Abstract:
Title: ENGINEERED NUCLEIC ACIDS AND METHODS OF USE THEREOF

(57) Abstract: Provided are compositions and methods for delivering biological moieties such as modified nucleic acids into cells to kill or reduce the growth of viruses. Such compositions and methods include the use of modified messenger RNAs, and are useful to treat or prevent viral infection, or to improve a subject's health or wellbeing.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US12/54574

A. CLASSIFICATION OF SUBJECT MATTER

IPC (8) - A61K 31/71 15; C12N 15/1 1 117 (2013.01)
USPC - 536/23.1 1 435/91 1.442 458

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)
IPC(8): A61K 48/00, 39/39, 12, 21, 245, 29, 31/7052, 7088, 7.115; C07H 21/00, 21/02, 21/04; C12N 15/1 1 (2013.01)
USPC: 536/23.1, 22.1, 18.7, 1.11, 23.74, 23.72; 435/91 1.1 91.51, 442, 455, 458, 465, 89, 87, 85, 84

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)

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>
<tbody>
<tr>
<td>X</td>
<td>WO 2001/092523 A2 (SHIMKETS, RA et al.), December 6, 2001; abstract; page 2, lines 3-6; page 3, lines 21-25; page 14, lines 17-23; page 17, lines 6-20; page 28, lines 17-27; page 31, lines 21-26; page 85, line 28 to page 86, line 6</td>
<td>1-4, 6-12, 14-23</td>
</tr>
<tr>
<td>Y</td>
<td>NGAL PHK et al. Agrocybin, An Antifungal Peptide From The Edible Mushroom Agrocybe Cylindracea, Peptides, 2005, Vol. 26, pp 191-196; DOI: 10.1016/j.peptides.2004.09.01 1; abstract; page 194, column 1, paragraph 2; Table 2</td>
<td>13</td>
</tr>
<tr>
<td>Y</td>
<td>US 7846895 B2 (ECKERT, RH et al.), December 7, 2010; abstract; page 18, paragraph 3</td>
<td>5</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search
21 June 2013 (21.06.2013)

Date of mailing of the international search report
01 JUL 2013

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:
Shane Thomas
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/2 10 (second sheet) (July 2009)
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).

This International Searching Authority found multiple inventions in this international application, as follows:

\*\* Please See Supplemental Page \*\*

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 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.:

Groups 1- Claims 1-23, SEQ ID NO: 1

**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.
"Continued from 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 I: Claims 1-23. SEQ ID NO: 1 are directed toward a pharmaceutical composition comprising: i) an effective amount of a synthetic messenger ribonucleic acid (mRNA) encoding an anti-viral polypeptide (AVP); and ii) a pharmaceutically acceptable carrier, wherein the synthetic mRNA comprises at least one nucleotide modification, and wherein the anti-viral polypeptide is about 6 to about 100 amino acids in length.

SEQ ID NO: 1 will be included within the search for Group I.

Additional SEQ ID NOs can be searched upon the payment of additional fees. An exemplary election would be SEQ ID NO: 2.

The limitations of Claim 1 are previously disclosed by WO 2001/092523 A2 to Shimkets, et al. (hereinafter 'Shimkets'). Shimkets discloses a pharmaceutical composition (abstract; Claim 13) comprising: i) an effective amount of a synthetic messenger ribonucleic acid (mRNA) (as used herein, the term 'nucleic acid molecule' is intended to include DNA molecules (e.g., cDNA or genomic DNA), RNA molecules (e.g., mRNA), analogs of the DNA or RNA generated using nucleotide analogs, and derivatives, fragments and homologs thereof; engineered/synthetically generated; page 14, lines 20-22; Claims 1, 29) encoding an anti-viral polypeptide (AVP) (costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention; page 85, lines 28-30 to page 86, lines 1-6); and ii) a pharmaceutically acceptable carrier (Claim 13), wherein the synthetic mRNA comprises at least one nucleotide modification (PNAs of ORFX can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to mRNA; a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, e.g., 5-(4-methoxytrityl) amino-5'-deoxy-uridine phosphoramidite can be used; page 29, lines 5-7; page 29, lines 14-17), and wherein the anti-viral polypeptide (costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention; page 85, lines 28-30 to page 86, lines 1-6) is about 6 to about 100 amino acids in length (a biologically active portion of a ORFX protein can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length; page 31, lines 25-26).

Since none of the special technical features of the Groups I., and additional SEQ ID NOs, is found in more than one of the inventions, and since the limitations of Claim 1 of the instant application are previously disclosed by the Shimkets reference, unity of invention is lacking.

Form PCT/ISA/210 (extra sheet) (July 2009)