

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

(19) World Intellectual Property  
Organization  
International Bureau



(10) International Publication Number  
**WO 2017/197141 A3**

(43) International Publication Date  
16 November 2017 (16.11.2017)

(51) International Patent Classification:

A61K 38/17 (2006.01) C12N 15/09 (2006.01)  
A61K 48/00 (2006.01) C12N 15/11 (2006.01)  
C12N 15/00 (2006.01)

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))

(21) International Application Number:

PCT/US2017/032202

(22) International Filing Date:

11 May 2017 (11.05.2017)

(88) Date of publication of the international search report:

07 December 2017 (07.12.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/335,952 13 May 2016 (13.05.2016) US

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(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, 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).

(54) Title: TARGETED TREATMENT OF ANDROGENIC ALOPECIA

(57) Abstract: Disclosed herein are methods and compositions for inactivating genes associated with androgenic alopecia, using engineered nucleases comprising a DNA binding domain and a cleavage domain or cleavage half-domain in conditions able to preserve cell viability. Polynucleotides encoding nucleases, vectors comprising polynucleotides encoding nucleases, and cells comprising polynucleotides encoding nucleases and/or cells comprising nucleases are also provided.



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INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US17/32202

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC - A61K 38/17, 48/00; C12N 15/00, 15/09, 15/11 (2017.01)  
 CPC - A61K 38/17, 38/1783, 48/00, 48/005, 48/0066; C12N 15/00, 15/09, 15/11, 15/1136

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	WO 2015/117021 A1 (FACTOR BIOSCIENCE INC.) 06 August 2015; Page 3 lines 6-10, Page 4, lines 9-22, page 11, lines 12-13 page 21, line 31 - page 22, line 2, page 30, lines 20-23, page 45, line 32 - page 46, line 6, lines 12-13	1-2, 10-11, 12/10-11
A	WO 2004/108899 A2 (THE GOVERNMENT OF THE UNITED STATES AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, CENTERS FOR DISEASE CONTROL AND PREVENTION) 16 December 2004; paragraph 58.	3/1-2
A	WO 01/88188 A2 (NIHON UNIVERSITY, SCHOOL JURIDICAL PERSON) 22 November 2001; page 4, lines 16-19	3/1-2

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	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 28 September 2017 (28.09.2017)	Date of mailing of the international search report <b>23 OCT 2017</b>
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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 <b>Shane Thomas</b>  PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/32202

**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.: 4-9 and 13-15  
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.:  
Groups I+, Claims 1-3, 10-12 and SEQ ID NO: 4

**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/US17/32202

\*\*\*-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 1-3, 10-12 and SEQ ID NO: 4 are directed toward a genetically modified cell in which expression of an AGA-related gene partially or completely inactivated; and a composition therefor.

The cell and composition will be searched to the extent the target gene encompasses SEQ ID NO: 4 (first exemplary target sequence). Applicant is invited to elect additional target sequence(s), with specified SEQ ID NO: for each, to be searched. Additional target sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1, 2, 3 (in-part) and 10-12 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 4 (target sequence). 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 target sequence encompassing SEQ ID NO: 5 (first exemplary elected target sequence).

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

Groups I+ share the technical features including: a genetically modified cell in which expression of an AGA-related gene partially or completely inactivated, the AGA-related gene comprising an insertion and/or deletion; and a composition for modifying one or more AGA-related genes in a cell of a mammalian subject, the composition comprising one or more nucleases, each nuclease comprising a DNA-binding domain that binds to the endogenous AGA-related gene and an endonuclease cleavage domain, wherein the nuclease cleaves the one or more endogenous AGA-related gene.

However, these shared technical features are previously disclosed by WO 2015/117021 A1 to Factor Bioscience Inc. (hereinafter 'Factor').

Factor discloses : a genetically modified cell (a cell produced using a gene-editing protein (a genetically modified cell); page 3, lines 6-10; page 4, lines 14-20) in which expression of an AGA-related gene is partially or completely inactivated (a method for reducing the expression of a protein of interest, including an AGA-related protein (in which expression of an AGA-related gene is partially or completely inactivated); page 21, line 31 - page 22, line 2; page 45, line 32- page 46, line 6), the AGA-related gene comprising an insertion and/or deletion (the AGA-related gene comprising a nick or double-strand break (insertion and/or deletion); page 46, lines 2-4); and a composition (a composition; page 3, lines 6-10) for modifying one or more AGA-related genes in a cell of a mammalian subject (for treating AGA by gene editing in cells of a subject (for modifying one or more AGA-related genes in a cell of a mammalian subject); page 21, line 31 - page 22, line 2), the composition comprising one or more nucleases (the composition comprising one or more nucleases; page 3, lines 6-10; page 4, lines 14-22; page 46, lines 12-13), comprising a DNA-binding domain (comprising a DNA-binding domain; page 4, lines 14-22) that binds to the endogenous AGA-related gene (that binds to the endogenous AGA-related gene; page 31, line 31 - page 22, line 2) and an endonuclease cleavage domain (and an endonuclease cleavage domain; page 4, lines 14-22), wherein the nuclease cleaves the endogenous AGA-related gene (wherein the nuclease cleaves the endogenous AGA-related gene; page 21, line 31 - page 22, line 2; page 45, line 32- page 46, line 6).

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 Factor reference, unity of invention is lacking.