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[54]	COMPOSITIONS AND METHODS OF USING				
	COMPOSITIONS WITH ACCELERATED				
	LYMPHOCYTE HOMING				
	IMMUNOSUPPRESSIVE PROPERTIES				

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[52] **U.S. Cl.** **424/278.1**; 514/487; 514/546; 514/653; 560/29; 560/163; 564/223; 564/355

[58] **Field of Search** 564/223, 355; 560/29, 163; 514/653, 487, 546; 424/278.1

[56] References Cited

U.S. PATENT DOCUMENTS

5,037,958 5,219,884		Hashimoto
5,604,229		Fujita et al
5,686,479	11/1997	Okumoto 514/383
5,719,175	2/1998	Fugita 514/440

FOREIGN PATENT DOCUMENTS

PCT/JP95/

01654 8/1995 Japan.

OTHER PUBLICATIONS

P. Cresswell, "Assembly, Transport, and Function of MHC Class II Molecules," Annu. Rev. Immunol., vol. 12, pp. 259-293 (1994).

M.R. Jackson et al., "Assembly and Intracellular Transport of MHC Class I Molecules," Annu. Rev. Cell Biol., vol. 9, pp. 207-235 (1993).

J.C. Howard, "Supply and transport of peptides presented by class I MHC molecules," Curr. Opin. Immunol., vol. 7, pp. 69-76 (1995).

B.D. Kahan, "Medical Intelligence, Drug Therapy, Cyclosporine," The New England Journal of Medicine, vol. 321, No. 25, pp. 1725-1738 (Dec. 21, 1989).

J. Fung et al., "A Randomized Trial of Primary Liver Transplantation Under Immunosuppression with FK 506 vs Cyclosporine," Transplantation Proceedings, vol. 23, No. 6, pp. 2977-2983 (Dec. 1991).

J.F. Borel et al., "Biological Effects of Cyclosporin A: A New Antilymphocytic Agent," Agents and Actions, vol. 6/4, pp. 468-475 (1976).

J. F. Borel, "Pharmacology of Cyclosporine (Sandimmune) IV. Pharmacological Properties in Vivo," Pharmacological Reviews, vol. 41, No. 3, pp. 259–371 (1989).

T. Kino et al., "FK-506, A Novel Immunosuppressant Isolated from a Streptomyces, I. Fermentation, Isolation and Physico-Chemical and Biological Characteristics," The Journal of Antibiotics, vol. 40, No. 9, pp. 1249-1255 (1987).

T. Kino et al., "FK-506, A Novel Immunosuppressant Isolated from a Streptomyces, II. Immunosuppressive Effect of FK-506 In Vitro," The Journal of Antibiotics, vol. 40, No. 9, pp. 1256-1265 (Sep. 1987).

N. Inamura et al., "Prolongation of Skin Allograft Survival in Rats by a Novel Immunosuppressive Agent, FK506," Transplantation, vol. 45, No. 1, pp. 206-209 (Jan. 1988).

J. Liu et al., "Calcineurin Is a Common Target of Cyclophilin-Cyclosporin A and FKBP-FK506 Complexes," Cell, vol. 66, pp. 807-815, (Aug. 23, 1991).

Y. Kokado et al., "Low-dose ciclosporin mizoribine and prednisolone in renal transplantation: A New triple-drug therapy," Clin. Transplantation, vol. 4, pp. 191–197 (1990). T. Fujita et al., "Fungal Metabolites, Part 11. A Potent Immunosuppressive Activity Found in Isaria sinclairii Metabolite," *The Journal of Antibiotics*, vol. 47, No. 2, pp. 208-215 (Feb. 1994).

T. Fujita et al., "Fungal Metabolites, Part 12. Potent Immunosuppressant, 14-Deoxomyriocin, (2S, 3R, 4R)—(E) -2-Amino-3,

4-Dihydroxy-2-Hydroxymethyleicos-6-Enoic Acid and Structure–Activity Relationships of Myriocin Derivatives," The Journal of Antibiotics, vol. 47, No. 2, pp. 216–224 (Feb. 1994).

S. Sasaki et al., "Fungal Metabolites. Part 14. Novel Potent Immunosuppressants, Mycestericins, Produced by Mycelia sterilia," The Journal of Antibiotics, vol. 47, No. 4, pp. 420-433 (Apr. 1994).

H.ff.S. Davies et al., "Long-Term Survival of Kidney Allografts in Dogs After Withdrawal of Immunosuppression with Ciclosporin and Azathioprine," Eur. Surg. Res., vol. 21, pp. 65–75 (1989).

