UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

PFIZER, INC. and
SAMSUNG BIOEPIS CO., LTD.,[1]
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

_____

Case IPR2017-01489
Patent 6,407,213

_____

PETITIONERS' REPLY TO PATENT OWNER RESPONSE

[1] Samsung Bioepis Co. Ltd.'s IPR2017-02140 has been joined with this proceeding. (IPR2017-02140, Paper 42.) Emphasis added unless otherwise noted.

TABLE OF CONTENTS

Page(s)

TABLE OF AUTHORITIES

Page(s)

Cases

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1501	U.S. Patent No. 6,407,213, *Method for making humanized antibodies* (filed July 17, 1993) (issued June 18, 2002)
1502 Vols. 1–10	File History for U.S. Patent No. 6,407,213
1503	Declaration of Dr. Foote in Support of Petition for *Inter Partes* Review of Patent No. 6,407,213
1503A	*Curriculum Vitae* of Dr. Foote
1503B	Materials Reviewed by Dr. Foote
1503C–Q	Exhibits C–Q of Dr. Foote's Declaration
1504	Declaration of Mr. Buss in Support of Petition for *Inter Partes* Review of Patent No. 6,407,213
1504A	*Curriculum Vitae* of Mr. Buss
1504B	Materials Reviewed by Mr. Buss
1505	Reserved
1506	Reserved
1507	Reserved
1508	Reserved
1509	Reserved
1510	Reserved
1511	Reserved
1512	Reserved
1513	Reserved
1514	Reserved
1515	Reserved
1516	Reserved
1517	Reserved
1518	Reserved
1519	Reserved
1520	Reserved

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1521	Hudziak *et al*., *p185^{HER2} Monoclonal Antibody Has Antiproliferative Effects In Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor*, 9(3) MOLECULAR CELLULAR BIOLOGY 1165–72 (1989) ("Hudziak")
1522	Köhler *et al*., *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256(5517) NATURE 495–97 (1975)
1523	Prabakaran, *The Quest for a Magic Bullet*, 349(6246) SCIENCE 389 (2015)
1524	Marks, *The Story of Cesar Milstein and Monoclonal Antibodies: A Healthcare Revolution in the Making*, http://www.whatisbiotechnology.org/exhibitions/milstein (last accessed March 23, 2017)
1525	Cosimi *et al*., *Treatment of Acute Renal Allograft Rejection with OKT3 Monoclonal Antibody*, 32(6) TRANSPLANTATION 535–39 (1981) ("Cosimi '81")
1526	Ortho Multicenter Transplant Study Group, *A Randomized Clinical Trial of OKT3 Monoclonal Antibody for Acute Rejection of Cadveric Renal Transplants*, 313(6) NEW ENG. J. MED. 337–42 (1985) ("OMTSG '85")
1527	Jaffers *et al*., *Monoclonal Antibody Therapy: Anti-Idiotypic and Non-Anti-Idiotypic Antibodies to OKT3 Arising Despite Intense Immunosuppression*, 41(5) TRANSPLANTATION 572–78 (1986) ("Jaffers '86")
1528	Sears *et al*., *Phase-I Clinical Trial of Monoclonal Antibody in Treatment of Gastrointestinal Tumours*, 1 LANCET 762–65 (1982)
1529	Sikora, *Monoclonal Antibodies in Oncology*, 35(4) J. CLINICAL PATHOLOGY 369–75 (1982)
1530	*Protein Data Bank - Chronology*, National Science Foundation, https://www.nsf.gov/news/news_summ.jsp?cntn_id=100689 (last accessed April 12, 2017)

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1531	Morrison *et al*., *Chimeric Human Antibody Molecules: Mouse Antigen-Binding Domains With Human Constant Region Domains*, 81(21) PROC. NAT'L ACAD. SCI. USA 6851–55 (1984) ("Morrison '84")
1532	Liu *et al*., *Chimeric Mouse-Human IgG1 Antibody that can Mediate Lysis of Cancer Cells*, 84(10) PROC. NAT'L ACAD. SCI. USA 3439–43 (1987) ("Liu '87")
1533	Jones *et al*., *Replacing the Complementarity-Determining Regions in a Human Antibody With Those From a Mouse*, 321(6069) NATURE 522–25 (1986) ("Jones '86")
1534	Queen *et al*., *A Humanized Antibody That Binds to the Interleukin 2 Receptor*, 86(24) PROC. NAT'L ACAD. SCI. USA 10029–33 (1989) ("Queen 1989")
1535	Kirkman *et al*., *Early Experience with Anti-Tac in Clinical Renal Transplantation*, 21(1) TRANSPLANTATION PROC. 1766–68 (1989) ("Kirkman '89")
1536	Waldmann *et al*., *The Interleukin-2 Receptor: A Target for Monoclonal Antibody Treatment of Human T-Cell Lymphotrophic Virus I-Induced Adult T-Cell Leukemia*, 82(6) BLOOD 1701–12 (1993) ("Waldman '93")
1537	Hakimi *et al*., *Reduced Immunogenicity and Improved Pharmacokinetics of Humanized ANTI-Tac in Cynomolgus Monkeys*, 147(4) J. IMMUNOLOGY 1352–59 (1991) ("Hakimi '91")
1538	Vincenti *et al*., *Interleukin 2-Receptor Blockade with Daclizumab to Prevent Acute Rejection in Renal Transplantation*, 338(3) NEW ENG. J. MED. 161–65 (1998) ("Vincenti '98")
1539	*SEER Stat Fact Sheets: Breast Cancer*, National Cancer Institute, http://seer.cancer.gov/statfacts/html/breast.html (last accessed March 17, 2017)
1540	Harris *et al*., *Medical Progress: Breast Cancer*, 327(5) NEW ENG. J. MED. 319–28 (1992) ("Harris '92")
1541	King *et al*., *Amplification of a Novel v-erbB-Related Gene in a Human Mammary Carcinoma*, 229(4717) SCIENCE 974–76 (1985) ("King '85")

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1542	Semba *et al*., *A v-erbB-Related Protooncogene, c-erbB-2, is Distinct from the c-erbB-1 / Epidermal Growth Factor-Receptor Gene and is Amplified in a Human Salivary Gland Adenocarcinoma*, 82(19) PROC. NAT'L ACAD. SCI. USA 6497–01 (1985) ("Semba '85")
1543	Coussens *et al*., *Tyrosine Kinase Receptor with Extensive Homology to EGF Receptor Shares Chromosomal Location with* neu *Oncogene*, 230(4730) SCIENCE 1132–39 (1985) ("Coussens '85")
1544	Fukushige *et al*., *Localization of a Novel v-erbB-Related Gene, c-erbB-2, on Human Chromosome 17 and its Amplification in a Gastric Cancer Cell Line*, 6(3) MOLECULAR CELLULAR BIOLOGY 955–58 (1986)
1545	Slamon *et al*., *Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu *Oncogene*, 235(4785) SCIENCE 177–82 (1987) ("Slamon '87")
1546	Kraus *et al*., *Overexpression of the EGF Receptor-Related Proto-Oncogene erbB-2 in Human Mammary Tumor Cell Lines by Different Molecular Mechanisms*, 6(3) The EMBO J. 605– 10 (1987)
1547	Hudziak *et al*., *Increased Expression of the Putative Growth Factor Receptor p185^{HER2} Causes Transformation and Tumorigenesis of NIH 3T3 Cells.*, 84(20) PROC. NAT'L ACAD. SCI. USA 7159–163 (1987) ("Hudziak '87")
1548	Shepard *et al*., *Monoclonal Antibody Therapy of Human Cancer: Taking the HER2 Protooncogene to the Clinic*, 11(3) J. CLINICAL IMMUNOLOGY, 117–27 (1991)
1549	Chothia *et al*., *Conformations of Immunoglobulin Hypervariable Regions*, 342(21) NATURE 877–83 (1989) ("Chothia '89")
1550	Queen, International Publication No. WO 1990/07861 (published July 26, 1990) ("Queen 1990")
1551	Tramontano *et al*., *Framework Residue 71 is a Major Determinant of the Position and Conformation of the Second Hypervariable Region in the V_H Domains of Immunoglobulins*, 215(1) J. MOLECULAR BIOLOGY 175–82 (1990) ("Tramontano")

