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(54) Title: ANTIBODIES THAT BLOCK RECEPTOR PROTEIN TYROSINE KINASE ACTIVATION, METHODS OF SCREENING FOR AND USES THEREOF

(57) Abstract: Molecules containing the antigen-binding portion of antibodies that block constitutive and/or ligand-dependent activation of a receptor protein tyrosine kinase, such as fibroblast growth factor receptor 3 (FGFR3), are found through screening methods, where a soluble dimeric form of a receptor protein tyrosine kinase is used as target for screening a library of antibody fragments displayed on the surface of bacteriophage. The molecules of the present invention which block constitutive activation can be administered to treat or inhibit skeletal dysplasia, craniosynostosis disorders, cell proliferative diseases or disorders, or tumor progression associated with the constitutive activation of a receptor protein tyrosine kinase.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL02/00494

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07K 16/00; A61K 39/395; G01N 33/53

US CL : 530/387.1, 388.1, 388.22, 388.8, 388.85, 300, 350; 424130.1, 143.1, 155.1, 156.1; 435/7.1

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)

U.S. : 530/387.1, 388.1, 388.22, 388.8, 388.85, 300, 350; 424130.1, 143.1, 155.1, 156.1; 435/7.1

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 practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,214,974 B1 (ROSENBLUM et al.) 10 April 2001 (10.04.01), see entire document, especially column 2, line 44-55.	1, 4-5, 7-9, 11 ----- 12
X --- Y	US 5,707,632 A (WILLIAMS et al.) 13 January 1998 (13.01.98), see entire document, especially column 21-23.	1-5, 7-11 ----- 12, 18, 32-33
X --- Y	US 6,165,464 A (HUDZIAK et al.) 26 December 2000 (26.12.00), see entire document, especially abstract.	1, 4, 7, 32-33 ----- 12
X --- Y	US 6,129,915 A (WELS et al.) 10 October 2000 (10.10.00), see entire document, especially abstract.	1-2, 4, 7, 18 ----- 11-12
A	US 6,183,975 B1 (GARGUS et al.) 06 February 2001 (06.02.01) see entire document, especially column 2, lines 7-30	13-24

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

06 May 2003 (06.05.2003)

Date of mailing of the international search report

29 MAY 2003

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL02/00494

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim Nos.: 41-85
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 41-85 could not be searched because the claims recite SEQ ID Nos and this application is not in sequence compliance.

3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
 2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/IL02/00494

Continuation of B. FIELDS SEARCHED Item 3:

CAPLUS, MEDLINE, WEST, BIOSIS, US PATFUL

Search terms: antibody, FGFR, FGFR3, her2/neu, EGFR, fibroblast growth factor receptor, cancer, bone, cartilage, SADDAN, achondroplasia, RPTK, receptor protein tyrosine kinase, carcinoma, tumor.