

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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COHERUS BIOSCIENCES, INC.,  
Petitioner,

v.

HOFFMANN-LA ROCHE INC.,  
Patent Owner

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Case IPR2017-01916  
Patent No. 8,163,522

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**PATENT OWNER'S PRELIMINARY RESPONSE**

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2096	Niles, “Brand of the year Enbrel (sales report of Enbrel),” <u>Highbeam Business</u> (June 1, 2006), <a href="https://business.highbeam.com/437048/article-1G1-148004990/brand-year-enbrel">https://business.highbeam.com/437048/article-1G1-148004990/brand-year-enbrel</a>
2097	“Prescription information,” <u>IQVIA</u> , <a href="https://www.iqvia.com/locations/united-states/commercial-operations/essential-information/prescription-information">https://www.iqvia.com/locations/united-states/commercial-operations/essential-information/prescription-information</a> (last visited Dec. 13, 2017) - PROTECTIVE ORDER MATERIAL
2098	[Reserved]
2099	Desai et al., “Temporal trends in use of biologic DMARDs for rheumatoid arthritis in the United States: A cohort study of publicly and privately insured patients,” <u>J. Managed Care &amp; Specialty Pharmacy</u> 23(8):809–814 (2017)
2100	Ward, “Medicare reimbursement and the use of biologic agents: Incentives, access, the public good, and optimal care,” <u>Arthritis Care Res (Hoboken)</u> 62(3):293–295 (2011)

2101	Zhang et al., "Trends in the use of biologic agents among rheumatoid arthritis patients enrolled in the US Medicare program," <u>Arthritis Care &amp; Research</u> 65(11):1743–1751 (2013)
2102	Promotional Pamphlet, Immunex Corp. & Wyeth-Ayerst Labs, "Introducing the first TNF-receptor: Enbrel™," (Nov. 1998)
2103	"Enbrel TV Ad 2004," <u>YouTube</u> (November 1, 2010), <a href="https://www.youtube.com/watch?v=kYR6U_qIiJw">https://www.youtube.com/watch?v=kYR6U_qIiJw</a>
2104	[Reserved]
2105	[Reserved]
2106	[Reserved]
2107	CD4 IgG Drug Profile, <u>AdisInsight</u> <a href="http://adisinsight.springer.com/drugs/800001201">http://adisinsight.springer.com/drugs/800001201</a> (last visited Dec. 13, 2017) ("CD4-IgG Drug Profile")
2108	FDA Briefing Document – Arthritis Advisory Committee Meeting (Ex. 2108) (July 13, 2016), <a href="https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM510493.pdf">https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM510493.pdf</a> ("AAC Briefing Document")
2109	U.S. Patent App. No. 08/444,790, Response to Non-Final Rejection (Mar. 29, 2011) ("3/29/2011 Response")
2110	U.S. Patent App. No. 08/444,791, Response to Non-Final Rejection (Mar. 15, 2011) ("3/15/2011 Response")
2111	Declaration of Andrew W. Carter ("Carter-Decl.") – REDACTED PUBLIC VERSION
2112	"Prescription information," <u>IQVIA</u> , <a href="https://www.iqvia.com/locations/united-states/commercial-operations/essential-information/prescription-information">https://www.iqvia.com/locations/united-states/commercial-operations/essential-information/prescription-information</a> (last visited Dec. 13, 2017) – REDACTED PUBLIC VERSION

## I. INTRODUCTION

Despite proffering obviousness theories substantively indistinguishable from those the Board twice has found unpersuasive, Petitioner asks the Board for the third time to find the claimed invention of U.S. Patent No. 8,163,522 (“the ’522 patent”) obvious over prior art describing non-TNFR fusion proteins having no functional relevance to TNF or treating inflammatory diseases. The Board need not revisit these obviousness theories again.

The ’522 patent claims polynucleotides and methods of using them to make a fusion protein from parts of two unrelated proteins – the extracellular portion of the p75 tumor necrosis factor receptor (“p75 TNFR”) and a strictly defined portion of a human IgG immunoglobulin heavy chain (*i.e.*, “all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain...”). The commercial embodiment of the resultant “p75 TNFR fusion protein” is etanercept, a novel protein having unexpected properties that have made it a potent and effective anti-inflammatory.

Etanercept is ground-breaking. As the active ingredient of Enbrel®, the first FDA-approved human therapeutic fusion protein, it has improved the lives of countless patients afflicted with debilitating inflammatory diseases such as rheumatoid arthritis (RA). Etanercept also was the first therapeutic to do more than merely treat the symptoms of RA – by capturing tumor necrosis factor

("TNF") (an inflammation-causing cytokine), it can slow and sometimes even stop the severe joint damage that are RA's hallmark. Etanercept is also unquestionably successful – immediately after it was launched, Enbrel® became physician's leading choice for treating RA patients, and it continues to be widely prescribed for this disease despite the subsequent launch of other biological products targeting TNF.

Etanercept's success is attributable to several of its unexpected properties tied to its unique structure. Etanercept binds TNF with much greater affinity and neutralizes TNF activity 1000-fold more effectively than p75 TNFR – properties that make it uniquely well-suited for treating diseases caused by uncontrolled inflammation. Etanercept also does not aggregate when it binds TNF ligands in solution, an unexpected result given that other bivalent proteins like anti-TNF antibodies do. And despite incorporating a portion of the IgG1 constant region, it does not cause meaningful antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) – a surprising result given that IgG1 antibodies are the most potent inducers of those activities. Adalimumab (Humira®) and infliximab (Remicade®) – which are high affinity IgG1 antibodies – cause such effects.

Given etanercept's therapeutic benefits and overwhelming clinical success, many companies, including Petitioner, are pursuing commercial strategies based on

copying it. And while Petitioner considers challenging patents covering etanercept and its production to be an integral part of Petitioner's commercial strategy,<sup>1</sup> that alone cannot justify institution of *inter partes* review of the '522 patent. Rather, Petitioner's must demonstrate "that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."<sup>2</sup> This Petition falls far short of that standard.

## II. SUMMARY OF RESPONSE

The Petition presents a textbook example of a petition that should be denied under either or both of 35 U.S.C. §§ 325(d) and 314(a). It not only advances obviousness theories substantively indistinguishable from those the Board has now twice rejected, but frames its arguments largely as a reply to the Board's past findings. Both of Petitioner's grounds rely on prior art teachings exhaustively considered during original examination and again during another request for *inter partes* review: the Smith patent (Ex. 1005) was central to both, and the fusion

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<sup>1</sup> Ex. 2029 (Coherus Press Release) at 2 ("[C]hallenging these patents in IPR aligns with our decision to refocus the priorities of our etanercept biosimilar program, CHS-0214, on the potential U.S. opportunity...."). All citations refer to the Exhibits' native page numbers.

<sup>2</sup> 35 U.S.C. § 314(a).

proteins disclosed in Petitioner's supposedly new references – Zettlmeissl (Ex. 1005) and Watson (Ex. 1003) – are the same fusion proteins described in the prior art the Board previously considered. Even Petitioner's supposed motivations are the same: a supposed desire for “practical yields,” half-life improvements, enhanced binding, and ease of purification. Permitting serial challenges under immaterially different obviousness theories based on the same or substantially the same teachings in the prior art is flatly contrary to the policies underlying §§ 325(d) and 314(a), and warrants non-institution.

During original examination, the Examiner rejected the recited fusion proteins as obvious over prior art showing “hybrid” proteins combining unrelated receptors with portions of immunoglobulin chains. The Board reversed those rejections, based on, *inter alia*, evidence of objective indicia of non-obviousness, including some of etanercept's unexpected properties.<sup>3</sup>

In 2015, the Board declined to institute *inter partes* review of the '522 patent based on a third party petition (“CFAD-IPR”) advancing an obviousness rationale substantively indistinguishable from those addressed during examination and presented again here, explaining:

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<sup>3</sup> See Ex. 1021 (11/22/2010 Decision) at 7 (“Appellants' evidence of unexpected results is convincing to rebut the Examiner's obviousness rejection.”).

[T]he generalized guidance in *Seed* and *Capon* [teaching non-TNFR “hybrid” proteins] would not have led one of ordinary skill in the art to produce a p75 TNFR-based fusion protein having a structure that corresponds to the expression products of the challenged claims or the protein encoded by the polynucleotides described in the challenged claims.<sup>4</sup>

Importantly, the Board rejected the proposition – which this Petitioner now repeats – that a need to achieve “practical yields” of a TNFR-based fusion protein would have led an Ordinary Artisan to “select the hinge- $C_{H2}$ - $C_{H3}$  constant region of the immunoglobulin.”<sup>5</sup>

The Board also found etanercept's unexpected properties to support non-obviousness. It specifically rejected CFAD's assertion this evidence had no nexus to the claims, finding “[t]he evidence of unexpected results is commensurate in scope with the claims.” It also faulted CFAD for not addressing this evidence (which the Board considered during original examination), observing “[t]he Petition, moreover, should have addressed the evidence of unexpected results as part of Petitioner's showing of a reasonable likelihood of success.”<sup>6</sup>

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<sup>4</sup> See Ex. 1010 (CFAD-Dec.) at 15.

<sup>5</sup> *Id.* at 16.

<sup>6</sup> *Id.* at 18.

Neither of the two grounds advanced in this Petition can be meaningfully differentiated from those the Board has repeatedly rejected. Each employs hindsight, using the claims as a roadmap for finding their constituent elements in the prior art. Each rests on an inaccurate portrayal of both the prior art's teachings and the Ordinary Artisan's beliefs in August 1990. And, as in the CFAD-IPR, each ignores compelling objective indicia of non-obviousness.

Petitioner's first ground ("Ground One") portrays the p75 TNFR fusion protein of the claims as an obvious variant of Watson's fusion protein. That fusion is made from part of the murine peripheral lymph node homing receptor ("pln-HR"), an "adhesion molecule" that facilitates the physical migration of lymphocytes through lymph nodes, and was used "as a histochemical reagent for the staining of pln HEV" and "analyzing the distribution of HR ligand(s) in normal as well as in inflammatory states."<sup>7</sup>

Aside from not providing any insights relevant to therapeutically targeting a soluble cytokine like TNF, Watson's pln-HR fusion protein does not use "the identical portion of the IgG heavy chain as claimed in the '522 patent" as Petitioner claims.<sup>8</sup> It uses a truncated IgG1 hinge in combination with the C<sub>H</sub>2 and

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<sup>7</sup> Ex. 1003 (Watson) at 2221.

<sup>8</sup> Pet. at 5 (original emphasis).

C<sub>H</sub>3 domains, while the claims require use of the complete hinge with those domains (*i.e.*, “all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region”). Consequently, following Petitioner’s “straightforward application of Watson’s method to the 75-kDa TNFR” does not yield the fusion proteins of the claims, a deficiency Petitioner neither acknowledges nor resolves.<sup>9</sup>

Petitioner’s second ground (“Ground Two”) is likewise hindsight-based and incorrectly portrays its cited references’ teachings. Notably, this ground is anchored in the Smith patent,<sup>10</sup> which the Board has twice found insufficient to render the recited fusion proteins obvious.

Smith described, *inter alia*, a p75 TNFR-based “chimeric” antibody that retains the starting immunoglobulin’s tetrameric structure, replacing only the variable regions in one or both of the heavy and light chains with “TNF-R” but otherwise retaining “unmodified constant region domains.”<sup>11</sup> As Petitioner admits,

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<sup>9</sup> *Id.* at 31.

<sup>10</sup> Ex. 1004 (Smith).

<sup>11</sup> Smith at 10:53–57.

the claims at issue here expressly exclude the C<sub>H</sub>1 domain and the light chain constant domain.<sup>12</sup>

To escape Smith's literal teachings, Petitioner simply invents a problem – supposedly suboptimal expression – and asserts that this would have led an Ordinary Artisan to a “well-known, optimized method of preparing fusion proteins” allegedly disclosed in Watson and another reference, Zettlmeissl (Ex. 1005).<sup>13</sup>

But that supposed motivation, conspicuously unsupported by expert testimony, is the same purported “practical yields” motivation the Board found unpersuasive in the CFAD-IPR:

Such motivation [‘for practical yields’] does not provide a reason for one of skill in the art to select the hinge-C<sub>H</sub>2-C<sub>H</sub>3 constant region of the immunoglobulin from the teachings of Seed or Capon to combine with Smith's TNF-R gene.<sup>14</sup>

Worse, Petitioner's arguments rest on inaccurate depictions of the secondary references. As it did with Watson's fusion protein, Petitioner incorrectly portrays

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<sup>12</sup> Pet. at 1.

<sup>13</sup> Pet. at 27.

<sup>14</sup> Ex. 1010 at 16.

Zettlmeissl's fusion proteins as consisting of a "receptor [that] is attached directly to the hinge-CH2-CH3 region of an IgG antibody's heavy chain."<sup>15</sup> But Zettlmeissl's proteins actually have a third component, a synthetic "5-amino-acid linker sequence," interposed between each protein's CD4 and IgG1 portions, a distinction Petitioner largely ignores.<sup>16</sup> Petitioner also incorrectly claims these proteins do not exhibit CDC, ignoring contrary indications in Zettlmeissl and a contemporaneous paper from the same researchers showing they "unequivocally" do.<sup>17</sup>

Petitioner's hindsight-driven obviousness theories, coupled with its inaccurate portrayal of the prior art, fall far short of the standards required for institution.

Independently, the Board should deny the Petition because substantial evidence of objective indicia supports the non-obviousness of the claims.

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<sup>15</sup> *E.g.*, Pet. at 4 (emphasis added); *id.* at 10 (claiming Zettlmeissl "discloses fusion proteins in which the CD4 receptor is fused to the hinge region of an IgG antibody.")

<sup>16</sup> Zettlmeissl at 348.