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1552	Kabat *et al.*, SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST: TABULATION AND ANALYSIS OF AMINO ACID AND NUCLEIC ACID SEQUENCES OF PRECURSORS, V-REGIONS, C-REGIONS, J-CHAIN, T-CELL RECEPTOR FOR ANTIGEN, T-CELL SURFACE ANTIGENS, β_2-MICROGLUBINS, MAJOR HISTOCOMPATIBILITY ANTIGENS, THY-1 COMPLEMENT, C-REACTIVE PROTEIN, THYMOPOIETIN, POST-GAMMA GLOBULIN, AND α_2-MACROGLOBULIN 41–175 (4th ed. 1987) ("Kabat 1987")
1553	Reserved
1554	Reserved
1555	Kabat *et al.*, 1 SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST: TABULATION AND ANALYSIS OF AMINO ACID AND NUCLEIC ACID SEQUENCES OF PRECURSORS, V-REGIONS, C-REGIONS, J-CHAIN, T-CELL RECEPTOR FOR ANTIGEN, T-CELL SURFACE ANTIGENS, β_2-MICROGLUBINS, MAJOR HISTOCOMPATIBILITY ANTIGENS, THY-1 COMPLEMENT, C-REACTIVE PROTEIN, THYMOPOIETIN, POST-GAMMA GLOBULIN, α_2-MACROGLOBULINS, AND OTHER RELATED PROTEINS 103–338 (5th ed. 1991) ("Kabat 1991")
1556	Reserved
1557	Reserved
1558	Davies & Metzger, *Structural Basics of Antibody Function*, 1 ANN. REV. IMMUNOLOGY 87–117 (1983) ("Davies & Metzger")
1559	Amit *et al.*, *Three-Dimensional Structure of an Antigen-Antibody Complex at 2.8 Å Resolution*, 233(4765) SCIENCE 747–53 (1986) ("Amit '86")
1560	Reserved
1561	Reserved
1562	Chothia & Lesk, *Canonical Structures for the Hypervariable Regions of Immunoglobulins*, 196(4) J. MOLECULAR BIOLOGY 901–17 (1987) ("Chothia & Lesk")
1563	Chothia *et al.*, *Domain Association in Immunoglobulin Molecules: The Packing of Variable Domains*, 186 J. MOLECULAR BIOLOGY 651–63 (1985)

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1564	Reserved
1565	Reserved
1566	Reserved
1567	Reserved
1568	Verhoeyen *et al*., *Reshaping Human Antibodies: Grafting an Antilysozyme Activity*, 239(4847) SCIENCE 1534–36 (1988) ("Verhoeyen '88")
1569	Riechmann *et al*., *Reshaping Human Antibodies for Therapy*, 332(6162) NATURE 323–27 (1988) ("Riechmann '88")
1570	Reserved
1571	Kurrle *et al*., EP Publication Number 0403156, *Improved Monoclonal Antibodies Against the Human Alphabeta T-Cell Receptor, Their Production and Use* (published December 19, 1990) ("Kurrle")
1572	Reserved
1573	Winter *et al*., EP Publication Number 0239400, *Recombinant Antibodies and Methods for Their Productions* (published September 30, 1987)
1574	Reserved
1575	Reserved
1576	Reserved
1577	Reserved
1578	Reserved
1579	Kabat *et al*., SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST: TABULATION AND ANALYSIS OF AMINO ACID AND NUCLEIC ACID SEQUENCES OF PRECURSORS, V-REGIONS, C-REGIONS, J-CHAIN, β_2 MICROGLOBULINS, MAJOR HISTOCOMPATIBILITY ANTIGENS, THY-1, COMPLEMENT, C-REACTIVE PROTEIN, THYMOPOIETIN, POST-GAMMA GLOBULIN, AND α_2-MACROGLOBULIN (1983)
1580	Bernstein *et al*., *The Protein Data Bank: A Computer-based Archival File for Macromolecular Structures*, 112(3) J. MOLECULAR BIOLOGY 535–42 (1977)

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1581	Sheriff *et al*., *Three-Dimensional Structure of an Antibody- Antigen Complex*, 84(22) PROC. NAT'L ACAD. SCI. USA. 8075–79 (1987) ("Sheriff '87")
1582	Marquart *et al*., *The Three-Dimensional Structure of Antibodies*, 3(6) IMMUNOLOGY TODAY 160–66 (1982)
1583	Saul *et al*., *Preliminary Refinement and Structural Analysis of the Fab Fragment from Human Immunoglobulin New at 2.0 Å Resolution**, 253(2) J. BIOLOGICAL CHEMISTRY 585–95 (1978) ("Saul '78")
1584	Reserved
1585	Satow *et al*., *Phosphocholine Binding Immunogloubulin Fab McPC306 An X-ray Diffraction Study at 2•7 Å*, 190(4) J. MOLECULAR BIOLOGY 593–604 (1986)
1586	Herron *et al*., *Three-Dimensional Structure of a Fluorescein-Fab Complex Crystallized in 2-Methyl-2,4-Pentanediol*, 5(4) PROTEINS 271–80 (1989)
1587	Padlan *et al*., *Structure of an Antibody-Antigen Complex: Crystal Structure of the HyHEL-10 Fab-Lysozyme Complex*, 86(15) PROC. NAT'L ACAD. SCI. USA 5938–42 (1989) ("Padlan '89")
1588	Kumar *et al*., *Regulation of Phosphorylation of the c-erbB-2/HER2 Gene Product by Monoclonal Antibody and Serum Growth Factor(s) in Human Mammary Carcinoma Cells*, 11(2) MOLECULAR CELLULAR BIOLOGY 979–86 (1991)
1589	Soomro *et al*., *C-erbB-2 Expression in Different Histological Types of Invasive Breast Carcinoma*, 44(3) J. CLINICAL PATHOLOGY 211–14 (1991)
1590	Wilson & Goulding, A BIOLOGIST'S GUIDE TO PRINCIPLES AND TECHNIQUES OF PRACTICAL BIOCHEMISTRY, §Protein Sequencing, 170–73 (3d ed. 1986)
1591	Edelman *et al*., *The Covalent Structure of an Entire γG Immunoglobulin Molecule**, 63(1) PROC. NAT'L ACAD. SCI. USA 78–85 (1969)

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1592	Capra & Kehoe, *Variable Region Sequences of Five Human Immunoglobulin Heavy Chains of the V_HIII Subgroup: Definitive Identification of Four Heavy Chain Hypervariable Regions*, 71(3) PROC. NAT'L ACAD. SCI. USA 845–48 (1974)
1593	Morin, *From Oncogene to Drug: Development of Small Molecule Tyrosine Kinase Inhibitors as Anti-Tumor and Anti-Angiogenic Agents*, 19(56) ONCOGENE 6574– 83 (2000)
1594	Reserved
1595 Vols. 1–15	Patent Interference No. 105,744 (Senior party Application No. 11/284,261, Inventors John Robert Adair *et al*., Junior Party, U.S. Patent 6,407,213, Inventors Paul J. Carter and Leonard G. Presta) ("Adair")
1596	U.S. Patent No. 5,677,171, *Monoclonal Antibodies Directed to the HER2 Receptor* (filed August 5, 1994) (issued October 14, 1997)
1597	Sambrook *et al*., MOLECULAR CLONING: A LABORATORY MANUAL (Cold Spring Harbor Laboratory Press, 2d ed. 1989)
1598	Reserved
1599	Reserved
1600	Colman *et al*., *Three-Dimensional Structure of a Complex of Antibody with Influenza Virus Neuraminidase*, 326(6111) NATURE 358–63 (1987) ("Colman '87")
1601	Reserved
1602	Bender *et al*., *Immunogenicity, Efficacy and Adverse Events of Adalimumab in RA Patients*, 27(3) RHEUMATOLOGY INT'L 269–74 (2007)
1603	Brient & Nisonoff, *Quantitative Investigations of Idiotypic Antibodies. IV. Inhibition by Specific Haptens of the Reaction of Anti-Hapten Antibody with Its Anti-Idiotypic Antibody*, 132 J. EXPERIMENTAL MED. 951–61 (1970)
1604	Koprowski *et al*., *Human Anti-Idiotype Antibodies in Cancer Patients: Is the Modulation of the Immune Response Beneficial for the Patient?*, 81(1) PROC. NAT'L. ACAD. SCI. USA 216–19 (1984) ("Koprowski '84")

