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(54) Title: VARIANT DOMAINS FOR MULTIMERIZING PROTEINS AND SEPARATION THEREOF

(57) Abstract: The current invention relates to means and methods for producing and isolating immunoglobulin proteins comprising a first and a second immunoglobulin polypeptide, in particular to means and methods for producing, and separating proteins comprising said first and second immunoglobulin polypeptide. By including variations to amino acids, and variant separation domains from a cell producing the desired immunoglobulin protein, a desired immunoglobulin protein as produced can be separated from mixtures of immunoglobulin proteins.

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/00 C07K16/06 C07K16/28 C07K16/36 C07K16/46 ADD.		
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) C07K		
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) EPO-Internal, BIOSIS, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/092925 A2 (XENCOR INC [US]; LAZAR GREGORY ALAN [US]; KARKI SHER BAHADUR [US]) 6 October 2005 (2005-10-06)	6-8, 61-63
Y	claim 7; table 4 -----	11,40-47
X	WO 01/40306 A1 (BIOSITE DIAGNOSTICS INC [US]; GENPHARM INTERNAT [US] ET AL.) 7 June 2001 (2001-06-07)	6-8, 61-63
Y	example 22 -----	11,40-47
X	US 7 135 287 B1 (LONBERG NILS [US] ET AL) 14 November 2006 (2006-11-14)	6-8, 61-63
Y	sequence 168 -----	11,40-47
Y	EP 2 009 101 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]) 31 December 2008 (2008-12-31) claims 1,6,20,21; examples 5,8,12-14 -----	11,40-47
	-/--	
☒ Further documents are listed in the continuation of Box C. ☒ See patent family 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 application or patent 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	Date of mailing of the international search report	
4 February 2021	14/04/2021	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Cilensek, Zoran	

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2020/050298

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAMILLA DE NARDIS ET AL: "A new approach for generating bispecific antibodies based on a common light chain format and the stable architecture of human immunoglobulin G 1", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 292, no. 35, 1 September 2017 (2017-09-01), pages 14706-14717, XP055403663, US ISSN: 0021-9258, DOI: 10.1074/jbc.M117.793497	46,47
A	figures 1-3; tables 1-4	6-8,11, 40-45, 61-63
A	----- WO 2017/213267 A1 (EISAI R&D MAN CO LTD [JP]) 14 December 2017 (2017-12-14) paragraphs [0013], [0091]; figure 7; sequence 23	6-8,11, 40-47, 61-63
A	----- WO 2013/055809 A1 (XENCOR INC [US]; BERNETT MATTHEW J [US] ET AL.) 18 April 2013 (2013-04-18) paragraphs [00420], [00422]; figure 2	6-8,11, 40-47, 61-63
A	----- WO 2016/016299 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 4 February 2016 (2016-02-04) sequences 18,25,28,44,50	6-8,11, 40-47, 61-63
A	----- EP 2 202 245 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]) 30 June 2010 (2010-06-30) the whole document -----	6-8,11, 40-47, 61-63

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☐ forming part of the international application as filed:
- ☐ in the form of an Annex C/ST.25 text file.
- ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
- ☒ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
- ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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:
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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 fees, this Authority did not invite payment of additional fees.
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.:
6-8, 11, 40-47, 61-63(all partially)
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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 6-8, 11, 40-47, 61-63(all partially)

An immunoglobulin CH1 region comprising a variation of an amino acid N159 (EU numbering), preferably to a negatively or positively charged amino acid.
Subject-matter related thereto.

2-11. claims: 6-8, 11, 40-47, 61-63(all partially)

An immunoglobulin CH1 region comprising a variation of an amino acid selected from N201, T120, K147, D148, Y149, V154, A172, Q175, S190, and K213 (EU-numbering), respectively, preferably wherein the variation is selected from

- a neutral amino acid to a negatively charged amino acid;
 - a positively charged amino acid to a neutral amino acid;
 - a positively charged amino acid to a negatively charged amino acid;
 - a neutral amino acid to a positively charged amino acid;
 - a negatively charged amino acid to a neutral amino acid;
- and
- a negatively charged amino acid to a positively charged amino acid.

Subject-matter related thereto.

12. claims: 12(completely); 40-47(partially)

An immunoglobulin CH2 region comprising a variation of amino acid V303.
Subject-matter related thereto.

13-15. claims: 13(completely); 40-47(partially)

An immunoglobulin CH3 region comprising a variation of an amino acid selected from K370, E382 and E388, respectively.
Subject-matter related thereto.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-5, 9, 10, 14-39, 48-60, 64-76(completely); 6-8, 11-13, 40-47, 61-63(partially)

The present application contains a total of 76 claims, with multiple independent claims in the same category.

The person skilled in the art is in the first place confronted with a research project which requires identification of "non-surface exposed residues". In the absence of any unequivocal definition of such residues, the claims cannot therefore be considered clear and cannot be searched.

The claims attempt to define the subject-matter by a "variation" present at a given position of the CH1/CH2/CH3 domain. The claims can thus be construed as product-by-process claims. Since neither the sequence of such domain to which modifications are made nor the numbering system is defined, this subject-matter cannot be searched. In other words, it is not possible to determine whether a CH1/CH2/CH3 domain in suit falls under the scope of the claims and thus a meaningful search cannot be carried out.

While some claims refer to the numbering system (claim 6 refers to the EU numbering), the other independent claims leave this undefined (see for instance claims 48-51 and 70-74), leaving the person skilled in the art in doubt as to which positions should be changed. The Applicant has failed to indicate the numbering system to be followed and such claims cannot be searched.

In the absence of any indication from the Applicant as to which subject-matter should be searched, the search can be carried out on the subject-matter of claims 6-8, 11-13, 40-47 and 61-63, insofar the requirements of clarity and unity of invention are met.

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 Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2020/050298

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Information on patent family members

International application No

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