<sup>17</sup> Ex. 2020 (Gregersen) at 41.

Importantly, Petitioner nowhere disputes the Board's past findings of a nexus between etanercept and the claims – that its unexpected properties are “commensurate in scope with the claims.”<sup>18</sup> But inexplicably, Petitioner ignores evidence of several objective indicia associated with etanercept of which it is certainly aware, including: (i) substantial commercial success, (ii) addressing a long-felt need for an effective RA treatment, and (iii) copying by Petitioner and others. Petitioner's sole challenge is to the unexpected results of etanercept. But that – like much of the petition – rests on an incorrect description of both the science and the Ordinary Artisan's knowledge and expectations in August 1990.

Petitioner has plainly failed to meet its burden, and the Board should decline to institute *inter partes* review.

### **III. THE '522 PATENT**

Petitioner filed two petitions – one against the '522 method patent and the other against its sister '182 composition patent. The two petitions advance nearly identical obviousness grounds, relying on the same references and arguments and

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<sup>18</sup> Ex. 1010 at 18; *see also* Ex. 1021 at 7.

using almost the same language. Petitioner also treats each patent's prosecution histories as establishing a common prosecution history applicable to both patents.<sup>19</sup>

#### **A. The Patent Disclosure**

The '522 patent describes fusion proteins made from DNA sequences derived from two different proteins. The first encodes the extracellular region of either the p55 or the p75 tumor necrosis factor receptor ("p55 TNFR" and "p75 TNFR").<sup>20</sup> The second encodes a human immunoglobulin heavy chain lacking the C<sub>H</sub>1 domain. As the '522 patent explains:

The invention is also concerned with DNA sequences which comprise a combination of two partial DNA sequences, with one of the partial sequences coding for those soluble fragments of non-soluble proteins which bind TNF (see above) and the other partial sequence coding for all domains other than the first domain of the constant region of the heavy chain of human immunoglobulins such as IgG, IgA, IgM or IgE, in particular IgG<sub>1</sub> or IgG<sub>3</sub> subtypes.<sup>21</sup>

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<sup>19</sup> See Pet. at 16 ("Prosecution of the '522 Patent Tracked that of the '182 Patent").

<sup>20</sup> '522 patent, 2:52–56, 2:65–3:5, Figs. 1A–1D, Figs. 4A–4D, Fig. 5. See also *id.* at 5:46–6:8 (indicating sequence deposited with ATCC).

<sup>21</sup> '522 patent at 6:9–16.

The specification portrays the invention as “TNF binding proteins” (“TNF-BP”) including “proteins which consist of a soluble fragment of non-soluble TNF-BP and an immunoglobulin fragment, i.e., all domains except the first of the constant region of the heavy chain.”<sup>22</sup> It explains these fusion proteins can be made using, among other things, vectors “pDC4-Hγ1 [sic] (DSM 5314)” and “pCD4-Hγ3 (DSM 5523).”<sup>23</sup> Example 11 illustrates production of one such TNF-BP example using the p55 TNFR, in which the TNFR's extracellular region was attached directly to the hinge-C<sub>H2</sub>-C<sub>H3</sub> sequence of an IgG3 heavy chain.<sup>24</sup> The specification also describes pharmaceutical preparations and uses for these TNF-BP's.<sup>25</sup>

## **B. Claim Construction**

Independent claims 1 and 7 define methods for producing a p75 TNFR-based fusion protein by culturing a host cell containing a polynucleotide encoding the protein and purifying its expression product. Independent claim 4 defines a polynucleotide encoding a p75 TNFR-based fusion protein. Claim 1 is illustrative.

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<sup>22</sup> *Id.* at 9:14–18.

<sup>23</sup> *Id.* at 9:14–32.

<sup>24</sup> *Id.* at 20:64–21:33; Ex. 2002 (Croft-Decl.) ¶¶46–47, 59.

<sup>25</sup> *Id.* at 6:48–57.

In the CFAD-IPR, the Board interpreted the terms “TNF receptor,” “all of the domains of the constant region of a human [IgG/ IgG1] immunoglobulin heavy chain other than the first domain of said constant region” and “about.”<sup>26</sup> Petitioner and its expert have accepted those constructions without comment.<sup>27</sup>

Patent Owner agrees with the Board's prior constructions, but believes a brief explanation is warranted due to significant errors in the Petition and Dr. Burton's declaration about the IgG element of the claims – both incorrectly claim that: (i) the IgG components of the fusion proteins in Watson and Zettlmeissl are “identical” to the claimed fusion proteins<sup>28</sup> (and thus necessarily to each other) and

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<sup>26</sup> *Id.* at 4–7.

<sup>27</sup> Pet. at 20–21; Ex. 1002 (Burton-Decl.) ¶¶33–34.

<sup>28</sup> *See, e.g.*, Pet. at 5 (“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.”); *id.* at 18 (“...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.”); *id.* at 30 (“Watson's fusion protein is identical to the fusion protein of the '522 patent claims, except that the receptor

(ii) that Zettlmeissl “discloses fusion proteins in which the CD4 receptor is fused to the hinge region of an IgG antibody.”<sup>29</sup>

Both assertions are demonstrably false – the Watson fusion protein uses a truncated human IgG1 heavy chain hinge- $C_{H2}$ - $C_{H3}$  sequence that omits the first five residues of the exon-encoded hinge domain, while the Zettlmeissl fusion proteins interpose an artificial linker sequence between the IgG1 and CD4 receptor sequences. A simple alignment of the relevant portions of the Watson and Zettlmeissl proteins reveals both errors:<sup>30</sup>

IgG1	[ IgG1-CH1 ]	EPKSCDKTHTCPPCP	APELLGGPSVFLF...
	CH1	HINGE	CH2
Watson	[mHRLEC]	-----DKTHTCPPCP	APELLGGPSVFLF...
	pln-HR	HINGE	CH2
Zettlmeissl	[CD4] -HADPE	EPKSCDKTHTCPPCP	APELLGGPSVFLF...
	CD4+Linker	HINGE	CH2

protein is different.”). *See also* Burton-Decl. ¶104 (“A POSA would have understood that Zettlmeissl and Watson each disclose [“the hinge- $C_{H2}$ - $C_{H3}$  region of a human IgG”] limitation.”); *id.* ¶139 (“Watson’s fusion protein is identical to the fusion protein of the ’522 patent claims, except that Watson’s receptor is the extracellular domain of pln HR....”).

<sup>29</sup> Pet. at 10.

<sup>30</sup> Croft-Decl. ¶¶119–121, 150–161; Ex. 1050 at Fig. 4; Zettlmeissl at Fig. 1.

Petitioner glosses over these errors. But a precise identification of the differences between the prior art fusion proteins relative to the claims is factual prerequisite of an obviousness assessment.

The Board should maintain its prior construction – that the IgG/IgG1 element of the claims requires use of the “-hinge-C<sub>H2</sub>-C<sub>H3</sub>’ region of a human IgG/IgG1 immunoglobulin heavy chain.” Under the plain and ordinary meaning of the claim language, and consistent with the specification and prosecution history, that means the claims require use of the entire hinge-C<sub>H2</sub>-C<sub>H3</sub> region of the IgG/IgG1 heavy chain, not a truncated portion of that region.

First, the claims expressly require use of all of a human IgG or IgG1 heavy chain constant region except for the first domain. Thus, by their terms, the claims require use of the entire amino acid sequence of the specified heavy chain except for the sequence within the first (*i.e.*, C<sub>H1</sub>) domain.

The plain and ordinary meaning of “C<sub>H1</sub> domain” is the amino acid sequence encoded by the “C<sub>H1</sub> domain” exon in the four IgG sub-type genes. As Dr. Elvin Kabat explained in his seminal work on immunoglobulin sequences:

The C<sub>H</sub> and hinge domains conform to the findings of Sakano et al. (172), who defined each domain precisely by sequencing the coding and intervening nucleotide sequences bordering each domain.

The extensive nucleotide sequence data on exons for the constant regions of heavy chains have provided exact boundaries for C<sub>H1</sub>, hinge, C<sub>H2</sub>, C<sub>H3</sub>, and C<sub>H4</sub>.<sup>31</sup>

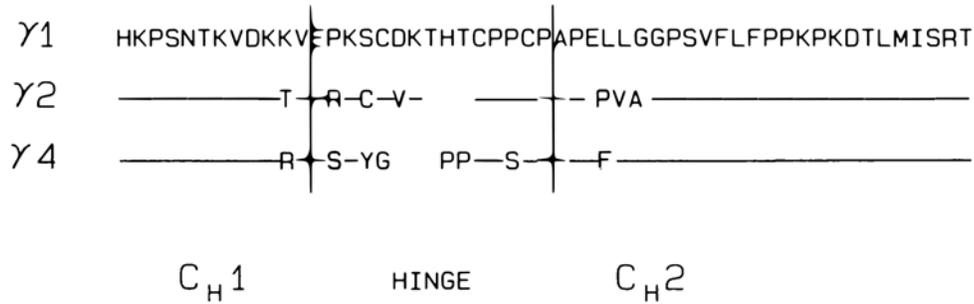
Ellison (Ex. 1050) likewise describes the amino sequence of the C<sub>H1</sub> domain (and of the other domains) of human IgG heavy chains as being those encoded by the C<sub>H1</sub>, hinge, C<sub>H2</sub> and C<sub>H3</sub> exons.<sup>32</sup>

Ellison also compared the boundaries of the C<sub>H1</sub>-hinge-C<sub>H2</sub> domains of three IgG isotype heavy chains as defined by their exons in its Figure 4 (below), illustrating that each begins with a glutamic acid (E) and ends with a proline (P):

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<sup>31</sup> Ex. 2012 (Kabat) at xix. *See also* Ex. 2014 (“Sakano”) at Fig. 4.

<sup>32</sup> Ellison at 4072 (CH1, hinge, CH2 and CH3 sequences in IgG1 polypeptide “are encoded in individual exons that are separated from one another by introns, the largest one lying between the CH1 and hinge exons.”); Croft-Decl. ¶¶62–64. Dr. Burton cites Ellison as proof that the DNA sequences encoding the various IgG heavy chains were “well known.” Burton-Decl. at ¶107 n.4.

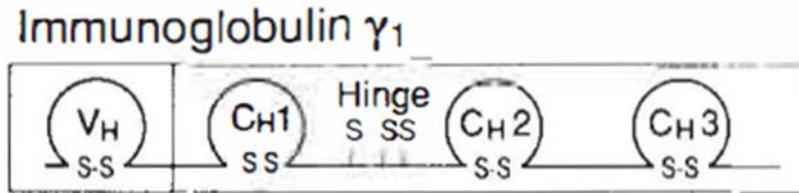


**Figure 4.** Comparison of amino acid residues in the hinge area of three  $C_{\gamma}$  polypeptides. Vertical lines separate the hinge residues from those contiguous amino acids which are encoded in the  $C_{H1}$  and  $C_{H2}$  exons. Amino acids are listed in the one-letter code. Solid lines represent identity of the  $\gamma_2$  and  $\gamma_4$  sequences to the  $\gamma_1$  sequence. The  $C_{H2}$  domain of the  $C_{\gamma_2}$  sequence contains one less amino acid than is found in the other genes.

Notably, Ellison shows the IgG1 hinge containing three cysteine residues. Capon (Ex. 1032) (“Capon”) (which Petitioner and its expert both cite<sup>33</sup>) likewise indicates the “hinge region of each [IgG1-based] immunoadhesin contains three cysteine residues, one normally involved in disulphide bonding to light chain, the other two in the intermolecular disulfide bonds between the two heavy chains in IgG.”<sup>34</sup> Capon also depicts the IgG1 heavy chain having three disulfide bonding sites in the hinge domain downstream from the  $C_{H1}$  domain:

<sup>33</sup> *E.g.*, Pet. at 34; Burton-Decl. ¶¶63–68.

<sup>34</sup> Ex. 1032 (Capon-1989) at 526.



The specification and prosecution history are consistent with this understanding of what the hinge-CH<sub>2</sub>-CH<sub>3</sub> of IgG and IgG1 heavy chains constitutes. For example, the specification describes examples of “especially suitable” vectors for expressing TNFR fusion proteins that contain sequences encoding the complete, exon-encoded hinge-CH<sub>2</sub>-CH<sub>3</sub> sequence of an IgG1 or IgG3 heavy chain (*i.e.*, sequences omitting only the amino acids in the exon-defined C<sub>H1</sub> domain).<sup>35</sup>

Likewise, during prosecution, Patent Owner distinguished the claims from other fusion proteins having “only a portion of a hinge domain,” stating “[b]oth are

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<sup>35</sup> *E.g.*, '522 patent at 9:14–32 (describing pCD4-H $\gamma$ 1 and pCD4-H $\gamma$ 3 vectors for use in “expression of proteins which consist of a soluble fragment of non-soluble TNF-BP and an immunoglobulin fragment, *i.e.*, all domains except the first of the constant region of the heavy chain” and citing to EP Appl. No. 90107393.2, which confirms that these vectors were made with “exons” encoding the full hinge, C<sub>H2</sub>, and C<sub>H3</sub> domains); Ex. 1011 ('393 Application); Croft-Decl. ¶¶40–45, 59.

missing the first several amino acids of this domain..."<sup>36</sup> Patent Owner also noted during the CFAD-IPR that the claims "were drafted to exclude other p75 TNFR/IgG fusion proteins (such as Delta 57 and Protein 3.5D) that contained only a portion of the hinge domain and did not display the unexpected properties."<sup>37</sup>

Consequently, the Board's prior interpretation of the meaning of the IgG element of the claims as requiring use of the hinge-CH2-CH3 portion of the IgG or IgG1 heavy chain should be maintained.<sup>38</sup>

### **C. Etanercept Is a Commercial Embodiment of the Invention**

Etanercept, Enbrel®'s active ingredient, is a fusion protein made by culturing CHO cells transfected with DNA encoding a protein consisting of the extracellular region of p75 TNFR fused directly to the hinge-CH<sub>2</sub>-CH<sub>3</sub> sequence of

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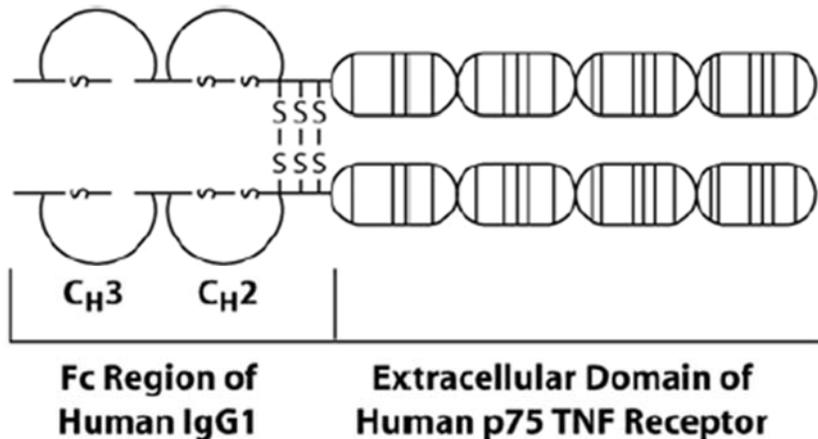
<sup>36</sup> Ex. 2110 (3/15/2011 Response) at 35.