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1605	Chanh *et al*., *Monoclonal Anti-Idiotypic Antibody Mimics the CD4 Receptor and Binds Human Immunodeficiency Virus*, 84 PROC. NAT'L. ACAD. SCI. USA 3891–95 (1987) ("Chanh '87")
1606	Schroff *et al*., *Human Anti-Murine Immunoglobulin Responses in Patients Receiving Monoclonal Antibody Therapy*, 45(2) CANCER RES. 879–85 (1985) ("Schroff '85")
1607	Abdou *et al*., *Network Theory in Autoimmunity. In Vitro Suppression of Serum Anti-DNA by Anti-idiotypic Antibody in Systemic Lupus Erythematosus*, 67(5) J. CLINICAL INVESTIGATION 1297–1304 (1981)
1608	Reserved
1609	Reserved
1610	Reserved
1611	Reserved
1612	Reserved
1613	Epp *et al*., *The Molecular Structure of a Dimer Composed of the Variable Portions of the Bence-Jones Protein REI Refined at 2.0-Å Resolution*, 14(22) BIOCHEMISTRY 4943–52 (1975)
1614	Mian, *Structure, Function and Properties of Antibody Binding Sites*, 217(1) J. MOLECULAR BIOLOGY 133–51 (1991)
1615	Poljak *et al*., *The Three-Dimensional Structure of the Fab Fragment of A Human Myeloma Immunoglobulin at 2.0-Å Resolution*, 71(9) PROC. NAT'L ACAD. SCI. USA. 3440–44 (1974)
1616	Padlan *et al*., *Model Building Studies of Antigen-binding Sites: the Hapten Binding Site of MOPC-315*, 41 COLD SPRING HARBOR SYMP. QUANTITATIVE BIOLOGY 627–37 (1977)
1617	Reserved
1618	Reserved
1619	Reserved
1620	Reserved
1621	Suh *et al*., *The Galactan-Binding Immunoglobulin Fab J539: An X-Ray Diffraction Study at 2.6-Å Resolution,* 1(1) PROTEINS 74–80 (1986) ("Suh '86")

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1622	Reserved
1623	Reserved
1624	Reserved
1625	Furey *et al*., *Structure of A Novel Bence-Jones Protein (Rhe) Fragment at 1.6Å Resolution*, 167(3) J. MOLECULAR BIOLOGY 661–92 (1983) ("Furey")
1626	Segal *et al*., *The Three-Dimensional Structure of a Phosphorylcholine-Binding Mouse Immunoglobulin Fab and the Nature of the Antigen Binding Site*, 71(11) PROC. NAT'L ACAD. SCI. USA 4298 (1974)
1627	Jones, *Diffraction Methods for Biological Macromolecules. Interactive Computer Graphics: FRODO*, 115 METHODS ENZYMOLOGY 157–71 (1985) ("Jones '85")
1628	Co *et al*., *Humanized Antibodies for Antiviral Therapy*, 88(7) PROC. NAT'L ACAD. SCI. USA 2869–73 (1991) ("Co '91")
1629	Excel Trick, *History of Microsoft Excel 1978–2013*, http://www.exceltrick.com/others/history-of-excel/ (last accessed April 13, 2017)
1630	U.S. Patent No. 4,891,762, *Method and Apparatus for Tracking, Mapping and Recognition of Spatial Patterns* (filed February 9, 1988) (issued January 2, 1990)
1631	Wallick *et al*., *Glycosylation of A V_H Residue of a Monoclonal Antibody Against α(L-6) Dextran Increases its Affinity for Antigen*, 168(3) J. EXPERIMENTAL MED. 1099–109 (1988) ("Wallick '88")
1632	Reserved
1633	Reserved
1634	Reserved
1635	Reserved
1636	Reserved
1637	Reserved
1638	Reserved
1639	Reserved

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1640	Reserved
1641	Library of Congress Copyright Record for Cosimi '81
1642	Library of Congress Copyright Record for OMTSG '85
1643	Library of Congress Copyright Record for Jaffers '86
1644	Library of Congress Copyright Record for Morrison '84
1645	Library of Congress Copyright Record for Liu '87
1646	Library of Congress Copyright Record for Jones '86
1647	Library of Congress Copyright Record for Queen 1989
1648	Library of Congress Copyright Record for Kirkman '89
1649	Library of Congress Copyright Record for Waldamnn '93
1650	Library of Congress Copyright Record for Hakimi '91
1651	Library of Congress Copyright Record for Vincenti '98
1652	Library of Congress Copyright Record for Harris '92
1653	Library of Congress Copyright Record for King '85
1654	Library of Congress Copyright Record for Semba '85
1655	Library of Congress Copyright Record for Coussens '85
1656	Library of Congress Copyright Record for Slamon '87
1657	Library of Congress Copyright Record for Hudziak '87
1658	Library of Congress Copyright Record for Chothia '89
1659	Library of Congress Copyright Record for Davies & Metzger
1660	Library of Congress Copyright Record for Amit '86
1661	Reserved
1662	Reserved
1663	Library of Congress Copyright Record for Verhoeyen '88
1664	Library of Congress Copyright Record for Riechmann '88
1665	Reserved
1666	Reserved
1667	Library of Congress Copyright Record for Sheriff '87
1668	Library of Congress Copyright Record for Saul '78
1669	Reserved

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1670	Library of Congress Copyright Record for Padlan '89
1671	Library of Congress Copyright Record for Colman '87
1672	Library of Congress Copyright Record for Koprowski '84
1673	Library of Congress Copyright Record for Chanh '87
1674	Library of Congress Copyright Record for Schroff '85
1675	Reserved
1676	Reserved
1677	Reserved
1678	Library of Congress Copyright Record for Suh '86
1679	Library of Congress Copyright Record for Jones '85
1680	Library of Congress Copyright Record for Co '91
1681	Library of Congress Copyright Record for Wallick '88
1682	Bodmer, International Publication No. WO 1989/01783 (published March 9, 1989)
1683	Gorman, International Publication No. WO 1992/05274 (published April 2, 1992)
1684	Declaration of Karen Younkins
1684A	*Three-Dimensional Structure of an Antibody-Antigen Complex*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/obsolete.do?obsoleteId=2HFL&evtc=Suggest&evta=PDBID&evtl=autosearch_SearchBar_querySuggest (last accessed April 25, 2017)
1684B	*The Three-Dimensional Structure of Antibodies*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/obsolete.do?obsoleteId=1FB4 (last accessed April 25, 2017)
1684C	*Preliminary Refinement and Structural Analysis of the FAB Fragment from Human Immunoglobulin New at 2.0 Angstroms Resolution*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/obsolete.do?obsoleteId=3FAB (last accessed April 25, 2017)

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1684D	*Refined Crystal Structure of the Galactan-Binding Immunoglobulin Fab J539 at 1.95-Angstroms Resolution*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/explore.do?structureId=2FBJ (last accessed May 4, 2017)
1684E	*Phosphocholine Binding Immunoglobulin Fab McPC603. An X-ray Diffraction Study at 2.7 A*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/explore.do?structureId=1MCP (last accessed May 4, 2017)
1684F	*Three-dimensional Structure of a Fluorescein-Fab Complex Crystallized in 2-methyl-2,4-pentanediol*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/explore.do?structureId=4FAB (last accessed May 4, 2017)
1684G	*Structure of an Antibody-Antigen Complex: Crystal Structure of the HyHEL-10 Fab-lysozyme Complex*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/explore.do?structureId=3HFM (last accessed May 4, 2017)
1684H	*The Molecular Structure of a Dimer Composed of the Variable Portions of the Bence-Jones Protein REI Refined at 2.0-A Resolution*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/explore.do?structureId=1REI (last accessed May 4, 2017)
1684I	*Structure of a Novel Bence-Jones Protein (Rhe) Fragment at 1.6 A Resolution*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/explore.do?structureId=2RHE (last accessed May 4, 2017)
1685	Miller, *To Build a Better Mousetrap, Use Human Parts*, 90(1) J. NAT'L CANCER INST. 1416 (1998) ("Miller '98")
1686	Library of Congress Copyright Record for Miller '98
1687	Declaration of Amanda Hollis
1688	Declaration of Christopher Lowden
1689	Declaration of Sarah K. Tsou in Support of Petitioner's Motion for the Pro Hac Vice Admission
1690	Declaration of Benjamin A. Lasky in Support of Petitioner's Motion for the Pro Hac Vice Admission

