

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

26 APR 2019

Applicant's or agent's file reference
M103034-1060

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 18/63175

International filing date (day/month/year)

29 November 2018 (29.11.2018)

Priority date (day/month/year)

29 November 2017 (29.11.2017)

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

IPC(8) - A61K 39/395, C07K 16/28 (2019.01)

CPC - A61K 35/28, A61K 39/395, A61L 27/3804, C07K 16/2866, C07K 16/2896, G01N 33/6854, A61K 2039/505

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 43bis.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 66.1bis(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
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

31 March 2019

Authorized officer

Lee W. Young

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

**WRITTEN OPINION OF THE
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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ 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. ☒ 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. ☒ forming part of the international application as filed:
 - ☒ 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:

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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. 13-85, 123-141, 148-166, 179-233

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. (please see below) are so unclear that no meaningful opinion could be formed (*specify*):

Claims 13-85, 123-141, 148-166, 179-233 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. 13-85, 123-141, 148-166, 179-233

- ☐ 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.

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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 1-12, 86-122, 167-178, drawn to a method of administering an anti-CD5 antibody or an anti-CD5 antibody-cytotoxin conjugate to a patient to deplete a population of CD5+ cells and a method of treating a disorder. The method will be searched to the extent that the anti-CD5 antibody encompasses CDR-H1, -H2, -H3 having SEQ ID NOs: 3, 4, 5, respectively; CDR-L1, -L2, -L3 having SEQ ID NOs: 6, 7, 8, respectively; VL SEQ ID NO: 1; and VH SEQ ID NO: 2; and the disorder encompasses stem cell disorder. It is believed that claims 1-10, 86-92, (118-120)(in part), 167-176 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 stem cell disorder. Additional anti-CD5 antibody(ies) and disorder(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected anti-CD5 antibody(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-CD5 antibody that encompasses CDR-H1, -H2, -H3 having SEQ ID NOs: 11, 12, 13, respectively; CDR-L1, -L2, -L3 having SEQ ID NOs: 14, 15, 16, respectively; VL SEQ ID NO: 9; and VH SEQ ID NO: 10; and that the disorder encompasses a myelodysplastic disorder (claims 1-8, 11, 12, 93, (118,121,122)(in part), 167-174, 177, 178).

Group II+: Claims 142-147, drawn to a conjugate represented by the formula anti-CD5-Cytotoxin. Group II+ will be searched upon payment of additional fees. The conjugate may be searched, for example, to the extent that the anti-CD5 antibody encompasses CDR-H1, -H2, -H3 having SEQ ID NOs: 3, 4, 5, respectively; CDR-L1, -L2, -L3 having SEQ ID NOs: 6, 7, 8, respectively; for an additional fee and election as such. It is believed that claims 142-144, 146, 147 read on this exemplary invention. Additional anti-CD5 antibody(ies) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected anti-CD5 antibody(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-CD5 antibody that encompasses CDR-H1, -H2, -H3 having SEQ ID NOs: 11, 12, 13, respectively; CDR-L1, -L2, -L3 having SEQ ID NOs: 14, 15, 16, respectively (claims 142-143, 145-147).

The inventions listed as Groups I+ and II+ 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+ include the special technical feature of a method of treating a disorder, not required by Groups II+.

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

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

No technical features are shared between the amino acid sequences of anti-CD5 antibodies of Groups I+ and II+ and, accordingly, these groups lack unity a priori.

-----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. 1-10, 86-92, (118-120)(in part), 167-176 limited to SEQ ID NOs: 1-8, stem cell disorder

