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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 spe cific 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 pro t eins 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 coul d 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. novel and innovative multi-disciplinary approaches have been applied to the elucidation of oncogenic and anti-oncogenic pathways.

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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.