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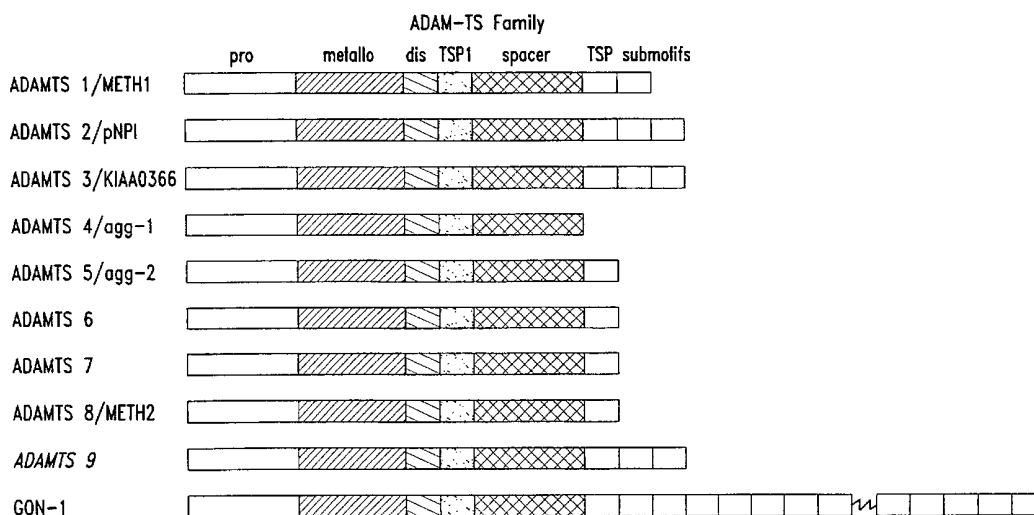
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(54) Title: METALLOPROTEINASES AND METHODS OF USE THEREFOR



(57) Abstract: Members of the ADAMTS family of metalloproteinases are provided, along with variants thereof and agents that modulate an activity of such metalloproteinases. The polypeptides and modulating agents may be used, for example, in the prevention and treatment of a variety of conditions associated with undesirable levels of metalloproteinase activity.



WO 00/53774 A3

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/06237

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 C12N15/57 C12N15/63 C12N9/64 A61K38/48 C07K16/40  
C12Q1/37

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 C12N A61K C07K C12Q

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	WO 98 55643 A (KUREHA CHEMICAL INDUSTRY CO., LTD.) 10 December 1998 (1998-12-10)  & EP 1 004 674 A (KUREHA CHEMICAL INDUSTRY CO., LTD.) 31 May 2000 (2000-05-31)  ---  -/--	1,3-11, 17-21, 28,29, 31,32

Further documents are listed in the continuation of box C.

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

29 June 2000

Date of mailing of the international search report

13.10.00

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

P./US 00/06237

## 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>KOUJI KUNO ET AL.: "Molecular cloning of a gene encoding a new type of metalloproteinase-disintegrin family protein with thrombospondin motifs as an inflammation associated gene"            JOURNAL OF BIOLOGICAL CHEMISTRY,            vol. 272, no. 1,            3 January 1997 (1997-01-03), pages            556-562, XP002076038            MD US            cited in the application            abstract            page 558, left-hand column, paragraph 2            -page 559, left-hand column, paragraph 2;            figure 2            page 559, left-hand column, paragraph 4            page 561, right-hand column, last            paragraph -page 562, left-hand column,            paragraph 1</p>	<p>1,3-11,            17,20,            21,28,            29,31,32</p>
X	<p>---            KOUJI KUNO ET AL.: "The exon/intron organization and chromosomal mapping of the mouse ADAMTS-1 gene encoding an ADAM family protein with TPS motifs"            GENOMICS,            vol. 46, no. 3,            15 December 1997 (1997-12-15), pages            466-471, XP000922766            cited in the application            page 466, right-hand column, paragraph 2            page 468, left-hand column, paragraph 5            -page 470, right-hand column, paragraph 2;            figure 3</p>	1,3-11
X	<p>---            BOR LUEN TANG ET AL.: "ADAMTS: A novel family of proteases with an ADAM protease domain and thrombospondin 1 repeats"            FEBS LETTERS, [Online]            vol. 445, 26 February 1999 (1999-02-26),            pages 223-225, XP002141413            AMSTERDAM NL            Retrieved from the Internet:            &lt;URL:http://gdbwww.gdb.org/gdb-bin/genera/            genera/hgd/Gene?!action=query&amp;displayName=            ADAMTS2&gt; [retrieved on 2000-06-22]            page 223, left-hand column, paragraph 2            -page 225, right-hand column, paragraph 2;            figure 2</p>	1,3-11
X	<p>---            EMBL Database Entry AI378857            Accession number AI378857; 28 January 1999            ROBERT STRAUSBERG:"tc67h11.x1            Soares_NhHMPu_S1 Homo sapiens cDNA clone"            XP002141415            the whole document            ---</p>	1,5-7
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## INTERNATIONAL SEARCH REPORT

International Application No

P ./US 00/06237

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>FRANCISCA VÁZQUEZ ET AL.: "METH-1, a human ortholog of ADAMTS-1, and METH-2 are members of a new family of proteins with angio-inhibitory activity"            JOURNAL OF BIOLOGICAL CHEMISTRY,            vol. 274, no. 33,            13 August 1999 (1999-08-13), pages            23349-23357, XP002141414            MD US            abstract            page 23349, right-hand column, paragraph 2            -page 23350, left-hand column, paragraph 1            page 23351, left-hand column, paragraph 1            -page 23352, right-hand column, paragraph 2; figure 1            page 23353, left-hand column, paragraph 4            -page 23357, left-hand column, paragraph 2            -----</p>	1,3-6, 8-11

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 00/06237

## 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.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 22-27, 30, 33-35  
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.:  
Claims 1-12, 17-35 (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.: 22-27, 30, 33-35

Present claims 22-27, 30 and 33-35 relate to an agent defined by reference to a desirable characteristic or property, namely decreasing or modulating expression or activity of an ADAMTS protein. The claims cover all agents having this characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any specific example of such agents. 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 agent 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, no search has been carried out for claims 22-27, 30 and 33-35.

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

## 1. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:1 or 23 encoding ADAMTS-2; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-2 polypeptide; ADAMTS-2 polypeptide of SEQ ID NO:2 or 24 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-2 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-2 protein

## 2. Claims: 36 and partially 1-12, 17-35

Polynucleotide of SEQ ID NO:3, 15 or 17 encoding ADAMTS-4; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-4 polypeptide; ADAMTS-4 polypeptide of SEQ ID NO:4, 16 or 18 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-4 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-4 protein

## 3. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:9 or 25 encoding ADAMTS-3; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-3 polypeptide; ADAMTS-3 polypeptide of SEQ ID NO:10 or 26 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-3 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-3 protein

## 4. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:13 or 21 encoding ADAMTS-5; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-5 polypeptide; ADAMTS-5 polypeptide of SEQ ID NO:13 or 21 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-5 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-5 protein

## 5. Claims: Partially, 1, 3-12, 17-35

Polynucleotide encoding an ADAMTS-9 protein of SEQ ID NO:27;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-9 polypeptide; ADAMTS-9 polypeptide of SEQ ID NO:27 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-9 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-9 protein

6. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:6 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:6 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

7. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:8 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:8 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

8. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:12 or 20 or variants thereof; ADAMTS polypeptide of SEQ ID NO:12 or 20 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

F . / US 00/06237

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9855643 A	10-12-1998	EP 1004674 A JP 11046781 A	31-05-2000 23-02-1999
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