

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 use the CRC to study normal volunteers or patients with chronic diseases.

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 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, consists of seven voting members plus 10 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.

Administrative Initiatives/Accomplishments

The CRC codirectors John Gabrieli, PhD, and Ravi Thadhani, MD, MPH, continue the outreach efforts started last year to engage MIT faculty and investigators and assist with research and pilot studies by providing infrastructure and resources as needed. This outreach has resulted in increased MIT-based protocols and collaboration with MIT investigators for additional studies. We have collaborated and assisted on studies with the following departments:

- Aeronautics and Astronautics—a protocol for NASA research completed in December 2007
- The Broad Institute—a new study to diagnose mitochondrial disorders was approved in January 2008
- Biology—we are engaged in an ongoing protocol with Professor Monty Krieger's laboratory
- Center for Environmental Health and Safety—a protocol to examine biomarkers for inflammatory bowel disease completed enrollment of subjects in May 2008 (The investigator, Leona Sampson, is looking to expand the study as a result.)
- D Lab—study with Amy Smith to test adherence to drug regimens was approved and initiated

- The Media Lab—a new study to examine trust behavior with Professor Ed Boyden was recently approved
- MIT Medical—study approved to test physical therapy rehabilitation via a simulator with Dr. Kane
- Whitehead Institute—new protocol approved to collaborate with biology professor Jaenisch
- Architecture—study collaboration between Stephen Intille and CRC bionutritionists

The CRC program directors and assistant directors enthusiastically sponsored and presented a lecture series for the January 2008 independent activities period, providing a discourse on clinical research issues, offering seminars such as “Optical Measurement of Cerebral Blood Flow to Guide Treatment in Brain Injury,” “Metabolic Abnormalities and Cardiovascular Risk in HIV Disease,” “Acupuncture and its Applications in Psychiatry,” and “Representation of the Self in the Human Brain: Alterations in Autism and Schizophrenia.”

The codirectors coordinated Clinical Translation Science Award (CTSA) discussions with Harvard Medical School and MIT’s vice president for research to ensure that the MIT CRC was represented as an ambulatory outpatient/outreach center in Harvard’s CTSA proposal submitted in November 2007. The Harvard CTSA proposal was awarded in May 2008.

The CRC also affords opportunities to MIT undergraduate and graduate students to participate in clinical research projects. In spring 2008, Dr. Thadhani, who in addition to being codirector of MIT CRC is also an associate professor of medicine at HMS, again taught a formal undergraduate course in clinical investigation. Fifteen undergraduate 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 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 Massachusetts General Hospital (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. The CRC website was maintained and revised for accessibility. Additionally, a private link was added to the website for secure access to the most current protocol documents. In addition to providing daily technological support to the staff and investigators at the MIT Clinical Research Center, Informatics became involved in additional projects. One endeavor involves WebCAMP. WebCAMP is a protocol authoring and scheduling web application in use by other CRCs and CTSA's. The Informatics department set up a prototype WebCAMP installation (WebCAMP software ColdFusion Server and MySQL database) that was evaluated by nursing and administration. It was decided to pursue the transition to WebCAMP. A Windows 2003 server was purchased and configured. ColdFusion MX8 application server software was purchased and configured to run WebCAMP. The IIS web server was configured. An additional Oracle database was added for WebCAMP. The WebCAMP software was installed and is now being configured.

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 of amino acids and malondialdehyde (an indicator of tissue oxidative stress), GC/mass spectrometry of metabolic intermediates (including amino acids, glucose, and glycerol), radio immunoassays and enzyme immunoassay of a variety of cytokines, inflammatory markers, and growth factors. 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.

Future Plans

Harvard Medical School was awarded a Clinical Translation Science Award (CTSA), which includes all current Harvard-affiliated GCRCs, including MIT. This new award went into effect June 1, 2008, overriding the current general clinical research center (GCRC) award, so the MIT CRC has migrated from a GCRC to a Clinical Translation Science Center (CTSC) for funding and organizational purposes. MIT will serve as the community outreach arm of the Harvard CTSC.

The CRC continues to expand its outreach to the MIT community, interacting with investigators from the Media Lab, MIT Medical, the Center for Environmental Health Sciences, 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.

