### PATENT COOPERATION TREATY

**PCT**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

<table>
<thead>
<tr>
<th>Applicant’s or agent’s file reference</th>
<th>FOR FURTHER ACTION</th>
<th>See item 4 below</th>
</tr>
</thead>
<tbody>
<tr>
<td>6964WO (51590)</td>
<td>International filing date <em>(day/month/year)</em></td>
<td>Priority date <em>(day/month/year)</em></td>
</tr>
</tbody>
</table>

International Patent Classification (8th edition unless older edition indicated)
See relevant information in Form PCT/ISA/237

**Applicant**
MEMORIAL SLOAN-KETTERING CANCER CENTER

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1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

   - Box No. I Basis of the report
   - Box No. II Priority
   - Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - Box No. IV Lack of unity of invention
   - Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - Box No. VI Certain documents cited
   - Box No. VII Certain defects in the international application
   - Box No. VIII Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

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**Date of issuance of this report**
06 October 2009 (06.10.2009)

**Authorized officer**
Yoshiko Kuwahara

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1211 Geneva 20, Switzerland

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Form PCT/I/373 (January 2004)
PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To
PETER C. LAURO
EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

PCT
WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) 21 AUG 2008

Applicant’s or agent’s file reference
66964WO (51590)

International application No.
PCT/US 08/04251
International filing date (day/month/year) 31 March 2008 (31.03.2008)
Priority date (day/month/year) 30 March 2007 (30.03.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A01N 63/00 (2008.04)
USPC - 424/93.71

Applicant MEMORIAL SLOAN-KETTERING CANCER CENTER

1. This opinion contains indications relating to the following items:
   - [ ] Box No. I Basis of the opinion
   - [ ] Box No. II Priority
   - [X] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [X] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI Certain documents cited
   - [ ] Box No. VII Certain defects in the international application
   - [ ] Box No. VIII Certain observations on the international application

2. FURTHER ACTION
   If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will be so considered.

   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

   For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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. 571-273-3201

Date of completion of this opinion
08 August 2008 (08.08.2008)

Authorized officer:
Lee W. Young

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

Form PCT/ISA/237 (cover sheet) (April 2007)
1. With regard to the language, this opinion has been established on the basis of:
   - [x] the international application in the language in which it was filed.
   - [ ] a translation of the international application into ____________ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:
   a. type of material
      - [ ] a sequence listing
      - [ ] table(s) related to the sequence listing
   b. format of material
      - [ ] on paper
      - [ ] in electronic form
   c. time of filing/furnishing
      - [ ] contained in the international application as filed
      - [ ] filed together with the international application in electronic form
      - [ ] furnished subsequently to this Authority for the purposes of search

4. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto 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.

5. Additional comments:
<table>
<thead>
<tr>
<th>Box No. III</th>
<th>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of</td>
</tr>
<tr>
<td></td>
<td>☐ the entire international application</td>
</tr>
<tr>
<td></td>
<td>☒ claims Nos. 13-15, 19-23, 32-41, 61-71 and 74</td>
</tr>
<tr>
<td></td>
<td>because:</td>
</tr>
<tr>
<td></td>
<td>☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (specify):</td>
</tr>
<tr>
<td></td>
<td>☒ the description, claims or drawings (indicate particular elements below) or said claims Nos. see below</td>
</tr>
<tr>
<td></td>
<td>Claims 13-15, 19-23, 32-41, 61-71 and 74 are dependent claims that are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.</td>
</tr>
<tr>
<td></td>
<td>☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (specify):</td>
</tr>
<tr>
<td></td>
<td>☒ no international search report has been established for said claims Nos. 13-15, 19-23, 32-41, 61-71 and 74</td>
</tr>
<tr>
<td></td>
<td>☐ a meaningful opinion could not be formed without the sequence listing: the applicant did not, within the prescribed time limit:</td>
</tr>
<tr>
<td></td>
<td>☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.</td>
</tr>
<tr>
<td></td>
<td>☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.</td>
</tr>
<tr>
<td></td>
<td>☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13 ter. 1(a) or (b).</td>
</tr>
<tr>
<td></td>
<td>☐ a meaningful opinion could not be formed without the tables related to the sequence listings: the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.</td>
</tr>
<tr>
<td></td>
<td>☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.</td>
</tr>
<tr>
<td></td>
<td>☐ See Supplemental Box for further details.</td>
</tr>
</tbody>
</table>

