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(54) Title: METHODS AND COMPOSITIONS FOR TREATMENT OF IMMUNE-RELATED DISEASES OR DISORDERS AND/OR THERAPY MONITORING

(57) Abstract: Described herein are methods and compositions for treatment of immune-related diseases or disorders and/or therapy monitoring based on the level of TIGIT, Flg2 and/or IL-33 expression and/or activity. In some embodiments, the methods and compositions described herein are directed to treatment and/or therapy monitoring of cancer and/or infections (e.g., chronic viral infection, intracellular and/or extracellular bacterial infection, and/or fungal infection). In some embodiments, the methods and compositions described herein are directed to treatment and/or therapy monitoring of autoimmune diseases and/or inflammation (e.g., caused by parasitic infection). In some embodiments, the methods and compositions described herein are directed to treatment and/or therapy monitoring of asthma, allergy, and/or atopy. Methods for identifying patients who are more likely to be responsive to and benefit from an immunotherapy that targets TIGIT, Flg2 and/or IL-33 are also described herein.
<table>
<thead>
<tr>
<th>Declarations under Rule 4.17:</th>
<th>Published:</th>
</tr>
</thead>
<tbody>
<tr>
<td>— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))</td>
<td>— with international search report (Art. 21(3))</td>
</tr>
<tr>
<td>— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi))</td>
<td>(88) Date of publication of the international search report: 24 March 2016</td>
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### INTERNATIONAL SEARCH REPORT

**INTERNATIONAL SEARCH REPORT**

**International application No.**

**PCT/US2015/021784**

**A. CLASSIFICATION OF SUBJECT MATTER**

**IP(C)8** - C12Q1/68(2015.01)

**CPC** - C12Q1/68 (2015.10)

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)

**IP(C)8** - A61 P 35/00, 37/00, C120 1/68, G01F 33/50 (2015.01)

**CPC** - A61K 38/00, 38/20, 39/3955, 2039/57, 2039/505, C07K 16/244: C12G 1/00, 1/68, 1/6886, 2600/158; G01N 33/574, 33/6869, 2800/52 (2015.10)

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

**CPC** - A61K 38/00, 38/20, 39/3955, 2039/57, 2039/505; C07K 16/244; C12Q 1/00, 1/68, 1/6886, 2600/158; G01N 33/574, 33/6869, 2800/52 (2015.10) (keyword delimited)

**USPC** - 435/8, 7.1: 436/501

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatBase, Google Patents, Google Scholar, Google, PubMed

Search terms used: Fgl2 Fibrinogen-Like 2 PT49 Fibro/teukin3 T49 TIGIT T Cell Ig And CD8 Domain V-Set And Immunoglobulin

Domain-Containing Protein 3 VSG9 VSTFG Washington University Cell Adhesion Molecule WUCAM IL-33

**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>
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</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

**Date of the actual completion of the international search**

01 October 2015

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

02 November 2015

**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**

Blaine Copenhaver

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

Form PCT/ISA/210 (second sheet) (January 2015)
<table>
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<td>Nucleotide and/or amino acid sequence(s) (Continuation of item 1c of the first sheet)</td>
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<tr>
<td>1.</td>
<td>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:</td>
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<tr>
<td></td>
<td>a. forming part of the international application as filed:</td>
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<td>b. furnished together with the international application under PCX Rule Iter. 1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.</td>
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<td>c. furnished subsequent to the international filing date for the purposes of international search only:</td>
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<td>on paper or in the form of an image file (Rule 13Iter.1(b) and Administrative Instructions, Section 713).</td>
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<td>2.</td>
<td>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.</td>
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<td>3.</td>
<td>Additional comments:</td>
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<td>SEQ ID NO:2 was searched.</td>
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</table>
### 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:

   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### 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 Extra Sheet(s).

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.: 1-3, 22-24, 28-39, 55-57, 76-79, 82-93, 110-114, and 128-138

### 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.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (January 2015)
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 need to be paid.

Group I: claims 1-3, 22-24, 28-39, 55-57, 76-79, 82-93, 110-114, and 128-138 are drawn to methods of identifying and/or treating a patient who is likely to be responsive to a TIGIT agonist or IL-33 agonist therapy.

Group II: claims 5-8, 11-13, 59-61, and 115-117 are drawn to methods of treating a patient diagnosed with a disease, the methods comprising administering to the patient a composition comprising an Fg2 inhibitor.

Group III: claims 40-52, 94-100, 102-108, and 139-151 are drawn to a pharmaceutical composition comprising an ST2 inhibitor.

