Title: IMMUNOMODULATORY AGENTS

Abstract: The invention provides antibodies that specifically bind to PD-L1 and fusion molecules comprising PD-L1 binding proteins constructed with an IL15 receptor-binding domain, nucleic acid molecules encoding the same, and therapeutic compositions thereof. The agents inhibit PD-L1-mediated immunosuppression and enhance cell and cytokine mediated immunity for the treatment of neoplastic and infectious diseases.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8)—A61K 39/395, C07K 16/28, C07K 16/24, C07K 16/46 (2015.01)
CPC—A61K 2039/505, C07K 16/2827, C07K 16/244, C07K 16/468
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 39/395, C07K 16/28, C07K 16/24, C07K 16/46 (2015.01)
CPC—A61K 2039/505, C07K 16/2827, C07K 16/244, C07K 16/468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC—C07K 2317/56, C07K 2317/565, C07K 2317/73, A61K 39/3955
(keyword limited; terms below)

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
PatBase, PCT/ISA/210 (second sheet) (January 2015)

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 2013/079174 A1 (NASTRI et al.) 06 June 2013 (06.06.2013) p 1, ll 5-6; p 11, In 30-32; p 11, In 33 - p 12, ln 2; p 14, ln 4-8; p 14, In 9-13; p 15, In 5-7; SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 26, SEQ ID NO: 27</td>
<td>1-2, 5(1,2), 8-14, 20</td>
</tr>
<tr>
<td>X</td>
<td>KERMER et al., Combining antibody-directed presentation of IL-15 and 4-1BB in a functional fusion protein for cancer immunotherapy, Mol Cancer Ther, published online 6 November 2013, Vol 13, No 1, p 112-21. Especially abstract; p 112, col 2, para 1.</td>
<td>21-22, 24-26</td>
</tr>
<tr>
<td>A</td>
<td>US 201 1/01 77074 A1 (SIVAKUMAR et al.) 21 July 201 1 (21.07.201 1) SEQ ID NO: 514</td>
<td>27</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
“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

Date of the actual completion of the international search
10 June 2015 (10.06.2015)

Date of mailing of the international search report
02 July 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. 571-273-8300

Authorized officer
Lee W. Young
PCT Referral: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)
### INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/US 15/11657

**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. X Claims Nos.: 6-7, 16-19, 23, 28-34
   - 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 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. X 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.:
   - claims 1-2, 5 (in part), 10, 13, 20 limited to SEQ ID NOs: 241, 243, 245, 246;
   - claims 8-9, 11, 14 limited to SEQ ID NOs: 247, 248, 249, 250; and
   - claims 21-22, 24-27

4. H 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.

Form PCTnSA/210 (continuation of first sheet (2)) (January 2015)
Continuation of:
Box No. Ill Observations where unity of invention is lacking

Group I: Claims 1-5, 10, 13, 15, 20, drawn to an antibody or fragment thereof that binds to PD-L1, which comprises heavy chain CDR-1H, CDR-2H, and CDR-3H. The PD-L1 antibody or fragment thereof will be searched to the extent that the heavy chain CDR-1H, CDR-2H, and CDR-3H, and heavy chain variable domain sequences encompass the CDR-1H sequence of SEQ ID NO: 241, the CDR-2H sequence of SEQ ID NO: 243, the CDR-3H sequence of SEQ ID NO: 245, and the heavy chain variable domain sequence of SEQ ID NO: 246 [mAB, tclambdab8, see Table 1 of instant Specification]. It is believed that claims 1-2, 5 (in part), 10, 13, 20 limited to SEQ ID NOs: 241, 243, 245, 246, encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass an antibody or fragment thereof that binds to PD-L1, which comprises heavy chain CDR-1H, CDR-2H, CDR-3H, and heavy chain variable domain sequences of SEQ ID NOs: 241, 243, 245, 246, respectively. {Note that claim 15 requires light chain sequences not encompassed by the first named invention and will only be searched if the light chain sequences are additionally elected for search. Additional heavy chain CDR-1H, CDR-2H, CDR-3H, heavy chain variable domain and light chain variable domain sequences will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected heavy chain CDR-1H, CDR-2H, CDR-3H, and heavy chain variable domain sequences. 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 dearly 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 an antibody or fragment thereof that binds to PD-L1, which comprises heavy chain CDR-1H, CDR-2H, CDR-3H, heavy chain variable domain and light chain variable domain sequences of SEQ ID NOs: 264, 243, 245, 265, 250 [mAB R101, Table 1, instant Specification], respectively, i.e. claims 1-2, 5 (in part), 10, 13, 20 limited to SEQ ID NOs: 264, 243, 245, 265, 250.}

