Abstract: In some aspects, the invention teaches pharmaceutical compositions that include a TGF-beta ligand trap, and methods of using a TGF-beta ligand trap to treat, prevent, or reduce the progression rate of pulmonary hypertension (PH). The invention also provides methods of using a TGF-beta ligand trap to treat, prevent, or reduce the progression rate of a variety of conditions including, but not limited to, pulmonary vascular remodeling, pulmonary fibrosis, right ventricular hypertrophy, diseases associated with excessive TGF-beta signaling, diseases associated with excessive GDF15 signaling, and diseases associated with excessive PAI-1 signaling. The invention further provides methods of using a TGF-beta ligand trap to reduce right ventricular systolic pressure in a subject.
(88) Date of publication of the international search report:
19 November 2015

Published:
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi))
— with international search report (Art. 21(3))
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) ... Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201
Form PCT/ISA/210 (second sheet) (July 2009)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C07K 16/00; C12N 5/07, 5/16; A61K 38/00, 39/00 (2015.01)
CPC: A61K 38/00, 2039/505; C07K 2317/24, 16/28, 16/18, 2319/00; USPC: 530/388.22, 388.2, 388.1, 387.1, 386, 380, 350; 435/334

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)
Databases and Files Searched) and Search Terms Used:
PatSeer (US, EP, WO, JP, DE, GB, CH, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; PubMed; ScienceDirect; 'TGFb,' TGF-beta, 'PAI-1,' 'GDF15,' 'pulmonary hypertension,' 'right ventricular systolic pressure,' 'pulmonary fibrosis'

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 2013/019805 A1 (TUFTS MEDICAL CENTER, INC.) February 07, 2013; page 1, lines 30-34; page 9, lines 18-20; page 12, lines 25-26; page 18, lines 18-35</td>
<td>1-3, 22, 25, 27, 30, 32, 34</td>
</tr>
<tr>
<td>X</td>
<td>WO 2012/145339 A1 (ACCELERON PHARMA, INC.) October 26, 2012; page 14, lines 9-11; page 38, lines 12-13; page 52, lines 30-31; page 53, lines 10-16; page 74, line 4</td>
<td>23</td>
</tr>
<tr>
<td>Y</td>
<td>GONZALEZ-NUNEZ, M et al. The ALK-1/Smad1 Pathway In Cardiovascular Physiopathology: A New Target for Therapy? Biochim Biophys Acta. 22 May 2013; Vol. 1832, No. 10; pages 1492-1510; page 1495; figure 1; page 1499, right column, fifth paragraph; page 1503, right column, fifth paragraph; page 1504, left column, third paragraph. DOI: 10.1016/j.bbadis.2013.05.016.</td>
<td>25, 32, 34</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* 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 ("earlier document")
  "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

"I" 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
"M" document member of the same patent family

Date of the actual completion of the international search
02 March 2015 (02.03.2015)

Date of mailing of the international search report
24 MAR 2015

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/210 (second sheet) (July 2009)
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 filed or furnished:

a. (means)
   - [x] in electronic form
   - [ ] on paper

b. (time)
   - [x] subsequently to this Authority for the purposes of search
   - [ ] in the international application as filed
   - [ ] together with the international application in electronic form

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 in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:
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:
   - 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.:** 4-21, 24, 26, 28, 31, 33, 35
   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:

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.:

**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.