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(12) **EX PARTE REEXAMINATION CERTIFICATE (6829th)****United States Patent****Cabilly et al.**(10) **Number: US 6,331,415 C1**(45) **Certificate Issued: May 19, 2009**(54) **METHODS OF PRODUCING IMMUNOGLOBULINS, VECTORS AND TRANSFORMED HOST CELLS FOR USE THEREIN**(75) Inventors: **Shmuel Cabilly**, Monrovia, CA (US); **Herbert L. Heyneker**, Burlingame, CA (US); **William E. Holmes**, Pacifica, CA (US); **Arthur D. Riggs**, La Verne, CA (US); **Ronald B. Wetzel**, San Francisco, CA (US)(73) Assignees: **Genentech, Inc.**, South San Francisco, CA (US); **City of Hope**, Duarte, CA (US)**Reexamination Request:**

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**C12N 15/63** (2006.01)(52) **U.S. Cl.** ..... **435/69.6**; 435/252.1; 435/252.3; 435/252.33; 435/254.11; 435/254.2; 435/254.21; 435/69.7; 435/70.21; 435/71.2; 435/71.1; 435/70.1; 435/320.1; 435/455; 435/483; 435/485; 435/471; 435/69.1(58) **Field of Classification Search** ..... None  
See application file for complete search history.(56) **References Cited**

## U.S. PATENT DOCUMENTS

4,224,404 A 9/1980 Viza  
4,348,376 A 9/1982 Goldenberg  
4,366,246 A 12/1982 Riggs  
4,370,417 A 1/1983 Hung  
4,399,216 A 8/1983 Axel et al.  
4,419,446 A 12/1983 Howley  
4,431,740 A 2/1984 Bell  
4,440,859 A 4/1984 Rutter  
4,500,637 A 2/1985 Neville, Jr. et al.  
4,511,502 A \* 4/1985 Builder et al.  
4,565,785 A 1/1986 Gilbert  
4,599,197 A 7/1986 Wetzel  
4,634,665 A 1/1987 Axel et al.  
4,642,334 A 2/1987 Moore  
4,668,629 A 5/1987 Kaplan et al.  
4,713,339 A 12/1987 Levinson et al.  
4,766,075 A 8/1988 Goeddel et al.4,792,447 A 12/1988 Uhr et al.  
4,816,567 A 3/1989 Cabilly et al.  
4,965,196 A 10/1990 Levinson et al.  
5,081,235 A 1/1992 Shively et al.  
5,098,833 A 3/1992 Lasky et al.  
5,116,964 A 5/1992 Capon et al.  
5,137,721 A 8/1992 Dallas  
5,179,017 A 1/1993 Axel et al.  
5,225,538 A 7/1993 Capon et al.  
5,336,603 A 8/1994 Capon et al.  
5,420,020 A 5/1995 Riggs  
5,428,130 A 6/1995 Capon et al.  
5,455,165 A 10/1995 Capon et al.  
5,500,362 A 3/1996 Robinson et al.  
5,514,582 A 5/1996 Capon et al.  
5,561,053 A 10/1996 Crowley  
5,583,013 A 12/1996 Itakura  
5,585,089 A 12/1996 Queen et al.  
5,605,689 A 2/1997 Ammann  
5,612,185 A 3/1997 Uhr et al.  
5,648,237 A 7/1997 Carter  
5,686,072 A 11/1997 Uhr et al.  
5,721,108 A 2/1998 Robinson et al.  
5,736,137 A 4/1998 Anderson et al.  
5,807,715 A 9/1998 Morrison et al.  
5,840,545 A 11/1998 Moore  
5,846,818 A 12/1998 Robinson et al.  
5,877,293 A 3/1999 Adair et al.  
5,965,405 A 10/1999 Winter  
5,997,867 A 12/1999 Waldmann et al.  
6,054,297 A 4/2000 Carter et al.  
6,054,561 A 4/2000 Ring  
6,120,767 A 9/2000 Robinson et al.  
6,204,023 B1 3/2001 Robinson et al.  
6,331,415 B1 12/2001 Cabilly et al.  
6,455,275 B1 9/2002 Axel et al.  
6,548,640 B1 4/2003 Winter

## FOREIGN PATENT DOCUMENTS

EP 0 036 776 3/1981  
EP 0 447 222 1/1982  
EP 0 044 722 1/1982

(Continued)

## OTHER PUBLICATIONS

Harvard Journal of Law &amp; Technology 17(2) (Spring 2004), pp. 583-618.\*

Jun. 5, 1995 preliminary amendment in the Moore U.S. Appl. No. 08/461,071.\*

Declaration of Dr. Richard Axel, submitted Oct. 5, 1989 in U.S. Appl. No. 08/422,187.\*

(Continued)

*Primary Examiner* Padmashri Ponnaluri(57) **ABSTRACT**

The invention relates to processes for producing an immunoglobulin or an immunologically functional immunoglobulin fragment containing at least the variable domains of the immunoglobulin heavy and light chains. The processes can use one or more vectors which produce both the heavy and light chains or fragments thereof in a single cell. The invention also relates to the vectors used to produce the immunoglobulin or fragment, and to cells transformed with the vectors.

