

signaling molecules. Thirty subtypes of PTPs have been identified in human genomes. Among PTPs, PTP1B has been suggested as a negative regulator of insulin signaling. Overexpression of this enzyme has been known as a cause of obesity and type II diabetes, so it is a target for drug discovery. However, PTPs are involved in several signaling pathways, it is possible that PTPs inhibition may give rise to unwanted side effects. Therefore, specific PTP1B inhibitors that may be free of side effects and highlight the potential of selective therapeutic efficacy in targeting PTP1B are required. The 73,000 compounds were screened using high-throughput experimental techniques for searching compounds that inhibited PTP1B. 4-nitrophenyl phosphate assay has been used for the first assay in the format 96-well plate. Using this assay system, we have discovered 61 hit compounds. For the second screening, hit compounds are assayed with phosphotyrosine peptide as substrate. Finally, we test isozymes selectivity of each compounds. In this schedule, we are screening for discovering the novel drug of anti-obesity and anti-diabetes.

[PA1-8] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Growth inhibition and cell cycle phase-specific apoptosis induced by celecoxib in human NSCLC cells in vitro.

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Cyclooxygenase-2 (COX-2) is an inducible enzyme which produces prostanoids by various stimuli. Overexpression of COX-2 in many tumor types indicates its association with tumor progression, which has been a promising target for chemoprevention and chemomodulation. We studied conc- and time-dependency of COX-2 inhibition, growth inhibition, and cell cycle arrest induced by celecoxib, a selective COX-2 inhibitor, in human non-small cell lung cancer (NSCLC) A549 cells. COX-2 activity IC₅₀ and IC₈₀ for 24hr exposure were approx. 0.1 and 1 μM, respectively. The inhibition increased with prolonged exposure, i.e., 20% at 6hr to 60% at 24hr when exposed to 0.1 μM. Cytotoxic IC₅₀ after 6hr exposure was 110 μM and decreased to 20 μM after 72hr exposure. These conc were about 600 fold higher than those of COX-2 inhibition. Fifty μM (cytotoxic IC_{80,72hr}) of celecoxib induced G1 phase arrest and apoptosis in cells in G1 phase. In summary, (1) the drug conc inducing COX-2 inhibition and cytotoxicity were different by more than 600 folds in human NSCLC cells, suggesting that these two effects may not have direct causal relationship, and (2) growth inhibition and apoptosis induced by celecoxib are associated with G1 phase arrest, which may be important in designing of combination regimen of celecoxib. Changes in expression level of COX-2 and other factors at higher conc are under investigation to elucidate the mechanism of growth inhibition by celecoxib in human NSCLC cells.

[PA1-9] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

4-Hydroxy nonenal (HNE) Induces Apoptosis and Cell Cycle Arrest in Bovine Aortic Endothelial Cells

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4-Hydroxy nonenal (HNE) is a lipid peroxidation product derived from oxidized ω-6 polyunsaturated fatty acids, such as arachidonic acid. HNE is widely used as a marker of lipid peroxidation. To study the hypothesis that HNE may induce apoptosis and cell cycle arrest, we estimated cytotoxicity of HNE