JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

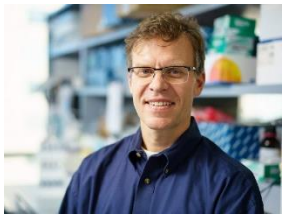
JDRF Center of Excellence in Northern California Progress Report 2022

Executive Summary

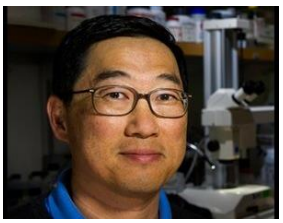
Two years ago, the generous support of JDRF donors helped launch the **JDRF Center of Excellence in Northern California.** This Center marks the first project in JDRF's 50-year history that formally unites academic institutions to form a high-impact research partnership toward accelerating cures for type 1 diabetes (T1D).

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

In the last two years, 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.



Matthias Hebrok, Ph.D.



Seung Kim, M.D., Ph.D.

Research Progress to Date

The JDRF Center of Excellence in Northern California is building on recent advances and state-of-the-art technologies to overcome the remaining challenges in bringing cell replacement therapies to market. Utilizing and combining expertise in stem cell biology, immunology, and computational biology, researchers aim to discover and test new approaches to prevent beta cell loss after transplantation and the rejection of transplanted islets and eliminate the need for recipients to receive chronic immunosuppression. Below are highlights of their current progress.

Project 1: Leveraging New Technologies to Create Stronger Beta Cells

In the first project, the teams are using several approaches to understand how the immune system affects the formation of T1D and how we may use these insights to develop cures. For example, **Linda Vo, Ph.D., and her team** are generating human stem cell-derived immune cells (T cells) that can be used in tandem with beta cells to protect them from the immune attack after transplantation. There is a subtype of immune cells, named regulatory T cells (Tregs), that can dampen the immune response induced by the transplanted beta cells and consequently can protect beta cells from the immune attack. Dr. Vo has successfully identified the initial step for making Tregs from human stem cells and is actively testing ways of completing the process. This novel method to protect insulin-producing beta cells is early in stages but, if successful, would help accelerate the development of cell-based cures for T1D.

Another collaborative team at UCSF consisting of **Dr. Hebrok, Jimmie Ye, Ph.D., Julie Sneddon, Ph.D.,** and **Alex Marson, M.D., Ph.D.,** is investigating how immune cells interact with beta cells in the human pancreas to obtain genetic information at the cell level and determine the spatial distribution of each cell within the pancreas. The team is currently conducting novel 3D imaging studies of the pancreas architecture in T1D to reveal how immune cells infiltrate the pancreas and distribute around the beta cells. Securing such detailed information from isolated single cells will be key to decoding interacting signals between the different cell types within the islet and, most importantly, interactions between islet cells and the specific immune cells that invade the pancreas leading to T1D. As an initial validation step, the team has performed a deeper analysis of gene expression data using the mouse pancreatic tissue and have started experiments on healthy adult human pancreas tissue.

Another team led by **Qizhi Tang, Ph.D.,** is working on controlling immune tolerance to the islets in T1D by capitalizing on Tregs. This team uses an innovative approach to create “smarter” Tregs by using a chimeric antigen receptor (CAR) approach. This approach of reprogramming T cells has been used in the cancer field to target T cells to specific tumor tissue. Here, Dr. Tang’s team is developing Tregs that express a CAR that can specifically suppress the immune response in the pancreatic islets.

Project 2: Cloaking Beta Cells

The project led by **Audrey Parent, Ph.D., Dr. Tang, and the Hebrok group** continues to work on hiding, or “cloaking,” 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. Previously, the team generated immunoengineered stem cells that are less immunogenic when transplanted in mice, meaning they are less likely to be attacked by the immune cells. However, these cells had not yet been differentiated into insulin-producing beta cells. Through their experiments in mice, they have generated and tested stem-cell-derived beta cells. Most recently, they have validated that their genome strategy of “cloaking” these beta cells does not result in a decrease in insulin production and impair their function—which is hugely important. There is no use generating cloaked cells if that process renders them ineffective.

Complementing this work, **Dr. Tang and her team** are identifying key molecular components from T cells, referred to as T cell receptors (TCR), that are responsible for recognizing and targeting beta cells in T1D. Their goal is to engineer T cells that can recognize insulin-producing beta cells and learn how T cells trigger the autoimmune attack and destruction of beta cells.

Work in Dr. Tang's lab in the previous two years has focused on three HLA-restricted TCRs reported to be specific for beta cells. The key learning has been that selected TCRs should meet three criteria: have high specificity, high affinity, and target highly abundant antigens in the islets. Based on these criteria, Dr. Tang will focus her research on one selected TCR. They have made impressive findings into specific gene mutations that appear to provoke and accelerate autoimmune diabetes in both mice and humans, a critical step in understanding how T1D works. They have also made an important discovery of which gene mutations in humans may contribute to T1D and can be transmitted in families. Having identified the pathway to target, these researchers are now testing a specific therapy, JAK inhibitors, to see if it can halt the progression of T1D.

Parallel to this work, they have recently generated a similar mouse model with a gain of function mutation in STAT1, which is also linked to many cases of type 1 diabetes. This model will also be tested for mechanisms by which type 1 diabetes occurs on how JAK inhibition can alter the course of the disease.

Project 3: Increasing Successful Islet Transplantations

Researchers at the JDRF Center of Excellence in Northern California focus on developing ways to increase successful islet transplantations.

Led by **Dr. Kim** with **Judith Shizuru, Ph.D.**, and **Everett Meyer, M.D., Ph.D.**, one strategy builds on the team's success in solid organ transplantation and consists of transplanting a combination of allogenic islet cells, which are islets from donors, and hematopoietic stem cells, 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.

Drs. Kim and Shizuru have made excellent progress in demonstrating the effectiveness of their strategy. The team is working on adapting these protocols in specialized T1D mouse models.

The generation of this novel mouse strain by the Kim lab addresses an important need in the diabetes community: an immunocompetent mouse strain with a genetic modification, allowing for efficient induction of diabetes without the side effects and variability that may be observed using alternative ways of making mice diabetic, such as treating mice with the chemical drug streptozotocin (STZ). The suitability of this mouse strain as a transplant recipient was confirmed by an islet transplant experiment using the islet allograft tolerance induction by mixed chimerism. The

Kim and Shizuru labs have made excellent progress in demonstrating the efficacy of an innovative conditioning regimen and cell transplant protocol for achieving mixed chimerism and islet graft tolerance. This team's work is crucial to help create a pathway to translate laboratory advances into achieving a cell-based cure for T1D.

Thank You

On behalf of the 1.4 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. We look forward to sharing more exciting updates on the impact of your philanthropy in 2023.