H. Amemiya et al., "Synergistic Effect of Cylcosporine and Mizoribine on Survival of Dog Renal Allografts," Transplantation, vol. 46, No. 5, pp. 768-771 (Nov. 1988).

M.L. Arbonés et al., "Lymphocyte Homing and Leukocyte Rolling and Migration are Impaired in L-Selectin-Deficient Mice," Immunity, vol. 1, pp. 247-260 (Jul. 1994).

(List continued on next page.)

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[57] **ABSTRACT**

The methods and compositions of the invention and the compounds used in the invention involve a novel immunosuppression mechanism, accelerated lymphocyte homing immunosuppression (ALH-immunosuppression). For example, the compound FTY720 specifically directs lymphocytes to the peripheral lymph nodes, mesenteric lymph nodes, and Peyer's patches. By reversibly sequestering lymphocytes in these tissues, the compounds can inhibit an immune response in a mammal. Understanding these mechanisms provides a novel immunosuppression therapy that can synergistically interact with other immunosuppressive compounds. Screening methods for identifying similar ALH-immunosuppression compounds are also described. The invention allows better treatments and therapies wherever an immunosuppression regimen is desired.

6 Claims, 11 Drawing Sheets



OTHER PUBLICATIONS

- A. Hamann et al., "Role of α_4 -Integrins in Lymphocyte Homing to Mucosal Tissues in Vivo," *Journal of Immunology*, vol. 152, pp. 3282–3293 (1994).
- Y. Imai et al., "Sulphation requirement for GlyCAM-1, an endothelial ligand for L-selectin," *Nature*, vol. 361, pp. 555-557 (Feb. 11, 1993).
- T. B. Issekutz, "Inhibition of In Vivo Lymphocyte Migration to Inflammation and Homing to Lymphoid Tissues by the TA–2 Monoclonal Antibody," *The Journal of Immunology*, vol. 147, No. 12, pp. 4178–4184 (Dec. 15, 1991).
- C. Berlin et al., " $\alpha 4\beta 7$ Integrin Mediates Lymphocyte Binding to the Mucosal Vascular Addressin MadCAM-1," *Cell*, vol. 74, pp. 185–195 (Jul. 16, 1993).
- B.D. Kahan et al., "Preclinical Evaluation of a New Potent Immunosuppressive Agent, Rapamycin," *Transplantation*, vol. 52, No. 2, pp. 185–191 (Aug. 1991).
- R. Schwartz et al., "Drug-induced Immunological Tolerance," *Nature*, vol. 183, p. 1682 (Jun. 13, 1959).
- L.A. Turka et al., "Guanine Ribonucleotide Depletion Inhibits T Cell Activation," *J. Clin. Invest.*, vol. 87, pp. 940–948 (Mar. 1991).
- W.A. Lee et al., "Bioavailability Improvement of Mycophenolic Acid Through Amino Ester Derivatization," *Pharmaceutical Research*, vol. 7, No. 2, pp. 161–166 (1990).
- D.V. Cramer et al., "The Effect of a New Immunosuppressive Drug, Brequinar Sodium, on Heart, Liver, and Kidney Allograft Rejection in the Rat," *Transplantation*, vol. 53, No. 2, pp. 303–308 (Feb. 1992).
- L.J. Picker et al., "Physiological and Molecular Mechanisms of Lymphocyte Homing," *Ann. Rev. Immunol.*, vol. 10, pp. 561–591 (1992).
- J.E. Miller et al., "A New Model of Heterotopic Rat Heart Transplantation with Application for In Vivo ³¹P Nuclear Magnetic Resonance Spectroscopy," *Transplantation*, vol. 39, No. 5, pp. 555–558 (May 1985).
- M.J. Dallman et al., "Cytokine Gene Expression: Analysis using Northern Blotting, Polymerase Chain Reaction and in situ Hybridization," *Immunological Reviews*, No. 119, pp. 163–179 (1991).
- M.J. Dallman et al., "Cytokine Gene Transcription in Vascularised Organ Grafts: Analysis Using Semiquantitative Polymerase Chain Reaction," *J. Exp. Med.*, vol. 174, pp. 493–496 (Aug. 1991).
- J. Wang et al., "Local Hormone Networks and Intestinal T Cell Homeostasis," *Science*, vol. 275, pp. 1937–1939 (Mar. 28, 1997).
- European FK506 Multicentre Liver Study Group, "Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection", *The Lancet*, vol. 344, pp. 423–428 (Aug. 13, 1994).
- T. Tanaka et al., "Characterization of a CD3-like Rat T Cell Surface Antigen Recognized by a Monoclonal Antibody," *The Journal of Immunology,* vol. 142, No. 8, pp. 2791–2795 (Apr. 15, 1989).
- G.R. Woollett et al., "Molecular and antigenic heterogeneity of the rat leukocyte-common antigen from thymocytes and T and B lymphocytes," *Eur. J. Immunol.*, vol. 15, pp. 168–173 (1985).
- Y. Masaki et al., "Microchimerism and Heart Allograft Acceptance," *Transplantation Proceedings*, vol. 27, No. 1, pp. 148–150 (Feb. 1995).

