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(54) Title: ANTI-INFLUENZA B VIRUS NEURAMINIDASE ANTIBODIES AND USES THEREOF

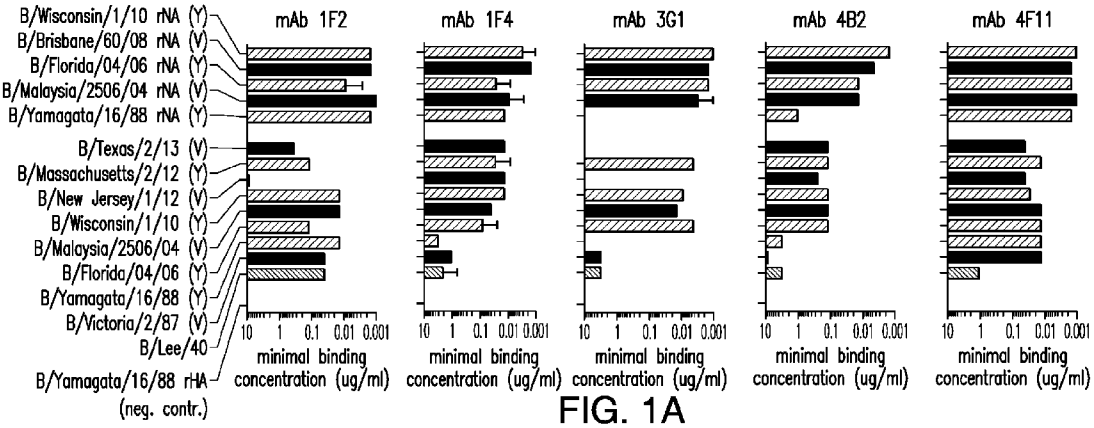


FIG. 1A

(57) Abstract: Provided herein are antibodies that bind to neuraminidase (NA) of different strains of influenza B virus, host cells for producing such antibodies, and kits comprising such antibodies. Also provided herein are compositions comprising antibodies that bind to NA of different strains of influenza B virus and methods of using such antibodies to diagnose, prevent or treat influenza virus disease.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/26489

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 39/145; C07K 14/435, 16/10; C12N 15/09; C12P 19/34 (2018.01)
CPC - A61K 39/145; C07K 14/435, 16/1018; C12N 15/09; C12P 19/34

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	(DOYLE, TM et al.) A monoclonal antibody targeting a highly conserved epitope in influenza B neuraminidase provides protection against drug resistant strains. Biochemical and Biophysical Research Communications. 8 November 2013, Epub 16 October 2013, Vol. 441, pages 226-229; page 226, 2nd column, 2nd paragraph; page 227, 1st column, 1st-2nd paragraphs; Figure 1; DOI: 10.1016/j.bbrc.2013.10.041	1, 5
A	(GRAVEL, C et al.) Qualitative and quantitative analyses of virtually all subtypes of influenza A and B viral neuraminidases using antibodies targeting the universally conserved sequences. Vaccine. 16 August 2010, Epub 9 July 2010, Vol. 28, pages 5774-5784; page 5777, 1st column, 1st paragraph; page 5778, 1st column, 4th paragraph; Table 1; DOI: 10.1016/j.vaccine.2010.06.075	2-3, 4/2-3, 6-8
A	(WOHLBOLD, TJ et al.) Vaccination with Adjuvanted Recombinant Neuraminidase Induces Broad Heterologous, but Not Heterosubtypic, Cross-Protection against Influenza Virus Infection in Mice. mBio. 10 March 2015, Vol. 6, Issue 2, e02556-14, pages 1-13; abstract; page 9, 2nd column, 2nd paragraph; DOI: 10.1128/mBio.02556-14	2-3, 4/2-3, 6-8
A	WO 2016/118937 A1 (ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI) 28 July 2016; paragraphs [00448], [00213], [00797]	2-3, 4/2-3, 6-8
A	(HU, W et al.) Fully human broadly neutralizing monoclonal antibodies against influenza A viruses generated from the memory B cells of a 2009 pandemic H1N1 influenza vaccine recipient. Virology. 20 January 2013, Epub 16 October 2012; Vol. 435, pages 320-328; page 321, 1st column, 3rd column; page 323, 1st column, 1st paragraph; Table 1; DOI: 10.1016/j.virol.2012.09.034	29, 104

