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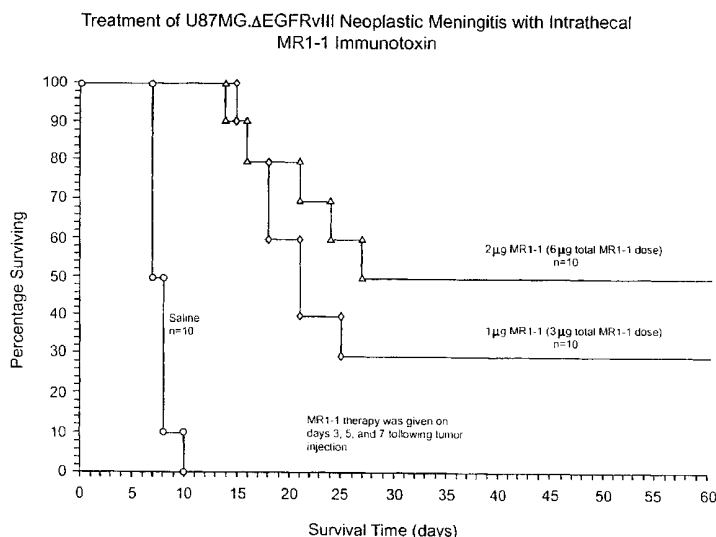
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(54) Title: ANTI-EGFRvIII SCFVS WITH IMPROVED CYTOTOXICITY AND YIELD, IMMUNOTOXINS BASED THEREON, AND METHODS OF USE THEREOF



(57) Abstract: The invention provides antibodies for a mutant form of the epidermal growth factor receptor known as EGFRvIII. This mutant is found only or primarily on the surface of glioblastoma cells, and on cells of breast, ovarian and non-small cell lung carcinomas. The antibodies provided by the invention have higher affinity for EGFRvIII, and form immunotoxins with higher cytotoxicity and yield, than prior art antibodies, including the scFv designated MR1. In particular, the invention provides an antibody, designated MR1-1, which mutates MR1 in the CDR3 of the VH and VL chains to provide an antibody with especially good cytotoxicity. The invention provides additional antibodies in which MR1 is mutated in the CDR1 and 2 of VH or VL, or both, with better binding to EGFRvIII than that of the parental MR1 antibody.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/13 C07K16/28 C12N15/62 C07K19/00 A61K47/48
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EMBASE, WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	C. KUAN ET AL.: "EGFRvIII as a promising target for antibody-based brain tumor therapy." BRAIN TUMOR PATHOLOGY, vol. 17, no. 2, 2000, pages 71-78, XP001016320 Tokyo, Japan page 75, left-hand column, line 21 - line 42 page 76, left-hand column, line 15 - line 27 page 76, right-hand column, line 8 - line 9 --- -/--	1-45

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- *Z* document member of the same patent family

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International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	I. LORIMER ET AL.: "Directed evolution of higher affinity single chain Fv antibodies specific for the mutant EGF receptor EGFRvIII." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 39, March 1998 (1998-03), page 65 XP002176478 Baltimore, MD, USA abstract #442	1-45
Y	P. CHOWDHURY ET AL.: "Improving antibody affinity by mimicking somatic hypermutation in vitro." NATURE BIOTECHNOLOGY, vol. 17, June 1999 (1999-06), pages 568-572, XP000918985 New York, NY, USA the whole document	1-45
A	G. ARCHER ET AL.: "MR1scFvPE38KDEL (MR1), a single chain immunotoxin for the treatment of tumors expressing EGFRvIII, a deletion mutation of the EGFR." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 39, March 1998 (1998-03), pages 438-439, XP002176479 Baltimore, MD, USA abstract #2985	1-45
A	I. LORIMER ET AL.: "Immunotoxins that target an oncogenic mutant epidermal growth factor receptor expressed in human tumors." CLINICAL CANCER RESEARCH, vol. 1, no. 8, August 1995 (1995-08), pages 859-864, XP000891452 Philadelphia, PA, USA the whole document	1-45
A	I. LORIMER ET AL.: "Recombinant immunotoxins specific for a mutant epidermal growth factor receptor: Targeting with a single chain antibody variable domain isolated by phage display." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE U.S.A., vol. 93, no. 25, 10 December 1996 (1996-12-10), pages 14815-14820, XP000652097 Washington, DC, USA cited in the application the whole document	1-45

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	R. BEERS ET AL.: "Immunotoxins with increased activity against epidermal growth factor receptor VIII-expressing cells produced by antibody phage display." CLINICAL CANCER RESEARCH, vol. 6, no. 7, July 2000 (2000-07), pages 2835-2843, XP002176480 Philadelphia, PA, USA the whole document	1-45
P,X	C. KUAN ET AL.: "Increased binding affinity enhances targeting of glioma xenografts by EGFRvIII-specific scFv." INTERNATIONAL JOURNAL OF CANCER, vol. 88, no. 6, 15 December 2000 (2000-12-15), pages 962-969, XP002176481 New York, NY, USA the whole document	1-45