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- (74) **Agents:** TERMES, Lance et al.; Alston & Bird LLP, Bank of America Plaza, 101 South Tryon Street, Suite 4000, Charlotte, NC 28280-4000 (US).
- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, 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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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27 December 2013



WO 2013/152001 A3

(54) **Title:** ANTI-HLA-B*27 ANTIBODIES AND USES THEREOF

(57) **Abstract:** The present invention provides antibodies and antigen-binding fragments thereof that specifically bind HLA-B*27 (also called HLA-B27). In certain embodiments, the antibodies of the invention bind soluble and/or cell surface-expressed forms of HLA-B*27. The antibodies of the present invention, in certain embodiments, inhibit HLA-B*27-mediated activation of T cells. Certain exemplary antibodies of the present invention exhibit enhanced binding to HLA-B*27 as compared to other HLA-B allelic variants (e.g., HLA-B*07). The present invention also provides anti-HLA-B*27 antibodies with pH-dependent binding characteristics (e.g., higher affinity binding at neutral pH than at acidic pH). The antibodies of the invention are useful for the treatment of diseases and disorders associated with HLA-B*27 expression, including ankylosing spondylitis and other spondyloarthropathies.

INTERNATIONAL SEARCH REPORT

International application No PCT/US2013/034952

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/28 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 A61K				
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) EPO-Internal, BIOSIS, WPI Data, EMBASE				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	Wilfried H.B.M. Levering ET AL: "Flow Cytometric Screening for the HLA-B27 Antigen on Peripheral Blood Lymphocytes" In: "Current Protocols in Cytometry", 1 May 2001 (2001-05-01), John Wiley & Sons, Inc., Hoboken, NJ, USA, XP055069131, ISBN: 978-0-47-114295-9 DOI: 10.1002/0471142956.cy0622s33, page 6.22.1, last paragraph - page 6.22.2, paragraph 1; tables 6.22.2, 6.22.4 page 6.22.7, left-hand column, paragraph 3 - right-hand column, paragraph 2 ----- -/--	1-9,21		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.</td> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> See patent family annex.</td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
<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 :				
"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	Date of mailing of the international search report			
5 November 2013	14/11/2013			
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 Loubradou, Gabriel			

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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>COATES E ET AL: "Routine HLA-B27 typing by flow cytometry: Differentiation of the products of HLA-B*2702, B*82705 and B*2708", EUROPEAN JOURNAL OF IMMUNOGENETICS, vol. 25, no. 1, February 1998 (1998-02), pages 29-37, XP002702758, ISSN: 0960-7420 abstract; tables 1,3</p>	1-9,21
X	<p>CHRIS DARKE ET AL: "One-tube HLA-B27/B2708 typing by flow cytometry using two "Anti-HLA-B27" monoclonal antibody reagents", CYTOMETRY PART B: CLINICAL CYTOMETRY, vol. 9999B, 1 January 2009 (2009-01-01), pages NA-NA, XP055069138, ISSN: 1552-4949, DOI: 10.1002/cyto.b.20490 abstract page 22, left-hand column, paragraph 3 - paragraph 5 page 23, left-hand column, last paragraph - page r, column 1; tables 1,2,5</p>	1-9,21
X	<p>EP 0 213 824 A2 (GENETIC SYSTEMS CORP [US]) 11 March 1987 (1987-03-11) claims; examples</p>	1-9,21
X	<p>WILFRIED H. B. M. LEVERING ET AL: "Flow cytometric HLA-B27 screening: Cross-reactivity patterns of commercially available anti-HLA-B27 monoclonal antibodies with other HLA-B antigens", CYTOMETRY, vol. 54B, no. 1, 1 July 2003 (2003-07-01), pages 28-38, XP055068775, ISSN: 0196-4763, DOI: 10.1002/cyto.b.10022 abstract; table 2</p>	1-9,21
A	<p>PEI R ET AL: "A Monospecific HLA-B27 Fluorescein isothiocyanate conjugated monoclonal antibody for rapid, simple and accurate HLA-B27 typing", HUMAN IMMUNOLOGY, NEW YORK, NY, US, vol. 36, no. 1, 1 January 1993 (1993-01-01), page 55, XP023851378, ISSN: 0198-8859, DOI: 10.1016/0198-8859(93)90057-8 [retrieved on 1993-01-01] abstract</p>	1-9,21
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/034952

