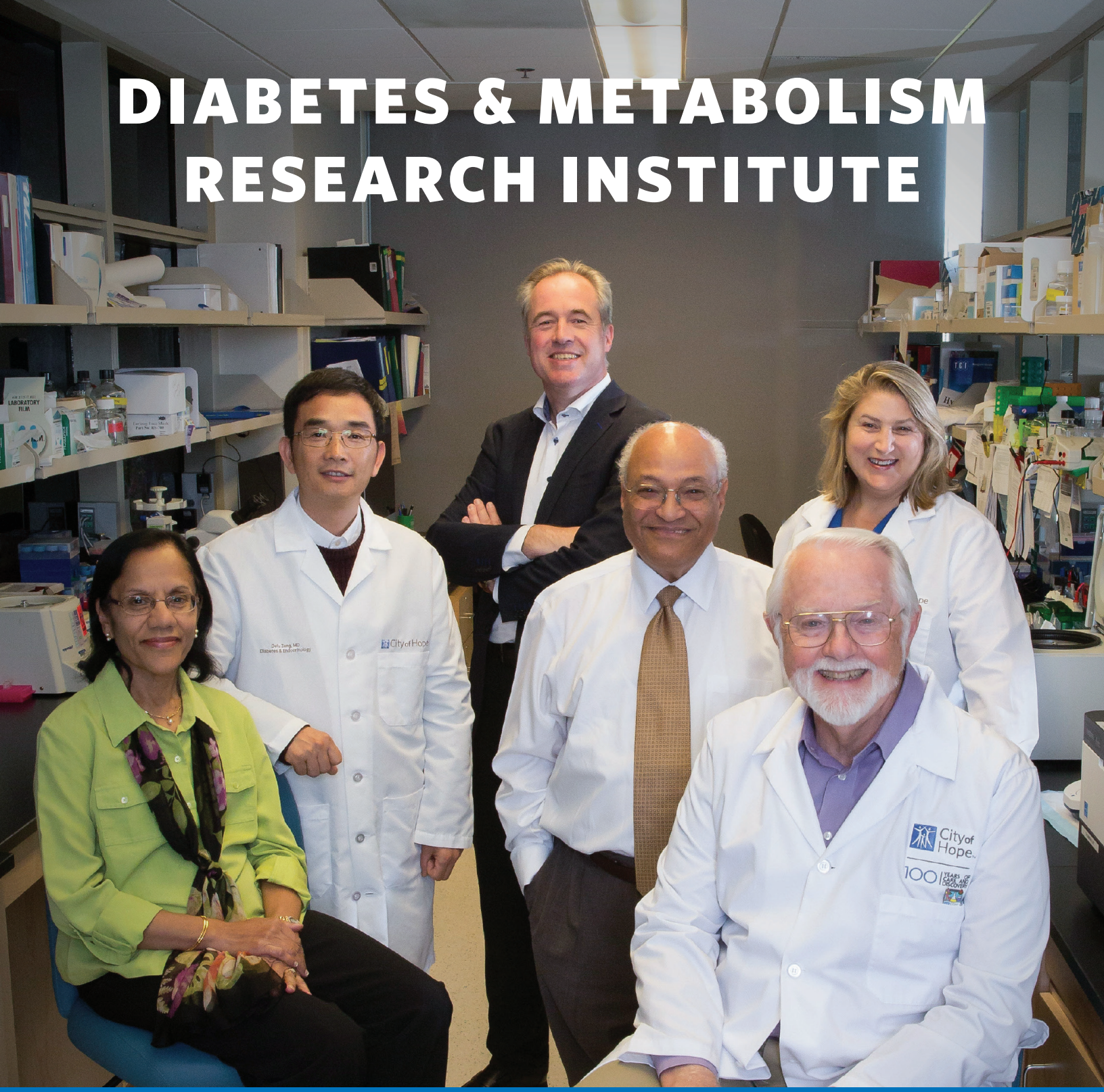
DIABETES & METABOLISM RESEARCH INSTITUTE



See what philanthropy has helped to accomplish, and what it will fuel going forward.

