



# Research Report



At the Diabetes Research Institute and Foundation, the vision is a world without diabetes. To make that vision a reality, we are laser-focused on one goal: to discover a biological cure. For millions of children and adults living with diabetes today, a cure would mean:

**The ability to restore natural insulin production and normalize blood sugar levels without imposing other risks.**



*“The reason we remain focused on a biological cure is that while we recognize there are other efforts to improve day-by-day life of patients with diabetes...these approaches don't deal with the eradication of the disease...”*

— DRI Director Camillo Ricordi, M.D.

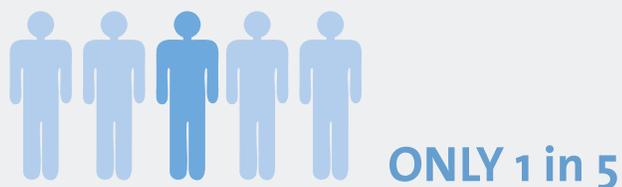
## Why a Biological Cure?

Cases of diabetes have been documented for several thousand years, though the term wasn't coined until the first century. For almost 2,000 years since then, the only treatment option for patients was starvation until the discovery of insulin in 1922.

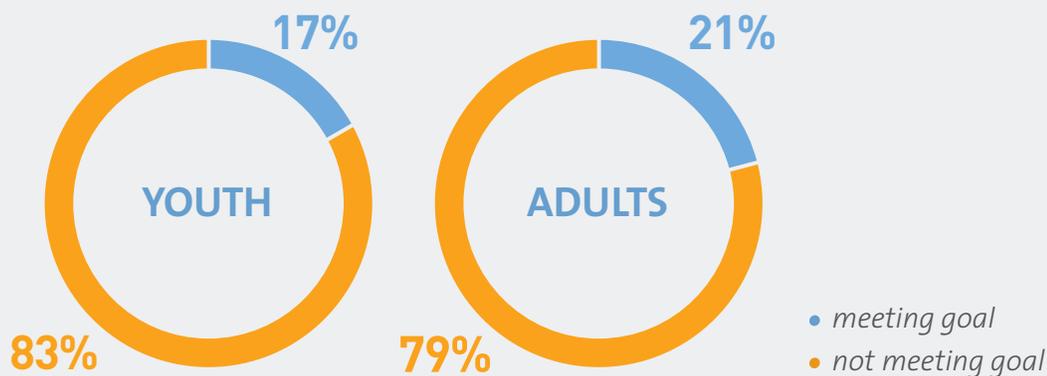
Over the last 100 years, insulin has saved the lives of millions of people with diabetes – **but insulin is not a cure**, and insulin therapy cannot ideally mimic the precise biological function of insulin-producing islet cells.

Despite patients' best attempts, managing diabetes remains a challenging, daily balancing act that requires constant vigilance. And while tremendous advances in new treatments and computer technology have helped people better manage the disease, recent studies show that the vast majority of children and adults are still unable to achieve optimal glucose control<sup>1,2</sup>.

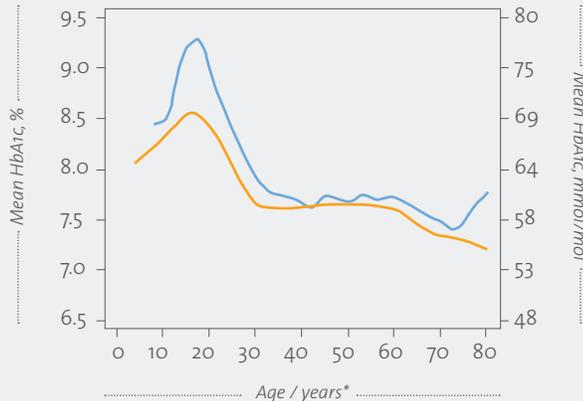
### Very few people with type 1 diabetes are achieving optimal blood sugar levels



### The number is even lower among young people

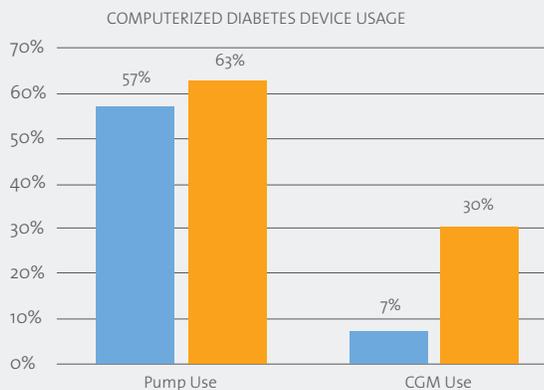


## Metabolic control has worsened over time



Glycemic control has not improved overall between 2010-2012 and 2016-2018 and appears to have worsened, particularly in adolescents...

- 2010 - 2012
- 2016 - 2018

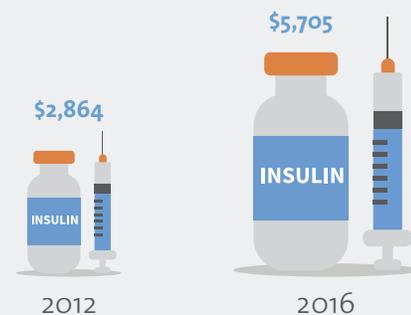


...despite increased use of computerized diabetes devices.

- 2010 - 2012
- 2016 - 2018

## And, the cost of insulin has skyrocketed

The price of insulin has doubled in recent years, causing some patients to ration their use of the life-saving drug. Many have lost their lives, having been forced to choose between buying insulin or food, housing and other necessities.



- Annual Spending Per Person (\$)³

## A biological cure is an urgent priority

The Diabetes Research Institute and Foundation are intensely focused on one single goal – the discovery of a biological cure – to restore natural insulin production in people living with this life-threatening disease.

Building upon decades of pioneering research accomplishments and significant contributions to the field of diabetes, DRI scientists are urgently working to overcome the challenges that stand in the way of a cure.

Sources: 1) Diabetes Technology & Therapeutics, Jan 2019; T1D Exchange; 2) American Diabetes Association (ADA) HbA1c goal of <7.5% (<58 mmol/mol) for youth; <7% (<53 mmol/mol for adults); 3) Health Care Cost Institute

Beyond the daily challenges  
of managing diabetes...

the freedom it robs from  
patients of all ages but  
especially from children...

