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**Published**:

— *with international search report (Art. 21(3))*

(88) **Date of publication of the international search report**:
30 December 2009

(54) **Title**: INHIBITORS OF ONCOGENIC ISOFORMS AND USES THEREOF

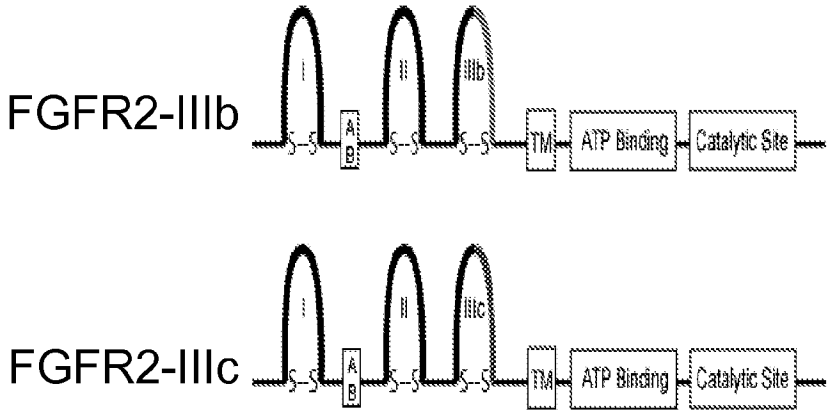


FIG. 1

(57) **Abstract**: Isoform-binding molecules that specifically bind to one or more isoforms expressed and/or associated with oncogenic phenotypes in a hyperproliferative cell (e.g., a cancerous or tumor cell) are disclosed. The isoform-binding molecules can be used to treat, prevent and/or diagnose cancerous conditions and/or disorders. Methods of using the isoform-binding molecules to selectively detect oncogenic isoforms, to reduce the activity and/or induce the killing of a hyperproliferative cell expressing an oncogenic isoform in vitro, ex vivo or in vivo are also disclosed. Diagnostic and/or screening methods and kits for evaluating the function or expression of an oncogenic isoform are also disclosed.

WO 2009/100105 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/33031

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/18, 16/46 (2009.01)
USPC - 424/138.1, 424/178.1
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)
IPC(8) - C07K 16/18, 16/46 (2009.01)
USPC - 424/138.1, 424/178.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - C07K 16/18, 16/46 (2009.01) - see keyword below
USPC - 424/138.1, 424/178.1 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google
Search terms: FGFR2, inhibitor, antibody, epitope, affinity, Kd, IIIc, ligand, cancer, prostate, refractory, signaling, IIIb, link, conjugate, toxin, radioisotope, cytotoxic, label, antagonist, pharmaceutical, extracellular, 212Bi, 90y, 131I, alpha, beta, carcinoma,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>----<br>Y | US 2007/0248605 A1 (HESTIR et al.) 25 October 2007 (25.10.2007), Abstract, para [0003], [0007], [0021], [0022], [0034], [0035], [0065], [0067], [0074], [0075], [0076], [0078], [0084], [0087], [0092], [0096], [0098], [0099], [0103], [0120], [0121], [0126], [0127], [0140], and Claim 3 | 1-9, 34-47<br>----------<br>28-32 |
| Y | US 2004/0044181 A1 (TANG et al.) 04 March 2004 (04.03.2004), para [0139], [0229], [0353], [0363], [0364], and [0377] | 28-32 |
| A | WO 2007/014123 A2 (WILLIAMS et al.) 01 February 2007 (01.02.2007), Fig A ? FGFR2 IIIc | 1-9, 28-32, 34-47 |
| A | HAJIHOSSEINI et al. "A splicing switch and gain-of-function mutation in FgfR2-IIIc hemizygotes causes ApertyPfeiffersyndrome-like phenotypes". Proc. Natl. Acad. Sci. USA. 27 March 2001, vol. 98(7), p.3855-3860. | 1-9, 28-32, 34-47 |

☐ 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 |
|---|---|
| 05 August 2009 (05.08.2009) | 21 AUG 2009 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (April 2007)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/33031

**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.: 20-22 and 48-54
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 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.

