PATHWAY TO STOP DIABETES®

2014 ANNUAL SUMMARY REPORT

American Diabetes Association®
Research Foundation

PATHWAY TO STOP DIABETES

Diabetes impacts nearly 30 million Americans today, with 86 million more at serious risk for developing the disease. Diabetes presents an enormous challenge for individuals and families, and it is a societal burden that threatens to overwhelm our healthcare system. Yet, diabetes research is critically underfunded, leading talented investigators to choose other areas of focus. This problem creates a disaster for future innovations in diabetes prevention, treatments and cures, because the next generation of diabetes researchers may be lost forever.

In 2013, the American Diabetes Association launched *Pathway to Stop Diabetes*, a transformational approach to address this crisis by creating a new generation of exceptional diabetes researchers. The prestigious, nomination-only, *Pathway* Awards are designed to attract brilliant scientists at the peak of their creativity, and accelerate research progress by providing the resources and support for conducting transformative science by:

- Focusing on exceptional scientists,
- Providing substantial and sustained funding that is unrestricted and portable,
- Guiding the researchers with a broad array of scientific and career mentoring,
- Creating systems and programs for collaboration, communication, and career advancement

Pathway provides crucial support to individuals focusing on innovative ideas and transformational approaches to Stop Diabetes.

With more than $35 million in generous gifts from individuals, foundations and corporations, including program sponsors Sanofi, Novo Nordisk, AstraZeneca and the Eli Lilly and Company Foundation, *Pathway* is making significant progress toward this objective.

HIGHLIGHTS FROM 2014

The year 2014 marked the first full year of funding for the *Pathway* program, which is off to a successful start by all measures.

- The first class of five *Pathway* scientists was announced in January 2014.
- Two high-profile papers were published by *Pathway* scientists within just six months of their awards.
- The two *Pathway* scientists who received Initiator awards successfully transitioned from training into their first faculty positions.
- One patent application was submitted by a *Pathway* scientist.
- *Pathway* scientists presented their work to the Mentor Advisory Group, Association leadership and *Pathway* sponsors and donors at the first *Pathway* Symposium.
- The second call for nominations led to the selection of six new *Pathway* scientists, announced in January 2015.

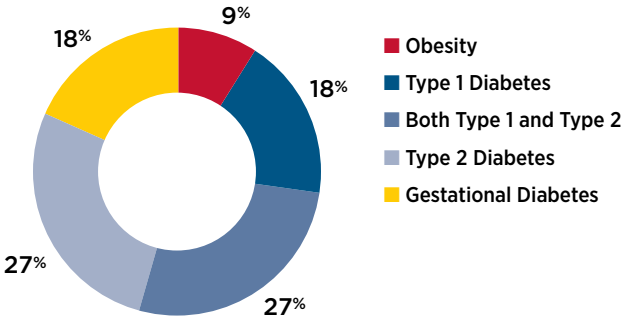
THE *PATHWAY* PORTFOLIO

Now 11 strong, *Pathway* scientists comprise a strong program portfolio representing the full breadth of diabetes research and achieving key program goals.

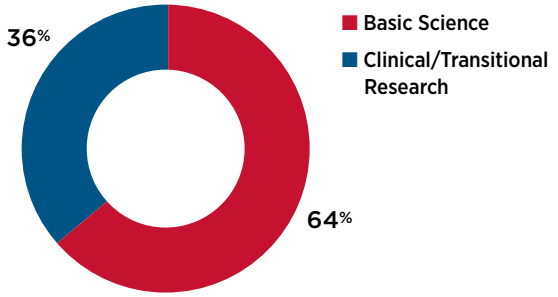
Highlights of the *Pathway* portfolio include:

- Balanced investments across diabetes types, including two projects dedicated to type 1 diabetes and three relevant to both type 1 and type 2 diabetes
- Collaborative, multi-disciplinary approaches, including a biomedical engineer working with biologists, endocrinologists and chemists to develop new ways to automate insulin and glucagon delivery using nano technologies
- Expertise from other fields applied to diabetes, including a scientist with experience successfully developing drugs for other diseases working to develop better ways to treat diabetic wounds, reducing diabetes-related amputations
- Diverse group of investigators (degree, gender, race/ethnicity)

