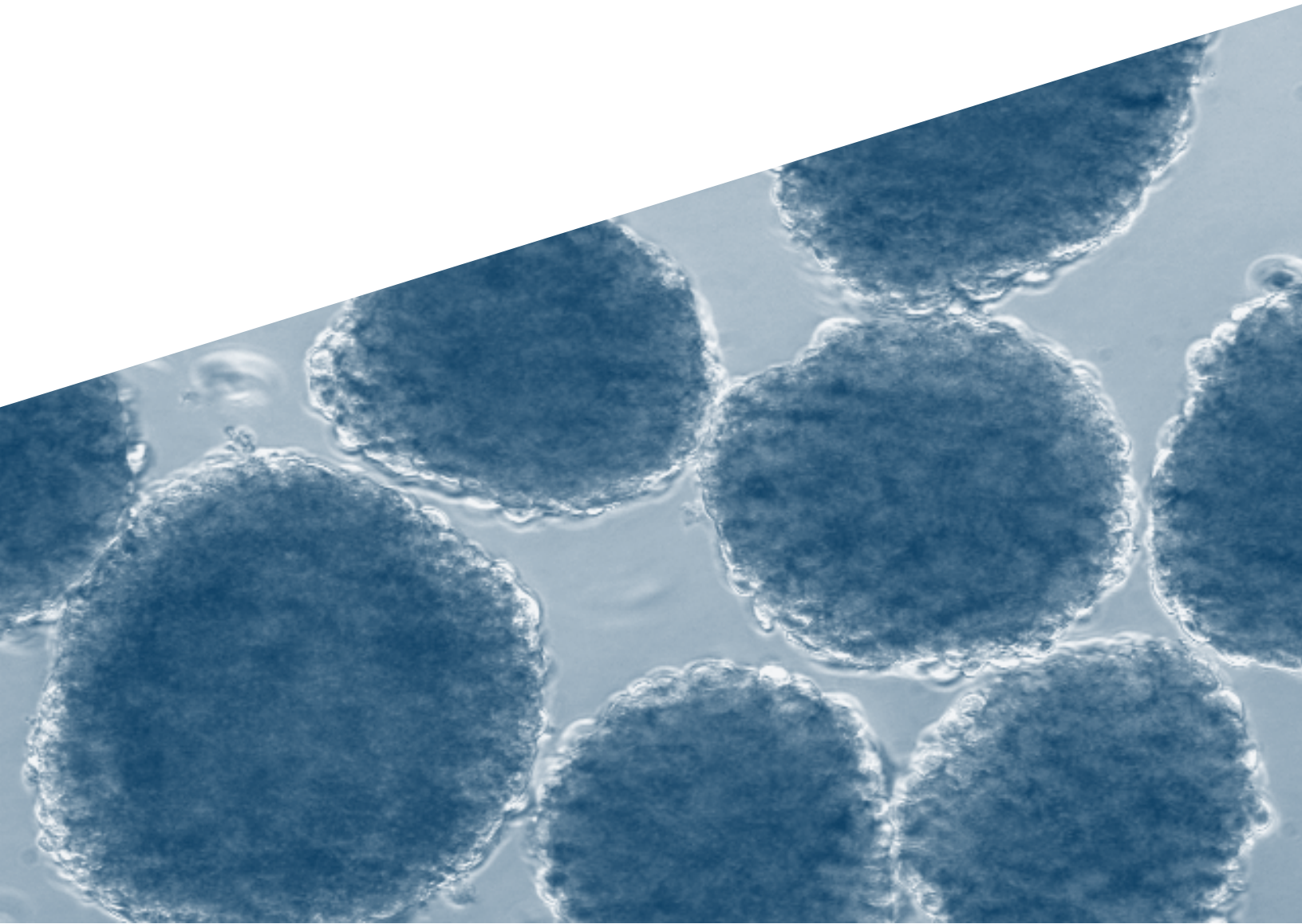
FUTURE OPPORTUNITIES FOR TYPE 1 DIABETES RESEARCH



The Special Statutory Funding Program for Type 1 Diabetes Research has supported great strides in the understanding of this disease, but much work remains to be done. Studies to identify how genetic propensities and environmental triggers initiate the disease process in humans are now critical. Continued research on animal and cellular models to understand molecular mechanisms will provide the basis for rational development of preventive agents for type 1 diabetes and its devastating complications. Ongoing investment in clinical trials and research will help scientists translate research advances into real improvements in patients' health. Thus, the research initiatives and resource development projects undertaken with the special funding program to date have sparked exciting new opportunities for future, cutting-edge research on understanding, preventing, and treating type 1 diabetes.

