



(51) International Patent Classification:

A61K 38/37 (2006.01) C12P 21/08 (2006.01)  
C12N 15/00 (2006.01)

(21) International Application Number:

PCT/US2013/049989

(22) International Filing Date:

10 July 2013 (10.07.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/670,401	11 July 2012 (11.07.2012)	US
61/759,819	1 February 2013 (01.02.2013)	US
61/801,504	15 March 2013 (15.03.2013)	US
61/801,544	15 March 2013 (15.03.2013)	US
61/827,158	24 May 2013 (24.05.2013)	US
61/840,811	28 June 2013 (28.06.2013)	US

(71) Applicants (for all designated States except US):

AMUNIX OPERATING INC. [US/US]; 500 Ellis Street, Mountain View, CA 94043-2206 (US). BIOGEN IDEC MA INC. [US/US]; 14 Cambridge Center, Cambridge, MA 02142 (US).

(72) Inventors; and

(71) Applicants (for US only): CHHABRA, Ekta, Seth [IN/US]; 1550 Worcester Road #128, Framingham, MA 01702 (US). LIU, Tongyao [US/US]; 53 Buckman Drive, Lexington, MA 02421 (US). CHANG, Pei-yun [—/US];

2395 Sharon Road, Menlo Park, CA 94025 (US). PETERS, Robert, T. [US/US]; 53 Parkinson Street, Needham, MA 02492 (US). KULMAN, John [US/US]; 88 Creeley Road, Belmont, MA 02478 (US).

(74) Agents: ORBAL, Lucian et al.; WILSON SONSINI GOODRICH & ROSATI, 650 Page Mill Road, Palo Alto, CA 94304-1050 (US).

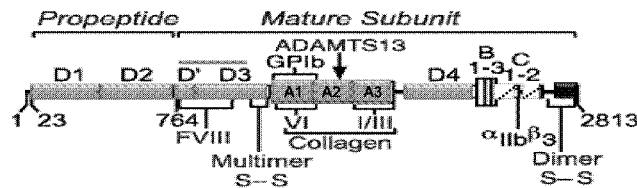
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: FACTOR VIII COMPLEX WITH XTEN AND VON WILLEBRAND FACTOR PROTEIN, AND USES THEREOF

Figure 1D. Von Willebrand Factor



- ~ 250 kDa protein, forms multimers (> 20 MDa) by disulfide bonding
  - Associates with FVIII (95-98%) in non-covalent complex
    - Protects FVIII from protease cleavage/activation
    - Stabilizes heavy & light chain
    - Prevents clearance of FVIII by scavenger receptors
  - Clearance of FVIII-vWF complex through vWF-receptors
    - Prevents pinocytosis and recycling of rFVIII Fc?
- } Extends half-life  
} Limits half-life

(57) Abstract: The present invention includes a chimeric protein comprising a VWF protein with D' domain and D3 domain of VWF, one or more XTEN sequence, and a FVIII protein, wherein the VWF fragment, the XTEN sequence, or the FVIII protein are linked to or associated with each other. The chimeric protein can further comprise one or more Ig constant region or a portion thereof (e.g., an Fc region). A polypeptide chain of a VWF fragment is associated with a FVIII polypeptide chain linked to an XTEN sequence. The VWF fragment polypeptide chain can prevent or inhibit binding of endogenous VWF to FVIII protein linked to the XTEN sequence. By preventing or inhibiting binding of endogenous VWF to FVIII protein, VWF fragment can extend half-life of chimeric protein comprising FVIII protein. The invention includes nucleotides, vectors, host cells, use of VWF fragment, or chimeric proteins.

WO 2014/011819 A3

**Published:**

- *with international search report (Art. 21(3))*
- *with sequence listing part of description (Rule 5.2(a))*

**(88) Date of publication of the international search report:**  
6 March 2014

**INTERNATIONAL SEARCH REPORT**

international application no.

PCT/US13/49989

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(8) - A61K 38/37; C12N 15/00; C12P 21/08 (2013.01)

USPC - 530/387.1, 380; 514/14.1

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): A61K 38/37; C12N 15/00; C12P 21/08 ; C07K 14/755 (2013.01)

USPC: 530/387.1, 380, 381, 383; 514/14.1, 13.7; 424/178.1

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)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ScienceDirect; Google; Google Scholar; IP.com; 'von Willebrand factor,' 'VWFL,' 'D domain,' 'D3 domain,' polypeptide, 'chimeric protein,' 'fusion protein,' 'FVIII,' 'XTEN,' sequence, 'coagulation factor'

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/060242 A2 (BARNETT, T) May 19, 2011; page 3, fifth paragraph; page 6, fourth paragraph; page 12, fifth paragraph; page 27, fifth paragraph; figures 2, 10, 11	1, 2, 3/1, 3/2, 4/3/1, 4/3/2, 8, 45, 46, 47/45, 47/46
Y	WO 2011/101242 A1 (PESCHKE, B et al.) August 25, 2011; page 7, lines 1-5, 7-10, 32-35; page 8, lines 1-5; page 12, lines 5-10	3/1, 3/2, 4/3/1, 4/3/2, 8, 27, 28, 29/27, 29/28, 30/29/27, 30/29/28, 45, 46, 47/45, 47/46
Y	SCHELLENBERGER, V et al. A Recombinant Polypeptide Extends The In-Vivo Half Life of peptides And Proteins In A Tunable Manner. Nature Biotechnology. 15 November 2009, Vol. 27, pp 1186-1192; abstract; Figure 1. DOI:10.1038/nbt.1588	1, 2, 3/1, 3/2, 4/3/1, 4/3/2, 8, 27, 28, 29/27, 29/28, 30/29/27, 30/29/28, 45, 46, 47/45, 47/46
Y	WO 2009/062100 A1 (SCHWARZ, HP et al.) May 14, 2009; paragraphs [0031]-[0033], [0084]	47/45, 47/46
Y	LEYTE, A et al. Sulfation of Tyr1680 of Human Blood Coagulation Factor VIII Is Essential For The Interaction of Factor VIII With Von Willebrand Factor. J Biol Chem. 15 January 1991, Vol. 266, pp 740-746; entire document.	30/29/27, 30/29/28
Y	SAENKO, EL et al. A Role For The C2 Domain Of Factor VIII In Binding To Von Willebrand Factor. J Biol Chem. 15 April 1994, Vol. 269, pp 11601-11605; entire document.	30/29/27, 30/29/28

Further documents are listed in the continuation of Box C.

* 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 but 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	

Date of the actual completion of the international search 04 December 2013 (04.12.2013)	Date of mailing of the international search report <b>16 DEC 2013</b>
--	--

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: <b>Shane Thomas</b>  PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774
---	---

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US13/49989

**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.: 5-7, 9-26, 31-44, 48-165  
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:

- 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.:

**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.