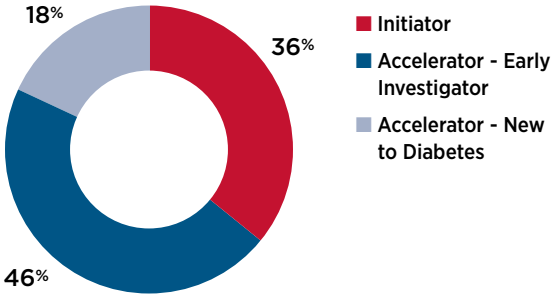
Pathway Portfolio by Diabetes Type



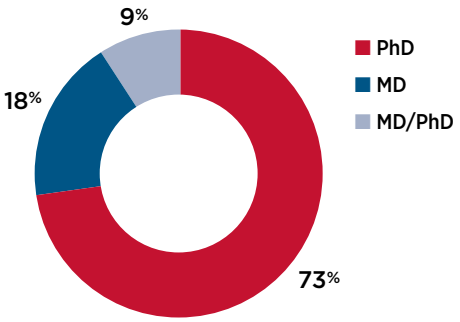
Pathway Portfolio by Research Type



Pathway Portfolio by Award Type



Pathway Scientists by Degree



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AVERAGE AGE OF *PATHWAY* INITIATOR AND ACCELERATOR – EARLY CAREER SCIENTISTS

Compared to **42** for initial NIH R01 awardees and **51** for NIH R01 awardees overall

KEY ACCOMPLISHMENTS OF *PATHWAY* SCIENTISTS IN 2014

The inaugural class of five *Pathway* scientists was announced in January 2014. The class comprised two Initiator Awards, two Accelerator – Early Investigator Awards and one Accelerator – New to Diabetes Award. In just the first year of funding, the successes of these scientists and of the program are impressive.

Publications and Presentations

Peer-reviewed publications are the currency of science. Two *Pathway* scientists published manuscripts in top-tier academic journals within the first six months of their *Pathway* funding. In addition, *Pathway* scientists presented a combined 10 poster and oral presentations and 24 invited lectures in 2014.

Krishnan N, Miller DH, Kragelj K, Ringkjøbing Jensen M, Gauss K, Xue B, Muthuswamy SK, Page R, Blackledge M, **Peti W**, Tonks NK. (2014) A novel mechanism of allosteric inhibition of protein tyrosine phosphatase PTP1B reveals a new strategy for therapeutic development, *Nature Chemical Biology*, 10(7), 558-566.

Dennis MD, Coleman CS, Jefferson LS, Kimball SR. (2014) REDD1 Enhances Protein Phosphatase 2A (PP2A)-Mediated Dephosphorylation of Akt to Repress mTORC1 Signaling. *Science Signaling* 7: ra68.

Promotions

The Initiator Awards are intended to assist *Pathway* scientists with making a successful transition from training to independent academic research. In 2014, both recipients of the Initiator Awards began their first faculty positions.

- Dr. Michael Dennis was promoted internally from Post-doctoral Fellow to Assistant Professor at Pennsylvania State University – Hershey.
- Dr. Stephen Parker transitioned to an independent faculty position at the University of Michigan after interviewing for seven positions and receiving an offer for each.

Patents

One patent was filed by a *Pathway* scientist in 2014. Dr. Wolfgang Peti filed a patent for *Methods and compounds for treatment of PTP1B-related diseases*. PTP1B is an important regulator of the insulin signaling pathway and a potential target for therapeutic development for diabetes.

The *Pathway* Symposium and Guidance from Accomplished Mentors

Members of the Mentor Advisory Group, in addition to corporate sponsors and philanthropic supporters of the program, attended the inaugural *Pathway* symposium, held in San Francisco, CA on June 13, 2014, preceding the commencement of the American Diabetes Association's 74th Scientific Sessions. This occasion offered all five *Pathway* scientists an intimate and rigorous platform to present their projects and progress and to receive critical feedback and new opportunities for collaboration.

The thought-provoking discussion following each presentation added a powerful component to the symposium, highlighted the incredible value of mentorship and collaboration, and demonstrated that the *Pathway* scientists are clearly thinking about and articulating how their work can be translated into real solutions for those living with and at risk for diabetes.

THE *PATHWAY* PROGRAM

The grant mechanisms in the *Pathway* program are designed to provide support to exceptionally creative scientists at two critical career stages: investigators early in their diabetes research careers, and investigators established in other disciplines, but interested in expanding their focus to diabetes research.

