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**Published**:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
19 February 2015

(54) Title: ANTIBODIES DIRECTED AGAINST PROGRAMMED DEATH-1 (PD-1)

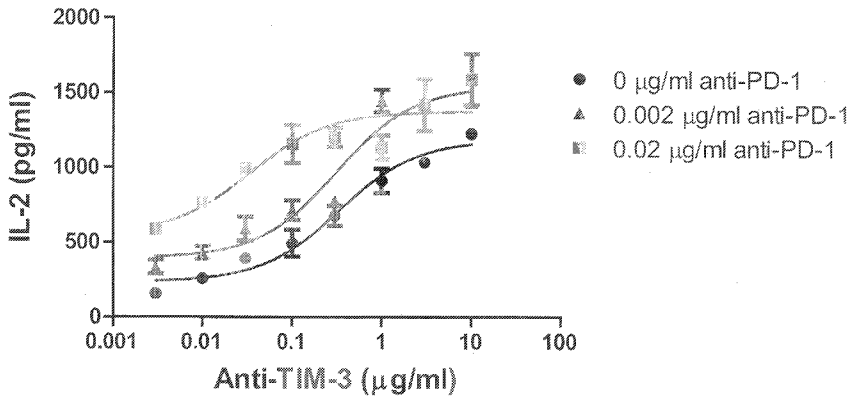


FIG. 2

(57) Abstract: The invention relates to an isolated immunoglobulin heavy chain polypeptide and an isolated immunoglobulin light chain polypeptide that bind to a programmed death-1 (PD-1) protein. The invention provides a PD-1-binding agent that comprises the aforementioned immunoglobulin heavy chain polypeptide and immunoglobulin light chain polypeptide. The invention also provides related vectors, compositions, and methods of using the PD-1-binding agent to treat a cancer or an infectious disease.

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# INTERNATIONAL SEARCH REPORT

International application N°
PCT/US2014/036525

**Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

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)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

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:

SEQ ID NOs: 4-11, 15-18, 22-25, 28, 29, 32-34, and 38-41 were searched.

# INTERNATIONAL SEARCH REPORT

International application N°
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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/28 (2014.01)
CPC - C07K 16/2896 (2014.12)
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)
IPC(8) - A61K 39/00, 39/395; A61P 31/00, 35/00, 35/02, 37/00, 37/04, 37/06; C07K 16/18, 16/22, 16/24, 16/28 (2014.01)
USPC - 424/139.1, 141.1, 145.1, 158.1; 435/331, 335, 336; 530/387.1, 387.9, 388.1, 388.23, 388.24

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

CPC - A61K 2039/505; C07K 16/2896, 16/2827, 2317/74, 2316/96, 2317/55 (2014.12) (keyword delimited)

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

PatBase, Google Patents, PubMed

Search terms used:programmed cell death 1, CD279, PD-1, PD1, SLEB2, hPD-1, hPD-l, hSLE1, antibody, immunoglobulin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2012/017003 A1 (F. HOFFMANN-LA ROCHE AG) 09 February 2012 (09.02.2012) entire document | 1-5, 17-21, 26-30, 32 |
| A | US 8,008,449 B2 (KORMAN et al) 30 August 2011 (30.08.2011) entire document | 1-5, 17-21, 26-30, 32 |
| A | US 2012/0039906 A1 (OLIVE) 16 February 2012 (16.02.2012) entire document | 1-5, 17-21, 26-30, 32 |
| A | WO 2004/056875 A1 (WYETH) 08 July 2004 (08.007.2004) entire document | 1-5, 17-21, 26-30, 32 |
| A | KASAGI et al. "Anti-Programmed Cell Death 1 Antibody Reduces CD4+PD-1+ T Cells and Relieves the Lupus-Like Nephritis of NZB/W F1 Mice," The Journal of Immunology, 05 February 2010 (05.02.2010), Vol. 184, Pgs. 2337-2347. entire document | 1-5, 17-21, 26-30, 32 |

☐ 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
"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
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 08 December 2014 | 24 DEC 2014 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Blaine R. Copenheaver<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

# INTERNATIONAL SEARCH REPORT

International application N°
PCT/US2014/036525

**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.: 6-8, 14-16, 31, 33-52
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 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.:
1-5, 17-21, 26-30, and 32 restricted to SEQ ID NOs: 4, 8, 23, 28, 29, and 40 only

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.

