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(71) Applicant *(for all designated States except US)*: **GENZYME CORPORATION** [US/US]; 500 Kendall Street, Cambridge, MA 02142 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KAPLAN, Johanne, M.** [US/US]; 123 Mill Street, Sherborn, MA 01770 (US). **ROBERTS, Bruce, L.** [US/US]; 108 Pine Hill Road, Southborough, MA 01772 (US). **SIDERS, William, M.** [US/US]; 618 Lisa Lane, Franklin, MA 02038 (US).

(74) Agents: **GUNNISON, Jane, T.** et al.; Ropes & Gray LLP, 1211 Avenue of the Americas, New York, NY 10036 (US).

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Published:

— *with international search report (Art. 21(3))*

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(54) Title: METHODS AND COMPOSITIONS FOR TREATMENT

(57) Abstract: The invention provides methods for improving the efficacy and reducing side effects of anti-CD52 antibody treatment. The methods can be used to treat patients who are in need of immunoregulation such as lymphocyte depletion and patients who have cancer. Also included are compositions useful for these methods.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/34780

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/395; A61K 39/395; C07K 16/00 (2010.01)
USPC - 424/130.1; 424/144.1; 530/389.6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/395; A61K 39/395; C07K 16/00 (2010.01)
USPC - 424/130.1; 424/144.1; 530/389.6

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

USPC - 424/85.5, 141.1; 173.1; 435/375, 377,70.1; 536/23.53; 530/387.1,387.3, 391.1 (keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google: anti-CD52, alemtuzumab, Campath-1H, CAMPATH, simulate, induce, neutrophils, natural killer, NK, side effect, infusion, autoimmunity, regulatory T cell, Treg, leukemia, lymphoma, T cell, malignancy, B cell, malignancy, non-Hodgkin's lymphoma (NHL), small lymphocytic, NHL, chronic lymphocytic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2007/0274948 A1 (HURST et al.) 29 November 2007 (29.11.2007) Abstract, para [0002]-0003], [0005], [0007]-[0010], [0018], [0024], [0031], [0037], [0039], [0061], [0076], [0100], [0186], and [0189]	1-3, 7, 17-19, 24-25, 27, 30, 33 --- 4-6, 8, 20-23, 26, 28-29, 31-32, 38-41
Y	US 2008/0267954 A1 (MARGOLIN et al.) 30 October 2008 (30.10.2008) Abstract, para [0002]-[0003], [0006], [0015], [0057], and [0070]	4, 20-23, 38-41
Y	Goodman. Alemtuzumab Found More Effective Than Interferon in Reducing Disability in Relapsing-Remitting MS, Neurology Today 2008, 8(10):17; pg 17, col 2-3	5
Y	KIM et al. Antibody Engineering for the Development of Therapeutic Antibodies. Mol Cells. 2005, Vol. 20(1), p.17-29. pg 19 Table 1, and pg 22, col 1, lower para	6
Y	MUTHUSAMY et al. Alemtuzumab Induction and Steroid-Free Maintenance Immunosuppression in Pancreas Transplantation. Am J Transplant. 2008, 8(10):2126-2131; Abstract; pg 2128, col 2, para 1 and para 2; and pg 2129, col 1	8
Y	US 2007/0292439 A1 (Luqman) 20 December 2007 (20.12.2007) para [0094], [0117], [0133], and [0140]	26, 28
Y	US 2008/0305075 A1 (CURD et al.) 11 December 2008 (11.12.2008) Abstract, para [0011], [0209], [0215], [0227], and [0324]	29

☒ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
25 September 2010 (25.09.2010)	19 NOV 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/34780

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.: 15-16
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:

Groups I+: claims 1-8, 17-33, 38-41, drawn to a method comprising administering to the patient an agent that stimulates neutrophils, or natural killer (NK) cells, or both; and administering to the patient a therapeutically effective amount of an anti-CD52 antibody. The first invention encompasses sargramostim. Should an additional fee(s) be paid, Applicant is invited to elect an additional cell type and stimulatory agent(s) to be searched. The exact claims searched will depend on the specifically elected cell type and stimulatory agent(s).

Group II, claims 9-14, 17-33, drawn to a method comprising administering to the patient an agent that stimulates CD4+CD25+FoxP3+ regulatory T cells; and administering to the patient a therapeutically effective amount of an anti-CD52 antibody.

