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[Lab. of Pharmacology]

**Facilitation of Apoptosis by Cyclosporin A and H, but not FK506 in Mouse
Bronchial Eosinophils.**

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This study was undertaken to clarify whether or not binding to cyclophilin is a prerequisite for cyclosporin A-induced modulation of apoptotic cell death in eosinophils (Eos). Eos was isolated from bronchoalveolar lavage fluid of mice challenged with inhaled allergen after sensitization. Apoptosis was determined by analysing the DNA content. At 72 h, 99% of the cells had died without addition of cytokines, whereas 55-60% of the cells survived in the presence of interleukin 5 (IL-5) or granulocyte macrophage-colony stimulating factor (GM-CSF). Apoptotic cell death at 72 h in the presence of IL-5 was increased by addition of an analogue of cyclosporin A without cyclophilin binding activity. Tacrolimus failed to augment apoptotic cell death. Thus, it is unlikely that binding of cyclosporin A to cyclophilin accounts for the increased apoptosis induced by cyclosporin A and its analogue in Eos.

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[Lab. of Pharmacology]

**FK-506 and Cyclosporin A Potentiate the IgE Antibody Production by
Contact Sensitization with Hapten in Mice.**

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Five repeated topical applications of 2,4-dinitrofluorobenzene to the ears of BALB/c mice resulted in contact dermatitis (CD) on the ears as well as significant elevation in dinitrophenol-specific and total IgE antibodies and total in the serum. FK-506 and cyclosporin A selectively inhibited the Th1 cell-mediated CD and potentiated the Th2 cell-mediated IgE antibody production in vivo. This potentiation is probably due to the down-regulation of interferon- γ production by Th1 cells after the treatment with these drugs. FK-506 and cyclosporin A inhibited the production of cytokines by both Th1 and Th2 cells in vitro and these two immunosuppressors showed higher selectivity toward inhibiting Th1 cell-mediated reactions by limitations in vivo experiments.

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[Lab. of Pharmacology]

The Effect of TRK-530 on Experimental Arthritis in Mice.

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TRK-530 is a newly synthesized diphosphonate derivative. We investigated the effect of TRK-530 on type II collagen-induced arthritis (CIA) in mice in comparison to those of prednisolone and indomethacin. TRK-530 inhibited the development of the CIA in terms of the progression of footpad swelling, bone damage and histopathological changes. TRK-530 also inhibited the delayed type hypersensitivity (DTH) response to type II collagen, but not the production of anti-type II collagen IgG antibody in arthritis mice. To investigate the inhibitory mechanism of TRK-530, the type of effect of TRK-530 on the production of IL-1 β in vitro was studied. TRK-530 inhibited LPS-induced IL-1 β production from J774.1 cells. In conclusion, TRK-530 inhibited CIA in mice. The inhibition of the DTH reaction to type II collagen and the inhibition of IL-1 β production may partly participate the anti-rheumatoid action of TRK-530.

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[Lab. of Pharmacology]

**Effects of cAMP-phosphodiesterase Isozyme Inhibitor on Cytokine Production
by Lipopolysaccharide-stimulated Human Peripheral Blood Mononuclear
Cells.**

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The effects of cAMP-phosphodiesterase (PDE) isozyme inhibitors, dibutyryl cAMP and β -adrenoceptor agonists on the production of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and IL-8 by lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (PBMCs) were investigated. Type IV PDE inhibitors were effective at inhibiting the production of TNF- α and IL-1 β , but not IL-8. Dibutyryl cyclic AMP also inhibited the production of TNF- α and IL-1 β , but not IL-8. Moreover, β -agonists increased the inhibitory effect of PDE inhibitors tested on the production of TNF- α and IL-1 β , but not IL-8.