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1691	Declaration of Mark C. McLennan in Support of Petitioner's Motion for the Pro Hac Vice Admission
1692	Declaration of Christopher J. Citro in Support of Petitioner's Motion for the Pro Hac Vice Admission
1693	Foote, *Humanized Antibodies*, 61(269) NOVA ACTA LEOPOLDINA 103-110 (1989)
1694	Kolbinger, *et al., Humunization of a Mouse Anti-Human IgE Antibody: A Potential Therapeutic for IgE-Mediated Allergies,* 6(8) PROTEIN ENGINEERING 971–980 (1993)
1695	DAVID J. KING, APPLICATIONS AND ENGINEERING OF MONOCLONAL ANTIBODIES (1998)
1696	Presta, Humanized Monoclonal Antibodies, 29 Ann. Rep. in Med. Chemistry 317-24 (1994)
1697	Deposition Transcript of Ian A. Wilson, dated April 21, 2018
1698	Deposition Transcript of Paul J. Carter, dated April 27, 2018
1699	Deposition Transcript of Leonard G. Presta, dated May 1, 2018
1700	Deposition Transcript of Irene Loeffler, dated May 1, 2018
1701	Deposition Transcript of John B. Ridgway Brady, dated April 27, 2018
1702	Reply Declaration of Jefferson Foote
1703	Reply Declaration of Christopher Lowden
1704	Reply Declaration of Benjamin Lasky
1705	Library of Congress Copyright Record for Presta '94
1706	Foote & Winter, *Antibody Framework Residues Affecting the Conformation of the Hypervariable Loops*, 224 J. MOLECULAR BIOLOGY 487-499 (1991).
1707	Hale *et al.*, *Remission Induction in Non-Hodgkin Lymphoma with Reshaped Human Monoclonal Antibody Campath-1H*, 332 LANCET 1394-1399 (1988).
1708	Mathieson *et al.*, *Monoclonal Antibody Therapy in Systemic Vasculitis*, 323(4) NEW ENG. J. MED. 250-254 (1990).

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1709	Kyle *et al.*, *Humanized Monoclonal Antibody Treatment in Rheumatoid Arthritis*, 18(11) J. RHEUMATOLOGY 1737-1738 (1991).
1710	Brown, Jr. *et al., Anti-Tac-H, a Humanized Antibody to the Interleukin 2 Receptor Prolongs Primate Cardiac Allograft Survival*, 88 PROC. NAT'L. ACAD. SCI. U.S. 2663-2667 (1991).
1711	Havrdova, *et. al.*, *Alemtuzumab in the Treatment of Multiple Sclerosis: Key Clinical Trial Results and Considerations for Us*e, 8(1) THERAPEUTIC ADVANCES IN NEUROLOGICAL. DISORDERS 31-45 (2015).

I. BACKGROUND AND ARGUMENT SUMMARY

The '213 patent does ***not*** "provide[] a broadly-applicable humanization platform," but rather claims vast genuses of humanized antibodies PO never made or tested, which are indistinguishable from the prior art. PO ***concedes*** claims 1-2, 25, 29, and 80-81 are invalid. The remaining claims also are invalid.

PO's expert and inventors concede it was known ***before*** the patent that:

- "overexpression of the HER2 protein led to a poor prognosis in cancer, including breast cancer";
- "work had been done to identify murine antibodies that would target the HER2 receptor," with "4D5" shown "to have the…greatest effect of relative cell proliferation";
- "[t]here was a concern that you might get a reaction against a mouse antibody if you give it to a human";
- scientists had succeeded in "humanizing" monoclonal antibodies by "taking…the CDRs, from the mouse monoclonal antibodies and placing them in [a] human antibody framework" in order to reduce their immunogenic potential;
- "[i]n some cases, humanizing an antibody by placing the CDRs from the mouse antibody into the human framework" would "retain some binding

affinity toward the original antigen…but it was hard to regain, often, the original affinity";

- "one approach to try to regain the binding affinity that was lost…was to make additional substitutions back to mouse in the human framework";
- investigators set forth "criteria" to identify framework residues to substitute back, including (1) "to look for framework residues that were likely to contact the antigen," (2) "to look for framework residues that were in contact with or in close proximity to the CDR residues," and (3) "to identify framework residues that may impact the binding affinity of humanized antibody by looking at residues that were known to affect the conformation of the antibody";
- a POSITA could "use 3-D structures of known antibodies identified in the protein data bank in computer modeling to predict which framework residues were likely to contact antigen or contact or be in close proximity to CDR residues"; and
- "framework residues that introduced a glycosylation site could impact binding of antigen," and "residues that participate in the interactions between the light and the heavy chain of an antibody could affect the

confirmation of the antibody" by "impact[ing] the folding of an antibody into the shape needed to bind antigen."[2]

PO's claims merely adopt these known humanization techniques, while reciting arbitrary numbers of FR substitutions previously-identified or readily-identifiable through known methods. The only aspects of PO's claims even ***allegedly*** new are: (1) humanization of ***anti-HER2*** antibodies (claims 30-33, 42, 60); (2) "***consensus***" human frameworks (claims 4, 62, 64); (3) specific recited FR substitution (all claims); and (4) antibodies having "up to three-fold more" binding affinity than their parents (claims 63, 65). PO cannot establish patentability.

First, PO does not dispute that "a [POSITA] would have been motivated to make a humanized version of the murine 4D5 antibody (which binds $p185^{HER2}$) based upon Hudziak." (POR_62.) This motivation is clear. HER2-overexpressing cancer was being intensely researched, anti-HER2 mouse antibodies showed promising anti-tumor activity, and mouse antibodies were known to need "humanization." Humanization of the 4D5 antibody was simply a matter of applying known humanization techniques. (Exs.1702¶¶3-12, 57;

---

[2] Ex.1697(Wilson)_19:7-23:15, 24:11-28:8, 51:3-53:13, 54:6-13, 55:19-56:17; Exs.1698(Carter)_22:13-24:7, 24:13-26:15, 27:7-28:20; 1699(Presta)_22:18-23, 23:19-25:23, 67:6-70:3, 70:11-25, 71:8-23, 72:9-21, 75:17-76:18, 156:24-159:10; 1501_1:58-4:23; 1521_8, 14, abstract; 1534_3-7; 1503¶¶97-120; 1504¶¶38-43, 56-67; 2041¶¶35-37, 46-63; 1702¶¶35-58.

1697(Wilson)_258:3-263:21; 264:9-267:18; 267:24-268:12; 1699(Presta)_92:9-93:9; 115:1-116:17.) That, in fact, is all the named inventors allegedly did.

Second, the "consensus" technique upon which PO relies was disclosed in prior art, including Queen-1989 and -1990.[3] Moreover, the '213 patent does not claim processes, and the consensus process confers no patentable distinction from humanized antibodies made using other approaches. *In re Kubin*, 561 F.3d 1351, 1356(Fed. Cir. 2009)(differences in prior art and patent processes irrelevant to product claims' obviousness).

Third, to the extent recited FR substitutions were not explicitly disclosed, they necessarily would have been identified by following the prior art. PO's criteria for identifying candidates are ***the same*** as in the prior art. And Dr. Presta admitted that "once you have the candidate list, the sequences that you're ultimately going to test is determined by whether the framework residue…and the mouse sequence differ at a given position," requiring a POSITA "to test approximately ten different variants" regardless of the criteria for identifying candidates. (Ex.1699(Presta)__99:6-20, 98:25-99:5.) Notably, PO asserts that the

---

[3] As described below (§III.B), PO's antedation attempt fails; its claims are unsupported by the parent application, and its evidence is unreliable and does not show invention of the ***claimed*** antibodies.

relevant level of ordinary skill is even higher than Petitioner proposes, yet identifies no aspect of the claimed invention under either side's definition that a POSITA would not know how to do.

Indeed, all of PO's attempts to distinguish the prior art—including "failure" to disclose specific sequences, substitutions and binding data—cannot be reconciled with the '213 patent's specification, which provides ***no*** sequences, substitutions, or binding data for the vast majority of the innumerable combinations it attempts to monopolize. It also explicitly admits that identifying antibodies that bind antigen is "***per se routine and well within the ordinary skill of the art***." (Ex.1501_10:31-33.)

Finally, the prior art teaches antibodies "lack[ing] immunogenicity" with "up to 3-fold more" affinity than their parents. Immunogenicity ***data*** cannot be necessary, as the patent provides none for ***any*** antibody.

The challenged claims are unpatentable.

II. CLAIM CONSTRUCTION

For this IPR, Petitioners adopt PO's definitions of "consensus human variable domain" ("a human variable domain which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure.") and "lacks immunogenicity" (this "refer[s] to a humanized antibody having reduced immunogenicity in a human

patient as compared to its non-humanized parent antibody").

