PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CRISTIN H. COWLES
WOMBLE BOND DICKINSON (US) LLP
TWO INTERNATIONAL PLACE
SUITE 2310
BOSTON, MA 02110

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	12 APR 2019
Applicant's or agent's file reference M103034-1050	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 18/63171	29 November 2018 (29.11.2018)	29 November 2017 (29.11.2017)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C07K 16/28, A61K 38/00 (2019.01)
CPC - C07K 16/2806, A61K 38/00, C07K 2317/24, C07K 2319/00

Applicant MAGENTA THERAPEUTICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ 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 Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and 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 66.1*bis*(b) that written opinions of this International Searching Authority will not 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.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	01 April 2019	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/63171

Box No. I Basis of this opinion

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 43*bis*.1(a)).

3. [x] 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 sequence listing:
   - a. [x] forming part of the international application as filed:
     - [x] in the form of an Annex C/ST.25 text file.
     - [ ] on paper or in the form of an image file.
   - b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   - c. [ ] furnished subsequent to the international filing date for the purposes of international search only:
     - [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
     - [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. [ ] 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.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/63171

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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:

☐ the entire international application.

☒ claims Nos. 10, 12-82, 117-139, 143-168, 178-185, 199-202, 206-217

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. see below are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 10, 12-82, 117-139, 143-168, 178-185, 199-202, 206-217 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. see above

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file 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 the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ 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).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/63171

Box No. IV 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.

   ☐ 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.

   ☒ not complied with for the following reasons:

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 searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-9, 11, 83-116, drawn to a method of administering an anti-CD2 antibody-cytotoxin conjugate to a patient to deplete a population of CD2+ cells and a method of treating a disorder. The method will be searched to the extent that the anti-CD2 antibody encompasses CDR-H1, -H2, -H3 as set forth in SEQ ID NOs: 1, 2, 3, respectively; CDR-L1, -L2, -L3 as set forth in SEQ ID NOs: 4, 5, 6, respectively; VH SEQ ID NO: 7; VL SEQ ID NO: 8; and the disorder encompasses a stem cell disorder. It is believed that claims 1-9, 11, 83-89, (115-116)(in part) encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass SEQ ID NOs: 1-8 and a stem cell disorder. Additional anti-CD2 antibod(ies) and disorder(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected anti-CD2 antibod(ies) and disorder(s). 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 an anti-CD2 antibody encompasses CDR-H1, -H2, -H3 as set forth in SEQ ID NOs: 14, 15, 16, respectively; CDR-L1, -L2, -L3 as set forth in SEQ ID NOs: 18, 19, 20, respectively; VH SEQ ID NO: 21; and VL SEQ ID NO: 22; and the disorder encompasses a myelodysplastic disorder (claims 1-9, 11, 90, (115-116)(in part)).

Group II+: Claims 140-142, drawn to a conjugate represented by the formula anti-CD2-Cytotoxin. Group II+ will be searched upon payment of additional fees. The conjugate may be searched, for example, to the extent that the anti-CD2 antibody encompasses CDR-H1, -H2, -H3 as set forth in SEQ ID NOs: 1, 2, 3, respectively; CDR-L1, -L2, -L3 as set forth in SEQ ID NOs: 4, 5, 6, respectively; VH SEQ ID NO: 7; and VL SEQ ID NO: 8; for an additional fee and election as such. It is believed that claims 140-142 read on this exemplary invention. Additional anti-CD2 antibod(ies) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected anti-CD2 antibod(ies). 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. Another exemplary election would be an anti-CD2 antibody that encompasses CDR-H1, -H2, -H3 as set forth in SEQ ID NOs: 14, 15, 16, respectively; CDR-L1, -L2, -L3 as set forth in SEQ ID NOs: 18, 19, 20, respectively (claims 140-142).

