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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
16 January 2014

WO 2013/165982 A3

(54) Title: ANTI-HUMAN CYTOMEGALVIRUS ANTIBODIES AND USE THEREOF

(57) Abstract: This disclosure provides anti-human cytomegalovirus antibodies and methods of treatment, prophylaxis, detection, and diagnosis using the same. In another aspect, the disclosure features therapeutic, prophylactic, and/or diagnostic compositions for human cytomegalovirus infection or for a human cytomegalovirus-related disease that include a binding agent (e.g., antibody) or polynucleotide disclosed herein. In some embodiments, the composition is formulated for ocular or topical administration. The compositions can further include one or more human cytomegalovirus-neutralizing antibodies, an intravenous immunoglobulin preparation, and/or one or more antiviral compounds (e.g., ganciclovir, foscamet, cidofovir, or valganciclovir).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/038814

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/42 (2013.01)
USPC - 424/159.1
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 39/395, 39/42; C07K 16/08 (2013.01)
USPC - 424/139.1, 142.1, 159.1; 530/287.1, 387.1, 388.15

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 39/395, 39/42; C07K 16/081, 16/085 (2013.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google, 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 2011/076883 A1 (GRAWUNDER et al) 30 June 2011 (30.06.2011) entire document	1-3, 8-18
A	POTZSCH et al., "B Cell Repertoire Analysis Identifies New Antigenic Domains on Glycoprotein B of Human Cytomegalovirus which Are Target of Neutralizing Antibodies," Plos Pathogens, Vol. 7, Issue 8, e1002172, Pgs. 1-14. 11 August 2011 (11.08.2011) entire document	1-3, 8-18
A	ISAACSON et al., "Human Cytomegalovirus Glycoprotein B Is Required for Virus Entry and Cell-to-Cell Spread but Not for Virion Attachment, Assembly, or Egress," Journal of Virology, Vol. 83, No. 8, Pgs. 3891-3903. 04 February 2009 (04.02.2009) entire document	1-3, 8-18

☐ 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	Date of mailing of the international search report
12 November 2013	22 NOV 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/038814

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 8-18 (in part), limited to SEQ ID NOs: 21, 22, 24, 26, 28, 66, 67, 69, 71, and 73.

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/038814

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 8-18 (in part) are drawn to a purified anti-human cytomegalovirus envelope glycoprotein B antibody, said antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 22, 31, 40, 49, or 58 or a light chain variable region comprising the sequence of SEQ ID NO: 67, 76, 85, 94, 103, 112, 121, 130, 139, 148, 157, 166, or 175.

Group II: claims 4-7 and 8-18 (in part) are drawn to a purified anti-human cytomegalovirus envelope glycoprotein B antibody that compete for binding to a polypeptide having an amino acid sequence consisting of SEQ ID NO: 2, said antibody comprising a heavy chain amino acid sequence consisting of SEQ ID NO: 3, 4, 5, 6, or 7 and a light chain amino acid sequence consisting of SEQ ID NO: 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17.

The first invention of Group I+ is restricted to a purified anti-human cytomegalovirus envelope glycoprotein B antibody comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:22, encoded by SEQ ID NO:21, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:24, CDR2 is selected to be SEQ ID NO:26, and CDR3 is selected to be SED ID NO:28; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:67, encoded by SEQ ID NO:66, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:69, CDR2 is selected to be SEQ ID NO:71, and CDR3 is selected to be SED ID NO:73. It is believed that claims 1-3 and 8-18 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: 21, 22, 24, 26, 28, 66, 67, 69, 71, and 73.

Applicant is invited to elect additional anti-human cytomegalovirus envelope glycoprotein B antibodies with a specified SEQ ID NO for each heavy and light chain CDR1, 2, and 3 to be searched in a specific combination by paying an additional fee for each set of election.

An exemplary election would be a purified anti-human cytomegalovirus envelope glycoprotein B antibody comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:22, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:24, CDR2 is selected to be SEQ ID NO:26, and CDR3 is selected to be SED ID NO:28; and a light chain, wherein the light chain variable region is selected to be SEQ ID NO:76, 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:78, CDR2 is selected to be SEQ ID NO:80, and CDR3 is selected to be SED ID NO:82.

