The present invention relates to antibodies and antigen-binding fragments thereof that bind to PD-1, and to methods of using such antibodies and antigen-binding fragments. For example, the present invention provides humanized anti-PD-1 antibodies and methods of use thereof.
**INTERNATIONAL SEARCH REPORT**

**International application No.**

PCT/US 15/41575

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**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(8) - A61K 39/395, C07K 16/18 (2015.01)

CPC - A61K 39/395, A61K 2039/505, C07K 16/2896

According to International Patent Classification (IPC) or to both national classification and IPC

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**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC - A61K 39/395, C07K 16/18

CPC - A61K 39/395, A61K 2039/505, C07K 16/2896

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

CPC - C07K 2317/50, C07K 16/28; USPC - 424/143.1

(knowledge limited; terms below)

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

PatBase, Google Patents, Google Scholar

Search terms: PD-1, PD1, programmed cell death 1, CD279, PDCD1, SLEB2, hPD-1, hPD1, hSLE1, antibody, immunoglobulin, mAb, 10D1, hybridoma, light chain, heavy chain, CDR1, CDR2, CDR3

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**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>A</td>
<td>US 2013/0133091 A1 (KORMAN et al.) 23 May 2013 (23.05.2013) para [0008], [0048], [0502]</td>
<td>1-3, 14-15, 35, 40</td>
</tr>
<tr>
<td>A</td>
<td>US 2011/0008369 A1 (FINNEFROCK et al.) 13 January 2011 (13.01.2011) SEQ ID NOs: 7, 12, 40</td>
<td>1-3, 14-15</td>
</tr>
<tr>
<td>A</td>
<td>CN 1687135 A (WANG ZHE) 26 October 2005 (26.10.2005) SEQ ID NO: 2</td>
<td>1-3</td>
</tr>
</tbody>
</table>

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Further documents are listed in the continuation of Box C.

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* 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
  * "Z" document member of the same patent family

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Date of the actual completion of the international search

14 December 2015

Date of mailing of the international search report

06 JAN 2016

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 Helpdesk: 571-272-4300
PCT OSP: 571-272-7714

Form PCT/ISA/210 (second sheet) (January 2015)
**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.: 22-26, 36-39, and 41-46
   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:

--------Please see continuation in 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.: 1-3, 14-15, 35, 40; limited to the antibody 10D1 (SEQ ID NOs: 18-21, 23-26)

**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

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 1-21, 35, 40, directed to an isolated antibody or fragment thereof that binds to PD-1, wherein the antibody comprises specific light chain and heavy chain sequences. The anti-PD-1 antibody or fragment thereof will be searched to the extent that it encompasses antibody 10D1, which comprises:
- light chain CDRs1-3 (10D1) SEQ ID NO: 24, 25, 26,
- heavy chain CDRs1-3 (10D1) SEQ ID NO: 19, 20, 21,
- light chain variable (10D1) SEQ ID NO: 23,
- heavy chain variable (10D1) SEQ ID NO: 18.

It is believed that claims 1-3, 14-15, 35, 40, limited to the antibody 10D1, encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass antibody 10D1 or a fragment thereof. Additional antibodies will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected antibody. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be antibody 4C10, which comprises light chain CDRs1-3 (4C10) SEQ ID NO: 34, 35, 36, heavy chain CDRs1-3 (4C10) SEQ ID NO: 29, 30, 31, light chain variable (4C10) SEQ ID NO: 33, heavy chain variable (4C10) SEQ ID NO: 28, i.e. claims 1-2, 4, 14-15, 35, 40, limited to the antibody 4C10.

Group II: Claims 27-32 and 34 drawn to an isolated antibody or fragment thereof that binds to PD-1, wherein the antibody has a specific binding affinity for PD-1.

Group III: Claim 33, drawn to an isolated antibody or fragment thereof that binds to PD-1, wherein the antibody or fragment increases T cell activation as measured by inflammatory cytokine production.

The inventions listed as Groups I, II, and 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 technical feature of each of the inventions listed as Group I is the specific antibody light chain CDR sequences, heavy chain CDR sequences, light chain variable sequences, and heavy chain variable sequences recited therein. Each invention requires antibody fragment sequences, not required by any of the other inventions, and not required by Groups II and III.

Group II requires specific binding affinity to PD-1, not required by Groups I and II.

Group III requires an increase in T cell activation as measured by inflammatory cytokine production, not required by Groups I and II.

Common Technical Features
The feature shared by Groups I, II, and III is an isolated antibody or fragment thereof that binds to PD-1.

The feature shared by the inventions of Group I is an antibody that binds to PD-1 and comprises light chain variable region comprising light chain CDRs1-3 and heavy chain variable region comprising heavy chain CDRs1-3.

However, these shared technical features do not represent a contribution over prior art, because the shared technical features are taught by US 2013/0133091 A1 to Korman et al. (hereinafter 'Korman').

Korman discloses an isolated antibody or fragment thereof that binds to PD-1 (para [0008] "The present invention provides isolated monoclonal antibodies, in particular human monoclonal antibodies, that bind to PD-1 and that exhibit numerous desirable properties").

Korman further discloses that the antibody that binds to PD-1 comprises light chain variable region comprising light chain CDRs1-3 and heavy chain variable region comprising heavy chain CDRs1-3 (para [0048] "a heavy chain variable region that comprises CDR1, CDR2, and CDR3 sequences; and a light chain variable region that comprises CDR1, CDR2, and CDR3").

Additionally, Korman teaches that the antibody that binds to PD-1 binds to human PD-1 with a K.sub.D of 1.times.10.sup.-7 M or less (para [0010J]) and increases T-cell activation (para [0499] "Without wishing to be bound by theory, it is possible that by raising the threshold of T cell activation by PD-1 and CTLA-4 blockade, anti-tumor responses may be activated in a host").

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

Groups I, II, and III therefore lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Item 4 (continued)

Claims 22-26, 36-39, and 41-46 have been held unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).