IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IMMUNEX CORPORATION, AMGEN MANUFACTURING, LIMITED, and HOFFMANN-LA ROCHE INC., Plaintiffs, v. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Honorable Claire C. Cecchi, U.S.D.J. Civil Action No.: 2:16-cv-01118-CCC-MF

DEFENDANTS' SECOND CORRECTED POST-TRIAL FINDINGS OF FACT AND CONCLUSIONS OF LAW

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FINDINGS OF FACT

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TABLE OF ABBREVIATIONS

Term	Definition
’182 patent	U.S. Patent No. 8,063,182 (JTX-1)
’522 patent	U.S. Patent No. 8,163,522 (JTX-2)
Patents-in-suit	The ’182 and ’522 patents
’029 patent	U.S. Patent No. 5,808,029 (PTX-1035)
ADCC	Antibody dependent cellular cytotoxicity
Amended specification	The specification of the ’182 and ’522 patents, as amended by Immunex on Nov. 10, 2006, and Aug. 30, 2007, respectively
Amgen	Plaintiff Amgen Manufacturing, Ltd.
Arora 2009	Arora, T., et al., Differences in binding and effector functions between classes of TNF antagonists, Cytokine 45:124-131(2009) (PTX-130)
Ashkenazi 1991	Ashkenazi, A., et al., Protection against endotoxic shock by a tumor necrosis factor receptor immunoadhesin, Proc. Natl. Acad. Sci. 88:10535-39 (1991) (JTX-69)
Asserted claims	Claims 11-12 and 35-36 of the ’182 patent and claims 3, 8, and 10 of the ’522 patent
BPCIA	The Biologics Price Competition and Innovation Act
Brennan 1989	Brennan FM et al., Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis, Lancet, 2 (8657):244-47, 247 (1989) (DTX-75)
Brockhaus ’279 patent	U.S. Patent 5,610,279 (JTX-5)
Byrn 1990	Byrn, R.A., et al., Biological properties of a CD4 immunoadhesion, Nature 344:667-670 (1990) (JTX-56)
Capon 1989	Capon, D., et al., Designing CD4 immunoadhesins for AIDS therapy, Nature 337:525-30 (1989) (JTX-58)
Capon ’964 patent	U.S. Patent No. 5,116,964 (JTX-61)

Term	Definition
CDC	Complement dependent cytotoxicity
Dembic 1990	Dembic et al., Two Human TNF Receptors Have Similar Extracellular, But Distinct Intracellular, Domain Sequences, Cytokine, 2(4): 231-237 (July 1990) (JTX-23)
Exon-encoded hinge-CH2-CH3 of a human IgG1	Hinge-CH2-CH3 of a human IgG1, as defined by Dr. Tonegawa according to the DNA that encodes a human IgG1
Figure 1	Figure 1 of the patents-in-suit
Figure 4	Figure 4 of the patents-in-suit
Finck '225 patent	U.S. Patent No. 7,915,225 (JTX-39)
Finck '605 patent	U.S. Patent No. 8,119,605 (JTX-40)
Finck '631 patent	U.S. Patent No. 8,722,631 (JTX-41)
IgG	Immunoglobulin of class G
IgG1	IgG subclass 1
IgG3	IgG subclass 3
Immunex	Plaintiff Immunex Corp.
Jacobs '690 patent	U.S. Patent 5,605,690 (JTX-42)
Karjalainen '827 publication	European Patent Application Publication No. 0 394 827 (JTX-60)
Kohno 2007	Kohno, *et al.*, Binding Characteristics of Tumor Necrosis Factor Receptor-Fc Fusion Proteins vs Anti-Tumor Necrosis Factor mAbs, Journal of Investigative Dermatology Symposium Proceedings (2007) (PTX-140)
Mitoma 2008	Mitoma H, et al., Mechanisms for Cytotoxic Effects of Anti-Tumor Necrosis Factor Agents on Transmembrane Tumor Necrosis Factor a-Expressing-Cells, Arthritis & Rheumatism, Vol. 58 No. 5, 1248-57 (May 2008) (DTX-213)
p55 TNFR	A human TNF receptor having an apparent molecular weight of 55 kilodaltons on a non-reducing SDS-polyacrylamide gel

Term	Definition
p75 TNFR	A human TNF receptor having an apparent molecular weight of 75 kilodaltons on a non-reducing SDS-polyacrylamide gel
p75 extracellular region	The portion of the p75 TNFR that protrudes outside the cell, which is amino acids 1-235 of the p75 TNFR
Peppel 1991	Peppel, K., et al., A tumor necrosis factor (TNF) receptor-IgG heavy chain chimeric protein as a bivalent antagonist of TNF activity, J. Exp. Med. 174:1483-89 (1991) (JTX-68)
POSA	Person of ordinary skill in the art
Psoriasis patents	The ’225, ’605, and ’631 patents
PTO	U.S. Patent and Trademark Office
Roche	Plaintiff Hoffmann-La Roche Inc.
Sandoz	Defendants Sandoz Inc., Sandoz International GmbH, and Sandoz GmbH
Seed ’262 publication	European Patent Application Publication No. 0 325 262 (JTX-57)
Smith 1990	Smith, C.A., et al., A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins, Science 248:1019-1023 (1990) (JTX-24)
Smith ’760 patent	U.S. Patent No. 5,395,760 (JTX-65)
Smith ’760 patent’s chimeric antibody	The “recombinant chimeric antibody molecule” described in the Smith ’760 patent at col. 10, ll. 53-68.
Smith protein	The p80 TNFR protein encoded by the amino acid sequence published by Immunex as Figure 3 in Smith 1990, now known as the full-length p75 TNFR
Specification	The original specification of EP 90116707, the priority application of the patents-in-suit, as filed on August 31, 1990
TNF	Tumor necrosis factor

Term	Definition
TNFR	TNF receptor
Traunecker 1989	Traunecker, A., et al., Highly efficient neutralization of HIV with recombinant CD4-immunoglobulin molecules, Nature 339:68-70 (1989) (JTX-25)
Watson 1990	Watson, S.R., et al., A Homing Receptor-IgG Chimera as a Probe for Adhesive Ligands of Lymph Node High Endothelial Venules, J. Cell Biol., 110:2221-29 (1990) (JTX-59)

TABLE OF WITNESSES

Witness	Live or By Deposition	Description
Peter Alliger, Ph.D.	By Deposition	Dr. Alliger is technical project leader at Sandoz for its GP2015 project
Taruna Arora, Ph.D.	By Deposition	Dr. Arora is a former principal scientist at Amgen who was involved in research related to etanercept. Dr. Arora submitted a declaration to the USPTO in support of the prosecution of the patents-in-suit
Carl P. Blobel, M.D., Ph.D.	Live	Dr. Blobel is Defendants' expert on obviousness, obviousness-type double patenting, and anticipation
Manfred Brockhaus, Ph.D.	By Deposition	Dr. Brockhaus is a named inventor on the patents-in-suit and a former employee of Hoffmann La-Roche
Daniel Capon, Ph.D.	Live	Dr. Capon is Defendants' expert on written description and enablement
Zlatko Dembic, Ph.D.	By Deposition	Dr. Dembic is a former senior scientist at Hoffman-LaRoche who is involved in research relating to TNF receptor. Dr. Dembic is a named inventor of the patents-in-suit
Roy Fleischmann, M.D.	Live	Dr. Fleischmann is Plaintiffs' expert on clinical success
Stephen Gillis, Ph.D.	By Deposition	Dr. Gillis is a former employee of Immunex. He served as Immunex's executive vice president and director of research and development during the development of etanercept

Witness	Live or By Deposition	Description
Raymond G. Goodwin, Ph.D.	By Deposition	Dr. Goodwin is a former employee of Immunex and was involved in the development of etanercept
Graham B. Jones, Ph.D.	By Deposition	Dr. Jones is Plaintiffs' expert on FDA's practices and policies regarding demonstrating biosimilarity
Warner C. Greene, M.D., Ph.D.	Live	Dr. Greene is Plaintiffs' expert on etanercept's properties with respect to aggregation, and CDC, and ADCC pathways
Ueli Gubler, Ph.D.	By Deposition	Dr. Gubler is a former senior research leader at Hoffmann-LaRoche, who was involved in research relating to TNF receptors
Johann Gudjonsson, M.D.	By Deposition	Dr. Gudjonsson is Plaintiffs' expert in dermatology
Jeffrey Kittendorf, Ph.D.	By Deposition	Dr. Kittendorf is Defendants' expert in biochemistry
Michael K. Kirschner	By Deposition	Mr. Kirschner is an intellectual property attorney who was formerly employed by Immunex and Amgen
Stephen G. Kunin	Live	Mr. Kunin is Plaintiffs' expert on in USPTO patent policy, practice, and procedure
Leandre Lauffer, Ph.D.	By Deposition	Dr. Lauffer was a research scientist and former employee of Behringwerke. During his time there he was involved in the development of fusion proteins

Witness	Live or By Deposition	Description
Werner K. Lesslauer, Ph.D.	By Deposition	Dr. Lesslauer is a named inventor of the patents-in-suit. He was a research scientist and former employee of Hoffmann-LaRoche
Stewart Lyman, Ph.D.	By Deposition	Dr. Lyman is a former director at Extramural Research at Immunex. Dr. Lyman submitted declarations to the United States Patent and Trademark Office in support of the patents-in-suit.
Mark A. McCamish, M.D., Ph.D.	Live	Dr. McCamish was the Global Head of the Biopharmaceutical Development at the Biopharmaceutical Division of Sandoz from 2009-2016
DeForest McDuff, Ph.D.	Live	Dr. McDuff is Defendants' expert responding to Dr. Vullturo's opinion on commercial success
James H. Naismith, Ph.D.	Live	Dr. Naismith is Plaintiffs' expert on written description and binding properties of etanercept
John P. Parise	By Deposition	Mr. Parise is the former senior counsel and managing attorney at Hoffman LaRoche who was involved in the negotiation and drafting of license agreements
Arne Skerra, Ph.D.	Live	Dr. Skerra is Defendants' expert on binding properties, aggregation, and CDC and ADCC activities of etanercept
Christopher A. Vellturo, Ph.D.	Live	Dr. Vellturo is Plaintiffs' expert on commercial success

Witness	Live or By Deposition	Description
Thomas R. Wall, Ph.D.	Live	Dr. Wall is Plaintiffs' expert on obviousness and enablement
Stuart Watt	Live	Mr. Watt is Amgen's Vice President, Law and Intellectual Property Officer

FINDINGS OF FACT

I. Background

A. The Race to Clone and Identify TNFRs.

1. By 1990, there was a high level of interest in studying TNF and investigating whether targeting TNF with a TNF-binding protein would provide a therapeutic benefit by inhibiting the binding of TNF to its cell-bound receptors. *E.g.*, 9/11 PM Tr. 26:6-27:1, 61:8-14, 65:15-66:7 (Blobel); 9/17 AM Tr. 61:1-18 (Loetscher); 9/18 Tr. AM 69:1-18 (Naismith). As such, academic and commercial groups alike (including Immunex, Genentech, Roche, and the Weizman Institute) were working on targeting this molecule. *See infra* Section IV.A.1.

2. By 1989, it was known that there were at least two TNF receptors ("TNFR"), what are now known as the p55 and p75 TNFRs. Both of them were expected to specifically bind TNF. 9/17 AM 61:1-18 (Loetscher); 9/11 PM Tr. 71:21-72:5 (Blobel). Whether there were additional TNFRs was not conclusively established at the time. 9/17 AM Tr. 91:2-20 (Loetscher) ("[A]t that time we certainly were aware of these two TNF receptors, but we conclude that there may be another one or other receptors…."); *see also* 9/11 PM Tr. 25:6-9 (Blobel); 9/13 AM Tr. 80:3-6 (Capon). But it is now known that there are only two TNFRs, the p55 and p75, encoded by different genes. 9/13 AM Tr. 85:8-13; 85:23-86:1 (Capon).

1. Immunex Successfully Developed Etanercept.

a. Immunex was First to Clone the p75 TNFR.

3. By October 1989, Immunex had cloned the full-length p75 TNFR. DTX-111 at 2; 9/11 PM Tr. 86:21-25, 89:15-19 (Blobel); JTX-73 (49:6-8, 11-12) (Gillis). Cloning means to isolate and identify the DNA sequence that encodes a protein. 9/17 AM Tr. 29:22-24 (Loetscher). The DNA sequence is necessary to make and express recombinant forms of the protein. *Id*. at 29:25-30:6.

4. On May 10, 1990, Immunex filed a patent application claiming DNA encoding of the p75 TNFR, which it designated at the time as "p80." JTX-65 at 3:47-49. This patent ultimately issued to Immunex as U.S. Patent No. 5,395,760. JTX-65. On May 25, 1990, Immunex published Smith 1990, disclosing the amino acid sequence of what it identified as a p80 TNFR. JTX-24 at 4 ("The receptor we have described may correspond to the 80-kD form."). Although referred to at that time as the p80 TNFR, this protein is known today as the p75 TNFR. 9/18 PM Tr. 39:20-40:7 (Naismith); 9/13 AM Tr. 2-14 (Capon).

b. Immunex Collaborated with Behringwerke on a p75 TNFR-IgG1 Fusion Protein.

5. In October 1989, representatives of Immunex and Behringwerke met to discuss the development of soluble TNFRs, including Immunex's p75 TNFR. 9/11 PM Tr. 86:21-25, 88:3-18, 89:15-19 (Blobel); DTX-111 at 1, 2; JTX-73 (49:6-8, 11-12) (Gillis); JTX-74 (43:20-24) (Goodwin). Behringwerke had experience creating Fc fusion proteins of receptors fused to the hinge-CH2-CH3 of human IgG1, including Dr. Lauffer's prior work with Dr. Brian Seed on CD4-IgG1 fusion

proteins. DTX-111 at 2; JTX-73 (49:13-14, 17-22) (Gillis); JTX-74 (50:25-51:1, 51:3-8) (Goodwin); JTX-78 (16:2-5, 16:11-17:1, 38:10-13) (Lauffer).

6. At the October 1989 meeting, Immunex and Behringwerke discussed creating Fc fusion proteins with a TNFR, fusing the soluble p75 TNFR to the IgG1 hinge-CH2-CH3. DTX-111 at 2; JTX-78 (26:23-27:5, 27:9-17, 37:17-25, 38:1-9) (Lauffer); JTX-73 (65:21-66:11) (Gillis); 9/11 PM Tr. 90:7-13 (Blobel). Immunex and Behringwerke were inspired to create a p75 TNFR-IgG1 fusion protein to create a drug with a longer *in vivo* half-life that could be readily purified by Protein A techniques. DTX-111 at 2; 9/11 PM Tr. 89:20-90:6 (Blobel); JTX-78 (39:15-40:5, 41:2-42:1) (Lauffer); JTX-73 (66:18-21, 66:24-67:2) (Gillis).

7. By June 25, 1990, Behringwerke had sent a sample of the TNFR-IgG1 fusion protein in cell culture supernatant. DTX-87; JTX-78 (52:1-53:9, 53:12) (Lauffer); JTX-73 (82:14-24, 84:10-24) (Gillis). This fusion protein consisted of amino acids 1 to 230 of the p75 extracellular region linked to the hinge-CH2-CH3 portion of a human IgG1 via a linker. 9/20 AM Tr. 88:14-23 (Wall); 9/18 PM Tr. 104:8-16 (Greene).

8. By July 20, 1990, Immunex had tested this fusion protein and had shown that it "does contain some binding inhibition activity compared to controls," "which is believable and comparable" to the activity of Immunex's "soluble TNF construct." DTX-114 at 1; JTX-78 (57:2-21) (Lauffer); JTX-73 (84:15-85:10, 85:13-

18, 86:13-18, 86:21-22) (Gillis); 9/11 PM Tr. 91:21-92:1 (Blobel).

9. By October 4, 1990, Immunex had received a cell line from Behringwerke "designated TNFRFc A2," producing the p75 TNFR-IgG1 fusion protein made by Behringwerke. DTX-967 at 1; JTX-78 (69:14-70:8) (Lauffer); JTX-73 (98:25-99:6, 99:15-100:7) (Gillis). Testing by Immunex showed that this fusion protein had a 50- to 100-fold higher affinity for binding to TNF compared to the monomeric TNFR. JTX-74 (51:25-52:15) (Goodwin).

10. Inspired by these binding results, Dr. Goodwin from Immunex decided to make Immunex's own p75 TNFR-IgG1 fusion protein, which was etanercept. JTX-74 (50:25-51:8, 52:11-15, 53:1-18, 54:10-12, 59:24-60:3) (Goodwin). Dr. Goodwin removed the three-amino acid linker between the p75 TNFR and the hinge-CH2-CH3 of the human IgG1. JTX-74 (55:21-24, 56:2-9, 64:7-11) (Goodwin); *see* JTX-78 (88:16-89:8) (Lauffer). Dr. Goodwin made etanercept in November or December 1990. JTX-74 (9:17-10:2, 53:20-54:12) (Goodwin); *see* JTX-73 (51:5-15) (Gillis). He expected that etanercept would have higher binding affinity to TNF compared to the TNFR. JTX-74 (54:24-55:1, 65:20:23, 65:25) (Goodwin).

11. Neither Behringwerke nor Immunex had contact with Roche regarding the TNFR fusion protein. JTX-78 (89:24-90:2) (Lauffer); JTX-73 (123:7-10, 123:12) (Gillis). Immunex is the only company that constructed etanercept. 9/20 AM Tr. 88:8-13 (Wall); 9/18 PM Tr. 130:8-16 (Greene); JTX-73 (50:10-15) (Gillis).

Roche never made etanercept, or any other p75 TNFR-IgG1 fusion protein. 9/18 PM Tr. 130:17-20 (Greene); 9/17 AM Tr. 24:18-20, 75:8-9 (Loetscher).

12. Etanercept is the active ingredient in Enbrel. *E.g.*, DTX-1083 at 2. Enbrel was first approved by the FDA in 1998 and has been on the market continuously since that time. DTX-1083; 9/25 Tr. 27:25-28:14 (McDuff).

13. By 1998, when Enbrel was first marketed, Immunex had obtained at least three patents, including the Smith '760 patent (claiming the DNA sequence encoding the p75 TNFR), the Jacobs '690 (claiming the etanercept molecule) and 5,712,155 (claiming DNA sequences and vectors), all of which it listed on Enbrel's label as covering Enbrel. DTX-1083 at 10; JTX-65; JTX-42.

2. Roche Researched the TNFRs.

14. In 1989, Roche started to investigate the potential therapeutic benefits of TNFRs and sought to clone TNFRs. 9/17 AM Tr. 29:18-21; 61:25-62:3 (Loetscher); JTX-85 53:4-9 (Dembic).

15. Roche's cloning method involved converting short stretches of amino acids called amino acid peptide sequences into oligonucleotide DNA probes to use as fishing hooks. JTX-86 (46:02-48:19) (Gubler); 9/17 AM Tr. 30:9-25 (Loetscher). Natural proteins are made from 20 amino acids and each is encoded by three DNA nucleotides ("a triplet codon") consisting of the letters G, A, T, and C. 9/13 AM Tr. 23:9-17 (Capon). Most amino acids are encoded by more than one triplet codon, and

many are encoded by up to six different triplet codons. JTX-86 (47:3-7, 52:7-19) (Gubler). Thus, a significant number of different, diverse DNA sequences can encode any given protein or peptide sequence. JTX-86 (46:23-48:19) (Gubler). Given this diversity, converting amino acid peptide sequences into DNA sequences to use as probes in 1990 was "technically very tricky." *Id.* Presuming a probe could be obtained, Roche would then use the probe to create primers to go "fishing" in a cDNA library for TNFR clones. 9/17 AM Tr. 30:16-21 (Loetscher).

a. Roche focused on the p55 TNFR.

16. Roche's early cloning efforts focused exclusively on the p55, resulting in Roche cloning the full-length p55 TNFR using its cDNA library fishing method by the summer of 1989. JTX-21; 9/17 AM Tr. 24:2-9; 32:12-21; 71:10-22 (Loetscher); JTX-80 (39:9-15, 72:3-9) (Parise); *see* JTX-72 (84:25-85:6; 85:21-23) (Brockhaus). Roche focused the majority of its characterization and development efforts thereafter on the p55 TNFR. JTX-21 (describing significant characterization of p55 to date); 9/17 AM Tr. 64:25-65:5, 65:10-14 (Loetscher).

17. On January 11, 1990, Roche submitted for publication the full-length p55 TNFR amino acid and DNA sequences. JTX-21 at Fig. 2; 9/17 AM Tr. 32:12-21 (Loetscher). Loetscher 1990 published on April 20, 1990. JTX-21. Roche's Loetscher 1990 and Genetech's Schall 1990, which were published simultaneously, were the first disclosure of the full-length DNA and amino acid sequence of the p55.

9/17 AM Tr. 32:22-25 (Loetscher); *see* JTX-21 at 3; JTX-64 at 3.

18. In the summer of 1989, Dr. Manfred Brockhaus (a named inventor) met with a former colleague from the Basel Institute of Technology, Andre Traunecker. JTX-72 (84:19-86:8, 86:17-87:4, 231:4-24) (Brockhaus); DTX-1141 at 1. During that meeting, Dr. Brockhaus explained that the Roche scientists had just cloned a TNFR and "d[id] not know" what they were going to do with it. JTX-72 (84:19-85:13; 231:4-13) (Brockhaus). Dr. Traunecker proposed the idea of making an IgG fusion protein with the p55 clone using human Ig vectors from Dr. Klaus Karjalainen, a collaborator at the Basel Institute, to construct the fusion proteins. *Id*. at 85:2-20; 231:14-19. Dr. Brockhaus returned to Roche and informed Dr. Lesslauer about Dr. Traunecker's idea. *Id*. at 86:9-16.

19. By February 15, 1990, Dr. Lesslauer had obtained Dr. Karjalainan's pcd4Hγ3 vector, which had been "gifted from Dr. Klaus Karjalainen." JTX-81 (123:10-124:9) (Lesslauer); PTX-745 at 63. This is the IgG3 vector discussed in the sole fusion protein DNA example of the patents-in-suit, Example 11. JTX-1 at 20:44-21:10. There is no documentary evidence that Roche conceived of TNF-IgG fusion proteins before Dr. Traunecker's proposal. JTX-82 (326:7-23) (Lesslauer); 9/17 AM Tr. 78:24-79:7 (Loetscher).

20. Roche's research led to the testing of a p55-IgG1 fusion protein in clinical trials. Specifically, Roche's clinical trials with the p55 TNFR fusion protein

started in 1993 and Roche prepared a New Drug Application for its clinical candidate. JTX-81 (89:25-90:2, 100:25-101:4) (Lesslauer); JTX-80 (39:9-15, 72:3-9) (Parise). By the early 2000s, Roche stopped clinical development of its p55-IgG1 fusion protein because it failed in clinical trials. JTX-80 (80:10-16, 20-22) (Parise); 9/24 PM Tr. 48:20-49:7 (Watt).

b. Roche Failed in Cloning the p75 TNFR and Instead, Cloned a Truncated, Mutated p75 TNFR.

21. While it was working on the p55 TNFR, in December 1989, Roche learned of Immunex's research into another TNFR. JTX-85 (51:14-51:25) (Dembic). Dr. Lesslauer recruited Dr. Dembic to clone the p75 TNFR. *Id*. at 53:4-5; 53:8-17. Although Roche had already cloned the full-length p55 TNFR, Dr. Dembic could not clone the full-length p75 TNFR using the same method. *Id*. at 58:3-20; JTX-81 (64:21-65:3) (Lesslauer).

22. In February 1990, Dr. Lesslauer recruited Dr. Eli Gubler to attempt a different approach using genomic DNA probes from two amino acid peptide sequences: one corresponding to what Roche thought was a p65 TNFR ("Nterm 65: LPAQVAFTPYAPEPGSTC") and the other corresponding to the p75 ("PKT15: SQLETPETLLGSTEEKPL"). JTX-86 (45:12-46:1, 61:16-24, 63:24-64:11, 64:17-19) (Gubler); JTX-81 (62:6-15, 65:4-12) (Lesslauer); DTX-1137 at 324.

23. The Nterm 65 sequence sent to Dr. Gubler was similar to, but more definite than, what is now disclosed as SEQ. ID 10 in the patents-in-suit. As shown

below, in place of the undetermined amino acid "X" in SEQ. ID 10, Nterm 65 included a "T" for the amino acid threonine. JTX-86 (109:15-20) (Gubler); DTX-1137 at 324; JTX-1 at 16:21-30.

Nterm 65	LPAQVAFTPYAPEPGSTC
SEQ. ID 10	LPAQVAFXPYAPEPGSTC

24. The PKT15 sequence sent to Dr. Gubler corresponds to what is now disclosed as SEQ. ID 7 in the patents-in-suit. JTX-86 (109:21-110:4; 112:9-24) (Gubler); DTX-1137 at 324; JTX-1 at 4:19-20.

25. Dr. Gubler worked on preparing DNA probes from the amino acid sequences of Nterm 65 and PKT15 for several weeks. DTX-1137 at 324-329. He failed to obtain a DNA sequence of Nterm 65 (SEQ. ID 10) that could be used as probe for fishing for a full-length p75 TNFR. JTX-86 (45:12-46:1) (Gubler); DTX-1137 at 329. Instead, he successfully converted PKT15 (SEQ. ID 7) into three probes denoted "clones 1, 2, and 14." JTX-86 (99:1-12) (Gubler); DTX-1137 at 324, 329. He sent one of those probes to Dr. Lesslauer in early March 1990. JTX-86 (50:19-51:06; 104:08-15) (Gubler). This amino acid sequence analysis is now reflected in Example 8 of the patents-in-suit. JTX-1 at 17:30-43; JTX-86 (110:22-114:7) (Gubler); 9/18 PM Tr. 30:10-13 (Naismith).

