JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

JDRF Center of Excellence in Northern California Progress Report Spring 2020

Executive Summary

Last fall, generous JDRF supporters provided the seed funding to launch the **JDRF Center of Excellence in Northern California.** This is the first JDRF Center of Excellence in our 50-year history that formally unites academic institutions to form a high impact research partnership. The JDRF Center of Excellence in Northern California combines the scientific expertise of Stanford University and the University of California, San Francisco (UCSF) to accelerate cures for type 1 diabetes (T1D).

Backed by JDRF supporters, research in T1D has led to critical advances in two key areas: beta cell therapy and immune therapy. Bringing these fields together, researchers at the JDRF Center of Excellence in Northern California are building on the current momentum 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 approaches and technologies used to reset and control the immune system.

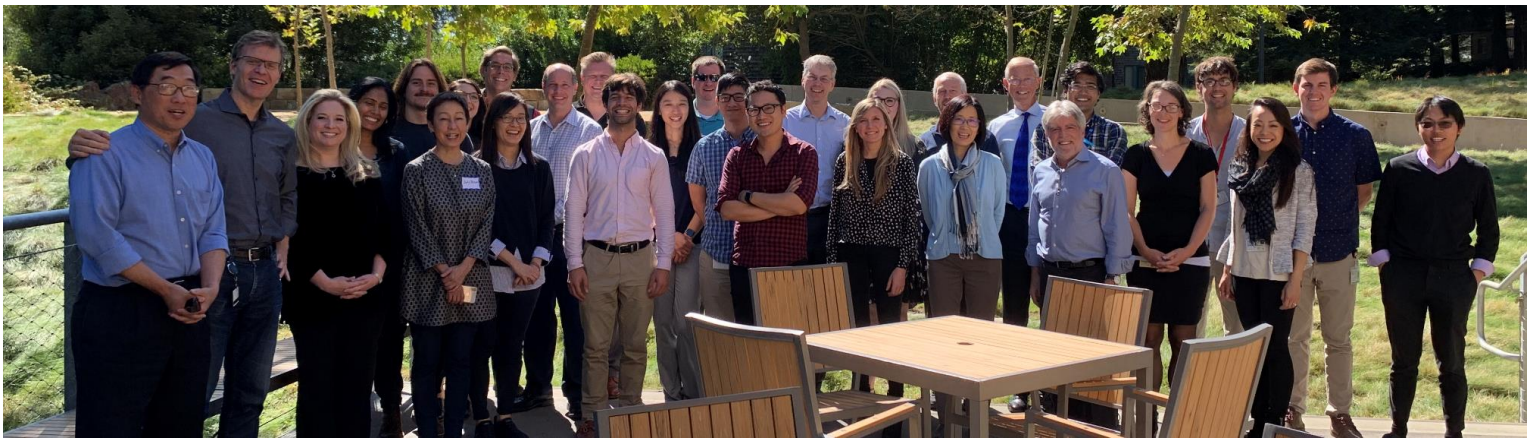
Led by **Matthias Hebrok, Ph.D. (UCSF)**, **Seung Kim, M.D., Ph.D. (Stanford University)**, and advised by **Esther Latres, Ph.D. (JDRF),** the **JDRF Center of Excellence in Northern California** aims to:

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

Right People + Right Opportunities = A Cure Accelerator

Islet transplantation has proven to be a viable cure for T1D since the late 1990s, but it is currently not widely available, because of a limited cell source (reliant upon organ donation) and the need to take immunosuppressive drugs for the recipient's lifetime. **Dr. Matthias Hebrok**'s team has developed a method to generate insulin producing beta cells from stem cells, which brings us closer to providing a reliable source of cells for transplantation.

JDRF Center of Excellence in Northern California is building on recent advances and state-of-the-art technologies to overcome the remaining challenges. The researchers are utilizing and combining expertise in stem cell biology, immunology and computational biology to discover and test new approaches aimed at preventing beta cell loss after transplantation and rejection of the transplanted islets, as well as eliminating the need for recipients to receive chronic immunosuppression.



