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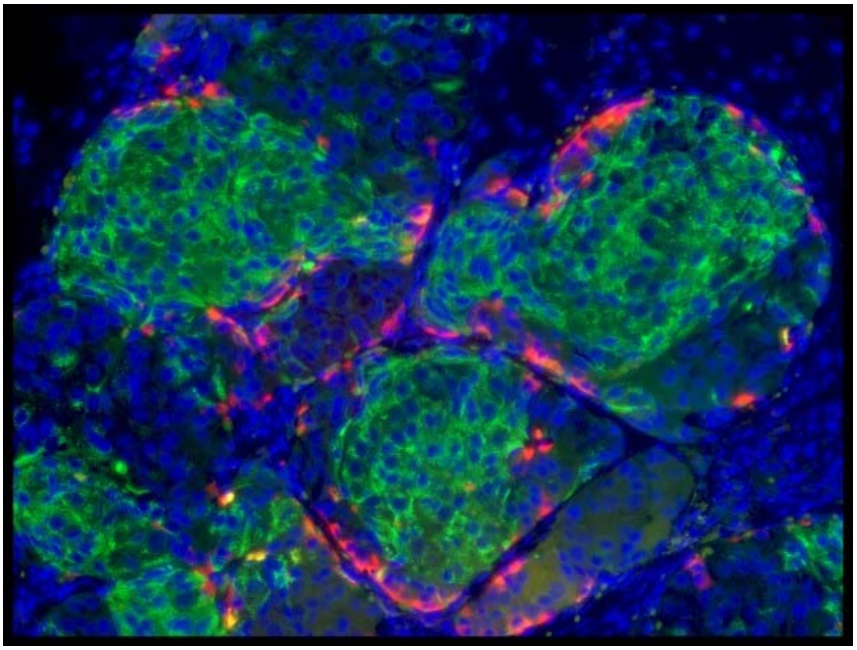
BREAKING NEWS

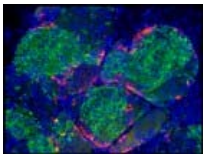
Stem-Cell Breakthrough in Treatment of Diabetes

Science



Images courtesy of Douglas Melton

The image shows human-stem-cell-derived beta cells that have formed islet-like clusters in a mouse. The cells were transplanted to the kidney capsule (the fibrous connective layer surrounding the kidneys); the photograph was taken two weeks later, by which time the beta cells were making insulin and had cured the diabetes in the mouse.



10.9.14 Print

IN WHAT MAY LEAD to the biggest breakthrough in the treatment of Type 1 diabetes in three decades, Xander University Professor Douglas Melton and colleagues have figured out the complex series of steps necessary to turn stem cells into beta cells. Beta cells are the sugar-sensing, insulin-secreting cells of the pancreas that are missing in Type 1 diabetics, casualties of the body's own immune attack on itself.

KEYWORDS

Douglas Melton, Harvard Stem Cell Institute, stem cell, stem cell and regenerative biology, stem cells, type 1 diabetes

Scientists first discovered in the 1920s that insulin is the necessary substance most diabetics lack. For decades thereafter, physicians injected the protein, which at the time was purified from animals, into patients as a treatment. In 1978, the gene for *human* insulin was cloned, says Melton, leading in the early 1980s to what is now a major industry: the production of injectable human insulin. "While there have been continual improvements in the types of

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insulins—long and short-acting—fundamentally since the 1980s, there have been no advances other than providing insulin to inject into patients," Melton explains. "This is a kind of life-support for diabetics. It doesn't cure the disease and leads to devastating and very costly complications...such as heart failure and peripheral neuropathy, and other unpleasant consequences of patients not being able to accurately control their blood sugars or their metabolism."

"We wanted to replace insulin injections" with "nature's own solution," says Melton, who has been a leading scientist in and advocate for the field of stem-cell biology ever since he switched from studying developmental biology in frogs after his young son, and later his daughter, were diagnosed with Type 1 diabetes.

He is now co-director of the Harvard Stem Cell Institute (HSCI) and co-chair of the Harvard department of stem cell and regenerative biology (in the Faculties of Medicine and of Arts and Sciences).

