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(54) Title: METHODS FOR THE IDENTIFICATION OF ALL-ANTIGENS AND THEIR USE FOR CANCER THERAPY AND TRANSPLANTATION

(57) Abstract: The present invention delivers a new concept with respect to the broad definition of allo-antigens that drive graft-versus-tumor (GVT) reactions and/ or graft-versus-host disease (GVHD). The new method for the identification of allo-antigens, which has so far been an unresolved technical problem, furthermore calls for new strategies in immunotherapy. Because the analysis of HLA-binding proteins can now be done with alloantigens for which the corresponding aminoacid sequence is known, the present invention also allows the separation of allo-reactive T cells that only recognize tumor cells from those that mediate GVHD. Antigens defined with the new technology are especially useful for diagnosis and vaccination in cancer and transplantation-related diseases.



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06251

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 G01N33/68 G01N33/569		
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) EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 00/42181 A (INTROGENE BV) 20 July 2000 (2000-07-20) claims 3,8-10,42	41 1-11, 28-31
A	----- WO 97/05169 A (UNIV LEIDEN; UNIV VIRGINIA) 13 February 1997 (1997-02-13) the whole document	1-11, 28-31
A	----- WO 01/78708 A (MILLENNIUM PHARM INC) 25 October 2001 (2001-10-25) page 1, line 10 - line 21	1-11, 28-31
A	----- US 2001/006792 A1 (GERMAIN ET AL) 5 July 2001 (2001-07-05) claims 10-14	1-11, 28-31
<input 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 28 October 2004	Date of mailing of the international search report 05/11/2004	
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 Gunster, M	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 27,37-39

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Claims Nos.: 12-26, 32-36, 40 and 42-49

Present claims 12-18 relate to peptides defined by reference to four desirable characteristics or properties, namely 1) that they are allelic variants of antigenic proteins or peptides, 2) that they are encoded by a DNA sequence containing a SNP, 3) that they bind MHC-protein complex to induce an immunogenic response, and 4) that they are not identical to a sequence that induces a GVHD.

The claims cover all peptides having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for none of such peptides.

The peptides disclosed in tables 1-6 cannot be taken into account for the purpose of support and disclosure within the meaning of Articles 5 and 6 PCT, because no sequence listing according to Rule 5.2(a) PCT has been provided. Consequently, no meaningful search can be carried out with regard to the peptides of tables 1-6 (Rule 13ter(c) PCT).

Therefore, 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 peptides 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 not been carried out for claims 12-18.

As the peptides of claims 12-18 could not be searched, the subject-matter of claims 19-26 - relating to cells expressing said peptides, pharmaceutical compositions containing said peptides and uses of said peptides - could also not be searched.

Present claims 32-36 relate to a method of screening for a protein which protein is defined by reference to a desirable characteristic or property namely that it binds HLA.

The claims cover all proteins having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for none of such proteins.

Therefore, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

is impossible. Consequently, the search has not been carried out for claims 32-36.

Present claim 40 relates to monitoring peptides (or antibodies or T cells that bind them) which peptides are defined by reference to a desirable characteristic or property, namely that they are identifiable by the method of claim 32.

The claim covers all peptides having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for none of such peptides.

Therefore, 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 not been carried out for claim 40.

Present claims 42-44 relate to agents defined by reference to a desirable characteristic or property, namely that they selectively enrich the presence of complexes formed by an HLA molecule and amino acid mismatched allelic protein variants representing human cancer allogen.

The claims cover all agents having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for none of such agents.

Therefore, 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 not been carried out for claims 42-44.

As the agents of claims 42-44 could not be searched, the subject-matter of claims 45-47 - relating to a pharmaceutical composition containing said agents and methods comprising administering said agents - could also not be searched.

Present claims 48 and 49 relate to antibodies against a complex comprising a peptide which peptide is defined by reference to a desirable characteristic or property, namely that the peptide binds to the HLA molecule to form an alloantigen/HLA complex.

The claims cover all antibodies against complexes with peptides having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for none of such peptides.

Therefore, 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 not been carried out for claims 48 and 49.

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/06251

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.: 27, 37-39
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. Claims Nos.: 12-26, 32-36, 40 and 42-49
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

Information on patent family members

International Application No

PCT/EP 03/06251

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0042181	A	20-07-2000	EP 1020519 A1	19-07-2000
			AU 2332000 A	01-08-2000
			CA 2359367 A1	20-07-2000
			EP 1141280 A1	10-10-2001
			WO 0042181 A1	20-07-2000

WO 9705169	A	13-02-1997	AU 716907 B2	09-03-2000
			AU 5409996 A	26-02-1997
			CA 2224909 A1	13-02-1997
			EP 0840750 A1	13-05-1998
			JP 11514340 T	07-12-1999
			WO 9705169 A1	13-02-1997
WO 0178708	A	25-10-2001	AU 5349601 A	30-10-2001
			WO 0178708 A1	25-10-2001
			US 2002018776 A1	14-02-2002

US 2001006792	A1	05-07-2001	US 5958712 A	28-09-1999
			US 5837477 A	17-11-1998
			US 2003077286 A1	24-04-2003
			US 2002187148 A1	12-12-2002
			US 2001016198 A1	23-08-2001
			US 5948409 A	07-09-1999
