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MONOCLONAL ANTIBODIES DIRECTED TO THE HER2 RECEPTOR

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70.21

[58] Field of Search 530/387.7, 388.8, 530/388.85, 381.1; 435/7.23, 240.27, 172.2,

References Cited [56]

U.S. PATENT DOCUMENTS

4,699,877	10/1987	Cline et al
4,753,894	6/1988	Frankel et al
4,906,646	3/1990	Honn et al 514/356
4,957,735	9/1990	Huang 424/85.8
4,968,603	11/1990	Slamon et al
5,108,934	4/1992	Rokugawa et al
5,288,477	2/1994	Bacus.
5,401,638	3/1995	Carney et al
. ,		•

FOREIGN PATENT DOCUMENTS

0118365	9/1984	European Pat. Off C12P 21/00
239400	8/1994	European Pat. Off C12N 15/00
85/03357	8/1985	WIPO.
87/07646	12/1987	WIPO.
WO 89/10412	11/1989	WIPO C12O 1/68

OTHER PUBLICATIONS

Park et al., "Development of anti-p185HER2 Immunoliposomes for Cancer Therapy" Proc. Natl. Acad. Sci. USA 92:1327-1331 (Feb. 1995).

Akiyama et al., "Potentation of Cytotoxic Activity of Immunotoxins on Cultured Human Cells" Cancer Research 45:1005-1007 (1985).

Akiyama et al., "The product of the human c-erbB-2 Gene: a 185-Kilodalton Glycoprotein with tyrosine Kinase Activity" Science 232:1644-1646 (1986).

Coussens et al., "Tyrosine Kinase Receptor with Extensive Homology to EGF Receptor Shares Chromosomal Location with neu Oncogene" Science 230:1132-1139 (1985).

Douillard et al., "Radioimmunotection of Human Tumors with Radiolabeled Monoclonal Antibodies" Oncogenes to Tumor Antigens, Geraldo et al. (eds.), Elsevier Sci. Publ. Drebin et al., "Development of Monoclonal Antibodies Reactive with the Product of the neu Oncogene" Symposium on Fundamental Cancer Research 38:277-289 (1986).

Drebin et al., "Down-Modulation of an Oncogene Protein Product an Reversion of the Transformed Phenotype by Monoclonal Antobodies" Cell 41(3):695-706 (1985).

Drebin et al., "Inhibition of tumor growth by a monoclonal antibody reactive with an oncogene-encoded tumor antigen" Proc. Natl. Acad. Sci. 83:9129-9133 (1986).

Drebin et al., "Monoclonal antibodies identify a cell-surface antigen associated with an activated cellular oncogene" Nature 312:545-548 (1984).

Fendly et al., "Characterization of murine monoclonal antibodies reactive to either the human epidermal growth factor receptor of HER2/neu gene product" Cancer Research 50:1550-1558 (1990).

Fukushige et al., "Localization of a Novel v-erbB-Related Gene, c-erbB-2, on Human Chromosomes 17 and its Amplification in a Gastric Cancer Cell Line" Molecular & Cellular Biology 6(3):955-58 (1986).

Gill et al., "Monoclonal Anti-epidermal Growth Factor Receptor Antibodies Which are Inhibitors of Epidermal Growth Factor Binding and Antagonists of Epidermal Growth Factor-stimulated Tyrosine Kinase Activity" Journal of Biological Chemistry 259:7755-60 (1984).

Hudziak et al., "Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells" Proc. Natl. Acad. Sci. 84:7159-7163 (1987).

Hudziak et al., "p185HER2 Monoclonal Antibody Has Antiproliferative Effects In Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor" Molecular & Cellular Biology 9(3):1165-1172 (1989).

King et al., "Amplification of a Novel v-erbB-Related Gene in a Human Mammary Carcinoma" Science 229:974-976 (1985).

Kipps et al., "Schemata for the production of monoclonal antibody-producing hybridomas" Handbook of Experimental Immunology, Herzenberg et al. (eds.), Blackwell Sci., Chapter 108, pp. 108.1 –108.9 (1986).

Lupu et al., "Direct interaction of a ligand for the erbB2 oncogene product with the EGF receptor and p185erbB2" Science 249:1552-1555 (1990).