*The JDRF Center of Excellence in Northern California team is led by **Drs. Seung Kim** and **Matthias Hebrok** (on left). They are joined at UCSF by: **Drs. Mark Anderson, Jeffrey Bluestone**, **Alexander Marson**, **Audrey Parent**, **Julie Sneddon**, **Qizhi Tang**, **Linda Vo** and **Jimmie Ye**. At Stanford, **Drs. Kyle Loh**, **Everett Meyer** and **Judith Shizuru** are part of the JDRF Center of Excellence in Northern California.*

Research Progress to Date

The JDRF Center of Excellence in Northern California is creating a model for effective cross-institutional collaboration to accelerate basic and translational research in T1D. Toward that goal, Center scientists are working together to understand the critical signals and processes involved in the initiation and progression of T1D and most importantly, the guided recognition of beta cells by immune cells that invade human islets and the surrounding pancreatic tissue.

As a first step, the JDRF Center of Excellence in Northern California has implemented two project teams referred to as Projects 1 and 2 as well as the supporting Cores A, B, and C. Administrative Core A, led by Drs. Seung Kim and Matthias Hebrok, will coordinate center activities including education, outreach, data storage and sharing, interaction among center members and reporting to JDRF. For example, the teams at UCSF and Stanford have already established regular team meetings between **Jeffrey Bluestone, Ph.D.**, and **Qizhi Tang, Ph.D.**, to discuss reagents *(a substance or mixture added to a system to cause a chemical reaction)*, and animal and experimental support.

Cores B and C, the research cores, will focus on supporting the scientific projects. The goal of these cores is not only to help synergize members from UCSF and Stanford but to make research and administrative activities more efficient.

Project 1: Leveraging New Technologies to Create Stronger Beta Cells

Advances in modern imaging technologies now allow for the visualization of signals on immune and beta cells in tissues from people with T1D, information critical in defining those signals that likely guide recognition of beta cells by immune cells. Project 1 will coordinate activities related to generating functional insulin-producing beta cells and immune cells from human stem cell populations with the intent of implementing gene editing approaches.

The Project 1 team will utilize these recently available technologies to understand the interactions between immune and insulin-producing beta cells that contribute to T1D development. The team will leverage these state-of-the-art technologies to determine the signals and signaling pathways involved in the immune/beta cell interactions with the goal of defining those that are critical for the initiation and progression of the disease. This team will catalog the relevant information, as well as modify expression of candidate factors in human stem cell derived immune and beta cells. What they aim to do is to understand:

1. How does the immune system recognize and trigger the destruction of beta cells?
2. Which are the genes/factors responsible for immune cell activation upon interaction with beta cells?
3. How can we identify genes/factors in human beta cells responsible for immune destruction?

Project 1's goal is to model immune/beta cell interactions in cell culture *(the process by which **cells** are grown under controlled conditions – e.g. in a lab)* and in mice to learn about how the cells communicate and how one might be able to perturb such cross talk to block beta cell destruction. This information would serve as the foundation for translational efforts aimed at generating therapies that prevent beta cell loss in people with T1D. For example, **Matthias Hebrok, Ph.D. with Jimmie Ye, Ph.D.**, **Julie Sneddon, Ph.D.**, **Qizhi Tang, Ph.D.,** and **Alex Marson, M.D., Ph.D.**, — lead investigators at UCSF with expertise in immunology, bioinformatics, human genetics, stem cell and beta cell biology and genome engineering — are combining their unique technologies to investigate how the immune cells interact with beta cells in the human pancreas.

One project currently underway is generating novel 3D imaging studies of the pancreas architecture in T1D, which will reveal how immune cells infiltrate the pancreas and distribute around the beta cells. While the ultimate goal is to investigate tissues from human pancreata, the team has been testing and optimizing the molecular and imaging methodologies using tissue from a T1D mouse model named non-obese diabetic or NOD. Once these technologies are optimized and validated in the NOD mouse model, the team will transition to test and investigate tissue from human pancreata.

To complement the imaging study, the team has been optimizing a technology to isolate and obtain molecular information from pancreatic islets at the single cell level. Securing such an up-close level of 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 unique immune cells that invade the pancreas. The team expects to have the first set of data analysis from the NOD mouse studies in the next few months.

