Whitaker College of Health Sciences and Technology

Center for Environmental Health Sciences

Overview

The overriding goal of MIT's Center for Environmental Health Sciences (CEHS) is to study the biological effects of exposure to environmental agents in order to understand, and predict, how such exposures affect human health. Three fundamental components influence the physiological effects of environmental exposures: the nature of the exposure, the duration of that exposure, and how well the exposed organism is equipped to deal with the exposure—in other words, the organism's genetic susceptibility. Environmental health research at MIT encompasses a wide range of disciplines, and the CEHS brings together 31 faculty members (29 from MIT plus 2 from Harvard University) who employ a diverse set of tools to tackle research relevant to the environmental health sciences.

The center has core funding from the National Institute of Environmental Health Sciences, and its research programs are funded through a variety of sources, including the National Institute of General Medical Sciences, National Cancer Institute, Department of Energy, National Science Foundation, American Cancer Society, and Defense Advanced Research Projects Agency. The many and varied research programs provide challenging interdisciplinary research problems for postdocs, graduate students, and undergraduates. Research in the center is organized into three research cores that build on the strengths of the center membership and reflect a vision for the future of environmental health research. These are (1) the Mutation and Cancer Research Core, (2) the Bioengineering for Toxicology Research Core, and (3) the Environmental Systems and Health Research Core. The theme of each core derives from the members' research interests, and all are linked by the center's overarching focus on defining the biological effects of exposure to environmental agents.

The Mutation and Cancer Research Core, directed by Professor Peter Dedon, addresses the relationships between DNA damage, DNA repair, mutation, and cancer associated with exposure to environmental and endogenous chemical and physical agents. The Bioengineering for Toxicology Research Core, directed by Professor Linda Griffith, was created to facilitate the development of new experimental tools and analysis methods relevant to environmental influences on human health, with a range of approaches that span the molecular-cellular-systems length scales. The mission of the Environmental Systems and Health Research Core, now directed by Professor David Schauer after its former director, Professor Harold Hemond, stepped down, is to understand the relationships that link environmental processes and human health in terms of exposure to chemical agents as well as biota. This is most aptly illustrated by the triad of dependent interactions of aflatoxin, hepatitis virus, and human liver cancer, which has been a research foundation for the center since its inception nearly three decades ago.

Three state-of-the-art facilities cores reflect CEHS's new research directions. The cores are heavily used by center researchers, with each contributing to the research of at least 10 members. Under the direction of Drs. John Wishnok, Koli Taghizadeh, and Paul Skipper, the Bioanalytical Facilities Core provides center members with the latest tools, techniques, and expertise in the characterization and quantification of chemical substances and modifications of cellular molecules such as DNA and protein. The core operates as a resource for the center, and it allows researchers to use the facilities as a service lab, for supervised analyses, or as fully trained users. The Genomics and Bioinformatics Facilities Core, directed by Professor Peter Sorger and Dr. Rebecca Fry, provides center members with an integrated facility for microarray fabrication and analysis, database storage, database management, data mining, and modeling. These tools are critical to the goal of moving center research to higher levels of complexity in an attempt to understand the response of the whole organism to environmental influences. The Animal Models and Pathology Facilities Core, directed by Professor James Fox, provides center members with the latest technology for the application of animal models to environmental health research, including the generation of genetically engineered mice, embryo rederivation of imported mice, colony management, and preparation and interpretation of murine tissue by histological and image analysis.

Research Cores

Mutation and Cancer Research Core

This research core was created in 2002 to provide an integrated and focused scientific program that addresses the relationships between DNA damage, DNA repair, mutation, and cancer associated with exposure to environmental and endogenous chemical and physical agents. One of the central questions is the degree to which environmental and endogenous processes contribute to the mutational burden of human cells. The specific aims of this core are:

- To further the development of center research projects and programs that address the mechanistic linkages between exposure to environmental and endogenous agents, genetic change, and cancer and other diseases
- To promote interaction among the members of the Mutation and Cancer Research Core, and interactions between members of this research core and those of the other two research cores, with the goal of creating new research projects and programs
- To promote the development and acquisition of new technologies in the CEHS Facilities Cores that will facilitate studies in the Mutation and Cancer Research Core

Core Members

- Peter C. Dedon, core director and associate director, Biological Engineering Division; deputy director, CEHS; professor of biological engineering and toxicology
- Jeffrey A. Coderre, associate professor of nuclear engineering

- Catherine L. Drennan, Cecil and Ida Green career development associate professor of chemistry
- Thomas E. Ellenberger, professor of biological chemistry and molecular pharmacology, Harvard Medical School
- Bevin P. Engelward, associate professor of biological engineering and toxicology
- John M. Essigmann, professor of toxicology and chemistry
- James G. Fox, professor of biological engineering and toxicology and director, Division of Comparative Medicine
- David J. Hunter, professor of epidemiology and nutrition, Harvard School of Public Health
- Leona D. Samson, professor of biological engineering and toxicology
- David B. Schauer, associate professor of biological engineering and toxicology
- James L. Sherley, associate professor of biological engineering and toxicology
- Steven R. Tannenbaum, Underwood-Prescott professor of toxicology and professor of chemistry
- Luk Van Parijs, associate professor of biology
- Graham C. Walker, professor of biology
- John S. Wishnok, senior research scientist in biological engineering
- Gerald N. Wogan, professor of toxicology and chemistry, emeritus
- Jacquelyn C. Yanch, professor of nuclear engineering

Bioengineering for Toxicology Research Core

This research core, created in 2002, builds on productive research collaborations fostered by a new academic structure at MIT. The Biological Engineering Division was formed in 1998 with the aim of strengthening the educational interface between engineering and molecular cell biology, and of melding molecular and systems toxicology (MST) research and educational programs with the nascent discipline of biological engineering. The evolution of the Biological Engineering Division has been strongly influenced by several productive research collaborations among the bioengineering and MST faculty; and, in turn, the research collaborations have grown since the formation of the division.

The Bioengineering for Toxicology Core was created to facilitate the development of new experimental tools and analysis methods relevant to the scientific foci of the two other research cores, with an initial emphasis on activities in the Mutation and Cancer Research Core. Its aim is to develop a range of approaches that span the molecular-cellular-systems length scales to solve problems in toxicology and environmental health. The experimental tools range from tissue-engineered physiological bioreactors that bridge the gap between cell culture, animal models, and humans; and multiphoton imaging methods that allow in situ quantification of events such as single cell apoptosis and DNA recombination by scanning large populations of cells in tissues and tissue models. Analytical methods include statistical (Bayesian) and deterministic models of signal transduction networks and computational models of protein interactions in the context of different cell compartments.

Core Members

- Linda G. Griffith, core director and professor of biological engineering
- Peter C. Dedon, associate director, Biological Engineering Division, and professor of biological engineering and toxicology
- Bevin P. Engelward, associate professor of biological engineering and toxicology
- Douglas A. Lauffenburger, director, Biological Engineering Division, and professor of biological engineering, chemical engineering, and biology
- Leona D. Samson, professor of biological engineering and toxicology
- Ram Sasisekharan, professor of biological engineering and toxicology
- James L. Sherley, MD, PhD, associate professor of biological engineering and toxicology
- Peter T. C. So, associate professor of mechanical engineering and biological engineering
- Peter K. Sorger, professor of biology and biological engineering
- Steven R. Tannenbaum, Underwood-Prescott professor of toxicology and professor of chemistry
- Bruce Tidor, associate professor of biological engineering and electrical engineering and computer science
- Forest White, assistant professor of biological engineering
- Michael B. Yaffe, associate professor of biology and biological engineering

Environmental Systems and Health Research Core

The mission of this new research core, created in 2002, is to understand the relationships linking environmental processes and human health. This requires improved understanding of the relationships between human health and environmental chemicals and their processes of transport and transformation. Increasingly, a broader view of environment-health linkages is required, one in which genomics and ecology play a growing role. The well-being of humans is inextricably interconnected with processes that may best be regarded as ecological, based on the recognition that environmental biota share with chemicals a linkage to human health.

Inasmuch as this emerging field cuts across traditional disciplines, the Environmental Systems and Health Research Core brings together researchers with expertise in microbiology, microbial ecology, analytical chemistry, hydrology, veterinary science, fluid mechanics, environmental chemistry, and instrumentation. Some members focus on understanding the diversity and movement of genes in the environment (environmental genomics, gene flow); others specialize in chemical transport and measurement; others focus on the physical processes, notably fluid movement, that are central to the transport of both biological and chemical entities. A unifying theme is that of ecology in the broad sense as researchers address processes that are rooted in the natural environment, yet have implications for human well-being.

Gene flow, for example, can affect the distribution of pathogenicity, the acquisition of antibiotic resistance, or the presence of biodegradative capability in microbial communities. Ecosystem processes govern the nature of coexisting populations at scales

from that of microbes to that of continents, with direct effects on humans at all scales. In 2003, core leadership changed from Professor Hemond to Professor Schauer.

Core Members

- David B. Schauer, core director and associate professor of biological engineering and toxicology
- Sallie W. Chisholm, professor of civil and environmental engineering and biology
- Peter C. Dedon, associate director, Biological Engineering Division, and professor of biological engineering and toxicology
- Edward DeLong, professor of civil and environmental engineering and biological engineering
- James G. Fox, professor of biological engineering and toxicology and director of the Division of Comparative Medicine
- Charles F. Harvey, associate professor of civil and environmental engineering
- Harold F. Hemond, professor of civil and environmental engineering
- Martin F. Polz, associate professor of civil and environmental engineering
- Graham C. Walker, professor of biology
- John S. Wishnok, senior research scientist in biological engineering

Core Facilities

Bioanalytical Facilities Core

The purpose of the Bioanalytical Facilities Core is to provide center members with state-of-the-art tools and techniques for the characterization and quantification of chemical substances and modifications of cellular molecules such as DNA and protein. The primary objective is to continually increase our abilities and effectiveness via the following aims:

- To assist center members in the purification, identification, and quantitation of unknown compounds, synthetic intermediates, and products of DNA and protein damage
- To maintain a broad range of cutting-edge major analytical instruments and assist in the acquisition of new instrumentation to meet the needs of center members
- To keep center members informed about developments in equipment and methods
- To provide expert assistance with method development, experimental design, and data analysis, with an emphasis on promoting collaborative research projects
- To teach students and postdoctoral scientists to become proficient in their own analyses

Major changes in the past year include (1) incorporation of the Accelerator Mass Spectrometry Core into the Bioanalytical Core, (2) moving a portion of the core to 500 Technology Square, and (3) the acquisition of several pieces of equipment. On the advice

of our External Advisory Committee, we incorporated the former Accelerator Mass Spectrometry Facilities Core into the Bioanalytical Facilities Core. This logical change will streamline the facilities cores structure in the center and enhance operations. In mid-July, the Bioanalytical Laboratory previously located in Building 16 was moved to the second floor of NE47 at 500 Technology Square. The increase in laboratory space by 400 square feet has allowed the center to acquire a new triple quadrupole mass spectrometer (ABI 3000) from Professor Steven Tannenbaum in the Biological Engineering Division. This expensive instrument is in high demand by center members and represents a major acquisition. Other equipment acquisitions are described below.

