Center for Biomedical Engineering

Executive Summary

The mission of the Center for Biomedical Engineering (CBE) is to combine engineering with molecular and cellular biology to develop new approaches to biomedical technology with applications to medicine and biology. CBE has played a leading role in the evolution of MIT's activities in tissue engineering. New initiatives have focused on the structure and function of biomembrane proteins for applications in sensors. In addition, fundamental discoveries in cellular and molecular mechanics and mechanobiology by CBE faculty and students have enabled critical advances for applications in musculoskeletal and cardiovascular tissue repair and regeneration. We are witnessing fundamental changes in MIT's approach to bioengineering research and education. To maintain intellectual leadership during this period of rapid evolution in bioengineering nationwide and during times of economic uncertainty, innovative approaches are needed to stimulate fundamental research and to facilitate timely translation of new discoveries into the biomedical industrial and health care sectors. With these goals in mind, CBE continues to identify new opportunities and connections with industry that are aligned with its set of core research thrusts. The center has also expanded and improved its core research facilities, which are provided at minimal user cost to the MIT community. Taken together, our aim is to pursue multidisciplinary biomedical research and create an outstanding training environment for a new generation of students/leaders in biomedical and biological engineering.

Major Research Areas

CBE's core faculty members represent a variety of academic units, primarily within the School of Engineering, but with substantial participation from School of Science faculty and collaborating faculty from Harvard Medical School, Colorado State University Medical School, and the Cleveland Clinic. These faculty participate in multi-investigator programs focusing on CBE's primary research areas: (1) cell and tissue engineering; (2) designer biomaterials and scaffolds for regenerative medicine and drug delivery; (3) membrane protein structural biology, design, and fabrication; and (4) mechanobiology and biophysical regulation of cell signaling and tissue function. Together, these research thrusts have direct applications to cardiovascular and musculoskeletal physiology, pathology, tissue regeneration and repair, drug discovery, environmental and biohazard sensors based on membrane proteins, and nanobiotechnology. CBE maintains a broad funding base with support from the Department of Health and Human Services (55%), industry (10%), the Department of Defense (25%), and a variety of other public (e.g., National Science Foundation) and private sponsors. CBE faculty members participate in many interdepartmental programs as well as collaborative interactions with other universities and industry research laboratories.

Major Research Initiatives

CBE researchers are participating in an exciting research initiative funded by the Defense Advanced Research Projects Agency involving membrane protein molecular structure and function and membrane protein nanobiotechnology. At the core of these studies

is a class of G-protein coupled receptors (GPCRs) that represents the largest family of receptors directly involved in the biological aspects of vision, smell, taste, and memory. GPCRs are also directly involved in cancer metastasis, cardiovascular problems, asthma, AIDS, and viral infection. The smell receptors represent the most abundant GPCRs (400 among the 800 GPCRs in humans) and are perhaps the oldest of the sensory GPCRs to evolve. Although olfaction is an important part of perception, the smell receptor molecular structure currently remains unknown. The question of how finite numbers of smell receptors recognize seemingly infinite odorants remains an enigma. This lack of understanding is mainly due to the difficulty in obtaining a sufficient amount of smell receptors for scientific studies. CBE researchers have now purified a large quantity of smell receptors and are undertaking structural and functional studies. Since most membrane proteins are natural molecular devices, membrane protein-based nanodevices can be modeled from these receptors for a wide range of applications including the detection of infinitesimal amounts of odorants emitted from the environment as well as biological and chemical warfare agents.

CBE researchers are forging new pathways in a multigroup collaboration involving the use of stem cells and self-assembling peptide scaffolds for tissue engineering, the basis of a large ongoing Bioengineering Research Partnerships grant from the National Institutes of Health centered on bone, cartilage, myocardium, and liver tissue. This work is related in part to our industry connections with 3-D Matrix Inc. (scaffold) and Olympus (bone tissue engineering) and our work with Centocor (Johnson & Johnson) on cartilage degradation in osteoarthritis and the need for regenerative technologies. Exciting progress has been made in the use of peptide scaffolds in cartilage tissue engineering. A recently completed study in rabbits has now shown the ability of specially designed peptide gels to be used as an injectable in vivo and to provide a new material that can fill full-thickness osteochondral defects and promote improved cartilage repair. These peptide scaffolds can also deliver growth factors and marrow-derived stem cells to the joint. Ongoing studies are under way to determine efficacious doses of growth factors. In addition, a major study using these peptides for repair of defects in the knees of horses has been initiated, motivated by the need to evaluate these materials in a defect of clinically relevant size with strenuous exercise, as would be the case for application to human clinical needs. These studies involve collaborators in the Clinical Sciences Department of Colorado State University and several CBE faculty laboratories at MIT, including biophysicists with expertise in the biophysics and rheology of biomolecular networks, and computational modeling and simulations at the level of molecular dynamics.

