Reexam

PTO/SB/21 (09-04)

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Total Number of Pages in This Submission | |

| | |
|---|---|
| Application Number | Pat. 6,653,104 |
| Filing Date | Issued 11/25/2003 |
| First Named Inventor | GOLDENBERG, David M. |
| Art Unit | |
| Examiner Name | |
| Attorney Docket Number | 015280-325300US |

## ENCLOSURES *(Check all that apply)*

- ☒ Fee Transmittal Form-**in duplicate**
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please identify below):

**1)-Request for *inter partes* Reexamination Under 37 CFR 1.915**
**w/forms PTO/SB/08A&B (1449)**
**w/Appendices A and B (35 refs.)**
**w/U.S. Pat. 6,653,104**
**w/Certificate of Service**
**2)-Return Postcard**

Remarks: The Commissioner is authorized to charge any additional fees to Deposit Account 20-1430.

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | Townsend and Townsend and Crew LLP | | |
| Signature | Kenneth A. Weber | | |
| Printed name | Kenneth A. Weber | | |
| Date | December 1, 2004 | Reg. No. | 31,677 |

## CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

| | | | |
|---|---|---|---|
| Signature | Malinda C. Dagit | | |
| Typed or printed name | Malinda C. Dagit | Date | 12/1/2004 |

12/07/2004 MTUITTY 00000011 201430 95000062
01 FC:1813 8800.00 DA

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

PATENT
015280-325300US

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On 1 Dec. 2004

TOWNSEND and TOWNSEND and CREW LLP

By: Malvida Dogs

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

*In re* Reexamination of:

David M. Goldenberg

U.S. Patent No.: 6,653,104

Issued: November 25, 2003

For: IMMUNOTOXINS, COMPRISING AN INTERNALIZED ANTIBODY DIRECTED AGAINST MALIGNANT AND NORMAL CELLS

REQUEST FOR *INTER PARTES* REEXAMINATION UNDER 37 CFR § 1.915

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The Department of Health and Human Services request *inter partes* reexamination of U.S. Patent 6,653,104 (the '104 patent). This request is accompanied by a fee authorization for the fee for requesting *inter partes* reexamination set forth in 37 CFR § 1.20(c)(2).

The estoppel provision of 37 CFR § 1.907 do not prohibit the *inter partes* reexamination.

[redacted]

## I. Claims for Which Reexamination Is Requested.

Reexamination is requested of claims 1-140 in view of U.S. Patent No. 5,840,840, which raise new questions of patentability that were not addressed during the prosecution of the '104 patent. The reference is listed on the attached Information Disclosure form and a copy of the reference is attached as Appendix A. Reexamination of specific claims, identified below, is requested in view U.S. Patent 5,840,840, and further in view of the additional references listed on the attached Information Disclosure form and included in Appendix B

## II. Explanation of relevance and manner of applying cited prior art to every claim for which reexamination is requested.

### A. The '104 patent family and independent claims

The '104 patent application (Application No. 09/986,119) was filed November 7, 2001, and is a CIP that claims priority to two parent applications, each of which claims priority to a respective provisional application. One parent is Serial No. 09/107,672, filed May 1, 1998, now U.S. Patent No. 6,395,276 (the '276 patent), issued May 28, 2002, which claims benefit of a provisional application filed May 5, 1997. The other parent is Serial No. 08/949,758 filed Oct. 14, 1997, now US Patent No. 6,083,477 (the '477 patent), issued July 4, 2000, which claims the benefit of a provisional application filed October 17, 1996.

The claims of the '104 patent are directed to immunoconjugates. Independent composition claims are:

> 1. A cytotoxic reagent comprising an antibody and a moiety having ribonucleolytic activity derived from a non-human ribonuclease, wherein said antibody and said moiety are linked through recombinant production.

> 2. A cytotoxic reagent comprising an internalizing antibody and a moiety having ribonucleolytic activity, wherein said internalizing antibody is direct against a lineage-dependent antigen or against an antigen associated with cancer cells, and wherein said internalizing antibody and said moiety are linked through recombinant production.

51. A cytotoxic reagent comprising an antibody and a moiety having ribonucleolytic activity derived from a non-human ribonuclease, wherein said antibody is directed against an antigen other than a B-cell antigen.

52. A cytotoxic reagent comprising an internalizing antibody and a moiety having ribonucleolytic activity, wherein said internalizing antibody is directed against a lineage-dependent antigen or against an antigen associated with cancer cells, and wherein said internalizing antibody is directed against an antigen selected from the group consisting of:

a) T-cell antigens;

(b) MUC1 antigens;

(c) EGP-1 antigens;

(d) EGP-2 antigens; and

(e) placental alkaline phosphatase antigen.

92. A cytotoxic reagent comprising an antibody and a moiety having ribonucleolytic activity derived from a non-human ribonuclease, wherein said antibody in human or humanized.

93. A cytotoxic reagent comprising an internalizing antibody and a moiety having ribonucleolytic activity, wherein said internalizing antibody is directed against a lineage-dependent antigen or against an antigen associated with cancer cells, and wherein said internalize antibody is human or humanized.

**B. U.S. Patent 5,840,840, filed September 22, 1993 (the '840 patent).**

The '840 patent issued on Nov. 24, 1998. The filing date is September 22, 1993. The patent is a continuation-in-part of Ser. No. 14,082, filed Feb. 4, 1993, abandoned; which is a continuation of Ser. No. 779,195, filed Oct. 22, 1991, abandoned; which is a continuation-in-part of Ser. No. 510,696, filed Apr. 20, 1990, abandoned. The patent is prior art to the '104 patent under 35 U.S.C. § 102. The disclosure anticipates particular claims of the '104 patent and renders other claims obvious. The '840 patent teaches cytotoxic reagents comprising RNases linked to recognition moieties that binds to specific cell surface markers (*see, e.g.,* the abstract). The teachings are applied to the claims 1-140 of the '104 patent as detailed below. The relevance

of the '840 patent to the independent claims is explained first. Tables that provide exemplary anticipatory passages in the '840 patent that are relevant to the independent claims 1, 2, 51, 52, 92, and 93 are provided on pages 20-26.

**C. The '840 patent anticipates independent claims of the '104 patent**

*1. Claim 1*

Claim 1 of the '104 patent is drawn to a cytotoxic reagent comprising an antibody and an RNase moiety derived from a nonhuman RNase where the antibody and RNase are linked recombinantly. The '840 patent discloses:

1) both human and nonhuman ribonucleases (*e.g.*, column 8, lines 1-11);

2) that the recognition moiety can be an antibody (*e.g.*, column 8, lines 50-53); and

3) that the moieties in the immunotoxin can be linked recombinantly (*e.g.*, column 9, lines 53-54). The '840 patent thus discloses all of the elements of claim 1 and accordingly, anticipates claim 1.

