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

- (88) **Date of publication of the international search report:**
12 March 2015

(54) **Title:** CHIMERIC FVII-XTEN MOLECULES AND USES THEREOF

(57) **Abstract:** The present invention provides chimeric FVII molecules comprising FVII, an XTEN polypeptide, and an antibody and antigen-binding molecules thereof which specifically bind the α and/or β subunits of the non-active form of the GPIIb/IIIa receptor. The antibodies and antigen-binding molecules can be genetically fused and/or conjugated to heterologous moieties, e.g., half-life extending moiety. The invention also includes methods of producing and using the chimeric molecules.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/040370

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 14/745 (2014.01)

CPC - C12N 9/647 (2014.12)

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 38/36, 38/43, 38/48, 39/395; A61P 7/04; C07K 14/745, 14/755, 16/28, 16/46, 19/00; C12N 9/96; C12P 21/02 (2014.01)
USPC - 424/94.3, 134.1; 435/69.6, 188, 219, 328; 530/383; 536/23.2, 23.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 38/00, 2039/505; C07K 14/745, 14/755, 16/28, 16/2848, 2317/622, 2319/00; C12N 9/96, 9/647 (2014.12) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, PubMed

Search terms used: 34D10 XTEN FVII Factor VII single chain light chain heavy chain

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/006633 A1 (BIOGEN IDEC HEMOPHILIA INC) 12 January 2012 (12.01.2012) entire document	64-67, 70-73
A	WO 2012/170969 A2 (BIOGEN IDEC MA INC) 13 December 2012 (13.12.2012) entire document	1-3, 6, 7, 12, 64-67, 70-73, 119-122
A	WO 2013/016454 A1 (BIOGEN IDEC HEMOPHILIA INC) 31 January 2013 (31.01.2013) entire document	1-3, 6, 7, 12, 64-67, 70-73, 119-122
A	US 2013/0108629 A1 (DUMONT et al) 02 May 2013 (02.05.2013) entire document	1-3, 6, 7, 12, 64-67, 70-73, 119-122
A	WO 2010/091122 A1 (AMUNIX, INC) 12 August 2010 (12.08.2010) entire document	1-3, 6, 7, 12, 64-67, 70-73, 119-122

☐ 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

23 December 2014

Date of mailing of the international search report

09 JAN 2015

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INTERNATIONAL SEARCH REPORT

0147040370 03.01.2018
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PCT/US2014/040370

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.: 13, 20, 21, 24, 25, 32, 33, 41, 42, 47-63, 68, 69, 74-118
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 Extra Sheet(s).

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.:
1-3, 6, 7, 12, 64-67, 70-73, and 119-122 will be searched to the extent that they read on a chimeric molecule comprising Factor VII ("FVII"), an XTEN polypeptide, and an anti-GPIIb/IIIa antibody or antigen-binding molecule thereof that is 34D10 antibody.

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.

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 need to be paid.

Group I+: claims 1-12, 14-19, 22, 26-31, 34-40, 43-45, 64-67, 70-73, and 119-122 are drawn to a chimeric molecule comprising Factor VII ("FVII"), an XTEN polypeptide, and an anti-GPIIb/IIIa antibody or antigen-binding molecule thereof.

The first invention of Group I+ is restricted to a chimeric molecule comprising Factor VII ("FVII"), an XTEN polypeptide, and an anti-GPIIb/IIIa antibody or antigen-binding molecule thereof, wherein the anti-GPIIb/IIIa antibody or antigen-binding molecule thereof is selected to be 34D10 antibody, wherein the 34D10 antibody comprises a heavy chain variable region wherein in the heavy chain variable region is SEQ ID NO:1, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is SEQ ID NO:31, CDR2 is SEQ ID NO:32, and CDR3 is SEQ ID NO:33; and a light chain variable region, wherein the light chain variable region is SEQ ID NO:2, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is SEQ ID NO:34, CDR2 is SEQ ID NO:35, and CDR3 is SEQ ID NO:36. It is believed that claims 1-3, 6, 7, 12, 64-67, 70-73, and 119-122 read on this first named invention and thus these claims will be searched without fee to the extent that they read on a chimeric molecule comprising Factor VII ("FVII"), an XTEN polypeptide, and an anti-GPIIb/IIIa antibody or antigen-binding molecule thereof that is 34D10 antibody.

