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A61K 39/42 (2006.01) *C07K 16/08* (2006.01)
C12N 15/09 (2006.01)
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- (74) **Agents:** **BRUKMAN, Alla** et al.; Cooley LLP, 1299 Pennsylvania, N.W., Suite 700, Washington, District of Columbia 20004-2400 (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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, 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, SA, 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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Published:

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- 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))

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WO 2015/127140 A3

(54) **Title:** MARBURG MONOCLONAL ANTIBODIES

(57) **Abstract:** The present invention relates to monoclonal antibodies and antigen-binding portions thereof that specifically bind to a filovirus (e.g., Marburg virus (MARV)), including antibodies that cross-react with at least two filoviruses. Such antibodies are useful for the prevention and treatment of filovirus infection. The invention also provides pharmaceutical compositions comprising the MARV-binding antibodies, nucleic acid molecules encoding these polypeptides and methods of making these molecules.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/16708

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 39/42; C12N 15/09; C07K 16/08 (2015.01) CPC - A61K 2039/505; C07K 14/005 According to International Patent Classification (IPC) or to both national classification and IPC</p>																																						
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) CPC: A61K 2039/505; C07K 14/005</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched CPC: A61K 2039/505; C07K 14/005 (text search) USPC: 530/388.1, 388.3; 424/130.1, 147.1; 435/69.1 (text search)</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Electronic data bases: PatBase; Google Scholar; Google Patents Search terms: filovirus, Marburg virus, Ebola virus, monoclonal, epitope, complementary determining region (CDR), light chain, heavy chain, glycoprotein, virus envelope</p>																																						
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</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>A</td> <td>US 2007/0298042 A1 (HART et al.) 27 December 2007 (27.12.2007). Especially para [0003], [0006],[0033-0042].</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>US 2013/0288927 A1 (SMITH et al.) 31 October 2013 (31.10.2013). Especially SEQ ID NO: 20</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>US 2013/0171152 A1 (SPRIGGS et al.) 4 July 2013 (04.07.2013). Especially SEQ ID NO: 27</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>US 2006/0270003 A1 (ARNOTT et al.) 30 November 2006 (30.11.2006). Especially SEQ ID NO: 10</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>US 2008/0166756 A1 (TSUCHIYA et al.) 10 July 2008 (10.07.2008). Especially SEQ ID NO: 62</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>US 2011/0250203 A1 (KLITGAARD et al.) 13 October 2011 (13.10.2011). Especially SEQ ID NO: 104</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>US 2008/0160035 A1 (STEVENS et al.) 3 July 2008 (03.07.2008). Especially SEQ ID NO: 271</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>US 2009/0275124 A1 (Muruganandam et al.) 5 November 2009 (05.11.2009). Especially SEQ ID NO: 70</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>US 2012/0034229 A1 (Rousselle et al.) 9 February 2012 (09.02.2012). Especially SEQ ID NO: 6</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>US 2003/0119018 A1 (Omura et al.) 26 June 2003 (26.06.2003). Especially SEQ ID NO: 14443</td> <td>1-3</td> </tr> <tr> <td>A</td> <td>WO2006017173 A1 (Bowdish et al.) 16 February 2006 (16.02.2006). Especially SEQ ID NO: 83</td> <td>1-3</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	US 2007/0298042 A1 (HART et al.) 27 December 2007 (27.12.2007). Especially para [0003], [0006],[0033-0042].	1-3	A	US 2013/0288927 A1 (SMITH et al.) 31 October 2013 (31.10.2013). Especially SEQ ID NO: 20	1-3	A	US 2013/0171152 A1 (SPRIGGS et al.) 4 July 2013 (04.07.2013). Especially SEQ ID NO: 27	1-3	A	US 2006/0270003 A1 (ARNOTT et al.) 30 November 2006 (30.11.2006). Especially SEQ ID NO: 10	1-3	A	US 2008/0166756 A1 (TSUCHIYA et al.) 10 July 2008 (10.07.2008). Especially SEQ ID NO: 62	1-3	A	US 2011/0250203 A1 (KLITGAARD et al.) 13 October 2011 (13.10.2011). Especially SEQ ID NO: 104	1-3	A	US 2008/0160035 A1 (STEVENS et al.) 3 July 2008 (03.07.2008). Especially SEQ ID NO: 271	1-3	A	US 2009/0275124 A1 (Muruganandam et al.) 5 November 2009 (05.11.2009). Especially SEQ ID NO: 70	1-3	A	US 2012/0034229 A1 (Rousselle et al.) 9 February 2012 (09.02.2012). Especially SEQ ID NO: 6	1-3	A	US 2003/0119018 A1 (Omura et al.) 26 June 2003 (26.06.2003). Especially SEQ ID NO: 14443	1-3	A	WO2006017173 A1 (Bowdish et al.) 16 February 2006 (16.02.2006). Especially SEQ ID NO: 83	1-3
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<p>Date of the actual completion of the international search 27 July 2015 (27.07.2015)</p>		<p>Date of mailing of the international search report 13 AUG 2015</p>																																				
<p>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. 571-273-8300</p>		<p>Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>																																				