## FOREIGN PATENT DOCUMENTS

EP	060057	9/1982
EP	0 114 506	12/1983
EP	102634	3/1984
EP	0171496	2/1986
EP	173494	3/1986
EP	177343	4/1986
EP	365997	5/1990
EP	0481790	4/1992
WO	81/02426	9/1981
WO	WO 82/03088	9/1982
WO	83/00164	1/1983
WO	87/02671	5/1987
WO	89/00999	2/1989
WO	89/01783	3/1989
WO	92/16553	10/1992
WO	93/07899	4/1993
WO	93/10817	6/1993
WO	93/21319	10/1993
WO	97/30087	8/1997

## OTHER PUBLICATIONS

- Accolla et al., *Proc. Nat'l Acad. Sci. USA* 77:563 (1980).
- Rice and Baltimore, *Proc. Nat'l Acad. Sci. USA* 79:7862 (1982).
- Deacon et al., Antibody Synthesis in *Xenopus* Oocytes with Messenger Ribonucleic Acid from Immunized Rats, *Biochemical Society Transactions*, vol. 4, pp. 818-820 (1976).
- Ochi et al., Transfer of a cloned immunoglobulin light-chain gene to mutant hybridoma cells restores specific antibody production, *Nature*, vol. 302, pp. 340342 (1983).
- Oi et al., Immunoglobulin gene expression in transformed lymphoid cells, *Proc. Natl. Acad. Sci. USA*, vol. 80, pp. 825-829 (1983).
- Rice et al., Regulated expression for an immunoglobulin  $\kappa$  gene introduced into a mouse lymphoid cell line, *Proc. Natl. Acad. Sci. USA*, vol. 79, pp. 7862-7865 (1982).
- Valle et al., Synthesis and secretion of mouse immunoglobulin chains from *Xenopus* oocytes, *Nature*, vol. 291, pp. 338-340 (1981).
- Valle et al., Anti-ovalbumin monoclonal antibodies interact with their antigen in internal membranes of *Xenopus* oocytes, *Nature*, vol. 300, pp. 71-74 (1982).
- U.S. Appl. No. 07/233,430, Boss et al.
- U.S. Appl. No. 07/930,821, Boss et al.
- U.S. Appl. No. 08/320,381, Boss et al.
- U.S. Appl. No. 08/450,727, Boss et al.
- U.S. Appl. No. 08/452,420, Boss et al.
- U.S. Appl. No. 08/453,449, Boss et al.
- Abbas et al., Cellular and Molecular Immunology, Second Edition pp. 38-39 (1994).
- Abstract, Journal of Nuclear Medicine, May 1990, No. 613 (Exhibit 1177, Int. No. 104,532).
- Abstract, The Society of Nuclear Medicine 37<sup>th</sup> Annual Meeting, Washington Convention Center—Washington, D.C., Tuesday, Jun. 19—Friday, Jun. 22, 1990 (Exhibit 1180, Int. No. 104,532).
- Abstract, World Federation of Nuclear Medicine & Biology, Abstract submitted Jan. 15, 1990 (Exhibit 1178, Int. No. 104,532).
- Achord et al. 1978. Human  $\beta$ -glucuronidase: in vivo clearance and in vitro uptake by a glycoprotein recognition system on reticuloendothelial cells. *Cell* 15:269-278.
- Alberts et al. Molecular Biology of The Cell, pp. 285 and 375. Garland Publishing, Inc., (1983).
- Alberts, B. Molekularbiologie der Zelle, Weinheim: VCH p. 1075 (1987).
- Alt et al. "Immunoglobulin heavy-chain expression and class switching in a murine leukaemia cell line," *Nature*, vol. 298, p. 325-31, (Mar. 25, 1982).
- Andrews, D.W. and J.D. Capra. 1980. Clinical Immunobiology. pp. 1-18, W.B. Sanders.
- Arathoon, et al.—Large-Scale Cell Culture in Biotechnology pp. 1390-1395, *Science*, vol. 232, Jun. 1986 (Exhibit 1157; Int. No. 104,532).
- Arthritis & Rheumatism, Abstract Suppl. vol. 39, No. 9, Sep. 1996, p. S244.
- Ashford et al. 1993 "Site-specific Glycosylation of Recombinant Rat and Human Soluble CD4 Variants Expressed in Chinese Hamster Ovary Cells", *J. Biol. Chem.*, 268, 3260-3267.
- Bagdasarian et al., "Activity of the hybrid trp-lac (tac) promoter of putida. Construction of broad-host-range, controlled-expression vectors" *Gen* 26 (2-3): 273-282 (Dec. 1983).
- Baldwin, R.W. et al. 1990. Monoclonal Antibodies and Immunoconjugates. The Parthenon Publishing Group (UK), p. 209.
- Banerji et al., "A Lymphocyte-Specific Cellular Enhancer Is Located Downstream of the Joining Region in Immunoglobulin Heavy Chain Genes," *Cell*, vol. 33, 729-740 (Jul. 1982).
- J. Baselga et al., "Recombinant Humanized Anti-HER2 Antibody (Herceptin™) Enhances the Antitumor Activity of Paclitaxel and Doxorubicin against HER2/neu Overexpressing Human Breast Cancer Xenografts", *Cancer Res.* (1988) 58: 2825-2831.
- Beatty et al., *Cancer Research* (Suppl.), 50:922s-926s (Feb. 1, 1990) (Exhibit 1011; Int. No. 104,532).
- Beatty et al., *Cancer Research* 49:1587-1594 (Mar. 15, 1989) (Exhibit 1010; Int. No. 104,532).
- Begent et al., *Br. J. Cancer*, 62:487 (1990) (Exhibit 1088; Int. No. 104,532).
- Benoist, C., et al., "In vivo sequence requirements of the SV40 early promoter region," *Nature*, 290: 304-310 (1981).
- Bergman, Y., et al., "Two regulatory elements for immunoglobulin kappa light chain gene expression," *Proc. Natl. Acad. Sci.*, 81: 7041-45 (1984).
- Berman et al., *Science*, Nov. 4, 1983; 222(4623): 524-7.
- Bernier, "Proliferative Disorders of the Immune System," Chapter 21 (pp. 622-643) in Bellanti, *Immunology II* (1978).
- Bindon et al. (1985). Therapeutic potential of monoclonal antibodies to the leukocyte-common antigen. Synergy and interference in complement-mediated lysis. *Transplantation* 40(5):538-44 (Exhibit 2072; Int. No. 104,532).
- Blatt, C. and J. Haimovich. 1981. The selective effect of tunicamycin on the secretion of IgM and IgG produced by the same cells. *European Journal Of Immunology* 11:65-66.
- Blair, DG, et al., "Activation of the transforming potential of a normal cell sequence: a molecular model for oncogenesis," *Science*, 212: 941-43 (1981).
- Breathnach, R., et al. "Corrected splicing of a chicken ovalbumin gene transcript in mouse L cells," *Proc. Natl. Acad. Sci.*, 77: 740-44 (1980).
- Bruggemann et al. 1987. Comparison of the effector functions of human immunoglobulins using a matched set of chimeric antibodies. *Journal of Experimental Medicine* 166(5):1351-61 (Exhibit 2079; Int. No. 104,532).

