Biotechnology Process Engineering Center

The Biotechnology Process Engineering Center (BPEC), as a National Science Foundation (NSF) engineering research center (ERC), is a multidisciplinary body with faculty members from the MIT departments of Biology, Chemistry, and Chemical Engineering, the Biological Engineering Division, and the Whitehead Institute for Biomedical Research, along with the University of Toronto Department of Chemical Engineering, Boston Children's Hospital, and the Brown University School of Medicine Liver Center.

Goals, Objectives, and Priorities

BPEC remains committed to its core mission of fusing engineering with molecular cell biology by emphasizing strategic problem solving in interdisciplinary research, education, and biotechnology industry interaction. The center's vision over the past seven years has been to define the engineering/biology partnership needed to create a "therapeutic gene" biotechnology industry, a vision modeled on its past success in influencing the ongoing "therapeutic protein" biotechnology industry. This vision is now evolving to a more comprehensive strategy for molecular and cellular therapeutics. Key components of achieving this goal are innovations in research, the graduating of highly prepared students into important roles at biotech companies, and our active exchanges with key partners in the industry.

BPEC's strategic plan focuses on two major engineered-system objectives to achieve successful transgene delivery and expression to blood and tissue cells. The first is an ex vivo approach employing genetically engineered stem cells to lay a basis for replacement therapies of injured tissues. Examples of treatment potential include degenerative diseases such as diabetes and the repair of tissues injured through trauma or stress, as in spinal cord injuries. The second is an in vivo approach employing targeted viral or synthetic vectors. This research attempts to identify or create compounds that will protectively shuttle therapeutic DNA to targeted cells. Once the DNA is safely delivered to the compromised cell's nucleus, therapeutic gene expression can result. Advances could give rise to noninvasive, curative treatments for any affliction that would benefit from the cellular production of new proteins—such as cancers—and also to preventive DNA vaccines that can arrest the onset of disease altogether.

The challenges involved in understanding the properties of stem cells that will lead to successful gene transduction—as well as in defining the barriers to successful transgene uptake and expression and designing vectors to overcome these barriers—require basic tools of engineering analysis, design, and synthesis combined with a forefront understanding of biology. Thus, the specific application problems funded through the NSF ERC core grant have provided a rich foundation for a more general approach to molecular and cellular therapeutics. The fundamental knowledge, enabling technologies, and engineered systems that have been produced by BPEC over the past eight years—focused on the problems above—are now being applied by BPEC researchers and their collaborators to a range of needs in the pharmaceutical and biotechnology industry, including generation of in vitro toxicity assays to replace animal testing and speed

drug development; designing better breast cancer–fighting drugs through molecular engineering of cytokines and receptors; and providing computational and analytical algorithms that allow standardization of experiments on the complex machinery of intracellular signal transduction.

Whereas in the past, BPEC research focused primarily on challenges in large-scale economic production of a target therapeutic molecule that had been discovered by biologists, the current and future BPEC research directions bring engineering into discovering new targets for therapeutic intervention and validating these targets, as well as in molecular engineering that optimizes the targets based on a detailed understanding of cellular pharmacology. Thus BPEC research has driven the evolution of "biological engineering" and is creating new pathways for engineers in drug discovery.

The educational programs of BPEC deal with the needs of undergraduates, graduates, and industrial personnel and serve MIT students, students visiting from the United States and abroad, and industry colleagues. The goal of the educational programs is to provide broad bioengineering perspectives to the students and to emphasize integration of engineering and biology. At the undergraduate level, we have continued to participate in the popular biomedical engineering minor offered by the Biological Engineering Division (BE) to students in all majors. Two signature subjects in the minor—7.37/BE.361/10.441 Molecular and Engineering Aspects of Biotechnology and BE.110/2.772 Statistical Thermodynamics of Biomolecular Systems—were developed to meet the needs of BPEC research and are taught by BPEC faculty members. The subject BE.110/2.772 was developed by BPEC faculty member Griffith, along with Kim Hamad-Schifferli, to provide a firm foundation in molecular thermodynamics relevant for biomolecular interactions (protein folding, protein-protein interactions, etc.) and has rapidly become a service subject for a wide audience at MIT, with 70 students enrolled in the spring 2005 offering. The MIT Biology Department now recommends this subject to fulfill the thermodynamics requirement for biology majors. A significant development in the course occurred this past year, with the participation of Dean Bob Silbey in teaching leading to a plan for coteaching the first half of BE.110 with 5.60 starting fall 2005, thus consolidating material for the benefit of students.