Philanthropic support of scientists in the Diabetes & Metabolism Research Institute at City of Hope advances the fight against diabetes. This report highlights just a few of the exciting projects that were made possible because of this partnership.

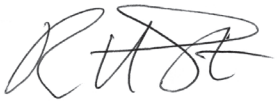
the MIRACLE of SCIENCE with SOUL™ City of Hope®

To Our City of Hope Community,

I am very proud to share this report on our Diabetes & Metabolism Research Institute, especially with the upcoming 40th anniversary of the seminal paper published by Dr. Arthur Riggs and his team. Building on that incredible milestone, which led to the first synthetic human insulin for patients, we celebrate the institute's collective accomplishments — work that has helped more than 100 million people worldwide.

This is only the beginning. As we look to the future, we continue to develop promising treatments and drive toward cures.

All of this is made possible through our philanthropic partnerships and committed supporters. Together we will turn hope into reality for the benefit of patients today and tomorrow.



Robert W. Stone

President and Chief Executive Officer

Dear Friends,

The Diabetes & Metabolism Research Institute had a banner year. Several new departments were launched, comprised of some of the most renowned faculty in the nation who are poised to make major contributions to the fields of diabetes, metabolism and immunology. As one of the top diabetes research groups in the country, especially for cell-based therapy, we are well-positioned to tackle this challenge.

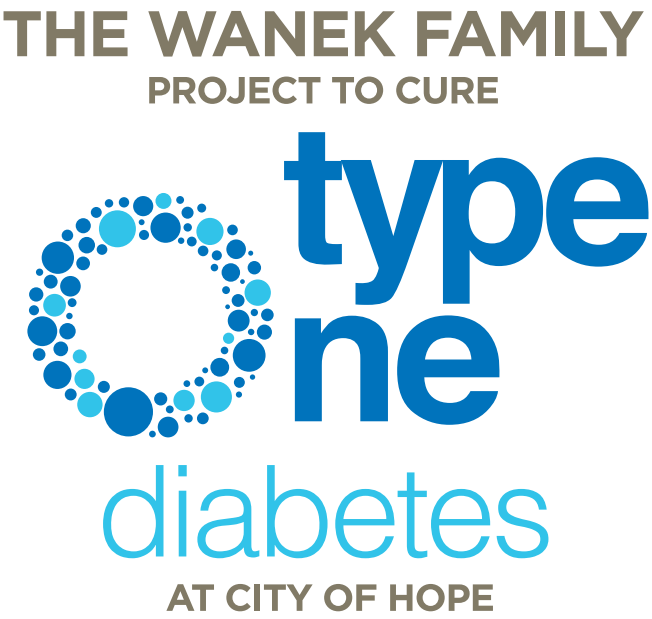
I hope you enjoy reading about some of the leading-edge research that is inspiring hope for millions of people.

Arthur Riggs, Ph.D.

Director, Diabetes & Metabolism Research Institute
Samuel Rahbar Chair in Diabetes & Drug Discovery
Emeritus Director, Beckman Research Institute of City of Hope

Diabetes impacts the lives of more than 422 million people worldwide. That's 1 in 11 adults

or about 40 times the population of L.A. County.



Update: The Wanek Family Project Year 1

At the start of 2017, the Diabetes & Metabolism Research Institute announced the inception of the Wanek Family Project for Type 1 Diabetes. The goal of this $50 million initiative is to find a cure for type 1 diabetes (T1D) in six years — an ambitious timeline. This funding has already set the stage to accelerate clinical trials of next-generation treatments and establish the first steps on the road to cure T1D.

During year one of the Wanek Family Project, 16 compelling projects were successfully launched, and 12 of these accomplished their ambitious first-year milestone(s). The first year also resulted in the filing of four patents to secure intellectual property and establish the foundation for synergy with the pharmaceutical industry to more quickly translate novel therapeutic strategies to the clinic. City of Hope provided funds to support 10 additional projects that will undoubtedly innovate, translate and accelerate strategies to narrow the gap to a cure for T1D.

