[*Anti-Cancer Drugs.*, **8**, 482-488 (1997)] [Lab. of Pharmacology]

Irreversible Cytotoxic Effect of a Novel Low Immunosuppressive Antitumor Fluorouridir Derivative, UK-21.

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To elucidate the molecular mechanism of antitumor activity of UK-21, we compared the effect of the four drugs on cell proliferation, cell cycle progression and macromolecular syntheses. When KB cells were exposed to the drugs for 4-96 h and washed out, UK-21 and 5-FUR inhibited the colony formation, whereas more higher doses was needed for the cytotoxicity of 5-FU and 5-FUDR. By exposure for 24-48 h, all these drugs inhibited cell growth and caused accumulation of the cells in S or G2 phase. In addition, the cells were treated with UK-21 and/or 5-FU for 1 h, and continued to be cultured for 1-7 days, resulting in the inhibition of cell growth by UK-21, but not by 5-FU. UK-21 also inhibited the incorporation of [^{3}H]-uridine like 5-FUR and [^{3}H]-thymidine like 5-FUDR. These results suggest that irreversible cytotoxic effects of UK-21 are exerted through inhibition of RNA synthesis.

[*Prostaglandins*, **54**, 805-820 (1997)] [Lab. of Pharmacology]

Time Course Study for Airway Inflammation and Responsiveness by Repeated Provocation of Aeroantigen in Guinea Pigs.

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To study the mechanisms of airway hyperresponsiveness (AHR), we examined the time course for asthmatic responses after the repeated antigen provocation of aeroantigen in sensitized guinea pigs. Moreover, we examined the effect of S-1452, a thromboxane A2 (TXA2) receptor antagonist, on the antigen-induced airway obstruction and AHR in guinea pigs. Immediate asthmatic response occurred 1 min after every antigen inhalations. Late asthmatic response (LAR) was observed every 4 h after the antigen challenge without 1st and 2nd challenge. AHR was initially observed 4 h after 5th antigen challenge, and then AHR was observed at every time measured even after the 6th antigen provocation. TXB2 and histamine in airways were detected after the first antigen provocation. In addition, S-1452 clearly inhibited LAR and AHR, assessed after the 6th challenge. These data suggest that repeated antigen challenge leads to the onset of LAR and AHR when became chronic, and TXA2 is an important factor in these phenomena.

[*J. Allergy Clin. Immunol.*, **100**, S39-44 (1997)] [Lab. of Pharmacology]

Immunoglobulin E Production in Mice by Means of Contact Sensitization with a Simple Chemical, Hapten.

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Production of IgE caused by repeated topical application of 2,4-dinitrofluorobenzene (DNFB) to the ears of BALB/c mice was investigated. After the fifth application, the mice showed as immediate cutaneous reaction in addition to delayed type hypersensitivity reaction (DTH). The strong expression of interferon γ and IL-2 mRNA in the skin lesions indicated the participation of Th1 cell in the DTH. Hapten-specific IgE was detected in serum from mice, and the expression of germline and productive Cε mRNA was detected in cervical lymph nodes, whereas productive Cε mRNA was also detected in spleen. These results indicate that eczematous dermatitis is mainly caused by Th1 cell, and IgE production is mediated by Th2 cells in the carvical lymph nodes. In addition, IgE production occurs in both lymph nodes and spleen.

[*Chem. Pharm. Bull.*, **45**, 418-420 (1997)] [Lab. of Pharmacognosy]

Inhibitory Activity of Xanthone Derivatives Isolated from Some Guttiferaeous Plants against DNA Topoisomerases I and II.

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Two major topoisomerases, types I and II, play a critical cellular role in alterations of the topological state of DNA such as supercoiling, knotting, and catenation. The prime importance of these enzymes makes them critical targets for the action of a wide variety of anticancer drugs. Camptothecin and etoposide analogs have been applied clinically, but their severe side effects remain a serious problem. The development of a new class of inhibitors of Topo is thus awaited. In the development of new drugas, natural products obtained from plants are sometimes useful directly or serve as starting material for semisynthesized active agents. Furthermore, naturally occurring compounds can supply suitable leads for the subsequent design of structurally related molecules that are more active or less toxic. In our search for physiologically active principles in Guttiferaeous plants, we report here on the inhibitory effects of xanthone and benzophenone derivatives against Topo I and II in *vitro* experiment.