The Inventions listed in Groups I-II do not relate to a single general inventive concept under PCT Rule 13.2 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, methods of identifying and/or treating a patient who is likely to be responsive to a TIGIT agonist or IL-33 agonist therapy, are not found in Groups II and III; the special technical features of Group II, methods of treating a patient diagnosed with a disease, the methods comprising administering to the patient a composition comprising an Fg2 inhibitor, are not found in Groups I and III; and the special technical features of Group III, a pharmaceutical composition comprising an ST2 inhibitor, are not found in Groups I and II.

Groups I-III share the technical features of a patient diagnosed with cancer and/or infection; proinflammatory immunotherapy; measuring the level of activity or expression in a sample from a patient; measuring a level of Fg2 activity or expression; a method of treating a patient diagnosed with cancer and/or infection; an agent that inhibits or agonizes IL-33 activity and/or TIGIT activity; a method of treating a patient diagnosed with cancer and/or Infection that exhibits an elevated level of IL-33; a method of treating a patient who is determined to have an autoimmune disease or disorder and/or parasitic infection; administering to the patient a composition comprising a TIGIT agonist and/or an IL-33 agonist; administering a TIGIT inhibitor or agonist, administering an Fg2 inhibitor or agonist, and a TH2 dampening therapy. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2008/0003199 A1 to Lee discloses a patient diagnosed with a disease (IL-33 has been found to be induced by cardiac strain and can be used in various methods of evaluating risk of developing a disease or disorder, diagnosis, determining the prognosis, Para. [0006]; a method for treating a subject having or at risk of developing a cardiac disease or disorder is provided, Para. [0007]; proinflammatory immunotherapy [the subject is also administered an anti-inflammatory or immunosuppressive agent or both, Para. [0028]; measuring the level of activity or expression in a sample from a patient [In one embodiment, the method includes the steps of determining the level of IL-33 in a subject (e.g., in a sample obtained from the subject), comparing the level of IL-33 to a predetermined value, and characterizing the subject’s risk, Para. [0053]]; a method of treating a patient diagnosed with a disease [In one aspect of the invention, a method for treating a subject having or at risk of developing a cardiac disease or disorder is provided, Para. [0007]]; a method of treating a patient diagnosed with a condition that exhibits an elevated level of IL-33 [In one embodiment, the method includes the steps of determining the level of IL-33 in a subject (e.g., in a sample obtained from the subject), comparing the level of IL-33 to a predetermined value, and characterizing the subject’s risk, Para. [0053]].

Further, US 2005/0169913 A1 to Levy et al. discloses a cancer and/or infection diagnosis (useful in the prevention, treatment and diagnosis of diseases associated therewith including bacterial and viral infections, glomerulonephritis [GN], cancer, Para. [0016]); a method of treating a patient who is determined to have a autoimmune disease or disorder and/or parasitic infection (useful in the prevention, treatment and diagnosis of diseases associated therewith including ...viral infections, Para. [0016]; the present invention have diagnostic and monitoring applications. In particular they may be used in conventional assays to monitor or diagnose conditions such as bacterial and viral infections, Para. [0016]; the pharmaceutical compositions can be prepared by per se known methods for the preparation of pharmaceutically acceptable compositions which can be administered to patients, Para. [0097]; measuring a level of Fg2 activity or expression (assay for fg2 prothrombinase was used to directly measure procoagulant activity, Para. [0286]); administering an Fg2 inhibitor or agonist (administering an effective amount of an antibody to Fg2 to an animal in need thereof, Para. [0011]; the inhibitor may be an antibody specific for Fg2, Para. [0019]).

Further still, US 2013/0251720 A1 to Clark et al. discloses an agent that inhibits or agonizes IL-33 activity and/or TIGIT activity (the invention provides an anti-TIGIT Antibody, Para. [0017]; administering at least one of ...an agonist of TIGIT expression and/or activity, or an antagonist of TIGIT expression and/or activity in vivo, Para. [0019]); administering to the patient a composition comprising a TIGIT agonist and/or an IL-33 agonist (the invention provides an anti-TIGIT Antibody, Para. [0017]; administering at least one of ...an agonist of TIGIT expression and/or activity, or an antagonist of TIGIT expression and/or activity in vivo, Para. [0019]); administration of compositions containing, treatment of a disease with, etc., to each polynucleotide of the invention, Para. [0067]; administering a TIGIT inhibitor or agonist (the invention provides an anti-TIGIT Antibody, Para. [0017]; administering at least one of ...an agonist of TIGIT expression and/or activity, or an antagonist of TIGIT expression and/or activity in vivo, Para. [0019]); TH2 dampening therapy (Molecules that inhibit the lymphocyte response in the MLR, Para [0365]; in activated and resting... Tnf2, Para. [0388]).

The Inventions listed in Groups I-III therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.