- Byrn, et al., *Nature* 344:667–670 (Apr. 12, 1990) (Exhibit 1055; Int. No. 104,532).
- Cabilly, S. and A.D. Riggs. 1985. Immunoglobulin transcripts and molecular history of a hybridoma that produces antibody to carcinoembryonic antigen. *Gene* 40(1):157–61 (Exhibit 2073; Int. No. 104,532).
- Cabilly, Shmuel, “Growth at sub-optimal temperatures allows the production of functional, antigen-binding Fab fragments in *Escherichia coli*” *Gene* 85:553–57 (1989).
- Cancer Principles & Practice of Oncology, 5th Edition, vol. 1, Chapter 18, pp. 360–372 (Exhibit 1181; Int. No. 104,532).
- Carter et al., “High Level *Escherichia coli* Expression and Production of a Bivalent Humanized Antibody Fragment.” *Bio/Technology* 10(2):153–167 (Feb. 1992).
- Chang, E., et al., “Transformation by cloned Harvey sarcoma virus DNA: efficiency increased by long terminal repeat DNA.” *Science*, 210: 1249–51 (1980).
- Chang et al., *Proc. Natl. Acad. Sci. USA*, vol. 84, pp. 5640–5644 (1987) (Exhibit 1107; Int. No. 104,532).
- Clynes et al., 2000 “Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor antigens” *Nature Med* 6: 443–446.
- Cobbold et al., *Bone Marrow Purging and Processing*, pp. 139–154 (Jan. 1, 1990) (Exhibit 1027; Int. No. 104,532).
- Cobbold, S.P. and H. Waldmann, “Therapeutic potential of monovalent monoclonal antibodies” *Nature* 308(5958):460–62 (1984) (Exhibit 2068; Int. No. 104,532).
- Code of Medical Ethics and Current Opinions, excerpts from pp. 339–379 (Exhibit 2269; Int. No. 104,532).
- Colcher et al., *Cancer Res.* 49:1738–1745 (1989) (Exhibit 1047; Int. No. 104,532).
- Crowe, et al., *A Clinical Experimental Immunology*, 1992, 87, pp. 105–110 (Exhibit 1070; Int. No. 104,532).
- Davies, J., et al., “A new selective agent for eukaryotic cloning vectors,” *Am J. Trop. Med. Hyg.*, 29 (5 Suppl): 1089–92 (1980).
- Davis et al. 1990, “High Level Expression in Chinese Hamster Ovary Cells of Soluble Forms of CD4 T Lymphocyte Glycoprotein Including Glycosylation Variants.” *J Biol. Chem.* 265, 10410–10418 (Exhibit 2189; Int. No. 104,532).
- Davis, “Immunoglobulin molecules and genes” *Microbiology Including Immunology and Molecular Genetics*, Third edition, 1980, Chapter 17, pp. 338–379, Harper & Row, Hagerstown, MD.
- De Waele et al. 1988. Expression in non-tymphoid cells of mouse recombinant immunoglobulin directed against the tumor marker human placental alkaline phosphatase. *European Journal of Biochemistry* 176:287–295 (Exhibit 2109; Int. No. 104,532).
- Dean, C.J. 1994. Preparation and characterization of monoclonal antibodies to proteins and other cellular components. *Methods in Molecular Biology* 32:361–379 (Exhibit 2026; Int. No. 104,532).
- DeBoer, “The tac promoter: A functional hybrid derived from the trp and lac Promoters” *Proc. Natl. Acad. Sci. USA* 80:21–25 (1983).
- Devita et al., *Cancer: Principles & Practice of Oncology*, 1997, 5th Ed., vol. 1, Chapter 18, VT. DeVita (Ed.), Lippincott-Raven, Philadelphia, PA.
- Duda et al., *J. Surgical Oncology* 44:73–77 (Jun. 1990) (Exhibit 1014; Int. No. 104,532).
- Dyer et al., *Blood* 73:1431–1439 (May 1, 1989) (Exhibit 1025; Int. No. 104,532).