The team will also build on the exciting progress made generating engineered immune cells from human stem cells (hSC). **Linda Vo, Ph.D.**, and **Jeff Bluestone, Ph.D.** have started making T cells (Immune cells) from hSC, 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.

The next round of experiments will be really interesting and innovative as the team will attempt to generate both immune T cells and insulin-producing beta cells from the same source of human stem cells. Stem cells can be differentiated into different lineages including immune cells and insulin-producing cells. By combining these human stem cell-derived T cells and beta cells in a petri dish and mimicking what occurs in T1D, the team will gain useful information on how to improve development of cell replacement therapies. Ultimately, these researchers aim to use gene editing technologies to make immune and beta cells for improved cell therapy.

Project 2: Increasing Successful Islet Transplantations

Project 2 will support the immune modulation and islet transplantation efforts. This includes the optimization of mouse models of autoimmunity and alloimmunity *(an immune response to nonself antigens from members of the same species)*, as well as supporting the procurement of immune cells from blood and bone marrow, which is required for the Center's unique "mixed chimerism" transplant approach. This team aims to modulate immune cell function to assist their translational efforts designed to optimize current islet replacement procedures. Their recent studies demonstrate how targeted elimination of bone marrow cells can increase islet transplantation efficiency. This technique, known as "mixed chimerism" for islet replacement would benefit from the team's ability to generate and manipulate the functionality and specificity of human T cell populations, in particular T regulatory cells known to modify activities of other immune cells. By combining gene editing, stem cell differentiation, and ablation of bone marrow cells, the Center team anticipates being able to optimize current islet transplantation strategies for people with T1D.

In addition, this group has already made progress on developing a clinical islet transplant protocol that will allow for the survival of insulin-producing cells without the need for chronic immunosuppression therapy. A major barrier to the successful transplantation of organ or cells is rejection by the recipient's immune system. Immunosuppressive drugs can prevent rejection but are associated with increased risk of undesired effects (e.g. infections, tissue damage). As an alternative approach to remove the need for strong immunosuppressive drugs, is the transplantation of organs or cells with selected immune cells from the same donor, which can result in a state of "immune tolerance" or absence of rejection.

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. The team is assessing and optimizing the protocols required for testing the new transplant therapy in laboratory animals. This is the first step required to maximize the efficiency and reliability of any future human clinical trials.

Furthermore, since the launch of this JDRF Center of Excellence in fall 2019, these researchers have selected the optimal combination of mouse strains to mimic the allogenic transplant setting that would occur between a human donor and a transplant recipient. This initial step will help enable the team to reach for their goal of eventually using lab-engineered islets developed by Dr. Hebrok's team instead of relying on donor islets. In addition, the team has successfully isolated hematopoietic cells (HSC) from the bone marrow and islet cells from donor mice, and transplanted them into a mouse recipient without any immunosuppression drugs. This

is an exciting development and the team is currently assessing lack of rejection and long-term survival of islets in transplanted mice. There will be additional exciting progress to come in the next reporting period.

Lastly, this Center started generating T1D mouse models that are more suitable to test and validate the Center's transplantation approach. The mouse colony is expanding, and it should be large enough in the next few months to start transplant experiments.

The progress above exemplifies the commitment and excitement of the researchers participating in the JDRF Center of Excellence in Northern California.

COVID-19 Impact on Research

As we continue to address the devastating impact of COVID-19 on JDRF funded research and the T1D community, JDRF's mission and commitment to people with T1D and their loved ones remain unwavering. Our efforts to cure, prevent, and treat T1D and its complications are more relevant than ever.

Some of the research progress with the JDRF Center of Excellence in Northern California has slowed, ever so slightly, due to the partial closure of labs and clinics during the stay at home ordinance. However, the investigators have been working remotely to maintain momentum and are anxious to get back into their labs full time.

The JDRF Center of Excellence researchers are deeply grateful for your commitments and, given all the challenges we are facing due to COVID-19, they want to extend a heartfelt thank you for stepping up to support this life changing work.

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. We look forward to sharing additional updates on the impact of your philanthropy in fall 2020.