26. Shortly after receiving the DNA probe corresponding to PKT15 (SEQ. ID 7) from Dr. Gubler, Dr. Lesslauer fished out with that probe "the first partial

cDNA of the p75 receptor." JTX-81 (62:13-19; 65:10-11) (Lesslauer). Dr. Lesslauer then transmitted the probe and partial cDNA of the p75 TNFR to Dr. Dembic for further sequencing. JTX-81 (62:13-19) (Lesslauer).

27. In April 1990, Roche filed a Swiss application disclosing the sequences for its truncated, mutated p75 protein, which was later filed with the patents-in-suit as Figure 4. JTX-45 at 50-51. Even now, Roche has no evidence or data regarding the binding of Figure 4 to TNF. 9/17 AM Tr. 87:2-10 (Loetscher).

28. Concurrently, in April and May 1990, Dr. Dembic continued working on cloning the p75 TNFR. JTX-81 (65:11-12) (Lesslauer). Using Dr. Gubler's probe generated from PKT15 (SEQ. ID 7), Dr. Dembic isolated a partial p75 cDNA clone, but he could not obtain the full p75 clone despite trying different techniques. JTX-85 (58:11-24; 68:25-69) (Dembic).

29. Roche learned of Immunex's Smith 1990 publication around May 1990. JTX-85 (50:21-24) (Dembic). After being rejected by Science over Smith 1990, Roche published Dembic 1990 in Cytokine in July 1990, reporting a partial p75 sequence lacking the first 14 amino acids at the N-terminal. JTX-85 (51:3-7) (Dembic); JTX-23 at Fig. 1; 9/17 AM Tr. 94:8-20 (Loetscher). Dembic 1990 reports that Dr. Gubler's probe derived from PKT15 (SEQ ID 7) was used. JTX-23 at 2.

30. Both the specifications of the patents-in-suit, as filed, and Dembic 1990 identified the Nterm 65 peptide *amino acid sequence* (SEQ. ID 10) as being

associated with a p65 TNFR. JTX-1 at 16:21-30; JTX-2 at 16:41-51; JTX-23 at Fig. 1. Dembic 1990 did not report the *DNA sequence* of Nterm 65, because Roche was unable to determine it. 9/17 AM Tr. 94:8-25 (Loetscher); JTX-86 (45:12-46:1) (Gubler); DTX-1137 at 329.

31. By September 1990, Roche still did not have the full-length p75 TNFR available in a purified form. JTX-72 133:3-134:9 (Brockhaus). Indeed, as of November 1990, Roche still had not successfully "fished out" the full N-terminal sequence of the p75 using either SEQ. IDs 7 or 10. PTX-858 at 6 ("[A]ttempts to determine the N-terminal sequence of the 75 kDa band were not successful."); 9/17 AM Tr. 98:14-99:5 (Loetscher). Roche continued to report in November 1990 that SEQ. ID 10 was associated with the 65 kD protein and that Roche could not obtain the N-terminus of the 75-kD protein. *Id*.

32. There is no evidence that Roche was ever able to sequence the full p75 TNFR with either SEQ. IDs 7 or 10 using the method described in the patents-in-suit. 9/17 AM Tr. 96:10-21, 54:1-22, 98:17-99:5 (Loetscher), 9/18 PM Tr. 31:2-7; 35:4-18 (Naismith); JTX-85 (58:11-20) (Dembic).

c. Roche Never Conceived of or Made Etanercept or any p75-IgG1 Fusion Protein.

33. Because Immunex had beat Roche by sequencing the p75 protein, Roche did not seriously pursue p75 fusion proteins. *See* FOF ¶¶ 3-4. Roche produced no contemporaneous evidence that it ever conceived of a p75-IgG1 fusion protein.

9/17 AM Tr. 78:24-79:7 (Loetscher). Roche never made etanercept or any p75-IgG1 TNFR fusion protein. *Id*. at 24:15-20, 75:8-9. Roche never sent a p75 TNFR fusion protein into clinical trials. JTX-81 (89:3-6, 105:14-22) (Lesslauer); JTX-80 (80:3-9) (Parise).

34. When Roche sought to use a p75-IgG1 fusion protein in an animal study to compare its efficacy against Roche's p55-IgG1 fusion protein, Roche had to borrow one (etanercept) from Immunex. DTX-144 at 2 ("The TNFR-IgG1 p75 fusion protein was kindly supplied by the Immunex Corporation (Seattle, WA).").

B. Roche's TNF Patent Estate

1. Roche's Patent Estate Reflects its TNF Contributions.

35. By April 1990, Roche had cloned the full-length p55 and the truncated, mutated p75 TNFR proteins. *See* FOF ¶¶ 17, 27; JTX-45 at 3, 46-47, 50-51. Armed with these proteins, on April 20, 1990, Roche filed Swiss Patent Application No. CH 1347/90, describing and claiming the full-length p55 TNFR in Figure 1 and the truncated, mutated p75 TNFR in Figure 4. JTX-45 at 3, 46-47, 50-51.

36. On August 31, 1990, Roche filed the European App. No. 90116707.2, a priority application to the patents-in-suit. JTX-7 at 2. Roche disclosed the amino acid and DNA sequences of the full-length p55 TNFR in Figure 1 and the truncated, mutated p75 TNFR in Figure 4, same as the Swiss application. *Id*. at 47-48; 51-52.

37. In its August 1990 application, although Roche could have described

Immunex's Smith p80 sequence or the longer partial sequence disclosed in Dembic 1990, it chose to describe Figure 4 instead because it possessed this unique protein in April 1990, before Immunex published Smith 1990. 9/18 PM Tr. 22:10-12; 25:3-12; 25:22-26:5 (Naismith); 9/17 AM Tr. 93:12-24 (Loetscher). Roche recognized that it had priority over the truncated, mutated p75 protein in Figure 4, but not the full-length p75 TNFR protein described in Smith 1990. PTX-1056 at 578-79.

38. On September 10, 1990, Roche filed U.S. Patent Application No. 07/580,013 ("the '013 application"). JTX-10 at 1. Like the Swiss and European applications, the '013 application also disclosed the amino acid and DNA sequences of the full-length p55 TNFR in Figure 1 and the truncated, mutated p75 TNFR in Figure 4. *Id.* at 64-65, 68-69. This application was later abandoned. JTX-5 at 1.

39. On July 21 1993, Roche filed U.S. Patent Application No. 08/095,640 ("the '640 application") as a continuation of the '013 application. JTX-5 at 1. The parent patent of the patents-in-suit, U.S. Patent No. 5,610,279 ("the '279 patent"), eventually issued from this application. *Id.* The '279 patent also disclosed the amino acid and DNA sequences of the full-length p55 TNFR in Figure 1 and the truncated, mutated p75 TNFR in Figure 4. *Id.* at 3-4, 7-8.

40. During the prosecution of the '279 patent, the examiner issued a restriction requirement requiring Roche to elect one of three distinct inventions: (I) protein and antibody; (II) DNA, vector, and host; and (III) a method of isolating the

claimed proteins. JTX-9 at 117. It also required Roche to elect between the p55 and p75 protein, among other things. *Id.* at 117-18. Roche elected to pursue claims related to the p55 protein in the '279 patent application. *Id.* at 123.

41. Following the restriction requirement, Roche filed divisional applications from the '279 patent application, three of which issued as patents. JTX-1 at 3; JTX-2 at 3; PTX-1035 at 1.

2. Roche Told the PTO that Its Trunacted Mutated p75 Protein Was Distinct from Immunex's p75 Protein.

42. Roche obtained U.S. Patent No. 5,808,029 ("the '029 patent") covering a polynucleotide encoding Figure 4. PTX-1035 at 1,7-8; 22:64-65; cl. 1.

43. During prosecution of the '029 patent, Roche filed claims directed to the p75 TNFR—a "polynucleotide encoding an insoluble protein which has an apparent molecular weight of about 75 kilodaltons . . . which protein or fragment binds human tumor necrosis factor." PTX-1056 at 494-95 (cl. 44). The examiner rejected the pending claims directed to the p75 TNFR as anticipated over Immunex's Smith '760 patent. PTX-1056 at 563.

44. On July 21, 1997, Roche filed a response denying that Immunex's Smith protein discloses a p75 TNFR. Roche represented that "Smith et al. teaches a cDNA sequence encoding a human TNF-R of about 80 kD, whereas applicants claim a purified and isolated polynucleotide encoding an insoluble protein which has an apparent molecule weight of about 75 kilodaltons." PTX-1056 at 579-80; *see id.* at

577. Roche furher distinguished its truncated, mutated Figure 4 protein from Smith's protein because Figure 4 contains three amino acid mutations and one extra amino acid. *Id*. at 578-79.

3. Roche's Prosecution of the '182 Patent Exclusively Focused on the p55 Fusion Protein.

45. On May 19, 1995, Roche filed another divisional of the '279 patent application, which led to the '182 patent. JTX-1 at 3. Roche filed the '182 patent application before the Uruguay Round Agreements Act ("GATT") went into effect so that it would be entitled to a patent term running 17 years from the date of issuance. JTX-80 (86:8-17, 25; 87:6-25) (Parise). This application was not published until the '182 patent issued. JTX-76 (137:2-20) (Kirschner).

46. Roche filed a preliminary amendment with the '182 patent application in which all claims other than claim 48 were directed to the p55 TNFR. JTX-3 at 10-11; JTX-80 (74:4-9) (Parise). Claim 48 was a generic claim that did not identify a specific weight for the claimed TNFR. JTX-3 at 10.

47. In May 1996, Roche amended claim 48 so that it related only to the p55 TNFR. JTX-3 at 269; JTX-80 (77:3-24; 78:6-23) (Parise). Under Roche's control from May 1996 until late 2004, when Immunex took over prosecution, all claims in the '182 patent application related only to the p55 TNFR. JTX-3 at 294-95, 311-13, 332-33, 487-89, 613-15; JTX-80 (84:1-9; 84:25-85:2; 91:7-15; 92:15-18; 94:4-7; 96:4-8, 11-17; 101:2-4, 16-18; 102:4-7, 11-14; 103:11-13, 103:18-104:9) (Parise).

4. Roche's Prosecution of the '522 Patent Focused on the p55 Fusion Protein.

48. On May 19, 1995 (pre-GATT), Roche filed a third divisional of the '279 patent application, which led to the '522 patent. JTX-2 at 3; JTX-80 (87:6-15; 115:17-22; 116:2-5) (Parise). The '522 patent was filed with a preliminary amendment in which all claims related to the p55 TNFR. JTX-4 at 74, 80-82; JTX-80 (115:16-22, 116:9-13, 15-16) (Parise).

49. On August 5, 1996, Roche copied generic claims from U.S. Patent No. 5,447,851 (Beutler, et al.) solely to provoke an interference. JTX-4 at 289-98, 317-321; JTX-80 (123:9-11, 16-23; 125:5-9, 14-16; 125:23-126:6, 126:25-127:6) (Parise). In August 2000, Roche withdrew its request for an interference with the Beutler patent after Beutler amended his claims during reexamination. JTX-4 at 77, 83-87, 344-51; JTX-80 (127:24-129:8) (Parise). At the same time it withdrew its request for an interference, Roche amended the '522 patent application claims to relate to both the p55 and p75 receptor. *Id.*

50. In response to the August 2000 amendment, the examiner issued a restriction requirement requiring Roche to elect claims related to either the p55 TNFR or the p75 TNFR. JTX-4 at 450-52; JTX-80 (131:3-5, 10-22) (Parise). Roche again elected the p55 TNFR. JTX-4 at 499; JTX-4 at 521, 528-30, 667-72.

C. Relationship Between Roche and Amgen/Immunex.

51. In the late 1990s, Immunex became aware that Roche filed patents

relating to TNFR fusion proteins and began to negotiate an agreement with Roche. JTX-76 (135:7-10) (Kirschner).

1. Under The 1998 Roche-Immunex Agreement Roche Retained Ownership of the Patents-in-Suit.

52. In 1998, Roche and Immunex entered into a cross-license agreement, in which Roche non-exclusively licensed Immunex under the applications which subsequently became the patents-in-suit and Immunex granted Roche the option to license its own patents and applications ("the 1998 Agreement"). JTX-13.

53. Under the terms of the 1998 Agreement, Immunex paid royalties to Roche equivalent to 2% of Enbrel sales. JTX-76 (168:24-169:4) (Kirschner); JTX-13 at 15; JTX-80 (45:18-20) (Parise); 9/24 PM Tr. at 83:25-84:5 (Watt). Roche explicitly "retain[ed] ownership or control" of the patent rights, maintained control of prosecution, had the sole right to enforce the patents, and had the right to grant sublicenses. JTX-13 at 9 (Sec. 3.1), 10 (Sec. 3.4), 10-11 (Sec. 3.5); 9/24 PM Tr. 50:3-7; 51:4-16; 51:25-52:8; 53:1-12; 53:18-24 (Watt). Under the agreement, Immunex received all of the protection it needed in order to market Enbrel without fear of potential infringement of Roche patents. 9/24 PM Tr. 50:8-12 (Watt).

2. The 2004 Roche/Immunex Agreement.

a. The 2004 Agreement Transferred All Substantial Rights to the Patents-in-Suit from Roche to Immunex.

54. In 2004, after Roche's p55 TNFR fusion protein failed in clinical trials, and after Amgen's 2002 acquisition of Immunex, Roche and Immunex entered into

an Accord and Satisfaction Agreement ("the 2004 Agreement"). JTX 12; 9/24 PM Tr. 21:18-20; 24:6-8 (Watt). Immunex's acquired the patents-in-suit, including control over their prosecution, to extend its monopoly over Enbrel. *Id*. at 47:24-48:2, 78:4-9, 104:15-22; JTX-84 at 50:04-52:5, 57:11-17 (Arora).

55. Stuart Watt, Vice President, Law and Intellectual Property Officer at Amgen, negotiated the 2004 Agreement on behalf of Immunex and contributed to the drafting of it. JTX 12; 9/24 PM Tr. 20:19-23; 25:15-18 (Watt). Mr. Watt acknowledged that one of his jobs at Amgen was to "maximize [Amgen's] intellectual property rights." 9/24 PM Tr. 47:24-48:2 (Watt).

56. At the time that he negotiated the 2004 Agreement on behalf of Immunex, Mr. Watt was aware of the doctrine of double patenting in the context of patent prosecution and litigation. *Id*. at 80:7-18. Mr. Watt was aware that common ownership (or common inventors) was a requirement in order for the double patenting doctrine to apply. *Id.* at 80:19-23.

57. Mr. Watt admitted at trial that Immunex already had all of the rights under the 1998 agreement that it needed in order to market Enbrel free from the risk of potential patent infringement. *Id*. at 50:8-12. While he claimed the purpose of the 2004 Agreement was to buy out Immunex's royalty obligation, the 2004 Agreement did much more than that. *Id.* at 56:10-15.

58. In fact, the stated purpose of the 2004 Agreement was for Immunex

(and Wyeth, which had the exclusive right to distribute etanercept outside North America) both "*to acquire all rights* licensed pursuant to the [1998] Roche-Immunex Agreement *and* to eliminate the continuing obligations to pay royalties to Roche" under the 1998 Agreement. JTX-12 at 1 (emphasis added). The 2004 Agreement further stated that "Roche is willing to *sell such rights* in accordance with the terms of" the 2004 Agreement. *Id.* (emphasis added).

59. Among other things, the 2004 Agreement gave Immunex:

- The exclusive, irrevocable right to make, use, sell, offer for sale, and import the claimed invention, JTX-12 at 4 (Sec. 3.1); 9/24 PM Tr. 57:12-15 (Watt);
- The absolute right to exclude anyone from commercializing the claimed invention, JTX-12 at 4 (Sec. 3.1);
- The complete, unfettered right to sublicense the patents, JTX-12 at 4 (Section 3.1); JTX-80 (109:22-110:5; 110:7) (Parise); 9/24 PM Tr. 58:15-24; 59:15-20; 67:24-68:2 (Watt);
- The first right to sue for infringement, JTX-12 at 5 (Sec. 3.5); JTX-80 (111:11-15) (Parise); 9/24 PM Tr. 65:11-66:10 (Watt);
- The complete, unfettered right to control the litigation, JTX-12 at 5 (Sec. 3.5); JTX-80 (111:16-18; 111:20-24; 112:1-4) (Parise); 9/24 PM Tr. 67:17-23 (Watt);
- The complete, unfettered right to collect all damages, JTX-12 at 5 (Sec. 3.5); JTX-80 (112:11-15) (Parise); 9/24 PM Tr. 67:9-16 (Watt);
- The complete, unfettered right to settle the litigation, JTX-12 at 5 (Sec. 3.5); 9/24 PM Tr. 71:10-12 (Watt); and
- The complete, unfettered right to control the prosecution of the patent applications, JTX-12 at 5 (Sec. 3.3); JTX-80 (110:9-15; 110:17-111:7) (Parise); 9/24 PM Tr. 59:25-60:17; 61:20-23; 68:3-6 (Watt).

60. Roche had no right to terminate the agreement for any reason. JTX-12 at 13 (Sec. 9.2).

61. Mr. Watt acknowledged that rights such as maintaining control of patent prosecution, enforcing patents, and having the ability to grant sublicenses are indicative of having control of a patent. 9/24 PM Tr. 51:20-24; 52:9-21; 53:13-21 (Watt). He also acknowledged that pursuant to the 2004 Agreement, Immunex "got control of the patents" and was in a better position than it was under the 1998 Agreement. *Id*. at 56:13-15; 58:6-14.

62. Under the 2004 Agreement, Roche only retained: (1) an ability to practice the patents for "internal, non-clinical research only"; and (2) an ability to "initiate an action" for infringement "in the event that Amgen fails to rectify" the infringement or fails to "bring an action for such infringement" within 180 days of Roche's written request to do so. JTX-12 at 4 (Sec. 3.2), 6 (Sec. 3.6).

63. Thus, Roche could no longer do clinical research and, by extension, could not commercialize a product. JTX-12 at 4 (Sec. 3.2); JTX-80 (112:16-19; 112:24-113:5) (Parise); 9/24 PM Tr. 69:3-10 (Watt).

64. Roche's back-up right to sue only gave Roche the right to "initiate an action" for infringement in the event that Immunex did not "rectify" the infringement or "initiate an action" for infringement within 180 days after written request by Roche. JTX-12 at 6 (Sec. 3.6). Immunex, by contrast, had the right to "rectify"

infringement "by sublicense, by instituting suit for infringement, or by causing the alleged infringement to cease." JTX-12 at 5 (Sec. 3.5). Thus, Immunex could "rectify" any infringement raised by Roche by exercising its unfettered right to grant a sublicense to the accused infringer. JTX-12 at 4 (Sec. 3.1), 5 (Sec. 3.5).

65. The 2004 Agreement also provided that "Roche may not enter into any settlement agreement rectifying such infringement without the prior written approval" of Immunex. JTX-12 at 6 (Sec. 3.6). Immunex, in contrast, had the unfettered control to settle litigation it initiated. 9/24 PM Tr. 71:2-12 (Watt).

b. Immunex Deliberately Structured the 2004 Agreement As A "License" In The U.S.

66. Roche's corporate witness, John Parise, who was involved in the drafting and negotiation of the 2004 Agreement, testified that Roche "wanted to assign all rights to Immunex and Amgen." JTX-80 (16:24-17:2; 62:16-20) (Parise). Indeed, Roche expected to receive "an offer from Amgen to purchase [the] patents covering Enbrel." DTX-1072. But, Roche "couldn't get [Immunex] to agree to have [the patents] assigned" to them because Immunex "preferred a license." JTX-80 (62:21-24; 66:23; 67:1-5) (Parise).

67. While the 2004 Agreement contained a provision under which Roche would execute an assignment of the patents to Immunex upon request and payment of $50,000, Roche would have been willing to assign without the $50,000 "from day one." JTX-12 at 5 (Sec. 3.3); JTX-80 (109:12-13; 109:17-20) (Parise).

68. Mr. Watt further testified that Immunex entered into the 2004 Agreement in order to "buy out or buy down . . . future royalties" on sales of Enbrel. 9/24 PM Tr. 25:1-14 (Watt). Not only could Immunex have accomplished that without obtaining control of the patent applications, but, pursuant to the 2004 Agreement, Immunex paid Roche only $45 million total. *Id*. at 86:2-5. At the time, that represented only approximately nine days of Enbrel's approximately $5.2 million daily revenue. *Id*. at 87:25-88:12. Compared to Enbrel's current sales of $5 billion per year, it represents approximately three days of Enbrel's $15 million daily revenue. *Id*. at 87:5-24.

69. And contrary to Mr. Watt's testimony that Immunex wanted Roche to "remain the patent owner" so that it would participate in proceedings in the PTO and in litigation, *Id*. at 29:11-30:2, the 2004 Agreement had specific provisions contractually obligating Roche to participate in patent prosecution and litigation. JTX-12 at 5 (Sec. 3.4, 3.5); 9/24 PM Tr. 63:11-64:7; 66:15-21; (Watt). Mr. Watt admitted he had no contemporaneous documents reflecting his purported rationale for maintaining Roche's ownership interest. 9/24 PM Tr. 63:1-7 (Watt).

70. While the transfer of the same substantial rights from Roche to Wyeth outside North America was labeled an "assignment," the transfer of rights involving Immunex was labeled a "license." JTX-12 at 3, 4, 12.

71. Mr. Watt acknowledged that assignments are required to be disclosed

to the PTO. *Id*. at 82:14-18. But the 2004 Agreement was never disclosed to the PTO. 9/24 PM Tr. 82:25-83:3 (Watt). Mr. Watt admitted that the PTO never considered a double patenting rejection using Immunex's patent applications as double patenting references. *Id*. at 83:4-19.

D. After Immunex Took Control Of The Patents-in-Suit, Immunex Changed The Patents.

72. As a result of the 2004 Agreement, on October 6, 2004, Roche revoked its own powers of attorney for the '182 and '522 patent applications and transferred them to attorneys controlled by Immunex. JTX-80 (104:10-12, 104:17-105:12; 137:14-16; 137:21-138:14; 138:17-18) (Parise); JTX-3 at 875-82; JTX-4 at 706-713. From that point forward, prosecutions of the '182 and '522 patent applications were controlled solely by Immunex—with Roche having no say in the prosecution. JTX-80 (68:23-69:5, 110:9-20) (Parise); 9/24 PM Tr. at 59:25-60:17, 61:20-23 (Watt).

73. After taking control of the prosecution of the '182 patent, Immunex amended Roche's claims, which all related to a p55 TNFR, which it had prosecuted for 10 years, to claim either a p55 ***or*** a p75 TNFR:Fc fusion protein on January 18, 2005. JTX-3 at 893, 899-903. Then, on October 5, 2005, Immunex amended the claims to remove all references to the p55 TNFR. JTX-3 at 3165, 3167-72. As amended by Immunex, all claims related exclusively to the p75 TNFR:Fc fusion protein for the first time. *Id*.; 9/21 Tr. 102:18-21 (Kunin); JTX-3 at 3167.

74. On November 14, 2006, Amgen amended the specification to include a

reference to an October 17, 2006 deposit of a plasmid related to the p75 TNFR. JTX-3 at 3658; 9/24 PM Tr. at 84:11-23 (Watt). Although Drs. Lesslauer and Loetscher contend Roche produced this plasmid before August 31, 1990 (JTX-3 at 3660; 9/17 AM Tr. at 55:17-22 (Loetscher)), no such evidence was presented at trial.

75. Roche did not deposit the plasmid related to the p75 TNFR when the priority application was filed in 1990, and only provided the plasmid after Immunex asked for it over 16 years after it was supposedly created. 9/17 AM Tr. 93:25-94:3 (Loetscher). Neither Amgen nor Roche provided any chain of custody evidence of the plasmid deposit related to the p75 TNFR. Dr. Lesslauer did not supervise the deposit and relied on Amgen's representation that Amgen made the deposit. JTX-81 (165:20-166:6) (Lesslauer).

76. The asserted claims were not added to the '182 patent application until December 16, 2010. JTX-3 at 5461, 5468, 6012. Immunex drafted the claims that issued in the '182 patent without any involvement from Roche. JTX-80 (68:11-22) (Parise); 9/24 PM Tr. at 68:3-6 (Watt).

77. During prosecution, the proposed claims were repeatedly rejected as obvious. *E.g.*, JTX-3 at 3399-402, 3770-376, 5508-5516. Ultimately, in an appeal before the Board in the '182 patent application, Immunex convinced the Board that its uncontested evidence of unexpected results, particularly lack of effector functions based on Immunex's etanercept, not any Roche construct, was sufficient to rebut the

examiner's prima facie obviousness rejection. JTX-3 at 5378-79. In its August 31, 2011 Notice of Allowance, the examiner expressly allowed the '182 patent solely because of Immunex's unrebutted evidence of unexpected results. JTX-3 at 6017.

1. Immunex Changed the Claim Scope of the '522 Application to Exclusively Relate to the p75 Fusion Protein.

78. On December 9, 2004, Immunex filed an amendment cancelling all pending claims, including all claims related to the p55 TNFR, and filed amended claims, each related to the p75 receptor. JTX-4 at 722-26.

79. On August 30, 2007, Immunex filed an amendment to the claims and specification. JTX-4 at 3564-85. Immunex amended the specification to, for the first time, specifically incorporate Smith 1990 by reference. JTX-4 at 3564; 9/24 PM Tr. 84:11-20 (Watt). Immunex copied and pasted Figure 3B of Smith 1990, which shows the deduced (correct) amino acid sequence for the full p75 cDNA clone into the '522 patent specification as Figure 5. JTX-4 at 3564, 3566-67; 9/24 PM Tr. 85:2-17 (Watt). While Roche was aware of Smith 1990 by May 1990, JTX-85 (50:21-24) (Dembic), it was only after Immunex took over prosecution that Smith 1990 was incorporated into the patent application. Immunex also copied the figure legend describing from Figure 3B of Smith into the specification. JTX-4 at 3564. Additionally, Immunex amended the specification to include a reference to the plasmid deposit it made in October 2006. JTX-4 at 3565; *see* FOF ¶¶ 74-75.

