"An Integrative Paradigm for the Discovery of Novel Tumor Subtypes and Associated Cancer Genes"

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Abstract: Cancer is a heterogeneous disease. Identifying clinically relevant tumor subtypes is an important yet difficult task because of tumor heterogeneity. In recent years, molecular classification based on microarray gene expression profiling has led to discovery of novel tumor subtypes with prognostic implications. However, the genetic complexity of a tumor manifests at multiple levels including genomic, epigenomic and transcriptomic alterations. Multidimensional genomic profiling would allow an integrated view of these changes for tumor characterization. The Cancer Genome Atlas (TCGA) project, as well as individual investigators, are generating multiple types of high-dimensional "omic" data from multiple cancer types. These include somatic mutations, DNA copy number alterations, DNA methylation, messenger RNA (mRNA) gene expression and microRNA expression. In contrast to the accumulating number of multidimensional data sets, there is a lack of effective statistical and bioinformatic tools for integrative data analysis. In this proposal, we aim to develop a new integrative paradigm for tumor subtype discovery that allows simultaneous inference from multiple "omic" data sets with continuous and discrete data types, as well as easily accessible software to implement the paradigm. In addition, for the case of hepatocellular carcinoma, the genes resulting from the integrated oncogenomic analysis will be functionally tested for oncogenic properties. This will be done using rapid and cost-effective *in vivo* RNAi and cDNA screening platforms that will filter out secondary alterations and pinpoint driver genes that render selective advantages for tumor development.