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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 September 2018 (13.09.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/165338 A3

(51) International Patent Classification:
*C07K 7/06* (2006.01) *A61K 38/08* (2006.01)
*C07K 14/705* (2006.01)

(21) International Application Number:
PCT/US2018/021404

(22) International Filing Date:
07 March 2018 (07.03.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/468,286 07 March 2017 (07.03.2017) US
62/536,924 25 July 2017 (25.07.2017) US

(71) Applicant: **UBIOME, INC.** [US/US]; 360 Langton Street, #301, San Fracisco, CA 94103 (US).

(72) Inventors: **APTE, Zachary**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **RICHMAN, Jessica**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **ALMONACID, Daniel**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **ALEGRIA, Melissa**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **MARQUEZ, Valeria**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **MORALES, Eduardo**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **ORTIZ, Rodrigo**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **TORRES, Janet**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **CORRUBIAS, Paulo**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **GIMPEL, Javier**; 360 Langton Street, #301, San Francisco, CA 94103 (US). **ARAYA, Ingrid**; 360 Langton Street, #301, San Francisco, CA 94103 (US).

(74) Agent: **SCHOX, Jeffrey**; 500 3rd Street, Suite 215, San Francisco, CA 94107 (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,

(54) Title: THERAPEUTIC & DIAGNOSTICS COMPOSITIONS TARGETING TOLL-LIKE RECEPTORS AND METHODS THEREOF

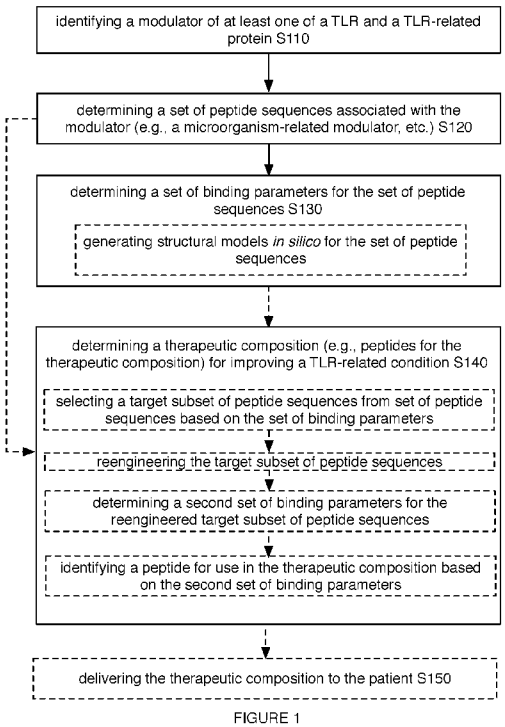


FIGURE 1

(57) Abstract: Therapeutic compositions and an associated method for improving a Toll-like receptor (TLR)-related condition, including determining a set of peptide sequences associated with a microorganism-related modulator of a TLR, determining a first set of binding parameters for the set of peptide sequences in relation to the TLR, selecting a target subset of peptide sequences from the set of peptide sequences based on the first set of binding parameters, reengineering the target subset of peptide sequences based on mutating amino acid residues of the target subset of peptide sequences, determining a second set of binding parameters for the reengineered target subset of peptide sequences in relation to the TLR, and identifying a first peptide for use in a therapeutic composition for improving the TLR-related condition, based on the second set of binding parameters for the reengineered target subset of peptide sequences.

WO 2018/165338 A3

*[Continued on next page]*

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))*

**(88) Date of publication of the international search report:**
11 October 2018 (11.10.2018)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/21404

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 7/06, 14/705, 14/705; A61K 38/08 (2018.01)
CPC - C07K 7/06, 14/705, 14/195; A61K 39/0208, 39/164, 38/08

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)
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<br>---<br>Y | WO 2016/177797 A1 (WAGENINGEN UNIVERSITEIT) 10 November 2016 (10.11.2016). Especially pg 4 ln 18-19, pg 12 ln 5-27, pg 18 ln 28-31, SEQ ID NO: 1. | 1, 2, 8-10, 29<br>----------<br>13, 14 |
| Y | US 2009/0028889 A1(NAKAAR et al.) 29 January 2009 (29.01.2009). Especially para [0144]. | 13, 14 |

☐ 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 |
|---|---|
| 21 June 2018 | 29 AUG 2018 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/21404

**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.:
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:
----Go to Extra Sheet for continuation------

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, 2, 8-10, 13, 14, 29 limited to the first motif, XXGFXLKXX

**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 18/21404

Continuation of 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.