Group II: Claims 8-9, 11-12, 14, drawn to an antibody or fragment thereof that binds to PD-L1, which comprises light chain CDR-1L, CDR-2L, CDR-3L. The PD-L1 antibody or fragment thereof may be searched, for example, to the extent that light chain CDR-1L, CDR-2L, CDR-3L, and light chain variable domain sequences encompass the CDR-1L sequence of SEQ ID NO: 247, the CDR-2L sequence of SEQ ID NO: 248, the CDR-3L sequence of SEQ ID NO: 249, and the light chain variable domain of SEQ ID NO: 250 [mAB, tcclambdab7], for an additional fee and election as such. Additional light chain CDR-1L, CDR-2L, CDR-3L, and light chain variable domain sequences will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected light chain CDR-1L, CDR-2L, CDR-3L, and light chain variable domain sequences. Failure to dearly 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. Another exemplary election would be an antibody or fragment thereof that binds to PD-L1, which comprises light chain CDR-1L, CDR-2L, CDR-3L, and light chain variable domain sequences of SEQ ID NOs: 7, 8, 9, 10 [mAB R2kappa3], i.e. claims 11-12, 14 limited to SEQ ID NOs: 7, 8, 9, 10.

Group III: Claims 21-22, 24-27, drawn to a fusion protein comprising a first domain that binds to PD-L1 and a second domain that binds to IL15 receptor.

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 heavy chain CDR-1H, CDR-2H, CDR-3H, and heavy chain variable domain sequences recited therein. Significant structural similarities cannot readily be ascertained among the heavy chain sequences. Without significant structural similarities, the heavy chain sequences do not have a shared special technical feature. Further, the heavy chain sequences are not required by Groups II and III.

The technical feature of each of the inventions listed as Group II is the specific light chain CDR-1L, CDR-2L, CDR-3L, and light chain variable domain sequences recited therein. Significant structural similarities cannot readily be ascertained among the light chain sequences. Without significant structural similarities, the light chain sequences do not have a shared special technical feature. Further, the light chain sequences are not required by Groups I and III.

Group III requires a fusion protein that binds to both PD-L1 and IL15 receptor, not required by Groups I and II.

Common Technical Features

The feature shared by Groups I, II, and III is an antibody or fragment thereof that binds to PD-L1. An additional feature shared by Groups I and II are PD-L1 antibody variable domains.

The feature shared by the inventions of Groups I is [claim 1] an antibody or fragment thereof that binds to PD-L1, which comprises a heavy chain CDR-1H which has the sequence X1YX2MX3 [SEQ ID NO:328] wherein X1 is A, G, M, O, S, Y, or W, X2 is A, L, M, Q, R, S, V, W, or Y, and X3 is A, F, L, M, S, T, V, or Y, a heavy chain CDR-2H which has SEQ ID NO:243, and a heavy chain CDR-3H which has the sequence of SEQ ID NO:245.

—please see continuation on next extra sheet—
INTERNATIONAL SEARCH REPORT

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

Another feature shared by the inventions of Groups I+ is [claim 10] an antibody or fragment thereof that binds to PD-L1, which comprises a heavy chain variable domain with a CDR-1H, a CDR-2H, and a CDR-3H as set forth in Table 1.

Another feature shared by the inventions of Groups I+ is [claim 13] an antibody or fragment thereof that binds to PD-L1, which comprises a heavy chain variable domain sequence set forth in Table 1, or a heavy chain variable domain sequence set forth in Table 1 with conservative substitutions such that it is at least 95% identical to the heavy chain variable domain sequence set forth in Table 1.

The feature shared by the inventions of Groups II+ is [claim 8] an antibody or fragment thereof that binds to PD-L1, wherein the light chain comprises a CDR-1L which has SEQ ID NO:247, a CDR-2L which has SEQ ID NO:248, and a CDR-3L which has SEQ ID NO:249.

Another feature shared by the Inventions of Groups II+ is [claim 11] an antibody or fragment thereof that binds to PD-L1, which comprises a light chain variable domain with a CDR-1L, a CDR-2L, and a CDR-3L as set forth in Table 1.