What Melton reports in the journal *Cell* on October 9 is that his lab, including co-first authors Felicia W. Pagliuca, Jeff Millman, and Mads Gurtler (as well as a Harvard undergraduate and others), have succeeded in developing a procedure for making hundreds of millions of pancreatic beta cells in vitro. These cells, Melton explains, "read the amount of sugar in the blood, and then secrete just the right amount insulin in a way that is so exquisitely accurate that I don't believe it will ever be reproduced by people injecting insulin or by a pump injecting that insulin."

The cells share key traits and markers characteristic of beta cells with those from healthy individuals, including the packaging of the insulin they secrete in granules. In diabetic mice, they cure diabetes right away, in fewer than 10 days, Melton reports.

The challenge of creating such cells was described in this magazine in 2004:

> Type 1 diabetes, the problem that concerns Melton, is well-suited to stem-cell therapy. It involves a single cell type, the beta cell, that is either missing or present in numbers too low to regulate blood-sugar levels. "If you could place that cell type back into a person [so] that it was not subjected to autoimmune attack, where it could be healthy and thrive, even outside the context of the pancreas, then you could cure diabetes." One current therapy for Type 1 diabetes — the Edmonton protocol —involves injecting beta cells from three cadavers into a patient's vein; the cells seed the liver and work from within that organ. But nonsteroidal immunosuppressants are required to control both autoimmune attacks and rejection of the foreign cells by the patient's body. Nevertheless, a first test of beta cells created through directed differentiation of human [embryonic stem] cells might be to use them in the Edmonton protocol. The next step might be to create a device—beta-cell tissue grown on a synthetic three-dimensional biomatrix—and encapsulate it in a Gore-Tex-like membrane that would allow glucose and insulin, but not immune cells, to pass through.

But the *how* of creating beta cells from embryonic stem (ES) cells—directing the process of differentiation in either embryonic stem cells or induced pluripotent stem cells (derived from adult cells) to make *any* specific cell type, for that matter—has eluded scientists for more than a decade. Recapitulating the normal development program in a petri dish has proven extremely complicated, because a protein signal that has a certain effect at one stage of the process—guiding an ES cell to become, for example, one of the embryonic "germ layers" such as endoderm (from which the gut, liver, and pancreas develop)—might have an entirely different effect at a later stage, or in a higher concentration, or within a different environmental niche in the body.

The discovery reported today in *Cell* was thus not the result of serendipitous biological code-breaking, says Melton, but rather of "hard work." "What we did to solve this problem is study all the genes that come on and go off during the normal

development of a beta cell in mice and in frogs and in the human material that we could get access to. Once we knew which genes come on and go off, we then had to find a way to manipulate their activity...with inducing agents." Melton and his team tested hundreds of combinations of small chemicals and growth factors before hitting on a six-step procedure in which two or three factors are added at each step, and in which the factor, its concentration, and the duration of its application all mattered.

The result was a scalable differentiation protocol that will be usable in industrial production of beta cells. "We are very excited about this," Melton says, because "it provides for Type 1 diabetics, in my view, half of the solution to their problem": victims lack beta cells, and have an immune system that attacks and kills those cells. "So problem one is replacing [beta cells], and these cells are suitable for that kind of replacement" in combination with some kind of immune protection.

Melton thanked not only the 50 or more students who have worked on this problem in his lab during the past 15 years, but also the philanthropists (including the Juvenile Diabetes Research Foundation, the Helmsley Trust, numerous donors to the Harvard Stem Cell Institute, the National Institutes of Health, the JPB Foundation, and Mike and Amy Barry) who supported it, especially during the period when government restrictions made work with human embryonic stem cells nearly impossible.

How soon could a transplant therapy protocol be ready for type 1 diabetics?

"PATIENTS ASK when these cures are coming," Melton said in a conference call with reporters, "and none of them touch me more than my own children, who ask me that all the time. I would say this. We now know we can make these cells. We have to transfer the protocol to what is called GMP, good manufacturing practice, so that it can be compliant with the very reasonable FDA regulations. So the protocol has to be done with highly purified factors. That is likely to take us about a year. And then...we have to choose the method for Type 1 diabetes that will allow us to put the cells in the patients and protect them from an immune attack."

