Research Highlight

Bi-Hormonal Closed Loop System to Treat Type I Diabetes Mellitus

The development of a bi-hormonal bionic pancreas system has the potential to revolutionize the management of type 1 diabetes, easing the demand on those afflicted and on their families.

Type 1 diabetes is an autoimmune disease characterized by the destruction of beta cells in the pancreas. These cells are necessary for monitoring blood glucose and responding to high glucose levels by signaling cell uptake of glucose to be used for energy. To date, treatment has primarily consisted of frequent measurement of glucose levels throughout the day and administration of insulin as necessary. Elevated glucose levels can over time lead to complications such as kidney damage and cardiovascular disease. However, too much insulin causes hypoglycemia, a condition of low glucose levels that leads to seizures, loss of consciousness and can, in some cases, be fatal. Additionally, decisions about how much insulin to take, made multiple times each day, place a significant amount of pressure on the person administering insulin. Thus, a diagnosis of type 1 diabetes means a life-long struggle to maintain the delicate balance between diet, exercise and medication.

Faced with these demands when his son was diagnosed at 11 months old with type 1 diabetes, Edward Damiano, PhD, Associate Professor of Biomedical Engineering at Boston University set out to develop a system that more closely mimics healthy pancreatic function. Dr. Damiano’s closed loop system uses glucose values measured every five minutes. These values are then used in an algorithm, developed by Firas El-Khatib, PhD, Senior Research Scientist at Boston University, that controls dosing of both insulin and glucagon, a hormone that increases blood glucose levels. Insulin and glucagon are given through FDA-approved insulin pumps and infusion sets. This is the first bionic pancreas to use glucagon in addition to insulin to regulate blood glucose, and therefore has the ability to automatically reduce and increase glucose levels.

The clinical studies of this closed-loop system are ongoing at the Massachusetts General Hospital Clinical Research Center, under the direction of Steven Russell, MD. In 2009 Dr. Russell and his team completed a study of 20 experiments in 11 participants with Type I diabetes, each lasting 24 hours. This study, published in the Journal of Science and Translational Medicine in April 2010, demonstrated that the bi-hormonal closed loop device could achieve near normal blood glucose levels when reference quality blood glucose (BG) measurements were the input to the system. Five of the 11 study participants absorbed insulin very slowly, which led to periods of hypoglycemia. After modifying algorithm (continued...
Research Highlight (continued)

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parameters related to modeling of insulin absorption the system was retested in the same participants and found to control blood glucose levels in the participants who were slow absorbers of insulin without hypoglycemia. Blood glucose was also effectively controlled in the participants with fast insulin absorption.

The group's most recent trials of a fully automated, portable system using a minimally invasive continuous glucose monitor as the input to the system included experiments that were 48 hours long with six large meals and a period of exercise, so they were closer than anything previously published to simulating what conditions would be like in outpatient use of a closed-loop device. The large, high carbohydrate meals represent a "worst case" scenario for control, yet blood glucose was well controlled. The average BG in a group of adults was 158 mg/dl, which would translate over time into an A1c of 7.1%, extremely close to the ADA goal of 7% for people with diabetes (mean BG of 154 mg/dl). This was achieved with minimal hypoglycemia (0.7% of time), all of which was associated with mild, if any, symptoms. A trial with the same design in children 12-17 years old produced similar results.

The next planned study will include five continuous days of closed-loop control using a fully wearable automated version of the bionic pancreas during which subjects will have no restrictions on their activity or food intake and will maintain daily routines as close as possible to their usual activities while living on the hospital campus. These studies will pave the way for pivotal outpatient trials.

HCCRC News

Junior Investigator Laboratory Awards

The Harvard Catalyst Clinical Research Center recently awarded 27 small grants for laboratory funding to junior investigators across the university and its affiliated health care centers.

This is the second award program of this type supported by the Harvard Catalyst Clinical Research Center. The previous laboratory pilot grant program was conducted in early 2010. Previous awardees found the funds very helpful in obtaining pilot data in support of grant applications and publications. "I used the results from my junior investigator lab award as additional preliminary data for my R01 re-submission, which got funded," says Monika Haack, PhD, a junior investigator from the HC-CRC at BIDMC.

As with the prior grant program, this award was targeted to Junior Investigators from a Harvard Catalyst affiliated institution with a rank less than or equal to Assistant Professor with limited research funding. Projects eligible for support were investigator-initiated, human studies with samples to be analyzed at one of the HC-CRC supported laboratories:

- Harvard Catalyst Central Laboratory (HCCL), a CLIA-certified research assay laboratory
- LabCorp, a commercial laboratory contracted by Harvard Catalyst to provide routine laboratory testing
- Harvard Catalyst-affiliated institutional genotyping facilities

Awardee information can be found at http://www.brighamandwomens.org/research/cci/jrnvestrfa.asp

Congratulations to all recipients!

Awards and Honors

We would like to congratulate Jose Florez, MD PhD, Associate Professor of Medicine at Massachusetts General Hospital for receiving the Presidential Early Career Scientist Award. This is the highest honor given by the US government to science and engineering professionals in the early stages of their independent research careers.

The awards were established by President Clinton in 1996. Awardees are selected for their pursuit of innovative research at the frontiers of science and technology and their commitment to community service as demonstrated through scientific leadership, public education or community outreach.

