

## 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 in which 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 CRC to study normal volunteers or patients with chronic diseases. The NIH Roadmap for Medical Research into the 21st century calls for developing community partnerships and providing a faster "bench to bedside" approach for more timely treatment for patients. The CRC is uniquely poised to translate basic science and engineering research at MIT into initial clinical applications for patients.

Scientists and physicians authorized to carry out research protocols using CRC 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 Harvard Medical School (HMS) and professor of health sciences at the Harvard-MIT Division of Health Sciences and Technology (HST), consists of eight voting members plus 12 nonvoting members from CRC's program and operating staffs. 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 CRC.

At the suggestion of NIH, the CRC developed a structured relationship with the Massachusetts General Hospital Mallinckrodt General Clinical Research Center (GCRC) in 2001. Since that time, the CRC has functioned as an autonomous satellite of the larger Massachusetts General Hospital (MGH) GCRC. The senior program staffs at the two institutions meet monthly to anticipate and solve potential problems related to their integration. Developing this type of relationship with MGH GCRC has allowed MIT CRC to solve a continuing chronic problem: the small size of the pool of medical doctors conducting clinical research in this facility, a consequence of the tendency of MIT's academic departments not to appoint such people as professors during recent decades. Moreover it has served as a source of physician scientists who can collaborate with MIT biomedical scientists who hold doctoral degrees. The reputations of the two GCRCs are excellent, and the strengths of each institution complements those of the other.

## **Administrative Initiatives/Accomplishments**

The CRC codirectors John Gabrieli, PhD and Ravi Thadhani, MD, MPH, are actively integrating CRC resources within the MIT community. A broad-based outreach program has been initiated to expand and incorporate the human clinical research currently occurring across campus with the resources and infrastructure that CRC can offer. We have collaborated and assisted on studies with the following departments:

- Brain and Cognitive Sciences—We worked with several investigators on varied projects, such as a virtual environment-based telerehabilitation system and a quantitative evaluation of students' psychological and physiological response during human-computer interactions.
- Aeronautics and Astronautics—We are engaged in an ongoing protocol for NASA research.
- The Broad Institute—We collaborated on metabolites for the Metabolic Abnormalities in College Students protocol (MACS).
- Biology—We are engaged in an ongoing protocol with Professor Monty Krieger's Laboratory.
- The Center for Environmental Health and Safety (CEHS)—A protocol to examine biomarkers for inflammatory bowel disease will be starting soon.
- The Media Lab—Protocols with several investigators are in final development stages.

The CRC program directors and assistant directors sponsored a lecture series for the January 2007 Independent Activities Period, providing a discourse on clinical research issues, offering classes such as the Brain Basis of Dyslexia, Pregnancy Diagnostics—Translated from Mice to Humans, Natural Remedies for the Treatment of Depression, and Medical Evidence for the Health Benefits of a Vegetarian Diet.

Joint Standard Operating Procedures were developed in conjunction with MGH GCRC for the NIH competitive renewal submitted in January 2007. These procedures were drafted to further assist investigators in a streamlined submission process for joint protocols.

NIH announced in June 2007 that MGH GCRC and MIT CRC were approved for funding as a result of the competitive renewal submitted in January 2007. This new funding will cover December 2007 through November 2010. The last competitive renewal was submitted five years ago in 2002. Since that time, 111 protocols have been active at MIT CRC, with 42 active protocols in the past year.

The CRC also affords opportunities to MIT undergraduate and graduate students to participate in clinical research projects. In the spring term of 2007, Dr. Thadhani, who in addition to being codirector of MIT CRC is also associate professor of medicine at HMS, again taught a formal undergraduate course in clinical investigation. Fifteen undergraduates students were enrolled for the semester and the course evaluations were very positive. This course has been offered for five years and has been very well received.

### **Bionutrition Core**

The Bionutrition Core of MIT CRC provides nutrition-related support to all CRC-approved research protocols. This includes nutritional methodology; protocol design; nutritional product establishment; research diet design, calculation, production, and monitoring; indirect calorimetry; clinical nutritional evaluation and assessment; nutrition intake quantification and analysis; and dual-energy X-ray absorptiometry (DXA) scanning, analysis, and management.

Since acquiring the Hologic 4500A DXA system in 1998, the Bionutrition Core has been responsible for operating and managing the scanning services for protocols requiring the measurement of bone density and body composition in both MIT and MGH CRCs. This quantitative digital radiography application of DXA technology provides accurate and precise measurement of small changes in bone mineral density (BMD) measured in grams per centimeter square. BMD measurements offer the investigator the most reliable means of recording the rate of bone loss or gain in health and disease and during drug/diet intervention.