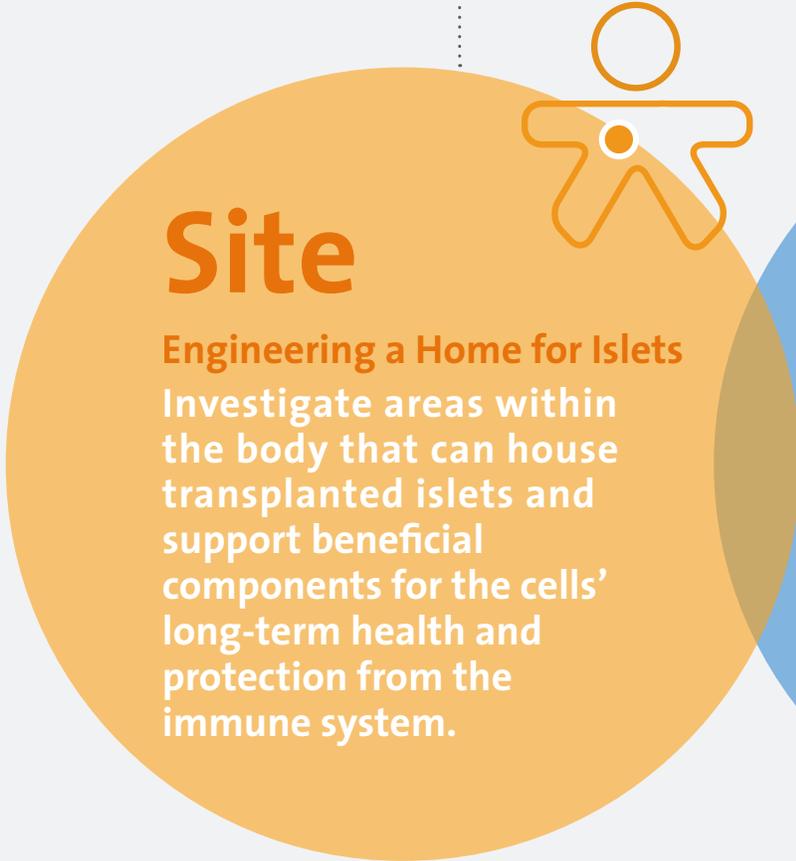
the immeasurable pain and  
suffering from complications...

and the billions of dollars in  
annual healthcare costs...

these alarming statistics  
further underscore the  
urgent need to discover  
a biological cure for this  
devastating disease.



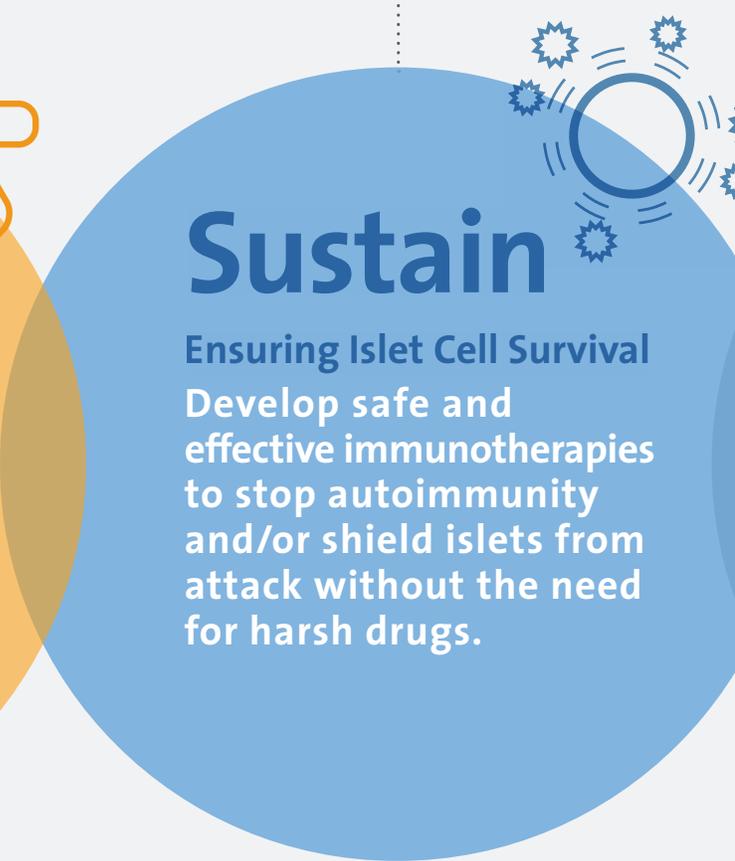
# 3 areas for a Biological C



## Site

### Engineering a Home for Islets

Investigate areas within the body that can house transplanted islets and support beneficial components for the cells' long-term health and protection from the immune system.



## Sustain

### Ensuring Islet Cell Survival

Develop safe and effective immunotherapies to stop autoimmunity and/or shield islets from attack without the need for harsh drugs.

# Cure

## Supply

### Creating More Insulin-Producing Cells

Create a reliable and plentiful supply of insulin-producing cells or regenerate a patient's own islets.

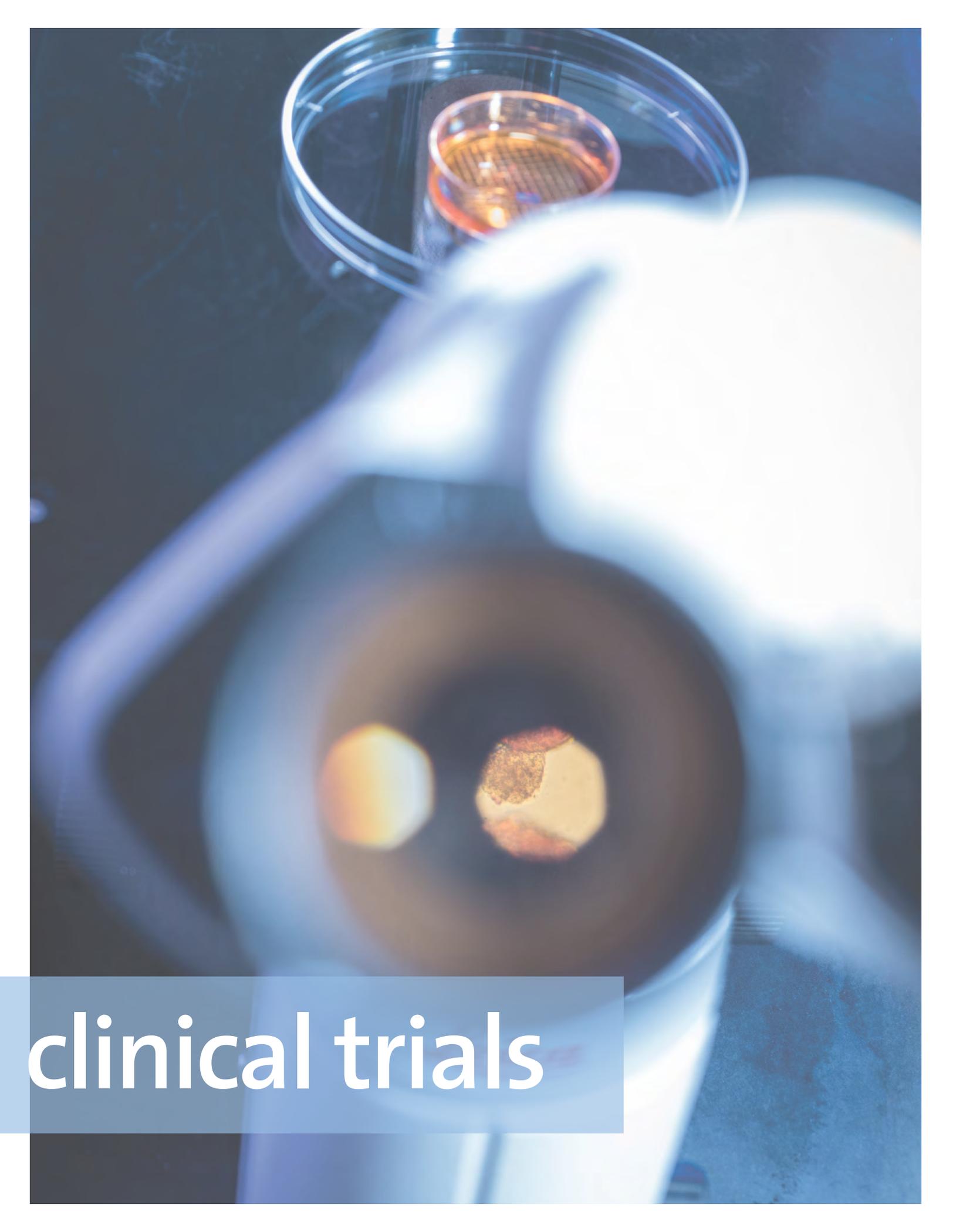
**How will we cure diabetes?** By targeting the major research areas needed to restore insulin production.