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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				
Novelty (N)	Claims	3-5, 7-10, 87-92, (118-120)/(86-92), 169-171, 173-176	YES	
	Claims	1, 2, 6, 86, 167-168, 172	NO	
Inventive step (IS)	Claims	NONE	YES	
	Claims	1-10, 86-92, (118-120)/(86-92), 167-176	NO	
Industrial applicability (IA)	Claims	1-10, 86-92, (118-120)/(86-92), 167-176	YES	
	Claims	NONE	NO	
2. Citations and explanations:				
Claims 1, 2, 6, 86, 167-168, 172 lack novelty under PCT Article 33(2) as being anticipated by the article "Combined In Vitro And In Vivo T Lymphocyte Depletion For The Control Of Graft-Versus-Host Disease Following Haploidentical Marrow Transplant" by Henslee-Downey et al. (hereinafter 'Downey'). Regarding claim 1, Downey teaches a method of depleting a population of CD5+ cells in a human patient (pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient an effective amount of an anti-CD5 antibody or antigen binding fragment thereof (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)) wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin (pg 3, para 5, H65-RTA IT is a murine, CD5-specific, IgG1 mAb coupled by disulfide bonding to ricin A chain. It was prepared by the Xoma Corporation, Inc. (Berkeley, CA)). Regarding claim 2, Downey teaches a method of depleting a population of CD5+ cells in a human patient in need of a hematopoietic stem cell transplant (pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient an effective amount of an anti-CD5 antibody, or antigen-binding fragment (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)), wherein the antibody, or antigen binding fragment thereof, is conjugated to a cytotoxin (pg 3, para 5, H65-RTA IT is a murine, CD5-specific, IgG1 mAb coupled by disulfide bonding to ricin A chain. It was prepared by the Xoma Corporation, Inc. (Berkeley, CA)). Regarding claim 6, Downey teaches a method comprising: a. administering to a human patient an anti-CD5 antibody or antigen-binding fragment thereof, that binds to CD5, in an amount sufficient to deplete a population of CD5+ cells in the patient, wherein the antibody or antigen-binding fragment thereof (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)), is conjugated to a cytotoxin (pg 3, para 5, H65-RTA IT is a murine, CD5-specific, IgG1 mAb coupled by disulfide bonding to ricin A chain. It was prepared by the Xoma Corporation, Inc. (Berkeley, CA)); and b. subsequently administering to the patient a transplant comprising hematopoietic stem cells (pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)).				
-----continued in Supplemental Box-----				

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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

Additionally, even if Groups I+ were considered to share the technical features of including: a method of depleting CD5+ cells and a method of treating a disorder; and Groups II+ were considered to share the technical features of including: an anti-CD5-cytotoxin conjugate; these shared technical features are previously disclosed by the article "Selective Depletion of Bone Marrow T Lymphocytes With Anti-CD5 Monoclonal Antibodies: Effective Prophylaxis for Graft-Versus-Host Disease in Patients With Hematologic Malignancies" by Antin et al. (hereinafter 'Antin') (Blood, Vol 78, No 8 (October 15). 1991: pp 2139-2149).

Antin teaches (instant claim 6) a method comprising:

a. administering to a human patient an anti-CD5 antibody or antigen-binding fragment thereof, that binds to CD5, in an amount sufficient to deplete a population of CD5+ cells in the patient, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin (abstract, Seventy-one patients with hematologic malignancies received bone marrow from a histocompatible sibling (n = 48) or a partially matched relative (n = 23) that had been depleted of CD5+ T cells with...an anti-CD5 MoAb conjugated to ricin A chain (ST1 immunotoxin [ST1-IT]). Both anti-Leu1 + C and ST1-IT ex vivo treatments effectively depleted bone marrow of T cells (97% and 95% respectively).), and

b. subsequently administering to the patient a transplant comprising hematopoietic stem cells (abstract, pg 2142, col 2, para 2, ST1-IT, The average nucleated cell dose administered was 1.15 +/- 0.51 x 10.exp.8/kg. All patients initially engrafted.....Two of 27 (7%) MHC-matched and 1 of 12 (8%) MHC-mismatched patients had late graft failures.).

Antin teaches (instant claim 86) a method of treating a stem cell disorder in a human patient (pg 2144, col 2, para 2, Patients at "low risk" had ANLL or acute lymphocytic leukemia (ALL) in first remission, chronic myelogenous leukemia (CML) in stable phase, or refractory anemia.), the method comprising

administering to the patient a therapeutically effective amount of an anti-CD5 antibody or antigen binding fragment thereof, wherein the antibody, or antigen-binding fragment thereof, is conjugated

to a cytotoxin (abstract, Seventy-one patients with hematologic malignancies received bone marrow from a histocompatible sibling (n = 48) or a partially matched relative (n = 23) that had been depleted of CD5+ T cells with...an anti-CD5 MoAb conjugated to ricin A chain (ST1 immunotoxin [ST1-IT]).

Antin teaches (instant claim 142) a conjugate represented by the formula Ab-Cy, wherein Ab is an antibody or antigen-binding fragment thereof that binds CD5 and Cy is a cytotoxin (abstract, an anti-CD5 MoAb conjugated to ricin A chain (ST1 immunotoxin [ST1-IT])).