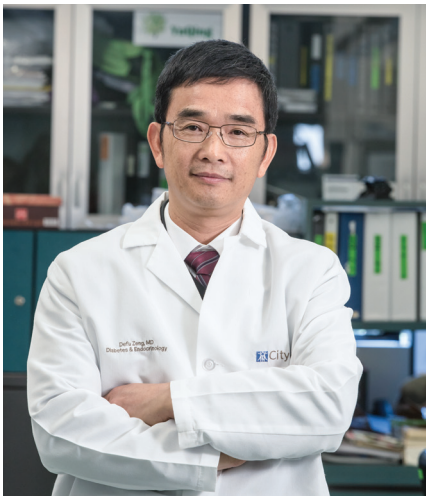
TYPE 1 DIABETES RESEARCH HIGHLIGHTS

Pillar 1: Modulating the Immune System

City of Hope is advancing breakthrough research to correct T1D's autoimmune attack by regulating — instead of suppressing — the immune system. Our innovative approaches aim to restore a balanced immune system to stop the attack on insulin-producing beta cells, as well as reawaken or boost remaining beta cells in order to help patients produce insulin on their own. Such therapies represent a radical shift in treatment — they target the cause of the disease, rather than just its consequences (insulin insufficiency).

Current Trials

Preclinical testing has shown that mixed chimerism — a state that is achieved when a donor's immune system is transplanted into a patient and coexists alongside his or her own immune system — could potentially cure autoimmune diseases like lupus and multiple sclerosis. In recent animal studies, **Defu Zeng**, in collaboration with Arthur Riggs, Ph.D., Samuel Rahbar Chair in Diabetes & Drug Discovery, demonstrated that achieving an enduring state of mixed chimerism can also potentially cure T1D.



Zeng, in partnership with Joseph Rosenthal, M.D., Barron Hilton Chair in Pediatrics, is conducting a safety trial of the regimen used to calm the immune system in preparation for inducing mixed chimerism. The first-in-human trial, which is enrolling patients with severe sickle cell anemia, will use it in an extremely creative and novel way that Zeng and Rosenthal believe has the ability to cure these patients of their potentially fatal genetic disorder. In support of this work, the California Institute of Regenerative Medicine recently awarded nearly $6 million to enable them to conduct this trial. Being able to prove safety in humans in that trial will then allow Zeng to move forward and evaluate his mixed chimerism strategy as a possible cure for T1D.

Building on the success of his trials in Europe, **Bart Roep, Ph.D.**, Chan Soon-Shiong Shapiro Distinguished Chair in Diabetes, is implementing a clinical trial for patients with T1D. Rather than resetting the immune system, Roep is testing a vaccine that uses vitamin D3, along with a unique form of insulin, to re-educate a patient's own immune cells to help decrease the inflammatory attack that causes T1D. The goal of his vaccine is to both prevent beta cell destruction and restore the islet-specific immune regulation that is lost in T1D. This exciting new approach shows the potential impact of precision medicine — using individual variations in genes, environment and lifestyle to develop therapies to target, treat and monitor chronic and life-threatening conditions.

Fouad Kandeel, M.D., Ph.D., will be launching a clinical trial to explore the effectiveness of mesenchymal stem cell-derived extracellular vesicles — particles released by cells that are able to significantly modify our immune response. His goal is to halt the autoimmunity that causes T1D while prompting a patient's natural ability to produce sufficient insulin on their own. This landmark study will represent the first Food and Drug Administration (FDA)-approved trial utilizing vesicles to treat T1D patients and has the potential of developing into an off-the-shelf biologic therapy.