Core Leadership

- John S. Wishnok, core director
- Paul L. Skipper, core codirector
- Koli Taghizadeh, core codirector

Usage and Benefits

The Bioanalytical Facilities Core provides state-of-the-art equipment and expertise in the purification, characterization, and quantitation of chemicals and modified biomolecules. Center members benefit from the core in several ways. Perhaps the most important is access to technology and expertise not generally available to MIT researchers. Though facets of the Facilities Core are available to researchers not affiliated with the center, CEHS members benefit by receiving top priority for use of equipment and services and they receive a 50 percent discount on all core services. The goal of the core staff is to attend to member needs and promote collaborations, including acquisition of new instruments, development of new analytical methods, and education of students and postdocs. This is illustrated by examples of methods that are now available on a routine basis:

- LC-MS/MS quantitation of ABP-dG adducts in human DNA
- GC-MS quantitation of ABP-hemoglobin adducts
- Enrichment and quanitification of nitrotyrosine-containing peptides
- LC-MS analysis of 8-oxo-dG oxidation and nitration products
- MS-MS-MS analysis of PAH-adducted peptides
- Sequencing of DNA oligos by exonuclease digestion and MALDI MS
- Peptide mass fingerprinting by MALDI-TOF MS
- Peptide sequencing by ion-trap or tandem quadrupole MS
- Quantitation of nitrate/nitrite in biological fluids
- Characterization and quantitation of mutagens in foods
- Quantitation of modified DNA bases

High demand for core services led to several major improvements in the past year. A ThermoFinnigan TSQ 7000 tandem quadrupole MS was replaced by an Applied Biosystems/Sciex API 3000 of greater sensitivity, and we acquired a MALDI-TOF instrument shared with the MIT Chemistry Department. The API 3000 was purchased with electrospray and atmospheric-pressure chemical ionization sources; we added a

custom nanoelectrospray source. The core has acquired a single-quadrupole LC/MS system and an ion-trap MS with a variety of ion sources, including nanoelectrospray, photoionization, and atmospheric-pressure MALDI. The quantitation capabilities of the API 3000 were enhanced by the addition of an automated online-desalting system. A new Agilent 5973 GC-MS with an autosampler and a positive- and negative-ion chemical ionization source was purchased, and we have completed construction of two laser-induced fluorescence systems.

Examples of specific use and benefits include:

—Accelerator mass spectrometry (AMS) is fundamentally a mass spectrometry technique for the detection of low-abundance isotopes, with a sensitivity some 1000-times greater than scintillation counting and attomole quantitation of ^{14}C. Several groups make use of the center's AMS: Professor John Essigmann's project on chemotherapeutic drug development uses AMS to assess drug targeting in cell culture and in murine tumor models; Professor Peter Dedon's studies of DNA strand breaks use AMS sensitivity to measure the formation of carbonyl termini by derivatization with ^{14}C-reagents; a pharmacokinetic study of acetaminophen in the rat was completed recently in the Tannenbaum lab.

—Professor Bevin Engelward's lab has shown that enzymes involved in base excision repair can modulate the susceptibility of microbial cells toward recombination events induced by alkylating agents and by NO delivered by a membrane-based system developed in the core. These experiments showed that recombinational repair can prevent NO-related cytoxicity and the NO can induce recombination, which suggests a mechanism linking inflammation with cancer.

—The Essigmann group is studying the relationships between the structures of specific DNA lesions and the biological endpoints of mutation and cell death. MALDI-TOF mass spectrometry was used to confirm the structures of synthetic oligos that contain specific DNA lesions formed by chemical carcinogens, oxidants, or radiation. The group is also involved in the design of anticancer drugs, and has used LC-MS to characterize the interactions of a potential anti-breast-tumor agent with DNA.

—The Sherley lab has recently proved the immortal strand hypothesis, in which the parent DNA strand is conservatively segregated to the stem cell during asymmetric cell division. GC-MS and LC-MS was used to search for evidence that nucleoside modifications were involved in the selection process.

—Using LC-MS, Prof. Tannenbaum's group showed that nitration of human serum albumin by peroxynitrite occurred with high regio-selectivity. Using both ion-trap and tandem quadrupole electrospray MS, they carried out an extensive investigation of the reaction of dG with peroxynitrite and showed that analogous reactions occurred in DNA. They demonstrated that the DNA lesions can be located and tentatively identified with controlled endonuclease digestion followed by MALDI-TOF analysis. They recently designed and synthesized nitrotyrosine-specific affinity probes that show

promise for purifying low levels of nitrotyrosine-containing proteins from complex mixtures of peptides from digests, prior to analysis by MS.

—In addition to the NO-related genetic damage, the Wogan group has characterized the DNA reaction products of aflatoxin B1 and developed LC-MS/MS and LC-LIF procedures of adequate sensitivity to measure DNA adduct levels in human tissues and serum albumin. They have recently developed a novel LC-LIF method for detection of DNA adducts of all classes of carcinogens, and—in collaboration with the Tannenbaum group—have developed an LC-MS/MS method for quantitation of the aminobiphenyl-dG adduct in bladder tissue.

—Professor Ram Sasisekharan's research is focused on the structure and function of heparin-like glycosaminoglycans. His group has regularly used MALDI-TOF mass spectrometry to characterize these molecules by carbohydrate-protein complexes.

—Prof. Dedon's group has made extensive use of the facilities core in the analysis of DNA damage products by LC-MS and GC-MS and in the development of a sensitive assay for strand breaks and abasic sites. They developed sensitive LC/MS methods to quantify the nucleobase deamination products arising from exposure of DNA to NO: dX, dO, dU, and dI. Controlled delivery of NO under biologically relevant conditions revealed the absence of dO and the formation of a significant number of abasic sites presumably derived from NO-mediated depurination. Other studies revealed that dX is a stable lesion in DNA with a half-life of > 2 yr at 37 °C.

—The Hemond group has studied respirable airborne particles, which penetrate deep into the lungs, contain toxins and carcinogens, and have been linked epidemiologically to various lung and heart diseases, including lung cancer, asthma, and cardiopulmonary distress. The risk of lung cancer is higher in urban areas than in rural areas, although the cause of this difference is not clear. Air samples from Massachusetts and upstate New York were tested for mutagenicity in the h1A1v2 human cell line. The results indicate that cold weather is significantly correlated with the human cell mutagenicity of respirable particles in the northeastern United States and furthermore show that populations of urban centers in this region are exposed to higher levels of airborne human cell mutagens than in nearby rural areas.

—Another benefit to CEHS members is the availability of Ms. Patricia Brown, a technical specialist available *ad hoc* for software and hardware consulting. To facilitate data-exchange and communication, a web-based network is being developed by Ms. Brown for our current facilities and should include secure-but-accessible data storage and real-time video conferencing.

Genomics and Bioinformatics Facilities Core

The Genomics and Bioinformatics Facilities Core was created to provide center members with integrated facilities for microarray fabrication, microarray analysis, database storage, large-scale database management, data mining, and data modeling. The core is comprised of the CEHS Bioinformatics Computing Facility tightly integrated with the

MIT BioMicro Center. The latter is a joint endeavor of the Center for Environmental Health Sciences, the Department of Biology, the Center for Cancer Research, and the Biological Engineering Division and was founded in 2000 as the central bio-fabrication and bio-information technology resource at MIT. The specific aims of the Genomics and Bioinformatics Facilities Core are:

- To provide integrated support for both commercial and custom microarrays. Though the current focus of most center members is on mRNA analysis, the capabilities of the core can be extended to the fabrication and analysis of other types of arrays, including protein arrays.
- To provide strong three-tier architecture for data storage, management, and processing.
- To provide networks of managed desktop computers for data analysis and mining.
- To provide training and educational programs in commercial and open-source bioinformatics software.
- To provide center members with technical assistance with programming, database administration, and data analysis.
- To work with center members in applying their results to the development of data models and quality control procedures and error modeling, as well as the development of new technologies.

Core Leadership

- Peter K. Sorger, core director
- Rebecca C. Fry, core codirector

Facilities and Equipment

The core provides two areas of focus: bio-fabrication and bio-IT. The largest effort in the bio-fabrication group involves oligo and cDNA based microarrays, while the primary focus of the bio-IT group is the desktop, server, and network infrastructure required for database-driven bioinformatics applications. The core is the central provider of experimental and computational facilities for DNA microarraying and for other high-throughput analytic methods in the center. A focus on new technology also helps to ensure that the core remains at the cutting edge of DNA microarray methods. Standardization, quality control, and data integrity are major issues in the analysis of DNA microarray data and are areas of active research in the core.

Major facilities and services available include:

- Biofabrication/liquid handling equipment for precision automation and experimentation
- Biofabrication: cDNA amplification systems
- Robotic printing for microarray production
- Spotted microarray and Affymetrix GeneChip hybridization equipment
- Spotted microarray and Affymetrix Genechip scanning equipment

- Prefabricated arrays and custom arrays
- Microarray experimentation training and support
- Core computing clusters and core workstations

Usage and Benefits

The Genomics and Bioinformatics Facilities Core provides state-of-the-art microarray and data mining technology for the study of cellular responses to environmental agents. The core was created to accommodate the growing needs of center investigators and it benefits center members in several ways. First, the core provides a 50 percent discount on all services for members of CEHS. Second, the core provides access to technology and expertise not generally available in the surrounding community. In its first year, the core has seen substantial use, with an increase in use projected in the next year. Ten center members are currently using the Genomics and Bioinformatics Facilities Core for studies ranging from creation of whole genome arrays for bacteria to expression profiling with mammalian cells. The following summaries illustrate the research projects utilizing the core:

—The Chisholm group has a long-standing interest in the ecology of ocean microorganisms. One of these, *Prochlorococcus,* is a prokaryotic oxygenic photoautotroph that is abundant in vast regions of the world's oceans and is responsible for a significant proportion of global carbon fixation by photosynthesis. To understand how *Prochlorococcus spp.* have become so successful in the oceanic environment, the Chisholm group is studying their response to changes in environmental parameters under controlled laboratory conditions. Three types of arrays have been used to this point. The first was is a 70-mer probe array spotted using core facilities. This array was used to optimize protocols for signal intensity and clarity. With this data, they have now switched to NimbleGen arrays in anticipation of forthcoming Affymetrix arrays. These studies will provide important information about the link between this ocean microorganism and human well-being.