As one of the largest and most comprehensive research centers in the world, the DRI houses teams of scientists, engineers, and clinicians with the expertise required to tackle this disease from many angles.

This integrated approach, combining technology and medicine, drives the vision behind the DRI BioHub, a multidisciplinary, three-pronged strategy to cure diabetes. The BioHub strategy builds upon decades of cure-focused research and addresses critical challenges that stand in the way of a biological cure. It is based upon the premise that:

- If we need to transplant insulin-producing islet cells to replace those that are destroyed by the immune system, then we must engineer a mini-pancreas in a **Site** within the body to house the cells.
- If we are to **Sustain** the survival of the transplanted islets, then they need protection from the immune system rejection, as well as from the autoimmune attack that initially caused the onset of the disease.
- If we can halt autoimmunity through safe and effective immunotherapies, then we may **Sustain** natural insulin production before all the insulin-producing cells are lost.
- If we can halt autoimmunity, we may regenerate a person's own insulin-producing cells, creating a natural **Supply** within the body.
- If we need more insulin-producing cells for transplant, then we must create an unlimited **Supply** for millions of people with diabetes who can benefit.

**These three principal research avenues, collectively referred to as the “Three S’s” – Site, Sustain, Supply – are being pursued simultaneously by the DRI’s investigators and global collaborators in a waste-no-time approach.**



clinical trials

The DRI conducts research with the goal of translating findings from the bench (in the lab) to the bedside (in patients) as quickly as possible. After a promising treatment is developed and its safety and effectiveness in the preclinical setting proven, clinical investigators obtain regulatory approval to conduct studies in patients.

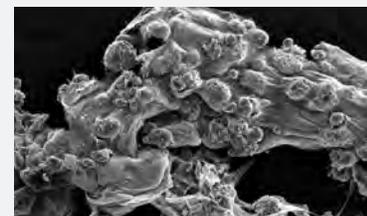
The DRI has received authorization from the Food and Drug Administration (FDA) to proceed with five clinical trials, some of which are ongoing or have begun recruiting patients this past year. The ability to advance this work to the clinical setting represents a significant step on the path toward a cure.

## BioHub Trial: Islet Transplantation onto the Omentum

The DRI's FDA-authorized Phase I/II clinical trial was the first step in testing the safety and efficacy of islets transplanted within a tissue-engineered platform in a new site, the omentum. In the study, donor islets were combined with the patient's blood plasma together with thrombin, a commonly used clot promoter. The mixture sticks to the omentum and holds the islets in place, providing them with spacing and support similar to the pancreas, their native home.

While the study is still ongoing, the early results have shown that the omentum appears to be very safe and the procedure is well tolerated by patients. The DRI team, led by **Rodolfo Alejandro**, M.D., director of clinical islet transplantation, and **David Baidal**, M.D., assistant professor of medicine, was also able to show in all patients that transplanted islets can function in the omentum, confirmed by measure of C-peptide, a by-product of endogenous (a person's own) insulin production. Overall, the patients had improved metabolic control and a better quality of life.

Further evaluation and testing will determine the long-term efficacy of this procedure, as well as how it compares to the long-standing data from islet transplantation in the liver.



*Electron microscope image of islets implanted within the biological scaffold.*

## DIPIT Trial (Diabetes Islet Preservation Immune Treatment)

There is growing evidence that type 1 diabetes is caused by many factors, and that inflammation and beta cell dysfunction may also be important in the development and progression of the disease process. However, the majority of approaches to combat T1D have involved single agents that primarily targeted the immune system. So far, these immune interventions have not demonstrated sustained beneficial effects on the function of the insulin-producing cells.

The DIPIT trial, led by **Camillo Ricordi**, M.D., DRI director, and **Jay Skyler**, M.D., deputy director of clinical research and academic programs, involves a first-ever combination strategy that targets four separate pathways that researchers believe are implicated in type 1 diabetes. Three of the interventions aim to block innate immunity, block adaptive immunity and enhance regulatory immunity, while another will simultaneously attempt to improve beta cell health.

Once fully funded, this innovative FDA-authorized trial will enroll adults with new-onset T1D (within four months of diagnosis). It will be conducted at the DRI and at multiple facilities throughout the United States. The data from this study may also provide vital information for developing treatment strategies in people with long-standing type 1 diabetes.

## Low-Dose IL-2 Trial

Interleukin-2 (IL-2), a naturally occurring protein, is important for immune system function. Not only does it stimulate the effector cells, the "attack arm" of the immune system that protects the body from infections and other harmful invaders, but IL-2 is also critical for the function of regulatory T cells (Tregs), the immune cells that prevent the destruction of the body's own tissues.



