(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
07 May 2020 (07.05.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/092694 A3

(51) International Patent Classification:
C12N 5/0789 (2010.01) *A61K 35/28* (2015.01)
A61K 35/12 (2015.01)

(21) International Application Number:
PCT/US2019/059039

(22) International Filing Date:
31 October 2019 (31.10.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/753,865 31 October 2018 (31.10.2018) US
62/860,866 13 June 2019 (13.06.2019) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
11 June 2020 (11.06.2020)

(54) Title: METHODS FOR HEMATOPOIETIC STEM AND PROGENITOR CELL TRANSPLANT THERAPY

(57) Abstract: Provided herein are compositions and methods useful for the transplantation of hematopoietic stem and progenitor cells, as well as for preparing patients for receipt of such therapy, such as patients suffering from a variety of inherited metabolic disorders.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference		FOR FURTHER ACTION
MGTX009001WO		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US19/59039	31 October 2019 (31.10.2019)	31 October 2018 (31.10.2018)
Applicant		
MAGENTA THERAPEUTICS INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   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).

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 19-82
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***- Please See within the Next Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Group I, Claims 1-3, 5-7, 10-17 and 18 (in-part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC - C12N 5/0789; A61K 35/12, 35/28 (2020.01)

CPC - C12N 5/0647; A61K 35/12, 35/28

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 1999/25367 A2 (THE GENERAL HOSPITAL CORPORATION) 27 May 1999; page 4, lines 11-16; page 16, lines 9-11; page 45, lines 23-29; claim 6	3 ------ 18/3
X -- Y	WO 2018/136606 A1 (PAPAYANNOPOULOU, T et al.) 26 July 2018; paragraphs [0025], [0028], [0066]; claims 1, 11	5-7, 10-12 ---------- 13-14, 18/5-7, 18/10-14
X -- Y	(XU, L et al.) The Consensus on Indications, Conditioning Regimen, and Donor Selection of Allogeneic Hematopoietic Cell Transplantation for Hematological Diseases in China—Recommendations from the Chinese Society of Hematology. Journal of Hematology and Oncology. 02 March 2018; Vol. 11, No. 1; pages 1-17; page 6, column 2, paragraph 2; page 10, column 1, paragraph 3; table 3; DOI: 10.1186/s13045-018-0564-x	15 ---------- 16-17, 18/15-17
Y	(FAULKNER, L et al.) ATG vs Thiotepa with Busulfan and Cyclophosphamide in Matched-Related Bone Marrow Transplantation for Thalassemia. Blood Advances. 23 May 2017; Vol. 1, No. 13; pages 792-801; abstract; page 793, column 2, paragraph 3; DOI: 10.1182/bloodadvances.2016004119	13-14, 16-17, 18/13-14, 18/16-17
Y	(HARRIS, LM et al.) Busulfan, Cyclophosphamide, and Antithymocyte Globulin Followed by Donor Stem Cell Transplant in Treating Patients with Hematologic Cancer. 03 April 2018; retrieved from the internet <https://clinicaltrials.gov/ct2/show/NCT00611351>; pages 1-9; page 3/9, paragraph 5 – page 4/9, paragraph 1	14, 17, 18/14, 18/17