<sup>37</sup> See Ex. 1008 (CFAD-POPR) at 40 (emphasis added); *id.* at 47 (Capon-964 preferred embodiments use "'the entire heavy chain constant region' (including CH1)" or "part but not all of the hinge domain").

<sup>38</sup> If the Board believes a clarification of its prior construction is warranted, it could add the words "complete, exon-encoded" before the phrase "-hinge-CH2-CH3" in its prior construction. Doing so would yield the meaning compelled by the claim language, the patent disclosure and the prosecution history.

a human IgG1 heavy chain and purifying the expression product.<sup>39</sup> Etanercept, as the claims specify, is a “protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to” a portion of the human IgG1 that “contains the C<sub>H</sub>2 domain, the C<sub>H</sub>3 domain and hinge region, but not the C<sub>H</sub>1 domain of IgG1.”<sup>40</sup>

Etanercept assembles as a homodimer, with the IgG hinge's three cysteine residues forming disulfide bonds with complementary cysteine residues in the hinge of its dimeric partner, yielding the structure depicted below:<sup>41</sup>



**Fig. 4.1. Chemical structure of etanercept. IgG1 immunoglobulin G1, TNF tumor necrosis factor**

<sup>39</sup> Ex. 2004 (Enbrel® Label) § 11.

<sup>40</sup> *Id.*

<sup>41</sup> Ex. 2007 (Molta) at 32, Fig. 4.1.

Etanercept thus embodies the '522 patent's claims,<sup>42</sup> which Petitioner nowhere disputes.

**IV. THE BOARD SHOULD EXERCISE ITS DISCRETION UNDER § 325(d) AND/OR § 314(a) AND NOT INSTITUTE TRIAL**

Under § 325(d), “[i]n determining whether to institute or order a proceeding,” including an IPR, the Board “may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” The Board has also relied on § 314(a) to decline to institute trial when a petition advances substantially the same challenge that had been earlier considered by the Board or the Office.<sup>43</sup> And the Board has found that § 314(a) applies to cases “in which a different petitioner filed

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<sup>42</sup> Croft-Decl. ¶¶48–53.

<sup>43</sup> *See, e.g., Gen. Plastic Indus. Co., Ltd., v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, at 16–17 (PTAB, Sept. 6, 2017) (declining to institute because petition fosters “abuse of the review process by repeated attacks on patents.”)

a petition challenging a patent that had been challenged already by previous petitions.”<sup>44</sup>

Under either standard, the Board should exercise its discretion and decline to institute trial. The Board has not only considered the substantive teachings of the prior art in both of Petitioner's grounds, but also the specific obviousness rationales Petitioner advances based on them.

**A. The Board Has Twice Found the Fusion Protein of the Claims Non-Obvious Over Unrelated Fusion Proteins**

**1. Examination of the '182 and '522 Patents**

During examination of U.S. Appl. No. 08/444,790 (“the '790 application”) (the '182 patent), the Examiner imposed written description and obviousness rejections, and for the latter, cited Dembic (Ex. 1018) as teaching the “full-length amino acid sequence of” p75 TNFR and U.S. Patent No. 5,116,964 (“Capon-964”) (Ex. 1019) as teaching attachment of a “truncated murine lymphocyte homing receptor (MHLR) to the Fc region of human IgG1.”<sup>45</sup>

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<sup>44</sup> *Netapp, Inc. v. Realtime Data, LLC*, IPR2017-01354, Paper 16, at 8–9 (PTAB Nov. 14, 2017).

<sup>45</sup> Ex. 2031 (2/23/2007 Final Rejection) at 14.

Patent Owner appealed, explaining an Ordinary Artisan “would have been discouraged from fusing an anti-inflammatory agent, such as soluble fragments of p75 TNFR, to the pro-inflammatory constant region of an immunoglobulin heavy chain.”<sup>46</sup> Patent Owner also cited evidence of unexpected results observed with etanercept, including “reduced pro-inflammatory effector functions,” “lack of aggregating ability,” “unexpected thousand-fold increased potency in TNF neutralization activity,” and “unexpectedly increased binding affinity and kinetic stability.”<sup>47</sup>

The Board reversed the Examiner's rejections. It found “the written description supports the pending claim scope.” It observed the Examiner did not dispute the unexpected results of etanercept, and found (as it did during original examination) that evidence “convincing to rebut the Examiner's obviousness rejection.”<sup>48</sup>

Despite the Board's decision, the Examiner again rejected the claims as obvious. He replaced Dembic with Smith, and used a continuation of Capon-964

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<sup>46</sup> Ex. 1006 (2/28/2008 Appeal Br.) at 42.

<sup>47</sup> *Id.* at 48–55.

<sup>48</sup> Ex. 1021 at 5, 7.

(U.S. Patent No. 5,428,130 (Ex. 1022, "Capon-130"), citing the latter as disclosing a "murine lymphocyte homing receptor (MHLR) extracellular domain" that is "fused to the Fc region of human IgG1"<sup>49</sup> and teaching a "variety of uses" for its fusion proteins, including "prolonging in vivo plasma half-life, facilitating purification."<sup>50</sup>

Patent Owner, citing the Board's decision, argued the rejections were improper, explaining, *inter alia*, that "[t]he ordinary skilled artisan following the teaching of Example 5, [of Capon-130], would have arrived at an embodiment outside the scope of the pending claims, i.e. missing a portion of the hinge domain."<sup>51</sup> The Examiner eventually agreed.<sup>52</sup>

Similar obviousness rejections based on Smith and Capon-130 were imposed during examination of U.S. Appl. No. 08/444,791 ("the '791 application"),<sup>53</sup>

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<sup>49</sup> Ex. 2034 (3/7/2011 Non-Final Rejection) at 8.

<sup>50</sup> *Id.* at 9.

<sup>51</sup> Ex. 2109 (3/29/2011 Response) at 19.

<sup>52</sup> Ex. 2035 (8/31/2011 Notice of Allowance).

<sup>53</sup> Ex. 1023 (6/24/2011 Final Rejection at 7).

which Patent Owner disputed using essentially the same rationale and unexpected results evidence.<sup>54</sup> The Examiner ultimately withdrew those rejections.<sup>55</sup>

## 2. The CFAD-IPR

In 2015, CFAD sought *inter partes* review of the '522 patent. Like the present Petition, it focused on supposed deficiencies in the original examination's obviousness rejections.<sup>56</sup> For example, it argued the Examiner should have relied on "Capon's 'typical' approach ... used in Examples 4 and 5, and FIG.8" of Capon-130, and on the statement in that patent contemplating "enhanced specific activity and modified plasma half-life."<sup>57</sup> CFAD also claimed that Capon-130 "disclosed a general method for making [ligand-binding partner]-Fc fusions."<sup>58</sup>

CFAD's obviousness ground was based on U.S. Patent No. 6,004,781 to Seed ("Seed" – Ex. 1027) in view of Smith and further in view of Capon-964. CFAD claimed that Seed and Capon-964 "consistently" demonstrated that

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<sup>54</sup> Ex. 1017 (11/23/2011 Response).

<sup>55</sup> Ex. 1025 (2/15/2012 Notice of Allowance).

<sup>56</sup> Ex. 1026 (CFAD-Pet.) at 6 ("The Examiner's Smith/Capon rejection was framed incorrectly.").

<sup>57</sup> *Id.* at 8–10.

<sup>58</sup> *Id.* at 7.

“chimeric molecules were ‘efficiently synthesized’ and secreted ‘in the absence of any light chain production’”<sup>59</sup> and that an Ordinary Artisan would have been “motivated to create chimeras containing [Smith’s] TNF receptor fused to [Seed or Capon-964’s] Fc regions because each was expected to express the protein from host cells, to dimerize, resulting in a product with enhanced binding affinity...and because the Fc region provides long serum half-life.”<sup>60</sup> CFAD did not directly challenge the unexpected results evidence the Board previously considered, arguing those properties were not “commensurate in scope” with the claims – that they lacked a nexus.<sup>61</sup>

The Board declined to institute review.<sup>62</sup> It observed the CFAD petition failed to “offer persuasive evidence to explain why one of skill in the art would choose the Fc portion of the immunoglobulin heavy chain from the choices taught in [Seed or Capon-964].”<sup>63</sup> The Board found (contrary to this Petitioner’s

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<sup>59</sup> *Id.* at 31.

<sup>60</sup> *Id.* at 32–33.

<sup>61</sup> *Id.* at 10–11.

<sup>62</sup> Ex. 1010 at 19.

<sup>63</sup> *Id.* at 16.

assertion) that the teaching in Smith regarding “use of the entire constant region would not point to selective deletion of the C<sub>H</sub>1 domain.”<sup>64</sup> The Board also found the unexpected results evidence “commensurate in scope with the claims” and “supports the non-obviousness of the challenged claims,” and noted the CFAD petitioner “...should have addressed the evidence of unexpected results as part of Petitioner’s showing of a reasonable likelihood of success on the merits.”<sup>65</sup>

**B. This Petition Presents a Textbook Case for Denying Institution under §§ 325(d)/314(a)**

Each of the criteria the Board has identified in its decisions declining to institute trial based on §§ 325(d) and 314(a) is present here.

First, the specific teachings of the prior art in this Petition were considered by the Board during original examination and in the CFAD-IPR:

- Smith was considered in both the CFAD-IPR and during examination.<sup>66</sup>
- Watson describes the same pln-HR fusion protein as Example 4 of Capon-964 (Ex. 1019) (upon which the CFAD petitioner based its

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<sup>64</sup> *Id.* at 16–17 (emphasis added).

<sup>65</sup> *Id.* at 18.

<sup>66</sup> *See supra* § IV.A.

denied challenge) and of Capon-130 (Ex. 1022) (which was at issue in the appeal to the Board in original examination).<sup>67</sup>

- Zettlmeissl discloses the same CD4-based fusion protein constructs described in the Seed patent (Ex. 1027), which the Board considered in the CFAD-IPR.<sup>68</sup>

The Board has found grounds presenting the same prior art teachings to warrant denial of *inter partes* review.<sup>69</sup> Using redundant secondary references (Zettlmeissl

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<sup>67</sup> Compare Watson at Fig. 1 with Ex. 1019 at 40:43–48 and Ex. 1022 at 40:24–31; compare also Watson at Fig. 1A with Ex. 1019 at Fig. 8 and Ex. 1022 at Fig. 8. Croft-Decl. ¶¶104–111. Watson was cited as Exhibit 1045 in the CFAD-IPR.

<sup>68</sup> Compare Zettlmeissl at 348 (“a 5-amino acid linker sequence (HADPE), and a synthetic splice donor sequence” was used) with Ex. 1027 at 13:20–38 and Table 2 (showing nucleotides 1292–1306 encoding the HADPE sequence); Croft-Decl. ¶¶162–163. Zettlmeissl also was considered during examination.

<sup>69</sup> See *Nu Mark LLC v. Fontem Holdings 1, B.V.*, IPR2016-01309, Paper 11 at 7–12 (PTAB Dec. 15, 2016).

in Ground Two) or reversing the order of the references (Ground One) does not cure this deficiency.<sup>70</sup>

Second, Petitioner employs the same obviousness rationales and justifications advanced in earlier proceedings and found unpersuasive by the Board – it asks the Board to consider Smith, Watson, and Zettlmeissl in substantially the same way and for the same purpose as before.<sup>71</sup> The table below maps the positions in this petition to those in the two prior proceedings:

<i>Purpose</i>	<i>Coherus Arguments</i>	<i>CFAD Arguments</i>	<i>Prosecution History</i>
General fusion method makes obvious claimed fusions	Pet. at 33.	CFAD-Pet. at 7. CFAD-Pet. at 42.	3/4/2009 Ex. Answer at 20.
Therapeutic uses provide motivation	Pet. at 34.	CFAD-Pet. at 19.	3/7/2011 Non-Final Rejection at 9.

<sup>70</sup> See *Neil Ziegman, N.P.Z., Inc. v. Stephens*, IPR2015-01860, Paper 13 at 21 (“Moreover, Section 325(d) does not mention anything about ‘relative strengths’ of secondary references; it only requires the prior art to be ‘substantially the same,’ and nothing more.”).

<sup>71</sup> See *Kingston Tech. v. Polaris Innovations LTD*, IPR2017-00974, Paper 8 at 13 (PTAB Aug. 14, 2017) (declining to institute where each reference “serve[s] the same purpose” as the previously considered art).

