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(54) Title: METHODS AND COMPOSITIONS RELATED TO MUTANT KUNITZ DOMAIN I OF TFPI-2

(57) Abstract: Disclosed are methods and compositions relating to plasmin inhibition.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/62723

A. CLASSIFICATION OF SUBJECT MATTER
 IPC: **C12N 15/09**(2006.01);**C12P 21/06**(2006.01);**C12N 15/00**(2006.01);**A61K 38/48**(2006.01);**38/00**(2006.01);**C07K 4/00**(2006.01)
 USPC: 435/69.1,320.1;424/94.64;514/12;530/300
 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)
 U.S. : 435/69.1,320.1;424/94.64;514/12;530/300

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)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,103,499 (MARKLAND et al.) 15 August 2000 (15.08.200), abstract; column 10, lines 55-58; column 14, lines 31-33, 56-60.	1,3,8 ----- 2,4,5,8,22
Y	CHAND et al. Structure-funtions analysis of the reactive site in the first Kunitz-type domain of human tissue factor pathway inhibitor-2. The Journal of Biological Chemistry. 23 April 2004, Vol 279, No.17, pages 17500-17507, especially page 17501 and Table 1.	2,4,5,7
Y	US 2004/0229312 A1 (BOUGLELERET et al.) 18 November 2004 (18.11.2004), especially page 8, paragraph 73.	2,4,5,7
Y	SCHMIDT et al. Crystal Struture of Kunitz domain 1 (KD1) of tissue factor pathway inhibitor-2 in comples with trypsin. The Journal of Chemistry. 29 July 2005, Vol 280, No. 30, 27832-27838, especially pages 27833, left column, lines 14-16, 27837, right column, last paragraph.	2,4,5,7

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

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Name and mailing address of the ISA/US: Mail Stop PCT, Attn: ISA/US, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, Facsimile No. (571) 273-3201
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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:
Please See Continuation 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 additional fees, this Authority did not invite payment of any 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.: 1-8 and 22

- 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.

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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.
Y	US 2005/0222023 A1 (HAUSER et al.) 6 October 2005 (06.10.2005), abstract, Table 4.	22

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contain the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under the PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional fees must be paid.

Group I, claims 1-8 and 22 are drawn to a polypeptide comprising SEQ ID NO:1 with one or more amino acid mutations.

Group II, claim 9 is drawn to a nucleic acid encoding the polypeptide.

Group III, claims 10 -19 and 24 are drawn to method of treating a subject in need of inhibition of a plasmin activity by administering to the subject the polypeptide.

Group IV, claim 20 is drawn to a method of identifying a plasmin inhibitor.

Group V, claim 21 is drawn to a method of inhibiting plasmin in a subject in need by administering to the subject the nucleic acid encoding the polypeptide.

Group VI, claim 23 is drawn to a transgenic animal comprising the nucleic acid encoding the polypeptide.

The International Searching Authority considers that the international applications does not comply with the requirement of unity of invention (PCT Rule 13.1, 13.2 and 13.3) for the reason indicated below:

The inventions are linked by the technical feature of mutations in the domain I of TFPI-2 that is plasmin inhibitor. However, this is not special because it does not constitute an advance over the prior art. Markland et al. (US6,103,499) teach a plasmin inhibitor derived from Human TFPI-2 domain 1 that contains substitutions Y11T, L17R, L18F, L19D, and R31E (column 10, lines 55-60).

Furthermore, each Group involves methods not required by the other.

Group I, a first product, requires substitutions in positions 10, 11, 16, 17 and 46 of the polypeptide of SEQ NO: 1, not required by any other group.

Group II, a second product, requires a nucleic acid, not required by any other group.

Group III, a first method, requires multiple plasmin inhibitor applications, not required by any other group.

Group IV, a second method, requires modeling a crystal structure of plasmin, not required by any other group.

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Group V, a third method, requires the nucleic acid to the protein directed to inhibiting plasmin, not required by any other group.

Group VI, a third product, requires a transgenic animal, not required by any other group.

Continuation of B. FIELDS SEARCHED Item 3:
USPAT, US-PGPUB, BIOSIS, CAPLUS, MEDLINE
Search terms: KDI, Kunitz domain, plasmin, inhibitor