Group III+: Claims 169-177, 186-198, 203-205, 218-226, drawn to a method of administering an anti-CD2 antibody to a patient to deplete a population of CD2+ cells and a method of treating a disorder. Group III+ will be searched upon payment of additional fees. The method may be searched, for example, to the extent that the anti-CD2 antibody encompasses CDR-H1, -H2, -H3 as set forth in SEQ ID NOs: 1, 2, 3, respectively; CDR-L1, -L2, -L3 as set forth in SEQ ID NOs: 4, 5, 6, respectively; VH SEQ ID NO: 7; VL SEQ ID NO: 8; and the disorder encompasses a myelodysplastic disorder; for an additional fee and election as such. It is believed that claims 169-177, 186-198, 203 read on this exemplary invention. Additional anti-CD2 antibod(ies) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected anti-CD2 antibod(ies). 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. Another exemplary election would be an anti-CD2 antibody that encompasses CDR-H1, -H2, -H3 as set forth in SEQ ID NOs: 14, 15, 16, respectively; CDR-L1, -L2, -L3 as set forth in SEQ ID NOs: 18, 19, 20, respectively; VH SEQ ID NO: 21; and VL SEQ ID NO: 22; and the disorder encompasses an immunodeficiency disorder (claims 169-177, 186-198, 203-205, 218).

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:

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

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-9, 11, 83-89, (115-116)/(83-89) limited to SEQ 1-8, stem cell disorder

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/63171

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

1. Statement

Novelty (N)	Claims	2-5, 7--9, 11, 83-89, (115-116)/(83-89)	YES
	Claims	1, 6	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-9, 11, 83-89, (115-116)/(83-89)	NO
Industrial applicability (IA)	Claims	1-9, 11, 83-89, (115-116)/(83-89)	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims.1, 6 lack novelty under PCT Article 33(2) as being anticipated by US 2011/0280868 A1 to Dingivan et al. (hereinafter 'Dingivan').

Regarding claim 1, Dingivan teaches a method of depleting a population of CD2+ cells in a human patient, the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen binding fragment thereof (para [0023], the use of MEDI-507, an analog, derivative or an antigen-binding fragment thereof as a single agent therapy for the prevention, treatment, management, or amelioration of cancer, particularly a T-cell malignancy.; [0115], In a specific embodiment, CD2 antagonists mediate the depletion of lymphocytes, in particular peripheral blood T-cells, in a subject with a T-cell malignancy.; [0237], human or humanized antibodies are administered to a human patient for therapy or prophylaxis.), wherein the antibody, or antigen-binding fragment thereof is conjugated to a cytotoxin (para [0161], an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response....., for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin.).

Regarding claim 6, Dingivan teaches a method comprising:
i) administering to a human patient an antibody, or antigen-binding fragment thereof, that binds to CD2 in an amount sufficient to deplete a population of CD2+ cells in the patient, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin (para [0023], the use of MEDI-507, an analog, derivative or an antigen-binding fragment thereof as a single agent therapy for the prevention, treatment, management, or amelioration of cancer, particularly a T-cell malignancy; [0024], Examples of therapeutic agents which may be conjugated to MEDI-507, an analog, derivative or an antigen-binding fragment thereof include, but are not limited to, cytokines, toxins, radioactive elements, and antimetabolites.; [0115], In a specific embodiment, CD2 antagonists mediate the depletion of lymphocytes, in particular peripheral blood T-cells, in a subject with a T-cell malignancy.), and
ii) subsequently administering to the patient a transplant comprising hematopoietic stem cells (para [0188], administering to a subject in need thereof a prophylactically or therapeutically effective amount of MEDI-507,....in combination with administration a prophylactically or therapeutically effective amount of other therapies used for ATL (adult T cell leukemia) therapy, including but not limited to:....Interferon-alpha therapy following autologous peripheral blood stem cell transplantation (Fujiwara H., et al., 2002, Acta Haematol., 107:213-219).).

Claims 2-5, (7-9, 11)/(2-5) lack an inventive step under PCT Article 33(3) as being obvious over US 7,592,006 B1 to Bazin et al. (hereinafter 'Bazin'), in view of Dingivan, as applied above.