Future Trials

Kandeel also aims to halt the autoimmune destruction of recently diagnosed T1D patients and eliminate the need for immune suppressive drugs for islet transplant recipients. In order to accomplish this, he is training regulatory T (Treg) cells to help block the progression of islet destruction in early phase T1D. Kandeel is currently planning clinical trials and plants to submit his investigational new drug (IND) application with the FDA in mid-2019.

The Importance of Precision Medicine:

"Diabetes is actually a spectrum of disease, which is why we need so many treatment options. Looking at people's individual genetic signature will give us insight into what's happening in their bodies."

— Debbie Thurmond, Ph.D., Ruth B. & Robert K. Lanman Chair in Gene Regulation and Drug Discovery Research

Pillar 2: Replacing or Revitalizing Beta Cells

Insulin producing beta cells, which are found in the pancreas, are destroyed by an autoimmune attack in T1D. Renowned for our work in producing beta cells, we are conducting vital research to expand and improve these cells in order to make them less susceptible to attack by the immune system. Our beta cell replacement platform is unique among our peers, and we are building on it to create improved methods of boosting and replacing beta cells, as well as imaging them in the body to understand and encourage long-term survival.

Current Trials

Kandeel is currently running a clinical trial to test his theory that gastrin, a hormone that has been shown to promote beta cell expansion in animal studies, might allow T1D patients to achieve insulin sufficiency with a single islet transplant.

Upcoming Trials

Kandeel is also finalizing the clinical protocol on the development of a noninvasive imaging probe that will allow doctors to monitor transplanted islet cells. This probe could be vital to establishing and evaluating the efficiency of pancreatic islet transplantation in order to improve transplant outcomes. He plans to submit an IND application to the FDA by mid-2019.

Advancing Research

This year, **Debbie Thurmond, Ph.D.**, discovered the mechanism by which a protein (STX4) protects pancreatic function and survival of beta cells, even when they are challenged with inflammatory stress that mimics T1D. What Thurmond found was that the presence of STX4 makes beta cells better at secreting insulin and makes muscle and fat cells more responsive to insulin. Thus, she hypothesizes that factors which enhance insulin activity, such as STX4, could counter difficulties and complications associated with either form of diabetes.

To test this hypothesis, Thurmond is collaborating with Roep to explore how they can restore or raise STX4 levels, in order to increase insulin secretion and overcome insulin resistance in patients with diabetes and those at risk of developing the disease. The team hopes create a way to deliver STX4 into human islet cells as a next step toward clinical trials.

Pillar 3: Preventing, Halting or Reversing Diabetic Complications

For patients living with diabetes, complications affecting multiple organs can persist even when the disease is well-controlled. Treatments that intervene at the epigenetic level to reverse complications have the power to bring healing. Investigators are developing novel interventions, built on their expertise in understanding the complex epigenetic modifications that cause complications.

