(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2018 (25.01.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/018047 A3

(51) International Patent Classification:
A61K 39/395 (2006.01) *C07K 14/47* (2006.01)
A61K 45/06 (2006.01)

(21) International Application Number:
PCT/US2017/043538

(22) International Filing Date:
24 July 2017 (24.07.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/365,921 22 July 2016 (22.07.2016) US
62/365,919 22 July 2016 (22.07.2016) US

(71) Applicant: **GLIKNIK INC.** [US/US]; 801 W. Baltimore Street, Suite 501A, Baltimore, Maryland 21201 (US).

(72) Inventors: **BLOCK, David S.**; c/o Gliknik Inc., 801 W. Baltimore Street, Suite 501A, Baltimore, Maryland 21201 (US). **OLSEN, Henrik**; c/o Gliknik Inc., 801 W. Baltimore Street, Suite 501A, Baltimore, Maryland 21201 (US).

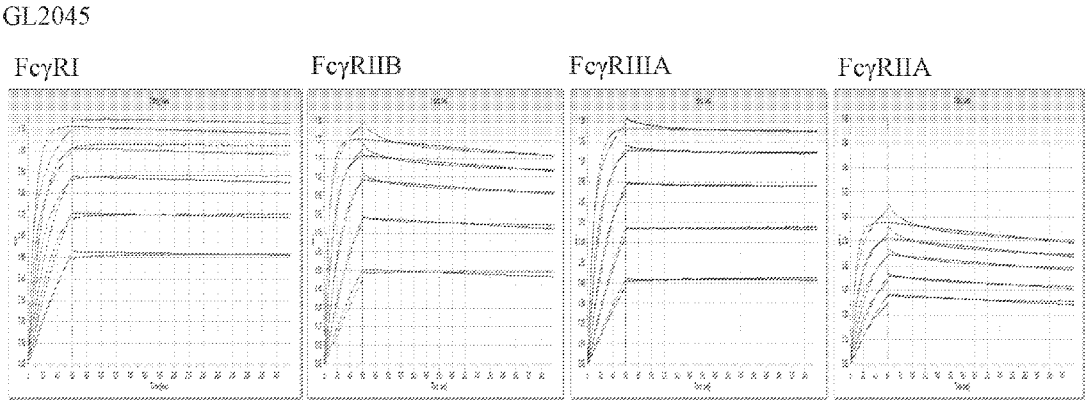
(74) Agent: **PHELAN, Jordan D.** et al.; Cooley LLP, 1299 Pennsylvania Avenue, NW, Suite 700, Washington, District of Columbia 20004 (US).

(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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, 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,

(54) Title: FUSION PROTEINS OF HUMAN PROTEIN FRAGMENTS TO CREATE ORDERLY MULTIMERIZED IMMUNOGLOBULIN FC COMPOSITIONS WITH ENHANCED FC RECEPTOR BINDING

FIG. 1



(57) Abstract: The present invention involves a series of fully recombinant multimerized forms of immunoglobulin Fc which thereby present polyvalent immunoglobulin Fc to immune cell receptors. The fusion proteins exist as both homodimeric and highly ordered multimeric fractions, termed stradomers. The invention involves fusion proteins that bind to FcγRs and complement and that are useful in the treatment and prevention of disease.

[Continued on next page]

WO 2018/018047 A3

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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:
01 March 2018 (01.03.2018)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/43538

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 39/395, 45/06; C07K 14/47 (2017.01)
CPC - A61K 31/573, 39/395, 45/06; C07K 14/47, 16/00

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.
Y	US 2013/0156765 A1 (BLOCK et al.) June 20, 2013; paragraphs [0014], [0015], [0019], [0020], [0031], [0033], [0035], [0044], [0064], [0074], [0078], [0081], [0085], [0086]; claims 165-166	1-3, 29-33, 35-38, 58/1, 59/58/1
Y	WO 2015/132364 A1 (UCB BIOPHARMA SPRL.) September 11, 2015; abstract; page 32, seventh paragraph; page 55, fourth paragraph; Table 4; Claim 40	1-3, 29-33, 35-38, 58/1, 59/58/1
Y	US 2015/0166636 A1 (CHUGAI SEIYAKU KABUSHIKI KAISHA) June 18, 2015; paragraph [0098]	29

☐ 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
04 December 2017 (04.12.2017)	05 JAN 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/US17/43538

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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/43538

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.: 64-76
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 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.:
1-3, 29-33, 35-38, 58/1, 59/58/1; SEQ ID NO: 7, a G236R mutation

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/US17/43538

-***-Continued from 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.

