(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 June 2008 (12.06.2008)

PCT

(10) International Publication Number
WO 2008/070325 A3

(51) International Patent Classification:
C12Q 1/68 (2006.01)

(21) International Application Number:
PCT/US2007/082397

(22) International Filing Date: 24 October 2007 (24.10.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/863,106 26 October 2006 (26.10.2006) US
60/917,814 14 May 2007 (14.05.2007) US

(71) Applicant *(for all designated States except US)*: **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KAN, Zhengyan** [CN/US]; 608 McLellan Drive, South San Francisco, CA 94080 (US). **KENSKI, Denise M.** [US/US]; 690 Guerrero Street, Apt. 5, San Francisco, CA 94110 (US). **PETERS, Brock** [US/US]; 43 Albion Street, San Francisco, CA 94103 (US). **SESHAGIRI, Somasekar** [IN/US]; 1012 Porto Marino Drive, San Carlos, CA 94070 (US).

(74) Agents: **PASQUALONE, Danielle, M.** et al.; c/o Genentech, INC., 1 DNA Way MS 49, South San Francisco, CA 94080 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

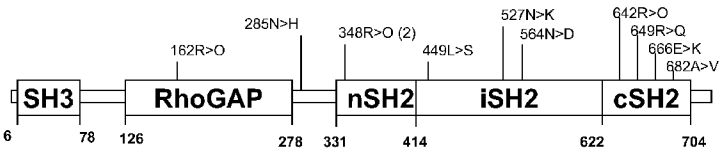
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

[Continued on next page]

(54) Title: GENETIC VARIATIONS ASSOCIATED WITH TUMORS

FIGURE 3

Somatic mutations in PIK3R1



Sample	p85 α (PIK3R1)	PTEN
Colon 1	HETSUB.285N>H, 527N>K, 564N>D	HETSUB.31N>H, 28I>M
Colon 2	HETSUB.162R>O, 666E>K	HETSUB.232R>O
Colon 3	HETSUB.642R>O	
Colon 4	HETSUB.348R>O	
Colon 5	HETSUB.348R>O, 574R>I	
Colon 6	HETSUB.682A>V	
Colon 7	HETSUB.649R>Q	
Breast	HETSUB.449L>S	

- 6.4% (7/108) of colorectal cancers have p85α mutation
- 1.6% (1/62) of breast cancers have p85α mutation

(57) Abstract: Nucleotide and amino acid variations associated with tumors are provided. Methods for detecting variations and for diagnosing and treating tumors are provided.

WO 2008/070325 A3

— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

(88) Date of publication of the international search report:
5 March 2009

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/082397

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68

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)
C12Q

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, BIOSIS, EMBASE, WPI Data, CHEM ABS Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SAMUELS Y ET AL: "High frequency of mutations of the PIK3CA gene in human cancers" SCIENCE, WASHINGTON, DC, vol. 304, no. 5670, 23 April 2004 (2004-04-23), page 554, XP002375241 ISSN: 0036-8075 ------ -/--	

[X] 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) 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
26 November 2008	13/01/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Mabit, Hélène

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/082397

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PHILP AMANDA J ET AL: "The phosphatidylinositol 3'-kinase p85alpha gene is an oncogene in human ovarian and colon tumors" CANCER RESEARCH, vol. 61, no. 20, 15 October 2001 (2001-10-15), pages 7426-7429, XP002505603 ISSN: 0008-5472 cited in the application	
A	PARSONS RAMON: "Human cancer, PTEN and the PI-3 kinase pathway." SEMINARS IN CELL & DEVELOPMENTAL BIOLOGY, vol. 15, no. 2, April 2004 (2004-04), pages 171-176, XP002505604 ISSN: 1084-9521	
P,A	CARPTEN JOHN D ET AL: "A transforming mutation in the pleckstrin homology domain of AKT1 in cancer" NATURE (LONDON), vol. 448, no. 7152, July 2007 (2007-07), page 439, XP002484330 ISSN: 0028-0836	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/082397

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.:
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:

see additional sheet

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.:

claims 35-43 and claims 1-34, 44-53 partially (inventions 1, 51, 52 and 60)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-34, 44-53 partially

Subject-matter of claims 1-34, 44-53 partially, wherein the polynucleotide comprises a nucleotide variation in the gene AKT-1

Invention 2: claims 1-34, 44-54 partially

Subject-matter of claims 1-34, 44-53 partially, wherein the polynucleotide comprises a nucleotide variation in AKT-2 gene

---

Inventions 3-50: claims 1-34, 44-54 partially

Subject-matter of claims 1-34, 44-53 partially, wherein the polynucleotide comprises a nucleotide variation in the genes ALK, ARAF, AXIN1, AXIN2, AXL, BAX, BCL-XL, B-raf, CBL, CBLB, CBLC, CDKN2A, CIAS1, cMet, CXCR4, DDR2, DUBA2, EDG1, EGFL11, EGFR, ERBB3, ERBB4, ETBR, FGFR1, FGFR2, FGFR3, FGFR4, FRAP1, GPR73, Her2, IGF1-R, JAG1, JAK2, KRAS, MAP2K1, MELK, Notch2, NOTCH3, NRP1, NTC1, NTRK1, NTRK2, NTRK3, OTUD1, PAK6, PDGFRB, PDK1 respectively

---

Invention 51: claims 40-41 and claims 1-34, 44-54 partially,

Subject-matter of claims 40-41, and of claims 1-34, 44-53 partially, wherein the polynucleotide comprises a nucleotide variation in the gene PIK3CA

Invention 52: claims 35-39 and claims 1-34, 44-54 partially

Subject-matter of claims 35-39, and of claims 1-34, 44-53 partially, wherein the polynucleotide comprises a nucleotide variation in the gene PIK3R1

Inventions 53-59: claims 1-34, 44-54 partially

Subject-matter of claims 1-34, 44-53 partially, wherein the polynucleotide comprises a nucleotide variation in the genes PIK3R2, PIK3R4, PIK3R5, PLK1, PRKCB1, PRKC1, PTCH respectively

---

Invention 60: claims 42, 43 and claims 1-34, 44-54 partially

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Subject-matter of claims 42-43, and of claims 1-34, 44-53 partially, wherein the polynucleotide comprises a nucleotide variation in the gene PTEN

Inventions 61-76: claims 1-34, 44-54 partially

Subject-matter of claims 1-34, 44-53 partially, wherein the polynucleotide comprises a nucleotide variation in the genes RB1, Rem2, RET, RON, SMAD2, Stk6, SUFU, TGFBR1, TGFBR2, TP53, USP21, USP24, USP25, USP28, USP35, VEGFR2 respectively

---