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60/386,411 7 June 2002 (07.06.2002) US
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(54) Title: NEUTROPHIL IMAGING METHODS IN CYCTIC FIBROSIS

(57) Abstract: The present invention is directed to an improved method to detect and monitor a subject having cystic fibrosis (CF) by employing at least one anti-granulocyte/neutrophil antibody or a fragment thereof and a diagnostic agent via various imaging methods, wherein said anti-granulocyte antibody is not a murine MN-3 antibody Fab' fragment that is radiolabeled with ^{99m}Tc. Pretargeting methods for improved imaging of granulocytes accumulated in CF are also described. It is further directed to a simple, noninvasive, and effective test that can assess neutrophil delivery to the lower airways of patients with CF and effective test that can assess neutrophil delivery to the lower airways of patients with other neutrophil-mediated lung diseases.



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INTERNATIONAL SEARCH REPORT

International Application No

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<p>A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K47/48 A61K51/04 A61K49/16 A61K49/04 A61K49/22 A61K49/00</p>		
<p>According to International Patent Classification (IPC) or to both national classification and IPC</p>		
<p>B. FIELDS SEARCHED</p>		
<p>Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K</p>		
<p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p>		
<p>Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ</p>		
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p>		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>"Teva-tuteur to market and distribute immunomedics' diagnostic imaging products in Latin America" CANDIDAD E INVESTIGACION AL SERVICIO DE LA SALUD, [Online] 17 May 2002 (2002-05-17), XP002253564 Retrieved from the Internet: <URL:www.tevatuteur.com.ar/nueva/htm/pagin_a_novedades.htm> [retrieved on 2003-09-18] Page 1, paragraph 4</p> <p style="text-align: center;">----- -/--</p>	<p>1-17, 34-37, 73-78</p>
<p><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.</p>		
<p>° Special categories of cited documents :</p>		
<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>		<p>"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</p> <p>"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</p> <p>"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.</p> <p>"&" document member of the same patent family</p>
<p>Date of the actual completion of the international search 19 November 2003</p>		<p>Date of mailing of the international search report - 4. 03. 2004</p>
<p>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</p>		<p>Authorized officer Vadot, P</p>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/02392

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 93/19668 A (IMMUNOMEDICS INC) 14 October 1993 (1993-10-14)</p> <p>Page 12, paragraph 1 and 4</p> <p>Page 25, paragraph 2</p> <p>Page 20, first and last paragraph</p> <p>Page 21, third paragraph</p> <p>Page 22, second paragraph abstract; claims 1,4-6</p> <p>-----</p>	<p>1-17, 34-37, 73-78</p>
Y	<p>KEICHER ET AL: "Omega-3 fatty acids suppress the enhanced production of 5-lipoxygenase products from polymorph neutrophil granulocytes in cystic fibrosis"</p> <p>EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, BLACKWELL SCIENTIFIC PUBLICATIONS, XX, vol. 25, 1995, pages 915-919, XP002108311 ISSN: 0014-2972 abstract</p> <p>-----</p>	<p>1-17, 34-37, 73-78</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/02392

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 1-7,73-78 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
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:

see additional sheet

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.:

1-3, 8-17, 34, 73, 74, 78 (all partially), 4-7, 35-37, 75-77

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

Present claim 1 relates to an extremely large number of possible methods. In fact, the claims contain so many options that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely examples 1 and 2.

Present claims 3-6 relate to an extremely large number of possible methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the methods claimed. 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. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the examples 1 and 2.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3,8-17,34,73,74,78 (partially), 4-7,35-37,75-77

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody; having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a non-pretargeting method and bound to a diagnostic agent being radioactive.

2. claims: 1-3,34,73,74,78 (partially), 8-11,38-41,79-81

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a non-pretargeting method and bound to a diagnostic agent being a radiological contrast agent (paramagnetic ion).

3. claims: 1-3,34,73,74 (partially), 12,13,42,43,82,83

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a non-pretargeting method and bound to a diagnostic agent being radiopaque.

4. claims: 1-3,34,73,74 (partially), 14-17,44-47,88-91

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a non-pretargeting method and bound to a diagnostic agent which is an ultrasound enhancing agent.

5. claims: 1-3,73,74 (partially), 84,85

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a non-pretargeting method and bound to a diagnostic agent which is a fluorescent compound.

6. claims: 1-3,73,74 (partially), 86,87

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a non-pretargeting method and bound to a diagnostic agent which is a chemi- or bioluminescent compound.

7. claims: 1-3,73,74 (partially)

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a non-pretargeting method and bound to a diagnostic agent which is an enzyme.

8. claims: 51-55,92-94 (partially), 56-58,95-97

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a pretargeting method and bound to a diagnostic agent which is radioactive.

9. claims: 51-55,92-94 (partially), 59-62,98-101

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a pretargeting method and bound to a diagnostic agent which is a metal (paramagnetic ion).

10. claims: 51-55,92-94 (partially), 63,64,102,103

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a pretargeting method and bound to a diagnostic agent which is radiopaque.

11. claims: 51,52,54,55,92-94,65,104 (partially), 66,105

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a pretargeting method and bound to a diagnostic agent which is fluorescent.

12. claims: 51,52,54,55,92-94 (partially), 67,68,106,107

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a pretargeting method and bound to a diagnostic agent which is luminescent.

13. claims: 51,52,54,55,92-94 (partially)

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a pretargeting method and bound to a diagnostic agent which is an enzyme.

14. claims: 51-55,92-94 (partially), 69-72,108-111

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody, having affinity toward a neutrophil/granulocyte epitope. The antibody is used in a pretargeting method and bound to a diagnostic agent which is an ultrasound contrast agent.

15. claims: 18-33,48-50

An antibody or fragment thereof; a multivalent, monospecific antibody; a multivalent, multispecific antibody having affinity toward a neutrophil/granulocyte epitope.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/02392

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9319668	A	14-10-1993	US 5776093 A	07-07-1998
			AU 1131899 A	04-03-1999
			AU 3937093 A	08-11-1993
			AU 702089 B2	11-02-1999
			AU 5945896 A	12-09-1996
			AU 5946096 A	12-09-1996
			CA 2133833 A1	14-10-1993
			EP 1384488 A2	28-01-2004
			EP 1375519 A2	02-01-2004
			EP 1393750 A2	03-03-2004
			EP 0637933 A1	15-02-1995
			IL 105302 A	11-04-1999
			IL 127509 A	19-03-2001
			IL 127510 A	11-01-2001
			JP 7508974 T	05-10-1995
			JP 2000226338 A	15-08-2000
			US 2002052594 A1	02-05-2002
			WO 9319668 A1	14-10-1993
			US 6331175 B1	18-12-2001
			US 5776094 A	07-07-1998
			US 5697902 A	16-12-1997
			US 5776095 A	07-07-1998