The impact of BPEC research is further translated into education with BPEC director Linda Griffith serving as chair of the Undergraduate Programs Committee for BE. A significant accomplishment of this committee in the past year was the development of a new undergraduate SB degree in biological engineering, which was approved by a unanimous vote of the MIT Faculty in February 2005 as MIT's first new undergraduate major in 29 years. We have energized our student leadership council, currently headed by BE PhD student Nate Tedford, with new members and activities including an industrial seminar series, cosponsorship of the BE Diversity Group, and a student research update series.

At the graduate level we participate in the bioengineering and toxicology PhD programs offered by BE, the new Computational and Systems Biology PhD program offered jointly by BE, Biology, and Electrical Engineering and Computer Science (EECS), along with the traditional PhD programs in the departments of Biology, Chemistry, and Chemical

Engineering. In addition, National Institutes of Health (NIH) training programs in biotechnology and computational systems biology are administered from the BPEC office, leveraging the NSF ERC to broader educational opportunities at the engineering/molecular-biology interface. Students in the biotechnology training grant program participate in three-month industry internships and are sought after by industry colleagues. Recent internship hosts are Merck, Astra Zeneca, and Biogen.

Undergraduate research is achieved through the Undergraduate Research Opportunities Program for MIT students and the Research Experience for Undergraduates (REU) for non–MIT students. The REU program has been highly competitive in the past three years, with over 150 applicants for 8 spaces this year, and it has attracted a highly talented and highly diverse cadre of students from across the country.

Industrial activities and planning are coordinated through our 15-member Therapeutic Gene Biotechnology Industrial Consortium Advisory Board, supervised by Matt Croughan, industrial liaison officer.

Accomplishments

BPEC investigators published BPEC–related work in a number of high-profile scientific journals last year, including *Science, PNAS, Nature Biotechnology, Nature Methods,* and *Blood.* Griffith presented an overview of tissue engineering at the Congressional Joint Biomedical Research Caucus in Washington.

BPEC has high visibility in the NSF ERC program and its activities are often featured in sessions at the annual ERC meeting. In November 2004, BPEC was featured in the plenary opening session of the meeting as an example of a successful graduating ERC. BPEC director Griffith and BPEC industrial liaison Croughan presented a one-hour overview of the history, accomplishments, and future directions of BPEC. The final summation site visit conducted in July 2004 was highly successful, and NSF program director Lynn Preston suggested that NSF would support a technical writer to compile a history of BPEC and its impact on the research and teaching environment at MIT.

Many of the activities initiated by the BPEC Student/Postdoctoral Leadership Council (SLC) have now been adopted by the BE Student Board, thus increasing participation and audience. An example is the "Meet the Lab" seminar series, initiated by the SLC, which is designed to showcase several students in a single lab through short talks united by a brief overview given by the faculty member who runs the lab; this is now part of the BE seminar series. The Industrial Consortium Advisory Board (ICAB) continues to operate to great mutual benefit, including specific research collaborations that involve sponsored research at MIT as well as student and industrial scientist exchanges.
Our summer Research Experience for Undergraduates program continues to attract undergraduates to MIT graduate programs. We have a transition plan in place for becoming an intradepartmental center within BE following the end of NSF funding.
Overall, we submit that we are making excellent progress in accord with our strategic plan and in response to input from ICAB and SLC.

