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AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
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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,
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TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
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Published:

- with international search report (Art. 21(3))
— with sequence listing part of description (Rule 5.2(a))

- (88) **Date of publication of the international search report:**
27 February 2014

(54) **Title:** ANTI-HEPATITIS B VIRUS ANTIBODIES AND USE THEREOF

(57) **Abstract:** This disclosure provides anti-hepatitis B virus antibodies and methods of treatment, prophylaxis, detection, and diagnosis using the same. In an aspect, the disclosure features methods of detecting a hepatitis B virus or hepatitis B surface antigen in a sample that include contacting a sample with a binding agent (e.g., antibody) disclosed herein; and detecting binding of the binding agent to the sample, thereby detecting a hepatitis B virus or hepatitis B surface antigen in the sample. In yet another aspect, the disclosure features methods of inhibiting hepatitis B virus infection of a cell (e.g., a hepatocyte) that include contacting the cell with a binding agent (e.g., antibody disclosed herein).



INTERNATIONAL SEARCH REPORT

107000002 22.11.2013

International application No.

PCT/US2013/038802

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 16/08 (2013.01)

USPC - 424/149.1

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) - A61K 9/08, 39/00, 39/29, 39/42, 39/395, 47/12, 47/14, 47/18, 47/26; A61P 31/12, 31/20; C07K 16/00, 16/08 (2013.01)

USPC - 424/141.1, 149.1, 161.1, 228.1; 530/300, 387.1, 388.15, 388.2

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

CPC - A61K 9/08, 39/00, 39/29, 39/42, 39/395, 47/12, 47/14, 47/18, 47/26; C07K 16/00, 16/08 (2013.01)

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

PatBase, Google Patents, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/017003 A1 (JENEWEIN et al) 09 February 2012 (09.02.2012) entire document	1-3, 6-15
A	WO 2004/050683 A2 (BABCOOK et al) 17 June 2004 (17.06.2004) entire document	1-3, 6-15
A	US 2008/0152658 A1 (DAGAN et al) 26 June 2008 (26.06.2008) entire document	1-3, 6-15
A	WO 1994/11495 A1 (OSTBERG) 26 May 1994 (26.05.1994) entire document	1-3, 6-15



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

08 November 2013

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/038802

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, the international search was carried out on the basis of a sequence listing filed or furnished:

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 purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing 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:

Specifically, SEQ ID NOs: 44, 45, 47, 49, 51, 215, 216, 218, 220, and 222 were searched.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/038802

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 Extra Sheets

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.:
1-3 and 6-15 (in part), limited to SEQ ID NOs: 44, 45, 47, 49, 51, 215, 216, 218, 220, and 222.

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.

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 need to be paid.

Group I+: claims 1-3 and 6-15 (in part) are drawn to a purified anti-hepatitis B surface antigen antibody, said antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 45, 54, 63, 72, 81, 90, 99, 108, 117, 126, 135, 144, 153, 162, 171, 180, 189, 198, 207, 405, 409, 412, 418, or 421 or a light chain variable region comprising the sequence of SEQ ID NO: 216, 225, 234, 243, 252, 261, 270, 279, 288, 297, 306, 315, 324, 333, 342, 351, 360, 369, 378, 387, or 396.

Group II: claims 4 and 5 and 6-15 (in part) are drawn to a purified anti-hepatitis B surface antigen antibody, said antibody binds to a polypeptide consisting of SEQ ID NO:41; said antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO:1-19 and a light chain variable region comprising the sequence of SEQ ID NO:20-40.

The first invention of Group I+ is restricted to a purified anti-hepatitis B surface antigen antibody comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:45, encoded by SEQ ID NO:44, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:47; CDR2 is selected to be SEQ ID NO:49, and CDR3 is selected to be SEQ ID NO:51; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:216, encoded by SEQ ID NO:215, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:218, CDR2 is selected to be SEQ ID NO:220, and CDR3 is selected to be SEQ ID NO:222. It is believed that claims 1-3 and 6-15 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NOs: 44, 45, 47, 49, 215, 216, 218, 220, and 222.

Applicant is invited to elect additional anti-hepatitis B surface antigen antibodies with specified SEQ ID NO for each heavy and light chain CDR1, 2, and 3 to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a purified anti-hepatitis B surface antigen antibody comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:54, the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:56, CDR2 is selected to be SEQ ID NO:58, and CDR3 is selected to be SEQ ID NO:60; and a light chain, wherein the light chain variable region is selected to be SEQ ID NO:234, the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:236, CDR2 is selected to be SEQ ID NO:238, and CDR3 is selected to be SEQ ID NO:240. Additional anti-hepatitis B surface antigen antibodies will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ and II 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 features of Groups I+, an antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 45, 54, 63, 72, 81, 90, 99, 108, 117, 126, 135, 144, 153, 162, 171, 180, 189, 198, 207, 405, 409, 412, 418, or 421 or a light chain variable region comprising the sequence of SEQ ID NO: 216, 225, 234, 243, 252, 261, 270, 279, 288, 297, 306, 315, 324, 333, 342, 351, 360, 369, 378, 387, or 396, are not found in Group II; the special technical features of Groups II, an antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO:1-19 and a light chain variable region comprising the sequence of SEQ ID NO:20-40, are not found in Groups I+.