*Left to right: Alberto Pugliese, M.D., deputy director of immune tolerance; Thomas Malek, Ph.D., professor and chair of immunology and microbiology; Jay Skyler, M.D., deputy director of clinical research and academic programs; David Baidal, M.D., assistant professor of medicine; Rodolfo Alejandro, M.D., director of the Clinical Cell Transplant Program.*

In patients with type 1 diabetes, the “regulatory arm” of the immune system is impaired and cannot provide the protective response against the effector cells. This loss of balance, or regulation, results in the continued destruction of the target, which in type 1 diabetes are the insulin-producing cells.

This clinical trial will test whether IL-2, used in low doses, can better regulate the immune system and correct autoimmunity in young people, ages 8 - 21, with established type 1 diabetes (from four months to one year post-diagnosis).

The DRI’s multi-center trial, led by **Alberto Pugliese**, M.D., deputy director of immune tolerance, and **Thomas Malek**, Ph.D., professor and chair of microbiology and immunology, will further test the safety of low-dose IL-2 and its effect on preventing beta cell loss. The trial will include patients who have been diagnosed with type 1 diabetes up to one year, widening the typical enrollment window of less than three months. The reason for this extended time period is that many patients maintain a significant amount of insulin production for at least two to three years after diagnosis, if not longer. The continued presence of insulin secretion may offer the opportunity for preserving the surviving beta cells.

## POSEIDON Trial



*The POSEIDON clinical study team: David Baidal, M.D., assistant professor of medicine, Rodolfo Alejandro, M.D., director of the Clinical Cell Transplant Program, Janine Sanchez, M.D., director, Pediatric Diabetes Program, University of Miami, Ana Alvarez Gil, ARNP, Camillo Ricordi, M.D., DRI director, and Raj Hirani, Ph.D., director, regulatory support.*

Several scientific reports have suggested that the use of high-dose omega-3 and vitamin D, both of which have known anti-inflammatory and immunomodulatory properties, may offer a potential beneficial effect on autoimmune conditions, like type 1 diabetes. Recent case studies led by DRI Director Dr. **Camillo Ricordi** together with collaborators in Italy have shown, anecdotally, a pattern of disease remission in young patients for up to two years following the use of these supplements at the time of disease onset. Additionally, the intervention appears to be well tolerated, affordable and sufficiently safe to be further tested in larger, controlled studies.

The DRI received authorization from the FDA to proceed with a Phase I/IIa clinical trial, named the POSEIDON study (Pilot Study of Omega-3 and Vitamin D High Doses in T1D) to compare the effects of this intervention in children and adults newly diagnosed and in those with longer-standing T1D to evaluate any benefit of early and late treatment.

The POSEIDON study, which has begun recruiting participants, will enroll children and adults, ages 6 – 65, who have been diagnosed with type 1 diabetes within the last 10 years.

## Intraocular Islet Transplant Trial

The anterior chamber of the eye, or the “Living Window,” has been a very innovative and useful tool for studying transplanted islets *in vivo* – in a living organism. DRI scientists have also used this site to study new islet transplant methods. The eye is one of few immune-privileged sites in the body: strong immunological reactions are dampened in these areas to avoid damage to vital tissues.



*Per-Olof Berggren, Ph.D., director, islet physiology, and Midhat Abdulreda, Ph.D., assistant professor of surgery.*

As such, the eye may offer potential benefits for protecting the transplanted islets from an immune attack and potentially controlling blood sugar levels in those with type 1 diabetes.

**Per-Olof Berggren**, Ph.D., head of cell biology and signal transduction, and **Midhat Abdulreda**, Ph.D., assistant professor of surgery, and their team have already demonstrated the long-term survival of intraocular (within the anterior chamber of the eye) islet transplants without continued anti-rejection drugs in preclinical models. The data suggest two possibilities for establishing long-term islet survival: either through local immune tolerance in the eye, or as a means to induce tolerance systemically. Results from their studies were recently published in the journal *Diabetologia*.

This clinical trial will test the safety and efficacy of this approach in a very select group of patients. The researchers have been actively searching for patient candidates to participate in the study.

Simultaneously, the team continues to use the Living Window model to further study the immune system reactions that lead to the attack on insulin-producing cells. A better understanding of these cell interactions may lead to new therapies to protect transplanted islets from destruction.





site





In addition to testing promising findings in clinical trials, the DRI's teams of scientists, engineers, and clinicians are advancing other research initiatives within the areas of the BioHub strategy — Site, Sustain, Supply — simultaneously tackling this disease from many angles. Over the last year, scientists jump-started new initiatives, delved further into ongoing projects, and continued to translate research closer to people living with diabetes.

## The SITE: Engineering an Ideal Home for Islets

Recent studies have confirmed that for those with type 1 diabetes who suffer frequent and severe hypoglycemia – a potentially fatal low blood glucose level – islet transplantation can significantly improve quality of life. But for the majority of people with T1D, islet transplantation is not ideal. Patients who are eligible for the still-experimental procedure require life-long anti-rejection drugs. Plus, the liver, the usual site of implantation, poses some limitations.

Moving beyond traditional islet transplantation, DRI scientists are combining engineering principles and cellular therapies to create a more hospitable environment for the insulin-producing cells. These next-generation strategies aim to deliver immune modulation and other protective factors locally to promote the long-term health and function of islets without the need for immunosuppression.

While alternative transplant sites in the body have been explored over time, the DRI is focusing on locations that can accommodate the hundreds of thousands of transplanted islets together with these novel technologies. It also needs to be safely accessed with minimally invasive surgery.

The omentum is one such site currently being tested by DRI researchers. The omentum is a tissue that covers abdominal organs and is rich with blood vessels, important for carrying oxygen and other nutrients to the transplanted islets. Researchers have found that the omentum can also be manipulated with cellular therapies and other interventions more easily than other sites in the body that have been explored with very limited clinical success.

Identifying a location where the cells can be safely implanted and produce insulin is the first step. Next: engineering the site to mimic the endocrine (insulin-producing) function of the pancreas and ensuring that the cells survive for the life of the recipient.



*The omentum is a highly vascularized tissue covering abdominal organs.*



sustain



## SUSTAIN: Ensuring Islet Cell Survival

Until scientists can protect transplanted islets without the use of immunosuppressive drugs and, most importantly halt autoimmunity, many research advances will remain limited to a select group of people with type 1 diabetes. For this reason, the Sustain area – ensuring long-term islet survival – is an urgent DRI research priority.

From developing safe and effective immunotherapies to safeguarding islets locally at the site of implantation, DRI scientists are pursuing a number of immune-related avenues to sustain the survival of the insulin-producing cells.

### The Role of Folic Acid: Immune Function and Cell Metabolism

DRI researchers have observed that the dramatic increase in type 1 and type 2 diabetes, as well as other autoimmune conditions worldwide, seems to coincide with the mandatory fortification of flour products with folic acid that was put into effect in the mid-1990s.