The '840 patent also teaches pharmaceutical compositions ("The present invention also relates to a pharmaceutical composition comprising a cytotoxic reagent of the present invention and a pharmaceutically acceptable carrier" (column 11, lines 31-34) and methods of selectively killing cells by administering the pharmaceutical compositions (column 11, lines 60-62). Claim 33 (drawn to a pharmaceutical composition comprising the cytotoxic reagent of claim 1 and a pharmaceutically acceptable carrier), claim 34 (drawn to a method of killing cancer cells by administering a reagent of claim 1), and claim 48 (drawn to a method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 33) are therefore also anticipated by the '840 patent disclosure.

For convenience, a claim chart comparing the elements of claim 1 and related claims 33, 34, and 48 to exemplary disclosure in the '840 patent is provided on page 20.

*2. Claim 2*

Claim 2 is drawn to a cytotoxic reagent comprising an internalizing antibody and an RNase moiety where the two components are linked recombinantly and where the internalizing antibody is to a lineage-dependent antigen or an antigen associated with cancer cells. As noted above, the '840 patent discloses recombinant linkage and an antibody moiety. Further, the patent discloses internalizing, lineage-specific antibodies. For example, column 13 discloses a human T cell-specific monoclonal antibody to CD5 (T101). The antibodies is lineage specific (*i.e.*, T cell-specific) and has the inherent property of being internalized (*see, e.g.*, Ravel, *et al. Blood* 79:1511-1517, 1992, attached as Appendix C). Thus, the '840 patent discloses each element of claim 2. Accordingly, it anticipates claim 2.

Claim 3 is also anticipated, as it is dependent from claim 2 and merely adds the requirement that the antibody is a monoclonal antibody (T101 is a monoclonal antibody, *supra*).

Claim 24 (drawn to a pharmaceutical composition comprising the cytotoxic reagent of claim 1 and a pharmaceutically acceptable carrier), claim 25 (drawn to a method of killing cancer cells by administering a reagent of claim 1), and claim 47 (drawn to a method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 24) are therefore also anticipated by the '840 patent in view of the passages indicated above under the heading "*Claim 1*".

For convenience, a claim chart comparing the elements of claim 2 and related claims 24, 25, and 47 to exemplary disclosure in the '840 patent is provided in Appendix B.

*3. Claim 51*

Claim 51 recites a reagent comprising an antibody and a nonhuman ribonuclease, where the antibody is directed against an antigen other than a B-cell antigen. The '840 patent discloses nonhuman ribonucleases and antibodies against cell types other than B-cells (*e.g.*, columns 10 and 11). Further, the patent discloses the human T-cell-specific antigen T101 linked to a nonhuman RNase (bovine RNase) (column 13). We note that RNase A in the context of the examples is disclosed to be bovine RNase A from Calbiochem in the Material and Methods section that accompanies the examples (first paragraph, column 13, and last full paragraph,

column 18). The '840 patent thus discloses each element of claim 51. Accordingly, it is anticipatory art.

Claim 75 (drawn to a pharmaceutical composition comprising the cytotoxic reagent of claim 51 and a pharmaceutically acceptable carrier), claim 76 (drawn to a method of killing cancer cells by administering a reagent of claim 51), and claim 89 (drawn to a method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 75) are also anticipated by the '840 patent in view of the passages indicated above under the heading "*Claim 1*".

For convenience, a claim chart comparing elements of claim 51 and related claims 75, 76, and 89 to exemplary disclosure in the '840 patent is provided on page 22.

*4. Claim 52*

Claim 52 is drawn to a reagent comprising an internalizing antibody and an RNase, in which the internalizing antibody is directed against an antigen selected from the group consisting of T cell antigens; MUC1 antigens, EGP-1 antigens, EGP-2 antigens, and placental alkaline phosphatase antigen.

As disclosed above, the '840 patent discloses a T-cell-specific antibody (T101) linked to an RNase and therefore anticipates claim 52.

Claim 53 is also anticipated, as it is dependent from claim 52 and merely adds the requirement that the antibody is a monoclonal antibody. T101 is a monoclonal antibody as taught in column 13 of the '840 patent.

Claim 67 (relating to a pharmaceutical composition comprising the cytotoxic reagent of claim 52 and a pharmaceutically acceptable carrier), claim 68 (relating to a method of killing cancer cells by administering a reagent of claim 52), and claim 88 (drawn to a method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 67) are also anticipated by the '840 patent in view of the passages indicated above under the heading "*Claim 1*".

For convenience, a claim chart comparing elements of claim 52 and related claims 67, 68, and 88 to exemplary disclosure in the '840 patent is provided on pages 23-24.

*5. Claim 92*

Claim 92 recites an antibody and a nonhuman ribonuclease, wherein the antibody is human or humanized. In an exemplary passage at column 10, the '840 patent discloses that the cytotoxic reagent can be a mammalian RNase and a humanized antibody. The '840 patent therefore anticipates claim 92.

Claim 123 (relating to a pharmaceutical composition comprising the cytotoxic reagent of claim 92 and a pharmaceutically acceptable carrier), claim 124 (relating to a method of killing cancer cells by administering a reagent of claim 92), and claim 138 (drawn to a method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 123) are also anticipated by the '840 patent in view of the passages indicated above under the heading "*Claim 1*".

For convenience, a claim chart comparing elements of claim 92 and related claims 123, 124, and 138 to exemplary disclosure in the '840 patent is provided on page 25.

*6. Claim 93*

Claim 93 is drawn to a reagent comprising a human or humanized internalizing antibody and an RNase moiety where the antibody is directed against a lineage-dependent antigen or against an antigen associated with cancer cells. The '840 patent discloses that a cytotoxic moiety can be human or humanized in order to reduce immunogenicity in humans; further the patent provides example of internalizing antibodies. The '840 patent therefore anticipates, or in the alternative, renders obvious, claim 93.

Claim 94, which depends from claim 93, recites that the antibody is a monoclonal antibody. The '840 patent provides examples of monoclonal antibodies (see, *e.g.*, column 13) and therefore anticipates, or in the alternative, renders obvious, claim 94.

Claim 114 (relating to a pharmaceutical composition comprising the cytotoxic reagent of claim 93 and a pharmaceutically acceptable carrier), claim 115 (relating to a method of killing cancer cells by administering a reagent of claim 93), and claim 137 (drawn to a method of selectively killing unwanted types of cells in a subject comprising administering to said

subject a pharmaceutical composition of claim 114) are also anticipated, or obvious, in view of the passages indicated above.

For convenience, a claim chart comparing elements of claim 93 and related claims 114, 115, and 137 to exemplary disclosure in the '840 patent is provided on page 26.