- Emery & Adair, *Exp. Opin. Invest. Drugs* (1994) 3(3):241–251 (Exhibit 1087; Int. No. 104,532).
- Estabrook A. and J. A. K. Patterson. “Immunotherapy using monoclonal antibodies,” *J. of Cutaneous Pathology* 10: 559–66 (1983).
- Ettinger, et al. *Cancer Treatment Reports* vol. 83, No. 1, pp. 131–134, Jan. 1979 (Exhibit 1129; Int. No. 104,532).
- Finnegan et al., *J. Rheumatology* 1997, 24:7, 1448–1449 (Exhibit 1069; Int. No. 104,532).
- Fittler et al., “Localization in Mouse–L–Cell Chromosomal Sites of Transferred Immunoglobulin Genes,” *Chromosoma (Berl.)* 84, 717–727 (1982).
- Fleischman, J. *BioScience Reports* 5:893–899 (1985) (Exhibit 1080 Case No. CIV S–00–1252 WBS GGII).
- Frenkel et al. 1980. Analysis and detection of B cell neoplasms. *Blood Cells* 6:783–793 (Exhibit 2123; Int. No. 104, 532).
- Friend et al., *Transplantation* 48:248–253 (Aug. 1, 1989) (Exhibit 1023; Int. No. 104,532).
- Fundenberg and Koistinen, “Human Allotype Detection by Passive Hemagglutination, with Special Reference to Immunoglobulin A Allotypes” Chapter 103 (pp. 767–774) in Rose and Friedman, *Manual of Clinical Immunology*, Second Edition (1980).
- Geisse et al. 1996. Eukaryotic expression systems: a comparison. *Protein Expression and Purification* 8:271–282 (Exhibit 2025; Int. No. 104,532).
- Gillics et al., “Expression of cloned immunoglobulin genes introduced into mouse L cells,” *Nucl. Acids. Res.*, vol. 11, No. 22, pp. 7982–7997 (1983).
- Glaser et al., “Functional interrelationship between two tandem *E. coli* ribosomal RNA promoters” *Nature* 302(59031):74–76 (Mar. 3, 1983).
- Goeddel et al. 1979. Direct expression in *Escherichia coli* of a DNA sequence coding for human growth hormone. *Nature* 281(5732):544–8 (Exhibit 2038; Int. No. 104,532).
- Goeddel et al., “Synthesis of Human Fibroblast Interferon by *E. coli*” *Nucleic Acids Research* 8(18):4057–4074 (1980).
- Goeddel, *Methods in Enzymology*, vol. 185, *AGene Expression Technology* (1990) (Exhibit 1077; Int. No. 104,532).
- Gold et al. 1978. Carcinoembryonic antigen (CEA) in clinical medicine. *Cancer* 42:1399–1405 (Exhibit 2135; Int. No. 104,532).
- Goochee et al. 1991, “The Oligosaccharides of Glycoproteins: BioProcess Factors Affecting Oligosaccharide Structure and Their Effect on Glycoprotein Properties”, *Bio Technology* 9, 1347–1355 (Exhibit 2187; Int. No. 104,532).
- Goochee, C. F., and T. Monica. 1990. Environmental effects on protein glycosylation. *Bio Technology* 8:421–427 (Exhibit 2023; Int. No. 104,532).
- Goodman and MacDonald, “Cloning of hormone genes from a mixture of cDNA molecules” *Methods in Enzymology* 68:75–90 (1979).
- Greipp, P. 1992. Advances in the diagnosis and management of myeloma. *Seminars in Hematology* 29(3: Suppl. 2):24–45 (Exhibit 2020; Int. No. 104,532).
- Grillo Lopez et al. 1999. Overview of the clinical development of rituximab: first monoclonal antibody treatment approved for the treatment of lymphoma. *Seminars in Oncology* 26:66–73 (Exhibit 2144; Int. No. 104,532).
- Gross et al., “Bone marrow Purging and Processing,” *International Symposium on Bone Marrow Purging and Processing* (2nd, Apr. 27 and 28, 1989 Cancun, Mexico) Gross et al. (Ed.), Wiley-Liss, NY.

