Title: NOVEL MULTIVALENT NANOPARTICLE-BASED VACCINES

Abstract: Novel, nanoparticle-based vaccines are provided that elicit an immune response to a broad range of infectious agents, such as influenza viruses. The nanoparticles comprise a heterogeneous population of fusion proteins, each comprising a monomeric subunit of a self-assembly protein, such as ferritin, joined to one or more immunogenic portions of a protein from an infectious agent, such as influenza virus. The fusion proteins self-assemble to form nanoparticles that display a heterogeneous population of immunogenic portions on their surface. When administered to an individual, such nanoparticles elicit an immune response to different strains, types, subtypes and species with in the same taxonomic family. Thus, such nanoparticles can be used to vaccinate an individual against infection by different Types, subtypes and/or strains of infectious agents. Also provided are specific fusion proteins, nucleic acid molecules encoding such fusion proteins and methods of using nanoparticles of the invention to vaccinate individuals.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K39/12

ADD.

According to International Patent Classification (IPC) into 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, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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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
  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

Date of the actual completion of the international search

23 March 2016

Date of mailing of the international search report

14/07/2016

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

Heder, Andreas

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>wo 2010/117786 AI (SINAI SCHOOL MEDICINE [US]; LOWEN ANICE C [US]; STEEL JOHN [US]; GARCI) 14 October 2010 (2010-10-14)</td>
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<td>JOHN STEEL ET AL: &quot;Influenza Virus Vaccine Based on the Conserved Hemagglutinin Stalk Domain&quot;, MBIO, AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 1, no. 1, 18 May 2010 (2010-05-18), pages e00018-10/l-9, XP002675042, ISSN: 2150-7511, DOI: 10.1128/MBIO.00018-10 Abstract* Figs. 1, 5, 6 * Tab. 1 * pages 5, 6</td>
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<td>YASSINE HADI M ET AL: &quot;Hemagglutinin-stem nanoparticles generate heterosubtypic influenza protection.&quot;, NATURE MEDICINE, vol. 21, no. 9, September 2015 (2015-09), XP002755796, ISSN: 1546-170X pages1065-1070, Online Methods ; the whole document</td>
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## INTERNATIONAL SEARCH REPORT

### 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.:

I-II(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.
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11 (partially)
   Nanoparticle comprising fusion proteins derived from at least two infectious agents, comprising HA-feritin fusions, methods for making the same, and medical use
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2-7. claims: 1-11 (partially)
   Like invention 1, but HA being fused (instead of feritin) to encapsulin, 03-33, SOR, LS, PDC protein, or Chikungunya virus structural polyprotein
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8-39. claims: 12, 13
   Fusion protein comprising an amino acid sequence having at least 80% identity to SEQ ID NO: 97, 100, 103, 106, 109, 112, 115, 118, 121, 124, 127, 130, 133, 136, 139, 142, 145, 148, 151, 154, 157, 160, 163, 166, 169, 172, 175, 178, 181, 184, 187, or 190
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