Improved yields and secretion suggest use of hinge-CH <sub>2</sub> -CH <sub>3</sub>	Pet. at 24. Pet. at 44. Pet. at 47.	CFAD-Pet. at 18. CFAD-Pet. at 44.	3/7/2011 Non-Final Rejection at 8–9.
Enhanced binding would motivate	Pet. at 34–35.	CFAD-Pet. at 32–33.	2/23/2007 Final Rejection at 17.
Increase serum half-Life would motivate	Pet. at 35.	CFAD-Pet. at 44.	3/7/2011 Non-Final Rejection at 9.
Purification reasons would motivate	Pet. at 37.	CFAD-Pet. at 11.	3/24/2009 Ex. Answer at 60.

Third, the Petition presents its arguments as a reply to the Board's past determinations – it thus aims to “second-guess the Office's previous decision on substantially the same issue.”<sup>72</sup> Indeed, Petitioner frames nearly all of its arguments as solving supposed deficiencies of prior decisions of the Board.<sup>73</sup>

<sup>72</sup> *Ziegman*, IPR2015-01860, Paper 11 at 12–14 (PTAB Feb. 24, 2016).

<sup>73</sup> Pet. at 17 (claiming CFAD petition failed to explain why an Ordinary Artisan would “choose the Fc [*i.e.*, hinge-CH<sub>2</sub>-CH<sub>3</sub>] portion of the immunoglobulin heavy chain from the choices taught in Seed or Capon.”); *see also id.* at 37 (“During prosecution, Patent Owner argued...”), 38 (“Patent Owner argued during prosecution....”), 39 (“Contrary to Patent Owner's arguments....”), 45 (“Patent Owner has previously argued....”). *See also* Ex. 2036 (Coherus Investor Slides) at 21 (publicly portraying Petition as “fundamentally different” from the CFAD-IPR).

Using a new petition to correct supposed deficiencies in an earlier, failed petition is plainly improper.<sup>74</sup>

Accordingly, the Board should exercise its discretion under §§ 325(d) or 314(a) and decline to institute trial.<sup>75</sup> Doing so will avoid wasting the Board's valuable time and resources in revisiting obviousness theories and evidence that have already been fully considered and rejected.<sup>76</sup>

## **V. THE PETITION FAILS TO PRESENT ANY BASIS FOR INSTITUTING TRIAL**

### **A. Ground One: The Claims Are Not Obvious Over Watson in View of Smith**

Petitioner asserts the “straightforward application of Watson’s method to the 75-kDa TNFR disclosed by Smith...results in exactly the same polynucleotides and

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<sup>74</sup> See *Gen. Plastic*, Paper 19 at 17–18, n.14 (using the Board’s prior decisions as a “roadmap” for future challenges is “unfair to patent owners and is an inefficient use of the *inter partes* review process”).

<sup>75</sup> *Huawei Tech. Co., Ltd. v. Pabst Licensing GmbH & Co. KG*, IPR2017-00449, Paper 7 at 9 (PTAB, June 12, 2017).

<sup>76</sup> *Hengdian Group Dmegc Magnetics Co., Ltd. v. Hitachi Metals, Ltd.*, IPR2017-01313, Paper 7, at 16 (PTAB Nov. 6, 2017); *Panacea Biotec, Ltd. v. Daiichi Sankyo Co. Ltd.*, IPR2015-01496, Paper 11, at 6 (PTAB, Jan. 7, 2016).

methods claimed in the '522 patent.”<sup>77</sup> According to Petitioner, an Ordinary Artisan would have been motivated to start with Watson because it supposedly: (i) “teaches use of the IgG fusion protein as an anti-inflammatory” by “block[ing] certain inflammatory pathways” in a manner that “is very similar to the use that Smith and others identified for therapeutics based on TNFR” and (ii) it “teaches a general method to make fusion proteins using various receptors.”<sup>78</sup> Petitioner then claims an Ordinary Artisan would have been further motivated to make the claimed TNFR-based fusion proteins because “receptor:IgG fusion proteins were likely to display increased affinity”; that “serum half-life could be greatly extended”; and that “incorporating IgG functionality into a fusion protein” would “simplify purification.”<sup>79</sup>

But each of Petitioner's foundational assumptions about Watson is false.

First, following Petitioner's proposed strategy of simply replacing the pln-HR component of Watson's “probe” with TNFR does not yield a fusion protein containing the complete, exon-encoded -hinge-C<sub>H</sub>2-C<sub>H</sub>3 portion of IgG, as each of

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<sup>77</sup> Pet. at 31.

<sup>78</sup> Pet. at 32–34.

<sup>79</sup> *Id.* at 36.

the claims requires – it would yield a fusion protein lacking part of the hinge, and thus fall outside the claims.

Second, Watson does not describe treating inflammation by inhibiting cell signaling pathways, much less in a manner “very similar” to how TNFR-based therapeutics do. Instead, Watson describes a research tool (*i.e.*, a “probe”) capable of binding to an unknown ligand and use of this “histochemical reagent” to study physical migration of lymphocytes through peripheral lymph nodes. Watson also did not announce a new, general strategy for making fusion proteins using the claimed hinge-CH2-CH3 portion of IgG heavy chains, but instead indicates the design of its pln-HR-fusion protein was influenced by many different considerations linked to use of its pln-HR fusion as a research tool.

Finally, Petitioner's assertions about supposedly predictable properties shared by the fusion proteins in Watson and the claims ignore numerous, material differences between the involved receptors, ligands and IgG elements, and rest on overgeneralized and scientifically implausible theories.

Petitioner's Ground One rationale also violates a central tenant of the law of obviousness – that an Ordinary Artisan would not make a change that renders a prior art molecule inoperable for its disclosed and intended use.<sup>80</sup> Petitioner's

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<sup>80</sup> *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

Ground One theory does precisely that – it claims an Ordinary Artisan would start with the Watson pln-HR-IgG protein but then discard the “pln homing receptor” portion of it, the one feature that is both central and necessary to the design, properties and all of the actual and theoretical uses identified in Watson for its “probe.”

Petitioner's Ground One theory thus lacks a rational basis based on an objective or accurate depiction of the teachings of the prior art.

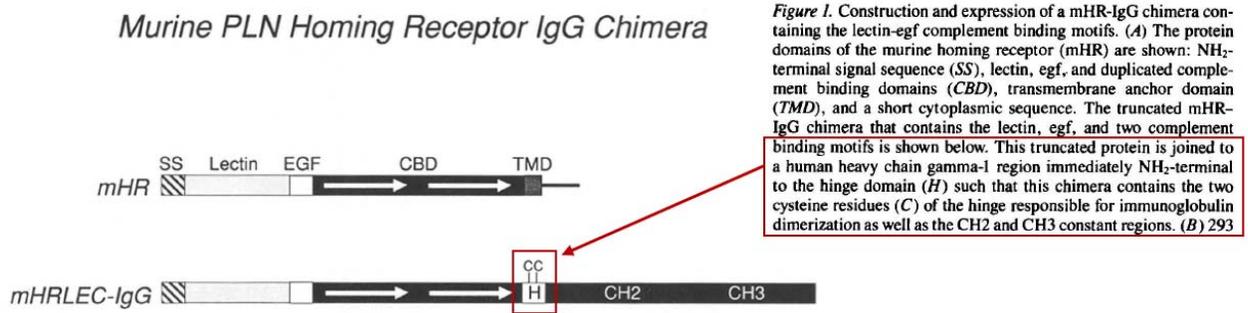
**1. Petitioner's Combination Would Not Yield the Recited Fusions**

Petitioner's Ground One obviousness theory would not have led the Ordinary Artisan to the fusion proteins of the claims for the simple reason that it would yield a fusion protein having a different portion of the IgG heavy chain than what the claims require, and Petitioner provides no reason why an Ordinary Artisan would further modify this fusion protein to contain the correct portion.

Contrary to Petitioner's assertion, Watson's fusion protein does not use the complete hinge-CH2-CH3 portion of the IgG1 heavy chain that the claims require – its protein lacks the first five amino acid sequences of the hinge (including the first cysteine residue) and therefore does not contain “all the domains of the

constant region of a heavy immunoglobulin IgG [IgG1] heavy chain other than the first domain of said constant region.”<sup>81</sup>

This difference is readily apparent from Watson and related publications describing the structure of Watson's protein. For example, in Figure 1A, Watson states its fusion has only two cysteine residues in its hinge:<sup>82</sup>



Example 4 of Capon-964, which describes the same pln-HR fusion protein as Watson<sup>83</sup>, likewise reports the protein contains only a portion of the hinge: “a sequence beginning in the hinge region just upstream of the papain cleavage site . .

<sup>81</sup> Croft-Decl. ¶¶112–118.

<sup>82</sup> Watson at Fig. 1A (adapted).

<sup>83</sup> Croft-Decl. ¶¶113–115.

. is described in the Example 4.”<sup>84</sup> Patent Owner noted this important difference during the CFAD-IPR, yet, inexplicably, Petitioner ignores it in its petition.<sup>85</sup>

As explained in § III.B above, before August 1990, it was well established that the hinge domain of the human IgG1 heavy chain contains three cysteine residues. For example, Ellison (Ex. 1050) shows the human IgG1 hinge domain contains three cysteine residues:<sup>86</sup>

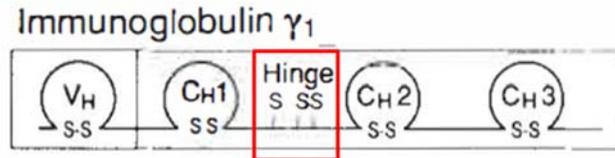


<sup>84</sup> Ex. 1019 at 15:11–18. *See also* Watson at 2228 (“We thank Dr. Dan Capon for the plasmid construct, containing the human IgG1 constant region, as well as advice on junction sites.”) (emphasis added); *cf.* Ex. 1019 at 44:63–66 (“The CD4-Ig plasmid is that described in Capon et al. supra, *modified by the deletion of the coding region for the CH1 domain and a portion of the hinge region up to the first cysteine residue.*”) (emphasis added).

<sup>85</sup> Ex. 1010 at 47 (Capon preferred embodiments may contain “...part but not all of the hinge domain...”).

<sup>86</sup> Ex. 1050 at Fig. 4 (adapted); Croft-Decl. ¶¶66–67.

The Capon Nature paper (Ex. 1032) describing Capon's related work similarly shows that the IgG1 hinge contains three cysteines, each capable of forming a disulfide bond.<sup>87</sup>



Petitioner's assertion that the "straightforward application of Watson's method to the 75-kDa TNFR disclosed by [Smith]...results in exactly the same polynucleotides and methods claimed in the '522 patent" is thus demonstrably false.<sup>88</sup>

Petitioner compounds its error by providing no reason why an Ordinary Artisan, after supposedly changing pln-HR to TNFR, would then modify Watson's IgG1 portion to add back in the missing hinge residues needed to yield the recited fusion proteins. Petitioner and its expert likewise offer no opinions about whether this change would have any consequences (*e.g.*, whether it would affect expression or secretion of the protein). Both omissions are notable because, throughout its

<sup>87</sup> Ex. 1032 at 526 ("The hinge region of each immunoadhesin contains three cysteine residues....").

<sup>88</sup> Pet. at 31.

Petition, Petitioner repeatedly emphasizes the supposed criticality of using the same IgG portion as the Watson protein to achieve its supposed benefits.<sup>89</sup>

Petitioner's failure to acknowledge and address this important difference between the IgG portion of Watson's fusion protein and the portion required by the claims is fatal to its Ground One theory.

## **2. Watson Provides No Motivation for a TNFR Therapeutic**

Petitioner's reliance on Watson is also fundamentally misplaced – Watson provides no relevant insights into designing TNF-targeting fusion proteins that can be used to treat inflammatory diseases.

Watson describes investigations of a protein found on murine lymphocytes termed the peripheral lymph node “homing receptor” (pln-HR). Homing receptors are “a set of diverse adhesion receptors on lymphocytes” that bind to carbohydrate

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<sup>89</sup> Pet. at 17 (Watson provides “a clear and compelling reason” to select its fusion location) (emphasis added); *id.* at 18 (“Watson identifies *only one* location as optimal for fusion...”) (emphasis in original); *id.* at 43 (modifying Smith based on Zettlmeissl and Watson “results in the exact fusion proteins recited” in the contested claims) (emphasis added).

structures in tissues and “may be involved in the ability of lymphocytes to home to different anatomical regions....”<sup>90</sup>

To study the physical migration (“trafficking”) of lymphocytes through “high endothelial venules” (HEV) within peripheral lymph nodes (pln), Watson prepared a “probe” that combined part of the murine pln-HR protein with part of the human IgG1 heavy chain.<sup>91</sup> Watson stained lymphoid tissue with its probe to identify tissues potentially involved in lymphocyte migration.<sup>92</sup>

Importantly, as Watson indicates, the cognate ligand of the murine pln homing receptor was “unknown” at the time of its publication.<sup>93</sup> That lack of knowledge plainly limited the conclusions that Watson could draw from its results. For example, while Watson indicates its fusion protein was able to block *in vitro* adherence of lymphocytes to HEV, uncertainty about the cognate ligand precluded

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<sup>90</sup> Watson at 2221; Croft-Decl. ¶¶73–74.

<sup>91</sup> *Id.* at 2221, Fig. 1.

<sup>92</sup> *Id.* (“This murine HR-IgG chimera should prove useful in analyzing the distribution of the HR ligand(s) in normal as well as in inflammatory states.”); *see also id.* at 2228 (“it allows for immunohistochemical analysis”).

<sup>93</sup> *Id.* at 2228 (“...the nature of the ligand is currently unknown...”).

