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- (81) **Designated States** (unless otherwise indicated, for every  
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BZ, CA, CH, CL, 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, IR, IS, JP, KE, KG, KN, KP, KR,

KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,  
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,  
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,  
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,  
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LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,  
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**Published:**

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the  
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- (88) **Date of publication of the international search report:**  
26 November 2015



WO 2015/153997 A3

(54) **Title:** NOTCH3 ANTIBODIES AND USES THEREOF

(57) **Abstract:** Novel antibodies that specifically bind human NOTCH3 are provided. Methods and kits using these antibodies to de-  
termine the level of NOTCH3 expression in tumor samples are provided.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/24291

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC(8) - A61K 39/00; C07K 16/00 (2015.01)  
 CPC - A61K 38/00, 39/00, 2039/505; C12Q 1/6886; C07K 16/30, 16/00, 2317/254  
 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): A61K 39/00; C07K 16/00 (2015.01)  
 CPC: A61K 38/00, 39/00, 2039/505; C12Q 1/6886; USPC: 435/7.23, 7.21, 7.2, 7.1, 4; 424/133.1, 130.1; 530/387.1, 386, 380, 350

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)

PatSeer; Google; Google Scholar; Dialog ProQuest; Entrez Pubmed; Science Direct; NCBI Protein BLAST; 'anti-Notch3,' antibody, 'heavy chain,' 'light chain,' 'CDR,' 'patient responsiveness,' 'pancreatic cancer,' 'tumor sample'

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0111958 A1 (GURNEY, AL et al.) May 6, 2010; figures 8, 12B; paragraphs [0015], [0018]-[0020], [0035], [0036], [0049], [0053], [0067], [0071], [0289], [0290], [0325], [0326]	1-6, 29-33
A	US 2009/0155250 A1 (CHEN, Z et al.) June 18, 2009; paragraphs [0014], [0041]; figure 6; SEQ ID NO: 49	1-6, 29-33
A	US 2014/0093497 A1 (REIMANN, KA et al.) April 3, 2014; paragraph [0031]; figure 1; SEQ ID NO: 2	1-6, 29-33
A	US 2012/0276099 A1 (POPPE, R) November 1, 2012; paragraphs [0069], [0073]; SEQ ID NO: 2	1-6, 29-33
A	US 2011/0274683 A1 (WONG, J et al.) November 10, 2011; paragraph [0019]; SEQ ID NO: 24	1-6, 29-33
A	US 2002/0010320 A1 (FETT, JW) January 24, 2002; paragraph [0101]; SEQ ID NO: 18	1-6, 29-33
A	WO 2002/059318 A1 (KOREA RESEARCH INSTITUTE OF BIOSCIENCE AND BIOTECHNOLOGY) August 1, 2002; page 20, lines 23-24; figure 6	1-6, 29-33
A	US 2012/0082659 A1 (LAND, H et al.) April 5, 2012; entire document	1-6, 29-33

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 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 02 September 2015 (02.09.2015)	Date of mailing of the international search report <b>23 SEP 2015</b>
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Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer  Shane Thomas  PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/24291

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a.  forming part of the international application as filed:
    - in the form of an Annex C/ST.25 text file.
    - on paper or in the form of an image file.
  - b.  furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
  - c.  furnished subsequent to the international filing date for the purposes of international search only:
    - in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
    - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2.  In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/24291

**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.: 7, 11-14, 16-28, 34-47.  
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 Supplemental Page-\*\*\*

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.:

Group I: Claims 1-6, 29-33

**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**  
Information on patent family members

International application No.  
PCT/US15/24291

\*\*\*-Continued from Box No. 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.

Group I: Claims 1-6 and 29-33 are directed toward an isolated antibody that specifically binds the extracellular domain of human NOTCH3, which comprises: (a) a heavy chain CDR1 comprising TKYTIH (SEQ ID NO: 39), a heavy chain CDR2 comprising YINPSNDYTNYNQTFKD (SEQ ID NO:40), and a heavy chain CDR3 comprising ARGTTPYSLDY (SEQ ID NO:41); and (b) a light chain CDR1 comprising RASESVDNYGMSFMN (SEQ ID NO:42), a light chain CDR2 comprising AASNQGS (SEQ ID NO: 43), and a light chain CDR3 comprising LQSKEVP (SEQ ID NO:44).

Groups II: Claims 8 and 9 are directed toward an isolated antibody comprising a heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-121156 and a light chain variable region encoded by the plasmid deposited with ATCC as PTA-121155.

Group III: Claim 10 is directed toward an antibody produced by a hybridoma deposited with ATCC as PTA-121154.

Group IV: Claim 15 is directed toward an isolated polynucleotide comprising SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:35, or SEQ ID NO:36.

Groups I-II share the technical features including an isolated antibody which comprises a heavy chain region and a light chain region. Groups I-III share the technical features including an antibody. Groups I and IV do not share any technical features and, accordingly, lack unity a priori.

However, these shared technical features are previously disclosed by US 8,524,234 B2 to Getts, et al. (hereinafter 'Getts').

Getts discloses an isolated antibody which comprises a heavy chain region and a light chain region (column 4, lines 54-65).

Since none of the special technical features of the Groups I-IV inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Getts reference, unity of invention is lacking.