JDRF Israel Initiative
Progress Report

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Spring 2014

JDRF: BUILDING A WORLD WITHOUT TYPE 1 DIABETES

JDRF is extremely grateful for your generous support, which has led to significant progress in type 1 diabetes (T1D) research in 2013. The following pages provide details on some of the strides JDRF has made in the past year.

JDRF's vision for the future is a world without T1D, where normal physiology, including reversal of complications, is restored for all those who live with the disease. This is also a world where universal childhood prevention exists, so that no one ever again suffers the day-to-day challenges of living with T1D or its long-term complications.

JDRF's T1D research programs have made extraordinary advances during the past decade and have increased our understanding of the disease. We are now able to detect antibodies in at-risk individuals long before they are diagnosed, identify genetics that create predisposition to the disease, and even slow the autoimmune attack in newly diagnosed individuals to maintain insulin production for some time after diagnosis. Thanks to the generosity of JDRF donors such as you and the commitment of researchers worldwide, we have made remarkable progress. Yet our vision still remains in the future.

JDRF believes that achieving this vision will require a multi-decade effort during which significant therapeutic advances must be developed to reduce the impact of T1D on people living with the disease and those who care for them. By focusing on the delivery of increasingly effective therapies, JDRF will progressively remove the daily disease burden and lessen the risk of premature death and long-term complications as we work toward the ultimate goal of restoring normal physiology.

JDRF's commitment to creating a world without T1D is the vision that underpins our comprehensive global strategies to reduce the impact of T1D in the lives of those affected by the disease—until one day Type One becomes Type None. JDRF's ability to expedite and sustain meaningful progress in bringing life-changing therapies from the lab to the community is made possible by donors like you. Thank you.

JDRF ISRAEL INITIATIVE

In 2010, JDRF established a Joint Program with the Israel Science Foundation (ISF), Israel's leading source of competitive grants for basic research. The ISF-JDRF Joint Program in Type 1 Diabetes Research was created to leverage JDRF's resources with those of the ISF and to advance T1D research by providing support to Israel's gifted researchers in the fields of autoimmunity and beta cell biology research. This joint venture is accelerating the practical application of basic scientific advances into novel therapies for T1D.

The goals of the ISF-JDRF Joint Program are to promote the highest quality of biomedical research in the areas of autoimmunity, beta cell biology, and the interaction between the immune system and the beta cell in the context of T1D; to expedite the practical application of basic scientific advances into novel therapies for T1D; and to issue collective grants to bring scientists from other fields into T1D research.

Over the past three years, the ISF-JDRF Joint Program has provided nearly $4 million in funding to support ten projects, each focused on one or more of the following areas:

- Beta cell encapsulation: restoring normal blood-glucose levels and insulin independence by implanting an encapsulated, replenishable source of glucose-responsive, insulin-secreting cells without the need for chronic immunosuppression;

- Beta cell restoration: restoring normal blood-glucose levels and insulin independence either by triggering the proliferation of existing beta cells and/or the growth of new beta cells, or by reprogramming of other cells to become insulin-producing beta cells;
- Beta cell biomarkers, imaging, and targeting: identifying and validating prognostic and predictive T1D immune and beta cell biomarkers and imaging tools to aid clinical development and clinical trials;
- Immune therapies: eliminating immune-mediated destruction of beta cells and restoring beta cell-specific immunoregulation to preserve residual beta cells and prevent destruction of regenerated beta cells.

Since the launch of the ISF-JDRF Joint Program in Type 1 Diabetes Research, three rounds of grant funding have been awarded to support a variety of T1D research projects. These projects and their progress to date are described below.

Year One Grant Awards

The first five grant recipients under the ISF-JDRF Joint Program were announced in August 2011, following a rigorous peer-review process to identify the highest quality basic or translational T1D research proposals. These five projects are:

Shimon Efrat, Ph.D.

