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| 62/244,855 | 22 October 2015 (22.10.2015) | US |
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- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH,

(54) Title: INFECTIOUS DISEASE VACCINES

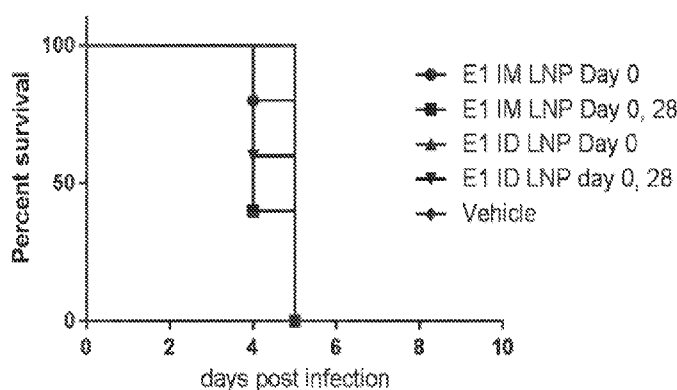


Fig. 4A

(57) Abstract: Aspects of the disclosure relate to nucleic acid vaccines. The vaccines include one or more RNA polynucleotides having an open reading frame encoding one or more Chikungunya antigen(s), one or more Zika virus antigens, and one or more Dengue antigens. Methods for preparing and using such vaccines are also described.



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).

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

26 April 2018 (26.04.2018)

**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:  
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
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 Supplemental Box for Details**

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.:

**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

International application No.  
**PCT/US2016/043348**

## A. CLASSIFICATION OF SUBJECT MATTER

**A61K 31/7105 (2006.01) A61K 39/12 (2006.01) A61P 31/14 (2006.01)**

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)

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)

HCAPLUS, MEDLINE, BIOSIS, EMBASE, PATENW, WPI &amp; Search Terms: ZIKA, DENGUE, CHIKUNGUNYA, RNA, vaccine and like terms

GenomeQuest: SEQ ID no: 13

Internal databases provided by IP Australia, Patentscope, PubMed: Applicant/Inventor search

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Documents are listed in the continuation of Box C		

 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  
22 March 2018Date of mailing of the international search report  
22 March 2018

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		<b>PCT/US2016/043348</b>
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/006834 A1 (NOVARTIS AG) 10 January 2013 whole document, particularly pages 13-28, 36-54, 62-66, Examples	1-16, 21-23, 29-103, 109-111, 112-128, 130-150, 157-159, 165-239, 245-247, 258-273, 278-280, 286-367, 373-375
P,X	RICHNER J. M. et al., "Modified mRNA vaccines protect against Zika virus infection", CELL, March 2017, vol. 168, pages 1114-1125 Summary, Figures 1-4, Results	1-16, 21-23, 29-103, 109-111
P,X	PARDI N. et al. "Zika virus protection by a single low dose nucleoside modified mRNA vaccination", Author manuscript [retrieved from internet, available in PMC 02 August 2017] < URL: <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5344708/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5344708/</a>  Published in final edited form as: NATURE, March 2017, vol. 543, no. 7644, pages 248-251. Whole document, particularly Abstract, pages 3-5, mRNA production, LNP formulation of the mRNA, Figures	1-16, 21-23, 29-103, 109-111
A	GARCIA-ARRIAZA J. et al., "A novel poxvirus-based vaccine, MVA-CHIKV, is highly immunogenic and protects mice against Chikungunya infection", JOURNAL OF VIROLOGY, 2014, vol. 88, no. 6, pages 3527-3547. Whole document	258-273, 278-280, 286-367, 373-375
P,A	MCSWEEGAN E. et al., "The global virus network: Challenging Chikungunya", Author manuscript [retrieved from internet, available in PMC 01 August 2016] < URL: <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4843800/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4843800/</a>  Published in final edited form as: ANTIVIRAL RESEARCH, August 2015, vol. 120, pages 147-152. Published online 2015 Jun 10. Whole document	258-273, 278-280, 286-367, 373-375
P,A	BURT F.J. et al., "Chikungunya virus: an update on the biology and pathogenesis of this emerging pathogen", THE LANCET, April 2017, vol. 17, e107-e117 Whole document	258-273, 278-280, 286-367, 373-375
P,A	WO 2017/021546 A1 (CUREVAC AG) 09 February 2017 Whole document, particularly pages 80, 81, 101-103, examples	112-128, 130-150, 157-159, 165-239, 245-247
P,A	WO 2017/020026 A1 (MODERNATX, INC) 02 February 2017 Whole document	1-16, 21-23, 29-103, 109-111, 112-128, 130-150, 157-159, 165-239, 245-247, 258-273, 278-280, 286-367, 373-375
P,A	WO 2017/162265 A1 (BIONTECH RNA PHARMACEUTICALS GMBH & TRON-TRANSLATIONALE ONKOLOGIE AN DER UNIVERSITÄTSMEDIZIN DER JOHANNES GUTENBERG-UNIVERSITÄT MAINZ GEMEINNUTZIGE GMBH) 28 September 2017 Whole document, Particularly Abstract, pages 5, 28, examples, claims	258-273, 278-280, 286-367, 373-375