Another feature shared by the inventions of Groups III+ is [claim 14] an antibody or fragment thereof that binds to PD-L1, which comprises a heavy chain variable domain with a CDR-1H, a CDR-2H, and a CDR-3H as set forth in Table 1.

However, these shared technical feature do not represent a contribution over prior art, because the shared technical features are taught by WO 2013/079174 A1 to Nastri et al. (hereinafter “Nastri”).

Nastri discloses an antibody or fragment thereof that binds to PD-L1 (p 1, in 5-6), wherein the anti-PD-L1 antibody or fragment thereof comprises heavy chain variable region (p 7, in 29-30 “heavy chain variable region polypeptide comprising an HVR-H1, HVR-H2 and HVR-H3 sequence”) and light chain variable region (p 8, in 23 “variable region light chain comprising an an HVR-L1, HVR-L2 and HVR-L3”).

Nastri further discloses [claim 1] an antibody or fragment thereof that binds to PD-L 1 (p 1, in 5-6), which comprises a heavy chain CDR-1H which has the sequence X1Y2X3 (SEQ ID NO:328) wherein X1 is A, G, M, O, S, Y, or W, X2 is A, L, M, O, R, S, V, W, or Y, and X3 is A, F, L, M, S, T, V, or Y (p 11, in 30-32; Nastri SEQ ID NO: 21 i exhibits 100% identity to SEQ ID NO: 328 MYMM (i.e. SEQ ID NO: 241)), a heavy chain CDR-2H which has SEQ ID NO:243 (p 11, in 30-32; Nastri SEQ ID NO: 22 exhibits 100% identity to SEQ ID NO:243), and a heavy chain CDR-3H which has the sequence of SEQ ID NO:245 (p 11, in 30-32; Nastri SEQ ID NO: 17 exhibits 100% identity to SEQ ID NO: 245).

Nastri further discloses [claim 10] an antibody or fragment thereof that binds to PD-L1 (p 1, in 5-6), which comprises a heavy chain variable domain with a CDR-1H, a CDR-2H, and a CDR-3H as set forth in Table 1 (p 11, in 30-32; Nastri SEQ ID NOs: 21, 22, 17 exhibit 100% identity to CDR-1H, CDR-2H, CDR-3H SEQ ID NOs: 241, 243, 245 respectively).

Nastri further discloses [claim 13] an antibody or fragment thereof that binds to PD-L1 (p 1, in 5-6), which comprises a heavy chain variable domain sequence set forth in Table 1 (p 14, in 4-8; Nastri SEQ ID NO: 26 exhibits 100% identity to heavy chain variable domain sequence SEQ ID NO: 246).

Nastri further discloses [claim 8] an antibody or fragment thereof that binds to PD-L1 (p 1, in 5-6), wherein the light chain comprises a CDR-1L which has SEQ ID NO:247 (p 11, in 33 - p 12, in 2; Nastri SEQ ID NO: 23 exhibits 100% identity to SEQ ID NO: 247 (TGTSSDVGYAVYNSV)), a CDR-2L which has SEQ ID NO: 248 (p 11, in 33 - p 12, in 2; Nastri SEQ ID NO: 19 exhibits 100% identity to SEQ ID NO: 248 (DVSNRPS)), and a CDR-3L which has SEQ ID NO:249 (p 11, in 33 - p 12, in 2; Nastri SEQ ID NO: 20 exhibits 100% identity to SEQ ID NO: 249 (SSYTSSTSRV)).

Nastri further discloses [claim 11] an antibody or fragment thereof that binds to PD-L1 (p 1, in 5-6), which comprises a light chain variable domain with a CDR-1L, a CDR-2L, and a CDR-3L as set forth in Table 1 (p 11, in 33 - p 12, in 2; Nastri SEQ ID NOs: 23, 19, 20 exhibit 100% identity to CDR-1L, CDR-2L, and CDR-3L SEQ ID NOs: 247, 248, and 249 respectively).

Nastri further discloses [claim 14] an antibody or fragment thereof that binds to PD-L1 (p 1, in 5-6), which comprises a light chain variable domain sequence set forth in Table 1 (p 14, in 9-13; Nastri SEQ ID NO: 27 exhibits 100% identity to light chain variable domain sequence SEQ ID NO: 250).

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.

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.