for U.S. regulatory approval and commercial

introduction an etanercept product for the treatment of disorders such as rheumatoid arthritis.

B. Challenge Under 37 C.F.R. § 42.104(b); Relief Requested

Coherus requests IPR and cancellation of all claims of the ’522 patent as unpatentable on the grounds listed below. The ’522 patent is to be reviewed under pre-AIA law.

Ground No.	Claims Challenged	Statutory Grounds for Unpatentability
1	1-10	Obvious under 35 U.S.C. § 103 in view of Watson (Ex. 1003) in combination with Smith (Ex. 1004).
2	1-10	Obvious under 35 U.S.C. § 103 in view of Smith in combination with Zettlmeissl (Ex. 1005) and Watson.

V. THE ’522 PATENT

A. The ’522 Patent Only Generically Encompasses Fusion Proteins Comprising the 75-kDa TNFR, and Does Not Specifically Disclose Etanercept

The ’522 patent is entitled “Human TNF Receptor,” and issued on April 24, 2012 from an application filed nearly seventeen years earlier, on May 19, 1995. Ex. 1001, cover. As explained in Section V.C. below, the ’522 patent is entitled to a priority date no earlier than August 31, 1990.

The ’522 specification includes the DNA and amino acid sequences for the 55-kDa and 75-kDa TNFR, but admits the latter sequence was taken from the May 1990 Smith Publication. *See* Ex. 1001, 2:52-56 (describing Fig. 1), 3:1-5

(describing Fig. 5 (SEQ ID NO:27)). The specification never specifically describes a fusion protein consisting of the extracellular region of the 75-kDa TNFR and the hinge-CH2-CH3 region of a human IgG1, and contains no description or examples describing etanercept. The specification does not report that any fusion proteins were purified, and does not report data or results obtained with any fusion protein. Ex. 1002 ¶¶43, 45.

The '522 patent's sole example of a fusion protein describes ligation of a cDNA fragment encoding the extracellular region of the *55-kDa* TNFR into the "pCD4-Hγ3" vector disclosed in European application EP 90107393.2. Ex. 1001, 20:65-21:18. That European application—like the Zettlmeissl reference relied on by Coherus—discloses fusion proteins in which the CD4 receptor is fused to the hinge region of an IgG antibody. Ex. 1002 ¶44; Ex. 1011, 7:39-45. The applicants simply removed the CD4 receptor DNA and substituted the 55-kDa TNFR sequence in its place using conventional recombinant DNA techniques. Ex. 1002 ¶¶44-46; Ex. 1001, 20:65-21:18. That is, the lone example of a TNFR fusion protein disclosed in the '522 patent replaced the portion of the vector encoding one known soluble receptor (*i.e.*, CD4, the subject of the Zettlmeissl reference) for another known soluble receptor (*i.e.*, TNFR) to produce the expected result of a fusion protein comprising that soluble receptor. Ex. 1002 ¶46.

B. The Claims of the '522 Patent Cover Standard Methods for Expressing a Fusion Protein in a Host Cell, Applied to 75-kDa TNFR:hinge IgG Fusions

Independent claims 1 and 4 are illustrative of the claimed subject matter. Ex. 1010, 3-4. Claim 1 recites a standard method of expressing a fusion protein in a host cell, where the fusion protein consists of the extracellular region of the 75-kDa TNFR and the hinge-CH2-CH3 region of a human IgG molecule. Ex. 1002 ¶93; Ex. 1010, 7. Claim 1 recites:

> 1. A method comprising the steps of:
>
> (a) culturing a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein consisting of:
>
> (i) the extracellular region of an insoluble human TNF receptor, wherein the insoluble human TNF receptor has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel and comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), and
>
> (ii) all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region, and
>
> (b) purifying an expression product of the polynucleotide from the cell mass or the culture medium.

Ex. 1001, claim 1.

Claim 4 recites a polynucleotide that encodes essentially the same fusion protein expressed in the method of claim 1, except that claim 4 specifies that the human IgG heavy chain is of the IgG1 isotype. Ex. 1002 ¶116.

Independent claim 7 is similar to claim 1, but recites the insoluble human TNF receptor as comprising "the amino acid sequence of SEQ ID NO: 27." *Id.* ¶124. "SEQ ID NO: 27" corresponds to the full-length 75-kDa TNF receptor published by Smith in May 1990, and includes the sequence recited in claims 1 and 4 (SEQ ID NO: 10). *Id.* ¶¶56, 60.

Various dependent claims require a "mammalian host cell," that the host cell is a "CHO cell," (claims 2, 6, 9, and 10), or that the IgG heavy chain is an IgG1 heavy chain (claims 3, 8).

C. The Priority Date of the '522 Patent Is No Earlier Than August 31, 1990.

The earliest effective filing date of the '522 patent is no earlier than August 31, 1990. All of the claims of the '522 patent require, among other things, a polynucleotide that encodes (1) the extracellular region of the 75-kDa human TNF receptor, and (2) "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region" (i.e., the hinge-CH2-CH3 region of a human IgG). Ex. 1001, 45:44-46:68; Ex. 1002 ¶48. The '522 patent claims priority to four foreign patent applications filed

between September 12, 1989 and August 31, 1990. *See* Ex. 1001, cover. None of the priority applications that pre-date August 31, 1990 describe either of these features. Ex. 1002 ¶48.

The Patent Owner amended the August 31, 1990 application to add, among other things, (1) a disclosure of recombinant proteins comprising portions of a TNFR and all of the domains, other than the first domain, of the constant region of the heavy chain of human immunoglobulins, and (2) Example 11. Ex. 1002 ¶¶49-50; Ex. 1012, 8, 29-30; Ex. 1013.

The August 31, 1990 priority application does not disclose the complete sequence for the *75-kDa* TNFR fusion protein. Ex. 1002 ¶49; Ex. 1012. The Applicants admitted that they rely on *the May 1990 Smith publication* for the necessary 75-kDa TNFR sequence. *See* Ex. 1016, 9 ("Two TNF receptors, an approximately 55 kD receptor (p55 TNFR) and an approximately 75 kD/65 kD receptor (p75 TNFR), were known in the art, and the DNA and amino acid sequences for both receptors … had been published ***before the August 31, 1990 priority date of the present application***.").[3] Indeed, Applicants admitted that the earliest possible priority date is August 31, 1990. *Id.*; *see Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569 (Fed. Cir. 1988) (holding "[a patentee's] own admission during prosecution … is binding upon him").

[3] All emphasis in ***bold italics*** is added.

D. The Prosecution History of the ’522 Patent

The ’522 patent was filed as U.S. Patent Application No. 08/444,791 on May 19, 1995. The Office only allowed the claims after 15 Office Actions, 19 responses and/or amendments, and several examiner interviews.

The ’522 patent was prosecuted in parallel with the related ’182 patent, has a similar specification, and claims priority to the same earlier applications. While the ’522 patent claims nucleotides and methods for culturing host cells to express fusion proteins, the ’182 patent claims the fusion proteins themselves. The prosecution history of the ’182 patent includes an appeal to the Board of Patent Appeals and Interferences. Ex. 1006. The Applicants relied on the outcome of that appeal in gaining allowance of the ’522 patent. Ex. 1017, 6.

1. The Board Found the Related ’182 Patent Nonobvious Based Solely on Alleged Evidence of Unexpected Results, Which the Examiner Did Not Substantively Address

During prosecution of the ’182 patent, the claims were rejected for failing to meet the written description requirement, for introducing new matter, and for obviousness over Dembic (Ex. 1017) and a Capon patent (Ex. 1019). *See* Ex. 1006, 10. Patent Owner responded to the obviousness rejection in part by providing evidence purporting to show unexpected results, specifically: (1) absence or marked reduction in effector function, (2) lack of ability to form aggregated complexes with TNF, (3) increased TNF neutralization potency, and

(4) improved TNF-binding properties. *See id.* at 48. The Examiner refused to consider the alleged unexpected results because they were based on fusion proteins containing the full length extracellular domain of the 75-kDa TNFR, and the Examiner had found such fusions were not described by the specification. *Id.* at 47-48.

Patent Owner appealed to the Board, arguing that the obviousness rejection should be reversed because: (1) the cited art allegedly "teaches away" from combining Dembic with Capon, (2) there was no reason to select the claimed hinge-CH2-CH3 fusion protein from the "many types of fusion proteins disclosed in Capon," (3) there was no reasonable expectation of success, and (4) the Examiner erred in refusing to consider Patent Owner's alleged evidence of unexpected results. *Id.* at 39.

Despite the Patent Owner's extensive arguments questioning the Examiner's *prima facie* case, the Board reversed the obviousness rejection *solely on the basis of unexpected results*. Ex. 1021, 6-7. The Board noted that the Examiner did not dispute Patent Owner's alleged unexpected results on the merits. *Id.* at 7. Because the Board determined that there was written description for fusion proteins containing the full extracellular 75-kDa TNFR, it held the corresponding "evidence of unexpected results is convincing to rebut the Examiner's obviousness rejection." *Id.*

2. Prosecution of the ’522 Patent Tracked that of the ’182 Patent

The Examiner’s final rejection of the claims of the ’522 patent was for obviousness over Smith (Ex. 1004) in view of Capon (U.S. Pat. No. 5,428,130, Ex. 1022). Ex. 1023, 7.

The Patent Owner responded that “obviousness had been dispositively addressed by the decision of the Board” in the ’182 patent, which reversed a rejection based on a similar combination of references. Ex. 1017, 6. The Patent Owner noted that in the ’182 patent prosecution, “Dembic, like the Smith Patent, had been cited for its disclosure of the p75 TNFR, and the Capon Patent disclosure had been cited for teaching the immunoglobulin portion of Ig fusion molecules that contain a ligand-binding portion of a receptor.” *Id.*

The Patent Owner also relied on a Declaration of Taruna Arora, which was not before the Board during the ’182 patent appeal, as additional alleged evidence of unexpected results. *Id.* at 11; Ex. 1024. The Patent Owner claimed that the Aurora Declaration shows the claimed fusion proteins surprisingly lack antibody effector functions. Ex. 1017, 11. A Notice of Allowance was mailed on February 15, 2012. Ex. 1025. The Examiner stated only that the rejections were withdrawn “in view of the cancellation of claims … and applicants [sic] arguments.” *Id.* at 6.