<b>INTERNATIONAL SEARCH REPORT</b>		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		<b>PCT/US2016/043348</b>
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2015/164674 A1 (MODERNA THERAPEUTICS, INC.) 29 October 2015 Abstract, pages 501, 643-652, Table 14, Examples 14, 17, Claims	112-114, 142, 143 159, 166-169, 178-180, 181-187, 190, 191, 195-238, 245, 246
P,X	WO 2017/140905 A1 (CUREVAC AG & SANOFI PASTEUR SA) 24 August 2017 Abstract, pages 21, 22, 30, 41, 45-50, 58, 61-72, 166-189, 207-208, 211, claims, Examples, Tables	1-9, 12, 21-23, 29-39, 42-103, 109-111
P,X	WO 2017/208191 A1 (GLAXOSMITHKLINE BIOLOGICALS) 07 December 2017 Abstract, pages 17-18, 26-28, Examples, Tables	1-9, 12, 21-23, 30-32, 35-39, 42-103, 109-111
P,X	WO 2017/210364 A1 (INFECTIOUS DISEASE RESEARCH INSTITUTE) 07 December 2017 abstract, examples, [0358]	1, 2, 51, 54
P,X	WO 2016/044023 A1 (THE UNIVERSITY OF IOWA RESEARCH) 24 March 2016 Abstract, pages 4-6, 14, 25, claims	112, 142, 143-146, 178-180, 187, 190-195

**Supplemental Box****Continuation of: Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

The application features multiple inventions defined in the 477 claims, and many of the claims make reference to numerous sequences and alternative combinations of features.

There are 4 overarching separate inventions encompassing vaccine constructs (in the main, RNA constructs) against 3 distinct viruses; however, there are multiple inventions within each of these 4 groups and also within the claims within each subgroup in each invention:

**Invention 1**

- Claims 1 to 101 relate to Zika virus (ZIKV) vaccine constructs comprising an RNA encoding a ZIKV antigenic polypeptide, and the therapeutic uses of these constructs.
- Claims 102 and 103 relate to nanoparticle formulations of ZIKV vaccine constructs comprising an RNA encoding ZIKV antigenic polypeptides with 5' cap and chemical modifications. Exemplary signal peptides are defined in SEQ ID NOs: 125, 126, 128 & 131.
- Claims 104 to 108 relate to vaccine constructs comprising a ZIKV envelope protein fused to a signal sequence, and nucleic acids encoding the same.
- Claims 109 to 111 relate to ZIKV vaccine constructs comprising an RNA encoding a ZIKV antigenic peptide linked to a signal peptide.

