



THE HARVARD CLINICAL  
AND TRANSLATIONAL  
SCIENCE CENTER

# Harvard Catalyst Clinical Research Center News

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## 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.



*Bionic Pancreas Study Team (from left) Steven Russell, MD, Firas El-Khatib, PhD, Edward Damiano, PhD, David Nathan, MD*

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

of 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

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# 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/jrinvestrfa.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 transforma-

tive 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/>

## MGH CRC Updates

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.