CIMIT MEETING SUMMARY 7/05/05

The meeting was the first in a CIMIT Forum Educational Series devoted to Molecular Imaging. Ralph Weissleder, MD, PhD, MGH gave an overview entitled "Introduction to in vivo Molecular Imaging". Imaging techniques form a continuum, with spatial images ranging from cell-size to whole-body size and information ranging from the molecular to the anatomic. Methodologically, clinically-relevant targets are selected and agents that will mark them sought; studies of model systems are followed by clinical trials. In the case of cancer, the targets were initially various kinases but, more recently, genetic screens have provided new targets. A variety of imaging agents are in use, including nanoparticles, optical sensors which fluoresce when activated by kinases, and isotopically-labeled small molecules. Magnetic nanoparticles consisting of monocrystalline iron oxide can be coated with agents which facilitate uptake by macrophages; the nanoparticles are not taken up by malignant nodes, allowing their detection with MRI. Fluorescence and MRI of long-circulating magnetofluorescent nanoparticles has been used to visualize micro-vascular leakage, an indicator of inflammation, in mouse models of type 1 diabetes. Libraries of nanoparticles with small-molecule targeting agents are being screened for differential uptake by human macrophages and endothelial cells as well as by prostate and pancreatic cancer tumor cells. Many of the targeting agents found have higher avidity than monoclonal antibodies. The MGH group is now focusing on high-throughput approaches for developing new markers.

King Li, MD, MBA, NIH, described "Combining Imaging and Tissue Analysis for Studying Systems Biology ". In light of the progress that has been made in genomics and proteomics as well as in functional and molecular imaging, the most productive avenue of research may now be designing experiments to integrate the in vivo imaging data with the powerful in vitro tissue analysis tools to try to understand the complex biologic processes. Once the important molecular targets for a physiologic or pathologic process are identified, imaging probes can be designed for visualizing changes of their concentration in vivo. This may allow the deciphering of complex reactions, such as a single protein-protein interaction initiating a large cascade of reactions. A cell rolling in the vasculature is an example of an event which sets off multiple reactions. Functional genomics and molecular biology would be linked in a "top-down" approach to discover what molecules are up or down regulated by an initial interaction using multiple injected molecular imaging agents. Drug delivery by nanoscale particles which encapsulate a drug and are in turn coated with polyvalent particles on their surface was described. At present the design of nanoparticles from first principles is not possible. Instead, efforts to better understand linking mechanisms are underway, using atomic-force microscopy to quantify the strength of a linkage. Further complicating the picture is the dependence of tumor genetics on location. Tumors that appear identical by histology can show different gene expression. An interventional suite which allows MRI-guided biopsies is being used to prescreen potential stroke patients before fMRI is performed. TOF mass spectroscopy has been used the analyze the biopsies and three of five peptide peaks discovered are sufficient for stroke potential discrimination.