Abstract: Provided herein are agents that inhibit binding domain I of LRPI and mimic the activity of prosaposin in stimulating Tsp-1. Further provided herein are agents that inhibit the function (e.g., the ability to repress Tsp-1) of Protease, Serine 2 (PRSS2) by inhibiting the binding of PRSS2 to LRPI. Methods of using these agents in treating cancer are also provided.
A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/00, A61K 38/10, A61K 38/17 (201 8.01)
CPC - A61K 38/00, C07K 231/93, A61K45/06

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>X</td>
<td>US 20130072125 A1 (WATNICK) 21 March 2013 (21.03.2013) para [0142], [0143], [0164], [0484]</td>
<td>27</td>
</tr>
<tr>
<td>Y</td>
<td>EP 2,322,204 A1 (FRAUNHOFER-GESELLSCHAFT ZUR FOERDERUNG DER ANGEWANDTEN FORSCHUNG E.V.) 18 May 2011 (18.05.2011) (Especially para [0001], [0003], [0004], [0038], [0079], [0078], [0094], [0100], [0102], [0103], [0108], [0111], [0115])</td>
<td>1-6, 10, 11, 27-33</td>
</tr>
<tr>
<td>Y</td>
<td>VAN GOOL et al., The Matricellular Receptor LRP1 Forms an Interface for Signaling and Endocytosis in Modulation of the Extracellular Tumor Environment. Front Pharmacol., 10 November 2015, Vol 6, Article 271, pp 1-9. Especially abstract, Fig 1</td>
<td>28, 30</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search: 17 October 2018
Date of mailing of the international search report: 1 JAN 2019

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. 571-273-8300

Authorized officer: Lee W. Young

PCT Hippdesk: 571-272-4300 PCT GDD: 571-272-7774

Form PCT/ISA/2 10 (second sheet) (January 2015)
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 13/er. 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:
ISA/225 mailed on 09 April 2018. The applicant did not, within the prescribed time limit, pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter. 1(a) or (b). Accordingly, ISA/US cannot consider the sequence listing submitted on 07 May 2018.
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. [34] Claims Nos.: 7-9, 12-18, 22-26
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:

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 1-6, 10, 11 and 27-33, directed to a method of treating cancer by administering an agent that binds Low Density Lipoprotein Receptor-related Protein 1 (LRP1).

Group II, claims 19-21, directed to an antibody that binds LRP1.

—please see continuation on extra 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 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.
1-6, 10, 11 and 27-33

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.
Continuation of Box No. III Observations where unity of invention is lacking

The inventions listed as Groups I-II do not relate to a single special technical feature 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:

Group I has the special technical feature of administering an agent that binds LRP1, that is not required by Group II.

Group II has the special technical feature of an antibody that binds LRP1, that is not required by Group I.

Common technical features:

Groups I-II share the common technical feature of an agent that binds to the binding domain I of LRP1. However, this shared technical feature does not represent a contribution over prior art, because this shared technical feature is made obvious by EP 2,322,204 A1 to Fraunhofer-Gesellschaft zur Foerderung der angewandten Forschung E.V. (hereinafter 'Fraunhofer') in view of an article by Mikhailenko et al., entitled "Recognition of alpha-2-Macroglobulin by the Low Density Lipoprotein Receptor-related Protein Requires the Cooperation of Two Ligand Binding Cluster Regions" (hereinafter 'Mikhailenko').

Fraunhofer teaches a method of treating cancer, the method comprising administering to a subject in need thereof activated alpha-2-macroglobulin that binds to the Low Density Lipoprotein Receptor-related Protein I (LRP 1) (para [0038]) The inventors of the present invention surprisingly found that binding of activated alpha-2-macroglobulin (also referred herein as A2M*) to human LRP1 receptor suppresses specific phenotypes of tumor cells and results in an inhibition of the Wnt/beta-catenin signaling pathway. The inventors of the present invention thus found that the binding of activated alpha-2-macroglobulin to the receptor does not only trigger receptor-mediated endocytosis but that A2M* is also an LRP1 receptor agonist; para [0039] "a pharmaceutical composition comprising an LRP1 receptor agonist for use in the treatment of cancer."; [0047] "the invention is administered parenterally or orally."; para [0131] "Native alpha-2-macroglobulin will be transformed inside the body of a subject, to which the pharmaceutical application according to the invention is applied, to its activated form (A2M*) which is capable of binding to the LRP1 receptor."

Fraunhofer does not teach that activated alpha-2-macroglobulin binds to domain I of LRP1. However, Mikhailenko teaches that activated alpha-2-macroglobulin binds to domain I of LRP1 (abstract "The low density lipoprotein receptor-related protein (LRP) is a scavenger receptor that binds several ligands including the activated form of the pan-proteinase inhibitor alpha-2-macroglobulin (alpha2M*)...". Together, these studies indicate that ligand binding repeats from both cluster I and II cooperate to generate a high affinity binding site for alpha2M*). It would have been obvious to one skilled in the art to have combined the cancer treatment method taught by Fraunhofer with the knowledge taught by Mikhailenko, to develop, for research or therapeutic purposes, a cancer treatment method comprising agents that bind to domain I of LRP1 since the anti-cancer agent activated alpha-2-macroglobulin binds to domain I of LRP1.

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I-II inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

Note: Claims 7-9, 12-18, 22-26 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Note: Claim 30 is objected to for lack of antecedent basis. As drafted, claim 30 depends from claims 26-29, but claim 26 fails to recite a "method". For the purpose of completing this lack of unity analysis, claim 30 is construed as though depending from claims 27-29.