Group I+: Claims 1-14, 29, drawn to a peptide configured to modulate a toll--like receptor (TLR) related functionality.
The peptide configured to modulate a TLR related functionality will be searched to the extent that the peptide sequence motif is the first named motif (motif1), XXGFXLKXX, where X is in the first motif comprises any amino acid or no amino acid (claim 1). It is believed that claims 1, 2, 8-10, 13, 14, 29 read on this first named invention and thus these claims will be searched without fee to the extent that they encompass peptide motif 1: XXGFXLKXX. Additional peptide motifs will be searched upon payment of additional fees. Applicant must specify the claims that encompass any additional elected peptide motifs. Applicants must further indicate, if applicable, the claims 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. An exemplary election would be: peptide motif 3, [X][Z][B]APW, where X=(I, F, W, Y, or A), Z=(D, A, Q, E, G, H, I, L, F, P, T, or Y), B=(Q, L, W, or Y) (claims 1, 2, 3, 8-10, 13, 14, 29).

Group II: Claims 15-28, drawn to a method for improving a TLR-related condition

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:

Technical Features:

Group I+ has the special technical feature of a composition of a reengineered peptide sequence associated with a microorganism related modulator of a TLR, not required by Group II.

Group II has the special technical feature of the method step of determining a set of binding parameters for a set of peptide sequences in relation to a TLR, not required by Group I+.

Group II has the special technical feature of specific method steps of reengineering a target subset of peptide sequences bases on mutating amino acid residues of the target subset of peptide sequences, not required by Group I+.

Group II has the special technical feature of the method step of determining a set of binding parameters for a set of reengineered peptide sequences in relation to a TLR, not required by Group I+.

No technical features are shared between the peptide motif polypeptide sequences of Group I+ (e.g., in instant application claim 1) and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ inventions and Croup II woro concidored to share the technical features of:

1. a Toll-like receptor related condition

2. a peptide configured to modulate TLR-related functionality and based on reengineering of a target peptide sequence associated with a microorganism-related modulator of a TLR.

3. a peptide motif sequence

these shared technical features are previously disclosed by the publication titled "Pili-like proteins of Akkermansia muciniphila modulate host immune responses and gut barrier function" by Ottman et al. (hereinafter "Ottman") [published 1 March 2017 in PLoS One Vol 12 No 3 Pages e0173004 1-18], in view of the publication titled "Identification of receptor ligands with phage display peptide libraries" by Koivunen et al. (hereinafter "Koivunen") [published May 1999 in J Nucl Med Vol 40 No 5 Pages 883-888], in view of the Uniprot database entry B2UR41 titled "Uncharacterized protein of gene Amuc_1100" (hereinafter "Uniprot B2UR41") [published 1 July 2008 available on the internet: < http://www.uniprot.org/uniprot/B2UR41>]

-----continued on next sheet------

----continued from previous sheet------

As to shared technical feature #1, a Toll-like receptor related condition, Ottman teaches (abstract; "Herein, we identify a highly abundant outer membrane pili-like protein of A. muciniphila MucT that is directly involved in immune regulation and enhancement of trans-epithelial resistance. The purified Amuc_1100 protein and enrichments containing all its associated proteins induced production of specific cytokines through activation of Toll-like receptor (TLR) 2 and TLR4. This mainly leads to high levels of IL-10 similar to those induced by the other beneficial immune suppressive microorganisms such as Faecalibacterium prausnitzii A2-165 and Lactobacillus plantarum WCFS1. Together these results indicate that outer membrane protein composition and particularly the newly identified highly abundant pili-like protein Amuc_1100 of A. muciniphila are involved in host immunological homeostasis at the gut mucosa, and improvement of gut barrier function").

As to shared technical feature #2, a peptide configured to modulate TLR-related functionality and based on reengineering of a target peptide sequence associated with a microorganism-related modulator of a TLR, Koivunen teaches (abstract; "Thus, peptides capable of binding target molecules in vitro and even target tissues in vivo can be identified. In recent years, a series of libraries that display degenerate peptides of different lengths have been constructed, and specific ligands to cell surface receptors, such as integrins, have been isolated"). Koivunen does not specifically teach a peptide configured to modulate TLR-related functionality and based on reengineering of a target peptide sequence associated with a microorganism-related modulator of a TLR. However, it would have been obvious that a degenerate peptide library based on peptide segments of expressed in a phage system and based on the sequence of Amuc_1100 of A. muciniphila, as taught above by Ottman, could have been utilized to identify "engineered" peptides capable of binding to TLR2 or TLR4, using the method of Koivunen.

As to shared technical feature #3, a peptide motif, the first motif of instant claim 1, comprising XXGFXLKXX, where X is any amino acid, was known in the art, as taught by Uniprot B2UR41 for the protein sequence for of A. muciniphila protein Amuc_1100 (pg 1; 149-TLGFELKAI-157).

As the shared technical features were known in the art at the time of the invention, they cannot be considered common special technical features that would otherwise unify the groups. The inventions lack unity with one another.

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