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(71) Applicant *(for all designated States except US)*: **THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA** [US/US]; Suite 300, 3700 Market Street, Philadephia, PA 19104-3147 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WASIK, Mariusz, A.** [US/US]; 210 Cedarbrook Road, Ardmore, PA 19003 (US). **SHAW, Leslie, M.** [US/US]; 705 Sunnyside Avenue, Audubon, PA 19403 (US).

(74) Agents: **COLBY, Gary, D.** et al.; Akin, Gump, Strauss, Hauer & Feld, L.L.P., One Commerce Square, 22nd floor, 2005 Market Street, Philadelphia, PA 19103-7986 (US).

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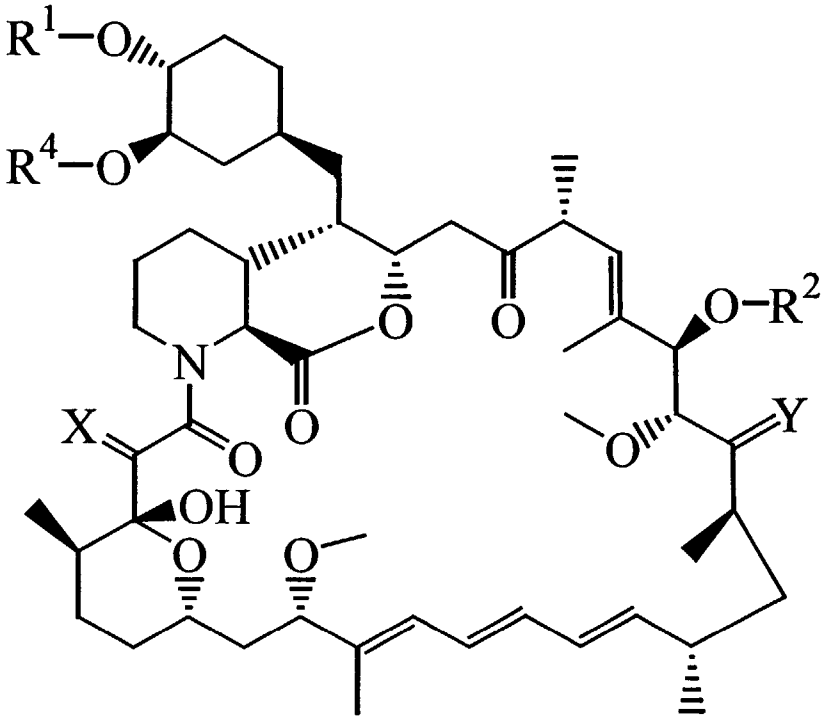
(54) Title: O-METHYLATED RAPAMYCIN DERIVATIVES FOR ALLEVIATION AND INHIBITION OF LYMPHOPROLIFERATIVE DISORDERS



(57) Abstract: The present invention relates to methods of alleviating and inhibiting a lymphoproliferative disorder in a mammal, the method comprising administering one or more rapamycin derivatives (including rapamycin) to the mammal (see figure 8). Further, the invention provides a method for identifying agents which are useful for alleviating and inhibiting lymphoproliferative disorders, as well as a method for identifying agents which are capable of inhibiting metastasis of lymphatic tumors in a mammal.

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TITLE

O-Methylated Rapamycin Derivatives for Alleviation and Inhibition of Lymphoproliferative Disorders

BACKGROUND OF THE INVENTION

Post-transplant lymphoproliferative disorders (PTLDs) which usually involve expansion of B lymphocytes infected with the Epstein-Barr virus (EBV), are a life-threatening complication of the immunosupressive therapy necessary to inhibit graft rejection (Morrison et al., 1994, Am. J. Med. 97:14-24; Warnke et a1., 1995, AFIP Fascicle 14:531-535). PTLDs comprise a whole spectrum of lymphoproliferative disorders ranging from a polyclonal atypical lymphoid hyperplasia to a monoclonal, overtly malignant B-cell lymphoma (Morrison et al., 1994, Am. J. Med. 97:14-24; Warnke et a1., 1995, AFIP Fascicle 14:531-535; Curtis et al., 1999, Blood 94:2208-2216; Harris et al., 1997, Semin. Diagn. Path. 14:8-14). Less advanced forms of PTLDs respond to a less aggressive course of immunosuppressive therapy (Morrison et al., 1994, Am. J. Med. 97:14-24; Sigal et al., 1992, Ann. Rev. Immunol. 10:519-60). However, lowering the dose of standard immunosuppressive drugs, which nullify the body's ability to reject and destroy foreign tissue, can jeopardize the survival of a graft. Moreover, this modification in treatment with conventional agents is not effective against malignant, lymphoma-type PTLDs which are usually fatal for the graft recipient.