—The Dedon group studies the role of deoxyribose damage in the cellular response to oxidizing agents. Deoxyribose oxidation plays a critical role in the genetic toxicology of oxidative stress, including involvement in complex DNA lesions, cross-linking with DNA repair proteins, and the formation of endogenous DNA adducts. The Dedon group is approaching this problem by applying the power of genomics (transcriptional profiling) and genetics (targeted knock-outs) to define the role of deoxyribose oxidation products in the responses of *S. cerevisiae* to oxidative insults. The key feature is the use of a series of deoxyribose-specific DNA-damaging agents (enediyne antibiotics), each of which differs in the proportion of single- and double-strand breaks produced and in the chemical products attached to the resulting strand breaks.

—The Samson group makes extensive use of the Genomics and Bioinformatics Facilities Core in studies of gene expression and phenotypic analysis with *E. coli*, yeast, and mice. One of these projects is entitled Transcriptional Responses of Mice to Alkylating Agents, and has a major goal of painting an integrated picture of how mammalian cells, in culture and in the intact organism, respond upon exposure to alkylating agents. The

specific agents are chosen to represent environmental toxicants as well as those commonly used for chemotherapy. Specifically, they are analyzing the global transcriptional responses of specific tissues in wild type, Mgmt and Aag null mice upon exposure to SN1 and SN2 alkylating agents, respectively. They will also analyze the global transcriptional responses of isogenic sets of mouse embryonic fibroblasts upon exposure to alkylating agents.

—The Griffith group has developed a microfabricated, perfused bioreactor that fosters development of 3D architecture of liver when seeded with primary cells isolated from liver. When both parenchymal and non-parenchymal cells are present, fenestrated endothelium with an accompanying high degree of liver function is observed. Griffith is a coinvestigator with Samson, Essigmann, and Sorger on the NIEHS project Global Responses to Aflatoxin B1 and Alkylating Agents, and as part of this grant is comparing the responses of the liver bioreactor to those of native liver under treatment by toxicants. Transcriptional profiling is used to compare the responses of cells maintained by standard cell culture methods, perfused bioreactor, to those in vivo.

—The Schauer group is currently using cDNA microarrays to characterize the expression profile of hepatocytes following infection with the cancer-causing bacterium *Helicobacter hepaticus.* Male A/J mice, which are susceptible to *Helicobacter hepatitis* and hepatocellular carcinoma, are experimentally infected with *H. hepaticus,* and are euthanized six to 12 months later. RNA is isolated from primary hepatocytes, after perfusion and isolation, and from whole liver tissue. Control RNA is isolated from hepatocytes and liver tissue collected from age-matched, uninfected male A/J mice. The goal of these studies is to ascertain the mechanism by which *H. hepaticus* infection causes persistent hepatitis and hepatocellular carcinoma.

—The core has allowed the Sherley lab to accelerate their efforts to identify genes that are specifically up-regulated during asymmetric cell kinetics. Asymmetric cell kinetics are a characteristic of adult stem cells. Therefore, their hypothesis is that some genes that are specifically up-regulated during asymmetric cell kinetics may also identify adult stem cells. Currently, genes that uniquely identify adult stem cells have not been discovered. The identification of such genes is highly desired in efforts to identify, isolate, and manipulate adult stem cells for new therapies.

—Sorger and Samson have undertaken a major study entitled Standardization Experiments of the Toxicogenomics Research Consortium, the goals of which are to determine sources of variation in gene expression profiling and microarray data analysis, to develop standards by which to minimize variation in gene profiling experiments, and to develop methods to harmonize data across different microarraying platforms.

—Research on gene expression analysis in the Essigmann lab divides into three areas. In the first, the gene expression response of human cells exposed to aflatoxin B1 is being defined. In parallel, DNA containing enriched DNA adduct pools (e.g., the aflatoxin-FAPY adduct) is introduced into cells by transfection to determine the elements of the transcriptional response that may be specific to individual adducts. The hypothesis

tested is that there will be certain gene expression patterns that reflect the level and type of challenge to the cell from this toxin. The second project is focused on a striking biological observation that, while adult mice are refractory to aflatoxin toxicity and carcinogenicity, infant mice have a window of sensitivity to aflatoxin in the first few weeks of life. The constellation of genes that are expressed or not during this critical time period is being examined. The third project concerns the response of cells to cisplatin, which forms DNA lesions that hijack transcription factors. Gene expression changes in *E. coli* that may result from cellular treatment with the toxin are being probed. In all experiments, Affymetrix arrays are used with the fluidics workstation and the data analyzed using the Spotfire software.

Animal Models and Pathology Facilities Core

The overall objective of the Animal Models and Pathology Facilities Core is to provide center members with state-of-the-art pathology support, transgenic resources, and a centrally managed, AAALAC-approved animal holding and surgical facility. The core is staffed with experienced personnel and is equipped with essential equipment:

- To generate transgenic animals by pronuclear microinjection of DNA constructs or embryonic stem cell manipulation and provide colony management of GEM for use by center members
- To rederive transgenic and other specialized mouse strains by embryo transfer to assure specific pathogen-free status of all mice used in this program
- To freeze and store embryos from GEM utilized by center members
- To provide histology, pathology, molecular characterization, and imaging expertise for extensive phenotyping and assessment of pathological damage of GEM and other animal models as needed

Core Leadership

- James G. Fox, core director and professor of biological engineering

Facilities and Equipment

Histopathology Service

The Histopathology Service is part of the Division of Comparative Medicine's research and service laboratories. Staff members assist in the preparation of tissue specimens for diagnosis and analysis of disease processes under the guidance of a board-certified veterinary pathologist. Histopathology staff include Dr. Arlin B. Rogers, Dr. Prashant Nambiar, Kathy Cormier, Jeff Bajko, and Erinn Stefanovich.

Colony Management Service

Approximately 125,000 GSF of centrally managed, AAALAC-approved facilities with the necessary equipment, space, and containment suite to conduct transgenic and germ-free work are available to center investigators. Colony management staff include Dr.

Susan E. Erdman, Jennifer Statile, Liz Horrigan, Erica Jarmon, Caroline Dudley, and Nate Rogers.

Transgenic Service

The Division of Comparative Medicine (DCM) operates a centralized transgenic facility for generation of novel genetically engineered rodents. The 1,652 square foot facility comprises four rooms in the division's barrier facility located in the sub-basement of Building 68. DCM staff advise investigators on health status or strain backcrossing that may contribute to the utility of the particular rodent model system. Transgenic Service staff include Dr. Alison Hayward, Dr. Susan Erdman, Peimin Qi, Alan Discua, and Tony Chavarria.

CEHS Imaging Facility

The CEHS Imaging Facility is led by Dr. Elena Gostjeva, an expert in the use of state-of-the-art microscopes and advanced digital imaging methods. Use of the instruments listed below is overseen by Dr. Gostjeva, and she trains lab members of the CEHS faculty in the methods required for preparation and analysis of biological materials for immunohistochemistry, molecular cytogenetics, cytotoxicity, and other related scanning microscopy and imaging methods.

- Nikon Eclipse E800 fluorescence microscope
- Nikon Labophot fluorescence phase-contrast microscope
- Zeiss fluorescence phase-contrast microscope
- CompuCyte LSC laser scanning cytometer
- Zeiss phase-contrast microscope
- Zeiss Axioskop 2 MOT fluorescence phase-contrast microscope

Usage and Benefits

Animals continue to be important models for the study of molecular mechanisms of complex biological processes. The Animal Models and Pathology Facilities Core provides and maintains genetically engineered mice that are increasingly being generated to model specific aspects of human diseases and have proven to be extremely valuable in examining how genetic alterations interact with environmental chemicals and microorganisms to induce disease. The core provides personnel with this expertise as well as centralized laboratory equipment as part of the center's program. Center members benefit from use of the core by receiving substantial discounts on services and technologies (including use that is free of charge up to $2,300–$5,000 per user depending on the service) that are generally available at higher cost to the MIT community.

Here are some examples of member use and benefits:

—The Engelward laboratory has developed one of the first models in which cells that have undergone spontaneous homologous recombination can be detected within the

tissues of a mouse. This mouse model has provided insights into the relative susceptibility of different cell types to mitotic recombination in mammals. In addition, studies are currently underway to develop technology for detecting recombinant cells within tissues in situ. Engelward's group also used the laser scanning cytometer to monitor recombination events in the mouse model.

—Three transgenic mouse strains for the Sherley lab were developed with the *L. donovani* xanthine phosphoribosyl transferase gene (XPRT). There is no mammalian enzyme with XPRT activity and xanthosine (Xn) exists in very low levels in mammalian tissues. In cell culture models, Sherley's group has shown that guanine nucleotide pools are elevated in mammalian cells that express a XPRT transgene when Xn is added to the culture medium. They propose to control the level of guanine nucleotide pools in the tissues of XPRT-transgenic mice in a controlled fashion by controlling Xn in the diet or by intravenous injection. Sherley's group also made use of the imaging facilties run by Dr. Gostjeva to detect asymmetrical kinetics in p53 mutant mouse cell lines.

K19-TGF b dominant-negative receptor II GEM were generated for the Fox lab. TGF b and its signaling effectors act as key determinants of carcinomatous cell behaviors, such as morphogenesis, growth arrest, and apoptosis. To assess the role of TGF b in more detail, a dominant-negative form of the TGF b II receptor (TGF b DNRII) was fused with the mouse cytokeratin 19 (K19) promoter in a DNA construct used to generate the K19-TGF b DNRII transgenic mouse. We plan to assess the histopathological changes in the gastric mucosa of the K19 TGF b DNRII genetically engineered mouse before and after infection with Helicobacter pylori to learn the role of the TGF b signaling pathway in the pathogenesis and carcinogenesis related to *H. pylori* infection.

—The Dedon group employed the core's fluorescence microscopy facilities in a collaboration with Dr. Gostjeva to develop a yeast comet assay technique to quantify strand breaks and base damage arising in yeast cells treated with a variety of oxidizing agents.

—In addition to the use of mouse models for tissue engineering, the Griffith group makes use of the laser scanning cytometer for monitoring liver cell function in a novel bioreactor.

—The generation and maintenance of a wide variety of transgenic and knock-out mouse strains, altered in various aspects of DNA alkylation repair, or in their responses to DNA damage, are a crucial part of the Samson lab's activities. The imaging facilities are also crucial to the Samson lab, to perform scanning and counting of sister chromatid exchanges in human cells and to visualize and label apoptotic human and mouse cells, and in various mouse tissues.

