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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

Internat	Application No
PCT/IB	02/03523

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7    C07K16/00    A61K38/17    C12N15/13    C12N15/10    C12Q1/00 A61P19/00    A61P35/00    C07K16/28				
According to International Patent Classification (IPC) or to both national classification and IPC				
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7    C07K    A61K				
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) <b>BIOSIS, MEDLINE, PAJ, EPO-Internal, WPI Data, EMBL</b>				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>				
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
<b>X</b>	OTSUKI TAKEMI ET AL: "Expression of fibroblast growth factor and FGF-receptor family genes in human myeloma cells, including lines possessing t(4;14)(q16.3;q32.3) and FGFR3 translocation." INTERNATIONAL JOURNAL OF ONCOLOGY, vol. 15, no. 6, December 1999 (1999-12), pages 1205-1212, XP000999866 ISSN: 1019-6439 the whole document  <div style="text-align: center;">--- -/--</div>	<b>1-6</b>		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.                 </td> <td style="width: 50%; border: none;"> <input checked="" type="checkbox"/> Patent family members are listed in annex.                 </td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.	<input checked="" type="checkbox"/> Patent family members are listed in annex.
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.	<input checked="" type="checkbox"/> Patent family members are listed in annex.			
° Special categories of cited documents :				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;">                 *A* document defining the general state of the art which is not considered to be of particular relevance                  *E* earlier document but published on or after the international filing date                  *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)                  *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             </td> <td style="width: 50%; border: none;">                 *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                  *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                  *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.                  *&amp;* document member of the same patent family             </td> </tr> </table>			*A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *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) *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	*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 *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 *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. *&* document member of the same patent family
*A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *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) *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	*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 *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 *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. *&* document member of the same patent family			
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">6 March 2003</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">13/03/2003</div>		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Mateo Rosell, A.M.</div>		

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/1B 02/03523

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FAN ZHEN ET AL: "Blockade of epidermal growth factor receptor function by bivalent and monovalent fragments of 225 anti-epidermal growth factor receptor monoclonal antibodies." CANCER RESEARCH, vol. 53, no. 18, 1993, pages 4322-4328, XP008014409 ISSN: 0008-5472 the whole document	1-4
X	MONTERO-JULIAN F A ET AL: "Characterization of two monoclonal antibodies against the RON tyrosine kinase receptor." HYBRIDOMA, vol. 17, no. 6, December 1998 (1998-12), pages 541-551, XP008014423 ISSN: 0272-457X the whole document	1-3
X	WO 97 08320 A (MORPHOSYS PROTEINOPTIMIERUNG ;KNAPPIK ACHIM (DE); PACK PETER (DE);) 6 March 1997 (1997-03-06) cited in the application	11,12
Y	page 5, line 1 -page 12, line 8; figure 5G	1-36
Y	YAYON A ET AL: "Isolation of peptides that inhibit binding of basic fibroblast growth factor to its receptor from a random phage-epitope library" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 90, no. 22, 15 November 1993 (1993-11-15), pages 10643-10647, XP002130209 ISSN: 0027-8424 the whole document	1-36

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5,9,21

Present claims 1-5,9,21 relate to a product defined by reference to a desirable characteristic or property, namely a molecule comprising the antibody binding portion of an isolated antibody which has increased activity for a receptor protein tyrosine kinase and which blocks constitutive activation of said receptor tyrosine kinase. The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to molecule(s) comprising the antibody binding portion of an isolated antibody which has increased activity for the FGFR3 and which blocks constitutive activation of said receptor.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 02/03523

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

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

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 22-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: 1-5, 9, 21  
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:  
see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims 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

International Application No  
PCT/IB 02/03523

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE 69621940 D1	25-07-2002
		DE 69621940 T2	16-01-2003
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		EP 0859841 A1	26-08-1998
		ES 2176484 T3	01-12-2002
		JP 2001519643 T	23-10-2001
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		US 6300064 B1	09-10-2001

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