80. The asserted claims were not added to the '522 patent application until

September 8, 2010. JTX-4 at 4247-48, 4286, 5364. Immunex drafted the claims that issued in the '522 patent without any involvement from Roche. JTX-80 (69:6-15) (Parise); 9/24 PM Tr. at 68:3-6 (Watt).

81. Similar to the '182 patent, when facing obviousness rejections, JTX-4 at 4210-15, 4609-16, 5299-302, Immunex ultimately relied on the Board's decision on the '182 patent to credit its unrebutted evidence of unexpected results to convince the PTO to issue the '522 patent. JTX-4 at 5325, 5328-32.

E. Immunex's Unprecedented Enbrel Monopoly.

82. Immunex has had patent protection and market exclusivity for Enbrel since 1998—for 20 years to date. DTX-1083 at 10; DTX-460 at 41; 9/25 Tr. 19:20-24 (McDuff). Faced with the expiration of its main patent in 2014, in 2004, Immunex obtained Roche's applications and changed the focus of the claims to cover etanercept. JTX-12; JTX-3 at 893, 899-903, 3167; JTX-4 at 723-26. Because the applications were strategically filed just weeks before GATT went into effect, the terms of the issued patents would be 17 years from the date of issuance. JTX-80 (86:8-17, 25; 87:6-25; 115:17-22; 116:2-5) (Parise).

83. The '182 patent issued on November 22, 2001 and expires on November 22, 2028. JTX-1. The '522 patent issued on April 24, 2012 and expires on April 24, 2029. JTX-2. If the '182 and '522 patents remain in force until their expiration dates, Immunex will have had over 30 years of market exclusivity for

Enbrel–something which is virtually unprecedented for a pharmaceutical or biologic product. 9/25 Tr. 27:25-28:14 (McDuff).

F. Sandoz's Development of Etanercept Biosimilar.

84. In 2010, Congress passed the BPCIA, intending to stimulate competition through biosimilars. 9/14 Tr. 13:13-22; 98:10-15 (McCamish). In the early 2000s, Europe was far ahead of the United States with respect to biosimilars, and Sandoz had the first biosimilar approved in Europe in 2006. *Id*. at 18:6-11.

85. Based in part on its experience in Europe, Sandoz began developing its biosimilar etanercept in the 2005-2006 timeframe. PTX-689; JTX-83 (105:4-9, 147:3-5) (Alliger). Sandoz named its etanercept project GP2015: "GP" stood for glycoprotein and 2015 was the year in which Sandoz expected to have freedom to operate globally. 9/14 Tr. 15:15-22; 19:22-20:3 (McCamish).

86. Sandoz's understanding that it would have freedom to operate globally in 2015 changed when Immunex issued a press release on November 22, 2011 that the '182 patent had issued and "describes and claims the fusion protein that is etanercept" and "has a term of 17 years from today." *Id*. at 20:4-21:13; DTX-1241.

87. By the end of 2011, when Immunex issued its press release, Sandoz had completed its technical process development and preclinical development for GP2015 and was poised to begin its Phase I clinical program. PTX-692 at 13. What remained to be done was "clinical confirmation" of GP2015's biosimilarity, DTX-

403 at 12; PTX-693 at 13; JTX-83 (157:4-11; 157:14-20; 157:23) (Alliger), the last part of establishing biosimilarity. 9/14 Tr. 97:12-17 (McCamish).

88. Having worked on GP2015 continuously since 2006, Sandoz filed its aBLA in July 2015. *Id*. at 27:16-28:1. GP2015 received FDA approval on August 30, 2016. *Id*. at 34:7-12.

II. The Asserted Claims Are Invalid for Obviousness-Type Double Patenting.

A. A POSA Would Have Been Highly Skilled.

89. A POSA is a scientist with an M.D. or a Ph.D. degree in biology, molecular biology, biochemistry, chemistry, or a similar field. Such a person would have 1-2 years of experience in the field of immunology or molecular immunology, including experience with cloning and expression of DNA, protein biochemistry on cell culture, protein purification, and immunological assays. 9/11 PM Tr. 30:14-31:18 (Blobel). Immunex has not offered a definition of the level of ordinary skill in the art that is materially different. 9/20 AM Tr. 18:5-22 (Wall).

B. Claim 1 Of The Psoriasis Patents Renders The Asserted Claims Invalid For Obviousness-Type Double Patenting.

90. U.S. Patent Nos. 7,915,225, 8,119,605, and 8,722,631 ("the psoriasis patents") claim priority to U.S. Patent Application No. 09/373,828, filed on August 13, 1999. JTX-39 at 1; JTX-40 at 1; JTX-41 at 1. Each of the psoriasis patents expire on August 13, 2019. Each of the psoriasis patents are owned by Immunex. *Id.*

91. Dr. Wall confirmed that he has offered no opinions for obviousness-

type double patenting on the psoriasis patents. 9/20 AM Tr. 100:12-19 (Wall).

92. Claim 1 of the psoriasis patents recites a method for treating a psoriatic condition by administering a therapeutically effective dose of "TNFR:Fc." JTX-39 at 16; JTX-40 at 16; JTX-41 at 17; *see* 9/11 PM Tr. 32:20-25 (Blobel). The specification defines "TNFR:Fc" to mean "etanercept." JTX-39 at 4:44-51; JTX-40 at 4:49-56; JTX-41 at 4:50-57; *see* 9/11 PM Tr. 35:22-36:15 (Blobel). As of August 1990, a POSA would have understood that the psoriasis patents claim a method of treatment comprising administering a therapeutically effective dose of etanercept to a patient having a psoriatic condition. 9/11 PM Tr. 33:14-35:1 (Blobel).

93. Claims 11 and 35 of the '182 patent are obvious in view of claim 1 of the psoriasis patents, which recites a method of treatment by administering "TNFR:Fc" (etanercept). 9/11 PM Tr. 41:10-17 (Blobel). The claimed "TNFR:Fc" (etanercept) is a fusion protein consisting of the extracellular region of the p75 TNFR fused to the full exon-encoded hinge-CH2-CH3 of a human IgG1. 9/11 PM Tr. 37:10-39:4 (Blobel). An inherent property of the claimed "TNFR:Fc" is specific binding to human TNF. 9/11 PM Tr. 39:5-20 (Blobel). The etanercept label reflects that, when administered to treat psoriatic conditions, etanercept functions as "a tumor necrosis factor (TNF) blocker" by specifically binding human TNF. DTX-44 at 1; 9/11 PM Tr. 39:21-40:16 (Blobel); *see also* JTX-75 (31:14-32:05) (Gudjonsson). The specification of the psoriasis patents also supports the inherent

TNF binding properties of etanercept. JTX-39 at 4:51-55; JTX-40 at 4:56-60; JTX-41 at 4:57-61; *see* 9/11 PM Tr. 40:18-41:6 (Blobel).

94. Claims 12 and 36 of the '182 patent are obvious in view of claim 1 of the psoriasis patents. 9/11 PM Tr. 41:25-42:19 (Blobel). To use etanercept for patient treatment, it would have been obvious to a POSA to deliver etanercept in a pharmaceutical composition with a pharmaceutically acceptable carrier material. *Id.*

95. Claims 3, 8, and 10 of the '522 patent are obvious in view of claim 1 of the psoriasis patents. 9/11 PM Tr. 45:10-14 (Blobel). To produce etanercept and make use of it, it would have been obvious to a POSA to culture a host cell comprising a polynucleotide encoding etanercept and to purify etanercept from the cell mass or culture medium. 9/11 PM Tr. 43:18-44:23 (Blobel); *see also id.* at 20:4-22:4 (Blobel). In August 1990, a CHO cell was one of the major host cell types that was used by scientists, and would have been an obvious choice. 9/11 PM Tr. 44:24-45:9 (Blobel); 9/20 AM Tr. 96:14-97:7 (Wall).

96. There is no dispute that a POSA in August 1990 would have had a reasonable expectation of success. As Dr. Wall concedes, such a person would have been able to produce etanercept by culturing a host cell and purifying etanercept using no more than ordinary skill. 9/20 AM Tr. 92:10-93:1 (Wall); *id.* at 96:14-97:7 (Wall); *id.* at 110:14-23 (Wall); 9/11 PM Tr. 20:4-22:4 (Blobel); 9/12 PM Tr. 55:2-56:5 (Blobel). Further, as admitted by Drs. Wall and Naismith, such a person would

have reasonably expected that etanercept would specifically bind to human TNF. 9/20 AM Tr. 112:4-11 (Wall); 9/18 PM Tr. 46:20-23, 47:8-14 (Naismith); 9/11 PM Tr. 118:11-16 (Blobel); 9/12 PM Tr. 56:6-13 (Blobel).

C. Claim 3 of the Jacobs '690 Patent Renders The Asserted Claims Invalid for Obviousness-Type Double Patenting.

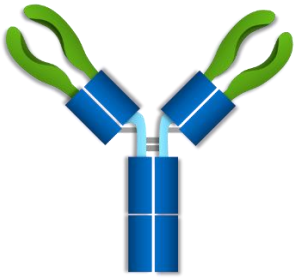
97. U.S. Patent No. 5,605,690 was filed on February 8, 1995 and issued on February 25, 1997. JTX-42 at 1. The Jacobs '690 patent expired on February 25, 2014. The Jacobs '690 patent is owned by Immunex Corporation. *Id.*

1. As Properly Construed, Claim 3 Of The Jacobs '690 Patent Covers A Method Of Administering Etanercept.

98. Claim 3 of the Jacobs '690 patent recites "a method for lowering the levels of active TNF-α in a mammal in need thereof which comprises administering to said mammal a TNF-lowering amount of a chimeric antibody comprising a TNFR comprising the sequence of amino acids 3-163 of SEQ ID NO:1 fused to the constant domain of an immunoglobulin molecule." JTX-42 at 26.

99. The parties dispute the meaning of the phrase "fused to the constant domain of an immunoglobulin molecule" which describes the structure of chimeric antibody of claim 3 of the Jacobs '690 patent. Defendants construe claim 3 to claim etanercept. 9/11 PM Tr. 46:5-47:8 (Blobel). Immunex construes claim 3 to claim a protein whereby the TNFR is fused to "a completely unchanged and unmodified constant region domain for the light chain and for the heavy chains." 9/20 AM Tr.

91:2-24 (Wall); *see* 9/11 PM Tr. 73:16-74:25 (Blobel). The parties' proposed claim constructions are illustrated below. *See* DDX-1002; PDX-11.21.

Defendants' Construction	Immunex's Construction
	

100. The claimed chimeric antibody recited in claim 3 of the Jacobs '690 patent covers etanercept. 9/11 PM Tr. 46:5-47:8 (Blobel). Etanercept is a "chimeric antibody" of the extracellular domain of the p75 TNFR (*i.e.*, amino acids 1-235 of SEQ ID NO:1) fused to the hinge-CH2-CH3 portion of a human IgG1 immunoglobulin. 9/11 PM Tr. 15:23-16:15, 55:10-56:19 (Blobel). The TNFR portion of etanercept comprises "the sequence of amino acids 3-163 of SEQ ID NO:1." *Id*. This TNFR portion of etanercept is "fused to the constant domain of an immunoglobulin molecule," *i.e.*, at the hinge-CH2-CH3 portion of an immunoglobulin molecule. *Id.*

101. Dr. Wall does not know whether the phrase "fused to the constant domain of an immunoglobulin molecule" precludes fusing the TNFR to the hinge-CH2-CH3 portion of an immunoglobulin. 9/20 PM Tr. 98:19-99:6.

a. The Specification Supports the Plain Meaning of Claim 3 as Covering Etanercept.

102. The specification of the Jacobs '690 patent shows that the claimed chimeric antibody covers etanercept. 9/11 PM Tr. 47:9-49:12 (Blobel). Figure 1 presents a schematic representation of a "recombinant human TNFR/Fc fusion protein," which is etanercept. JTX-42 at Fig. 1; *id.* at 2:11-18; 9/11 PM Tr. 47:9-25 (Blobel); 9/20 PM Tr. 90:3-10 (Wall). Figure 2 shows the construction of a plasmid encoding for etanercept. JTX-42 at Fig. 2; *id.* at 2:19-25. Figures 3-7 report the effect of administering etanercept. *Id.* at Figs. 3-7; *id.* at 2:26-47.

103. The single paragraph in the specification of the Jacobs '690 patent that discusses a "chimeric antibody" describes etanercept (the TNFR/Fc fusion protein):

> ***A recombinant chimeric antibody molecule may also be produced having TNFR sequences substituted for the variable domains of either or both of the immunoglobulin molecule heavy and light chains and having unmodified constant region domains.*** For example, chimeric TNFR/IgG1 may be produced from two chimeric genes--a TNFR/human κ light chain chimera (TNFR/G_κ) and a TNFR/human γ1 heavy chain chimera (TNFR/C_γ-1). Following transcription and translation of the two chimeric genes, the gene products assemble into a single chimeric antibody molecule having TNFR displayed bivalently. Such polyvalent forms of TNFR may have enhanced binding affinity for TNF ligand. ***One specific example of a TNFR/Fc fusion protein is disclosed in SEQ ID NO:3 and SEQ ID NO:4. Additional details relating to the construction of such chimeric antibody molecules are disclosed in WO 89/09622 and EP 315062.***

JTX-42 at 7:42-58 (emphasis added). As Dr. Wall admits, human IgG1 has multiple constant region domains. 9/20 PM Tr. 87:7-24 (Wall). Etanercept has the unmodified exon-encoded hinge domain, CH2 domain, and CH3 domain of a human IgG1. 9/11

PM Tr. 15:23-16:15 (Blobel). The TNFR/Fc fusion protein of SEQ ID NOS: 3 and 4 is etanercept. 9/11 PM Tr. 49:3-12 (Blobel); 9/20 PM Tr. 89:15-24 (Wall).

104. The specification calls out two embodiments of the claimed invention: the p75 extracellular region and etanercept. Examples 1 and 3 teach the production of the p75 extracellular region—referred to as a "soluble human TNFRI protein having the sequence of amino acids 1-235" or a "monomeric soluble TNF receptor." JTX-42 at 14:15-53, 15:61-17:14; 9/11 PM Tr. 55:10-56:19 (Blobel); 9/20 PM Tr. 91:17-92:6 (Wall). Example 2 describes the production of etanercept—referred to as a "TNFR/Fc fusion protein." JTX-42 at 14:55-15:60; 9/11 PM Tr. 48:1-9 (Blobel); 9/20 PM Tr. 90:11-91:1 (Wall). Example 4 describes the use of the p75 extracellular region and etanercept to suppress the effects of arthritic conditions, and Examples 5 and 6 describe further testing with just etanercept. JTX-42 at 17:16-20:43; 9/11 PM Tr. 48:10-29:2 (Blobel); 9/20 PM Tr. 91:2-92:19 (Wall).

b. The Prosecution History Supports the Plain Meaning of Claim 3 as Covering Etanercept.

105. The prosecution history of the Jacobs '690 patent (DTX-18), which Dr. Wall did not consider, reflects that the chimeric antibody recited in claim 3 was defined to cover etanercept. 9/20 AM Tr. 88:12-17 (Wall). The Jacobs '690 patent was filed as U.S. Patent Application No. 08/385,229, which is a continuation of U.S. Patent Application No. 07/946,236. JTX-42 at 1. The only fusion protein construct claimed in the originally filed Jacobs '236 application was a protein "wherein the

soluble human TNFR is fused to the Fc region of a human immunoglobulin molecule," *i.e.*, etanercept. DTX-18 at 17.

106. During prosecution of the Jacobs '690 patent, the applicants amended the claims to specify that an example of a "chimeric antibody comprising a TNF receptor and the constant domain of an immunoglobulin molecule" was a "soluble human TNFR is fused to the Fc region of the human immunoglobulin molecule." Specifically, the applicants amended the claims of the Jacobs '236 application as follows, with additions in underline and deletions in strikethrough:

> 1. A method for treating TNF-mediated inflammatory diseases which comprises administering to a mammal in need thereof a therapeutically effective amount of a TNF antagonist selected from the group consisting of a TNF receptor, ~~a TNF binding protein~~ and a chimeric antibody comprising a TNF receptor and the constant domain of an immunoglobulin molecule.
>
> . . .
>
> 6. A method according to claim 4 [ultimately depending on claim 1], wherein the soluble human TNFR is fused to the Fc region of a human immunoglobulin molecule.

See DTX-18 at 17 (originally presented claims); *id.* at 173; *id.* at 220. Claim 6 depends upon claim 1. DTX-18 at 17. The TNFR:Fc protein recited in claim 6 is thus a species of the "chimeric antibody comprising a TNF receptor and the constant domain of an immunoglobulin molecule" recited in claim 1. *Id.*

107. During prosecution of the Jacobs '690 patent, to claim an earlier priority date, the applicants relied on their earlier applications' disclosure of

"chimeric antibodies" to support the claimed TNFR:Fc fusion proteins. DTX-18 at 226. They explained that the "construction of Fc fusions was known, and the ordinary artisan at the time the instant application was filed would have known how to make Fc fusions in general. See for example, EP 315062 and WO 89/09622 . . . ." *Id.* Both EP 315062 and WO 89/09622 are identified in the earlier applications and the Jacobs '690 patent as detailing "the construction of such chimeric antibody molecules." *See* DTX-18 at 25; JTX-42 at 7:56-58.

108. The applicants also submitted a declaration by Dr. Moreland explaining the utility of administering a "soluble TNFR:Fc fusion protein" (*i.e.*, etanercept) to treat patients suffering from inflammatory conditions, such as rheumatoid arthritis. DTX-18 at 224, 237-38; *id.* at 231-81; 9/11 PM Tr. 49:13-51:6 (Blobel). After the claims were amended to recite a method for inhibiting TNF-α activity by administering a TNF antagonist, including "a chimeric antibody comprising a Type I TNF receptor fused to the constant domain of an immunoglobulin molecule," the applicants maintained that Dr. Moreland's declaration describing the administration of etanercept "conclusively proves the utility *in vivo* of the claimed method." DTX-18 at 293-94, 297.

109. The applicants further argued that the claimed chimeric antibody was nonobvious in view of the Fc fusion protein prior art (*e.g.*, the Capon '964 patent), because there was no motivation to construct an Fc fusion protein with a TNFR.

DTX-18 at 301. The applicants did not argue that the claimed chimeric antibody excludes an Fc fusion protein. *Id.*

c. Extrinsic Evidence Supports the Intrinsic Record Regarding the Meaning of Claim 3.

110. The Enbrel label lists the Jacobs '690 patent among the "patents covering methods, vectors, and/or host cells for making [etanercept] or methods for using [etanercept]." DTX-44 at 29; *see also* DTX-460 at 41; DTX-1083 at 10.

2. As Properly Construed, Claim 3 of the Jacobs '690 Patent's Renders Obvious the Asserted Claims.

111. Asserted claims 11 and 35 of the '182 patent are obvious in view of claim 3 of the Jacobs '690 patent. 9/11 PM Tr. 51:20-52:5, 55:10-58:18 (Blobel).

112. The Jacobs '690 patent's chimeric antibody (etanercept) comprises "the sequence of amino acids 3-163 of SEQ ID NO: 1," whereby SEQ ID NO: 1 is the full sequence of the p75 TNFR. JTX-42 at 26; 9/11 PM Tr. 51:20-52:2 (Blobel). In August 1990, a POSA would have been motivated to use the entire p75 extracellular region. 9/11 PM Tr. 52:3-5 (Blobel). The prior art Smith '760 patent teaches that the entire p75 extracellular region (*i.e.*, amino acids 1-235 of SEQ ID NO: 1) "retains its ability to bind TNF" and is a "particularly preferred" soluble TNFR construct. JTX-65 at 9:17-29; 9/11 PM Tr. 55:10-56:19 (Blobel).

113. Furthermore, in August 1990, a POSA would have selected the human IgG1, because the IgG1 is the most common immunoglobulin found in human

bodies and was the best studied and most understood. 9/11 PM Tr. 57:7-23 (Blobel); JTX-72 (188:3-14) (Brockhaus); *see* 9/17 AM Tr. 70:10-13 (Loetscher); JTX-81 (80:7-80:21) (Lesslauer). The Smith '760 patent teaches fusing a portion of a TNFR to a human IgG1. JTX-65 at 10:53-68; 9/11 PM Tr. 57:24-58:8 (Blobel).

114. Claim 3 of the Jacobs '690 patent specifies that a TNF-lowering amount of the chimeric antibody is administered to a mammal. JTX-42 at 26. An inherent property of administering a TNF-lowering amount of etanercept would be specific binding to human TNF. 9/11 PM Tr. 58:9-18 (Blobel); FOF ¶¶ 93, 230.

115. Asserted claims 12 and 36 of the '182 patent are obvious in view of claim 3 of the Jacobs '690 patent. 9/11 PM Tr. 58:19-59:4 (Blobel). As discussed with respect to the psoriasis patents, for the same reasons, it would have been obvious to a POSA to deliver etanercept in a pharmaceutical composition with a pharmaceutically acceptable carrier. *Id.*; *see also* FOF ¶ 94.

116. Asserted claims 3, 8, and 10 of the '522 patent are obvious in view of claim 3 of the Jacobs '690 patent. 9/11 PM Tr. 59:5-60:3 (Blobel). As discussed with respect to claim 1 of the psoriasis patents, for the same reasons, as of the relevant time, it would have been obvious for a POSA to culture a host cell (*e.g.*, CHO cells) comprising a polynucleotide encoding etanercept and to purify etanercept from the cell mass or culture medium. *Id.*; *see also* FOF ¶ 95.

3. Under Dr. Wall's Construction, Claim 3 of the Jacobs '690 Patent's Renders Obvious the Asserted Claims.

117. Under Dr. Wall's construction, claim 3 of the Jacobs '690 patent recites the same chimeric antibody as described in the Smith '760 patent. 9/20 AM Tr. 91:2-24 (Wall); *see* JTX-65 at 10:53-68. For the same reasons as discussed below with respect to the Smith '760 patent, the asserted claims would have been obvious in view of Dr. Wall's construction of claim 3 of the Jacobs '690 patent. *See infra* Section IV.B.

D. Claim 5 of the Brockhaus '279 Patent Renders The '182 Patent Asserted Claims Obvious.

118. U.S. Patent No. 5,610,279 was filed on July 21, 1993 and issued on March 11, 1997. JTX-5 at 1. The Brockhaus '279 patent expired on March 11, 2014. The Brockhaus '279 patent and the '182 patent have the same named inventors in common. *Compare* JTX-5 at 1, *with* JTX-1 at 1.

119. A POSA, as of the relevant time, would have understood that claim 5 of the '279 patent is directed to a fusion protein comprising a soluble fragment of the p55 TNFR (*e.g.*, the extracellular domain of the p55 TNFR) fused to the hinge-CH2-CH3 potion of a human IgG1. JTX-5 at 20; 9/11 PM Tr. 122:1-25 (Blobel).

120. Claims 11 and 35 of the '182 patent are obvious in view of claim 5 of the Brockhaus '279 patent. The only difference between these claims is the use of the extracellular domain of the p75 TNFR instead of a soluble fragment of the p55 TNFR. 9/11 PM Tr. 123:1-12 (Blobel); 9/18 PM Tr. 111:9-19 (Greene). The full extracellular region of the p75 TNFR would be an obvious substitution for the p55

soluble fragment in claim 5 of the '279 patent, as the soluble forms of both p55 and p75 TNFRs were known to perform the same function of inhibiting TNF activity. 9/11 PM Tr. 52:3-5, 55:10-56:19, 123:13-16 (Blobel). A POSA would have reasonably expected that such a fusion protein would inherently and specifically bind human TNF. 9/11 PM Tr. 123:17-21 (Blobel).

121. Claims 12 and 36 of the '182 patent are obvious in view of claim 5 of the Brockhaus '279 patent, for the same reasons discussed above. *See* FOF ¶ 94.

III. Lack of Written Description and Enablement

A. There is No Written Description of Etanercept.

122. A POSA in the art reading the specification would not have understood that the Roche inventors had invented and possessed the claimed invention as of August 1990. 9/13 AM Tr. 113:5-114:8, 115:1-11 (Capon).

1. There is No Description of Amino Acids 1-235, the Extracellular Region of a p75-TNFR.

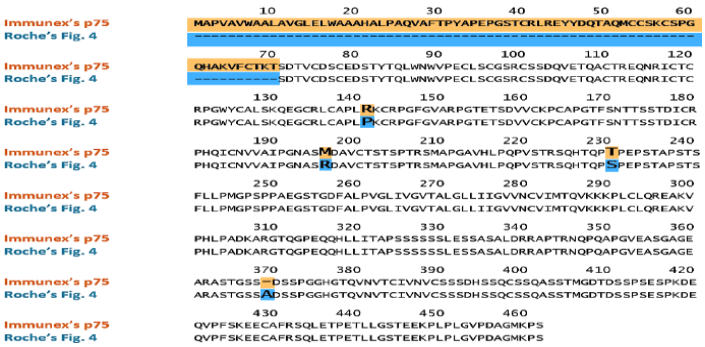
123. There is no dispute that all of the asserted claims require the extracellular region of a p75 TNFR. 9/13 AM Tr. 19:20-20:18 (Capon); 9/18 AM Tr. 45:19-46:2 (Naismith). Moreover, both parties' experts agree that there is no disclosure of the full p75 extracellular region or the full-length p75 TNFR. 9/13 AM Tr. 21:20-25 (Capon); 9/18 PM Tr. 17:5-9 (Naismith); 9/17 AM Tr. 86:10-15 (Loetscher). In fact, the specification of the priority application directs a POSA away from the full-length p75 TNFR. 9/13 AM Tr. 36:24-37:13 (Capon).