—Much of the research in the Schauer lab relies heavily on the services of this core. As an example, the immunohistochemistry services played a significant part in the characterization of experimental inflammatory bowel disease in lymphocyte (Rag2)-deficient mice with or without adoptive transfer of regulatory T cells.

—The Yanch group made use of the imaging facilities to visualize a track of damaged cells produced by a high-LET alpha particle beam that delivers single alpha particles to subcellular locations in cells and thin tissue explants.

Community Outreach and Education Program

The primary goal of CEHS's Community Outreach and Education Program (COEP) is to promote community-level scientific literacy through a variety of programs targeted to students and their teachers from grade four through the undergraduate curriculum. The programs represent extensions of the research activities of the center, including those of the Environmental Systems and Health Research Core and the Mutation and Cancer Research Core. Future programs will also include the work of the Bioengineering and Toxicology Core. Under the direction of Professor Samson and Katy Wack , COEP is committed to:

- Developing supplemental materials and activities that augment existing K–12 science curricula and that reflect recent advances in environmental health sciences
- Providing support and learning enrichment for Boston-area K–12 teachers
- Mentoring and training young scientists and graduate students in the mechanisms and importance of outreach
- Engaging CEHS members in these and other COEP activities

The involvement of center members in COEP activities has been promoted along several lines. First, COEP has initiated the NIEHS Summer Teaching Fellows Program that each summer pairs local K–12 teachers with CEHS members to collaborate in ongoing research and the development of novel teaching activities. Second, COEP offers funding to encourage CEHS members to participate in the development of outreach activities. Members participating in recent outreach activities include Drs. Gostjeva, Hemond, Schauer, Polz, Harvey, and Yanch. Finally, COEP has initiated an annual MIT Museum and Outreach Day that involves exhibits developed by center members and family-oriented activities at the MIT Museum.

COEP is reviewed annually by the Internal Advisory Committee to assess performance in meeting the objectives of the center. Review criteria may include:

- Evidence of tangible outcomes, e.g., implementation of new K–12 curricula and development of teaching tools such as kits and videotapes
- Feedback from teachers participating in COEP activities
- The numbers of students, teachers, and CEHS members participating in COEP activities

COEP Leadership

- Leona D. Samson, program director
- Katy Wack, program codirector

- Amy S. Fitzgerald, program coordinator
- Kathleen Vandiver, program coordinator

COEP Programs

Groundwater Pollution Curriculum Package

COEP created a new teacher- ready, student-friendly curriculum package on groundwater pollution and the Superfund program. The curriculum package includes a 45-minute video that walks students through the investigation of a contaminated site and the process by which a site is added to the National Priorities List. A 66-page curriculum guide outlines supporting activities such as hands-on experiments, web-based learning exercises, and suggestions for library and community research. The package is available through the NIEHS COEP Resource Center, the Teacher as Scholars Program, and MIT's Edgerton Center. Portions of the video have already been adopted by the Advanced Technology Environmental Education Center (ATEEC) for use in a new curriculum for junior college students.

Grungy Groundwater

Grungy Groundwater is a hands-on activity that challenges students to discover how water and pollutants move underground, and how pollutants impact surface and drinking water supplies. During the four-hour activity, students first explore how fluids travel through different soil types. Then, students build their own models of the underground using the different soil types they have just investigated. The students use these models to discover how buried and surface contamination enter and travel through the subsurface. Over 500 students took part this year. With cooperation from the Cambridge Public Schools science coordinator, Dr. Melanie Barron, this activity will be integrated into the pollution and ecosystem health unit of every fifth grade class in the CPS system.

The Road to the Double Helix

This activity uses a unique LEGO kit developed by Dr. Kathy Vandiver to visualize the structure of DNA. At the start of the activity, students are given a box of LEGO pieces that represent the four nucleotides. Distinctly colored magnets differentiate between adenine, guanine, cytosine, and thymine. The polarity of the magnets are arranged such that adenine can only join with thymine and guanine can only join with cytosine. The students use the pieces to create models of DNA and to discover how DNA replicates itself. In the second part of the activity students extract DNA from a variety of fruits to better understand how real DNA behaves and how it is different from the LEGO models.

CEHS Summer Teaching Fellows at MIT

To foster even stronger links between CEHS and the local teaching community, one or possibly more teachers from the Boston area are to be selected each year from a pool of

applicants to be NIEHS Summer Teaching Fellows at MIT. The fellows will be given an office in the center and a ten-week stipend. Prior to arriving at MIT, the fellows will work with the COEP directors to identify areas of interest shared with center researchers. Each fellow will then be linked with one, or possibly two, researchers who will serve as their official hosts.

During the orientation week, the fellows will meet with members of each research core and be given tours of each lab. Also, during the first week the fellows will work with Amy Fitzgerald, the COEP directors, and the host researchers to define specific goals for the summer. These might include (1) participation in current research, (2) creation of a hands-on activity for the Edgerton Center, (3) creation of new classroom activities for Boston-area schools, or (4) development of a teacher-training course for the fellow's home district.

Pilot Project Program

The goals of CEHS's Pilot Project Program are:

- To provide initial support for new investigators to establish new lines of research in environmental health
- To allow exploration of possible innovative new directions representing a significant departure from ongoing funded research for established investigators in environmental health sciences
- To stimulate investigators from other areas of endeavor to apply their expertise to environmental health research

These goals are achieved by providing $20,000 to $30,000 of funding for four or five novel and innovative research projects related to toxicology and environmental health issues. The center received 14 proposals for review in 2003, of which four were funded. Each application was reviewed by at least two members of the Internal Advisory Committee and scored using the NIH scale in four areas:

- intrinsic quality of proposed research
- relevance to the stated CEHS mission
- likelihood that the project will lead to formal RO1 or equivalent funding
- likelihood of the project leading to collaborative interactions with Center members

Pilot Projects for 2003

- Mechanisms of Chemotherapy-induced Genetic Instability, Professor Bevin Engelward, Biological Engineering
- The Role of Exogenous Pathogens and Intestinal Microbiota in Colorectal Cancer, Professor Martin Polz, Civil and Environmental Engineering
- Microfluidic Platform for High-density Multiplexed Genetic Analysis, Professor Todd Thorson, Mechanical Engineering

- Phosphoproteomics of DNA Damage Repair, Professors Forest White, Biological Engineering, and Michael Yaffee, Biology

Positive Outcome of Previously Awarded Pilot Projects

The $195,000 awarded to Pilot Projects in 2002 has been leveraged into NIH grant awards totaling $3,091,300 so far, and CEHS has good reason to expect further leverage from its $195,000 investment.

Details of these projects, as well as of the successes enjoyed by the Pilot Projects funded in 2001, are available at http://cehs.mit.edu/pilotprojects.html.

Plans for 2005

- We await the conclusion of our recent competitive-renewal revised application to the National Institute of Environmental Health Sciences for continuation of the center grant.
- We are planning a retreat for center members in January 2005 at the Endicott House. This will be the first of what we intend to be an annual CEHS retreat to discuss the science and engineering projects and programs driving center research, as well as to promote interactions among center members.
- We will be continuing our successful Friday Forum series in which CEHS core directors and center members make research presentations at a monthly event intended to promote interaction among center members in an informal social setting.
- CEHS Annual Poster Session: this event was launched in 2004 with over 100 people in attendance.
- CEHS Sponsored Seminars: the center will sponsor or cosponsor five to ten seminar speakers on topics related to center research activities.
- DNA Repair and Mutagenesis (DRAM) Meeting: a continuation of the "Boston Mutagenesis Group" seminar series, Boston DRAM will continue to be hosted by CEHS each month to share results and ideas pertinent to a molecular-level understanding of DNA damage/repair, mutagenesis, and carcinogenesis.
- We will be site visited by our highly distinguished External Advisory Committee in the spring of 2005, an opportunity to gain further input and advice on the growth and development of MIT's Center for Environmental Health Sciences.

Leona D. Samson, Director and Professor of Biological Engineering and Toxicology
Peter C. Dedon, Deputy Director and Professor of Biological Engineering and Toxicology

More information about the Center for Environmental Health Sciences can be found online at http://cehs.mit.edu/.

Clinical Research Center

The Clinical Research Center (CRC) was established in 1964, with grant support from the National Institutes of Health (NIH), to provide a facility where MIT investigators and their collaborators could apply the Institute's expertise in basic biochemical and biophysical mechanisms to the analysis of normal and pathologic processes in humans.

MIT's CRC was the first federally supported clinical research center located in a university and not within a hospital, and remains one of only two or three such centers. It was anticipated that in spite of its university venue, numerous qualified physicians and clinical scientists from MIT's faculty and staff would utilize the CRC to study normal volunteers, or patients with chronic diseases.

Scientists and physicians authorized to carry out research protocols using the CRC's facilities include professors, research scientists who work exclusively at MIT, and investigators with primary appointments in local medical institutions whose research interests overlap extensively with those of MIT investigators. Research protocols must be approved by the MIT Committee on the Use of Humans as Experimental Subjects (COUHES) and the CRC Advisory Committee before they can be implemented.

The CRC Advisory Committee, chaired by Dr. Daniel Shannon, professor of pediatrics at the Harvard Medical School and professor of health sciences at the Harvard-MIT Division of Health Sciences and Technology, consists of ten voting members plus nine nonvoting members from the CRC's program and operating staffs. The committee has reported to the principal investigator of the CRC's NIH Grant, Martha Gray, professor and codirector of the Harvard-MIT Division of Health Sciences and Technology (HST). With the CRC's administrative merger with the Massachusetts General Hospital's CRC, it now reports (for NIH grant purposes) to Peter L. Slavin, MD, principal investigator of the joint NIH grant and president of MGH. The Advisory Committee meets bimonthly to evaluate protocols for their scientific quality, experimental design, ultimate statistical validity, and potential risk to human subjects. The committee also sets general policies and reviews the operations of the CRC.

Administration

The CRC has a dual administrative locus within MIT. As a research unit, the CRC reports through the Harvard-MIT Division of HST to the vice president and dean for research, Professor Alice Gast. However as a patient-care unit, the CRC is a part of the MIT Medical Department and reports to Dr. William M. Kettyle, director of the Medical Department. Members of the CRC participate in the Medical Department's activities—for example, its Quality Improvement, Pharmacy and Therapeutics, Medical Records, and Safety committees.

