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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 June 2018 (14.06.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/106956 A3

(51) International Patent Classification:
C07K 14/54 (2006.01) *C12N 15/63* (2006.01)
C12N 15/09 (2006.01) *C12P 21/04* (2006.01)

(21) International Application Number:
PCT/US2017/065173

(22) International Filing Date:
07 December 2017 (07.12.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/431,336 07 December 2016 (07.12.2016) US
62/486,944 18 April 2017 (18.04.2017) US

(71) Applicant: **UNIVERSITY OF FLORIDA RESEARCH FOUNDATION, INCORPORATED** [US/US]; 223 Grinter Hall, Gainesville, FL 32611 (US).

(72) Inventor: **GHIVIZZANI, Steven C.**; 9916 SW 19th Lane, Gainesville, FL 32607 (US).

(74) Agent: **WALLER, Patrick R.H.**; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210-2206 (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, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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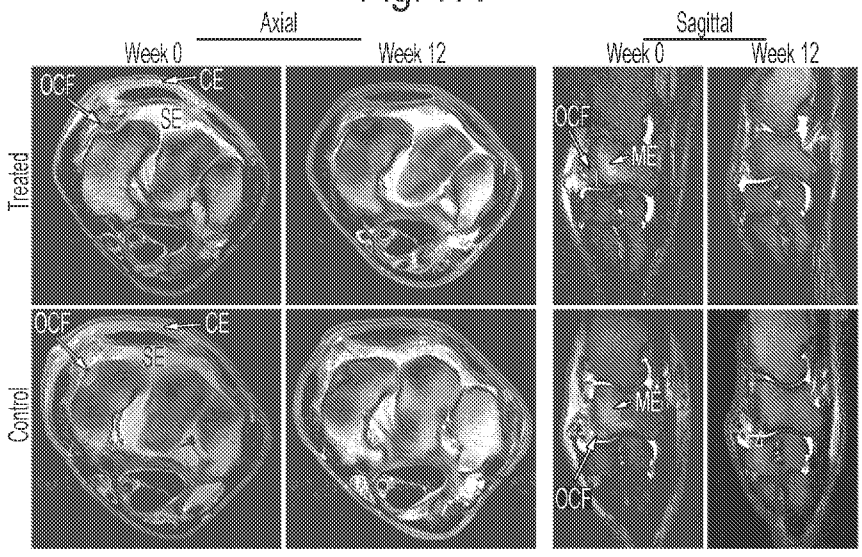
(54) Title: IL-1RA CDNAs

Fig. 7A



(57) Abstract: The present disclosure relates to compositions and methods for treatment of degenerative conditions of large weight-bearing joints, such as osteoarthritis, by intra-articular delivery of a codon-modified IL-1Ra encoding gene.

[Continued on next page]

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:
12 July 2018 (12.07.2018)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/65173

A. CLASSIFICATION OF SUBJECT MATTER
IPC - C07K 14/54, C12N 15/09, 15/63; C12P 21/04 (2018.01)
CPC - C07K 14/54, C12N 15/09, 15/63

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	US 2008/0166762 A1 (SHIVRAJ, L et al.) July 10, 2008; paragraphs [0013], [0017]	1
X	GOODRICH, LR et al. Optimization of scAAVIL-1ra In Vitro and In Vivo to Deliver High Levels of Therapeutic Protein for Treatment of Osteoarthritis. Molecular Therapy–Nucleic Acids. 05 February 2013; Vol. 2:e70; pages 1-10; DOI: 10.1038/mtna.2012.61	1
A	US 2014/0107189 A1 (BANCEL, S et al.) April 17, 2014; Table 146	2, 4/2
A	US 2012/0237587 A1 (WEHLING, P et al.) September 20, 2012; paragraph [0030]	2, 4/2

☐ 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
26 March 2018 (26.03.2018)	09 MAY 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/US17/65173

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.: 5-13
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.:
1-2, 4/2; SEQ ID NOs: 2-3, 11

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/US17/65173

-***-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 1-4, SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 11; are directed toward a recombinant, codon-modified gene encoding IL-1R, an aadeno-associated virus (rAAV) particle comprising said IL-1Ra; and a method administering the rAAV particle to treat degenerative conditions of large weight-bearing joints.

The recombinant nucleic acid will be searched to the extent they encompass SEQ ID NO: 2 (eqIL-1Ra), SEQ ID NO: 3 (Kozak sequence) and SEQ ID NO: 11 (eqIL-1Ra with Kozak). Applicant is invited to elect additional nucleic acid(s), with specified SEQ ID NO: for each, to be searched. Additional nucleic acid sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1, 2 and 4 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 2 (eqIL-1Ra), SEQ ID NO: 3 (Kozak sequence) and SEQ ID NO: 11 (eqIL-1Ra with Kozak). Applicants must specify the claims that encompass any additionally elected nucleic acid 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 nucleic acid encompassing SEQ ID NO: 10 (human IL-1Ra).

No technical features are shared between the IL1-Ra nucleic acid sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of: a recombinant adeno-associated virus (rAAV) particle comprising a recombinant nucleic acid comprising a codon-modified gene encoding IL-1Ra; these shared technical features are previously disclosed by US 2008/0187576 A1 to Ghivizzani et al. (hereinafter 'Ghivizzani').

Ghivizzani discloses a recombinant adeno-associated virus (rAAV) particle (recombinant AAV vectors and particles; paragraph [0025]) comprising a recombinant nucleic acid (recombinant DNA or RNA; paragraph [0152]) comprising a gene encoding IL-1Ra (viral vector encoding IL-1ra; paragraph [0022]). Ghivizzani does not disclose wherein the particle comprises a codon-modified gene encoding IL-1Ra.

Cho discloses a recombinant (vector-transfected) IL-1Ra (paragraphs [0058], [0084]) wherein the IL-1Ra is comprises a codon-modified gene encoding IL-1Ra (codon-optimized IL-1Ra; paragraph [0047]). It would have been obvious to one of ordinary skill in the art at the time of the invention to have modified the disclosure of Ghivizzani to provide wherein the rAAV particle comprises a codon-modified gene encoding IL-1Ra, because codon-modification of nucleic acid encoding IL-1Ra for use in vector transfection as disclosed by Cho would have motivated the use of codon-optimized IL-1Ra for delivery in the recombinant adeno-associated virus as previously disclosed by Ghivizzani in order to enhance the recombinant yield of IL-1Ra.

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 the combination of the Ghivizzani and Cho references, unity of invention is lacking.