

(12) **United States Patent**  
**Dedrick et al.**

(10) **Patent No.:** **US 6,582,698 B1**  
(45) **Date of Patent:** **Jun. 24, 2003**

(54) **TREATMENT METHOD**

(75) Inventors: **Russell L. Dedrick**, Kensington, CA (US); **Marvin R. Garovoy**, San Anselmo, CA (US); **Susan M. Kramer**, San Francisco, CA (US); **Karen M. Starko**, Hillsborough, CA (US)

(73) Assignees: **Genentech, Inc.**, South San Francisco, CA (US); **XOMA Technology, Ltd.**, Berkeley, CA (US)

(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/819,921**

(22) Filed: **Mar. 28, 2001**

**Related U.S. Application Data**

(62) Division of application No. 09/527,957, filed on Mar. 17, 2000, now abandoned.

(60) Provisional application No. 60/125,228, filed on Mar. 19, 1999, and provisional application No. 60/125,351, filed on Mar. 19, 1999.

(51) **Int. Cl.**<sup>7</sup> ..... **A61K 39/395**

(52) **U.S. Cl.** ..... **424/133.1**; 424/173.1;  
424/144.1; 424/154.1

(58) **Field of Search** ..... 424/144.1, 130.1,  
424/143.1, 152.1, 153.1, 154.1, 173.1, 133.1

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

5,002,869 A 3/1991 Schlossman et al.  
5,071,964 A 12/1991 Dustin et al.  
5,622,700 A \* 4/1997 Jardieu et al.

**FOREIGN PATENT DOCUMENTS**

AU	8815518	11/1988
CA	2008368	6/1991
EP	289949	11/1988
EP	346078	12/1989
EP	379904	8/1990
EP	387668	9/1990
WO	WO 88/06592	9/1988
WO	WO 90/10652	9/1990
WO	WO 90/15076	12/1990
WO	WO 91/16927	11/1991
WO	WO 91/16928	11/1991
WO	WO 91/18011	11/1991
WO	WO 94/02175	2/1994
WO	WO 94/04188	3/1994
WO	WO 98/23761	6/1998

**OTHER PUBLICATIONS**

Abramowicz et al., "Release of tumor necrosis factor, interleukin-2, and gamma-interferon in serum after injection of OKT3 monoclonal antibody in kidney transplant recipients" *Transplantation* 47(4):606-608 (Apr. 1989).

Azzawi et al., "Identification of Activated T Lymphocytes and Eosinophils in Bronchial Biopsies in Stable Atopic Asthma" *Am. Rev. Resp. Dis.* 142:1407-1413 (1990).

Bauer et al., "Population pharmacokinetics and pharmacodynamics of the anti-CD11a antibody hull24 in human subjects with psoriasis" *J. Pharmacokinetics and Biopharmaceutics* 27(4):397-420 (1999).

Benjamin et al., "Mechanisms of Monoclonal Antibody-Facilitated Tolerance Induction: A Possible Role for the CD4(L3T4) and CD11a (LFA-1) Molecules in Self-Non-Self Discrimination" *European Journal of Immunology* 18:1079-1088 (1988).

Campana et al., "Human leukocyte function-associated antigens on lympho-hemopoietic precursor cells" *European Journal of Immunology* 16(5):537-542 (May 1986).

Cavazzana-Calvo et al., "A phase II trial of partially incompatible bone marrow transplantation for high-risk acute lymphoblastic leukaemia in children: prevention of graft rejection with anti-LFA-1 and anti-CD2 antibodies." *British Journal of Haematology* 93(1):131-138 (Apr. 1996).

Cavazzana-Calvo et al., "Prevention of bone marrow and cardiac graft rejection in an H-2 haplotype disparate mouse combination by an anti-LFA-1 antibody" *Transplantation* 59(11):1576-1582 (Jun. 15, 1995).

Chatenoud et al., "In vivo cell activation following OKT3 administration: Systemic cytokine release and modulation by corticosteroids" *Transplantation* 49(4):697-702 (Apr. 1990).