Additional anti-human cytomegalovirus envelope glycoprotein B 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: 22, 31, 40, 49, or 58 or a light chain variable region comprising the sequence of SEQ ID NO: 67, 76, 85, 94, 103, 112, 121, 130, 139, 148, 157, 166, or 175, are not found in Group II; the special technical features of Groups II, an antibody comprising a heavy chain amino acid sequence consisting of SEQ ID NO: 3, 4, 5, 6, or 7 and a light chain amino acid sequence consisting of SEQ ID NO: 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17, are not found in Groups I+.

The Groups I+ and II share the technical features of a purified anti-human cytomegalovirus envelope glycoprotein B 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 2011/076883 A1 to Grawunder et al. discloses a purified anti-human cytomegalovirus envelope glycoprotein B antibody (this invention relates to binding members, especially antibody molecules, which neutralize the biological effects of human cytomegalovirus (hCMV), Pg. 1, Lns. 4-6; we have developed hCMV neutralizing human antibodies, which bind with high affinity to the gB (glycoprotein B) protein of hCMV, Pg. 8, Lns. 10-12), the antibody comprising a heavy chain variable region (binding member of the invention may comprise an antibody molecule, e.g. an antibody molecule with fully human amino acid sequence. The binding member normally comprises an antibody VH and/or VL domain. VH and VL domains of binding members are also disclosed as part of the invention, Pg. 15, Lns. 26-30), the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3 (antibody VH domain comprises three HCDR regions, designated HCDR1, HCDR2, and HCDR3, Pg. 15, Lns. 32-33 and Pg. 16, Ln. 1); and a light chain variable region (binding member of the invention may comprise an antibody molecule, e.g. an antibody molecule with fully human amino acid sequence. The binding member normally comprises an antibody VH and/or VL domain. VH and VL domains of binding members are also disclosed as part of the invention, Pg. 15, Lns. 26-30), the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3 (antibody VL domain comprises three LCDR regions, designated LCDR1, LCDR2, and LCDR3, pg. 16, Lns. 1-2).

The Groups I+ antibodies do not share a significant structural element responsible for binding a human cytomegalovirus envelope glycoprotein B 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: 22, 31, 40, 49, or 58 or a light chain variable region comprising the sequence of SEQ ID NO: 67, 76, 85, 94, 103, 112, 121, 130, 139, 148, 157, 166, or 175".

The Groups I+ share the technical features of a purified anti-human cytomegalovirus envelope glycoprotein B 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 2011/076883 A1 to Grawunder et al. discloses a purified anti-human cytomegalovirus envelope glycoprotein B antibody (this invention relates to binding members, especially antibody molecules, which neutralize the biological effects of human cytomegalovirus (hCMV), Pg. 1, Lns. 4-6; we have developed hCMV neutralizing human antibodies, which bind with high affinity to the gB (glycoprotein B) protein of hCMV, Pg. 8, Lns. 10-12), the antibody comprising a heavy chain variable region (binding member of the invention may comprise an antibody molecule, e.g. an antibody molecule with fully human amino acid sequence. The binding member normally comprises an antibody VH and/or VL domain. VH and VL domains of binding members are also disclosed as part of the invention, Pg. 15, Lns. 26-30), the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3 (antibody VH domain comprises three HCDR regions, designated HCDR1, HCDR2, and HCDR3, Pg. 15, Lns. 32-33 and Pg. 16, Ln. 1); and a light chain variable region (binding member of the invention may comprise an antibody molecule, e.g. an antibody molecule with fully human amino acid sequence. The binding member normally comprises an antibody VH and/or VL domain. VH and VL domains of binding members are also disclosed as part of the invention, Pg. 15, Lns. 26-30), the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3 (antibody VL domain comprises three LCDR regions, designated LCDR1, LCDR2, and LCDR3, pg. 16, Lns. 1-2).

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.