Dr. Florez, an active HC-CRC investigator conducts his project "Study to Understand the Genetics of the Acute Response to Metformin and Glipizide in Humans" at the HC-CRC sites at Massachusetts General and Brigham and Women’s Hospital. Also, Dr. Florez is a recipient of the HC-CRC Junior Investigator Laboratory Pilot Award.
Harvard Catalyst Spotlights

**SHRINE – Shared Research Information Network**

The Shared Health Research Information Network, or SHRINE, is a web-based tool that allows investigators to request aggregate numbers of patients seen at participating hospitals who meet criteria of interest. Supported by Harvard Catalyst, SHRINE was launched in 2010 to help researchers overcome one of the greatest problems in population-based research: compiling large groups of well-characterized patients. By aggregating large numbers of de-identified patients, studies can have greater power and at the same time protect patient privacy.

Investigators who have used SHRINE call the network not only a powerful engine for research, but also a transformative tool for patient care. "Patients are treated every day, yet it can be surprisingly difficult to answer even basic questions about how well a medication is working or how often patients are diagnosed with related illnesses," said Andrew McMurry, an informatics team lead at the HMS Center for Biomedical Informatics who helped develop SHRINE. "These clinical data can help us ask better questions on a population scale." The collaboration required the approval of each Institutional Review Board and multiple safeguards to protect the privacy of 6 million patients.

Building the network required not only technological innovation but a delicate administrative dance among five hospitals that do not routinely share clinical data for research: Brigham and Women’s Hospital, Beth Israel Deaconess Medical Center, Dana-Farber Cancer Institute, Children’s Hospital Boston and Massachusetts General Hospital. "The success of SHRINE is the result of an extraordinary collaboration across the Harvard research community," said Doug MacFadden, program director for SHRINE.

This fall, Isaac Kohane, professor of Pediatrics and Health Sciences Technology, MacFadden, McMurry and their collaborators are working to extend the network to include facilities in Michigan, Texas, North Carolina, Ohio, California and Washington.

For more information about this tool:  [http://catalyst.harvard.edu/services/shrine/](http://catalyst.harvard.edu/services/shrine/)

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**CRC Updates**

**BIDMC UPDATE**

**New DXA Service**

The Nutrition Service at the BIDMC Clinical Research Center will be expanding its services in early 2012 to include DXA scanning. DXA, or Dual-Energy X-Ray Absorptiometry, is a tool to allow investigators to measure bone mineral density (BMD) and body-composition as part of research protocols.

The DEX Discovery A by Hologic offers a variety of bone density tests: AP Lumbar Spine, AP/Supine lateral Lumbar Spine, Proximal Femur, Dual Hip, Forearm Whole Body BMD, Supine lateral BMD, Scolitic Spine, Automatic Low Density spine, Automatic Low Density hip, as well as Body Composition with Sub Region analysis.

For more information about this service please contact Joanna Radziejowska, MS RD LDN at jradziej@bidmc.harvard.edu

**BWH UPDATE**

**Did you know…..**

The BWH Center for Clinical Investigation ultrasound service offers a comprehensive non-invasive assessment of cardiac and vascular structure and function utilizing both ultrasound and arterial tonometry. High-quality cardiac ECHO, brachial artery reactivity, carotid IMT, cerebral and renal resistive index, and aortic augmentation index and pulse wave velocity are available to investigators. Please contact us at cci@partners.org if you are interested in utilizing this resource.
CRC Updates (continued)

CHB UPDATE

1. Increase in Nursing ~ Starting in January, the CTSU will have a 3rd nurse on staff which will increase the available hours for nursing visits.

2. CTREC/Departmental Matching Fund Award ~ On behalf of the Clinical and Translational Research Executive Committee (CTREC), there is availability of matching funds to help pay for the costs of ancillary tests, (radiology studies, lab studies in excess of the $60 per day per patient available through Harvard Catalyst, nutritionist support, DXA scans, and other related services) for clinical trials protocols of junior investigators. For more information, click here:

   http://web2.tch.harvard.edu/ctsu/mainpageS2803P71.html

3. The Clinical Research Center ~ Effective 10/1, the CTSU and CRP have merged to a new Center. The four cores are: CTSU, Education, Design & Analysis and Development & Operations. One goal of the new Center is to help investigators navigate the CHB research maze. Whoever you contact, we’ll be sure to point you in the right direction! Click here for more information: http://www.childrenshospital.org/cfapps/research/data_admin/Site2734/mainpageS2734P0.html

4. Labs required for appointments ~ When requesting an appointment that will require labs, please indicate this in your email request. This helps us schedule your appointment appropriately.

5. Re-consenting of patients ~ Please notify the CTSU nursing staff (ivy.dang@childrens.harvard.edu or Courtney.silver@childrens.harvard.edu) ASAP if at the time of your appointment, the patient needs to be re-consented.

6. Snack Service ~ The CTSU is offering free, healthy snacks for those patients that are on the floor for more than 4 hours. Click here for a list of our options: http://web2.tch.harvard.edu/ctsu/Documents/CTSU%20snack%20menu.doc. For day-before or same-day requests, please contact Nicolle Quinn (Nicolle.quinn@childrens.harvard.edu)

GHG UPDATE

The MGH Clinical Research Center provides comprehensive nursing and nutrition support. We support studies conducted on our main unit of White 13 and our satellite unit at Building 149 of the Charlestown Navy Yard, in addition to conducting visits at sites both on the main campus and at Partners-affiliated locations outside of the main campus. These services include specialized inpatient and outpatient facilities to carry out a wide variety of studies in healthy volunteers and patients with diverse diseases, routine and specialized nursing care, routine and specialized nutrition services including assessment equipment such as DXA, treadmill and metabolic cart and services such as food record analysis and preparation of weighed meals.