The three *Pathway* grant types are:

- ***Pathway* Initiator** — For scientists currently in training positions, as they transition to independence
- ***Pathway* Accelerator-Early Investigator** — For scientists early in their independent careers
- ***Pathway* Accelerator-New to Diabetes** — For well-established scientists with a track record of success in another field of study, who wish to apply their expertise to diabetes research

Game-changing scientific breakthroughs of many Nobel laureates came in fields that were not their original fields of research. Fredrick Banting, who discovered insulin, was a surgeon who had not previously worked in diabetes research.

Through its Accelerator – New to Diabetes grants, *Pathway* is bringing new perspectives to diabetes research. *Pathway* scientist Wolfgang Peti is applying structural biology expertise to diabetes and *Pathway* scientist Mayland Chang, who has expertise in neurology and antibiotic development, is working on drug development to improve wound-healing in diabetes.

Pathway accepts nominations directed toward all topics relevant to the prevention, treatment and cure of any type of diabetes (type 1, type 2 and gestational), diabetes-related disease state (obesity, pre-diabetes, and other insulin resistant states) or diabetes complication.

Applications are accepted by institutional nomination only, and each institution is allowed only a single nomination. Institutions perform internal searches and select their best candidates to nominate. All scientists who are selected by their institution to submit an application have been evaluated and nominated by the people who best know their work and their potential.

Pathway Awards provide $1.625M in unrestricted, flexible, long-term support for research. These funds are granted to the individual, rather than the institution, and are portable should the investigator change institutions. Thus, *Pathway* scientists are able to seek positions where they will receive the strongest institutional support, and follow their science, wherever it takes them.

In addition to the financial aspect of the grants, the *Pathway* Program provides awardees ongoing mentorship from the Mentor Advisory Group for the duration of their grant, and opportunities to integrate into the diabetes research community and develop lifelong relationships and collaborations.

> **“ I am immensely grateful for the access to mentorship and resources that being part of this community brings. ”**
>
> – Stephen C.J. Parker, PhD, 2014 *Pathway* Initiator Award Recipient

THE 2015 NOMINEES

For the 2015 competition, 116 institutions in 37 states nominated candidates. The 116 nominations included 17 *Initiator*, 47 *Accelerator – Early Investigator*, and 52 *Accelerator – New to Diabetes* applications (Figure 1). Sixty percent of the nominees had never applied for any type of American Diabetes Association research grant support in the past, and 8 individuals (7%) had submitted previous *Pathway* applications for 2014 and were re-nominated by their institutions for 2015. Clearly, ***the initiative continues to attract a new group of investigators to the field of diabetes research,*** one of the key objectives of the program.

The majority of applicants were from departments related to biomedical sciences, including biology, medicine, endocrinology, biochemistry and physiology. However, nearly 10% were from less traditional departments including engineering, mathematics, physics, chemistry and geography, suggesting that ***the program is reaching individuals from new areas and with novel approaches to diabetes research.***

The nominations were distributed among basic (62%), translational (27%) and clinical (11%) research, in very similar proportions to the inaugural year. Together, clinical and translational research (including various aspects of clinical therapeutics, behavioral science, epidemiology, and nutrition) represented nearly 40% of the applications, suggesting that the nomination and application process was amenable to various research approaches.

Finally, ***the program attracted investigators in all types of research that are relevant to diabetes,*** as the distribution of applications across diabetes types (Figure 2) was also diverse. There was a notable increase in type 1 diabetes nominations this year.

Figure 1: *Pathway* Nominees by Grant Type (Comparing 2014 & 2015)

