Embryonic Stem Cells in Trial for Diabetes

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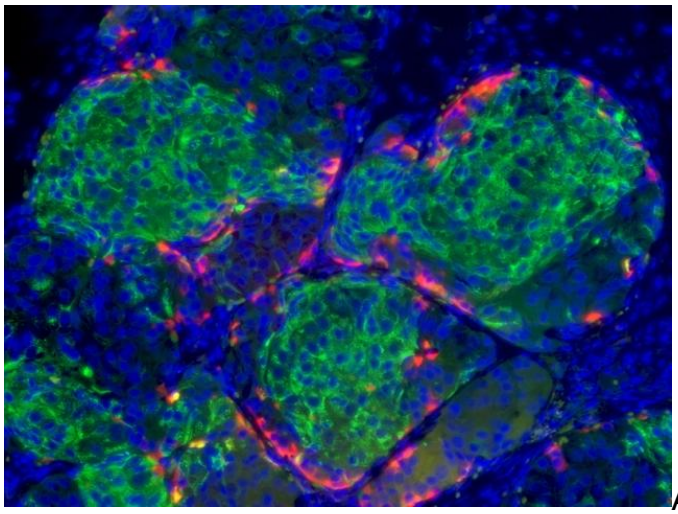 As San Diego's ViaCyte was in the midst of launching the first FDA-approved embryonic stem (ES) cell clinical trial for diabetes last week, Boston's Harvard University reported that beta cells from ES cells "cured" diabetic mouse-models.

Both teams worked for years to painstakingly recreate the natural development of pancreatic islet cells— if Harvard took it further in the dish, and ViaCyte took it further to the clinic.

"A remarkable tenacity has been displayed by these two teams, on opposite sides of the country," said Scripps Research Institute ES cell expert Jeanne Loring by email to *Bioscience.* "Both should be congratulated. This is a notable moment in the history of human stem cell research— I would dare to hope that it's the beginning of the golden age of stem cell therapeutics. Diabetes has been an important target for stem cell therapy. Ever since islets from cadavers were first transplanted in the 1990s (the Edmonton Protocol) it's been clear that a better source of islet cells would be the key to real long term therapeutic benefit."

That better source appears to be found, she said, if "we still can't use the word 'cure.'"

Harvard's 'extraordinary' pre-clinical work

The "c-word" can be used with regard to animal models--if in quotation marks--Melton feels, also speaking via email. After 15 years of systematically testing 150 combinations of more than 70 compounds in pancreas development, his team finally made fully mature beta cells from both human ES cells, and human induced pluripotent stem cells (iPSCs, pluripotent cells made from mature cells).

The final recipe, published in Cell *[1]*, was 11 compounds applied in step-

wise fashion for four weeks.

“The cells we make respond to glucose and secrete insulin, and do so multiple times,” said Melton, who has two children with diabetes. “When our cells are transplanted into mice, they ‘cure’ the mice in a few days.”

Cadaver islet cells are rare, and only last up to five years. Melton’s ES and iPS cells are robust, and can theoretically expand infinitely. His cells do need to be placed in a yet-to-be-devised capsule, to protect them from the immune system, and contain them should they go awry.

 But the field has reacted with alacrity.

“The new study of Doug Melton is a true milestone in the use of pluripotent stem cells in diabetes,” Hebrew University Stem Cell Unit Director Nissim Benvenisty told *Bioscience* via email. “The generation of pancreatic beta cells was an elusive target in the past decade. The new study demonstrates an efficient methology for generating the cells, and shows many of the characteristics of authentic beta cells both *in vitro* and *in vivo*.”

Emailed Tim Kieffer, a University of British Columbia expert in stem cells and diabetes: “I congratulate Dr. Melton’s team for this work.”

Harvard president Drew Faust issued a press statement noting she was “excited” by the “extraordinary” work.

“I’m very happy for Doug," said Loring. “He’s been working on this a very long time, and had to start from the beginning again and again. This seems to be the

inevitable requirement for figuring out how to differentiate human pluripotent stem cells. By using what is known about embryonic development of the pancreas, and applying that knowledge to cells in culture dishes, Melton's team was able to coax human ES cells into becoming pancreatic islet cells that are very similar to the cells in our bodies."

ViaCyte's 'careful' clinic-ready approach

Still, she noted, Melton has competition. ViaCyte "started working toward the same goal of treating diabetes with human ES cell-derived islets more than 10 years ago. They published [2] their method for making islet cells— less mature than the ones made by Melton's group— nearly eight years ago, and they worked for many years on designing a device to deliver the cells to the body that would allow them to thrive and not be rejected as foreign cells."