The CRC nursing staff collaborated with Kathleen Vandiver at MIT's Center for Environmental Health Sciences to plan a two-day continuing education workshop for

Boston-area nurses and health care professionals. The nursing focus group occurred in May 2008, and the workshop is scheduled for January 2009. The workshop will provide needed continuing educational requirements for nurses and will demonstrate correlation of molecular biology to disease process. This collaboration is focused to reach out to Boston-area health care professionals and MIT researchers to highlight current translational science.

Research Activities and Highlights

During FY2008, the CRC patient census totaled 1,139 outpatient visits. During the past year, the CRC has not used inpatient days; protocols requiring inpatient stays are now conducted at MGH GCRC.

Emilio Bizzi and Maureen Holden

Bizzi and Holden's study was the first to develop and clinically test a system for the remote delivery of virtual environment-based rehabilitation (VE) for patients with stroke using telerehabilitation. While other descriptions of systems have been published, this study was the first to show efficacy of treatment in a group of patients with chronic stroke ($n = 12$; 1 drop out, 11 completed study, mean duration post stroke 3.8 ± 3.1 year).

The goal was to test the feasibility of developing a relatively low-cost telerehabilitation system using off-the-shelf hardware components and commercially available broadband internet providers to enhance our laboratory-developed virtual environment motor retraining software. We hypothesized that subjects with stroke, who were less than six months post-injury, discharged from therapy with stabilized upper extremity motor recovery, would be able to show significant continued improvement on standard clinical measures following training in VE for a total of 30 hours over six weeks (five one-hour sessions per week), and at least partially maintain these improvements at a four month follow-up appointment.

The training involved practice of upper extremity movements and tasks under the guidance of a virtual teacher, as well as a real therapist, who was located remotely, but viewable by camera on a second computer monitor. During training sessions subjects received various types of enhanced feedback about performance.

The feedback was based on a quantitative comparison of patient and "teacher"-generated 3D kinematic trajectories, which were recorded and could be displayed in real time during practice or following practice. Improvement following VE training was assessed using four measures: (1) Fugl-Meyer Test of Motor Recovery [FM], (2) Wolf Motor Test [WMT], (3) shoulder strength [ShS], and (4) grip strength.

Results, after 30 hours of treatment, showed significant improvement on FM ($p < 0.0001$), WMT ($p < 0.0097$), ShS ($p < 0.0027$), and a trend toward improvement in grip strength ($p < 0.025$). These changes were maintained, for the most part, at a four months follow-up (FM, +7.6 pts; WMT, -18.4 sec; ShS, +169%; grip, +53%). These results are important because they show that subjects were able to generalize motor training received in VE to real-world performance, even to tasks not specifically trained in VE, and to retain gains for four months. They also confirm findings reported by others, that subjects with stroke

are still capable of significant motor improvement even many years after the stroke. The home-based VE treatment tested in this study offered significant benefits to patients in terms of logistics and energy cost (no travel to clinic) but made the treatment much more difficult for the therapist (e.g., the patient could not be touched, could be viewed only via camera, many verbal commands were required, running the VE setup remotely was more complex than standard treatment). Despite these constraints, our patients improved significantly, with a magnitude of improvement larger than reports for other VE-based treatments reported in the literature. Together these findings indicate that this novel treatment approach holds promise for the future benefit of patients with stroke.

Woodie Flowers and Kailius Narendram

Robot-assisted exercise shows promise as a means of providing exercise therapy for weakness resulting from stroke or other neurological conditions. Exoskeletal or “wearable” robots can, in principle, provide therapeutic exercise and/or function as powered orthoses to help compensate for chronic weakness. A novel electromyography (EMG)-controlled exoskeletal robotic brace for the elbow (the active joint brace) was developed and the results of a pilot study conducted using this brace for exercise training in individuals with chronic hemiparesis after stroke.

Eight stroke survivors with severe chronic hemiparesis were enrolled in this pilot study. One subject withdrew from the study because of scheduling conflicts. A second subject was unable to participate in the training protocol because of insufficient surface EMG activity to control the active joint brace. The six remaining subjects each underwent 18 hours of exercise training using the device for a period of six weeks. Outcome measures included the upper-extremity component of the Fugl-Meyer scale and the modified Ashworth scale of muscle hypertonicity.