- Grossbard, M.L. 1998. Monoclonal Antibody Based Therapy of Cancer. Marcel Dekker, p. 451 (Exhibit 2094; Int. No. 104,532).
- Gruss, P., et al., "Simian virus 40 tandem repeated sequences as an element of the early promoter," *Proc. Natl. Acad. Sci.*, 78:943-47 (1981).
- Habara et al. "Rauscher Murine Leukemia Virus: Molecular Cloning of Infectious Integrated Proviral DNA," *J. of Virology*, vol. 44, No. 2, pp. 731-735 (No. v 1982).
- Halc et al. 1985. Reactivity of rat monoclonal antibody CAMPATH-1 with human leukemia cells and its possible application for autologous bone marrow transplantation. *British Journal of Hematology* 60(1):41-8 (Exhibit 2074; Int. No. 104,532).
- Hale et al. 1988. Remission induction in non Hodgkin lymphoma with reshaped human monoclonal antibody CAMPATH-1 H. *Lancet* 2 (8625): 1394-1399 (Exhibit 2015 and 1024; Int. No. 104,532).
- Hale et al., 1990. The Campath-1 antigen (CDw52). *Tissue Antigens* 35:118-127 (Exhibit 2049 Int. No. 104,532).
- Hale, "Effects of Monoclonal Anti lymphocyte Antibodies in Vivo in Monkeys and Humans", *Mol Biol Med* (1983) 1, 321-334 (Exhibit 2240; Int. No. 104,532).
- Hale, Progress Report (May 1990-Dec. 31, 1990), MRC Wellcome Therapeutic Antibody Center (Exhibit 1072; Int. No. 104,532).
- Hamilton, R., "Application of engineered chimeric antibodies to the calibration of human antibody standards" *Annales de Biologie Clinique* 49 (4):242-248 (1991).
- Harris "Expression of Eukaryotic Genes in *E. coli*" *Genetic Engineering*, R. Williamson, 4<sup>th</sup> edition pp. 127-185 (1983).
- Harris, et al., Proceedings of the 34th Oholo Conference, Eilat, Israel (1990) (Exhibit 1073; Int. No. 104,532).
- Haynes and Weissmann, "Constitutive, long-term production of human interferons by hamster cells containing multiple copies of a cloned interferon gene," (1983) *Nucl. Acid. Res.*, vol. 11 No. 3, pp. 687-706 (Exhibit 1109; Int. No. 104,532).
- Hodge, J.W. 1996. carcinoembryonic antigen as a target for cancer vaccines. *Cancer Immunol and Immunother* 43:127-134 (Exhibit 2032; Int. No. 104,532).
- Hutchins et al., *Proc. Natl. Acad. Sci. USA*, vol. 92, pp. 11980-11984 (1995).
- Huynh et al., 1984. Constructing and screening cDNA libraries in kgt IO and kgtl 1. *DNA Cloning*, vol. I—A practical Approach 49-78. Glover, D(Editor), IRL Press, Oxford (Exhibit 2050; Int. No. 104,532).
- Jackson and Davis, "Quantitation of Immunoglobulins," Chapter 14 (pp. 109-120) in Rose and Friedman, *Manual of Clinical Immunology*, Second Edition (1980).
- Jefferis et al. 1998. IgG-Fc-mediated effector functions: molecular definition of interaction sites for effector ligands and the role of glycosylation. *Immunological Reviews* 163:59-76 (Exhibit 2095; Int. No. 104,532).
- Joziasse, et al., 2000 "a3-Galactosylated glycoproteins can bind to the heptasialin glycoprotein receptor" *Eur. J. Biochem.* 267:6501-6508 (Exhibit 1037; Int. No. 104,532).
- Kabat et al. Sequences of Proteins of Immunological Interest, Bethesda, MD: National Institute of Health pp. i, xxi, xxii (1983).
- Khazaeli, et al., *Cancer Research*, 51, 5461-5466 (1991) (Exhibit 1074; Int. No. 104,532).