124. The specification describes two acts as the invention, the first act: a full-length p55 TNFR (Figure 1), and the second act: a truncated, mutated p75 TNFR distinct from the full-length p75 TNFR (Figure 4). JTX-10 at 64-65; 9/13 AM Tr. 22:1-18, 23:23-24:17, 36:24-37:13 (Capon); 9/17 AM Tr. 21:18-22:1 (Loetscher); 9/18 PM Tr. 16:22-17:4 (Naismith). There is no dispute that Figure 4 is the only p75 TNFR sequence disclosed in the specification. 9/13 AM Tr. (22:1-7) (Capon); 9/18 AM Tr. 52:19-53:1 (Naismith).

125. The p55 and p75 TNFRs are distinct proteins with different extracellular regions. 9/18 PM Tr. 16:22-17:4 (Naismith); 9/18 PM Tr. 133:4-24 (Greene). The specification identifies the extracellular, intracellular, and transmembrane regions of the p55 TNFR, but does not identify or even mention the corresponding regions of the Figure 4 protein. JTX-10 at 64-65; 9/18 PM Tr. 17:10-18 (Naismith).

a. Roche's Truncated, Mutated Figure 4 p75 TNFR is a Distinct Protein from the Full-Length p75 TNFR.

126. Immunex published Smith 1990 in May 1990 and disclosed what is now known to be the full-length p75 TNFR. JTX-24; 9/13 AM Tr. 24:18-20 (Capon). Smith 1990 disclosed that the Smith protein "may correspond to the 80-kD form." JTX-24 at 4; 9/13 AM Tr. 25:6-14 (Capon). As shown below, Roche's Figure 4 Protein is different from Immunex's Smith Protein in five important ways. DDX-2006; 9/13 AM Tr. 26:7-27:3 (Capon); 9/17 AM Tr. 85:13-19 (Loetscher).



127. First, as compared to the actual sequence of 235 amino acids comprising the full p75 extracellular region, the Figure 4 protein deletes the first 70 amino acids, as shown in blue highlighting above. 9/13 AM Tr. 24:11-17; 27:4-14 (Capon); 9/18 AM Tr. 127:5-16 (Naismith); 9/17 AM Tr. 85:13-15 (Loetscher). The first 22 deleted amino acids comprise the signal sequence, which is essential to protein excretion from the cell. 9/13 AM Tr. 27:15-28:4 (Capon). The next 48 deleted amino acids comprise the N-terminus of the p75 extracellular region, which is a substantial portion—20 percent—of the extracellular region. 9/13 AM Tr. 28:5-13 (Capon); 9/18 AM Tr. 128:12-18 (Naismith).

128. Although it was not known in August 1990, scientists have since discovered that the 48 deleted amino acids are likely important to TNF binding. 9/13 AM Tr. 28:5-29:14 (Capon); DTX-180 at 1; DTX-145 at 1. In light of these studies published 10 and 20 years after August 1990, it is possible that Figure 4 is missing critical sequences for binding to TNF, but this is still unclear. DTX-180 at 1; DTX-145 at 1; 9/13 AM Tr. (30:10-18) (Capon); 9/17 AM Tr. 70:6-8, 87:2-14 (Loetscher); JTX-81 (138:16-19) (Lesslauer); JTX-82 (195:1-15) (Lesslauer).

129. Second, as compared to the actual sequence of 235 amino acids comprising the full p75 extracellular region, the Figure 4 protein contains three amino acid mutations. 9/13 AM Tr. 31:10-13 (Capon); 9/17 AM Tr. 85:16-19 (Loetscher). A POSA would call these mutations "non-conservative" because they are drastic, they arise in nature, and they result in two different proteins by virtue of the changes. 9/13 AM Tr. 31:10-13, 31:16-19 (Capon).

130. The first amino acid mutation is located at amino acid residue 141. 9/13 AM Tr. 30:20-31:3 (Capon). In the Smith protein, this amino acid is an R, or Arginine. 9/13 AM Tr. 31:4-9 (Capon). In the Figure 4 protein, this amino acid is a P, or proline. 9/13 AM Tr. 31:9-10 (Capon). A POSA in 1990 would have understood that changing R to P is a non-conservative change: while R leads to a smooth protein "necklace," P causes a sharp kink in the necklace resulting in an entirely different structure. *Id*. A POSA would have understood that this R to P mutation may confer some advantages, but would not necessarily believe one is better or worse than the other. 9/13 AM Tr. 31:14-32:14 (Capon).

131. The second amino acid mutation is located at amino acid residue 196. 9/13 AM Tr. 32:15-33:11 (Capon). In the Smith protein, the amino acid at position 196 is an M, or methionine. *Id*. In the Figure 4 protein, the amino acid at position 196 is an R, or arginine. *Id*. A POSA in 1990 would have understood that changing M to R is also a non-conservative mutation: whereas the methionine has no effect

on the protein necklace at that point, the arginine, being charged, seeks out and gravitates toward other charged parts of the necklace, resulting in a protein with a different shape and possibly a different function. *Id*. Indeed, this M to R mutation is very drastic because we now know it is associated with susceptibility to the disease lupus. 9/13 AM Tr. 33:12-19 (Capon).

132. The third amino acid mutation is located at amino acid residue 230. 9/13 AM Tr. 33:23-34:18 (Capon). In the Smith protein, this amino acid at position 230 is a T, or threonine. *Id*. In the Figure 4 protein, this amino acid at position 230 is an S, or serine. *Id*. A POSA in 1990 would have understood that changing a T to an S is associated with the attachment of sugar at this residue, which can affect both its structure and biological activity. *Id*.

133. Given the deletion of amino acids 1 through 70 and the three mutations, a POSA in 1990 looking at the sequences of the Smith protein and the Figure 4 protein would have understood that they correspond to two very different proteins. 9/13 AM Tr. 35:9-19 (Capon); 9/18 AM Tr. 98:4-6 (Naismith).

134. Third, as compared to the actual sequence of 235 amino acids comprising the full p75 extracellular region, the Figure 4 protein has one extra amino acid, an A, or alanine, at residue 369. 9/13 AM Tr. 34:19-35:8 (Capon). A POSA in 1990 would have understood that deleting an amino acid, as the Smith protein does, is also a drastic mutation resulting in a different protein with significant structural

differences. *Id*.

135. In sum, a POSA would have understood, that the Figure 4 protein and its variants, with its particular structure and biological activities, is the subject of the invention, not the Smith protein. 9/13 AM Tr. 35:9-19 (Capon); 9/17 AM Tr. 85:6-19, 87:11-14 (Loetscher).

b. The Specification Describes the Figure 4 Protein as the Invention Relating to p75 TNFR.

136. The specification as of September 1990 describes as the invention the Figure 4 protein—not a protein with the full p75 extracellular region. 9/13 AM Tr. 22:1-7 (Capon).

137. Starting at Summary of the Invention, the specification unambiguously identifies the Figure 4 protein as the "present invention." 9/13 AM Tr. 35:23-36:3 (Capon). Specifically, it describes as the "invention" "TNF-binding proteins containing amino acid sequences of Figure 1 or Figure 4, proteins containing fragments of these sequences, and proteins analogous [*sic*] to the sequences of Figure 1 or Figure 4 or to fragments thereof." JTX-10 at 8:25-29.

138. A POSA would have understood from this description that there are two acts to the invention: a Figure 1 (p55) protein, and a truncated, mutated Figure 4 protein, or analogues thereof in which amino acids have been replaced or deleted in a known way without affecting binding. 9/13 AM Tr. 36:4-19 (Capon).

139. Notably, Figure 4, and smaller fragments of it, is the ***only*** p75 TNFR

mentioned in the Summary of the Invention. 9/18 PM Tr. 11:6-12:7 (Naismith). A POSA would have understood from this that the invention, with respect to the p75, is Figure 4 and not any other p75 TNFR protein. 9/13 AM Tr. 36:16-19 (Capon).

140. The Detailed Description of the Invention likewise defines Figure 4 as the p75 portion of the invention. JTX-10 at 10; 9/13 AM Tr. 36:20-37:13 (Capon). The Detailed Description describes the "present invention" as TNF-binding proteins "containing the amino acid sequence depicted in Figure l or in Figure 4…." JTX-10 at 10:11-13. A POSA would have understood from this description that the inventors are reiterating that there are two acts to the invention: a Figure 1 (p55) protein, and a truncated, mutated Figure 4 protein. 9/13 AM Tr. 36:24-37:13 (Capon).

141. The Detailed Description further describes the present invention as "proteins containing fragments of either sequence, and analogues of any such proteins for example proteins containing amino acid sequences analogous to the amino acid sequences of Figure l or Figure 4 or to fragments thereof." JTX-10 at 10:13-17. A POSA in 1990 would have understood from this description that the POSA should start with the sequences identified in Figures 1 or 4 and make deletions. 9/13 AM Tr. 37:15-38:2 (Capon).

142. The Smith protein is not an analogue of Figure 4 because the specification limits the definition of an analogue, in relevant part, to "a protein….in which one or more amino acids have been replaced or deleted, without thereby

eliminating TNF-binding ability." JTX-10 at 10:17-23; 9/13 AM Tr. 38:3-19 (Capon). The Smith protein does not arise from the Figure 4 protein by replacing or deleting any sequence. 9/13 AM Tr. 38:14-19 (Capon).

143. The Detailed Description further explains that:

> The present invention embraces not only allelic variants, but also those DNA sequences which result from deletions, substitutions and additions from one or more nucleotides of the sequences given in Figure 1 or Figure 4, whereby in the case of the proteins coded thereby there come into consideration, just as before, TNF-BP. One sequence which results from such a deletion is described, for example, in Science 248, 1019-1023, (1990).

JTX-10 at 15:1-10. The Science paper is Smith 1990. 9/13 AM Tr. 39:6-8 (Capon).

144. A POSA in 1990 would have understood from this paragraph that the Smith protein is cited in a singular context as a deletion of an amino acid residue from the Figure 4 protein. 9/13 AM Tr. 39:9-18 (Capon). Indeed, the Smith protein contains a deletion at amino acid residue 369 relative to the Figure 4 protein. 9/13 AM Tr. 39:16-40:2 (Capon). Other than this sentence, the specification makes no other mention of Smith 1990 or the Smith protein. 9/13 AM Tr. 40:22-25 (Capon). Thus, the specification teaches a POSA in 1990 not to use the Smith protein because it specifically describes Smith 1990 sequence as a deletion only, not as a substitution or addition. 9/13 AM Tr. 39:9-18 (Capon).

145. There is no dispute that a POSA in 1990 would have understood from the sole mention of Smith 1990 in the specification that the Smith protein is not

incorporated. 9/13 AM Tr. 40:3-14 (Capon); 9/13 PM Tr. 91:6-9 (Capon); 9/18 PM Tr. 24:8-10 (Naismith); JTX-79 (134:6-11) (Lyman). Dr. Naismith explained that the sentence was "confusing" and he "could not make sense of it because it's on its face ridiculous." 9/18 PM Tr. 22:19-23, 23:20-24, 52:23-7 (Naismith).

146. Dr. Naismith further admitted that the the sole mention of Smith 1990 in the specification does not say where in the Smith 1990 paper to find the invention, does not cite any specific part of Smith 1990 or the full-length p75 sequence in Figure 3b, and does not explain what Smith 1990 is in the context of the invention. 9/18 PM Tr. 24:4-7, 24:19-25:2, 25:22-26:5 (Naismith).

147. The Roche applicants could have specifically incorporated Smith 1990 by reference or added the Smith protein to the specification, as Immunex did in 2007, but they did not. 9/18 PM Tr. 25:3-21 (Naismith).

148. Dr. Lyman, who filed a declaration in support of both applications to overcome written description rejections (9/13 PM Tr. 86:2-7 (Capon)), agrees with Dr. Naismith. In its decision overturning a written description rejection, the Appeals Board cited Dr. Lyman's May 22, 2007 declaration ("Lyman PTO Declaration 1"), which primarily rely on prior art and not the specification's written description. 9/13 PM Tr. 85:5-9, 94:21-95:3, 97:21-24 (Capon).

149. Like Dr. Naismith, Dr. Lyman testified at trial that Smith 1990 is referenced as a deletion of an amino acid only, and not an addition of amino acids.

JTX-79 (133:18-134:5) (Lyman). He admitted the reference to Smith 1990 in the specification does not direct a POSA to "[u]se Smith to complete the sequence of Figure 4." JTX-79 (134:6-11) (Lyman). This testimony is inconsistent with his sworn declarations to the PTO stating, "I would interpret this paragraph to mean that the Smith sequence was contemplated by the inventors because the Smith (1990) article is specifically cited" (PTX-6.396 at ¶ 20) and "the application clearly conveys an intent to incorporate by reference the sequences in Smith (1990) of soluble or non-soluble TNF receptors" (JTX-4 at 4396 ¶ 13 ("Lyman PTO Declaration 2")).

150. Further, the Lyman declarations misleadingly state, "[s]ince the amino acid sequence of Figure 4 is ***almost identical (almost 99% identical)*** to that of Smith, it would be clear to one of skill in the art that the protein represented by the Figure 4 sequence was the same protein described in Smith" (PTX-6.396 at ¶ 16; JTX-4 at 4394 ¶ 9) and "[d]espite differences between the sequences disclosed in the application and those in the Smith (1990) article, the amino acid sequences are nearly ***99% identical overall***" (JTX-4 at 4395 ¶ 10).

151. These statements in Lyman's declarations are inaccurate and misleading. 9/13 PM Tr. 104:24-13, 109:13-110:2 (Capon); 9/18 AM Tr. 126:11-20, 127:17-128:4 (Naismith). The extracellular region of the Figure 4 protein is over 20 percent different from the Smith protein and ***15 percent different overall***. 9/13 PM Tr. 109:18-110:10, 111:4-10 (Capon); 9/18 AM Tr. 127:17-128:18 (Naismith).

152. The next sentence of the Lyman PTO Declaration 1 says, "[a]ttached as Exhibit D is an alignment of the Figure 4 sequence with the ***complete sequence*** of p75 TNFR to illustrate this point." PTX-6.396 at ¶ 16 (emphasis added). This statement in the Lyman PTO Declaration 1 is also inaccurate and misleading. 9/13 PM Tr. 105:14-106:2, 109:8-25 (Capon). Exhibit D only compares the portions that overlap, not the "complete sequences." 9/13 PM Tr. 105:14-106:6, 108:21-24, 109:8-12 (Capon); 9/18 AM Tr. 128:1-18 (Naismith). A POSA in 1990 would have compared the entire length of the protein, not just the overlapping portion because comparing only the overlapping portion does not provide an accurate assessment of similarity. 9/13 PM Tr. 105:14-106:6, 108:21-24 (Capon); 9/18 AM Tr. 120:24-25, 121:17-21 (Naismith).

153. The Detailed Description defines, as the first act, "preferred first of all those DNA sequences which code for such a protein having an apparent molecular weight of about 55 kD, whereby the sequence given in Figure l is especially preferred…." JTX-10 at 15:12-15; 9/13 AM Tr. 41:1-15 (Capon).

154. The Detailed Description further defines as the second act "also preferred DNA sequences which code for a protein of about 75/65 kD, whereby those which contain the partial cDNA sequences shown in Figure 4 are preferred. Especially preferred DNA sequences in this case are the sequences of the open reading frame of nucleotide 2 to 1,177." JTX-10 at 15:23-28; 9/13 AM Tr. 41:16-

42:3 (Capon). This disclosure would have plainly told a POSA in 1990 that the invention is about the Figure 4 protein. 9/13 AM Tr. 41:25-42:14 (Capon). This disclosure would have also told a POSA that an especially preferred embodiment is one nucleotide less, with the first 71 amino acids deleted. 9/13 AM Tr. 42:15-43:7 (Capon).

155. The Detailed Description further provides that "DNA sequences which code for insoluble as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred." JTX-10 at 15:33-35. This disclosure does not describe the full-length p75 TNFR because it mentions soluble and insoluble proteins without giving any description of any specific sequence at all. 9/13 AM Tr. 43:8-22 (Capon).

156. The examples in the specification are likewise directed primarily to the p55 TNFR. 9/13 AM Tr. 44:3-9, 69:13-18 (Capon). None of the examples describe a full-length p75 TNFR, a method for obtaining a full-length p75 TNFR, or a p75 fusion protein, much less a p75-IgG1 fusion protein, much less etanercept. JTX-82 at 91:12-194:7, 297:21-298:7 (Lesslauer).

157. Example 8 describes the cloning of the p55 and truncated, mutated p75 leading up to filing the priority application. JTX-10 at 38-39; 9/13 AM Tr. 43:23-44:9 (Capon). With respect to the p75, the applicants describe adapting the method they used to clone the p55. 9/13 AM Tr. 43:23-44:9 (Capon); 9/17 AM Tr. 96:3-21

(Loetscher); JTX-86 (111:10-112:24) (Gubler); 9/18 PM Tr. 30:10-13 (Naismith). They obtained several clones, but they provided no information on these clones other than the Figure 4 clone. 9/13 AM Tr. 44:10-16 (Capon). A POSA would have understood this as a clear signal that the Figure 4 protein—and not other clones—is the intended and described invention. 9/13 AM Tr. 44:17-20 (Capon).

158. A POSA would have been aware of prior art that may correspond to the p75 TNFR (i.e., Smith 1990 and Dembic 1990). 9/13 AM Tr. 44:21-45:2 (Capon). Dembic 1990, which is authored by a number of the inventors of the patents-in-suit, published in July 1990. JTX-23 at 1; 9/13 AM Tr. 45:3-15 (Capon). But, Dembic 1990 reports another truncated receptor missing the signal sequence and the first 14 amino acids of the p75 TNFR. 9/13 AM Tr. 45:16-21 (Capon). The authors chose different starting materials and used an additional library to fish for p75 sequences. 9/13 AM Tr. 45:22-46:8 (Capon).

159. The specification does not reference Dembic 1990. 9/13 AM Tr. 46:9-10 (Capon); 9/17 AM Tr. 92:23-93:24 (Loetscher). A POSA in 1990 would have understood from the absence of any reference to or incorporation by reference of Dembic 1990 and Smith 1990 that the larger sequences disclosed therein are not part of the disclosure. 9/13 AM Tr. 46:9-15 (Capon). A POSA in 1990 would have understood that the Roche inventors, in their wisdom, direct the POSA to the Figure 4 protein or deletions or allelic variants thereof. 9/13 AM Tr. 46:9-15 (Capon); 9/13

PM Tr. 98:16-22 (Capon).

c. There is No Description to Use Amino Acids 1-235 of the Extracellular Region of a p75 TNFR.

160. Although the claims require a fusion protein comprising amino acids 1-235 of the extracellular region of the p75 TNFR, there is no description of or direction to use this sequence in the specification. Even if a POSA considered using the Smith protein, there is no direction in the specification directing the POSA to use amino acids 1-235 as claimed.

161. The term "extracellular region" does not appear anywhere in the specification in relation to p75. 9/18 PM Tr. 19:25-20:6 (Naismith). A POSA would have understood that "soluble binding fragment" does not specifically describe the entire extracellular region of the p75 TNFR, which is the portion claimed and used in etanercept. JTX-79 at 106:1-4 (Lyman). A POSA would have understood that the term "soluble binding fragments" could encompass amino acids 1-235 of the extracellular region or a portion thereof. JTX-79 at 94:21-25, 100:2-8 (Lyman); 9/18 PM Tr. 19:8-18 (Naismith). The soluble fragments that could be used as part of the fusion protein could encompass a significant number of possibilities. JTX-79 at 101:22-102:3, 105:12-15 (Lyman).

2. There is No Description of An Exon-Encoded Hinge-CH2-CH3 of An IgG1.

162. Pursuant to the parties' agreed claim construction, all of the asserted

claims require the exon-encoded hinge-CH2-CH3 of a human IgG1. 9/13 AM Tr. 19:20-20:18 (Capon). There is no disclosure of an exon-encoded hinge-CH2-CH3 of a human IgG1 in the specification. 9/13 AM Tr. 56:25-57:10 (Capon). The words "hinge" and "exon" and the expressions "exon-encoded," "exon-encoded hinge," or "hinge-CH2-CH3" do not appear in the specification. 9/13 AM Tr. 56:25-57:10 (Capon).

163. The specification describes the immunoglobulin portion of the invention as a "partial sequence encoding all domains except the first domain of the constant region of the heavy chain of human immunoglobulin IgG, IgA, IgM, or IgE." JTX-10 at 8:37-9:4; 9/13 AM Tr. 57:11-24 (Capon). A POSA understood that there were seven subtypes of immunoglobulins within these classes, resulting in 11 potential immunoglobulins. PTX-3 at 22-23; JTX-49 at 9-10.

164. This broad statement in the specification does not describe an exon-encoded hinge-CH2-CH3 to a POSA in 1990. 9/13 AM Tr. 57:25-58:7 (Capon). The statement encompasses a pantheon of potential hinges and almost a universe of variants, and provides no hint of what the hinge might look like to a POSA in 1990. 9/13 AM Tr. 57:25-58:13 (Capon).

165. The specification mentions, among other suitable vectors, the two vector deposits from Dr. Karjalainen: pDC4-Hγl and pDC4-Hγ3. JTX-10 at 22:26; 9/13 PM Tr. 107:18-23 (Capon). Dr. Karjalainen's pCD4-Hγ3 deposit contains DNA

encoding a portion of a human IgG3. 9/13 AM Tr. 100:14-25 (Capon). Example 11 specifies exact "restriction cleavage sites" unique to the human IgG3 instructing a POSA where in the pCD4-Hγ3 vector to "cut" out the full exon-encoded IgG3 hinge-CH2-CH3, similar to instructing a builder where to cut a board. 9/13 AM Tr. 101:11-19 (Capon).

166. Dr. Karjalainen's pDC4-Hγ1 deposit contains DNA encoding a human IgG1. 9/13 PM Tr. 75:13-76:1 (Capon). The examples do not discuss the pCD4-Hγ1 deposit. 9/13 AM Tr. 71:9-15 (Capon). The specification does not describe the restriction sites telling a POSA where to "cut" the IgG1 hinge or provide any other description of which hinge to use. 9/13 PM Tr. 107:21-108:1 (Capon).

167. A POSA in 1990 was aware of at least two definitions of an IgG1 hinge-CH2-CH3. 9/13 AM Tr. 58:14-19 (Capon). In his Nobel Prize-winning work, Dr. Gerald Edelman named the amino acid stretches of the IgG1 the CH1 domain, CH2 domain, and CH3 domain and identified the specific sequences corresponding to those domains. DTX-157 at 1; DTX-152 at 1; 9/13 AM Tr. 59:5-60:5 (Capon). Dr. Edelman defined the CH1 domain as ending with the sequence DKKVEPKSC. DTX-152 at 1; 9/13 AM Tr. 59:22-25 (Capon). Dr. Edelman defined the hinge as having the following sequence: DKTHTCPPCPAPE. DTX-152 at 1; 9/13 AM Tr. 60:1-5 (Capon).

168. Later, scientists began to investigate how DNA encodes the IgG1

protein. 9/13 AM Tr. 61:4-12 (Capon). Dr. Susumu Tonegawa answered this question by defining the hinge-CH2-CH3 of an IgG1 according to its genomic structure. 9/13 AM Tr. 61:13-18 (Capon). Dr. Tonegawa thus proposed defining the IgG1 according to the DNA that encodes the protein, not its amino acid sequence. 9/13 AM Tr. 61:13-20 (Capon). Dr. Tonegawa referred to the areas of the IgG1 as "exons," not "domains." 9/13 AM Tr. 61:21-23 (Capon). Dr. Tonegawa defined the CH1 exon as ending with the sequence DKKV. Dr. Tonewgawa defined the hinge as having the following amino acid sequence: EPKSCDKTHTCPPCP. DDX-2021; 9/13 AM Tr. 62:12-63:1 (Capon).

169. Because of the prominence of his work and his use of the term "domains," a POSA would have first considered the Edelman definition when considering all domains other than the first constant domain, as the term "domain," and not "exon," is used in the patents-in-suit. 9/13 AM Tr. 56:25-57:10, 62:21-63:6 (Capon).

170. Etanercept contains the amino acids "EPKSC" found in Dr. Edelman's CH1 domain and Dr. Tonegawa's hinge exon. 9/13 AM Tr. 63:2-6 (Capon). If a POSA applied the Edelman hinge definition to the asserted claims, the POSA would have obtained a fusion protein different than etanercept. Not would the resulting fusion protein be covered by the claims because it would be missing the amino acids "EPKSC." 9/13 AM Tr. 63:2-6 (Capon).

171. The specification does not describe whether to use the Edelman or Tonegawa hinge of an IgG1, or some other hinge. 9/13 AM Tr. 56:25-57:10 (Capon). The specification could have described the exon-encoded hinge by including specific restriction sites or by identifying the amino acid residue to include in the hinge, but did not. 9/13 AM Tr. 101:16-19 (Capon); 9/13 PM Tr. 107:18-108:1 (Capon).

172. In their 1998 License Agreement concerning the '790 and '791 applications, Immunex and Roche understood that the specification of the applications described the Edelman definition of the hinge, not the Tonegawa definition of the hinge. JTX-13 § 1.4; 9/13 AM Tr. 63:18-64:17 (Capon). In fact, Immunex's and Roche's definition of etanercept applied the Edelman definition of hinge. DDX-2024; 9/13 AM Tr. 63:18-64:17, 65:7-24; JTX-13 § 1.4. Immunex and Roche applied the same Edelman definition of the hinge in their 2004 Accord and Satisfaction Agreement. JTX-12 §1.5.

