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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

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Published:

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(88) Date of publication of the international search report:

4 June 2015

(54) Title: MATRIX METALLOPROTEINASE SUBSTRATES AND OTHER CLEAVABLE MOIETIES AND METHODS OF USE THEREOF

FIGURE 1A

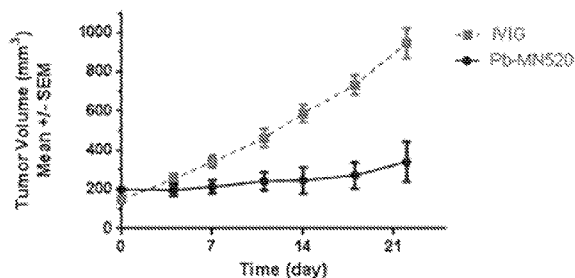
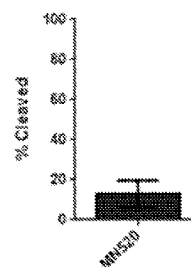


FIGURE 1B



(57) Abstract: The invention relates generally to polypeptides that include a cleavable moiety that is a substrate for at least one matrix metalloprotease (MMP), to activatable antibodies and other larger molecules that include the cleavable moiety that is a substrate for at least one MMP protease, and to methods of making and using these polypeptides that include a cleavable moiety that is a substrate for at least one MMP protease in a variety of therapeutic, diagnostic and prophylactic indications.

WO 2015/048329 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/057523

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 C07K16/18 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)
A61K 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	WO 2010/081173 A2 (CYTOMX THERAPEUTICS LLC [US]; STAGLIANO NANCY E [US]; WEST JAMES W [US] 15 July 2010 (2010-07-15) Whole doc., in particular para. [0174, Table 3, 0123, 0026, 0018, 00144, 00145, 00158]	1,2,4,5, 20,22-41
X	US 2013/150558 A1 (WILLIAMS JOHN C [US] ET AL) 13 June 2013 (2013-06-13) Whole doc., in particular example 2, Fig. 8, Seq.3, 5	1,2,4,5, 20,22-41
X	WO 2009/025846 A2 (UNIV CALIFORNIA [US]; CYTOMX LLC [US]; DAUGHERTY PATRICK SEAN [US]; ST) 26 February 2009 (2009-02-26) Whole doc., in particular para. [0173-0175, 00213], examples 9-10, Fig.38-40	1,2,4,5, 20,22-41
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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 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)

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"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 2 April 2015	Date of mailing of the international search report 10/04/2015
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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 Roscoe, Richard
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/057523

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	WO 2014/052462 A2 (CYTOMX THERAPEUTICS INC [US]) 3 April 2014 (2014-04-03) Whole doc., in particular para. [00060-00061; esp. Seq. 183] -----	1,2,4,5, 20,22-41
X	TURK B E ET AL: "Determination of protease cleavage site motifs using mixture-based oriented peptide libraries", NATURE BIOTECHNOLOGY, NATURE PUBLISHING GROUP, NEW YORK, NY, US, vol. 19, no. 7, 1 July 2001 (2001-07-01), pages 661-667, XP002254824, ISSN: 1087-0156, DOI: 10.1038/90273 the whole document -----	1,2,4,5, 20,22-25
X	KRIDEL S J ET AL: "Substrate hydrolysis by matrix metalloproteinase-9", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 276, no. 23, 1 June 2001 (2001-06-01), pages 20572-20578, XP002963030, ISSN: 0021-9258, DOI: 10.1074/JBC.M100900200 the whole document -----	1,2,4,5, 20,22-25
X	DATABASE UniProt [Online] 3 March 2009 (2009-03-03), "SubName: Full=Uncharacterized protein {ECO:0000313 EMBL:ACL49164.1}"; XP002734545, retrieved from EBI accession no. UNIPROT:B8J087 Database accession no. B8J087 sequence -----	1,2,5, 20,22-25
X	DATABASE UniProt [Online] 1 May 1999 (1999-05-01), "RecName: Full=Cytochrome b {ECO:0000256 RuleBase:RU000300}; Flags: Fragment"; XP002734546, retrieved from EBI accession no. UNIPROT:Q9ZZR8 Database accession no. Q9ZZR8 sequence ----- -/--	1,2,5, 20,22-25

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/057523

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>DATABASE Geneseq [Online]</p> <p>9 April 2001 (2001-04-09), "B. brevis tyrocidin synthetase activating domain #9.", XP002734547, retrieved from EBI accession no. GSP:AAB46481 Database accession no. AAB46481 sequence</p> <p>-----</p>	1,2,5, 20,22-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/057523

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.:

5(completely); 1, 2, 4, 20, 22-41(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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 5(completely); 1, 2, 4, 20, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM5 (Seq. ID Nos. 353-363, 364-370, 19)

2. claims: 6(completely); 1, 2, 4, 20, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM6 (Seq. ID Nos. 372-375, 379-393)

3. claims: 7(completely); 1, 2, 4, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM6A (Seq. ID Nos. 376-378)

4. claims: 8(completely); 1, 2, 4, 20, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM7 (Seq. ID Nos. 395-401, 403-408)

5. claims: 9(completely); 1, 2, 4, 20, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM8 (Seq. ID Nos. 411-419, 420-424)

6. claims: 10(completely); 1, 2, 4, 20, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM9 (Seq. ID Nos. 426-433, 434, 435)

7. claims: 11(completely); 1, 2, 4, 20, 22-41(partially)

Subject-matter relating to peptides comprising cleavable

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM10 (Seq. ID Nos. 437-449,450-452)

8. claims: 12(completely); 1, 2, 4, 20, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM11 (Seq. ID Nos. 454-456,457)

9. claims: 13(completely); 1, 2, 4, 20, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM12 (Seq. ID Nos. 459-469,470-472)

10. claims: 14(completely); 1, 2, 4, 20, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM13 (Seq. ID Nos. 475-482,474,483)

11. claims: 15(completely); 1, 2, 4, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM8A (Seq. ID Nos. 487-495)

12. claims: 16(completely); 1, 3, 4, 22-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM1 (Seq. ID Nos. 318-323)

13. claims: 17(completely); 1, 3, 4, 21-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM2 (Seq. ID Nos. 325-328)

14. claims: 18(completely); 1, 3, 4, 21-41(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM3 (Seq. ID Nos. 330-339)

15. claims: 19(completely); 1, 3, 4, 21-41(partially)

Subject-matter relating to peptides comprising cleavable moieties (i.e. protease substrate sites) wherein the sites are defined by an amino acid sequence according to core consensus (CM) sequence CM4 (Seq. ID Nos. 341-351)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2014/057523

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