Analysis revealed that the mean upper-extremity component of the Fugl-Meyer scale increased from 15.5 (SD 3.88) to 19 (SD 3.95) (P 0.04) at the conclusion of training for the six subjects who completed training. Combined (summated) modified Ashworth scale for the elbow flexors and extensors improved from 4.67 (1.2 SD) to 2.33 (0.653 SD) (P 0.009) and improved for the entire upper limb as well. All subjects tolerated the device, and no complications occurred.

The conclusion of this work is that EMG-controlled powered elbow orthoses can be successfully controlled by severely impaired hemiparetic stroke survivors. This technique shows promise as a new modality for assisted exercise training after stroke.

Steven Grinspoon

Recent studies suggest that bone loss occurs among HIV-infected women. This study examined the effects of reduced androgen levels, changes in weight, body composition, and menstrual dysfunction on bone mineral density (BMD) among 152 HIV-infected women characterized by normal weight ($> 90\%$ ideal body weight [IBW], $n = 124$) and low weight ($\leq 90\%$ IBW, $n = 28$) compared with 100 non-HIV-infected control subjects. BMD was assessed by dual x-ray absorptiometry, and free testosterone was assessed by equilibrium dialysis. Abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were determined by computed tomography scan.

A significant difference was seen in BMD between groups at the lumbar spine ($0.92 \pm 0.02 \text{ g/cm}^2$ versus $1.01 \pm 0.01 \text{ g/cm}^2$ versus $1.07 \pm 0.01 \text{ g/cm}^2$; $P < 0.0001$), total hip ($0.84 \pm 0.03 \text{ g/cm}^2$ versus $0.94 \pm 0.01 \text{ g/cm}^2$ versus $0.98 \pm 0.01 \text{ g/cm}^2$; $P < 0.0001$), and femoral neck ($0.73 \pm 0.03 \text{ g/cm}^2$ versus $0.83 \pm 0.01 \text{ g/cm}^2$ versus $0.87 \pm 0.01 \text{ g/cm}^2$; $P < 0.0001$) (HIV-infected low-weight group, HIV-infected normal-weight group, and non-HIV-infected control subjects, respectively, for each comparison; mean \pm SEM). Among the HIV-infected subjects, lumbar BMD correlated with percent IBW ($r = 0.37$, $P < 0.0001$), total body lean mass ($r = 0.43$, $P < 0.0001$), total body fat mass ($r = 0.35$, $P < 0.0001$), and SAT ($r = 0.41$, $P < 0.0001$), but not VAT ($r = 0.07$, $P = 0.417$).

Clinical risk factors for osteopenia and osteoporosis in the HIV population identified in univariate analysis included low free testosterone ($< 1.1 \text{ pg/mL}$ [lower limit of the normal range of free testosterone for women] or 3.8 pmol/L ; $P = 0.0007$), low weight ($P = 0.014$), and oligomenorrhea ($P = 0.0006$).

In multivariate regression analysis, lean body mass was most significantly associated with BMD among those with HIV. These data demonstrate that BMD is reduced among HIV-infected women in association with low weight, reduced lean mass, reduced androgen levels, and abnormal menstrual function.

Broad Institute

The Metabolic Abnormalities in College Students study has been ongoing at the CRC for several years, with Ravi Thadhani and Catherine Ricciardi as investigators. Recently they collaborated with Vamsi Mootha from Broad and his PhD research student, Oded Shaham, to measure additional metabolites, which revealed insight into insulin sensitivity and laid the groundwork for using metabolic profiling to pinpoint an individual's insulin-resistant pathway. The article "Metabolic Profiling of the Human Response to the Glucose Challenge Reveals Distinct Axes of Insulin Sensitivity," authored by Oded Shaham, Ru Weil, Thomas J. Wang, Catherine Ricciardi, Gregory D. Lewis, Ramachandran S. Vasam, Steven A. Carr, Ravi Thadhani, Robert E. Gerszten, and Vamsi K. Mootha, was accepted for publication in *Molecular Systems Biology* on June 30, 2008 and will appear in print on August 4, 2008.

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