3. CFAD's Prior Petition for IPR Challenging the '522 Patent Relied on Different Prior Art than Coherus' Petition, and Failed to Substantively Address Unexpected Results

The Coalition for Affordable Drugs V LLC ("CFAD") filed a Petition for IPR of the '522 patent (IPR No. 2015-01792), which the Board denied. Ex. 1026; Ex. 1010. As the Patent Owner has admitted, CFAD took a "less-than-rigorous approach" to its IPR (Ex. 1008, 2), which is fundamentally different from Coherus's challenge here.

First, CFAD's sole argument was obviousness over Seed (Ex. 1027) in view of Smith and Capon (Ex. 1032). The Board correctly found that CFAD "fail[ed] to offer persuasive evidence to explain why one of skill in the art would choose the Fc [*i.e.*, hinge-CH2-CH3] portion of the immunoglobulin heavy chain from the choices taught in Seed or Capon." Ex. 1010, 16.[4] Seed and Capon teach a variety of different possible locations at which to fuse a receptor protein to an immunoglobulin fragment, without providing clear guidance as to the best location. *See id.* at 15-16.

Coherus' invalidity grounds are entirely different in this respect. Watson and Zettlmeissl both provide a clear and compelling reason why a POSA would have specifically selected a fusion protein incorporating the hinge-CH2-CH3

[4] Patent Owner refers to the hinge-CH2-CH3 region interchangeably as the "Fc" portion of the antibody. *See* Ex. 1008, 1-2, n.1.

region of an IgG. Zettlmeissl, not cited by either the Examiner or CFAD, specifically compares fusion proteins in which the receptor protein is attached at different locations on the immunoglobulin molecule, and reports that "[i]n general, ***poor expression was observed for fusion proteins bearing CH1 domains***...." Ex. 1005, 348. Zettlmeissl reports excellent expression for a dimeric fusion protein in which the receptor protein is joined to the hinge-CH2-CH3 region of a human IgG1. *Id.* The hinge-CH2-CH3 fusion protein also displayed favorable binding characteristics and long serum half-life. *Id.*

Similarly, Watson identifies *only one* location as optimal for fusion of a receptor protein to the immunoglobulin.[5] Watson states that the "choice of junctional sites between the mHR [receptor sequence] and human IgG sequences was guided by work with human CD4-IgG chimeras that ***demonstrated that the joining of the molecules near the hinge region resulted in chimeric molecules that were both efficiently synthesized and dimerized*** in the absence of any light chain production." Ex. 1003, 2224. Both Watson and Zettlmeissl expressly directed the POSA to choose exactly the immunoglobulin fragment claimed in the '522 patent—the "hinge-CH2-CH3" region of a human IgG heavy chain. Ex. 1002 ¶¶104-106, 151-157.

[5] Watson was referred to in a single sentence in the CFAD Petition, as an example of a fusion protein made in the prior art. Ex. 1026, 20.

Second, the Board correctly found CFAD failed to "address adequately the objective indicia of nonobviousness presented to the Office during the prosecution of the '522 patent, merely asserting that such evidence was not commensurate in scope with the claims." Ex. 1010, 17. Indeed, CFAD's petition nowhere addresses the merits of the claimed unexpected results. *See* Ex. 1026.

This petition and the accompanying Declaration of Dr. Burton directly respond to Patent Owner's allegations of unexpected results. *See* § IX.C. *infra*. Coherus demonstrates that the vast majority of the alleged "unexpected results" are exactly what a POSA would have expected based on the prior art. Certain other results relied upon by Patent Owner are scientifically unreliable, legally deficient, and of questionable practical importance. In short, Patent Owner's alleged unexpected results cannot overcome the strong showing of obviousness presented in Coherus' present petition.

VI. LEVEL OF SKILL IN THE ART

The relevant field of the '522 patent is recombinant DNA processes for the production, isolation, and use of chimeric proteins. A person of ordinary skill in the field would have held an advanced degree, such as a Ph.D., in molecular biology, biochemistry, cell biology, molecular genetics, or a related field, and would have experience using recombinant DNA processes to construct chimeric

proteins, as well as experience using techniques for the expression, isolation, and purification of proteins. *See* Ex. 1002 ¶30.

VII. CLAIM CONSTRUCTION UNDER 37 C.F.R. 42.104(B)(3)

A claim in an unexpired patent subject to *inter partes* review is to be given its "broadest reasonable interpretation in light of the specification in which it appears." 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Tech., LLC v. Lee,* 136 S. Ct. 2131, 2146 (2016).[6]

The Board has previously addressed claim construction for the '522 patent in the CFAD proceedings, as discussed below. All other claim terms not addressed below should be given their plain and ordinary meaning. Coherus reserves the right to address any claim construction issue raised by Patent Owner.

A. "all of the domains of the constant region…other than the first domain of said constant region"

As previously held by the Board, when given its broadest reasonable interpretation in light of the specification of the '522 patent, the claim term "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region" means "-hinge-CH2-CH3

[6] Because the claim construction standard in an IPR is different than that used in litigation, Coherus expressly reserves the right to present different constructions of terms in any related litigation, as well as to challenge the claims under 35 U.S.C. § 112. *See In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1369 (Fed. Cir. 2004).

region of a human IgG immunoglobulin heavy chain." Ex. 1010, 7. Claims that specifically recite a human IgG1 immunoglobulin are construed analogously. *Id.*

B. "TNF receptor" and "about"

The Board previously determined that the terms "TNF receptor" and "about" did not require an express construction. Ex. 1010, 5, 7. Coherus agrees that both terms should be given their ordinary meaning in this proceeding.

VIII. PATENTS AND PRINTED PUBLICATIONS RELIED ON IN THIS PETITION

Claims 1-10 of the '522 patent are unpatentable under 35 U.S.C. § 103(a) as obvious over the prior art identified below, which teaches every element of the claimed invention, a motivation to combine those elements, and a reasonable expectation of success in doing so.

A. U.S. Patent No. 5,395,760 ("Smith") – May 10, 1990

Smith issued on March 7, 1995, directly from an application filed on May 10, 1990, and therefore is available as prior art under 35 U.S.C. § 102(e) (pre-AIA). Ex. 1004.

Smith Figure 2A discloses the full length cDNA and amino acid sequences of the 75-kDa TNFR, including SEQ ID NO: 27 and SEQ ID NO: 10 as claimed in the '522 patent. Ex. 1004, Fig. 2A; Ex. 1002 ¶56. Smith specifically identifies the sequence corresponding to the "entire extracellular region of the TNF-R," stating that it is a "particularly preferred soluble TNF-R construct." Ex. 1004, 9:25-29;

Ex. 1002 ¶¶55-56.

Smith teaches that "purified TNF receptor compositions may be used directly in therapy to bind or scavenge TNF, thereby providing a means for regulating the immune activities of this cytokine." Ex. 1004, 3:3-6. Moreover, Smith teaches making TNFR:IgG fusion proteins because bivalent expression of the receptor was expected to increase the affinity for TNF. Ex. 1002 ¶¶57-58. Smith states:

> 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…. Following transcription and translation of the two chimeric genes, the gene products assemble into a single chimeric antibody molecule having TNF-R displayed bivalently.

Ex. 1004, 10:53-64. Smith explains that "[s]uch polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand." *Id.* at 10:64-66.

Smith also discloses methods of obtaining purified TNFR by cloning and expressing genes that encode the receptor using recombinant DNA technology. *Id.* at 2:23-26; Ex. 1002 ¶¶54, 110. Smith teaches that "[r]ecombinant proteins are preferably expressed … in a mammalian host cell, such as Chinese Hamster Ovary (CHO) cells…" Ex. 1004, 15:46-48; *see also* 22:45-24:15 (Example 7).

B. Watson et al., "A Homing Receptor-IgG Chimera as a Probe for Adhesive Ligands of Lymph Node High Endothelial Venules" ("Watson") – June 1990

Watson published in the Journal of Cell Biology on June 1, 1990 and was received at libraries no later than June 14, 1990. Ex. 1003; Ex. 1028; Ex. 1029; Fed. R. Evid. 803(16), 901(b)(8). Watson was published in a recognized periodical, publicly disseminated, and readily accessible to the interested public before August 31, 1990 (the earliest possible priority date of the '522 patent). Ex. 1029; Ex. 1002 ¶76. It therefore is a printed publication that qualifies as prior art under 35 U.S.C. § 102(a) (pre-AIA); *Suffolk Techs., LLC v. AOL Inc.*, 752 F.3d 1358, 1364 (Fed. Cir. 2014) ("A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.") (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

Watson discloses procedures of "general applicability" for preparing fusion proteins comprising a receptor and the hinge-CH2-CH3 portion of the human IgG1 heavy chain. Ex. 1003, 2228; Ex. 1002 ¶¶76-82, 140. Watson builds on earlier work performed by Capon and others, who had prepared fusion proteins combining the CD4 receptor with portions of an IgG antibody. Ex. 1002 ¶82; Ex. 1003, 2224. Watson's fusion protein combines the extracellular region of a different receptor

protein, murine peripheral lymph node homing receptor ("pln HR" or "mHR"), with the hinge region of a human IgG1 heavy chain. Ex. 1003, 2223 (Fig. 1A); Ex. 1002 ¶¶76-79. Watson explains that "[t]he choice of junctional sites between the mHR and human IgG sequences was guided by work with human CD4-IgG chimeras that demonstrated that the ***joining of the molecules near the hinge region resulted in chimeric molecules that were both efficiently synthesized and dimerized*** in the absence of any light chain production." Ex. 1003, 2224.