Regarding claim 2, Bazin teaches a method of depleting a population of CD2+ cells in a human patient in need of a hematopoietic stem cell transplant (col 6, ln 20-28, antibodies of the present invention have
the characteristics of binding to an epitope of a CD2 antigen (CD2 positive human T-cells)....to inhibit T-cell activation or proliferation.; col 9, ln 50-61, LO-CD2a antibody or other molecule of the present invention is administered in vivo in an amount effective to inhibit graft rejection.), the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen- binding fragment thereof (col 21, ln 53-67, The patient who was suffering from severe graft versus host disease (severe skin, gut, renal and CNS toxicity resistant to high dose prednisone) after an allogeneic bone marrow transplant received 12 days of LO-CD2a at 10 mg/day. His symptoms improved.). Bazin does not specifically teach wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin. Dingivan teaches a method depleting a population of CD2+ cells in a human patient, the method comprising administering to the patient an effective amount of an anti-CD2 antibody (para [0115], In a specific embodiment, CD2 antagonists mediate the depletion of lymphocytes, in particular peripheral blood T-cells, in a subject with a T-cell malignancy.) wherein said CD2 antagonist can be conjugated to toxins (para [0161], an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response....., for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin.). It would have been obvious to one of ordinary skill in the art to have applied the CD2-toxin immunoconjugate of Dingivan to the method of Bazin, facilitating the process of depleting a population of CD2+ T cells.

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

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/63171

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. IV. Lack of unity of invention

Special Technical Features

Groups I+ include the special technical feature of a method of treating a disorder comprising administering an antibody-cytotoxin conjugate, not required by Groups II+ and III+.

Groups II+ include the special technical feature of a composition comprising antibody cytotoxin conjugate, not required by Groups I+ and III+.

Groups III+ include the special technical feature of a method of treating a disorder comprising administering an antibody, not required by Groups I+ and II+.

The inventions of Groups I+ and III+ each include the special technical feature of a specific disorder, recited therein, not required by any of the other inventions of Groups I+ or III+.

No technical features are shared between the amino acid sequences of anti-CD2 antibodies of Groups I+, II+ and III+ and, accordingly, these groups lack unity a priori.

Common Technical Features

The inventions of Groups I+, II+ and III+ share the technical features of an anti-CD2 antibody.

The inventions of Groups I+ and III+ share the technical features of depleting CD2+ cells, transplanting hematopoietic stem cells, and a method of treating a disorder.

However, these shared technical features do not represent a contribution over prior art in view of US 2011/0280868 A1 to Dingivan et al. (hereinafter 'Dingivan').

Dingivan teaches (instant claim 6) a method comprising: i) administering to a human patient an antibody, or antigen-binding fragment thereof, that binds to CD2 in an amount sufficient to deplete a population of CD2+ cells in the patient, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin (para [0023], the use of MEDI-507, an analog, derivative or an antigen-binding fragment thereof as a single agent therapy for the prevention, treatment, management, or amelioration of cancer, particularly a T-cell malignancy; [0024], Examples of therapeutic agents which may be conjugated to MEDI-507, an analog, derivative or an antigen-binding fragment thereof include, but are not limited to, cytokines, toxins, radioactive elements, and antimetabolites.; [0115], In a specific embodiment, CD2 antagonists mediate the depletion of lymphocytes, in particular peripheral blood T-cells, in a subject with a T-cell malignancy.), and
ii) subsequently administering to the patient a transplant comprising hematopoietic stem cells (para [0188], administering to a subject in need thereof a prophylactically or therapeutically effective amount of MEDI-507,....in combination with administration a prophylactically or therapeutically effective amount of other therapies used for ATL (adult T cell leukemia) therapy, including but not limited to:....Interferon-alpha therapy following autologous peripheral blood stem cell transplantation (Fujiwara H., et al., 2002, Acta Haematol., 107:213-219).).