*7. Summary--independent claims and dependent claims 3 and 53*

It is our understanding that the determination that the art raises new issue with respect to one claim of the patent for which reexamination is requested, results in the reexamination of the patent, *i.e.,* all of the claims. At a minimum, the '840 patent raises substantial new questions of patentability with respect to claims 1-3, 24, 25, 33, 34, 47, 48, 51, 52, 53, 67, 68, 75, 76, 88, 89, 92, 93, 114, 115, 123, 124, 137, and 138 for the reasons explained above. Accordingly, all of the claims of the '104 patent should be subject to reexamination based on these new questions alone.

**D. Dependent Claims Are Anticipated Or Obvious Over The Prior Art**

We further maintain that the dependent claims are anticipated, or rendered obvious, by the '840 patent disclosure. Thus, reexamination of claim 1-140 is requested. The manner of applying additional art in view of the '840 patent is detailed below.

*1. The '840 patent provides a proper motivation and reasonable expectation of success*

With regard to obviousness (35 U.S.C. § 103), the '840 patent discloses the general desirability of making immunotoxins to target particular cell types (*e.g.,* column 1, lines 42-50, where it teaches the therapeutic relevance of immunotoxins to cancer; and column 10, lines 54-63, where it teaches the desirability of using immunotoxins to target cells infected by an infectious agent). The '840 patent also teaches RNases, both human and nonhuman, that can be used as the toxic moiety in such immunotoxins (*see,* for example, the passages cited above with regard to the independent claims) and provides examples using RNase molecules. Accordingly, teachings of the '840 patent provide a motivation to make immunotoxins comprising RNase molecules. Further, the '840 patent discloses that such immunotoxins are in fact cytotoxic,

thereby providing a reasonable expectation that such immunotoxins will work. Specific antibodies, target antigens, and cell types, as recited in various dependent claims were known, as detailed below in the designated sections. Thus, in the absence of evidence to the contrary, it would have been *prima facie* obvious to make and use such RNase-containing immunotoxins to target a desired cell or tissue.

*2. Claims drawn to various types of antibodies are anticipated or obvious*

As noted above, the '840 patent discloses that antibodies for use in the invention can be humanized in order to minimize immunogenicity. *See, e.g.,* the exemplary passage at column 8, lines 58-60 referred to with regard to claim 92. ("For example, a preferred recognition moiety for a cytotoxic reagent for use in human is a "humanized" chimeric antibody against a cell receptors"...). Thus, dependent claims 4 and 54, which recite that the antibody is humanized, are anticipated, or in the alternative, obvious variants of the cytotoxic reagents disclosed in the '840 patent.

Claims 5, 55, and 95 recite single chain antibodies. The '840 patent discloses that "the recognition moiety may be an antibody or a modified form thereof (for example, a Fab fragment or a single chain antibody)" at column 8, lines 50-52. Accordingly, claims 5, 55, and 95, are anticipated or alternatively, rendered obvious in view of the teachings of the '840 patent disclosure.

Further, the disclosure of the '840 patent and the extensive disclosure in the prior art of internalizing antibodies renders claims 6, 7, 10, 12, 14, 16, 18, 19, 20, 21, 23, 29, 31, 32, 40, 53, 56, 60, 62, 64, 65, 66, 71, 73, 74, 119, 121, 122, 130, 94, 96, 97, 100, 102, 104, 106, 109, 110, 111, 113, 119, 121, 122, and 130 anticipated, or alternatively, rendered obvious. As explained above regarding claims 2, 3, 52, and 93, the '840 patent discloses an immunotoxin where the antibody is an internalizing antibody. The use of such antibodies to target various antigens is known in the art, as detailed below for specific antibodies and antigens. Accordingly, it would have been *prima facie* obvious, in the absence of evidence to the contrary, to make and use immunotoxins comprising internalizing antibodies to target a particular cell type that expresses the antigen.

The prior art describing particular antigens, antibodies, or cell types is discussed below and applied to each claim. Copies of the references cited below are provided in Appendix B.

*3. Antibodies directed against particular antigens*

Claims 6, 7,8, 9, 11, 13, 15, 17, 26, 31, 40, 56, 57, 58, 59, 61, 63, 73, 96, 97, 98, 99, 101, 103, 105, 107, 112, 116, 121, and 130 recite an antibody directed against particular antigens, B-cell antigens, T-cell antigens, plasma cell antigens, HLA-DR lineage antigens, MUC1 antigens, EGP-1 antigens, EGP-2 antigens, placental alkaline phosphatase antigen, CD19, CD22, CD40, IL-15, CD74, CD33, PSMA, PSA, and PAP. The knowledge of cell-specific antigens, and antibodies that target such antigens, is well known in the art. The use of antibodies directed to cell-specific or tumor specific antigens for the purpose of immunotherapy is known, as discussed above. Exemplary art describing the recited antibodies or antigens is cited below. It is noted that claims that recite antibodies targeting some of these particular antigens *e.g.*, MUC1, EGP-1, EGP-2, PSMA, PSA, PAP, placental alkaline phosphatase, as components of cytotoxic RNase reagents are not entitled to the parent application filing dates. These antigens were not described in the parent applications; accordingly, claims that specifically recite the antigens are entitled only to the filing date of the '104 application.

***a. B-cell Antigens.*** The prior art discloses antibodies directed to B-cell antigens targeted to cancer cells. For example, Zhang *et al.* (*Ther Immunol* 2(4):191-202, Aug. 1995) discloses monoclonal antibodies directed to the B-cell antigen CD79 bind with specificity to human tumor biopsies. This disclosure, in combination with teachings of the '840 patent as cited above, renders claims 6, 7, 97 (7 and 97 claiming an internalizing antibody "directed against a target antigen associated with a B- or T-cell lymphoma"), 26, 19, 109 (19 and 109 claiming a lineage-dependent antibody of a B-cell), 96, and 116 *prima facie* obvious in the absence of proper evidence to the contrary.

***b. T-cell Antigens.*** The prior art discloses antibodies directed to T-cell antigens used for immunotherapy in cancer patients. For example, Waldmann (*Important Adv Oncol* 131-41, 1994) used monoclonal antibodies directed to T-cell antigens to treat T-cell lymphoma. This

disclosure, in combination with the '840 patent as cited above, renders claims 6, 7, 97 (7 and 97 claiming an internalizing antibody "directed against a target antigen associated with a B- or T-cell lymphoma"), 26, 27, 29, 69, 117, 119 (27, 29, 69 117, and 119 claiming an antibody associating with, *inter alia*, T-cells), 20, 65, 110 (20, 65 and 110 claiming a lineage-dependant antibody of a T-cell), 52 (claiming an antibody directed against, *inter alia*, T-cell antigens), 56, 71 (56 and 71 claiming an antibody directed against an antigen associated with T-cell lymphoma), 96 and 116 *prima facie* obvious, in the absence of proper evidence to the contrary.