**********Continued in the Supplemental Box **********

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.:
1-8, 17-33, 38-41, limited to sargramostim

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

International application No.
PCT/US 10/34780

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0093399 A1 (DEFREES et al.) 09 April 2009 (09.04.2009) para [0670] and [1149]	31
Y	Stull. Colony-stimulating factors: beyond the effects on hematopoiesis. Am J Health Syst Pharm. 2002, 59(7 Suppl 2):S12-S20. [Retrieved from the Internet on 2010.09.25: <URL: http://www.ncbi.nlm.nih.gov/pubmed/11944610>]; Abstract	32
Y	US 2007/0172947 A1 (Shirwan) 26 July 2007 (26.07.2007) Abstract, para [0004]-[0005], [0027], [0070], [0073], [0142], and [0146]	38-41
Y	TUOVINEN et al. The FOXP3+ subset of human CD4+CD8+ thymocytes is immature and subject to intrathymic selection. Immunol Cell Biol. 2008, 86(6):523-529; Abstract	38-41

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/34780

********** Supplemental Box **********

Continuation of: Box No. III (unity of invention is lacking)

Group III, claims 34-37, 42-45 , drawn to an immunoconjugate comprising an anti-CD52 anti.body fused to an agent that stimulates neutrophils or NK cells, or both.

The inventions listed as Groups I+ 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:

The inventions of Group I+ and II do not include the inventive concept of an immunoconjugate comprising an anti-CD52 anti.body fused to an agent that stimulates neutrophils or NK cells, or both, as required by Group III.

The inventions of Group I+ do not include the inventive concept of administering to the patient an agent that stimulates CD4+CD25+FoxP3+ regulatory T cells, as required by Group II.

The inventions of Group I+ and II share the technical feature of administering to the patient a therapeutically effective amount of an anti-CD52 antibody. However, this shared technical feature does not represent a contribution over prior art. Specifically, US 2007/0274948 A1 (HURST et al.) (hereinafter 'Hurst') discloses a method of treating a patient in need thereof (Abstract - 'Methods for treating a human with chronic lymphocytic leukemia using a combination of an interleukin-2 and an anti-CD52 antibody'), comprising dministering to the patient a therapeutically effective amount of an anti-CD52 antibody(para [0024] - 'the cycle comprises administering a therapeutically effective dose of an anti-CD52 antibody in combination with administration of a two-level dosing regimen of IL-2'). As said administering to the patient a therapeutically effective amount of an anti-CD52 antibody was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

The inventions of Group I+ share the technical feature of a method comprising administering to the patient an agent that stimulates neutrophils, or natural killer (NK) cells, or both; and administering to the patient a therapeutically effective amount of an anti-CD52 antibody. However, this shared technical feature does not represent a contribution over prior art. Specifically, Hurst discloses a method of treating a patient in need thereof (Abstract - 'Methods for treating a human with chronic lymphocytic leukemia using a combination of an interleukin-2 and an anti-CD52 antibody'), comprising:
---administering to the patient an agent that stimulates natural killer (NK) cells (para [0005] - 'These two therapeutic agents are administered as separate pharmaceutical compositions, one containing an IL-2, the other containing at least one anti-CD52 antibody...Following one cycle of dosing of an IL-2 and an anti-CD52 antibody'; para [0031] - 'the total weekly dose of an IL-2 is an amount that provides at least 60% of the NK stimulatory activity ... at least 70% of the NK stimulatory activity ...or at least 80% of the NK stimulatory activity... or at least 90% of the NK stimulatory activity of a total weekly dose of aldesleukin administered'; para [0186] - 'unglycosylated human IL-2 mutein, called aldesleukin'; para [0002] - 'Interleukin-2 (IL-2) is a potent stimulator of natural killer (NK)'); and
---administering to the patient a therapeutically effective amount of an anti-CD52 antibody (para [0024] - 'the cycle comprises administering a therapeutically effective dose of an anti-CD52 antibody in combination with administration of a two-level dosing regimen of IL-2'). As said method was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another technical feature of the inventions listed as Group I+ is the specific activatory compound recited therein. The inventions do not share a special technical feature, because no significant structural similarities can readily be ascertained among said compounds. Without a shared special technical feature, the inventions lack unity with one another.

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