- Kabat et al., "Sequences of immunoglobulin chains: tabulation and analysis of amino acid sequences of precursors, V-regions, C-regions, J-chain and [beta]2-microglobulins . . .," *The Kabat Database of Sequences of Proteins of Immunological Interest*, 1979, Publication No. 80 2008, p. 185, National Institute of Health, Bethesda, MD. (GNE-MED 52680).
- Kaetzel et al. 1985. Expression of biologically active bovine luteinizing hormone in Chinese hamster ovary cells. *Proc. Natl. Acad. Sci. USA* 82:7280-7283 (Exhibit 2152; Int. No. 104,532).
- Kagawa Y; *J Biol Chem* Nov. 25, 1988:263(33):17508-15 (Exhibit 1153; Int. No. 104,532).
- Kaufman et al. 1987. Coamplification and coexpression of human tissue-type plasminogen activator and murine dihydrofolate reductase sequences in Chinese hamster ovary cells. *Molecular and Cellular Biology* 5:1750-1759 (Exhibit 2075; Int. No. 104,532).
- Khazaeli et al., Manuscript—Frequent Anti-V Region Immune Response to Mouse B72.3 Monoclonal Antibody (pp. 25-63).
- Kipriyanov et al. 1999. Generation of recombinant antibodies. *Molecular Biotechnology* 12:173-201 (Exhibit 2017; Int. No. 104,532).
- Klausner, A. "Genentech makes monoclonal precursors from *E. coli*" *Bio/Technology* 1(5):396-397 (1983).
- Kohler, G., et al., "Immunoglobulin chain loss in hybridoma cell lines," *Proc. Natl. Acad. Sci.*, 77:2197-99 (1980).
- Kohler, G. *BioScience Reports* 5:533-549 (1985) (Plaintiff Exhibit 1108, Case No. CIV S 00 1252 WBS GGH).
- Krag et al., *J. Biological Chemistry*, vol. 257, No. 14, p. 8424 (1983) (Exhibit 1115; Int. No. 104,532).
- Krag, *J. Biol. Chem.* 254:9167-9177 (1979) (Exhibit 1043; Int. No. 104,532).
- Krolick et al. 1982. In vivo therapy of a Murine B cell tumor (BC1.1) using antibody-ricin A chain immunotoxins. *J Exp. Med.* 155:1797-1809 (Exhibit 2122; Int. No. 104,532).
- Kyle, "Classification and Diagnosis of Monoclonal Gammopathies," Chapter 16 (pp. 135-150) in Rose and Friedman, *Manual of Clinical Immunology*, Second Edition (1980).
- I. Levy, R. and R.A. Miller. 1983. Biological and clinical implications of lymphocyte hybridomas: tumor therapy with monoclonal antibodies. *Ann. Rev. Med.*—34:107-116 (Exhibit 2121; Int. No. 104,532).
- Lifely et al., *Glycobiology*, vol. 5 No. 8; 813-822, 1995 (Exhibit 1170; Int. No. 104,532).
- Lingappa et al. 1980. Signal sequences for early events in protein secretion and membrane assembly. *Ann. NYAcad. Sci.* 343:356-61 (Exhibit 2147; Int. No. 104,532).
- Linscott's Directory (formerly Catalog) of Immunological and Biological Reagents, second edition 1982-83, pp. 1-57.
- LoBuglio and Saleh, *Am. J. Medical Sciences*, Sep. 1992 vol. 304, No. 3, pp. 214-224 (Exhibit 1160; Int. No. 104,532).
- Liu et al., "Expression of mouse: human immunoglobulin heavy-chain cDNA in lymphoid cells" *Gene* 54(1):33-40 (1987).
- M.D. Pegram et al., "Antibody dependent cell-mediated cytotoxicity in breast cancer patients in Phase III clinical trials of a humanized anti-HFR2 antibody", *Proc. Am. Assoc. Cancer Res.*, 1997, 38:602 (#4044) (Exhibit 2248; Int. No. 104,532).

