Greater Pittsburgh Diabetes Club Newsletter
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A Cure for Diabetes: Is this Possible in the Next Decade?

Michelle Roberts, MD

It is estimated that 415 million people in the world are living with diabetes. This reflects approximately 1 in 11 of the world's adult population. The majority of people with diabetes have type 2 diabetes mellitus (T2DM), with only about 5% having type 1 diabetes mellitus (T1DM). Due to the rising incidence of obesity and sedentary lifestyles, the total number of people with diabetes is predicted to increase to over 640 million people worldwide by 2040.

Both T1DM and T2DM result from a deficiency of functional pancreatic insulin producing beta cells. The discovery of insulin in 1921 provided the first option for treatment of diabetes. Before 1921, life expectancy after a diagnosis of diabetes was little more than a year or two. Since its first clinical use in January 1922, insulin remains the only effective treatment for people with T1DM today.

In contrast, a variety of treatments are available for T2DM. These include drugs that stimulate insulin

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Watch Your E-mail for news about our Fall 2021 Program Speaker and Date

A Message from the GPDC President

Noah Lubowsky, MD
Premier Medical Associates, Monroeville, PA

Welcome to the first Greater Pittsburgh Diabetes Club newsletter of 2021. I have the pleasure of serving as President for 2021-2022, succeeding Jacqueline Wesche-Thobaben. I am lucky to be able to follow in her footsteps and am really glad to have her help in leading this group. For those who don't know me, I am a clinical endocrinologist working for Premier Medical Associates in Monroeville. I've been a member of the GPDC for 4 years and have served on the board since 2019.

Since we were unable to hold 2 meetings last year, your 2020 membership dues were rolled over and will be effective until the end of 2021.

Our spring 2021 meeting will be virtual, with Dr. Andrew Stewart speaking about beta cell regeneration for diabetes. If you attended the fall 2020 meeting with Dr. William Lowe, the platform will be the same. This program was well received and highly rated, and we expect Dr. Stewart's will be just as good. We hope you will join us. All members can view the presentation for free. The Fall 2021 meeting, date, and presenter, still to be determined, will also be included in your 2021 membership. If you know someone who is not a member, encourage them to join for just $25.

2020 was a challenging year; with several vaccines available, hopefully 2021 will be a better one. Who knows — perhaps the pandemic will be controlled well enough that the Fall meeting can be in person?

While we are all excited for better times in the upcoming year, please remember to stay safe, wear your mask, stay socially distant as much as possible, and get vaccinated when you are able.

We are looking forward to seeing you, virtually, on April 28, at 6pm. ■

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release, increase insulin sensitivity, lower renal threshold for glucose excretion, and mimic action of glucagon-like peptide to reduce blood glucose. However, none of

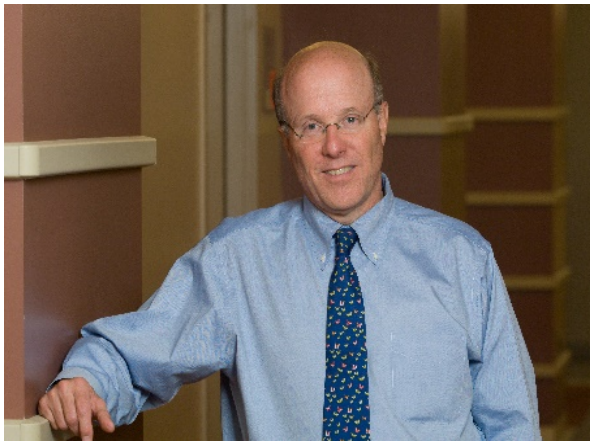
these treatments address the fundamental abnormality in T2DM, which is the loss of pancreatic beta cell mass.

Insulin-producing beta cells proliferate in humans only during a brief window beginning around the time of birth. After early childhood, beta cell replication is barely detectable. Treatment of diabetes with islet cell transplants was initially thought to be a viable strategy, but use was limited by the need for a donor pancreas and the downside risks of immunosuppression. On the other hand, targeting endogenous beta cells to induce proliferation is a novel and exciting therapeutic option for people with diabetes.

Dr. Andrew F. Stewart (former chief of Endocrinology and Metabolism at the University of Pittsburgh) currently the Director, Diabetes Obesity and Metabolism Institute, Irene and Dr. Arthur M. Fishberg Professor of Medicine, Icahn School of Medicine at Mount Sinai, NY has focused his research on identifying compounds that can induce regeneration and expansion of adult human beta cells. Using state of the art molecular screening techniques, his lab has identified a new class of human beta cell mitogenic compounds. These small molecules, known as harmines, target transcription factors that mediate human beta cell proliferation and differentiation. The goal is to induce beta cell proliferation, increase islet cell mass, and improve glycemic control.

