



(43) International Publication Date
23 July 2015 (23.07.2015)

(10) International Publication Number
WO 2015/108967 A3

- (51) **International Patent Classification:**
A61K 39/42 (2006.01) *A61K 39/155* (2006.01)
- (21) **International Application Number:**
PCT/US2015/011391
- (22) **International Filing Date:**
14 January 2015 (14.01.2015)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/927,819 15 January 2014 (15.01.2014) US
- (71) **Applicant:** **MEDIMMUNE, LLC** [US/US]; One Medimmune Way, Gaithersburg, MD 20878 (US).
- (72) **Inventors:** **ULBRANDT, Nacy**; One Medimmune Way, Gaithersburg, MD 20878 (US). **KALLE-WAARD-LELAY, Nicole**; One Medimmune Way, Gaithersburg, MD 20878 (US). **YUAN, Andy Q.**; One Medimmune Way, Gaithersburg, MD 20878 (US). **RICHTER, Bettina**; One Medimmune Way, Gaithersburg, MD 20878 (US).
- (74) **Agent:** **SANDBERG, Victoria A.**; Muetting, Raasch & Gebhardt, P.A., P.O. Box 581336, Minneapolis, MN 55458-1336 (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.

- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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:**
3 September 2015

(54) **Title:** RSV-SPECIFIC ANTIBODIES AND FUNCTIONAL PARTS THEREOF

(57) **Abstract:** This application provides antibodies and functional equivalents thereof which are capable of specifically binding RSV, as well as means and methods for producing them.



WO 2015/108967 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/11391

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/42, A61K 39/155 (2015.01)

CPC - A61K 39/39575, A61K 2039/505, C07K 2316/96, C07K 16/1027, C07K 2317/60, C07K 2317/565

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)

CPC- A61K 39/39575, A61K 2039/505, C07K 2316/96, C07K 16/1027, C07K 2317/60, C07K 2317/565

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

CPC- C07K 2317/567

USPC- 424/159.1, 424/211.1, 435/388.3

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

PubWEST(PGPB,USPT,USOC,EPAB,JPAB); PatBase, Google/Scholar: RSV, D25, monoclonal antibody, FR1, framework residue substitutions, improve the CDR conformation, M19K substitution; nongermine framework, germline framework...

GenCore 6.4.1: SEQ ID NO: 7

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 8,562,996 B2 (Spits, et al.) 22 October 2013 (22.10.2013) claims 1, 4; SEQ ID NO: 1-7; col 1, ln 40-55; Fig 11B	1-3
A	US 2012/0157662 A1 (Beaumont, et al.) 21 June 2012 (21.06.2012) Fig 2a; para [0049]-[0050]	1-3
A	Sela-Culang, et al. The structural basis of antibody-antigen recognition. Front Immunol. 2013, 4:302; pg 7, col 1 to col 2	1-3
A	McLellan, et al. Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. Science 2013, 340(6136):1113-7; Abstract; pg 9 [according to the posted document], Fig 1 and its legend; pg 3, last para	1-3



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

14 June 2015 (14.06.2015)

Date of mailing of the international search report

70 JUL 2015

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

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/11391

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.: 14-31, 34-45
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:

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.

..... 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.: 1-3 restricted to SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and the M19K substitution

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 15/11391

***** Supplemental Sheet *****

In Continuation of Box III. Observations where unity of invention is lacking:

Group I+: claims 1-13, 32, 33, drawn to a synthetic or recombinant anti- RSV antibody. The anti- RSV antibody will be searched to the extent that the antibody heavy chain variable region encompasses CDR1 of SEQ ID NO:1, CDR2 of SEQ ID NO:2, CDR3 of SEQ ID NO:3, and the M19K substitution in SEQ ID NO:7, i.e., the first claimed substitution in the framework of heavy chain of SEQ ID NO:7. It is believed that claims 1-3 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass an anti- RSV antibody comprising heavy chain variable region encompasses CDR1 of SEQ ID NO:1, CDR2 of SEQ ID NO:2, CDR3 of SEQ ID NO:3, light chain variable region encompasses CDR1 of SEQ ID NO:4, CDR2 of SEQ ID NO: 5, CDR3 of SEQ ID NO:6, and the M19K substitution in SEQ ID NO:7. Additional combination(s) of heavy chain variable region CDR1, 2, and 3 and/or specific substitution(s) in the framework regions of heavy chain of SEQ ID NO:7 will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected combination(s) of heavy chain variable region CDR1, 2, and 3 and/or specific substitution(s) in the framework regions of heavy chain of SEQ ID NO:7. 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 an anti-RSV antibody comprising HC CDR1 of SEQ ID NO:9, CDR2 of SEQ ID NO:10, CDR3 of SEQ ID NO:11, and a substitution Q23K in SEQ ID NO:7, i.e., claims 1-3, 32.