However in populations where folic acid is readily available in food along with vitamin supplements, the additive might not be necessary and may actually be detrimental to certain people, according to **Chris Fraker**, Ph.D., research assistant professor of surgery and cell transplantation, and **Allison Bayer**, Ph.D., research assistant professor of microbiology and immunology.

The researchers have been examining the effect of folic acid on critical immune system cells called natural killer (NK) cells, in conjunction with the viral hypothesis related to the onset of type 1 diabetes. Drs. Fraker and Bayer believe that folic acid may cause a general weakening in the immune systems of those who are susceptible to diabetes or other autoimmune conditions. Their data shows that even a minimal increase in folic acid may impair insulin secretion and glucose uptake in experimental models. Building upon their initial findings, published in *Frontiers in Endocrinology*, the team is further studying the potential effect of folic acid on NK cells to develop strategies to combat it.



*Chris Fraker, Ph.D., research assistant professor of surgery (left), and Allison Bayer, Ph.D., research assistant professor of microbiology and immunology.*

### Engineering New Techniques for Treg Therapy

Dr. **Allison Bayer** and her team continue to develop novel immunotherapies using Regulatory T cells (Tregs), immune cells that prevent the attack cells (effector cells) from destroying “self” tissues. Their unique protocol, called adoptive Treg therapy, was able to reverse diabetes and reset autoimmunity in experimental models. In their studies, which tested islet-specific Tregs, they achieved disease remission in 100% of the recipients without the need for chronic immunosuppression.

*Dr. Allison Bayer, and Alice Tomei, Ph.D., assistant professor of biomedical engineering.*



Along with this success comes additional challenges, including how to obtain a sufficient number of islet-specific Tregs that are needed for the clinical setting. To address this issue, Dr. Bayer is collaborating with **Alice Tomei**, Ph.D., director of the DRI's Islet Immunoengineering Laboratory, to engineer a new technique for releasing biomaterials that increase the numbers of these special Tregs.

In recognition of her pioneering research in this area, Dr. Bayer was awarded two new grants that will help her build upon these promising findings: a multi-year grant from the American Diabetes Association and the *Marc S. Goodman Prize for an Outstanding Young Scientist*.

In next steps, Dr. Bayer and her team are combining the Treg therapy with immunomodulatory agents to test whether this approach can further enhance transplant success and prolong the survival of the islets.

## **Engineering Protective Cell Therapies: MSCs and Other Helper Agents**

The DRI's leadership in cell-based therapies has attracted several investigators with extensive expertise in the field of mesenchymal stem cells (MSCs) and immunology. Institute scientists are exploring the critical role MSCs, together with other agents, may play in developing safer and more effective T1D treatments that eliminate the need for anti-rejection drugs.

MSCs are adult stem cells that are typically found in the bone marrow. They can also be taken from the umbilical cord, fat, skin, and other areas of the body. MSCs have features of stem cells, as they can self-renew and lead to the development of different tissues, like bone, cartilage, muscle and fat, to name a few.

Those alone are vital functions, but MSCs have other therapeutic advantages. Early DRI findings have shown that transplanting MSCs together with islets can help create a tolerant environment that prevents the insulin-producing cells from being destroyed by the immune system.

In addition to suppressing an immune attack, MSCs can also decrease inflammation and promote the growth of new blood vessels, all of which are critical for successful islet transplant outcomes. For these reasons, MSCs are the focus of many DRI projects.

**Norma Kenyon**, Ph.D., deputy director and Martin Kleiman professor of surgery, microbiology and immunology and biomedical engineering, and **Dora Berman-Weinberg**, Ph.D., research assistant professor of surgery, together with their team, are testing a unique combination of cells and agents that may help islets survive and function without the need for harsh immune-suppressing drugs.

Drs. Kenyon and Berman-Weinberg have intensely studied the effects of MSCs transplanted with islets in pre-clinical models (non-human). Through a recently completed National Institutes of Health (NIH)-funded project, they found that MSCs taken from the bone marrow promoted the long-term survival of the insulin-producing cells. These results build upon their earlier pre-clinical studies which first demonstrated the positive results of MSCs in islet transplantation.



*Norma S. Kenyon, Ph.D., deputy director, and Dora Berman-Weinberg, Ph.D., research associate professor of surgery.*



In another key project, the team has shown strong evidence that an immunotherapy agent, anti-CD40L, can create a more tolerant environment for the transplanted islets. Dr. Kenyon's studies with anti-CD40L allowed the islets to survive long-term without anti-rejection drugs, and even improved their function. This exceptional finding has not been replicated with any other immunological agent. The team is now studying a newly developed version of anti-CD40L with promising initial results.

The researchers are also testing whether the natural protection of pregnancy can help safeguard transplanted insulin-producing cells from an immune attack. PIF, or preimplantation factor, plays a critical role in the mother's ability to recognize and accept the embryo. Without PIF, the mother's immune system would reject it. They are investigating whether PIF, combined with transplanted islets, can help eliminate the need for anti-rejection drugs. Recently, Dr. Kenyon was awarded a JDRF Innovative Grant to further explore this novel research avenue.

While these three projects are moving ahead in parallel, the team envisions these approaches coming together in a combination therapy. The next step is to test this strategy in pre-clinical models and collect the data needed for a clinical trial.

**Diego Correa**, M.D., Ph.D., research assistant professor, and his team are focusing on the growth-promoting and immune-suppressing effects of MSCs. They discovered that a particular subset of these cells (from either bone marrow or fat) have a natural ability to control immune responses, which is further enhanced when they face inflammation.

Their innovative approach involves combining these particular MSCs with islets prior to transplantation. They have found that this method helps prevent an immune attack to the islets contained within this cell cluster, while improving their function. In a related project, they are studying the effects of adding cell-derived vesicles – sacs that contain certain signals – into the mix for even greater protection.

Dr. Correa is obtaining proof-of-concept results showing that this approach could help islets evade destruction and enhance their survival and function. The team's next steps involve transplanting the cells into diabetic mice to confirm their early findings.

**Giacomo Lanzoni**, Ph.D., is combining MSCs with islets and pancreatic stem cells (progenitors). He and his team are comparing the effects of MSCs derived from different tissues of the body. The goal is to create a welcoming "home" that defends islets from an immune attack and that mimics the pancreas – so that the insulin-producing cells sense that they are in a familiar place to perform their function.

The MSCs will be put to the test *in vivo* (within recipients), with the difficult task of counteracting the autoimmune attack against the insulin-producing cells. Ongoing studies will show whether MSCs can help islets survive and function, prevent autoimmunity and inflammation, and help the pancreatic stem cells grow into islets.

In a set of exciting – but still ongoing – studies in mice, MSCs are showing a beneficial effect on the autoimmune response that targets beta cells.