In addition to reviewing the special statutory funding program to date, the advisory panel of leading scientific experts convened at the NIH in May 2002 also assessed accomplishments and considered new research opportunities that have emerged as a result of the program's investment. The panel was encouraged both by the scientific progress supported by the special funds, as well as by the establishment of collaborative research infrastructure, such as consortia and trial networks, that will synergize future research efforts in the field. The advisors' recommendations for future research focused on: new research questions and goals that are critical to continuing advances in type 1 diabetes; the potential to apply new research methodologies to the study of type 1 diabetes; and research resources and infrastructure that would facilitate multidisciplinary approaches to the complex problems of type 1 diabetes and its complications. Following are highlights of specific research opportunities identified by the advisory panel.

Photo
Purified human islets
for transplantation.

(Photo Credit: Over Cabrera and Camillo Ricordi, University of Miami, Diabetes Research Institute)

Important Questions and Research Goals

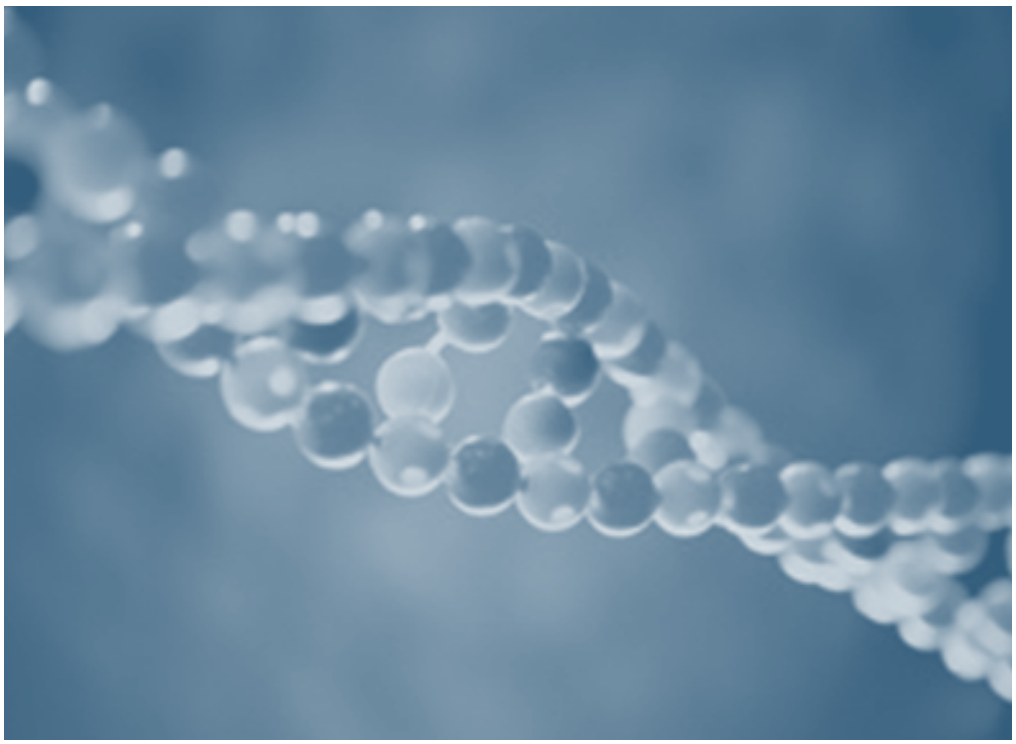
- Understand the role of Histocompatibility Leukocyte Antigens (HLA)—which are genetically linked to type 1 diabetes susceptibility—in the development of autoimmunity;
- Define the mechanism of T cell-mediated destruction of the pancreatic beta cells;
- Find methods to reverse autoimmunity by promoting central tolerance and reprogramming of T cells;
- Understand the contributions of autoantibodies to the pathogenesis of type 1 diabetes;
- Identify beta cell antigens that initiate the autoimmune process;
- Examine environmental factors during gestation that potentially modulate future susceptibility to type 1 diabetes;
- Investigate the effect of parental type 1 diabetes on possible immune tolerization of offspring during pregnancy;
- Study infectious agents, including viruses, as possible triggers of the autoimmune reaction leading to type 1 diabetes;
- Use type 1 diabetes as a platform for understanding immunology and autoimmunity.