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* 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
6 August 2018 (06.08.2018)	27 AUG 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/26489

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	(AIR, GM) Influenza virus antigenicity and broadly neutralizing epitopes. Current Opinion in Virology. 4 April 2015; Vol. 11, Pages 113-121; page 113, 2nd column, 2nd paragraph; page 115, 1st column, 3rd paragraph; Table 1; DOI: 10.1016/j.coviro.2015.03.006	29, 104
A	CN 103665155 A (SHANGHAI INST BIOL SCIENCE) 26 March 2014; abstract; page 4, lines 38-39; page 6, lines 33-34	29, 104
A	WO 2017/021893 A1 (NOVARTIS AG et al.) 9 February 2017; page 8, 8th paragraph; claim 23	30-31, 63, 69, 74
A	US 2008/0193455 A1 (Stassen, JM et al.) 14 August 2008; claim 1	30-31, 63, 69, 74
A	US 2015/0266951 A1 (SNU R&DB FOUNDATION) 24 September 2015; claims 1, 5-7	30, 63, 69, 74
A	US 2004/0073011 A1 (HAGAY, Y et al.) 14 April 2004; claim 25	30
A	US 2016/0017025 A1 (RAMOT AT TEL AVIV UNIVERSITY LTD. et al.) 21 January 2016; claim 1	31, 44, 51, 63, 69, 74
A	US 2015/0252103 A1 (GANYMED PHARMACEUTICALS AG) 10 September 2015; paragraph [0092]	31, 44, 51
A	US 2013/0224187 A1 (Rother, RP et al.) 29 August 2013; paragraph [0397]; Table 7	44, 51
A	US 2009/0169547 A1 (SAHIN, U et al.) 2 July 2009; paragraph [0093]	44, 51
A	US 2016/0185860 A1 (GANYMED PHARMACEUTICALS AG) 30 June 2016; paragraphs [0090]-[0091]	58
A	US 2016/0355590 A1 (Epstein, AL) 8 December 2016; paragraph [0128]; Table 2	58
A	US 2016/0015828 A1 (STEMCENTRX, INC.) 21 January 2016; claim 7	58
A	WO 2005/000901 A2 (DUKE UNIVERSITY et al.) 6 January 2005; page 19, lines 25-27; Figure 17D	58
P, X	(WOHLBOLD, TJ et al.) Broadly protective murine monoclonal antibodies against influenza B virus target highly conserved neuraminidase epitopes. Nature Microbiology. October 2017, Epub 21 August 2017, Vol. 2, pages 1415-1424; entire document; DOI: 10.1038/s41564-017-0011-8	1-3, 4/2-3, 5-8, 29-31, 44, 57-58, 63, 69, 74, 104

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/26489

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.: 9-28, 45-56, 59-62, 68, 75-103
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:

-***-Please See on Next Supplemental Page-***-

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.:
1-8, 29-31, 44 (in-part), 57 (in-part), 58 (in-part), 63, 69, 74 (in-part), and 104 (in-part)

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
Information on patent family members

International application No.
PCT/US18/26489

-***-Continued from Box 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.

Groups I+, Claims 1-8, 29-44, 57, 58, 63-67, 69-74, 104, antibody 1F2, an epitope bound by 1F2, and SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 81 and 82 are directed toward an isolated antibody that binds to and inhibits a neuraminidase (NA) of an influenza B virus strain of the Victoria lineage and the Yamagata lineage; an isolated polynucleotide sequence encoding the antibody; and a vector and host cell comprising the polynucleotide; and an epitope bound by the antibody.

