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(54) Title: ANTIBODIES FOR THE DETECTION OF INTEGRIN COMPLEXES IN FFPE MATERIAL

(57) Abstract: The invention relates to antibodies that are capable to bind the extracellular domain of integrin. Another object of the invention concerns the use of said antibodies for detecting integrins in archival formalin fixed paraffin embedded (FFPE) tissue. The invention also relates to methods for preparing monoclonal rabbit antibodies, wherein the immunogen is an insect expression culture-derived recombinant extracellular integrin domain, and another method for screening anti-integrin antibodies that discriminate between closest integrin homologues and that are especially suited for immunohistochemistry in FFPE material.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2010/004313

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. (means)
 - on paper
 - in electronic form
 - b. (time)
 - in the international application as filed
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A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/28 G01N33/53 C07K16/00 C12N15/13 ADD.				
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 G01N				
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, Sequence Search, BIOSIS, EMBASE, 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	HII L L ET AL: "Endometrial vascular and glandular expression of integrin alpha(v)beta3 in women with and without endometriosis.", HUMAN REPRODUCTION (OXFORD, ENGLAND) APR 1998 LNKD- PUBMED:9619566, vol. 13, no. 4, April 1998 (1998-04), pages 1030-1035, XP002604680, ISSN: 0268-1161 page 1034 - page 1035 ----- -/--	1,2,7, 13,14		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.				
* Special categories of cited documents : <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> </tr> </table>			"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
"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			
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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, Fax: (+31-70) 340-3016	Authorized officer Wagner, René			

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/004313

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LAURENS NANCY ET AL: "Single and combined effects of alphavbeta3- and alpha5beta1-integrins on capillary tube formation in a human fibrinous matrix.", ANGIOGENESIS 2009 LNKD- PUBMED:19449108, vol. 12, no. 3, 16 May 2009 (2009-05-16), pages 275-285, XP002615474, ISSN: 1573-7209 figure 1	1,2,7, 13,14
X	----- SINGH B ET AL: "Vascular expression of the alpha(v)beta(3)-integrin in lung and other organs.", AMERICAN JOURNAL OF PHYSIOLOGY. LUNG CELLULAR AND MOLECULAR PHYSIOLOGY JAN 2000 LNKD- PUBMED:10645910, vol. 278, no. 1, January 2000 (2000-01), pages L217-L226, XP002615475, ISSN: 1040-0605 figure 1	1,2,7, 13,14
X	----- MITJANS F ET AL: "In vivo therapy of malignant melanoma by means of antagonists of alphav integrins.", INTERNATIONAL JOURNAL OF CANCER. JOURNAL INTERNATIONAL DU CANCER 1 SEP 2000 LNKD- PUBMED:10925366, vol. 87, no. 5, 1 September 2000 (2000-09-01), pages 716-723, XP002604681, ISSN: 0020-7136 figure 1	1,2,7, 13,14
X	----- WO 89/05155 A1 (SCRIPPS CLINIC RES [US]) 15 June 1989 (1989-06-15) page 17	1,2,7, 13,14
A	----- MITJANS F ET AL: "An anti-alpha v-integrin antibody that blocks integrin function inhibits the development of a human melanoma in nude mice.", JOURNAL OF CELL SCIENCE AUG 1995 LNKD- PUBMED:7593323, vol. 108 (Pt 8), August 1995 (1995-08), pages 2825-2838, XP002615476, ISSN: 0021-9533 page 2825 - page 2835 ----- -/--	1,2,7, 13,14

