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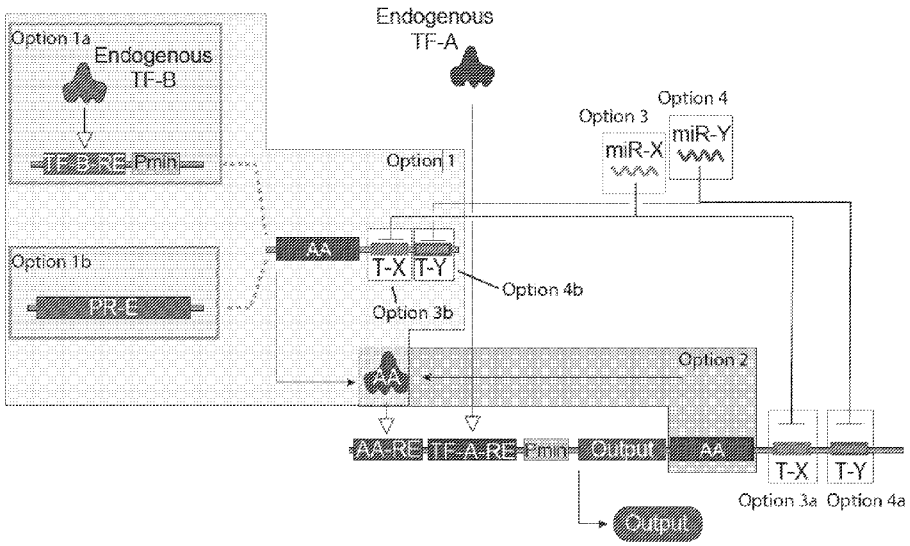
(54) Title: A METHOD TO TREAT DISEASE USING A NUCLEIC ACID VECTOR ENCODING A HIGHLY COMPACT MULTI-INPUT LOGIC GATE

FIG. 1A



(57) Abstract: Disclosed herein are contiguous DNA sequences encoding highly compact multi-input genetic logic gates for precise *in vivo* cell targeting, and methods of treating disease using a combination of *in vivo* delivery and such contiguous DNA sequences.

[Continued on next page]

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/85 C12N15/11
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 C40B

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, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NIELS HEINZ ET AL: "Graded or threshold response of the tet-controlled gene expression: all depends on the concentration of the transactivator", BMC BIOTECHNOLOGY, BIOMED CENTRAL LTD. LONDON, GB, vol. 13, no. 1, 22 January 2013 (2013-01-22), page 5, XP021135814, ISSN: 1472-6750, DOI: 10.1186/1472-6750-13-5	1-4, 8-11, 13-16, 25,26, 33-36
Y	abstract; figure 1	4-7,12, 62,64-79

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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
30 January 2020	01/04/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Mossier, Birgit

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SZYMANSKI PAUL ET AL: "Development and validation of a robust and versatile one-plasmid regulated gene expression system", MOLECULAR THERAPY, NATURE PUBLISHING GROUP, GB, vol. 15, no. 7, 1 July 2007 (2007-07-01), pages 1340-1347, XP002516079, ISSN: 1525-0024, DOI: 10.1038/SJ.MT.6300171 [retrieved on 2007-05-01] abstract; figures 2,5	1-3,11, 13-16, 26-29, 32-36
Y	BARTOLOMEO ANGELICI ET AL: "Synthetic Biology Platform for Sensing and Integrating Endogenous Transcriptional Inputs in Mammalian Cells", CELL REPORTS, vol. 16, no. 9, 1 August 2016 (2016-08-01) , pages 2525-2537, XP055662433, US ISSN: 2211-1247, DOI: 10.1016/j.celrep.2016.07.061 abstract page 2527, column 2 - page 2531 page 2533, column 1, paragraph 2 - page 2535; figures 2,3,6	4-7,12
Y	Bartolomeo Angelici: "Design and Implementation of Transcription Factor Based Gene Classifier Circuits", , 1 January 2017 (2017-01-01), XP055662696, DOI: 10.3929/ETHZ-B-000253961 Retrieved from the Internet: URL:https://search.datacite.org/works/10.3929/ethz-b-000253961 abstract page 39 - page 45 page 105 - page 107	4-7,12, 17-24, 30,31, 62,64-79
Y	MARIO AMENDOLA ET AL: "A Double-Switch Vector System Positively Regulates Transgene Expression by Endogenous microRNA Expression (miR-ON Vector)", MOLECULAR THERAPY : THE JOURNAL OF THE AMERICAN SOCIETY OF GENE THERAPY, vol. 21, no. 5, 1 May 2013 (2013-05-01), pages 934-946, XP055630166, US ISSN: 1525-0016, DOI: 10.1038/mt.2013.12 cited in the application abstract page 940, column 2, paragraph 2 - page 942, column 2, paragraph 1; figure 5	17-23