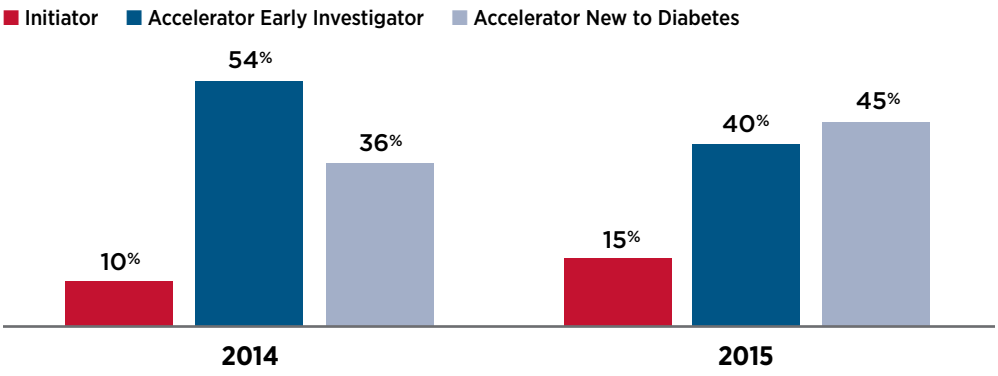
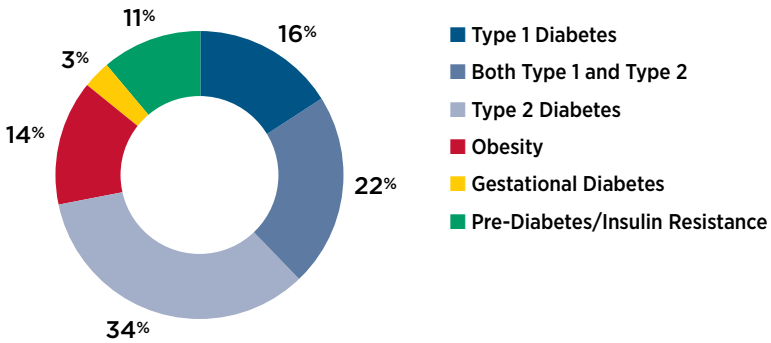


Figure 2: *Pathway* Nominees by Diabetes Type (2015)



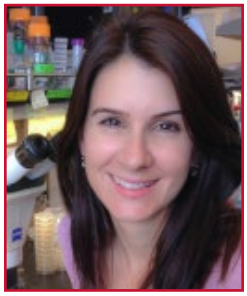
SELECTING THE *PATHWAY* SCIENTISTS

The 2015 *Pathway* candidates were outstanding, proposing innovative and novel approaches focused on improving the lives of people with diabetes. Of the initial 116 applications, 33 finalists were selected for detailed discussion at an in-person review meeting of the Mentor Advisory Group. At this meeting, each application was reviewed and scored. The Mentor Advisory Committee then ranked the grants within each category and provided funding recommendations to the American Diabetes Association National Research Policy Committee for final approval. In the 2015 competition, six applicants were ultimately selected to receive prestigious *Pathway* Awards.

This second class of *Pathway* scientists brings another exciting new set of projects to the *Pathway* portfolio, including two projects focused on type 1 diabetes. These awardees exemplify the qualities that the *Pathway* initiative seeks to attract: a diverse group of the highest quality scientists with bold and innovative approaches that are poised to change the face of diabetes. Expectations for success are high for these scientists and the program.

ANNOUNCING THE 2015 AWARDEES

Initiator Awards



Celine Emmanuelle Riera, PhD
University of California, Berkeley, Berkeley, CA
Identification of Sensory Neural Circuits Controlling Metabolic Disorders

In order to adapt quickly to changes in environmental conditions and perception of internal senses (such as digestion, temperature, hunger, pain and blood pressure), mammals rely on a part of the brain called the hypothalamus to integrate a variety of signals into appropriate responses and meet energy demand. However, it is not well understood whether neurons involved in sensory perception have the ability to translate sensory information into metabolic responses through communication with the hypothalamus and other brain regions. By focusing on the critical senses of pain and smell, which play important roles in the perception of harmful conditions and nutrient availability, this project will identify components of the metabolic response that become disrupted in type 2 diabetes.

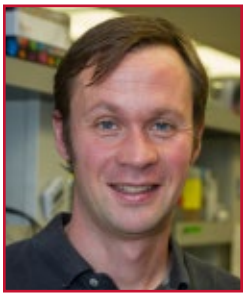
Through better understanding of these sensory systems, and how they impact metabolic activity, new therapies to treat type 2 diabetes may be identified.