Form PCT/ISA/237 (Box No. III) (April 2007)
Lack of unity of invention

1. In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - [ ] paid additional fees
   - [ ] paid additional fees under protest and, where applicable, the protest fee
   - [X] paid additional fees under protest but the applicable protest fee was not paid
   - [ ] not paid additional fees

2. [ ] This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - [ ] complied with
   - [X] not complied with for the following reasons:

   Group I, claims 1-12, 16-18, 72 and 73, drawn to an immunoresponsive cell comprising a receptor that binds an antigen and an exogenous co-stimulatory ligand (claims 1-12); drawn to a T cell expressing a vector encoding a polypeptide selected from the group consisting of CD80, 4-IBBL, OX40L, CD70 and CD30L (claims 16-18).

   Group II, claims 24-31, drawn to a method comprising administering an effective amount of an immunoresponsive cell comprising a receptor that binds a tumor antigen and a vector encoding a co-stimulatory ligand.

   Group III, claims 42-48, 51-57, drawn to a method for producing an antigen-specific immunoresponsive cell, the method comprising
   - introducing into the immunoresponsive cell a nucleic acid sequence that encodes a chimeric antigen receptor,
   - wherein the chimeric antigen receptor comprises an antigen-binding domain coupled to an intracellular signaling domain that activates an immunoresponsive cell.

   Group IV, claims 49-60, drawn to a method comprising
   - administering to the subject a therapeutically effective amount of a T cell or a NK cell comprising
     - a tumor antigen and an antigen presenting complex comprising at least two co-stimulatory ligands,
   - wherein at least one of the two co-stimulatory ligands, thereby treating cancer in the subject.

   The inventions listed as Groups I-IV 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:

   Groups I, II, and IV do not include the inventive concept of an immunoresponsive cell comprising a nucleic acid sequence that encodes a chimeric antigen receptor, as required by Group III.

   Groups I-III do not include the inventive concept of an immunoresponsive cell comprising a tumor antigen and an antigen presenting complex comprising at least two co-stimulatory ligands, as required by Group IV.

   Although Groups I-IV do share the technical feature of an immunoresponsive cell comprising a receptor that binds an antigen and an exogenous co-stimulatory ligand, this shared technical feature does not represent a contribution over the prior art. Specifically, the article entitled "Targeting Tumours With Genetically Enhanced T Lymphocytes" by Sadefain et al. (Nature Reviews Cancer 2003, 3: 35-45) teaches said cell (tumour-infiltrating lymphocytes were transduced with the tumour necrosis factor-? (TNF-?)) cDNA, pg 40, col 1). As the above immunoresponsive cell comprising a receptor that binds an antigen and an exogenous co-stimulatory ligand was known at the time, as evidenced by the teaching of Sadefain et al, this cannot be considered a special technical feature that would otherwise unify the groups.

   Groups I-IV therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - [ ] all parts
   - [X] the parts relating to claims Nos. 1-12, 16-18, 72, and 73
WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

Box No. V  Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

<table>
<thead>
<tr>
<th>Novelty (N)</th>
<th>Claims</th>
<th>YES or NO</th>
</tr>
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<tbody>
<tr>
<td>Claims 2, 3, 11, 12, 16-18, 72, 73</td>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>Claims 1-4-10</td>
<td></td>
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<table>
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<tr>
<th>Inventive step (IS)</th>
<th>Claims</th>
<th>YES or NO</th>
</tr>
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<tbody>
<tr>
<td>Claims none</td>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>Claims 1-12, 16-18, 72, 73</td>
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</tr>
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</table>

