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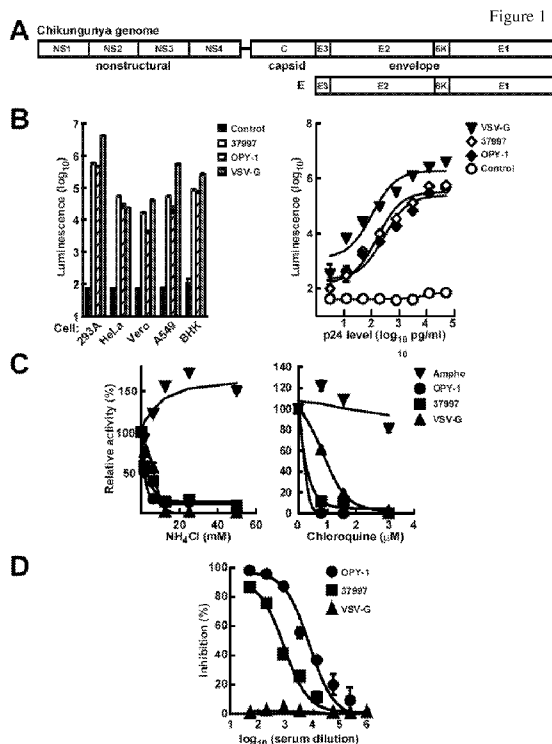
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[Continued on next page]

(54) Title: VIRUS-LIKE PARTICLES AND METHODS OF USE



(57) Abstract: The invention features modified alphavirus or flavivirus virus-like particles (VLPs). The invention provides methods, compositions, and kits featuring the modified VLPs. The invention also features methods for enhancing production of modified VLPs for use in the prevention or treatment of alphavirus and flavivirus-mediated diseases. The invention also provides methods for delivering agents to a cell using the modified VLPs.



SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, (88) **Date of publication of the international search report:**
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/023361

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/12 C12N7/00
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)
A61K 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, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/062396 A2 (US GOV HEALTH & HUMAN SERV [US]; NABEL GARY J [US]; AKAHATA WATARU [US) 3 June 2010 (2010-06-03)	1-9,12, 13, 18-30, 33-44, 63-66, 69,70, 87-95, 102
Y	the whole document ----- -/--	1-9,12, 13, 18-30, 33-44, 63-66, 69,70, 87-95, 102

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 28 September 2012	Date of mailing of the international search report 22/01/2013
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 Wimmer, Georg

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/023361

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PALUCHA ANDRZEJ ET AL: "Virus-like particles: Models for assembly studies and foreign epitope carriers", PROGRESS IN NUCLEIC ACID RESEARCH AND MOLECULAR BIOLOGY, ACADEMIC PRESS, US, vol. 80, 1 January 2005 (2005-01-01), pages 135-168, XP008111583, ISSN: 0079-6603	1-3,6, 12,13, 15,16, 20-22, 24,63, 65,66, 69,70, 87-91,93
Y	the whole document	1-9,12, 13, 18-30, 33-44, 63-66, 69,70, 87-95, 102
A	----- CHAMBERS T J ET AL: "FLAVIVIRUS GENOME ORGANIZATION, EXPRESSION, AND REPLICATION", ANNUAL REVIEW OF MICROBIOLOGY, ANNUAL REVIEWS, US, vol. 44, 1 January 1990 (1990-01-01), pages 649-688, XP008034574, ISSN: 0066-4227, DOI: 10.1146/ANNUREV.MI.44.100190.003245 the whole document	15-17, 49-51, 57-60
A	----- YAO J S ET AL: "Interactions between PE2, E1 and 6K required for assembly of alphaviruses studied with chimeric viruses", JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 70, no. 11, 1 November 1996 (1996-11-01), pages 7910-7920, XP002964147, ISSN: 0022-538X the whole document	1-9,12, 13, 15-30, 33-54, 57-70, 87-95, 102
A	----- WEST JOHN ET AL: "Mutations in the endodomain of Sindbis virus glycoprotein E2 define sequences critical for virus assembly", JOURNAL OF VIROLOGY, vol. 80, no. 9, May 2006 (2006-05), pages 4458-4468, XP002681816, ISSN: 0022-538X the whole document -----	1-9,12, 13, 15-30, 33-54, 57-70, 87-95, 102

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/023361

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.:

67, 68(completely); 1-9, 12, 13, 15-30, 33-54, 57-66, 69, 70, 87-95
102(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: 67, 68(completely); 1-9, 12, 13, 15-30, 33-54, 57-66, 69, 70, 87-95, 102(partially)

A virus-like particle (VLP) comprising one or more alterations that enhance VLP production, wherein the alteration is at an amino acid corresponding to amino acid 233 in a Chikungunya virus E2 protein; corresponding immunogenic compositions, methods of producing a VLP by modification of position 233 of the E2 protein, etc.

2. claims: 10, 14, 55(completely); 1-9, 12, 13, 15-30, 33-54, 57-66, 69, 70, 87-95, 102(partially)

As invention 1, but wherein the alteration is at an amino acid corresponding to amino acid 234 in a Chikungunya virus E2 protein

3. claims: 11, 56(completely); 1-9, 12, 13, 18-30, 33-48, 52-54, 61-66, 69, 70, 87-95, 102(partially)

As invention 1, but wherein the alteration is at an amino acid corresponding to amino acid 251 in a Chikungunya virus E2 protein

4. claims: 71-86, 99-101, 103(completely); 1, 35-44, 69, 70, 87-95, 102(partially)

As invention 1, but wherein the alteration is in an alphavirus capsid protein nuclear localization signal

5. claims: 31, 96-98(completely); 38-44(partially)

An immunogenic composition comprising at least two VLPs selected from the group consisting of EEEV, WEEV, VEEV, SFV, CHIKV, O'nyong-nyong virus, Sindbis virus, Mayaro virus, Ross River virus, Barmah forest virus, or Ockelbo virus.

6. claims: 32(completely); 38-44(partially)

An immunogenic composition comprising at least two VLPs selected from the group consisting of Yellow fever virus, Dengue Virus, JEV, TBEV, or WNV.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/023361

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010062396	A2	03-06-2010	
		AU 2009320287 A1	30-06-2011
		CN 102317308 A	11-01-2012
		EP 2370455 A2	05-10-2011
		SG 171828 A1	28-07-2011
		US 2012003266 A1	05-01-2012
		WO 2010062396 A2	03-06-2010