Dingivan teaches (instant claim 83) a method of treating a stem cell disorder in a human patient (para [0060], human; [0342], hematological events (anemia, lymphopenia, leukopenia, thrombocytopenia).), the method comprising administering to the patient a therapeutically effective amount of an antibody, or antigen binding fragment thereof, that binds to CD2, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin (para [0023]-[0024]).

Dingivan teaches (instant claim 140) a conjugate represented by the formula Ab-Z-L-Cy, wherein Ab is an antibody or antigen-binding fragment thereof that binds CD2, Z is a chemical moiety, L is a linker, and Cy is a cytotoxin (para [0161], an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety.... for example, a toxin such as abrin, ricin A, pseudomonas exotoxin.; [0162], an antibody can be conjugated to therapeutic moieties such as...which can be attached to the antibody via a linker molecule.). Although Dingivan does not specifically teach Z (a chemical moiety), however, it is well known to one of ordinary skill in the art that a bifunctional linker comprises reactive moieties on both ends.

The inventions of Groups III+ further share the technical features of claims 174 and 203. However, these shared technical features do not represent a contribution over prior art in view of US 6,558,662 B2 to Sykes et al. (hereinafter 'Sykes').

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

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/63171

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. IV. Lack of unity of invention

Sykes teaches (instant claim 174) a method comprising:
a. administering to a human patient an antibody, or antigen-binding fragment thereof, that binds to CD2 in an amount sufficient to deplete a population of CD2+ cells in the patient (col 1, ln 57 to col 2, ln 23, a method for treating a subject having a hematologic disorder comprising: (i) administering a myeloreductive nonmyeloablative treatment to the subject in sufficient amount such that mixed hematopoietic chimerism can be induced in the subject,....the myeloreductive treatment includes treating the subject with an immunosuppressant regimen, prior to introduction of the donor stem cells, in an amount sufficient to prevent rejection of the donor stem cells. Such immunosuppressant regimens can include...Lo-CD2a.; col 11, ln 16-32, the administration of anti-T cell antibodies, e.g.,....polyclonal or monoclonal antibody directed against CD4, CD8, or CD2 (an anti-CD2 antibody, e.g., the anti-CD2 monoclonal antibody BTI-322 or a humanized version thereof, or an antibody which overlaps or binds the epitope recognized by BTI-322, are particularly useful).; col 12, ln 12-27, Typically, a pre-stem cell treatment, e.g., the administration of antibodies,....and about 80, 90, or 99% depletion of peripheral T cells and then to perform the stem cell transplantation.); and
b. subsequently administering to the patient a transplant comprising hematopoietic stem cells. (col 1, ln 57-65, a method for treating a subject having a hematologic disorder comprising: ..and (ii) introducing into the subject, allogeneic donor hematopoietic stem cells (donor stem cells) to form chimeric bone marrow in the subject.).

Sykes teaches (instant claim 203) wherein the patient is suffering from a myelodysplastic disorder or an immunodeficiency disorder (col 3, ln 19-27, the present invention can be used to treat a wide range of hematologic disorders, including neoplastic proliferation of hematopoetic cells, such as....myelodysplastic syndrome.).

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

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

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/63171

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V2. Citations and explanation