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 1-5, 9-13, 17-30, and 32 are drawn to an isolated immunoglobulin comprising a heavy chain polypeptide and a light chain polypeptide.

The first invention of Group I+ is restricted to an isolated immunoglobulin comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:4, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:1, CDR2 is selected to be SEQ ID NO:2, and CDR3 is selected to be SEQ ID NO:3; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:28, the light chain further comprising light chain complementary determining regions CDR1 and CDR2, where CDR1 is selected to be SEQ ID NO:26, and CDR2 is selected to be SEQ ID NO:27. It is believed that claims 1, 19-21, and 32 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NOs: 1, 2, 3, 4, 26, 27, and 28.

Applicant is invited to elect additional isolated immunoglobulins with specified SEQ ID NO to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an isolated immunoglobulin comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:15, the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:12, CDR2 is selected to be SEQ ID NO:13, and CDR3 is selected to be SEQ ID NO:14; and a light chain, wherein the light chain variable region is selected to be SEQ ID NO:38, the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:35, CDR2 is selected to be SEQ ID NO:36, and CDR3 is selected to be SEQ ID NO:37. Additional isolated immunoglobulins will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on 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/examined.

The inventions listed in Groups I+ 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:

The Groups I+ isolated immunoglobulins do not share a significant structural element, requiring the selection of alternatives for the light and heavy chain variable regions of the antibody, where "immunoglobulin heavy chain polypeptide which comprises a complementarity determining region 1 (CDR) amino acid sequence of SEQ ID NO: 1, a CDR2 amino acid sequence of SEQ ID NO: 2, and a CDR3 amino acid sequence of SEQ ID NO: 3, wherein (a) residue 9 of SEQ ID NO: 1 is replaced with a different amino acid residue, (b) one or more of residues 7, 8, and 9 of SEQ ID NO: 2 is replaced with a different amino acid residue, (c) one or more of residues 1, 2, and 5 of SEQ ID NO: 3 is replaced with a different amino acid residue, or (d) any combination of (a)-(c)" and "isolated immunoglobulin heavy chain polypeptide which comprises a complementarity determining region 1 (CDR) amino acid sequence of SEQ ID NO: 12, a CDR2 amino acid sequence of SEQ ID NO: 13, and a CDR3 amino acid sequence of SEQ ID NO: 14, wherein optionally (a) residue 9 of SEQ ID NO: 12 is replaced with a different amino acid residue, (b) residue 8 and/or residue 9 of SEQ ID NO: 13 is replaced with a different amino acid residue, (c) residue 5 of SEQ ID NO: 14 is replaced with a different amino acid residue, or (d) any combination of (a)-(c)".

The Groups I+ share the technical features of an isolated immunoglobulin, the immunoglobulin comprising a heavy chain variable region, the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3; and a light chain variable region, the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3. However, these shared technical features do not represent a contribution over the prior art. Specifically, WO 2012/017003 A1 to Jenewein et al. discloses an isolated immunoglobulin (an antibody, Abstract; provided are isolated nucleic acids encoding an antibody heavy chain as reported herein. Further provided is an isolated nucleic acid encoding the antibody light chain as reported herein, Pg. 5, Lns. 18-20), the antibody comprising a heavy chain variable region (provided are isolated nucleic acids encoding an antibody heavy chain as reported herein, Pg. 5, Lns. 18-19; In one embodiment the antibody comprises a VH sequence of SEQ ID NO: 35, Pg. 5, Ln. 12), the heavy chain variable region further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3 (SEQ ID NO:4, CDR-H1 amino acid sequence of c18/A2 mAb; SEQ ID NO:5, CDR-H2 amino acid sequence of c18/A2 mAb; SEQ ID NO:6, CDR-H3 amino acid sequence of c18/A2 mAb, Pg. 43, Lns. 20-23); and a light chain variable region (further provided is an isolated nucleic acid encoding the antibody light chain as reported herein, Pg. 5, Lns. 19-20; In one embodiment the antibody comprises a VL sequence of SEQ ID NO: 39, Pg. 5, Ln. 14), the light chain variable region further comprising light chain complementary determining regions CDR1, CDR2, and CDR3 (SEQ ID NO:8, CDR-H1 amino acid sequence of c18/A2 mAb; SEQ ID NO:9, CDR-H2 amino acid sequence of c18/A2 mAb; SEQ ID NO:10, CDR-H3 amino acid sequence of c18/A2 mAb, Pg. 43, Lns. 24-26).

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