Applicant is invited to elect additional anti-GPIIb/IIIa antibodies or antigen-binding molecules thereof with specified SEQ ID NO for each heavy and light chain CDR1, 2, and 3 to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a chimeric molecule comprising Factor VII ("FVII"), an XTEN polypeptide, and an anti-GPIIb/IIIa antibody or antigen-binding molecule thereof, wherein the anti-GPIIb/IIIa antibody or antigen-binding molecule thereof is selected to be 12B2 antibody, wherein the 12B2 antibody comprises a heavy chain variable region wherein in the heavy chain variable region is SEQ ID NO:14, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is SEQ ID NO:64, CDR2 is SEQ ID NO:65, and CDR3 is SEQ ID NO:66; and a light chain variable region, wherein the light chain variable region is SEQ ID NO:15, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is SEQ ID NO:67, CDR2 is SEQ ID NO:68, and CDR3 is SEQ ID NO:69. Additional anti-GPIIb/IIIa antibodies or antigen-binding molecules thereof will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ 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 Groups I+ antibodies do not share a significant structural element responsible for binding GPIIb/IIIa, requiring the selection of alternatives for the light and heavy chain variable regions of the antibody, where "an anti-GPIIb/IIIa antibody or antigen-binding molecule thereof which comprises: (i) a variable heavy chain CDR-1 (VH-CDR1) sequence at least about 60%, 70%, 80%, 90%, 95%, or 100% identical to any one of SEQ ID NOS: 25, 31, 37, 43 or 111; (ii) a variable heavy chain CDR-2 (VH-CDR2) sequence at least about 60%, 70%, 80%, 90%, 95%, or 100% identical to any one of SEQ ID NOS:26, 32, 38, 44, or 112; - 158- (iii) a variable heavy chain CDR-3 (VH-CDR3) sequence at least about 60%, 70%, 80%, 90%, 95%, or 100% identical to any one of SEQ ID NOS: 27, 33, 39, 45, or 113; (iv) a variable light chain CDR-1 (VL-CDR1) sequence at least about 60%, 70%, 80%, 90%, 95%, or 100% identical to any one of SEQ ID NOS: 28, 34, 40, 117, or 114; (v) a variable light chain CDR-2 (VL-CDR2) sequence at least about 60%, 70%, 80%, 90%, 95%, or 100% identical to any one of SEQ ID NOS: 29, 35, 41, 118, or 115; and, (vi) a variable light chain CDR-3 (VL-CDR3) sequence at least about 60, 70, 80, 90, or 95% identical to any one of SEQ ID NOS: 30, 36, 42, 119, or 116".

The Groups I+ share the technical features of a chimeric molecule comprising Factor VII ("FVII"), an XTEN polypeptide, and an anti-GPIIb/IIIa antibody or antigen-binding molecule thereof, wherein the anti-GPIIb/IIIa antibody or antigen-binding molecule thereof comprises a heavy chain variable region and a light chain variable region. However, these shared technical features do not represent a contribution over the prior art. Specifically, WO 2012/006633 A1 to Salas et al. discloses a chimeric molecule (chimeric clotting factors, Abstract) comprising Factor VII ("FVII"), an XTEN polypeptide, and an anti-GPIIb/IIIa antibody or antigen-binding molecule thereof, wherein the anti-GPIIb/IIIa antibody or antigen-binding molecule thereof (a chimeric clotting factor which comprises a clotting factor ...and a targeting moiety which binds to platelets, Para. [0009]; In one embodiment, the clotting factor is Factor VII, Para. [0028]; the targeting moiety selectively binds to a target selected from the group consisting of: GPIIb, GPVI, and the nonactive form of GPIIb/IIIaIn one embodiment, the targeting moiety selectively binds to a target selected from the group consisting of: the active form of GPIIb/IIIa, Para. [0027]; the clotting factor comprises a scaffold moiety ...the scaffold moiety, if present, is selected from the group consisting of albumin and XTEN, Para. [0033]), wherein the anti-GPIIb/IIIa antibody or antigen-binding molecule thereof comprises a heavy chain variable region and a light chain variable region (chimeric clotting factor of the invention comprises an antigen binding site or region ...both variable domains, such that the VL and VH domain, Para. [00228]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.