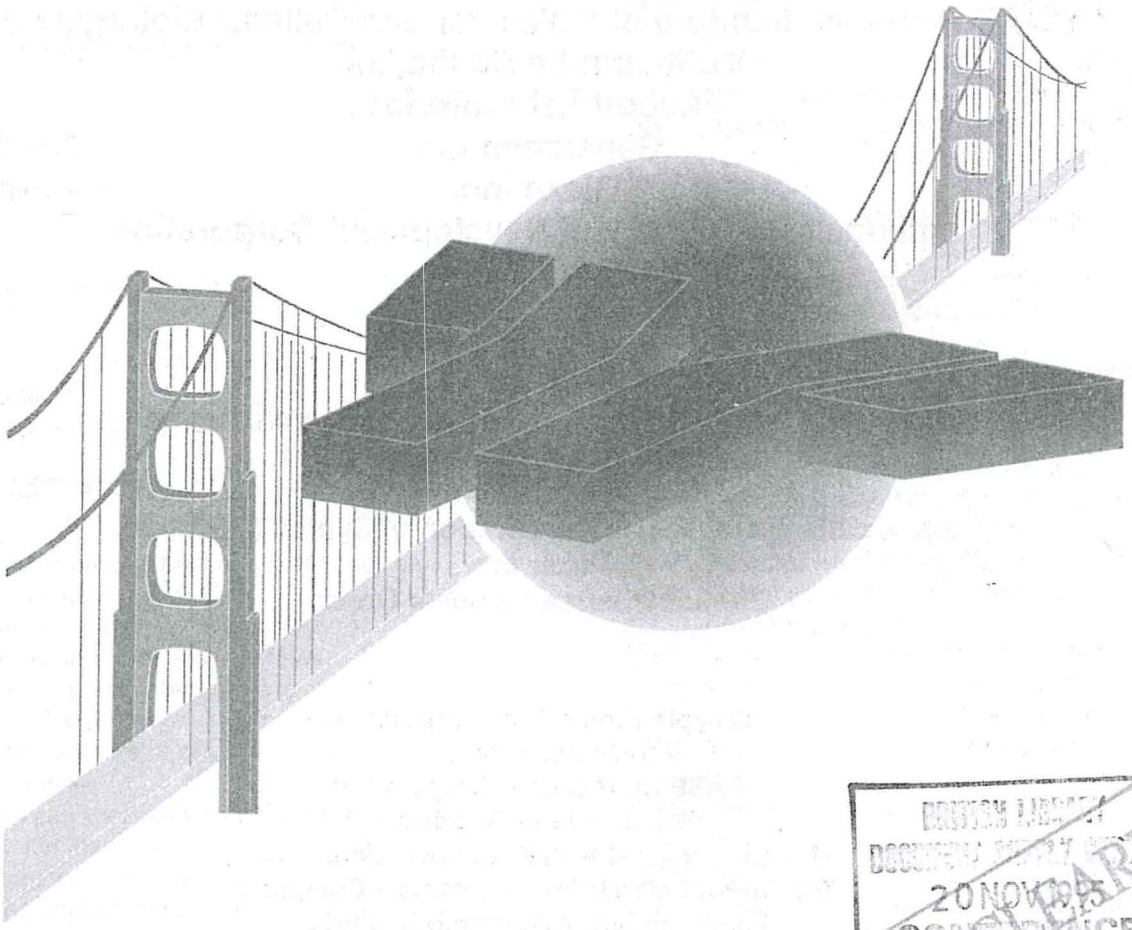
9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY



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CYCLOSPORIN A (SANDIMMUN) TREATMENT IN DERMATO/POLYMYOSITIS. K. Dankó, Gy. Szegedi. 3rd Dept. of Med. Univ. Med. School, Debrecen, Hungary.

A treatment with Cyclosporin A(Sandimmun) of 23 patients with dermato/-polymyositis (DM/PM) is described. In 14 of the 23 patients Azathioprine, in 3 of them Lycurim, in 2 of them Cyclophosphamid treatments had been tried earlier but were discontinued because of side effects or lack of efficacy. At the time of starting Cyclosporin A treatment(initial dose 5 mg/kg/day), all patients had serious involvement of the disease. The duration of DM/PM ranged from 6 months to 16 years at the time of initiation of Cyclosporin A treatment. The response to Cyclosporin A included recovery of muscle strength and function. It was possible to stop or reduce the steroid dose, which had previously been difficult in all 23 patients. In these patients a maintenance daily dose was between 2.5-3 mg/kg/day. Levels of CK and LDH returned to normal after 2-3 months of treatment. 2 patients discontinued Cyclosporin A because of hypertension. Minor side effects occurred in 4 patients (hypertrichosis in 2, nausea in 1, gingiva hyperplasia in 1). Because Cyclosporin A is a fast-acting immunosuppressive drug, it appears to be a good candidate for the treatment of refractory forms of DM/PM, with no increased risk of adverse effects compared with those associated with other drugs.

