CIMIT Forum Summary – July 11, 2006

Avrum Spira, MD, MSc, Boston University Medical Center, discussed "Developing Lung Cancer Biomarkers in the Post Genomic Era." Lung cancer is the most deadly cancer in the U.S., and it occurs predominantly in smokers and former smokers. Five-year survival rates are quite low, largely because the disease is rarely detected at a local level. Only 10 - 15 % of smokers will develop lung cancer in their lifetimes, so Dr. Spira's team is attempting to find a set of biomarkers that could identify those smokers at high risk. Bronchoscopies performed on patients with lung cancer often do not yield cancerous cells, so when treating patients with suspected lung cancer and uninformative bronchoscopies, clinicians must decide whether to perform a risky surgical biopsy or to "watch and wait." Using Affymetrix microarray technology, Dr. Spira's team looked for differences in airway gene expression between smokers who were ultimately diagnosed with lung cancer and smokers who did not have cancer. Usable cell samples were obtained from the uninvolved bronchial epithelium of 129 patients with suspected lung cancer, and eventually, 60 of these patients were diagnosed with the disease. The level of expression of 165 genes differed significantly ($p<0.000002$) between the smokers with cancer and those without cancer. A weighted voting method was used to identify a set of 80 predictive genes. This set was able to identify those patients with lung cancer with high sensitivity (80%) and specificity (84%), potentially enabling clinicians to better decide whether or not to perform an aggressive biopsy. Dr. Spira's current research focuses on validating his results in a large multicenter cohort study and using biomarkers to create a screening test for lung cancer in smokers and former smokers. He also plans to study more readily accessible biomarkers in cells from buccal and nasal mucus membranes.

Sui Huang, MD, PhD, Children's Hospital/Harvard Medical School, discussed the "Systems Biology of Cell Fate Decisions." His research seeks to determine how one progenitor cell can give rise to many discrete phenotypes. In the 1940s, C.F. Waddington proposed the concept of an epigenetic landscape to explain cell differentiation. Using Waddington's concept, Dr. Huang's team considers an n-dimensional hyperspace that encompasses the entire human genome. In this landscape, each point represents a potential gene expression profile. "Hills" in this n-dimensional hyperspace correspond to unstable patterns of expression, and "valleys" correspond to stable states (attractors). If one assumes that each gene can be either "on" or "off" and that any pattern of gene expression is possible, then there exist more possible gene expression profiles than there are atoms in the universe. Only a fraction of these possible profiles, however, are actually observed. Genetic interactions such as cross-inhibition and auto-regulation limit the number of states that are stable. Dr. Huang's team compared two ways of artificially inducing an HL60 progenitor cell to differentiate into a neutrophil, and they found that the two pathways of gene expression diverged and then converged, suggesting that a neutrophil occupies a stable state of expression that can be reached in multiple ways. The idea that many pathways can funnel into a few attractor states is also supported by the fact that, despite a huge variety of carcinogens and possible mutations, only four major types of malignant cells are observed in the lung. On a more specific level, Dr. Huang's team studied the interplay between the genes GATA1 and PU.1 and this interplay's effect on a progenitor cell's differentiation into an erythroid or a myeloid cell. GATA1 and

PU.1 are self-activating and cross-inhibiting, so their behavior can be easily predicted mathematically. The two genes can be used to map the course of differentiation. It appears that differentiation from a progenitor cell into an erthyroid or a myeloid cell takes place in two steps. First, the progenitor cell is destabilized. Second, the destabilized cell, which is now sensitive to stochastic noise or to deterministic signals, moves to either of two stable states. Dr. Huang's results suggest that cell fates can be viewed as attractors on the epigenetic landscape. Undifferentiated cells are cells perched on watersheds, capable of moving in many directions.