Beta cell replacement by human islet beta cells expanded in vitro

Tel Aviv University

Ramat Aviv, Israel

Using innovative tools in genetics and biochemistry, Dr. Efrat is working to create a replenishable source of human beta cells. Scientists have long understood that stem cells taken from either embryos or adults have the potential to turn into many different types of cell, including insulin-producing beta cells. In this project, Dr. Efrat and his team are examining whether cells taken from the pancreas can be redifferentiated into insulin-producing beta cells due to their genetic "memory." The team has found that, to some degree, adult stem cells retain a "memory" of what they once were—meaning that cells created from pancreatic beta cells prove more efficient than their embryonic counterparts in creating insulin-producing beta cells. The preliminary results of this study were recently published in the journal *Cell Stem Cell*, and could advance the development of cell replacement therapy as a treatment for T1D. When coupled with therapies to prevent or block the immune system from attaching the newly introduced beta cells, this research offers a possible route to a cure.

Gideon Gross, Ph.D.

Redirecting regulatory T cells against diabetogenic T cells for the immunotherapy of type 1 diabetes

Tel-Hai Academic College

Upper Galilee, Israel

Dr. Gross is testing the hypothesis that islet-specific regulatory T cells can suppress T1D. Dr. Gross and his team are investigating ways to recruit, induce, or engineer specific regulatory T cells to control the autoimmunity associated with the disease. The team has performed a number of experiments aimed at establishing the experimental procedures for separating $CD4^{+}CD25^{-}$ T cells and $CD4^{+}CD25^{+}$ cells, characterizing each population, identifying useful markers and functional properties of each. If successful, this project could lead to new therapies to treat and prevent T1D.

Shulamit Levenberg, Ph.D.

In vitro reconstruction of a vascular niche to support pancreatic islet survival and function and improve islet transplantation efficacy

Technion - Israel Institute of Technology

Haifa, Israel

Using bioengineered tissues, Dr. Levenberg aims to reconstruct a healthy environment for transplanted islets in humans. Dr. Levenberg and her team have built pancreatic tissue with insulin-secreting cells, surrounded by a three-dimensional network of blood vessels and have tested the use of this tissue with diabetic mice. To date, the team has found that these engineered tissues have some significant advantages over traditional transplant material that has been harvested from healthy pancreatic tissue. The insulin-producing cells survive longer in the engineered tissue, produce more insulin and other essential hormones, and function well enough to lower blood sugar levels in the mice. Currently, Dr. Levenberg is beginning to test the use of this engineered tissue in humans, in the hope that it will have the same effectiveness in humans. If successful, these studies could pave the way for improved tissue transplants to treat T1D.

Eli Lewis, Ph.D.

The involvement of B lymphocytes in the protective activity of alpha-1-antitrypsin during diabetes and islet transplantation

Ben Gurion University of the Negev

Beer-Sheva, Israel

Dr. Lewis is exploring whether and how B lymphocytes—a component of the immune system—may contribute to the activity of a protein known as alpha-1-antitrypsin, which is currently being administered to preserve beta cell function in new-onset T1D clinical trials. Alpha-1-antitrypsin, which is produced by the body and is known to exert tissue-protective effects and anti-inflammatory activities, is inactivated in the serum of people with T1D. Dr. Lewis and his team are working to identify the cellular targets of the protein and are examining beta cells for their responses to alpha-1-antitrypsin. If successful, this study could lead to new therapies for islet transplant recipients to protect the transplanted islets from immune attack without the use of immunosuppressive drugs.

Yair Reisner, Ph.D.

Correction of diabetes by transplantation of embryonic pig pancreatic tissue

Weizmann Institute of Science

Rehovot, Israel

Dr. Reisner is studying the use of tissue from embryonic pig pancreases to replenish depleted stores of beta cells in humans. The primary aim of this study is to define the feasibility of using reduced immune suppression and to optimize the tissue dose required for long-term correction of T1D in non-human primates. Despite some delays in the arrival of the monkeys to be used in the study, Dr. Reisner and his team are now moving forward with the project as planned. During the current year, they will focus their efforts on defining the minimal tissue dose that can result in a cure for diabetes in the monkeys, both with and without the use of immune suppression. If successful, this project could lead to a new source of transplantable tissue for use in treating T1D.

Year Two Grant Awards

In July of 2012, five new project grants were awarded by the ISF-JDRF Joint Program, again following a thorough peer-review process. Descriptions of these projects are:

Benjamin Glaser, M.D.