Chatenoud et al., "Systemic reaction to the anti-T-cell monoclonal antibody OKT3 in relation to serum levels of tumor necrosis factor and interferon- $\alpha$ " *New England J. of Medicine* 320(21):1420-1421 (May 25, 1989).

Cockcroft et al., "Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine" *Am. Rev. Respir. Dis.* 135:264-267 (1987).

Collins, T., "Adhesion molecules in leukocyte emigration" *Science and Medicine* pp. 28-37 (1995).

Connolly et al., "Treatment of murine lupus with monoclonal antibodies to lymphocyte function-associated antigen-1: dose-dependent inhibition of autoantibody production and blockade of the immune response to therapy" *Clinical Immunology & Immunopathology* 72(2):198-203 (Aug. 1994).

(List continued on next page.)

*Primary Examiner*—Christina Chan  
*Assistant Examiner*—Maher Haddad  
(74) *Attorney, Agent, or Firm*—Lee Tan

(57) **ABSTRACT**

A method is provided for reducing the occurrence of fever, headache, nausea and/or vomiting associated with administration of a therapeutic compound to a mammal in need thereof, comprising administering to the mammal a first conditioning dose of a non-target cell depleting compound which binds to a cell surface receptor on a target mammalian cell; and administering a second therapeutic dose of the compound, wherein the second dose is higher than the first dose.

