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George, D. [US/US]; 118 Salisbury Road, Brookline, MA 02445 (US).

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(74) Agent: **HARDING, Tanya, M.**; Klarquist Sparkman, LLP, One World Trade Center, Suite 1600, 121 SW Salmon Street, Portland, OR 97204 (US).

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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ACTIVATING MUTATIONS OF PLATELET DERIVED GROWTH FACTOR RECEPTOR ALPHA (PDGFRA) AS DIAGNOSTIC MARKERS AND THERAPEUTIC TARGETS:

(57) Abstract: This disclosure provides tyrosine kinase protein and nucleic acid variants, particularly PDGFRA variants, which are activating forms of these molecules and are linked to neoplasms and/or the development or progression of cancer. The disclosure further provides methods of diagnosis and prognosis, and development of new therapeutic agents using these molecules and fragments thereof, and kits for employing these methods and compositions.



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International application No.

PCT/US03/18901

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C07K 14/71(2007.01),16/28(2007.01);C07H 21/04(2007.01);C12N 1/21(2007.01),15/63(2007.01);G01N 33/567(2007.01)

USPC: 530/350,387.7;536/23.5;435/7.21,252.3,320.1

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)

U.S. : 530/350,387.7;536/23.5;435/7.21,252.3,320.1

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)
USPTO Sequence Database; EAST; STN; MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,833,986 A (LAROCHELLE et al) 10 November 1998 (10.11.1998), Column 12, line 62 through column 13, line 12 (Example 1); column 16, lines 33-64 (Example 7).	1, 11, 14, 15, 57-62 ----- 48-51, 54-56
X	OMURA, T. et al. Immunoglobulin-like Domain 4-mediated Receptor-Receptor Interactions Contribute to Platelet-derived Growth Factor-induced Receptor Dimerization. Journal of Biological Chemistry. 9 May 1997, Vol. 272, No. 19, pages 12676-12682, especially pages 12676, 12677 (Fig 1) and 12678 (Fig 2).	1, 11, 14, 15, 62
X --- Y	BAXTER, E. J. et al. The t(4:22)(q12;q11) in Atypical Chronic Myeloid Leukaemia fuses BCR to PDGFRA. 1 June 2002, Vol. 11, No. 12, pages 1391-1397, especially page 1393 (Figure 3).	11 ----- 1, 14, 15, 48-51, 54-56, 62
Y	BAI, R. Y. et al. The SH2-containing Adapter Protein GRB10 interacts with BCR-ABL. 1998, Vol. 17, pages 941-948, especially page 948.	1, 14, 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	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Authorized officer

Zachary C. Howard

Telephone No. 571-272-1600

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International application No.

PCT/US03/18901

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 16-47, 52, 53
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:
Please See Continuation Sheet
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 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 an additional fee, this Authority did not invite payment of any additional fee.
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.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

Continuation of Box I Reason 2:**The following claims are unsearchable:**

- The listing of claims includes two claims numbered 15. Only the first of the two claims will be searched.
- Claims 16-22, 27-39 and 41 are unsearchable because they depend from claim 15 but there are two claims numbered 15, and it is therefore impossible to determine which of the two claims the dependent claims depend from.
- Claims 23-26 are unsearchable because claim 23 depends from "claim 1520", but there is no claim 1520.
- There is no claim 40 presented in the claim listing.
- The listing of claims includes two claims numbered 41. Only the first of the two would be searched, however, the first claim 41 is also unsearchable as indicated above.
- Claims 42-47 are unsearchable because they depend from claim 41, but because there are two claims numbered 41 presented in the listing of claims, it is impossible to determine which of the two claims the dependent claims depend from.
- Claims 52 and 53 are unsearchable because they recite a "method of claim 48"; however, claim 48 is drawn to a kit and not a method.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I, claims 1-15 and 48-51, drawn to polypeptides, nucleic acids, vectors, host cells, kits and compositions comprising said polypeptides and nucleic acids, and a method of detecting whether a subject has a mutation in a nucleic acid.