***c. Plasma Cell Antigens.*** The prior art discloses antibodies directed to plasma cell antigens. Barker *et al.* (*Leuk Lymphoma* 8(3):189-96, Oct. 1992) discusses antigens present on the surface of plasma cells - in particular, ICAM-1 (CD54) and H-CAM (CD44) are on human plasma cells and antigens such as N-CAM (CD56) and LFA-3 (CD58) are found on malignant plasma cells. This disclosure, in combination with the '840 patent as cited above, renders claims 6, 26, 27, 29, 117, 119 (27, 29, 117, and 119 claiming an antibody associating with, *inter alia*, plasma cells), 21, 111 (21 and 111 claiming a lineage-dependent antibody of a plasma cell), 96 and 116 *prima facie* obvious in the absence of proper evidence to the contrary.

***d. HLA-DR Lineage Antigens.*** The prior art discloses antibodies directed to HLA-DR lineage antigens. For example, Mittelman *et al.* (*Am J Hematol* 43(3):165-71, Jul. 1993) describes monoclonal antibodies directed to myelomonocytic surface antigens, including HLA-DR antigens. Claim 8 and Claim 9 of the '104 patent claims antibodies directed against B- or T-cell antigens including HLA-DR antigens. This disclosure, in combination with the teachings of the '840 patent as noted above, renders claims 6, 8, 9, 99 (9 and 99 claiming a HLA-DR antibody), 26, 27, 29, 117, 119 (27, 29, 117, and 119 claiming an antibody associating with, *inter alia*, myeloid cells), 96, 98 (see below), and 116 *prima facie* obvious in the absence of proper evidence to the contrary.

***e. MUC1 Antigens.*** The prior art also discloses antibodies directed to MUC1 for use in immunotherapy in cancer patients. Apostolopoulos and McKenzie (*Crit Rev Immunol* 14(3-4):293-309, 1994) reviewed the use of antibodies against mucins and specifically MUC1 in cancer immunotherapy. Takahashi *et al.* (*J Immunol* 153(5):2102-9, Sep 1, 1994) describe the expression of MUC1 on myeloma cells, cancerous B-cells, and in the sera of multiple myeloma

patients. Claim 8 and claim 13 of the '104 patent claims antibodies directed to B- or T-cell antigens including MUC1 antigens. The combination of Apostolopoulos and McKenzie (disclosing MUC1 specific antibodies) and Takahashi *et al.* (disclosing the presence of MUC1 on myeloma cells) in conjunction with the teachings of the '840 patent as cited above renders claims 6, 8, 13, 103 (13 and 103 claiming a MUC1 antibody), 26, 27, 29, 20, 110 (20 and 110 claiming a lineage-dependant antibody of a T-cell), 52, 57 (52 and 57 claiming an antibody directed against, *inter alia*, MUC1 antigens), 59 (claiming a MUC1 antibody), 96, 98 (see below) and 116 *prima facie* obvious in the absence of proper evidence to the contrary.

***f. EGP-1 Antigens*** **(not entitled to priority date of parent applications).** De Leij (*Int J Cancer Suppl* 8:60-3., 1994) describes the identification of antibodies directed to the epithelium-associated EGP-1 and EGP-2 antigens. Basu *et al.* (*Int J Cancer* 62(4):472-9, Aug 9, 1995) describe a monoclonal antibody to the "epithelial/carcinoma antigen EGP-1." This reference, in conjunction with the '840 patent teachings as noted above, renders claims 6, 26, 52, 57(52 and 57 claiming an antibody directed against EGP-1 antigens), 61 (claiming an EGP-1 antibody), 96, and 116 *prima facie* obvious in the absence of proper evidence to the contrary.

***g. EGP-2 Antigens*** **(not entitled to priority date of parent applications).**. De Leij (*Int J Cancer Suppl* 8:60-3, 1994) describes the identification of antibodies directed to the epithelium-associated EGP-1 and EGP-2 antigens. Kroesen *et al.* (*J Hematother* 4(5):409-14, Oct. 1995) describe the use of bispecific monoclonal antibodies directed to EGP-2 for treatment of renal cell carcinoma in humans. These references, in combination with art cited above, renders claims 6, 26, 52, 57 (52 and 57 claiming an antibody directed against EGP-1 antigens), 63 (claiming an EGP-2 antibody), 96, and 116 *prima facie* obvious in the absence of evidence to the contrary.

***h. Placental Alkaline Phosphatase Antigen*** **(not entitled to priority date of parent applications).**. The prior art discloses antibodies directed to placental alkaline phosphatase that are used to identify tumors. Jacobs and Haskell (*Curr Probl Cancer* 15(6):299-360, Nov-Dec 1991) review tumor markers used in oncology and specifically identify placental alkaline phosphatase antigen as one such marker. This reference in conjunction with the '840

patent teachings as indicated above, renders claims 6, 26, 52, 96, and 116 *prima facie* obvious in the absence of proper evidence to the contrary.

***i. B- or T-cell lymphoma antigens.*** Claim 8 and 98 recites internalizing antibodies directed to B- or T-cell lymphoma antigens selected from the group consisting of CD19, CD22, CD40, MUC1, HLA-DR, EGP-1, EGP-2, and IL-15. See, *e.g.,* art cited above for a discussion of prior art disclosures of antibodies directed to MUC1 and HLA-DR antigens.

***CD19.*** The prior art discloses antibodies directed to CD19 antigens used for immunotherapy. For example, Scheuermann and Racila (*Leuk Lymphoma* 18(5-6):385-97 Aug 1995) describe the use of anti-CD19 mAbs coupled to biological toxin in immunotherapy of lymphocytic leukemia and non-Hodgkin's lymphoma. This reference in conjunction with the '840 patent teachings as outlined above renders the claims *prima facie* obvious in the absence of proper evidence to the contrary.

***CD22.*** The art discloses antibodies directed to CD22 antigens used for targeting toxins to cancer cells. For example, Kreitman and Pastan (*Semin Cancer Biol* 6(5):297-306, Oct 1995) describe the use of monoclonal antibodies to cell surface antigens for targeting toxins to cancer cells, naming CD22 as one such antigen. French *et al.* (*Lancet* 346(8969):223-4, Jul 22, 1995) describe the use of bispecific antibodies linked to saporin and that recognize the surface antigen CD22 for treatment of B-cell lymphoma. These references in conjunction with the teachings of the '840 patent renders claims 8, 11, 22, 101, 112 (11, 22, 101, 112 claiming a CD22 antibody), and 98 *prima facie* obvious in the absence of proper evidence to the contrary.