Unlike CD4, pln HR is not part of the IgG superfamily, but it still folded correctly when fused to the hinge-CH2-CH3 region of IgG1. Ex. 1002 ¶82. Watson explains that "[t]he work described here establishes that nonimmunoglobulin superfamily receptors, such as the mHR, can also be converted to mAb-like molecules." Ex. 1003, 2228. Moreover, "the fact that a nonimmunoglobulin superfamily member was successfully produced and employed here suggests that this procedure may be of general applicability." *Id.*

Watson teaches that its fusion protein "may find utility as an anti-inflammatory reagent by virtue of its ability to block the binding of leukocytes to endothelium." *Id.*; Ex. 1002 ¶¶80, 132-133. In that respect, the Watson fusion protein is similar to TNFR fusion proteins, which POSAs expected to be useful as anti-inflammatory agents. Ex. 1002 ¶134; Ex. 1004, 3:3-6.

C. Zettlmeissl et al., "Expression and Characterization of Human CD4:Immunoglobulin Fusion Proteins" ("Zettlmeissl") – June 1990

Zettlmeissl published in the June 1990 issue of DNA & Cell Biology, which was received at libraries no later than July 10, 1990. Ex. 1005; Ex. 1028; Ex. 1030; FED. R. EVID. 803(16), 901(b)(8). Zettlmeissl was published in a recognized periodical, publicly disseminated, and readily accessible to the interested public before the earliest possible priority date of the '522 patent. Ex. 1002 ¶83; Ex. 1028, Ex. 1030. Like Watson, Zettlmeissl therefore is a printed publication that qualifies as prior art under 35 U.S.C. § 102(a) (pre-AIA).

Zettlmeissl studies several variations of CD4:IgG fusion proteins, including fusions in which CD4 is bound to: (1) the CH1 domain; (2) the hinge region; and (3) the CH2 domain of an IgG1 molecule. Ex. 1005, 348, 349 (Fig. 1); Ex. 1002 ¶84. Zettlmeissl expressed each of its constructs in mammalian host cells, and found that "***in general poor expression was observed for fusion proteins bearing CH1 domains*** …." Ex. 1005, 348; Ex. 1002 ¶¶85-87.

In contrast, fusion proteins in which CD4 was fused to the hinge-CH2-CH3 region of IgG1 were highly expressed in two mammalian cell lines (COS cells and BHK cells). Ex. 1005, 348; Ex. 1002 ¶¶85-86, 123, 154. The CD4:IgG1 hinge fusion protein was "effective at blocking HIV-1 replication in a long-term virus neutralization assay over 5 weeks." Ex. 1005, 350; Ex. 1002 ¶87. However, the

CD4:IgG1 hinge fusion protein did not display "significant complement-dependent activity in a short-term chromium release assay." Ex. 1005, 350; Ex. 1002 ¶¶193-194.

The serum half-life of Zettlmeissl's hinge fusion protein was "about 50-fold higher than the reported value for the half-life of soluble CD4 in rabbits." Ex. 1005, 350-51; Ex. 1002 ¶89. Zettlmeissl observed no adverse reactions in preliminary toxicology studies in mice. Ex. 1005, 351; Ex. 1002 ¶89.

D. Prior Art Informing the General Knowledge of the POSA

In addition to the prior art relied upon in Coherus's grounds of unpatentablility, this Petition addresses additional publications confirming the general knowledge of a POSA as of the earliest possible priority date. These additional publications, which include articles reporting the production of other fusion proteins leading up to Watson's and Zettlmeissl's work, further confirm that a POSA would have been motivated to make TNFR-IgG hinge fusion proteins with a reasonable expectation of success. *See, e.g.*, Ex. 1002 ¶¶59-75, 211; Ex. 1032; Ex. 1033. The additional publications also confirm that POSAs were motivated to use the TNF receptor clinically to scavenge TNF as a means to treat inflammatory disorders. *See* Ex. 1007. Moreover, the art confirms that POSAs recognized that anti-TNF therapies incorporating the Fc domain of a human IgG antibody would be effective in treating inflammatory disorders mediated by TNF. *See* Ex. 1034.

IX. THE CHALLENGED CLAIMS ARE OBVIOUS OVER THE PRIOR ART

Claims 1-10 of the ’522 patent are unpatentable under 35 U.S.C. § 103(a) as obvious. Obviousness is determined based on an analysis of: (1) the scope and content of the prior art; (2) differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A patent claim is unpatentable under 35 U.S.C. § 103 if “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

The claimed invention of the ’522 patent is no more than the combination of a well-known receptor (*i.e.*, the 75-kDa TNFR) with a well-known, optimized method of preparing fusion proteins (*i.e.*, attaching DNA encoding the extracellular portion of a receptor to the DNA encoding the hinge-CH2-CH3 region of an IgG heavy chain, and expressing the fusion protein in host cells), to yield a predictable result (*i.e.*, a fusion protein with a high affinity for TNF). Thus, the claims are obvious. *KSR*, 550 U.S. at 416 (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”).

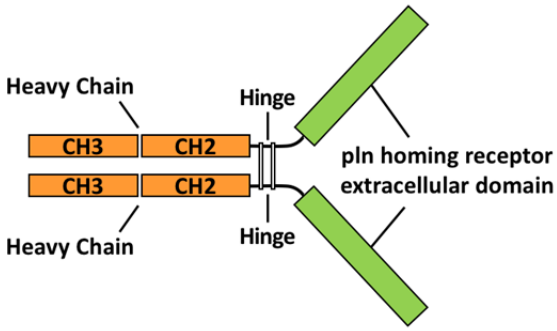
For the same reason, this case is entirely unlike *Millennium Pharms., Inc. v. Sandoz Inc.*, No. 2015-2066, 2017 U.S. App. LEXIS 12702, at *12 (Fed. Cir. July 17, 2017), in which the Federal Circuit found an unexpectedly-formed new compound nonobvious, supported by undisputed evidence that the new compound "provided unexpected properties, solving the problems that accompanied [the prior art compound]." As detailed below, here, the routine preparation of fusion proteins as taught by the prior art led to the *expected* result of a TNFR:hinge IgG fusion protein with improved binding affinity and serum half-life, among other benefits. Ex. 1002 ¶¶126-131, 136-139, 162-164.

A. Ground 1: The Claims of the '522 Patent Are Obvious Over Watson in view of Smith '760

The '522 patent claims polynucleotides and conventional methods for expressing a fusion protein in host cells, applied to fusions consisting of the extracellular region of the 75-kDa TNFR and the hinge-CH2-CH3 region of a human IgG. Ex. 1002 ¶¶93-94, 116. The POSA was motivated to apply Watson's general method for preparing fusion proteins to the TNFR sequences taught by Smith in order to make a TNFR:IgG fusion protein to bind and scavenge TNF, and had a reasonable expectation of success in doing so. That process results in the exact methods and nucleotides claimed in the '522 patent. Indeed, each and every limitation of claims 1-10 of the '522 patent was obvious.

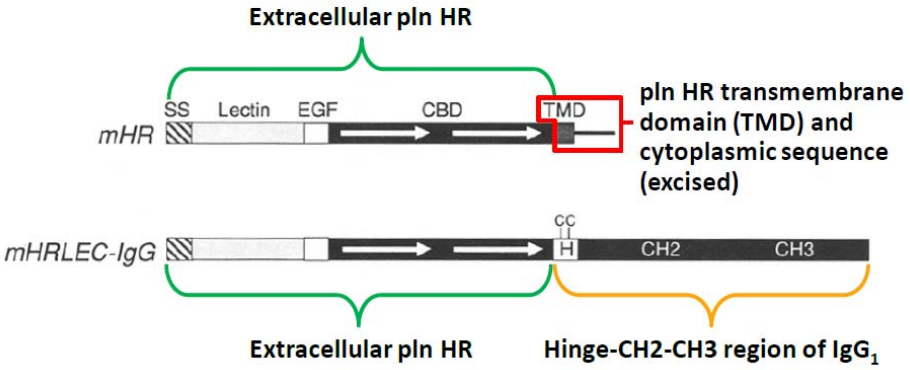
1. Applying Watson's General Method for Efficiently Expressing Fusion Proteins in Host Cells to the TNFR Sequences Taught by Smith Results in the Exact Methods and Nucleotides Claimed in the '522 Patent

Watson describes a dimeric fusion protein that combines the extracellular region of the pln homing receptor ("pln HR") with the hinge-CH2-CH3 region of a human IgG1 heavy chain:



Ex. 1002 ¶76; Ex. 1003, 2223-24.

The fusion protein is encoded by a polynucleotide assembled using conventional recombinant DNA technology. Ex. 1002 ¶142. Watson fused DNA encoding the extracellular region of pln HR to DNA encoding the hinge-CH2-CH3 region of human IgG1:



Ex. 1003, 2223 (Fig. 1A (as annotated by Dr. Burton)); Ex. 1002 ¶79. Watson transfected this polynucleotide into human kidney 293 cells, and purified the cultured host cells' expression product to obtain the fusion protein. Ex. 1003, 2222; Ex. 1002 ¶¶77, 112.

Watson's decision to use the hinge-CH2-CH3 region of an IgG1 antibody was not arbitrary. Based on prior work with CD4 receptor:IgG fusion proteins, Watson knew that "the joining of the molecules near the hinge region resulted in chimeric molecules that were both efficiently synthesized and dimerized in the absence of any light chain production." Ex. 1002 ¶¶78, 148, 157; Ex. 1003, 2224; Ex. 1032, 526 (Fig. 1). As Dr. Burton explains, Watson teaches the POSA that an "ideal location for joining a receptor to an IgG1 heavy chain is the point just N-terminal to the hinge region, so that the hinge-CH2-CH3 region is included." Ex. 1002 ¶157.

Watson's fusion protein is identical to the fusion protein of the '522 patent claims, except that the receptor protein is different. While Watson's receptor is the extracellular region of pln HR, the '522 patent claims recite that the receptor is the extracellular region of the 75-kDa TNFR. Ex. 1002 ¶132.