Watson from knowing how it achieved that result.<sup>94</sup> Watson also observed that “[a]dditional work will be required to address the physiologic or pathophysiologic significance of the expression of pln HR ligands on pp HEV when it occurs.”<sup>95</sup>

Contrary to Petitioner's assertions, Watson nowhere suggests that its fusion protein was able “to block certain inflammatory pathways.”<sup>96</sup> Instead, Watson suggested its fusion protein might be able to influence inflammation by interfering with the physical transit of lymphocytes to sites of inflammation, stating:

The demonstrated activity of the chimera in blocking the *in vitro* adherence of lymphocytes to HEV supports the possibility that leukocyte-endothelial interactions preceding inflammatory responses might be blocked *in vivo*.<sup>97</sup>

Petitioner and its expert fail to appreciate (much less explain) the implications of this observation in Watson. As Patent Owner's expert, Dr. Croft explains, one

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<sup>94</sup> *Id.* (explaining that “[w]hether this [pln endothelial] antigen is the cognate ligand of the mHR-IgG chimera or is sterically close to the ligand is a subject for future investigations.”).

<sup>95</sup> *Id.* at 2228.

<sup>96</sup> Pet. at 34.

<sup>97</sup> Watson at 2228.

possible consequence of inhibiting the adherence of lymphocytes to HEV tissue is that those lymphocytes will be diverted to sites in the body where they will exacerbate inflammation – precisely the opposite therapeutic effect.<sup>98</sup>

In fact, Watson itself questions whether its fusion protein could ever be developed into a therapeutic agent. After observing the complexity of the lymphocyte trafficking system, it states:

[T]he likely involvement of a multiplicity of parallel adhesion systems in leukocyte-endothelial interactions during inflammatory reactions ... may limit the efficacy of any particular blocking reagent as an anti-inflammatory drug.<sup>99</sup>

Before August of 1990, similar uncertainty existed over therapeutically targeting the cytokine TNF. By that time, TNF was known to bind to two different cell surface receptors (*i.e.*, p55 or p75 TNFR) with high affinity.<sup>100</sup> The physiological impact of TNF binding to each receptor, however, was not clearly

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<sup>98</sup> Croft-Decl. ¶¶90–92.

<sup>99</sup> Watson at 2228.

<sup>100</sup> Ex. 1018 (Dembic) at 231.

defined.<sup>101</sup> While some suggested soluble forms of TNFRs had a potential role in mediating the effects of TNF by acting as “scavenge[r]” molecules that blocked messages within the body that lead to or propagated inflammation,<sup>102</sup> others, while acknowledging TNF “may” play a role in inflammatory processes, made clear the “nature of the signal transduced following [TNF-TNFR] association has not been clarified.”<sup>103</sup> Moreover, in August of 1990, at least twenty other cytokines had been implicated in inflammation signaling pathways.<sup>104</sup> Indeed, one of the references Petitioner's expert cites explains that IL-1, IL-6, IFN- $\gamma$ , GM-CSF, PDGF, FGF, and TGB $\beta$  were all cytokines “capable of mediating both stimulatory

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<sup>101</sup> Ex. 2016 (Heller) (“The physiological significance of soluble [TNF] receptors can at best be only surmised.”).

<sup>102</sup> Smith at 3:3–6.

<sup>103</sup> Ex. 1056 (Beutler) at 514–15 (emphasis added).

<sup>104</sup> Ex. 2039 (Lipsky) at 128–129. In August of 1990, IL-1 was believed to have the strongest link to RA. Ex. 2040 (Jacob) at 254 (“The cytokine with the strongest link with rheumatoid arthritis is IL-1.”).

(agonist) and inhibitory (antagonist) effects” on RA, and the role of TNF “remains to be determined.”<sup>105</sup>

In August 1990, an Ordinary Artisan would have recognized the way pln-HR and its unknown ligand might influence an inflammation response (*i.e.*, by regulating migration of lymphocytes to a site of inflammation which could either dampen or enhance inflammation) was materially different than the way TNF and its two receptors (p75 and p55 TNFR) might do so (*i.e.*, influencing intracellular signaling pathways), and that substantial ongoing uncertainty existed about each system.<sup>106</sup>

Petitioner nonetheless claims:

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.<sup>107</sup>

But that assertion is supported only by attorney argument – the paragraphs of Dr. Burton's declaration Petitioner cites as support<sup>108</sup> nowhere suggest that an

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<sup>105</sup> Ex. 1057 (Arend) at 310, 312.

<sup>106</sup> Croft-Decl. ¶¶93–97.

<sup>107</sup> Pet. at 34 (emphasis added).

<sup>108</sup> Burton-Decl. ¶¶132–134

Ordinary Artisan would have considered the way in which a pln-HR fusion protein might “block” inflammation to be “very similar” to the way that a TNF-targeting agent might do so. The lack of evidence supporting this proposition is unsurprising given the very different roles the pln homing receptor and TNF receptors play in the body.<sup>109</sup> The predicate of Petitioner's Watson-based obviousness theory – that pln-HR and TNFR play equivalent roles in inflammation signaling pathways and could be substituted for one another to yield the same result – is false.

### **3. Petitioner's Proposed Change Would Render Watson's Fusion Protein Useless for Its Specified Applications**

Petitioner also ignores that its proposed modification to Watson's pln-HR fusion protein (*i.e.*, replacing the pln-HR component with a TNFR component) would remove from Watson's fusion protein its one feature – the pln-HR receptor – that is central to and necessary for every one of the utilities and applications identified in Watson for pln-HR-based fusion proteins. Such modifications are prohibited under the obviousness law.

Watson identifies several utilities for its fusion protein, explaining:

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<sup>109</sup> *Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043–44 (Fed. Cir. 2017) (“[a]ttorney argument is not evidence”).

In the present study, we demonstrate that this chimera exhibits the lectin properties and the adhesion-blocking activity of the native receptor. Additionally, we establish the utility of this protein as a histochemical reagent for staining of pln HEV. The results suggests that the receptor-IgG chimera may prove exceptionally useful in both the isolation of the HEV ligand(s) as well as in the examination of the role of this adhesion system in various inflammatory states.<sup>110</sup>

Every one of these utilities would be vitiated by Petitioner's proposed replacement of the pln-HR element of Watson's fusion protein with a p75 TNFR protein sequence. Without its pln-HR element, Watson's fusion protein could not be used to stain tissues or investigate the role of the unidentified pln-HR ligand(s).<sup>111</sup> Even Watson's speculated therapeutic use of a pln-HR-based fusion protein would be abrogated by the change proposed by Petitioner – the modified TNFR-containing fusion protein proposed by Petitioner would be unable to bind to the unidentified ligand of pln-HR and thus be unable to influence migration of lymphocytes.<sup>112</sup>

Remarkably, Petitioner nowhere acknowledges that its proposed modification would render Watson's fusion protein inoperative for every one of its

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<sup>110</sup> Watson at 2222.

<sup>111</sup> Croft-Decl. ¶¶98–102.

<sup>112</sup> *Id.* ¶101.

identified utilities. Instead, Petitioner simply presumes the Ordinary Artisan would make the change, and then tries to justify it post-hoc. Such an analysis is the epitome of hindsight.

Ground One thus fails to meet the central requirement for *prima facie* obviousness – an articulated reason with a rational underpinning as to why an Ordinary Artisan would have selected Watson's pln-HR-based protein and then swapped out its central feature to make a TNFR-based fusion protein.

#### **4. Watson Provides No General Guidance on Fusion Protein Design**

Petitioner also contends 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.”<sup>113</sup> Petitioner's assertions rest on a single sentence in Watson: “the fact that a nonimmunoglobulin superfamily member was successfully produced and employed here suggests that this procedure may be of general applicability.”<sup>114</sup>

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<sup>113</sup> Pet. at 23, 29.

<sup>114</sup> Watson at 2228; Pet. at 23.

An Ordinary Artisan would not have read Watson as Petitioner contends (*i.e.*, as being a general guide for producing fusion proteins that calls for use of the particular hinge- $C_{H2}$ - $C_{H3}$  sequence required by the claims).

Contrary to Petitioner's contention, Watson did not indicate the design of its fusion protein was chosen solely to increase expression. Instead, it identifies numerous factors that influenced that design, including enabling "use of the chimeric protein in histochemical studies employing readily accessible reagents" and that "use of the human IgG1 constant region would eliminate cross-reactivity with endogenous murine IgGs in immunohistochemical staining of mouse lymphoid organs."<sup>115</sup>

Moreover, Watson downplays the criticality of which portion of the IgG heavy chain to use in a fusion protein, explaining:

The 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 (9).<sup>116</sup>

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<sup>115</sup> Watson at 2224.

<sup>116</sup> *Id.* (emphasis added).

Watson also credited Capon (Ex. 1032) for its design choices, which describes fusion proteins with many different designs, including some with a complete (three cysteines) IgG1 hinge plus a C<sub>H</sub>1 domain and others with a truncated (two cysteines) IgG1 hinge lacking the C<sub>H</sub>1 domain.<sup>117</sup> Importantly, Capon nowhere correlates increased expression of fusion proteins to the use of different immunoglobulin fragments.<sup>118</sup>

In the CFAD-IPR, the Board considered the Capon group's work as it was described in Capon-964, and found it “does not distinguish the hinge-C<sub>H</sub>2-C<sub>H</sub>3 construct as offering any advantage that would lead one of skill in the art to choose it...”<sup>119</sup> According to the Board:

In fact, [Capon-964] specifically states that the precise site at which the fusion protein is made is not critical, but can be determined by routine experimentation.<sup>120</sup>

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<sup>117</sup> Ex. 1032 at Fig. 1; Croft-Decl. ¶¶146–148.

<sup>118</sup> Croft-Decl. ¶148.

<sup>119</sup> Ex. 1010 at 15; Ex. 1019 at 15:4–11 (fusion proteins having full C<sub>H</sub>1 domain are “particularly preferred embodiments,” along with other immunoglobulin constructs).

<sup>120</sup> Ex. 1010 at 15 (emphasis added).

The Board also considered the guidance in the Seed patent (Ex. 1027), and found it to likewise not suggest use of the particular IgG portion required by the claims, but to instead suggest multiple potential sites for fusions.<sup>121</sup> The Board thus found the “generalized guidance” that Petitioner flags in Watson insufficient to render the fusion proteins recited in the '522 patent claims obvious.<sup>122</sup>

Petitioner attempts to differentiate its arguments from those in the CFAD-IPR, claiming the references CFAD relied on did not provide “clear guidance as to the best location” for fusion, whereas “Watson identifies only one location as optimal.”<sup>123</sup> That is incorrect on both points. First, Example 4 of Capon-964 described the same pln-HR fusion protein described in Watson, and was specifically referenced in the CFAD-IPR.<sup>124</sup> Second, Watson (like Capon-964 and Capon) indicated the precise location of fusion is not important, citing Capon, which reported successful expression of fusion proteins with an intact C<sub>H</sub>1 domain

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<sup>121</sup> *Id.* at 16.

<sup>122</sup> *Id.* at 15.

<sup>123</sup> Pet. at 17–18 (emphasis added).

<sup>124</sup> Croft-Decl. ¶¶103–111; Ex. 1010 at 10–11.

and different portions of the hinge domain.<sup>125</sup> And, of course, Watson described a fusion protein that contains a different portion of the IgG1 hinge than what the claims require.<sup>126</sup>

Watson thus did not teach (as Petitioner contends) a method of “general applicability” for preparing fusion proteins having the same IgG portion required by the claims. Instead, it taught the same thing as Capon-964 – that there is no criticality of the precise portion of the IgG heavy chain to use in a fusion protein.

#### **5. Petitioner's Hindsight-Based Reasons Would Not Have Motivated an Ordinary Artisan to Make the Proteins**

Petitioner lists a number of supposedly desirable properties of a p75 TNFR fusion protein, such as binding affinity, half-life, and ease of purification, and asserts that to achieve them, an Ordinary Artisan “was motivated to apply Watson's method to Smith's TNFR to make a TNFR:hinge IgG fusion protein.”<sup>127</sup> But under Petitioner's Ground One obviousness rationale, an Ordinary Artisan would supposedly start with Watson's pln-HR fusion protein and then modify it to include the TNFR sequence disclosed in Smith. Given that the “solutions” to these

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<sup>125</sup> *Id.* ¶¶146–147.

<sup>126</sup> *See supra* § V.A.1.

<sup>127</sup> *Pet.* at 33–36.

various theoretical problems are not provided by Smith, there would have been no reason for the Ordinary Artisan to consider the latter reference for motivation. In reality, each of Petitioner's supposed motivations is simply a post hoc justification based on hindsight, not the beliefs of an Ordinary Artisan in August of 1990. None would have led the Ordinary Artisan to the claimed fusion proteins.

a. Binding Affinity Would Not Have Provided a Motivation

Petitioner asserts an Ordinary Artisan would have been motivated to make the claimed TNFR-fusion proteins because such proteins “were likely to display increased affinity for their target compared to the soluble receptor alone.”<sup>128</sup> But Petitioner identifies nothing to suggest that in August 1990 an Ordinary Artisan would have believed increasing the binding affinity of p75 TNFR was necessary or would provide any specific therapeutic benefits.

Initially, Petitioner ignores knowledge in the prior art that soluble and cell-bound forms of p75 TNFR already bind TNF with high affinity. Smith, for

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<sup>128</sup> Pet. at 35.

example, reports  $K_a$  values of  $1 \times 10^{10} M^{-1}$  and  $1 \times 10^8 M^{-1}$ .<sup>129</sup> These affinities are comparable to “high affinity” monoclonal antibodies.<sup>130</sup>

Petitioner also provides no reason why an Ordinary Artisan would have believed enhancing the binding affinity of p75 TNFR would have been desirable or necessary to use TNFR fusion as an anti-inflammatory. Watson, for example, does not suggest it is necessary – it reports that its bivalent pln-HR fusion protein bound in a “quantitatively similar” way relative to soluble pln HR.<sup>131</sup>

Finally, while Petitioner cites Smith as observing that “polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand,” Petitioner ignores that Smith already describes a “polyvalent” “chimeric” antibody,<sup>132</sup> as well as other

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<sup>129</sup> Smith at 18:41–49; *see also* Ex. 1058 (Engelmann-1990) at 1532–33 (soluble p75 TNFR “specifically binds” TNF”).

