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**WO 2005/100556 A3**

(54) Title: CLEAVAGE OF VEGF AND VEGF RECEPTOR BY WILD-TYPE AND MUTANT PROTEASES

(57) Abstract: Disclosed herein are methods for creating and using mutein proteases with altered specificity for the target molecules they cleave. The invention further discloses methods of using wild-type and mutein granzyme B to target VEGFR proteins to treat diseases, such as cancer. Cleaving VEGFR at certain substrate sequences with wild-type and mutein granzyme B proteases is a method for treating pathologies associated with angiogenesis.

**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/US2005/012243

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> C12N9/64  According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) C12N  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, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data, Sequence Search		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2004/031733 A (CATALYST BIOSCIENCES; NGUYEN, JACK; THANOS, CHRIS; RUGGLES, SANDRA, WA) 15 April 2004 (2004-04-15) *Whole document, in particular: Abstract, tables 3-5, examples and claims*  ----- -/--	3-7, 21-29
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <span style="margin-left: 200px;"><input checked="" type="checkbox"/> Patent family members are listed in annex.</span>		
° 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	Date of mailing of the international search report	
15 November 2005	01/12/2005	
Name and mailing address of the ISA	Authorized officer	
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	BULCAO DE MELO BARRE	

## INTERNATIONAL SEARCH REPORT

Internat

Application No

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## 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>RUGGLES SANDRA WAUGH ET AL:  "Characterization of structural determinants of granzyme B reveals potent mediators of extended substrate specificity"  JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 279, no. 29, 16 July 2004 (2004-07-16), pages 30751-30759, XP002304824  ISSN: 0021-9258  *Whole document, in particular: Abstract and figures 2-5*</p>	3,4
A	<p>-----  HARRIS J L ET AL: "Definition and redesign of the extended substrate specificity of granzyme B"  JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 273, no. 42, 16 October 1998 (1998-10-16), pages 27364-27373, XP002296677  ISSN: 0021-9258  cited in the application  *Whole document, in particular: Abstract*</p>	3,4
A	<p>-----  WAUGH S M ET AL: "The structure of the pro-apoptotic protease granzyme B reveals the molecular determinants of its specificity"  NATURE STRUCTURAL BIOLOGY, NEW YORK, NY, US, vol. 7, no. 9, September 2000 (2000-09), pages 762-765, XP002307284  ISSN: 1072-8368  cited in the application  *Whole document, in particular: Abstract*</p>	3,4
A	<p>-----  FRIEDRICH R ET AL: "Catalytic domain structures of MT-SP1/matriptase, a matrix-degrading transmembrane serine proteinase"  JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 277, no. 3, 18 January 2002 (2002-01-18), pages 2160-2168, XP002244714  ISSN: 0021-9258  cited in the application  *Whole document, in particular: Abstract*</p>	5-7
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INTERNATIONAL SEARCH REPORT

Intern | Application No  
PCT/US2005/012243

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>US 2002/022243 A1 (HARRIS JENNIFER L ET AL) 21 February 2002 (2002-02-21)                      cited in the application                      *Whole document, in particular: Abstract and claims*                      -----</p>	3-7

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2005/012243

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
- a. type of material
- a sequence listing
- table(s) related to the sequence listing
- b. format of material
- in written format
- in computer readable form
- c. time of filing/furnishing
- contained in the international application as filed
- filed together with the international application in computer readable form
- furnished subsequently to this Authority for the purpose of search
2.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

# INTERNATIONAL SEARCH REPORT

In... onal application No.  
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## Box 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.: 21-29  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 21-29 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/composition.
2.  Claims Nos.: 1, 2, 8-20  
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 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:

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.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

Continuation of Box II.1

Although claims 21-29 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/composition.

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Continuation of Box II.2

Claims Nos.: 1, 2, 8-20

Claims 1, 2 and 8-20 attempt to define the mutein serine protease/granzyme B/MT-SP1 merely by reference to a result to be achieved, namely to cleave a target polypeptide, such as VEGF or VEGF receptor, contrary to the requirements of clarity of Article 6 PCT. The result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. This lack of clarity is such as to render a meaningful search of the claimed subject-matter impossible. Consequently, no search report can be established for the present claims 1, 2 and 8-20.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern

Application No

PCT/US2005/012243

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004031733 A	15-04-2004	AU 2003282724 A1 CA 2501295 A1	23-04-2004 15-04-2004
US 2002022243 A1	21-02-2002	AU 6509201 A WO 0194332 A1 US 2004175777 A1	17-12-2001 13-12-2001 09-09-2004