Several years ago the CRC was approached by the General Clinical Research Centers administration of the NIH, which funds this and all other CRCs, and asked to consider becoming a "network" CRC. This would involve implementing at the MIT CRC some research projects generated at other local CRCs, and, conversely, implementing some of

our projects (e.g., those involving very sick patients) at those other centers. Additionally, the CRC would, where possible, coordinate the activities of the core laboratories, nutrition programs, and nursing programs with those of other local institutions, in order to increase their efficiency, and would use this networking as a platform from which to solicit additional common NIH grants. As a consequence, the CRC has successfully been developing a structured relationship with the CRC at the Massachusetts General Hospital, and in 2001 the MGH CRC and MIT CRC administratively merged.

To date, 37 MGH protocols have been approved and implemented at the MIT CRC. The senior program staffs at the two institutions meet monthly to anticipate and solve potential problems related to their integration and to streamline the protocol review process; COUHES and its MGH counterpart also work together to evaluate network protocols from the standpoint of safety. The MIT and MGH centers successfully collaborated on a joint NIH renewal grant application, for five years of support, which was funded by the NIH, starting in December 2002. The score, reflecting the reviewers' analysis of the joint application, was the best that MIT has received for its applications. MIT is now identified by the NIH as a "satellite" to the MGH CRC, but is suffering no loss of "sovereignty" or autonomy, or any decrease in funding.

Developing this type of "network" relationship with the MGH CRC allows the CRC to solve a continuing chronic problem—the small and shrinking pool of medical doctors conducting clinical research in this facility, a consequence of the failure, during the last decade, of MIT's academic departments to appoint such people as professors. Most important, it guarantees the longevity of the CRC until such time as the pool again expands, and provides a source of physician scientists to collaborate with MIT biomedical scientists who hold doctoral degrees. The reputations of the two CRCs apparently are excellent, and the strengths of each institution complement those of the other. The CRC also continues to "network" with other Boston-area GCRCs (e.g., Beth Israel Deaconess Medical Center) and all interested parties agree that the CRC should continue to do so in the future.

Education

The MIT CRC provides formal training in clinical investigation to advanced postdoctoral fellows taking a graduate degree (in clinical research) at Harvard Medical School, and to individual postdoctoral (medical) fellows working with CRC principal investigators and other researchers. These fellows and students utilize the CRC's facilities to initiate research protocols and participate in ongoing projects supervised by senior investigators and faculty (see the section below on the Center for Experimental Pharmacology and Therapeutics).

The MIT CRC also affords opportunities to MIT undergraduate and graduate students to participate in clinical research projects**.** In the spring semester of 2004**,** Ravi Thadhani, MD, assistant professor of medicine at Harvard Medical School and an assistant program director at MIT CRC, again taught a formal undergraduate course in clinical investigation. This course was very well received and will be offered again in the spring semester of 2005.

Affirmative Action

The hiring of women and minorities continues to be a high-priority commitment of the CRC. The CRC does have one continuing problem in meeting affirmative action objectives—namely, in attracting qualified minority members. The traditional means of locating such personnel, by advertising and posting positions in local colleges, universities, medical institutions, and minority organizations, have not generated a significant response. The two **v**isiting scientists appointed by the CRC in 2003–2004 were both women and minorities. The CRC will continue its efforts to increase the pool of qualified minority applicants, as positions become available.

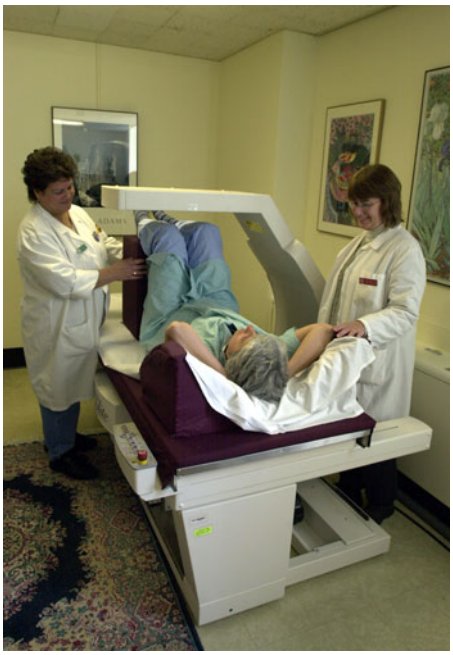
The CRC has, however, been highly successful in recruiting women and minorities as study subjects. During 2003–2004, approximately 65% of all study subjects were women and 25% of the total study population were minorities (Black 20%, Asian 4%, and 1% American Indian).

Research Activities

During 2003–2004, the CRC continued to maintain major commitments to the research activities associated with three clinical areas, each led by a senior professor:

- *Nutrition/ Metabolism.* In March 2004, the CRC and the MIT community were deeply saddened by the death of Dr. Vernon Young, a long-time contributor to the CRC, the MIT community, and the field of nutrition. A memorial lecture is planned for November 2004. Although his own research program thereupon terminated, two components of that program have now become core CRC facilities, and will be used by numerous other investigators. These are a laboratory for assaying compounds in human body fluids by GCMS and a team (led by Dr. Colleen Hadigan) that conducts infusions.
- *Neurochemistry/Neuropsychopharmacology* (Richard J. Wurtman, MD, Cecil H. Green distinguished professor and program director, MIT CRC). This group studies the effects of drugs, foods, and hormones on brain composition and behavior, the effects of melatonin on sleep, and a set of diseases characterized by affective and appetitive symptoms (depression, premenstrual syndrome, smoking withdrawal, carbohydrate craving, obesity) that relate to brain serotonin.
- *Behavioral Neuroscience* (Emilio Bizzi, MD, Institute Professor, and Lee H. Schwamm, MD, associate professor of neurology at Harvard Medical School and an assistant program director at MIT CRC) and *Neuroendocrinology* (Steven K. Grinspoon, MD, associate professor of medicine at Harvard Medical School and an assistant program director at MIT CRC, and Anne Klibanski, MD, professor of medicine at Harvard Medical School and codirector of MGH CRC). The behavioral neuroscience component now focuses on strategies for accelerating the return of various brain functions in people who have suffered strokes; the neuroendocrinology component focuses on neuroendocrine concomitants of AIDS, pituitary malfunction, and gender-dependent changes in calcium metabolism.

Center for Experimental Pharmacology and Therapeutics



The HST Center for Experimental Pharmacology and Therapeutics (CEPT), based at the MIT CRC, continues to have educational and research missions. This center, directed by Dr. Robert Rubin (HST), Osbourne professor of health sciences and technology, annually admits 10 MDs who have completed their clinical training. They enter a two-year program that provides both "hands-on" research experience and didactic training in clinical investigation and experimental pharmacology. At the end of this period, after passing a qualifying examination and fulfilling a thesis requirement, the graduates receive a Master/Medical Science degree in clinical investigation from HST. A parallel program for PhD scientists is in the process of being established as well. This will involve HST, the Sloan School, the Department of Biology, and the School of Engineering, and will again be centered in the CRC. In research, the emphasis of the CEPT has been in the application of positron emission tomography, magnetic resonance imagery, ultrasound, and other measurement technologies to the development of new drugs. With the development of imaging at MIT, these technologies will be greatly facilitated.

Computer Facility

The CRC computer facility provides hardware and software support for the CRC staff and investigators and statistical assistance to all researchers. The computer staff continues to develop and upgrade the CRC Operations System with the addition of computer systems for the CRC and investigators. These systems use an ORACLE relational database and support the day-to-day operations of the CRC. During 2003–2004, the computer staff has been working with their MGH counterparts to maintain and customize the Turbo software package, which has streamlined the protocol application process and NIH annual reporting requirement for both CRCs. Researchers also continue to make use of the SAS statistical software available on the CRC computer system.

Core Laboratory/Mass Spectrometry Facility

The Core Laboratory specializes in assays that directly support the research efforts of CRC investigators and are not readily available commercially. The most important and complex assays are undertaken by the Mass Spectrometry Facility, where stable isotope tracer analyses are performed. The Mass Spectrometry Facility is a shared instrument facility that allows CRC investigators to conduct human metabolic studies using stable nuclide tracers. Principal areas of investigation concern the regulation of energy substrate metabolism in health and disease, and the regulation of whole body amino

acid metabolism, with particular reference to the nutritional requirements for indispensable and conditionally indispensable amino acids. Research at the MIT CRC has made important contributions to the further development of national and international dietary standards and the establishment of sound food and nutrition policies and programs.

The Core Laboratory also utilizes high-performance liquid chromatography (HPLC) techniques. A Beckman System Gold Amino Acid Analyzer HPLC provides resolution of up to 42 physiologic amino acids. Other HPLC assays include tests for choline, tryptophan, the catecholamines, cytidine, and melatonin.

MIT Core Laboratory personnel are in frequent contact with their counterparts at MGH. This facilitates coordination of services and study planning (anticipating freezer space and reviewing core laboratory components of submitted protocols). Also, in an effort to recruit more core laboratory users, the MIT Core Laboratory actively networks with other GCRC labs. The MIT Core Laboratory posts a list of available assays on the National GCRC Core Laboratory site and a Core Laboratory representative attends the GCRC National Annual Conference. This networking has generated a number of Core Lab Only protocols.

Research Highlights

Bandini, L.
Dr. Linda Bandini and her colleagues have concluded their longitudinal study of the effect of energy expenditure on growth and development in preadolescent girls; however, Dr. Bandini continues to prepare and publish articles concerning this study, which sometimes requires her continued presence at the CRC. During the past year, six articles have been submitted to journals on various aspects of this study.

Bizzi, L. and Schwamm, L.
The Bizzi group, including Drs. Emilio Bizzi, Lee Schwamm, Maureen Holden, and Karen Furie, has continued to develop and test new methods of treating upper extremity impairments. A novel computerized learning system, developed for these studies, is designed to facilitate motor retraining in patients with stroke. The system makes use of a virtual environment (VE) to provide augmented feedback to subjects about their performance. The system has been used to study motor learning and generalization in patients with stroke. Improvements were found in patients' upper extremity movements following the training on standard clinical tests of motor recovery, functional performance, and strength assessment. In addition, improvements were noted in the more quantitative kinematic measures developed to assess motor generalization. Many subjects not only improve on the movements they practice with the VE system, but also improve on other movements or aspects of movements, that have not been specifically practiced. These findings were presented at the 2003 International Stroke Conference. Also, an NIH grant was received that will provide funding for a tele-medicine enabled virtual environment. This system is designed to provide motor retraining of stroke patients in their homes. Patients are connected, via the internet, to a remotely located

therapist who then directs treatment sessions through software on the patient's home computer.

