The present invention is directed to enhancing the immune response of a human in need of protection against IV infection by administering in vivo, into a tissue of the human, at least one polynucleotide comprising one or more regions of nucleic acid encoding an IV protein or a fragment, a variant, or a derivative thereof. The present invention is further directed to enhancing the immune response of a human in need of protection against IV infection by administering, in vivo, into a tissue of the human, at least one IV protein or a fragment, a variant, or derivative thereof. The IV protein can be, for example, in purified form or can be an inactivated IV, such as those present in inactivated IV vaccines. The polynucleotide is incorporated into the cells of the human in vivo, and an immunologically effective amount of an immunogenic epitope of an IV, or a fragment, variant, or derivative thereof is produced in vivo. The IV protein (in purified form or in the form of an inactivated IV vaccine) is also administered in an immunologically effective amount.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC: C12N 15/44(2006.01);A61K 31/711(2006.01);39/145(2006.01)

USPC: 536/23.72;514/44;424/209.1;435/320.1
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)
U.S. : 536/23.72;514/44;424/209.1;435/320.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

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 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

"P" 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

"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

"Y" document of particular relevance; the claimed invention cannot be considered novel or 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

"&" document member of the same patent family

Date of the actual completion of the international search
05 September 2007 (05.09.2007)

Date of mailing of the international search report
25 OCT 2007

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Mary E. Mosher, Ph.D.
Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (April 2005)
### INTERNATIONAL SEARCH REPORT

#### C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>NAKAMURA et al. Codon usage tabulated from international DNA sequence databases:</td>
<td>1-18, 311, 312, 335-343</td>
</tr>
<tr>
<td>Y</td>
<td>ITO et al. Evolutionary Analysis of the Influenza A Virus M gene with Comparison of the M1 and M2 Proteins. October 1991. Journal of Virology, vol. 65, no. 10, pages 5491-5498, see Figure 2 (B).</td>
<td>310-317, 335-343</td>
</tr>
<tr>
<td>Y</td>
<td>BRYDER et al. Improved immunogenicity of HIV-1 epitopes in HBsAg chimeric DNA vaccine plasmids by structural mutations of HBsAg. March 1999. DNA and cell biology, vol.18. no. 3, pages p219-25, see entire document.</td>
<td>315, 316, 342, 343</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (April 2005)
### 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.  
<table>
<thead>
<tr>
<th>Claims Nos.:</th>
</tr>
</thead>
<tbody>
<tr>
<td>because they relate to subject matter not required to be searched by this Authority, namely:</td>
</tr>
</tbody>
</table>

2.  
<table>
<thead>
<tr>
<th>Claims Nos.:</th>
</tr>
</thead>
<tbody>
<tr>
<td>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:</td>
</tr>
</tbody>
</table>

3.  
<table>
<thead>
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<th></th>
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</thead>
<tbody>
<tr>
<td>because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</td>
</tr>
</tbody>
</table>

### 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:

Please See Continuation 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 additional fees, this Authority did not invite payment of any 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.: 1-18, 310-317 and 335-343 |

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 not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.
BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-18, drawn to codon-optimized Type A NP SEQ ID NO: ID NO: 2.

Group 2, claim(s) 41-47, 50-63, drawn to codon-optimized M1 SEQ ID NO: 4.

Group 3, claim(s) 79-86, 89-97, drawn to codon-optimized M2 SEQ ID NO: 5.

Group 4, claim(s) 119-123, 125-133, 150-154, 156-165, drawn to codon-optimized M2e/NP fusions SEQ ID NO: 7 or 9.

Group 5, claim(s) 181-198, drawn to codon-optimized Type B NP SEQ ID NO: 16.

Group 6, claim(s) 240-250, drawn to consensus NP polypeptide SEQ ID NO: 76.

Group 7, claim(s) 254-261, drawn to nucleic acid encoding SEQ ID NO: 76.

Group 8, claim(s) 284-292, 335-343, drawn to nucleic acid encoding consensus M1 polypeptide SEQ ID NO: 77.

Group 9, claim(s) 307-309, drawn to Nucleic acid encoding consensus M1 polypeptide SEQ ID NO: 77.

Group 10, claim(s) 310-317, 335-343, drawn to nucleic acid encoding consensus M2 polypeptide SEQ ID NO: 78.

Group 11, claim(s) 332-334, drawn to consensus M2 polypeptide SEQ ID NO: 78.

The inventions listed as Groups 1-11 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The only feature common to the groups is the concept of codon optimization, which is old in the art, see for example Deml et al and Liu et al. Therefore no special technical feature unites the groups.
Continuation of B. FIELDS SEARCHED Item 3:
EAST USPAT, PG PUB, EPO, JPO, DERWENT; DIALOG FILES 155, 357. SEARCH TERMS: INFLUENZA, NP, NUCLEOPROTEIN, M2. DNA, VACCINE?, PY<2004, HBV, HEPATITIS (W) "B", CORE, HBV CAG, FUSION, CARRIER, CODON, CODONS, OPTIM?, PREFER?