

Biotechnology Process Engineering Center

The Biotechnology Process Engineering Center (BPEC), as a National Science Foundation (NSF) engineering research center, 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 six 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 preventative 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 Engineering Research Center (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 and 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 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.011/2.772 Statistical Thermodynamics of Biomolecular Systems—were developed to meet the needs of BPEC research and are taught by BPEC faculty members. The subject 7.37, cotaught by BPEC faculty Lodish and Griffith, underwent significant evolution this year, adapting to the new research directions in molecular engineering of therapeutics; it maintains a large (~70 students) enrollment, with students drawn from a variety of engineering and science majors.

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. This committee is in the final stages of developing a new undergraduate SB degree in biological engineering. 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, 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 in genomics 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 two years, with over 100 applicants for 8 spaces, and has attracted a highly talented and highly diverse cadre of students from across the country. Special one-week summer courses are offered to industrial personnel.

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*, *Nature*, *PNAS*, *Immunity*, and *Blood*, along with several articles in the top bioengineering journal *Biotechnology & Bioengineering*. The stem cell work published by George Daley in *Nature* in January 2004 created a worldwide sensation, with commentaries in prominent scientific journals as well as coverage in the popular press. Daley has been a featured speaker at many events in Washington that are aimed at educating legislators and their staff about the promises and realities of stem cell research. Work by Bob Langer on stem cell differentiation has also been featured in the public press.

BPEC has high visibility in the NSF ERC program, and its activities are often featured in sessions at the annual ERC meeting. Last November, BPEC director Griffith cochaired a session on "Bioengineering Education" for the eight bioengineering ERC centers, along with NSF program director Sohi Rastegar. The focus of the session was delineation of educational frontiers, and a consensus view emerged that "biomedical engineering" has evolved in two distinct directions: "biological engineering" as an emerging new engineering discipline, with a foundation in the basic science of modern molecular cell biology, and "medical engineering," in which tools from all engineering disciplines are applied to an array of problems in medicine and no particular underlying knowledge of biology is required. Medical engineering remains strongly rooted in the traditional engineering departments, as it is applications-driven.

The 2004 annual ERC meeting in November will feature a plenary session celebrating the accomplishments of BPEC as an exemplary ERC. BPEC just passed its final site visit with enthusiastic endorsement of the future plans for moving more broadly into molecular and cellular therapies.

The Student/Postdoctoral Leadership Council's (SLC) activities are at an all-time BPEC high for centerwide participation and impact. These activities include a well-attended monthly seminar series highlighting the research of the BPEC and MIT faculty, as well as the research of BPEC's industrial member representatives. 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. We have begun collaborations with the Cambridge Public Schools in building K-12 outreach, along with continuing our summer REU Program

and the Research Experience for Teachers Program. We are at the final stages of formulating a plan toward attaining self-sufficiency status within approximately a year, and we have begun to implement aspects of that plan.

Overall, we submit that we are making excellent progress in accord with our strategic plan and in response to input from ICAB and SLC. A total of 125 people took part in BPEC's NSF research strategic plan during fiscal year 2003.

The DuPont–MIT Alliance (DMA), administered through BPEC, is in its fifth year of funding. The Steering Committee agreed to extend the present agreement another year to December 2005, while the negotiation toward a five-year renewal progresses. DMA continues to credit the success of its research and education programs to the collaborative efforts between MIT administrative and principle 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 of DuPont and MIT is fostered through the multidisciplinary team effort in the alliance research program. Thirty-three projects have been sponsored, and each has had one or two DuPont investigators as liaisons who work closely with MIT investigators on the individual projects. The portfolio of projects is reviewed and revised annually by the Steering Committee. At present there are 19 principal investigators, 16 coinvestigators, and 49 graduate students. Fifteen projects have been closed. 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, the Center for Biomedical Engineering, the Research Laboratory of Electronics, Ocean Engineering, the Sloan School, Mechanical Engineering, Physics, the Center for Learning and Memory, the School of Science, Electrical Engineering and Computer Science (EECS), and the Whitehead Institute.

The process of white papers and proposal submission relies on the participation of the MIT Internal Advisory Committee (IAC). We gratefully acknowledge their assistance in reviewing 109 white papers and 44 proposals over the past four years. The present IAC member list includes professors Yet-Ming Chiang, Rebecca Henderson, Klavs Jensen, Philip Sharp, Anthony Sinskey, and Bruce Tidor.

The DMA has sponsored numerous research papers and 15 patent applications. As the alliance continues to grow, DMA remains dedicated to the principles of novelty and excellence in the research program.