- Ma, S. and W. Nashabeh. 1999. Carbohydrate analysis of a chimeric recombinant monoclonal antibody by capillary electrophoresis with laser-induced fluorescence detection. *Analytical Chemistry* 71:5185–5192 (Exhibit 2145; Int. No. 104,532).
- Maniatis, T., E.F. Fritsch, and J. Sambrook. 1982. Table of Contents; “Extraction, Purification, and Analysis of mRNA from Eukaryotic Cells”, 187–209; “Synthesis and Cloning of cDNA”, 211–246; and “Construction of Genomic Libraries”, 269–307. In *Molecular Cloning A Laboratory Manual*, New York: Cold Spring Harbor Laboratory (Exhibit 2008; Int. No. 104,532).
- Margulies et al., “Regulation of immunoglobulin expression in mouse myeloma cells” *Immunoglobulin Expression* pp. 781–791 (1977) (GNE–MED 31462).
- Marx, J. *Science* 229:455–456 (1985) (Plaintiff Exhibit No. 1118, Case No. CIV S–00–1252 WBS GGH).
- Martinis et al., “Monoclonal antibodies with dual antigen specificity” *Oncology* pp. 311–316.
- Matsuuchi et al. 1981. An analysis of heavy chain glycopeptides of hybridoma antibodies: correlation between antibody specificity and sialic acid content. *Journal of Immunology* 127(5):2188–90 (Exhibit 2060; Int. No. 104,532).
- Mercola et al., “Transcriptional Enhancer Elements in the Mouse Immunoglobulin Heavy Chain Locus,” *Science*, vol. 221, No. 4611, p. 663–65 (Aug. 12, 1983).
- Meredith et al., *J. Nucl. Med.*, Jan. 1992, 33:23–29 (pp. 13–19).
- Meredith et al., *J. Nucl. Med.*, vol. 33, No. 9: 1648–1653, Sep. 1992.
- Meredith, et al., *Hum. Antibod. Hybridomas*, 1993, 4:190–197 (Exhibit 1083; Int. No. 104,532).
- Miles *Biochemicals* 1979–80, p. 140–142.
- Miller et al., “Transfection of human lymphoblastoid cells with herpes simplex viral DNA,” *Proc. Natl. Acad. Sci.*, vol. 76, No. 2, pp. 949–953 (Feb. 1979).
- Morell et al. 1971. The role of sialic acid in determining the survival of glycoproteins in the circulation. *J. Biol. Chem.* 246:1461–1467 (Exhibit 2117; Int. No. 104,532).
- Morrison SL, et al., “A mouse myeloma variant with a defect in light chain synthesis,” *Eur. J. Immunol.*, 9:461–65 (1979).
- Morrison et al. 1988. Genetically engineered antibody molecules: new tools for cancer therapy. *Cancer Investigation* 6(2):185–92 (Exhibit 2085; Int. No. 104,532).
- Morrison et al. 1988. Production and characterization of genetically engineered antibody molecules. *Clinical Chemistry* 34(9):1668–75 (Defendant Exhibit 5009, Case No. CIV S 00 1252 WBS GGH).
- Morrison, S. *Hospital Practice* 24(10):65–80 (1989) (GNE–MED 077476).
- Morrison, S., “In vitro antibodies: strategies for production and application” *Annual Review of Immunology* 10:239–265 (1992).
- Mulligan, RC, et al., “Selection for animal cells that express the *Escherichia coli* gene coding for xanthine-guanine phosphorihosyltransferase,” *Proc. Natl. Acad. Sci.*, 78 :2072–76 (1980).
- Munro, “Uses of chimeric antibodies,” *Nature* 312:597 (1984).
- Neuberger, M. *TIBS* 347–349 (1985) (Plaintiff Exhibit 1130 (Case No. CIV S–00–1252 WBS GGH)).
- Neuhaus et al., *JACC* 14:1566–1569 (Nov. 15, 1989) (Exhibit 1032; Int. No. 104,532).