1. Diego Correa, M.D., Ph.D., research assistant professor.  
2. Giacomo Lanzoni, Ph.D., research assistant professor.



Peter Buchwald, Ph.D., director of drug discovery, and Oscar Alcazar, senior research associate.

## Targeting a Key Immune Pathway

While several types of immune interactions are involved in the rejection of transplanted tissue, DRI researchers have focused their attention on one interaction in particular, known as CD40-CD40L, because it is particularly promising for islet transplantation.

In a parallel project to Dr. Kenyon's work with anti-CD40L, the DRI's Drug Discovery team, led by **Peter Buchwald**, Ph.D., is focusing on developing small molecules that do not need to be administered as injections.

The team has identified the first small molecules that were capable of interfering with the CD40-CD40L pathway in research published in 2009. They have now developed the first set of promising compounds that can inhibit this pathway in experimental models.

The findings were published in the *Journal of Medicinal Chemistry* and more recently in *Molecules*. The ultimate goal is to develop clinically approved therapies that can be taken orally as tablets or capsules. This could lead to treatments in transplant recipients and possibly to prevent onset of autoimmunity in those likely to develop type 1 diabetes.

In next steps, Dr. Buchwald and his team will be working to further advance the compounds that they have identified and confirm their effectiveness in pre-clinical models.

## Using Advances in Cancer Therapy to Protect Insulin-Producing Cells

Type 1 diabetes and cancer are mirror diseases in some aspects: the same immune system that should normally destroy cancerous cells, but sometimes can give them a "pass," can also go into overdrive and attack and destroy a person's own insulin-producing cells. For fighting cancer, researchers have now discovered a way to force an attack on cancerous tumors using agents that "tweak" the immune system. These new cancer drugs are called checkpoint inhibitors, and immuno-oncology has revolutionized cancer treatment in the last five years.

The immune system's job is to destroy harmful or foreign invaders. In doing so it is guided by "checkpoints." Checkpoints are controlled by molecules on the surface of immune cells that give instructions about what to attack or not attack. Some cancer cells have learned to take advantage of this by tricking the immune system and escaping destruction. The new cancer-fighting drugs, which are called checkpoint inhibitors, interfere with this and allow the patient's immune system to destroy the tumor-causing cells.

Very recently, these drugs have been observed to cause the sudden onset of diabetes as an unwanted side effect in some patients—highlighting the mirror nature of these diseases. DRI researchers are exploring the possibility of controlling these checkpoints in the reverse direction to protect the insulin-producing cells in type 1 diabetes. The DRI team, led by Dr. **Buchwald**, is developing agents to deliver protective signals either to transplanted islets to improve their survival or to the pancreas to protect native islets from the autoimmune attack in new-onset patients or those highly likely to develop the disease. In either case, the goal is to allow the molecules on the surface of the immune cells to encounter these agents and give insulin-producing cells a "pass" from being destroyed.



## Encapsulation: Scaling Up, Refining Conformal Coatings

DRI scientists have taken major steps to overcome the challenges that have limited the clinical application of islet encapsulation strategies by engineering a unique technology called conformal coating. Developed by **Alice Tomei**, Ph.D., director of the Immuno-engineering Lab, and collaborators, conformal coating minimizes the space between the capsule wall and the islet within, offering many benefits over traditional cell encapsulation methods. The team has already shown that their conformal-coated islets can reverse diabetes and normalize blood sugar levels without immunosuppression in experimental models.

This past year, Dr. Tomei has begun designing and testing a new device that can produce the large numbers of capsules needed to translate this approach to pre-clinical models and humans. Working in collaboration with DRI colleagues Drs. **Norma Kenyon** and **Dora Berman-Weinberg**, the investigators will assess the safety and efficacy of this technology, as well as the duration of diabetes remission after transplantation. To support her ongoing research in this area, Dr. Tomei was awarded a JDRF Career Development Award.



Additionally, Dr. Tomei is working with DRI colleagues Drs. **Allison Bayer** and **Peter Buchwald** to refine the conformal coatings to include therapeutic biomaterials that can help eliminate the need for anti-rejection drugs, deliver oxygen to the islet within, or dampen inflammation, among other benefits. Drs. Tomei, Bayer and Buchwald were awarded a prestigious R01 grant from the National Institutes of Health (NIH) to further support this promising research.

## Optimizing the Capsule Environment

One of the major reasons for the limited success of islet encapsulation is the inability to deliver sufficient oxygen and nutrients to the cells. While teams of DRI scientists are engineering tighter-fitting coatings that can improve the delivery of these critical factors, others are taking a closer look at the environment within the capsules themselves, which can also affect islet survival.

When encapsulated islets lack oxygen, they begin to die off and cause an immune reaction – the body’s way of cleaning out waste that it doesn’t need. This process produces harmful free-radicals, further accelerating transplant failure. **Chris Fraker**, Ph.D., and his team are working on an innovative way to address this problem through a chemical reaction. The researchers have developed unique metal particles that immediately convert the free-radicals into oxygen, which is exactly what is needed by the islets.

Dr. Fraker and his team published their initial findings in the journal *Acta Biomaterialia*. The next step is to translate this research into experimental models of diabetes and test this encapsulation strategy *in vivo* (in recipients).

Dr. Fraker is also testing additional strategies to enhance oxygen delivery to the islets prior to transplantation, a vital yet overlooked aspect for transplant success. They were recently awarded a five-year, \$2 million grant from the National Institutes of Health (NIH) to further develop and test innovative ways to maximize oxygen transport to the encapsulated cells throughout the entire islet transplant process.



1. Alice Tomei, Ph.D., director and assistant professor of biomedical engineering.

2. Chris Fraker, Ph.D., research assistant professor of surgery, and Mohammed Tootoonchi, Ph.D., post-doctoral associate.



supply

# SUPPLY: Creating More Insulin-Producing Cells

Currently, islets used for transplantation come from the pancreases of deceased donors. With organ donation in the United States at critically low levels, there are clearly not enough cells for everyone who needs them. The DRI's cell supply and islet regeneration program is focused on finding alternative sources of islets to address this significant challenge.

Scientists have discovered that different types of cells within the non-insulin-producing portion of the pancreas, which makes up 98% of the organ, have the ability to become insulin-producing cells. In particular, they have focused on a unique population of stem cells that *remain intact after the autoimmune attack* in a large percentage of patients. The DRI's Cell Supply team has been developing methods to stimulate these pancreatic stem cells to turn into insulin-producing cells with very promising results.