The DuPont–MIT Alliance (DMA), administered through BPEC, is in its sixth year of funding. Significantly, DuPont renewed the DMA program in spring 2005. At the press conference announcing the renewal, DuPont featured BPEC research in the Griffith lab as an example of a successful collaboration; the *Boston Herald* ran a favorable story with the headline, "$25 Million is not chopped liver," and BPEC director Griffith was interviewed on National Public Radio regarding commercialization plans for the research. DMA continues to credit the success of its research and education programs to the collaborative efforts between MIT administrative and principal investigators and DuPont executives and technical liaisons.

There is a unique cooperation between DuPont and MIT to promote the basic principle of cutting-edge collaborative research that will have a significant impact on the long-term commercial goals of DuPont and the continuously evolving educational culture of MIT. The close relationship between DuPont and MIT is fostered through the multidisciplinary team effort in the alliance research program. Over 30 projects have been sponsored, and each has had one or two DuPont investigators as a liaison who works closely with MIT investigators on the individual projects. The portfolio of projects is reviewed and revised annually by the Steering Committee. The following 15 departments and centers across campus have received funding from DMA over the past four years: Biology, Biological Engineering Division, Chemistry, Chemical Engineering, Materials Science and Engineering, Center for Biomedical Engineering, Research Laboratory of Electronics, Ocean Engineering, Sloan School of Management, Mechanical Engineering, Physics, Center for Learning and Memory, School of Science, EECS, and Whitehead Institute. The process of white papers and proposal submission relies on the participation of the MIT Internal Advisory Committee. We gratefully acknowledge their assistance. The DMA has sponsored numerous research papers and around 20 patent applications. As the alliance continues to grow, DMA remains dedicated to the principles of novelty and excellence in the research program.

The NIH Biotechnology Training Program (BTP), now in its 15th year of funding, continues to be administered from the BPEC office, leveraging the NSF ERC to broader educational opportunities at the engineering/molecular-biology interface. Professor K. Dane Wittrup serves as director and principal investigator; Darlene Ray, BPEC's education coordinator, is the administrator for this program. The NIH BTP provides funds to support 20 predoctoral students who will provide future leadership in all aspects of biotechnology and the biotechnology industry. This requires that students be educated more broadly than would normally occur within their own discipline in order to solve problems when they arise and work with others from diverse backgrounds. The interdisciplinary program provides a formal mechanism for this broader education through specific research, education, and industrial interaction requirements. Activities include a yearly retreat, periodic trips to biotechnology company sites, and workshops on ethics in research. Currently, 22 faculty members participate in the program from the Biological Engineering Division and the departments of Biology, Chemistry, Chemical Engineering, and Mathematics.

In addition to the outreach activities described above, BPEC has participated in several activities that involve dissemination of the research and educational accomplishments of

BPEC to other academic institutions. For example, BPEC, along with the Georgia Tech/ Emory Center for the Engineering of Living Tissues and the University of Washington's Engineered Biomaterials Engineering Research Center, cosponsor a four-day winter conference in the field of tissue engineering. At the meeting in March 2005, BPEC student Joe Shuga was one of four awarded "Best Poster" prizes out of over 100 posters at the meeting.

Administrative Initiatives

BPEC is having an increasing role in career development of undergraduates. Through a Bioengineering Education grant from the Cambridge–MIT Institute (CMI), BPEC education and outreach coordinator Dan Darling has begun to build a formal internship program linking MIT undergraduates in bioengineering with new opportunities in industry, particularly in industries that have not previously considered hiring engineers. In these endeavors, he is working closely with the MIT student chapter of the Biomedical Engineering Society as well as the MIT Careers Office, and he placed several students in internships for summer 2005.