Mansi et al., "In vivo Evaluation of an Anti-Melanoma Antibody, F(ab')2, Labelled with TC-99m" Oncogenes to Tumor Antigens, Geraldo et al., eds., Elsevier Sci. Publ. (1985).

(List continued on next page.)

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ABSTRACT

Monoclonal antibodies which bind to the extracellular domain of the HER2 receptor and inhibit growth of SK-BR-3 breast tumor cells, which overexpress HER2, are disclosed. The monoclonal antibodies can be used for in vitro assays for detecting a tumor characterized by amplified expression of HER2.

39 Claims, 6 Drawing Sheets



OTHER PUBLICATIONS

Masui et al., "Mechanism of Antitumor Activity in Mice for Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies with Different Isotypes" Cancer Research 46;5592–5598 (1986).

Morrison, "Transfectomas Provide Novel Chimeric Antibodies" Science 229:1202–1207 (1985).

Padhy et al., "Identification of a Phosphoprotein Specifically Induced by the Transforming DNA of Rat Neuroblastomas" Cell 28:865–871 (1982).

Rodeck et al., "Interactions between growth factor receptors and corresponding monoclonal antibodies in human tumors" *J. Cellular Biochem.* 35(4):315–320 (1987).

Rodeck et al., "Tumor Growth Modulation by a Monoclonal Antibody to the Epidermal Growth Factor Receptor: Immunologically Mediated and Effector Cell-independent Effects" Cancer Research 47(14):3692–3696 (1987).

Rosenthal et al., "Expression in Rat Fibroblasts of a Human Transforming Growth Factor- α cDNA Results in Transformation" *Cell* 46:301-309 (1986).

Sato et al., "Biological Effects in Vitro of Monoclonal Antibodies to Human Epidermal Growth Factor Receptors" *Mol. Biol. Med.* 1:511-529 (1983).

Schechter et al., "The neu Gene: An erbB-Homologous Gene Distinct from and Unliked to the Gene Encoding the EGF Receptor" *Science* 229:976–978 (1985).

Schlom et al., "Basic Principles and Applications of Monoclonal Antibodies on the Management of Carcinomas: The Richard and Hinda Rosenthal Foundation Award Lecture" Cancer Research 46:3225–3238 (1986).

Semba et al., "A v-erbB-related protooncogene c-erbB-2, is distinct from the c-erb-B-1/epidermal growth factor-receptor gene and is amplified in a human salivary gland adenocarcinoma" *Proc. Natl. Acad. Sci. USA* 82:6497-6501 (1985).

Slamon et al., "Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene" Science 235:177-182 (1987).

Sobol et al., "Epidermal Growth Factor Receptor Expression in Human Lung Carcinoma Defined by a Monclonal Antibody" J. Natl. Cancer Institute 79(3):403–407 (1987).

Sugarman et al., "Effects of Growth Factors on the Antiproliferative Activity of Tumor Necrosis Factor" Cancer Research 47:780–786 (1987).

Sugarman et al., "Recombinant Human Tumor Necrosis Factor-α: Effects on Proliferation of Normal and Transformed Cells in Vitro" Science 230:943-945 (1985).

Takahashi et al., "Radioimmunodetection of Human Glioma Xenografts by Monoclonal Antibody to Epidermal Growth Factor Receptor" *Cancer Reserch* 47:3847–3850 (1987).

Urban et al., "Tumor necrosis factor: A potent effector molecule for tumor cell killing by activated macrophages" *Proc. Natl. Acad. Sci.* 83:5233-5237 (1986).

Van de Vijver et al., "Amplification of the neu (c-erbB-2) Oncogene in Human Mammary Tumors Is Relatively Frequent and Is Often Accompanied by Amplification of the Linked c-erbA Oncogene" *Molecular & Cellular Biology* 7(5):2019-2023 (1987).

Venter et al., "Overexpression of the c-erbB-2 Oncoprotein in Human Breast Carcinomas: Immunohistological Assessment Correlates with Gene Amplification" *Lancet* pp. 69-72 (1987).

Vitetta et al., "Redesigning nature's poisons to create anti-tumor reagents" *Science* 238:1098–1104 (1987).

