[PC1-9] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Computer-based screening for novel inhibitors of human topoisomerase I with FlexiDock docking protocol

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DNA topoisomerases I (topo I) and II are essential enzymes that relax DNA supercoiling and relieve torsional strain during DNA processing, including replication, transcription, and repair. Topo I relaxes DNA by cleaving one strand of DNA by attacking a backbone phosphate with a catalytic tyrosine (Tyr723, human topo I). This enzyme has recently been investigated as a new target for antineoplastic drugs. Inhibitors to the enzyme intercalate between the DNA base pairs, interfering religation of cleaved DNA, therefore inhibit the activity of topo I. To search novel inhibitors of topo I from existing chemicals, molecules that are known to act as antitumor, anti-inflammatory or anti-invasion drugs have been selected and docked into the human topo I-DNA complex. Among 13 molecules that have been tested, seven molecules showed intercalative binding modes like known inhibitors. Their structures are mainly composed of multi-rings and planar which are characteristics required to intercalate DNA. Although these results should be substantiated by further biological activity study with human topo I, the docking results suggest the possibility of these molecules being novel topo I inhibitors.

[PC1-10] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Binding modes of artemisinin to malarial TCTP demonstrated by computer modeling

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The translationally controlled tumor-associated proteins (TCTPs) are a highly conserved and abundantly expressed family of eukaryotic proteins that are implicated in both cell growth and human acute allergic response but whose intracellular biochemical function has remained elusive. There are reports that antimalarial drug, artemisinin, binds to *Plasmodium falciparum* TCTP, however, its 3D structure has not been known. To illustrate the action mechanism of artemisinin, 3D structure of *P. falciparum* TCTP was constructed by homology modeling using NMR structure of *Schizosaccharomyces pombe* TCTP (PDB code 1H6Q) as a template. Whose sequence is 39% identical and 56% similar to *P. falciparum* TCTP. The final model was chosen out of 5 models obtained after evaluation by PROSAII and PROCHECK. With this structure, docking experiment was carried out with Flexidock to determine the binding modes between the protein and the ligand. Since the TCTP has been shown to react with dihydroartemisinin in the presence of heme, docking simulation of artemisinin with heme was first performed and then the activated artemisinin was docked into the *P. falciparum* TCTP. The results show that the activated C^4 of artemisinin interacts with CYS14 of the TCTP, conforming the experimental data reported.

[PC1-11] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

β-ketoacyl-acyl carrier protein synthases for fatty acid biosynthesis in bacteria

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A universal set of genes encodes the components of dissociated, type II, fatty acid synthase system that is responsible for producing the multitude of fatty acid structures found in bacterial membranes. We examined the biochemical basis for the production of fatty acids by bacteria. Several genes from *Haemophilus influenzae* Rd

and three genes from *Enterococcus faecalis* V583 were predicted to encode homologs of the β-ketoacyl-acyl carrier protein synthases I or II or III of *Escherichia coli* (FabB or FabF, or FabH) were identified in the genomic database. The protein products were expressed, purified, and biochemically characterized. efFabH and hFabH carried out the initial condensation reaction of fatty acid biosynthesis with acetyl-Coenzyme A as a primer, and hFabB and efFabF1 carried out the elongation condensation reaction of fatty acid biosynthesis with myristoyl-ACP.

[PC1-12] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Purification and Characterization of Dermatan Sulfate from Eel Skin, *Anguilla japonica*

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Dermatan sulfate (DS) was isolated from eel skin (*Anguilla japonica*) by actinase and endonuclease digestions followed by β-elimination reaction and DEAE-Sephacel chromatography. DS was a major glycosaminoglycan in eel skin with 88% of the total uronic acid. The content of IdoA2Sα1→4GalNAc4S sequence in eel skin, which is known to be a binding site to heparin cofactor II, was two times higher than that of dermatan sulfate from porcine skin. The anti-IIa activity of eel skin dermatan sulfate mediated through heparin cofactor II (HCII) was 25 units/mg, whereas DS from porcine skin shows 23.2 units/mg. The average molecular weight was determined as 14 kDa by gel chromatography on a TSKgel G3000SWXL column. Based on H1 NMR spectroscopy, we suggest that 3-sulfated and/or 2,3-sulfated IdoA residues are present in the chain.

[PC1-13] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Induction of apoptosis in human promyelocytic leukaemia HL-60 cells by manassatin B involves release of cytochrome c and activation of caspases

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Manassantin B classified into dineolignans have been isolated from Saururus chinensis Manassantin B was found to induce apoptosis in human promyelocytic leukaemia HL-60 cells with characteristic apoptotic features like increase of nucleosomal ladder, apoptotic body ormation, flipping of membrane phosphatidylserine. Manassantin B induced FAS and FAS ligand expression, and activated caspase 8 which cleaved bid to tbid in cytosol. The release of cytochrome c to cytosol was accompanied with decrease of bcl-2 protein and increase of tbid and bax protein in mitochondria. Released cytochrome c activated caspase 9 and -3, but these effects were completely attenuated by the treatment of broad caspase inhibitor, Z-VAD fmk. These results indicate that manassatin B induce apoptosis through upregulation of FAS, caspase family and mitochondria -related proteins.

[PC1-14] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Induction of Differentiation in HI-60 Human leukemia cells by Acteoside.

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