BPEC interacts substantially with other MIT centers, notably the Center for Environmental Health Sciences and the Computational and Systems Biology Initiative. As BPEC research efforts move toward having a broad impact in the pharmaceutical and biotech industries, activities in BPEC are best leveraged by the strengths in computation and toxicology found in these centers. Approximately 15 MIT faculty members are affiliated with at least two of the centers, which have a combined total affiliation of around 60 members.

Finances and Funding

The center's NSF Cooperative Agreement ends August 31, 2005, and will have a no-cost extension until January 15, 2006, to allow completion of thesis work by BPEC students. In addition to the DMA, several sponsored research projects begun within the past two years provide a foundation for continuing the strategic plan for BPEC following the end of NSF funding. These projects include "3D Rat and Human Liver in Vitro Transport, Metabolism, and Toxicology Assay," supported by Pfizer; "Systems Biology of Stem Cells Knowledge Integration Community," funded by CMI; the "Bioengineering Education" grant funded by CMI; and sponsored research from Lexigen, Astra Zeneca, and others. These will continue to be administered by the current BPEC financial assistant, Michelle Berry, when BPEC becomes an intradepartmental center in BE.

Future Plans

The NSF core funding for BPEC, as noted, ends in 2005 and BPEC will become an intradepartmental center in Biological Engineering. BPEC will continue to provide a nexus for industry interaction through the industrial consortium, as well as a home for several multi-investigator grants. As BPEC research has evolved to address problems related to drug design and discovery—that is, far upstream of production—a new research core has emerged to address needs in the pharmaceutical industry for complex physiological models for drug discovery and development. "Complex physiological models" encompasses a range of approaches to develop living analogues of human

tissues that can be used to predict human responses to new therapies, as well as the analytical and computational methods needed to interpret the response of these models to therapeutics. BPEC has added a new faculty member, Darrell Irvine, in this area. We anticipate that this new research direction will become a thrust area in the larger "center for biomedical innovation" under development by Frank Douglas. As the industry needs coalesce, we anticipate developing a large multi-investigator center grant to support basic research in this area.

Personnel

Professor Linda Griffith is director of BPEC. Professor Douglas Lauffenburger, who replaced Professor Daniel Wang as director in 1998, has taken on full-time service as director of the Biological Engineering Division, the primary educational partner for BPEC. He also serves as BPEC executive director for development. Professor Harvey Lodish remains executive director for research. Professor Dane Wittrup is executive director for education, appropriately in his role as director of the NIH Biotechnology Training Grant administered by BPEC. Dan Darling is the outreach coordinator, assisting in BPEC outreach and student activities, and is also the administrative coordinator for a Biological Engineering Internship Program that is funded through the Cambridge–MIT Institute. Darlene Ray is the educational coordinator, assisting the director and executive director for education in educational activities and in operation of the three NIH training grants and assisting with preparation of new proposals relating to training at the graduate level. Aran Parillo is the information technologies specialist, a role he shares with the Biological Engineering Division. Nils Nordal is the director of administration.

BPEC faculty garnered a number of awards this year, including the R&D 100 Award (Wittrup); the Lifetime Achievement Award, Society of In Vitro Biology (Langer); Albany Medical Center Prize in Medicine and Biomedical Research (Langer); the Stohlman Scholar Award, Leukemia and Lymphoma Society of America (Daley); the NIH Director's Pioneer Award (Daley); and the UC Davis Smith Lecture (Lauffenburger). Lodish completed his term this past year as president of the American Society for Cell Biology and has been influential in bringing the technological applications of cell biology to the forefront through new symposia at the Annual Meeting as well as summer conferences. Griffith served as cochair of the first "Engineering Cell Biology: The Cell in Context" conference jointly sponsored by the American Society for Cell Biology and Engineering Conferences International.

Linda Griffith
Director
Professor of Biological and Mechanical Engineering

More information about the Biotechnology Process Engineering Center can be found online at http://web.mit.edu/bpec/.