Smith teaches the extracellular region of the 75-kDa TNFR, and states that this region is a "particularly preferred" form of soluble TNFR. Ex. 1004, 9:25-29; Ex. 1002 ¶¶102-103. The extracellular region is part of the full-length insoluble

human TNFR sequence reported in Smith Figure 2A, which is identical to "SEQ ID NO. 27," as claimed in claim 7. Ex. 1002 ¶¶101-102, 125. Amino acids 1-18 of Smith's Figure 2A correspond to SEQ ID NO. 10, as claimed in claims 1 and 4. *Id.* ¶101. Smith identifies amino acids 1-235 as the "entire extracellular region of TNF-R." Ex. 1004, 9:25-29.

Using the extracellular region of TNFR in a fusion protein was obvious, because Watson (and other prior art fusion proteins) used the extracellular receptor sequence. Ex. 1002 ¶¶103, 105-106; Ex. 1003, 2223 (Fig. 1A); Ex. 1005, 347. Additionally, Smith teaches that the extracellular region of 75-kDa TNFR retains the ability to bind TNF, and eliminating the intracellular and transmembrane domains facilitates expression in host cells. Ex. 1002 ¶103; Ex. 1004, 9:18-24.

The straightforward application of Watson's method to the 75-kDa TNFR disclosed by Smith (*i.e.*, joining the extracellular receptor to the hinge-CH2-CH3 region of IgG1) results in exactly the same polynucleotides and methods claimed in the '522 patent. Ex. 1002 ¶¶141-142, 158. Smith also teaches similar host cell expression and purification methods for preparing soluble TNFR. *See, e.g.*, Ex. 1004, 15:61-65, 22:45-24:15 (Example 7). The following claim chart for exemplary claim 1 demonstrates that the claimed method was an obvious combination of Watson and Smith. *See also* Ex. 1002, Appendix.

Claim 1	**Representative Disclosure**
A method comprising the steps of: (a) culturing a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein consisting of:	"The construct was transfected into human kidney cells and the synthesized protein … was recovered …" Ex. 1003, 2224. "CHO cells are transfected with an expression vector containing genes for both TNF-R and GS…." Ex. 1004, 22:45-24:15 (Example 7).
(i) the extracellular region of an insoluble human TNF receptor,	"A particularly preferred soluble TNF-R construct is TNF-RΔ235 (the sequence of amino acids 1-235 of FIG. 2A), which comprises the entire extracellular region of TNF-R." Ex. 1004, 9:25-28.
wherein the insoluble human TNF receptor has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel and	"The native human TNF-R molecules are recovered from cell lysates as glycoproteins having an apparent molecular weight by SDS-PAGE of about 80 kilodaltons (kDa)." Ex. 1004, 7:14-18.
comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), and	Amino acids 1-18 of Smith Fig. 2A are LPAQVAFTPYAPEPGSTC. Ex. 1004, Fig. 2A.
all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region, and	"This truncated [receptor] protein is joined to a human heavy chain gamma-1 region immediately NH_2-terminal to the hinge domain (H) such that this chimera contains the two cysteine residues (c) of the hinge

	responsible for immunoglobulin dimerization as well as the CH2 and CH3 constant regions." Ex. 1003, 2223.
(b) purifying an expression product of the polynucleotide from the cell mass or the culture medium.	"The construct was transfected into human kidney cells, and the synthesized protein … was recovered by affinity chromatography with protein A-Sepharose beads." Ex. 1003, 2224. "Purified mammalian TNF receptors or analogs are prepared by culturing suitable host/vector systems to express the recombinant translation products of the DNAs of the present invention, which are then purified from culture media or cell extracts." Ex. 1004, 15:61-65.

2. The Prior Art Motivated the POSA to Combine Watson and Smith

The POSA was motivated to apply Watson's method to Smith's TNFR to make a TNFR:hinge IgG fusion protein for several reasons.

First, Watson expressly teaches a general method to make fusion proteins using various receptors. Ex. 1002 ¶140; Ex. 1003, 2228. Watson points out that the method was successful even though, unlike the CD4 receptor, the pln HR is not a member of the immunoglobulin gene superfamily. Ex. 1003, 2228; Ex. 1002 ¶144. Watson explains that "the fact that a nonimmunoglobulin superfamily

member was successfully produced and employed here suggests that this procedure may be of general applicability." Ex. 1003, 2228. Watson thus teaches the POSA that various receptors, including TNFR, would likely fold compatibly with the hinge-CH2-CH3 region of an IgG heavy chain to produce a functional fusion protein. Ex. 1002 ¶¶82, 144.

Second, Watson teaches use of the IgG fusion protein as an anti-inflammatory. Ex. 1003, 2228 (stating the pln HR:IgG1 hinge fusion protein "may find utility as an antinflammatory [sic] reagent by virtue of its ability to block the binding of leukocytes to endothelium."). Watson's proposed use of a receptor:IgG fusion protein to block certain inflammatory pathways is very similar to the use that Smith and others identified for therapeutics based on TNFR. Ex. 1002 ¶¶132-134. Smith teaches that "purified TNF receptor compositions may be used directly in therapy to bind or scavenge TNF, thereby providing a means for regulating the immune activities of this cytokine." Ex. 1004, 3:3-6; *see also id.* at 16:63-66 (disclosing "methods for suppressing TNF-dependent inflammatory responses in humans" by administering soluble TNFR). Indeed, the Patent Owner has admitted that the *known* "proposed benefit of soluble forms of TNFR was for administration clinically to inhibit TNF, a known pro-inflammatory cytokine." Ex. 1006, 42 (citing Ex. 1007, 1019, 1022). The POSA was motivated to make a TNFR fusion protein using Watson's method, for the purpose of preparing an anti-inflammatory

agent that could suppress TNF-dependent inflammation.

Third, POSAs understood that receptor:IgG fusion proteins were likely to display increased affinity for their target compared to the soluble receptor alone. Ex. 1002 ¶¶136-137, 167-173. Watson explains that one reason for making a receptor:IgG fusion protein was that the molecule dimerizes (and therefore displays two copies of the receptor), which "might be expected to add to the avidity of the interaction between the receptor and its ligand." Ex. 1003, 2224; Ex. 1002 ¶136. Smith expressly suggests making TNFR:IgG fusion proteins for the same reason. Ex. 1002 ¶137. Smith states that IgG fusion proteins "having TNF-R displayed bivalently," may "result in ***enhanced binding affinity*** for TNF ligand." Ex. 1004, 10:61-66. As Dr. Burton explains, increased binding affinity would have been particularly expected for TNF, because it was known that multiple TNF receptors bind a single TNF molecule. Ex. 1002 ¶¶167-173; Ex. 1036; Ex. 1037; Ex. 1007.

Fourth, POSAs knew that serum half-life could be greatly extended by fusing the soluble receptor to portions of an IgG heavy chain, improving the receptor's usefulness as a therapeutic. Ex. 1002 ¶138; Ex. 1032, 527; Ex. 1005, 347. For example, Zettlmeissl reports that the serum half-life of a CD4:IgG1 hinge fusion protein was "about 50-fold higher than the reported value for the half-life of soluble CD4 in rabbits." Ex. 1005, 350-51. As Patent Owner admitted during

prosecution, soluble TNFR has a very short half-life that is unsuitable for use therapeutically. *See* Ex. 1020 ("The rapid elimination and thus the short half-life of p75sTNFR in vivo, however, made it imperative to enlarge the molecule."). This provided yet another reason to prepare a TNFR:hinge IgG fusion protein.

Fifth, Smith notes that to use TNFR therapeutically, it is necessary to first obtain practical yields of purified TNFR via host cell expression of the recombinant protein. Ex. 1004, 2:15-25. Watson explains that one advantage of incorporating IgG functionality into a fusion protein is that it simplifies purification from cell culture. Ex. 1003, 2224; Ex. 1002 ¶135. POSAs were therefore also motivated to prepare a TNFR fusion protein to simplify purification of the receptor. Ex. 1002 ¶135.

3. The POSA Had a Reasonable Expectation of Success in Preparing the Fusion Proteins Recited in the '522 Patent Claims

The POSA had a reasonable expectation of success in preparing the fusion proteins recited in the '522 patent claims by applying Watson's method to the soluble TNFR disclosed by Smith. Ex. 1002 ¶¶140-144. Watson's method had been used successfully with receptors from two different protein families: CD4 and pln HR. Ex. 1003, 2228; Ex. 1002 ¶¶140, 142. Moreover, Watson expressly suggests using the method to make fusion proteins with other receptors, stating "[t]he work described here ***establishes*** that nonimmunoglobulin superfamily receptors … can also be converted into [IgG fusion proteins]." Ex. 1003, 2228;

Ex. 1002 ¶¶140, 161. The DNA sequences and host cell expression techniques needed to prepare TNFR:IgG1 hinge fusion proteins were well known in the art. Ex. 1002 ¶¶94-97, 107, 141 (noting Watson and Capon used the same IgG1 heavy chain sequence); Ex. 1050.

During prosecution, Patent Owner argued that "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 TNFa." Ex. 1020. There is no basis in the prior art for this speculation. Ex. 1002 ¶143-144. Multiple groups had prepared fusion proteins that successfully bound their target molecules. *Id.* ¶¶130, 143 (citing Watson, Byrn, and Zettlmeissl). Moreover, Smith expressly predicted that binding affinity for TNF would be *increased* by preparing a dimeric fusion protein. Ex. 1004, 10:61-66. This expectation was supported by knowledge in the art that multiple TNFR proteins bind a single TNF molecule. Ex. 1002 ¶¶171-172; *see* Ex. 1037. A POSA would not have been discouraged by some vague possibility that the fusion protein would not bind TNF. Ex. 1002 ¶¶143-144. Based on the record of success in the art in preparing various fusion proteins, the POSA had a very reasonable expectation of success in preparing the claimed TNFR fusions. *See, e.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[O]nly a reasonable expectation of success, not a guarantee, is needed.").