<sup>130</sup> Ex. 2041 (Huston) at 5879 (“The [anti-digoxin] antibody exhibits a high digoxin binding affinity ( $K_a=5.4 \times 10^9 M^{-1}$ )...providing a baseline for comparison with the biosynthetic sFv.”).

<sup>131</sup> Watson at 2224.

<sup>132</sup> Smith at 10:53–68

“polyvalent forms of TNF-R” (e.g., chemically conjugating two “TNF-R” molecules using polyethylene glycol).<sup>133</sup>

b. Half-Life Would Not Have Provided a Motivation

Petitioner next asserts an Ordinary Artisan would have been motivated to produce TNFR-based fusion proteins to improve its half-life in the body.<sup>134</sup> But Petitioner again points to nothing that shows in August 1990 an Ordinary Artisan would have believed increasing the half-life of a p75 TNFR protein was necessary or desirable.

The pre-1990 literature actually suggests the contrary. For example, one group hypothesized in 1989 that native forms of soluble TNFR “might prolong the exposure of the organism to endogenously produced TNF by binding the cytokine and then releasing it slowly in an active form.”<sup>135</sup> Petitioner and its expert cite other work from this research group (Ex. 1058) but ignore this disclosure.

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<sup>133</sup> *Id.* at 10:33–44. In fact, others had tried this latter approach with the p55 TNFR around the time of the invention, but failed. *See* Ex. 2042 (’866 patent) at 38:67–39:2.

<sup>134</sup> Pet. at 35–36.

<sup>135</sup> Ex. 2021 (Engelmann-1989) at 11979.

Even if an Ordinary Artisan had a reason to increase the half-life of a p75 TNFR-based protein, that person would have had no reason to look to Watson for a solution. For example, Smith explains a protein's half-life can be increased using PEGylation or through chemical linkage of two TNFR molecules.<sup>136</sup> It also had been shown before August 1990 that the half-life of cytokines, such as IL-2, could be increased by pegylation.<sup>137</sup>

Petitioner attempts to remedy these analytical gaps by citing the inventors' own subjective insights regarding half-life.<sup>138</sup> That is improper and cannot provide a motivation for establishing obviousness.<sup>139</sup>

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<sup>136</sup> Smith at 10:33–44.

<sup>137</sup> Ex. 2043 (Katre) at 209 (pegylated IL-2 exhibited “enhanced solubility, longer circulatory life, and increased potency”).

<sup>138</sup> Pet. at 35–36; Burton-Decl. ¶151.

<sup>139</sup> *Zoltek Corp. v. U.S.*, 815 F.3d 1302, 1313 (Fed. Cir. 2016) (“arguments reliant upon ex post reasoning,” including expert testimony that relies on the teachings of the patent itself and the other disclosures of the inventor, shows “hindsight bias”).

c. Purification Would Not Have Provided a Motivation

Petitioner next asserts an Ordinary Artisan would have been motivated to combine Watson and Smith to obtain “practical yields” of TNFR and to “simplify purification of the receptor.”<sup>140</sup> But Examples 7 and 8 of Smith describe examples where soluble TNFR was successfully produced in CHO cells and in yeast, and Smith describes well-known techniques (*e.g.*, affinity chromatography using the target ligand or monoclonal antibodies, reverse phase high performance liquid chromatography,<sup>141</sup> or use of poly-histidine (“poly-His”) tags or linkage to other amino acid sequences<sup>142</sup>) to purify the receptor. Many of these methods had been used to purify soluble forms of TNFR before August of 1990.<sup>143</sup>

If Petitioner's Ground One arguments are based on a desire to make a p75 TNFR-based therapeutic, there is simply no reason why an Ordinary Artisan would

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<sup>140</sup> Pet. at 36.

<sup>141</sup> Smith at 16:4–23.

<sup>142</sup> *Id.* at 7:54–66.

<sup>143</sup> Ex. 1058 at Abstract (use of “ligand (TNF)-affinity purification, followed by reversed phase high performance liquid chromatography.”); Ex. 2044 (Brockhaus) at 3129 (“TNF binding proteins were enriched from cell lysates by TNF- $\alpha$  affinity chromatography”).

have started with Watson. All the benefits that Petitioner claims the IgG component of Watson provides are addressed using other means in Smith. Only through the lens of hindsight would the two references be considered together.

**B. Ground Two: The Claims Are Not Obvious Over Smith in View Of Zettlmeissl and Watson**

Petitioner's Ground Two posits that an Ordinary Artisan would have found each of the claims obvious based on Smith in view of both the Zettlmeissl and Watson references.<sup>144</sup> Supposedly, the Ordinary Artisan would start with the "chimeric" TNFR substituted antibody structures disclosed in Smith and modify them to instead use only the hinge- $C_{H2}$ - $C_{H3}$  IgG sequence. The sole reason Petitioner offers for doing this is that, purportedly:

Zettlmeissl and Watson taught that removing the  $C_{H1}$  region and the light chain of the IgG immunoglobulin would optimize expression of the fusion protein.<sup>145</sup>

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<sup>144</sup> Pet. at 43. The Petition improperly intermingles quotes from these two references, rather than clearly identifying what is missing from the various combinations of each with Smith.

<sup>145</sup> Pet. at 43 (emphasis added).

According to Petitioner, a “POSA would have recognized that Zettlmeissl and Watson report optimized methods for preparing fusion proteins compared to the earlier disclosure by Smith.”<sup>146</sup>

But this rationale is based entirely on attorney argument – Petitioner cites no evidence suggesting any problem actually existed with expressing the decidedly different TNFR fusion proteins described in Smith. Zettlmeissl also nowhere “compare[s]” expression of fusion proteins like those in Smith (*i.e.*, with light chains), as Petitioner suggests.<sup>147</sup> Further, Petitioner’s theory requires the Ordinary Artisan to ignore the explicit guidance in Smith to use “unmodified constant region domains” in TNFR-based fusion proteins. And Petitioner’s rationale is also the same one the Board specifically rejected in the CFAD-IPR as being insufficient to suggest modifying Smith’s TNFR-based fusion proteins to obtain “practical yields.” The Board should reject this rationale again.

### **1. Ordinary Artisans Would Not Disobey Smith’s Guidance**

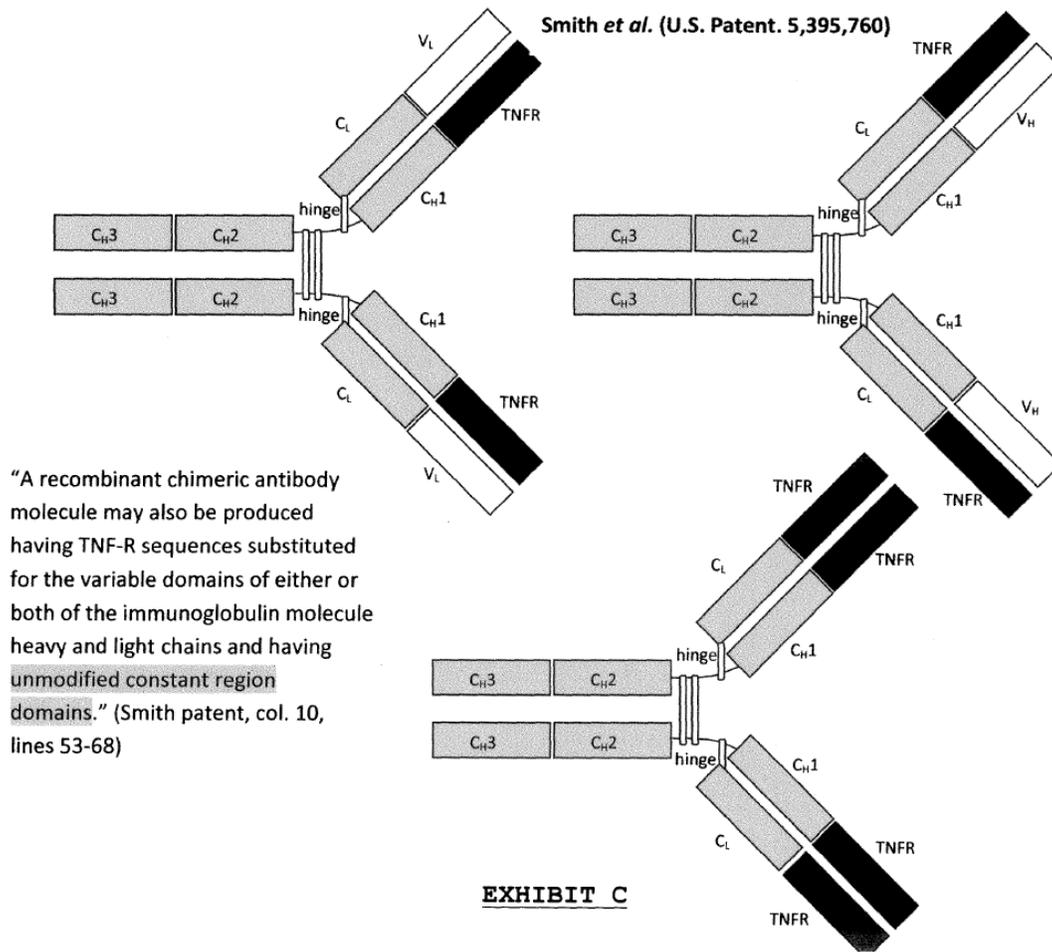
Smith describes very different TNFR-based fusion proteins than the claims – in which the variable domain of one or both of the heavy and light chains is replaced with a TNFR sequence, but which otherwise retain the conventional

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<sup>146</sup> Pet. at 47–48 (emphasis added).

<sup>147</sup> *Id.*

tetrameric structure of an immunoglobulin, including the C<sub>H</sub>1 and C<sub>L</sub> domains  
(illustrated in figure below).<sup>148</sup>



Smith also makes clear that TNFR-based fusion proteins should retain “unmodified” heavy and light constant regions.<sup>149</sup> Smith cites two different patent publications where “[a]dditional details relating to the construction of such

<sup>148</sup> Ex. 2037 (8/11/2011 Response) at Ex. C. See also Pet. at 3.

<sup>149</sup> Smith at 10:53–61.

chimeric antibody molecules” can be found.<sup>150</sup> Neither suggests modifying the design of the fusion proteins in Smith.<sup>151</sup>

As the Board found in the CFAD-IPR, an Ordinary Artisan would find no reason within Smith to modify the tetrameric fusion proteins it describes, particularly in a way that disobeys its explicit guidance to use “unmodified” constant regions (*i.e.*, that include the light chain constant domain and the heavy chain C<sub>H</sub>1 domain).<sup>152</sup>

## 2. Zettlmeissl's Teachings Belie Any “Expression” Problem

The linchpin of Petitioner's Ground Two rationale is its theory that an Ordinary Artisan would have been motivated to “optimize” expression of Smith's tetrameric TNFR fusion proteins because Zettlmeissl and Watson supposedly teach this goal can be achieved by “attach[ing] the extracellular receptor at the hinge region of the IgG heavy chain.”<sup>153</sup> But Zettlmeissl's comments concerning relative

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<sup>150</sup> *Id.* at 10:66–68.

<sup>151</sup> Croft-Decl. ¶143.

<sup>152</sup> Ex. 1010 at 15–16.

<sup>153</sup> Pet. at 45, 47–48 (“POSA would have recognized that Zettlmeissl and Watson reported optimized methods for preparing fusion proteins compared to the earlier disclosure in Smith.”) (citing Burton-Decl. ¶¶147, 153).

expression levels of fusion proteins relate to fusion proteins that, like Watson's protein, were not expressed with a light chain constant domain.<sup>154</sup> That is a critical point – as Zettlmeissl itself makes clear, expression problems are not ordinarily encountered when immunoglobulin structures are expressed with a light chain constant region:

The presence of either IgG or IgM C<sub>H1</sub> domains correlated with markedly reduced fusion expression, a result not entirely unexpected, given that C<sub>H1</sub> is normally found associated with either a light-chain constant region or heavy-chain binding protein during the course of synthesis in B cells (Haas and Meo, 1988).<sup>155</sup>

An Ordinary Artisan thus would have understood Zettlmeissl's observations about expression to concern fusion proteins not expressed with a light chain constant

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<sup>154</sup> Zettlmeissl reports preparation of two kinds of "CD4:IgG" fusion proteins.

Zettlmeissl at Fig. 1. One retained the C<sub>H1</sub> domain, but did not include the associated C<sub>L</sub> domain, while the other removed both the C<sub>H1</sub> and C<sub>L</sub> domains. *Id.* Zettlmeissl reports the presence of the C<sub>H1</sub> domain "correlated with markedly reduced fusion expression." *Id.* at 352; Croft-Decl. ¶¶138–142.

<sup>155</sup> Zettlmeissl at 352.

domain.<sup>156</sup> Indeed, Capon shows these types of expression problems were not even consistently observed.<sup>157</sup>

Petitioner and its expert nowhere discuss the implication of this critical observation in Zettlmeissl – that expression problems would not have been expected for Smith's tetrameric fusion proteins.<sup>158</sup> It is all the more remarkable because Petitioner and its expert plainly recognized that Smith's fusion proteins are

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<sup>156</sup> Croft-Decl. ¶142.