Stephanie Stanford, PhD
La Jolla Institute for Allergy and Immunology, La Jolla, CA
PTPN22: Model Gene to Unravel the Interaction between Genetics and Environment in Type 1 Diabetes

A mutation in a gene called PTPN22 is one of the strongest known genetic risk factors for type 1 diabetes (T1D). Viral infections are important risk factors for development of T1D, and the PTPN22 gene may play a critical role in defense against viruses. This project will study whether the mutated PTPN22 gene predisposes to T1D by

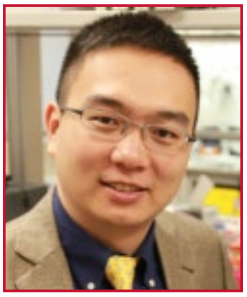
decreasing the response to viral infections. The results from this study will elucidate the mechanism by which a genetic T1D risk factor combines with an environmental trigger to confer disease susceptibility. Importantly, if correct, this model suggests that protection from and/or aggressive treatment of viral infections could prevent T1D in people with this genetic risk factor, and will pave the way to preventative treatment strategies for individuals at high risk of developing T1D.

Accelerator – Early Investigator Awards



Thomas Delong, PhD
University of Colorado Denver, Denver, CO
The Role of Hybrid Insulin Peptides in the Development of Type 1 Diabetes

Type 1 diabetes (T1D) is an autoimmune disease that is mediated by the immune system's own T cells. Normally, T cells fight infection by mounting a response to foreign bodies, called antigens, when they are detected in the circulation. While the immune system has mechanisms to prevent T cells from recognizing self-antigens, in T1D those mechanisms fail and T cells inappropriately attack the body's own insulin-producing beta cells. In order to prevent or reverse the development of T1D it is therefore critical to understand why and how T cells are misguided. This project describes a modification to self-antigens that are recognized by T cells that trigger diabetes in a major animal model for T1D. The researchers hypothesize that the same modification is relevant in the development of human T1D. They will test this hypothesis using T cells that were isolated from the remaining islet tissue of deceased human T1D patients. Additionally, the researchers have identified a potential mechanism that leads to these antigen modifications. They will study the mechanism and test whether the formation of modified antigens can be chemically inhibited, thereby blocking destruction of insulin-producing beta cells and preventing type 1 diabetes.



Zhen Gu, PhD
North Carolina State University, Raleigh, NC and University of North Carolina at Chapel Hill
Bio-Inspired Synthetic Pathway for Closed-Loop Delivery of Insulin and Glucagon

A therapeutic system capable of automatically regulating insulin delivery in proportion to blood glucose levels is highly desirable for people with type 1 and advanced type 2 diabetes. Several synthetic glucose-responsive formulations for self-regulated delivery of insulin have been developed. However, there are numerous remaining challenges to crafting a biocompatible system that would be easy to administer, provide a sufficiently fast insulin response, and prevent hypoglycemia. Inspired by the natural insulin vesicles in pancreatic beta cells, this project will develop artificial "synthetic insulin vesicles". The hypothesis is that the materials will be able to regulate release of insulin at high blood glucose levels and inhibit its release within the normal glucose range. To prevent potential hypoglycemia, the project includes design of "synthetic glucagon vesicles" to counteract unexpected large releases of insulin. If successful, these systems can fundamentally change how type 1 diabetes is managed and reduce the burden of monitoring and treatment.

Marie-France Hivert, MD
Harvard Pilgrim Health Care Institute, Harvard Medical School, Boston, MA
Understanding Pathways of Fetal Metabolic Programming to Stop the Transgenerational Risk of Diabetes

Exposure to maternal hyperglycemia in the womb is associated with significantly higher lifetime risk of type 2 diabetes (T2D). The exact mechanisms explaining this phenomenon are still unknown. This project will apply recent technological advances to examine differences in how epigenetic regulation (one of the mechanisms that controls gene expression) is linked to *in utero* exposure to diabetes. By following mother-child pairs throughout pregnancy and childhood, the study is expected to identify new information about which epigenetic adaptations across the human genome are implicated in linking maternal blood glucose to the offspring's future T2D risk. Revealing new information about how T2D is triggered in these children could aid development of early life prevention measures to reduce rates of diabetes in future generations.

