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16 April 2009

(54) Title: ACTIVATING MUTATIONS IN NOTCH-1

(57) Abstract: The present invention relates to certain methods and compositions for diagnosing, preventing, treating, and/or ameliorating the effects of various conditions in a mammal, such as T-cell lymphoblastic leukemia and lymphoma. The present invention also relates, inter alia, to methods of determining whether reducing or blocking NOTCH 1 activation will be effective to treat, prevent, or ameliorate the effects of a cancer in a patient. Such methods may include determining if the patient harbors one or more mutations in exon 28 or intron 27 of the NOTCH1 gene.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/07958

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - G01N 33/48; C12Q 1/00 (2009.01)

USPC - 435/4; 436/64

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) - G01N 33/48; C12Q 1/00 (2009.01)

USPC - 435/4; 436/64

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 424/144.1; 435/69.1 and freeform (search terms provided below)

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

PubWest, DialogPRO, Google Patent, Google Scholar, PubMed/Medline, WIPO

Search Terms Used: notch-1, mutations, expression, juxtamembrane, expansion, gene, neuroblastoma, breast cancer, ovarian cancer, T-cell leukemia, myeloleukemia, solid, tumor, and combinations thereof.

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 2007/0077245 A1 (ASTER et al.) 5 April 2007 (05.04.2007), para [0003], [0010], [0012], [0015], [0017], [0023], [0026], [0027], [0034], [0036], [0043], [0050], [0055], [0081], [0113].	1 - 9, 11, 13 - 16 ----- 10, 12
Y	US 2007/0083334 A1 (MINTZ et al.) 12 April 2007 (12.04.2007), para [0260], [0474], SEQ ID NO: 332143 (100% match to SEQ ID NO:1).	10
Y	Mann et al., "Complete Human NOTCH 1 (hN1) cDNA Sequence", direct submission to GenBank, 22 November 2000, Accession No: AF308602. Internet document downloaded 22 January 2009.	12
A	US 6,703,221 B1 (CHAN et al.) 9 March 2004 (09.04.2004).	5

☐ 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

20 January 2009 (20.01.2009)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/07958

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:

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 1-16, directed to an assay for identifying compounds to treat cancer comprising: *determining if Notch1 expression is affected in cells treated with a candidate compound.*

Group II: claims 17-31, directed to a method of making a cell line that overexpresses Notch1 by introducing a mutation into the juxtamembrane region of a Notch1 receptor

Group III: claims 32-43, directed to an isolated polynucleotide that encodes a Notch1 receptor having a mutation in the extracellular juxtamembrane region.

- Please see extra sheet for continuation -

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.:
1-16

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.

Continuation of Box III:

Group IV: claims 44-64, directed to a method of determining whether altering Notch1 activation will be effective to treat cancer in a patient comprising screening the patient for mutations in exon 28 or intron 27 of a Notch1 gene.

The inventions listed as Groups I - IV 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 special technical feature of the Group I claims is an assay for identifying compounds to treat cancer by determining if Notch1 expression is affected - not required by the claims of Groups II-IV. The special technical feature of the Group II claims is a method of making a cell line that over expresses Notch1 by introducing a mutation into the juxtamembrane region - not required by the claims of Groups I, III or IV. The special technical feature of the Group III claims is an isolated nucleic acid encoding a mutation to Notch1 in the extracellular juxtamembrane region - not required by the claims of Groups I, II or IV. The special technical feature of the Group IV claims is a genetic screen for patients to assess the probability of inhibitors of Notch1 activation to be useful for treatment of cancer - not required of the claims of Groups I-III.

The only common technical element shared by the above groups is that they are related to mutation of Notch1 in the juxtmembrane region, and its possible association with cancer. However, this common technical element does not improve over the prior art of US 2007/0077245 A1 to Aster et al. (see abstract, para [0113]), wherein Aster teaches both the association of mutations in Notch1 to cancer, and the requirement of the juxtamembrane region to be subject to proteolytic cleavage for activation. Therefore, the inventions of Groups I -IV lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.