Vollmar et al., "Toxicity of Ligand and Antibody-Directed Ricin A-Chain Conjugates Recognizing the Epidermal Growth Factor Receptor" J. Cellular Physiology 131:418-425 (1987).

Yamamoto et al., "Similarity of protein encoded by the human c-erb-B-2 gene to epidermal growth factor receptor" *Nature* 319:230-34 (1986).

McKenzie et al., "Generation and characterization of monoclonal antibodies specific for the human neu oncogene product, p185" Oncogene 4:543-548 (1989).

Muller et al., "Single-Step Induction of Mammary Adenocarcinoma in Transgenic Mice Bearing the Activated c-neu Oncogene" *Cell* 54:105-115 (1988).

Myers et al., "Biological Effects of Monoclonal Antireceptor Antibodies Reactive with neu Oncogene Product, p185^{neu}" Methods in Enzymology 198:277-290.

Drebin et al., "Monoclonal Antibodies Specific for the neu Oncogene Product Directly Mediate Anti-tumor Effects In Vivo" Oncogene 2 (4):387-394 (1988).

Hudziak et al., "Amplified Expression of the HER2/ERBB2 Oncogene Induces Resistance to Tumor Necrosis Factor α in NIH 3T3 Cells" *Proc. Natl. Acad. Sci. USA* 85:5102–5106. Aboud-Pirak et al., "Efficacy of Antibodies to Epidermal Growth Factor Receptor Against KB Carcinoma In Vitro and in Nude Mice" *Journal of the National Cancer Institute* 80(20):1605–1611 (Dec. 21, 1988).

Ballet et al., "Evaluation of a Nude Mouse-Human Tumor Panel as a Predictive Secondary Screen for Cancer Chemotherapeutic Agenst" *J. Natl. Canc. Inst* 63(5):1185-1188 (1979).

Bernards et al., "Effective Tumor Immunotherapy Directed Against an Oncogene-encoded Product Using a Vaccine Virus Vector" *Proc. Natl. Acad. Sci. USA* 84:6854-6858 (Oct. 1987).

Bucholtz, J.D., "Radiolabeled Antibody Therapy" Semin. Oncol. Nurs. (abstract only) 3(1):67-73 (1987).

Drebin et al., "Monoclonal antibodies reactive with distinct domains of the neu oncogene—encoded p185 molecule exert synergistic anti-tumor effects in vivo" *Oncogene* 2:273–277 (1988).

Hancock et al., "A Monoclonal Antibody Against the c-erbB-2 Protein Enhances the Cytotoxicity of cis-Diamminedichloroplatinum Against Human Breast and Ovarian Tumor Cell Lines" *Cancer Research* 51:4575-4580 (Sep. 1, 1991).

Masuko et al., "A murine Monoclonal Antibody That Recognizes an Extracellular Domain of the Human c-erB-2 Protooncogene Product" *Jpn J. Cancer Res.* 80:10-14 (Jan. 1989).

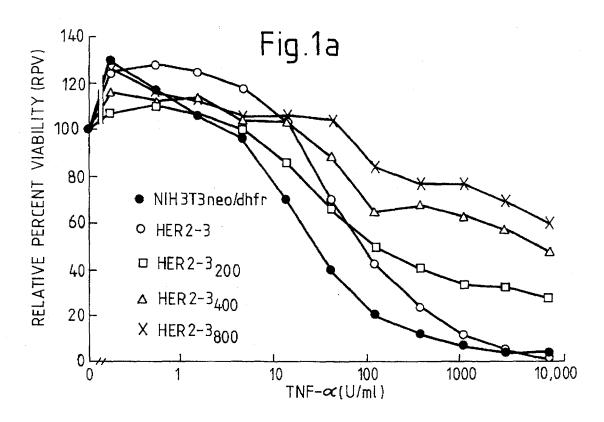
Pennica et al., "Human Tumour Necrosis Factor: Precursor Structure, Expression and Homology to Lymphotoxin" *Nature* 312:724–729 (1984).