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 April 2020 (07.04.2020)	28 APR 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	(BARTELINK, IH et al.) Association between Busulfan Exposure and Outcome in Children Receiving Intravenous Busulfan before Hematologic Stem Cell Transplantation. Biology Bone Marrow Transplant. 2009; Vol. 15; pages 231-241; abstract; table 2; DOI:10.1016/j.bbmt.2008.11.022	16, 18/16
Y	(MOHTY, M et al.) New Directions for Rabbit Antithymocyte Globulin (Thymoglobulin) in Solid Organ Transplants, Stem Cell Transplants and Autoimmunity. Drugs. September 2014; Vol. 74, No. 14; pages 1605-1634; page 1607, column 1, paragraph 1; DOI: 10.1007/s40265-014-0277-6	16-17, 18/16-17
Y	(BARI, S et al.) Ex Vivo Expansion of CD34+CD90+CD49f+ Hematopoietic Stem and Progenitor Cells from Non-Enriched Umbilical Cord Blood with Azole Compounds. Stem Cells Translational Medicine. May 2018; Vol. 7, No. 5; pages 376-393; abstract; page 391, column 2, paragraph 1 – page 392, column 1, paragraph 2; figure 5B; DOI: 10.1002/sctm.17-0251	18/3, 18/5-7, 18/10-17
A	(GRATWOHL, A et al.) Autografting: Autologous Hematopoietic Stem Cell Transplantation for Autoimmune Diseases. Bone Marrow Transplantation. May 2005; Vol. 35, No. 9; pages 869-879; page 870, column 2, paragraph 2; page 871, column 1, paragraph 1; DOI: 10.1038/sj.bmt.1704892	1-2, 18/1-2
A	(HWANG-BO, S et al.) Treatment and Response of Autoimmune Cytopenia Occurring after Allogeneic Hematopoietic Cell Transplantation in Children. Blood Research. June 2017; Vol. 52, No. 2; pages 119-124; abstract; page 120, column 1, paragraphs 3-4; DOI: 10.5045/br.2017.52.2.119	1-2, 18/1-2
A	WO 1998/20932 A2 (BAXTER INTERNATIONAL INC., etc.) 22 May 1998; page 5, lines 23-27	1-2, 18/1-2

INTERNATIONAL SEARCH REPORT
Information on patent family members

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-***-Continued from Box III Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, Claims 1-3, 5-7, 10-17 and 18 (in-part) are directed toward methods of administering hematopoietic stem or progenitor cells transplant therapy comprising a conditioning regimen comprising busulfan, cyclophosphamide and anti-thymocyte globulin.

Group II, Claims 4, 9, and 18 (in-part) are directed toward method of preventing, or reducing the risk of, autoimmune cytopenia in a patient in need thereof, the method comprising: i) conditioning the patient with a conditioning regimen that does not comprise busulfan plus fludarabine (BuFlu)

Group III, Claims 8 and 18 (in-part) are directed toward method of preventing or reducing the risk of autoimmune cytopenia in a patient in need thereof, the method comprising: administering a prophylactic agent prior to, during, or following transplant with expanded cord blood.

The inventions listed as Groups I-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: the special technical features of Group I include anti-thymocyte globulin, not present in either of Groups II or III; the special technical features of Group II include a conditioning regimen does not comprise busulfan plus fludarabine (BuFlu), not present in either of Groups I or III; the special technical features of Group III include administration of a prophylactic agent that inhibits the production of antibodies in a patient, not present in either of Groups I or II.

Groups I-III share the technical features including: preventing or reducing the risk of autoimmune cytopenia in a patient; and transplanting the patient with expanded cord blood. Groups I and II share the technical features including a conditioning regimen.

However, these shared technical features are previously disclosed by the article 'Posttransplant Autoimmune Hemolytic Anemia and Other Autoimmune Cytopenias are Increased in Very Young Infants Undergoing Unrelated Donor Umbilical Cord Blood Transplantation' by Page et al. (hereinafter 'Page') in view of US 2012/0093782 A1 to Grove et al. (hereinafter 'Grove').

Page discloses preventing or reducing the risk of autoimmune cytopenia in a patient (GVHD and autoimmune cytopenia prophylaxis (preventing or reducing the risk of autoimmune cytopenia in a patient); abstract); transplanting the patient with cord blood (transplanting the patient with cord blood; abstract); and a conditioning regimen (a conditioning regimen; abstract).

Page does not disclose transplanting the patient with expanded cord blood.

Grove discloses improving hematologic transplantation, including cord blood transplantations (improving hematologic transplantation, including cord blood transplantations; paragraphs [0012], [0013]), comprising expanded cord blood and HSCs therefrom (comprising expanded cord blood and HSCs therefrom; paragraph [0015]).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the disclosure of Page to have used expanded cord blood, and stem cells therefrom, as a more effective means of enriching the transplanted cells for stem cells in order to have an enhanced therapeutic effect.

Since none of the special technical features of the Groups I-III inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Page and Grove references, unity of invention is lacking.