

# Researchers Outline Steps to Artificial Pancreas

*Automated pump shut-off in response to pending low blood sugar is one of the next advances to come.*

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BETHESDA, MD. — Diabetes researchers are slowly getting closer to one of their biggest goals: creating an artificial pancreas.

The diabetes community has long awaited the announcement that researchers have “closed the loop” by fully automating insulin delivery to mimic the function of a normal pancreas. The development of continuous glucose monitoring (CGM) in the last few years was a major step in that direction. Now, the challenge remains to coordinate the CGM sensor and insulin pump technologies so that they work in tandem as a completely automated system.

Federal health officials, along with the Juvenile Diabetes Research Foundation, met with experts from academia, industry, and other stakeholders to share state-of-the-art information and to map out the intermediate steps that will need to be taken to ultimately close the loop.

“We need people to do better with their diabetes than they’re doing now. What we’ve heard from this conference is that it can be done,” Aaron Kowalski, Ph.D., director of strategic research projects for the JDRF, said in a press briefing held at the conclusion of the conference.

“Will it be just like someone who does not have diabetes? Probably not in the near term. But people with diabetes are struggling right now. They’re having low blood sugar that can be severe. They’re getting high blood sugar that causes expensive and painful and terrible diabetic complications. We can do much, much better. There’s no doubt in my mind,” Dr. Kowalski said.

The movement has been spearheaded by the JDRF, which in 2006 launched its Artificial Pancreas Project ([www.artificialpancreas.org](http://www.artificialpancreas.org)) with the goal of speeding the development of the technology. In the fiscal year ending July 2008, the organization spent approximately 6% of its total \$165-million research budget on the project. Both that proportion of the budget and the dollar amount are expected to grow in the coming years. Included is funding for the Artificial Pancreas Consortium, which currently supports seven academic research centers for the testing of prototype closed-loop systems. Those that prove successful would then be licensed by the device manufacturers.

The JDRF also lobbies Congress for funding, and was rewarded in mid-July with the passage of a 2-year extension of the federal government’s Special Diabetes Program, with \$300 million earmarked for diabetes type 1 research, Larry Soler, JDRF vice president of government relations, said in introductory comments at the 2-day meeting.

For its part, the Food and Drug Administration had designated the development of an artificial pancreas to be a priority within its “Critical Path Initiative” in 2006 ([www.fda.gov/oc/initiatives/criti](http://www.fda.gov/oc/initiatives/criti)

calpath), said Arleen Pinkos, chair of the FDA’s Interagency Artificial Pancreas Working Group.

Since 2006, a clearer path toward the artificial pancreas has emerged. “The project evolved to a specific laundry list of problems. ... Now we know where we are going exactly, and which are the specific problems to be solved. They are well defined now, there are ideas for solutions for most of them, and they are not infinitely many,” said Boris P. Kovatchev, Ph.D., head of the section of computational neuroscience and director of the diabetes technology program at the University of Virginia, Charlottesville, during the press briefing.

Intermediate steps on that list include the following:

► **Automated pump shut-off.** It’s likely that the first piece of information communicated from the sensor to the pump will be a signal to shut off insulin delivery in response to a pending low blood sugar level, said Dr. Bruce Buckingham, professor of pediatrics at Stanford (Calif.) University and director of pediatric diabetes at Lucile Packard Children’s Hospital, Palo Alto, Calif.

In early July, the FDA approved an investigational device exemption for the study of five potential mathematical control algorithms designed to do that. In preliminary studies conducted in 42 patients at Stanford and in Denver, programming a pump to turn off for 90 minutes in response to a CGM signal of a pending low blood sugar level prevented 91% of hypoglycemic events, without inducing rebound hyperglycemia.

Those studies were done during the day, whereas all subsequent studies using the predictive algorithms will be conducted during sleep, the time when 75% of severe hypoglycemic episodes occur in children. “There’s a 6% lifetime risk of death from nocturnal hypoglycemia. If you could have a sensor with the ability to shut off insulin infusion overnight, you could potentially prevent that,” Dr. Buckingham said.

► **“Hybrid” glucose control.** Previously, Medtronic Inc. had demonstrated the feasibility of a fully automated closed-loop system in 10 adults with type 1 diabetes, using an external pump and sensor with a variable insulin infusion rate algorithm designed to emulate physiological  $\beta$ -cell action (*Diabetes* 2006;55:3344-50).

However, there were still significant postprandial glucose excursions with that system because of delays in insulin absorption associated with subcutaneous delivery, said Dr. Stuart Weinzimer of the department of pediatrics at Yale University, New Haven, Conn.

To get around that problem, Dr. Weinzimer and his associates explored the possibility of using small manual “priming” bolus doses given 15 minutes prior to meals during closed-loop control in a 34-hour study of 17 adolescents with type 1 diabetes. Mean blood glucose levels were 135 mg/dL



“We can do much, much better” at helping people who are struggling with their diabetes, Dr. Aaron Kowalski said.

“I’m pretty convinced that you need a counterregulatory hormone. In real life, tremendous precipitous drops in blood sugar can happen due to changes in insulin sensitivity in a very short space of time. ... There’s no way a machine can prevent something like that, that quickly. Glucagon works extremely fast,” he said.

His group has now begun a hu-

man study at Massachusetts General Hospital, Boston, in adults with type 1 diabetes. In addition to investigating the ability to regulate glucose levels, they will also investigate the ability of the controller to resume function in the event of a pump/infusion site failure or a sensor signal dropout, Dr. Damiano said.

► **In silico modeling.** The need for studying animal models before moving to human trials is also controversial, as animal testing is both costly and time consuming. Computer simulations of patient and device variables, also known as “in silico” modeling, can rapidly assess the feasibility of various algorithms for human trials. “In silico testing can save years,” Dr. Kovatchev said.

This spring, both the University of Virginia and the University of Padua (Italy) received regulatory approval for clinical trials of closed-loop systems based entirely on in silico testing, he noted.

► **In-hospital closed-loop systems.** Most of the initial clinical trials of closed-loop systems are taking place in the hospital setting, where patient variables can be more easily controlled than in the real world. Moreover, closed-loop technology is seen as potentially extremely beneficial for hospitalized patients themselves: Glucose control often worsens when diabetes patients are hospitalized, because of the lack of nursing staff time available for close monitoring of blood glucose levels on busy wards, said Dr. Jeffrey I. Josephs of Jefferson Medical College, Philadelphia.

Dr. Josephs discussed several investigational devices that measure glucose directly in the blood via optical sensing. Such devices, which get around the time-lag problem of interstitial fluid measurement used by current CGM devices, are—for now at least—restricted to hospital use.

Other issues and challenges discussed at the meeting include the use of closed-loop systems in newly diagnosed patients or in conjunction with islet cell transplants; behavioral considerations; what to do about radiofrequency interference and biofouling; and the potential for implantable closed-loop systems.

Dr. Kowalski noted, “This meeting really did a nice job of benchmarking where we are and where we need to go, and how this is going to have to be a collaborative effort to get there.”