III. ARGUMENT

A. Claims 1, 2, 25, 29, 80, 81 Are Unpatentable

Petitioners previously demonstrated these claims are unpatentable because they are obvious in view of Queen 1989 or Queen 1990, and the PDB Database. (Pet._29-40, 52-53; Ex.1503¶¶252-316.) The POR does not rebut these grounds, and Dr. Wilson admitted he did "not consider those claims." (Ex.1697(Wilson)_61:4-16.) PO, apparently interested in keeping the claims it is not willing to defend, did not do the right thing and disclaim them. The Board should rule these claims unpatentable.

B. Grounds 2-4, 7: Queen 1990 And Tramontano Are Prior Art

PO only seeks to antedate these references for claims 12, 42, 60, 65, 71, 73-74, and 79. (POR_23.) Its attempt fails.

1. No priority to the '272 application

For priority, a parent application must "reasonably convey to those skilled in the art that as of the claimed priority date the inventor was in possession of the later claimed subject matter." *Los Angeles Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1057(Fed. Cir. 2017). That is not the case here.

Each challenged claim recites ***any*** humanized antibody or variable domain comprising CDR residues from ***any*** non-human antibody (or anti-HER2 antibody

for claims 42, 60) incorporated into a human framework, comprising one or more substitutions at ***up to 28*** different positions. But the '272 application does not show the inventors were in possession of any claimed antibody much less the full scope.

The '272 application identifies only eight humanized antibody variants made by the inventors—huMAb4D5-1 through 8. (Ex.2032_93.) Yet, each variant has CDRs with both human and mouse residues, notwithstanding Dr. Presta testified that the claims require the ***entire*** CDRs to be from mouse. (Exs.1501_48:52-49:1; 1702¶¶85-86; 1699(Presta)_86:20-87:7.) Furthermore, each variant with FR substitutions has at least one ***outside*** the recited Markush groups. (Ex.1702¶¶87-89.) PO previously conceded these claims "recite *Markush* groups of framework substitutions." (Paper 7_18, 34.) Thus, it is presumed with respect to the substitution element that "th[e] claim element is 'closed' and therefore 'exclude[s] any elements…not specified in the claim.'" *Shire Dev. LLC v. Watson Pharm., Inc.*, 848 F.3d 981, 984(Fed. Cir. 2017). Notably, PO's expert admitted he did ***not*** consider the Markush groups to be closed. (Ex.1697(Wilson)_77:17-81:21, 162:7-168:10.) In arguing priority, PO contends antibodies with non-recited FR substitutions embody the claims. (POR_36-39; Ex.2041¶¶88-95.) Because PO has not rebutted the presumption the Markush groups are closed, the variants fall outside the claims and cannot demonstrate possession. *Shire*, 848 F.3d 981 at 984. The '272 application thus does not show possession of any ***claimed*** embodiment.

Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1350-51(Fed. Cir. 2011)(no possession where patent "does not describe a single antibody that satisfies the claim limitations").

Moreover, the claims also encompass any combination of recited substitutions, most being unrepresented in any '272 embodiment. (Exs.2032_93; 1702¶90.) The only other working examples were added to the ***later*** application, which PO's expert and inventor admitted was critical to generalize the invention beyond 4D5 variants. (Exs.2041¶89; 1697(Wilson)_75:5-77:13, 97:19-101:18, 137:21-138:20, 143:1-144:24; 1698(Carter)_89:18-94:7, 110:6-129:8.) Thus, the '272 application certainly fails to support the ***full claim scope***. *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1253(Fed. Cir. 2004)("[P]rior application must enable…[POSITA] to practice the ***full scope*** of the claimed invention.").

Thus, Queen-1990 and Tramontano are §102(b) art and cannot be antedated.

2. No antedation in any event

PO's flawed antedation argument rests on its assertion that its "inventors conceived and ***actually reduced to practice*** [the claimed invention] prior to the publication of" the prior art. (POR_2) But that is not borne out by the evidence. "To demonstrate reduction to practice, a party must prove that the inventor: (1) constructed an embodiment or performed a process that met all the limitations and (2) determined that the invention would work for its intended purpose." *In re*

Omeprazole Patent Litig., 536 F.3d 1361, 1373(Fed. Cir. 2008). Inventor testimony must be independently corroborated. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 999(Fed. Cir. 2009).

Here, PO relies on inventor declarations, supported by notebooks. But the inventors' testimony lacks credibility; they could not even agree on key aspects of the alleged invention story. (Exs.1699(Presta)_26:7-27:13; 1698(Carter)_50:17-51:11.) Moreover, the inventors rely on notebooks that are ***unwitnessed*** and, on some pages, ***unsigned***, despite PO's notebook policies. (Exs.2001_4, 13-90; 2002_13-68; 2003_4, 13-110; 2004_4, 13-109; 1698(Carter)_169:14-173:14, 174:9-13, 175:3-10; 1699(Presta)_63:12-64:10, 65:1-67:5, 180:16-181:24.) Dr. Presta even admitted he ***changed dates*** without following PO's procedures. (Ex.1699(Presta)_178:24-179:6, 179:14-180:15.) Both inventors admittedly understood the importance of notebook procedures, yet ignored them. (Exs.1698(Carter)_169:14-173:14, 174:9-13, 175:3-10; 1699(Presta)_65:13-67:5.) Such undated, unwitnessed notebooks ***cannot*** corroborate invention. *Medichem S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1170(Fed. Cir. 2006)(unwitnessed notebook alone insufficient to support reduction to practice).

The only other evidence PO presents is a declaration from lab technician John Ridgeway, and his and other technicians' notebooks describing testing of antibody variants. (POR_24-41; Exs. 2005-8, 2018.) Yet none corroborates the

design (*e.g.*, Markush selection of framework residues) of tested antibodies. (Exs.1701_9:1-12:12; 1698(Carter)_141:12-145:13.) Thus, no corroboration evidence shows the tested antibodies embody the claims. *Medichem*, 437 F.3d at 1172(corroboration evidence must show ***claimed invention***).[4]

Furthermore, no variant made by the inventors is an "embodiment" that meets "all the limitations." (*See* Section 1 *supra*.) PO provides no expert testimony comparing the inventors' work to the claims. (Exs.1697(Wilson)_255:20-257:3; 1698(Carter)_37:19-39:15; 1699(Presta)_84:3-85:2.) Unsubstantiated attorney argument is insufficient. *Zimmer Tech. Inc. v. Howmedica Osteonics Corp.*, 476 F. Supp. 2d 1024, 1049(N.D. Ind. 2007).

Finally, the inventors had ***not*** established any variant "would work for its intended purpose." *Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery*, 514 F.

---

[4] PO produced notebook copies scanned in late 2016, rather than original microfilmed versions. (Ex.1700_15:1-12.) PO's records manager admitted storage and access was the responsibility of the notebook assignees, and she had no knowledge of how they were filled out, where and how they were stored, or if entries were altered. (*Id.*_18:2-20:6, 21:1-22:7, 23:18-27:24, 28:2-38:11, 41:18-42:4, 46:14-50:3.) The remaining notebooks/documents (Exs.2007-15) were not authenticated by any non-inventor. (Ex.1700_38:20-39:2.)

Supp. 2d 351, 360(D. Conn. 2007). The "intended purpose" was to treat humans, requiring both sufficient target binding ***and*** reduced immunogenicity. (Exs.1698(Carter)_29:17-32:15; 1699(Presta)_110:21-111:22; 1697(Wilson)_101:19-103:5; 1501_4:24-40.) Yet, PO shows no immunogenicity testing of ***any*** variant, despite asserting such data is necessary for obviousness. (Exs.1698(Carter)_112:7-112:19; 1699(Presta)_109:24-112:21; 1702¶¶91-93.)

PO also asserts that, for grounds 1, 3, and 6, "Petitioners' obviousness theory for Queen-1989 actually rests on Queen-1990, which is not prior art…." (POR_44-45.) But Queen 1990 ***is*** prior art as discussed above. Petitioners' Queen-1989 obviousness theory does not ***rest*** on Queen-1990. Although Dr. Foote pointed to Queen-1990 as showing FR residues interact with CDRs within 3.3 Angstroms, that was well-known; PO's own expert acknowledges a POSA "would know that Van der Waals and hydrophobic interactions [between CDR and FR residues] can occur at distances of ***3.5 to 4 Angstroms***," citing a ***1964*** paper. (Ex.2041¶186 (citing Ex.2045(Bondi 1964).)

