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Integrative Functional Genomics to Decode Human Cancer Signatures

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Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, accounting for an estimated 600,000 deaths annually. However, its heterogeneous etiologies hamper the ability to uncover the disease mechanisms and to develop efficient treatment modalities. Recently, microarray technologies have been applied in several studies to define the global gene expression patterns in human cancers and gain insight into mechanism(s) of tumorigenesis. The majority of gene expression profiling studies in cancer has focused on identifying gene sets and their expression signatures that are prognostic. The research focus has now shifted toward identifying genetic determinants that are components of the specific regulatory pathways altered in cancers, leading to the discovery of novel therapeutic targets. However, it is not easy to select only a few candidate genes for further studies from the lengthy gene lists generated in gene expression profiling studies of human cancer tissues because many confounding factors influence the interpretation of data. These factors include patient ages, hospital care, different treatments administered, nonparallel progression of cancer, and unspecified environment factors that are irrelevant to cancer development. Moreover, the gene expression profile provides only a “snap shot” of gene-to-gene interactions and lacks information on time-course changes of interaction during tumorigenesis; it is therefore almost impossible to discriminate the driver genes from passenger genes in these profiles.

Cross-comparison of gene expression data from human tumor samples with well-defined gene expression patterns from in vitro and in vivo models will help us define gene expression signatures that are associated with clinicopathologic conditions. In this

presentation, I will describe novel approaches of gene expression data analysis that integrate multiple data sets from human and animal models as well as gene copy number data from microarray-based comparative genomic hybridization. These novel approaches will provide a framework to: (1) stratify HCC patients into groups with homogeneous prognosis; (2) identify gene expression signatures that reflect the cellular origins of HCC; and (3) define the oncogenic mechanisms that drive the development of HCC.