Biotechnology Process Engineering Center

Massachusetts Institute of Technology

A National Science Foundation Engineering Research Center since 1985

Making advances in the knowledge-base and technology-base aimed at overcoming crucial "bottlenecks" of nucleic acid therapeutics

The MIT Biotechnology Process Engineering Center (BPEC) is a world leader in the training of students in biotechnology. BPEC emphasizes a fundamental but interdisciplinary approach to integrating molecular and cell biology with process engineering, with the simultaneous goals of creating advanced biological technologies, focusing on protein and nucleic acid therapeutics, and preparing top-quality individuals for leadership in this industry. BPEC now features two major thrust areas: Therapeutic Gene Biotechnology and Therapeutic Protein Biotechnology.

Research

The BPEC is moving its primary research direction from therapeutic protein biotechnology to therapeutic gene biotechnology, in order to attack bottleneck problems in this highly promising new area using the multidisciplinary approach proven in the Center's early years. The Center continues to maintain its emphasis on solving fundamental problems of generic importance for aiding the growth of a nascent industry.

It is widely recognized that, at the present time, the crucial bottleneck holding gene therapy back from reliable implementation lies predominantly in the area of delivery. In particular, effective delivery of a therapeutic transgene is typically limited by one or more of the following issues, depending on the approach and application: (1) longevity, or repeatability, of transgene expression; (2) selectivity of transgene expression; (3) efficiency of transgene expression; (4) regulation of transgene expression. Our new BPEC program is dedicated to creating new fundamental knowledge, enabling technology, and a systems perspective addressing these issues in focused manner, synergistically combining bio/chemical engineering with molecular cell biology.

Recognizing that different applications will require differing delivery vehicles, we are currently focusing our research efforts on two chief approach categories motivated by the issues listed above — representing *ex vivo* and *in vivo* approaches, respectively. One approach category is the use of pluripotent stem cells transfected via chromosomal-integrating retroviral vectors, as an *ex vivo* gene delivery vehicle that can potentially offer expression longevity. Critical problems for this approach are expanding these cells to significant numbers in culture, and obtaining high transfection efficiencies for reimplantation. The second approach category is the use of nonviral targeted polyplexes as an *in vivo* gene delivery vehicle that can potentially offer expression selectivity and repeatable retransfection. A critical problem for this approach is transfecting cells with adequate efficiency. In both of these two approaches — *ex vivo* stem cell delivery and *in vivo* targeted polyplex delivery — a capability for regulating transgene expression at the tissue level using small molecule drugs is needed. We are therefore pursuing research directed toward this capability in relation to both delivery approaches. As ultimate aims we are focusing on hematopoietic stem cell gene therapy via retroviral vehicles as an *ex vivo* target application and on liver gene therapy via molecular conjugate vehicles as an *in vivo* target application. Accordingly, a centerpiece of our efforts is the development of tissue-engineered "vascularized" hematopoietic and liver cell microarrays to serve as a unique model testbed integrating all research projects.

Our efforts in the area of production and delivery of therapeutic proteins also continue vigorously. Directions of current emphasis include protein folding and glycosylation, formulation issues for protein stability, novel delivery technologies, and protein engineering for enhanced potency.

Education

Undergraduate. At the undergraduate level, our goal is to ensure that the students are integrated into our research thrusts for both MIT students, through MIT's Undergraduate Research Opportunities Program (UROP), and students from other institutions through the Research Experiences for Undergraduates (REU) Program. To expose the students to cross-disciplinary activities and teamwork, the projects are selected carefully and critically. The BPEC provides initial experiences to undergraduates and encourages students to work in industry as internees.

Graduate. At the graduate level, one of the goals of the BPEC is to provide research experience related to the Center's thrusts. We ensure that the research is conducted with a spirit of teamwork and cross-disciplinary input. This is achieved by having joint faculty advisors on the doctoral thesis committees and/or thesis committee members who are from different departments and disciplines. To provide industrial perspectives on the students' training program, industrial personnel are often members of doctoral thesis committees.

An Interdepartmental Biotechnology Training Grant (BTG) program funded by the National Institutes of Health (NIGMS) is available at the BPEC. Training faculty participate from the Departments of Biology, Chemistry, Chemical Engineering, and Mathematics and the recently established department-level Division of Bioengineering & Environmental Health (which includes doctoral programs in Bioengineering and in Toxicology). The objective of the BTG is to continue to provide cross-disciplinary graduate education in

biotechnology. The program extends into new directions related to innovative biology-based therapeutics, such as nucleic acids (e.g., vaccines, anti-sense therapies, gene therapies), engineered cell and tissue implants, and new biomaterials useful for stimulating wound healing and tissue regeneration.

Industrial and Continual Education. To ensure that the educational needs of industry are met, the BPEC provides one-week special summer courses. These one-week courses provide training on such topics as Fermentation Technology; Biotechnology; Principles and Processing; Modeling, Simulation, and Optimization; and Down-stream Processing.

Other Student Outreach. Laboratory tours familiarize the public with the Center's ongoing cutting-edge research. These tours are designed for both the layman and the scientist. One important focus of this program is to reach out to both high school teachers and their students. To help pre-college students dispel any fear of science, they are given a strong insight into the ethics of laboratory research and information that helps build a curiosity and interest in biotech research.

Industrial Collaboration/Technology Transfer

The industrial activities and planning are achieved through the Industrial Consortium Advisory Board. Research collaborations and technology transfer are achieved through the Center's Industrial Consortia. Direct industrial collaborations involve BPEC's students, research staff, and faculty. These collaborative efforts involve the Center personnel working directly with companies either at the Center or at the industrial sites. Transfer of technology and information is also routinely accomplished through several other avenues, including publications, participation in thesis committees, retreats, presentations, seminars, and theses.

Facilities

Research and educational programs are conducted in a variety of environments. The BPEC's Core Facility consists of ~12,000 square feet of laboratory space and houses state-of-the-art equipment. Additional facilities associated with the BPEC's faculty are available in support of the Center's programs. Due to the multi-departmental participation in this Center, our researchers have access to a number of instrumentation facilities that are operated and maintained by different MIT departments.

Center Organization and Leadership

The Director of BPEC reports directly to the Dean of Engineering and to a member of Engineering Council. The Center's Industrial Consortium Advisory Board assists in the planning and assessment of the Center's activities. The Executive Director for Research, the Executive Director for Education, the Assistant Director for Operations and Administration, and the Industrial Liaison Officer all report to the Center Director.

One-week cultures of mouse embryonic stem cells in through-channels etched in silicon wafers; channel dimensions range from 250 microns to 600 microns.

Center Headquarters

Biotechnology Process Engineering Center
Massachusetts Institute of Technology
Room 16-429
77 Massachusetts Avenue
Cambridge, MA 02139-4307
Tel (617) 253-0805 • Fax (617) 253-2400
Email: bpec-www@mit.edu
Homepage: http://web.mit.edu/bpec/

Center Director: Dr. Douglas A. Lauffenburger
(617) 253-4480 • lauffen@mit.edu

Assistant Director for Administration and Operations: Ms. Audrey Jones Childs
(617) 253-2504 • childs@mit.edu

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