C. Grounds 1-4, 6-7: Each Queen Reference With The PDB Database Would Have Led To The Claimed Inventions With A Reasonable Expectation Of Success

POSITAs using Queen's roadmap and the PDB Database would have made the claimed antibodies as a matter of course. (Pet._34-37.) Notably, indisputably invalid claims 1-2, 25, 29, and 80-81 recite humanized antibodies comprising non-

human CDRs incorporated into human frameworks, with FR substitutions at any one or more of ***29 different positions***, including 66L, 73H, 78H and 93H, with the remaining claims differing in only unpatentable insignificant ways.

PO argues that the Queen references "do not teach using the PDB database as Petitioners use it" but rather "describe modeling the ***parent murine antibody*** to identify residues that may interact with the CDRs." (POR_45-46.) This is wrong.

PO and Dr. Wilson acknowledge Queen teaches to generate a "***plausible*** molecular model" of the donor. (POR_45; Exs.2041¶¶180-83; 1536_5.) At the time of the invention, only a small number of antibody crystal structures were solved and made public. (Exs.1503¶¶140-41; 1699(Presta)_157:19-22.) To generate a "plausible molecular model" for others, Queen taught "***known antibody structures, which are available from the Brookhaven Protein Data Bank***, ***can be used*** if necessary as rough models of other antibodies." (Ex.1550_14:32-36.) Thus, if a POSITA "needed an antibody structure, they either would have to get those coordinates from the Protein Data Bank or ask the authors themselves to send the coordinates." (Ex.1699(Presta)_156:25-157:8; *id.*_157:10-17.) Dr. Foote's analysis merely follows Queen's teachings. Using ***human*** antibody structures made sense since the task is to identify ***human*** FR residues proximate to the CDRs. (Ex.1702¶135-144.)

PO further argues the analysis "would have led to a broad genus of potential

framework substitutions, and Petitioners have provided no reason a POSITA would have selected the specific framework substitutions recited in the challenged claims." (POR_46-49.) PO contends "Petitioners have presented no evidence that a [POSITA] would have had a reasonable expectation of success that humanized antibodies containing the claimed substitutions" would "bind to an antigen." (*Id.*_49-50.) But the inventors and the patent itself contradict this argument.

As an initial matter, the patent's criteria for identifying candidate substitutions are ***the same*** as the prior art. Two criteria in claim 64—"(a) noncovalently binds antigen directly"; and "(b) interacts with a CDR"—are explicitly identified by Queen. (Exs.1534_5; 1550_14-16; 1697(Wilson)_258:3-263:21, 264:9-267:18; 267:24-268:12; 2039(Foote)_324:13-325:2; 1699(Presta)_92:9-93:9, 115:1-116:17.) It is undisputed these criteria may identify "a large number" of candidate FR positions for any humanization. (Exs.1697(Wilson)_112:12-21; 1699(Presta)_76:19-80:13, 90:1-102:25.) The patent identifies ***47*** different candidates, up to ***28*** in certain claims—encompassing millions or more antibodies—yet describes only a handful of variants actually made, with most substitutions unrepresented. (Exs.1501_5:12-6:22, 47:30-60:16, 85:44-90:30; 2039(Foote)_320:13-324:16; 1699(Presta)_96:14-97:13; 1698(Carter)_92:18-94:7.) The patent provides no further guidance on which "may be important for any given antibody." (Ex.1702¶¶164-165.)

The patent seeks to traverse this problem, stating that identifying antibodies that bind antigen is "per se routine and well within the ordinary skill of the art." (Ex.1501_10:31-33.) Dr. Presta agreed, testifying that "once you have the candidate list, the sequences that you're ultimately going to test is determined by whether the framework residue…and the mouse sequence differ at a given position," which is "a simple comparison of the letters to determine if they differ." (*Id.*_99:6-20, 101:24-102:9.) A POSITA would then "try each of [the substitutions] individually and then in combination" which, according to Dr. Presta, would require "test[ing] approximately ***ten*** different variants," whatever the candidate set. (*Id.*_98:25-99:5, 100:11-101:23.) According to that approach, if the mouse antibody happens to differ from the human acceptor at one or more recited positions, the resulting humanized antibodies will fall within the claims as a matter of course. (*Id.*; Ex.1702¶¶166.)[5] If the patent satisfies written description/enablement, identifying working antibodies from the prior art also must be "per se routine." *See Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559,

[5] In Queen's anti-Tac humanization, the residues at 66L were the same, whereas for the sequences Dr. Presta reviewed, they were different. (Ex.1697(Wilson)_225:17-229:24; 1702¶¶167-171.) The fact that Queen did not substitute 66L thus does not show it would not be obvious.

1567(Fed. Cir. 1997)("[A] description that does not render a claimed invention obvious does not sufficiently describe that invention for purposes of §112,¶1.").

PO's contrary arguments rely on Dr. Wilson, who admitted he applied an incorrect obviousness standard requiring ***every*** recited FR substitution to be obvious. (Ex.1697(Wilson)_84:11-15, 91:3-13, 92:3-14, 93:4-12.) PO presented no evidence that humanized antibodies with ***at least one*** recited substitution would be non-obvious. *In re Kubin*, 561 F.3d at 1361(obviousness of one embodiment sufficient).

PO criticizes Dr. Foote for relying on Dr. Padlan, an expert in earlier IPR proceedings. (POR_46.) Dr. Padlan used 3-D residue coordinates for known antibodies from the PDB Database and identified which FR residues were within 3.3 Angstroms of a CDR (one of Queen's criteria). (Ex.1503¶¶258-66, Exs.G-Q.) Dr. Foote did not blindly adopt Dr. Padlan's analysis. Rather, his reliance was "really the way a peer-reviewed paper would work," where scientists rely on and adopt others' work. (Ex.2039(Foote)_280:7-281:10.) Dr. Foote had "known [Padlan] by reputation for quite a long time" as "someone who's contributed…loads of findings to the antibody field," and "had great respect for him." (*Id.*_28:25-29:9.) Dr. Wilson admitted Dr. Padlan was "an expert in antibody structures" with a "good reputation," and that he was "someone who an antibody engineer might rely upon to perform analysis of 3-D modeling of antibody

structures." (Ex.1697(Wilson)_236:7-238:5.) Critically, he acknowledged that "[i]n ***re-doing*** the analysis that Dr. Padlan did in order to identify residues that would fall within criterion 4 from Queen that Dr. Foote…adopted and in doing [his own] ***good analysis*** of that data, [he] identified the residues in paragraph 186 of [his] declaration," ***including 66L, 71H, 73H, 78H, and 93H***. (*Id.*_242:4-244:7.) Thus, PO's own "good analysis" identified residues within all challenged claims. (Ex.1702¶¶139-141.)

Finally, PO's doomsday warnings about "sweeping consequences" that would arise from an obviousness finding are meritless. The claims are obvious because PO claims vast genuses of humanized antibodies that would be identified as a matter of course following the prior art, having tested only a handful while relying on "routine" skill to fill in the gaps. Petitioners do not contend ***all*** humanized antibodies would be obvious.

D. Grounds 1-2, 5, 7: The Prior Art Discloses Or Renders Obvious The "Consensus" Sequence Limitations

1. Queen teaches a "consensus" sequence

In Criterion I, Queen-1990 teaches POSITAs to use as "acceptor" either a framework identified using the "best fit" approach, ***or*** "a ***consensus framework*** from many antibodies." (Pet._36; Ex.1550_12:17-20.) PO argues the word "many" contradicts the patent definition, which requires a sequence generated from ***all*** antibody sequences of a particular subclass. (POR_52.) But a "consensus

framework from ***many*** antibodies" necessarily includes one from ***all*** antibodies in a subclass. Indeed, the "consensus" sequence used for the patent variants was generated using information from ***Kabat(1987)***. (Exs.2016¶¶24-25; 2017¶¶18-19; 1698(Carter)_56:20-61:24; 1699(Presta)_27:14-28:13, 29:25-36:2, 57:1-58:6, 115:7-17, 165:17-169:9; 1501_11:26-12:5.) Dr. Presta agreed a POSITA using a "consensus" approach would rely on, or recreate, Kabat(1987). (Ex.1699(Presta)_30:5-13, 33:7-34:9; Ex.1702¶¶94-96, 119, 156-163.) Yet PO's expert and inventors conceded that Kabat(1987) does ***not*** describe ***all*** human antibodies of a given subclass, and not even ***all*** those known. (Exs.1698(Carter)_56:20-61:24; 1697(Wilson)_33:18-36:3, 183:14-184:4, 212:8-217:22; 1699(Presta)_30:14-32:9.) Rather, it identifies only "***many***" antibodies of each subclass. (Ex.1697(Wilson)_33:18-36:32.) To the extent using Kabat(1987) meets the claims as PO asserts, it also does so for the prior art. *TVIIM, LLC v. McAfee, Inc.*, 851 F.3d 1356, 1362(Fed. Cir. 2017).