3. There is No Description of A p75-IgG1 Fusion Protein.

173. The principle of fusion proteins is that a POSA would take specific proteins or parts thereof and combine them at a specific place. 9/13 AM Tr. 66:9-67:3, 70:21-71:8, 89:14-22 (Capon). This teaching of the claimed p75-IgG1 protein is completely absent from the specification because none of the requisite parts are described and, therefore, there is no teaching of how to arrange the parts and, therefore, there is no fusion protein described. 9/13 AM Tr. 66:9-67:3 (Capon). The

specification does not describe the p75 TNFR extracellular region or the use of amino acids 1-235, the exon-encoded hinge-CH2-CH3 of an IgG1, where to cut the hinge, or the amino acid residue for fusion. *See* ¶¶ *supra* Sections III.A.1-3. There is no description of a polynucleotide that would encode a p75-IgG1 fusion protein. 9/13 AM Tr. 67:4-25 (Capon). There is no description of or way to make an expression vector containing the regulatory elements to produce the fusion protein. *Id*. There is no cell line described to produce a p75-IgG1 fusion protein. *Id*. There is no p75-IgG1 fusion protein described in part or full. *Id*. And because there is no p75-IgG1 fusion protein described, there is nothing to measure for specific binding of human TNF as required by the claims. *Id*.

174. The specification provides only one example of DNA that could be used to make a p55-IgG3 fusion protein. 9/13 AM Tr. 69:13-18, 88:5-12, 89:9-25 (Capon). The DNA is an instruction set, not the actual fusion protein. 9/13 AM Tr. 89:9-25 (Capon). It does not provide an example of a p75 fusion protein, much less a p75-IgG1 protein. 9/13 AM Tr. (70:4-17) (Capon).

175. The p55 is a very different gene product than the p75. 9/13 AM Tr. 69:13-18 (Capon). The IgG3 is a different immunoglobulin from an IgG1, with different structures. 9/13 AM Tr. 69:19-25 (Capon). Specifically, the IgG3 hinge is four times as long and has a very different sequence compared to the IgG1 hinge. 9/13 AM Tr. 69:19-25 (Capon). Because of these differences, a POSA could not

have used Example 11 to make a p75-IgG1 fusion protein. 9/13 AM Tr. 70:1-3 (Capon). Example 11 directs to use the SSTI restriction enzyme. 9/13 AM Tr. 70:21-71:3 (Capon). In doing so, a POSA would come up not with etanercept, or not even with a p75-IgG1 fusion protein, but rather a fusion protein of three parts: p75-CD4-IgG1. 9/13 AM Tr. 71:3-8 (Capon); DDX-2029.

176. The specification does not describe how to cut and splice the DNA to remove the third extra part from this construct. 9/13 AM Tr. 92:10-21, 93:17-94:7 (Capon). A POSA in 1990 understood that the ability to cut and splice DNA depended upon the sequences, and there were some plasmids that could never be made. 9/13 AM Tr. 92:10-21, 93:17-94:7 (Capon).

177. Further, because Example 11 describes producing a protein in a myeloma cell line that produces a light chain, the fusion protein could have light chains attached, making it significantly different from etanercept which does not have light chains. 9/13 AM Tr. 99:21-100:3 (Capon); 9/12 PM Tr. 20:14-17 (Blobel); 9/20 PM Tr. 5:16-20 (Wall).

178. Moreover, there is no description in the specification of the ability to specifically bind TNF for any fusion protein. 9/13 AM Tr. 72:2-10 (Capon). Further, because there is no description of a p75-IgG1 fusion protein, there is no description of its biological activity and no way to measure this biological property. 9/13 AM Tr. 72:11-14 (Capon). Given what is known today, it would be unclear to a POSA

whether a fusion protein with the Figure 4 protein would specifically bind human TNF. 9/13 AM Tr. 72:15-18 (Capon).

179. A POSA reading the specification and Example 11 in particular would not believe that the inventors possessed the claimed p75-IgG1 fusion protein, much less etanercept. 9/13 AM Tr. 95:24-96:16, 99:7-100:6 (Capon).

B. Lack of Enablement

180. The asserted claims are not enabled because lacking any written description, there is nothing that the priority application contributes beyond what was already known in the prior art. 9/13 AM Tr. 19:20-20:18, 73:12-21 (Capon).

C. Immunex Was Compelled To Amend the Specification In an Attempt To Describe Etanercept.

181. When Immunex took over prosecution, it made several amendments to the specifications of the patents-in-suit. On Nov. 10, 2006, Immunex amended the specification of the '182 patent to add the following underlined new subject matter: "DNA sequences which code for insoluble (deposited on October 17, 2006 with the American Type Culture Collection under Accession No. PTA 7942) as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred." JTX-3 at 3658; 9/13 AM Tr. 49:18-50:20 (Capon). By that time, Enbrel had been on sale and publicly available for eight years. DTX-1083; 9/25/Tr. 27:25-28:14 (McDuff); *see* 9/11 PM Tr. 121:5-15 (Blobel).

182. The amendment added a reference to a deposit made 16 years after the

priority date containing DNA for the PTA 7942 plasmid, which contains the full-length p75 TNFR. 9/13 AM Tr. 50:9-51:1 (Capon); JTX-16 at 29-31.

183. The amendment added new subject matter because the specification, as filed, only described the Figure 4 protein, not the full-length p75 TNFR. *See* FOF ¶¶ 123-24, 136-37, 154; 9/13 AM Tr. 21:20-25, 51:2-6 (Capon). Moreover, the plasmid PTA 7942 does not describe the claimed p75-IgG1 fusion protein, which Roche never possessed and which is not reflected in the specification. 9/13 AM Tr. 50:9-51:6 (Capon); DTX-1196 at 30-31.

184. Dr. Lesslauer filed a declaration dated November 9, 2006 indicating that plasmid N227 from Roche is the same as PTA 7942. JTX-3 at 3660-3661; JTX-81 (166:1-6) (Lesslauer). Immunex, not Roche, made the PTA 7942 deposit. 9/13 AM Tr. 52:1-7 (Capon); JTX-81 (166:1-6) (Lesslauer). It was transferred from Roche to Immunex in 2006. 9/13 PM Tr. 80:20-81:5 (Capon). Dr. Lesslauer did not supervise the deposit. JTX-81 (166:1-3) (Lesslauer). Instead, he relied upon a declaration by Amgen that the plasmid deposited in October 2006 was the construct created by Roche in September 1990. JTX-81 (166:4-6) (Lesslauer).

185. In his declaration, Dr. Lesslauer did not provide the sequence of PTA 7942 and/or compare it to Roche's Figure 4 Protein and there is no evidence that anyone, including Roche, sequenced PTA 7942 before this litigation. JTX-3 at 3660-3661; 9/13 AM Tr. 50:21-23 (Capon). In fact, there is no contemporaneous evidence

of the sequence of plasmid N227 from 1990. 9/18 PM Tr. 36:11-16 (Naismith). And, Dr. Brockhaus confirmed that Roche did not have a full-length p75 TNFR available in a purified form by September 1990. JTX-72 (133:20-134:9) (Brockhaus).

186. On August 30, 2007, Immunex amended the specification of the '522 patent to add new subject matter by importing whole swaths of its Smith 1990 paper into the specification and adding the 2006 PTA 7926 plasmid deposit. JTX-4 at 3565; 9/13 AM Tr. 55:20-56:3 (Capon).

187. Immunex added new Figure 5 to the four figures in the specification. JTX-4 at 3564, 3567; 9/13 AM Tr. 52:9-25 (Capon). Figure 5 is the full-length p75 sequence cut and pasted from Figure 3(B) of Smith 1990. 9/13 AM Tr. 52:22-25, 55:2-19 (Capon); JTX-24 at Fig. 3(B); JTX-4 at 3564, 3567. Immunex also copied jot-for-jot and inserted the figure legend for Figure 3(B) and added it as the figure legend for Figure 5. 9/13 AM Tr. 53:1-9, 54:1-24 (Capon).

188. Immunex added the following underlined language to incorporate Smith 1990 by reference: "One sequence which results from such a deletion is described, for example, in Smith et al., Science *248*, 1019-1023, (1990), which is incorporated by reference herein." JTX-4 at 3564; 9/13 AM Tr. 53:10-25 (Capon). Although as Dr. Naismith conceded the priority application did not incorporate Smith 1990 by reference (FOF ¶¶ 79, 147), this amendment added new subject matter by doing just that. 9/13 AM Tr. 53:10-25 (Capon). Instead, Immunex

expressly "incorporated by reference" Smith 1990 in 2007, as is made clear by Drs. Naismith's and Lyman's testimony. 9/18 PM Tr. 23:21-24:10, 25:13-26:5 (Naismith); JTX-79 (133:15-134:8, 134:11) (Lyman).

189. Immunex's amendments to Roche's 1990 specification transformed them into new applications covering an entirely new subject matter: Immunex's etanercept. 9/13 AM Tr. 56:7-10 (Capon).

1. A POSA in 1990 Could Not Use Sequence ID Numbers 7 or 10 To Get A Full-Length p75 TNFR

190. The specification identifies four amino acid peptide sequences for various bands on a gel: "55 kD band" (SEQ. ID 5 and 6); "51 kD and 38 kD bands" (SEQ. ID 15); "65 kD band" (SEQ. ID. 10), reflecting the uncertainty at the time about how many different TNFRs might exist. JTX-10 at 36-38.

191. The specification also identifies seven amino acid peptide sequences, later identified in the patents-in-suit by SEQ. ID Number for the "75(65) kDa-TNF-BP" (SEQ. ID 7, 8, 9, 11, 12, 13, and 14). JTX-10 at 37-38.

192. SEQ. ID NO: 10 is identified as belonging to the p65 TNFR. 9/18 PM Tr. 29:13-23 (Naismith); 9/13 PM Tr. 106:23-107:17 (Capon). The specification described the X in SEQ. ID Number 10 (Leu-Pro-Ala-Gln-Val-Ala-Phe-X-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr-Cys) as "an amino acid residue which could not be determined." JTX-10 at 37. The X could be any one of 20 amino acids or a mixture of two or more amino acids. 9/18 PM Tr. (32:13-22) (Naismith); 9/13 PM Tr. 13:24-

14:9, 106:23-107:7 (Capon).

193. The specification does not teach a POSA to combine any one or more of the listed peptides to obtain a protein. 9/18 PM Tr. 31:8-15 (Naismith). There is no teaching in the specification directing a POSA to combine SEQ. IDs 7 and 10 to obtain a TNF-binding protein. 9/18 PM Tr. 30:10-31:15 (Naismith).

194. Before filing the application in August 1990, Roche was unable to convert a sequence similar to SEQ ID 10—with a T (threonine) in the place of the X—to DNA to use as a probe to fish for a full-length p75 TNFR. JTX-86 45:12-46:1 (Gubler); 9/18 PM Tr. (34:21-24 (Naismith); *see supra* Section I.A.2.b.

IV. Obviousness

195. Etanercept and the claimed method of producing etanercept recited in the asserted claims would have been obvious to a POSA in view of the prior art as of August 1990. The prior art teaches each of the elements of the asserted claims. 9/11 PM Tr. 114:10-118:10 (Blobel). A POSA would have been motivated to combine the teachings of the prior art to produce etanercept, and would have been able to produce etanercept using ordinary skill with a reasonable expectation that it would specifically bind human TNF. 9/11 PM Tr. 118:11-16 (Blobel); 9/12 PM Tr. 27:10-25, 55:20-56:5 (Blobel); *see also* 9/20 AM Tr. 92:10-93:1, 112:4-11 (Wall).

A. A POSA Would Have Been Motivated to Construct an IgG1 Fusion Protein with the p75 TNFR

1. In August 1990, There Was Significant Interest in Studying

TNF Activity And TNFRs.

196. When TNF binds to its cell-surface receptors, it transmits a signal into the cell triggering a localized immune response. 9/11 PM Tr. 22:8-24:9 (Blobel). While TNF can be beneficial, too much TNF can cause dysregulated activity and contribute to TNF-mediated diseases. *Id.* By August 1990, several diseases were associated with overactive TNF, including rheumatoid arthritis, graft-versus-host disease, cachexia, and septic shock. *Id.*; DTX-75 at 1; JTX-62 at 2:10-23; 9/11 PM Tr. 61:18-63:5, 64:2-21 (Blobel); 9/18 PM Tr. 128:24-129:19 (Greene); *see also* 9/17 AM Tr. 61:1-10 (Loetscher); JTX-81 (67:5-67:17) (Lesslauer).

197. In August 1990, there was a tremendous interest in studying TNF activity and whether inhibiting the binding of TNF to its cell-surface receptors would provide a therapeutic benefit. 9/11 PM Tr. 26:6-27:1, 61:8-14, 65:15-66:7 (Blobel); 9/17 AM Tr. 61:1-24 (Loetscher); 9/18 AM Tr. 69:3-18 (Naismith). Based on studies of TNF in inducing rheumatoid arthritis, Brennan 1989 suggests that "drug therapy to inhibit TNFα production or to neutralise its effects may help to control the inflammatory process in rheumatoid arthritis." DTX-75 at 3; 9/20 PM Tr. 67:3-16 (Wall). To a POSA, Brennan 1989 and similar references provide a strong incentive to identify TNF inhibitors that may have therapeutic use. 9/11 PM Tr. 62:2-63:5 (Blobel); DTX-75 at 1, 3; *see also* JTX-62 at 2:57-3:11; JTX-47 at 6. In view of the prior art, a POSA would have been motivated to construct a soluble TNF-binding

protein that may serve as a potential therapeutic to scavenge TNF. JTX-65 at 3:3-6; 9/11 PM Tr. 26:6-27:1, 64:22-65:14 (Blobel); 9/20 AM Tr. 34:20-35:11 (Wall).

198. The prior art further suggests using TNF-binding proteins as a tool in "diagnostic assays for TNF." JTX-65 at 2:67-3:6; 9/11 PM Tr. 71:9-72:11 (Blobel). Such proteins would have been useful for *in vitro* studies to determine the biological activity of TNF. 9/17 AM Tr. 62:4-13 (Loetscher); JTX-81 (70:11-18) (Lesslauer).

199. By August 1990, there was a high level of interest in the TNFRs. 9/11 PM Tr. 65:15-21 (Blobel). Examples of major biotech institutions contributing to the research into the TNFRs prior to August 1990 included Genentech, Immunex, Roche, and the Weizmann Institute. 9/11 PM Tr. 65:24-66:7 (Blobel).

200. In late 1989 and early 1990, the Weizmann Institute published its research relating to proteins derived from human urine, which had the "ability to inhibit the binding of TNF-alpha to its cells surface receptors." JTX-62 at 4:1-9; *see* 9/11 PM Tr. 66:13-67:9 (Blobel); 9/20 AM Tr. 27:16-28:8 (Wall); 9/17 AM Tr. 61:1-18 (Loetscher). These proteins provided "protection against the *in vitro* cytocidal effect of [TNF]," suggesting that they "block[] the function of TNF by competing for TNF with the TNF receptor …." JTX-46 at 1; *see* JTX-47 at 1; DTX-49 at 1. Sequencing of the TNFRs by August 1990 confirmed that these urinary proteins were the extracellular regions of the full-length TNFRs that had been naturally cut off at the cell surface. 9/11 PM Tr. 66:13-67:9, 26:6-15 (Blobel); *see* 9/20 AM Tr.

27:16-28:19 (Wall).

201. In April 1990, the sequence of the p55 TNFR was first published by Genentech and Roche in independent but simultaneous publications. 9/11 PM Tr. 67:25-68:16 (Blobel). Figure 1 of Genentech's Schall 1990 and Figure 2 of Roche's Loetscher 1990 report the cDNA and amino acid sequences of the p55 TNFR. JTX-64 at 3; JTX-21 at 3; *see* 9/17 AM Tr. 31:22-32:21 (Loetscher).

202. In May 1990, the sequence of what is now known as the p75 TNFR was first published by Immunex. 9/11 PM Tr. 68:17-69:9 (Blobel); 9/20 AM Tr. 33:16-25 (Wall). Figure 3 of Immunex's Smith 1990 reports the amino acid sequence, and Figures 2A-2B of Immunex's Smith '760 patent report the cDNA and amino acid sequences of the TNFR. *Id.*; JTX-24 at 3; JTX-65 at Figs. 2A-2B, 3:16-25; 9/18 AM Tr. 69:5-70:1 (Naismith); *see* 9/20 AM Tr. 55:17-23 (Wall).

203. DNA sequencing of the TNFRs allowed for creating soluble forms of the TNFR for study of their protective mechanisms against TNF and as potential therapeutics to inhibit TNF activity. 9/11 PM Tr. 26:6-27:1 (Blobel); 9/20 AM Tr. 34:1-35:11 (Wall); JTX-72 (84:19-85:20, 231:4-232:5) (Brockhaus); *see, e.g.*, JTX-64 at 7; JTX-24 at 4; JTX-65 at 3:3-6; DTX-49 at 6.

2. Fusing Soluble Receptors to Human IgG1 Would Enhance the Properties of the Soluble Receptors.

204. In August 1990, a POSA would have been motivated to construct receptor-IgG1 fusion proteins to enhance the properties of the soluble receptors, for

example, by: (i) extending the *in vivo* half-life of soluble receptors, (ii) taking advantage of standard and efficient purification techniques, and (iii) increasing the binding strength between the fusion protein and its multivalent target.

205. Receptor-IgG1 fusion proteins were known to extend *in vivo* half-life of small soluble receptors. Half-life is a measure of the time that a drug will circulate within a patient's bloodstream following administration. 9/11 PM Tr. 94:8-95:5 (Blobel). By August 1990, a POSA would have expected that proteins of small molecular size (*i.e.*, a size below a limit of about 60 kD) to be rapidly lost in the bloodstream and secreted into the urine. *Id.* A primary objective of fusing a soluble receptor to a human IgG1 was to extend the *in vivo* half-life of the soluble receptor. 9/11 PM Tr. 95:9-96:6 (Blobel); 9/20 PM Tr. 42:1-24 (Wall); 9/17 AM Tr. 68:22-15, 69:5-11 (Loetscher); JTX-56 at 1; JTX-61 at 1:6-14, 4:38-43, 30:67-31:4; PTX-23 at 15; DTX-111 at 2; *see also* JTX-58 at 1, 3, 6.

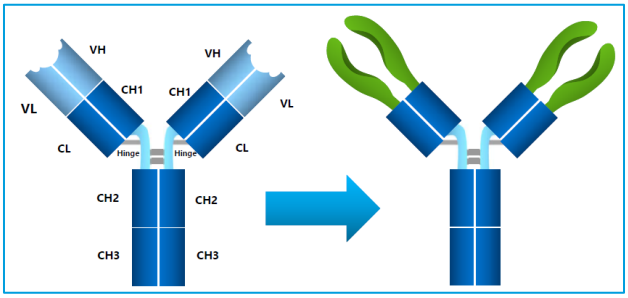
206. A POSA would have recognized that the receptor-IgG1 fusion proteins could be purified using standard and efficient techniques, specifically, by Protein A. 9/11 PM Tr. 96:7-97:1 (Blobel). A key advantage of the receptor-IgG1 fusion proteins is the ease of using of Protein A purification to isolate the protein to near homogeneity. 9/11 PM Tr. 97:2-98:10 (Blobel); 9/20 PM Tr. 42:9-43:7 (Wall); JTX-57 at 7:22-24; JTX-56 at 2, Fig. 1; JTX-61 at 4:38-43; JTX-59 at 4; DTX-111 at 2.

207. A POSA would have recognized that the receptor-IgG1 fusion proteins

may also provide for stronger binding interactions. The receptor-IgG1 fusion proteins form a dimeric protein that has two soluble receptors attached. 9/11 PM Tr. 98:11-99:19 (Blobel). When binding to a multivalent target (*i.e.*, a target with more than one binding site), the presence of two soluble receptors would permit two binding interactions between the receptor-IgG1 fusion protein and its target, resulting in a significantly stronger bond, *i.e.*, the avidity effect. *Id.*; JTX-59 at 4; *see also* JTX-65 at 10:53-68; 9/17 AM Tr. 69:14-70:5 (Loetscher). The advantage of the avidity effect is it can provide for a 1,000-fold greater binding compared to a single binding interaction between a soluble receptor and its target. 9/11 PM Tr. 99:20-100:16, 111:24-113:8 (Blobel); 9/24 AM Tr. 42:6-46:1 (Skerra); DTX-84 at 5.

B. A POSA Would Have Been Motivated To Modify the Smith '760 Patent's Chimeric Antibody to Create Etanercept.

208. The Smith '760 patent teaches the construction of a chimeric antibody, which is a fusion protein of a p75 TNFR fused to a human IgG1. JTX-65 at 10:53-68. As illustrated below, the VL and/or VH domains have been replaced with the p75 extracellular region. DDX-1049; 9/11 PM Tr. 72:12-74:11 (Blobel); 9/20 AM Tr. 115:7-118:2 (Wall).



209. The Smith '760 patent teaches that this chimeric antibody may have enhanced binding affinity for TNF. JTX-65 at 10:53-68; 9/11 PM Tr. 72:12-74:11 (Blobel). It also teaches that the chimeric antibody is useful in therapy to bind or scavenge for TNF. JTX-65 at 2:67-3:6; 9/11 PM Tr. 71:21-72:11 (Blobel).

1. The Smith '760 Patent's Chimeric Antibody Was Expected to Have Advantageous Properties.

210. A POSA in August 1990 would have identified the Smith '760 patent's chimeric antibody as a promising candidate. 9/12 PM Tr. 27:10-28:7 (Blobel). A POSA would have expected that it would provide for extended *in vivo* half-life, ease of purification, and enhanced TNF binding relative to a soluble TNFR (*e.g.*, the p75 extracellular region). *Id.* As Dr. Wall conceded, "this chimeric antibody would have addressed all three" of these properties. 9/20 AM Tr. 73:20-74:6 (Wall).

211. First, the Smith '760 patent's chimeric antibody was expected to provide for a longer *in vivo* half-life than a soluble p75 TNFR. 9/12 PM Tr. 27:10-28:7 (Blobel); 9/20 AM Tr. 73:20-74:4 (Wall). The soluble p75 TNFR was known to be a small protein, with a molecular size of at most about 30,000 Daltons (or 30 kD), which is well within the size cutoff that a POSA would have expected the protein to be rapidly lost in the bloodstream. 9/11 PM Tr. 94:8-95:5, 90:17-91:20 (Blobel); JTX-47 at 1. A POSA would have been motivated to make a TNFR-IgG1 fusion protein to keep it available in the bloodstream for a longer period of time. *Id.*; *see* DTX-111 at 2; JTX-73 (66:12-67:7) (Gillis); JTX-81 (78:15-21, 80:7-80:21,

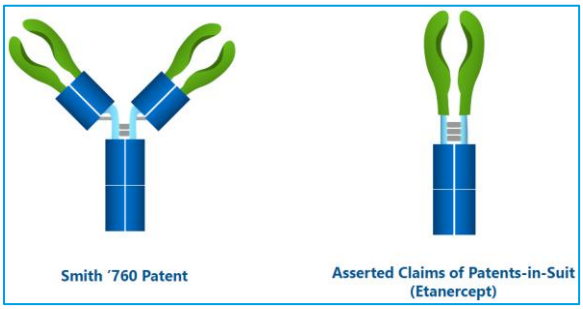
81:4-11, 82:5-10) (Lesslauer); JTX-82 (331:4-23) (Lesslauer); 9/17 AM Tr. 68:22-15, 69:5-11 (Loetscher).

212. Second, the Smith '760 patent's chimeric antibody was expected to be easier to purify than a soluble p75 TNFR. 9/12 PM Tr. 27:10-28:7 (Blobel); 9/20 AM Tr. 73:20-74:4 (Wall). While methods were available to purify the soluble p75 TNFR, these methods required successive purification steps and relied upon an available supply of non-standard materials. 9/12 PM Tr. 29:9-30:7 (Blobel). The prior art reported that the receptor-IgG1 fusion proteins may be purified to near homogeneity (< 99% purity) by using the single step of Protein A purification. 9/11 PM Tr. 97:2-98:10 (Blobel); JTX-57 at 7:22-24; JTX-56 at 2, Fig. 1; JTX-61 at 4:38-43; JTX-59 at 4. A POSA would have been motivated to make a TNFR-IgG1 fusion protein for the ease of purification. DTX-111 at 2; JTX-73 (66:12-17) (Gillis); JTX-81 (81:4-11) (Lesslauer).

213. Third, the Smith '760 patent's chimeric antibody was expected to bind TNF more strongly than a soluble TNFR due to its ability to take advantage of the avidity effect. 9/11 PM Tr. 72:12-73:11 (Blobel); 9/12 PM Tr. 24:22-25:19 (Blobel); JTX-65 at 10:53-67; *see* 9/24 AM Tr. 42:6-46:1, 49:18-51:4 (Skerra). Enhanced binding is an advantageous property for a competitive inhibitor, because it will bind to TNF better than the cell-bound receptors. 9/11 PM Tr. 98:11-99:19 (Blobel).

214. There are only two differences between the Smith '760 patent's

chimeric antibody and etanercept: (i) the light chain; and (ii) the CH1 domain. 9/11 PM Tr. 75:1-16 (Blobel); *see* DDX-1051; 9/20 PM Tr. 5:16-25 (Wall).



2. A POSA Would Have Been Motivated to Remove the Light Chain and CH1 Domain from the Smith '760 Patents' Chimeric Antibody.

215. A POSA would have been motivated to improve upon the Smith '760 patent's fusion protein by removing the light chain and the CH1 domain of the human IgG1. 9/11 PM Tr. 75:8-24, 85:5-86:5 (Blobel); 9/12 PM Tr. 18:4-19:21, 88:13-23 (Blobel); *see* DDX-1056.