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FTY720, A NOVEL IMMUNOSUPPRESSANT, POSSESSING UNIQUE MECHANISMS. I .Relationship between immunosuppressive effects and selective decrease of peripheral mature T cells. K. Chiba, K. Teshima, A. Fujii, Y. Masubuchi, C. Suzuki, K. Adachi, T. Mishina, S. Sasaki* and T. Fujita † Yoshitomi Pharmaceutical Industries LTD., Saitama, Taito Company*, Kobe, and Kyoto Univ. †, Kyoto Japan.

FTY720, a novel synthetic immunosuppressive agent, was found through chemical modification of ISP-I, a natural product from *Isaria sinclairii*. In vivo administration of FTY720 resulted in a marked prolongation of rat skin allograft survival at a dose more than 0.1mg/kg p.o. and its effect was 10-fold more potent than that of FK506. However, FTY720, at a concentration up to 100nM, had no effect on IL-2 and IL-3 productions, which were inhibited by both Ciclosporin and FK506, from alloantigen-stimulated T cells. When 0.1mg/kg of FTY720 was administrated orally to rat, the number of CD3-positive T cells in peripheral blood markedly decreased within 3 h, whereas the number of peripheral B cells and PMNs were unaffected. After the administration for 5 days, CD3-positive T cells in the spleen were selectively depleted, however bone marrow cells, thymocytes, and splenic B cells were not affected. Furthermore, DNA of FTY720-administered rat spleen cells showed ladder degradation by agarose gel electrophoresis. These results indicate that FTY720 possesses powerful immunosuppressive activity with unique mechanisms distinct from those of FK506 and Ciclosporin, and that the mechanisms of action of FTY720 is related to selective decrease of mature T cells by homing and apoptosis.

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FTY720, A NOVEL IMMUNOSUPPRESSANT, POSSESSING UNIQUE MECHANISMS. II. Synergistic prolongation of allograft survival in combination with Ciclosporin in rat and dog. Y. Hoshino, K. Chiba, F. Rahman, T. Kawaguchi, Y. Amano, H. Higashi, K. Teshima, T. Kakefuda* and S. Suzuki* Yoshitomi Pharmaceutical Industries LTD. Saitama, and National Children Hospital*, Tokyo, Japan.

FTY720, a novel synthetic immunosuppressive agent, posseses powerful immunosuppressive activity with unique mechanisms distinct from those of FK506 and Ciclosporin. Effects of FTY720 on rat skin, rat heart and dog kidney allografts were examined. In rat skin allogeneic transplantation with WKAH donor and F344 recipient, FTY720 prolonged the allogaft survival at a dose more than 0.1mg/kg p.o. in a dose-dependent manner, and showed synergistic effects in combination with suboptimal dose of Ciclosporin. In rat heterotropic heart allogaft with WKAH and ACI strain combination, FTY720 was also effective at a dose of more than 0.1mg/kg p.o. , and longterm graft survivals (>100days) were observed in high dose (10mg/kg p.o.). Furthermore, in dog kidney allogaft with Mongrel donor and Beagle recipient, longterm survivals (>70days) were also obtained by oral administration of FTY720 5mg/kg in combination with Ciclosporin 10mg/kg p.o.. These results suggest that the combination of FTY720 and Ciclosporin shows synergistic effects in various animal allogeneic transplantations because of the unique mechanisms of FTY720 distinct from those of FK506 and Ciclosporin, thus, FTY720 is expected to have clinical potential for organ transplantations.

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FTY720, A NOVEL IMMUNOSUPPRESSANT, POSSESSING UNIQUE MECHANISMS. III. Pharmacological activities in several autoimmune and inflammatory models. K. Teshima, T. Imayoshi*, M. Matsuura*, S. Yamaguchi*, K. Chiba, and M. Terasawa* Yoshitomi Pharmaceutical Industries, LTD. Saitama and Fukuoka*, Japan.