The Groups I+ and II share the technical features of a purified anti-hepatitis B surface antigen antibody, the antibody comprising a heavy chain variable region, the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3; and a light chain variable region, the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3. However, these shared technical features do not represent a contribution over the prior art. Specifically, WO 2012/017003 A1 to Jenewein et al. discloses a purified anti-hepatitis B surface antigen antibody (an antibody that binds to a human major histocompatibility complex presenting a peptidic fragment of a hepatitis- B-virus protein, Abstract; the hepatitis-B-virus protein is the hepatitis-B-virus envelope surface protein, Pg. 2, Lns. 16-17), the antibody comprising a heavy chain variable region (provided are isolated nucleic acids encoding an antibody heavy chain as reported herein, Pg. 5, Lns. 18-19; In one embodiment the antibody comprises a VH sequence of SEQ ID NO: 35, Pg. 5, Ln. 12), the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3 (SEQ ID NO:4, CDR-H1 amino acid sequence of c18/A2 mAb; SEQ ID NO:5, CDR-H2 amino acid sequence of c18/A2 mAb; SEQ ID NO:6, CDR-H3 amino acid sequence of c18/A2 mAb, Pg. 43, Lns. 20-23); and a light chain variable region (further provided is an isolated nucleic acid encoding the antibody light chain as reported herein, Pg. 5, Lns. 19-20; In one embodiment the antibody comprises a VL sequence of SEQ ID NO: 39, Pg. 5, Ln. 14), the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3 (SEQ ID NO:8, CDR-H1 amino acid sequence of c18/A2 mAb; SEQ ID NO:9, CDR-H2 amino acid sequence of c18/A2 mAb; SEQ ID NO:10, CDR-H3 amino acid sequence of c18/A2 mAb, Pg. 43, Lns. 24-26).

The Groups I+ antibodies do not share a significant structural element responsible for binding a hepatitis B surface antigen, requiring the selection of alternatives for the light and heavy chain variable regions of the antibody, where "a heavy chain variable region comprising the sequence of SEQ ID NO: 45, 54, 63, 72, 81, 90, 99, 108, 117, 126, 135, 144, 153, 162, 171, 180, 189, 198, 207, 405, 409, 412, 418, or 421 ...a light chain variable region comprising the sequence of SEQ ID NO: 216, 225, 234, 243, 252, 261, 270, 279, 288, 297, 306, 315, 324, 333, 342, 351, 360, 369, 378, 387, or 396".

The Groups I+ share the technical features of a purified anti-hepatitis B surface antigen antibody, the antibody comprising a heavy chain variable region, the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3; and a light chain variable region, the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3. However, these shared technical features do not represent a contribution over the prior art. Specifically, WO 2012/017003 A1 to Jenewein et al. discloses a purified anti-hepatitis B surface antigen antibody (an antibody that binds to a human major histocompatibility complex presenting a peptidic fragment of a hepatitis-B-virus protein, Abstract; the hepatitis-B-virus protein is the hepatitis-B-virus envelope surface protein, Pg. 2, Lns. 16-17), the antibody comprising a heavy chain variable region (provided are isolated nucleic acids encoding an antibody heavy chain as reported herein, Pg. 5, Lns. 18-19; In one embodiment the antibody comprises a VH sequence of SEQ ID NO: 35, Pg. 5, Ln. 12), the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3 (SEQ ID NO:4, CDR-H1 amino acid sequence of c18/A2 mAb; SEQ ID NO:5, CDR-H2 amino acid sequence of c18/A2 mAb; SEQ ID NO:6, CDR-H3 amino acid sequence of c18/A2 mAb, Pg. 43, Lns. 20-23); and a light chain variable region (further provided is an isolated nucleic acid encoding the antibody light chain as reported herein, Pg. 5, Lns. 19-20; In one embodiment the antibody comprises a VL sequence of SEQ ID NO: 39, Pg. 5, Ln. 14), the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3 (SEQ ID NO:8, CDR-H1 amino acid sequence of c18/A2 mAb; SEQ ID NO:9, CDR-H2 amino acid sequence of c18/A2 mAb; SEQ ID NO:10, CDR-H3 amino acid sequence of c18/A2 mAb, Pg. 43, Lns. 24-26), said anti-hepatitis B surface antigen antibody binds to a polypeptide 91% identical to SEQ ID NO: 41 (the hepatitis-B-virus protein is the hepatitis-B-virus envelope surface protein and the peptidic fragments corresponds to amino acid residues 172 to 180 thereof, or the hepatitis-B-virus protein is the hepatitis-B-virus envelope surface protein and the peptidic fragments corresponds to amino acid residues 183 to 191 thereof, or the hepatitis-B-virus protein is the hepatitis-B-virus core protein and the peptidic fragments corresponds to amino acid residues 18 to 27 thereof In one embodiment the peptidic fragment has the amino acid sequence of amino acid residues 172 to 180 of SEQ ID NO: 01, or has the amino acid sequence of amino acid residues 182 to 190 of SEQ ID NO: 01, Pg. 2, Lns. 16-24 (where SEQ ID NO:1 of Jenewein et al. comprises a 91% identity match to SEQ ID NO:41 of the instant application)) with a dissociation constant of 2×10^{-8} M or less, an association rate of $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, or a dissociation rate of $2 \times 10^{-3} \text{ s}^{-1}$ (an antibody that binds to a human major histocompatibility complex presenting a peptidic fragment of an hepatitis-B-virus protein has a dissociation constant (K_d) of less than or equal to 10 nM, less than or equal to 1 nM, less than or equal to 0.001 nM, e.g. less than 10^{-8} M, e.g. from 10^{-8} M to 10^{-13} M, e.g. from 10^{-9} M to 10^{-13} M, Pg. 9, Lns. 2-6).

The inventions listed in Groups I+ and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.