**Invention 2**

- Claims 112 to 237 relate to Dengue virus (DENV) vaccine constructs comprising an RNA encoding a DENV antigenic polypeptide (in the main, a DENV2 prME polypeptide), and the therapeutic uses of these constructs.
- Claims 238 and 239 relate to nanoparticle formulations of DENV vaccine constructs comprising an RNA encoding DENV antigenic polypeptides with 5' cap and chemical modifications. Exemplary signal peptides sequences are the same as for invention 1.
- Claims 240 to 244 relate to vaccine constructs comprising a DENV envelope protein fused to a signal sequence and nucleic acids encoding the same.
- Claims 245 to 247 relate to vaccine constructs comprising a DENV RNA encoding a DENV antigenic peptide linked to a signal peptide.
- Claims 248 to 257 relate to vaccine construct comprising an antigen presentation enhancer sequence linked to a DENV antigenic polypeptide.

**Invention 3**

- Claims 258 to 365 relate to Chikungunya virus (CHIKV) vaccine constructs comprising an RNA encoding a CHIKV antigenic polypeptide (including concatemeric constructs of DENV2 prME peptide epitopes), and the therapeutic uses of these constructs.

**Supplemental Box**

- Claims 366 and 367 relate to nanoparticle formulations of CHIKV vaccine constructs comprising an RNA encoding CHIKV antigenic polypeptides with 5' cap and chemical modifications. Exemplary signal peptides sequences are the same as for invention 1.
- Claims 368 to 372 relate to CHIKV vaccine constructs comprising a CHIKV envelope protein fused to a signal sequence and nucleic acids encoding the same.
- Claims 373 to 375 relate to vaccine constructs comprising a CHIKV RNA encoding a CHIKV antigenic peptide linked to a signal peptide.

**Invention 4**

- Claims 376 to 477, in summary, relate to combination RNA vaccines of CHIKV and/or, DENV and/or ZIKV comprising RNA polynucleotides constructs encoding antigenic polypeptides, and the uses of the combination vaccines.

Under Rule 33.3(b) it is considered not practical or economically feasible to identify the exact number of inventions and search and report on the full scope of all the claims in any one of the inventions.

Also, please note not all the claims comply with the descriptive support requirements of Article 6 of the PCT.

Therefore the search and examination will be limited to the first 3 inventions with the following limitations:

With respect to invention 1 (ZIKV):

- The search and opinion is limited to claims **1-16, 21-23, 29-103, 109-111** only in so far as they relate in a meaningful way to the concept of RNA vaccines encoding ZIKV polypeptides and the various construct derivatives such as these polypeptides with a 5' cap.
- No search will be undertaken on the ZIKV sequences.

With respect to invention 2 (DENV):

- This search and opinion is limited to claims **112-128, 130-150, 157-159, 165-239, 245-247** only in so far as they relate in a meaningful way to RNA constructs encoding DENV2 polypeptides in general and the various derivative constructs such as DENV concatemeric constructs in general and these polypeptides with a 5' cap.
- No search will be undertaken on the DENV sequences.

With respect to invention 3 (CHIKV):

- The search and opinion is limited to claims **258-273, 278-280, 286-367, 373-375** when relating to the general concept of RNA constructs encoding CHIKV polypeptides including the construct of SEQ ID No:3

With respect to invention 4 (combinations vaccines):

- No search nor examination will be undertaken.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2016/043348**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

<b>Patent Document/s Cited in Search Report</b>		<b>Patent Family Member/s</b>	
<b>Publication Number</b>	<b>Publication Date</b>	<b>Publication Number</b>	<b>Publication Date</b>
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2016/043348**

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<b>Patent Document/s Cited in Search Report</b>		<b>Patent Family Member/s</b>	
<b>Publication Number</b>	<b>Publication Date</b>	<b>Publication Number</b>	<b>Publication Date</b>
		WO 2017162461 A1	28 Sep 2017
WO 2015/164674 A1	29 October 2015	WO 2015164674 A1	29 Oct 2015
		AU 2015249553 A1	10 Nov 2016
		CA 2946751 A1	29 Oct 2015
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		EP 3134131 A1	01 Mar 2017
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**End of Annex**

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)