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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.

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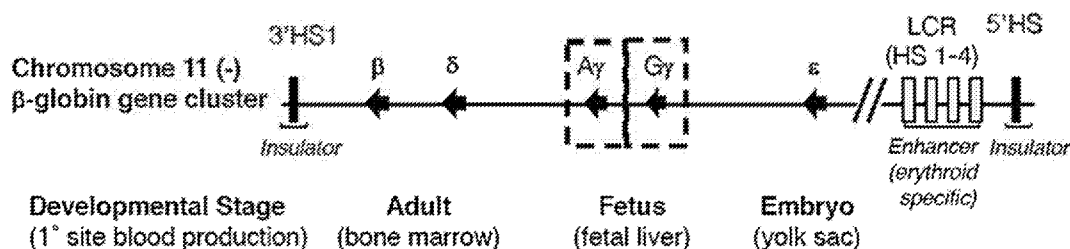
- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

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

24 October 2019 (24.10.2019)

(54) Title: SYSTEMS AND METHODS FOR THE TREATMENT OF HEMOGLOBINOPATHIES

FIG 1



(57) Abstract: Genome editing systems, guide RNAs, and CRISPR-mediated methods are provided for altering portions of the *HBG1* and *HBG2* loci in cells and increasing expression of fetal hemoglobin.



INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2019/021244

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C12N15/113 A61K31/713 A61P7/00  
ADD.  
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)  
C12N A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
EPO-Internal, WPI Data, BIOSIS, Sequence Search, EMBASE, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2017/160890 A1 (EDITAS MEDICINE INC [US]) 21 September 2017 (2017-09-21) claims 1,11,155-160,194,332; examples 1-3; sequences 345, 362, 915 -----	1-43
Y	WO 2016/011080 A2 (UNIV CALIFORNIA [US]) 21 January 2016 (2016-01-21) claims 1, 10, 50, 54; sequences 75438, 75441, 75443, 75445 -----	1-43
Y	WO 2016/135557 A2 (CRISPR THERAPEUTICS AG [CH]) 1 September 2016 (2016-09-01) claims 1, 7, 20-25, 46-55; examples 1,2; table 1; sequence 122 ----- -/--	1-43

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  2 July 2019	Date of mailing of the international search report  10/09/2019
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Bucka, Alexander
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2019/021244

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>ELIZABETH A TRAXLER ET AL: "A genome-editing strategy to treat beta-hemoglobinopathies that recapitulates a mutation associated with a benign genetic condition", NATURE MEDICINE, vol. 22, no. 9, 15 August 2016 (2016-08-15), pages 987-990, XP055372350, New York ISSN: 1078-8956, DOI: 10.1038/nm.4170 figures 1,2</p> <p style="text-align: center;">-----</p>	1-43
A	<p>CARSTEN LEDERER ET AL: "Beta testing: preclinical genome editing in [beta]-globin disorders", CELL AND GENE THERAPY INSIGHTS, vol. 1, no. 2, 10 December 2015 (2015-12-10), XP055462737, ISSN: 2059-7800, DOI: 10.18609/cgti.2015.021 table 1</p> <p style="text-align: center;">-----</p>	1-43
A	<p>MEGAN D HOBAN ET AL: "A genome editing primer for the hematologist", BLOOD, vol. 127, no. 21, 6 April 2016 (2016-04-06), pages 2525-2535, XP055552885, DOI: 10.1182/blood-2016-01- figures 1,2</p> <p style="text-align: center;">-----</p>	1-43
A	<p>MARIA ROSA LIDONNICI ET AL: "Gene therapy and gene editing strategies for hemoglobinopathies", BLOOD CELLS, MOLECULES AND DISEASES, vol. 70, 3 January 2018 (2018-01-03), pages 87-101, XP055597660, US ISSN: 1079-9796, DOI: 10.1016/j.bcnd.2017.12.001 page 95 - page 96</p> <p style="text-align: center;">-----</p>	1-43

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2019/021244
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017160890 A1	21-09-2017	AU 2017235333 A1	04-10-2018
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WO 2016135557 A2	01-09-2016		
WO 2016135558 A2	01-09-2016		
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2019/021244

## 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:

see additional sheet

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 an 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.:

1-43(partially)

### 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.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

## 1. claims: 1-43(partially)

A genome editing system, comprising an RNA-guided nuclease; and at least one guide RNA (gRNA) configured to provide an editing event within the region of Chr 11 (NC 000011.10): 5,247,883 -5,248,186, wherein the guide RNA is a guide RNA differing by no more than 3 nucleotides from the first guide RNA mentioned in table 12, i. e. SEQ ID NO: 1214, related products and methods.

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## 2-237. claims: 1-43(partially)

A genome editing system, comprising an RNA-guided nuclease; and at least one guide RNA (gRNA) configured to provide an editing event within one or more regions selected from Chr 11 (NC 000011.10): 5,247,883 -5,248,186; 5,248,509 - 5,249,173; 5,249,198 - 5,249,362; 5,249,591- 5,249,712; 5,249,904 - 5,249,927; 5,249,955 - 5,249,987, 5,250,040 - 5,250,075; 5,250,089 - 5,250,129; 5,250,141 - 5,250,254; 5,250,464 - 5,250,549; 5,250,594 - 5,250,735; 5,253,425 - 5,254,121; 5,254,122 - 5,254,306; 5,254,511 - 5,254,648; 5,254,829 - 5,254,866; 5,254,935 - 5,255,009; 5,255,025 - 5,255,053; 5,255,076 - 5,255,179; 5,255,255 - 5,255,292; and/or 5,255,518 - 5,255,641, wherein in each separate invention the guide RNA is selected from any one guide RNA differing by no more than 3 nucleotides from any one of the guide RNAs mentioned in table 12 and comprised in one of the regions of claim 1 (i. e. SEQ ID NO: 1067, 1068, 1215, 1216, etc.), related products and methods.

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