Antin teaches (instant claim 172) a method comprising:

a. administering to a human patient an anti-CD5 antibody or antigen-binding fragment thereof in an amount sufficient to deplete a population of CD5+ cells in the patient (abstract, Seventy-one patients with hematologic malignancies received bone marrow from a histocompatible sibling (n = 48)

or a partially matched relative (n = 23) that had been depleted of CD5+ T cells with either an anti-CD5 monoclonal antibody (MoAb) plus complement (anti-Leu1 + C)....Both anti-Leu1 + C and ST1-IT ex vivo treatments effectively depleted bone marrow of T cells (97% and 95% respectively).); and

b. subsequently administering to the patient a transplant comprising hematopoietic stem cells (abstract, pg 2142, col 2, para 2, ST1-IT, The average nucleated cell dose administered was 1.15 +/- 0.51 x 10.exp.8/kg. All patients initially engrafted.....Two of 27 (7%) MHC-matched and 1 of 12 (8%) MHC-mismatched patients had late graft failures.).

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

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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 86, Downey teaches a method of treating a stem cell disorder in a human patient (abstract, This carries an increased risk of graft failure and acute graft-versus-host disease (GVHD).; pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient a therapeutically effective amount of an anti-CD5 antibody or antigen binding fragment thereof (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)), wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin (pg 3, para 5, H65-RTA IT is a murine, CD5-specific, IgG1 mAb coupled by disulfide bonding to ricin A chain. It was prepared by the Xoma Corporation, Inc. (Berkeley, CA)).

Regarding claim 167, Downey teaches a method of depleting a population of CD5+ cells in a human patient (abstract, This carries an increased risk of graft failure and acute graft-versus-host disease (GVHD).; pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient an effective amount of an anti-CD5 antibody or antigen binding fragment thereof (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)).

Regarding claim 168, Downey teaches a method of depleting a population of CD5+ cells in a human patient in need of a hematopoietic stem cell transplant (abstract, This carries an increased risk of graft failure and acute graft-versus-host disease (GVHD).; pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient an effective amount of an anti-CD5 antibody, or antigen-binding fragment (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)).

Regarding claim 172, Downey teaches a method comprising:

- a. administering to a human patient an anti-CD5 antibody or antigen-binding fragment thereof in an amount sufficient to deplete a population of CD5+ cells in the patient (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)), is conjugated to a cytotoxin (pg 3, para 5, H65-RTA IT is a murine, CD5-specific, IgG1 mAb coupled by disulfide bonding to ricin A chain. It was prepared by the Xoma Corporation, Inc. (Berkeley, CA)); and
- b. subsequently administering to the patient a transplant comprising hematopoietic stem cells (pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)).

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

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box No. V2. Citations and explanation

Claims 3-5, 169-171 lack an inventive step under PCT Article 33(3) as being obvious over Downey, as applied above.

Regarding claim 3, Downey teaches a method of preventing rejection of a hematopoietic stem cell graft in a human patient in need of a hematopoietic stem cell transplant (abstract, This carries an increased risk of graft failure and acute graft-versus-host disease (GVHD).; pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient an effective amount of an anti-CD5 antibody, or antigen-binding fragment thereof, to the human patient receiving a transplant comprising hematopoietic stem cells (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)), wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin (pg 3, para 5, H65-RTA IT is a murine, CD5-specific, IgG1 mAb coupled by disulfide bonding to ricin A chain. It was prepared by the Xoma Corporation, Inc. (Berkeley, CA)).

Downey does not specifically teach administering anti-CD5 antibody prior to the human patient receiving a transplant. Downey further teaches that the incidence of GVHD is further reduced in patients receiving anti-CD5 antibody earlier (pg 5, para 2, The probability of developing > grade I acute GVHD was significantly reduced in the study group....There was a trend for a diminishing incidence of > grade I acute GVHD in patients given H65-RTA earlier posttransplant, occurring in 56% of patients in subgroup 1, 40% of patients in subgroup 2, and 17% of patients in subgroup 3, although this did not reach significance (P=0.12; Fig. 3A). see Fig. 1, subgroup 3 is started on day 5 post-BMT). Thus, it would have been obvious to one of ordinary skill in the art to have examined whether administering anti-CD5 antibody prior to graft would have further reduced the incidence of the risk of GVHD.