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/004313

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Unknown: "Product data sheet of anti-integrin alpha v antibody Mouse Mab (272-17E6) and corresponding safety data sheet dated 29-05-2003", E. Merck chemicals 29 May 2003 (2003-05-29), XP002615477, Retrieved from the Internet: URL:http://www.merck-chemicals.com/usa/life-science-research/anti-integrin-alpha-v-alpha-b-1-mouse-mab-272-17e6/EMD_BIO-407286/p_JR6b.s1LruAAAAEWZmEfVhTm [retrieved on 2010-12-23] the whole document	1,6,7,15
X	----- WO 2009/010290 A2 (MERCK PATENT GMBH [DE]; GOODMAN SIMON [DE]; HAHN DIANE [DE]; MITJANS F) 22 January 2009 (2009-01-22) page 2 - line 24	1,6,7,14
X	----- VAN AARSEN LOUISE A KOOPMAN ET AL: "Antibody-mediated blockade of integrin alpha v beta 6 inhibits tumor progression in vivo by a transforming growth factor-beta-regulated mechanism.", CANCER RESEARCH 15 JAN 2008 LNKD-PUBMED:18199553, vol. 68, no. 2, 15 January 2008 (2008-01-15), pages 561-570, XP002615478, ISSN: 1538-7445 page 562	1,4,7,14
X	----- US 2005/255102 A1 (VIOLETTE SHELIA M [US] ET AL) 17 November 2005 (2005-11-17) paragraph [0101]; table 1	1,4,7,14
X	----- WO 2004/007530 A2 (BLOOD RES CENTER [US]; SPRINGER TIMOTHY A [US]; TAKAGI JUNICHI [US]) 22 January 2004 (2004-01-22) page 56 - line 4	8-11
Y	page 73; sequence 15	12
X	----- DATABASE Geneseq [Online] 17 June 2004 (2004-06-17), "Human integrin beta3 subunit 1JV2 (chain B) mature protein.", XP002604682, retrieved from EBI accession no. GSP:ADM99600 Database accession no. ADM99600 the whole document ----- -/--	8-11

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/004313

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	XIONG JIAN-PING ET AL: "Purification, analysis, and crystal structure of integrins", METHODS IN ENZYMOLOGY; [METHODS IN ENZYMOLOGY], ACADEMIC PRESS INC, SAN DIEGO, CA, US, vol. 426, 1 January 2007 (2007-01-01), pages 307-336, XP009142830, ISSN: 0076-6879	8-11
Y	page 313	12
X	----- US 2007/178098 A1 (WAY JEFFREY [US] ET AL) 2 August 2007 (2007-08-02) paragraph [0049] - paragraph [0050]	12
X	----- MEHTA R J ET AL: "Transmembrane-truncated alphavbeta3 integrin retains high affinity for ligand binding: evidence for an 'inside-out' suppressor?", THE BIOCHEMICAL JOURNAL 1 MAR 1998 LNKD-PUBMED:9480902, vol. 330 (Pt 2), 1 March 1998 (1998-03-01), pages 861-869, XP002615479, ISSN: 0264-6021 page 862	8-10
A	----- Unknown: "integrin alpha-V:sc-9969", Santa Cruz biotechnology catalogue 2004, XP002604683, Retrieved from the Internet: URL:http://datasheets.scbt.com/sc-9969.pdf [retrieved on 2010-10-11] the whole document	1,2,7-15
A	----- US 2004/001835 A1 (WOESSNER RICHARD [US] ET AL) 1 January 2004 (2004-01-01) the whole document	1,2,7-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/EP2010/004313

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8905155	A1	15-06-1989	AU 2807189 A 05-07-1989
			EP 0341303 A1 15-11-1989
			FI 893475 A 18-07-1989
			JP 2502156 T 19-07-1990

WO 2009010290	A2	22-01-2009	AU 2008277907 A1 22-01-2009
			CA 2693863 A1 22-01-2009
			CN 101687039 A 31-03-2010
			EA 201070150 A1 30-08-2010
			EP 2167128 A2 31-03-2010
			JP 2010533480 T 28-10-2010
			KR 20100057010 A 28-05-2010
			US 2010254977 A1 07-10-2010

US 2005255102	A1	17-11-2005	US 2009186036 A1 23-07-2009

WO 2004007530	A2	22-01-2004	AU 2003256584 A1 02-02-2004

US 2007178098	A1	02-08-2007	US 2011038877 A1 17-02-2011

US 2004001835	A1	01-01-2004	US 2009148459 A1 11-06-2009