For the past five years, DMA has also supported MIT first-year graduate students named as DuPont fellows. The total number of fellowships has grown to 92, distributed through 10 academic departments: Biology, Biological Engineering, Chemistry, Chemical Engineering, Materials Science and Engineering, Mechanical Engineering, EECS, the Technology and Policy Program, Physics, and the Sloan School of

Management. After their first year, the graduate students are supported by the funded research programs of their faculty thesis advisors.

Another important second thrust of DMA's education program has been the short courses and tutorials offered by MIT to the DuPont personnel, including senior executives and investigators. This program continues to impact the strategic planning and management within DuPont's Central Research and Development Division. DMA has sponsored 10 tutorials and 6 short courses.

The NIH Biotechnology Training Program (BTP), now in its 14th 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; Ms. 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 and periodic trips to biotechnology company sites. Currently, 22 faculty members participate in the program from the Biological Engineering Division and the departments of Biology, Chemistry, Chemical Engineering, and Mathematics. Five BPEC faculty members are currently participating in the BTP. They are professors Griffith, Langer, Lauffenburger, Sherley, and Wittrup.

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, cosponsored a four-day winter conference in the field of tissue engineering.

BPEC faculty members have continued to lead special one-week summer courses to industrial personnel on and off campus.

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 (BMES) as well as the MIT career services office. BPEC ICAB members as well as several other companies will be participating in the program when it launches next year. Professor James Sherley assumed the role of primary faculty advisor

for the MIT student chapter of the BMES in fall 2002 and continues to coordinate joint BPEC–BMES activities.

BPEC is forming strategic alliances with other MIT centers, notably the Center for Environmental Health Sciences (CEHS) and the Computational and Systems Biology Initiative (CSBi). As the BPEC research efforts move more toward having a broad impact in the pharmaceutical and biotech industries, the activities in BPEC are best leveraged by the strengths in computation and in 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. The directors of the three centers, along with appropriate MIT administrative members, are in advanced stages of discussing an administrative merger of the centers that would combine the basic financial and personnel functions along with communications, industry liaison, and outreach functions to achieve a more visible presence outside MIT.

The core BPEC lab space underwent reorganization in December 2003. Long-time lab manager Jean-Francois Hamel moved to space in Chemical Engineering to focus on bioprocess engineering education and research. Space was reorganized to accommodate some students in the research group of BPEC faculty member Dane Wittrup, as well as a new junior faculty member, Darrell Irvine, who is anticipated to join BPEC activities, although he is not directly funded by the NSF core grant. Major equipment acquired in the past year includes a deconvolution microscope and an RT-PCR analyzer.

Finances and Funding

After the last NSF critical site visit, the center's NSF Cooperative Agreement was extended to August 31, 2005. Over the past year, several new projects have been funded that provide a base for continuing the strategic plan of BPEC following the end of NSF funding. These projects include the "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.

Future Plans

In addition to new multi-investigator grants that have been funded, several multi-investigator grants are in the planning stages and will be helpful in keeping the core funding of BPEC at a level commensurate with remaining an MIT center and providing a nexus for industry interaction. The potential administrative merger with CEHS and CSBi is expected to facilitate the preparation of multi-investigator grants and the industry interface. The membership of the ICAB is expected to undergo significant evolution at the fall and spring meetings as we invite potential members from new industry sectors, and again the interactions with CSBi have the potential to greatly enhance these interactions.

Personnel

Professor Linda Griffith became director of BPEC in July 2003. 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 will also serve as BPEC executive director for development, now replacing Wang. Professor Harvey Lodish remains executive director for research. Professor Dane Wittrup replaced Griffith as executive director for education, appropriately in his role as director of the NIH Biotechnology Training Grant administered by BPEC. In order to more formally address outreach and education activities as recommended by the site visit panel, Daniel Darling is the outreach coordinator, assisting in BPEC outreach and student activities, and has in the past year become the administrative coordinator for a nascent Biological Engineering Internship Program. Darlene Ray is the educational coordinator, assisting the director and executive director for education in educational activities and in operation of the NIH Biotechnology Training Grant and assisting with preparation of new proposals relating to training at the graduate level. Mr. Nils Nordal is the director of administration. He joined BPEC in February 2004 to replace Audrey Childs, who left MIT in January 2004.

BPEC faculty garnered a number of awards this year, including the Biomedical Engineering Society Distinguished Lecturer (Lauffenburger), the Harvey Prize (Langer), the John Fritz Award (Langer), and the General Motors Kettering Award for Cancer Research (Langer). Lodish served 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. Griffith gave a keynote lecture at the American Association of Pharmaceutical Scientists annual meeting.

Linda Griffith **Director**

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