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(54) **Title:** METHODS OF RAISING AN IMMUNE RESPONSE BY DELIVERY OF RNA

(57) **Abstract:** RNA encoding an immunogen is co-delivered to non-immune cells at the site of delivery and also to immune cells which infiltrate the site of delivery. The responses of these two cell types to the same delivered RNA lead to two different effects, which interact to produce a strong immune response against the immunogen. The non-immune cells translate the RNA and express the immunogen. Infiltrating immune cells respond to the RNA by expressing type I interferons and pro-inflammatory cytokines which produce a local adjuvant effect which acts on the immunogen-expressing non-immune cells to upregulate major histocompatibility complex expression, thereby increasing presentation of the translated protein to T cells. The effects on the immune and non-immune cells can be achieved by a single delivery of a single RNA e.g. by a single injection.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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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)
A61K

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, MEDLINE, 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 | wo 99/11808 AI (CONNAUGHT LAB [CA] ; PARRINGTON MARK [CA]) 11 March 1999 (1999-03-11) the whole document | 1-12 |
| X | wo 2009/042794 A2 (UNIV VANDERBILT [US] ; CROWE JAMES E JR [US] ; MOK HOYIN [US] ; JOHNSTON) 2 April 2009 (2009-04-02) the whole document | 1-12 |

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See patent family annex.

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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>GREER ET AL: "A chimeric alphavirus RNA replicon gene-based vaccine for human parainfluenza virus type 3 induces protective immunity against intranasal virus challenge", VACCINE, ELSEVIER LTD, GB, vol. 25, no. 3, 8 December 2006 (2006-12-08), pages 481-489, XP005798901, ISSN: 0264-410X, DOI: 10.1016/J.VACCINE.2006.07.048 the whole document</p> <p style="text-align: center;">-----</p> | 1-11 |
| X | <p>CHENG W F ET AL: "Enhancement of Sindbis Virus self-replicating RNA vaccine potency by linkage of Herpes Simplex Virus type 1 VP22 protein to Antigen", JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 75, no. 5, 1 March 2001 (2001-03-01), pages 2368-2376, XP002201711, ISSN: 0022-538X, DOI: 10.1128/JVI.75.5.2368-2376.2001 the whole document</p> <p style="text-align: center;">-----</p> | 1-11 |
| A | <p>DI EBOLD SANDRA S ET AL: "Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA.", SCIENCE (WASHINGTON D C), vol. 303, no. 5663, 5 March 2004 (2004-03-05), pages 1529-1531, XP002675306, ISSN: 0036-8075 the whole document</p> <p style="text-align: center;">-----</p> | 1-12 |
| A | <p>CARRALOT J-P ET AL: "Polarization of immunity induced by direct injection of naked sequence-stabilized mRNA vaccines", CMLS CELLULAR AND MOLECULAR LIFE SCIENCES, BIRKHAUSER VERLAG, HEIDELBERG, DE, vol. 61, no. 18, 1 September 2004 (2004-09-01), pages 2418-2424, XP002355208, ISSN: 1420-682X, DOI: 10.1007/S00018-004-4255-0 the whole document</p> <p style="text-align: center;">-----</p> | 1-12 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/043104

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date | | |
|--|------------------|-------------------------|----------------------------|----|------------|
| W0 9911808 | A1 | 11-03-1999 | AT 361368 T 15-05-2007 | | |
| | | | AU 742046 B2 13-12-2001 | | |
| | | | AU 9056998 A 22-03-1999 | | |
| | | | BR 9815642 A 31-12-2002 | | |
| | | | CA 2301891 A1 11-03-1999 | | |
| | | | DE 69837708 T2 10-01-2008 | | |
| | | | EP 1009846 A1 21-06-2000 | | |
| | | | JP 2001514857 A 18-09-2001 | | |
| | | | US 6060308 A 09-05-2000 | | |
| | | | US 6428324 B1 06-08-2002 | | |
| | | | WO 9911808 A1 11-03-1999 | | |
| | | | ----- | | |
| | | | W0 2009042794 | A2 | 02-04-2009 |
| EP 2205751 A2 14-07-2010 | | | | | |
| US 2009162395 A1 25-06-2009 | | | | | |
| WO 2009042794 A2 02-04-2009 | | | | | |
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