In parallel studies, his lab has focused on gene sequencing of insulinomas. These are very rare slowly proliferating pancreatic beta cell adenomas which cause symptomatic hypoglycemia. By studying the molecular pathophysiology of these tumors, high impact mutations have been identified that may provide therapeutic targets for human beta cell expansion. Using an integrative genomics approach and state of the art computational network analysis, these studies bring us close to the elusive goal of a “cure for diabetes.”

Dr. Stewart is a dynamic and energetic speaker and we look forward to his visit at our virtual meeting on April 28, 2021 ■



Dr. Andrew Stewart, Director, Diabetes, Obesity and Metabolism Institute, Irene & Dr Arthur M. Fishberg Professor of Medicine, Icahn School of Medicine at Mount Sinai, NY

Pancreatic Acinar to B-cell Conversion in mice and non-human primates

Dr Farzad Esni, Ph.D
Associate Professor of Surgery, University of Pittsburgh
UPMC Hillman Cancer Center
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Diabetes is a syndrome defined by high blood glucose levels caused by either reduction in number of insulin-producing cells (Type 1 diabetes), or the ability of our cells to respond to insulin in combination with declined numbers of insulin-producing cells (Type 2 diabetes). Thus, a cure for diabetes should entail replacement of insulin-producing β-cells. There have been tremendous efforts throughout the years to generate β-cells from different sources, not only from embryonic stem cells, and adult stem or somatic cells, but also from non-β-cells residing in the pancreas. One such cell type is the amylase-producing pancreatic acinar cell. These cells are primarily responsible for producing and secreting enzymes that would help us digest the food we eat. Reprogramming of acinar cells toward functional β-like cells would offer an abundant and autologous source of insulin-producing cells.

In the past six years, Dr. Esni’s research group has generated data demonstrating that genetic as well as pharmacological inactivation of focal adhesion kinase (FAK) results in trans-differentiation of pancreatic acinar cells into insulin-producing cells. Notably, the acinar-derived insulin producing (ADIP) cells infiltrate the pre-existing endocrine islets and are able to restore normoglycemia in non-autoimmune **diabetic** and **non-human primates**. The advantage with this approach is that first, unlike embryonic stem cells or iPS cells; there is no

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Are Stem Cell Therapies for Type 1 Diabetes on the Horizon?

Jagdeesh Ullal, MD

Clinical Associate Professor of Medicine, UPMC Center for Diabetes and Endocrinology

Type 1 diabetes is characterized by loss of beta cells of the islets due to autoimmune destruction. The cure for type 1 diabetes has long been discussed and one form of this is pancreas transplantation or islet transplantation. However, donor pancreata are becoming increasingly limited. There is a shortage of islets derived from human organs and the cost and complications associated with transplantation are high. The first pancreatic transplant was performed in 1966. Approximately 50,000 pancreas transplants have occurred across the world till 2015 based on the international pancreas transplant registry. Stem cell therapy offers a potential cure because these cells can multiply, differentiate into specialized cells and regenerate. Over the past two decades, intense studies have been conducted towards the development of insulin-producing cells (IPC) in vitro from human multipotent stem cells. The cells are referred to as islet organoids and are either human embryonic stem cells or human-induced pluripotent stem cells. Adult stem cells and differentiated status cells from mature tissue have been trans-differentiated into insulin-producing cells in vitro. Embryonic stem cells (ESC) are pluripotent cells derived from the inner cell mass of blastocysts. These cells possess an infinite capacity to multiply and differentiate into multiple types of adult cells in vitro and have the capacity for self-renewal. Induced pluripotent stem cells (iPSC) are adults' cells that are re-programmed into embryonic stem cell-like states by the introduction of genes that convert these cells into cells that resemble embryonic stem cells. This technique is called nuclear reprogramming and involves inducing a change in the nucleus of an immature cell that can be maintained and replicated through the process of mitosis. At the molecular level, iPSC and ESC appear indistinguishable but genomic analysis revealed subtle differences in therapy genetic methods relation between the 2 types of stem cells. There is experimental evidence to suggest that individual iPSC lines of cells are epigenetically unique and can give rise to a specific lineage of cells. Thus, this can prove challenging in testing that clinical behavior and in vivo human studies.

The first trial of stem cell therapy clinical trials was conducted in 2015 but was met with failure due to poor cell survival and vascularization. A subsequent study in 2017 showed some success in about 30% of transplanted patients. Trials are about to commence with human ESC-derived multipotent pancreatic progenitors and immature hormone-producing cells. The upcoming trials will test islet-like organoids which will be delivered through the portal vein and bolstered with an immunosuppressive regimen. Preclinical studies with this method have revealed a 60% reduction in insulin requirement. Newer methods include the use of micro-and macroencapsulation devices that cloak the transplant from the immune system. Transplant surgeon Dr. Martin Wijskstrom from the UPMC Starzl Transplantation Institute is partnering with UPMC Endocrinology in conducting the next generation of Stem cell transplantation therapies and is actively recruiting patients with type 1 diabetes.