Regarding claim 4, Downey teaches a method of depleting a population of CD5+ cells in a human patient in need of a hematopoietic stem cell transplant (abstract, This carries an increased risk of graft failure and acute graft-versus-host disease (GVHD).; pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient an effective amount of an anti-CD5 antibody, or antigen-binding fragment thereof, to the patient receiving a transplant comprising hematopoietic stem cells (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)), wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin (pg 3, para 5, H65-RTA IT is a murine, CD5-specific, IgG1 mAb coupled by disulfide bonding to ricin A chain. It was prepared by the Xoma Corporation, Inc. (Berkeley, CA)).

Downey does not specifically teach administering anti-CD5 antibody prior to the human patient receiving a transplant. Downey further teaches that the incidence of GVHD is further reduced in patients receiving anti-CD5 antibody earlier (pg 5, para 2, The probability of developing > grade I acute GVHD was significantly reduced in the study group....There was a trend for a diminishing incidence of > grade I acute GVHD in patients given H65-RTA earlier posttransplant, occurring in 56% of patients in subgroup 1, 40% of patients in subgroup 2, and 17% of patients in subgroup 3, although this did not reach significance (P=0.12; Fig. 3A). see Fig. 1, subgroup 3 is started on day 5 post-BMT). Thus, it would have been obvious to one of ordinary skill in the art to have examined whether administering anti-CD5 antibody prior to graft would have further reduced the incidence of the risk of GVHD.

Regarding claim 5, Downey teaches a method comprising administering to a human patient a transplant comprising hematopoietic stem cells (abstract, This carries an increased risk of graft failure and acute graft-versus-host disease (GVHD).; pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient an effective amount of an anti-CD5 antibody, or, wherein the patient is administered an anti-CD5 antibody or antigen-binding fragment thereof, in an amount sufficient to deplete a population of CD5+ cells in the patient (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT)), wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin (pg 3, para 5, H65-RTA IT is a murine, CD5-specific, IgG1 mAb coupled by disulfide bonding to ricin A chain. It was prepared by the Xoma Corporation, Inc. (Berkeley, CA)).

Downey does not specifically teach that said patient has been administered an anti-CD5 antibody prior to the human patient receiving a transplant. Downey further teaches that the incidence of GVHD is further reduced in patients receiving anti-CD5 antibody earlier (pg 5, para 2, The probability of developing > grade I acute GVHD was significantly reduced in the study group....There was a trend for a diminishing incidence of > grade I acute GVHD in patients given H65-RTA earlier posttransplant, occurring in 56% of patients in subgroup 1, 40% of patients in subgroup 2, and 17% of patients in subgroup 3, although this did not reach significance (P=0.12; Fig. 3A). see Fig. 1, subgroup 3 is started on day 5 post-BMT). Thus, it would have been obvious to one of ordinary skill in the art to have examined whether administering anti-CD5 antibody prior to graft would have further reduced the incidence of the risk of GVHD.

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Continuation of:
Box No. V2. Citations and explanation

Regarding claim 169, Downey teaches a method of preventing rejection of a hematopoietic stem cell graft in a human patient in need of a hematopoietic stem cell transplant (abstract, This carries an increased risk of graft failure and acute graft-versus-host disease (GVHD).; pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient an effective amount of an anti-CD5 antibody, or antigen-binding fragment thereof, to the human patient receiving a transplant comprising hematopoietic stem cells (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)).

Downey does not specifically teach administering anti-CD5 antibody prior to the human patient receiving a transplant. Downey further teaches that the incidence of GVHD is further reduced in patients receiving anti-CD5 antibody earlier (pg 5, para 2, The probability of developing > grade I acute GVHD was significantly reduced in the study group,...There was a trend for a diminishing incidence of > grade I acute GVHD in patients given H65-RTA earlier posttransplant, occurring in 56% of patients in subgroup 1, 40% of patients in subgroup 2, and 17% of patients in subgroup 3, although this did not reach significance (P=0.12; Fig. 3A). see Fig. 1, subgroup 3 is started on day 5 post-BMT). Thus, it would have been obvious to one of ordinary skill in the art to have examined whether administering anti-CD5 antibody prior to graft would have further reduced the incidence of the risk of GVHD.

Regarding claim 170, Downey teaches a method of depleting a population of CD5+ cells in a human patient in need of a hematopoietic stem cell transplant (abstract, This carries an increased risk of graft failure and acute graft-versus-host disease (GVHD).; pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), the method comprising administering to the patient an effective amount of an anti-CD5 antibody, or antigen-binding fragment thereof, to the patient receiving a transplant comprising hematopoietic stem cells (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)).

