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