Stem cell therapies are becoming a tangible reality. There appears to be some advantage of iPSC over ESC in terms of alloimmunity but tends to be more time-consuming and potentially more expensive. Currently, immune evasive cell lines are being studied opening yet another frontier in this field. A tremendous effort is now necessary to prove the safety, efficacy, durability, and cost-effectiveness of stem cell therapies. This decade is going to prove to be an exciting one in this endeavor.

References:

https://stemcells.nih.gov/info/Regenerative_Medicine/2006Chapter10.htm (accessed 3/23/21)

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Dr. Ullal can be reached at ullalj@upmc.edu OR call the Study Coordinator, Shari Reynolds at 412-383-0570 for more information about his research or to refer patients for the Type 1 Diabetes Stem Cell Therapy Clinical Research Trials.

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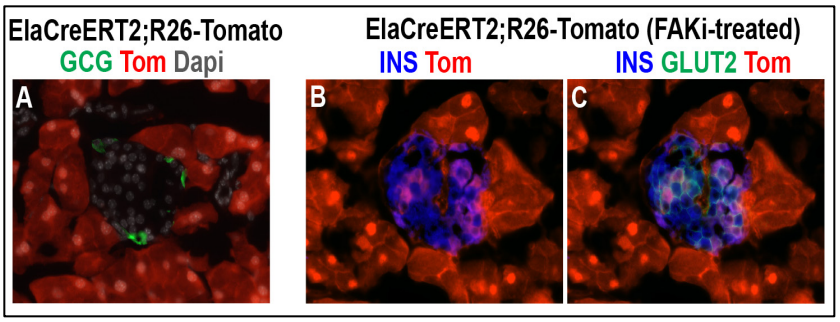
need to initially direct pancreatic acinar cell toward the pancreatic fate. Second, inhibition of FAK-function converts acinar cells, which represent the majority of cells in the pancreas, into functioning insulin-producing cells in vivo without genetic modification or viral-based therapy. Third, this approach does not involve any surgical procedure. Fourth, since the compound used in this study to inhibit FAK is already in several clinical trials for cancer therapy, the timeline for a potential transfer to a clinical trial for diabetes will be significantly reduced. Finally, as this study entails autologous acinar cells converting into insulin-producing cells, there is no risk for an alloimmune rejection of the newly formed β-like cells.

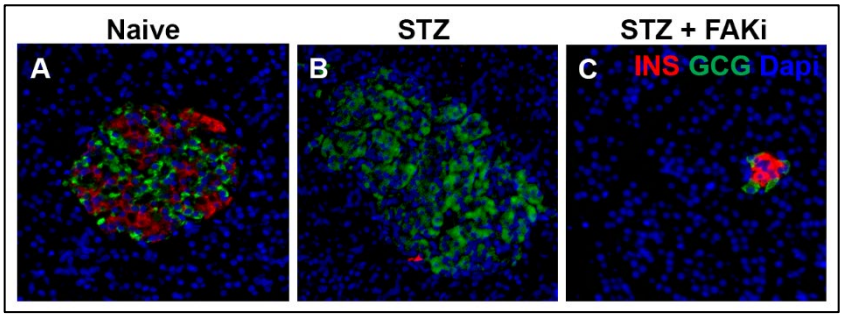
Despite these encouraging results, the questions remain: (i) what is the mechanism resulting in this conversion; (ii) would the ADIP cells be recognized and attacked by the immune cells in a type 1 setting, and perhaps more importantly (iii) could FAKi treatment convert human acinar cells into insulin-producing cells? Dr. Esni's research group is determined to find the answers to these questions in the upcoming years. He is funded by the NIH to study the effect of FAKi treatment on acinar-to-β-cell conversion in an autoimmune setting. If successful, the outcome of these studies should position them well in preparation for clinical trials in humans with diabetes.

Declaration of Interests: *Dr. Esni has a US national phase patent for the use of FAK inhibition in diabetes treatment.*

You may contact Dr. Esni at farzad.esni@chp.edu www.esnilab@pitt.edu ■



Pharmacological inhibition of FAK converts acinar cells into insulin-producing cells. *(A) Tamoxifen treatment in ElaCreERT2;R26^{Tomato} mice specifically labels the acinar cells (red cells). Glucagon staining has been used to highlight the periphery of an endocrine islet. (B) Immunostaining for insulin shows Tomato^{+}/insulin^{+} cells in the pancreas of ElaCreERT2;R26^{Tomato} mice treated with FAK inhibitor. (C) Immunostaining showing that the infiltrating Tomato^{+}/insulin^{+} cells also express Glut2, which is found in mature β-cells.*



Pharmacological inhibition of FAK induces β-cell neogenesis in diabetic NHP. *Treatment of a **diabetic NHP** with FAKi for only 8 days resulted in 50% reduction of exogenous insulin dependence. The NHP gained weight and maintained similar blood glucose levels without additional treatments until it was euthanized 4 months later. (A-C) Immunostaining for insulin (red) and glucagon (green) in the pancreas of control (A), STZ-treated diabetic (B) or STZ- and FAKi-treated recovered (C) NHP.*

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