

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
5 August 2004 (05.08.2004)

PCT

(10) International Publication Number
WO 2004/064595 A3

(51) International Patent Classification⁷: **A61K 38/00**,
C07K 19/00

(21) International Application Number:
PCT/US2003/028838

(22) International Filing Date:
11 September 2003 (11.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/440,201 15 January 2003 (15.01.2003) US
10/379,287 3 March 2003 (03.03.2003) US

(71) Applicants (*for all designated States except US*):
BRACCO INTERNATIONAL BV [IT/IT]; Strawin-
skyiaan 3051, NL-1077 ZX Amsterdam (NL). **DYAX**
CORPORATION [US/US]; 300 Technology Square,
Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **ARBOGAST**,
Christophe [FR/FR]; La Sardagne, F-74250 Viuz-en-Sal-
laz (FR). **BUSSAT, Philippe** [FR/FR]; Allee du Saleve
46, F-74160 Feigers (FR). **DRANSFIELD, Daniel, T.**
[US/US]; 14 George Street, Hanson, MA 02341 (US).
FAN, Hong [US/US]; 3 Barley Court, Plainsboro, NJ
08536 (US). **LINDER, Karen** [US/US]; 14 Basin Street,
Kingston, NJ 08528 (US). **MARINELLI, Edmund**,
R. [US/US]; 190 Eldridge Avenue, Lawrenceville, NJ
08648 (US). **NANJAPPAN, Palaniappa** [US/US]; 30
Liberty Avenue, Dayton, NJ 08810 (US). **NUNN, Adrian**
[US/US]; 33 Mill Road, Lamberville, NJ 08530 (US).
PILLAI, Radhakrishna [US/US]; 12 Walnut Court, Cran-
bury, NJ 08512 (US). **POCHON, Sybille** [CH/CH]; Route
de Bossey 76, CH-1256 Troinex (CH). **RAMALINGAM**,

Kondareddiar [US/US]; 46 Liberty Place, Dayton, NJ
08810 (US). **SATO, Aaron** [GB/US]; 19 Central Street,
#21, Somerville, MA 02143 (US). **SHRIVASTAVA**,
Ajay [IN/US]; 18-16 Pheasant Hollow Drive, Plainsboro,
NJ 08536 (US). **SONG, Bo** [US/US]; 1 English Lane,
Princeton, NJ 08540 (US). **SWENSON, Rolf, E.** [US/US];
35 Fieldston Road, Princeton, NJ 08540 (US). **VON**
WRONSKI, Mathew, A. [US/US]; 604 Oldershaw Av-
enue, Moorestown, NJ 08057 (US). **WALKER, Sharon**,
Michele [US/US]; 128 West Concord Street, #2, Boston,
MA 02118 (US).

(74) Agent: **MCNEES, Scott, W.**; Kramer Levin Naftalis &
Frankel LLP, 919 Third Avenue, New York, NY 10022
(US).

(81) Designated States (*national*): AL, AM, AT, AU, AZ, BA,
BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES,
FI, GB, GD, GE, GH, HU, ID, IL, IN, IS, JP, KE, KG, KP,
KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL,
TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
31 March 2005

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: MULTIVALENT CONSTRUCTS FOR THERAPEUTIC AND DIAGNOSTIC APPLICATIONS

(57) Abstract: The invention provides compositions and methods for therapeutic and diagnostic applications.



WO 2004/064595 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/28838

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/00, C07K 19/00
 US CL : 514/2, 530/300, 530/333

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. : 514/2, 530/300, 530/333

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)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	LU, D. et al. Identification of the Residues in the Extracellular Region of KDR Important for Interaction with Vascular Endothelial Growth Factor and Neutralizing Anti-KDR Antibodies. J. Biol. Chem. May 2000, Vol. 275, No. 19, pages 14321-14330, especially pages 14321-14324.	1,2,4,5,11-20,27-29,53,54,75,76,78-80,82-90 ----- 3,6,7,55,95,98,102,104,105,109,110
X --- Y	TAMURA, S. et al. Expression and Function of c-Met, a Receptor for Hepatocyte Growth Factor, During T-Cell Development. Scand. J. Immunol. 1998, Vol. 47, pages 296-301, see entire document.	1,2,4,5,11,12,14,21-23,27,30,31,91,92 ----- 3,6,7,53,54
X	WEI, K. et al. Quantification of Renal Blood Flow With Contrast-Enhanced Ultrasound. J. Am. Coll. Cardiol. 2001, Vol. 37, No. 4, pages 1135-40, especially pates 1135-1136.	68-73

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	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family


Date of the actual completion of the international search

31 August 2004 (31.08.2004)

Date of mailing of the international search report

12 OCT 2004

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. (703) 305-3230

Authorized officer

 Andrew D. Kosar
 Telephone No. (571)272-1600

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/28838

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.:
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. Claim Nos.: 10, 74, 76-77, 80-87, 93-94, 97
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**
- | | |
|--------------------------|---|
| <input type="checkbox"/> | The additional search fees were accompanied by the applicant's protest. |
| <input type="checkbox"/> | No protest accompanied the payment of additional search fees. |

INTERNATIONAL SEARCH REPORT

PCT/US03/28838

BOX II. 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.

Group I, claim(s) 1-18, 24,25,27-29,33,35-70,96,99,103-108,112, drawn to KDR targeting compounds.

Group II, claim(s) 1-11,19-23,26,30,31,34-70,96,99,103-108,112, drawn to cMet targeting compounds.

Group III, claim(s) 71-73,77, drawn to diagnostic methods.

Group IV, claim(s) 74,77,78,80-87,93,95,98,101, drawn to methods of treating a disease.

Group V, claim(s) 75,78,80-87,90,93,95,98,101, drawn to methods of using KDR targeting compounds.

Group VI, claim(s) 76,78,80-87,91-95,97,98,100,101, drawn to methods of using cMet targeting compounds.

Group VII, claim(s) 79, drawn to a method of screening compounds.

Group VIII, claim(s) 109-111, drawn to methods of making compounds.

The inventions listed as Groups I-VIII 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: Lu teaches an antibody to KDR which binds multiple domains. Further, instant Claim 1 reads upon an antibody.

Continuation of B. FIELDS SEARCHED Item 3:

PUBMED, GOOGLE. Search terms: mucrobubble,contrast,imaging,agent,cmet,hgf,antibody,kdr,vegf,tumor,binding,peptide,dimer.
STN: structure of non-peptide component of claims 57-67,112.