

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte LAWRENCE S. LAMB JR.

Appeal No. 2005-1511
Application No. 09/879,398

ON BRIEF

ELLIS, MILLS and GREEN, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 2-7, 11, 12, 16 and 18, all the claims remaining in the application. Claims 1, 8-10, 13-15, 17 and 19-23 have been cancelled.

Claims 6, 4 and 11 are representative of the subject matter on appeal and read as follows:

6. A method of treating a patient with acute lymphoblastic leukemia comprising the steps of:

obtaining a donor material comprising bone marrow or peripheral blood collected from a donor;

depleting said donor material in vitro of $\alpha\beta$ + T cells, thereby rendering the donor material rich in $\gamma\delta$ + T cells;

activating said $\gamma\delta$ + T cells in vitro by treating said cells with a media comprising leukemia cells extracted from the patient and irradiated ex vivo, alone or in combination with an anti-T cell receptor (TCR) pan- δ antibody; and

administering an effective amount of said activated $\gamma\delta$ + T cells to said leukemia patient, wherein said activated $\gamma\delta$ + T cells are cytolytic to the patient's leukemia cells but minimally cytotoxic to the patient's other cells.
4. The method in accordance with claim 6, wherein said activated $\gamma\delta$ + T cells predominantly express the V δ 1 phenotype.
11. The method in accordance with claim 6, wherein said media consists essentially of irradiated leukemia blast cells extracted from said patient, an anti-TCR-pan- δ antibody, and interleukin-2.

The references relied upon by the examiner are:

Bell et al.(Bell) WO 98/33891 Aug. 6, 1998

Ensslin et al. (Ensslin), "Comparison of cytolytic and proliferative activities of human $\gamma\delta$ and $\alpha\beta$ T cells from peripheral blood against various human tumor cell lines," J. of National Cancer Institute, Vol. 83, pp. 1564-1569 (1991).

Lamb et al. (Lamb), "Increased frequency of TCR $\gamma\delta$ + T cells in disease-free survivors following T cell-depleted, partially mismatched, related donor bone marrow transplantation for leukemia," J. Hematotherapy, Vol. 5, pp. 503-509 (1996).

Coligan et al. (Coligan), Current Protocols in Immunology, Vol. 2, Chapter 7.4, pp. 7.4.1-7.4.6, John Wiley & Sons, Inc. (1995).

Falkenburg et al. (Falkenburg), "Generation of donor-derived antileukemic cytotoxic T-lymphocyte responses for treatment of relapsed leukemia after allogeneic HLA-identical bone marrow transplantation." J. Immunotherapy, Vol. 14, pp. 305-309 (1993).

Viale et al. (Viale), "TCR $\gamma\delta$ positive lymphocytes after allogeneic bone marrow transplantation," Bone Marrow Transplantation, Vol. 10, pp. 249-253 (1992).

Duval et al. (Duval), "Potential antileukemic effect of $\gamma\delta$ T cells in acute lymphoblastic leukemia," Leukemia, Vol. 9, pp. 863-868 (1995).

Bigby et al. (Bigby), "Most $\gamma\delta$ T cells develop normally in the absence of MHC class II molecules," J. of Immunology, Vol. 151, pp. 4465-75 (1993).

Skyes et al. (Skyes), "Interleukin 2 prevents graft-versus-host disease while preserving the graft-versus-leukemia effect of allogeneic T cells," Proc. Natl. Acad. Sci., USA, Vol. 87, pp. 5633-37 (1990).

The claims stand rejected as follows:

- I. Claims 2, 3, 6, 7, 12, 16 and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bell, Ensslin, Lamb, Coligan and Falkenburg.
- II. Claims 4 and 5 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bell, Ensslin, Lamb, Coligan and Falkenburg as applied to claims 2, 3, 6, 7, 12, 16 and 18, above, and in further view of Viale and Duval.
- III. Claim 11 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Bell, Ensslin, Lamb, Coligan and Falkenburg as applied to claims 2, 3, 6, 7, 12, 16 and 18, above, and in further view of Bigby and Sykes.

We have carefully considered the respective positions of both the appellant and the examiner and find ourselves in substantial agreement with that of the appellant. Accordingly, we reverse.

Background

The present invention is directed to the treatment of acute lymphoblastic leukemia using a selected population of white blood cell (lymphocyte) known as $\gamma\delta$ + T cells. Prior to the present invention, it was known in the art that

Lymphocytes are short-lived cells produced from bone marrow stem cells that give rise to B cells, T cells and natural killer (NK) cells, in addition to all other blood cells. A key feature of stem cells is their ability to provide a constant source of progenitor cells that possess a high proliferative capacity, but are committed to produce cells of one or more blood cell lineage. Cells of the immune system are collectively referred to as lymphoid cells and are believed to be descended from a common lymphoid progenitor cell. [Bell, p. 2, para. 1].

