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(57) Abstract: An isolated human antibody or a fragment of a human antibody which specifically binds to human delta-like ligand 4 (hDII4) and blocks hDII4 binding to a Notch receptor. The human anti- hDII4 antibody or antibody fragment binds hDII4 with an affinity of ≤ 500 pM, as measured by surface plasmon resonance.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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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)
 C07K A61K A61P

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 , EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	LAURET E ET AL: "Membrane-bound Delta-4 Notch ligand reduces the proliferative activity of primitive human hematopoietic CD34+CD3810W cells while maintaining their LTC-IC potential" 20040401; 20040400, vol. 18, no. 4, 1 April 2004 (2004-04-01), pages 788-797, XP002421237 page 789, left-hand column, paragraph 5 - right-hand column, paragraph 1 page 790, right-hand column, paragraphs 3,4 page 791; figure 1 <div style="text-align: center;">----- -/--</div>	1-17

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
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Name and mailing address of the ISA/ European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Ci Iensek , Zoran
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International application No

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X	<p>WILLIAMS CASSIN KIMMEL ET AL: "Up-regulation of the Notch ligand Delta-like 4 inhibits VEGF-i induced endothelial cell function" BLOOD, W.B.SAUNDERS COMPANY, ORLANDO, FL, vol. 107, no. 3, 1 February 2006 (2006-02-01), pages 931-939, XP002457722 ISSN: 0006-4971 page 932, right-hand column, paragraph 3 page 933; figure 1 page 934, left-hand column, paragraphs 3,4 -----</p>	1-17
X	<p>HAINAUD PATRICIA ET AL: "The role of the vascular endothelial growth factor-Del ta-1 like 4 ligand/Notch4-ephrin B2 cascade in tumor vessel remodeling and endothelial cell functions." CANCER RESEARCH 1 SEP 2006, vol. 66, no. 17, 1 September 2006 (2006-09-01), pages 8501-8510, XP002484535 ISSN: 1538-7445 page 8502, right-hand column, paragraph 2 page 8503, right-hand column figures 2,3,5 -----</p>	1-17
X	<p>DANDO JONATHAN S ET AL: "Notch/Del ta4 interaction in human embryonic liver CD34+ CD38- cells: positive influence on BFU-E production and LTC-IC potential maintenance." STEM CELLS (DAYTON, OHIO) APR 2005, vol. 23, no. 4, April 2005 (2005-04), pages 550-560, XP002484536 ISSN: 1066-5099 page 551, right-hand column, paragraph 3; figure 1 -----</p>	1-17
X	<p>SUGIMOTO ET AL: "Delta-4 Notch ligand promotes erythroid differentiation of human umbilical cord blood CD34<+> cells" EXPERIMENTAL HEMATOLOGY, NEW YORK, NY, US, vol. 34, no. 4, 1 April 2006 (2006-04-01), pages 424-432, XP005353748 ISSN: 0301-472X the whole document ----- -/--</p>	1-17

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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	<p>DORSCH MARION ET AL: "Ectopic expression of Delta4 impairs hematopoietic development and leads to lymphoprol iterative disease." BLOOD 15 SEP 2002, vol. 100, no. 6, 15 September 2002 (2002-09-15), pages 2046-2055, XP002484537 ISSN: 0006-4971 page 2047, right-hand column, paragraph 8 - page 2048, left-hand column, paragraph 1 figure 1</p>	1-17
X	<p>LIU ZHAO-JUN ET AL: "Inhibition of endothelial cell proliferation by Notchl signaling is mediated by repressing MAPK and PI3K/Akt pathways and requires MAM11." THE FASEB JOURNAL : OFFICIAL PUBLICATION OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY MAY 2006, vol. 20, no. 7, May 2006 (2006-05), pages E201-E210, XP002484538 ISSN: 1530-6860 page E202, right-hand column, paragraph 2 page E203, right-hand column, paragraph 4 page E204; figure 1</p>	1-17
A	<p>US 2006/134121 A1 (THURSTON GAVIN [US] ET AL) 22 June 2006 (2006-06-22) page 4, left-hand column - page 6, left-hand column</p>	1-17
P, X	<p>NOGUERA-TROISE IRENE ET AL: "Blockade of Dll4 inhibits tumour growth by promoting non-productive angiogenesis" NATURE, NATURE PUBLISHING GROUP, LONDON, vol. 444, no. 7122, 21 December 2006 (2006-12-21), pages 1032-1037, XP002452162 ISSN: 0028-0836 the whole document</p>	1-17
E	<p>WO 2008/060705 A (GENENTECH INC [US]; YAN MINHONG [US]; WU YAN [US]) 22 May 2008 (2008-05-22) the whole document</p>	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006134121	A1	NONE	
WO 2008060705	A	NONE	