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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:
15 July 2010

(54) Title: MODULATION OF FACTOR 11 EXPRESSION

(57) Abstract: Disclosed herein are antisense compounds and methods for decreasing Factor 11 and treating or preventing thromboembolic complications in an individual in need thereof. Examples of disease conditions that can be ameliorated with the administration of antisense compounds targeted to Factor 11 include thrombosis, embolism, and thromboembolism, such as, deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. Antisense compounds targeting Factor 11 can also be used as a prophylactic treatment to prevent individuals at risk for thrombosis and embolism.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/70 (2010.01)
USPC - 424/44A
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)
USPC- 424/44A

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 424/44R, 424/44; 536/23.1; 536/24.5

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar, PubMed: Human factor XI, Factor XI light chain, coagulation factor XIa, Factor XI, coagulation factor XIa, Factor 11, Factor 11, oligonucleotide, antithrombotic, Aptamer, FXI zymogen, antisense, inhibitory RNA. GenCore 6.3: SEQ ID NO: 223

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2002/072882 A2 (Cullen et al.) 19 September 2002 (19.09.2002) Abstract, AX609519	1-2
Y	US 2008/0219998 A1 (Gruber) 11 September 2008 (11.09.2008) Abstract; claims 13 and 18; para [0016, [0077], [0092], [0101]	1-2, 4-18, 29, 31-42
Y	GenBank Submission AY402921/c. 03 February 2006 [Retrieved from the Internet 03 February 2010:<http://www.ncbi.nlm.nih.gov/nucgss/39758904>] nucleotides 974-955	1-2, 4-18, 31-33
Y	Davis, et al. Improved targeting of miRNA with antisense oligonucleotides. Nucleic Acids Research, 2006, 34(8):2294-2304; pg 2296, col 1	12
Y	WO 2007027894 A2 (Esau, et al.) 08 March 2007 (08.03.2007) Abstract; pg 3, ln 24-25; pg 8, ln 14-15; pg 11, ln 16-18; pg 12, ln 25-28, pg 18, ln 6-26; pg 29, ln 26-28; pg 32, ln 32-34;	6-10, 13-18, 29, 31-42
Y	US 2008/0146788 A1 (Bhat, et al.) 19 June 2008 (19.06.2008) para [0009], [0011], [0089]	2, 4-5, 11-12
Y	Howard, et al. Factor IXa Inhibitors as Novel Anticoagulants. Arterioscler Thromb Vasc Biol 2007, 27(4):722-727; pg 724 Fig 3 and its legend; pg 726, col 1	40-42
Y	US 2005/0181978 A1 (Rojkjaer, et al.) 18 August 2005 (18.08.2005) Abstract, claim 1	42
A	GenBank Direct Submission AX609519. Sequence 544 from Patent WO02072882. 17 February 2003. [Retrieved from the Internet 02 February: <http://www.ncbi.nlm.nih.gov/nuccore/28404948>]	1-2

☐ 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
01 February 2010 (01.02.2010)	26 MAY 2010

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	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 09/60922

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.: 19-28 and 30
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 from 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 1-18, 29, 31-42 and 50-54 are drawn to a compound comprising a modified oligonucleotide, a composition comprising a modified oligonucleotid, and a method of administering a modified oligonucleotide, where the first named invention will be searched (claims 1, 2, 4-18, 29, and 31-42) and includes a search for SEQ ID NO 223. Applicant may have SEQ ID NO: 1 in its entirety (e.g. claim 3), or a specific fragment thereof (e.g. nucleobases 738 to 762 of SEQ ID NO: 1, as recited in claim 50) searched for an additional search fee per sequence.

Group II: Claims 43-49 are drawn to a method comprising administering a Factor 11 specific inhibitor and anti-platelet therapy.

********** SEE SUPPLEMENTAL BOX TO CONTINUE **********

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.:
Claims 1, 2, 4-18, 29, and 31-42

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 09/60922

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	Crosby, et al. Antisense Oligonucleotide Mediated Depletion of Factor XI Results in Effective Anticoagulation with a Favorable Risk/Benefit Profile in Mice. ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY JUL 2009, 29(7):E21-E21; Abstract	1-2, 4-18, 29, 31-42
A	Gailani. Gene targeting in hemostasis: factor XI. Front Biosci. 2001, 6:D201-D207	1-2, 4-18, 29, 31-42
A	Gaynor, et al. Synthesis, Properties and Application of Nucleic Acids Containing Phosphorothiolate Linkages. Current Organic Chemistry EPub March 2008, 12(4):291-308	1-2, 4-18, 29, 31-42
A	US 5,252,217 A. Burnouf-Radosevich, et al. 12 October 1993 (12.10.1993)	42
A	US 2008/0058266 A1 (Rojkjaer, et al.) 06 March 2008 (06.03.2008)	42

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********** SUPPLEMENTAL BOX **********

The groups listed above 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 technical features that links Groups I+ and II are a Factor 11 inhibitor and a method of administering such. However, this does not represent an improvement over the prior art of WO 1995/017420 to Walsh et al., which teaches a Factor 11 inhibitor (Factor XI analog and competitive inhibitor of Factor XI; abstract) and a method of treating thrombosis with such (pg 8, ln 8-10 and claim 59).

In addition, the inventions of Group I+ do not relate to a single general inventive concept because they are drawn to distinct sequences with different structure and function. As SEQ ID NO: 223 is old in the art (SEQ ID NO: 250856 of US 2006/0134663 A1 to Harkin), SEQ ID NO 223 and SEQ ID NO: 1 do not relate to a single inventive concept. Further, although the various sequences recited by claims 50-54 are all fragments of SEQ ID NO: 1, they do not relate to a single inventive concept because they are non-overlapping fragments, and because a sequence of at least 90% identity to SEQ ID NO: 1, as recited by claims 50-54, is old in the art (94.8% - SEQ ID NO 418345 of US 2007/0083334 A1 to Mintz).

Accordingly, unity of invention is lacking.