The antibody, polynucleotide, vector and host cell, and epitope will be searched to the extent they encompass antibody 1F2 (first exemplary antibody), encompassing a variable heavy chain region encompassing SEQ ID NO: 1 (first exemplary HCVR), encompassing a CDR1 encompassing SEQ ID NO: 3 (first exemplary HCDR1), a CDR2 encompassing SEQ ID NO: 4 (first exemplary HCDR2), and a CDR3 encompassing SEQ ID NO: 5 (first exemplary HCDR3), and encoded by a nucleic acid encompassing SEQ ID NO: 81 (first exemplary HCVR-encoding nucleic acid); and a variable light chain region encompassing SEQ ID NO: 2 (first exemplary LCVR) encompassing a CDR1 encompassing SEQ ID NO: 6 (first exemplary LCDR1), a CDR2 encompassing SEQ ID NO: 7 (first exemplary LCDR2) and a CDR3 encompassing SEQ ID NO: 8 (first exemplary LCDR3), and encoded by a nucleic acid encompassing SEQ ID NO: 82 (first exemplary LCVR-encoding nucleic acid); and an epitope bound by 1F2 (first exemplary epitope). Applicant is invited to elect additional antibody(ies) with associated HCVR(s), LCVR(s), nucleic acid sequences encoding the antibody(ies) and CDRs associated therewith, with specified SEQ ID NO: for each, or with specified substitution(s) at specified site(s) of a SEQ ID NO:, such that the sequence of each elected species is fully specified (i.e. no optional or variable residues or substituents), and the corresponding epitope (s) bound by said elected antibody(ies), to be searched. Additional antibody(ies), sequence(s) and epitope(s) will be searched upon the payment of additional fees. It is believed that claims 1-8, 29-31, 44 (in-part), 57 (in-part), 58 (in-part), 63, 69, 74 (in-part), and 104 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass antibody 1F2 (antibody), SEQ ID NO: 1 (HCVR), SEQ ID NO: 3 (HCDR1), SEQ ID NO: 4 (HCDR2), SEQ ID NO: 5 (HCDR3), SEQ ID NO: 81 (HCVR-encoding nucleic acid), SEQ ID NO: 2 (LCVR), SEQ ID NO: 6 (LCDR1), SEQ ID NO: 7 (LCDR2), SEQ ID NO: 8 (LCDR3), SEQ ID NO: 82 (LCVR-encoding nucleic acid); and an epitope bound by 1F2 (epitope). Applicants must specify the claims that encompass any additionally antibody(ies), sequence(s) and epitope(s). 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/examined. An exemplary election would be antibody 1F4 (antibody), SEQ ID NO: 17 (HCVR), SEQ ID NO: 19 (HCDR1), SEQ ID NO: 20 (HCDR2), SEQ ID NO: 21 (HCDR3), SEQ ID NO: 83 (HCVR-encoding nucleic acid), SEQ ID NO: 18 (LCVR), SEQ ID NO: 22 (LCDR1), SEQ ID NO: 23 (LCDR2), SEQ ID NO: 24 (LCDR3), SEQ ID NO: 84 (LCVR-encoding nucleic acid); and an epitope bound by 1F4 (epitope).

No technical features are shared between the antibodies and antibody sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: an isolated antibody that binds to a neuraminidase (NA) of an influenza B virus strain of the Victoria lineage and an NA of an influenza B virus strain of the Yamagata lineage, wherein said antibody inhibits the enzymatic activity of the NA of the influenza B virus strains of the Victoria and Yamagata lineages; an isolated polynucleotide sequence and vector encoding an antibody that binds to an NA of an influenza B virus strain; a host cell comprising: (a) (I) a polynucleotide encoding a variable heavy chain region comprising a variable heavy chain region complementarity determining region (CDR) 1, a variable heavy chain region CDR2, and a variable heavy chain region CDR3; and (II) a polynucleotide encoding a variable light chain region comprising a variable light chain region complementarity determining region (CDR) 1, a variable light chain region CDR2, and a variable light chain region CDR3; and an isolated influenza virus neuraminidase antigenic peptide comprising an epitope of an antibody; these shared technical features are previously disclosed by WO 2016/124682 A1 to Janssen Vaccines & Prevention B.V. (hereinafter 'Janssen') in view of the abstract of the article 'A monoclonal antibody targeting a highly conserved epitope in influenza B neuraminidase provides protection against drug resistant strains' by Doyle, T.M. et al. (hereinafter 'Doyle').