***CD40.*** The prior art discloses antibodies directed to CD40 antigens used for targeting toxins to CD40-expressing cancer cells. For example, Francisco *et al.* (*Cancer Res.* 55(14):3099-104, Jul 15, 1995) describe the use of *Pseudomonas* exotoxin attached to monoclonal antibodies directed to CD40 as immunotoxins to kill B-cells expressing the CD40 antigen. This reference, in combination with the '840 patent teachings, renders claims 8, 57 (claiming, *inter alia*, an antibody directed against CD40), and 98 *prima facie* obvious in the absence of proper evidence to the contrary.

***IL-15.*** The prior art discloses antibodies directed to IL-15 antigens. For example, Azzarone *et al.* (*Eur Cytokine Netw* 7(1):27-36, Jan-Mar 1996) describe the presence of

IL-15 antigens in melanoma cells. This reference in combination with the '840 patent as noted above, renders the *prima facie* obvious in the absence of proper evidence to the contrary.

***CD74*** Ohsawa (*J Clin Pathol* 47(10):928-32, Oct. 1994) describes immunoreactivity of monocytoid B-cell lymphoma to antibodies directed to CD74, and makes note of the presence of the CD74 antigen in "neoplastic disease tumor cells." This reference in combination with the '840 patent as noted above renders claims 8, 22, 112, 130 (22, 112, and 130 claiming a CD74 antibody), 39 and 40 (Claims 39 and 40 are method claims that describe the use of antibodies directed to lymphomas and specifically CD74, respectively) *prima facie* obvious in the absence of prpoper evidence to the contrary.

***j. CD33, PSMA, PSA, and PA antigens.*** Claim 31 and 121 recite internalizing antibodies directed to antigens selected from the group consisting of CD33, PSMA, PSA, and PAP. Claim 73 recites internalizing antibodies directed to antigens selected from the group consisting of PSMA, PSA, and PAP

***CD33.*** The prior art discloses antibodies directed to CD33 antigens. For example, Drexler (*Leukemia* 1(10):697-705, Oct 1987) reviews the use of, *inter alia*, CD33 mAbs to immunophenotype cells. Ball (*Bone Marrow Transplant* 3(5):387-92, Sep 1988) describes the use of CD33 mAbs to target antigens on the surface of leukemia cells. This reference in conjunction with the '840 patent teachings as noted above, renders claims 31 and 121 *prima facie* obvious in the absence of proper evidence to the contrary.

***PSMA*** (not entitled to the priority application filing dates). Troyer *et al.* describe PSMA (prostate-specific membrane antigen) as a "novel prostate biomarker," determined by immunohistochemical staining and western blot analysis using PSMA-specific monoclonal antibodies. This reference in conjunction with the '840 patent as noted above, therefore renders claims 31, 73, and 121 *prima facie* obvious in the absence of proper evidence to the contrary.

***PSA*** (not entitled to the priority application filing dates). The art discloses antibodies directed to PSA (prostate specific antigen) that are used to identify tumors. Jacobs and Haskell (*Curr Probl Cancer* 15(6):299-360, Nov-Dec 1991) review tumor markers used in oncology and specifically identify PSA antigen as one such marker. This reference in

conjunction with the '840 patent teachings renders claims 31, 73, and 121 *prima facie* obvious in the absence of proper evidence to the contrary.

***PAP*** (not entitled to the priority application filing dates). The art discloses antibodies directed to PAP (prostatic acid phosphatase) that are used to identify tumors. Jacobs and Haskell (*Curr Probl Cancer* 15(6):299-360, Nov-Dec 1991) review tumor markers used in oncology and specifically identify PAP antigen as one such marker. In the absence of proper evidence to the contrary, this reference renders claims 31, 73, and 121 *prima facie* obvious in view of the teachings of the '840 patent.

*3. Particular Tissues, Cells, or Diseases*

***a. Solid Cancers.*** Claims 27, 29, 69, 71, 117, and 119 recite antibodies associated, *inter alia*, with solid tumors. Dependent claims 28, 30, 70, 72, 118, and 120 recite solid cancers from the group consisting of neuroblastoma, malignant melanoma, breast, ovarian, prostate, lung, kidney, and pancreas cancers. In the absence of proper evidence to the contrary, these claims are *prima facie* obvious in view of the teachings of the '840 patent as set forth in the following discussion.

***Neuroblastoma***. Larson (*Cancer* 67(4 Suppl):1253-60, Feb 15, 1991) reviews radioimmunotherapy and cites several examples of antibodies that target neuroblastoma.

***Malignant melanoma***. Merimsky *et al.* (*Tumour Biol* 15(4):188-202, 1994) discusses the use of antigens and antibodies in the treatment of melanoma.

***Breast***. The MUC1 antigen is expressed in a variety of cancers including breast, pancreas and ovary (*see* Apostolopoulos and McKenzie, *Crit Rev Immunol* 14(3-4):293-309, 1994).

***Ovarian***. The MUC1 antigen is expressed in a variety of cancers including breast, pancreas and ovary (*see* Apostolopoulos and McKenzie, *Crit Rev Immunol* 14(3-4):293-309, 1994).

***Prostate***. Maguire *et al.* (*Cancer* 72(11 Suppl):3453-62, Dec 1, 1993) discuss the use of prostate tumor specific monoclonal antibodies for use in immunoscintigraphy.

***Lung***. RS7-3G11 is a monoclonal antibody against small-cell lung carcinoma, recognizing the antigen EGP-1 (Basu *et al.*, *Int J Cancer* 62(4):472-9, Aug 9, 1995).

***Kidney.*** McCarley and Weiner (*Semin Surg Oncol* 5(4):293-301, 1989) discuss the use of monoclonal antibodies in diagnosing and treating various types of cancers including renal cancer.

***Pancreas***. PAM4 is an antibody that specifically targets pancreatic cells and prior publications (see below) renders claims 27, 29, 69, 71, 117, 119 (previous claims recite antibody against solid cancer), 28, 30, 70, 72, 118, 120 (previous claims recite antibody against, *inter alia*, pancreas cancers) *prima facie* obvious in view of the teachings of the '840 patent as cited above.

***b. Cancer Cells.*** Claims 41, 42, 82, 83, 131, and 132 recite a list of cancer cells that would be targeted by the claimed pharmaceutical reagent, including breast, ovarian, prostate, lung, kidney, and pancreatic cancers, melanomas, neuroblastomas, and myelomas. Also, claims 39, 81 and 129 recite cancer cells selected from cancers from the group consisting of lymphomas, melanomas, neuroblastomas and myelomas. Such cells and tissues are *prima facie* obvious, in the absence of evidence to the contrary, in view of the art cited, *e.g.*, the previous section relating to solid tumors, and the sections relating to B-cell antigens and MUC1, in combination with the teaching set forth in the '840 patent.