With respect to T cells in particular, it was also known by prior investigators that they

. . . recognize antigenic determinants through a surface receptor called the T cell receptor (TcR). . . . T cells mediate their prime immunological function through direct contact with infected host cells. These infected cells cooperate by displaying (presenting) antigenic fragments of foreign proteins on their surface as a means of signaling to T cells that they are infected. While T cells recognize antigens presented on all host cells, T cells are first activated to recognize these antigens by specialized antigen-presenting cells such as dendritic cells, B cells and macrophages. . . . Together with macrophages, T cells are the main component of the cell-mediated immune response and, through the release of soluble factors, are required for virtually all aspects of the immune response. In addition to the T cell receptor, T cells are characterized by two major T cell-specific surface markers, CD4 and CD8, which define functionally distinct T cell populations. CD4 T cells, called T helper cells, are activated through interaction with antigen-presenting cells and function primarily to activate CD8 T cells, also known as cytotoxic or killer T cells (CTL). CTLs are the main effector T cell mediating the destruction of infected host cells and

only recognize foreign antigens that are bound to specialized molecules found on virtually all cells. Thus, most infected cells of the body may serve as CTL targets [Bell, p. 3].

Leukocytes express a variety of surface molecular markers that provide a basis for distinguishing progenitor and mature cells. The clusters of differentiation (CD) numbering system has been devised to provide a universal means for identifying various types of leukocytes. Surface markers on leukocytes are antigenic and can be bound by monoclonal antibodies. By agreement, CD numbers have been assigned to those surface markers to which are bound antibodies having similar specificity characteristics. For example, T cells were found to be distinguished from B cells by their ability to bind to sheep erythrocytes via the CD2 surface marker. Thus, CD2 is a marker for T cells. Of course, the primary surface marker distinguishing T cells is the T cell antigen receptor (TcR), which forms a complex with another T cell specific surface marker, CD3. Most T cells express a T cell receptor composed of an alpha (α) chain and a beta (β) chain (TcR $\alpha\beta$), while a small subset express a TcR composed of gamma (γ) chain and a delta (δ) chain (TcR $\gamma\delta$) [Bell, p. 7].

With regard to T cells specifically, the vast majority of T cells can be subdivided into either CD4+ or CD8+ cells, i.e., T cells which express either the CD4 or CD8 marker. CD4+ T cells are also known as helper T cells, and function to positively or negatively influence the immune response of B cells and other T cells. CD8+ T cells are called cytotoxic or killer T cells. Suppressor T cells, which are activated by CD4+ cells, also are CD8+. Other lymphocytes which exhibit a cytotoxic function include natural killer (NK) cells and lymphokine activated killer (LAK) cells, which cells are both CD4- and CD8-, cytokine induced killer cells (CIK) which co-express CD56, CD3, TcR $\alpha\beta$ and CD8, and TcR $\gamma\delta$ + cells which are either CD4-/CD8- or CD4-/CD8+ [Bell, para. bridging pp. 7-8].

According to the appellant, he

. . . previously reported an improved survival advantage for patients who develop an increased number of $\gamma\delta$ + T cells following allogeneic BMT [bone marrow transplant]. (Lamb, et al., J Hematotherapy, 1996 - of record). Appellant posited that this increase played a role in graft-versus-leukemia effect. Accordingly, he isolated the leukemia cells and phenotypically characterized them. He was then able to replicate in vitro the process which presumably occurs in vivo: intentionally selecting for $\gamma\delta$ + T cells in the donor material and subsequently activating them through exposure to the recipient's own leukemia blast cells so as to render the activated $\gamma\delta$ + T

cells selectively cytolytic to recipient's leukemia cells yet minimally cytotoxic to his other "normal" cells. When these activated $\gamma\delta$ + T cells are subsequently transplanted into the leukemia patient (i.e., the original donor of [the] activating blast cells), they, like their naturally arising analogs, correlate to lower relapse rates and improved survival [Brief, para. bridging pp. 4-5].

Discussion

Rejection I

Bell discloses methods of "producing an expanded culture of lymphocytes containing an enriched fraction of a desired population of lymphocytes." Bell, p. 8, lines 25-26. Bell further discloses that "[t]he target lymphocyte population to be expanded can be selected from any mammalian lymphocyte population, preferably a primary mammalian lymphocyte population, and more preferably a primary human lymphocyte population [emphasis added]". . . for example, from a patient's peripheral blood, "bone marrow, lymph or lymph node, or other cells or tissues of the lymphohematopoietic system [p. 12, lines 23-28]." The cell populations which "can be expanded and enriched in the starting population include, for example, stem cells, progenitor cells, precursor cells and fully differentiated cells (i.e. cells at all stages of differentiation) [sentence bridging pp. 12-13]."

