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Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:  
24 September 2009

(54) Title: METHODS AND MATERIALS FOR TARGETED AFFINITY ENHANCEMENT

(57) Abstract: The present disclosure relates to materials and methods for enhancing the binding affinity of antibodies by introducing a number of targeted amino acid changes in antibody variable domains. The present disclosure provides novel methods of flowcharted amino acid change cycles, of identifying residues as members of unique proximity groups and of determining the degree of conspicuousness of amino acid residues in antibody variable regions. The disclosed methods are useful for the selection of variable region amino acid residues that are candidates for change to produce antibody variable domains with enhanced affinity for their binding partners.



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INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2008/088631

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K16/00 C07K16/30 C07K16/46

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 practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 849 425 B1 (HUSE WILLIAM D [US] ET AL) 1 February 2005 (2005-02-01) column 2, line 38 - line 51 column 4, line 1 - column 5, line 3 column 10, line 6 - line 64 column 12, line 47 - column 14, line 52 column 17, line 52 - column 18, line 24 column 19, line 41 - column 20, line 13 column 21, line 4 - line 42	1-95
Y	WO 98/17792 A (SUNOL MOLECULAR CORP [US]) 30 April 1998 (1998-04-30) page 4, line 11 - page 6, line 4 page 7, line 22 - page 10, line 12 page 15, line 6 - line 28 page 16, line 10 - page 24, line 25 claims 1-10; examples 2,4,6-8	1-95
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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 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

24 March 2009

Date of mailing of the international search report

20/07/2009

Name and mailing address of the ISA/

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2008/088631

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/020267 A1 (FUH GERMAINE [US] ET AL) 25 January 2007 (2007-01-25) paragraphs [0020] - [0022], [0065] - [0069], [0118], [0119], [0143], [0175] - [0211], [0281] - [0285]; examples 1-11 -----	1-95
Y	RAJPAL A ET AL: "A general method for greatly improving the affinity of antibodies by using combinatorial libraries" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC.; US, vol. 102, no. 24, 1 June 2005 (2005-06-01), pages 8466-8471, XP002347095 ISSN: 0027-8424 the whole document -----	1-95
Y	US 5 766 886 A (STUDNICKA GARY M [US] ET AL) 16 June 1998 (1998-06-16) the whole document, especially column 7, line 31 - column 10, line 22; figures 16A, 16B -----	1-95
Y	CHOTHIA C ET AL: "Canonical structures for the hypervariable regions of immunoglobulins" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 196, no. 4, 20 August 1987 (1987-08-20), pages 901-917, XP024010426 ISSN: 0022-2836 [retrieved on 1987-08-20] the whole document, especially table 6 -----	1-95
A	MACCALLUM R M ET AL: "Antibody-antigen interactions: Contact analysis and binding site topography" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 262, no. 5, 1 January 1996 (1996-01-01), pages 732-745, XP002242391 ISSN: 0022-2836 cited in the application the whole document -----	

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2008/088631

## 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:
  
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 allsearchable 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.:
  
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.:

see additional sheet(s)

### 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: 1-95

A method for enhancing the binding affinity of an antibody variable domain to a binding partner as recited in present claims 1, 20, 39, 58 and 77.

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2. claims: 96-113

A method for enhancing the binding affinity of an antibody variable domain to a binding partner as recited in present claim 96.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2008/088631
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
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