Group I: claims 1-7, 8 (limited to SEQ ID NO: 2 or SEQ ID NO: 1), 9, 28-32, 34-39 (limited to SEQ ID NO: 2 or SEQ ID NO: 1), 40 (limited to SEQ ID NO: 2 or SEQ ID NO: 1), 41-47, directed to an isoform-specific inhibitor of an oncogenic polypeptide or nucleic acid, wherein the inhibitor comprises an antibody, and wherein the oncogenic isoform polypeptide is an isoform of FGFR2.
Group II: claims 1, 4, 5, 10, 11, and 39, 40 (both limited to SEQ ID NO: 10; SEQ ID NO: 9) directed to an an isoform-specific inhibitor *comprising an antibody that binds to human FGFR1L.*

*- Please see extra sheet for continuation -*

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.:
1-7, 8 (limited to SEQ ID NO: 2 or SEQ ID NO: 1), 9, 28-32, 34-39 (limited to SEQ ID NO: 2 or SEQ ID NO: 1), 40 (limited to SEQ ID NO: 2 or SEQ ID NO: 1), 41-47

**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 09/33031

Continuation of Box III: Lack of Unity of Invention

Group III: claims 1, 4, 5, 12 13, and 39, 40 (both limited to SEQ ID NO: 12; SEQ ID NO: 11), directed to an isoform-specific inhibitor comprising an antibody that binds to human RON.delta.160.
Group IV: claims 1, 4, 5, 14, 15, and 39, 40 (both limited to SEQ ID NO: 14; SEQ ID NO: 13), directed to an isoform-specific inhibitor comprising an antibody that binds to human exon 11-deleted KIT.
Group V: claims 1, 4, 5, 16, 17, and 39, 40 (both limited to SEQ ID NO: 16; SEQ ID NO: 15), directed to an isoform-specific inhibitor comprising an antibody that binds to human exon 6-deleted PDGF.
Group VI: claims 1, 4, 5, 18, 19, and 39, 40 (both limited to SEQ ID NO: 18; SEQ ID NO: 17), directed to an isoform-specific inhibitor comprising an antibody that binds to human exon 7/8-deleted PDGFR-alpha.
Group VII: claims 1 and 23-26, directed to an isoform specific inhibitor which comprises a soluble receptor or receptor fusion.
Group VIII: claims 1, 27 (limited to SEQ ID NO: 2 or SEQ ID NO: 1), directed to an isoform specific inhibitor which comprises a peptide or functional variant thereof. (applicant may elect to search additional sequence pairs by specifying the pair and paying for each search as an additional invention).
Group IX: claims 1, 33, directed to an isoform specific inhibitor which comprises a nucleic acid inhibitor.
Group X: claims 1, 2, and 55-65, directed to a method of detecting the presence of an oncogenic isoform of a polypeptide in samples in vitro.

The inventions listed as Groups I - X 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 special technical feature of the claims of Groups I-VI is an isoform-specific inhibitor of an oncogenic polypeptide or nucleic acid, wherein the inhibitor comprises an antibody, and wherein the oncogenic isoform polypeptide is an isoform of FGFR2, FGFR1L, RON.delta.160, exon 11-deleted KIT, exon 6-deleted PDGF, and exon 7/8-deleted PDGFR-alpha, respectively. The special technical feature of the Group VII claims is an isoform specific inhibitor which comprises a soluble receptor or receptor fusion. The special technical feature of the Group VIII claims is an isoform specific inhibitor which comprises a peptide or functional variant thereof. The special technical feature of the Group IX claims is an isoform specific inhibitor which comprises a nucleic acid inhibitor. The special technical feature of the Group X claims is a method of detecting the presence of an oncogenic isoform of a polypeptide in samples in vitro.

The only common technical element shared by the above groups is that they are related to isoforms of polypeptides that may be associated with cancer. This common technical element does not represent an improvement over the prior art of US 2007/0248605 A1 to Hestir et al. (See abstract, Claims 1, 3 and SEQ ID NO: 21). Therefore, the inventions of Groups I-X lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.