Bell still further discloses that the target cell population must be cultured in a conditioned medium (CM) in order to achieve expansion of the target lymphocytes. Bell, p. 8, line 24- p. 9, line 1. The starting cell population which is used to produce a conditioned medium (CM) is said to be "preferably selected from peripheral blood cells, umbilical cord blood cells or bone marrow cells"

(sentence bridging) pp. 13-14. The conditioned medium is preferably produced by culturing the starting cell population with mitogens which include, inter alia, “plant lectins such as concanavalin A (ConA) or phytohemagglutinin (PHA), T-cell mitogens such as mezerein (Mzn) or tetradecanoyl phorbol acetate (TPA) or a T-cell antibody such as those directed against the CD3 or CD28 antigen” [p. 9; see also, pp. 14-15]; as well as “Staphylococcal enterotoxin A (SEA), Steptococcal protein A, galactase oxidase and T cell antibodies such as anti-CD3 antibodies (e.g. OKT3) or anti-CD28 antibodies” [p. 15, lines 14-16]. Bell still further discloses that the “CM can be selectively modified by removing or adding specific factors to favor the proliferation of a different target cell population.” Id., p. 9, lines 18-19.

Briefly summarized, we find that Bell discloses a method which involves growing a starting cell population of a donor (which can comprise, for example, bone marrow or peripheral blood), in the presence of at least two mitogens to produce a conditioned medium. Claim 1 and Example 1, pp. 17-18. The conditioned medium is then used to culture the population of lymphohematopoietic cells to obtain an expanded population of the target lymphocytes. Id. We find that Bell mentions $\gamma\delta$ T cells; but does not teach or suggest any methods of selectively enriching this subset of T cells from the aforementioned expanded lymphocyte population as required by the claimed invention.

Ensslin discloses the enrichment of $\gamma\delta$ T cells from peripheal blood lymphocytes (PBL) using anti-TCR δ 1 monoclonal antibody. Ensslin, the

abstract; p. 1565, col. 1, second para. and col. 3, para. 1. Ensslin further discloses that the cytolytic activity of the enriched $\gamma\delta$ T cells (i) was four (4) to fifteen (15) times greater against tumor cells than $\alpha\beta$ T cells; (ii) was not major histocompatibility complex (MHC) restricted; and (iii) did not involve the $\gamma\delta$ T cell antigen receptor (TcR). Id., the abstract. Ensslin still further discloses that the enriched $\gamma\delta$ T cells proliferated in response to Ovcar-3 tumor cells. Id., the abstract; p. 1568, col. 3, first complete para. According to Ensslin, these results “opens the possibility of generating tumor-specific $\gamma\delta$ T cells and expanding these cells into numbers adequate for adoptive immunotherapy.” Id.

Lamb discloses that it is necessary to use allogeneic (genetically different, but from the same species) bone marrow transplant (BMT) in patients to produce a graft-versus-leukemia (GVL) effect in patients. Lamb, p. 503, col. 1, para. 1. Lamb further discloses that leukemia patients who received “partially HLA-mismatched grafts from related donors that were T cell depleted with the anti-TCR $\alpha\beta$ monoclonal antibody T10B9.1A-31 and complement” (i.e., T cells that were enriched for $\gamma\delta^+$ T cells by negative selection), “survived for at least 100 days following [bone marrow] transplantation.” Id., the abstract. Moreover, “[t]en patients (23.2%) were found to have an increased ($\geq 10\%$) proportion of $\gamma\delta^+$ T cells in the peripheral blood at 60-270 days after BMT. All of these patients remain alive, and 9 (90% of patients with $\geq 10\%$ $\gamma\delta^+$ cells) are free of disease at 2.5 years compared with a disease-free survival probability of 31% among patients with a normal proportion and concentration of $\gamma\delta^+$ T cells.” Id.

Falkenburg discloses the use of allogeneic bone marrow transplantation (BMT) for the treatment of leukemias, including acute lymphoblastic leukemia (ALL), in order to increase the likelihood of a graft-versus-leukemia (GVL) response in the patient. See, e.g., the abstract and p. 306, col. 1, first complete para. Falkenburg further discloses that since the use of T cell-depleted BMTs “reduce[s] the incidence and severity of graft-versus-host disease (GVHD)[,]” but increases the risk of relapse, “GVL reactivity has been attributed to the T lymphocytes from the graft.” Id., the abstract. Falkenburg still further discloses that “leukemia-reactive cytotoxic T-lymphocyte (CTL) lines and clones could be generated from the peripheral blood of HLA-genotypically identical siblings of patients with leukemia by stimulation of the donor cells with irradiated leukemic cells from the patients.” Id., the abstract; see also, p. 306, col. 2, para. 1. Falkenburg still further discloses using irradiated leukemic cells from patients who relapsed after receiving an allogeneic HLA-identical BMT for three types of leukemias, including ALL, to stimulate the patient’s own CTL lines to reduce the risk of GvHD. Id., the abstract; p. 306, col. 2, last para.; p. 307, col. 1, first complete para. According to Falkenburg this latter procedure produces antileukemic cell lines which “will be used in a phase I/II trial for the treatment of relapsed leukemia after allogeneic BMT.” Id., p. 308, col. 2, last sentence.