Regarding claim 3, Bazin teaches a method of preventing rejection of a hematopoietic stem cell graft in a human patient in need of a hematopoietic stem cell transplant (col 6, ln 20-28, antibodies of the present invention have the characteristics of binding to an epitope of a CD2 antigen (CD2 positive human T-cells)....to inhibit T-cell activation or proliferation.; col 9, ln 50-61, LO-CD2a antibody or other molecule of the present invention is administered in vivo in an amount effective to inhibit graft rejection.), the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof (col 21, ln 53-67, The patient who was suffering from severe graft versus host disease (severe skin, gut, renal and CNS toxicity resistant to high dose prednisone) after an allogeneic bone marrow transplant received 12 days of LO-CD2a at 10 mg/day. His symptoms improved.), prior to the human patient receiving a transplant comprising hematopoietic stem cells (col 10, ln 1-14, Such treatment for graft rejection is preferably started at, or immediately prior to, or shortly after transplantation or when graft rejection occurs.). Bazin does not specifically teach wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.
Dingivan teaches a method depleting a population of CD2+ cells in a human patient, the method comprising administering to the patient an effective amount of an anti-CD2 antibody (para [0115], In a specific embodiment, CD2 antagonists mediate the depletion of lymphocytes, in particular peripheral blood T-cells, in a subject with a T-cell malignancy.) wherein said CD2 antagonist can be conjugated to toxins (para [0161], an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response....., for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin.). It would have been obvious to one of ordinary skill in the art to have applied the CD2-toxin immunoconjugate of Dingivan to the method of Bazin, facilitating the process of depleting a population of CD2+ T cells.

Regarding claim 4. Bazin teaches a method of depleting a population of CD2+ cells in a human patient in need of a hematopoietic stem cell transplant (col 6, ln 20-28, antibodies of the present invention have the characteristics of binding to an epitope of a CD2 antigen (CD2 positive human T-cells)....to inhibit T-cell activation or proliferation.; col 9, ln 50-61, LO-CD2a antibody or other molecule of the present invention is administered in vivo in an amount effective to inhibit graft rejection.), the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof (col 21, ln 53-67, The patient who was suffering from severe graft versus host disease (severe skin, gut, renal and CNS toxicity resistant to high dose prednisone) after an allogeneic bone marrow transplant received 12 days of LO-CD2a at 10 mg/day. His symptoms improved.), prior to the patient receiving a transplant comprising hematopoietic stem cells (col 10, ln 1-14, Such treatment for graft rejection is preferably started at, or immediately prior to, or shortly after transplantation or when graft rejection occurs.). Bazin does not specifically teach wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.
Dingivan teaches a method depleting a population of CD2+ cells in a human patient, the method comprising administering to the patient an effective amount of an anti-CD2 antibody (para [0115], In a specific embodiment, CD2 antagonists mediate the depletion of lymphocytes, in particular peripheral blood T-cells, in a subject with a T-cell malignancy.) wherein said CD2 antagonist can be conjugated to toxins (para [0161], an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response....., for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin.). It would have been obvious to one of ordinary skill in the art to have applied the CD2-toxin immunoconjugate of Dingivan to the method of Bazin, facilitating the process of depleting a population of CD2+ T cells.

Regarding claim 5, Bazin teaches a method comprising administering to a human patient a transplant comprising hematopoietic stem cells (col 21, ln 53-67, The patient who was suffering from severe graft versus host disease (severe skin, gut, renal and CNS toxicity resistant to high dose prednisone) after an allogeneic bone marrow transplant received 12 days of LO-CD2a at 10 mg/day. His symptoms improved.), wherein the patient has been previously administered an anti-CD2 antibody or antigen-binding fragment thereof (col 10, ln 1-14, Such treatment for graft rejection is preferably started at, or immediately prior to, or shortly after transplantation or when graft rejection occurs.), in an amount sufficient to deplete a population of
CD2+ cells in the patient (col 6, ln 20-28, antibodies of the present invention have the characteristics of binding to an epitope of a CD2 antigen (CD2 positive human T-cells)....to inhibit T-cell activation or proliferation.; col 9, ln 50-61, LO-CD2a antibody or other molecule of the present invention is administered in vivo in an amount effective to inhibit graft rejection.). Bazin does not specifically teach wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.
Dingivan teaches a method depleting a population of CD2+ cells in a human patient, the method comprising administering to the patient an effective amount of an anti-CD2 antibody (para [0115], In a specific embodiment, CD2 antagonists mediate the depletion of lymphocytes, in particular peripheral blood T-cells, in a subject with a T-cell malignancy.) wherein said CD2 antagonist can be conjugated to toxins (para [0161], an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response....., for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin.). It would have been obvious to one of ordinary skill in the art to have applied the CD2-toxin immunoconjugate of Dingivan to the method of Bazin, facilitating the process of depleting a population of CD2+ T cells.

