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30 November 2006

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(54) Title: METHODS FOR MEASURING TRANSFORMING GROWTH FACTOR BETA (TGF- β) RECEPTOR SIGNALING ACTIVITY AND USES THEREOF

(57) Abstract: Methods are disclosed for determining the optimal biologic dose of a TGF β receptor kinase inhibitor for administration to patients in need of such therapy and for monitoring the effectiveness of therapy with a TGF β receptor kinase inhibitor in patients receiving such therapy. Kits comprising antibodies and reagents useful in such methods are also disclosed.

WO 2005/069935 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/01703

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC: G01N 33/53(2006.01);A61K 49/00(2006.01)</p> <p>USPC: 435/7.1;424/9.1,130.1 According to International Patent Classification (IPC) or to both national classification and IPC</p>													
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) U.S. : 435/7.1; 424/9.1,130.1</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Please See Continuation Sheet</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet</p>													
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>YINGLING et al. Development of TGF-beta signalling inhibitors for cancer therapy. Nature Reviews, Drug Discovery. December 2004, Vol. 3, pages 1011-1022, entire document, Particularly Table 2.</td> <td>1-5, 7-11, 13-17, 19-23 and 26</td> </tr> <tr> <td>A</td> <td>REISS. TGF-beta and Cancer. Microbes and Infection. 1999, Vol. 1, pages 1327-1347, entire document, see especially section 7.2.</td> <td>1-5, 7-11, 13-17 and 19-23</td> </tr> <tr> <td>A</td> <td>US 2005/0079559 A1 (MATSUZAKI et al.) 14 April 2005 (14.04.2005), see paragraphs [0024-0029], [0041] and [0075-0080].</td> <td>1-5, 7-11, 13-17 and 19-23</td> </tr> </tbody> </table>		Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	YINGLING et al. Development of TGF-beta signalling inhibitors for cancer therapy. Nature Reviews, Drug Discovery. December 2004, Vol. 3, pages 1011-1022, entire document, Particularly Table 2.	1-5, 7-11, 13-17, 19-23 and 26	A	REISS. TGF-beta and Cancer. Microbes and Infection. 1999, Vol. 1, pages 1327-1347, entire document, see especially section 7.2.	1-5, 7-11, 13-17 and 19-23	A	US 2005/0079559 A1 (MATSUZAKI et al.) 14 April 2005 (14.04.2005), see paragraphs [0024-0029], [0041] and [0075-0080].	1-5, 7-11, 13-17 and 19-23
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<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.</p>													
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="vertical-align: top;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>		<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>										
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<p>Date of the actual completion of the international search 05 July 2006 (05.07.2006)</p>	<p>Date of mailing of the international search report 28 JUL 2006</p>												
<p>Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201</p>	<p>Authorized officer Shulamith H. Shafer <i>J. Roberts for</i> Telephone No. 571-272-0600</p>												

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/01703

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.: 6,12,18 and 24
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:
Please See Continuation Sheet

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 any 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.: 1-5,7-11,13-17,19-23 and 26
- 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/US05/01703

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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 must be paid.

- I. Claims 1-5, 7-11, 13-17, 19-23 and 26, drawn to method for determining dose of TGF-beta receptor kinase inhibitor
- II. Claims 25, drawn to method of identifying agent by high throughput screening
- III. Claim 27, drawn to method of treatment

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1, 13.2, and 13.2 for the reasons indicated below:

Group I recites the unifying technical feature of obtaining a tissue sample from a patient prior to and after treatment and measuring the amount of psmad 2/3, a technical feature not required by claims of Groups II or III

Continuation of B. FIELDS SEARCHED Item 2:

US-PGPUB; USPAT; USOCR; EPO; JPO; Derwent.
CAPLUS, MEDLINE, EMBASE, BIOSIS, SCISEARCH on STN

Continuation of B. FIELDS SEARCHED Item 3:

CAPLUS, MEDLINE, EMBASE, BIOSIS, SCISEARCH on STN
search terms: TGF-beta, receptor kinase inhibitor, smad2/3