

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 Massachusetts Institute of Technology (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 MIT 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. Since CRC's administrative merger with Massachusetts General Hospital's General Clinical Research Center (MGH GCRC), 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 CRC.

Administration

CRC, under the new leadership of codirectors John Gabrieli, PhD and Ravi Thadhani, MD, MPH (after the retirement of Dick Wurtman, MD in July 2005), is 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:

- Mechanical Engineering—A medical device study was conducted.
- Brain and Cognitive Sciences—We worked with several investigators on several 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 developed a protocol for a NASA study thesis.
- Broad Institute—We collaborated on metabolites for the Metabolic Abnormalities in College Students protocol (MACS).
- Biology—CRC assisted Professor Monty Krieger to improve an ongoing study related to lipoprotein metabolism.
- Center for Environmental Health and Safety (CEHS)—Researchers are eager to start several studies before year-end following collaborative discussions.
- Center for Biomedical Innovation—We have initiated contact.

CRC has a dual administrative locus within MIT. As a research unit, CRC reports through HST to the vice president for research and associate provost. As a patient-care unit, CRC is a part of the MIT Medical Department and reports to Dr. William M. Kettle, the director of the Medical Department. Members of CRC participate in the Medical Department's activities, e.g., its Quality Improvement, Pharmacy and Therapeutics, Medical Records, and Safety committees.

Several years ago 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, 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, CRC successfully developed a structured relationship with the MGH GCRC in 2001. Since that time, the MIT CRC has functioned as an autonomous satellite of the larger MGH GCRC. The senior program staffs at the two institutions meet monthly to anticipate and solve potential problems related to their integration. 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, starting in December 2002. The score, reflecting the reviewers' analysis of the joint application, was the best that MIT has received for its applications. The next MGH-MIT competitive grant renewal is due at NIH in February 2007 to carry funding through 2010.

Developing this type of “network” relationship with the MGH GCRC has allowed the MIT CRC to solve a continuing chronic problem, i.e., 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 CRCs apparently are excellent, and the strengths of each institution complement those of the other.

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 CRC's facilities to initiate research protocols and participate in ongoing projects supervised by senior investigators and faculty. (See section 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 term of 2006, 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. This course has been offered for four years and has been very well received.

Affirmative Action

The hiring of women and minorities continues to be a high priority commitment for CRC. Of the eight visiting scientists appointed by CRC in 2005–2006, six were women and three were minorities. CRC will continue its efforts to increase the pool of qualified minority applicants as positions become available.

CRC has been highly successful in recruiting women and minorities as study subjects. During 2005–2006, approximately 68% of all study subjects were women and 17% of the total study population were minorities (black 14%, Asian 2%, 1% American Indian, and 1% other).

Research Activities

During 2005–2006, the CRC patient census totaled 1,375 outpatient visits. The CRC branch of the NIH had, based on prior years' activities, provided support for up to 2,172 outpatient visits. During the past year, CRC has not used inpatient days; protocols requiring inpatient stays are now conducted at the MGH GCRC.

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 of 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 MIT Sloan School of Management the Department of Biology, and the School of Engineering and will again be centered in CRC. Research-wise, the emphasis of CEPT has been in the application of positron emission tomography (PET), magnetic resonance imagery (MRI), ultrasound, and other measurement technologies to the development of new drugs. With the development of imaging at MIT, these technologies will be greatly facilitated.

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; 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 the 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.

The addition of TrueOne 2400 Indirect Calorimetry last year to our two other existing Deltatrac II systems has provided more strength to the Bionutrition Core in the capacity of measuring a subject's resting energy expenditure for various studies.

Computer Facility

The CRC computer facility provides hardware and software support for 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 CRC and investigators. These systems use an ORACLE relational database and support the day-to-day operations of CRC. During 2005–2006, the computer staff has continued to work with its 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 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. Studies continue to examine the role of dietary arginine as a precursor of the signal transducer nitric oxide. The novel doubly labeled water ($^2\text{H}_2^{18}\text{O}$) method is being used to define the

energy requirements for adolescent and elderly subjects, and the factors that affect these needs. These various investigations offer new basic knowledge about the physiology of human energy substrate and amino acid metabolism and, additionally, make practical contributions to problems in human nutrition.

The Core Laboratory also utilizes high performance liquid chromatography (HPLC) techniques. A Beckman System Gold HPLC amino acid analyzer 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 communication 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 Lab users, the Core Lab actively networks with other GCRC labs. The MIT Core Lab posts a list of available assays on the national GCRC Core Laboratories website and a Core Lab representative attends the GCRC National Annual Conference. This networking has generated a number of Core Lab-only protocols.

Research Highlights

Steven Grinspoon

Dr. Grinspoon has made a number of important contributions in the past year. The significant question of relative growth hormone (GH) deficiency among HIV-infected patients with lipodystrophy was investigated. Reduced GH secretion was seen in association with visceral adiposity, and was demonstrated to occur in up to 33% of such patients. The clinical significance of this finding relates to the potential cardiovascular complications of relative GH deficiency in this population. Bone loss has also been recently identified in HIV-infected patients with fat maldistribution. In a paper published during the reporting period, novel effects of growth hormone-releasing hormone (GHRH) are shown on bone turnover among HIV-infected patients with excess visceral adiposity. This study suggests for the first time that physiologic augmentation with a GH secretagogue may improve bone turnover and ultimately bone density in this population.

Colleen Hadigan

Dr. Hadigan's group, in collaboration with the MGH Department of Radiology, made important progress in establishing the use of MRI and magnetic resonance spectroscopy at MGH for the assessment of fatty liver in HIV-infected patients and other populations. There is currently an open protocol assessing the prevalence of fatty liver in HIV disease and its contribution to insulin resistance. They also published a report on the use of PET techniques to evaluate in vivo glucose dynamics in various adipose tissue compartments and in muscle in humans with HIV.

Ravi Thadhani

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 some 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. Based at MGH, this study, one of the largest of its kind in the world, has to date enrolled more than 8,000 women, 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 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 group has focused on alterations in the first trimester that identify those at risk for adverse outcomes later in pregnancy. The focus has been on metabolic alterations, inflammation, and alterations in angiogenesis evident in the first trimester, and the investigators have uncovered important interactions between these alterations. Finally, this group brings a subset of women back to the MIT CRC one year after pregnancy (more than 150 to date) and has begun to uncover alterations in insulin resistance and angiogenesis that persist one year postpartum, which may explain why these women develop hypertension and diabetes in future years.

San Wang

Dr. San Wang and his group (Heather Herrington, MD, and Frances Yang, PhD) have started a 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. It is hoped that this study will be extended next year, in collaboration with Robert Schrieber, MD, as an outpatient community-based study, which would bring a large number of subjects to the MIT CRC for screening tests, dietary guidance, and bionutrition activities.

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/wwww/>.