

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
12 March 2009 (12.03.2009)

PCT

(10) International Publication Number  
**WO 2009/033009 A3**

(51) International Patent Classification:  
A01N 37/18 (2006.01) A61K 39/40 (2006.01)

(21) International Application Number:  
PCT/US2008/075383

(22) International Filing Date:  
5 September 2008 (05.09.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/967,718 5 September 2007 (05.09.2007) US

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(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, BR, BW, BY, BZ, CA, CH, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- with sequence listing part of description published separately in electronic form and available upon request from the International Bureau

(88) Date of publication of the international search report:  
30 April 2009

(54) Title: ANTIBODIES AGAINST FLAGELLIN AND USES THEREOF

(57) Abstract: The present invention provides a novel class of monoclonal antibodies which have a high affinity, broad spectrum neutralizing reactivity to flagellin from various Gram-negative bacteria including, but not limited to, E. coli, Salmonella, Serratia, Proteus, Enterobacter, Citrobacter, Campylobacter and Pseudomonas. The present invention further provides methods of treating inflammatory bowel disease (IBD) and methods of treating enterobacterial infections using anti-flagellin antibodies in humans, other animals and birds.



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**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US 08/75383

<p><b>A. CLASSIFICATION OF SUBJECT MATTER</b>                  IPC(8) - A01N 37/18; A61K 39/40 (2009.01)                  USPC - 514/2; 424/150.1                  According to International Patent Classification (IPC) or to both national classification and IPC</p>														
<p><b>B. FIELDS SEARCHED</b></p> <p>Minimum documentation searched (classification system followed by classification symbols)                  USPC: 514/2; 424/150.1</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched                  USPC: 514/2; 424/130.1, 141.1, 150.1, 164.1, 169.1, 170.1, 800, 801, 803; 530/388.1, 388.2, 388.4, 389.5 (text search)</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)                  Electronic Databases Searched: (EPAB, JPAB, USPT, PBPB); Google Scholar, GenCore Sequence Search (AA)                  Search Terms Used: flagellin, IBD (inflammatory bowel disease), Crohn's disease, ulcerative colitis, antibody monoclonal antibody (mAbs), enterobacteria, gram negative, therapy, SEQ ID NO:1, SEQ ID NO:3</p>														
<p><b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b></p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X --- Y --- A</td> <td>US 2004/0043931 A1 (HERSBERG et al.) 4 March 2004 (04.03.2004). Especially abstract; para [0027], [0040], [0360]</td> <td>1, 8 ----- 9 ----- 4</td> </tr> <tr> <td>X --- Y --- A</td> <td>MATSUMOTO et al. Effect of anti-flagellar human monoclonal antibody on gut-derived Pseudomonas aeruginosa sepsis in mice. Clin Diagn Lab Immunol. July 1999 (07.1999), Vol 6, No 4, Pg 537-541. Especially abstract.</td> <td>2 ----- 10-11 ----- 4</td> </tr> <tr> <td>X --- Y --- A</td> <td>DE VRIES et al. Production of monoclonal antibodies specific for the i and 1,2 flagellar antigens of Salmonella typhimurium and characterization of their respective epitopes. Appl Environ Microbiol. Dec 1998 (12.1998), Vol 64, No 12, Pg 5033-5038. Especially abstract; pg 5033, para 1, 3; pg 5033, para 5 - pg 5034, para 1</td> <td>3, 12 ----- 10-11 ----- 4</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X --- Y --- A	US 2004/0043931 A1 (HERSBERG et al.) 4 March 2004 (04.03.2004). Especially abstract; para [0027], [0040], [0360]	1, 8 ----- 9 ----- 4	X --- Y --- A	MATSUMOTO et al. Effect of anti-flagellar human monoclonal antibody on gut-derived Pseudomonas aeruginosa sepsis in mice. Clin Diagn Lab Immunol. July 1999 (07.1999), Vol 6, No 4, Pg 537-541. Especially abstract.	2 ----- 10-11 ----- 4	X --- Y --- A	DE VRIES et al. Production of monoclonal antibodies specific for the i and 1,2 flagellar antigens of Salmonella typhimurium and characterization of their respective epitopes. Appl Environ Microbiol. Dec 1998 (12.1998), Vol 64, No 12, Pg 5033-5038. Especially abstract; pg 5033, para 1, 3; pg 5033, para 5 - pg 5034, para 1	3, 12 ----- 10-11 ----- 4
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<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/></p>														
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"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</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"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</td> </tr> <tr> <td>"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)</td> <td>"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</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&amp;" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"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	"E" earlier application or patent but published on or after the international filing date	"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	"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)	"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	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed			
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"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family													
"P" document published prior to the international filing date but later than the priority date claimed														
<p>Date of the actual completion of the international search</p> <p>22 January 2009 (22.01.2009)</p>		<p>Date of mailing of the international search report</p> <p><b>02 MAR 2009</b></p>												
<p>Name and mailing address of the ISA/US</p> <p>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents                  P.O. Box 1450, Alexandria, Virginia 22313-1450                  Facsimile No. 571-273-3201</p>		<p>Authorized officer:</p> <p>Lee W. Young</p> <p>PCT Helpdesk: 571-272-4300                  PCT OSP: 571-272-7774</p>												