Janssen discloses an isolated antibody that binds to a neuraminidase (NA) of an influenza virus strain (an isolated antibody that binds to a neuraminidase (NA) of an influenza virus strain; abstract, page 8, fourth paragraph); an isolated polynucleotide sequence (an isolated polynucleotide sequence; page 14, second paragraph) and vector (and vector; page 14, fifth paragraph) encoding an antibody that binds to the NA of an influenza virus strain (encoding an antibody that binds to the NA of an influenza virus strain; page 8, fourth paragraph, page 14, second paragraph); a host cell comprising: (a) (I) a polynucleotide encoding (a host cell comprising: (a) (I) a polynucleotide encoding; page 14, second paragraph, fifth paragraph; page 15, second paragraph) a variable heavy chain region (a variable heavy chain region; page 11, third paragraph) comprising a variable heavy chain region complementarity determining region (CDR) 1, a variable heavy chain region CDR2, and a variable heavy chain region CDR3 (comprising a variable heavy chain region complementarity determining region (CDR) 1, a variable heavy chain region CDR2, and a variable heavy chain region CDR3; page 11, first paragraph); and (II) a polynucleotide encoding (a polynucleotide encoding; page 14, second paragraph, fifth paragraph; page 15, second paragraph) a variable light chain region (a variable light chain region; page 12, first paragraph) comprising a variable light chain region complementarity determining region (CDR) 1, a variable light chain region CDR2, and a variable light chain region CDR3 (comprising a variable light chain region complementarity determining region (CDR) 1, a variable light chain region CDR2, and a variable light chain region CDR3; page 11, second paragraph).

Janssesn does not disclose an isolated antibody that binds to a neuraminidase (NA) of an influenza B virus strain of the Victoria lineage and an NA of an influenza B virus strain of the Yamagata lineage, wherein said antibody inhibits the enzymatic activity of the NA of the influenza B virus strains of the Victoria and Yamagata lineages; an isolated polynucleotide sequence and vector encoding an antibody that binds to an NA of an influenza B virus strain; and an isolated influenza virus neuraminidase antigenic peptide comprising an epitope of an antibody.

-***-Continued Within the Next Supplemental Box-***-

-***-Continued From Previous Supplemental Box-***-

Doyle discloses an isolated antibody that binds to a neuraminidase (NA) of an influenza B virus strain of the Victoria lineage and an NA of an influenza B virus strain of the Yamagata lineage (an isolated antibody that binds to a neuraminidase (NA) of an influenza B virus strain of the Victoria lineage and an NA of an influenza B virus strain of the Yamagata lineage; abstract), wherein said antibody inhibits the enzymatic activity of the NA of the influenza B virus strains of the Victoria and Yamagata lineages (wherein said antibody inhibits the enzymatic activity of the NA of the influenza B virus strains of the Victoria and Yamagata lineages; abstract); and a highly conserved NA epitope bound by said antibody (a highly conserved NA epitope bound by said antibody; abstract); and wherein the antibody is also capable of binding all nine types of influenza A NA (wherein the antibody is also capable of binding all nine types of influenza A NA; abstract).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Janssen to have produced the antibodies disclosed by Doyle, in order to enable the production of antibodies capable of neutralizing a broad range of both influenza A neuraminidase and the Yamagata and Victoria strains of influenza B neuraminidase polypeptides in order to better treat a broad range of influenza infections.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Janssen and Doyle references, unity of invention is lacking.