Non-neoplastic replication of adult human pancreatic beta cells—transformative study based on focal hyperinsulinism of infancy

Hadassah-Hebrew University Medical Center
Jerusalem, Israel

Dr. Glaser is investigating how to direct the replication of adult human beta cells in a way that does not lead to out-of-control cancerous growth. To achieve this goal, Dr. Glaser and his team are studying five genes associated with focal hyperinsulinism of infancy, a condition characterized by severe hypoglycemia that is due, in part, to excessive numbers of pancreatic beta cells. The team is inserting each of these genes into normal adult beta cells to determine whether any of the genes, alone or in combination, can cause the cells to divide and produce new, fully functional and differentiated beta cells. Progress to date has confirmed for the first time that inhibition of $p57^{kip2}$ expression resulted in increased beta cell proliferation. In addition, Dr. Glaser and his team have demonstrated that these replicated beta cells maintain their functionality and enhance the overall functional beta cell mass. In the coming year, the team will perform initial transplant experiments, by transducing human islets with a cocktail of lent-viruses designed to suppress all four imprinted genes and to overexpress IGF2. Transduced islets will be transplanted under the kidney capsule of immunodeficient mice, which will allow for longer survival of the islets, their revascularization, and exposure to host factors. If successful, Dr. Glaser's research will be an important step toward generating a safe, abundant, and replenishable supply of human beta cells for replacement therapy for T1D.

Ofer Mandelboim, Ph.D.; Angel Porgador, Ph.D.

Inhibition of the activity of the NK killer receptor NKp46 for the treatment of type 1 diabetes

Hebrew University; Ben-Gurion University of the Negev
Jerusalem, Israel; Beer-Sheva, Israel

Natural killer (NK) cells play a critical role in the immune system by killing tumor cells, as well as cells infected by viruses or other pathogens. NK cell function is controlled by receptors, specialized proteins on the cell surface, that recognize other proteins derived from pathogens (e.g., bacteria, viruses), tumor cells, or even self-proteins, which are normally produced by the body. Drs. Mandelboim and Porgador previously reported that one such NK cell receptor, named NKp46, targets an unknown protein produced by pancreatic beta cells. Further, they showed that mouse and human beta cells can be killed by NK cells through a mechanism that depends on NKp46, thus implicating NK cells and the receptor NKp46 in the development of T1D. During the current project, the team has succeeded in generating specific antibodies that block the function of NKp46. Furthermore, they demonstrated that the anti-Ncrl monoclonal antibody blocked the development of T1D in mice. Based on the success of this project, the pharmaceutical company BioLine is now developing these antibodies for the treatment of T1D.

Yoram Reiter, Ph.D.

Antigen-specific immunotherapy for T1D by novel recombinant antibodies directed to diabetes-associated autoreactive T cell epitopes

Technion—Israel Institute of Technology

Haifa, Israel

A major goal of T1D research is to develop therapies that halt or reverse the misguided autoimmune attack that destroys the pancreatic beta cells. To address this goal, researchers are working to develop antigen-specific immune therapies that can selectively block beta cell destruction without interfering with other, beneficial functions of the immune system, such as protection from foreign organisms and abnormal cells. In this project, Dr. Reiter is engineering a family of novel antibodies called T cell receptor-like (TCRL) antibodies, which could serve as T1D-specific immunotherapeutic agents. Dr. Reiter and his team are investigating the mechanisms by which these TCRL antibodies may prevent the autoimmune destruction of beta cells and studying whether these antibodies can establish antigen-specific immune tolerance to beta cells in a mouse model of T1D. If successful, this research would provide preclinical proof of concept for the development of TCRL antibodies as an antigen-specific immune therapy for people with T1D, or those at risk of developing the disease. To date, Dr. Reiter has successfully shown that TCRL antibodies are 70% effective in inhibiting T cell proliferation in mice, and that the antibodies can be administered in a range of doses in order to induce antigen-specific inhibition of T cells without upsetting the activation and function of other T-cell activities.

Michael Walker, Ph.D.; Yoav Soen, Ph.D.