Applying New Methodologies

- Apply proteomics approaches to the study of insulitis and the identification of circulating beta cell markers;
- Design beta cell imaging technology for use in assessing progression of autoimmune destruction of beta cells;
- Develop assays for identifying pathogenic T cells involved in triggering type 1 diabetes;
- Utilize synteny mapping and haplotype mapping approaches to the identification of genes conferring susceptibility to or protection from development of type 1 diabetes;
- Use PCR-based RNA or DNA analyses to identify infectious agents that may trigger autoimmune diabetes.

Resources and Infrastructure

- Devise a system for procurement of pancreata from organ donors, who had been identified as new-onset type 1 patients or autoantibody positive, pre-diabetic individuals, to facilitate research on insulitis—the inflammation of islets by infiltrating T cells;
- Promote cross-talk among databases and integration of bioinformatics resources to improve coordination and data-sharing among related consortia and research networks;
- Expand the type 1 diabetes animal repository to include non-NOD mouse backgrounds and inbred strains for studies of genetic and environmental susceptibility factors and drug testing;
- Establish human sample repositories to facilitate transfer of data and resources among research groups;
- Develop new research consortia to expedite the study of genes and environmental factors affecting diabetes susceptibility;
- Foster industry collaboration and participation in consortia to bring needed expertise in drug development;
- Establish type 1 diabetes as a reportable illness throughout the U.S. to shed light on the magnitude of the type 1 diabetes epidemic.



DNA double helix.

Important Questions and Research Goals

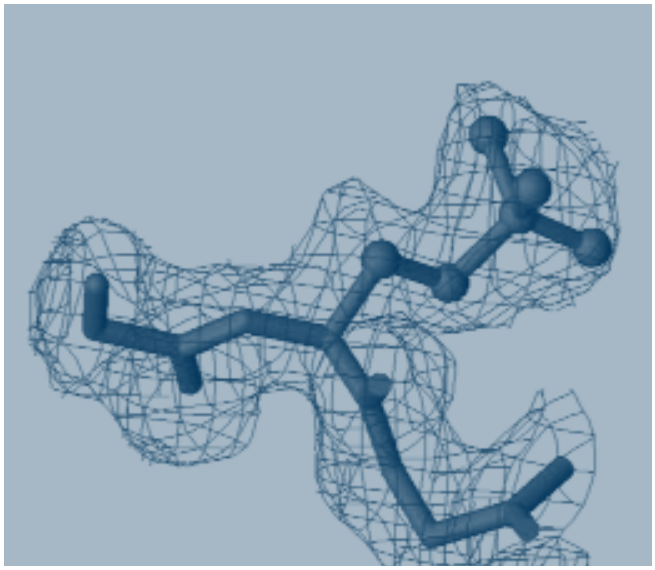
- Develop safe and effective approaches to preventing type 1 diabetes;
- Design methods to preserve or restore residual beta cell function in new-onset patients;
- Improve assays for identifying those at risk of developing type 1 diabetes;
- Generate new technologies for monitoring disease progression.

Applying New Methodologies

- Ensure that pathogenic T cell assays are included in the design of future prevention trials;
- Develop beta cell function assays that can be used as a clinical endpoint sufficient for drug approval.

Resources and Infrastructure

- Establish a central resource to facilitate preclinical studies of new drug efficacy and safety in animals;
- Create "humanized" animal models for the development of more specifically targeted therapies;
- Develop a non-human primate model of autoimmune beta cell destruction that closely mimics the human disease;
- Improve the standardization of C-peptide assays to reduce laboratory variability;
- Enhance human research consortia and interactions;
- Create a centralized Institutional Review Board (IRB) to expedite multi-center clinical trials.



Antibody structure.

Important Questions and Research Goals

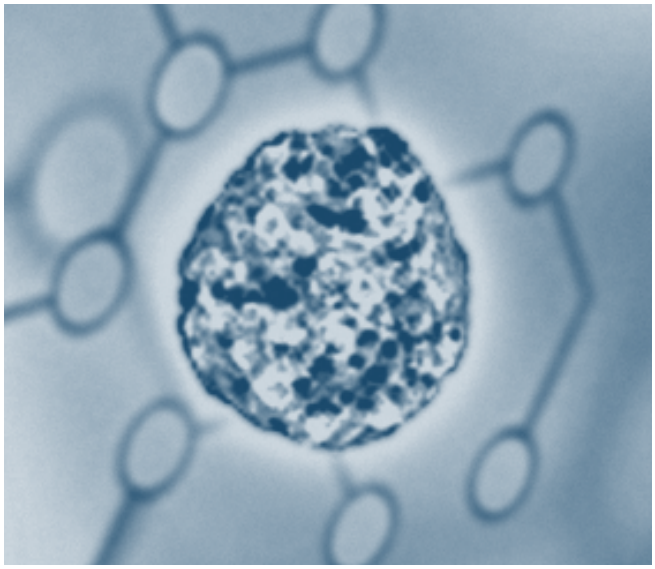
- Pursue stem cells or stimulators of stem cells as a source of beta cells that could overcome the short supply of islets available for transplantation by current protocols;
- Delineate the immune components of stem cells as they differentiate to determine whether stem cell-derived replacement beta cells can resist autoimmunity;
- Understand the biology of stressed or injured cells to optimize islet isolation techniques;
- Improve islet transplantation procedures;
- Document risks and benefits of islet transplantation, including issues of cost effectiveness, quality-of-life, and the development of complications.

