Abstract:

Compositions for treating autoimmune, allergic, or atopic disease comprising a compound that inhibits hyaluronan synthesis and a pharmaceutically acceptable carrier are described. In some embodiments, the compound that inhibits hyaluronan synthesis is 4-methylumbelliferone or a metabolite of 4-methylumbelliferone. Methods for treating autoimmune diabetes, multiple sclerosis and/or autoimmune demyelination, including administering to the subject a composition having a compound in an amount effective to inhibit hyaluronan synthesis in a mammalian subject, are also described.

FIG. 1A

[Continued on next page]
Date of publication of the international search report:
9 April 2015
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 5/0636; A61K 38/00; C12N 2501/23
CPC - C12N 5/0636; A61K 38/00; C12N 2501/23
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): C12N 5/0636; A61K 38/00; C12N 2501/23
CPC: C12N 5/0636; A61K 38/00; C12N 2501/23

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/372.3; 435/372.2; 514/789; 435/15; 435/193

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>US 6,376,475 B1 (March et al.) 23 April 2002 (23.04.2002) entire document especially title; claim 9; col 18, In 64 to col 19, In 3; col 19, In 50-54; col 2, In 28-31</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Kult et al. 4-Methylumbelliferone inhibits hyaluronan synthesis by depletion of cellular UDP-glucuronic acid and downregulation of hyaluronan synthase 2 and 37, Experimental Cell Res, Volume 315, Issue 11, 1 July 2009, Pages 1914-1923</td>
<td>7-8</td>
</tr>
</tbody>
</table>

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
& - document member of the same patent family

Date of the actual completion of the international search: 12 January 2015 (12.01.2015)
Date of mailing of the international search report: 22 JAN 2015

Name and mailing address of the ISA/US
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P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer: Lee W. Young

Form PCT/ISA/2 I (second sheet) (July 2009)
Box III: LACK OF UNITY

Group I: Claims 1-9 directed to composition for treating an autoimmune, allergic, or atopic disease

Group II: Claims 10-23, directed to a method for treating an autoimmune, allergic, or atopic disease in a mammalian subject in need thereof, the method comprising administering to the subject a composition comprising a compound in an amount effective to inhibit hyaluronan synthesis

Group III: Claims 24-35, directed to a method for treating multiple sclerosis in a mammalian subject in need thereof, the method comprising administering to the subject a composition comprising a compound in an amount effective to inhibit hyaluronan synthesis

The inventions listed as Group I-III 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:

Special technical features:

The special technical feature of group I is a method for treating an autoimmune, allergic, or atopic disease in a mammalian subject in need thereof, the method comprising administering to the subject a composition comprising a compound in an amount effective to inhibit hyaluronan synthesis, not required by groups I and III.

The special technical feature of group III is a method for treating multiple sclerosis in a mammalian subject in need thereof, the method comprising administering to the subject a composition comprising a compound in an amount effective to inhibit hyaluronan synthesis, not required by groups I and II.

Common technical features:

Groups I-III share the technical features of compound that inhibits hyaluronan synthesis, and (ii) a pharmaceutically acceptable carrier.

Group I and II share the technical features of composition for treating an autoimmune, allergic, or atopic disease comprising (i) a compound that inhibits hyaluronan synthesis, and (ii) a pharmaceutically acceptable carrier.

Groups II and III share the technical feature of administering a composition comprising a compound in an amount effective to inhibit hyaluronan synthesis in the mammalian subject.

These shared technical features, however, do not provide a contribution over the prior art as being anticipated by US 6,376,475 B1 to Marth et al. (hereafter 'Marth'). Marth teaches composition for treating an autoimmune, allergic, or atopic disease comprising (title; claim 9) (i) a compound that inhibits hyaluronan synthesis (compound that inhibits hyaluronan synthesis is a UD P-glycosyltransferase inhibitor ...col 18, In 64 to col 19, In 3, '... Compositions that contain glycosyltransferase inhibitors...'), and (ii) a pharmaceutically acceptable carrier (col 19, In 50-54, '...compositions for parenteral administration which comprise a solution of the glycosyltransferase inhibiting agent dissolved or suspended in an acceptable carrier, preferably an aqueous carrier...') and administering teh composition to a mammalian subject (col 2, In 28-31 '...inhibiting an immune response in a mammal by administering to the mammal a therapeutically effective amount of an agent ...col 18, In 64 to col 19, In 3, '... Compositions that contain glycosyltransferase inhibitors...')

As said compound, composition and method were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify Groups I-III.

Groups I-III, thus lack unity under PCT Rule 13.2, because they do not share a same or corresponding special technical feature providing a contribution over the prior art.
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:

---see supplemental box---

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.:

   Claims 1-9

**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.