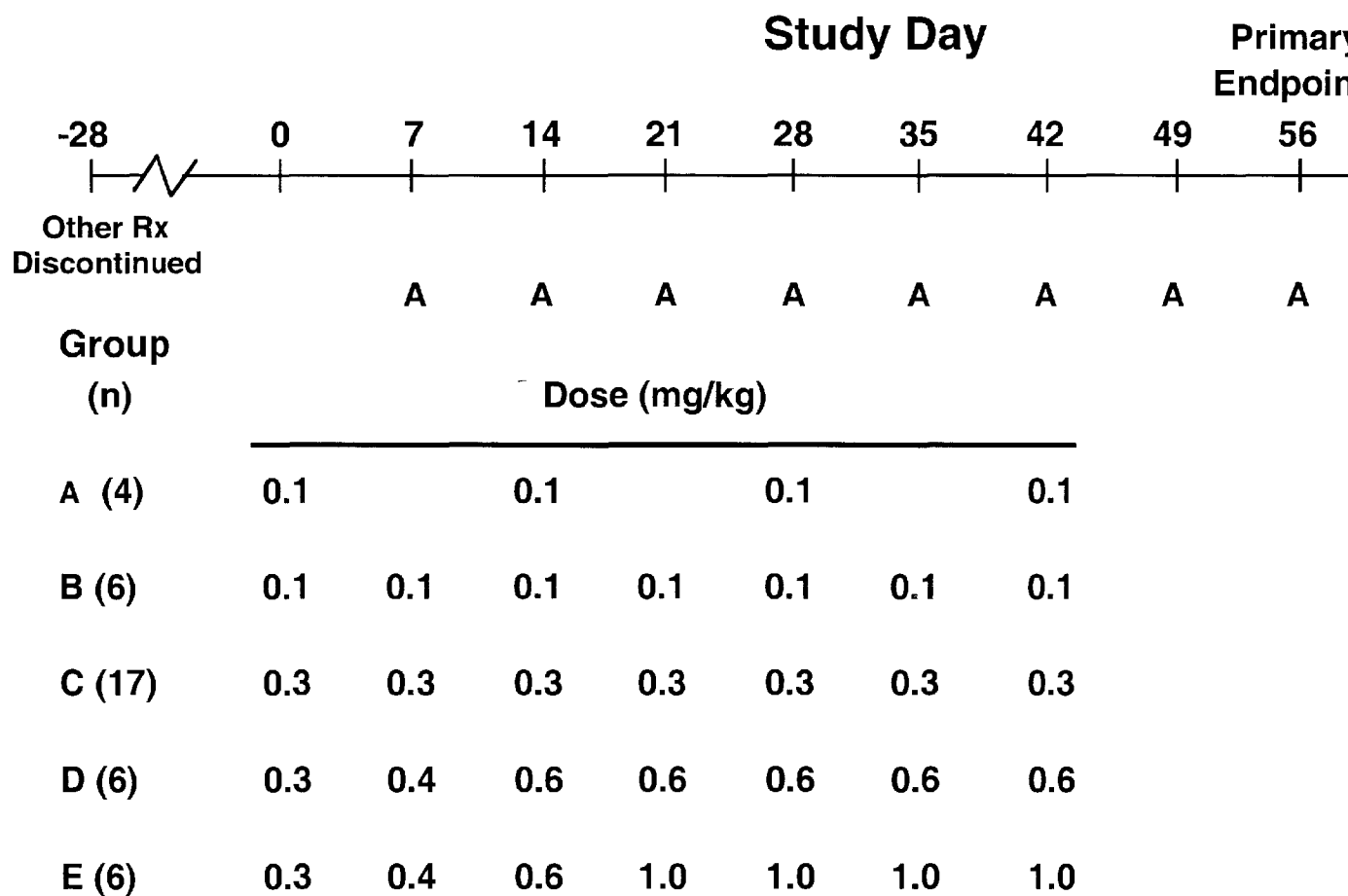
**8 Claims, 10 Drawing Sheets**

## OTHER PUBLICATIONS

- Corrigan & Kay, "CD4 T-Lymphocyte Activation in Acute Severe Asthma" *Am. Rev. Respir. Dis.* 141:970-977 (1990).
- Cosimi et al., "Use of monoclonal antibodies to T-cell subsets for immunologic monitoring and treatment in recipients of renal allografts" *New England J. of Medicine* 305(6):308-314 (Aug. 6, 1981).
- Crescioli et al., "Theophylline inhibits early and late asthmatic reactions induced by allergens in asthmatic subjects" *Ann. Allergy* 66:245-251 (Mar. 1991).
- Curnow, R., "Clinical experience with CD64-directed immunotherapy. An overview" *Cancer Immunology and Immunotherapy* 45(3-4):210-215 (Nov.-Dec. 1997).
- de Fougerolles et al., "Characterization of the function of intercellular adhesion molecule (ICAM)-3 and comparison with ICAM-1 and ICAM-2 in immune responses" *Journal of Experimental Medicine* 179(2):619-629 (Feb. 1, 1994).
- Desroches et al., "Regulation and Functional Involvement of Distinct Determinants of Leucocyte Function-Associated Antigen 1 (LFA-1) in T-Cell Activation In Vitro" *Scand. J. Immunol.* 33:277-286 (1991).
- Djukanovic et al., "Effect of an Inhaled Corticosteroid on Airway Inflammation and Symptoms in Asthma" *Am. Rev. Respir. Dis.* 145:669-674 (1992).
- Dustin and Springer, "Lymphocyte function-associated antigen-1 (LFA-1) interaction with intercellular adhesion molecule-1 (ICAM-1) is one of at least three mechanisms for lymphocyte adhesion to cultured endothelial cells" *Journal of Cell Biology* 107(1):321-331 (Jul. 1988).
- Dustin and Springer, "Role of lymphocyte adhesion receptors in transient interactions and cell locomotion" *Annual Review of Immunology* 9:27-66 (1991).
- Dustin et al., "Induction By IL 1 and Interferon- $\gamma$ : Tissue Distribution, Biochemistry, and Function of a Natural Adherence Molecule (ICAM-1)" *The Journal of Immunology* 137(1):245-254 (Jul. 1, 1986).
- Fekete et al., "Involvement of Lymphocyte Function-Associated Antigen-1 (LFA-1) But Not ICAM-1 in a Radioactive Leukocyte Cell-Mediated Immunity (LA-CMI) Assay" *J. Clin. Lab. Immunol.* 31:145-149 (1990).
- First et al., "The effect of indomethacin on the febrile response following OKT3 therapy" *Transplantation* 53(1):91-94 (Jan. 1992).
- Fischer et al., "Reduction of Graft Failure by a Monoclonal Antibody (Anti-LFA-1 CD11a) After HLA Nonidentical Bone Marrow Transplantation in Children with Immunodeficiencies, Osteopetrosis, and Fanconi's Anemia" *Blood* 77(2):249-256 (Jan. 15, 1991).
- Fischer et al., "Role of the LFA-1 Molecule in Cellular Interactions Required For Antibody Production in Humans" *The Journal of Immunology* 136(9):3198-3203 (May 1, 1986).
- Goldman et al., "OKT3-induced cytokine release attenuation by high-dose methylprednisolone" *Lancet* 2(8666):802-803 (Sep. 30, 1989).
- Goldstein et al., "A randomized clinical trial of OKT3 monoclonal antibody for acute rejection of cadaveric renal transplants. Ortho Multicenter Transplant Study Group" *New England J. of Medicine* 313(6):337-342 (Aug. 8, 1985).
- Gordon et al., "Both anti-CD11a (LFA-1) and anti-CD11b (MAC-1) therapy delay the onset and diminish the severity of experimental autoimmune encephalomyelitis" *Journal of Neuroimmunology* 62(2):153-160 (Nov. 1995).
