Title: C1-INHIBITOR PREVENTS NON-SPECIFIC PLASMINOGEN ACTIVATION BY A PROUKINASE MUTANT WITHOUT IMPEDING FIBRIN-SPECIFIC FIBRINOLYSIS

Abstract: A mutant prourokinase plasminogen activator (M5) was developed to make prouPA less subject to spontaneous activation during fibrinolysis. C1- inhibitor complexes with tcM5. The effect of C1- inhibitor on fibrinolysis and fibrinogenolysis by M5 was determined. Supplemenal C1-inhibitor restores the stability of M5 but not that of prouPA. Clot lysis by M5 with supplemental C1-inhibitor showed no attenuation of the rate of fibrinolysis, whereas fibrinogenolysis was prevented by C1-inhibitor. Due to higher dose tolerance of M5 with C1-inhibitor, the rate of fibrin-specific lysis reached that achievable by nonspecific fibrinolysis without inhibitor. Plasma C1-inhibitor stabilized M5 in plasma by inhibiting tcM5 and thereby non-specific plasminogen activation. At the same time, fibrin-specific plasminogen activation remained unimpaired. This unusual dissociation of effects has significant implications for improving the safety and efficacy of fibrinolysis. Methods of reducing bleeding and non-specific plasminogen activation during fibrinolysis by administering M5 along with exogenous C1-inhibitor are disclosed.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 38/49(2006.01),38/36(2006.01);C12N 9/72(2006.01),9/64(2006.01);C07H 21/04(2006.01)

USPC: 424/94.63,435/215,226;514/12,536/23.2

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.: 424/94.63; 435/215,226; 514/12; 536/23.2

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)

STN-Online:C/plus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>

☐ 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
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Date of the actual completion of the international search 30 July 2008 (30.07.2008)

Date of mailing of the international search report 30 SEP 2008

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Form PCT/ISA/210 (second sheet) (July 1998)