Downey does not specifically teach administering anti-CD5 antibody prior to the human patient receiving a transplant. Downey further teaches that the incidence of GVHD is further reduced in patients receiving anti-CD5 antibody earlier (pg 5, para 2, The probability of developing > grade I acute GVHD was significantly reduced in the study group,...There was a trend for a diminishing incidence of > grade I acute GVHD in patients given H65-RTA earlier posttransplant, occurring in 56% of patients in subgroup 1, 40% of patients in subgroup 2, and 17% of patients in subgroup 3, although this did not reach significance (P=0.12; Fig. 3A). see Fig. 1, subgroup 3 is started on day 5 post-BMT). Thus, it would have been obvious to one of ordinary skill in the art to have examined whether administering anti-CD5 antibody prior to graft would have further reduced the incidence of the risk of GVHD.

Regarding claim 171, Downey teaches a method comprising administering to a human patient a transplant comprising hematopoietic stem cells (abstract, This carries an increased risk of graft failure and acute graft-versus-host disease (GVHD).; pg 3, para 2, The study group consisted of 40 consecutive patients accrued between August 1987 and January 1990 on a clinical trial....Study patients received conditioning therapy.....; pg 4, para 3, Patient characteristics are shown in Table 1. Most patients in both groups were transplanted for advanced hematologic malignancies), wherein the patient is administered an anti-CD5 antibody or antigen-binding fragment thereof, in an amount sufficient to deplete a population of CD5+ cells in the patient (abstract, This study of 40 patients used a novel approach combining in vitro and in vivo T cell depletion with T lymphocyte targeted monoclonal antibodies (mAb) and intensified conditioning therapy....Grafts were treated with T10B9.1A-31 mAb, directed against the alpha-beta heterodimer of the T cell receptor, and rabbit complement. In vivo depletion was attempted with an anti-CD5 mAb-Ricin A-chain (H65-RTA) immunotoxin (IT).; pg 3, para 4, The study group received H65-RTA beginning at 1 of 3 different time intervals (subgroups 1, 2, and 3) after BMT (bone marrow transplantation), at a daily dose of 0.1 mg/kg i.v. (Fig. 1)).

Downey does not specifically teach administering anti-CD5 antibody prior to the human patient receiving a transplant. Downey further teaches that the incidence of GVHD is further reduced in patients receiving anti-CD5 antibody earlier (pg 5, para 2, The probability of developing > grade I acute GVHD was significantly reduced in the study group,...There was a trend for a diminishing incidence of > grade I acute GVHD in patients given H65-RTA earlier posttransplant, occurring in 56% of patients in subgroup 1, 40% of patients in subgroup 2, and 17% of patients in subgroup 3, although this did not reach significance (P=0.12; Fig. 3A). see Fig. 1, subgroup 3 is started on day 5 post-BMT). Thus, it would have been obvious to one of ordinary skill in the art to have examined whether administering anti-CD5 antibody prior to graft would have further reduced the incidence of the risk of GVHD.

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Continuation of:
Box No. V2. Citations and explanation

Claims 87-88, 90, (118-120)/(87,88,90) lack an inventive step under PCT Article 33(3) as being obvious over US 5,770,196 A (Studnicka).

Regarding claim 87, Studnicka teaches a method of treating a hemoglobinopathy disorder in a human patient (col 15, In 46-64, Humanized antibodies of the present invention may be administered to patients with a disease having targetable cellular markers. Such diseases include, but are not limited to, autoimmune diseases such as.....aplastic anemia), the method comprising administering to the patient a therapeutically effective amount of an anti-CD5 antibody or antigen-binding fragment thereof (col 41, In 50-60, Systemic Lupus Erythematosus ("SLE"))....Some of the more frequent manifestations include fatigue, anemia,.....Anti-CD5 antibody prepared as described above is administered to patients at doses of about 0.005 to 2.0 mg/kg/day). Studnicka does not specifically teach wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin. However, Studnicka does teach an anti-CD5-cytotoxin conjugate (col 41, In 2-17, CD5 Plus, a murine H65 antibody linked to ricin toxin A). Given the potent cytotoxicity of said anti-CD5 immunoconjugate (col 41, Table 10), it would have been obvious to one of ordinary skill in the art to have administered anti-CD5 immunoconjugate to treat a hemoglobinopathy disorder.

Regarding claims 88, 90, Studnicka teaches the method of claim 87, wherein the hemoglobinopathy disorder is selected from aplastic anemia (col 15, In 46-64).