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/16708

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:

- a. forming part of the international application as filed:
 - in the form of an Annex C/ST.25 text file.
 - on paper or in the form of an image file.
- b. furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. furnished subsequent to the international filing date for the purposes of international search only:
 - in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

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 forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

GenCore ver 6.4.1 SEQ ID NOs: 2, 6, 7, 8, 14, 18, 19, 20, 74, 78, 79, 80, 86, 90, 91, 92 specifically searched by ISA for ISR

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/16708

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.: 4-43
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:
-----go to Extra Sheet for continuation-----

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.:
Claims 1-3 limited to the first named LCDR1-3, HCDR1-3, light chain and heavy chain sequence of a Mab directed against a filovirus.(claims 1-3; SEQ ID NOs: 2, 6,7,8,14, 18, 19, 20) and applicant elected LCDR1-3, HCDR1-3, light chain and heavy chain sequence of a Mab directed against a filovirus.(claims 1-3; SEQ ID NOs: 74, 78, 79, 80, 86, 90, 91, 92)
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.

INTERNATIONAL SEARCH REPORT

International application No.

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-----continuation of Box III (Lack of Unity of Invention)-----

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.

Group I+: Claims 1-3, drawn to a monoclonal antibody, or an antigen-binding portion thereof, that specifically binds to a filovirus, wherein the antibody or antigen-binding portion comprises (i) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and (ii) an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3.

The monoclonal antibody composition will be searched to the extent that it comprises the first named invention (claim 1 (a)): the LCDR1, LCDR2 and LCDR3 comprise the amino acid sequences set forth in SEQ ID NOs: 6, 7 and 8, respectively, and the HCDR1, HCDR2, and HCDR3 comprise the amino acid sequences set forth in SEQ ID NOs: 18, 19 and 20, respectively. In addition, the antibody composition is limited to the first named light chain and first named heavy chain (claims 2 and 3 (a)): the immunoglobulin light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 2 and the immunoglobulin heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 14. It is believed that claims 1-3 read on this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NOs: 6, 7, 8, 18, 19, 20, 2 and 14. Additional monoclonal antibody LCDRs, HCDRs, light and heavy chains will be searched upon payment of additional fees. Applicant must specify the claims that encompass any additional elected sequences. 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. An exemplary election would be (claim 1(b)): the LCDR1, LCDR2 and LCDR3 comprise the amino acid sequences set forth in SEQ ID NOs: 30, 31 and 32, respectively, and the HCDR1, HCDR2, and HCDR3 comprise the amino acid sequences set forth in SEQ ID NOs: 42, 43 and 44, respectively, and (claims 2 and 3(b)): the immunoglobulin light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:26 and the immunoglobulin heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 38 (claims 1-3).

The inventions listed as Group I+ 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:

Special Technical Features:

Among the inventions listed as Groups I+ is the specific sequences of LCDRs, HCDRs, light chain variable region, and heavy chain variable region recited therein. The inventions do not share a special technical feature, because no significant structural similarities can readily be ascertained among sequences for LCDRs, HCDRs, light chain variable region, and heavy chain variable region.

Common Technical Feature:

Group I+ claims teach share the common technical feature of a monoclonal antibody, or an antigen-binding portion thereof, that specifically binds to a filovirus, wherein the antibody or antigen-binding portion comprises (i) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and (ii) an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3.

However, said common technical feature does not represent an advance over the prior art, and is anticipated by US 2007/0298042 A1 to HART et al. (hereinafter "Hart").

Hart teaches a monoclonal antibody that specifically binds to a filovirus (para [0006]; "One embodiment of this invention relates to monoclonal antibodies that protect against Ebola virus and bind to epitopes on the Ebola virus GP"; para [0003]-"Ebola virus GP is a type I transmembrane glycoprotein"), wherein the antibody or antigen-binding portion comprises (i) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3 (para [0033]; "the complementarity-determining regions of the light chain are between amino acids 24-34 (CDR1), 50-56 (CDR2) and 89-97 (95 a-f, CDR3) [note: see para [0039] for complete light chain sequence of Mab EGP13C6-I-1, and para [0040], [0041], [0042] for the sequence of LCDR1, LCDR2, and LCDR3 respectively]) and (ii) an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3.(para [0033]; "complementarity- determining regions of the heavy chain are between amino acids 31-35 (35 a-b, CDR1), 50-65 (52 a-c, CDR2), and 95-102 (100 a-k, CDR3)" [note: see para [0034] for complete heavy chain sequence of Mab EGP13C6-I-1, and para [0035], [0036], [0037] for the sequence of HCDR1, HCDR2, and HCDR3 respectively])

As the common technical feature was known in the art at the time of the invention, this cannot be considered a common special technical feature that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Group I+ lacks unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature

Note concerning item 4: Claims 4-43 are multiple dependent claims and are held unsearchable because they are not drafted according to the second and third sentences of PCT Rule 6.4(a).