***c. Vascular Endothelium or Angiogenesis Receptor Antibody.*** Claim 66 recites an antibody directed against a vascular endothelium or angiogenesis receptor antibody. Ruiter *et al.* (*J Invest Dermatol* 93(2 Suppl):25S-32S, Aug 1989); Pandey *et al.* (*Science* 268(5210):567-9, Apr 28, 1995) review many types of monoclonal antibodies used to recognize vascular endothelium. This claim is therefore *prima facie* obvious in the absence of proper evidence to the contrary.

***d. Autoimmune Disease.*** Claims 90 and 139 recite unwanted types of cells that are involve in the development and progression of one or more autoimmune disease. Claims 91 and 140 recites autoimmune diseases selected from the group consisting of rheumatoid arthritis, systemic lupus erythematosis, immune thrombocytopenic pupura, and Sjogren's syndrome. Targeting autoimmune disease with immunotoxins is well known in the art. U.S. Patent No.

5,167,956 teaches the desirability of targeting these unwanted cells using an immunotoxin (*see, e.g.,* the abstract and column 2, lines 35-41). It would therefore be *prima facie* obvious to target such unwanted types of cells in the absence of evidence to the contrary.

*4. Particular Antibodies*

***An antibody LL1*** is recited in claims 10, 23, 100, and 113. An LL1 antibody is described in Hansen *et al.* (*Biochem J* 320 ( Pt 1):293-300, Nov 15, 1996) as an class II invariant chain or CD74 antibody (see, the abstract). The '104 patent priority claim to U.S. Serial No. 08/949,758, which issued July 4, 2000 as U.S. Patent 6,083,477 and claims benefit of provisional application 60/028,430, filed October 17, 1996, is not valid, as it was not co-pending at the time of the filing of the '104 patent (November 7, 2001). Accordingly, Hansen *et al.* is prior art.

***An antibody LL2*** is recited in claims 12, 23, 102, and 113. An LL2 antibody is described as a CD22-specific monoclonal antibody reactive with B-cells and non-Hodgkin's B-cell lymphoma by Stein *et al.* (*Cancer Immunol Immunother* 37(5):293-8, Oct. 1993).

***A PAM4 antibody*** is recited in claims 14, 60 and 104. A PAM4 antibody is described by Gold *et al.* (*Int J Cancer* 57(2):204-10, Apr 15, 1994) as a pancreatic carcinoma tissue-specific antibody.

***An antibody RS7*** is recited in claims 16, 62, and 106. An RS7 antibody is described by Stein *et al.* (*Cancer Res.* 50(4):1330-6, Feb 15, 1990) as RS7-3G11. RS7-3G11 binds to a wide variety of tumors.

***An antibody RS11*** is recited in claims 18, 64, and 108. A RS11 antibody is described by Stein *et al.* (*Cancer Res.* 50(4):1330-6, Feb 15, 1990) as RS11-51. RS11-51 binds to a wide variety of tumors. T

***An antibody 17-1A*** is recited in claims 18, 64, and 108. A 17-1A antibody is described in U.S. Patent 5,130,116. as a monoclonal antibody that is useful for the treatment of umors bearing the antigen 17-1A. It is an internalizing antibody (*see, e.g.,* column 10, lines 8-11).

***An antibody M195*** is recited in claims 32 and 122. A humanized M195 antibody is described by Caron *et al.* (*J. Exp. Med.* 176:1191-1195, 1992) for the treatment of leukemia (*see, e.g.*, abstract).

***An antibody G250*** is recited in claims 32, 74, and 122. A G250 antibody is described by Oosterwijk *et al.* (*Semin Oncol* 22(1):34-41, Feb 1995) as a monoclonal antibody used in the therapy of renal-cell carcinoma.

***An antibody RFB4*** is recited in claims 32 and 122. An RFB4 antibody is described by Vitetta *et al.* (*Cancer Res* 51(15):4052-8, Aug 1, 1991) as a CD22-specific antibody used as a Fab fragment connected to the toxin ricin A in clinical trials as an immunotoxin for B-cell lymphoma patients.

The prior art disclosure of the specific antibodies, in combination with the teachings of the '840 patent, renders the claims indicated above *prima facie* obvious, in the absence of proper evidence to the contrary.

*5. Methods of administering pharmaceutical compositions*

Claims 35-38, 77-80, and 125-128 of the '104 patent are drawn to particular method of administering pharmaceutical compositions comprising the cytotoxic reagent: administration via intranasal or by aerosol (claims 35, 37, 77, 79, 125, and 127) ; or administration via micropheres, liposomes, or microparticles (claims 36, 38, 78, 80, 126, and 128). The '840 patent teaches that the cytotoxic reagents "may be administered by various means appropriate for different purposes, for example, for treating tumors in various parts of the body, according to methods known in the art for immunotoxins" (column 11, lines 36-40, references cited at lines 41-42). The patent also discloses that administration can be "in the form a [sic] spray into the bronchi or nasopharyngeal cavity" (column 11, lines 49-50) and that the invention "relates to pharmaceutical compositions comprising a cytotoxic reagent of this invention and a pharmaceutically acceptable carrier, particularly such compositions which are suitable for the above means of administration" (column 11, lines 55-59). Thus, the '840 patent anticipates (in the case of claims reciting intranasal or aerosol administration) or renders obvious (claims reciting microspheres, liposomes, or microparticles), the invention of claims 35, 36, 37, 38, 77,

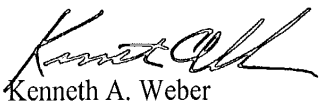
78, 79, 80, 125, 126, 126, and 128, in the absence of evidence to the contrary, for example, demonstrable, unexpected benefits of these particular administration methods.

Claims 44-46, 85-87, and 134-136 recite the following administration regimens: the pharmaceutical composition is administered more than once (claims 44, 85, and 134); or is administered at 0.1 to about 1000 mg per day (claims 45, 46, 86, 87, 135, or 136). As described above, the '840 patent discloses administering a pharmaceutical composition comprising an RNase and a recognition moiety for therapeutic purposes, *e.g.,* administering a chemo-therapeutically alleviating amount of the reagent for the treatment of cancer or infectious disease (column 12, lines 13-22). Accordingly, the '840 patent renders obvious claims 44-46, 85-87, and 134-136 in the absence of proper evidence to the contrary.

## III. New Question of Patentability (37 CFR § 1.915)

The '840 reference described above was of record during the prosecution of the '104 patent. The reference was cited in an IDS during the prosecution of parent application 09/071,672, now U.S. Patent No. 6,395,276. However, none of the art cited on the IDS, including this reference, was addressed by the Examiner. The '840 patent therefore raises new issues of patentability that were not considered during the prosecution of the '104 patent.