Group II, claims 54-56, drawn to a kit comprising a specific binding agent for a PDGFRA protein (including antibodies to PDGFRA protein).

Group III, claims 57-59, drawn to a method of screening for a compound that binds to or interacts with a polypeptide.

Group IV, claims 60 and 61, drawn to a compound that binds to or interacts with a polypeptide.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

A) The first species of isolated PDGRA variant protein is SEQ ID NO: 4 and the 2nd through 8th species are SEQ ID NO: 6, 8, 10, 12, 21, 23 and 25. These variants are encoded, respectively, by the nucleic acids of SEQ ID NO: 3, 5, 7, 9, 11, 20, 22, and 24.

The claims correspond to the species listed above in the following manner:

Claim 3 corresponds to the species of SEQ ID NO: 4.

Claim 4 corresponds to the species of SEQ ID NO: 6.

Claim 5 corresponds to the species of SEQ ID NO: 8.

Claim 6 corresponds to the species of SEQ ID NO: 10.

Claim 7 corresponds to the species of SEQ ID NO: 12.

Claim 8 corresponds to the species of SEQ ID NO: 21.

Claim 9 corresponds to the species of SEQ ID NO: 23.

Claim 10 corresponds to the species of SEQ ID NO: 25.

Claims 2, 13, 16 and 62 recite each of the species listed above.

The following claim(s) are generic: 1, 11, 12, 14-15, 48-51 and 54-59.

The fees previously paid cover the first group (I) and first species. In order for more than one group or more than one species to be examined, the appropriate additional fees must be paid. Each additional species counts as an additional group. There are 3 additional groups of inventions (II-IV above) and 7 additional species of PDGRA variant protein. Therefore, for all of the groups and species to be searched, search fees for an additional 10 groups must be paid.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT rule 12.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Pursuant to 37 C.F.R. 1.475 (B-D), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly, the main invention (Group I) comprises the first product (a variant polypeptide and fragments thereof), nucleic acids encoding the product and

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fragments thereof (including vector and host cells), a kit comprising oligonucleotide fragments of the nucleic acid, and the first method of use of said product (a method of detecting a nucleic acid mutation in a sample from a subject). Group II does not share the same technical feature because it is drawn to a different product, a specific binding agent for a PDGFRA mutant protein (such as an antibody) which is a structurally and functionally different product than the product of Group I, each of which can be made and used without each other, and thus do not relate to a single general invention concept within the meaning of PCT Rule 13.1. Groups III does not share the same or corresponding technical feature because it is drawn to a different method that has different method steps and goals, and these method steps and goals are not required by the method of Group I. Group IV does not share the same technical feature because it is drawn to a different product, a compound that binds to or interact with a PDGFRA variant polypeptide, which is a structurally and functionally different product than the product of Group I, each of which can be made and used without each other, and thus do not relate to a single general invention concept within the meaning of PCT Rule 13.1.

The species of PDGFRA mutant proteins, listed above do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each species (sequence) is drawn to a nucleic acid/encoded polypeptide pair which is a structurally and functionally different nucleic acid/encoded polypeptide pair from the other species (sequence) in the respective genus, thus the sequences are independent and distinct from one another.

The Authority therefore considers that the four inventions do not share a special technical feature within the meaning of PCT Rule 13.2 and thus do not relate to a single general inventive concept within the meaning of PCT Rule 13.1.

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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	US 6,187,536 B1 (WEINBERG et al) 13 February 2001 (13.02.2001), column 25, line 44 through column 26, line 64; column 29, line 66 through column 31, line 19.	48-51, 54-56
Y	US 5,795,976 A (OEFNER et al) 18 August 1991 (18.08.1991), entire document.	49
A	HIROTA, S. et al. Gain-of-Function Mutations of Platelet-Derived Growth Factor Receptor alpha Gene in Gastrointestinal Stromal Tumors. Gastroenterology. 2003, Vol. 125, pages 660-667.	1-15, 48-51, 54-56, 57-62