Regarding claim 7/(2-5), Bazin and Dingivan teach the method of any one of claims 2-5, wherein the antibody or antigen-binding fragment thereof is produced by the hybridoma cell line ATCC HB 11423 (Bazin, col 6, ln 36-43, A cell line which produces LO-CD2a, was....given the ATCC accession number ATCC HB 11423.).

Regarding claim 8/(2-5), Bazin and Dingivan teach the method of any one of claims 2-5, wherein the antibody or antigen-binding fragment thereof comprises antibody LO-CD2A produced by the hybridoma cell line having ATCC accession number HB 11423 (Bazin, col 6, ln 36-43, A cell line which produces LO-CD2a, was....given the ATCC accession number ATCC HB 11423.; col 5, ln 25-35, Amino acid sequences of the light chain variable region of...humanized LO-CD2a (SEQ ID NO:88).....Amino acid sequences of the heavy chain variable region of....humanized LO-CD2a (SEQ ID NO:93).).

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

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/63171

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V2. Citations and explanation

Regarding claim 9/(2-5), Bazin and Dingivan teach the method of any one of claims 2-5, wherein the antibody, or antigen-binding fragment thereof, is iii) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 7 (Bazin, col 5, ln 25-35, Amino acid sequences of the heavy chain variable region of....humanized LO-CD2a (SEQ ID NO:93).; 100% match to claimed SEQ ID NO: 7.) and comprising a light chain variable region as set forth in SEQ ID NO: 8 (Bazin, col 5, ln 25-35, Amino acid sequences of the light chain variable region of...humanized LO-CD2a (SEQ ID NO:88).; 100% match to claimed SEQ ID NO: 8.).

Regarding claim 11/(2-5), Bazin and Dingivan teach the method of any one of claims 2-5, wherein the antibody or antigen-binding fragment thereof is a monoclonal antibody (Bazin, col 6, ln 3-14, a monoclonal antibody or fragment thereof) which binds to the same epitope (or a portion thereof) on human lymphocytes as the monoclonal antibody produced by the cell line deposited as ATCC Deposit No. HB 11423.).

Claims (7-9, 11)/(1,6) lack an inventive step under PCT Article 33(3) as being obvious over Dingivan, in view of Bazin, as applied above.

Regarding claim 7/(1,6), Dingivan teaches the method of any one of claims 1, 6, but does not specifically teach wherein the antibody or antigen-binding fragment thereof is produced by the hybridoma cell line ATCC HB 11423. Bazin teaches an anti-CD2 antibody that is produced by the hybridoma cell line ATCC HB 11423 (col 6, ln 36-43, A cell line which produces LO-CD2a, was....given the ATCC accession number ATCC HB 11423.). It would have been obvious to one of ordinary skill in the art to have applied the anti-CD2 antibody of Bazin to the method of Dingivan, as said antibody is well known to one of ordinary skill in the art.

Regarding claim 8/(1,6), Dingivan teaches the method of any one of claims 1, 6, but does not specifically teach wherein the antibody or antigen-binding fragment thereof comprises antibody LO-CD2A produced by the hybridoma cell line having ATCC accession number HB 11423. Bazin teaches a heavy chain variable region CDR set (CDR1, CDR2, and CDR3) and a light chain variable region CDR set (CDR1, CDR2, and CDR3) of antibody LO-CD2A produced by the hybridoma cell line having ATCC accession number HB 11423 (col 6, ln 36-43, A cell line which produces LO-CD2a, was....given the ATCC accession number ATCC HB 11423.; col 5, ln 25-35, Amino acid sequences of the light chain variable region of...humanized LO-CD2a (SEQ ID NO:88).....Amino acid sequences of the heavy chain variable region of....humanized LO-CD2a (SEQ ID NO:93).). It would have been obvious to one of ordinary skill in the art to have applied the anti-CD2 antibody of Bazin to the method of Dingivan, as said antibody is well known to one of ordinary skill in the art.

