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**WO 01/098365 A3**

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60/212,998 21 June 2000 (21.06.2000) US
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



**WO 01/098365 A3**

(54) Title: PEPTIDE AND POLYPEPTIDE INHIBITORS OF COMPLEMENT C1S

(57) Abstract: The complement system plays an important role in providing resistance to infections and in the pathogenesis of tissue injury. Yet an inappropriate activation of complement can result in a variety of disorders. The present invention provides C1s catalytic site-directed moieties, C1s exosite binding moieties, and bivalent polypeptide inhibitors comprising such moieties, which can be used to treat conditions characterized by inappropriate complement activation.

INTERNATIONAL SEARCH REPORT

Interr. I Application No  
PCT/US 01/19405

<p><b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 C07K14/815 A61K38/58 A61P29/00</p> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>											
<p><b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K A61K A61P</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, BIOSIS</p>											
<p><b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b></p> <table border="1"> <thead> <tr> <th>Category °</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>WO 99 36439 A (BIO DISCOVERY LTD ;FINNEY SARAH (GB); SEALE LISA (GB)) 22 July 1999 (1999-07-22) the whole document</td> <td>1-5,9-23</td> </tr> <tr> <td>A</td> <td>--- LIN W-H ET AL: "RECOGNITION OF SUBSTRATES BY TYROSYLPROTEIN SULFOTRANSFERASE DETERMINATION OF AFFINITY BY ACIDIC AMINO ACIDS NEAR THE TARGET SITES" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 5, 1992, pages 2876-2879, XP001094163 ISSN: 0021-9258 the whole document --- -/--</td> <td>1-5,9-23</td> </tr> </tbody> </table>			Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	WO 99 36439 A (BIO DISCOVERY LTD ;FINNEY SARAH (GB); SEALE LISA (GB)) 22 July 1999 (1999-07-22) the whole document	1-5,9-23	A	--- LIN W-H ET AL: "RECOGNITION OF SUBSTRATES BY TYROSYLPROTEIN SULFOTRANSFERASE DETERMINATION OF AFFINITY BY ACIDIC AMINO ACIDS NEAR THE TARGET SITES" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 5, 1992, pages 2876-2879, XP001094163 ISSN: 0021-9258 the whole document --- -/--	1-5,9-23
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<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> <table border="0"> <tr> <td style="vertical-align: top;"> <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> </td> <td style="vertical-align: top;"> <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>"&amp;" document member of the same patent family</p> </td> </tr> </table>			<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>"&amp;" document member of the same patent family</p>							
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<p>Date of the actual completion of the international search <b>18 September 2002</b></p>		<p>Date of mailing of the international search report <b>31. 01. 03</b></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 <b>Lüdemann, S</b></p>									

## INTERNATIONAL SEARCH REPORT

Inter... al Application No

PCT/US 01/19405

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>YUNG YU C: "THE COMPLETE EXON-INTRON STRUCTURE OF A HUMAN COMPLEMENT COMPONENT C4A GENE DNA SEQUENCES, POLYMORPHISM, AND LINKAGE TO THE 21-HYDROXYLASE GENE" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 146, no. 3, 1 February 1991 (1991-02-01), pages 1057-1066, XP000993298 ISSN: 0022-1767 the whole document</p> <p style="text-align: center;">---</p>	1-5,9-23
A	<p>MATHIAS P ET AL: "MUTANTS OF COMPLEMENT COMPONENT C3 CLEAVED BY THE C4-SPECIFIC C1S PROTEASE" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 89, no. 17, 1 September 1992 (1992-09-01), pages 8125-8129, XP002017958 ISSN: 0027-8424 the whole document</p> <p style="text-align: center;">-----</p>	1-5,9-23

INTERNATIONAL SEARCH REPORT

international application No.  
PCT/US 01/19405

**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.: 22,23  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 20-23 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 or composition.
- 2.  Claims Nos.: 1,9  
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.:  
1-5, 9-17, 18 (partially), 19, 20-23 (partially)

**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.: 1,9

Present claims 1-3, 5,9 and 16 and dependent claims lack clarity within the meaning of Art. 6 PCT to such extent as to render a meaningful search of the claims impossible, the reason being the following:

(i) There is an inconsistency between the general formula given in said claims and the corresponding seq. id's cited in the same claims, e.g. claim 1 states the general formula

P-N-[DE](2)-[YX1X2X3]-[DE](2)-[YX1X2X3]-[DE]-[YX1X2X3]-[DE](1,2) and seq. id 127 corresponds to the seq:

ProAsnXaaXaaTyrXaaXaaXaaXaaXaaTyrXaaXaaXaaXaaTyrXaaXaaXaaXaaXaa, with the def's for Xaa as given in the seq listing. The inconsistency is to be found in the fact that the amino acids in brackets are defined as alternative residues, i.e. [DE](2) appears to correspond to 2 residues, which can be either D or E. Consequently, [YX1X2X3] is to be interpreted as either Y or X1 or X2 or X3, i.e. 1 residue which can alternatively be Y or X1 or X2 or X3, which is in contrast to the sequence listing.

Furthermore, the applicant is informed that seq. id's 2-27 (as give in table 1) do also not correspond to the building principle of claim 1, since the 6th amino acid is a single E. This would rather correpond to the building principle: P-N-[DE](2)-[YX1X2X3]-[DE](1,2)...Therefore claim 4 cannot be considered to lie within the scope of claim 1.

(ii) The applicant is furthermore informed that the term "acceptable" (the terms in square brackets rather refer to "alternative" residues) is not clear within the meaning of Art. 6 PCT.

Consequently, the search has been carried out for those parts of the application which do appear to be clear namely the example sequences of table 1 combined with the formula of claims 1 and 3.

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 1-5,9-17, 18 (partially), 19, 20-23 (partially)

C1s exosite binding moiety peptides as characterized by the formulas of claims 1-5

2. Claims: 6-8,18 (partially), 20-23 (partially)

C1s catalytic site directed peptides with the general formula given in claim 6.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter	al Application No
PCT/US 01/19405	

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9936439	A	22-07-1999	AU	2068599 A	02-08-1999
			CA	2318358 A1	22-07-1999
			EP	1045862 A1	25-10-2000
			WO	9936439 A1	22-07-1999
			JP	2002508953 T	26-03-2002
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