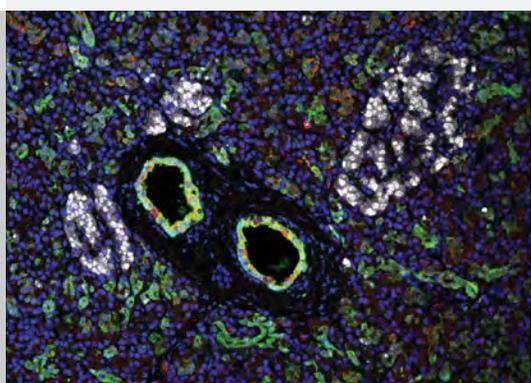
## Beyond Transplantation: Regenerating a Patient's Own Islets

Using a naturally occurring protein called bone morphogenetic protein 7 (BMP-7), DRI researchers demonstrated that those stem cells within the non-endocrine cells in the pancreas can become new islets when cultured in a lab. In itself, that discovery could allow researchers to transplant multiple patients from a single organ.

The promise of this approach, however, also lies in the potential to regenerate a person's own insulin-producing cells using this method. Recently, the DRI team, headed by **Juan Dominguez-Bendala**, Ph.D., director of stem cell development for translational research, and **Ricardo Pastori**, Ph.D., director of molecular biology, confirmed the existence and exact location of these pancreatic progenitor cells that have the potential to regenerate islets. The significant findings, published in *Cell Reports*, open the door to developing regenerative cell therapies for those living with type 1 diabetes.

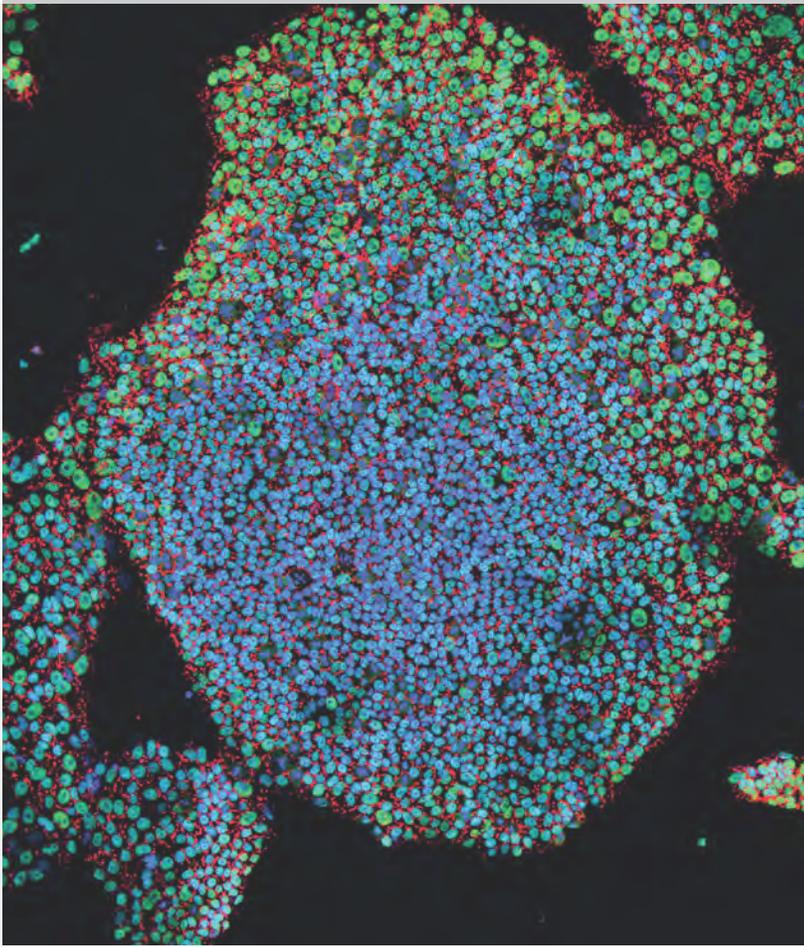
The team plans to extensively test the regeneration of insulin-producing cells by using this method. They envision this approach advancing to clinical trials as part of a "combination therapy" that also addresses autoimmunity, another key challenge in T1D.

The addition of this type of molecule, which is already in clinical use for other conditions, to any approach designed to stop autoimmunity – including those being explored in DRI clinical trials – may result in permanent, functional beta cell regeneration.



1. Juan Dominguez-Bendala, Ph.D., director of stem cell development for translational research, and Ricardo Pastori, Ph.D., professor of medicine.

2. Pancreatic progenitor cells reside within large ducts of the human pancreas. Two such ducts (green), surrounded by three islets (white), are shown in this picture.



*The DRI team engineered stem cells with a double fail-safe approach to prevent the formation of tumors and the development of unwanted cells.*

## Engineering a Safe Cell Supply

The Cell Supply team's efforts are also focused on finding alternative sources of insulin-producing cells for transplant. One option: human pluripotent stem cells (hPSC), which are capable of becoming any type of cell in the body.

However, the use of hPSC poses some safety risks, such as the development of tumors or the growth of the stem cells into cells that are not islets. Drs. **Dominguez-Bendala** and **Pastori** are now at the forefront of developing safeguard approaches to eliminate these risks.

For the first time, the researchers have engineered a stem cell line containing two "suicide genes" that can eliminate all but the desired insulin-producing cells. Their pioneering findings were recently published in *Stem Cell Reports*.

With clinical trials already underway using stem cell-derived beta-like cells and other approaches on the horizon, the need to ensure patient safety is of paramount importance. Their double fail-safe approach works in two ways. First, it destroys any cell that may form a tumor. Second, it selectively destroys cells that do not produce insulin, like liver, brain, muscle cells and others that stem cells tend to grow into.

No other research method reported thus far offers the same degree of safety and targeting of certain cells. While the team focused on deriving insulin-producing cells, this strategy, if clinically successful, may benefit other conditions beyond diabetes.

In next steps, the team will further enhance the safety of this method using a technology called CRISPR, which can precisely insert the suicide genes into the stem cells. CRISPR is a powerful tool for editing genes and is used for many applications, including correcting genetic defects, treating and preventing diseases, and improving farm crops, to name a few.

# Multicenter Initiatives

JDRF nPOD (Network for Pancreatic Donors with Diabetes)



To combat type 1 diabetes, researchers need more knowledge about the disease and the mechanisms of the immune system that trigger an attack on insulin-producing beta cells. Historically, researchers could only collect blood samples from those with T1D in order to conduct patient studies; access to pancreata and other disease-related tissues was severely limited.

To overcome this challenge, in 2007 JDRF seeded the creation of the Network for Pancreatic Organ Donors with Diabetes (JDRF nPOD), a global network that procures and distributes pancreatic tissue from organ donors with type 1 diabetes to further study the key immunological, histological, viral and metabolic questions related to how the disease develops. The DRI's **Alberto Pugliese**, M.D., deputy director and head of immunogenetics, and the University of Florida's **Mark Atkinson**, M.D., director of the UF Diabetes Institute, serve as co-executive directors of nPOD, together with a multidisciplinary team of diabetes investigators.