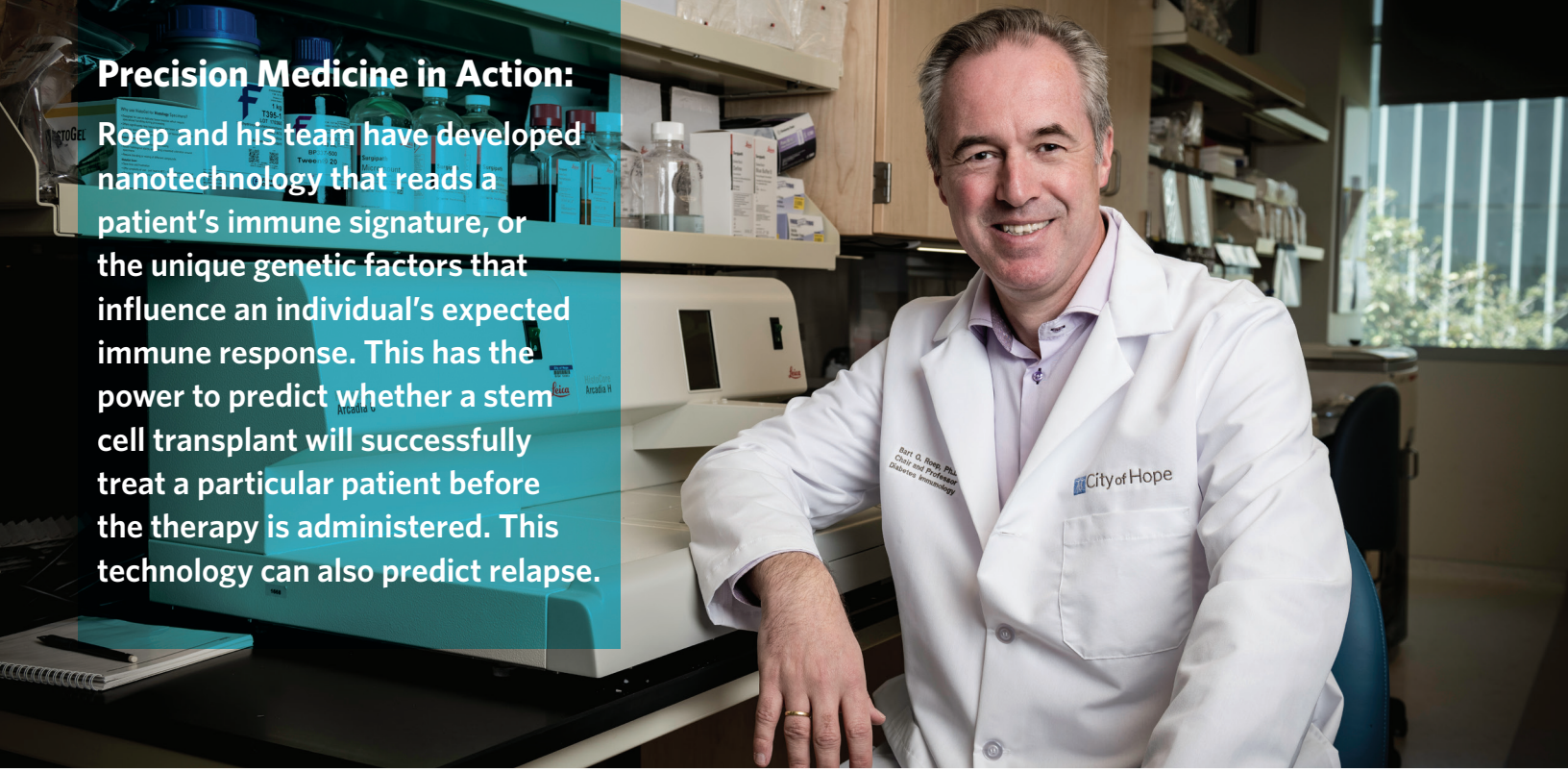
Advancing Research

Riggs and **James Figarola, Ph.D.**, are in the process of developing an innovative drug that aims to decrease diabetic neuropathy — nerve-related pain and/or loss of feeling in the limbs. Affecting as many as 60-70 percent of people with diabetes, neuropathy is one of the most common and debilitating complications associated with both T1D and type 2 diabetes (T2D).

In initial animal studies, the new compound has shown a reduction in the occurrence and severity of neuropathy with no major side effects. Next, the team will conduct additional preclinical studies and apply for FDA approval to run an in-human trial.

Rama Natarajan, Ph.D., National Business Products Industry Professor in Diabetes Research, studies the causes of devastating complications associated with diabetes and how to treat them. One such project focuses on metabolic memory, a phenomenon in which cells "remember" diabetes and act like they are still diseased, even after normal glucose levels are achieved. This means that the development of heart, eye and kidney complications can persist despite sugar control. Natarajan has made seminal contributions to the field by showing the role of epigenetics for the first time in metabolic memory — specifically in a particularly harmful gene called TXNIP. She and her team are focused on developing a small molecule drug that will inhibit TXNIP to interrupt and reverse metabolic memory in order to intervene in the progression of T1D and its complications.