4. Nothing in the Prior Art "Teaches Away" from Preparing TNFR:hinge IgG Fusion Proteins

Patent Owner argued during prosecution that the prior art "teaches away" from fusion proteins that combine the hinge-CH2-CH3 region of an IgG antibody with TNFR, because Smith teaches a different form of TNFR fusion protein (*i.e.*, one in which the IgG fragment includes the light chain and the CH1 region of the heavy chain). Specifically, Patent Owner claimed that Smith's teaching to use an "unmodified" constant region (Ex. 1004, 10:57) is inconsistent with use of a heavy chain that is truncated to exclude the CH1 region (but is otherwise unmodified). *See* Ex. 1008, 48-49. Patent Owner's argument amounts to a contention that because Smith does not *anticipate* the claims, it "teaches away." That is not the law. *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) ("A reference does not teach away … if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.") (quotation omitted).

Watson was published *after* Smith was filed, and indicates that it has *optimized* the location for attaching a receptor to an IgG to make a fusion protein. Ex. 1002 ¶¶129, 157-158; Ex. 1003, 2224; *see also* § IX.B.2 *infra* (discussing Zettlmeissl's teaching of the same optimization). A POSA would have readily applied Watson's optimized technique of attaching the soluble receptor to the

hinge-CH2-CH3 portion of an IgG1 (which Watson teaches results in efficient synthesis and dimerization), to improve on Smith's recommendation to prepare a TNFR:IgG1 fusion protein. Ex. 1002 ¶¶142, 145, 156-158; Ex. 1003, 2224; Ex. 1004, 10:53-66. Smith was "a piece of prior art ready for the improvement" taught by Watson. *KSR*, 550 U.S. at 417.

The prior art also did not "teach away" from fusing an anti-inflammatory agent, such as soluble TNFR, to the constant region of an IgG heavy chain. Patent Owner has argued that CD4 receptor fusion proteins were developed in part to take advantage of "effector functions" of antibodies: the triggering of complement-mediated ("CDC") and cell-mediated ("ADCC") responses by which the body kills unwanted cells and viruses. Ex. 1008, 28-31; Ex. 1002 ¶¶35, 186-188, 196-197. Patent Owner then leaps to misleadingly labeling the antibody Fc fragment "pro-inflammatory," while failing to show that any prior art taught away from using an IgG fusion protein as an anti-inflammatory treatment. Ex. 1002 ¶¶208-211; *see also* § IX.C.3 *infra* (explaining prior art indicated that Fc fusion proteins do not retain all antibody effector functions).

Contrary to Patent Owner's arguments, both Watson and Smith suggest use of an IgG-receptor fusion protein as an anti-inflammatory therapy. Ex. 1002 ¶¶132-134; Ex. 1003, 2228; Ex. 1004, 3:3-6, 10:53-66; 16:60-66. Moreover, POSAs expressly suggested that "[a]ntibodies to TNFα injected locally into a

rheumatoid joint may be a useful therapy in severe rheumatoid arthritis." Ex. 1034, 246. This demonstrates that POSAs did not believe that the presence of an IgG Fc region, or any antibody effector functions that may be activated by that region, would significantly detract from the anti-inflammatory benefits of scavenging TNF. Ex. 1002 ¶211.

5. The Claimed Methods and Polynucleotides Were Obvious (Claims 1, 4, 7)

As demonstrated above, it was obvious to prepare the fusion proteins recited in the '522 patent claims by applying Watson's generally applicable method to Smith's TNFR sequences. The claimed nucleotides and methods also were obvious because they simply represent the known means to prepare those fusion proteins. Ex. 1002 ¶¶93-97, 107-112.

POSAs routinely used recombinant DNA techniques to combine known polynucleotide sequences. Ex. 1002 ¶¶107, 142; *see* Ex. 1003, 2222 (describing the preparation of a polynucleotide encoding a receptor:IgG fusion protein). The '522 patent also admits that "standard procedures" are used for cultivating and cloning the host cells, and that "usual methods of protein chemistry" are used to purify the expression product secreted by the host cells. Ex. 1001, 21:26-33; Ex. 1002 ¶¶45-46.

Section IX.A.1 above presents a claim chart demonstrating that each element of claim 1 was taught by the combination of Watson and Smith. Independent

claim 4 claims essentially the same "polynucleotide encoding" the TNFR:hinge IgG fusion protein that is recited as part of the method of claim 1. Ex. 1002 ¶¶116-117. The only difference is that claim 4 specifies that the IgG heavy chain is of the IgG1 isotype. Ex. 1002 ¶117. This element also was obvious, because Watson specifically uses the IgG1 isotype (as did other prior art fusion proteins). *Id.* at ¶¶115-117; Ex. 1003, 2224 (stating that the fusion protein's "constant domain is derived from the human IgG_1 heavy chain"); Ex. 1005, 347. Smith also suggests using an IgG1-isotype antibody to prepare a TNFR:IgG fusion protein. Ex. 1004, 10:57-61.

Independent claim 7 recites essentially the same method as claim 1, but it defines the insoluble TNFR (from which the extracellular region is used) as one that "comprises the amino acid sequence of SEQ ID NO: 27." Ex. 1002 ¶124. Smith Figure 2A presents the identical amino acid sequence as in SEQ ID NO: 27 of the '522 patent, and identifies amino acids 1-235 of that sequence as the soluble, extracellular region. Ex. 1004, Fig. 2A, 9:17-29; Ex. 1002 ¶125.

Accordingly, the methods and polynucleotides claimed in independent claims 1, 4, and 7 are invalid as obvious.

6. The Use of Mammalian CHO Cells Was Obvious (Claims 2, 6, 9, 10)

Dependent claims 2, 9, and 10 require that "the host cell is a CHO cell." Dependent claim 6 requires "A mammalian host cell comprising the

polynucleotide of claim 4." Each of these limitations was obvious.

POSAs knew that CHO cells are one of the most common mammalian host cell lines used for expression of recombinant proteins. Ex. 1002 ¶¶113-114 (citing Ex. 1051). Smith uses CHO cells to express soluble TNFR, and further states "[e]xpression of recombinant proteins in mammalian cells is particularly preferred because such proteins are generally correctly folded, appropriately modified and completely functional." Ex. 1004, 14:7-15, 22:48-52. Although Watson uses human kidney 293 cells to express its fusion proteins, POSAs knew that other mammalian cell lines could be used as an alternative expression system for the fusion protein recited in the '522 patent claims. Ex. 1002 ¶¶114, 123. Accordingly, each of claims 2, 6, 9, and 10 is invalid as obvious.

7. The Use of an IgG1 Heavy Chain Was Obvious (Claims 3, 8)

Claims 3 and 8 depend from claims 1 and 7, respectively, and specify that "the IgG heavy chain is an IgG_1 heavy chain." This limitation is also present in independent claim 4, and was obvious for the reasons stated in section IX.A.5 above.

8. The Vector of Claim 5 Was Obvious

Claim 5 requires "a vector comprising the polynucleotide of claim 4." Vectors (also referred to as expression plasmids) are the vehicle used to introduce a polynucleotide that encodes a particular protein into a host cell. Ex. 1002 ¶118.

Unsurprisingly, Smith and Watson both teach the use of vectors comprising a polynucleotide encoding the target protein. Ex. 1004, 22:62-23:24; Ex. 1003, 2222; Ex. 1002 ¶¶119-121. It was obvious to make a vector comprising the polynucleotide of claim 4, for the same reasons it was obvious to make the corresponding fusion protein.

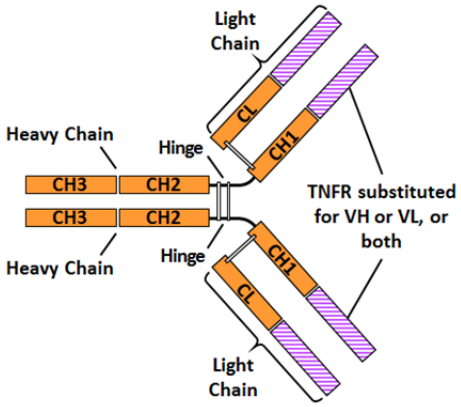
B. Ground 2: The Claims of the '522 Patent Are Obvious Over Smith in view of Zettlmeissl and Watson

As demonstrated in Section IX.A. above, it was obvious to modify Watson's method by applying it to the TNFR sequences taught by Smith, and doing so results in the exact methods, polynucleotides, and vectors claimed in claims 1-10 of the '522 patent. Alternatively, it was obvious to modify the TNFR:IgG fusion proteins expressly taught by Smith to arrive at the claimed subject matter, because Zettlmeissl and Watson taught that removing the CH1 region and the light chain of the IgG immunoglobulin would optimize expression of the fusion protein. Ex. 1002 ¶¶145-161; Ex. 1003, 224; Ex. 1005, 347 (Abstract). Smith in view of Zettlmeissl and Watson therefore also render every claim of the '522 patent invalid as obvious.

1. Modifying Smith's TNFR:IgG Fusion Proteins As Taught By Zettlmeissl and Watson Results in the Exact Fusion Proteins Recited in the '522 Patent Claims

Smith expressly suggests preparing a fusion protein in which TNFR sequences are "substituted for the variable domains of either or both of the

immunoglobulin molecule heavy and light chains and having unmodified constant region domains." Ex. 1004, 10:53-57. Smith thus teaches a fusion protein wherein the TNF receptor has been attached directly to the CH1 domains of the IgG molecule, much like the early CD4 fusion protein constructs disclosed by Capon:



Id. at 10:53-61; Ex. 1002 ¶¶57-58, 146; Ex. 1032, 526.

As detailed in Section IX.A.1 above, Smith discloses the same TNFR receptor sequences recited in claims 1, 4, and 7 of the '522 patent. A POSA would understand Smith's fusion proteins to employ the soluble, extracellular region of TNFR. Ex. 1002 ¶¶102-103, 134, 146. Smith defines "TNFR" to include soluble TNFR, specifically including the complete extracellular region. Ex. 1004, 3:66-4:21. Moreover, Smith teaches that the extracellular region contains the TNF binding site and can be expressed in cell culture. Ex. 1004, 9:17-29. The complete extracellular region also was commonly used in prior art fusion proteins. Ex. 1002 ¶103 (citing Ex. 1003, Ex. 1005).