Cell surface markers of pancreatic beta cells as a tool for identifying, isolating, and characterizing precursor and mature cell populations

Weizmann Institute of Science

Rehovot, Israel

The severe shortage of human donor islets is one of the major challenges to making islet transplantation widely available as a treatment for T1D. A potential solution to this shortage is to generate an abundant and replenishable supply of beta cells through the differentiation of human embryonic stem cells. Drs. Walker and Soen have developed a technology platform known as a "differential cell-capture antibody array" and have used it to identify unique cell surface markers that distinguish among cells at various stages of beta cell differentiation. They have also identified, purified, and characterized uniform populations of beta cell precursors in intermediate stages of differentiation, as well as mature, fully differentiated beta cells. This research will facilitate further understanding of beta cell development and differentiation and represents an important step toward generating and purifying functional beta cells that are suitable for replacement therapies for people with T1D. To date, Drs. Walker and Soen have been successful in developing a method of identifying markers designating cells with specific functions. The approach, known as designated functional cell-capture assay (FCCS) dramatically increases the ability of the array approach to identify cells with desired functionality. In the current year, the team is working to use the FCCS approach to identify additional markers and to test the utility of the identified markers individually and in combination for characterization and enrichment of de-differentiated and re-differentiated islets.

Yehiel Zick, Ph.D.

Characterization of TM7SF3—a novel receptor that affects beta cell survival and resistance to ER stress

Weizmann Institute of Science

Rehovot, Israel

Preventing beta cell death due to autoimmunity in individuals with T1D might require a combination of strategies. Some researchers are looking for ways to control the immune system so that it no longer attacks and kills the pancreatic beta cells. Others, like Dr. Zick, are developing methods to genetically modify the beta cells themselves in order to help them better resist an autoimmune attack. Recently, Dr. Zick's laboratory set up an experiment to identify proteins that are involved in beta cell survival and growth. One protein they identified, called TM7SF3, appears to protect beta cells from proinflammatory cytokines—small proteins released by immune cells that trigger beta cell death. Dr. Zick also showed that TM7SF3 has a role in preserving beta cell mass and maintaining insulin secretion from beta cells in response to glucose. Now, Dr. Zick is continuing to investigate the mechanisms through which TM7SF3 protects beta cells from death induced by cytokines or other stressors. This research will improve our understanding of beta cell survival and growth and might reveal new targets for the discovery and development of drugs that can promote beta cell survival, proliferation, or regeneration. To date, Dr. Zick has successfully shown that promoting the expression of "survival and growth" genes such as TM7SF3 can better protect beta cells from death, preserve their mass, and maintain their functionality when subjected to different forms of cellular stress.

Year Three Grant Awards

In September 2013, two new project grants were awarded by the ISF-JDRF Joint Program, again following a thorough peer-review process. The two projects are:

Sarah Ferber, Ph.D.

Characterization of transdifferentiation-prone human liver cells to be used in cell-replacement therapy for diabetics

Chaim Sheba Medical Center

Ramat Gan, Israel

Dr. Ferber is studying the subpopulation of human liver cells that are prone to self-reprogramming into beta cells. She aims to characterize the cells at the molecular, cellular, and functional levels and to determine whether they carry potential for cell-replacement therapy. Further goals include developing methods to isolate these cells before reprogramming. Dr. Ferber was one of the first scientists to champion the potential for transdifferentiation of human liver cells, and this current project could ultimately lead to more efficient ways of isolating and growing replacement beta cells.

Yoram Reiter, Ph.D.

Antigen-specific immunomodulation for T1D by novel recombinant antibodies directed against diabetes-associated auto-receptive T cell epitope

Technion—Israel Institute of Technology

Haifa, Israel

Building upon the pilot/feasibility grant he received from the ISF-JDRF Joint Program last year, Dr. Reiter will study antigen-specific immunotherapy for T1D by novel recombinant autoantibodies. The project will focus on T cell receptor-like antibody to induce tolerance of an epitope of glutamic acid decarboxylase (GAD), an autoantigen believed to be centrally involved in triggering T1D. Dr. Reiter will collaborate with Gerald T. Nepom, M.D., Ph.D., director of the Benaroya Research Institute in Seattle. This collaboration represents an exciting opportunity to bring new perspectives from cancer, autoimmunity, and inflammation to translational question in T1D.

