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33/68, 33/561, C07K 14/47

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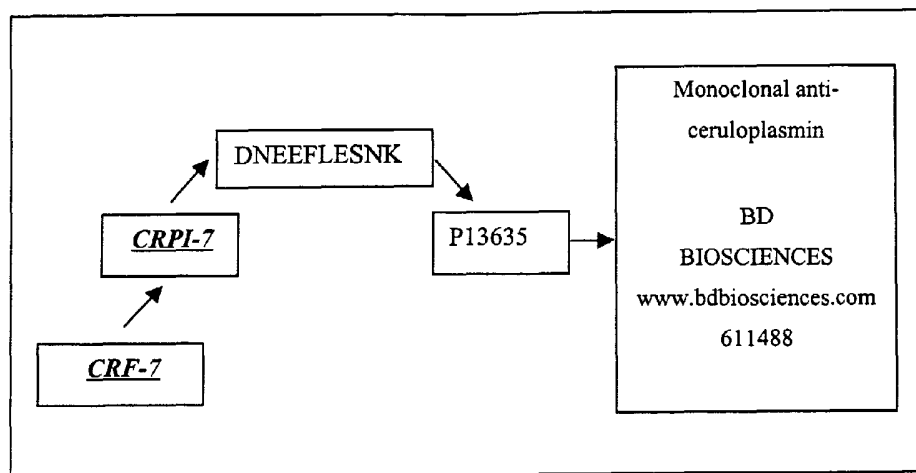
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[Continued on next page]

(54) Title: PROTEINS, GENES AND THEIR USE FOR DIAGNOSIS AND TREATMENT OF CARDIAC RESPONSE

Characterization of a Feature and the relationship of a Feature and Protein Isoform(s)



(57) Abstract: The present invention provides methods and compositions for screening, diagnosis and prognosis of Cardiac Response, for monitoring the effectiveness of Cardiac Response treatment and for drug development. Cardiac Response-Associated Features (CRFs) detectable by two-dimensional electrophoresis of blood are described. The invention further provides Cardiac Response-Associated Protein Isoforms (CRPIs) detectable in biological sample preparations comprising isolated CRPIs, antibodies specific for CRPIs and kits comprising the aforesaid.



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MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
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INTERNATIONAL SEARCH REPORT

PCT/GB 01/05763

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 G01N33/50 G01N33/68 G01N33/561 C07K14/47		
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) IPC 7 G01N		
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)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BOOTH D R ET AL: "A novel variant of transthyretin, 59Thr-->Lys, associated with autosomal dominant cardiac amyloidosis in an Italian family." CIRCULATION. UNITED STATES 15 FEB 1995, vol. 91, no. 4, 15 February 1995 (1995-02-15), pages 962-967, XP002224261 ISSN: 0009-7322 the whole document ---	14-16, 18-22
<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 :		
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 13 December 2002		Date of mailing of the international search report 28. 03. 03
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 Stricker, J-E

INTERNATIONAL SEARCH REPORT

PCT/GB 01/05763

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE MEDLINE 'Online! August 1993 (1993-08) HESSE A ET AL: "Cardiac amyloidosis: a review and report of a new transthyretin (prealbumin) variant." Database accession no. NLM8038017 XP002224264 abstract & BRITISH HEART JOURNAL. ENGLAND AUG 1993, vol. 70, no. 2, August 1993 (1993-08), pages 111-115, ISSN: 0007-0769</p>	14-16
X	<p>OZA V B ET AL: "Synthesis and Evaluation of Anthranilic Acid-Based Transthyretin Amyloid Fibril Inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 1, January 1999 (1999-01), pages 1-6, XP004154767 ISSN: 0960-894X the whole document</p>	30,43
Y	<p>LI XIN PING ET AL: "A two-dimensional electrophoresis database of rat heart proteins." ELECTROPHORESIS, vol. 20, no. 4-5, April 1999 (1999-04), pages 891-897, XP002224262 ISSN: 0173-0835 abstract page 897, column 1, line 9-11</p>	1-13, 24-27, 31-42, 44-50,55
Y	<p>WO 99 47925 A (OXFORD GLYCOSCIENCES UK LTD ;PAREKH RAJESH BHIKHU (GB); PATEL THAK) 23 September 1999 (1999-09-23) claims</p>	1-13, 24-27, 31-42, 44-50,55
Y	<p>RIDKER PAUL M: "Evaluating novel cardiovascular risk factors: Can we better predict heart attacks?" ANNALS OF INTERNAL MEDICINE, vol. 130, no. 11, 1 June 1999 (1999-06-01), pages 933-937, XP002224263 ISSN: 0003-4819 abstract; tables 1,2</p>	1-13, 24-27, 31-42, 44-50,55

INTERNATIONAL SEARCH REPORT

PCT/GB 01/05763

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LABUGGER RALF ET AL: "Extensive troponin I and T modification detected in serum from patients with acute myocardial infarction." CIRCULATION, vol. 102, no. 11, 12 September 2000 (2000-09-12), pages 1221-1226, XP001080442 ISSN: 0009-7322 abstract ---	
A	MANABE T ET AL: "A NONDENATURING PROTEIN MAP OF HUMAN PLASMA PROTEINS CORRELATED WITH A DENATURING POLYPEPTIDE MAP COMBINING TECHNIQUES OF MICRO TWO-DIMENSIONAL GEL ELECTROPHORESIS" ELECTROPHORESIS, WEINHEIM, DE, vol. 20, no. 4/5, April 1999 (1999-04), pages 830-835, XP001070186 ISSN: 0173-0835 abstract -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 01/05763

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9947925 A	23-09-1999	AU 2942999 A	11-10-1999
		CA 2323238 A	23-09-1999
		CN 1300367 T	20-06-2001
		EP 1062509 A	27-12-2000
		JP 2002507723 T	12-03-2002
		ZA 9902079 A	10-10-2000

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 01/05763

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.: 25-29, 36-42, 50, 54
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. Claims Nos.: 51-54
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.:

Invention 1: claims 1-16, 18-22, 24-27, 30-50, 55 (in part)

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.1

Although claims 25-29, 50 and 54 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.

Continuation of Box I.1

Claims Nos.: 25-29, 36-42, 50,54

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery (Claims 36-42)

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy (Claims 25-29,50,54)

Continuation of Box I.2

Claims Nos.: 51-54

Present claims 51-54 relate to a substance and its use defined by reference to a desirable characteristic or property, namely a modulator of a CRPI.

The said claims cover all substances 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 no such substances. 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 substances 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.

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 application No.

PCT/GB 01/05763

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

Invention 1: claims 1-16,18-22,24-27,30-50,
55 (in part)

Method for diagnosis of cardiac response using CRF-1 or
CRPI-1 as a marker.

Inventions 2-190: Claims 1-50, 55 (in part)

Method for diagnosis of cardiac response using CRF-2 or the
isoform CRPI-2, ..., CRF-190 as a marker.