Groups I+, Claims 1-63 and SEQ ID NO: 7, comprising a mutation corresponding to a G236R mutation are directed toward a stradomer unit comprising: at least one homodimeric IgG1 Fc domain comprising one or more point mutations corresponding to at least one of positions 236, 267, 268, 324, and/or 299 of the Fc domain; and at least one multimerization domain; and a cluster stradomer comprising two or more such units.

The stradomer and cluster stradomer will be searched to the extent it encompasses SEQ ID NO: 7, comprising a mutation corresponding to a G236R mutation (first exemplary stradomer). Applicant is invited to elect additional stradomer(s), 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 is fully specified, to be searched. Additional stradomer sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 3 (in-part), 29 (in-part), 30 (in-part), 31 (in-part), 32 (in-part), 33 (in-part), 35 (in-part), 36 (in-part), 37 (in-part), 38 (in-part), 58 (in-part) and 59 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 7, comprising a mutation corresponding to a G236R mutation (stradomer). Applicants must specify the claims that encompass any additionally elected stradomer sequence(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 a stradomer comprising SEQ ID NO: 7 with mutations corresponding to a E233P mutation, a G236E mutation, an H268F mutation, and a S324T mutation (first exemplary elected stradomer).

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

Groups I+ share the technical features including: a stradomer unit comprising: at least one homodimeric IgG1 Fc domain comprising a point mutation at any one of positions 236, 267, 268, 324, 299, 430, 440 and/or 345 of the IgG1 Fc domain, and an IgG2 hinge multimerization domain located on the C-terminus of the at least one homodimeric IgG1 Fc domain, wherein said stradomer units multimerize into a hexameric stradomer structure; an enriched heterogeneous composition comprising high molecular weight species multimers comprising the multimerized homodimers; a cluster stradomer comprising two or more stradomer units; and a composition comprising the cluster stradomer.

However, these shared technical features are previously disclosed by US 2013/0156765 A1 to Block et al. (hereinafter 'Block') in view of WO 2015/132364 A1 to UCB Biopharma Sprl. (hereinafter 'UCB').

Block discloses a stradomer unit (a stradomer unit; abstract) comprising: at least one homodimeric IgG1 Fc domain (comprising: at least one homodimeric IgG1 Fc domain; paragraphs [0014], [0064]) comprising a point mutation of the IgG1 Fc domain (comprising a point mutation of the IgG1 Fc domain; paragraph [0026]), and an IgG2 hinge multimerization domain located on the C-terminus of the at least one homodimeric IgG1 Fc domain (an IgG2 hinge multimerization domain located on the C-terminus of the at least one homodimeric IgG1 Fc domain; paragraphs [0016], [0019]), wherein said stradomer units multimerize into a hexameric stradomer structure (wherein said stradomer units multimerize into a hexameric stradomer structure; paragraph [0183]); an enriched heterogeneous composition comprising high molecular weight species multimers comprising the multimerized homodimers (a composition comprising multimeric stradomers including a mixture of naturally occurring Fc domains and Fc domains with altered amino acid sequences (an enriched heterogeneous composition comprising high molecular weight species multimers comprising the multimerized homodimers); paragraphs [0012] [0103], [0183]); a cluster stradomer comprising two or more stradomer units (a cluster stradomer comprising two or more stradomer units; paragraph [0027]); and a composition comprising the cluster stradomer (a composition comprising the cluster stradomer; paragraphs [0012], [0027]).

Block does not disclose an IgG1 Fc domain comprising a point mutation at any one of positions 236, 267, 268, 324, 299, 430 or 440.

UCB discloses multimeric fusion proteins which bind to Fc receptors (multimeric fusion proteins which bind to Fc receptors; abstract), wherein the fusion proteins comprise IgG1 mutations (wherein the fusion proteins comprise IgG1 mutations; page 55, fourth paragraph), including an H268Q mutation (including an H268Q mutation; Table 4), and a G236R mutation (and a G236R mutation; page 32, seventh paragraph; Claim 40) to modulate binding to specific Fc receptors (to modulate binding to Fc receptors; Page 32, second paragraph).

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 Block to have provided mutations in the IgG1 Fc domains, as disclosed by UCB, in order to increase or decrease the binding of the stradomers comprising the mutated Fc regions to specific Fc receptors.

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 Block and UCB references, unity of invention is lacking.