Regarding claim 9/(1,6), Dingivan teaches the method of any one of claims 1, 6, but does not specifically teach wherein the antibody, or antigen-binding fragment thereof, is iii) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 7 and comprising a light chain variable region as set forth in SEQ ID NO: 8.
Bazin teaches an anti-CD2 antibody, LO-CD2a, comprising a heavy chain variable region as set forth in SEQ ID NO: 7 (col 5, ln 25-35, Amino acid sequences of the heavy chain variable region of....humanized LO-CD2a (SEQ ID NO:93).; 100% match to claimed SEQ ID NO: 7.) and comprising a light chain variable region as set forth in SEQ ID NO: 8 (col 5, ln 25-35, Amino acid sequences of the light chain variable region of...humanized LO-CD2a (SEQ ID NO:88).; 100% match to claimed SEQ ID NO: 8.). It would have been obvious to one of ordinary skill in the art to have applied the anti-CD2 antibody of Bazin to the method of Dingivan, as said antibody is well known to one of ordinary skill in the art.

Regarding claim 11/(1,6), Dingivan teaches the method of any one of claims 1, 6, but does not specifically teach wherein the antibody or antigen-binding fragment thereof is a monoclonal antibody. Bazin teaches a monoclonal anti-CD2 antibody (col 6, ln 3-14, a monoclonal antibody or fragment thereof) which binds to the same epitope (or a portion thereof) on human lymphocytes as the monoclonal antibody produced by the cell line deposited as ATCC Deposit No. HB 11423.). It would have been obvious to one of ordinary skill in the art to have applied the anti-CD2 antibody of Bazin to the method of Dingivan, as said antibody is well known to one of ordinary skill in the art.

Claims 83-89 lack an inventive step under PCT Article 33(3) as being obvious over US 6,558,662 B2 to Sykes et al. (hereinafter 'Sykes'), in view of Dingivan, as applied above.

Regarding claim 83, Sykes teaches a method of treating a stem cell disorder in a human patient (col 1, ln 58-65, a method for treating a subject having a hematologic disorder comprising: (i) administering a myeloreductive non-myeloablative treatment to the subject..., and (ii) introducing into the subject, allogeneic donor hemato poietic stem cells (donor stem cells).), the method comprising administering to the patient a therapeutically effective amount of an antibody, or antigen binding fragment thereof, that binds to CD2 (col 2, ln 9-19, Such immunosuppressant regimens can include, independently for pre- and post-transplantation....depletes host T-lymphocytes and/or natural killer (NK) cells in the subject....includes treatment with T cell-depleting....LO-CD2a.). Sykes does not specifically teach wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.
Dingivan teaches a method depleting a population of CD2+ cells in a human patient, the method comprising administering to the patient an effective amount of an anti-CD2 antibody (para [0115], In a specific embodiment, CD2 antagonists mediate the depletion of lymphocytes, in particular peripheral blood T-cells, in a subject with a T-cell malignancy.) wherein said CD2 antagonist can be conjugated to toxins (para [0161], an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response....., for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin.). It would have been obvious to one of ordinary skill in the art to have applied the CD2-toxin immunoconjugate of Dingivan to the method of Sykes, facilitating the process of depleting a population of CD2+ T cells.

