Abstract: The invention relates to aortopathy, and in particular, to compositions and methods for the diagnosis and treatment of aortopathy.
### A. CLASSIFICATION OF SUBJECT MATTER

**INV.** A61K38/19 A61K39/395 A61P9/10

ADD.

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)

A61K A61P

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

### 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>Y</td>
<td>PING YE ET AL: &quot;GM-CSF contributes to aortic aneurysms resulting from SMAD3 deficiency (includes supplemental material)&quot; JOURNAL OF CLINICAL INVESTIGATION, vol. 123, no. 5, 1 May 2013 (2013-05-01), pages 2317-60, XP05527 1723, US ISSN: 0021-9738, DOI: 10.1172/JCI67356 page 2318 -/-</td>
<td>1-5,11, 12</td>
</tr>
</tbody>
</table>

[X] 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) on 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 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**

11 May 2016

**Date of mailing of the international search report**

22/09/20 16

**Name and mailing address of the ISA**

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Form PCT/ISA/210 (second sheet) (April 2006)
**INTERNATIONAL SEARCH REPORT**

**Box No. 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 No. 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 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.:
   - 1-5, 11, 12 (all partially)

**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.
<table>
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<tr>
<td>Y</td>
<td>LINZHAO NIU ET AL: &quot;High-affinity binding to the GM-CSF receptor requires intact N-glycosylation sites in the extracellular domain of the beta subunit α&quot;, BLOOD, vol. 95, no. 11, 1 June 2000 (2000-06-01), pages 3357-3362, XP055271662, US ISSN: 0006-4971 page 3358</td>
<td>1-5</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>
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</tbody>
</table>
This International Search Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5, 11, 12 (all partially)

A granulocyte macrophage colony-stimulating factor (GM-CSF) negative modulator, for use in treating, preventing or ameliorating aortopathy, wherein the GM-CSF negative modulator is confi gured to: (i) alter the conformational state of the GM-CSF receptor, for example by destabilizing the active conformation of that macrophage receptor and/or maintaining the receptor in its inactive conformation to thereby prevent it from binding its natural ligand, i.e. GM-CSF.

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2. claims: 1-5, 11, 12 (all partially)

As invention 1, but wherein the GM-CSF negative modulator is confi gured to: (i) alter the conformational state of a signal transduction molecule through which GM-CSF signalling is achieved.

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3. claims: 1-5, 11, 12 (all partially)

As invention 1, but wherein the GM-CSF negative modulator is confi gured to: (ii) bind to the GM-CSF receptor through which GM-CSF signalling is achieved, and prevent, decrease or attenuate transmission at that receptor.

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4. claims: 1-5, 11, 12 (all partially)

As invention 1, but wherein the GM-CSF negative modulator is confi gured to: (iii) down-regulate or de-activate the downstream signalling pathways activated by the negative modulator binding to the GM-CSF receptor.

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5. claims: 6-10 (completely); 1-5, 11, 12 (partially)

As invention 1, but wherein the GM-CSF negative modulator is confi gured to: (iii) down-regulate or de-activate the downstream signalling pathways activated by the negative modulator binding to GM-CSF itself.

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6. claims: 1-5, 11, 12 (all partially)

As invention 1, but wherein the GM-CSF negative modulator is confi gured to: (iv) decrease, prevent or attenuate transcription, translation or expression of GM-CSF.

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7. claims: 1-5, 11, 12 (all partly)

As invention 1, but where in the GM-CSF negative modulator is configured to: (v) inhibit synthesis or release, from intracellular stores, of GM-CSF.

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8. claims: 1-5, 11, 12 (all partly)

As invention 1, but where in the GM-CSF negative modulator is configured to: (vi) increase the rate of degradation of GM-CSF.

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9. claims: 1-5, 11, 12 (all partly)

As invention 1, but where in the GM-CSF negative modulator is configured to perform more than one of the functions as described in (i) - (vi) of claim 5 as filed.

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10. claims: 13-22

Use of granulocyte macrophage colony-stimulating factor (GM-CSF), or a variant or fragment thereof, as a biomarker for detecting or diagnosing aortopathy, the kit of claim 16 or the method of diagnosing of claim 17.