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PEI R ET AL: "A monospecific HLA-B27 fluorescein isothiocyanate-conjugated monoclonal antibody for rapid, simple and accurate HLA-B27 typing", TISSUE ANTIGENS, vol. 41, no. 4, 1993, pages 200-203, XP002702759, ISSN: 0001-2815 page 202, left-hand column, last paragraph - right-hand column, paragraph 1; tables 3,5</p>	1-9,21
A	<p>WEYL D ET AL: "Epitope mapping of human monoclonal antibodies to HLA-B27 by using natural and mutated antigenic variants", HUMAN IMMUNOLOGY, NEW YORK, NY, US, vol. 31, no. 4, 1 August 1991 (1991-08-01) , pages 271-276, XP025810286, ISSN: 0198-8859, DOI: 10.1016/0198-8859(91)90099-U [retrieved on 1991-08-01] page 275, left-hand column, last paragraph - right-hand column, paragraph 1; figure 4 page 272, left-hand column, paragraph 2</p>	1-9,21
A	<p>TRAPANI J A ET AL: "Description of a mouse monoclonal anti-HLA-B27 antibody HLA-ABC-m3", HUMAN IMMUNOLOGY, NEW YORK, NY, US, vol. 7, no. 4, 1 August 1983 (1983-08-01), pages 205-216, XP023940472, ISSN: 0198-8859, DOI: 10.1016/0198-8859(83)90058-7 [retrieved on 1983-08-01] abstract</p>	1-9,21
A	<p>MCHUGH K ET AL: "HD6: a novel monoclonal antibody that recognises a subset of HLA-B27 molecules strongly implicated in spondyloarthritis disease pathogenesis", IMMUNOLOGY, BLACKWELL PUBLISHING, OXFORD, GB, vol. 135, no. Suppl. 1, 1 December 2011 (2011-12-01), page 155, XP009170698, ISSN: 0019-2805 abstract</p>	1-9, 21-24
A,P	<p>WO 2012/047294 A2 (LUDWIG INST FOR CANCER RES LTD [US]; UNIV ZUERICH [CH]; CHANCELLOR MAS) 12 April 2012 (2012-04-12) examples</p>	1-9, 21-24
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INTERNATIONAL SEARCH REPORT

International application No PCT/US2013/034952

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	<p>SRAVAN K. PAYELI ET AL: "Inhibiting HLA-B27 homodimer-driven immune cell inflammation in spondylarthritis", ARTHRITIS & RHEUMATISM, vol. 64, no. 10, 28 October 2012 (2012-10-28), pages 3139-3149, XP055069158, ISSN: 0004-3591, DOI: 10.1002/art.34538 abstract</p> <p align="center">-----</p>	<p>1-9, 21-24</p>

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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 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
 - together with the international application in electronic form
 - subsequently to this Authority for the purpose of search
2. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto 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:

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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:

see additional sheet

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 an 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.:

1-9, 21-24(all partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9, 21-24(all partially)

Subject-matter of claims 1 to 9 and 21 to 24 as far as the heavy chain variable region has the complementary determining regions of the heavy chain variable region having the amino acid sequence consisting in SEQ ID N°2 and the light chain variable region has the complementary determining regions of the light chain variable region having the amino acid sequence consisting in SEQ ID N°10.

2-24. claims: 1-9, 12-18, 21-24(all partially)

Subject-matter of claims 1 to 9, 12-18 and 21 to 24 as far as the heavy chain variable region has the complementary determining regions of the heavy chain variable region having the amino acid sequence consisting in SEQ ID N°X and the light chain variable region has the complementary determining regions of the light chain variable region having the amino acid sequence consisting in SEQ ID N°Y wherein the pairs X/Y are as disclosed in claim 10, namely 18/28, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, and 370/378. Each pair corresponds to a separate invention.

25. claims: 10, 19(completely); 22-24(partially)

Subject-matter of claims 10 and 19 and subject-matter of claims 22 to 24 as far as it refers to claims 9 and 10.

26. claims: 11, 20(completely); 21-24(partially)

Subject-matter of claims 11 and 20 and subject-matter of claims 22 to 24 as far as it refers to claims 11 and 20.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP 0213824	A2	11-03-1987	CA 1340610 C	29-06-1999
			DE 3650327 D1	29-06-1995
			DE 3650327 T2	04-01-1996
			EP 0213824 A2	11-03-1987
			JP 2536851 B2	25-09-1996
			JP S6240297 A	21-02-1987

WO 2012047294	A2	12-04-2012	NONE	