### **Computer Facility**

The CRC computer facility provides hardware and software support for CRC staff and investigators. During FY2007, changes were made to the CRC operations system, which is an in-house developed Oracle application. The CRC website was redesigned using Dreamweaver software. Cascading Style Sheets design was implemented. A website Google search was included. The CRC Calendar was designed using the MIT Custom Calendar. The CRC mailing list was established. All CRC PCs were upgraded to Office 2003 which included Oracle Connector for Outlook. An Oracle Database schedule was scripted for use in Outlook. A database with data entry began being designed for the protocol investigating MACS. In addition, much data and information was collected for the grant renewal application.

### **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. Assays include: gas chromatography (GC) of fatty acids, high performance liquid chromatography (HPLC) of amino acids and malondialdehyde (an indicator of tissue oxidative stress), GC/mass spectrometry (GC/MS) of metabolic intermediates (including amino acids, glucose, and glycerol), radio immunoassays and enzyme immunoassay of a variety of cytokines, inflammatory markers, and growth factors. Principle 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.

### **Future Plans**

Harvard Medical School is drafting a Clinical Translation Science Award (CTSA) proposal which will include all current Harvard-affiliated GCRCs, including MIT's. This proposal will be submitted in October 2007. If the proposed grant is awarded, MIT CRC would migrate from a GCRC to a CTSA for funding and organizational purposes.

The CRC continues to expand its outreach to the MIT community, interacting with investigators from the Media Lab, MIT Medical, CEHS, and the MIT Sloan School of Management. We envision expanding our protocol development consulting which allows us to collaborate with new MIT investigators to help define or focus their research and also match MIT investigators with physicians from MGH or other area hospitals to collaborate on MIT investigator-initiated studies.

We hope to expand the outreach of the CRC core lab facilities, which offers GC/MS, GC, and HPLC equipment, to MIT investigators. The CRC core lab can facilitate use of this equipment even if the research was not conducted at the CRC.

### **Research Activities and Highlights**

During FY 2007, the CRC patient census totaled 1,190 outpatient visits. During the past year, the CRC has not used inpatient days; protocols requiring inpatient stays are now conducted at MGH GCRC.

#### **Steven Grinspoon**

Dr. Grinspoon has investigated both the short and longer-term effects of inhibition of lipolysis, using detailed spectroscopic, isotope, and clamp techniques uniquely available on the MIT GCRC. These novel studies have shown that lipolysis is increased and that inhibition markedly improves insulin sensitivity and hypertriglyceridemia. In addition, Dr. Grinspoon continues to perform metabolic studies in non HIV-infected patients, most recently providing the first evidence that inhibition of TNF-alpha in patients with the metabolic syndrome improves inflammatory indices and adiponectin. These detailed physiological studies, enabling determination of nutrient flux, detailed body composition parameters, and substrate metabolism, could not have been performed without the facilities at MIT. These studies have had a direct impact on the prevention and treatment of cardiovascular disease in HIV-infected patients.

#### **Ravi Thadhani**

The GCRC serves as the central investigative site for a postpartum study conducted by Dr. Thadhani in which women with prior complications of pregnancy are brought to the GCRC approximately one year after giving birth. The aims of this study are to identify subclinical alterations in women with a prior history of preeclampsia, gestational diabetes, or normal pregnancies. Two recent studies (Wolf, Myles, et al. "Preeclampsia and Future Cardiovascular Disease: Potential Role of Altered Angiogenesis and Insulin Resistance," *Journal of Clinical Endocrinology & Metabolism* 89 [2004]: 6239-6243, and Hubel, Carl, et al. "Agonistic AT-1 Receptor Autoantibodies in Postpartum Women with a History of Preeclampsia," *Hypertension* [2007, In press]) highlight the postpartum studies currently ongoing at MIT GCRC. In addition, Dr. Thadhani is the principal investigator of the ongoing MACS study, a cross-sectional study assessing the burden of metabolic syndrome among 1,000 college age students at MIT.

**San Wang**

Dr. San Wang and his group (Heather Herrington, MD, and Frances Yang, PhD) have continued their nutritional study, A Nutritional Approach to Reducing Cardiovascular Risk Factors, at the MIT CRC during the past year. This study tests whether older subjects following healthy omnivore and vegetarian diets based on the US government's 2005 Dietary Guidelines for Americans will have improvements in a range of cardiovascular risk factors including blood pressure, lipid profiles, and fasting glucose levels. In this study, all foods are provided to the subjects for three four-week diet blocks. Other nutritional measurements such as resting metabolic rate, food frequency and dietary satisfaction questionnaires, and body composition tests are performed at each diet phase.

**John Gabrieli****Codirector****Grover Hermann Professor in Health Sciences and Technology and Cognitive Neuroscience****Ravi Thadhani****Codirector****Associate Professor of Medicine, Harvard Medical School**

*More information about the MIT Clinical Research Center can be found at <http://web.mit.edu/crc/www/>.*