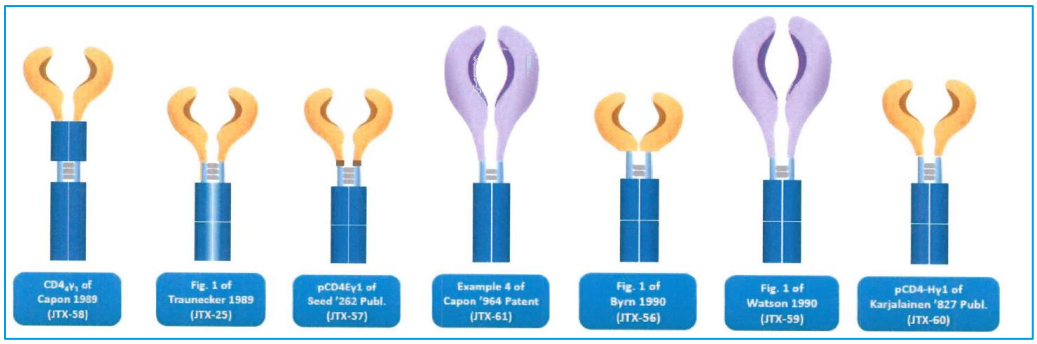
216. By August 1990, a POSA would have known that the receptor-IgG fusion proteins lacking the light chain were much easier to synthesize, worked, and had many advantages. 9/11 PM Tr. 80:5-12 (Blobel). Even Dr. Wall acknowledges that "there was a good reason for removing the light chain" from the receptor-IgG fusion proteins, because the light chain "didn't add anything." 9/20 PM Tr. 7:2-22 (Wall). Capon 1989 made several fusion proteins, including ones that retained the light chains, but selected for further development the fusion proteins lacking the light chain. JTX-58 at 1-2 ($CD4_2\gamma_1$ and $CD4_4\gamma_1$ constructs); 9/12 AM Tr. 19:2-12 (Blobel); 9/20 PM Tr. 8:17-9:4 (Wall).

217. It is undisputed that by August 1990, the receptor-IgG fusion protein art had evolved such that the fusion proteins either removed or did not have a light chain. 9/12 PM Tr. 18:4-19:21 (Blobel); *see* 9/20 PM Tr. 7:2-22, 10:9-11, 12:13-21 (Wall). For example, Capon 1989 (JTX-58 at 2), Traunecker 1989 (JTX-25 at 1), Seed '262 publication (JTX-57 at 10:57-11:2), Capon '964 patent (JTX-61 at 15:4-18), Byrn 1990 (JTX-56 at 2), Watson 1990 (JTX-59 at 3), and the pCD4-Hγ1 deposit identified in Karjalainen '827 publication (JTX-60 at 12) describe fusion proteins that lack a light chain. *See* PDX-14.3; DDX-1056.

218. A POSA would also have been motivated to remove the CH1 domain (in addition to the IgG1 light chain) in constructing a TNFR-IgG1 fusion protein. 9/11 PM Tr. 77:19-78:9, 85:6-86:5 (Blobel); 9/20 PM Tr. 11:3-12:8 (Wall); JTX-81 (128:19-129:5) (Lesslauer). Removal of the CH1 domain improved the production and secretion of receptor-IgG fusion proteins that lacked a light chain. 9/11 PM Tr. 79:1-15 (Blobel); 9/20 PM Tr. 11:3-12:8 (Wall). Traunecker 1989 reported that "deletion of the CH1 domain may allow the association and secretion of heavy chains in the absence of light chains." JTX-25 at 1; *see id.* at 3. Traunecker 1989 suggested that this basic design "may be generally and usefully applied." *Id.* at 1; *see id.* at 3; 9/11 PM Tr. 79:1-15 (Blobel). Others followed the teaching of Traunecker 1989 in constructing human CD4-IgG1 fusion proteins. 9/18 Tr. 87:5-11 (Greene); JTX-56 at 1. As Dr. Wall conceded, experimental evidence comparing

CD4-IgG fusion proteins with and without the CH1 domain in the absence of the light chain showed that "poor expression was observed for fusion proteins bearing CH1 domains from either murine or human immunoglobulins." PTX-26 at 5-6; 9/20 PM Tr. 11:3-12:8 (Wall).

219. By August 1990, the receptor-IgG fusion protein art had evolved such that the preferred fusion proteins included those that lack the light chain and CH1 domain. 9/11 PM Tr. 85:6-86:5 (Blobel); *see* 9/20 PM Tr. 7:9-14, 11:3-12:8, 12:13-24, 25:1-11 (Wall); 9/18 Tr. 87:5-11 (Greene). For example, as illustrated below, Traunecker 1989 (JTX-25 at 1; 9/11 PM Tr. 79:1-15 (Blobel)), Seed '262 publication (JTX-57 at 10:57-11:2; 9/11 PM Tr. 81:7-82:1 (Blobel)), Capon '964 patent (JTX-61 at 15:4-18), Byrn 1990 (JTX-56 at 2; 9/11 PM Tr. 80:13-18 (Blobel)), Watson 1990 (JTX-59 at 3), and the pCD4-Hγ1 deposit identified in Karjalainen '827 publication (JTX-60 at 12; 9/11 PM Tr. 82:2-8 (Blobel)) describe fusion proteins that lack a light chain and CH1 domain. *See* PDX-14.3; DDX-1056.



220. While the patent references describe receptor-IgG fusion proteins that retained the CH1 domain, each of those references selected those fusion proteins that

lacked the CH1 for further testing. For instance, Seed '262 publication selected the pCD4Eγ1 construct, lacking the CH1, for further testing in the assays described in Examples 5-9. JTX-57 at 10:57-11:2, 57:1-58:64; 9/12 AM Tr. 22:24-23:16 (Blobel). The Capon '964 patent did the same. JTX-61 at 15:4-18, 40:26-43, Figs. 8 and 9; *see also* 9/12 AM Tr. 64:5-16 (Blobel); 9/12 PM Tr. 86:2-14 (Blobel). The prior art as a whole taught a POSA in August 1990 to construct a receptor-IgG fusion protein without a light chain and CH1 domain. 9/11 PM Tr. 85:6-86:5 (Blobel).

3. It Would Have Been Obvious to Directly Fuse the p75 Extracellular Region to the Full Exon-Encoded Hinge.

221. A POSA would have been motivated to directly fuse p75 extracellular region to the full exon-encoded hinge-CH2-CH3 portion of the human IgG1. 9/11 PM Tr. 113:9-114:9 (Blobel); 9/12 AM Tr. 79:3-14 (Blobel). In his analysis, Dr. Wall incorrectly assumed that a reference must be "exactly the same" and "incorporate whatever the claimed invention is" for obviousness. 9/20 PM Tr. 14:4-23, 15:20-16:11 (Wall). As Dr. Wall conceded, there were only a limited number of options for constructing the fusion site of a soluble receptor to the hinge-CH2-CH3 portion of the human IgG1. 9/20 PM Tr. 17:3-7, 18:6-17 (Wall). A POSA as of August 1990 would have needed to make only two choices, with each choice having only two options. *Id.*

222. First, with respect to the hinge, the prior art fusion proteins included either the full exon-encoded hinge or truncated hinge (lacking the 5-amino acid

sequence EPKSC). 9/20 PM Tr. 18:13-17, 19:7-10 (Wall). The fusion proteins containing a full hinge included Figure 1 of Traunecker 1989 (JTX-25 at 1), the pCD4Eγ1 construct of the Seed '262 publication (JTX-57 at 10:29-11:12), and the pCD4-Hγ1 deposit identified in Karjalainen '827 publication (JTX-60 at 12), which was publicly available by April 1989 (JTX-60 at 5:25-30; JTX-1 at 8:64), and the Smith '760 patent's chimeric antibody (JTX-65 at 10:53-67; 9/20 AM Tr. 117:22-118:2 (Wall)). The receptor-IgG1 fusion proteins containing a truncated hinge included Example 4 of Capon '964 patent (JTX-61 at 40:26-59), Figure 1 of Byrn 1990 (JTX-56 at 2), and Figure 1 of Watson 1990 (JTX-59 at 3). While a POSA could have used either hinge, such a person would have preferred the full exon-encoded hinge, which was expected to hold the two TNFRs in an orientation that would favor the avidity effect. 9/11 PM Tr. 113:9-114:9 (Blobel).

223. Second, with respect to the linker, the prior art fusion proteins included either no linker or a 3-amino acid linker of the sequence DPE. 9/20 PM Tr. 17:3-7 (Wall). The fusion proteins containing no linker included Figure 1 of Traunecker 1989 (JTX-25 at 1), Example 4 of Capon '964 patent (JTX-61 at 40:26-59), Figure 1 of Byrn 1990 (JTX-56 at 2), and Figure 1 of Watson 1990 (JTX-59 at 3), and the pCD4-Hγ1 deposit identified in Karjalainen '827 publication (JTX-60 at 12). The fusion proteins containing a linker included the pCD4Eγ1 construct of the Seed '262 publication (JTX-57 at 10:29-11:12). A POSA would have preferred to construct a

potential drug candidate without a linker. 9/12 AM Tr. 79:3-14 (Blobel). Indeed, that is exactly what Dr. Goodwin did when he made etanercept: he removed the three-amino-acid linker from Behringwerke's TNFR-IgG1 fusion protein, which Dr. Lauffer derived from the Seed '262 publication's pCD4Eγ1 construct. JTX-74 (55:21-24, 56:2-9, 64:7-11) (Goodwin); JTX-78 (16:2-5, 16:11-17:1) (Lauffer). As Dr. Wall conceded, there is no suggestion in the art that a fusion protein cannot be made without a linker and be successful. 9/20 PM Tr. 18:6-12 (Wall).

224. Dr. Wall has not opined that the different choices in a hinge and/or linker would have affected the function of the fusion protein. As Dr. Greene admitted, many of these IgG fusion protein "constructs mirrored precisely the structure of etanercept in terms of its immunoglobulin domain." 9/18 PM Tr. 71:21-72:12 (Greene). Even Immunex's experts agreed that a POSA in August 1990 would have expected that a p75 TNFR-IgG1 fusion protein would specifically bind to human TNF. 9/11 PM Tr. 118:11-16 (Blobel); 9/12 PM Tr. 56:6-13 (Blobel); 9/20 AM Tr. 112:4-11 (Wall); 9/18 PM Tr. 46:20-23, 47:8-14 (Naismith). The teachings of the prior art to remove the light chain and CH1 domain from the Smith '760 patent's fusion protein would have created etanercept with a reasonable expectation of success. 9/11 PM Tr. 75:1-24 (Blobel); *see* 9/20 PM Tr. 5:16-25 (Wall).

4. Dr. Wall's Hypothetical Concerns Of Effector Functions Would Not Have Discouraged A POSA.

225. Dr. Wall opines that a POSA would have been dissuaded from creating

an IgG1 fusion protein with a TNFR (*e.g.*, etanercept) "because of the effector function of the Ig portion" would have made it unsuitable for use as a therapeutic in patients with an autoimmune disease, like rheumatoid arthritis. 9/20 AM Tr. 39:13-40:9, 113:23-114:4 (Wall). Dr. Wall has not presented any prior art reference expressly discouraging the construction of an IgG1 fusion protein with a TNFR. In fact, the Smith '760 patent's fusion protein is a prior art example of an IgG1 fusion protein with a TNFR. 9/11 PM Tr. 119:5-23 (Blobel); JTX-65 at 10:53-67.

226. According to Dr. Wall, a POSA would have expected that anti-TNF antibodies would elicit effector functions. 9/20 PM Tr. 50:9-24 (Wall). But the prior art expressly encouraged development of anti-TNF antibodies as potential therapeutics to block TNF activity and did not report any negative effects of effector functions. 9/11 PM Tr. 119:9-121:4 (Blobel); *see* DTX-79 at 1; JTX-62 at 2:24-31; DTX-82 at 1, 6. For example, Brennan 1989 reports that anti-TNF antibodies had been used successfully in animal models to protect against the negative effects of TNF-alpha and may be useful in treating rheumatoid arthritis. 9/20 PM Tr. 70:13-73:7 (Wall); DTX-75 at 2, 3. It does not mention any concern of effector functions. 9/20 PM Tr. 72:14-73:7 (Wall).

227. The prior art also teaches receptor-IgG fusion proteins for the treatment of inflammatory conditions, including rheumatoid arthritis, without expressing any concerns of the negative effects of effector functions. 9/11 PM Tr. 119:9-121:4

(Blobel); 9/20 PM Tr. 50:9-24 (Wall). For example, Capon '964 patent reflects that effector functions were not a concern for fusion proteins used for the treatment of inflammatory diseases, such as rheumatoid arthritis. 9/12 AM Tr. 59:17-61:13 (Blobel); JTX-61 at 30:42-51. Watson 1990 teaches the same. 9/12 AM Tr. 73:16-74:16 (Blobel); 9/20 PM Tr. 40:16-41:6 (Wall); JTX-59 at 1, 2, 8.

228. Real-world evidence of simultaneous invention of TNFR-IgG fusion proteins by Genentech, Behringwerke, Immunex, and UT Southwestern show that scientists at the time were not discouraged by effector functions. Instead, they were encouraged to make TNFR-IgG fusion proteins. 9/11 PM Tr. 119:9-121:4 (Blobel); DTX-111 at 2, 3; DTX-114 at 1; JTX-69 at 2; JTX-68 at 3; *see also* FOF ¶¶ 5-11, 231-36. Immunex's Dr. Goodwin, who created etanercept in November or December 1990, testified that he wasn't aware of any conversations of whether etanercept would fix complement until the mid-to-late 1990s. JTX-74 (53:20-54:12, 67:8-25) (Goodwin). Dr. Lesslauer testified that any potential complement fixation "did not concern" him and "didn't think it was of sufficient relevance not to continue that avenue" of creating a fusion protein with a TNFR, because targeting TNF "would not have the same situation" as the CD4 fusion proteins. JTX-81 (82:11-85:17, 85:22-85:24, 86:2) (Lesslauer). Testing of etanercept for effector functions were not published until more than a decade after August 1990, and several years after FDA approval of infliximab and etanercept in 2000. *See* DTX-213; PTX-130;

PTX-138. As Dr. Arora testified, these CDC and ADCC assays were conducted to provide "post-marketing support" for etanercept. JTX-84 (45:2-9, 178:10-179:10) (Arora). Even by 2009, Dr. Arora reported that "[t]he role of the TNF antagonist Fc regions in mediating FcγR-related events has not been thoroughly investigated." PTX-130 at 2; JTX-84 (117:22-118:15) (Arora).

C. A POSA Using Ordinary Skill Would Have Been Able To Produce Etanercept With A Reasonable Expectation Of Success.

229. By August 1990, the prior art provided all of the information needed to construct etanercept. 9/20 AM Tr. 92:10-93:1 (Wall). The cDNA and amino acid sequences of the p75 TNFR were reported and publicly available. 9/12 PM Tr. 53:9-54:4 (Blobel); 9/11 PM Tr. at 115:4-116:10 (Blobel); JTX-65 at 2:67–3:6, 3:16-26, 9:16-29, 10:53-68, 16:60-66, Figs. 2A-2B. The cDNA and amino acid sequences for the constant domains of the human IgG1 were also reported and publicly available. 9/12 PM Tr. 54:5-12 (Blobel); JTX-19 at 4. The prior art further teaches fusion proteins consisting of a receptor fused to the hinge-CH2-CH3 of a human IgG1, including the deposit of a vector for the full exon-encoded hinge-CH2-CH3 portion of a human IgG1. 9/20 AM Tr. 92:10-93:1 (Wall); 9/11 PM Tr. at 116:11-117:11 (Blobel); JTX-57 at 10:56-11:2, Table 2, 57:1-58:55; JTX-56 at 1, 2, 3-4, Fig. 1; JTX-59 at 1, 2, Fig. 1A; JTX-60 at 6:44-7:45, Fig. 2; JTX-61 at 1:8-14, 4:16-43, 7:13-19, 15:4-18, Example 4; JTX-25 at 1-3, Fig. 1. With the complete DNA sequences, modifying genes to construct recombinant molecules was routine by

August 1990. 9/12 PM Tr. 54:13-55:1 (Blobel). The prior art teaches methods for expressing receptor-IgG1 fusion proteins and purifying them. 9/12 PM Tr. 55:2-56:5 (Blobel); 9/11 PM Tr. 117:12-118:10 (Blobel); 9/17 AM Tr. 79:19-80:19 (Loetscher); JTX-65 at 14:5-15, 15:60-16:56; JTX-57 at 6:23-24, 6:28-32, 7:20-26, 57:16-58:55; JTX-56 at 2, Fig. 1; JTX-59 at 2, 4; JTX-61 at 16:10-11, 29:30-48, 30:26-37, 40:68-41:2, 44:67-45:9; JTX-25 at Fig. 2.

230. A POSA in August 1990 would have been able to construct the fusion protein using ordinary skill. 9/12 PM Tr. 20:4-22:4, 55:2-56:5 (Blobel); 9/20 AM Tr. 92:10-93:1, 96:14-97:7, 110:14-23 (Wall). A POSA in August 1990 would have reasonably expected that etanercept would specifically bind to human TNF. 9/11 PM Tr. 118:11-16 (Blobel); 9/12 PM Tr. 56:6-13 (Blobel); 9/20 AM Tr. 112:4-11 (Wall); 9/18 PM Tr. 46:20-23, 47:8-14 (Naismith).

D. The Objective Indicia Supports Obviousness.

1. Simultaneous Inventions Show That Others Created TNFR-IgG1 Fusion Proteins, Including Etanercept.

231. At least three other research groups had, within a short time frame around August 1990, independently conceived of and developed proteins of a TNFR extracellular region fused to the hinge-CH2-CH3 of an immunogloublin. 9/11 PM Tr. 86:6-87:12 (Blobel); 9/18 PM Tr. 131:21-132: 24 (Greene).

232. As discussed, Immunex collaborated with Berengwerke to develop etanercept, and came up with the specific claimed construct wholly independently

of the Roche inventors. FOF ¶¶ 5-11.

233. In addition, scientists at Genentech developed a p55 TNFR-IgG1 fusion protein in which the p55 extracellular region was directly linked to a truncated hinge, which in turn was linked to CH2-CH3 domains of a human IgG1. 9/11 PM Tr. 86:14-87:6 (Blobel); 9/20 AM Tr. 89:10-18 (Wall); 9/18 PM Tr. 103:25-104:3 (Greene). Genentech's p55 TNFR-IgG1 fusion protein is described in a paper by Ashkenazi, which was received for review on June 13, 1991, and published in December 1991. JTX-69 at 1, 2.

234. Genentech scientists relied on the CD4-IgG1 fusion protein, which were found to have "two functional HIV binding sites and a markedly longer plasma half-life than soluble extracellular portion of CD4," and the advantage of Protein A "to recover and purify the protein." JTX-69 at 1, 2; 9/20 PM Tr. 85:2-24 (Wall).

235. UT Southwestern scientists developed a p55 TNFR-IgG fusion protein consisting of the p55 extracellular region fused via a cleavable linker to the hinge-CH2-CH3 of a mouse IgG1. 9/11 PM Tr. 86:14-87:6 (Blobel); 9/18 PM Tr. 103:12-21 (Greene). Their fusion protein is described in a paper by Peppel, which was received for publication on August 8, 1991, JTX-68 at 6, and published in December 1991. JTX-68 at 1, 3; *see also* DTX-1164.

236. Peppel 1991 explains that "[t]he TNF inhibitor that we have produced and characterized finds precedent" in the CD4-IgG fusion proteins. JTX-68 at 5.

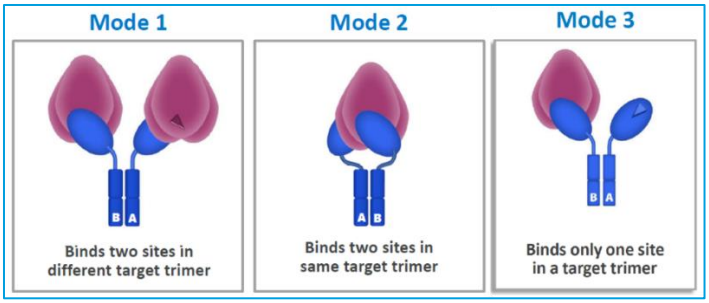
Peppel 1991 explains that the soluble TNFRs are highly unstable *in vivo*, univalent with far lower binding than a bivalent protein, produced at low levels, and difficult to purify. *Id.* at 1. They created a TNFR-IgG fusion protein to "circumvent these problems." *Id.* Since the fusion protein is produced "in considerable abundance" and "can easily be purified," Peppel 1991 explains that "it will be possible to produce large quantities of the protein for investigational use" and that "a homologous construct utilizing the human IgG heavy chain could readily be prepared." *Id.*

2. Unexpected Results Do Not Support Nonobviousness.

a. Etanercept's Binding Strength Would Be Expected.

237. By August 1990, TNF was known to exist in the form of a soluble trimer consisting of three identical parts and three binding sites. JTX-26 at 4; 9/24 AM Tr. 35:17-36:10 (Skerra); 9/18 AM Tr. 107:16-21 (Naismith).

238. Dr. Naismith presented three theoretical modes by which a bivalent protein with two binding sites (*e.g.*, etanercept) may bind to a trimeric target with three binding sites (*e.g.*, TNF): monovalent binding (Mode 1), bivalent binding (Mode 2), and an intermediate step (Mode 3) that could lead to either Mode 1 or Mode 2 binding. 9/24 AM Tr. 39:25-41:24 (Skerra); 9/18 Tr. 110:10-111:13 (Naismith); DTX-84 at 5; *see* DDX-3017, DDX-3012.



Mode 1 is a monovalent binding interaction, because the protein binds to each TNF trimer at only one binding site; this is known as "affinity." 9/24 AM Tr. 40:16-20, 44:22-45:3 (Skerra); DTX-84 at 5. Mode 2 is a bivalent binding interaction, because the bivalent binding protein binds to each TNF trimer at two binding sites; this is known as "avidity." 9/24 AM Tr. 40:22-41:2, 45:18-20 (Skerra); DTX-84 at 5.

239. By August 1990, due to the avidity effect, bivalent binding (binding Mode 2) was expected to provide on average a 1,000-fold stronger bond than monovalent binding (binding Mode 1). 9/24 AM Tr. 45:6-46:1 (Skerra); DTX-84 at 5. As a result of the stronger binding interaction, a POSA would have expected that bivalent binding, forming a 1:1 complex, to be the default mode and predominate over monovalent binding. 9/24 AM Tr. 39: 11-24, 42:2-3, 48:23-49:17, 53:8-10 (Skerra); DTX-84 at 5.

240. Dr. Naismith did not consider the avidity effect but instead assumed that, to bind the same TNF trimer, the two arms of a bivalent binding protein would need to cross in a complicated manner. 9/18 AM Tr. 109:25-110:9, 111:14-112:5 (Naismith). As Dr. Skerra explained, however, the two binding arms of a bivalent

binding protein can rotate 360 degrees around an axis, and thus they can bind to the same TNF trimer without crossing. 9/24 AM Tr. 48:1-21 (Skerra); *see* 9/18 AM Tr. 109:25-110:9 (Naismith).

241. By August 1990, to a POSA, bivalent binding was expected on average to lead to a 1,000-fold increase in binding strength compared to monovalent binding. 9/24 AM Tr. 49:18-51:4 (Skerra); 9/11 PM Tr. 99:20-102:6, 111:24-113:8 (Blobel); DTX-84 at 5. Thus, a POSA in 1990 would fully expect a bivalent molecule like etanercept to provide 50-times stronger binding to TNF and 1,000-times higher neutralization activity as compared to the soluble monomeric TNFR. *Id*.

b. A POSA Would Not Expect Etanercept To Aggregate.

242. The expected bivalent binding (Mode 2) would also lead a POSA to expect fewer, if any, aggregates to form. For a bivalent TNF-binding protein to form aggregates, the predominant mode of binding would need to be monovalent binding, whereby each TNF-binding protein binds to more than one TNF trimer, creating large cross-links between many TNF-binding proteins. 9/18 AM Tr. 112:6-19 (Naismith); 9/24 AM Tr. 54:22-55:24, 56:7-22 (Skerra). But, it was well-established in the prior art that "[i]n situations where multisite adherence to a single particle [*i.e.*, bivalent binding] and cross-linking of discrete particles [*i.e.*, monovalent binding] are both possible, *the former is predicted to predominate strongly*." JTX-70 at 1; 9/24 AM Tr. 52:4-53:7 (Skerra). Thus, in August 1990, a POSA would have

expected that etanercept's preference for bivalent binding for the TNF trimer would preclude aggregation. 9/24 AM Tr. 51:14-53:10, 37:8-21 (Skerra); JTX-70. The observed lack of aggregation would not have been surprising. 9/24 AM Tr. 48:23-49:17, 51:11-52:4, 57:25-58:7 (Skerra).

243. In contrast, in Dr. Capon's sheep red blood cell agglutination studies, relied upon by Immunex's experts, the target of his CD4-IgG1 fusion protein was gp120, which was known to be a monomer (*i.e.*, having one binding site) in this experimental setting. 9/18 AM Tr. 114:5 (Naismith); 9/24 AM Tr. 59:5-13 (Skerra). Since the monomeric gp120 has only a single binding site, bivalent binding is not possible. Thus, monovalent binding would lead to cross-linking (*i.e.*, agglutination) of several red blood cells. 9/18 AM Tr. 114:5-10 (Naismith); 9/24 AM Tr. 59:5-9 (Skerra). Due to the differences between a monomeric target (gp120) and a trimeric target (TNF), a POSA would not have expected etanercept to show the same results as the CD4-IgG1 fusion proteins. 9/24 AM Tr. 58:22-59:5 (Skerra).

244. Moreover, Dr. Naismith relied upon a comparison of etanercept to the anti-TNF antibodies infliximab (Remicade®) and adalimumab (Humira®) in forming his opinion that etanercept's lack of aggregation was unexpected. 9/18 AM Tr. 115:13-20 (Naismith); PTX-140; 9/24 AM Tr. 53:11-19 (Skerra). But infliximab and adalimumab did not exist in August 1990. 9/18 PM Tr. 118:19-119: 6 (Greene); 9/24 AM Tr. 53:11-19 (Skerra). Dr. Naismith did not present prior art testing of any

anti-TNF antibody. Dr. Greene admitted that he is not aware of any prior art showing aggregation by an anti-TNF antibody in the presence of soluble TNF. 9/18 PM Tr. 122:13-21 (Greene).

