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*Searching for the " molecular triggers" for diabetes prevention*

# Lauded Diabetes Researcher May be Closing in on Preventing Childhood Diabetes

*By Todd Neff*

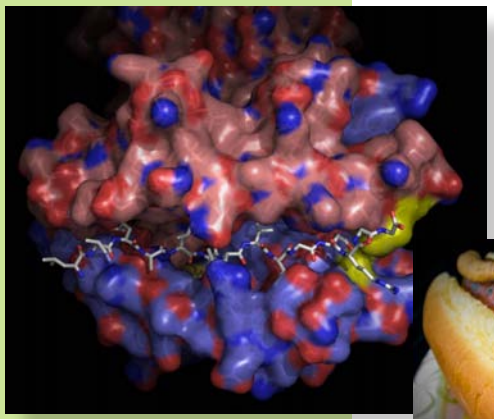
*George Eisenbarth, MD, PhD, diabetes research pioneer and executive director of the Barbara Davis Center for Childhood Diabetes.*

The Barbara Davis Center's George Eisenbarth may be on the cusp of understanding how to stop the body from killing off its own insulin-producing cells, the internal war that causes type 1 diabetes.

Eisenbarth, MD, PhD, already has helped pioneer medical science's understanding of how genetics and the body's own immune system can conspire to bring on type 1 diabetes, in which white blood cells attack insulin-producing cells in the pancreas.

***Stopping the immune system's response to a particular insulin protein may be the key to a vaccine for diabetes.***

That's one reason why in May Eisenbarth, the center's executive director and professor of Pediatrics, Medicine and Immunology at the University of Colorado Denver School of Medicine, was awarded the American Diabetes Association's highest honor, the Banting Medal for Scientific Achievement.



*The crystal structure of antigen-presenting protein I-Ag7 with an insulin peptide in its cleft. Certain immune system T cells are trained to mistake the insulin peptide for a foreign invader, attacking insulin-producing cells in the pancreas and leading to type 1 diabetes.*

*A hot dog. Eisenbarth says think of it and its mustard as the things that make insulin. The trick: make them look unappetizing to T-cells.*

It's the sort of lifetime achievement award that goes to "an individual who has made significant, long-term contributions to our understanding of diabetes, its treatment and/or prevention," the ADA explained.

But Eisenbarth isn't done yet. In addition to leading the Barbara Davis Center, which serves 5,000 children and adults with type 1 diabetes, he remains a fixture in the center's immunology lab. Thanks in no small mea-

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sure to his work, type 1 diabetes can be predicted.

Now he wants to prevent it, Eisenbarth says, and the latest science might just make it possible.

***"The really important thing is to be able to turn this into a therapy that prevents diabetes."***

Type 1 diabetes occurs when the cells in the body's pancreas produce very little or no insulin. Without insulin, the body's cells can't process sugar. That, in turn, can produce short-term problems like hypoglycemia – low blood sugar – which can trigger confusion, lethargy and even lead to coma and death. In the long-term, high blood sugar levels increase the risk of eye, kidney, nerve and heart damage and other debilitating problems.

**Like a bloodhound.** Eisenbarth says his main research interest these days is "interrupting the targeting of insulin in a safe way." Key to the effort, he believes, is interfering with the way certain T cells (a type of immune system white blood cell) interact with a particular insulin protein thought to be central to teaching T cells to attack insulin-producing beta cells in the pancreas.

Due to a genetic quirk, some T cells in the bodies of potential type 1 diabetics have receptors that recognize a particular insulin protein as a foe. If such T cells find their way to the pancreas, they start killing insulin-producing beta cells.

The thymus, where T cells are born, wipes out most of these rogue T cells, but many survive to go through what amounts to training for an attack on the pancreas. The T cells do this through encounters with a piece of the aforementioned insulin that's nestled in an human leukocite antigen (HLA) protein called I-Ag7.

HLA proteins stick to cell walls and present antigens to the immune system much as an escaped prisoner's scent might be presented to a bloodhound. The I-Ag7 protein is shaped something like a hot dog bun, Eisenbarth explains, with a long cleft in which the "meat and mustard" (the insulin piece) are presented to the T-cell receptors. The idea is to somehow make the hot dog as unappetizing as possible to T-cells to prevent them from attacking.

**Hold the mustard.** There are two promising ways to manage this, Eisenbarth says. One is to develop an antibody to block the T cell's access to the "mustard" peptide in the insulin protein – in effect, a vaccine. A second would be to develop "small molecules" to be taken as medicine. The small molecules would physically interfere with the T cells' ability to get a "taste" of the I-Ag7-bound insulin peptide.

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This is all still in the laboratory phase, Eisenbarth says, with therapies a decade or longer away from prescription pads. In the meantime, he's hopeful that clinical trials for less targeted but promising approaches to stemming or slowing the destruction of insulin-producing cells bear fruit.

The work involves collaborations with researchers all over the country. National Jewish Health researchers John Kappler and Brian Stadinski figured out the shape of the I-Ag7 insulin peptide complex; University of Florida scientist David Ostrov's group uses supercomputers to narrow a list of 140,000 possible small molecules to shorter lists of possible drug candidates.

But the idea that type 1 diabetes could tamed by highly targeted therapy – and thus, one hopes, with few side effects – is compelling, Eisenbarth says.

"The really important thing is to be able to turn this into a therapy that prevents diabetes," Eisenbarth said.

*Those with blood relatives who are diagnosed with type 1 diabetes can schedule a free diabetes screening at the Barbara Davis Center. Call 303-724-6772 for more information. In addition, National Institutes of Health clinical trials related to the prevention of diabetes and the preservation of insulin-production cells are available to relatives of patients with type 1 diabetes. Call 1-800-HALT-DM1 or visit the Barbara Davis Center web page at www.barbaradaviscenter.org.*

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