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

The special technical feature of each invention of Group I+ is a specific combination of heavy chain CDR1, CDR2, CDR3, because said CDRs were known in the art at the time of the invention (please see US 2012/0263715 A1 to Richter et al. (18 October 2012) (hereinafter "Richter"); pg 175-176, Human antibody D25, VH CDR1, SEQ ID NO:344; VH CDR2, SEQ ID: 345; VH CDR3, SEQ ID NO: 346 are 100% identical to the claimed CDR1 of SEQ ID NO:1, CDR2 of SEQ ID NO:2, CDR3 of SEQ ID NO:3, respectively).

The special technical feature of some inventions of Group I+ is a substitution(s) and/or combination thereof in the framework regions of SEQ ID NO:7, because no significant structural similarities can readily be ascertained among the substitution(s), and further because SEQ ID NO:7 was known in the art at the time of the invention (please see Richter, as above, pg 177, Human antibody D25-VH chain, SEQ ID NO:350, 100% identity).

Common Technical Features

The inventions of Group I+ share the technical feature of a synthetic or recombinant anti- RSV antibody, comprising light chain variable region CDR1 of SEQ ID NO:4, CDR2 of SEQ ID NO:5, CDR3 of SEQ ID NO:6. However, this shared technical feature does not represent a contribution over prior art as being anticipated by Richter, as above, disclosing a recombinant anti-RSV antibody (pg 175-177, Human antibody D25) comprising a light chain variable region CDR1 of SEQ ID NO:4 (pg 176, SEQ ID NO:347, 100% identity), CDR2 of SEQ ID NO:5 (pg 176, SEQ ID NO:348, 100% identity), CDR3 of SEQ ID NO:6 (pg 176, SEQ ID NO:349, 100% identity). 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.

Some inventions of Group I+ share the technical feature of a recombinant anti-RSV antibody having at least one framework substitution in the heavy chain of SEQ ID NO:7. However, this shared technical feature does not represent a contribution over prior art as being obvious over Richter, as above, in view of a paper titled "The structural basis of antibody-antigen recognition" by Sela-Culang, et al. (Front Immunol. 2013, 4:302) (hereinafter "Sela-Culang").

Richter discloses a recombinant anti-RSV antibody comprising heavy chain variable region of SEQ ID NO:7 (pg 177, Human antibody D25-VH chain, SEQ ID NO:350, 100% identity). Richter does not provide a sufficient motivation to one of ordinary skill in the art to introduce a substitution(s) into the framework regions of heavy chain variable region of SEQ ID NO:7. Sela-Culang discloses that "[f]ramework region residues that affect Ag binding can be divided into two categories. The first are FR residues that contact the Ag, thus are part of the binding-site... Other residues are those that are far from the CDRs in sequence, but are in close proximity to it in the 3-D structure. In particular, a loop in the heavy chain FR-3, sometimes referred to as CDR-H4, accounts for 1.3% of human Ab-Ag contacts... In the second category of FR residues that affect Ag binding, are residues that are not in contact with the Ag, but affect Ag binding indirectly..." (pg 7, col 1 to col 2), thereby motivating one of ordinary skill in the art to introduce, in the course of routine experimentation and with a reasonable expectation of success, a substitution(s) into the framework regions of heavy chain variable region of SEQ ID NO:7, to improve the antibody affinity to RSV. As said technical feature would have been obvious to one of ordinary skill in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the groups.

The inventions of Group I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.