CIMIT MEETING SUMMARY 7/20/2004

In the last of a series of tutorial lecture on biomaterials, Joachim Kohn, PhD, Rutgers University, spoke on “Integration of Combinatorial Synthesis, Rapid Screening, and Computational Modeling in Biomaterials Development”. To date, the available polymeric biomaterials lack chemical diversity, in part because new biomaterials have been synthesized one at a time and not fully characterized. Biomaterials design requires the simultaneous optimization of a large number of interconnected parameters, much like the design of the optimal aircraft for a particular application. The development of new biomaterials could impact numerous medical applications, including controlled drug delivery using polymeric systems and tissue-engineered structures based on biodegradable polymer scaffolds. To be of practical utility, combinatorial approaches to biomaterials design require (i) the availability of parallel synthesis techniques to generate libraries of polymers, (ii) efficient assays for the rapid characterization of bio-relevant material properties, and (iii) computational methods to efficiently model different biological responses in the presence of polymers. Parallel synthesis techniques involve the generation of combinatorial polymer libraries, typically using all possible combinations of polymers based on small systematic variations of two or more monomers. These combinations are synthesized using a robotic system. Typical characterizations involves the determination of a specific property, such as the glass transition temperature, for each combination and its correlation with polymer structure. In the transition temperature example, a systematic variation with structure was found. Since there are many bio-relevant properties, rapid screens for some highly-relevant ones, protein adsorption and gene expression of inflammation, were developed. For example, a screen for fibrogen adsorption was developed using a high-throughput immunofluorescence assay and a screen for macrophage activation based on RT-PCR developed. These bio-relevant properties were then correlated with the surface of different polymers. In order to computationally model biological response as a function of structure a number of polymer descriptors were developed and an artificial neural network used find the most relevant descriptors from a training set. These descriptors were then used to predict the biological response to a different set of polymers and the model predictions compared with experimental results; the correlation was generally good. A current clinical project involves the development of a resorbable polymer stent; while this is a work in progress, the screening techniques described have allowed 10,000 polymer structures to be characterized in 9 months.

John T. Santini, Jr, PhD, President, MicroCHIPS Inc., described “Microchips as Intelligent Drug Delivery Devices”. Existing devices that can release combinations of multiple drugs, provide control over the timing of drug release, and increase patient compliance with prescribed drug regimens were surveyed. They include the implantable “Gliadel” polymeric drug-delivery system for brain tumors, the Ti-rod-based leuprolide delivery system for prostate cancer and implantable pumps for morphine delivery in the control of chronic pain. Transdermal delivery systems for insulin and other drugs have been developed using a number of technologies, including microneedles, iontophoresis, nanoporous membranes and functionalized microparticles that carry drug. The technology developed by MicroCHIPS is based on solid state fabrication techniques for

silicon. Anisotropic etching is used to produce multiple reservoirs, typically 400 microns square, in silicon wafers. The reservoirs, filled with drug, are sealed with a metal membrane which can be “blown” open like a fuse by on-chip electronics, which can involve pre-programmed microprocessors, wireless telemetry, or biosensors. The metals used have been chosen for stability in the body and for low electrical energy to “blow”. On-demand release of drugs stored inside a microchip device has been demonstrated both in vitro and in vivo. A prototype device for closed-loop control of drug delivery for congestive-heart-failure management has been developed; the clinical goal is to keep the patient out of the ER. Another effort involves overcoming the current degradation of implanted glucose biosensors by using multiple protected sensors which can be sequentially activated when an existing sensor fouls.