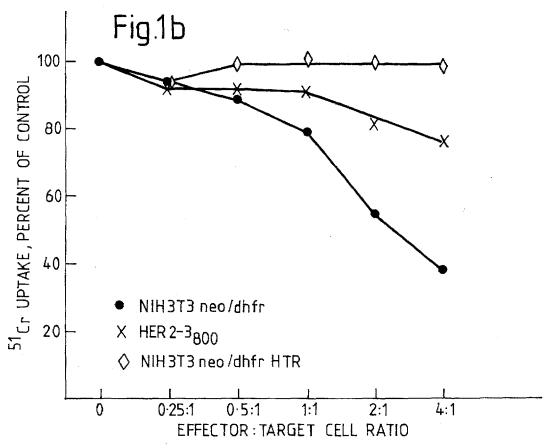
Ring et al., "Identity of BCA200 and c-erB-2 Indicated by Reactivity of Monoclonal Antibodies with Recombinant c-erbB-2" *Molecular Immunology* 28(8):915-917 (1991).

King, C.R. DHHS Patent Application 6/836.414. National Technical Information Service, Springfield, VA. 22161 Pub. 86–197928.

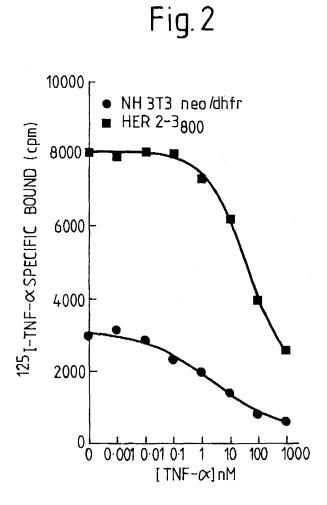


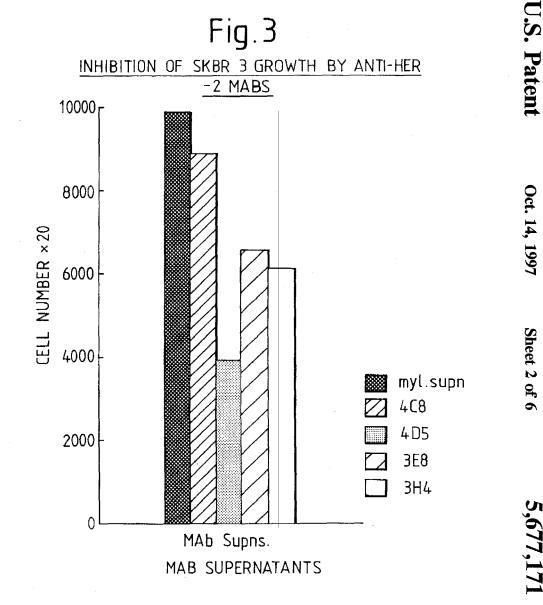
U.S. Patent





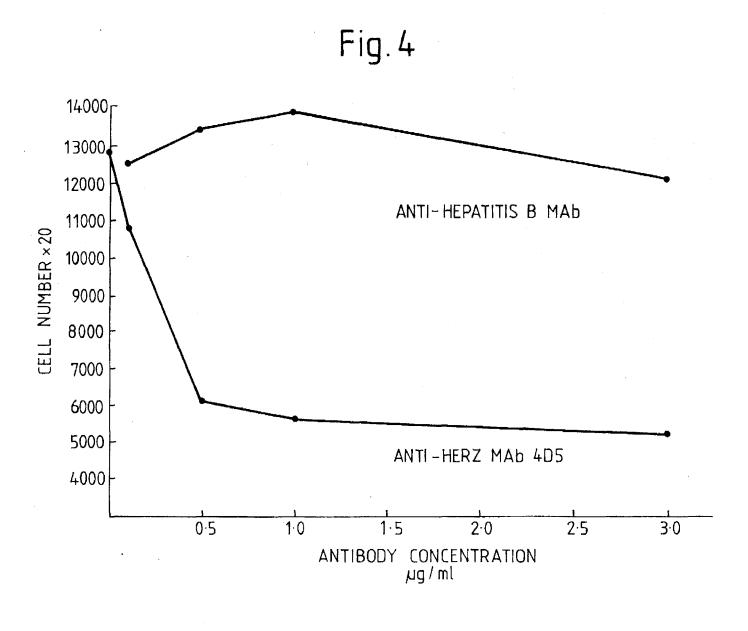






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