- Gottlieb et al., "Psoriasis is clinically and histologically improved by treatment with a humanized anti-CD11a monoclonal antibody (hu1124): results of a multicenter, multiple ascending dose study" *J. Investigative Dermatology* (abstract only) 112(4):647 (Apr. 1999).
- He et al., "A Human Lymphocyte-associated Antigen Involved in Cell-mediated Lympholysis" *European Journal of Immunology* 13:202-208 (1983).
- Hourmant et al., "A randomized multicenter trial comparing leukocyte function-associated antigen-1 monoclonal antibody with rabbit antithymocyte globulin as induction treatment in first kidney transplantations" *Transplantation* 62(11):1565-1570 (Dec. 15, 1996).
- Hourmant et al., "Administration of an Anti-CD11a Monoclonal Antibody in Recipients of Kidney Transplantation" *Transplantation* 58(3):377-380 (Aug. 1994).
- Isaacs et al., "Humanized anti-CD4 monoclonal antibody therapy of autoimmune and inflammatory disease" *Clinical & Experimental Immunology* 110(2):158-166 (Nov. 1997).
- Isobe et al., "Specific acceptance of cardiac allograft after treatment with antibodies to ICAM-1 and LFA-1" *Science* 255(5048):1125-1127 (Feb. 28, 1992).
- Kato et al., "Specific acceptance of fetal bowel allograft in mice after combined treatment with anti-intercellular adhesion molecule-1 and leukocyte function-associated antigen-1 antibodies" *Annals of Surgery* 223(1):94-100 (Jan. 1996).
- Krensky et al., "The Functional Significance, Distribution, and Structure of LFA-1, LFA-2, and LFA-3: Cell Surface Antigens Associated with CTL-Target Interactions" *The Journal of Immunology* 131(2):611-616 (Aug. 1983).
- Kuypers et al., "Leukocyte Membrane Adhesion Proteins LFA-1, CR3 and p150,95: A Review of Functional and Regulatory Aspects" *Res. Immunol.* 140:461-486 (1989).
- Le Mauff et al., "Effect of anti-LFA1 (CD11a) monoclonal antibodies in acute rejection in human kidney transplantation" *Transplantation* 52(2):291-296 (Aug. 1991).
- Nakakura et al., "Potent and Effective Prolongation by Anti-LFA-1 Monoclonal Antibody Monotherapy of Non-Primarily Vascularized Heart Allograft Survival in Mice Without T Cell Depletion" *Transplantation* 55(2):412-417 (Feb. 1993).
- Nishihara et al., "Potent immunosuppressive effect of anti-LFA-1 monoclonal antibody on islet allograft rejection" *Transplantation Proc.* 27:372 (1995).
- Nishimura et al., "Lymphokine-activated cell-associated antigen involved in broad-reactive killer cell-mediated cytotoxicity" *Cellular Immunology* 94(1):122-132 (Aug. 1985).
- Nishimura et al., "The role of lymphokine-activated cell-associated antigen. III. Inhibition of T-cell activation by monoclonal killer-blocking antibody" *Cellular Immunology* 107(1):32-39 (Jun. 1987).
- Raasveld et al., "Complement activation during OKT3 treatment: a possible explanation for respiratory side effects" *Kidney International* 43(5):1140-1149 (May 1993).
- Sanchez-Madrid et al., "Mapping of antigenic and functional epitopes on the  $\alpha$ - and  $\beta$ -subunits of two related mouse glycoproteins involved in cell interactions, LFA-1 and MAC-1" *Journal of Experimental Medicine* 158(2):586-602 (Aug. 1, 1983).