- Neumaier et al., *Cancer Research* 50:2128–2134 (Apr. 1, 1990) (Exhibit 1013; Int. No. 104,532).
- Nose, M. and H. Wigzell. 1983. Biological significance of carbohydrate chains on monoclonal antibodies. *Proc. Natl. Acad. Sci. USA* 80:6632–6636 (Exhibit 2022; Int. No. 104, 532).
- Oi et al., “Immunoglobulin Gene Expressin in Transformed Lymphoid Cells,” *Proc. Natl. Acad. Sci.*, vol. 80, No. 3, p. 825–59 (Feb. 1, 1983).
- Oi & Morrison *BioTechniques* 4(3):214–221 (1986) (Plaintiff Exhibit 1135, Case No. CIV S–00–1252 WBS GGH).
- Oldham, R. 1983. Monoclonal antibodies in cancer therapy. *Journal of Clinical Oncology* 1:582–590 (Exhibit 2119; Int. 104,532).
- Orfila et al., “Immunofluorescence study of “non-idiopathic” renal amyloidosis,” *Hum. Pathol.* 14(4):362–7 (1983).
- Peakman et al., *Hum. Antibod. Hybridomas* 5:65–74 (1994) (Exhibit 1038; Int. No. 104,532).
- Page et al., *Biotech*, 9:64–68 (1991).
- Picard et al., “Correct transcription of a cloned mouse immunoglobulin gene in vivo,” *Proc. Natl. Acad. Sci.*, vol. 80, pp. 417–421 (Jan. 1983).
- Potamianos et al. 2000. Radioimmunosctigraphy and Radioimmunotherapy in Cancer: Principles and Application, *Anticancer Research* 20, 925–948 (Exhibit 2185, Int. No. 104,532).
- Primus et al., *Cancer Immunol. Immunotherapy* (1990) 31:349–357 (Exhibit 1164; Int. No. 104,532).
- Queen and Baltimore, “Immunoglobulin gene transcription is activated by downstream sequence elements” *Cell* 33(3):741–748 (Jul. 1983).
- Queen, C., “Comparison of mouse and human V–kappa domains” (Submitted by PDL Mar. 27, 1997).
- Queen, C., “Comparison of human and mouse VH domains” (Submitted by PDL on Mar. 27, 1997).
- Rademacher et al. (1988) *Ann. Rev. Biochem.* 57:785–838 (Exhibit 2165; Int. No. 104,532).
- Raju et al. 2000. Species-specific variation in glycosylation of IgG: evidence for the species-specific sialylation and branch-specific galactosylation and importance for engineering recombinant glycoprotein therapeutics. *Glycobiology* 10(5):477–486 (Exhibit 2027; Int. No. 104,532).
- Reff et al., *Blood*, vol. 83, No. 2, pp. 435–445 (1994) (Exhibit 1111; Int. No. 104,532).
- Renner et al. 1997. Monoclonal antibodies in the treatment of non-Hodgkin’s lymphoma: recent results and future prospects. *Leukemia* 11(2):S55–S59 (Exhibit 2019; Int. No. 104, 532).
- Rhodes and Birch *Biotechnology* 6:518, 521, 523 (1988) (Exhibit 1046; Int. No. 104,532).
- Rhodes, *Adv. Anim. Cell. Biol. Technol. Bioprocess.*, 472–74 (1988) (Exhibit 1045; Int. No. 104,532).
- Riechmann et al. 1988. Expression of an antibody Fv fragment in myeloma cells. *Journal of Molecular Biology* 203(3):825–8 (Exhibit 2087; Int. No. 104,532).
- Riechmann et al. 1988. Reshaping human antibodies for therapy. *Nature* 322:323–327 (Exhibit 1022; Int. No. 104, 532).
- Rosen et al. 1983. Application of monoclonal antibodies to tumor diagnosis and therapy. *Annals of Clinical and Laboratory Science* 13:173–184 (Exhibit 2120; Int. No. 104,532).
- Routledge et al., *Eur. J. Immunol.* 1991, 21:2717–2725 (Exhibit 1068; Int. No. 104,532).

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