CONCLUSION

The ISF-JDRF Joint Program in Type 1 Diabetes Research is accelerating research into life-changing treatments and a cure for T1D; increasing support of Israel's rising talent and expertise in the areas of autoimmunity and beta cell biology; and fostering cross-disciplinary collaboration between T1D experts and scientists in other fields. The groundbreaking projects being carried out through this partnership are helping JDRF move forward with our plan to progressively remove T1D from people's lives until it is finally gone. Thanks to the support of donors like you, JDRF has made tremendous strides in the past year in our critical areas of T1D research—each of which has the potential to lead to truly life-changing therapies for people with T1D.

As the world's leading private funder of research to cure T1D, JDRF is only able to continue our vitally important research with the continued support of our many donors, and we are extremely grateful for your ongoing belief in our work. With dedicated partners like you, JDRF is confident that we will turn Type One into Type None.

Thank you again for your generosity.

JDRF STAFF FOR THE ISF-JDRF JOINT PROGRAM IN TYPE 1 DIABETES

Adrianne Wong, Ph.D.
Senior Scientific Program Manager, Beta Cell Therapies, Replacement

Adrianne Wong, Ph.D., is currently a senior scientific program manager at JDRF, where she is responsible for developing cell therapies and noninvasive imaging in the area of beta cell replacement. She is also involved in negotiating and implementing international partnerships with public and private agencies to create funding opportunities for T1D research. In her role, Dr. Wong has gained unique perspectives on the commercialization potential for cell therapy in T1D, having represented JDRF on numerous occasions in stem cell translation and policy programs at the National Institutes of Health and the U.S. Food and Drug Administration. In her biomarkers and beta cell imaging program, she works closely with two European Union-supported framework programs: as JDRF's liaison to BetaImage and an Industrial Advisory Board member of Vibrant. In the United States, she is also a liaison to the Foundation for the National Institutes of Health, an independent nonprofit organization that facilitates the development of public-private partnerships, including The Biomarkers Consortium. Dr. Wong has expertise in intellectual property strategy and management, which she gained as a science advisor at Darby & Darby. Dr. Wong received her undergraduate degree in biology from Brown University and her doctorate in cell biology from Duke University, where she studied cellular signaling in angiogenesis as a United States Army MRMC Breast Cancer Research Program fellow under the guidance of Dr. Kevin G. Peters. She continued her training in developmental biology as a postdoctoral fellow at Columbia University, studying murine kidney development. Her scientific communication experience encompasses teaching, independent writing, and completing a production internship with National Public Radio's *Science Friday*. Dr. Wong is also committed to mentoring young scientists.

Julia L. Greenstein, Ph.D.
Vice President, Discovery Research

Julia L. Greenstein, Ph.D., originally joined JDRF as a consultant in 2005 and currently serves as the JDRF vice president of discovery research, one of JDRF's core research initiatives. Projects in the discovery research portfolio also contribute toward our goal of preventing, treating and curing T1D. In her more than 20 years of experience in the corporate biotechnology arena, Dr. Greenstein has held various leadership positions that have helped accelerate discoveries to market. From 2000 to 2005, Dr. Greenstein was the chief executive officer and president of Immerge BioTherapeutics, a Novartis and BioTransplant joint venture focused on the development of pig xenotransplantation for clinical practice. Prior to this position, she held the roles of chief scientific officer and senior vice president of research at BioTransplant and vice president of discovery research at ImmuLogic Pharmaceutical Corp. Dr. Greenstein currently serves on the Board of Directors of Massachusetts General Hospital Institute of Health Professions. She also served on the board of the Massachusetts Biotechnology Council, MassBioEd Foundation and the Massachusetts Society for Medical Research. Dr. Greenstein received her bachelor's degree in biochemistry from Russell Sage College and her doctorate in microbiology from University of Rochester School of Medicine and Dentistry, under the direction of Philippa Marrack, Ph.D. Dr. Greenstein was an assistant professor at the Dana-Farber Cancer Institute of Harvard Medical School after completing her postdoctoral work there and at the University of Rochester.