Grinspoon, S.
Over the course of the past year, substantial progress has been made by Dr. Steven Grinspoon and his group to investigate the mechanisms and consequences of insulin resistance in HIV lipodystrophy. Dr. Grinspoon's group has shown that loss of subcutaneous fat is a significant predictor of insulin resistance in this population. In a recent article published in the *Annals of Internal Medicine*, his group reported the first randomized, placebo-controlled study to demonstrate increased subcutaneous fat with the use of rosiglitazone, a PPAR gamma agonist. This study also showed improvements in insulin sensitivity and, importantly, increased adiponetin. This work highlights a potentially important, novel therapeutic strategy for this population.

Hadigan, C.
Dr. Colleen Hadigan, whose previous investigations evaluated the utility of insulin sensitizing agents for HIV lipodystrophy, is currently conducting a randomized, placebo-controlled trial investigating the benefits of extended lipolytic blockade to treat hyperlipidemia and insulin resistance in patients with HIV infection.

Thadhani, R.
Dr. Ravi Thadhani and his group have continued to examine hypertension and diabetes in pregnancy. Hypertension and diabetes represent the most common medical complications of pregnancy, affecting about 500,000 women each year. The cause for each of these conditions remains unclear. Importantly, most pregnancy-related studies have been cross-sectional in design, tremendously limiting any conclusion about potential causal mechanisms. In 1999, this group initiated a prospective cohort study of pregnant women, collecting blood and urine samples in the first and second trimester of pregnancy. As of May 1, 2004, this study based at MGH has enrolled more than 8,000 women (one of the largest studies of its kind in the world), has yielded more than 15 original manuscripts and over 25 abstracts, funded four investigators by agencies such as the NIH, American Heart Association, and American Diabetes Association, and has been the centerpiece of collaborations with Harvard Dental School, Channing Laboratories, Beth Israel Deaconess Medical Center, University of Pittsburgh, University of California at San Francisco, National Institutes of Child Health and Disease, and the National Cancer Institute. The primary goal of this research is to understand alterations that antedate clinical disease in pregnancy; hence the focus has been on alterations in the first trimester that identify those at risk for adverse outcomes later in pregnancy. The research focuses on metabolic alterations, inflammation, and alterations in angiogenesis evident in the first trimester, and has uncovered important interactions between these alterations. Finally, this group brings a subset of women back to the MIT CRC one year after pregnancy (n>130 to date) and have begun to uncover alterations in insulin resistance and angiogenesis that persist one year post-partum, which may explain why these women develop hypertension and diabetes in future years.

Wurtman, R.
Dr. Richard Wurtman and his colleagues have continued to examine the effects of drugs,

foods, and hormones on brain composition and behavior. Pharmacokinetic studies continue to be performed on compounds, preliminary to using these compounds, to study behavioral or physiological mechanisms. These are (1) melatonin, (2) 5-hydroxytryptophan (5HTP), and (3) uridine monophosphate (UMP).

Other studies are examining the ability of a carbohydrate-rich supplement, which changes plasma amino acid levels in a manner previously shown to increase brain serotonin, to enhance a standard weight loss regimen in obese subjects.

CRC Investigator-Initiated Programs

Three investigator-initiated programs continue to contribute to the MIT CRC. In addition to fulfilling their scientific goals, these programs also provide opportunities for increased collaboration between the MIT and MGH CRCs.

—The Program in Nutrition and Metabolism, directed by Steven Grinspoon, MD, is investigating the relationships among nutrition, body composition, and hormonal function. One of the program's chief therapeutic targets is HIV-lipodystrophy, which involves potentially unhealthy redistribution of body fat and changes in blood lipid levels that are often found in persons affected with the virus that causes AIDS.

—The Program in Women's Health, directed by Judith Wurtman, PhD, was established to study the psychological aspects of premenstrual syndrome and of menopause. This effort will hopefully identify promising leads for new treatments for the discomfort that may accompany these normal components of the human female life cycle.

—The Program in Applied Technology & Communications in Healthcare (PATCH), directed by Lee Schwamm, MD, seeks to develop new avenues for healthcare delivery through the strategic application of novel technologies. The program targets areas where barriers exist to the clinical implementation of evidence-based medicine, and seeks out technological solutions to overcome these barriers. Focus areas include low bandwidth transmission of medical multimedia content for education or decision-support, high bandwidth interactive medical evaluation or therapy, and wireless and handheld extensions of conventional bandwidth applications.

Richard J. Wurtman
Director
Cecil H. Green Distinguished Professor of Neuropharmacology and Health Sciences and Technology

More information about the MIT Clinical Research Center can be found on the World Wide Web at http://web.mit.edu/crc/www/.

Division of Comparative Medicine

The Division of Comparative Medicine (DCM) provides animal husbandry and clinical care for all research animals on the MIT campus. From its inception in 1974, DCM has evolved into a comprehensive laboratory animal program that provides a full range of veterinary and surgical support. Additionally, DCM has a National Institutes of Health (NIH) grant for training veterinarians for careers in biomedical research. DCM also has an active research program funded by numerous R01 grants from NIH.

Total personnel in the division now comprises 145 individuals. The administrative headquarters, together with diagnostic and research laboratories, are located on the eighth floor of Building 16. This space is contiguous to the eighth floor of Building 56, which houses quarantine, diagnostic, and research space for DCM. The division now encompasses approximately 115,000 square feet devoted to animal research activities. In addition, a new 57,600 gross square foot vivarium is being constructed as part of the neuroscience complex currently under construction.

Facility Management and Animal Care

The average daily census of laboratory animals increased 5 percent during FY04. Mice remain the primary species used by MIT investigators and represent more than 98 percent of the animal population. The animal facilities support transgenic and gene-knockout in vivo experiments. DCM now operates a transgenic core and performs a range of transgenic services, including in vivo embryo transfer for rederivation of mice with endemic disease which have been imported to MIT from laboratories worldwide, in vitro fertilization, and genotyping of mice. It also provides genetically engineered mice and veterinary support for the large zebra fish colonies maintained at MIT. The animal resource program was recertified by the Association for Assessment and Accreditation for Laboratory Animal Care (AAALAC) during the summer of 2002. The division collaborated with the Environment Health and Safety Office to produce an ergonomic training video for animal technicians involved in animal care.

Research Activities

Currently there are 12 NIH-funded grants that support in vivo study of nitrite carcinogenesis, in vivo study of *Helicobacter hepaticus* and tumorigenesis, in vivo study of the pathogenesis of inflammatory bowel disease, in vivo study of *H. pylori* pathogenesis, in vivo study of gastric cancer, studies of heat shock protein and *H. pylori* pathogenesis, study of microflora induced colitis, studies involving diet and *H. pylori* infection, and in vivo study of micro-ecology of the gut and the pathogenesis of colitis. Total research expenditures were $2.3 million in FY04.

FY04 was the sixteenth year of DCM's NIH postdoctoral training grant. There are currently eight postdoctoral trainees, one of whom is enrolled in the graduate program in the Biological Engineering Division. Thirty-one trainees have completed our postdoctoral training program and 23 of them have passed the board examination of the American College of Laboratory Animal Medicine. Many of our former trainees hold

leadership positions in academia as well as pharmaceutical and biotechnology companies. The training grant also provides short-term training opportunities for veterinary students interested in careers in comparative medicine. During FY04 the Division had 10 short-term trainees for periods ranging from four to 12 weeks.

DCM faculty and staff published three chapters, 17 papers and 30 abstracts in FY04 and presented numerous research papers at national and international meetings. Dr. Fox is the senior editor for the second edition of a four-volume series entitled "The Mouse in Biomedical Research."

Academic Activities

Dr. James Fox continues to serve on the NIH Scientific Advisory Council of the National Center for Research Resources. Dr. Fox also chaired a National Academy of Sciences Committee on "The Need for Veterinarians in Biomedical Research." A report on the subject was published by the academy in 2004. Dr Prashant Nambiar joined the Division as a comparative pathologist in October 2003. Both Dr. Nambiar and Dr. Arlin Rogers earned board certification from the American College of Veterinary Pathologists this past year. DCM faculty and staff taught two graduate courses in the Biological Engineering Division (BE 202 and 214).

Committee on Animal Care Activities

All students, staff, visiting scientists, and principal investigators who use animals in teaching or research must be certified by the Committee on Animal Care. To enable protocol submission and personnel training, the website for the Committee on Animal Care provides required forms, continuing education material, and information on the CAC's activities.

DCM staff in conjunction with the Committee on Animal Care has developed an online training program that is combined with individual orientation and training in animal use by the veterinary staff at the Institute. Periodically, individual and group didactic training sessions for Institute personnel on topics pertaining to the care and use of laboratory animals are also offered. The CAC has also developed an occupational health screen for animal-related occupational health issues and periodically sponsors seminars on health issues such as zoonotic diseases. The CAC continued to distribute to other institutions in the United States and abroad two instructional videos, one focusing on the role and responsibilities of Institutional Committees for the Care and Use of Animals and the other focusing on the use of anesthesia in laboratory animals. Both are available to MIT researchers at the division or in the Hayden Science Library.

James G. Fox
Director
Professor of Toxicology

Harvard-MIT Division of Health Sciences and Technology

Founded 30 years ago, the Harvard-MIT Division of Health Sciences and Technology (HST) is the longest-standing collaboration between Harvard University and the Massachusetts Institute of Technology. From its inception, HST pioneered a new way of thinking about the processes that govern life and disease, breaking down barriers that impede interdisciplinary education and collaborative research and creating an environment that brings innovation from the laboratory bench to the bedside, and clinical insight from the bedside to the bench. HST has one of the nation's oldest and largest biomedical engineering (PhD) and physician-scientist (MD and MD/PhD) programs, and in effect, serves as MIT's "medical school."

HST's administrative home is located at the Whitaker College of Health Sciences and Technology at MIT. As one of the five medical societies at Harvard Medical School, HST also maintains an office at the medical school's quadrangle campus in Boston. HST's directors, Martha L. Gray, PhD (HST '86), for MIT and Joseph Bonventre, MD, PhD (HST '76), for HMS, report to the provost and the vice president for research at MIT, as well as to the HMS executive dean for academic programs and the dean of Harvard Medical School. Richard N. Mitchell, MD, PhD, and Lee Gehrke, PhD, serve as the Division's associate directors.

Highlights of Events

2004 HST graduates Stephanie Misono, MD, Dan Mazzucco, PhD, Emaneula Binello, PhD, and Ugwuii Maduekwe, MD. Photo by Ralph Lindenfeld

George Q. Daley. Photo by Ralph Lindenfeld

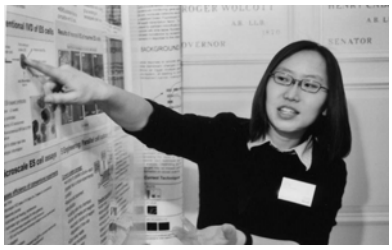
Robert A. Brown, PhD, provost of MIT and the Warren K. Lewis professor of chemical engineering, delivered the keynote address at HST's graduation on June 07, 2004.

