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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, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(54) **Title:** NOVEL POLYNUCLEOTIDES, CELLS AND METHODS

Flow cytometry-based quantification of the silencing efficiency of B2M GEIGS solutions ectopically expressed in human iPSCs

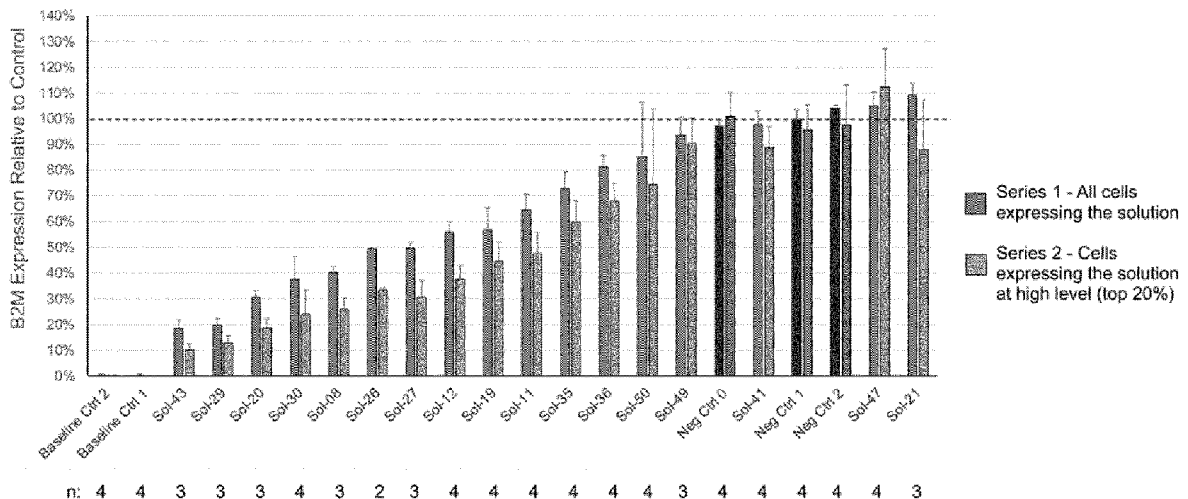


Fig. 8

(57) **Abstract:** There are disclosed *inter alia* novel inhibitory RNAs, or a polynucleotide sequence encoding an inhibitory RNA, and expression cassettes, vectors, virions, synthetic microRNA, synthetic pre-microRNA molecules and cells, and associated medical uses and methods of modifying protein expression, especially B2M protein expression.



(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, 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, ME, 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))*
- *with sequence listing part of description (Rule 5.2(a))*
- *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

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22 August 2024 (22.08.2024)

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER INV. C12N15/113 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		
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, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/033023 A1 (BAYLOR COLLEGE MEDICINE [US]) 14 February 2019 (2019-02-14)	1-6, 13-30, 33, 35-43, 45-47, 49-54, 56-59, 66-69
Y	paragraphs [0024], [0062], [0066], [0074], [0124]; claims 1-18; examples 1,4; sequences 3,7 <div style="text-align: center;">-----</div> <div style="text-align: center;">- / - -</div>	25,31, 32,34, 44,48, 55,60-65
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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	
2 May 2024	15/07/2024	
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	

INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/192286 A1 (TCR2 THERAPEUTICS INC [US]) 15 September 2022 (2022-09-15)	1-30,33, 35-43, 45-47, 49-54, 56-59, 66-69
Y	paragraph [0431] - paragraph [0434]; claims 1-25,32,62-64,179-240; example 2; sequences 167,185,187	31,32,34
X	WO 2021/011936 A2 (UNIV ROCHESTER [US]) 21 January 2021 (2021-01-21)	1-30,33, 35-42, 45,47, 51-54, 56-59, 66-69
	claims 1-7,25,38-42,50; examples 1-3; sequence 55	
A	WO 2020/206248 A1 (PREC BIOSCIENCES INC [US]) 8 October 2020 (2020-10-08) claims 1-14,126-128,174,306-308; examples 5,11,13,15; sequences 7-20,60,61	1-69
Y	WO 2020/221939 A1 (CELYAD [BE]) 5 November 2020 (2020-11-05)	44,48
A	pages 5,21; claims 1,17-20; figures 5,13,14; example 9 page 24 - page 25	1-43, 45-47, 49-69
A	CN 102 899 327 A (UNIV TSINGHUA GRADUATE SCHOOL ET AL.) 30 January 2013 (2013-01-30) claims 1-9; figure 3; sequence 6	1-69
Y	WO 2019/058253 A1 (TROPIC BIOSCIENCES UK LTD [GB]) 28 March 2019 (2019-03-28) page 35; claims 1-42; examples 1,2,5	25,55, 60-65
A	WO 2022/226353 A1 (BAYLOR COLLEGE MEDICINE [US]) 27 October 2022 (2022-10-27) claims 1-16,21; figure 1; examples 2,3,5	1-69
A	WO 2016/160721 A1 (HARVARD COLLEGE [US]) 6 October 2016 (2016-10-06) claims 1-23,35; example 2; sequence 13149	1-69
A	WO 2021/016608 A1 (PREC BIOSCIENCES INC [US]) 28 January 2021 (2021-01-28) paragraph [0102]; sequence 22	1-69
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International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	<p>SEITAN V: "759: Engineering Therapeutic Cells through Rewiring of the miRNA Network", MOLECULAR THERAPY; 26TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF GENE & CELL THERAPY 20230516 TO 20230520 LOS ANGELES, ELSEVIER INC, US, [Online] vol. 31, no. 4, Supplement 1, 2 May 2023 (2023-05-02), page 377, XP009552411, ISSN: 1525-0016 Retrieved from the Internet: URL:https://www.sciencedirect.com/science/article/pii/S1525001623002484?via%3Dihub> abstract</p> <p style="text-align: center;">-----</p>	1 - 69

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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.
 - b. furnished subsequent to the international filing date for the purposes of international search (Rule 13^{ter}.1(a)).
 accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

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PCT/EP2024/050828

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 - 69 (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: 1-69 (partially)

An inhibitory RNA, or a polynucleotide sequence encoding an inhibitory RNA, the inhibitory RNA comprising a sequence selected from: (i) SEQ ID NO: 1, 4, 71, 78, 109-111, 114, 125, 126 or 127; (ii) a variant of SEQ ID NO: 1, 4, 71, 78, 109-111, 114, 125, 126 or 127; (iii) a fragment of any one of SEQ ID NO: 1, 4, 71, 78, 109-111, 114, 125, 126 or 127; and (iv) a DNA sequence complementary to any one of (i), (ii) or (iii).

2-71. claims: 1-69 (partially)

An inhibitory RNA, or a polynucleotide sequence encoding an inhibitory RNA, wherein in each separate invention the inhibitory RNA comprises a sequence selected from: (i) any one of SEQ ID NOs: 2, 3, 5-17, 64-70, 72-77, 79-108, 112, 113, 115-124, 127; (ii) a variant of any one of SEQ ID NOs: 2, 3, 5-17, 64-70, 72-77, 79-108, 112, 113, 115-124, 127; (iii) a fragment of any one of SEQ ID NOs: 2, 3, 5-17, 64-70, 72-77, 79-108, 112, 113, 115-124, 127; and (iv) a DNA sequence complementary to any one of (i), (ii) or (iii).

INTERNATIONAL SEARCH REPORT

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International application No PCT/EP2024/050828

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