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/001100

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NURIA VILABOA ET AL: "Gene Switches for Deliberate Regulation of Transgene Expression: Recent Advances in System Development and Uses", JOURNAL OF GENETIC SYNDROMES & GENE THERAPY, vol. 02, no. 03, 1 January 2011 (2011-01-01), XP055555286, DOI: 10.4172/2157-7412.1000107 abstract page 14, column 1, paragraph 2 - page 15, column 1, paragraph 1 page 18, column 2, paragraph 3	17-23
Y	WO 2017/064566 A2 (ASTRAZENECA AB [SE]) 20 April 2017 (2017-04-20) abstract page 6, line 10 - page 7, line 5 page 12, line 31 - page 15, line 7 page 19, line 10 - line 32	24,30,31
A	SIMON AUSL?NDER ET AL: "From gene switches to mammalian designer cells: present and future prospects", TRENDS IN BIOTECHNOLOGY, vol. 31, no. 3, 1 March 2013 (2013-03-01), pages 155-168, XP055117371, ISSN: 0167-7799, DOI: 10.1016/j.tibtech.2012.11.006 abstract page 166, column 1, paragraph 2 - column 2; figures 1-3; table 2	1-36,62, 64-79
A	YAAKOV BENENSON: "Biomolecular computing systems: principles, progress and potential", NATURE REVIEWS GENETICS, vol. 13, no. 7, 12 June 2012 (2012-06-12), pages 455-468, XP055107191, ISSN: 1471-0056, DOI: 10.1038/nrg3197 cited in the application abstract; figures 1-7	1-36,62, 64-79

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/001100

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.:

1-36, 62(completely); 64-79(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: 1-36, 62(completely); 64-79(partially)

A contiguous polynucleic acid molecule encoding at least two cassettes, wherein each cassette comprises a regulatory component and a response component, wherein: (i) at least one cassette comprises: a 5' regulatory component comprising a transactivator response element and a 3' response component comprising an output; and (ii) at least one cassette comprises: a 5' regulatory component and a 3' response component comprising a nucleic acid sequence encoding a transactivator protein; and wherein the transactivator of (ii), when expressed as a protein, binds and transactivates the transactivator response element of (i) and the subject-matter relating thereto.

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2. claims: 37-61, 63(completely); 64-79(partially)

A contiguous polynucleic acid molecule encoding at least one cassette, wherein the cassette comprises:(i) a 5' regulatory component comprising a transactivator response element; and (ii) a 3' response component comprising an output, a transactivator, wherein transcription of the response component generates a single mRNA; and wherein the transactivator of (ii), when expressed as a protein, binds and transactivates the transactivator response element of (i) and the subject-matter relating thereto.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/001100

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017064566 A2	20-04-2017	AU 2016337408 A1	26-04-2018
		CA 3001518 A1	20-04-2017
		CN 108431225 A	21-08-2018
		EP 3362561 A2	22-08-2018
		JP 2018531013 A	25-10-2018
		US 2018305714 A1	25-10-2018
		WO 2017064566 A2	20-04-2017