Regarding claims 118/(87,88,90), Studnicka teaches the method of any one of claims 87, 88, 90, but does not specifically teach wherein the antibody or antigen-binding fragment thereof is produced by the hybridoma cell line ATCC CRL 8000. Studnicka teaches an anti-CD5 antibody hybridoma cell line deposited in ATCC (Claim 13, said anti-CD5 immunoglobulin molecule is that produced by the hybridoma having ATCC Accession No. HB 11206). It would have been obvious to one of ordinary skill in the art to have deposited an anti-CD5 antibody hybridoma cell line in ATCC, as commonly practiced in the art.

Regarding claims 119/(87,88,90), Studnicka teaches the method of any one of claims 87, 88, 90, wherein the antibody or antigen-binding fragment thereof comprises:

- a. a VL having the amino acid sequence
DIQMTQSPSSMSASLGDRVTITCRASQDINSYLSWFQKPKGKSPKTLIYRANRLVDGVPSRFSGSGSGTDYTL
TISSLQYEDFGIYCCQQYDESPWTFGGGTKLEIK (SEQ ID NO: 1); and
- b. a VH having the amino acid sequence
QIQLVQSGPGLKPKGGSVRISCAASGYTFTNYGMNWWKQAPGKGLRWGMWI
NTHTGEPTYADDFKGRFTFSLDTSKSTAYLQINSLRAEDTATYFCTRRGYDWY
FDVWGQGTITVTVSS (SEQ ID NO: 2) (col 27, In 23-32, the sequences of the light and heavy chains of the H65 antibody variable domain....FIGS. 6A and 6B set out the amino acid sequences of humanized light (SEQ ID NO: 27) and heavy chains (SEQ ID NO: 29) of the H65 antibody variable domain. Note, SEQ ID NOs: 27 and 29 are 100% match to SEQ ID NOs: 1 and 2 of instant claim, respectively).

Regarding claims 120/(87,88,90), Studnicka teaches the method of any one of claims 87, 88, 90, wherein the antibody or antigen-binding fragment thereof comprises the following CDRs:

- a. a CDR-H1 having the amino acid sequence GYTFTNY (SEQ ID NO: 3) (amino acid residues 26-32 of SEQ ID NO: 29 displays 100% match);
- b. a CDR-H2 having the amino acid sequence NTHTGE (SEQ ID NO: 4) (amino acid residues 52-57 of SEQ ID NO: 29 displays 100% match);
- c. a CDR-H3 having the amino acid sequence RGYDWYFDV (SEQ ID NO: 5) (amino acid residues 99-107 of SEQ ID NO: 29 displays 100% match);
- d. a CDR-L1 having the amino acid sequence RASQDINSYLS (SEQ ID NO: 6) (amino acid residues 24-34 of SEQ ID NO: 27 displays 100% match);
- e. a CDR-L2 having the amino acid sequence RANRLVD (SEQ ID NO: 7) (amino acid residues 50-56 of SEQ ID NO: 27 displays 100% match); and
- f. a CDR-L3 having the amino acid sequence QQYDESPWT (SEQ ID NO: 8) (amino acid residues 89-97 of SEQ ID NO: 27 displays 100% match).

Claims 7-10, (118-120)/86, 173-176 lack an inventive step under PCT Article 33(3) as being obvious over Downey, in view of Studnicka.

Regarding claims 7, 118/86, 173, Downey teaches the method of any one of claims 1-6, 86 and 167-172, but does not specifically teach wherein the antibody or antigen-binding fragment thereof is produced by the hybridoma cell line ATCC CRL 8000. Studnicka teaches an anti-CD5 antibody hybridoma cell line deposited in ATCC (Claim 13, said anti-CD5 immunoglobulin molecule is that produced by the hybridoma having ATCC Accession No. HB 11206). It would have been obvious to one of ordinary skill in the art to have deposited an anti-CD5 antibody hybridoma cell line in ATCC, as commonly practiced in the art.

Regarding claims 8, 174, Downey teaches the method of any one of claims 1-6 and 167-172, but does not specifically teach wherein the antibody or antigen-binding fragment thereof comprises 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 OKT1 produced by the hybridoma cell line having ATCC accession number CRL 8000. Studnicka teaches an anti-CD5 antibody hybridoma cell line deposited in ATCC wherein said antibody comprises a heavy chain variable region CDR set (CDR1, CDR2, and CDR3) and a light chain variable region CDR set (CDR1, CDR2, and CDR3) of H65 (col 27, In 23-32, the sequences of the light and heavy chains of the H65 antibody variable domain....FIGS. 6A and 6B set out the amino acid sequences of humanized light (SEQ ID NO: 27) and heavy chains (SEQ ID NO: 29) of the H65 antibody variable domain). It would have been obvious to one of ordinary skill in the art to have deposited an anti-CD5 antibody of choice and the associated hybridoma cell line in ATCC, as commonly practiced in the art.