Lymphoma causes significant morbidity and mortality, accounting for more than 50,000 new diagnoses annually in the United States alone. Many lymphomas are either Hodgkin's or non-Hodgkin's lymphomas, which can be derived from peripheral, mature B, T, or NK lymphomas. Based on their natural course, non-Hodgkin's lymphomas are classified into low, intermediate, and high grades. Low grade lymphomas are usually slowly progressive, but are essentially non-curable. The current 5-year disease-free, post-therapy survival rate for the intermediate and high grade lymphomas is approximately 60%. These aggressive types of lymphoma result in a rapid demise of the patients who do not respond to therapy. Prognosis of lymphomas occurring in patients who are

immunocompromised such as AIDS and post-transplant patients, is particularly poor. Therefore, new treatment modalities are needed to improve cure rate of lymphoma.

SDZ RAD (40-O-{2-hydroxyethyl}-rapamycin) is one of a class of rapamycin derivatives which exhibit immunosuppressive activities (PCT application WO 94/09010; Schuurman et al., 1997, Transplantation 64:32-5; Schuler et al. 1997, Transplantation 64:36-42; Sedrani, et al., 1998, Transplant. Proc. 30:2192-2194; Schuurman et al., 1998, Transplant Proc. 30:2198-2199; Hausen et al., 1999, J. Heart Lung Transplant 18:150-159). Compounds of this class, including rapamycin, have several points of action in normal T lymphocytes. They inhibit primarily down-stream signaling events mediated by the IL-2 receptor (Seghal, 1998, Clin. Biochem. 31:335-340) and other cytokine receptors (Sakata et al., 1999, Immunology Letters 68:301-309), but also affect cell-cycle progression at the early G_1 phase (Terada et al., 1993, J. Cell Physiol. 154:7-15; Flanagan et al., 1993, Ann. N.Y. Acad. Sci. 696:31-37). The multi-faceted immunosuppressive activities exhibited by SDZ RAD and other O-alkylated rapamycin derivatives compounds make these compounds versatile immunosuppressive agents.

There is a significant need for more effective therapeutic and prophylactic methods for limiting the severity and frequency of lymphoproliferative disorders such as lymphomas and PTLDs. The present invention satisfies this need.

BRIEF SUMMARY OF THE INVENTION

The invention includes a method of alleviating a lymphoproliferative disorder in a human patient. The method comprises administering to the patient, in an amount sufficient to alleviating the disorder, a rapamycin derivative having the chemical structure shown in Formula I in Figure 8. In a preferred embodiment, the rapamycin derivative is 40-O-(2-hydroxy)ethyl-rapamycin. Numerous other useful rapamycin derivatives (including rapamycin itself) are described in this disclosure. Lymphoproliferative disorders that can be alleviated using this method include, for example, PTLDs and lymphatic cancers such as lymphomas. The method can also be used to alleviate lymphoproliferative disorders caused or associated with

treatment of the patient by immunosuppressive therapy (e.g., immunosuppressive therapy associated with tissue transplantation).

In another method included in the invention, a lymphoproliferative disorder is inhibited or prevented in a patient at risk for developing such a disorder (e.g., an immunocompromised patient or a patient undergoing immunosuppressive therapy).

In these methods, the rapamycin derivative can be co-administered (in a single composition or in discretely-administered compositions) with a second pharmacologically active agent, such as an immunosuppressive agent. Immunosuppressive agents are known for use in methods of inhibiting graft rejection, and those known methods can be improved by administering both the immunosuppressive agent and a rapamycin derivative disclosed herein to a patient who has received a graft.

The invention also includes a method of inhibiting metastasis of a lymphatic tumor in a human patient afflicted with a lymphatic cancer. This method comprising administering to the patient, in an amount sufficient to inhibit lymphocyte proliferation, a rapamycin derivative having the chemical structure shown in Formula I.

In another aspect, the invention includes a method of assessing whether an agent is useful for alleviating or inhibiting a lymphoproliferative disorder in a human patient. This method comprising transforming a B lymphocyte with an Epstein-Barr virus, injecting the lymphocyte into a mouse having a severe combined immunodeficiency, administering the agent to the mouse, and monitoring tumor growth in the mouse for at least about 21 days. If one or more of tumor regression, tumor eradication, and absence of a second tumor is observed in the mouse, then this is an indication that the agent is useful for alleviating or inhibiting a post-transplant lymphoproliferative disorder in a mammal.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph which illustrates SDZ RAD-mediated inhibition of in vitro proliferation of PTLD-like EBV+ B cells. BC-1 is an EBV+/HSV8+ B-

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