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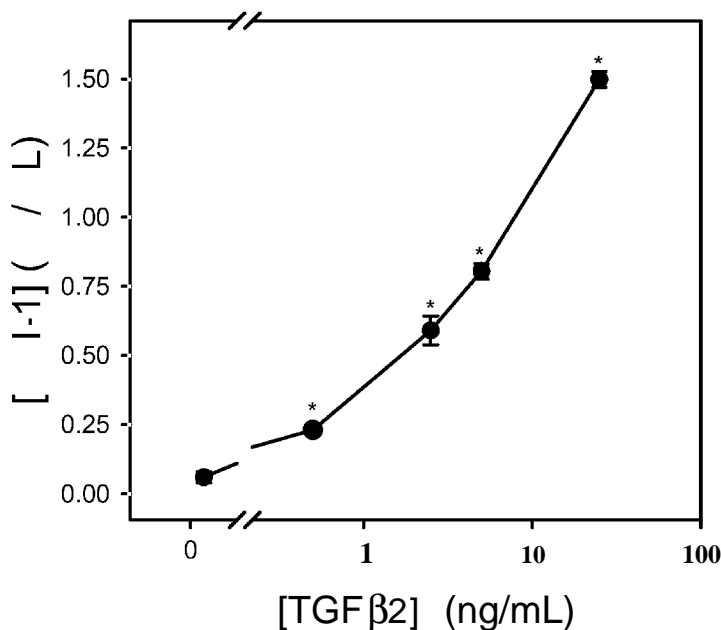
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[Continued on next page]

(54) Title: PAI-I BINDING MODULATORS FOR THE TREATMENT OF OCULAR DISORDERS



(57) Abstract: The invention concerns in one embodiment a method for treating glaucoma or elevated IOP in a patient comprising administering to the patient an effective amount of a composition comprising an agent that modulates PAI-I binding to vitronectin. In another embodiment, the invention concerns a method of manufacturing a compound to be used as a treatment for glaucoma or elevated IOP comprising providing a candidate substance suspected of modulating PAI-I binding, selecting the compound by assessing the ability of the candidate substance to decrease the amount of active PAI-I in the trabecular meshwork of a subject suffering from glaucoma or elevated PAI-I, and manufacturing the selected compound.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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INTERNATIONAL SEARCH REPORT

International application No

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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/122 A61K31/19 A61K31/41 A61P35/00

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)

A61K

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 practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DAN JACOB; BELYEA DAVID; GERTNER GREGORY; LESHEM ISRAEL; LUSKY MOSHE; MISKIN RUTH: "Plasminogen activator inhibitor-1 in the aqueous Humor of patients with and without glaucoma" ARCHIVES OF OPHTHALMOLOGY, vol. 123, no. 2, February 2005 (2005-02), pages 220-224, XP002480460 page 223, right-hand column -----	1-15
Y	MISKIN R; DAN J; BELYEA D: "Plasminogen activator inhibitor-I (PAL-I) in the murine and human eye: implications for glaucoma" THROMBOSIS AND HAEMOSTASIS, vol. 93, no. 4, April 2005 (2005-04), page A21, XP009100300 abstract ----- -/-	1-15



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 document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) for 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

16 May 2008

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10/06/2008

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/083170

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PARMLEY V C ; JENSEN H ; FOWLER W C ; STONECIPHER K G ; SCOTT M H ; SCHROUF D G ; ROWSEY J J : "INHIBITION OF PLASMINOGEN ACTIVATOR AND PLASMIN BY EPSILON AMINOCAPROIC ACID BASIS FOR TOPICAL THERAPY IN OCULAR SURFACE DISORDERS" INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, vol. 32, no. 4 , 1991, page 1071, XP009100312 abstract</p>	1-15
Y	<p>WIMMER I ; FUCHSHOFER R ; GREHN F ; LUETJEN-DRECOLL E : "Plasminogen activator inhibitor (PAI)-I in the aqueous humor of glaucoma and the correlation to bleb scarring after trabeculectomy" IOVS, vol. 45, no. Suppl.1, April 2004 (2004-04), page U373, XP009100305 abstract</p>	1-15
A	<p>LIANG A ET AL: "Characterization of a small molecule PAI-I inhibitor, ZK4044" THROMBOSIS RESEARCH, TARRYTOWN, NY, US, vol. 115, no. 4 , 1 January 2005 (2005-01-01), pages 341-350, XP004820342 ISSN: 0049-3848 page 341, abstract</p>	
A	<p>GILS ANN; DECLERCK PAUL J : "Plasminogen activator inhibitor-1" CURRENT MEDICINAL CHEMISTRY, vol. 11, no. 17, September 2004 (2004-09), pages 2323-2334, XP002480461 the whole document</p>	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos. : -

The present claims 1 and 7 encompass compounds defined only by their desired function ("agent that modulates PAI-I binding to vitronectin"), contrary to the requirements of clarity of Article 6 PCT, because the result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed, except for the compounds disclosed in the description and claim 6. Undue experimentation would be required to screen compounds randomly. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search for claims 1 and 7.

The search of claims 1 and 7 was consequently restricted to compounds listed in claim 6 (ZK4044, PAI-039, WAY-140312, HP-129, T-686, XR5967, XR334, XR330, XR5118, PAI-I antibodies and PAI-I peptidomimetics).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/083170

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:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
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 allsearchable claims.

2. ☐ As all searchable claims could be searched without effort Justifying an 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 reportcovers 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.