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Regarding claims 9, 119/86, 175, Downey teaches the method of any one of claims 1-6, 86 and 167-172, but does not specifically teach wherein said antibody or antigen-binding fragment thereof comprises VL of SEQ ID NO: 1 and VH of SEQ ID NO: 2. Studnicka teaches an anti-CD5 antibody H65 comprising a light chain variable domain SEQ ID NO: 27 and a heavy chain variable domain SEQ ID NO: 29 that is 100% match to:

a. a VL having the amino acid sequence
DIQMTQSPSSMSASLGDRVTITCRASQDINSYLSWFQQKPGKSPKTLIYRANRLVDGVPSRFSGSGSGTDYTL
TISSLQYEDFGIYYCQQYDESPWTFGGGTKLEIK (SEQ ID NO: 1); and

b. a VH having the amino acid sequence
QIQLVQSGPGLKKPGGSRISCAASGYTFTNYGMNWWKQAPGKGLRWMGWI
NTHTGEPTYADDFKGRFTFSLDTSKSTAYLQINSLRAEDTATYFCTRRGYDWY
FDVWGQGTITVTVSS (SEQ ID NO: 2) (col 27, In 23-32, the sequences of the light and heavy chains of the H65 antibody variable domain....FIGS. 6A and 6B set out the amino acid sequences of humanized light (SEQ ID NO: 27) and heavy chains (SEQ ID NO: 29) of the H65 antibody variable domain). It would have been obvious to one of ordinary skill in the art to have applied the H65 antibody of Studnicka to the method of Downey, as the amino acid sequences of VL and VH of H65 antibody are known.

Regarding claims 10, 120/86, 176, Downey teaches the method of any one of claims 1-6, 86 and 167-172, but does not specifically teach wherein said antibody or antigen-binding fragment thereof comprises CDR-H1-H3 and CDR-L1-L3 of SEQ ID NOs: 3, 4, 5, 6, 7, 8. Studnicka teaches an anti-CD5 antibody H65 comprising a light chain variable domain SEQ ID NO: 27 and a heavy chain variable domain SEQ ID NO: 29 (col 27, In 23-32, the sequences of the light and heavy chains of the H65 antibody variable domain....FIGS. 6A and 6B set out the amino acid sequences of humanized light (SEQ ID NO: 27) and heavy chains (SEQ ID NO: 29) of the H65 antibody variable domain); wherein

a. amino acid residues 26-32 of SEQ ID NO: 29 is 100% match to CDR-H1 having the amino acid sequence GYTFTNY (SEQ ID NO: 3);
b. amino acid residues 52-57 of SEQ ID NO: 29 is 100% match to CDR-H2 having the amino acid sequence NTHTGE (SEQ ID NO: 4);
c. amino acid residues 99-107 of SEQ ID NO: 29 is 100% match to CDR-H3 having the amino acid sequence RGYDWYFDV (SEQ ID NO: 5);
d. amino acid residues 24-34 of SEQ ID NO: 27 is 100% match to CDR-L1 having the amino acid sequence RASQDINSYLS (SEQ ID NO: 6);
e. amino acid residues 50-56 of SEQ ID NO: 27 is 100% match to CDR-L2 having the amino acid sequence RANRLVD (SEQ ID NO: 7);
and
f. amino acid residues 89-97 of SEQ ID NO: 27 is 100% match to CDR-L3 having the amino acid sequence QQYDESPWT (SEQ ID NO: 8).

It would have been obvious to one of ordinary skill in the art to have applied the H65 antibody of Studnicka to the method of Downey, as the amino acid sequences of VL and VH of H65 antibody are known.

Claims 89, 91, 92, (118-120)/(89,91,92) lack an inventive step under PCT Article 33(3) as being obvious over Studnicka, in view of US 2015/0004145 A1 to Icahn School of Medicine at Mount Sinai (hereinafter 'ISMMS').

