MicroRNAs can be used to decrease expression of apolipoprotein B (apoB), increase expression of apolipoprotein A (apoA), and decrease expression of NCOR1. Use of these microRNAs can simultaneously reduce LDL and increase HDL in circulation and have applications in prevention and treatment of atherosclerosis, hyperlipidemia, and cardiovascular disease as well as other disorders associated with high apoB and/or low apoA1 levels.

Figure 8
Published:
— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(b))

(88) Date of publication of the international search report:
1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ✔ forming part of the international application as filed:
      - in the form of an Annex C/ST.25 text file.
      - on paper or in the form of an image file.
   b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
      - in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
      - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:
INTERNATIONAL SEARCH REPORT

International application No. PCT/US17/3120

Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

<table>
<thead>
<tr>
<th>Box No. II</th>
<th>Observations where certain claims were found unsearchable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ☐ Claims Nos.:</td>
<td>because they relate to subject matter not required to be searched by this Authority, namely:</td>
</tr>
<tr>
<td>2. ☐ Claims Nos.:</td>
<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>
<tr>
<td>3. ☐ Claims Nos.:</td>
<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)

<table>
<thead>
<tr>
<th>Box No. III</th>
<th>Observations where unity of invention is lacking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.</td>
<td></td>
</tr>
<tr>
<td>2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.</td>
<td></td>
</tr>
<tr>
<td>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.:</td>
<td></td>
</tr>
</tbody>
</table>

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.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/71.3, 48/00; C07H 21/04, 15/1 13 (2017.01)
CPC - A61 K 31/71 3: C12N 15/1 13, 15/1 137, 15/1 138

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

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>A</td>
<td>US 2003/0026801 A1 (WEINER et al.) February 6, 2003; Table 4</td>
<td>1-28, 52/1, 54/1, 55-56, 57/55-56, 59/55-56, 59/55-56, 60/55-56, 61/55-56,</td>
</tr>
</tbody>
</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 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
  "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
  "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 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
  "Z" document member of the same patent family

Date of the actual completion of the international search

26 September 2017 (26.09.2017)

Date of mailing of the international search report

20 OCT 2077

Name and mailing address of the ISA

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

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

Form PCT/ISA/2 10 (second sheet) (January 2015)
<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>A</td>
<td>US 2014/0363469 A1 (ALNYLAM PHARMACEUTICALS, INC.) December 11, 2014; Table 3 95/87/83</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Citation of document, with indication, where appropriate, of the relevant passages</td>
<td>Relevant to claim No.</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
</tbody>
</table>
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 1-98 and 124-152 are directed toward methods of treating or preventing atherosclerosis, cardiovascular disease, hyperlipidemia, dyslipidemia, obesity, type II diabetes, or metabolic syndrome by increasing ApoAI and/or HDL using an inhibitor of BCL11B; and miRNAs therefor.

Group II, Claims 99-123 are directed toward methods of increasing ApoAI and HDL, comprising an inhibitor of NRIP1.

The inventions listed as Groups I and II 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 special technical features of Group I include BCL11B, not present in Group II; the special technical features of Group II include NRIP1, not present in Group I.

Groups I and II share the technical features including: a method of increasing ApoAI expression or secretion by a cell, comprising contacting the cell with an inhibitor, thereby increasing expression or secretion of ApoAI; and a method of increasing HDL in a subject in need thereof, comprising administering a therapeutically effective amount of an inhibitor, thereby increasing HDL, and an inhibitor comprising a modulatory nucleic acid.

However, these shared technical features are previously disclosed by US 2016/0024506 A1 to CuRNA Inc. (hereinafter 'CuRNA').

CuRNA discloses a method of increasing ApoAI expression or secretion by a cell (a method of increasing ApoAI expression or secretion by a cell; paragraphs [0006], [0031]), comprising contacting the cell with an inhibitor (comprising contacting the cell with an inhibitor; paragraph [0006]), thereby increasing expression or secretion of ApoAI (thereby increasing expression or secretion of ApoAI; paragraphs [0006], [0034]); and a method of increasing HDL in a subject in need thereof (a method of increasing HDL in a subject with an HDL deficiency (in need thereof); paragraphs [0006], [0122], [0141]), comprising administering a therapeutically effective amount of an inhibitor (comprising administering a therapeutically effective amount of an inhibitor; paragraphs [0006], [0014], [0034]), thereby increasing HDL (thereby increasing HDL; paragraphs [0006], [0034], [0141]); and an inhibitor comprising a modulatory nucleic acid (an inhibitor comprising a modulatory nucleic acid; paragraphs [0005], [0006]).

Since none of the special technical features of the Groups I and II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the CuRNA reference, unity of invention is lacking.