<table>
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<tr>
<th>Industrial applicability (IA)</th>
<th>Claims</th>
<th>YES or NO</th>
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<tbody>
<tr>
<td>Claims 1-12, 16-18, 72, 73</td>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>Claims none</td>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

2. Citations and explanations:

Claims 1 and 4-10 lack novelty according to PCT Article 33(2) as anticipated by the publication "Integrated CD28 and 4-1BB Signals Strongly Potentiate CD8+ T Cell Mediated Radiation of Metastatic Prostate Cancer" by Zhong et al. (hereinafter "Zhong").

As to claim 1, Zhong teaches an immune-responsive cell comprising a receptor that binds an antigen (abstract; "T cell receptor directed to prostate-specific membrane antigen (PMSA)^") and an exogenous co-stimulatory ligand (abstract; "ligand for receptor CD28 (i.e. ligand is CD80, also known as B7-1)").

As to claim 4, Zhong further teaches that the cell is a T cell (abstract).

As to claim 5, Zhong further teaches that the antigen is a tumor antigen (abstract; "prostate-specific membrane antigen (PMSA)^")

As to claim 6, Zhong further teaches that the antigen is prostate-specific membrane antigen (PSMA) (abstract).

As to claim 7, Zhong further teaches that the cell expresses a recombinant or an endogenous antigen receptor P26z. (abstract).

As to claim 8, Zhong teaches that the co-stimulatory ligand is a tumour necrosis factor (TNF) ligand (abstract; ligand for 4-1BB receptor, where ligand would be 4-1BB).

As to claim 9, Zhong further teaches that the TNF ligand is selected from the group consisting of 4-1BB/1 (abstract; ligand for 4-1BB receptor, where ligand would be 4-1BB).

As to claim 10, Zhong further teaches that the Ig superfamily ligand is selected from the group consisting of CD80 (abstract, ligand for CD28 receptor, where ligand would be CD80, also known as B7-1).

Claims 72 and 73 lack an inventive step according to PCT Article 33(3) as obvious over Zhong, as above.

As to claims 72 and 73, Zhong teaches -- an immune-responsive cell comprising a receptor that binds an antigen (abstract; "T cell receptor directed to prostate-specific membrane antigen (PMSA)^") and

-- an exogenous co-stimulatory ligand (abstract; "ligand for receptor CD28 (i.e. ligand is CD80, also known as B7-1)").

Zhong does not specifically teach a kit for treatment of a neoplasia, the kit comprising the above components and written instructions for using it. However, based on the teaching of Zhong (abstract), one of ordinary skill in the art would have known how to assemble the claimed kit and provide instructions for its use, with the aim of simplifying administration of the claimed composition.

Claims 2, 3 and 18 lack an inventive step according to PCT Article 33(3) as obvious over Zhong, as above, in view of the article entitled "4-1BB Ligand Induces Cell Division, Sustains Survival, and Enhances Effector Function of CD4 and CD8 T Cells with Similar Efficacy" by Cannons et al. (hereinafter "Cannons").

As to claim 2, Zhong teaches receptor (abstract; CD28) for a co-stimulatory ligand but does not mention ligand itself. However, Cannons teaches constitutive ligand for CD28 as B7-1, also known as CD80 (pg 1313 left col para 1; "[the interaction of CD28 on T cells with its ligands B7-1 and B7-2]"). It would have been obvious to one skilled in the art to combine the report of the receptor CD28 of Zhong with the information about the ligand for it, as taught by Cannons, so that full knowledge of the receptor-ligand signaling pair would be available to understand functional interactions and their consequences.

As to claim 3, Zhong, in addition to teaching a first receptor (abstract; CD28) for a co-stimulatory ligand, further teaches a second receptor (abstract; 4-1BB) for a second co-stimulatory ligand as constitutively expressed, but does not specifically teach the name of the ligand. However, Cannons teaches that 4-1BB is the second constitutively expressed co-stimulatory ligand (pg 1313 left col para 1; "[a number of additional receptor ligand pairs are up-regulated on the T cell and APCs, respectively. These receptor ligands may be involved in sustaining, diversifying, and/or amplifying the immune response. In particular, members of the TNFR/TNF ligand family, including 4-1BB/4-1BB]").