245. Moreover, the authors of Kohno 2007, the publication that Dr. Naismith relied upon to compare etanercept to the anti-TNF antibodies, explained that the monoclonal antibodies "*typically do not* form precipitable complexes [*i.e.*, aggregates] in these types of assays." PTX-140 at 3. Kohno 2007 is consistent with the expectation of a POSA that, unless experimental evidence proved otherwise, aggregates were not expected to form. 9/24 PM Tr. 11: 14-12:5 (Skerra).

c. Etanercept's Role in CDC and ADCC Is Not Unexpected.

246. Both CDC and ADCC are antibody effector functions. 9/18 PM Tr. 76:24-77:2 (Greene); 9/11 PM Tr. 118:22-119:4 (Blobel). The acronym "CDC" stands for complement dependent cytotoxicity. 9/18 PM Tr. 64:19-22 (Greene). The first step of the CDC pathway is called "complement fixation." 9/18 PM Tr. 125:13-22 (Greene). The acronym "ADCC" stands for antibody dependent cellular cytotoxicity. 9/18 PM Tr. 67:15-18 (Greene). Both cause "cytotoxicity," which means cell death. 9/18 PM Tr. 64:23-25, 67:19-20 (Greene).

247. By August 1990, it was known that aggregation of IgGs is "absolutely critical" for CDC and ADCC to occur. 9/18 PM Tr. 98:7-8, 122:22-25, 123:11-124:21, 127:7-19 (Greene); 9/24 AM Tr. 62:18-21 (Skerra); JTX-50 at 9. The need

for aggregation is "built for own protection so that we're not triggering this pathway willy-nilly." 9/18 PM Tr. 127:7-19 (Greene); *id.* at 123:25-124:21 (Greene).

248. The primary target of etanercept is the soluble (i.e., non-membrane bound) trimeric TNF. 9/24 AM Tr. 63:1-2 (Skerra); 9/12 AM Tr. 85:20-86:21 (Blobel); JTX-84 (86:17-20) (Arora). By August 1990, it was known that the active form of TNF involved in endotoxic shock and many inflammatory diseases was the soluble trimeric TNF, which is not attached to any cell membrane and thus would not trigger cell death. 9/18 PM Tr. 128:24-129:19 (Greene).

249. In addition, in August 1990, a POSA would have expected etanercept to prefer bivalent binding to the TNF trimer, forming a 1:1 complex, which would not aggregate. 9/24 AM Tr. 63:2-4 (Skerra); *see also supra* Sections IV.D.2.a and IV.D.2.b. Even in the presence of excess etanercept, the largest complex expected to form between etanercept and TNF would have been a 3:2 complex. 9/24 AM Tr. 57:15-23 (Skerra). This 3:2 complex is not sufficient to trigger either CDC or ADCC, whether the TNF is membrane bound or soluble. 9/24 AM Tr. 58:9-19 (Skerra); 9/18 PM Tr. 123:11-19, 127:7-19 (Greene).

250. Because aggregation was known to be critical for triggering both the CDC and the ADCC pathways, it would not have been surprising that etanercept does not cause CDC or ADCC. 9/24 AM Tr. 63:4-6 (Skerra). Dr. Greene admitted that he is not aware of any prior art ADCC or CDC testing of an anti-TNF antibody

or of the soluble TNFR. 9/18 PM Tr. 119: 9-14, 122:7-21 (Greene); *see also* 9/24 AM Tr. 64:5-8 (Skerra).

251. Dr. Greene relied upon the CD4-IgG1 studies to form his opinion with respect to etanercept's CDC and ADCC activity. 9/18 PM Tr. 119: 21-25 (Greene). In disease states, the targets for CD4-IgG1 and etanercept are fundamentally different. The CD4-IgG1's target, gp120, was a membrane-bound protein attached to the membrane of HIV-infected cells. 9/18 PM Tr. 115:9-19, 117:5-7, 121:15-19 (Greene). Etanercept's target is the TNF trimer, which in its active form in disease states is soluble (not bound to a cell). 9/24 AM Tr. 63:1-2 (Skerra); 9/12 AM Tr. 85:20-86:21 (Blobel); 9/18 PM Tr. 128:24-129:19 (Greene); JTX-84 (86:17-20) (Arora); JTX-26 at 1.

252. Dr. Greene also relied upon a post-filing date comparison of etanercept to infliximab and adalimumab, which did not exist in August 1990. 9/18 PM Tr. 118:19-119:6 (Greene); 9/24 AM Tr. 53:11-19 (Skerra). The data reported in Arora 2009 and Mitoma 2008 comparing the CDC and ADCC activities of infliximab, adalimumab, and etanercept were collected using mutated, membrane-bound TNF under artificial experimental settings that are not representative of human physiological conditions. PTX-130 at 2; DTX-213 at 2; 9/24 AM Tr. 64:10-65:3, 65:21-24, 67:12-22, 68:7-8 (Skerra); JTX-84 (86:3-87:10, 127:1-128:1) (Arora); 9/12 AM Tr. 100:8-24 (Blobel). Both Arora 2009 and Mitoma 2008 identified the

use of mutated, membrane-bound TNF as limitations of applying their studies to physiological conditions. PTX-130 at 6; 9/24 AM Tr. 65:10-24 (Skerra); 9/24 PM Tr. 7:9-15 (Skerra); JTX-84 (127:6-128:24) (Arora); DTX-213 at 8; 9/24 AM Tr. 67:25-68:8 (Skerra).

253. During prosecution of the patents-in-suit, Dr. Arora submitted a declaration to the PTO reporting the same results of the CDC and ADCC studies reported in Arora 2009. PTX-6.459 at 2; 9/24 AM Tr. 66:8-15 (Skerra). At her deposition, despite repeated questions from Immunex's counsel, Dr. Arora would not agree that the results reported in Arora 2009 or in her declaration to the Patent Office were surprising or unexpected. JTX-84 (170:4-19) (Arora) ("I don't remember the sequence of design of the study and results were surprising or not."); JTX-84 (175:3-18) (Arora) ("In this case, I don't think there was surprise or no surprise question. We were just evaluating some variants without having any pre-formed conclusions."); *see* JTX-84 (178:18-179:2) (Arora) ("How they may perform in our ADCC or CDC assay, I did not have any speculation."). Dr. Arora testified only that it would have been unexpected if etanercept had shown *higher*, not lower, effector function (such as ADCC activity) than infliximab and adalimumab. JTX-84 (172:10-14, 172: 19-20) (Arora); *see also id.* (170:4-9, 170:13-19); PTX-130 at 1.

254. Mitoma 2008 reported that "ADCC activities were almost equal among" etanercept, infliximab, and adalimumab. DTX-213 at 1 (Results); 9/24 AM

Tr. 68:12-15 (Skerra). Dr. Greene testified that these conflicting results, as compared to Arora, are due to different experimental conditions used in each study. 9/18 PM Tr. 97:14-18 (Greene). Thus, etanercept's role in ADCC was not settled even almost 20 years after the priority date. 9/24 AM Tr. 68:19-21 (Skerra).

255. In addition, etanercept's lack of effector function activity is not a superior property. Despite higher ADCC and/or CDC activities compared to etanercept, infliximab and adamlimumab are both FDA-approved to treat rheumatoid arthritis. 9/18 PM Tr. 92:7-8, 95:9-15, 96:16-17, 134:14-17 (Greene).

256. And infliximab and adalimumab are FDA-approved for treating more TNF-mediated diseases, including Crohn's disease and ulcerative colitis, than etanercept. 9/20 PM Tr. 162:18-25; 163:13-18 (Fleischmann); 9/21 Tr. 48:8-10, 49:6-11 (Vellturo); 9/18 PM Tr. 134:12-135:6 (Greene); *see* 9/12 AM Tr. 93:20-94:6 (Blobel). Etanercept has not been shown to be safe and effective for treating these conditions. PTX-130 at 7; DTX-214 at 10.

257. Indeed, infliximab and adalimumab's therapeutic safety and efficacy for treating more TNF-mediated conditions than etanercept is due to their ability to elicit the effector functions of CDC and ADCC. 9/12 AM Tr. 93:20-94:6 (Blobel). For example, Arora 2009 reports that etanercept's lack of CDC activity may explain "major clinical differences" between etanercept and anti-TNF antibodies, including the fact that Remicade (Infliximab) "is efficacious in the treatment of Crohn's

disease [] and Wegener's granulomatosis [], whereas etanercept has not demonstrated clinical benefits in these diseases." PTX-130 at 7. As another example, Dr. Kohno explained that the differences between etanercept and anti-TNF antibodies in initiating the first steps of ADCC and CDC "may lead to differences in immunologic mechanisms, and explain the varying disease states for which these agents are effective treatments. For example, in contrast to the soluble TNFR etanercept, the anti-TNF antibody infliximab is effective in the treatment of Crohn's disease." PTX-138. Likewise, Mitoma 2008 explained that their "finding suggests that CDC and outside-to-inside signals by anti-TNFα antibodies may explain the successful clinical efficacy of adalimumab and infliximab in Crohn's disease and Wegener's granulomatosis [WG]." DTX-213 at 1. As Dr. Greene admitted, the anti-TNF antibodies' "ability to act with the TNF trimers that are present on a unique set of cells probably explains their extended clinical capabilities." 9/18 PM Tr. 135:4-6 (Greene).

3. Copying

258. Sandoz selected the amino acid sequence for GP2015 years prior to the

issuance of the patents-in-suit, and based on the commercial product, Enbrel, which it obtained from the market. 9/14 Tr. 6:24-7:2; 17:10-16; 17:10-21 (McCamish); JTX-83 (105:17-25) (Alliger). Sandoz copied the primary amino acid sequence for etanercept, not the patents-in-suit, only because Sandoz wanted to meet the FDA standards for approval of biosimilar products under the BPCIA. 9/14 Tr. 17:22-18:5; 23:19-24:2; 24:16-27:10 (McCamish); JTX-83 (213:10-16; 213:19-214:4; 214:6; 214:9-11; 218:17-25) (Alliger); DTX-931 at 12.

259. Immunex itself understood this. In correspondence to the FDA in response to the draft Guidance document, Amgen took the position that a "biosimilar product must have an identical amino acid sequence" and "the BPCIA prohibits virtually all differences in amino acid sequence." DTX-1187 at 17; JTX-87 (276:22-277:3) (Jones).

4. Clinical Success and Failure of Others

260. The named inventors did not succeed: Roche's p55 TNFR fusion protein failed in clinical trials. 9/20 PM Tr. 176:24-177:5 (Fleischman); JTX-80 (80:10-16; 80:20-22) (Parise); 9/24 PM Tr. 48:20-49:7 (Watt). Instead, it was others who succeeded: specifically, scientists at Immunex who developed Enbrel as an FDA-approved and commercial product. JTX-74 (54:10-12; 59:24-60:1; 60:3) (Goodwin).

261. Moreover, the claimed clinical success of Enbrel does not encompass

the full scope of the asserted claims, which do not claim use of etanercept for treatment of any particular disease. JTX-1; JTX-2; 9/20 AM Tr. 105:14-106:3 (Wall). The asserted claims only require, at most, that Enbrel "specifically bind TNF." JTX-1; 9/20 AM tr. 106:4-8 (Wall). As discussed, Enbrel is not effective in treating diseases that infliximab and adalimumab are effective in treating precisely because of its lack of effector function. 9/20 PM Tr. 162:9-25, 163:13-18 (Fleischmann); 9/21 Tr. 48:8-10 (Vellturo); 9/18 PM Tr. 134:12-135:6 (Greene).

262. Finally, Immunex's expert, Dr. Vellturo, looked at 1998-2008, before the patents-in-suit issued and while Immunex's other patents were providing market exclusivity for Enbrel. JTX-1; JTX-2; 9/25 Tr. 19:4-19, 20:17-21:18, 26:13-27:10, 27:13-24 (McDuff); 9/21 AM Tr. 62:3-6 (Vellturo); DTX-460 at 41; DTX-1083 at 10. Dr. Vellturo did not evaluate what was novel about the patents-in-suit compared to the earlier issued patents. 9/25 Tr. 21:19-23 (McDuff); *see* 9/21 AM Tr. 58:14-59:3; 59:19-60:4 (Vellturo).

CONCLUSIONS OF LAW

I. Obviousness-Type Double Patenting

263. The asserted claims of the patents-in-suit are invalid for obviousness-type double patenting over the psoriasis patents and the '690 patent.

264. Obviousness-type double patenting "is a judicially created doctrine grounded in public policy (a policy reflected in the patent statute) rather than based

purely on the precise terms of the statute." *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). "[I]t is a bedrock principle of our patent system that when a patent expires, the public is free to use not only the same invention claimed in the expired patent but also obvious or patentably indistinct modifications of that invention." *Gilead Sci., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1214 (Fed. Cir. 2014); *accord Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1347 (Fed. Cir. 2010); *Longi*, 759 F.2d at 892. Thus, the purpose of the defense "is to prevent the extension of the term of a patent, even where an express statutory basis for the rejection is missing, by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." *Longi*, 759 F.2d at 892.

265. The obviousness-type double patenting doctrine applies when the reference patent and the patent-in-suit are either commonly owned or assigned, or there is at least one common inventor. *In re Hubbell*, 709 F.3d 1140, 1146 (Fed. Cir. 2013). If "the later expiring patent is merely an obvious variation of an invention disclosed and claimed in the reference patent, the later expiring patent is invalid for obviousness-type double patenting." *Abbvie, Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1379 (Fed. Cir. 2014) (internal quotation marks omitted).

A. Common Ownership/Assignment Between The Patents-In-Suit And The Psoriasis And '690 Patents.

266. With respect to Sandoz's double patenting defenses based on the

psoriasis patents and the '690 patent, which Immunex indisputably owns, the first issue to address is whether Immunex also owns the patents-in-suit. Under Federal Circuit law, it does.

1. Ownership Under The Patent Act.

267. The Federal Circuit has well-settled rules for determining who is the owner of a patent, and has set them out in a series of cases addressing standing under the Patent Act. *See, e.g.*, *Diamond Coating Techs., LLC v. Hyundai Motor Am.*, 823 F.3d 615, 618 (Fed. Cir. 2016); *Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1349 (Fed. Cir. 2016); *Speedplay, Inc. v. BeBop, Inc.*, 211 F.3d 1245, 1250 (Fed. Cir. 2000). Under these rules, if a licensee to a patent has received "all substantial rights" in the patent from the licensor, it becomes the patent owner or assignee "regardless of how the parties characterize the transaction that conveyed those rights." *Speedplay*, 211 F.3d at 1250.

268. The "all substantial rights" test is the only test for patent ownership the Federal Circuit has ever set forth or adopted in any context. While this test has not been applied specifically in the context of double patenting, it is nonetheless applicable here, as it addresses the same issues: who owns the right to exclude others from practicing an invention and for how long that party controls that right. Indeed, "[t]he fundamental reason for the rule [of obviousness-type double patenting] is to prevent unjustified timewise extension of the right to exclude granted by a patent *no*

matter how the extension is brought about." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001) (quoting *In re Van Ornum*, 686 F.2d 937, 943-44 (C.C.P.A 1982)) (emphasis added). Possession of all substantial rights by a party in both the reference patents and later-expiring, obvious variations thereof, could unjustifiably extend that party's patent rights beyond the initial term. Immunex has not pointed to cases applying any other test for ownership, and for good reason: where the party controls the substantial rights in the patent, that party should be the owner for all purposes under patent laws, including for double patenting purposes.

269. Under the Federal Circuit's "all substantial rights" test, Immunex owns the patents-in-suit. The two most critical substantial rights in determining patent ownership are the exclusive right to make, use, and sell the patented product and the right to sue for infringement. *Diamond Coating Techs.*, 823 F.3d at 619. Immunex holds both of these critical rights.

270. Immunex has the exclusive right to make, use, sell, offer for sale, and import the claimed invention. FOF ¶ 59. Moreover, Immunex has the sole right to sublicense the patents, without restriction. *Id*. In addition, Immunex has the first right to rectify any alleged infringement, either by suing, sublicensing, or causing the alleged infringement to cease. *Id*. ¶ 59, 64. If Immunex sues, it exclusively finances and controls the litigation, including settlement, and obtains all proceeds from such a lawsuit. *Id*. Importantly, Immunex holds these rights until patent expiration and

Roche has no right whatsoever to terminate the agreement for any reason. *Id*. ¶ 60.

271. These are the hallmarks of patent ownership. *Diamond Coating Techs.*, 823 F.3d at 619 ("We have observed that (1) the exclusive right to make, use, and sell . . . is *vitally important*,' and (2) 'the nature and scope of the [patentee's[retained right to sue accused infringers [and to license the patent are] the most important factor[s] in determining whether an [agreement] . . . transfers sufficient rights to render the [other party] the owner of the patent.'"); *EMC Corp. v. Pure Storage, Inc.*, 165 F. Supp. 3d 170, 178 (D. Del. 2016) ("A party's right to sue for infringement is complete if it includes the 'right to indulge infringements.'") (emphasis in original); *Vaupel Textilmaschinen KG v. Meccanica Euro Italia SPA*, 944 F.2d 870, 875 (Fed. Cir. 1991) (finding assignment even though licensor retained "a veto right on sublicensing"); *Speedplay*, 211 F.3d at 1250 (finding assignment where licensee obtained exclusive right to make, use, and sell, and right to enforce the patents).

272. In addition, Immunex obtained another critical right: the exclusive right to control the prosecution of the patents-in-suit. Roche had no right to direct the prosecution of the patents and did not even retain a right to review or comment on any patent prosecution submissions. FOF ¶¶ 59, 61. This substantial right gave Immunex the ability to draft patent claims and amend the specification to ensure its right to exclude was fully protected. *Id*. ¶¶ 59, 72. And most importantly here, to ensure that the patents that ultimately issued covered and extended the existing

monopoly on Immunex's etanercept product. *Id*. ¶¶ 54-55, 72-83.

273. The rights that Roche retained under the 2004 Agreement are not substantial rights. First, Roche only retained the right to practice the invention for internal, non-commercial uses. *Id*. ¶¶ 62-63. The Federal Circuit has held that this is not a substantial right: "A patentee that merely retains the right to practice the patent does not risk *losing* a substantial right if the claims are invalidated or the patent held unenforceable." *Luminara*, 814 F.3d at 1351 (emphasis in original). Indeed, here, Roche would have *more* rights if the patent claims were held invalid or unenforceable because it would gain the right to commercialize the patented product, which it currently lacks.

274. Second, Roche retained a right to sue only if Immunex does not. FOF ¶¶ 62, 65. This, under Federal Circuit law, is an illusory right "because [Immunex] could 'render that right nugatory by granting the alleged infringer a royalty-free sublicense.'" *AssymetRx, Inc. v. Biocare Med., LLC*, 582 F.3d 1314, 1320 (Fed. Cir. 2009); *accord Speedplay*, 211 F.3d at 1251; *EMC Corp.*, 165 F. Supp. 3d at 174-75. As such, it is not a substantial right.

275. Simply put, Roche did not retain any substantial rights in the patents, instead transferring all of them to Immunex under the 2004 Agreement. FOF ¶¶ 54-65. Accordingly, Immunex is the owner of the patents-in-suit and the doctrine of obviousness-type double patenting applies. To find otherwise would reward

Immunex's gamesmanship by extending its monopoly by another 10 years—for a total of over 30 years of market exclusivity.

276. Immunex contends that because it is labeled an "exclusive licensee" under the 2004 Agreement, it cannot be an owner for purposes of double-patenting. But the Federal Circuit has made clear that the label the parties place on the transaction is irrelevant; rather, it is the substantive effect of the agreement: "A party that has been granted all substantial rights under the patent is considered the owner *regardless of how the parties characterize the transaction that conveyed those rights*." *Speedplay,*211 F.3d at 1250 (Fed. Cir. 2000) (emphasis added).

277. Immunex further contends, based on the MPEP, that common ownership must exist at the time the claimed invention was made.

278. In no case has the Federal Circuit or any District Court imposed this timing requirement. On the contrary, the Federal Circuit has applied obviousness-type double patenting, even when the patents only became commonly owned later, e.g., via merger. *See Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377, 1382-86 (Fed. Cir. 2003) (holding patents invalid for obviousness-type double patenting where the patentee "own[ed] the [reference] patents because [it] has merged with the original assignees of those patents").

279. The Federal Circuit also has found that double patenting can apply in situations where a later-filed reference patent did not exist at the time that the

invention claimed in the target patent was made, and therefore could not have been commonly owned at that time. *See Lilly*, 251 F.3d 955; *see also Ex parte Pfizer, Inc.*, Appeal No. 2009-004106, 2010 WL 532133, at *21 (B.P.A.I. Feb. 12, 2010).

280. In addition, the MPEP is not binding on this Court. *Regents of Univ. of New Mexico v. Knight*, 321 F.3d 1111, 1121 (Fed. Cir. 2003) ("The MPEP sets forth PTO procedures; it is not a statement of law.")

281. But even if it were, the MPEP does not require that, for purposes of double-patenting, common ownership must exist at the time the application is filed. The "at the time the claimed invention was made" language quoted in the MPEP comes directly from 35 U.S.C. § 103(c)(1). The MPEP simply states that, in cases where a reference patent is not prior art for purposes of obviousness because it is commonly owned as defined in 35 U.S.C. § 103(c)(1), it will be treated as commonly owned for purposes of double patenting. The MPEP also provides that a party who is not a common owner at the time of invention can still face a potential double-patenting rejection. MPEP 804.03 ¶ 8.28.fti.

282. The reason for requiring common ownership at the time the invention was made in the context of obviousness is to prevent the patentee from strategically assigning a patent after filing in order to avoid it being used as prior art—it is a *restriction* on patentee gamesmanship. MPEP § 706.02(*l*)(2) ("The requirement for common ownership at the time the claimed invention was made is intended to

preclude obtaining ownership of subject matter after the claimed invention was made in order to disqualify that subject matter as prior art against the claimed invention.").

283. There is no corresponding statutory language for obviousness-type double patenting, and the MPEP recognizes that equitable principles should prevail in double patenting cases. MPEP § 804.II.B.3 ("In some circumstances a nonstatutory double patenting rejection is applicable based on equitable principles. Occasionally the fundamental reason for nonstatutory double patenting – to prevent unjustified timewise extension of patent rights – is itself enforceable no matter how the extension is brought about."). Applying a requirement that the patents also be commonly owned at the time of filing for purposes of double-patenting would *promote* patentee gamesmanship of exactly the kind presented here: permitting a patentee to later acquire a patent (even a day after filing), use that patent to exclude a party from practicing invention, and thereby extend its right to exclude. There is simply no rationale, in the case law or for purposes of equity, to impose this sort of timing requirement in cases of double patenting.

284. Accordingly, it is appropriate to apply the Federal Circuit's established rules on patent ownership in the context of double patenting, regardless of when the transfer of ownership occurred.

B. The Patents-In-Suit Are Invalid Over The Psoriasis Patent Claims.

285. Sandoz presented unrebutted testimony at trial demonstrating by clear

and convincing evidence that the claims of the psoriasis patents render the asserted claims of the patents-in-suit invalid. FOF ¶¶ 90-96; *see, e.g.*, *Geneva*, 349 F.3d at 1383 (holding that the earlier expiring claim was "basically a species of the [later expiring claims, which]…[o]verall recite limitations that are either broader than or obvious variants of corresponding limitations in the [earlier expiring] claim"); *Lilly*, 231 F.3d at 968-70 (holding that claim directed to a method of blocking the uptake of serotonin by administering fluoxetine was invalid for double patenting in view of a claim directed to treating anxiety by administering fluoxetine, which inherently resulted in blocking the uptake of serotonin).

286. Specifically, the psoriasis patents each claim a specific use for etanercept: to treat psoriatic conditions. FOF ¶ 92. The asserted claims are broader, claiming etanercept and a method of making it. *Id*. ¶¶ 93-95. It is undisputed that etanercept specifically binds TNF when administered to treat psoriasis, so that property, claimed in the =''182 patent asserted claims, is inherent. *Id*. ¶ 93. It is also undisputed that the process steps in the '522 patent claims are obvious and within the routine skill of a person of ordinary skill in the art. *Id*. ¶¶ 95-96. Given this undisputed, clear, and convincing evidence, the asserted claims are invalid for obviousness-type double patenting in view of the psoriasis patent claims.

C. The Patents-In-Suit Are Invalid Over Claim 3 Of The '690 Patent.

287. The asserted claims of the patents-in-suit are invalid in view of claim 3

of the '690 patent. FOF ¶¶ 97-117. Properly construed, claim 3 of the '690 patent specifically claims or covers etanercept. *Id*. ¶¶ 98-110. This is clear from the intrinsic record, that is, the specification and the prosecution history of the '690 patent. *See, e.g., Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) ("To ascertain the meaning of claims, we consider three sources: The claims, the specification, and the prosecution history.").

288. Etanercept is featured prominently in the '690 patent specification. Figure 1 depicts etanercept, and is entitled "TNFR:Fc." FOF ¶ 102. The remaining figures relate to the construction of and effects of administering etanercept. *Id*. Example 2 describes the construction and expression of etanercept. *Id*. ¶ 104. Examples 4, 5, and 6 describe the use of etanercept to suppress the effects of arthritic conditions. *Id*. Moreover, SEQ ID NOS. 3 and 4, which are expressly described in the specification as *embodiments* of the claimed invention, are directed to a p75 TNFR:Fc fusion protein—i.e., in which the TNFR is fused at the hinge of an IgG1. *Id*. ¶ 103.

289. The prosecution history confirms that the '690 patent covers etanercept. Immunex used results from studies performed with etanercept to support its claims and, importantly, drafted dependent claims directed specifically to etanercept that fell within independent claims with the "chimeric antibody" language. *Id*. ¶¶ 106, 108. Immunex also emphasized that "neither of the constructs supposedly obvious

to one of skill in the art results in ***the claimed TNFR:Fc***." *Id*. ¶ 107. Thus, the '690 patent covers etanercept. *See Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1095 (Fed. Cir. 2013) (when the patentee "disavows a certain meaning to obtain a patent, the doctrine of prosecution history disclaimer narrows the meaning of the claim consistent with the scope of the claim surrendered").