Respectfully submitted,



Kenneth A. Weber
Reg. 31,677

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300

## Claim 1 and related claims 33, 34, and 48

| '104 Patent Claim | Exemplary '840 Patent Disclosure |
|---|---|
| 1. A cytotoxic reagent | The present invention relates a selective RNase reagent. The reagent comprises a toxic moiety that is an RNase linked to a recognition moiety that binds a specific cell surface marker. (Abstract, line 1-4) |
| comprising an antibody | "The recognition moiety may be an antibody or a modified form thereof..." (column 8, line 50-53) |
| and a moiety having ribonucleolytic activity derived from a non-human ribonuclease, i | The RNase cytotoxic reagent has ribonucleotytic activity, for example, bovine ribonuclease A or, most preferably for human applications, human angiogenin. (column 7, lines 65-67)<br>Preferably the RNase is one in the pancreatic RNase A superfamily. Many of such members are known an include, but are not limited to, frog lectin from *Rana Catesbaiana*...; onconase....bovine seminal RNase; and bovine pancreatic RNase. (column 8, lines 1-11) |
| wherein said antibody and said moiety are linked through recombinant production. | Further, recombinant DNA techniques can be used to link together the toxic moiety and the recognition moiety. (column 9, lines 53-54) |

| | |
|---|---|
| 33. A pharmaceutical composition comprising a cytotoxic reagent of claim 1 and a pharmaceutically acceptable carrier. | The present invention also relates to a pharmaceutical composition comprising a cytotoxic reagent of the present invention, and a pharmaceutically acceptable carrier (column 11, lines 31-34) |

| | |
|---|---|
| 34. A method of killing cancer cells comprising administering to a subject in need thereof a pharmaceutical composition of claim 33. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62)<br><br>For example, the cytotoxic reagent of this invention includes those with a recognition moiety that binds to a tumor cellpspecific surface marker, of which many are known in the art. (column 10, lines 46-49). |

| | |
|---|---|
| 48. A method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 33. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62) |

[redacted]

## Claim 2 and related claims 24, 25, and 27

| '104 Patent Claim | Exemplary '840 Patent Disclosure |
|---|---|
| 2. A cytotoxic reagent | The present invention relates a selective RNase reagent. The reagent comprises a toxic moiety that is an RNase linked to a recognition moiety that binds a specific cell surface marker. (Abstract, line 1-4) |
| comprising an internalizing antibody | RNase A was conjugated to an antibody to the human T cell-specific antigen CD5 (T101) (column 13, lines 34-35) |
| and a moiety having ribonucleolytic activity, | The RNase cytotoxic reagent has ribonucleotytic activity, for example, bovine ribonuclease A or, most preferably for human applications, human angiogenin. (column 7, lines 65-67)<br>Preferably the RNase is one in the pancreatic RNase A superfamily. Many of such members are known an include, but are not limited to, frog lectin from *Rana Catesbaiana*...; onconase....bovine seminal RNase; and bovine pancreatic RNase. (column 8, lines 1-11) |
| wherein said internalizing antibody is directed against a lineage-dependent antigen or against and antigen associated with cancer cells, and | RNase A was conjugated to an antibody to the human T cell-specific antigen CD5 (T101) (column 13, lines 34-35) |
| wherein said internalizing antibody and said moiety are linked through recombinant production. | Further, recombinant DNA techniques can be used to link together the toxic moiety and the recognition moiety. (column 9, lines 53-54) |

| | |
|---|---|
| 24. A pharmaceutical composition comprising a cytotoxic reagent of claim 1 and a pharmaceutically acceptable carrier. | The present invention also relates to a pharmaceutical composition comprising a cytotoxic reagent of the present invention, and a pharmaceutically acceptable carrier (column 11, lines 31-34) |

| | |
|---|---|
| 25. A method of killing cancer cells comprising administering to a subject in need thereof a pharmaceutical composition of claim 24. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62)<br><br>For example, the cytotoxic reagent of this invention includes those with a recognition moiety that binds to a tumor cellpspecific surface marker, of which many are known in the art. (column 10, lines 46-49). |

| | |
|---|---|
| 47. A method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 24. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62) |

## Claim 51 and related claims 75, 76, and 89

| '104 Patent Claim | Exemplary '840 Patent Disclosure |
|---|---|
| 51. A cytotoxic reagent | The present invention relates a selective RNase reagent. The reagent comprises a toxic moiety that is an RNase linked to a recognition moiety that binds a specific cell surface marker. (Abstract, line 1-4) |
| comprising an antibody | The recognition moiety may be an antibody or a modified form thereof... (column 8, line 50-53) |
| and a moiety having ribonucleolytic activity derived from a non-human ribonuclease, | The RNase cytotoxic reagent has ribonucleotytic activity, for example, bovine ribonuclease A or, most preferably for human applications, human angiogenin. (column 7, lines 65-67)<br>Preferably the RNase is one in the pancreatic RNase A superfamily. Many of such members are known an include, but are not limited to, frog lectin from *Rana Catesbaiana*...; onconase....bovine seminal RNase; and bovine pancreatic RNase. (column 8, lines 1-11) |
| wherein said antibody is directed to an antibody against an antigen other than a B-cell antigen. | The cytotoxic agents of the present invention may also be directed toward immune dysfunctional cells in immune and autoimmune disease. The recognition moiety of such cytotoxic reagents is directed towards T-cell antigens or subsets thereof; (column 11, lines 21-25) |

| | |
|---|---|
| 75. A pharmaceutical composition comprising a cytotoxic reagent of claim 1 and a pharmaceutically acceptable carrier. | The present invention also relates to a pharmaceutical composition comprising a cytotoxic reagent of the present invention, and a pharmaceutically acceptable carrier (column 11, lines 31-34) |

| | |
|---|---|
| 76. A method of killing cancer cells comprising administering to a subject in need thereof a pharmaceutical composition of claim 75. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62)<br><br>For example, the cytotoxic reagent of this invention includes those with a recognition moiety that binds to a tumor cellpspecific surface marker, of which many are known in the art. (column 10, lines 46-49). |

| | |
|---|---|
| 89. A method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 75. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62) |

[redacted]