- C. Legendre et al., "Prediction of Successful Allograft Rejection Retreatment with OKT3," *Transplantation*, vol. 53, No. 1, pp. 87–90 (Jan. 1992).
- T. Tamatani et al., Characterization of rat LECAM-1 (L-selectin) by the use of monoclonal antibodies and evidence for the presence of soluble LECAM-1 in rat sera, *Eur. J. Immunol.*, vol. 23, pp. 2181–2188, (1993).
- L.M. McEvoy et al., "Anti-CD43 inhibition of T Cell homing," *J. Exp. Med.*, vol. 185, No. 8, pp. 1493–1498 (Apr. 21, 1997) (Abstract only).
- T. Tamatani et al., "Characterization of the rat leukocyte integrin, CD11/CD18, by the use of LFA-1 subunit-specific monoclonal antibodies," *Eur. J. Immunol.*, vol. 21, pp. 627–633 (1991).
- A. Siegling et al., "A novel multispecific competitor fragment for quantitative PCR analysis of cytokine gene expression in rats," *Journal of Immunological Methods*, vol. 177, pp. 23–28 (1994).
- Copending U.S. Application Serial No. 08/801,390, filed Feb. 20, 1997.
- Tetsuro Fujita et al., "Simple Compounds, 2–alkyl–2–amino–1,3–propanediols Have Potent Immunosuppressive Activity", *BioMed. Chem. Lett.*, vol. 5, No. 8, pp. 847–852 (1995).
- T. Fujita et al., "Potent Immunosuppressants, 2–alkyl–2–aminopropane–1,3–diols", *J. Med. Chem.*, vol. 39, pp. 4451–4459 (1996).
- Kunitomo Adachi et al., "Design, Synthesis, And Structure–Activity Relationships of 2–substituted–2–amino–1,3–propanediols: Discovery of a Novel Immunosuppressant, FTY720", *BioMed. Chem. Lett.*, vol. 5, No. 8, pp. 853–856 (1995).
- K. Chiba et al., "FTY720, A Novel Immunosuppressant Possessing Unique Mechanisms. I. Prolongation of Skin Allograft Survival and Synergistic Effect in Combination with Cyclosporine in Rats", *Transplant. Proc.*, vol. 28, No. 2, pp. 1056–1059 (1996).
- Barry D. Kahan et al., "The Synergistic Interactions In Vitro and In Vivo of Brequinar Sodium with Cyclosporine or Rapamycin aAone and in Triple Combination", *Transplantation*, vol. 55, No. 4, pp. 894–900 (1993).
- Y. Hoshino et al., "FTY720, A Novel Immunosuppressant Possessing Unique Mechanisms. II. Long—Term Graft Survival Induction in Rat Heterotopic Cardiac Allografts and Synergistic Effect in Combination with Cyclosporine A", *Transplant. Proc.*, vol. 28, No. 2, pp. 1060–1061 (1996).
- T. Kawaguchi et al., "FTY720, A Novel Immunosuppressant Possessing Unique Mechanisms. III. Synergistic Prolongation of Canine Renal Allograft Survival in Combination With Cyclosporine A", *Transplant. Proc.*, vol. 28, No. 2, pp. 1062–1063 (1996).
- Seiichi Suzuki et al., "A Novel Immunosuppressant, FTY720, With A Unique Mechanism of Action, Induces Long-Term Graft Acceptance in Rat and Dog Allotransplantation", *Transplantation*, vol. 61, No. 2, pp. 200–205 (1996).
- S. Suzuki et al., "Long-Term Graft Acceptance in Allografted Rats and Dogs by Treatment With a Novel Immunosuppressant, FTY720", *Transplant. Proc.*, vol. 28, No. 3, pp. 1375–1376 (1996).
- Y. Masubuchi et al., "FTY720, A Novel Immunosuppressant, Possessing Unique Mechanisms. IV. Prevention of Graft Versus Host Reactions in Rats", *Transplant. Proc.*, vol. 28, No. 2, pp. 1064–1065 (1996).