Natarajan and her team are also developing novel gene therapies to address a new target with the hope of slowing down the progression of diabetic kidney disease and other complications. They have already filed two patent applications for this discovery.



Precision Medicine in Action:
Roep and his team have developed nanotechnology that reads a patient's immune signature, or the unique genetic factors that influence an individual's expected immune response. This has the power to predict whether a stem cell transplant will successfully treat a particular patient before the therapy is administered. This technology can also predict relapse.

PROMISING TYPE 1 DIABETES INNOVATIONS

Roep recently made a unique discovery that redefines both the process and the culprit involved in the immune attack that leads to T1D.

Taking note of how successful cancer immunotherapy treatments "remind" the immune system to recognize and then target specific cancer molecules, Roep and his team looked at one such target, a so-called nonsense protein that is produced by misread DNA sequences. Of interest, this same type of protein error is also produced by stressed beta cells in T1D. Therefore, Roep and his collaborators believe it is a "wrong read" of DNA sequences in the insulin gene itself that results in our beta cells being targeted by our immune system, in the same way that these nonsense proteins become a target in cancer.

Before Roep's discovery, common medical knowledge held that the root cause of T1D was the immune system mistakenly identifying insulin-secreting beta cells as a danger and, in turn, destroying them. However, Roep contends that T1D results from a mistake of the beta cell, not a mistake of the immune system. The immune system is responding to these error proteins with the best intentions, when they are mistakenly produced by beta cells, identifying and attacking them as it would when they are seen during infection or cancer.

This groundbreaking knowledge paves the way for new generations of therapies targeting beta cells to be combined with immunotherapy, radically changing treatment options from simply coping with T1D to halting its development by treating the immune system directly.

Vaccine for Diabetes:

Rates of T1D are increasing worldwide, so there is an urgent need for an inexpensive but effective way to restore the body's regulatory mechanisms. Mohamed Elsayed, Ph.D., is exploring how to prevent T1D through the creation of an oral vaccine that could potentially be easy to produce and administer.

Increasing Stem Cell Transplant Effectiveness

Graft-versus-host disease (GVHD) is a long-term side effect that occurs in approximately half of people receiving allogeneic stem cell transplants, used to treat specific forms of blood cancer and in certain acute cases of blood-related genetic disorders like sickle cell anemia. GVHD occurs when the newly transplanted donor cells do not recognize the patient's cells and decide to attack them.

Zeng's recent studies showed that PD-L1 (a cell surface molecule that regulates how the immune system responds to changes like stem cell transplants, for example) working in combination with PD-1 (another protein related to this process) can regulate the survival of a protective intestinal immune cell called CX3CR1hi, and balance intestinal bacteria that are involved in immunologic response. Now, he is working to develop novel ways to expand the protective CX3CR1hi cells to prevent severe GVHD in the gut, the most critical step for preventing systemic GVHD.

The team is also developing an additional molecule (PD-L1-Ig) with the potential to grow Treg cells in vivo and reduce disease-causing T cells in people with GVHD. This work, once perfected for use in people, will exponentially increase the effectiveness of stem cell transplants and possibly translate to a true cure for patients with hematological malignancies.

Using Immunotherapeutics to Target T1D

Roep discovered that many islet cells survive the immune system's attack by halting their insulin production and activity. Using immunotherapeutics, he hopes to stop and reverse diabetes by preventing the destruction of surviving islets and, in parallel, reawaken hibernating cells to start producing insulin again.

Patient results from Roep's initial trial in the Netherlands have been extraordinary, prompting him to accelerate a U.S.-based trial to assess this novel immune intervention strategy. This will be the first trial of its kind, targeting people with T1D years after receiving a diagnosis.

Furthering Islet Cell Research

In T1D, the body's immune system mistakenly destroys insulin-producing beta cells, a type of cell within islet cells. City of Hope plays a key role in distributing islet cells and coordinating information-sharing efforts across institutions in order to drive research conducted around the world in the search for a cure.