While that could be achieved with immunosuppressants, Melton favors an encapsulation device and cited an "encouraging collaboration" with the lab of Daniel Anderson [Goldblith professor of applied biology at MIT's Koch Institute for Integrative Cancer Research], who has developed a chemically modified alginate that coats and protects islets, clusters of beta cells. Melton estimates that an encapsulation device would be about the size of a credit card.

Elaine Fuchs, Lancefield professor at Rockefeller University and a Howard Hughes Medical Institute Investigator who is not involved in the work, hailed the discovery as "one of the most important advances to date in the stem-cell field, and I join the many people throughout the world in applauding my colleague for this remarkable achievement. For decades, researchers have tried to generate human pancreatic beta cells that could be cultured and passaged long term under conditions where they produce insulin. Melton and his colleagues have now overcome this hurdle and opened the door for drug discovery and transplantation therapy in diabetes."

Jose Oberholtzer, associate professor of surgery, endocrinology and diabetes, and of bioengineering at the University of Illinois at Chicago, director of its islet and pancreas transplant program and chief of its division of transplantation, said the work described in today's *Cell* "will leave a dent in the history of diabetes. Doug Melton has put in a lifetime of hard work in finding a way of generating human islet cells in vitro. He made it. This is a phenomenal accomplishment."

Corrected 2014-10-23 *to clarify that beginning in the 1920s and for decades thereafter, physicians injected the protein purified from animals into their patients. Beginning in 1923, it was pharmaceutical companies, not physicans, who purified the insulin from animals, when the University of Toronto gave the license for producing insulin to the pharmaceutical industry.*

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MysticYooper • 6 months ago

My wife was told "they" were within five years of a cure when she was diagnosed with type 1 diabetes at age nine. Our daughter was told "they" were within five years of a cure when she was diagnosed with type 1 diabetes at age ten. She is now 27 and if this pans out to be what they say it is.... it will be the happiest day in my 58 years to see both my wife and daughter be cured and live the rest of their lives without having to do several daily injections. Thank you Professor Melton and your colleagues for not giving up....:-)

20 • Reply • Share ›

hal carnes • 6 months ago

Can the unprotected beta cells be injected into the diabetic and then be done again when they are destroyed?

11 • Reply • Share ›

Rick • 5 months ago

Great news....but just another discovery/cure for Type I Diabetics that will be swept under the rug and never to be heard again. This just in, the diabetes hospitals, drug companies, government will not allow a cure for this or any other diseases like it. Type I Diabetes is a trillion dollar business and people like myself will continue to live with it. The money makers will continue to makes trillions on all Type I Diabetics. Fact and extremely unfortunate.

8 • Reply • Share ›

عبود • 5 months ago

يارب نستفيد منكم يا كفار

5 • Reply • Share ›

lol ➔ عبود • 3 months ago

haha!

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SF • 5 months ago

I'm not in the beta cell field but I know that there was a 100 times better paper published a month before this one in nature biotech with a better protocol and way more solid data. And even those cells are not nearly as good or useful for therapy as they claim. These overselling is very dangerous for future of stem cell research as a few failed clinical trials would be enough to destroy everything and discourage future fundings...

4 • Reply • Share ›

Peter ➔ SF • 5 months ago

About the paper in Nature Biotech you mention. Who are the author/s, title of paper, Volume, Number?

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Guest ➔ Peter • 5 months ago

Nature Biotech, Sep. 11th, 2014 - Rezania et al. (Dr. Kieffer's lab) But I wouldn't say the other paper was a better protocol (if anything, it's harder, and requires a 40 day maturation period in the host, which isn't great) - but at lest in that paper they show the stem cells REVERSE diabetes, whilst Melton's paper shows it prevents onset. It probably does, or at the very least, with a few tweaks, could - also reverse the symptoms of diabetes.... but they didn't show it so...

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Kevin McDermott • 6 months ago

God Bless you Dr Melton

2 • Reply • Share ›