## S4-3

## Chemical Genetics and Chemical Genomics: High Throughput Profiling of Drugs, Therapeutic Genes and Disease Networks

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With advances in determining the entire DNA sequence of the human genome, it is now critical to identify and catalog genes/proteins for specific cellular pathways and ultimately to formulate and modulate complex biological systems. My efforts have focused on the development of a "chemical genetic" approach that uses small molecules to probe the function of specific pathways and genes/proteins in human cells. Chemical genetics involves: (1) identifying small molecules that affect specific cellular pathways with unbiased phenotype-based screens (2) characterizing their action mechanisms and identifying the proteins whose activity is affected by these chemical ligands and (3) studying the biological consequences of inhibition or activation of the target protein using the small molecules as a tool. These procedures yield information that is similar to what could be learned from cloning a mutant gene from a genetic screen and using a conditional allele to study the function of the protein that it encodes. Chemical genetic approach has been complemented by various functional genomics/proteomic s and systems biology approaches, which will provide the relevant and creative directions for: (1) high throughput discovery of drugs and therapeutic disease genes and (2) chemical (drug) - and genome (disease genes)-based probe, control and formulation of disease networks in human bio-systems in the "chemical genomic s and medicinal bio-systemics" approaches, tovel and innovative multi-disciplinary approaches have been applied to the elucidation of oncogenic and anti-oncogenic pathways.

## S4-4

## Genetic Epidemiology and Pharmacogenetics in Common Diseases

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The completion of the whole human genome sequences is now a reality. Emphasis on the analysis of genetic variations on both an individual level and a population level is more important than ever. The identification and characterization of single nucleotide polymorphisms (SNPs) in target genes or candidate genes plays a crucial role in identification of disease genes and in expediting drug discovery/d evelopment. This presentation will cover the recent accomplishments of genetic epidemiology studies, in concentration of the role of IL10 haplotype in HCC development and HBV progression. Interleukin 10 (IL10) is a powerful Th-2 cell cytokine produced by lymphoid cells that exerts its functions by inhibiting macrophage/monocyte and T-cell lymphocyte replication and secretion of inflammatory cytokines (IL1, TNFA, TGFB, IL6, IL8 and IL12). Genetic association analysis of well-characterized HBV cohort revealed that one of IL10 haplotypes, IL10-ht2, was strongly associated with hepatocellular carcinoma (HCC) occurrence in gene dose-dependent manner. The frequency of susceptible IL10-ht2 was much higher in HCC patients and significantly increased in order of susc eptibility to HBV progression from CH (chronic hepatitis) to LC (liver cirrhosis) and HCC among hepatitis B patients. In addition, survival analysis clearly showed that the onset age of HCC was also accelerated among chronic hepatitis B patients who carrying IL10-ht2. Increased IL10 production mediated by IL10-ht2 suggests that up-regulated IL10 accelerate progression of chronic HBV infection, especially to HCC development.