Accelerator – New To Diabetes Award

Mayland Chang, PhD
University of Notre Dame, Notre Dame, IN
A Strategy to Accelerate Diabetic Wound Repair

A serious complication of diabetes is the inability of wounds to heal, which contributed to 73,000 lower-limb amputations in the United States in 2010. Currently, no therapeutic agents for the treatment of diabetic wounds are approved and there is a paucity of research to understand why diabetic wounds are difficult to heal. Preliminary work has identified enzymes called "matrix metalloproteinases" (MMPs) that seem to influence wound healing in diabetic mice. In addition, a drug has been identified that selectively blocks the detrimental MMP, is not toxic to mice, and is poised for development as a topical therapy for diabetic wound healing. This project proposes to validate the beneficial and detrimental roles of MMPs in human samples and to understand how MMP inhibitor drugs may improve diabetic wound healing. The combination of studies applying selective MMP inhibitors and using samples from people with diabetes is expected to lead to a new treatment for this serious complication of diabetes.

THE FUTURE

The third annual* Pathway *call for nominations opened in January 2015, with an application deadline of July 1, 2015.

On June 5, 2015, in Boston, Massachusetts, prior to the start of American Diabetes Association's 75th Annual Scientific Sessions, the* Pathway *scientists will assemble for the 2nd Annual* Pathway *Symposium. The invitation-only symposium includes the Mentor Advisory Group and Association leadership, as well as the individual donors and sponsors of the program. The *Pathway* scientists will present their research plans and progress to date. The Mentor Advisory Group will provide feedback, assess progress, and challenge traditional thinking in order to accelerate the *Pathway* scientists' research progress. Through events like the *Pathway* Symposium, the *Pathway* program creates a culture of excellence, and provides opportunities for the *Pathway* scientists to develop lasting professional and personal relationships that will enhance their research and careers.

MENTOR ADVISORY GROUP

The *Pathway* proposals are reviewed in detail by the *Pathway* Mentor Advisory Group — eminent scientists who seek in the *Pathway* applicants the core elements for exceptional science: rigorous thought processes, keen intellect, and capacity for innovation, creativity, and productivity.

C. Ronald Kahn, MD
Chair, Mentor Advisory Group
Joslin Diabetes Center and
Harvard Medical School
Boston, MA

John B. Buse, MD, PhD
University of North Carolina School of Medicine
Chapel Hill, NC

Barbara J. Anderson, PhD
Baylor College of Medicine
Houston, TX

Lawrence Chan, MD
Baylor College of Medicine
Houston, TX

Mark A. Atkinson, PhD
The University of Florida
Gainesville, FL

Silvia Corvera, MD
University of Massachusetts Medical School
Worcester, MA

Richard N. Bergman, PhD
Cedars-Sinai Medical Center
Los Angeles, CA

Robert H. Eckel, MD
University of Colorado Anschutz Medical Campus
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San Francisco, CA

Michael S. German, MD
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University of Michigan Medical School
Ann Arbor, MI

Margaret Grey, DrPH, RN, FAAN
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Alvin C. Powers, MD
Vanderbilt University School of Medicine
Nashville, TN

Barbara V. Howard, PhD
MedStar Research Institute and Georgetown University
Hyattsville, MD

Christopher J. Rhodes, PhD
The University of Chicago School of Medicine, Kovler Diabetes Center
Chicago, IL

Barbara Kahn, MD
Beth Israel Deaconess Medical Center
Boston, MA

Philipp E. Scherer, PhD
University of Texas Southwestern Medical Center
Dallas, TX

Steven Kahn, MB, ChB
VA Puget Sound Health Care System and University of Washington School of Medicine
Seattle, WA

Elizabeth Seaquist, MD
University of Minnesota
Minneapolis, MN

Francine R. Kaufman, MD
Medtronic Diabetes and USC School of Medicine, Children's Hospital
Los Angeles, CA

Randy J. Seeley, PhD
University of Michigan
Ann Arbor, MI

Christopher Newgard, PhD
Duke University
Durham, NC

Alan R. Shuldiner, MD
University of Maryland School of Medicine, Baltimore, MD and Regeneron Genetics Center
Tarrytown, NY

Jeffrey E. Pessin, PhD
Albert Einstein College of Medicine
Bronx, NY

Gerald I. Shulman, MD, PhD
Yale University School of Medicine
New Haven, CT

Pathway to Stop Diabetes Corporate Sponsors and Philanthropic Supporters

Through the tremendous generosity of four founding corporate sponsors and many philanthropic supporters who embrace new ways of thinking, *Pathway to Stop Diabetes* is accelerating the types of scientific investigations needed to discover solutions and ultimately end diabetes.

The Association extends deep appreciation for the investments that contribute toward the successes of this bold research initiative*.

Corporate Sponsors

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Bess Weatherman

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