Title: ANTIBODY-MEDIATED NEUTRALIZATION OF CHIKUNGUNYA VIRUS

[Continued on next page]

FIG. 4

Abstract: The present disclosure is directed to antibodies binding to and neutralizing Chikungunya virus (CHIKV) and methods for use thereof.
Published:

— with international search report (Art. 21(3))
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/027466

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/12; A61K 39/395; C07K 16/10; C12N 5/12; C12N 15/13 (2016.01)
CPC - C07K 16/1081; C07K 2317/56; C07K 2317/76; C07K 2317/565 (2016.08)

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 - A61K 39/12; A61K 39/395; C07K 16/10; C12N 5/12; C12N 15/13
CPC - A61K 39/12; C07K 16/1081; C07K 2317/21; C07K 2317/24; C07K 2317/34; C07K 2317/56; C07K 2317/565; C07K 2317/76; C07K 2317/92; C12N 2740/10023; C12N 2770/36123; C12N 2770/36134

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/147.1; 435/5; 435/7.1; 530/387.3; 530/388.3; 530/389.4 (keyword delimited)

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

Search terms used: Chikungunya OR CHIKV antibod* OR immunoglob in OR (antigen binding) E2 W3 glycoprotein%

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<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>WO 2015/010125 A1 (INTEGRAL MOLECULAR, INC. et al) 22 January 2015 (22.01.2015) entire document</td>
<td>1, 2, 13, 14, 17-19, 26-31, 36-42</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search
19 August 2016

Date of mailing of the international search report
07 OCT 2016

Name and mailing address of the ISA/
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300

Authorized officer
Blaine R. Copenhaver

Form PCT/ISA/210 (second sheet) (January 2015)
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.:** 3-12, 15, 16, 20-25, 32-35, 43-46
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

see Extra Sheet(s).

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.:**

**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

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, 2, 13, 14, 17-19, 26-31, and 36-42 are drawn to an anti-E2 Chikungunya virus glycoprotein antibody, and methods comprising the same.

The first invention of Group I is restricted to an anti-E2 Chikungunya virus glycoprotein antibody, and methods comprising the same, wherein the anti-E2 Chikungunya virus glycoprotein antibody is selected to be 1H12 comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:53, encoded by SEQ ID NO:2, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:103, CDR2 is selected to be SEQ ID NO:104, and CDR3 is selected to be SEQ ID NO:105; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:54, encoded by SEQ ID NO:3, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:187, CDR2 is selected to be SEQ ID NO:188, and CDR3 is selected to be SEQ ID NO:189. It is believed that claims 1, 2, 13, 14, 17-19, 26-31, and 36-42 read on this first named invention and thus these claims will be searched without fee to the extent that they read on 1H12 antibody and SEQ ID NOs: 2, 3, 53, 54, 103, 104, 105, 187, 188, and 189.

Applicant is invited to elect additional anti-E2 Chikungunya virus glycoprotein antibodies with specified SEQ ID NO for each heavy and light variable chains and corresponding CDR1, CDR2, and CDR3 to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be anti-E2 Chikungunya virus glycoprotein antibody, wherein the anti-E2 Chikungunya virus glycoprotein antibody is selected to be 2B4 comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:55, encoded by SEQ ID NO:4, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:106, CDR2 is selected to be SEQ ID NO:107, and CDR3 is selected to be SEQ ID NO:108; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:56, encoded by SEQ ID NO:5, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:190, CDR2 is selected to be SEQ ID NO:191, and CDR3 is selected to be SEQ ID NO:192. Additional anti-E2 Chikungunya virus glycoprotein antibodies with specified SEQ ID NO for each heavy and light variable chains and corresponding CDR1, CDR2, and CDR3 will be searched upon payment of additional fees.

Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the combinations 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 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 Groups I formulas do not share a significant structural element responsible for binding an E2 Chikungunya virus glycoprotein antigen, requiring the selection of alternatives for the light and heavy chain variable regions of the antibody, where "said antibody or antibody fragment is encoded by light and heavy chain variable sequences having 70%, 80%, or 90% identity to clone-paired sequences from Table 1 and said antibody or antibody fragment comprises light and heavy chain variable sequences having 70%, 80% or 90% identity to clone-paired sequences from Table 2 and the antibody or antigen fragment is characterized by cloned-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively."

The Groups I share the technical features of a method of detecting a Chikungunya virus infection in a subject comprising: (a) contacting a sample from said subject with an antibody or antibody fragment having clone-paired heavy and light chain CDR, respectively; and (b) detecting Chikungunya virus glycoprotein E2 in in said sample by binding of said antibody or antibody fragment to E2 in said sample; a method of treating a subject infected with Chikungunya Virus, or reducing the likelihood of infection of a subject at risk of contracting Chikungunya virus, comprising delivering to said subject an antibody or antibody fragment having clone paired heavy and light chain CDR sequences; a monoclonal antibody, wherein the antibody or antigen fragment is characterized by clone-paired heavy and light chain CDR fragment is characterized by clone-paired heavy and light chain CDR sequences. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2015/010125 A1 to Integral Molecular, Inc. et al. discloses a method of detecting a Chikungunya virus infection in a subject (methods of detecting the presence or absence of a CHIKV antigen in a sample are provided, Para. [0014]; methods of identifying antibodies, including neutralizing antibodies, against Chikungunya virus. Abstract) comprising: (a) contacting a sample from said subject with an antibody or antibody fragment having clone-paired heavy and light chain CDR (in some embodiments, the methods comprise contacting a sample with an antibody, such as those described herein, and detecting the binding to a CHIKV antigen by the antibody, Para. [0014]); clones expressing antibodies of identical specificity, [0052]); CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, Para. [0045]); and (b) detecting Chikungunya virus glycoprotein E2 in said sample by binding of said antibody or antibody fragment to E2 in said sample (the CHIKV antigen is the E1 protein, E2 protein, 6k protein, or E3 protein. The CHIKV antigen can also be referred to as the CHIKV protein, Para. [0073]); a method of treating a subject infected with Chikungunya Virus (Embodiments provided herein also provide methods of treating, inhibiting or ameliorating a CHIKV infection comprising administering an antibody described herein, Para. [00121]) comprising delivering to said subject an antibody or antibody fragment having clone paired heavy and light chain CDR sequences; a monoclonal antibody, wherein the antibody or antigen fragment is characterized by cloned-paired heavy and light chain CDR sequences (the antibody can be a monoclonal antibody, Para. [00122]); CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, Para. [0045]); hybridoma or engineered cell encoding an antibody or antibody fragment wherein the antibody or antigen fragment is characterized by clone-paired heavy and light chain CDR sequences (hybridoma producing a mAb of the present invention may be cultivated in vitro, in situ or in vivo. Production of high titers of mAbs in vivo or in situ makes this the presently preferred method.
of production, Para. [0050]; CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, Para. [0045]).

The inventions listed in Groups 1+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.