Of the 70 graduates that received degrees, 17 graduated with PhD degrees, 33 received MD degrees, and 25 received master's degrees. Eleven MD students graduated with honors: six *cum laude* and five *magna cum laude*. HST's graduating class of 2004 represented 17 states and 14 foreign countries.

Robert A. Brown, keynote speaker at HST's commencement. Photo by Ralph Lindenfeld

The 17th annual HST Forum, "Stem Cells and Therapeutic Cloning Regenerative Medicine and Reproductive Biology," featured keynote speaker George Q. Daley, PhD ('89), MD ('91), HST faculty and alumnus, associate professor of biological chemistry and molecular pharmacology at Harvard Medical School and Children's Hospital Medical Center, who gave the audience a glimpse of what the future of medicine may very well be.

There were 93 posters presented at the 17th annual HST Forum, a 20 percent increase from 2003. The poster session was underwritten by a generous grant from the Guidant Foundation.



MEMP student Lily Y. Kim explains "Parallel Embryonic Stem Cell Culture on a Chip."

HST's annual John F. and Virginia B. Taplin Awards Symposium was held on May 6, and the Taplins were in attendance. This year's award builds on a grant from the Alex and Brit d'Arbeloff Fund for Excellence in MIT Education in 2000, which seeded an innovative mentoring program—BioMatrix—for students with an interest in the biomedical or life sciences. During the past year, not only has the BioMatrix program thrived, but it also has attracted the support of donors whose generosity will ensure the continuation of this program for the next five years. It is with great pleasure and deep appreciation that HST acknowledges the gifts of Larry G. Benedict, dean for student life, Phillip L. Clay, chancellor, Isaac M. Colbert, dean for graduate students, Robert P. Redwine, dean for undergraduate education, and Anthony Williams, HST Advisory Board member.

Milestones

In the four years that the BioMatrix program has been in existent, it has hosted 28 dinners, created dozens of mentorship opportunities, and dutifully watched its inaugural members transition from undergraduates to graduate students. Six of HST's 29 matriculating students are BioMatrix members.

Bernd Comjean, Lisa Coviello, Lisa Desforge, Terrill Gadde, and John Suparyo were awarded MIT's Excellence Award in the Innovation Solutions category. The Innovation Solutions category acknowledges those in the MIT community that participate in collaborative problem solving; approach problems as opportunities for learning and growth; create more efficient and/or less costly ways of performing work functions; break down boundaries and/or create new relationships to improve the way work gets done; and take a proactive and innovative approach toward finding solutions to business and workplace challenges.

Excellence Award winners(left to right) John Suparyo, Lisa Coviello, Bernd Comjean, and Terrill Gadde. Photo by Alison N. Haughton

Master's degrees were conferred on the first graduates of the Biomedical Enterprise Program, a dual-degree master's program jointly administered by HST and the MIT Sloan School of Management.

External Relations

Biomedical Enterprise Program graduates (left to right) Richard Wehby, Peter Smith, Adrian Gottschalk, and Matthew Strobeck. Photo by Ralph Lindenfeld

- A memorandum of understanding was signed by HST and the Food and Drug Administration designed to foster collaboration in the pharmaceutical development and regulatory approval process, and to finding ways to continue interdisciplinary scientific training for regulatory scientists, academicians, and students.
- A cosponsorship agreement was signed by HST and the FDA's Center for Biologics Evaluation and Research for a workshop entitled "Adaptive Clinical Trial Design: Ready for Primetime?" scheduled for October 19, 2004, at the University of Maryland, Shady Grove Campus.
- Five new members were added to HST's Advisory Council: Anthony K. Asnes, managing director of Eagle Capital Management; Joshua Makower, MD, venture partner at New Enterprise Associates and founder and CEO of ExploraMed II; James E. Nicholson, founder of Cortek, Inc.; Tom Sommer, president of the Massachusetts Medical Device Industry Council; and Joseph M. Smith, MD ('87), PhD ('85), senior vice president/chief medical officer of Guidant-CRM.
- HST Advisory Council meetings were held on November 18, 2003, and March 18, 2004. In the November meeting, members laid the groundwork for an FDA-Industry collaboration focused on reducing the time and cost of bringing products to market; and in the March meeting, members discussed the development of a center in HST's Biomedical Enterprise Program to sustain, grow, and improve practices in the biomedical industry.
- Groundwork was laid for the establishment of a new HST Alumni Council designed to foster increased communication between HST's growing alumni community and its present students, faculty, and administrators.
- In 2003, the Irving M. London Society, HST's annual giving program, increased donor participation by 7 percent and raised more than $180,000, an increase of nearly 100 percent in donor dollars from the previous year.

HST Admissions

- HST's PhD Admissions Committee received 239 applications during the 2003–2004 academic year. While applications were down by 6 percent from the previous year, the decrease is in line with similar trends at peer schools and programs. The average applicant age is 25. Forty-one students from 25 different undergraduate institutions and 10 different countries, and with 20 different undergraduate degrees, will matriculate. Seventeen percent of the matriculating students are women.
- The Biomedical Enterprise Program, HST's dual MS-MBA program offered jointly with Sloan, received 26 applications, representing a 75 percent increase over the previous year, and 16 applicants were interviewed. From these, 9 new

students (including 2 women) were offered admission, 4 as BEP-Sloan Fellows, 3 for the BEP-Sloan MBA, and 2 for the BEP-HBS MBA. The applicants' range of work experience is 3.5 to 12 years, and the average years of experience is 8. The average applicant age is 32. Nearly half of those admitted hold advanced degrees (two PhDs, one MD, and one MS).

- The MD Admissions Committee received 570 applications—a 4 percent increase from last fiscal year—and 145 applicants were invited for interviews. Forty-four were offered admission, and nearly one-third of the matriculating students are women. Of those admitted, about half have undergraduate degrees in engineering or physical sciences, substantially more than any MD program of which we are aware. Virtually all have had prior research experience, in keeping with the objective of the MD program to train physician-scientists.
- In 2003–2004, a total of 429 matriculated students were enrolled and 438 degrees were sought in the following HST programs:

  PhD (180)
  Medical Engineering and Medical Physics Program (109)
  Radiological Sciences Joint Program (8)
  Speech and Hearing Bioscience and Technology Doctoral Program (63)
  MD (194)
  Medical Sciences (MD)
  MD/PhD Program
  Master's (55)
  Biomedical Enterprise Program (10)
  Biomedical Informatics Program (21)
  Clinical Investigator Training Program (22)
  Master's of Engineering in Biomedical Engineering (2)

- The following new classes were added in 2003–2004:

  HST 205 Enterprise Experience in Medical Engineering & Medical Physics
  HST 452J Statistical Physics in Biology
  HST 527 Blood Vessels and Endothelial Phenotypes in Health and Disease
  HST 535 Principles and Practice of Tissue Engineering
  HST 592 Seminar in Computational Biology
  HST 725 Music Perception and Cognition
  HST 975 Clinical Trials in Biomedical Enterprise

Student Honors, Awards, and Fellowships

Research Awards

Daniel Mazzucco received the 2004 John Charnley Award from the Hip Society for *The Role of Joint Fluid in the Tribology of Total Joint Arthroplasty*, a paper describing findings made in his doctoral thesis. The Charnley Award recognizes innovative research encompassing important advances in the management of hip disorders.

Jacob Wesley Ulm won second prize in the annual Neurofibromatosis Prize for Research Ideas competition, sponsored by the National Neurofibromatosis Foundation and the International Neurofibromatosis Association.

Research Fellowships

Howard Hughes Medical Institute Award (new and continuing)	David Berry, Christina Boulton, Robert Den, Sang D. Kim, Kevin S. King, Stephanie Misono, Yvonne Ou, Mohammad Siddiqui, Ryuji Suzuki, David Ting, Vladimir Vinarsky, Nikhil Wagle
NIH Individual National Research Service Award	David O'Gorman
American Heart Association Predoctoral Fellowship	Pak Wai (Patrick) Au
Hugh Hampton Young Memorial Fellowship	Fabio Thiers
Hertz Foundation Fellowships(new and continuing)	Lily Y. Kim, Andrew Levin, E. Courtenay Wilson
Alexandra J. Miliotis Research Fellows in Pediatric Oncology	Steven Corsello, Navid Redjal, Annemarie Stroustrup Smith
National Science Foundation Fellowships (new and continuing)	Jose O. Aleman, Lauren J. O'Donnell, Laura C. Redi, Adam Rosenthal, Jocelyn E. Songer, Lauryn R. Zipse.
Whitaker Foundation Fellowships (new and continuing)	Gil Alterovitz, Aaron B. Baker, Erika L. Brown, Steven K. Charles, David A. Eavarone, Paul Matthew George, Kevin R. King, Tony H. Ko, Sylaja Murikipudi, David N. Nguyen, Eric A. Osborn, Andrew G. Richardson, Christina E. Silcox, Joshua Tam, Juwell W. Wu, Peter I. Wu, Ernest N. Yeh.
Zakhartchenko Fellowship	David O'Gorman

Community Leadership and Teaching Awards

HST Student Leadership Award	David Ting
HST Directors' Award	Adrian H. Gottschalk, Shunmugavelu D. Sokka
William L. Stewart Award	David Berry
Goodwin Medal	Raj Malhotra

Competitive Industry Awards

H. Hocking Cheng and teammates were selected as the Robert P. Goldberg Grand Prize winner of the 15th annual MIT 50K Entrepreneurship Competition. The team won for its work on the Active Joint Brace, an affordable, wearable, unencumbering exoskeleton that augments physical capability by working in tandem with existing musculature.

H. Hocking Cheng and teammates, winners of the Robert P. Goldberg Grand Prize in MIT's 50K Entrepreneurship Competition

Alumni

Sangeeta Bhatia, PhD ('97), MD ('99), named one of *Technology Review*'s 100 brilliant young innovators under 35 in its October 2003 issue, has coauthored *Tissue Engineering*, the first book in its field to lay a foundation for the study of tissue engineering by covering quantitative cell and tissue biology, cell and tissue characterization, engineering methods and design, and clinical implementation.

Sangeeta Bhatia

George Q. Daley, PhD ('89), MD ('91), associate professor of biological chemistry and molecular pharmacology at Harvard Medical School and HST, and David C. Page, MD ('84), an affiliated faculty member of HST and professor of biology at MIT, were mentioned in *Science Magazine*'s coverage of the top scientific advances of 2003.