Joyce Niland, Ph.D., the Estelle & Edward Alexander Chair in Information Sciences, oversees both the Human Islet Research Network's Coordinating Center (HIRN-CC) and the Integrated Islet Distribution Program's Coordinating Center (IIDP-CC). The HIRN-CC helps facilitate scientific communications and resource sharing across the HIRN and with the scientific community at large. The IIDP provides high quality, cost effective international islet distribution. As head of the coordinating center, Niland and her team worked with five human islet isolation centers to distribute 927,691 islets from donors with T2D and 7,094,179 islets from other donors last year!

TYPE 2 DIABETES

Maintaining Balance - The Key to Staving off Disease

Normally, there is a delicate balance between various molecules as they interact within a cell. When these processes are disturbed, imbalances (such as high blood sugar) can result and promote metabolic diseases like cancer and diabtes. **Lei Jiang, Ph.D.**, looks to expand our understanding of how cells maintain balance and pinpoint what goes wrong in cancer and diabetes.

In order to accomplish this, Jiang tracks the levels of various molecules within healthy and diseased cells to see how they differ, which may provide clues as to what causes the disease. He has found that one of the major contributors to maintaining balance in the cell is the mitochondria — the tiny "machines" in our cells that burn sugar to produce energy that cells need. Jiang is currently delving into the details at the molecular level of what makes the mitochondria less effective under conditions of disease, and how to target the mitochondria to help them work better in patients with diabetes or cancer.

Understanding Susceptibility to Obesity and Metabolic Disease

Natarajan's goal is to understand why some individuals are more susceptible to obesity and metabolic disease, as well as why some metabolic dysfunction persists despite lifestyle modifications. The answer, she hypothesizes, is in our epigenetics. She is currently exploring how environmental factors such as a high fat diet can contribute to epigenetic changes leading to obesity, diabetes, inflammation and related complications.

Activating Fat Cells to Improve Insulin Resistance

Annabel (Qiong) Wang, Ph.D., is focused on understanding the development and treatment of obesity, T2D and related metabolic syndromes. One way she is tackling this challenge is by researching brown adipocyte tissue (BAT), which is a specific kind of fat that actually looks brown in color and burns sugar to produce heat much faster than regular fat cells.

Having larger amounts of BAT or stimulating BAT to be more active could correct hyperlipidemia (high levels of fat in the blood), prevent diet-induced obesity and improve insulin resistance. Wang and her team recently discovered that there are two types of fat cells present in BAT: "active" cells that burn sugar and generate heat, and "resting" cells. She is currently studying how various genes control this activity in order to identify potential targets that could make more of these cells "active."

Exercise in a Pill?

Janice Huss, Ph.D., has discovered that activating a particular pathway in the skeletal muscle allowed mice to run long distances on a treadmill without tiring despite their "couch potato" lifestyles. These changes also improved their ability to handle insulin and glucose. The notion of "exercise in a pill" is an attractive therapeutic option — especially for patients unable to perform regular exercise — but this aspiration requires a better understanding of how this happens. Over the next year, Huss aims to explore exactly how this pathway is involved in controlling metabolic genes in response to exercise. Eventually, she hopes to identify factors to trigger controlled activation of this pathway in order to create targeted therapies for T2D.

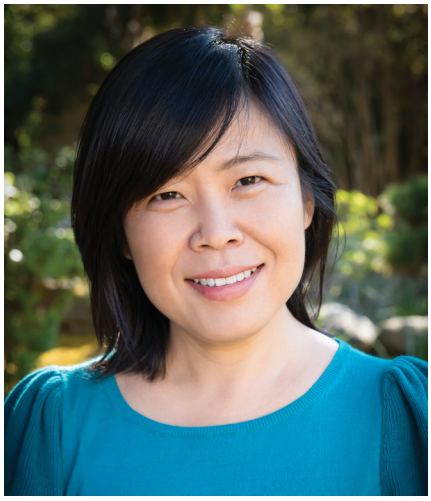
Developing a Compound that Targets a Harmful Protein

Patrick Fueger, Ph.D., has discovered that a protein called Mig6 is harmful to both the insulin-producing beta cells and the liver in T2D. In collaboration with others at City of Hope, he is developing compounds to block the negative effects of Mig6 with the hope of preventing or reversing the disease. Over the next year, Fueger and his team will test these compounds in the laboratory and in animal models in order to create a new potential therapy for T2D.