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

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/63171

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V2. Citations and explanation

Regarding claim 84, Sykes teaches a method of treating a hemoglobinopathy disorder in a human patient (col 3, ln 28-35, For example, the instant method can be used to treat hemoglobinopathies, e.g., sickle cell anemia, aplastic anemia or thalassemia.), the method comprising administering to the patient a therapeutically effective amount of an antibody, or antigen-binding fragment thereof, that binds to CD2 (col 2, ln 9-19, Such immunosuppressant regimens can include, independently for pre- and post-transplantation....depletes host T-lymphocytes and/or natural killer (NK) cells in the subject....includes treatment with T cell-depleting....LO-CD2a.). Sykes does not specifically teach wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.
Dingivan teaches a method depleting a population of CD2+ cells in a human patient, the method comprising administering to the patient an effective amount of an anti-CD2 antibody (para [0115], In a specific embodiment, CD2 antagonists mediate the depletion of lymphocytes, in particular peripheral blood T-cells, in a subject with a T-cell malignancy.) wherein said CD2 antagonist can be conjugated to toxins (para [0161], an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response....., for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin.). It would have been obvious to one of ordinary skill in the art to have applied the CD2-toxin immunoconjugate of Dingivan to the method of Sykes, facilitating the process of depleting a population of CD2+ T cells.

Regarding claim 85, Sykes and Dingivan teach the method of claim 84, wherein the hemoglobinopathy disorder is selected from the group consisting of sickle cell anemia, thalassemia, Fanconi anemia, aplastic anemia, and Wiskott-Aldrich syndrome (Sykes, col 3, ln 28-35).

Regarding claim 86, Sykes and Dingivan teach the method of claim 84, comprising treating the hemoglobinopathy disorder (Sykes, col 3, ln 28-35). Although Sykes does not specifically teach Fanconi anemia, however, it would have been obvious to one of ordinary skill in the art to have determined whether anti-CD2 antibody can be used to treat Fanconi anemia, given that Sykes teaches that anti-CD2 antibody can be used to treat sickle cell anemia, thalassemia, and aplastic anemia.

Regarding claim 87, Sykes and Dingivan teach the method of claim 84, wherein the hemoglobinopathy disorder is aplastic anemia (Sykes, col 3, ln 28-35).

Regarding claim 88, Sykes and Dingivan teach the method of claim 84, wherein the hemoglobinopathy disorder is sickle cell anemia (Sykes, col 3, ln 28-35).

Regarding claim 89, Sykes and Dingivan teach the method of claim 84, wherein the hemoglobinopathy disorder is thalassemia (Sykes, col 3, ln 28-35).

Claims (115-116)/(83-89) lack an inventive step under PCT Article 33(3) as being obvious over Sykes and Dingivan, in view of Bazin, as applied above.

Regarding claim 115/(83-89), Sykes and Dingivan teach the method of any one of claims 83-89, but does not specifically teach wherein the antibody or antigen-binding fragment thereof is produced by the hybridoma cell line ATCC HB 11423. Bazin teaches an anti-CD2 antibody that is produced by the hybridoma cell line ATCC HB 11423 (col 6, ln 36-43, A cell line which produces LO-CD2a, was....given the ATCC accession number ATCC HB 11423.). It would have been obvious to one of ordinary skill in the art to have applied the anti-CD2 antibody of Bazin to the method of Sykes and Dingivan, as said antibody is well known to one of ordinary skill in the art.

Regarding claim 116/(83-89), Dingivan teaches the method of any one of claims 1, 6, but does not specifically teach wherein the antibody, or antigen-binding fragment thereof, is iii) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 7 and comprising a light chain variable region as set forth in SEQ ID NO: 8.
Bazin teaches an anti-CD2 antibody, LO-CD2a, comprising a heavy chain variable region as set forth in SEQ ID NO: 7 (col 5, ln 25-35, Amino acid sequences of the heavy chain variable region of....humanized LO-CD2a (SEQ ID NO:93).; 100% match to claimed SEQ ID NO: 7.) and comprising a light chain variable region as set forth in SEQ ID NO: 8 (col 5, ln 25-35, Amino acid sequences of the light chain variable region of...humanized LO-CD2a (SEQ ID NO:88).; 100% match to claimed SEQ ID NO: 8.). It would have been obvious to one of ordinary skill in the art to have applied the anti-CD2 antibody of Bazin to the method of Dingivan, as said antibody is well known to one of ordinary skill in the art.

Claims 1-9, 11, 83-89, (115-116)/(83-89) have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.