During the past three years, The Helmsley Charitable Trust (HCT) has supported nPOD with the George Eisenbarth nPOD Award for Team Science, providing critical funds for infrastructure, pilot studies and working groups. Last year, HCT renewed this vital funding source to support continued pilot studies conducted throughout nPOD working groups.



The nPOD working groups investigate specific interest areas in diabetes research. Among these is nPOD-V, a self-assembled group of collaborators who investigate the role of viruses in type 1 diabetes through the study of nPOD samples. This past year, the nPOD-V group was awarded renewed grant support by JDRF in gaining a better understanding of the causes of T1D as it relates to the role of viruses. The goal of this research is to generate critical evidence to support and guide the production of an anti-viral vaccine and anti-viral therapies that are important for disease prevention, as well as treatment, given the chronic nature of autoimmunity and viral infections.

1. Alberto Pugliese, M.D., co-executive director of nPOD (left of sign), together with DRI colleagues at the nPOD meeting in Florida.

2. David Baidal, M.D., assistant professor of medicine, is the TrialNet site principal investigator.

3. Ronald B. Goldberg, M.D., professor of medicine, is director of the Diabetes Prevention Program.

*Working closely with colleagues throughout the U.S. and globally, DRI researchers investigate more strategies, share more ideas, and accomplish more success for those living with diabetes.*

## Type 1 Diabetes TrialNet



The Diabetes Research Institute is one of 25 participating centers in TrialNet, an international consortium of clinical research centers that conduct studies to prevent or delay type 1 diabetes. Led by **David Baidal**, M.D., the DRI's TrialNet team collaborates with investigators throughout the entire network to recruit those who are eligible to participate in and carry out the clinical studies.

TrialNet has conducted a number of clinical trials designed to prevent diabetes onset and preserve beta cell function in recent-onset T1D using different agents and treatment strategies. At the 2019 ADA Scientific Sessions, TrialNet reported on the first drug that can delay the onset of type 1 diabetes in children and adults at high risk for the disease. The results of this multi-center study, of which the DRI was a part, showed that teplizumab (anti-CD3) allowed people to live diabetes-free an extra two years, on average. For people who are at risk for developing the disease, this is good news. This is the first study to show any drug can delay T1D.

TrialNet is supported by the National Institutes of Health (NIH), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), JDRF, American Diabetes Association (ADA), and Helmsley Charitable Trust.

## Diabetes Prevention Program Outcomes Study (DPPOS) Phase 3



Under the direction of **Ronald B. Goldberg**, M.D., professor of medicine, and his team, the Diabetes Research Institute has played a key role in the Diabetes Prevention Program (DPP) and DPPOS since the study's inception in 1994.

Sponsored by the National Institutes of Health, the DPP was a major multicenter study that examined if intensive lifestyle changes (dietary changes and physical activity) or treatment with the medication metformin would prevent or delay the development of type 2 diabetes in people at high risk for the disease.

The DPP Outcomes Study (DPPOS) explored the longer-term effects of the interventions on the further development of type 2 diabetes and diabetes complications, including heart, kidney and eye diseases. The DPPOS demonstrated that these effects were durable over the subsequent 10 years of follow-up.

The fact that DPPOS is the longest-running clinical trial testing the effects of metformin has made this aspect of the study the centerpiece of the new DPPOS Phase 3 trial. Two years ago, Dr. Goldberg was awarded a five-year, \$1.7 million grant, which initiated Phase 3 of the DPPOS.

DPPOS Phase 3 will study the DPPOS patient cohort for 10 more years and examine outcomes that are of an increasing public health concern in the aging population with pre-diabetes and type 2 diabetes. The overarching goals of the DPPOS Phase 3 include examining the long-term effects of metformin therapy on the risk for cardiovascular disease and cancer, the effects on microvascular complications, and the clinical course of pre-diabetes and new onset diabetes.

To learn more visit: [nPOD jdrfnpod.org](http://nPOD.jdrfnpod.org) [TrialNet trialnet.org](http://TrialNet.trialnet.org) [Diabetes Prevention Program dppos.org](http://Diabetes Prevention Program.dppos.org)



# mission

To provide the Diabetes Research Institute with the funding necessary to cure diabetes *now*.

The Diabetes Research Institute Foundation (DRIF) is the organization of choice for those who are serious, passionate and committed to curing diabetes. Its mission – to provide the Diabetes Research Institute with the funding necessary to cure diabetes *now* – is a testament to the belief that tomorrow is not soon enough to cure those living with diabetes.

## About The Diabetes Research Institute Foundation

The Diabetes Research Institute has become the world leader it is today through the substantial funding provided by the Foundation. Supported by private philanthropy, the DRIF seeds the funding of new ideas and ensures the continuation of innovative research projects that remain cure-focused and will ultimately benefit those with diabetes.

The DRIF's history of commitment dates back to 1971 when it was founded by a small group of parents of children with diabetes who were dedicated to finding a cure. Driven by a shared mission, they banded together to support a promising research program at the University of Miami solely aimed at curing those living with diabetes. In an unprecedented partnership that spans more than three decades and continues today, North America's Building Trades Unions joined with the Foundation's leadership to help fulfill its mission to cure diabetes. The DRIF's largest contributor, the Building Trades committed to funding – and building – the Diabetes Research Institute facility. The unions have raised more than \$50 million for the DRI and today, under the banner of Blueprint for Cure, thousands of union members undertake fundraising projects nationwide to provide ongoing support.

The DRI Foundation is recognized as one of the world's most respected diabetes organizations. Garnering the attention of influential people who are personally affected by diabetes, the Foundation has grown into an international coalition of business leaders, celebrities, scientists, clinicians, families and other concerned individuals who have elevated the importance of cure-focused research and provided meaningful support for the DRI's multidisciplinary research program.

This funding is provided through individual and corporate donations, special events, sponsorships, cause marketing relationships and planned giving, which allows donors to provide a gift in the form of a will, trust or other deferred giving vehicle.

In an effort to increase awareness about the latest advances toward a cure, the Foundation conducts a wide variety of activities both online and offline, hosts research updates and workshops for people with diabetes and their families, and produces numerous printed publications and e-communications to make this information accessible to people nationally and internationally. A 501(c)(3) not-for-profit corporation, the DRI Foundation has thousands of supporters in the United States and worldwide.

The Diabetes Research Institute Foundation was created for one reason – to cure diabetes – which is and will continue to be its singular focus until that goal is reached. For the millions of individuals and families affected by diabetes, the Diabetes Research Institute Foundation is the best hope for a cure.



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