Exploring Related Diseases

An abnormality in the way lipids are stored in the liver can lead to nonalcoholic fatty liver disease (NAFLD), a health threat which, if not treated, can lead to metabolic diseases such as T2D. **John Shively, Ph.D.**, is working to better understand NAFLD and the role of a gene called CEACAM1 in metabolic disease, lipid regulation in the liver and control of inflammation in the immune system. He and his team have recently discovered a novel mechanism that they are testing to see if it provides insight into how NAFLD works and potential treatments for the condition.

Understanding the Circadian Clock's Role in T2D



Circadian rhythm is a term that refers to how the human body has a natural cycle and follows patterns of wakefulness and sleep. These changes are driven by internal "clocks" that are present in different tissues and organs, and are controlled by clock genes.

In the past year, **Ke Ma, M.D., Ph.D.**, and her team have discovered that the circadian clock in muscle plays a key role in the body's ability to determine whether more food should be stored as fat or broken down to generate energy. When this clocks malfunctions, it markedly impairs our body's ability to handle glucose and utilize fat properly. Ma's research team is currently exploring the specific reasons underlying the circadian clock system's role in causing metabolic disorders like T2D. Based on these studies, they will explore different ways to target the genes and pathways that control the clocks in order to mitigate the adverse effects of dysfunctional clocks on metabolism.

Understanding the Molecular Mechanisms of Bariatric Surgery

Wendong Huang, Ph.D., is working on a way to treat diabetes and obesity by mimicking bariatric surgery — a procedure that induces weight loss — with medicine. Specifically, he and his team are currently determining the roles of bile acid receptors and how they reproduce the anti-obesity and anti-diabetes effects of this surgery.

Molecular Factors Underlying Vascular Complications in Diabetes and Cancer

Patients with diabetes or obesity are at higher risk of cardiovascular disease, and **Zhen Chen, B. Med., Ph.D.**, is taking a closer look at a molecule called nitric oxide synthase (NOS) that is important for maintaining healthy blood vessels and proper insulin levels. NOS is made by the endothelial cells that line the surface of blood vessels, and levels of NOS can decrease in response to stress conditions, particularly those associated with obesity and diabetes.

In the past year, Chen and her team have shown for the first time that a specific type of molecule called long noncoding RNA helps turn on the gene that makes NOS. Pinpointing an exact molecule that can turn up the levels of NOS is a major achievement that provides important insight into understanding the connection between vascular health and diseases such as diabetes.

Strengthening Our Defense Mechanisms

The human genome is littered with repetitive genetic elements that have accumulated throughout evolutionary history. In order to keep these repetitions in check, our bodies have developed defense mechanisms. However, when these mechanisms break down or become less effective, the results can lead to a number of metabolic diseases, including diabetes and obesity. **Dustin Schones, Ph.D.** and his lab have demonstrated that obesity leads to changes in these defense mechanisms and increases peoples' risk for other diseases, including cancer. Schones and his team are currently trying to understand obesity's role in these changes with the hope of creating targeted therapies that could prevent or reverse diabetes and other related diseases.

PHILANTHROPIC DOLLARS AT WORK IN 2018*

380 DONORS GAVE 447 GIFTS

TOTALING $18,047,741**

*based on City of Hope's fiscal year that runs from October through September
**includes gifts and pledges

INVESTING IN A FUTURE FREE FROM DIABETES

If you would like more information on the projects in this report, or any others that are being conducted at City of Hope's Diabetes & Metabolism Research Institute, please contact:

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