Regarding claims 89, 91 and 92, Studnicka teaches the method of claim 87, but does not specifically teach wherein the hemoglobinopathy disorder is Fanconi anemia, sickle cell anemia, or thalassemia. Studnicka further teaches that anti-CD5 antibody can be used to treat GVHD disorder (Claim 1, A method of depleting CD5+ cells in an animal comprising the step of administering, to said animal, an effective amount of a cytotoxic protein that comprises...an anti-CD5 immunoglobulin molecule.; col 4, In 32-35, T cell-mediated diseases such as graft-versus-host disease or tissue transplant rejection may be treated with proteins). ISMMS teaches that hemoglobinopathy disorder is Fanconi anemia, sickle cell anemia, or thalassemia can be benefited with hematopoietic stem cell transplantation (Claim 15, A method for treating a subject who suffers from a condition or a disease that would benefit from hematopoietic stem cell transplantation, wherein the condition or disease is selected from the group consisting of...aplastic anemia,...Fanconi anemia, Thalassemia major, sickle cell anemia). It would have been obvious to one of ordinary skill in the art to have administered anti-CD5 immunoconjugate to treat a hemoglobinopathy disorder such as Fanconi anemia, sickle cell anemia, or thalassemia.

Regarding claims 118/(89,91,92), Studnicka and ISMMS teaches the method of any one of claims 89, 91, 92, but does not specifically teach wherein the antibody or antigen-binding fragment thereof is produced by the hybridoma cell line ATCC CRL 8000. Studnicka teaches an anti-CD5 antibody hybridoma cell line deposited in ATCC (Claim 13, said anti-CD5 immunoglobulin molecule is that produced by the hybridoma having ATCC Accession No. HB 11206). It would have been obvious to one of ordinary skill in the art to have deposited an anti-CD5 antibody hybridoma cell line in ATCC, as commonly practiced in the art.

Regarding claims 119/(89,91,92), Studnicka and ISMMS teaches the method of any one of claims 89, 91, 92, wherein the antibody or antigen-binding fragment thereof comprises:

a. a VL having the amino acid sequence
DIQMTQSPSSMSASLGDRVTITCRASQDINSYLSWFQQKPGKSPKTLIYRANRLVDGVPSRFSGSGSGTDYTL
TISSLQYEDFGIYYCQQYDESPWTFGGGTKLEIK (SEQ ID NO: 1); and

b. a VH having the amino acid sequence
QIQLVQSGPGLKKPGGSRISCAASGYTFTNYGMNWWKQAPGKGLRWMGWI
NTHTGEPTYADDFKGRFTFSLDTSKSTAYLQINSLRAEDTATYFCTRRGYDWY
FDVWGQGTITVTVSS (SEQ ID NO: 2) (Studnicka, col 27, In 23-32, the sequences of the light and heavy chains of the H65 antibody variable domain....FIGS. 6A and 6B set out the amino acid sequences of humanized light (SEQ ID NO: 27) and heavy chains (SEQ ID NO: 29) of the H65 antibody variable domain. Note, SEQ ID NOs: 27 and 29 are 100% match to SEQ ID NOs: 1 and 2 of instant claim, respectively).

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Regarding claims 120/(89,91,92), Studnicka and ISMMs teaches the method of any one of claims 89, 91, 92, wherein the antibody or antigen-binding fragment thereof comprises the following CDRs:

- a. a CDR-H1 having the amino acid sequence GYTFTNY (SEQ ID NO: 3) (Studnicka, amino acid residues 26-32 of SEQ ID NO: 29 displays 100% match);
- b. a CDR-H2 having the amino acid sequence NTHTGE (SEQ ID NO: 4) (Studnicka, amino acid residues 52-57 of SEQ ID NO: 29 displays 100% match);
- c. a CDR-H3 having the amino acid sequence RGYDWYFDV (SEQ ID NO: 5) (Studnicka, amino acid residues 99-107 of SEQ ID NO: 29 displays 100% match);
- d. a CDR-L1 having the amino acid sequence RASQDINSYLS (SEQ ID NO: 6) (Studnicka, amino acid residues 24-34 of SEQ ID NO: 27 displays 100% match);
- e. a CDR-L2 having the amino acid sequence RANRLVD (SEQ ID NO: 7) (Studnicka, amino acid residues 50-56 of SEQ ID NO: 27 displays 100% match); and
- f. a CDR-L3 having the amino acid sequence QQYDESPWT (SEQ ID NO: 8) (Studnicka, amino acid residues 89-97 of SEQ ID NO: 27 displays 100% match).

Claims 1-10, 86-92, (118-120)/(86-92), 167-176 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.