JDRF Center of Excellence in Northern California Progress Report Fall 2020

Executive Summary

The JDRF Center of Excellence in Northern California brings the scientific expertise of Stanford University and the University of California, San Francisco (UCSF) together to enable **stem cell-based cures for type 1 diabetes (T1D)** by identifying and targeting the interactions between the immune system and the beta cells. The discoveries will then be applied to approaches and technologies used to reset and control the immune system.

Over the last 12 months, this Center, led by **Matthias Hebrok, Ph.D. (UCSF)**, and **Seung Kim, M.D., Ph.D. (Stanford University)**, has made significant progress toward its scientific goals and setting an example of intra-institutional collaborations in T1D. Overall, the Center researchers will work to:

Analyze the interactions between the immune system and beta cells to illuminate the processes driving development of T1D, helping to reveal a path to therapies	Generate islets and immune cells from stem cells as the basis for next-generation cell therapies	Develop an islet transplant protocol that will induce tolerance and not require immunosuppression

Research Progress to Date

Project 1: Leveraging New Technologies to Create Stronger Beta Cells

Project 1 is modeling the interactions between beta and immune cells in mice and in the lab to learn how these cells communicate and how to prevent beta cell destruction by the immune cells. This information is key to generating therapies that prevent beta cell loss in people with T1D.

This project is a collaboration between **Matthias Hebrok, Ph.D.**, **Jimmie Ye, Ph.D.**, **Julie Sneddon, Ph.D.**, **Qizhi Tang, Ph.D.**, and **Alex Marson, M.D., Ph.D.** These investigators are using the most advanced science and technology to investigate how the immune cells interact with beta cells in the human pancreas to obtain genetic information from each single cell and to determine the spatial distribution within the tissue.

One example is the work being done by Drs. Parent, Tang and the Hebrok group focuses on the cloaking of beta cells to prevent immune recognition. If the immune system does not recognize transplanted beta cells as foreign and can spare them from rejection, these beta cells can remain safe and continue to produce insulin. Through their experiments in mice, they have generated and tested stem-cell derived beta cells that are less

immunogenic, meaning they are less likely to be attacked by the immune cells.

Another example of this team's progress is their work into generating engineered immune cells from human stem cells (hSC). **Linda Vo, Ph.D.**, and **Jeff Bluestone, Ph.D.** continue to make T cells (immune cells) and **Qizhi Tang, Ph.D. and Mark Anderson, M.D. Ph.D.** are focusing on identifying the key molecular components from T cells, referred to as T cell receptors, that are responsible for specifically recognizing and targeting beta cells in T1D. The goal is to engineer T cells that can recognize insulin-producing beta cells and to learn how T cells trigger the autoimmune attack and destruction of beta cells.

Dr. Anderson and colleagues are testing if selected gene mutations found in humans are associated with developing T1D. Since the last report, they have made impressive findings into specific gene mutations that appear to provoke and accelerate autoimmune diabetes in both humans and a mouse model engineered to carry the same gene mutation. They have also determined other gene mutations in humans that can be transmitted in families and may contribute to T1D. The team will continue to investigate these mutations to further define the mechanisms underlying human T1D formation.

Additionally, Dr. Tang, who is focused on designing immune cells that can protect beta cells from immune attacks. These specific immune cells, if successfully engineered, would protect the transplanted beta cells. Dr. Tang has produced several viable candidates to achieve this goal. Once verified, these immune cells can be incorporated into the work being done by Dr. Vo and combined with their stem cell derived beta cells (all from the same genetic source). Dr. Tang and colleague will continue to evaluate the functionality of these cells in vivo in islet transplantation.

Project 2: Increasing Successful Islet Transplantations

The study, led by **Seung Kim, M.D., Ph.D.** with **Judith Shizuru, Ph.D.**, and **Everett Meyer, M.D., Ph.D.**, builds on the team's success in solid organ transplantation, and consists of transplanting a combination of allogenic islet cells from donors and hematopoietic stem cells (HSC), which are stem cells that live in the bone marrow that turn into mature blood cells. The team is assessing whether this mixed approach of host and donor stem cells, called mixed chimerism, will help reduce the rejection of transplanted beta cells. They are also optimizing the protocols required for testing the new transplant therapy in laboratory animals. This is a required step to maximize the efficiency and reliability of any future human clinical trials.

Since the last report, this group has successfully established a NOD (non-obese diabetic) mouse colony for studies of islet transplantation that are ongoing. They are working with researchers at The Jackson Laboratory in Maine, a lead research organization creating mouse models of human diseases and disorders, where they now have 87 mice awaiting conditioning, HSC transplantation and islet transplantation--the only line of mice needed for the specific study.

Due to the complexity of the gene modifications that these mouse colonies entail, researchers have also generated a new method for genotyping, which is the process of determining differences in the genetic make-up of an individual by examining the individual's DNA -- and confirming the accuracy of the modifications -- a crucial step for performing transplantation studies in the coming year.

Thank You

On behalf of the 1.6 million Americans diagnosed with T1D and their loved ones, we thank you for your generous support of the JDRF Center of Excellence in Northern California.

For more details about this JDRF Center of Excellence and to view previous progress reports, please visit: https://www.jdrf.org/impact/research/centers-of-excellence/northern-california/

We look forward to sharing additional updates on the impact of your philanthropy in 2021.

Thank you and happy holidays!