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(54) Title: ADMINISTRATION OF THE REG1 ANTICOAGULATION SYSTEM

(57) Abstract: An improved method of administration of an aptamer and antidote system to regulate blood coagulation in a host is provided based on weight adjusted or body mass index-adjusted dosing of the components of the system to provide a desired pharmacodynamic response. In addition, a method of reversing activity of the aptamer to a desired extent is provided where an antidote dose is based solely on its relationship to the aptamer dose.



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# INTERNATIONAL SEARCH REPORT

International application no.

PCT/US07/12625

## A. CLASSIFICATION OF SUBJECT MATTER

IPC: A01N 43/04( 2006.01);A61K 31/70( 2006.01)  
C12N 15/00( 2006.01);A61K 38/00( 2006.01),31/715( 2006.01)

USPC: 514/44;435/455;514/12;514/54

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. : 514/44;435/455;514/12;514/54

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)  
MEDLINE, AGRICOLA, BIOSIS, SCISEARCH, CAPLUS, PCGB, USPT, EPAB, JPAB, DWPI

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                        | Relevant to claim No. |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | SULLENGER, B. A. et al., (US2003/0083294 A1) May 1, 2003 (01.5.2003). Modulators of Pharmacological Agents. (entire article especially p.27 &29.) (entire article and especially Abstract and paragraphs 0047, 0196-0198, 0205, 0225-0226, 0241)                                                                                                                                                                                          | 1-30                  |
| P, X       | DYKE, C.K, Steinhubl SR, Kleiman NS, Cannon RO, Aberle LG, Lin M, Myles SK, Melloni C, Harrington RA, Alexander JH, Becker RC, Rusconi CP. First-in-human experience of an antidote-controlled anticoagulant using RNA aptamer technology: a phase Ia pharmacodynamic evaluation of a drug-antidote pair for the controlled regulation of factor IXa activity. Circulation. 2006 Dec 5;114(23):2490-7. Epub 2006 Nov 13. (entire article) | 1-30                  |
| A          | DROLET, D.W., Nelson J, Tucker CE, Zack PM, Nixon K, Bolin R, Judkins, MB, Farmer JA, Wolf JL, Gill SC, Bendele RA. Pharmacokinetics and safety of an anti-vascular endothelial growth factor aptamer (NX1838) following injection into the vitreous humor of rhesus monkeys. Pharm Res. 2000 Dec;17(12):1503-10. PMID: 11303960 (entire article)                                                                                         | 1-30                  |

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

☐ See patent family annex.

\* 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 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

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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          | RUSCONI, C.P., Scardino E, Layzer J, Pitoc GA, Ortel TL, Monroe D, Sullenger BA. RNA aptamers as reversible antagonists of coagulation factor IXa. Nature. 2002 Sep 5;419(6902):90-4. (entire article)                                                                              | 1-30                  |
| A          | GOPINATH, S.C., Shikamoto Y, Mizuno H, Kumar PK. A potent anti-coagulant RNA aptamer inhibits blood coagulation by specifically blocking the extrinsic clotting pathway. Thromb Haemost. 2006 May;95(5):767-71. (entire article)                                                    | 1-30                  |
| X          | RUSCONI, C.P., Roberts JD, Pitoc GA, Nimjee SM, White RR, Quick G Jr, Scardino E, Fay WP, Sullenger BA. Antidote-mediated control of an anticoagulant aptamer in vivo. Nat Biotechnol. 2004 Nov;22(11):1423-8. Epub 2004 Oct 17 (entire article)                                    | 1-30                  |
| A          | Boomer RM, Lewis SD, Healy JM, Kurz M, Wilson C, McCauley TG. Conjugation to polyethylene glycol polymer promotes aptamer biodistribution to healthy and inflamed tissues. Oligonucleotides. 2005 Fall;15(3):183-95. PMID: 16201906 [PubMed - indexed for MEDLINE (entire article)] | 1-30                  |