Coligan discloses a method for the negative selection of T cells from peripheral blood mononuclear cells using immunomagnetic microspheres coated with CD4+ and CD8+ antibodies.

The examiner argues that it would have been obvious to one of ordinary skill in the art to enrich $\gamma\delta^+$ T cells by negative selection as taught Lamb and Coligan,

. . . then activate the isolated gamma delta T cells in vitro by treating said cells with a media consisting essentially of leukemia cells extracted from the patient that have been irradiated ex vivo and IL-2 as taught by Falkenburg [] to render them cytolytic only to the patient's leukemia cells instead of other tumor cells and/or in combination with anti-T cell receptor (TCR) pan- δ antibody as taught by Ensslin et al to render $\gamma\delta^+$ T cells cytolytic only to the patient's leukemia cells but minimally cytotoxic to other cells as taught by Ensslin et al and Falkenburg et al and then administering activated donor gamma delta + T cells to leukemia patient with ALL as taught by [Bell], Falkenburg, Lamb et al and Ensslin et al. It would have been obvious to one of ordin[ar]y skill in the cancer art at the time the invention was made to substitute the [] human tumor cell lines as taught by Ensslin or any tumor cells as taught by [Bell] for the patient's leukemia cells as taught by Falkenburg for a method of activating gamma delta T cells that [are] specific for the patient's leukemia cells as taught by Falkenburg and Ensslin et al because Ensslin et al teach "the ability of $\gamma\delta^+$ T cells to proliferate in response to class I MHC expressed Ovar-3 tumor cells opens the possibility of generating tumor-specific $\gamma\delta^+$ T cells and expanding these cells into numbers adequate for adoptive immunotherapy. . . . From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have a reasonable [expectation] of success in producing the claimed invention [Answer, pp. 6-7].

The examiner further argues that one of ordinary skill in the art would have been motivated to apply the teachings Lamb, Ensslin, Falkenburg and Coligan "to the teachings of [Bell] because in leukemia patients who survived following transplantation using partially HLA-mismatched grafts from related donors that were T cell depleted with the anti-TCR $\alpha\beta$ monoclonal [antibody] and complement have an increase in frequency of $\gamma\delta^+$ T cells." Answer, p. 7.

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). To that end, it is the examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). This the examiner has not done.

Although Falkenburg and Lamb disclose different aspects of the claimed method of treating ALL patients, we agree with the appellants that neither these nor any of the other cited references teaches or suggests the present invention. Lamb discloses administering $\gamma\delta$ + T cells derived from an allogeneic donor to an ALL patient, but we do not find any suggestion therein to first prime the donor cells with irradiated leukemia cells derived from the patient. Falkenburg discloses irradiating leukemia cells and culturing them with CTL (cytotoxic T cells) from a donor, but the reference does not mention the use of $\gamma\delta$ + T cells. To the contrary, as pointed out by the appellant, the CTL lines taught by Falkenburg "were phenotyped with antibodies to CD2, CD3, CD4, CD8 and CD56 (see page 307), indicating that they were expecting to generate $\alpha\beta$ + T cells." Brief, p. 12. Thus, on this record, the only suggestion we find of culturing an ALL patient's own leukemia cells which have been irradiated ex vivo with an enriched population of a donor $\gamma\delta$ + T cells and to administer said T cells said ALL

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patient is in the appellant's disclosure. Accordingly, we find that the examiner has engaged in impermissible hindsight to arrive at the conclusion that the claimed invention would have been obvious over Bell, Ensslin, Lamb, Falkenburg and Coligan. In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985); W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-313 (Fed. Cir. 1983) cert. denied 469 U.S. 851 (1984) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher").

In view of the foregoing, Rejection I is reversed.

Rejections II and III

The examiner's rejection of claims 4, 5 and 11 (Rejections II and III) is based on an initial finding of the obviousness of independent claim 6 in view of the teachings of Bell, Ensslin, Lamb, Falkenburg and Coligan. Since we find that the examiner did not sustain his burden of establishing a prima facie case in this regard, these rejections fail for the reasons set forth above.

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Accordingly, in view of the foregoing, the decision of the examiner is reversed.

REVERSED

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Joan Ellis)	
Administrative Patent Judge)	
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Administrative Patent Judge)	APPEALS AND
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