## INTERNATIONAL SEARCH REPORT

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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.
Y	WO 2004/048600 A2 (GEWIRTZ et al.) 10 June 2004 (10.06.2004). Especially pg 10, para 5 - pg 11, para 1	9
A	WO 2004/110369 A2 (MCWHIRTER) 23 December 2004 (23.12.2004). Especially claim 23; SEQ ID NO:31; Fig 19; pg 71, para 2	4, 24, 26
A	UniProtKB/TrEMBL ENTRY Q8VDD0. Anti-MOG Z12 variable light chain. 1 March 2002 (01.03.2002). Retrieved from the internet at <<URL: <a href="http://www.uniprot.org/uniprot/Q8VDD0">http://www.uniprot.org/uniprot/Q8VDD0</a> >>.	25-26

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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.: 13-23  
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.

Groups 1-2: Claims 1-12, directed to a method of treating inflammatory bowel disease (IBD) in a subject, treating a gram-negative bacterial infection in a subject, or neutralizing enterobacteria, comprising administering to the subject a monoclonal antibody that binds to and neutralizes flagellin, SEQ ID NO:1 will be searched without an additional search fee. The applicant is required to pay an additional search fee for SEQ ID NO:3.

Group 3-4: Claims 24-26, directed to a chimeric monoclonal antibody that binds to flagellin. SEQ ID NO:1 will be searched without an additional search within Group 3. The applicant is required to pay an additional search fee for SEQ ID NO:3.

-----continued in Supplemental Box-----

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.:  
Group 1: claims 1-12 limited to SEQ ID NO:1  
Group 3: claims 24-26, limited to SEQ ID NO:1  
Group 4: claims 24-26, limited to SEQ ID NO:3  
Note: claims 5-7 are removed from Group 1 because they require a search of nonelected sequences
  
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.:

- 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.

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continuation of Box III:

Group 5: Claim 27, directed to a chimeric monoclonal antibody that binds to flagellin, comprising SEQ ID NO:5, 7, 9, 11, 13, and 15.

The inventions listed as Groups 1-5 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:

Each sequence does not share a common utility, and/or share a substantial structural feature disclosed as being essential to that utility.

Additionally, the common technical feature is a monoclonal antibody that binds to flagellin. However, this feature is taught by WO 2004/048600 A2 to Gewirtz et al. (abstract; pg 13, para 3). The compositions of Groups 3-5 do not require the method steps of Groups 1-2.

Thus, Groups 1-5 do not share a special technical feature as defined by PCT Rule 13.2.

Note: claims 5-7 are removed from Group 1 because they require a search of nonelected sequences