Thus, the only difference between Smith's TNFR:IgG1 fusion proteins and

those claimed in the '522 patent is the location at which the receptor sequence is attached to the IgG sequence. Ex. 1002 ¶146. Modifying Smith's fusion proteins to attach the extracellular receptor at the hinge region of the IgG heavy chain, which both Zettlmeissl and Watson teach as a means to optimize expression of the resulting fusion protein, results in the exact fusion proteins recited in every claim of the '522 patent. *Id.* ¶158.

Patent Owner has previously argued that Smith taught only *tetravalent* fusion proteins, and did not specifically teach bivalent fusions. Ex. 1008, 49-50. This is simply incorrect. Smith teaches fusing TNFR to "*either* or both of the immunoglobulin molecule heavy and light chains." Ex. 1004, 10:53-57. Fusions to *either* light chain or heavy chain result in bivalent expression of TNFR. Ex. 1002 ¶¶57-58. Smith expressly refers to the resulting fusion proteins as "having TNF-R displayed ***bivalently***," and then states that "such polyvalent forms of TNF-R may have enhanced binding affinity for TNF." Ex. 1004, 10:61-66. Smith clearly contemplates bivalent TNFR:IgG fusions, so it was no leap for the POSA to modify Smith's fusion proteins by employing only the IgG heavy chain, as taught by Zettlmeissl, Watson, and others before them.[7] Ex. 1002 ¶¶146-149; Ex. 1003,

[7] Patent Owner also criticized Smith for not having produced the fusion proteins or described their properties. Ex. 1008, 49. The '522 patent never describes production of a fusion protein within the scope of the claims, and nowhere

2224; Ex. 1005, 347 (Abstract); Ex. 1032, 526.

As detailed below, the POSA was strongly motivated to modify Smith's TNFR:IgG1 fusion proteins as taught by Zettlmeissl and Watson, and would have had a reasonable expectation of success in doing so.

2. Zettlmeissl and Watson Motivated the POSA to Modify Smith's Fusion Proteins to Optimize Expression

Smith was filed in May 1990, before either Zettlmeissl or Watson was published. Ex. 1004, cover; Ex. 1003 (Watson, June 1990); Ex. 1005 (Zettlmeissl, June 1990). Zettlmeissl's later publication details a rigorous study comparing fusion proteins in which an extracellular receptor protein was fused to different parts of an immunoglobulin heavy chain constant region. *See* Ex. 1005; Ex. 1002 ¶¶84-86. Zettlmeissl builds on work by Capon, which had already demonstrated that expression of the immunoglobulin light chain was unnecessary in fusion proteins based on human IgG. Ex. 1002 ¶¶64, 150-152; Ex. 1005, 347 (citing Ex. 1032); Ex. 1032, 526.

After preparing various fusion proteins, including fusions to the CH1, hinge, or CH2 regions of IgG and IgM immunoglobulins, Zettlmeissl reports that "[i]n general, ***poor expression was observed for fusion proteins bearing CH1 domains***

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describes the properties of *any* fusion protein. Ex. 1002 ¶¶43-45. There is "no relevant distinction" between Smith and the '522 patent here. *Merck & Co. v. Teva Pharms. USA*, 395 F.3d 1364, 1374 (Fed. Cir. 2005).

from either murine or human immunoglobulins." Ex. 1005, 348; *see also id.* at 347 (Abstract) ("For both IgG1 and IgM fusion proteins, the ***best expression*** in COS cells was observed for molecules lacking the CH1 domain of the heavy-chain constant region.") The fusion protein in which the receptor was fused to the hinge region of an IgG1 heavy chain (*i.e.*, incorporating the hinge-CH2-CH3 region) was "highly expressed" in two different mammalian cell lines (COS cells and BHK cells). Ex. 1005, 348 ("The properties of the most efficiently secreted CD4:IgG_1 hinge fusion protein were analyzed …."); Ex. 1002 ¶153. Moreover, the CD4:IgG1 hinge fusion protein was biologically active, had good affinity, low toxicity, and a serum half-life about 50-fold higher than the reported values for the corresponding soluble receptor. Ex. 1002 ¶¶87-89; Ex. 1005, 350-52.

Watson likewise achieved optimized expression by joining the extracellular receptor sequence to the hinge region of an IgG1 heavy chain. Ex. 1003, 2224; Ex. 1002 ¶157. Watson explains that the junctional site was chosen based on work with two different receptors: CD4 and pln HR. Ex. 1003, 2224. Watson's resulting IgG1 hinge fusion protein displayed high neutralization potency, and Watson touts its potential for use as an anti-inflammatory therapy. Ex. 1002 ¶¶133, 160, 177-179; Ex. 1003, 2225, 2228.

A POSA would have recognized that Zettlmeissl and Watson reported optimized methods for preparing fusion proteins compared to the earlier disclosure

by Smith. Ex. 1002 ¶¶147, 153. It therefore was obvious to improve on Smith's TNFR:IgG1 fusion proteins by joining the extracellular TNFR to the IgG1 heavy chain at the hinge region, omitting the light chain and the CH1 region of the heavy chain. Ex. 1002 ¶158. The POSA also was motivated to prepare TNFR:IgG fusion proteins for all the reasons discussed in Section IX.A.2 above.

3. The POSA Had a Reasonable Expectation of Success in Preparing the Fusion Proteins Recited in the '522 Patent Claims

The POSA had a reasonable expectation of success in modifying Smith's TNFR:IgG fusion proteins to develop a TNFR:IgG fusion protein without the light chain or CH1 domain. The literature contained several examples of fusion proteins lacking the light chain and CH1 domain, and these fusions all bound their target protein at least as well as the monomeric receptor. Ex. 1002 ¶143 (citing Ex. 1003, Ex. 1005, Ex. 1033), ¶159. Given the demonstrated success with other receptor:IgG hinge fusion proteins, a POSA had a reasonable expectation of success in modifying the fusion protein disclosed in Smith to obtain a TNFR:IgG hinge fusion protein. *Id.* ¶¶159-161.

For all of the reasons discussed in Sections IX.A.3-4 above, the POSA had a reasonable expectation of success in preparing TNFR:IgG hinge fusion proteins exactly as claimed in the '522 patent, and nothing in the prior art taught away from combining Smith's TNFR fusion proteins with the optimized receptor:IgG hinge fusions taught by Zettlmeissl and Watson.

4. The Claimed Polynucleotides and Host Cell Culturing Methods Were Obvious (Claims 1, 4, 7)

As demonstrated in Sections IX.B.1-3 above, it would have been obvious to the POSA to prepare the fusion proteins recited in independent claims 1, 4, and 7 by modifying Smith's TNFR:IgG fusion proteins to include only the "hinge-CH2-CH3" region of the IgG heavy chain, because Zettlmeissl and Watson taught that doing so leads to much better expression of the fusion protein. The nucleotides and methods claimed in the '522 patent were obvious because they simply represent the known means to prepare those optimized fusion proteins. *See* §§ IX.A.1, IX.A.5 *supra*.

As shown in Section IX.A.1, the limitations of independent claims 1 and 7 requiring "culturing a host cell comprising a polynucleotide" and "purifying an expression product of the polynucleotide from the cell mass or the culture medium" are only routine steps in producing fusion proteins, and are taught by Watson and Smith. Ex. 1002 ¶¶93-97, 107-112. Zettlmeissl also teaches these elements. Zettlmeissl describes transfecting an expression vector (polynucleotide) that encodes a fusion protein comprising the extracellular CD4 receptor and the hinge-CH2-CH3 region of human IgG1, culturing the host cells, and purifying the fusion protein (*i.e.*, the "expression product"). Ex. 1005, 348; Ex. 1002 ¶¶84, 96, 111, 121.

The polynucleotides of claim 4 are identical to those recited in the method of

claim 1, except that claim 4 specifies that the IgG heavy chain is of the IgG1 isotype. Ex. 1002 ¶¶116-117. Like Smith and Watson (discussed in Section IX.A.5), Zettlmeissl also specifies that the hinge-CH2-CH3 region of the fusion protein is derived from human IgG1, as required by claim 4. Ex. 1005, 348; Ex. 1002 ¶¶115, 117.

5. The Use of CHO Cells Was Obvious (Claims 2, 6, 9, 10)

The limitations of dependent claims 2, 9, and 10 requiring that "the host cell is a CHO cell," and of dependent claim 6 requiring a "mammalian host cell" were obvious for the reasons stated in Section IX.A.6 above. Ex. 1002 ¶¶113-114, 122-123. Additionally, Zettlmeissl taught the use of mammalian host cells (COS and BHK cells). Ex. 1005, 348-50; Ex. 1002 ¶123.

A POSA would have reasonably expected Zettlmeissl's teachings regarding expression levels attained in COS cells to hold true for other common mammalian cell lines. Ex. 1002 ¶154. Zettlmeissl itself demonstrates successful expression of CD4:hinge IgG1 in BHK cells in addition to COS cells, Watson taught efficient expression of mHR:hinge IgG1 in a third mammalian cell line (human kidney cells), and Smith taught expression of soluble TNFR in CHO cells. *Id.*; Ex. 1003, 2222; Ex. 1004, 22:45-24:15; Ex. 1005, 348-49. POSAs understood that CHO cells could be used as an alternative expression system for the TNFR:hinge IgG1 fusion proteins recited in the claims of the '522 patent. Ex. 1002 ¶114.

6. The Use of an IgG1 Heavy Chain Was Obvious (Claims 3, 8)

Dependent claims 3 and 8 specify that "the IgG heavy chain is an IgG_1 heavy chain." This limitation was obvious for all the reasons stated in Section IX.A.7 above. Additionally, Zettlmeissl specified the use of an IgG1 heavy chain. Ex. 1005, 347 (Abstract); Ex. 1002 ¶115.

7. The Vector of Claim 5 Was Obvious

The "vector comprising the polynucleotide of claim 4," as claimed in claim 5 was obvious for all the reasons stated in Section IX.A.8 above. Consistent with that discussion, Zettlmeissl also used vectors to transfect host cells with the polynucleotide encoding the CD4:hinge IgG1 fusion protein. Ex. 1002 ¶121; Ex. 1005, 348.