<sup>157</sup> Ex. 1032 at 526 (“CD4-heavy-chain hybrids...containing either the first two or all four immunoglobulin-like domains of CD4 (named 2γ1 and 4γ1 respectively), were secreted in the absence of wild-type or hybrid light chains (Fig. 2a).”) (emphasis added); Croft-Decl. ¶148.

<sup>158</sup> Petitioner makes no mention of Zettlmeissl's observation in the petition. Dr. Burton quotes it twice but nowhere addresses its significance. *See* Burton-Decl. ¶¶85, 152.

expressed with light chains.<sup>159</sup> Petitioner's supposed motivation to "optimize" expression of Smith's fusion proteins is thus illusory.<sup>160</sup>

Petitioner next claims that an Ordinary Artisan would have been somehow motivated to alter Smith's 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."<sup>161</sup> But Petitioner and its expert identify nothing in Zettlmeissl or Watson that supports that proposition. Instead, they simply presume doing that would be desirable for all fusion proteins, regardless of the nature of the fusion.<sup>162</sup> Petitioner's non-existent expression level problem thus cannot support a finding of obviousness.<sup>163</sup>

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<sup>159</sup> See, e.g., Pet. at 3, 44 (showing Smith fusion protein containing light chains); Burton-Decl. ¶57 (identifying the "Light Chain").

<sup>160</sup> Croft-Decl. ¶¶141–142.

<sup>161</sup> Pet. at 48 (emphasis added).

<sup>162</sup> *Id.* at 47–48.

<sup>163</sup> *Leo Pharm. Products Ltd. v. U.S.P.T.O.*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) ("[B]ecause neither Dikstein nor Serup recognized or disclosed the stability

Petitioner also argues that “[t]he POSA also was motivated to prepare TNFR:IgG fusion proteins for all the reasons discussed in Section IX.A.2 above” (Ground One).<sup>164</sup> The same reasons why Ground One is deficient apply to Ground Two. Also, Petitioner nowhere explains why an Ordinary Artisan would have believed Smith’s “chimeric” antibody would need binding, half-life, or purification improvements.<sup>165</sup>

### **3. Petitioner’s Ground Two Combination Would Not Yield the Recited Fusions**

As it did in Ground One, Petitioner glosses over material differences in the structures of Zettlmeissl’s and Watson’s fusion proteins relative to what the claims require, and incorrectly contends that “modifying Smith’s TNFR:IgG fusion proteins as taught by Zettlmeissl and Watson results in the exact fusion proteins recited in the ’522 Patent claims.”<sup>166</sup>

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problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi.”).

<sup>164</sup> Pet. at 48.

<sup>165</sup> Croft-Decl. ¶¶138, 140, 142–143.

<sup>166</sup> Pet. at 43. *See also* Pet. at 5 (arguing Watson and Zettlmeissl use “the identical portion of the IgG heavy chain as” in the contested claims).

As explained in § V.A.1, Watson's fusion protein does not use the same IgG1 sequence required by the claims. Zettlmeissl similarly has material differences in the design of its fusion proteins relative to the claims – each interposes an artificial five amino acid linker sequence between the receptor and immunoglobulin sequences.<sup>167</sup> Following Petitioner's rationale of replacing only the "receptor" in its proposed combination of Smith with both Zettlmeissl and Watson would thus yield fusion proteins that include a third component (*i.e.*, an artificial "linker") between the receptor and IgG components and omit part of the hinge. Remarkably, Petitioner ignores both differences – it provides no explanation why an Ordinary Artisan would omit Zettlmeissl's linker and add residues to Watson's IgG component to yield the complete hinge required by the claims.<sup>168</sup>

Petitioner thus has entirely failed to articulate a rational basis why an Ordinary Artisan would have modified the teachings of Smith based on the

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<sup>167</sup> Zettlmeissl at 348 ("The fusions were accomplished with the aid of a joining oligonucleotide encoding a 5-amino-acid linker sequence (HADPE) ...."); Croft-Decl. ¶¶154–156.

<sup>168</sup> Pet. at 45–46.

disclosures of Zettlmeissl and Watson in a way that would yield the claimed invention. The Board should decline to institute trial on Ground Two.

## **VI. OBJECTIVE INDICIA OF NON-OBVIOUSNESS CONFIRM THE PATENTABILITY OF THE INVENTION**

The Federal Circuit has emphasized that real-world evidence concerning how a patent has been received is a critical safeguard against hindsight.<sup>169</sup> Such objective indicia are important in any obviousness analysis and “it is an error not to consider them.”<sup>170</sup>

Surprisingly, while the petition takes issue with certain unexpected results of etanercept previously considered by the Board, it is entirely silent on other objective indicia associated with etanercept, including that it: (i) met a long-felt need and was praised, (ii) enjoys substantial commercial success, (iii) was copied by others, and (iv) succeeded where other fusion proteins failed. Petitioner's silence is inexcusable, given that it recognizes the claims cover etanercept,<sup>171</sup> that etanercept is one of the world's most successful RA drugs, and that Petitioner is

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<sup>169</sup> *Crocs, Inc. v. ITC*, 598 F.3d 1294, 1310 (Fed. Cir. 2010).

<sup>170</sup> *In re Kao*, 639 F.3d 1057, 1067 (Fed. Cir. 2011).

<sup>171</sup> Ex. 2003 (Coherus 10-K) at 50 (“...Brockhaus, et al., U.S. patents 8,063,182 and 8,163,522...are directed to the fusion protein in Enbrel.”).

most certainly aware of etanercept's remarkable attributes given its multi-year campaign to copy it.

Consequently, even if Petitioner had somehow made out its *prima facie* case (it did not), the Board should deny institution due to the numerous uncontested objective indicia of non-obviousness associated with etanercept.

**A. Etanercept Has a Nexus to the Contested Claims**

Despite being a central issue during prosecution of the '182 patent and the CFAD-IPR, Petitioner does not dispute that a nexus exists between the objective indicia of etanercept and the claims of both the '182 and '522 patents – it nowhere suggests the Board's prior findings of such a nexus were wrong.<sup>172</sup> A nexus is presumed here because etanercept falls within the scope of the claims,<sup>173</sup> as Petitioner itself admits.<sup>174</sup> The Board should not revisit this issue, but should instead maintain its prior findings regarding nexus.

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<sup>172</sup> See Ex. 1021 at 7 (crediting unexpected results of etanercept as objective indicia of non-obviousness); Ex. 1010 at 18 (finding objective indicia evidence based on etanercept to be “commensurate in scope with the claims.”).

<sup>173</sup> E.g., *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016); Croft-Decl. ¶¶32–35, 53.

<sup>174</sup> Ex. 2003 at 50; see also Croft-Decl. ¶¶32–35, 53.

**B. Numerous Uncontested Objective Indicia of Etanercept Demonstrate the Claims Are Not Obvious**

Petitioner, despite its intimate familiarity with the commercial and clinical profile of etanercept, presents no arguments and no evidence concerning numerous types of objective indicia of non-obviousness linked to etanercept. Given that each has a nexus to the claims, the Board should credit them – individually and collectively – as supporting the non-obviousness of the claims.

**1. Etanercept Is Praised and Met a Long-Felt Unmet Medical Need**

Before etanercept, drugs used to treat RA patients failed to control clinical signs and symptoms of the disease, halt advancement of the disease, or maintain patient function in a majority of patients.<sup>175</sup> These pre-etanercept treatments included NSAIDs, steroids, and conventional synthetic disease modifying anti-rheumatic drugs (“csDMARDs”), such as sulfasalazine.<sup>176</sup> Even the cornerstone RA therapy, methotrexate (“MTX”), provided benefits in only about 30% of patients using one standard RA metric; MTX also was associated with severe side effects.<sup>177</sup> Thus, before etanercept, there was a demonstrated need for a safe and

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<sup>175</sup> Ex. 2046 (Fleischmann-Decl.) ¶¶23–30.

<sup>176</sup> *Id.* ¶¶24–26.

<sup>177</sup> *Id.* ¶27–28.

effective treatment that would halt disease progression (*e.g.*, joint destruction) in rheumatoid arthritis patients.<sup>178</sup> Indeed, such a drug was considered by some to be the “holy grail.”<sup>179</sup>

As Petitioner is well-aware, etanercept met that long-felt unmet medical need – it is able to halt the progression of the debilitating symptoms of RA in the vast majority of treated patients, and has dramatically improved the lives of many patients.<sup>180</sup> Etanercept also has been hailed as a “breakthrough” therapy<sup>181</sup> that set the precedent for other TNF-inhibitor drugs, such as Humira® (adalimumab) and Remicade® (infliximab), which the FDA has recognized have “revolutionized” the treatment of inflammatory diseases.<sup>182</sup>

Indeed, respected rheumatologists have observed that etanercept is such a “dramatic drug that many patients now appreciate a new way of life,” and that TNF-inhibitors like etanercept were “an exciting development” that gave doctors a

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<sup>178</sup> *Id.* ¶¶29–30.

<sup>179</sup> *Id.* ¶30.

<sup>180</sup> *Id.* ¶36.

<sup>181</sup> *Id.* ¶34.

<sup>182</sup> Ex. 2030 (FDA AAC Transcript) at 134.

powerful new tool in the control of a potentially fatal disease.<sup>183</sup>

Notably, neither Dr. Burton nor Petitioner even acknowledge the unmet medical need etanercept addressed or its praise from others.

## 2. Etanercept Is Commercially Successful

“When ‘a product attains a high degree of commercial success, there is a basis for inferring that attempts to a solution have been made and have failed.’”<sup>184</sup>

Petitioner turns a blind eye to the clinical, commercial success of etanercept.

Within two years of its approval, most rheumatologists began using etanercept as the treatment of choice in the approximately 70% of patients who still had active disease despite treatment with methotrexate.<sup>185</sup> The demand for etanercept exceeded all expectations.<sup>186</sup> By December 2001, approximately 121,000 patients had been treated with etanercept – a rare accomplishment for an injectable drug based on an entirely new mechanism of action – and about 20,000 patients were on the waiting list for etanercept by 2002.<sup>187</sup>

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<sup>183</sup> Fleischmann-Decl. ¶41.

<sup>184</sup> *WBIP*, 829 F.3d at 1330–31.

<sup>185</sup> Fleischmann-Decl. ¶37.

<sup>186</sup> *Id.* ¶38.

<sup>187</sup> *Id.*

Etanercept had (and continues to have) a substantial share of the RA therapy market. For example, after its launch in 1998, etanercept use grew rapidly to over half a million monthly prescriptions per year by 2000, remained around that level through 2002, then sharply grew to just under two million monthly prescriptions by 2006 and remained around that level through 2008.<sup>188</sup> This growth occurred despite the market entry of two other biological-DMARDs (“b-DMARDs”), Remicade® and Humira® in 1999 and 2003, respectively.<sup>189</sup>

Etanercept's high utilization was reflected among all categories of RA patients. Among privately insured patients, etanercept was the most prescribed first-line b-DMARD from 2005-2008.<sup>190</sup> Among Medicaid patients, etanercept was the most prescribed first-line b-DMARD from 2001-2008.<sup>191</sup> Thus, there was a “sustained preference for etanercept as the agent of choice for patients initiating new treatment episodes with bDMARDs.”<sup>192</sup> Etanercept was also the most used

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<sup>188</sup> Ex. 2083 (Carter-Decl.) ¶25.

<sup>189</sup> *Id.* ¶27.

<sup>190</sup> *Id.* ¶29.

<sup>191</sup> *Id.* ¶¶29–30.

<sup>192</sup> *Id.* ¶29.

self-injectable biologic for treating RA among the Medicare population in 2007-2008, following its inclusion in the Medicare plan after the implementation of Medicare Part D in 2006.<sup>193</sup>

Etanercept's commercial success is plainly attributable to its properties, which in turn are based on its unique structure.<sup>194</sup> Enbrel®'s rapid and sustained utilization confirms that etanercept's efficacy and safety profile, as confirmed by its long history of physician and patient demand and use, is primarily responsible for its commercial success, as compared to other extraneous factors.<sup>195</sup>

Petitioner is plainly aware of etanercept's commercial success. It based its decision to copy this product on that knowledge. In its Annual Report, Petitioner also identifies etanercept as a "blockbuster drug" and indicates it selected etanercept for biosimilar development because it presents a "[l]arge market

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<sup>193</sup> *Id.* ¶30.

<sup>194</sup> Ex. 2079 (Moreland-1998) at 582 ("The resulting immunoglobulin-like dimer...has a substantially higher affinity for TNF- $\alpha$  than monomeric soluble receptor...[and] the immunoglobulin-like Fc structure results in a longer half-life of the molecule in vivo.").

<sup>195</sup> Carter-Decl. ¶¶35-37, 39-40, Figs. 2-4.

opportunity.”<sup>196</sup> Petitioner inexplicably fails to even mention the clinical and commercial success of etanercept.

### **3. Etanercept Has Been Copied by Others**

Within the United States, at least two companies – including Petitioner Coherus – have expended substantial efforts and resources to copy etanercept. For example, Sandoz Inc. represented to the FDA that it sought to make its product as identical as possible to etanercept in Enbrel®, copying not only its exact amino acid sequence but its CHO-cell production method.<sup>197</sup>

Petitioner makes no observations on this copying evidence, despite being one of the entities most knowledgeable about it.

### **4. Failure of Others**

Petitioner devotes extensive efforts portraying the fusion proteins described in Smith, Watson and Zettlmeissl as rendering obvious the recited fusion proteins of the claims. But Petitioner nowhere reveals that none of those prior art fusion proteins was successfully advanced as a clinical or commercial product.

For example, CD4 receptor proteins started clinical trials for HIV, but were

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<sup>196</sup> Ex. 2003 at 4, 12.

