Various biopolymers to prepare the drug carrier have been used by many investigator due to their biocompatibility and biodegradability. Among these polymers, PLGA, the copolymer of lactide and glycolide, is suitable material as drug carrier in this point. They were approved by the Food and Drug Administration (FDA) for several therapeutic products and can formulate to release macromolecules over a long period. In this study, we prepared the nanoparticle utilizing PLGA by dialysis method without surfactant and physicochemical properties such as particle size and drug contents were investigated against various solvents. And the nanoparticles of PLGA showed good spherical shapes from scanning electron microscopy (SEM) and transmission electron microscopy (TEM) observations. Biodegradation rate of PLGA nanoparticles prepared from DMF was faster than that of acetone, indicating that the biodegradation of PLGA nanoparticles was size-dependent. Resultantly, the higher drug contents and the larger particle size resulted in slower the drug release.

[PA1-3] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

The mechanism of C2-ceramide-induced contraction of smooth muscle cells in cat esophagus

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We previously have shown that C_2-ceramide (C_2) plays a role in mediating contraction of cat esophagus. We have isolated smooth muscle cells by enzymatic digestion with collagenase F.C_2 induced contraction of smooth muscle cells in cat esophagus, which is blocked by PKC inhibitors, H-7 or chelerythrine. To confirm that PKC-mediated contraction may be isozyme specific, we examined the effect of different PKC antibodies on the contraction. PKC-ϵ antibody inhibited the contraction by C_2, which suggest that PKC-ϵ may mediate the contraction induced by C_2. To characterize the specific PKC isozymes that mediate contraction of the smooth muscle cells, we used N-myristoylated peptides (Myr-PKC) derived from the pseudosubstrate sequences of PKC-$\alpha\beta\gamma$, -α, -δ, and -ϵ. Myr-PKC-ϵ only inhibited the contraction, which was concentration-dependent, suggesting that PKC-ϵ isozyme is involved in the contraction. To examine which MAP kinase is involved in C_2-induced contraction, p44/p42 MAP kinase inhibitor, PD98059, or p38 MAP kinase inhibitor, SB202190 was used. Preincubation of PD98059 only blocked the contraction induced by C_2 in a concentration dependent manner. C_2 increased the intensity of the bands identified by phosphospecific p44/p42 MAP kinase antibody and preincubation of PD98059 decreased the intensity of bands as compared with C_2 stimulated cells.

In conclusion, C_2 produced the contraction of smooth muscle cells. The contraction is mediated by PKC-ϵ-protein, resulting in the activation of p44/p42 MAP kinase

[PA1-4] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

Reversal of multidrug-resistance by benzodiazepin and benzotriazepin analogues in cancer cells

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A major mechanism by which tumor cells can develop resistance to anticancer drugs is by decreasing the intracellular bioavailability of the anticancer drug. Such a multidrug-resistance (MDR) phenotype of tumor cells is usually mediated by the overexpression of a membrane protein, P-glycoprotein (Pgp),

which directly binds cytotoxic compounds and reduces intracellular drug accumulation through an energy-dependent drug efflux mechanism. Accordingly, considerable effort has been directed towards the development of compounds that inhibit Pgp, reverse the MDR phenotype and sensitize cancer cells to conventional chemotherapy without undesired toxicological effects. In an effort to search for novel MDR reversal agent, we tested the derivatives of benzodiazepain and benzotrizepin. We tested the cytotoxicity of paclitaxel, a well-known substrate of Pgp, against Pgp-expressing colorectal cancer cells in the presence or absence of those compounds, as well as against Pgp-negative ovarian cancer cells in vitro. Among the compounds tested, N-(4-fluoro-phenyl)-2-(1-methyl-2-oxo-5-phenyl-1,2-dihydro-benzo[e][1,2,4]triazepin-3-yl)-acetamide and 2-(7-Chloro-1-methyl-2-oxo-5-phenyl-1,2-dihydro-benzo[e][1,2,4]triazepin-3-yl)-N-o-tolyl-acetamide remarkably increased the cytotoxicity of paclitaxel to Pgp-expressing cancer cells, but not to Pgp-negative cancer cells.

[PA1-5] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

Inhibition of the Processing of Oncogenic Ras by Farnesyltransferase Inhibitor, YH3817

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The Ras proteins have been the focus of oncology drug discovery efforts because of their ability to cause malignant transformation. To function in signal transduction and cell transformation, Ras must attach to the plasma membrane and this membrane localization requires their post-translational modification by FTase. For this reason, inhibition of Ras farnesylation is being pursued as a way of developing anticancer drugs. YH3817 blocks farnesylation of H-ras and K-ras4B by purified human FTase with IC50 values of less than 1.0 nM. Kinetic studies of YH3817 have demonstrated that it is competitive with ras protein substrate. YH3817 also inhibits anchorage dependent and independent growth, soft agar growth of human tumor cells which express mutated K-ras. Furthermore, the prenylation of oncogenic ras in A549 human lung tumor cell lines was disrupted by YH3817. This accounts for the ability of YH3817 to inhibit tumor cell growth and to abolish the malignancy of cancer cells. Therefore, our findings indicate that YH3817 is a potent inhibitor of Ras processing with anti-tumor properties.
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[PA1-6] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

Comparative studies of signaling pathway of D2 and D3 dopamine receptors for mitogen-activated protein kinase activation

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D2 and D3 dopamine receptors that belong to G-protein coupled receptor family, share similar structural architecture and signaling pathways. In some brain areas, they are co-expressed but in some brain areas, they are distributed in distinct brain regions, more D3 receptors are expressed in limbic area than D2 receptors. Here we studied, using HEK-293 cells, the regulation of MAPKs by D2 and D3 receptors, side by side to see whether they are employing different signaling pathways for the regulation of MAPK activation. MAPK activations by D2 and D3 receptors were both pertussis toxin-sensitive and they did not require the sequestration of receptors to initiate MAPK activation. They were