C. Any Objective Indicia Cannot Overcome the Strong Showing of Obviousness

A strong case of obviousness cannot be overcome by objective indicia of nonobviousness. *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1365 (Fed. Cir. 2012); *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) ("While secondary considerations must be taken into account, they do not necessarily control the obviousness determination.").

The only secondary consideration that Patent Owner has alleged, during prosecution and in its preliminary response to CFAD's prior IPR petition, is

unexpected results. Patent Owner previously alleged that the claimed TNFR:IgG fusions unexpectedly exhibit: (1) increased "kinetic stability" or binding affinity for TNF; (2) superior neutralization of TNF activity; and (3) a decrease in allegedly "pro-inflammatory" functions of antibodies: CDC, ADCC, and aggregation. *See* Ex. 1006, 48-54; Ex. 1008, 12-15.

Patent Owner's claims of unexpected results were not substantively challenged during prosecution or in CFAD's prior petition, and therefore the Board has never evaluated the merits of Patent Owner's claims. Ex. 1010, 17-18; Ex. 1021, 7. The Examiners had no access to expert testimony to assess the credibility of Patent Owner's alleged evidence. During Patent Owner's appeal to the Board in the related '182 patent, the Examiner entirely failed to dispute the alleged unexpected results due to his conviction that the claims lacked written description support. *See* Ex. 1021, 7. CFAD did not substantively address unexpected results, arguing only that Patent Owner's evidence was not commensurate in scope with the claims because the evidence relates to fusion proteins while the claims relate to methods and polynucleotides. *See* Ex. 1010, 13-14, 17-18.

In sharp contrast to those prior proceedings, Coherus' expert, Dr. Burton—a renowned expert in antibody engineering—has carefully analyzed Patent Owner's purported evidence, and establishes that it falls far short of demonstrating any unexpectedly superior results that could support a finding of nonobviousness. *See*

Ex. 1002 ¶¶162-211.

1. Increased Binding Affinity for TNF Compared to the Soluble Receptor Was Expected, and Motivated the POSA to Make the Claimed Fusion Proteins

Patent Owner asserts that the claimed fusion proteins exhibit surprisingly improved binding affinity and unexpectedly higher kinetic stability when compared to the soluble TNFR protein. Ex. 1006, 54. As an initial matter, the "binding affinity" and "kinetic stability" reported by Patent Owner are two equivalent measurements of the *same property*: the strength of the interaction between the TNFR fusion protein and its binding partner (TNF). Ex. 1002 ¶166.

It was entirely expected that the measured binding affinity of a TNFR:IgG fusion protein, which displays TNFR bivalently, would be increased relative to the affinity of the monovalent soluble receptor. Ex. 1002 ¶¶165-173. That was an express reason stated in the prior art that motivated POSAs to make the claimed fusion proteins. *See* § IX.A.2 *supra.*

It was well-known that, when multiple interactions are possible between a molecule and its target ligand (such as when a multivalent receptor fusion protein binds a multivalent target), the measured binding affinity reflects the accumulated strength of the multiple binding events. Ex. 1002 ¶¶167-169 (citing Ex. 1038). The apparent binding strength is multiplied due to proximity effects. *Id.* ¶168. If one binding event is interrupted, the molecule remains bound to the target via the

second binding event, and the first interaction is likely to be restored because the binding site remains in close proximity to the target. *Id.*

The apparent affinity of a bivalent antibody for a multivalent target has been measured as ***150-450 fold greater*** (or even higher) than the affinity of the equivalent monovalent antibody for the same target. *Id.* ¶173; Ex. 1039, 428; Ex. 1038, 219. The reported 50-fold increase in apparent binding affinity for the bivalent TNFR:IgG fusion protein, compared to the monovalent soluble TNFR, was not unexpected to a POSA. Ex. 1002 ¶¶172-173. Indeed, the article relied on by Patent Owner explains that because it was known that TNF is trimeric, it was considered "***likely*** that dimeric soluble receptor constructs should possess a higher affinity for TNF and therefore function as considerably more potent competitive inhibitors than monomeric sTNFR." Ex. 1040, 1549 (citing a prior art study); Ex. 1007, 1020.

Patent Owner has argued that a POSA would not have expected improved binding affinity because Capon reported that its CD4 fusion protein bound its target (gp120) with the same affinity as the soluble CD4 receptor. Ex. 1006, 54. However, the POSA knew from the very reference that Patent Owner cites that "gp120 has only a single binding site for CD4." Ex. 1032, 530. Because gp120 can only bind *one* CD4 receptor, no increase in binding affinity was expected (or even possible) for the fusion protein. Ex. 1002 ¶170. By contrast, POSAs knew

that TNF is a trimeric molecule that is "intrinsically capable of multivalent binding." Ex. 1007, 1020. POSAs also knew that multiple TNF receptors bind a single TNF molecule. Ex. 1002 ¶171; Ex. 1036, 6954; *see also* Ex. 1037, 14650. Increased binding affinity for the claimed fusions was expected, because both TNF and the TNFR:IgG fusion are multivalent. Ex. 1002 ¶¶171-173. That is exactly why Smith suggested making TNFR:IgG fusions: because such chimeras "having TNF-R displayed bivalently … may have enhanced binding affinity for TNF." Ex. 1004, 10:61-66.

2. Superior Neutralization of TNF Compared to the Soluble Receptor Was Expected, and Motivated the POSA to Make the Claimed Fusion Proteins

Patent Owner asserts that the claimed fusion proteins exhibit an unexpectedly greater ability to neutralize TNF in *in vitro* assays when compared to soluble TNFR. Ex. 1006, 53. Neutralization potency (the molecule's ability to exert a biological effect) was well-known to increase with increased binding affinity. Ex. 1002 ¶¶175-176. It was not at all unexpected that a bivalent TNFR fusion protein, which was expected to display enhanced binding affinity for the trimeric TNF molecule (*see* § IX.C.1 *supra*), would also display increased neutralization potency. Ex. 1002 ¶178.

Patent Owner again misleadingly compares to Capon's ***CD4***:IgG fusions, which showed equivalent potency to the soluble receptor. Ex. 1006, 53; Ex. 1002

¶¶174-175. As with binding affinity, a POSA would not have expected the CD4 fusion protein to display increased neutralization potential, because the gp120 ligand is ***monovalent*** (i.e., it can bind only one CD4 receptor). Ex. 1002 ¶175. A POSA would not have drawn conclusions about the neutralization potential of ***TNFR***-fusion proteins—which were expected to bind ***multivalently*** with the trimeric TNF molecule—based on Capon's CD4 fusion proteins. *Id.*

Patent Owner relies on neutralization results for TNFR:hinge IgG fusions reported in the Lesslauer Declaration (Ex. 1020) and in a journal article by Mohler (Ex. 1040). *See* Ex. 1008, 55. The Lesslauer Declaration reports an improvement in cell growth inhibition by a TNFR:hinge IgG_3 fusion protein (~86% inhibition) over soluble TNFR (~68% inhibition), corresponding to approximately 26% improvement. Ex. 1020, 1, 10-11; Ex. 1002 ¶178. Dr. Lesslauer asserts that the claimed fusion proteins thus display "a surprisingly superior neutralization of the TNF activity." Ex. 1020, 11. Lesslauer's improvement, however, is ***weaker than*** that seen in the prior art for Watson's fusion protein (Ex. 1003, Fig 3). Ex. 1002 ¶178. Watson reported an improvement in inhibition of lymphocyte attachment by the mHR-IgG chimera (~75% inhibition) over the corresponding soluble receptor (~50% inhibition), corresponding to approximately 50% improvement. *Id.*; Ex. 1003, 2225 (Fig. 3).

Measuring neutralization potency a different way (by the dose required to

prevent TNF-induced cytolysis), Mohler reported that a TNFR:hinge IgG1 fusion protein was "1000-fold more efficient" than soluble TNFR. Ex. 1040, 1550-51. This level of improvement is within the ***expected*** range of increased binding affinity and neutralization potency due to the multivalent nature of both the claimed TNFR fusion and the TNF ligand. Ex. 1002 ¶179; Ex. 1003, 2225; Ex. 1041, 672 (reporting that "bivalent antibodies neutralized ***1000 to 2000 times better*** than monovalent antibodies"). Moreover, the increased neutralization potency touted by Patent Owner does not support nonobviousness because unexpected results must be "different in kind and not merely in degree from the results of the prior art." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (quotation omitted).

3. Differences Between the Claimed Fusion Proteins and Antibodies Were Expected, and Patent Owner Has Not Demonstrated Any Surprisingly Superior Results

Patent Owner argues that etanercept (a TNFR:hinge IgG1 fusion protein) unexpectedly displays decreased antibody effector functions (CDC and ADCC) and aggregation. *See* Ex. 1008, 53-54. These claims are unsupported for several reasons. *First*, prior art receptor:IgG fusion proteins did not induce CDC, so the claimed fusions were not expected to induce CDC. *Second*, Patent Owner's data allegedly showing etanercept does not induce ADCC are unreliable, and contradicted by a peer reviewed publication. *Third*, Patent Owner has not shown

that TNFR:IgG fusion proteins were expected to form large aggregates with TNF. *Fourth*, Patent Owner has not compared the closest prior art. Moreover, the alleged differences between the claimed fusion proteins and antibodies are of no practical significance, as evidenced by the fact that two anti-TNF antibodies (infliximab and adalimumab) are FDA approved for the same indications as etanercept.

a. **Lack of CDC Was Expected**

Several prior art studies showed that fusion proteins did *not* display a CDC response. Ex. 1002 ¶¶185, 188, 190. Zettlmeissl expressly reported *no CDC response* for its CD4:hinge IgG1 fusion protein in the standard short-term assay. Ex. 1005, 350; Ex. 1002 ¶¶193-195. As Patent Owner admits, Capon reported its CD4:human-IgG fusion proteins did *not* bind C1q, which is the necessary first step in the protein binding cascade that initiates CDC. Ex. 1006, 50-51, nn.105-106; Ex. 1002 ¶¶68, 185, 190.

