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Robert [US/US]; 116 Amberleigh Drive, Silver Spring, MD 20905 (US). FRASCH, Carl, E. [US/US]; 13100 Burlwood Drive, Rockville, MD 20853 (US).

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(74) Agent: SIMPSON, Andrew, H.; Knobbe, Martens, Olson and Bear, LLP, 2040 Main Street, Fourteenth Floor, Irvine, CA 92614 (US).

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(71) Applicant (for all designated States except US): THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Office of Technology Transfer, 6011 Executive Blvd, Suite 325, Rockville, MD 20852-3804 (US).

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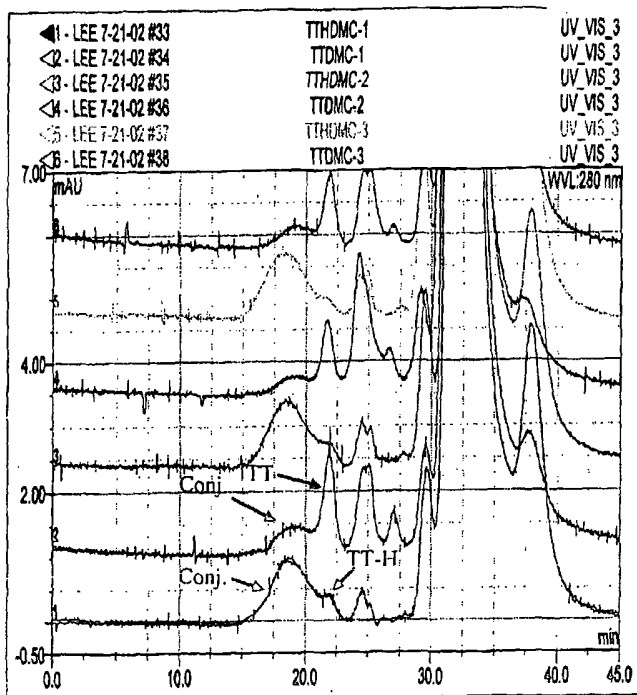
(72) Inventors; and

(75) Inventors/Applicants (for US only): LEE, Che-Hung,

[Continued on next page]

(54) Title: POLYSACCHARIDE-PROTEIN CONJUGATE VACCINES

Comparison between conjugation Method A and conventional reductive amination conjugation by HPSEC at 280 nm using a Waters Ultrahydrogel 2000 column



(57) Abstract: Abstract of the Disclosure Methods for synthesis and manufacture of polysaccharide-protein conjugate vaccines at high yield are provided. The methods involve reaction of a hydrazide group on one reactant with an aldehyde or cyanate ester group on the other reactant. The reaction proceeds rapidly with a high conjugation efficiency, such that a simplified purification process can be employed to separate the conjugate product from the unconjugated protein and polysaccharide and other small molecule by-products.

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FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

— *before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments*

Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv)) for US only*

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

26 January 2006

Published:

— *with international search report*

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/025477

<p>A. CLASSIFICATION OF SUBJECT MATTER A61K39/02 A61K39/385 A61K39/39</p>		
<p>According to international Patent Classification (IPC) or to both national classification and IPC</p>		
<p>B. FIELDS SEARCHED</p>		
<p>Minimum documentation searched (classification system followed by classification symbols) A61K</p>		
<p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p>		
<p>Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, EMBASE, PAJ, WPI Data</p>		
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEE CHI-JEN: "Quality control of polyvalent pneumococcal polysaccharide-protein conjugate vaccine by nephelometry" BIOLOGICALS, vol. 30, no. 2, June 2002 (2002-06), pages 97-103, XP002330498 ISSN: 1045-1056 figure 1	1-8, 19-22
X	US 4 356 170 A (JENNINGS ET AL) 26 October 1982 (1982-10-26) the whole document	1-8, 19-22
-/--		
<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.</p>		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document 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>		
<p>Date of the actual completion of the international search 30 November 2005</p>		<p>Date of mailing of the international search report 05. 12. 2005</p>
<p>Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016</p>		<p>Authorized officer Perez, F</p>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/025477

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>SHAFER DOUGLAS E ET AL: "Activation of soluble polysaccharides with 1-cyano-4-dimethylaminopyridinium tetrafluoroborate (CDAP) for use in protein-polysaccharide conjugate vaccines and immunological reagents. II. Selective crosslinking of proteins to CDAP-activated polysaccharides"</p> <p>VACCINE, vol. 18, no. 13, January 2000 (2000-01), pages 1273-1281, XP002330499 ISSN: 0264-410X the whole document</p>	9-12, 23-26
X	<p>LEES A ET AL: "Activation of soluble polysaccharides with 1-cyano-4-dimethylaminopyridinium tetrafluoroborate for use in protein-polysaccharide conjugate vaccines and immunological reagents."</p> <p>VACCINE. FEB 1996, vol. 14, no. 3, February 1996 (1996-02), pages 190-198, XP004057339 ISSN: 0264-410X the whole document</p>	9-12, 23-26
X	<p>KONADU EDWARD Y ET AL: "Phase 1 and phase 2 studies of Salmonella enterica serovar Paratyphi A 0-specific polysaccharide-tetanus toxoid conjugates in adults, teenagers, and 2- to 4-year-old children in Vietnam"</p> <p>INFECTION AND IMMUNITY, vol. 68, no. 3, March 2000 (2000-03), pages 1529-1534, XP002330501 ISSN: 0019-9567 the whole document</p>	9-12, 23-26
A	<p>MULARD L ET AL: "Vaccins polyosidiques"</p> <p>ANNALES DE L'INSTITUT PASTEUR ACTUALITES, vol. 12, no. 2, May 2002 (2002-05), pages 37-54, XP004476966 ISSN: 0924-4204 the whole document</p>	1-32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/025477

Box 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 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 fee, this Authority did not invite payment of any additional fee.
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.
- 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: 1-8, 19-22 (all completely) and 31-32 (in part)

Conjugate vaccines and methods for preparing them by reacting aldehyde activated polysaccharide with hydrazine activated protein.

- 1.1. claims: 9-12, 23-26 (all completely) and 31-32 (in part)

Conjugate vaccines and methods for preparing them by reacting CDAP activated polysaccharide with hydrazine activated protein.

2. claims: 13-18, 27-30 (all completely) and 31-32 (in part)

Conjugate vaccines and methods for preparing them by reacting hydrazine activated polysaccharide with APDO activated protein.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/025477

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4356170	A	26-10-1982 CA 1181344 A1	22-01-1985