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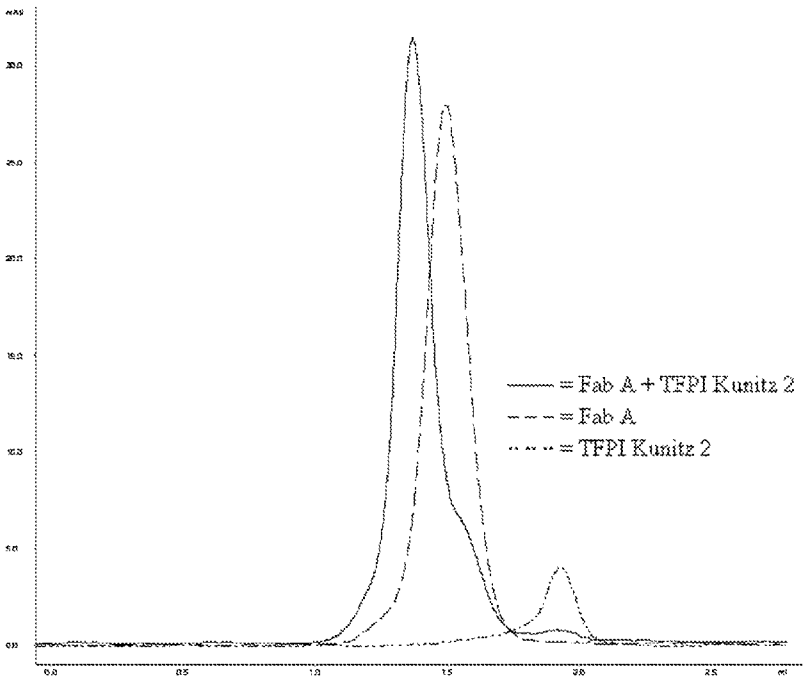
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[Continued on next page]

(54) Title: MONOCLONAL ANTIBODIES AGAINST TISSUE FACTOR PATHWAY INHIBITOR (TFPI)

Figure 1



(57) Abstract: Isolated monoclonal antibodies that bind to specific epitopes of human tissue factor pathway inhibitor (TFPI) and the isolated nucleic acid molecules encoding them are provided. Pharmaceutical compositions comprising the anti-TFPI monoclonal antibodies and methods of treating deficiencies or defects in coagulation by administration of the antibodies are also provided.

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SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

Published:

— *with international search report (Art. 21(3))*

— *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))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
13 December 2012

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/31538

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/18, A61K 39/395 (2012.01)
USPC - 530/388.15
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(8): C07K 16/18, A61K 39/395 (2012.01)
USPC: 530/388.15

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 530/388.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST, Google Scholar: Human, tissue, factor, pathway, inhibitor, antibody, bind, bound, human tissue factor pathway inhibitor, monoclonal, isolated, epitope, residue, Glu100, E100, glutamic acid 100, Glu101, E101, glutamic acid 101, Asp102, aspartic acid 102, D102, Pro103, proline 103, P103, Gly104, glycine 104, G104, Ile105, Isoleucine 105, I1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/0072691 A1 (HILDEN et al.) 01 July 2010 (01.07.2010); page 2, para 3; page 12, para 2-4; page 16, para 4-5	1-5
Y	UniProt submission P10646, TFPI1_HUMAN, 01 July 1989 [online]. [Retrieved on 2012-06-11]. Retrieved from the internet <URL: http://www.uniprot.org/uniprot/P10646.txt?version=151>	1-5
Y	WO 2010/017196 A2 (WANG et al.) 11 February 2010 (11.02.2010) para [0014], [0028], [0029]	1-5

☐ Further documents are listed in the continuation of Box C. ☐

* 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
30 August 2012 (30.08.2012)	01 OCT 2012
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	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/31538

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.: 29-37
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:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-5, drawn to an isolated monoclonal antibody that binds to an epitope of human tissue factor pathway inhibitor (SEQ ID NO:1), wherein said epitope comprises one or more residues selected from the group consisting of Glu100, Glu101 , Asp102, Pro103, Gly104, ne105, Cys106, Arg107, Gly108, Tyr109, Lys126, Gly128, Gly129, Cys130, Leu131, Gly132, and Asn133 of SEQ ID NO:1

Group II: Claims 6-11, drawn to an isolated monoclonal antibody that binds to an epitope of human tissue factor pathway inhibitor (SEQ ID NO:1), wherein said epitope comprises two amino acid loops linked by a disulfide bridge between residues Cys106 and Cys130 of SEQ ID NO:1

---please see continuation on extra 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 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.:
1-5

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

International application No.
PCT/US 12/31538

Continuation of Box No III Observations where unity of invention is lacking

Group III: Claims 12-23, drawn to an isolated monoclonal antibody that binds to an epitope of human tissue factor pathway inhibitor (SEQ ID NO:1), wherein said epitope comprises one or more residues of Kunitz domain 1 and one or more residues of Kunitz domain 2

Group IV: Claims 24-28, drawn to an isolated monoclonal antibody that binds to an epitope of human tissue factor pathway inhibitor (SEQ ID NO:1), wherein said epitope comprises two amino acid loops linked by a disulfide bridge between residues Cys35 and Cys59 of SEQ ID NO: 1

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The shared technical feature of the inventions listed as Groups I-IV is an isolated monoclonal antibody that binds to an epitope of human tissue factor pathway inhibitor (SEQ ID NO:1). This shared technical feature fails to provide a contribution over the prior art, as evidenced by WO 2010/017196 A2 to Wang et al. (published 11 February 2010; hereinafter 'Wang') in view of UniProt submission P10646 (published 01 July 1989; retrieved from the internet <URL:http://www.uniprot.org/uniprot/P10646.txt?version=151>; hereinafter 'P10646'). Wang disclsoes an isolated (para [0029]) monoclonal antibody that binds to an epitope of human tissue factor pathway inhibitor (para [0014] - "Monoclonal antibodies to human tissue factor pathway inhibitor (TFPI) are provided"; para [0028] - "A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope"). Although Wang does not teach taht the human tissue factor pathway inhibitor comprises the sequence of SEQ ID NO:1, P10646 discloses a sequence that exhibits 100% identity with SEQ ID NO:1 (sequence of P10646). One of ordinary skill in the art would have found it obvious that the human tissue factor pathway inhibitor of Wang may comprise the sequence disclosed by P10646 because the sequence of P10646 is that of human tissue factor pathway inhibitor. In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

Further, the special technical feature of the inventions listed as Group I is an epitope that comprises one or more residues selected from the group consisting of Glu100, Glu101, Asp102, Pro103, Gly104, ne105, Cys106, Arg107, Gly108, Tyr109, Lys126, Gly128, Gly129, Cys130, Leu131, Gly132, and Asn133. This special technical feature is not shared by the inventions of Groups II-IV. The special technical feature of the inventions listed as Group II is an epitope that comprises two amino acid loops linked by a disulfide bridge between residues Cys106 and Cys130. This special technical feature is not shared by the inventions of Groups I and III-IV. The special technical feature of the inventions listed as Group III is an epitope that comprises one or more residues of Kunitz domain 1 and one or more residues of Kunitz domain 2. This special technical feature is not shared by the inventions of Groups I-II and IV. The special technical feature of the inventions listed as Group IV is an epitope that comprises two amino acid loops linked by a disulfide bridge between residues Cys35 and Cys59. This special technical feature is not shared by the inventions of Groups I-III.

Unity of invention exists only when the same or corresponding technical feature is shared by the claimed inventions. Without a shared special technical feature, the inventions of Groups I-IV lack unity with one another.