--------------------------------------------------------------- continued in Supplemental Box ------------------------------------------
Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V(2): 

As to claim 16, Zhong teaches tumor antigen-specific T cell (abstract; "specific for prostate-specific membrane antigen (PMSA)") expressing a vector encoding 4-1BB. Zhong does not teach a T cell co-expressing the ligand for 4-1BB, known as 4-1BBL. However, Cannons teaches 4-1BBL vector (pg 1314 left col para 3). It would have been obvious to one skilled in the art to combine the tumor antigen specific T cell, as taught by Zhong, with the 4-1BBL vector taught by Cannons, thereby achieving a virus specific T cell that co-expresses 4-1BB and 4-1BBL.

Claims 11 lacks an inventive step according to PCT Article 33(3) as obvious Zhong, as above, in view of the article entitled "CD152 Ligation by CD80 on T Cells Is Required for the Induction of Unresponsiveness by Costimulation-Deficient Antigen Presentation" by Chai et al. (hereinafter "Chai").

As to claim 11, Zhong teaches T cell expression and secretion of TNF (abstract) but does not teach the immunoresponsive cell expresses both a TNF ligand and an Ig superfamily ligand. However, Chai teaches expression of a Ig superfamily ligand by T cells (pg 3041 left col para 2; "the unusual ratio of B7 molecules expressed by T cells. The 5-fold excess of CD80 has not been described for any other B7+ cell population"). It would have been obvious to one skilled in the arts to combine the immunoresponsive cells taught by Zhong that express and secrete TNF, with the B7, i.e. CD80, expression by Tcells, as taught by Chai, thereby achieving T cells with desired transcostimulatory/autocostimulatory properties for tumor or virus-infected cell destruction.

Claims 16 and 17 lack an inventive step according to PCT Article 33(3) as obvious over Chai, as above, in view of the article entitled "Virus-specific CD4+ T cells: ready for direct attack" by Heller (hereinafter *Heller*).

As to claim 16, Chai teaches a T cell that expresses CD80 —i.e. B7-1— (pg 3041 left col para 2; "the unusual ratio of B7 molecules expressed by T cells. The 5-fold excess of CD80 has not been described for any other B7+ cell population") but does not teach virus specific T cells. However Heller teaches a virus specific T cell (abstract). It would have been obvious to one skilled in the art that the CD80 expressing T cells would have novel autocostimulatory and transcostimulatory properties. It would have been further obvious to combine the CD 80 expressing T cell as taught by Chai with the virus specific T cell of Heller because expressing the CD80 molecule by vector in the virus specific T cell would have generated a virus specific T cell with novel autocostimulatory or transcostimulatory properties.

As to claim 17, Heller further teaches the T cell recognizes Epstein Barr Virus antigens (abstract).

Claims 12 lacks an inventive step according to PCT 33(3) as obvious over Zhong, in view of Chai, as above, and further in view of Cannons.

As to claim 12, Chai further teaches the Ig superfamily ligand is CD80 (pg 3041 left col para 2; "the unusual ratio of B7 molecules expressed by T cells. The 5-fold excess of CD80 has not been described for any other B7+ cell population"). However, neither Chai nor Zhong teaches that the TNF ligand is 4-1BBL. However, Cannons teaches 4-1BBL vector (pg 1314 left col para 1). It would have been obvious that the immunoresponsive cell, as taught by Zhong or Chai, could be transfected with a 4-1BBL expression vector, as taught by Cannons, to enable the construction of novel immunoresponsive T cells with desired autocostimulatory/transcostimulatory properties for tumor or virus-infected cell destruction.

Claims 1-12, 16-18, and 72-73 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry.