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- with international search report (Art. 21(3))
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(54) **Title:** MONOCLONAL ANTIBODIES DIRECTED AGAINST ENVELOPE GLYCOPROTEINS FROM MULTIPLE FILOVIRUS SPECIES

(57) **Abstract:** The disclosure provides binding molecules, e.g., antibodies or antigen-binding fragments thereof, that can bind to orthologous epitopes found on two or more filovirus species or strains.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/37493

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 16/10, A61K 39/00, A61K 39/42 (2015.01)

CPC - C07K 16/10, A61K 39/00, C07K 2317/76, C12N 2760/14011

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): C07K 16/10, A61K 39/00, A61K 39/42 (2015.01)

CPC: C07K 16/10, A61K 39/00, C07K 2317/76, C12N 2760/14011

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/133.1, 530/387.3, 530/387.9, 424/159.1, 424/130.1Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar, Google Web, search terms: filovirus, ebola virus, EBOV, Marburg virus, MARV, Ravn virus, RAVV, Tai Forest virus, TAFV, Reston virus, RESTV, Sudan virus, SUDV Bundibugyo virus, BDBV, binding fragment, antibody, bispecific, neutralizing, epitopes, orthologous, glycoprotein epitope, host cell endosomes

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Ou et al. Development and characterization of rabbit and mouse antibodies against ebolavirus envelope glycoproteins. Journal of Virological Methods (June 2011) vol 174, no 1-2, pp 99-109, pg 100, col 1, para 3, pg 104, col 1, para 3, Fig. 3, 5, 9, Table 1	1-4 ---- 10
Y	US 2011/0280904 A1 Bavari et al. 17 November 2011 (17.11.2011), para, [0013], [0130] Fig. 11	10
Y	Maruyama et al. Ebola Virus Can Be Effectively Neutralized by Antibody Produced in Natural Human Infection. Journal of Virology (July 1999) vol 73, no 7, pp 6024-6030, abstract	10
A	US 2011/0052582 A1 (Auer et al.) 03 March 2011 (03.03.2011) para [0007], SEQ ID NO: 1	11-12
A	US 2013/0224191 A1 (Stull et al.) 29 August 2013 (29.08.2013) para [0375], SEQ ID NO: 66	11-12

 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

26 October 2015 (26.10.2015)

Date of mailing of the international search report

12 JAN 2016

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/37493

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.: 5-9, 25-74
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 Supplemental Sheet to continue *****

- 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.: 1-4,10-12, limited to SEQ ID NOs: 22 and 27

- 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/US 15/37493

Continuation of Box No. III, Observations where unity of invention is lacking:

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 1-4, 10-24, directed to an isolated binding molecule or antigen-binding fragment thereof comprising a first binding domain that specifically binds to an orthologous filovirus glycoprotein epitope. The isolated binding molecule will be searched to the extent that the antibody VH and VL encompasses amino acid sequences SEQ ID NO: 22 and SEQ ID NO: 27. It is believed that claims 1-4, 10-12 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass SEQ ID NOs: 22 and 27. Additional antibody VH and VL sequences will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected VH and VL sequences. Applicants must further indicate, if applicable, the claims which encompass 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. An exemplary election would be SEQ ID NO: 32 and SEQ ID NO: 37 (claims 1-4, 13-15).

Group II: claim 75, drawn to a method of neutralizing a virus.

The inventions listed as 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:

Special Technical Features

Group I+ includes the special technical feature of an isolated binding molecule or antigen-binding fragment thereof comprising a first binding domain that specifically binds to an orthologous filovirus glycoprotein epitope, not required by Group II.

Group II includes the special technical feature of a method of neutralizing a virus, not required by Group I+.

Another special technical feature of the inventions listed as Group I+ is the specific VH and VL amino acid sequences recited therein. Each pair of VH and VL amino acid sequences is considered a distinct technical feature, because there is no significant structural similarities can readily be ascertained among these sequences.

Common Technical Features

The inventions of Groups I+ and II share the technical feature of a binding molecule or antigen-binding fragment thereof comprising a first binding domain that specifically binds to an epitope of a virus.
The inventions of Groups I+ share the technical feature of claim 1.

However, these shared technical feature do not represent a contribution over prior art in view of the article entitled "Development and characterization of rabbit and mouse antibodies against ebolavirus envelope glycoproteins" et al. (hereinafter 'Ou') [Journal of Virological Methods 174 (2011) 99 - 109]. Ou discloses (claim 1) an isolated binding molecules, or antigen-binding fragment thereof comprising a first binding domain that specifically binds to an orthologous filovirus glycoprotein epitope, wherein the binding domain specifically binds to the epitope on two or more filovirus species or strains (pg 100, col 1, para 3 "This report describes the development and characterization of a new panel of ebolavirus-specific antibodies. Some of these antibodies are broadly cross-reactive to glycoprotein GP1,2 of different ebolaviruses.", pg 104, col 1, para 3 "one rabbit polyclonal antibody against the conserved F88 peptide (R.F88-2), two mouse monoclonal antibodies against the F88 peptide (M.F88-H3D5, M.F88-H3C8) ... were developed..... four rabbit monoclonal antibodies (R.GP-S-46-12, R.GP-S-53-4, R.GP-S-53-7, R.GP-S-55-1) against the GP-S protein were developed.", See Table 1 for crossreactivity of the monoclonal antibodies.).

As said technical feature was known in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the groups.

Groups I+ and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.