Indeed, they recently received FDA approval to give their cells to patients in immunoprotective capsules. They will implant the cells at a more immature stage than Melton's, as they found they "worked better" if allowed to mature post-transplant, in the bodies of lab animals. "This careful approach got them FDA approval," said Loring.

Melton said "the progenitors ViaCyte makes do not respond to glucose [in that earlier stage], and when differentiated in the dish, they report the cells express more than one hormone, they are polyhormonal." (Melton's final cells, as noted, repeatedly respond to glucose, and make only the key hormone regulating it: insulin. Many believe this may prove a major advantage.)

Melton added that, while his cells "'cure'" mice in days, ViaCyte's cells "'cure' the mice in a few months." A reason: ViaCyte's cells need the host environment to differentiate to a stage where they can respond to glucose.

Speaking to *Bioscience* by interview and email, ViaCyte CEO Paul Laikind and CSO Kevin D'Amour said their immature cells do not respond to glucose *in vitro,* but said they do [3] *in* vivo *[4]*. They also noted their cells take less production time *ex vivo*: two weeks to Melton's four. Their cells are highly scalable. They believe their cells' heterogeneous output may be an asset, mimicking natural environments.

They settled on that immature state years ago, they said, because accessible spots

just under the skin for ideal placement tend to be hypoxic, a condition progenitors tolerate better than mature cells.

“Our stepwise changes also mimic the developmental biology of the pancreas,” said D’Amour. He noted Melton’s work built on theirs, as Melton stated in his paper.

Elaine Fuchs, a Rockfeller University ES cell researcher, told *Bioscience* by email that “ViaCyte generated primitive endoderm cells from human ES cells that upon transplantation into athymic mice could generate islet-like structures." But, she felt, "the extent of endocrine cell formation and secretory function was not sufficient to be clinically relevant, and the mechanisms underlying the *in vivo* steps that progressed these cells to becoming fully functional mature beta cells remained unclear. Melton's group overcame these hurdles." Melton's group also "succeeded in generating theoretically an infinite supply of functional beta cells, which can now be used by basic scientists and clinicians to move therapies for Type I diabetes forward. There will be much more to learn, particularly with immune attack of host beta cells. Melton's achievement in my view is a landmark, and will long be remembered as such. They've really paved the way for facing these next challenges and overcoming them.”

D’Amour responded ViaCyte has published much work “on the robust *in vivo* efficacy of the pancreatic progenitor-containing populations (pancreatic endoderm cells). Two [5] papers establish [4] clinically relevant levels of *in vivo* function based on glucose-responsive human C-peptide and insulin in the sera of the implanted mice, as well as control of glycemia verified through graft explant. Also, in a paper [6] from University of California San Diego collaborators, C-peptide from device-encapsulated grafts is presented. These levels are very high relative to what is presented in the Melton report.”

D’Amour added that, in two [3] other papers [7], “the functional starting cell (multipotent pancreatic progenitor) is defined and the cellular differentiation transitions are characterized, establishing that the cellular intermediates *in vivo* are essentially the same as the *in vitro* protocols. What is not known is the *signals* provided by the host/environment, unlike the recent in vitro protocols.”

Certainly, the big difference right now is the fact that ViaCyte is in trial. Harvard plans to first finish designing its own capsule, and to try cells in primates. (ViaCyte did no primate studies.)

“We are screening our first patient now, as we speak,” said Laikind. “We expect to implant the cells in the next couple of weeks.” Forty patients will be treated in ViaCyte’s Phase 1 trial.

Even more competition

BetaLogics published a paper in Nature Biotechnology *[8]* four weeks ago describing similar pre-clinical success with ES cells for diabetes. Both BetaLogic and ViaCyte have agreements with Johnson & Johnson.

ES cells are also in trial for macular degeneration [9]. They are headed for trial in heart failure [10].

Video courtesy Harvard University/Mikey Segel.

Links:
[1] http://www.cell.com/abstract/S0092-8674(14)01228-8
[2] http://www.nature.com/nbt/journal/v24/n11/abs/nbt1259.html
[3] http://www.nature.com/nbt/journal/v29/n8/full/nbt.1931.html?wt.ec_id=nbt-201108
[4] http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0037004
[5] http://www.nature.com/nbt/journal/v26/n4/abs/nbt1393.html
[6] http://www.cell.com/cell-stem-cell/abstract/S1934-5909(12)00706-0
[7] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3402300/
[8] http://www.nature.com/nbt/journal/vaop/ncurrent/full/nbt.3033.html
[9] http://download.thelancet.com/flatcontentassets/pdfs/S0140673612600282.pdf
[10] http://clinicaltrials.gov/show/NCT02057900