F. Shanahan, "A Gut Reaction: Lymphoepithelial Communication in the Intestine", *Science*, vol. 275, pp. 1897–1898 (1997).

C. Legendre et al., "Prediction of Successful Allograft Rejection Retreatment With OKT3", *Transplantation*, vol. 53, pp. 94–94 (1992).

Hirose, R, et al., Bioorgan. Med. Chem. Let. 6(22)2647–2650, 1996.

Fujita, T., et al., Bioorgan. Med. Chem. Let. 5(16)1857–1860, 1995.

Chiba, K. Adachi, K. Drugs of the Future. 22(1)18–22, Mar. 26, 1997.

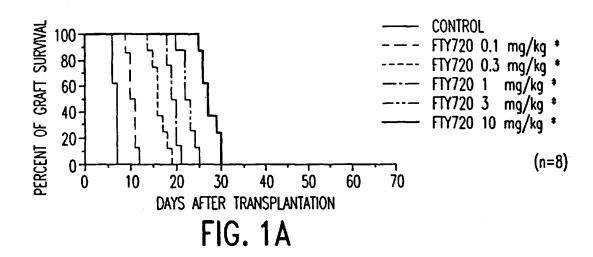
Suzuki, S. et al., Transplant. Proc. 28(4)2049-2050, Apr. 1996.

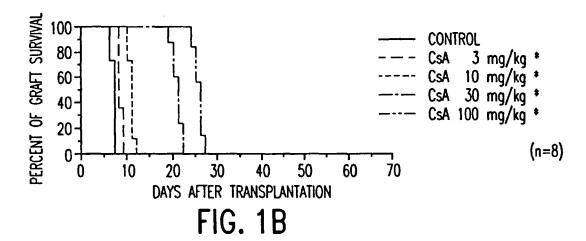
Enosawa, S., et al., Immunopharmacology 34:171–179, 1996.

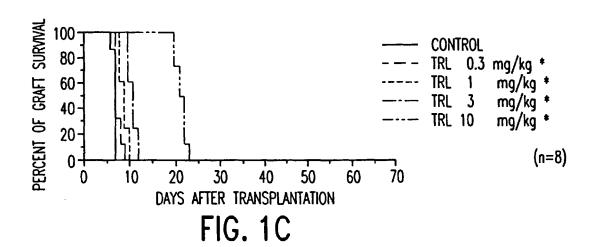
Suzuki, S., et al., Immunology. 89:518-523, 1996.

M. Slapak et al., "The Use of Low-Dose Cyclosporine in Combination With Azathioprine and Steriods in Renal Transplantation," *Transplantation Proceedings*, vol. XVII, No. 1, Feb. 1985, pp. 1222–1226.

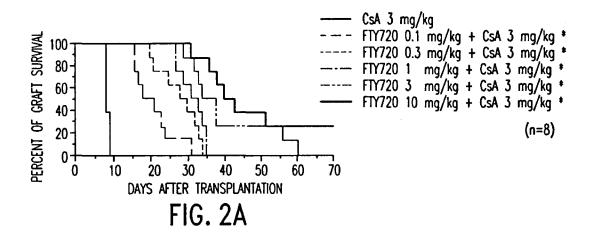


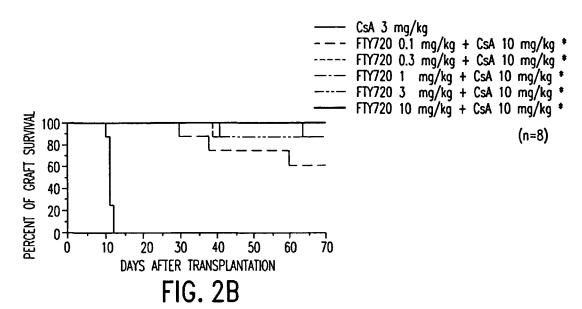


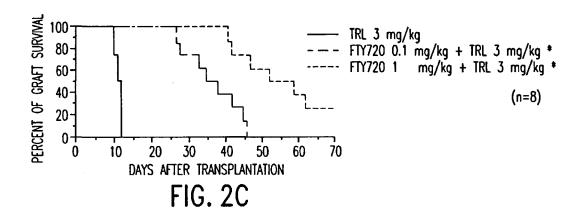














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