- Springer et al., "The lymphocyte function-associated LFA-1, CD2, and LFA-3 molecules: cell adhesion receptors of the immune system" *Annual Review of Immunology* 5:223-252 (1987).
- Stoppa et al., "Anti-LFA1 Monoclonal Antibody (25.3) for Treatment of Steroid-resistant Grade III-IV Acute Graft-versus-host Disease" *Transplant International* 4:3-7 (1991).
- Talento et al., "A single administration of LFA-1 antibody confers prolonged allograft survival" *Transplantation* 55:418-422 (1993).
- Tanaka et al., "Prolonged inhibition of an antigen-specific IgE response in vivo by monoclonal antibody against lymphocyte function-associated antigen-1" *European Journal of Immunology* 25:1555-1558 (1995).
- Taylor et al., "The expression of CD18 is increased on Trisomy 21 (Down syndrome) lymphoblastoid cells" *Clinical & Experimental Immunology* 71(2):324-328 (Feb. 1988).
- ten Berge et al., "Consequences of OKT3 administration via continuous infusion as compared to bolus infusion" *Transplantation Proceedings* 28(6):3217-3220 (Dec. 1996).
- Van Dijken et al., "Evidence That Anti-LFA-1 in vivo Improves Engraftment and Survival After Allogeneic Bone Marrow Transplantation" *Transplantation* 49(5):882-886 (May 1990).
- Vasconcellos et al., "Cytotoxic Lymphocyte Gene Expression in Peripheral Blood Leukocytes Correlates with Rejecting Renal Allografts" *Transplantation* 66:562-566 (1998).
- Walker et al., "T Cell Subsets and Their Soluble Products Regulate Eosinophilia in Allergic and Nonallergic Asthma" *J. Immunol.* 146(6):1829-1935 (Mar. 15, 1991).
- Ward et al., "Blocking of Adhesion Molecules in vivo as Anti-Inflammatory Therapy" *Therapeutic Immunology* 1:165-171 (1994).
- Ward et al., "Theophylline—an Immunomodulatory Role In Asthma?" *Am. Rev. Respir. Dis.* 147(3):518-523 (1993).
- Werther et al., "Humanization of an Anti-Lymphocyte Function-Associated Antigen (LFA)-1 Monoclonal Antibody and Reengineering of the Humanized Antibody for Binding to Rhesus LFA-1" *J. of Immunology* 157:4986-4995 (1996).
- Woodle et al., "OKT3 escalating dose regimens provide effective therapy for renal allograft rejection" *Clinical Transplantation* 10(4):389-395 (Aug. 1996).

\* cited by examiner



**Figure 1**

<b>Group</b>	<b>Dose (mg/kg)</b>	<b>n</b>	<b>Day 0</b>	<b>Day 28</b>
<b>A</b>	<b>0.1/qow</b>	<b>4</b>	<b>23.6 ± 8.1</b>	<b>-11.3 ± 15.1</b>
<b>B</b>	<b>0.1</b>	<b>6</b>	<b>21.2 ± 6.5</b>	<b>-8.2 ± 15.1</b>
<b>C</b>	<b>0.3*</b>	<b>17</b>	<b>25.6 ± 7.4</b>	<b>-24.5 ± 21.7</b>
<b>D</b>	<b>0.3-0.6</b>	<b>6</b>	<b>23.8 ± 4.5</b>	<b>-30.1 ± 13.7</b>
<b>E</b>	<b>0.3-1.0</b>	<b>6</b>	<b>28.1 ± 6.1</b>	<b>-38.6 ± 16.7</b>
<b>Total</b>		<b>39</b>	<b>24.8 ± 6.8</b>	<b>-23.7 ± 20.0</b>

**Figure 2**

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.