## Claim 52 and related claims 67, 68, and 88

| '104 Patent Claim | Exemplary '840 Patent Disclosure |
|---|---|
| 52. A cytotoxic reagent | The present invention relates a selective RNase reagent. The reagent comprises a toxic moiety that is an RNase linked to a recognition moiety that binds a specific cell surface marker. (Abstract, line 1-4) |
| comprising an internalizing antibody | RNase A was conjugated to an antibody to the human T cell-specific antigen CD5 (T101) (column 13, lines 34-35) |
| and a moiety having ribonucleolytic activity, | The RNase cytotoxic reagent has ribonucleotytic activity, for example, bovine ribonuclease A or, most preferably for human applications, human angiogenin. (column 7, lines 65-67)<br>Preferably the RNase is one in the pancreatic RNase A superfamily. Many of such members are known an include, but are not limited to, frog lectin from *Rana Catesbaiana*...; onconase....bovine seminal RNase; and bovine pancreatic RNase. (column 8, lines 1-11) |
| wherein said internalizing antibody is directed against a lineage-dependent antigen or against an antigen associated with cancers cells, and wherein said internalizing antibody is directed against an antigen selected from the group consisting of:<br>a) T cell antigens:<br>(b) MUC1 antigens;<br>(c) EGP-1 antigens:<br>(d) EGP-2 antigens; and<br>(e) placental alkaline phosphatase antigen. | RNase A was conjugated to an antibody to the human T cell-specific antigen CD5 (T101) (column 13, lines 34-35) |

| | |
|---|---|
| 67. A pharmaceutical composition comprising a cytotoxic reagent of claim 1 and a pharmaceutically acceptable carrier. | The present invention also relates to a pharmaceutical composition comprising a cytotoxic reagent of the present invention, and a pharmaceutically acceptable carrier (column 11, lines 31-34) |

| | |
|---|---|
| 68. A method of killing cancer cells comprising administering to a subject in need thereof a pharmaceutical composition of claim 67. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62)<br><br>For example, the cytotoxic reagent of this invention includes those with a recognition moiety that binds to a tumor cellpspecific surface marker, of which many are known in the art. (column 10, lines 46-49). |

| | |
|---|---|
| 88. A method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 67. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62) |

## Claim 92 and related claims 123, 124, and 138

| '104 Patent Claim | Exemplary '840 Patent Disclosure |
|---|---|
| 92. A cytotoxic reagent | The present invention relates a selective RNase reagent. The reagent comprises a toxic moiety that is an RNase linked to a recognition moiety that binds a specific cell surface marker. (Abstract, line 1-4) |
| comprising an antibody | "The recognition moiety may be an antibody or a modified form thereof..." (column 8, line 50-53) |
| and a moiety having ribonucleolytic activity derived from a nonhuman ribonuclease, | The RNase cytotoxic reagent has ribonucleotytic activity, for example, bovine ribonuclease A or, most preferably for human applications, human angiogenin. (column 7, lines 65-67)<br>Preferably the RNase is one in the pancreatic RNase A superfamily. Many of such members are known an include, but are not limited to, frog lectin from *Rana Catesbaiana*...; onconase....bovine seminal RNase; and bovine pancreatic RNase. (column 8, lines 1-11) |
| wherein said antibody is human or humanized. | For example, a preferred recognition moiety for a cytotoxic reagent for use in human is a "humanized" chimeric antibody against a cell receptors...(column 8, lines 58-60) |

| | |
|---|---|
| 123. A pharmaceutical composition comprising a cytotoxic reagent of claim 1 and a pharmaceutically acceptable carrier. | The present invention also relates to a pharmaceutical composition comprising a cytotoxic reagent of the present invention, and a pharmaceutically acceptable carrier (column 11, lines 31-34) |

| | |
|---|---|
| 124. A method of killing cancer cells comprising administering to a subject in need thereof a pharmaceutical composition of claim 123. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62)<br><br>For example, the cytotoxic reagent of this invention includes those with a recognition moiety that binds to a tumor cellpspecific surface marker, of which many are known in the art. (column 10, lines 46-49). |

| | |
|---|---|
| 138. A method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 124. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62) |

## Claim 93 and related claims 114, 115, and 137

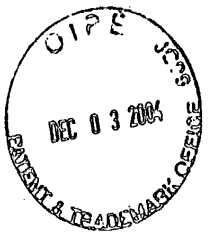
| '104 Patent Claim | Exemplary '840 Patent Disclosure |
|---|---|
| 93. A cytotoxic reagent | The present invention relates a selective RNase reagent. The reagent comprises a toxic moiety that is an RNase linked to a recognition moiety that binds a specific cell surface marker. (Abstract, line 1-4) |
| comprising an internalizing antibody | RNase A was conjugated to an antibody to the human T cell-specific antigen CD5 (T101) (column 13, lines 34-35) |
| and a moiety having ribonucleolytic activity, | The RNase cytotoxic reagent has ribonucleotytic activity, for example, bovine ribonuclease A or, most preferably for human applications, human angiogenin. (column 7, lines 65-67)<br>Preferably the RNase is one in the pancreatic RNase A superfamily. Many of such members are known an include, but are not limited to, frog lectin from *Rana Catesbaiana*...; onconase....bovine seminal RNase; and bovine pancreatic RNase. (column 8, lines 1-11) |
| wherein said internalizing antibody is directed against a lineage-dependent antigen or against an antigen associated with cancers cells, and | RNase A was conjugated to an antibody to the human T cell-specific antigen CD5 (T101) (column 13, lines 34-35) |
| wherein said internalizing antibody is human or humanized. | For example, a preferred recognition moiety for a cytotoxic reagent fur use in human is a "humanized" chimeric antibody against a cell receptors.....(column 8, lines 58-60). |

| | |
|---|---|
| 114. A pharmaceutical composition comprising a cytotoxic reagent of claim 1 and a pharmaceutically acceptable carrier. | The present invention also relates to a pharmaceutical composition comprising a cytotoxic reagent of the present invention, and a pharmaceutically acceptable carrier (column 11, lines 31-34) |

| | |
|---|---|
| 115. A method of killing cancer cells comprising administering to a subject in need thereof a pharmaceutical composition of claim 114. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62)<br><br>For example, the cytotoxic reagent of this invention includes those with a recognition moiety that binds to a tumor cell specific surface marker, of which many are known in the art. (column 10, lines 46-49). |

| | |
|---|---|
| 137. A method of selectively killing unwanted types of cells in a subject comprising administering to said subject a pharmaceutical composition of claim 114. | Further, the present invention relates to a method of selectively killing cells using a selective cytotoxic reagent of the present invention (column 11, lines 60-62) |

[redacted]






CERTIFICATE OF SERVICE

It is hereby certified that a true copy of this REQUEST FOR *INTER PARTES* REEXAMINATION UNDER 37 CFR §1.915 with APPENDICES A and B and a copy of U.S. PATENT NO. 6,653,104 was served on this 1st day of December 2004 by FedEx Priority to the patent owner and their attorney of record:

David M. Goldenberg
Immunomedics, Inc.
300 American Road
Morris Plains, NJ 07950

Stephen B. Maebius
FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143

Kenneth A. Weber

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, CA 94111-3834
Telephone: 415-576-0200
Telefax: 415-576-0300