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61/183,244 2 June 2009 (02.06.2009) US(71) Applicant (for all designated States except US): **MERCK SHARP & DOHME CORP.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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[Continued on next page]

(54) Title: GENERATION, CHARACTERIZATION AND USES THEREOF OF ANTI-NOTCH3 ANTIBODIES

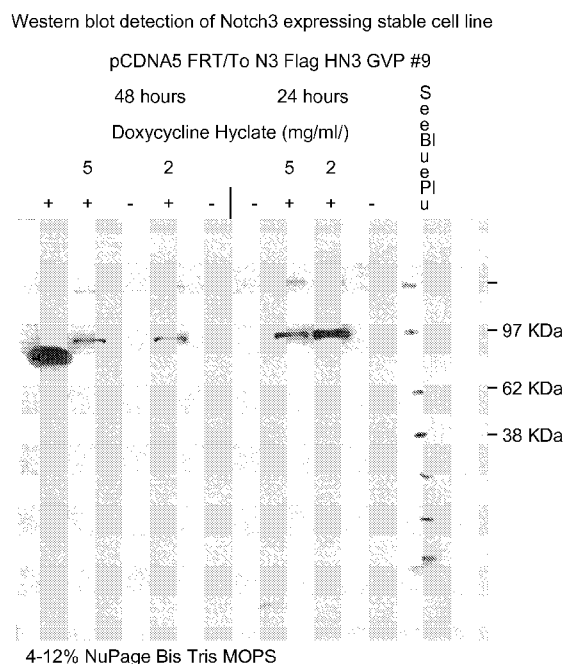


FIG. 1

(57) Abstract: The present invention relates to mammalian antibodies, preferably fully human monoclonal antibodies and antigen-binding portions thereof that specifically bind to a cell surface receptor, wherein the receptor protein is a Notch3 receptor protein. Some of the disclosed antibodies bind Notch3 to the exclusion of other members of the Notch receptor family, while other antibodies bind Notch 1 and Notch3. Nucleic acid molecules encoding the Notch antibodies as well as methods of use thereof are also disclosed. Also included are pharmaceutical compositions comprising these antibodies and methods of using the antibodies and compositions thereof for treatment and diagnosis of pathological hyperproliferative oncogenic disorders associated with expression of Notch3 including aberrant activation of each of these receptors.

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

Published:

- with international search report (Art. 21(3))

(88) Date of publication of the international search report:

27 January 2011

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/35920

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 16/00; G01N 33/53 (2010.01)

USPC - 530/388.1; 435/7.1

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 16/00; G01N 33/53 (2010.01)

USPC - 530/388.1; 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 530/387.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google Scholar: notch3, notch 3, notch-3, notch protein 3, notch homolog 3, notch homolog protein 3, casil, cadasil, antibod\$, immunog\$, anti, ab, mutat\$, mutant, substitut\$, variable, heavy, light, glycosyl\$, cancer, cancerous, tumor, tumor\$, hyperprolif\$, malign\$, threshold. GenCore 6.3: SEQ ID NO:888 and 793

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/0047285 A1 (GURNEY et al.) 19 February 2009 (19.02.2009) para [0069]-[0071]; [0083]-[0084]; [0088]	10
A	US 2008/0118520 A1 (LI et al.) 22 May 2008 (22.05.2008) para [0009]-[0010]; [0033]-[0034]; [0044]; [0051]; [0140]-[0142]; [0176]	1-10, 12-55, 57-81
A	US 2006/0062789 A1 (RUBEN et al.) 23 March 2006 (23.03.2006) para [0013]; [0166]-[0167]; Table 1; SEQ ID NOs: 1184, 1606, 1729, 1910	1-10, 12-55, 57-81

☐ 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

16 November 2010 (16.11.2010)

Date of mailing of the international search report

29 NOV 2010

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/35920

Box No. I 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 filed or furnished:

a. (means)

☐

on paper

☒

in electronic form

b. (time)

☐

in the international application as filed

☒

together with the international application in electronic form

☐

subsequently to this Authority for the purposes of search

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 in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

GenCore 6.3: SEQ ID NO:888 and 793

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/35920

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.: 11 and 56
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.

Group I+: claims 1-81, drawn to an isolated Notch-3 specific antibody. The first invention is restricted to an antibody comprising a light chain of SEQ ID NO: 888, the first entry listed in Table 6, and a heavy chain of SEQ ID NO: 793, the first entry listed in Table 5. Due to the number of sequences in this application, an additional invention(s) of Group I+ will be defined as necessary depending on Applicant's ultimate payment of additional fees. The additional sequences will be searched if applicant pays for each additional sequence or shows that the sequences share a special technical feature, i.e. a common structure or feature that defines a contribution over the prior art. Note that each additional sequence to be searched must be specified by the Applicant in the response to this invitation and must either (1) have an additional invention fee paid or (2) have a showing that the sequences share a common structure or feature that defines a contribution over the prior art.

[NOTE: Claims 11 and 56 were excluded from the search, because they are improper multiple dependent claims.]

***** See Supplemental Box to continue *****

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.: 1-10, 12-55, 57-81, limited to SEQ ID NOs: 793, 888

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 10/35920

***** Supplemental Box *****

continuation of Box No. III: Observations where unity of invention is lacking

The inventions listed as Group I+ 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 inventions of Group I+ share the technical feature of an isolated Notch-3 specific antibody. However, this shared technical feature does not represent a contribution over prior art. Specifically, a paper titled "The ectodomain of the Notch3 receptor accumulates within the cerebrovasculature of CADASIL patients" by Joutel, et al. (J. Clin. Invest. 2000, 105:597-605) discloses a such an antibody (pg 598, col 2, "The following primary antibodies were used: anti-Notch3 extracellular domain (1E4 and 2E11 hybridoma supernatant, 1:5 dilution); anti- Notch3 intracellular domain (6A10 hybridoma supernatant, 1:2 dilution)"). As said antibody was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another technical feature of the inventions listed as Group I+ is a light chain of the specific amino acid sequence and a heavy chain of the specific amino acid sequence recited therein. As no significant structural similarities can readily be ascertained 1) among the amino acid sequences of the light chains, and 2) among the amino acid sequences of the heavy chains the inventions do not share a special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

The inventions of Group I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.