FTY720, a potent immunosuppressive agent that prevents organ graft rejection on animal models of transplantation, possesses mechanisms of actions distinct from those of Ciclosporin and FK506. In this study, pharmacological activities of FTY720 in several autoimmune and inflammatory models were assessed in order to make clear its potential utility as a drug for autoimmune diseases. FTY720 significantly inhibited methylated human serum albumin-induced delayed-type hypersensitivity in a dose-dependent manner at a dose of more than 0.03 mg/kg p.o. daily in mice. In rat adjuvant-induced arthritis, FTY720 inhibited joint destruction completely as well as paw edema at a dose of more than 0.1 mg/kg p.o. on a daily dosing schedule. FTY720 was also effective in collagen-induced arthritis at a dose of more than 0.3 mg/kg p.o. daily in rats. Furthermore, in another T cell-mediated model, experimental allergic encephalomyelitis, FTY720 inhibited the paralysis completely at a dose of more than 0.1mg/kg p.o. daily in rats. These results indicate that FTY720 may be effective in the treatment of rheumatoid arthritis, multiple sclerosis and other autoimmune diseases.

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RAPAMYCIN INHIBITS SYNTHESIS OF IL-2 BY T CELLS. J. Zhang, O. Xiang and N. K. Damle. Wyeth-Ayerst Research, Princeton, NJ 08543, USA.

Upon activation via the CD3/TCR complex, T cells synthesize both IL-2 and functional receptors for IL-2 to bring about T-cell clonal expansion. Rapamycin (RAPA) mediates its immunosuppressive effects by interfering in the cell cycle progression from G1 to S phase, and thereby inhibiting cellular proliferation. It is commonly believed that RAPA inhibits growth factor-induced intracellular responses rather than the synthesis of the growth factor(s). The present study examines the effect of RAPA on the production of IL-2 as well as IL-2 responsiveness of murine T cells. Plastic-immobilized anti-CD3 mAb induced a strong proliferative response by $CD4^+$ T cells. This response was largely dependent on the IL-2 : IL-2R interaction as evidenced by the inhibitory effect of anti-IL-2R mAb. Stimulation of T cells with anti-CD3 in the presence but not absence of anti-IL-2R mAb allowed significant accumulation of soluble IL-2 in the culture supernatants reflective of the inhibition of consumption of endogenous IL-2. Under these conditions, a combination of anti-IL-2R mAb and RAPA, but not its nonimmunosuppressive analog, caused a profound reduction in the accumulation of IL-2. While Cyclosporin A almost completely blocked the expression of both IL-2 and IL-2R, RAPA had no effect on the expression of IL-2R. These results suggest that RAPA can inhibit T-cell proliferation not only by interfering with IL-2-induced cell-cycle progression but also by

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CYTOKINE SECRETION IN SMALL CELL LUNG CANCER MAY BE MODULATED BY TUMOR-DERIVED, ENDOGENOUS AND THERAPEUTIC FACTORS

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We investigated immunosuppressive effects of soluble factors secreted by small cell lung cancer (SCLC) cell-lines. We found that the SCLC cell-line NCI-N417 secretes a cytokine that inhibits IL-2 mediated T cell growth. The SCLC cell-line NCI-H69 did not secrete this activity. The immunosuppressive cytokine secreted by NCI-N417 was serologically identified as Transforming growth factor β1 (TGF β1). TGF β1 mRNA was expressed in NCI-N417 but not in NCI-H69. Further investigation showed that TGF β1 protein was secreted by 4 of 8 SCLC lines tested. TGF β1 inhibited secretion of IL-2, IFN α, IFN γ, TNF α, but not of IL-1α, IL-1β in whole blood cell culture from normal individuals.

To investigate the clinical relevance of TGF β1 secretion by SCLC, we evaluated cytokine concentrations of IL-2, IFN α, IFN γ, TNF α, IL-1α, IL-1β in whole blood cell culture from 58 SCLC patients by enzyme-linked immunosorbent assay (ELISA). Compared to 44 normal controls, immunocompetent cells from SCLC patients secreted significantly lower amounts of IL-2, IFN α, IFN γ upon mitogen-stimulation. TNF α secretion was significantly reduced in extensive disease but not in limited disease SCLC. Secretion of IL-1α and IL-1β was not reduced. This selective cytokine suppression in SCLC patients corresponds to the selectively suppressed cytokine profile induced by TGF β1 in whole blood cell culture from healthy controls. Further investigation demonstrated that cytokine secretion is reconstituted upon tumor reduction by chemotherapy, but not upon ineffective chemotherapy. These results provide further evidence for an interaction between tumor cells and the immune system. This interaction may play an important role in the pathogenesis and treatment of SCLC. Since TGF β1 is secreted by SCLC lines and induces the selective cytokine suppression found in SCLC patients, tumor-derived TGF β1 may be one factor mediating selective immunosuppression in SCLC patients.

Using whole blood cell culture and ELISA for assessment of cytokine concentrations, we found in additional experiments that cortisol, noradrenaline (NA) and ethanol significantly inhibit secretion of different cytokines. Furthermore, suppression of mitogen-induced cytokine secretion by TGF β1 was further inhibited by NA in an additive way. GM-CSF but not G-CSF selectively stimulated secretion of