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### **Biomagnetics and Cell-Based Biochips**

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This presentation will review various micro- and nanotechnologies that we have developed over the past decade in our efforts to manipulate and probe living cells. In early studies, we used magnetic micro-particles to apply controlled mechanical forces to surface membrane receptors. We did this to probe cellular mechanical properties, and to investigate the molecular basis of mechanotransduction – how mechanical forces are transduced into changes in intracellular biochemistry. The magnetic beads were coated with ligands for adhesion receptors, such as synthetic RGD (arginine-glycine-aspartate) peptides or antibodies that bind to membrane integrin receptors. Controlled twisting (torque) or pulling (tension) forces were exerted on the integrin-bound beads using magnetic twisting or pulling cytometry. To investigate the cellular response to dynamic forces, and to increase the level of stress applied, an electromagnetic needle was developed to apply a temporally varying magnetic field controlled by a user-defined solenoidal current; the end of the needle also was electropolished to produce a nanoscale pole tip. Magnetic forces applied to integrin receptors, but not other cell-surface receptors, induced force-dependent recruitment of cytoskeletal linker (focal adhesion) proteins to the site of bead binding, resulting in assembly and mechanical strengthening of the adhesions. Stress application to integrins also resulted in force-dependent increases in cAMP signaling and induction of gene transcription. These experiments revealed that integrins and the cytoskeleton play a central role in cellular mechanotransduction. In collaboration with George Whitesides (Harvard U.), we used microcontact printing techniques with self-assembled monolayers of alkanethiols to microfabricate extracellular matrix-coated adhesive islands of defined size, shape, and position on the micrometer scale. When cells were plated on these islands, the spread to take on the form of the island. These studies revealed that cells can be switched between growth, differentiation, and death (apoptosis) by varying the degree to which a cell physically can distend. When cells grown on islands with corners (e.g., squares, triangles) were stimulated with motility factors, the cells preferentially extended new motile processes from the corner regions, whereas cells on circular islands showed no bias. These findings demonstrated that much of cell behavior is controlled through physical interactions between cells and their adhesive substrate, and that microfabrication methods may be useful for tissue engineering, as well as creation of “laboratories on a chip” or biosensor devices that incorporate living mammalian cells. In addition, in experiments with Bob Westervelt and Donhee Ham (Harvard U.), we have demonstrated the feasibility of using microelectromagnetic circuits and CMOS technology to physically pull cells out from medium magnetically, and to move them in a directed manner. This approach may have great value for cell separation applications. Finally, with Whitesides group, we also demonstrated that microfluidics technologies may be used to deliver chemicals or probes to different regions of the same living cell under flow conditions. This provides a novel way to create chemical gradients at the subcellular scale and thereby probe the relation between cell structure and function. We also are currently exploring novel uses of microfluidics technologies, including their application for clinical cell separation applications. Taken together, this body of his work clearly