290. In short, the specification and file history point to the same conclusion: the '690 patent claims "the claimed TNFR:Fc" of Fig. 1, which is etanercept.

291. Because claim 3 of the '690 patent covers etanercept, the asserted claims of the patents-in-suit are invalid for obviousness-type double patenting for the same reasons as discussed above with respect to the psoriasis patent claims. FOF ¶¶ 111-16; *see* COL ¶¶ 285-86.

292. Moreover, even if claim 3 of the '690 patent were construed to require fusing the TNFR to the entire heavy and light chains of the IgG1 constant regions, as Immunex suggests, the asserted claims of the patents-in-suit would be obvious. Immunex does not dispute that it would be obvious to use the full extracellular region of the p75 TNFR in a fusion protein and to use an IgG1 for the immunoglobulin portion of a fusion protein. *Id*. ¶¶ 112-13. They also do not dispute that any fusion protein using that receptor would specifically bind TNF and would obviously be made by the process claimed in the '522 patent. *Id*. ¶¶ 114-16. The sole dispute is whether it would be obvious to fuse the TNFR directly to the hinge. The evidence at

trial demonstrates, clearly and convincingly, that fusing the receptor directly to the hinge would be obvious.

293. Indeed, the state of the art at the time pointed directly to fusing the receptor to the hinge. By August 1990, the receptor-IgG fusion protein art had evolved such that the preferred receptor-IgG fusion proteins removed both the light chain and the CH1 domain, because both were unnecessary and this simplified the construction of the fusion proteins. *Id*. ¶¶ 215-20.

294. A person of skill in the art would not be deterred from removing the CH1 for fear of effector functions or aggregation. *Id*. ¶¶ 225-28. This is so for several reasons. First, the asserted claims are not directed to any specific treatment or in vivo effects and only require the fusion protein to, at most, specifically bind TNF. *Id*. ¶ 225. Such fusion protein would indisputably be useful for in vitro testing and diagnostics at a minimum. *Id*. ¶¶ 198, 225. Second, it was also possible that, in some clinical treatments, effector functions or aggregation of the fusion protein might be desirable, such as to treat Crohn's disease. *Id*. ¶¶ 255-57. Third, even for treatment of rheumatoid arthritis, specifically, the target would be soluble, non-membrane bound TNF, which would make effector functions irrelevant. *Id*. ¶¶ 248-51. Fourth, a person of skill in the art would not expect aggregation because of the expected 1:1 binding of fusion protein to TNF, which would avoid aggregation. *Id*. ¶¶ 242-45. Accordingly, the art did not teach away from removing the CH1 domain.

295. In sum, the most obvious construct to make, in view of claim 3 of the '690 patent, would be a construct in which the full p75 extracellular region was fused directly to the hinge of an IgG1—i.e., etanercept. For this additional reason, the asserted claims of the patents-in-suit are invalid for obviousness-type double patenting.

D. The '182 Patent Claims Are Invalid As Obvious Over '279 Patent Claim 5.

296. The asserted claims of the '182 patent are invalid as obvious in view of claim 5 of the '279 patent. There is no dispute that the double patenting doctrine applies because the '182 patent and '279 patent share common inventors. FOF ¶ 118; *see Hubbell*, 709 F.3d 1146. The sole difference between the asserted claims and '279 patent claim 5 is the use of the extracellular domain of the p75 TNFR in place of a soluble fragment of the p55 TNFR. *Id*. ¶¶ 119-21. It would be obvious to make that modification.

297. Both the p55 and p75 TNFRs were known in the art, and were known to specifically bind TNF. *Id*. ¶¶ 120, 201-02. Accordingly, it would have been obvious to use the full extracellular region of the p75 TNFR in place of a p55 TNFR fragment. *Id*. ¶ 120.

298. Furthermore, the '182 patent is not entitled to safe harbor protection under 35 U.S.C. § 121 because the applicants failed to maintain consonance throughout the prosecution of the '182 patent application. It is black letter law that

"a divisional application filed as a result of a restriction requirement *may not* contain claims drawn to the invention set forth in the claims elected and prosecuted to patent in the parent application. The divisional application *must* have claims *drawn only to the 'other invention.'*" *Gerber Garment Tech., Inc., v. Lectra Sys., Inc.*, 916 F.2d 683, 687 (Fed. Cir. 1990) (emphasis added). Moreover, "[c]onsonance requires that the line of demarcation between the 'independent and distinct inventions' that prompted the restriction requirement be maintained. . . . Where that line is crossed the [§ 121 safe harbor] does not apply." *Id.*

299. In response to a restriction requirement, the Roche inventors selected the p55 fusion protein in both the '279 patent prosecution *and* the '182 patent prosecution. FOF ¶¶ 40-41, 45, 47. It was not until ten years later, after Immunex assumed control of the prosecution, that Immunex changed the '182 patent application claims to the p75 TNFR. *Id*. ¶ 73.

300. Immunex relies on a single case, in which the applicant *mistakenly* copied the claims of the parent application and corrected that mistake within a few months. *See Boehringer Ingelheim*, 592 F.3d at 1344. There was no such mistake here. Instead, the Roche applicants made a deliberate decision to select the p55 protein claims and prosecuted them for ten years before Immunex switched the claims to cover etanercept.

301. The applicants failed to maintain consonance. Accordingly, the § 121

safe harbor does not apply. Because the safe harbor does not apply, and Sandoz has proven by clear and convincing evidence that the asserted '182 patent claims would be obvious in view of '279 patent claim 5, the asserted '182 patent claims are invalid for obviousness-type double patenting.

II. Lack Of Written Description And Enablement

302. The asserted claims of the patents-in-suit are invalid for lack of written description and enablement. A patent's specification is required to contain a written description of the invention in sufficient detail to enable a person of skill in the art to make and use it. 35 U.S.C. § 112. To comply with the written description requirement, a patentee must describe "the invention, with all its claimed limitations" as of the filing date. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The specification must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The Court must make "an objective inquiry into the four corners of the specification" to determine whether it "show[s] that the inventor actually invented the invention claimed. *Id*. A "description that merely renders the invention obvious does not satisfy the [written description] requirement." *Id*. at 1352.

303. Patents claiming chemical compounds, such as the proteins claimed here, must provide enough information about those compounds to distinguish them

from other materials. Such distinguishing information may include functional descriptions of chemical compounds where "the disclosed function is sufficiently correlated to a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003).

304. Similarly, the enablement requirement is not met "when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The patentee may not establish enablement by "asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Id.*

A. The Specifications as Filed Describe a Structurally Different Protein Than the Claimed Fusion Protein.

305. The specifications of the patents-in-suit are primarily directed to the p55 TNFR and fusion proteins containing the p55 TNFR—*not* to the claimed fusion protein containing the extracellular portion of the p75 TNFR.

1. The Specifications of the Patents-in-Suit Do Not Describe the Extracellular Region of p75.

306. The specifications of the patents-in-suit, as filed, did not describe the full amino acid sequence for the p75 TNFR. Rather, they recited, in Figure 4, a truncated and mutated p75 TNFR sequence that is missing 70 amino acids from the

N-terminus (including 48 from the extracellular region) and contains three specific mutations, each of which potentially could change the shape or function of the molecule. FOF ¶¶ 36-44, 124-135. A person of skill in the art would not have been able to predict the activity of the Figure 4 protein as of the filing date, although it was discovered, decades later, that this Figure 4 sequence was lacking a large portion of the region that is responsible for TNF binding activity. *Id*.¶¶ 127-128.

307. The specifications repeatedly reference the p55 TNFR and Figure 4 as the claimed invention and the preferred sequence. *Id*. ¶¶ 136-155. The specification, including the examples, is primarily directed to the p55 TNFR and only secondarily to Figure 4. *Id*. ¶¶ 156-157 The sole example related to Figure 4, Example 8, does not provide sufficient information to obtain the full p75 TNFR. Indeed, the inventors themselves, were unable to do so using that technique. *Id*. ¶¶ 25-32, 157. Such a disclosure in the specification of the patents-in-suit is insufficient to establish adequate written description of the claimed extracellular region of the p75 TNFR: "[A]dequate description of claimed DNA requires a precise definition of the DNA sequence itself—not merely a recitation of its function or a reference to a potential method for isolating it." *Amgen,* 314 F.3d at 1332.

308. Moreover, the specification does not mention the extracellular region of the p75 TNFR as required in the claims, nor does it provide the sequence for that protein. FOF ¶¶ 161, 173.

309. A POSA also would have understood that truncated, mutated Figure 4 sequence is a distinct protein from the full p75 TNFR disclosed in Smith 1990, which would have a distinct shape and function. *Id*. ¶¶ 36-44, 124-135. Moreover, a POSA would have understood that the inventors did not describe or possess the full p75 TNFR sequence because, while it was disclosed in the art in Smith 1990, they did not describe it in their patent or indicate that it was part of their invention. *Id*. ¶¶ 34-37, 143-147. In fact, they distinguished their Figure 4 sequence from the Smith 1990 sequence in a related application. *Id*. ¶¶ 42-44. Accordingly, the specification, as filed, lacks written description of the extracellular region of a p75 TNFR.

B. There is No Written Description Support for an Exon-Encoded Hinge CH2-CH3 of an IgG1.

310. The specifications also fail to describe the immunoglobulin portion of the molecule with the requisite particularity. *Id*. ¶¶ 162-172. There is no mention of the hinge or a suggestion that it must be the exon-encoded definition of a hinge. The specification contains references to "domains" of the IgG, which would suggest a construct that contains a different hinge than that contained in etanercept—not the exon-encoded hinge. *Id*. ¶ 162. The sole fusion protein example in the specification, Example 11, is directed to a p55/IgG3 construct that does not describe where to cut an IgG1 immunoglobulin to provide the fusion site. *Id*.¶¶ 173-176. Moreover, the reference to a CD4/IgG1 deposit provides no such information either. *Id*. ¶¶ 165-166. Accordingly, the specifications do not adequately describe the immunoglobulin

portion of the molecule, either.

C. There is No Written Description Support for a p75-IgG1 Fusion Protein that Specifically Binds TNF.

311. The specifications of the patents-in-suit do not describe the construction of a p75/IgG1 fusion protein or any binding studies demonstrating the function of the molecule. *Id*. ¶¶ 174-178. Lacking a description of either of the individual parts that are the starting materials, the specification fails to provide any of the information needed to create the claimed fusion protein. Indeed, following the instructions in Example 11, applied to a p75/IgG1 protein instead of the described p55/IgG3, would lead to a molecule that is not etanercept and contains a portion of CD4. *Id*.¶¶ 175-176. Immunex is, again, relying solely on the knowledge in the art at the time, not in the specification, in a hindsight analysis.

312. A "description that merely renders the invention obvious does not satisfy the [written description] requirement." *Ariad*, 598 F.3d at 1351. Moreover, "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech*, 108 F.3d at 1366. The patents-in-suit are invalid for lack of written description and lack of enablement.

D. The Sole Reference in the Specification of the Patents-in-Suit to Smith 1990 Does Not Cure the Written Description Problem.

313. Under the law, Immunex cannot cure the written description deficiency

based on a hindsight analysis that attempts to piece together the disclosure for the p75 TNFR extracellular region from ambiguous hints in the specification and mostly prior art disclosures: "Working backward from a knowledge of [the claims], that is by hindsight, . . . to derive written description support from an amalgam of disclosures plucked selectively from the" application does not satisfy the written description requirement. *Novozymes A/s v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) (first alteration in original).

314. Immunex cannot supplement the written description solely with prior art, and specifically, the Smith 1990 sequence for p75. First, while the full amino acid sequence for the p75 TNFR had been published by Immunex, not the inventors, in the May 1990 Smith article, a person of skill in the art would not have understood the inventors to be describing or claiming that specific receptor. The art, as of the filing date of the patents-in-suit, had definitively identified two TNFRs, but it was not sufficiently advanced for a person of skill in the art to say with certainty that these were the only two receptors. *Id*.¶ 2. In fact, Dr. Loetscher testified "at that time we certainly were aware of these two TNF receptors, but we conclude that there may be another one or other receptors…." *Id*. Indeed, the specifications of the patents-in-suit reference at least seven different TNFRs that the inventors identified. *Id*. ¶¶ 36, 190-192.

315. Moreover, under the law, "[i]t is not sufficient . . . that the disclosure,

when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood*, 107 F.3d at 1572. Rather, the original disclosure must provide adequate direction which reasonably would lead persons skilled in the art to "single out" the invention from the various alternatives discussed in the disclosure. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326 (Fed. Cir. 2000). The only p75 sequence that the disclosure "singles out" is the truncated, mutated Figure 4 sequence. And, that disclosure is for a different protein than p75.

316. The written description problem of the patents in suit cannot be remedied by the sole passing reference to the Smith 1990 article. That sole reference is not sufficient to incorporate Smith by reference. "To incorporate material by reference, the host document must identify *with detailed particularity* what *specific material* it incorporates and clearly indicate where that material is found in the various documents." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (emphasis added). The Smith 1990 reference in the specification does no such thing. Instead the specification refers solely to a "deletion" in the Smith 1990 that could constitute a modification. Even Dr. Naismith agreed this reference to Smith was "confusing," "made no sense to [him]," and he "could not make sense of it because it's on its face ridiculous." FOF ¶¶ 144-146. The Smith 1990 reference in the specification is wholly insufficient to incorporate the

Smith protein by reference, let alone specifically identify the claimed extracellular region of the Smith 1990 p75 TNFR as the invention. *See Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1379 (Fed. Cir. 2007) (holding that language in specification that limited incorporation to specific subject matter did not effectively incorporate the whole subject matter claimed).

E. Generic References Do Not Cure the Written Description Problem.

317. Finally, Immunex relies on various pieces of the specification to piece together the claimed invention. SEQ ID NO: 10, which is mentioned in the patent specification and contains 18 of the missing amino acids from Figure 4, does not describe the claimed fusion protein. The specification identifies SEQ ID NO: 10 as belonging to a p65 TNFR, not a p75 TNFR. FOF ¶ 192. In addition, it has an unidentified amino acid. *Id*.. One of skill in the art would not have been able to take SEQ ID NO: 10 and obtain a probe that could fish out the full p75 TNFR sequence. Indeed, even the Roche inventors were unable, despite many attempts, to do that prior to filing the application. *Id*. ¶¶ 15, 21-32, 193-194.

318. Immunex further relies on references to the p75 receptor, and references to "analogues, additions, and deletions," which appear in the specification in no more than generic broad terms. Under controlling Federal Circuit case law, this is insufficient to describe the p75 extracellular region with the requisite particularity. *See Novozymes*, 723 F.3d at 1349 (holding that specification with "formal textual

support" was insufficient because claimed combination was not described and the bulk of the specification focused on a different molecule).

III. Obviousness

319. The asserted claims of the patents-in-suit are invalid for obviousness. A patent is invalid for obviousness, even "though the invention is not identically disclosed or described" in the art if the differences between the asserted claims and the prior art are "such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a); *see also KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416.

320. An obviousness inquiry requires analysis of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, and any relevant objective indicia of obviousness or non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). The Supreme Court requires an "expansive and flexible approach" to the question of obviousness. *KSR*, 550 U.S. at 415. Applying this approach, the asserted claims are obvious.

A. The Art Provided A Motivation To Combine Known Elements With A Reasonable Expectation Of Success.

321. The motivation to combine "need not be found in the references sought to be combined, but may be found in any number of sources, including common

knowledge, the prior art as a whole, or the nature of the problem itself." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006).

322. At the time the applications were filed, TNF binding proteins, and especially TNFRs, were of great interest as potential molecules to bind TNF for in vitro studies, diagnostic assays, and potential therapeutic uses to scavenge excess TNF in the body. FOF ¶¶ 196-203. The p75 TNFR was known and was a TNF binding molecule that, along with the p55 TNFR, generated a great deal of research and development interest. *Id*. ¶¶ 201-203. Multiple groups were working on and publishing information about the p55 and p75 TNFRs prior to August 1990, including Roche, Immunex, Genentech, and the Weitzman Institute. *Id*.¶¶ 199-203.

323. Multiple groups were working on and publishing information about fusion proteins, which fused receptors to portions of human immunoglobulins. *Id.* ¶¶ 204-207. These fusion proteins provided the advantages of extending the plasma half-life of the receptors, simplifying protein purification, and creating a dimerized molecule that could strongly and stably bind trimeric targets like TNF. *Id*.

324. In May 1990, Immunex filed the '760 patent, which specifically suggested a p75 TNFR-IgG1 fusion protein. *Id.* ¶ 208. At the time, the combination was an attractive one for researchers working in the field. *Id.* ¶¶ 210-13. The TNFRs were known to have a short half-life and a TNFR fusion protein would provide all

the advantages disclosed for the other receptor fusion proteins. *Id.* And the art specifically suggested anti-inflammatory receptors, such as the lymphocyte homing receptor, as fusion proteins, including specifically for rheumatoid arthritis. *Id.* ¶ 227.

325. After Dr. Capon published his landmark paper in Nature on fusion proteins that described a CD4 fusion protein lacking the light chains (*id.* ¶ 216), Dr. Karajalinen followed with a publication in Nature of a fusion protein that also deleted the CH1 domain (*id.* ¶ 218). In both cases, the references taught that removal of these domains resulted in ready secretion of the fusion protein from the cell. *Id.* Following these publications, the preferred structure for every fusion protein was the one lacking the light chains and CH1. *Id.* ¶¶ 216-20.

326. Following this teaching in the art, a person of skill would modify the '760 patent construct by removing the light chain and CH1, thereby arriving exactly at etanercept. *Id.* ¶¶ 214-15, 224. While there would be a choice between an exon-encoded hinge and a domain defined hinge, either could be used but the undisputed evidence at trial established that person of skill would prefer the exon-encoded hinge, like etanercept. *Id.* ¶¶ 221-24.

327. Immunex does not dispute that a person of skill in the art would reasonably expect any TNFR fusion protein that used the full extracellular region would specifically bind TNF, as the '182 patent claims require. *Id.* ¶ 230.

328. The real-world evidence also demonstrates that motivation to modify

the '760 patent construct existed. "Independently made, simultaneous inventions . . . are persuasive evidence that the claimed apparatus 'was the product only of ordinary . . . skill.'" *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305-06 (Fed. Cir. 2010) (finding "only a year later" near-simultaneous). Here, multiple groups, including Roche and Immunex, were working on TNFR fusion proteins right around the time the patent applications were filed. FOF ¶¶ 5-11, 231-36. All deleted the light chains and the CH1 domain. *Id.* ¶¶ 7, 10, 233, 235. And the group that created the p75/IgG1 fusion protein that is, in fact, etanercept, was not the named inventors, but Immunex, which was a third party at that time. *Id.* ¶ 10. This is powerful, real-world evidence of motivation and obviousness.

329. Immunex argues that a person of skill in the art would not be motivated to fuse a TNFR to a portion of a human IgG1 because of a concern about aggregation and effector functions potentially caused by the Fc portion of the IgG1. But a "reference does not teach away . . . if it merely expresses a general preference for an alternative intervention but does not 'criticize, discredit, or otherwise discourage' investigation into the invention claimed." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009).

330. The claims do not require any therapeutic effect. It is undisputed that fusion proteins were considered useful for both *in vitro* and diagnostic assays, which wouldn't present concerns about aggregation or effector functions. FOF ¶¶ 198, 225.

331. Even in therapeutic uses, neither aggregation or effector functions would discourage the person of skill in the art to make TNFR fusion proteins. With respect to effector functions, the therapeutic target would be non-membrane bound TNF, which would not implicate effector functions. *Id.* ¶¶ 248-51. The existence and prevalence of membrane bound TNF was not a concern because it was known that TNF readily cleaved off cells and became the soluble protein. *Id.* ¶ 248. With respect to aggregation, the expected binding of one fusion protein to one TNF trimer would lead a person of skill in the art to believe aggregation would not occur. *Id.* ¶¶ 242-45. And, both effector functions and aggregation could potentially provide therapeutic benefits, which would provide further motivation. *Id.* ¶¶ 255-57.

332. Immunex has cited no contemporaneous evidence that effector functions and aggregation would, or in fact did, discourage the construction of TNFR fusion proteins, instead relying on hindsight from its experts that contradict Immunex's own contemporaneous activities. This is insufficient to establish that the art taught away from TNFR fusion proteins. The evidence at trial proved, clearly and convincingly, that persons of skill in the art would be motivated to combine the elements to create etanercept with a reasonable expectation of success.

B. Objective Indicia Further Support Obviousness

333. In addition to the prior art, objective indicia, the real-world evidence, provides proof of obviousness. Importantly, "evidence rising out of the so-called

[objective indicia] . . . may often be the most probative and cogent evidence in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

334. First, the simultaneous invention by four separate groups is strong evidence that persons of skill in the art were motivated to combine TNFRs with immunoglobulins to create fusion proteins—specifically those lacking light chains and CH1. FOF ¶¶ 5-11, 231-36. *Int'l Glass Co. v. U.S.*, 408 F.2d 395, 405 (Ct. Cl. 1969) ("The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art."); *Trustees of Columbia Univ. in City of New York v. Illumina, Inc.*, 620 F. App'x 916, 930 (Fed. Cir. 2015)*; Spectrum Pharm., Inc. v. Sandoz Inc.*, No. 2:12-cv-111, 2015 WL 794674, *14 (D. Nev. Feb. 25, 2015), *aff'd*, 802 F.3d 1326, 1335 (Fed. Cir. 2015); *Warner Chilcott Co. v. Teva Pharm. USA, Inc.*, 37 F. Supp. 3d 731, 739 (D. Del. 2014).

335. Second, the alleged clinical and commercial success, industry praise, and failure of others actually supports obviousness, not non-obviousness. These successes belonged to Immunex, not the inventors, based on work done completely independently. And "others" did not fail. Immunex, an "other," succeeded. It was Roche and the inventors who failed. Moreover, Immunex has failed to demonstrate that these successes bear a nexus to the asserted claims of the patents-in-suit rather than to Immunex's other patents (like the '760, '690, and psoriasis patents). *In re*

Huai-Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011) ("Where the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention."). Immunex artificially restricted the evidence its experts reviewed to include only those treatments for which etanercept had been approved and only those years of commercial sales that were best for etanercept. This selective review of evidence is improper. *Crowley v. Chait*, 322 F. Supp. 2d 530, 542 (D.N.J. 2004).

336. Third, Roche's "licensing" of the patents to Immunex shows how little value these patent applications really had at the time of the 2004 Agreement. Immunex only paid $45 million to Roche to purchase the patents, at a time when it was taking in revenues of $2 billion to $3 billion per year. FOF ¶ 68. Again, this objective consideration demonstrates obviousness rather than non-obviousness.

337. Fourth, Sandoz's alleged copying is irrelevant. Copying in the context of regulatory approval of a pharmaceutical product is not probative evidence of nonobviousness. *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (copying is "not probative of nonobviousness" because "a showing of bioequivalence is required for FDA approval"); *Hoffman-La Roche Inc. v. Apotex Inc.*, No. 07 4417, 2012 WL 1637736, at *20 (D.N.J. May 7, 2012) (same). Indeed, the evidence at trial established that Sandoz, as a factual matter, copied etanercept because it believed it would be required to have complete identity

in order to get FDA approval. FOF ¶¶ 84-88, 258-59. Thus, copying is irrelevant.

338. Finally, Immunex's evidence of unexpected results is insufficient to demonstrate non-obviousness. As an initial matter, they all relate to Immunex's invention, not the claimed invention. Thus, Immunex cannot establish nexus. In addition, Immunex fails to compare etanercept to the closest prior art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

339. But Immunex's arguments fail on the merits as well. "Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013); *accord Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014) (holding that showing that results were greater than expected was insufficient to demonstrate nonobviousness). Each of Immunex's alleged unexpected results is either expected or insufficient.

340. Immunex first argues that etanercept demonstrated surprising binding strength of up to 1,000x improved binding over the TNR receptor alone. This was not unexpected. In fact, it was expressly predicted in the prior art, which taught that a bivalent molecule like etanercept would be expected to have 1,000x better binding than a monomer like the TNFR alone. FOF ¶¶ 237-41.

341. Immunex next argues that etanercept unexpectedly does not cause effector functions on membrane bound TNF. Immunex bases this argument on

studies conducted in vitro under highly artificial conditions that do not simulate the in vivo environment. *Id.* ¶¶ 252-53. Moreover, the results, at least with respect to ADCC, conflicted. *Id.* ¶ 254. Thus, they are not results at all.

342. Immunex finally argues that etanercept unexpectedly does not aggregate. There are two problems with this argument. First, because of the expected 1:1 binding of etanercept to TNF, a person of skill would not expect etanercept to form aggregates or agglutination. *Id.* ¶ 242.

343. Second, Immunex improperly tries to limit the scope of the claims solely to treating rheumatoid arthritis. The claims say nothing about rheumatoid arthritis and cover any situation in which specific TNF binding occurs. *Id.* ¶ 261. One such situation is the treatment of Crohn's disease, for which etanercept is ineffective. *Id.* ¶¶ 256, 261. In contrast, molecules like Remicade and Humira, which do form aggregates, are highly effective in treating Crohn's disease. *Id.* ¶ 255-56. "It is well settled that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). Immunex's proffered evidence fails this requirement. In sum, the objective indicia all either support a finding of obviousness, or are irrelevant or insufficient to support a finding of nonobviousness. Viewed as a whole, the evidence at trial proved by clear and convincing evidence that the asserted claims are invalid for obviousness.

Dated: October 26, 2018

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CERTIFICATION OF SERVICE

The undersigned attorney certifies that copies of the foregoing **DEFENDANTS' SECOND CORRECTED POST-TRIAL FINDINGS OF FACT AND CONCLUSIONS OF LAW** and supporting documents were served by electronic mail on October 26, 2018, upon all counsel of record.

Dated: October 26, 2018

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