Vamsi Mootha, MD ('98), and Collin Stultz, MD ('97), PhD ('97), received Burroughs Wellcome Fund Career Awards in the biomedical sciences. Dr. Mootha, a postdoctoral fellow at the Broad Institute, and Dr. Stultz, an assistant professor in the Department of Electrical Engineering and Computer Science and HST, will each receive $500,000 over five years toward postdoctoral training and the early years of faculty service.

Mark B. McClellan. Photo by L. Barry Hetherington

Mark B. McClellan, MD ('92), PhD, commissioner of the Food and Drug Administration, was nominated by President George W. Bush to head the Center for Medicine and Medical Services, a $500 billion agency implementing new regulations to expand drug coverage. The Senate unanimously confirmed Dr. McClellan on March 12, 2004.

Robert L. Satcher, Jr., PhD ('93), MD ('94), is one of 11 members chosen for NASA's 2004 class of astronaut candidates. Dr. Satcher is an orthopedic surgeon at Northwestern Memorial Hospital and

Robert L. Satcher, Jr. Photo courtesy NASA

Children's Memorial Hospital in Chicago, specializing in child and adult orthopedic oncology.

Personnel Information

Mario Casal and Amy Magiera were hired to fill positions in the Finance & Personnel Office and the Academic Office, respectively.

Bernd Comjean and Terrill Gadde are jointly sharing the position of administrative officer.

Lee Gehrke was appointed associate director of HST Faculty Affairs.

Julie Greenberg was appointed director of education and academic affairs.

Faculty Appointments

Junior Faculty

Elfar Adalsteinsson, PhD, will be based both at the Martinos Center in Charlestown and the Research Laboratory of Electronics at MIT. He comes from the Richard M. Lucas Center for Magnetic Resonance Spectroscopy and Imaging at Stanford University, where he served as senior research engineer in the Department of Radiology. Dr. Adalsteinsson's research area is medical imaging with magnetic resonance, focusing on optimal methods for acquisition, reconstruction, and processing of in vivo imaging data.

Collin Stultz, MD ('97), PhD, comes to HST from a postdoctoral fellowship at Brigham and Women's Hospital and HST where he developed novel methods to understand the role of collagen degradation in atherosclerosis. His research interests revolve around understanding conformational changes in macromolecules and the effect of structural transitions on common human diseases. Dr. Stultz will be based in the Stata Center with auxiliary lab space in E25.

Senior Faculty

John Gabrieli will have a dual appointment in HST and the Department of Brain and Cognitive Sciences. Dr. Gabrieli will serve as associate director of the Martinos Center and will be initiating a footprint for the Athinoula A. Martinos Center on the MIT campus. A cognitive neuroscientist, he is currently a professor of psychology at Stanford, where he studies human memory systems using functional magnetic resonance imaging.

Newly Appointed Joint/Second Faculty Members

David Cohen, MD, PhD ('87), is joining HST from Albert Einstein College of Medicine, where he has conducted innovative studies in the fields of molecular biophysics, biology, and genetics of biliary lipid metabolism, including a focus on cholesterol transfer from plasma to bile.

Lucila Ohno-Machado, MD, PhD, associate professor of radiology at Harvard Medical School and Brigham and Women's Hospital, and associate director of Decision Systems, researches predictive modeling of diseases using machine learning and statistical techniques with a major focus in modeling medical prognosis using neural networks.

Anthony Sinskey, PhD, professor of biology at MIT, will continue his key role in the development of the Biomedical Enterprise Program. Currently, Professor Sinskey serves as codirector of MIT's Program on the Pharmaceutical Industry—convened to study the economics of drug discovery and development and the process of technological, regulatory, and policy changes in the pharmaceutical industry. His broad-based research takes an interdisciplinary approach to metabolic engineering, focusing on the fundamental physiology, biochemistry, and molecular genetics of important organisms.

Daniel Sodickson, MD ('99), PhD ('87), assistant professor of radiology at Beth Israel Deaconess Medical Center, will continue serving as director of HST 590. His research centers on the development of new techniques for rapid biomedical imaging—with particular focus on projects involving novel rapid MRI techniques using a new paradigm of parallel image acquisition.

Gregory Sorensen, MD ('89), associate professor of radiology at Harvard Medical School and Massachusetts General Hospital, and associate director of the Athinoula A. Martinos Center for Biomedical Imaging, has focused his research on bringing novel technical developments in MRI to the investigation of neurological diseases and the care of patients. His primary interests are perfusion/diffusion imaging of stroke; functional MRI of migraine and migraine aura; and the transfer of technology from the laboratory into clinical practice and research.

Promotions of HST Faculty

George Daley has been promoted to associate professor of biological chemistry and molecular pharmacology at Harvard Medical School and associate professor of pediatrics at HMS and Children's Hospital Medical Center.

Promotions of HST Affiliated Faculty

R. Rox Anderson, MD ('84), has been promoted to professor of dermatology at Harvard Medical School and Massachusetts General Hospital.

Alan D. D'Andrea, MD ('83), has been awarded a second appointment as Alvan T. and Viola D. Fuller-American Cancer Society professor of radiation oncology at Harvard

Medical School. He is professor of pediatrics at Harvard Medical School and Children's Hospital Medical Center and chief, Division of Radiation and Cancer Biology at Dana Farber Cancer Institute.

Kenneth Falchuk, MD, has been promoted to professor of medicine at Harvard Medical School and Brigham Women's Hospital.

Charles Hatem, MD, has been promoted to professor of medicine at Harvard Medical School and Beth Israel Deaconess Medical Center.

Dava J. Newman, PhD, has been promoted to professor of aeronautics and astronautics at MIT.

Carl Rosow, MD, PhD, has been promoted to professor of anesthesia at Harvard Medical School and Massachusetts General Hospital.

Faculty Awards and Honors

Lee Gehrke, PhD, the Hermann von Helmholtz professor of health sciences and technology, received an MIT award for excellence in graduate student teaching and an honorable mention for excellence in direct teaching—as demonstrated by teaching awards, student evaluations, and recommendations by colleagues—in the preclinical years from Harvard Medical School.

Lucila Ohno-Machado, MD, PhD, associate professor of radiology, received the Clifford Barger Excellence in Mentoring Award—an annual HMS award based on nomination letters and testimonials of former students and trainees.

Robert H. Rubin, MD, the Gordon and Marjorie Osborne professor of health sciences and technology, received the 2004 American Society of Transplantation/ Wyeth Senior Achievement Award in Clinical Transplantation.

Ken Stevens, ScD, the Clarence J. Lebel professor of electrical engineering and health sciences and technology, received the IEEE's 2004 James L. Flanagan Speech Audio Processing Award for "fundamental contributions to theory and practice and special perceptions."

In Memory

HST faculty, staff, students, and alumni were deeply sadden by the passing of:

- John A. Badwey, PhD, codirector of HST 146 Human Biochemistry and Metabolic Diseases, and a principal investigator in the Center for Experimental Therapeutics and Reperfusion Injury at Brigham and Women's Hospital.
- William C. Quist, MD, PhD, associate director of HST 30 Human Pathology. In 1999, Bill was the recipient of the Irving London Teaching Award, which

recognizes faculty who have made outstanding contributions to the training of HST students.

HST will remember both John and Bill for their significant contributions.

Research

The research of HST's faculty and research staff encompasses initiatives based at laboratories at MIT, Harvard University, and Harvard Medical School, as well as collaborations at area teaching hospitals including Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Children's Hospital, Dana Farber Cancer Institute, Massachusetts Eye and Ear Infirmary, and Massachusetts General Hospital.

In addition to individual research efforts at these locations, HST research also comprises work undertaken at several area research centers, including the Children's/HST Center for Biomedical Informatics, the HST Division of Brigham and Women's Hospital, the MIT site for the MGH-MIT General Clinical Research Center, the Athinoula A. Martinos Center for Biomedical Imaging, the Boston Heart Foundation, the Center for Experimental, Pharmacology and Therapeutics, and the Harvard-MIT Biomedical Engineering Center.

This year's report highlights the research activities at the Athinoula A. Martinos Center for Biomedical Imaging.

MIND Consortium

HST's Athinoula A. Martinos Center has been asked by the Mental Illness and Neuroscience Discovery (MIND) Institute, a multi-institutional research foundation, to participate and indeed take a lead in their newly established Schizophrenia Consortium Study. The project developed jointly by members of the MIND Consortium Group, including Nancy Andreasen, Robert McCarley, Dara Manoach, Randy Gollub, Vince Clark, John Lauriello, Lee Friedman, Kelvin Lim, Chuck Schultz, Dan O'Learly, and Vince Magnotta, aims to answer basic questions about the progression of schizophrenia in young adults, and the underlying changes in the brains of these patients.

Acupuncture Center of Excellence

HST's ongoing efforts to investigate the neural basis of acupuncture effects have been bolstered recently by the award of a Center of Excellence for Research on Complementary and Alternative Medicine grant from the National Center of Alternative and Complementary Medicine. Bruce Rosen, MD, PhD, director of the Nuclear Magnetic Resonance Center at MGH and HST's Athinoula A. Martinos Center for Biomedical Imaging, is the principal investigator of a project entitled "Neuroimaging Acupuncture Effects on Human Brain Activity," the overall goal of which is to investigate in a rigorous and scientific way the neurobiology of acupuncture.

Phenotype Genotype Project for Depression and Addictions

The Office of National Drug Control Policy's Counter-drug Technology Assessment Center (CTAC) awarded $8 million in funding to a large-scale proof-of-concept project proposed by Hans Breiter, MD, an HST-Martinos Center investigator. Dr. Breiter will develop the experimental infrastructure to link alterations in specific brain circuits associated with addiction and related disorders such as depression, to the genes that confer susceptibilities to them. The goal is to understand the genetic basis underlying brain circuitry alterations that confer susceptibility and resistance to cocaine (and nicotine) dependence and/or mood disorders in humans.

Future Plans

HST plans to execute a multi-faceted strategy to expand its research presence, including:

- Establishing HST research facilities in HST stakeholder institutions, including the teaching hospitals
- Recruiting faculty in biomedical imaging, biomedical informatics and integrative biology, and regenerative and functional biomedical technologies
- Creating centers of excellence that have strong foundations in the medical, academic, and business communities
- Continuing to explore mechanisms to optimize impact on education and research at the interface of biomedical/bioengineering in the health sciences
- Expanding HST's faculty and its visibility in research in the Harvard and MIT communities, as well as in industry
- Raising new sources of funding to support HST students and faculty

Martha L. Gray
Director
Edward Hood Taplin Professor of Medical and Electrical Engineering

More information about the Harvard-MIT Division of Health Sciences and Technology can be found online at http://hst.mit.edu/.