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

not blocked by βARKct that inhibits Gβγ-mediated signaling, and not by βarrestin1-V53D, a dominant negative mutant of βarrestin 1. We also tested several kinase inhibitors (wortmannin, genistein, and PKC inhibitors) and dominant negative mutants for c-Src, PI3-Kinase, mSOS, Ras, and Raf to see whether they follow the same signaling pathways. It was generally concluded that they show the similar time-dependency and dose-dependency, but D2 receptors are more potent than D3 receptor for the activation of MAPK. So far we have tested, D2 and D3 receptors seem to employ the same signaling components for the regulation of MAPK.

[PA1-7] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

Effects of dopamine agonists and antagonists on the degranulation of mast cells and LPS-induced nitric oxide production in macrophage cells

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Generally dopamine agonists or antagonists for the treatment of Parkinson's disease or Schizophrenia are used on the long-term basis. It would be important to see whether they have any effect on physiological functions, such as hormonal or immune functions. In this study, we tested whether they have any effects on the degranulation of mast cell (RBL-2H3) and nitric oxide production from macrophage cells (RAW 264.7), which presumably represent the allergic and inflammation, respectively. Among dopamine agonists (dopamine, bromocriptine, 7-OH-DPAT) and antagonists (Sulpiride, U99194A) tested, bromocriptine and 7-OH-DPAT showed potent inhibitions of mast cell degranualtion (IC50 value, 10μM). On the other hand, nitric oxide induction from RAW 264.7 cell was markedly reduced by bromocriptine and dopamine (IC50 value, 10μM). When bromocriptine was tested for the effects on LPS-induced iNOS expression, bromocriptine showed a time-dependent and concentration-dependent inhibtion of iNOS expression. These results suggest that some of dopamine agonists, like bromocriptine, could have some effects on immune functions, and it would be necessary to be more careful for some patients depending on the their immunological status.

[PA1-8] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

Reversal of multidrug-resistance by synthetic alkaloids in cancer cells

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The occurrence of resistance to chemotherapeutic drugs is a major problem for successful cancer treatment. Frequently, this resistant phenotype of cancer cell reveals a broad spectrum to structurally and/or functionally unrelated anticancer drugs, termed multidrug resistance (MDR). Overexpression of P-glycoprotein (Pgp), a transmembrane drug efflux pump, is a major mechanism of MDR. The MDR associated with Pgp-overexpression can be reversed or modulated by inhibition of Pgp-mediated transport, via increasing cellular accumulation of anticancer drugs with various agents such as calcium channel blockers, calmodulin inhibitors, antiarrythmics, steroids, antiestrogens cyclic peptide antibiotics and etc. To date, however, the usefulness of MDR-reversal agents has been limited since the undesired side effects such as cardiac toxicity or immunosuppression. The present study was performed to evaluate the ability of some synthetic alkaloids to overcome multidrug resistance by measuring the cytotoxicity of paclitaxel, a well-known Pgp substrate. Among the compounds tested, 2-(2-ethoxy-ethyl)-N,N'-bis-(2-methoxy-phenyl)-malonamide and [1-(N'-benzyl-hydrazinocarbonyl)-2-phenyl-ethyl]-carbamic acid benzyl ester revealed significantly inhancing of paclitaxel induced cytotoxicity to Pgp-positive cancer cells but not to Pgp-negative cancer cells in