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| 61/782,613 | 14 March 2013 (14.03.2013) | US |
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

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- 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))
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(54) Title: VARIANTS OF TISSUE INHIBITOR OF METALLOPROTEINASE TYPE THREE (TIMP-3), COMPOSITIONS AND METHODS

(57) Abstract: There are disclosed TIMP-3 mutants, variants and derivatives, nucleic acids encoding them, and methods of making and using them.

INTERNATIONAL SEARCH REPORT

International application No PCT/US2014/026811
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A. CLASSIFICATION OF SUBJECT MATTER INV. C07K14/435 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, Sequence Search		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LANGTON KEVIN P ET AL: "Localization of the functional domains of human tissue inhibitor of metalloproteinases-3 and the effects of a Sorsby's fundus dystrophy mutation", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 273, no. 27, 3 July 1998 (1998-07-03), pages 16778-16781, XP002417706, ISSN: 0021-9258, DOI: 10.1074/JBC.273.27.16778 Abstract, Figs. 1, 4-5, p. 16778 col. 2 li. 6-9, p. 16778 col. 2 li. 25-26, p. 16779 col. 1 li. 1-4, p. 16779 col. 1 li.18-53, p. 16779 col. 2 li. 59-69, p. 16780 col. 1 li. 30-p. 16780 col. 2 li. 6, p. 16780 col. 2 li. 19-24, p. 16780 col. 2 li. 29-33, p. 16781 col. 12 li. 3-6 -/--	1,4-19
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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	
26 August 2015	02/09/2015	
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 Landré, Julien	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/026811

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>-----</p> <p>Anonymous: "Tissue inhibitor of metalloproteinase 3 (Predicted) - TIMP3 - Rhinolophus ferrumequinum (Greater horseshoe bat)",</p> <p>10 June 2008 (2008-06-10), XP055122276, Retrieved from the Internet: URL:http://www.uniprot.org/uniprot/B2KII1 [retrieved on 2014-06-10]</p>	4-8
Y	the whole document	1,9-19
X	<p>-----</p> <p>DATABASE UniProt [Online]</p> <p>6 March 2013 (2013-03-06), "SubName: Full=Metalloproteinase inhibitor 3;" XP002725522, retrieved from EBI accession no. UNIPROT:L5KF25 Database accession no. L5KF25</p>	4-8
Y	the whole document	1,9-19
X	<p>-----</p> <p>WO 2008/109433 A2 (CLEVELAND CLINIC FOUNDATION [US]; ANAND-APTE BELA [US]) 12 September 2008 (2008-09-12)</p>	4-8
Y	<p>0039], [0043], [0052], [0058], [0064], [0071], [00105], [00108], [00136], [00138], [00141]-[00142], [00147], [00157]-[00159], [00172], [00244], [00255], [00261], [00265], [00281]-[00282], [00295], [00307]-[00309]</p>	1,9-19
Y	<p>-----</p> <p>EP 0 648 838 A1 (AMGEN INC [US]) 19 April 1995 (1995-04-19) Abstract, Fig. 1, p. 4, li. 41-47, p. 7 li. 57-p. 8 li. 12, p. 9 li. 9-11, p. 9 li. 39-41, p. 10 li. 35-52, p. 11 li. 47-57, p. 15 li. 46-p. 18 li. 46, examples 2, 4</p>	1,9-19
Y	<p>-----</p> <p>WO 2007/016482 A2 (IMP INNOVATIONS LTD [GB]; NAGASE HIDEAKI [GB]; BREW KEITH [US]) 8 February 2007 (2007-02-08) p. 1 li. 30-p. 2 li. 2, p. 3 li. 14-19, p. 4 li. 27, p. 5 li. 2-5, p. 8 li. 5-8, p. 8 li. 19-24, p. 9 li. 19-20, p. 12 li. 20-23, p. 15 li. 25-30, example 1</p> <p>-----</p>	1,9-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/026811

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 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.:
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, 4-19(all partially)

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2014/026811

Patent document cited in search report	A2	Publication date		Patent family member(s)	Publication date
WO 2008109433	A2	12-09-2008		EP 2136831 A2	30-12-2009
				US 2010099611 A1	22-04-2010
				WO 2008109433 A2	12-09-2008

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				US 2009318342 A1	24-12-2009
				WO 2007016482 A2	08-02-2007

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, 4-19(all partially)

TIMP-3 muteins, vectors, cells and a method of producing TIMP-3 muteins, composition, method of treatment wherein the mature region is at least 95% identical to SEQ. ID. No. 2 and the at least mutation is at position 45.

2-8. claims: 1, 4-19(all partially)

TIMP-3 muteins, vectors, cells and a method of producing TIMP-3 muteins, composition, method of treatment wherein the mature region is at least 95% identical to SEQ. ID. No. 2 and the at least mutation is each of the other positions.

9. claims: 2, 3(completely); 1, 4-19(partially)

TIMP-3 muteins, vectors, cells and a method of producing TIMP-3 muteins, composition, method of treatment wherein the mature region is at least 95% identical to SEQ. ID. No. 2 and the at least mutation is at position 57.

10-42. claims: 1, 4-19(all partially)

TIMP-3 muteins, vectors, cells and a method of producing TIMP-3 muteins, composition, method of treatment wherein the mature region is at least 95% identical to SEQ. ID. No. 2 and the at least mutation is each of the other positions.