None of the prior art Patent Owner cites shows that a receptor:IgG fusion protein actually triggered a CDC response. Ex. 1002 ¶¶71, 73, 188-191; Ex. 1008, 54; Ex. 1006, 50-51. Patent Owner relies on Traunecker's report that its fusion protein (CD4 fused to the hinge region of a *mouse* IgG) retained the ability to bind C1q. Ex. 1008, 54. However, POSAs knew that binding of C1q to the Fc portion of an immunoglobulin is only the *first step* in the carefully-controlled CDC

pathway, and that additional events must occur to initiate CDC. Ex. 1002 ¶¶186-187, 191-192; Ex. 1045, 148-151. A POSA therefore would not expect a CDC response based solely on whether the fusion protein can bind C1q. Ex. 1002 ¶192.

Given the express evidence in the prior art that human hinge-IgG fusion proteins neither bind C1q nor mediate a CDC response, a POSA would have found it entirely unsurprising that etanercept does not initiate a CDC response. Ex. 1002 ¶¶185, 189, 194.

Additionally, Capon notes that the CD4:IgG fusion proteins' inability to mediate complement fixation may be explained by issues relating to segmental flexibility. Ex. 1032, 529. Segmental flexibility (e.g., movement of the Fab arms) was recognized to be important for antibody effector functions. Ex. 1002 ¶¶182-185, 207; Ex. 1043. The CH1 region—deleted in the claimed fusion proteins—was known to play an important role in determining antibody flexibility. Ex. 1002 ¶¶182-183, 207; Ex. 1042, 2509. For this reason as well, a POSA would not have found it surprising that the claimed fusion proteins had a reduced ability to exert effector functions such as CDC and ADCC. Ex. 1002 ¶¶182, 185.

b. **Patent Owner's Evidence Regarding ADCC Is Unreliable**

Patent Owner also falls far short of demonstrating unexpected results with respect to ADCC. Patent Owner has relied on the Arora Declaration as allegedly demonstrating that etanercept shows a surprisingly low ADCC response relative to

infliximab and adalimumab—two monoclonal antibodies that, like etanercept, are FDA-approved treatments for rheumatoid arthritis. Ex. 1002 ¶¶181, 201; Ex. 1024; Ex. 1048, 1248. Patent Owner has also cited Amgen poster presentations (not peer-reviewed articles) reporting similar results. Ex. 1006, 49-50; Ex. 1046; Ex. 1047.

ADCC assays are complicated and highly variable experiments that must be conducted carefully. Ex. 1002 ¶200. Despite this variability, the relative percent ADCC observed from one antagonist to the next should be consistent across experiments. *Id.* ADCC assays should also show a dose-dependent response. Ex. 1002 ¶203. The Arora Declaration, however, fails to show a dose-dependent response, and the data vary wildly from one experiment to the next. *Id.* Aurora's data also inexplicably fail to show an ADCC response for adalimumab in donor 2, even though adalimumab is accepted as being able to mediate ADCC. *Id.* ¶204. A POSA would have found the data in the Arora Declaration unreliable, and would not have accepted the results as support for the proposition that etanercept causes little or no ADCC. Ex. 1002 ¶¶201-205.

In addition, third party publications in peer-reviewed journals have reached differing conclusions over etanercept's ability to mediate ADCC. Ex. 1002 ¶205. An article by Mitoma, et al. tested the same three drugs as Arora (etancercept, adalimumab, and infliximab) and concluded that "ADCC activities were almost

equal among these 3 agents." Ex. 1048, 1248. The lack of scientific consensus and the poor data quality in Patent Owner's declaration cannot support a claim of unexpectedly superior results to overcome the overwhelming evidence of obviousness in this case.

Moreover, even if etanercept did cause a reduced ADCC response compared to anti-TNF antibodies (which has not been established), Patent Owner has not demonstrated that the level is unexpected. Patent Owner has relied on Byrn's report that its CD4:IgG fusion protein mediated ADCC towards HIV-infected cells. Ex. 1008, 54; Ex. 1033, 668-69. Byrn does not, however, compare the level of ADCC response to that obtained with an anti-gp120 antibody control. Ex. 1002 ¶199. Moreover, a POSA would not anticipate a certain level of ADCC response from a TNFR fusion protein based on results obtained in an assay employing an entirely different cell line, antigen, and fusion protein. *Id.* Accordingly, a POSA could not have expected based on Byrn that the ADCC response from a fusion protein would be as robust as for monoclonal antibodies. *Id.*

Patent Owner also points to articles showing that some prior art fusion proteins bind FcγR. Ex. 1002 ¶198; Ex. 1006, 50-51 (citing Ex. 1035); Ex. 1032. However, just as binding of C1q is only the first step in triggering CDC, binding of FcγR alone does not trigger ADCC—multiple molecules also must bind and cross-link together. Ex. 1002 ¶¶197-198. Accordingly, data showing FcγR binding

would not alone lead a POSA to expect a robust ADCC response. Ex. 1002 ¶198.

c. **Lack of Aggregation Was Not Unexpected**

Patent Owner asserts that it was unexpected that the claimed fusion protein does not aggregate in the presence of TNF, while infliximab and adalimumab do. Ex. 1006, 51-53. Patent Owner has not identified any teaching in the prior art showing that similar fusion proteins aggregated. *See id.*

Patent Owner makes the unsupported assertion that a POSA would have expected each dimeric TNFR fusion protein to bind *two* trimeric TNF ligands. Ex. 1006, 53. There is no basis in the prior art for that assertion. Ex. 1002 ¶206. Because Patent Owner cannot show that the lack of aggregation would have been *unexpected*, this property is irrelevant. *See Pfizer*, 480 F.3d at 1371 ("[Patentee's] evidence must fail because the record is devoid of any evidence of what the skilled artisan would have expected."). Moreover, POSAs had good reason to expect that both receptors on the dimeric TNFR:IgG fusion protein would bind a single TNF ligand, because it was known that multiple TNF receptors on the cell surface bind to a single TNF molecule. Ex. 1002 ¶206; Ex. 1037.

d. **Patent Owner Has Not Compared the Closest Prior Art and Has Not Shown that Any Unexpected Results are Significant**

Patent Owner's evidence regarding CDC, ADCC, and aggregation compares etanercept to anti-TNF antibodies that were not reported in the prior art. Ex. 1002

¶181; Ex. 1024; Ex. 1046. Binding affinity and neutralization potential were compared to monomeric soluble TNFR. Ex. 1002 ¶¶165, 174. None of these comparators are the closest prior art. Smith's TNFR:IgG fusion proteins are the closest prior art because they include (1) the 75-kDa TNFR, (2) displayed bivalently, like the fusion proteins recited in the claims of the '522 patent. Ex. 1002 ¶181. Because evidence of unexpected results should establish "a difference between the results obtained and those of ***the closest prior art***," Patent Owner's evidence is legally insufficient. *Bristol-Myers*, 752 F.3d at 977.[8]

Finally, any reduction in effector functions or aggregation for etanercept compared to anti-TNF antibodies is not of practical significance and thus cannot support a finding of nonobviousness. *Id.* ("When assessing unexpected properties, … we must evaluate the significance and 'kind' of expected results along with the unexpected results."); *Wrigley*, 683 F.3d at 1363 (quoting *Ex parte NutraSweet Co.*, 19 U.S.P.Q.2d 1586, 1589 (BPAI 1991)) (holding unexpected results must be "of some significant, practical advantage"). Patent Owner's argument that POSAs would have avoided pairing the anti-inflammatory TNFR with a "pro-inflammatory" Fc portion of IgG are belied by the fact that Smith and Watson both

[8] In *Millennium*, the Patent Owner was not required to compare to a hypothetical compound that was not "specifically disclosed or actually identified" in any prior art reference. 2017 U.S. App. LEXIS 12702, at *23. Here, Smith specifically describes TNFR:IgG1 fusion proteins. Ex. 1004, 10:57-64.

taught anti-inflammatory IgG fusion proteins, as well as the fact that POSAs recognized the therapeutic potential of anti-TNF antibodies. Ex. 1002 ¶¶132-134, 211.

Even if Patent Owner's ADCC data were credited (which it should not be), Patent Owner would have shown only that etanercept mediates reduced effector function and aggregation compared to two monoclonal antibodies that are *FDA-approved for the same indication* as etanercept: rheumatoid arthritis. Ex. 1048, 1248. Clearly, the ability of those antibodies to form aggregates and induce ADCC and CDC has not diminished their clinical utility as anti-inflammatories. As to safety, etanercept carries the same FDA warnings regarding risks of tuberculosis and other infections as the anti-TNF antibodies. *See* Ex. 1049, 1. Patent Owner has not shown that any alleged reduced effector function or aggregation by the claimed fusion proteins solves any problem or need in the art. Ex. 1002 ¶¶208-211. For that reason as well, these purported unexpected results are unpersuasive of nonobviousness.

X. CONCLUSION

For all the reasons above, Petitioner respectfully requests that the Board institute IPR of claims 1-10 of the '522 patent on the grounds set forth in this Petition.

Respectfully submitted,

Date: August 4, 2017 By: */s/ Joseph A. Hynds*

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4) and 42.105(a), the undersigned certifies that on August 4, 2017, a complete and entire copy of the foregoing Coherus BioSciences, Inc.'s **Petition to Institute an *Inter Partes* Review of U.S. Patent No. 8,163,522 under 37 C.F.R. § 42.100 *et seq.***, along with **Exhibits 1001-1058** and **Petitioner's Power of Attorney**, were served, via Federal Express overnight courier, on the following counsel of record for Patent Owner:

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CERTIFICATE OF COMPLIANCE

In accordance with 37 C.F.R. 42.24, as amended, the undersigned certifies that this Petition complies with the applicable type-volume limitations of 37 C.F.R. 42.24(a)(1)(i). Exclusive of the portions exempted by 37 C.F.R. 42.24(a)(1), this Petition contains 13,921 words as counted by the word processing program used for its preparation (Microsoft Word 2007) , with the addition of all words in figures as counted manually.

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