Queen-1990's discussion of "a representative collection of at least about 10 to 20 distinct human heavy chains" is in the context of using a "homologous" sequence ("best fit"), as is Criterion II, which involves identifying "rare" amino acids that would not be present under the "consensus" approach. (Ex.1550_13:3-11, 22-37; 1702¶158.) Queen-1990 states not all criteria apply in all circumstances, and POSITAs would know these applied only to the "best fit" option.

(Ex.1550_12:12-15; 1702¶158.)

The use of a "consensus" sequence also would have been obvious from Queen-1989, alone or in view of Kabat(1987). Queen-1989 does ***not*** teach using a human sequence with "unusual residues," but rather ***replacing*** such residues with "***more typical***" ones making the resulting antibody more human and less immunogenic, and moving toward "consensus." (Exs.1534_5-6; 1503¶320.) As with Queen-1990, a POSITA implementing this instruction would have looked to Kabat(1987). (Exs.1503¶¶319-20; 1699(Presta)_29:25-30:13.) To the extent the antibody identified by "best fit" differed from "consensus" only at the positions where residues were "rare" in humans, or where FR substitutions were indicated by Queen's criteria, then following Queen-1989 would result in a humanized antibody with every human FR residue the same as the "consensus." This is exemplified in Kurrle, where a "best fit" approach was initially used, but after FR substitutions to mouse the remaining human framework residues were identical to those of "consensus." (Exs.1571_8; 1697(Wilson)_258:3-263:21, 264:9-267:18, 267:24-268:12; 2039(Foote)_313:7-320:11; 1702¶¶7, 104-106, 160-162.) To the extent a POSITA ***also*** made substitutions to ***mouse*** amino acids (POR_55), they would be considered FR substitutions, not impacting the "consensus" limitation. (Ex.1702¶159.)

This highlights the lack of a meaningful difference between a humanized

antibody generated by "consensus" and "best fit" approaches, as the same sequence can arise from both. PO's contrary assertion—that the "patent's consensus sequence ***starts*** with 'the most frequently occurring amino acid residues at each location'" (POR_54-55)—is nonsensical. The patent does not claim methods. (Ex.1501, claim 62 ("A ***humanized antibody variable domain*** comprising non-human…CDR…amino acid residues that bind an antigen ***incorporated into a consensus human variable domain***….").) How the claimed antibodies are made is irrelevant.

2. The prior art teaches humanized antibodies with the recited substitutions that bind antigen

PO next argues "the Queen references do not disclose ***any*** antibody with the claimed framework substitutions and non-human CDRs in a human consensus framework that 'bind an antigen.'" (POR_56-57.) But Queen-1989 teaches antibodies made using the described methods are designed "to select a combination of mouse and human sequence elements that would reduce immunogenicity ***while retaining high binding affinity***." (Ex.1534_3.) Queen-1990 teaches its antibodies "retain substantially the ***same affinity*** as the donor immunoglobulin to the antigen." (Pet._41; Ex._1550_Abstract.) PO does not dispute that Queen's criteria for identifying candidate FR substitutions necessarily identifies positions recited in

each challenged claim, including ***4L***, ***98L***, ***36H***, ***69H***, ***71H***[6], ***73H***, and ***76H***. (Ex.1503¶¶33-38, 121-137, 155-199.)

PO argues there is no "binding affinity data" for sequences within the claims and thus "no evidence an antibody with the claimed framework substitutions will bind antigen." (POR_57.) But lack of "binding affinity data" is not determinative. As noted above, the patent provides no binding data for the vast majority of claimed FR substitutions, or indeed ***any*** antibody within the closed Markush groups. The patent thus relies on inherent properties of humanized antibodies or routine knowledge and skill. According to that approach, to the extent "bind[ing] an antigen" is not explicitly disclosed, it is inherently disclosed. *In re Kubin*, 561 F.3d at 1357.

3. Grounds 1-4: Claim 65's "up to 3-fold more" binding affinity limitation would have been obvious

Queen-1990 explains, for antibodies humanized using its criteria, "affinity levels…may be ***within about 4 fold*** of the donor immunoglobulin's original affinity to the antigen." (Pet._55-56; Ex.1550_6:26-28.) PO asserts this "does not

---

[6] Contrary to PO's assertion, Tramontano teaches importance of considering 71H for substitution, and that it can improve binding. (Exs.1551_6; 1503¶¶142-143; 1702¶¶113-116, 145-148.)

indicate that the humanized antibody's binding affinity is ***more*** than the…parent…." (POR_57.) But the basis for Queen's statement is testing of parent and humanized antibodies, which "show[ed] that these antibodies have approximately the same affinity (within 3 to 4 fold)." (Ex.1550_31:28-32:2, Fig._10B.) In other words, Queen's testing showed its humanized antibodies may have 3 to 4 fold ***more*** binding affinity than the parent, within limits of testing. (Ex.1702¶¶103, 176-177.)

This is consistent with Dr. Wilson's testimony that there were "examples" in the prior art where "using the humanization techniques that were known prior to the '213 patent invention," a POSITA "could achieve about the same binding affinity as the parent" and that "in achieving around about the same binding affinity as the parent, that might include ***a little bit more*** or a little bit less." (Ex.1697(Wilson)_104:12-105:5.) No more is required. (*Id.*_103:12-25 (agreeing "it could be ***any*** amount more, up to threefold more").)

Moreover, claim 65 encompasses infinite humanized antibodies with unlimited FR substitutions, while the patent identifies only ***two*** variants able to achieve more binding affinity than the parent, and then only because of ***CDR*** substitutions. (Ex.1501_50:63-54:62, 88:63-65, 90:2-9; 1697(Wilson)_146:9-176:14, 280:24-284:15; 1699(Presta)_117:10-125:15; 1698(Carter)_114:9-129:8; 1702¶¶178.) There is ***no*** embodiment able to achieve this requirement through the

claimed ***FR*** substitutions. (*Id*.) To the extent claim 65 satisfies written description/enablement, identifying working humanized antibodies with up to 3-fold more binding affinity must be "per se routine and well within the ordinary skill in the art." (Ex.1501_10:28-24.)

4. Queen 1989 and 1990 explicitly or inherently disclose the "lacks immunogenicity" limitation of claim 63

Queen-1989 teaches that making humanized antibodies according to its criteria "would ***reduce immunogenicity*** while retaining high binding affinity." (Pet._41; Ex.1534_3.) Queen-1990 teaches that "[w]hen combined into an intact antibody, the humanized immunoglobulins of the present invention ***will be substantially non-immunogenic*** in humans." (Paper 1_38; Ex.1550_Abstract.)

PO argues this limitation is not described because the prior art "cite[s] no data showing any antibody produced according to Queen-1989 or Queen-1990 'lacks immunogenicity,'" which "can only be determined through clinical trials." (POR_60-61.) This again is inconsistent with the patent, which includes ***no*** immunogenicity data for ***any*** humanized antibody. (Ex.1697(Wilson)_244:9-245:15, 245:22-246:19; 1698(Carter)_112:7-112:19.) At most, the patent states "it is anticipated that the optimal MAb4D5 variant molecule for therapy will have low immunogenicity …," providing no more disclosure than the prior art. (Ex.1501_52:55-57.) To the extent the patent satisfies written description/enablement, Queen-1989 and -1990 explicitly or inherently disclose

this limitation. *In re Kubin*, 561 F.3d at 1357. (Exs.1702¶¶149-155.) At the very least, it would have been obvious.

E. Grounds 6-7: It would have been obvious to make humanized antibodies with the recited FR substitutions that bind $p185^{HER2}$

Although PO asserts that "Hudziak doesn't discuss humanized antibodies," PO does not and cannot dispute that POSITAs would have been motivated to humanize Hudziak's 4D5 antibody. Dr. Wilson admitted it was known that "overexpression of the HER2 protein led to a poor prognosis in cancer, including breast cancer," "work had been done to identify murine antibodies that would target the HER2 receptor," with 4D5 shown "to have the…greatest effect of relative cell proliferation," and "[t]here was a concern that you might get a reaction against a mouse antibody if you give it to a human." (Ex.1697(Wilson)_19:7-21:8; *see also* Ex.1503¶¶39-40.)