<sup>197</sup> Ex. 2008 (Advisory-Committee Slides) at CA-5, CA-14; Ex. 2027 (Summary-Review) at 4.

discontinued in Phase I in 2005.<sup>198</sup> Likewise, there is no evidence Watson's fusion proteins were ever successfully developed, especially a therapeutic for treating inflammation, an unsurprising outcome given Watson's own skepticism.<sup>199</sup>

Petitioner also ignores the failed efforts of others to develop TNFR-based products. For example, one group tried but failed to develop a dimeric pegylated p55 TNFR product but, as one report explained, "[t]his TNFbp will not be a viable option for treating patients with RA secondary to immunogenicity."<sup>200</sup>

"While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure."<sup>201</sup>

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<sup>198</sup> Ex. 2107 (CD4-IgG Drug Profile) at 1.

<sup>199</sup> Watson at 2228.

<sup>200</sup> Ex. 2032 (Moreland-2000) at 601, 607 ("further development of the TNFbp dimer for chronic RA [rheumatoid arthritis] became a concern because of the immunogenicity of this dimerically linked PEGylated molecule").

<sup>201</sup> *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003).

**C. Petitioner's Flawed Scientific Analysis is Inadequate to Explain Away Evidence of Etanercept's Unexpected Results**

Ignoring other known objective indicia of non-obviousness having a nexus to etanercept, Petitioner takes issue with only certain of the unexpected results the Board considered during original examination and in the CFAD-IPR. But even for those, Petitioner's criticisms lack any merit.

**1. Etanercept's Binding Properties Were Unexpected**

Petitioner first contends the enhanced binding and neutralization properties of etanercept and its lack of aggregation were all somehow expected because it was known before August of 1990 that "multiple" soluble TNFR monomers can bind the TNF trimer.<sup>202</sup> All of Petitioner's arguments concerning unexpected results rest on this assertion, and because it is false, each of those arguments should be dismissed.<sup>203</sup>

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<sup>202</sup> Pet. at 53–57, 62.

<sup>203</sup> Pet. at 55 (binding: "POSAs also knew that multiple TNF receptors bind a single TNF molecule."); *id.* at 56 (neutralization: "TNFR-fusion proteins" "were expected to bind multivalently with the trimeric TNF molecule."); *id.* at 62 (aggregation: "POSAs had good reason to expect that both receptors on the dimeric

Petitioner's expert, Dr. Burton, cites two papers for the proposition that it was established by August 1990 that multiple soluble TNFRs bind a single TNF trimer.<sup>204</sup> Neither paper supports his assertions. The first simply confirms that TNF exists in solution as a trimer while the second reports that multiple proteins, including at least one TNFR, on the cell surface interact with the TNF trimer. Neither paper provides insights into how many soluble TNFRs can separately bind a TNF trimer.<sup>205</sup> And subsequent papers, citing this same work, confirm Dr. Burton's reading is wrong – one explained that cell-bound TNFRs self-associate (*i.e.*, “crosslink”) rather than separately bind different TNF ligands within a TNF trimer,<sup>206</sup> while another observes that “one TNF $\alpha$  trimer binds to one receptor molecule” citing the second paper Dr. Burton relies upon.<sup>207</sup>

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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.”).

<sup>204</sup> Burton-Decl. ¶171 (citing Ex. 1036 at 6951; Ex. 1037 at 14646).

<sup>205</sup> Croft-Decl. ¶¶196–202.

<sup>206</sup> Ex. 2010 (Schall) at 367–68; Croft-Decl. ¶200.

<sup>207</sup> Ex. 2022 (Hohmann) at 14929 (emphasis added); Croft-Decl. ¶201.

In short, the premise underpinning each of Petitioner's challenges to etanercept's unexpected binding, neutralization, and aggregation properties is false – in August 1990, it was not known how many soluble TNFR proteins could simultaneously bind to a single TNF trimer. An Ordinary Artisan – even under Petitioner's reasoning – could not have predicted that the TNFR fusion protein of the claims binds TNF with a 50-fold greater affinity than a TNFR monomer, exhibits a 1000-fold increase in neutralization of TNF $\alpha$  and does not cause aggregation.<sup>208</sup>

Moreover, knowledge of the stoichiometry of soluble TNFR binding to TNF trimers would not have enabled an Ordinary Artisan to predict how a bivalent TNFR fusion protein – which presents two TNFRs in an unnatural configuration – might interact with TNF trimers.<sup>209</sup> And without any information illuminating how a bivalent TNFR-based fusion protein interacts with TNF trimers, an Ordinary Artisan could only have made the most general of assumptions.

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<sup>208</sup> Croft-Decl. ¶¶190–191, 210–216.

<sup>209</sup> Croft-Decl. ¶202 (explaining stoichiometry would not explain whether TNFR presented in constrained IgG-based molecule could bind multiple TNF ligands or cause aggregation).

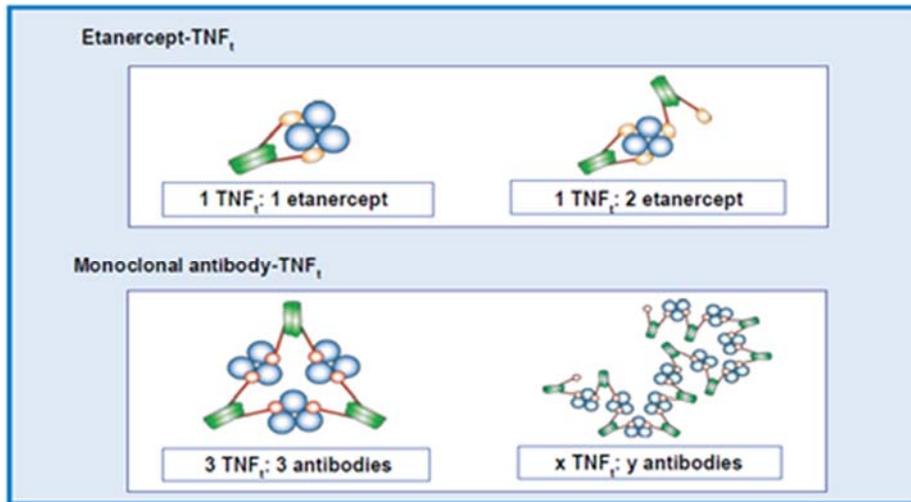
For example, an Ordinary Artisan might have envisioned a bivalent TNFR fusion protein interacting with a TNF trimer in the ways an antibody can interact with a multimeric antigen – by binding two TNF ligands in separate trimers, by binding two TNF ligands in the same trimer, and/or by binding only one TNF ligand if its other arm cannot bind another TNF ligand (whether in the same or a different trimer).<sup>210</sup>

An Ordinary Artisan likewise would have expected etanercept to cause aggregation like anti-TNF antibodies because it is bivalent, like an antibody. Aggregation results when many bivalent TNF-binding molecules (*e.g.*, antibodies or TNFR multimers) bind different TNF trimers with their different arms, leading to the formation of higher order oligomeric complexes of antibodies and TNF trimers (shown in bottom panel below).<sup>211</sup>

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<sup>210</sup> See Croft-Decl. ¶¶204–209 (citing Ex. 2023 (Thomas) as explaining antibodies have ability to exhibit “monogamous” and “bigamous” binding interactions with a multimeric antigen).

<sup>211</sup> Ex. 2024 (Kohno 2005); Croft-Decl. ¶208.



Etanercept surprisingly does not cause aggregation while anti-TNF antibodies do – testing showed it binds only a single TNF trimer, and does not cause higher order oligomeric complexes to form, unlike anti-TNF antibodies.<sup>212</sup> Neither the flexibility of an Ig structure lacking the C<sub>H1</sub> domain nor anything else known in August of 1990 would have enabled an Ordinary Artisan to predict this effect. Indeed, Petitioner seeks to have it both ways: it cites etanercept's similarity to conventional antibodies to claim its binding and neutralization properties were

<sup>212</sup> Croft-Decl. ¶¶207–208, 210–216 (explaining aggregation results when a bivalent TNF binding molecule binds to distinct TNF trimers, ultimately forming oligomeric structures that, when they reach a certain size, become insoluble).

expected, but its differences from conventional antibodies to claim its lack of aggregation was expected.<sup>213</sup> Both assertions are simply hindsight.

## **2. Etanercept's ADCC and CDC Profile Was Unexpected**

Petitioner also disputes it was surprising that etanercept exhibited low ADCC and CDC activities despite its incorporation of portion of an IgG1 heavy chain.<sup>214</sup> Here, it asserts that nothing in the prior art “taught away from using an IgG fusion protein as an anti-inflammatory treatment,”<sup>215</sup> citing Zettlmeissl as supposedly showing a CD4-IgG1 fusion protein that did not exhibit CDC activity.

But the Zettlmeissl scientists unequivocally state the contrary, both in Zettlmeissl and in a contemporaneous paper.<sup>216</sup> And Zettlmeissl specifically cites

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<sup>213</sup> Pet. at 53–57, 62.

<sup>214</sup> Ex. 2028 (Bruggemann) at 1359 (“[F]or many therapeutic purposes, an IgG1 antibody might be greatly preferred to other IgG subclasses as it appears to be considerably more effective in mediating both complement-dependent lysis and ADCC.”).

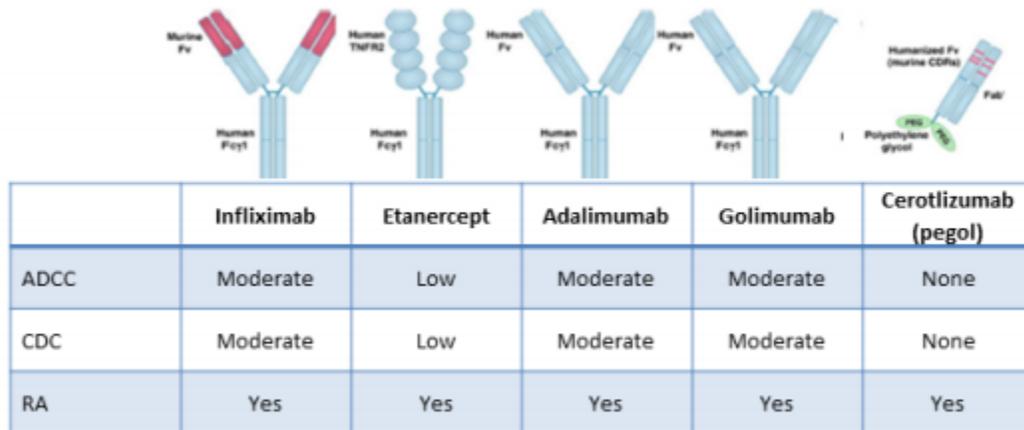
<sup>215</sup> Pet. at 39.

<sup>216</sup> Croft-Decl. ¶¶180–189; Zettlmeissl at 348, 352; Ex. 2020 at 42.

concerns over IgG1-based fusions with high-affinity receptors causing autoimmune damage due to CDC activity.<sup>217</sup>

Petitioner also criticizes a declaration submitted by Dr. Arora during examination showing etanercept exhibits unexpectedly low ADCC relative to Humira® and Remicade®. Petitioner attacks those results for not being in a peer-reviewed publication, ignoring that Dr. Arora reported similar results reaching the same conclusion in a refereed journal.<sup>218</sup> And Petitioner cannot seriously dispute the substance of Dr. Arora’s findings – the FDA reached the same conclusion, citing, among other things, Dr. Arora’s peer-reviewed publication:<sup>219</sup>

**Figure 12. The Role of Fc in the Anti-TNF-α Class Mechanism(s) of Action**



Source: FDA summary of existing literature on the topic of Fc functions of TNF-blockers.<sup>19</sup>

<sup>217</sup> Croft-Decl. ¶¶171, 189; Zettlmeissl at 352.

<sup>218</sup> Pet. at 60; Ex. 2026 (Arora-2009) at 124–30.

<sup>219</sup> Ex. 2108 (AAC Briefing Document) at 34, n.15 (citing Ex. 2026).

Petitioner's criticisms of Dr. Arora's declaration are plainly unwarranted.

Petitioner also claims that properties such as the binding affinity, neutralization effects, and ADCC/CDC effects of etanercept would not be considered important to its clinical activity. But these are quality attributes the FDA can demand a biosimilar sponsor to evaluate as part of proving their drug is safe and effective.<sup>220</sup> And Coherus itself conducted ADCC and CDC studies to show "CHS-0214 to have highly similar pharmacological activity to Enbrel."<sup>221</sup>

**D. Petitioner's Closest Prior Art Assertion is Baseless**

Petitioner criticizes Patent Owner for not allegedly comparing the invention to the closest prior art, which Petitioner contends is the "chimeric" antibody in Smith.<sup>222</sup> But Smith does not disclose a single TNFR fusion protein – it describes many different molecules – and its fusion proteins all include a C<sub>H</sub>1 domain.<sup>223</sup> More directly, etanercept's properties are unexpected and clinically important as

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<sup>220</sup> Ex. 2018 at 20 (ADCC, CDC, "binding," and "neutralization" are "quality attributes").

<sup>221</sup> Ex. 2003 at 12.

<sup>222</sup> Pet. at 63.

<sup>223</sup> See Smith at 7:21–28 and *supra* § V.B.1; *Millennium Pharms., Inc. v.*

*Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017).

measured against any prior art – they are what allow etanercept to halt the progression of RA in the vast majority of patients and have its groundbreaking profile that “revolutionized” the treatment of this disease. Petitioner's contrary arguments all miss the mark.

## **VII. CONCLUSION**

In view of the above remarks, the Board should decline to institute trial on either of the grounds presented in the petition.

Respectfully submitted,

Dated: December 13, 2017

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**CERTIFICATE OF COMPLIANCE**

I hereby certify that the foregoing, Patent Owner's Preliminary Response, contains 13,914 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

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I hereby certify that, on this 13th day of December, 2017, I caused to be served a true and correct copy of the foregoing materials and any accompanying exhibits by email on the following counsel:

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