A new family of designer bioactive peptide scaffolds have been developed that enable mouse preosteoblast cells and human umbilical vein endothelial cells to migrate into and within the designer peptide scaffolds without additional extra growth factors. Fibroblasts not only migrate into these scaffolds because of their biologically active motifs, they also produce abundant type I and type III collagen, typical fibroblast collagen types that are important in the engineering and regeneration of fibrous connective tissues. Collaborating CBE biophysicists have also perfected atomic force microscope–based tools to quantify, in a high-throughput fashion, the kinetics of gelation of these peptide scaffolds as well as the associated time dependence of the

evolution of their mechanical properties after gelation has occurred. These mechanical properties have been found to be extremely important determinants in the spreading, adhesion, and differentiation of stem cells into specific desired phenotypes. Using novel microfluidic devices, CBE researchers have also discovered the effects of interstitial fluid flow within peptide gel scaffolds on vascular sprouting. These studies have provided new insights on angiogenesis and the combined effects of physical forces and gradients in selected growth factors on endothelial cell behavior.

In collaboration with scientists at the Brigham and Women's Hospital, CBE researchers have discovered a means for local delivery of insulin-like growth factor-1 (IGF-1) with applications in the repair of cardiovascular and musculoskeletal tissues and organs. IGF-1 is a polypeptide protein hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults as a stimulator of tissue growth and repair. However, systemic delivery of this growth factor is not practical because of its short half-life in vivo and, additionally, systemic delivery can lead to deleterious side effects. New discoveries have shown that a fusion protein construct, HB-IGF-1, composed of IGF-1 with a positively charged heparin binding domain at the protein's amino terminus, will bind within tissues that contain a high density of negatively charged glycosaminoglycans (GAGs) in their extracellular matrix. This binding interaction enables sequestration of HB-IGF-1 in the neighborhood of cell targets within the tissue. As a result, the tissue GAGs provide a depot-like local, sustained delivery of IGF-1 to desired cells, eliminating the need for continuous systemic delivery. CBE researchers showed that such binding of HB-IGF-1 to GAGs in cartilage tissue occurs in living organ culture samples in vitro. Now, Brigham scientists have further demonstrated that this binding can occur in a rat knee model providing bioavailable IGF-1 to selected tissues in vivo. Ipsen Pharmaceuticals is working with CBE's Brigham collaborators to provide GMP-grade HB-IGF-1, which will further enable progress in ongoing in vivo and in vitro research aimed at translating this discovery into the clinic.

A collaboration between investigators spanning engineering, science, and medicine has focused on the goal of creating a physiologically relevant microenvironment for liver morphogenesis and growth using self-assembling peptide gels with adhesive modifications and tethered epidermal growth factor under conditions of interstitial flow. Recent results showed that peptide biogels are promising substrates for the long-term culture of primary hepatocytes in a format such as the microfluidic system. In addition, new studies revealed that the seeding of hepatocytes under an interstitial "packing flow" (forcing the cells onto the surface of a 3D gel matrix) was successful in creating a liver-like mass of rat hepatocytes on one surface of the gel. These studies represent the first published triculture system for studying the development of vascularized liver tissue. They have led to new insights into the role of interstitial flow in hepatocyte growth and function and the nature of interactions among hepatocytes, endothelial cells, and stellate cells in developing liver tissue.

Core Facilities

One of the critically important missions of CBE is to maintain and expand a set of central core research facilities. These core facilities are made available to faculty, staff, and students, MIT-wide, at no or minimal user cost, and are particularly relevant for CBE's major research areas. New instruments added this past year include the Attana 200 dual-channel, label-free, temperature-controlled, continuous-flow system for analysis of molecular interactions (e.g., kinetics, affinity and off-rate screening) and a Rigaku X-ray diffraction facility for protein and molecular crystallography and analysis. In addition, CBE continues to maintain facilities including an Applied Biosystems (AB) 7900HT fast real-time 384-well plate quantitative polymerase chain reaction (qPCR) instrument and associated peripherals and a NanoDrop ND-1000 Spectrophotometric Analyzer to measure RNA quality (which is useful in assessing samples prior to amplification using the AB 7900HT qPCR facility). An Alpha Innotech Gel Imaging Facility has been added for quantitative analysis of electrophoresis gels, along with a multiphoton microscopy facility, a Cressington Quick-Freeze Deep Etch facility to prepare specimens for follow-on electron microscopy, and a BiaCore 2000 surface plasmon resonance instrument to quantify binding reaction constants between molecules and between molecules and surfaces. CBE also continues to run a large cell, tissue, and organ culture facility including four six-foot biosafety cabinets and eight incubators. These are available to faculty and students MIT-wide who would otherwise not be able to explore new ventures in biomedical engineering involving living cells because of a lack of specialized facilities in their own laboratories (including an array of associated instruments and peripherals needed for maintaining and experimenting with living cells and tissues). All of these instruments are located in the second- and third-floor laboratories of CBE in NE47 (500 Technology Square).

UROP Activities

CBE continues to connect outstanding undergraduate students in several departments at MIT to laboratories at Boston's Beth Israel Deaconess Medical Center working in cancer-related research. CBE provides logistical and administrative support to ensure the continued success of this long-standing partnership.

Alan J. Grodzinsky
Director
Professor of Mechanical, Electrical, and Biological Engineering

More information about the Center for Biomedical Engineering can be found at http://web.mit.edu/cbe/www/.