Thus, any question about qualifications of Timothy Buss (POR_63-64), whose opinions are limited to this issue, is moot. Nevertheless, at the priority date, Mr. Buss had the "equivalent of a Ph.D." in biochemistry with practical academic experience in antibody development, meeting PO's POSITA definition. (Ex. 2040(Buss)_34:19-25, 40:3-6; Ex. 1504¶¶4-6; Paper 27_8.) And in any event, an expert need not meet the POSITA definition to provide opinions helpful to the Board. IPR2017-00860, Paper 34 at 2 (Apr. 23, 2018).

Once POSITAs decided to humanize 4D5, it was a matter of routine skill to

transfer CDRs to a human framework ("consensus" or "best fit"), identify candidate residues following the prior art, narrow to those differing between 4D5 and human framework, substitute FR residues at those positions individually and in combination, and test the few (per Dr. Presta) resulting variants. (*See* Section III.C, *supra*.) This would result in humanized antibodies with one or more recited substitutions as a matter of course, with identification of working variants that bind $p185^{HER2}$ being "per se routine and well within the ordinary skill in the art."

That is not to say humanized antibodies for ***any antigen*** would be obvious (POR_63), only that PO's incredibly broad claims, covering countless antibodies that bind ***any*** anti-HER2 antigen comprising any of a multitude of untested candidate substitutions, are *per se* obvious. *See Application of Mraz*, 455 F.2d 1069, 1072-73(C.C.P.A 1972)("[C]laims are unpatentable when they are so broad as to read on obvious subject matter even though they likewise read on non-obvious subject matter.").

F. "Objective Indicia" Do Not Establish Non-Obviousness

Alleged "objective indicia" (POR_64-68) do not assist PO.

1. No unexpected results

As discussed above, the "results" achieved in humanizing 4D5 following the prior art were in no way "unexpected." The patent does not claim a "broadly-applicable platform that could be used to humanize different antibodies" (POR_64-

66), but rather specific antibodies with specific FR substitutions. PO has not even shown the patent's variants fall within the claims. (Section III.B.1, *supra*.) PO certainly has not shown any other antibodies do so. For example, PO's expert and inventors identify several drugs they claim were designed using "the '213 patent invention," but provided (and performed) no analysis comparing these drugs to the claims. (Exs.2016¶5; 2017¶4; 2041¶¶130, 266; 1697(Wilson)_252:12-254:21; 1698(Carter)_32:25-39:15; 1699(Presta)_41:10-44:4.) At most they assert these drugs were designed using the common "consensus" framework from Kabat(1987). (Exs.2016¶5; 2017¶4; 2041¶¶130, 266.) But the "consensus" approach is not recited in most challenged claims and, even where it is, the claims include other unmet limitations.

PO's assertion that the '213 patent's approach results in antibodies with "unexpectedly superior properties," *i.e.*, lacking immunogenicity with "superior binding," also fails. First, PO's expert and inventors admitted there is no evidence that the "consensus" approach has ***any*** advantage over the "best fit" approach in terms of binding affinity or immunogenicity. (Exs.1697(Wilson)_184:16-185:7, 187:21-193:6; 1699(Presta)_131:10-141:22; 1698(Carter)_83:7-18; 1694.) The only publication identified as comparing the approaches concluded there is "***no clear advantage*** to designing reshaped human antibodies based on consensus sequences for human antibodies or on sequences from individual human

antibodies," and the consensus approach "may lead to a reshaped human variable region that has unnatural frameworks that are the result of averaging many sequences" and "***this could lead to a higher risk of immunogenicity***." (Exs.1694_9; 1697(Wilson)_187:21-193:6; 1699(Presta)_137:24-141:22; 1502_3:1362.) Dr. Presta wrote soon after that "***Dr. Queen's best fit method*** has remained the more popular method for designing the sequence of the humanized antibody than the consensus method" and the two approaches "both may function well with regard to acceptance by the human immune system with perhaps an occasional aberration." (Exs.1696_5-6; 1699(Presta)_131:10-136:14.)

Notably, as PO acknowledged during prosecution, the "prior art humanized antibodies" PO criticizes as producing immunogenic responses (POR_66)—as described in Ex. 2025, Riechmann (1988)—***were made using the consensus approach***, as PO admitted during prosecution. (Exs.1502_5:2500 ("Applicants have now learnt that the humanized light chain gene of the CAMPATH-1 antibody in Riechmann *et al.* was converted from an anti-lysozyme construct (see page 108 of Foote, J., *Nova acta Leopoldina* NF **61(269)**:103-110 (1989), of record). Foote's antilysozyme construct was prepared by combining CDR sequences from the kappa light chain of the anti-lysozyme antibody ***with consensus human kappa***

frameworks (see page 106, third paragraph of Foote, supra).");[7] 1693_9-11; 1697(Wilson)_176:25-178:23; 2039(Foote)_327:12-331:11; 1702¶¶41-43, 79-.) Queen's "best fit" antibodies showed ***no*** immunogenicity. (Exs. 1695_45; 1697(Wilson)_218:3-224:13.)

Thus, to the extent the "results" PO identifies were even achieved—which PO has not established—they bear no nexus to the claims. *Merck & Co. Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); IPR2014-00784 at 12 (Sep. 24, 2015) ("If objective indicia of nonobviousness are 'due to an element in the prior art, no nexus exists.'"). They also would not be commensurate with claim scope (*contra* POR_66-67), as the vast majority of substitutions in countless antibodies encompassed by the immensely broad claims are not even represented in ***any*** generated and tested variant, much less ones shown to achieve the alleged "unexpected results." *Ex Parte Takeshi*, Appeal 2013-003410 2015 WL 1952506 at *4 (Apr. 29, 2015) ("Evidence of secondary considerations must be reasonably commensurate with the scope of the claims.") (citing *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)).

---

[7] Both inventors admitted they received and analyzed Dr. Foote's unpublished sequence while working on the invention but could not say how they acquired it. (Exs.1698(Carter)_61:25-70:4; 1699(Presta)_159:22 -163:1.)

2. No commercial success

PO's "commercial success" argument similarly fails. Neither PO nor its witnesses have provided any analysis showing ***any*** identified drug—Herceptin®, Perjeta®, Avastin®, Lucentis®, and Xolair®—actually embodies ***any***, much less all, challenged claims. (Exs.2016¶5; 2017¶4; 2041¶¶130, 266; 1697(Wilson)_252:12-254:21; 1698(Carter)_32:25-39:15; 1699(Presta)_41:10-44:4.) Nor has PO shown any commercial success attributable to this patent. At most, PO identifies the "patent's consensus sequence approach, which allows good binding affinity while minimizing immunogenicity" but, as discussed above, there is no evidence these alleged advantages are in any way attributable to the "consensus" approach. IPR2014-00652, Paper 68 at 35 ("[E]vidence of commercial success is 'only significant if there is a nexus between the claimed invention and the commercial success.'"). Nor has PO provided evidence customers buy these drugs because of the claimed invention rather than, for example, their ability to bind HER-2, as previously taught. *Id.* at 35-36 (nexus requires "proof that the sales [of the allegedly successful product] were a direct result of the unique characteristics of the claimed invention—as opposed to other…factors unrelated to the quality of the patented subject matter.'").

G. These Proceedings Are Constitutional

This IPR is constitutional. *Oil States Energy Servs. LLC v. Greene's Energy Grp.*, 138 S. Ct. 1365, 1379 (2018).

IV. CONCLUSION

The challenged claims are invalid.

Date: May 25, 2018

Respectfully submitted,

/Amanda Hollis/

Amanda Hollis (Reg. No. 55,629)

Attorney For Petitioner

CERTIFICATE OF COMPLIANCE

This Reply complies with the type-volume limitations as mandated in 37 C.F.R § 42.24, totaling 5600 words. Counsel has relied upon the word count feature provided by Microsoft Word.

/Amanda Hollis/
Amanda Hollis

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Reply to Patent Owner Response was served on May 25, 2018, via electronic service on lead and back up counsel:

david.cavanaugh@wilmerhale.com

lauren.blakely@wilmerhale.com

robert.gunther@wilmerhale.com

abrausa@durietangri.com

ddurie@durietangri.com

andrew.danford@wilmerhale.com

kevin.prussia@wilmerhale.com

lisa.pirozzolo@wilmerhale.com

/Amanda Hollis/
Amanda Hollis