Applying New Methodologies

- Perform a systematic evaluation of approaches to islet transplantation, including the optimization of:
  - pancreas harvesting;
  - islet isolation, evaluation, and preservation;
  - site and method of islet transplantation;
  - immunosuppression, tolerance induction, and other aspects of immunomodulation;
- Apply insights from angiogenesis research to the study of islet graft vascularization;
- Adapt proteomics approaches to measure beta cell specific proteins in plasma for monitoring insulitis and autoimmunity recurrence.

Resources and Infrastructure

- Strengthen mechanisms for data sharing and cross-talk among consortia;
- Expand international collaborations; for example, extend data collection through the islet transplant registry to include international transplantation procedures;
- Improve access to state-of-the-art immunology measurements for transplant trials;
- Explore ongoing opportunities for initiating research support as justified by emerging preliminary data.



Pancreatic islet.

GOAL IV Prevent or Reduce Hypoglycemia in Type 1 Diabetes

Important Questions and Research Goals

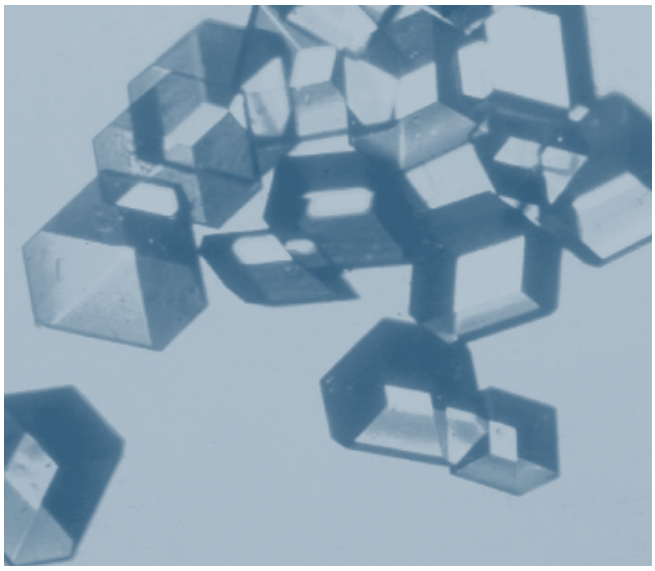
- Understand the mechanisms of hypoglycemia unawareness and nocturnal hypoglycemia;
- Examine the role of glucose transporters and monocarboxylic acid in sensing and responding to hypoglycemia;
- Identify long-term consequences of recurrent hypoglycemia, particularly in young children;
- Develop new therapies, such as insulin analogs, that reduce the occurrence of hypoglycemia;
- Elucidate mechanisms of the reversal of hypoglycemia unawareness and defective counter-regulation to inform the development of pharmaceutical approaches to restore counter-regulation;
- Intensify research on glucose sensors and the development of closed-loop systems for glucose sensing and insulin delivery;
- Evaluate the clinical utility of new glucose sensors and insulin delivery devices, including the effects of these technologies on patients' quality-of-life.

Applying New Methodologies

- Investigate the problem of hypoglycemia unawareness in new islet transplant recipients;
- Recruit neuroscientists and brain-imaging specialists to study similarities in the glucose-sensing mechanisms of the pancreatic beta cells and the brain;
- Develop neuronal cell lines for the study of glucose sensing;
- Use new sensors that measure neurotransmitter substrates in the brain for investigation of brain glucose sensing;
- Use MRI spectroscopy, brain volume measurement, and other advanced imaging technologies to identify brain changes after recurrent and/or severe hypoglycemia;
- Apply new glucose sensor technology to the development of methods for metabolic screening in research animals.

Resources and Infrastructure

- Establish multidisciplinary research consortia to foster new approaches to the problem of hypoglycemia.



Insulin crystals.

GOAL V Prevent or Reduce Complications of Type 1 Diabetes

Important Questions and Research Goals

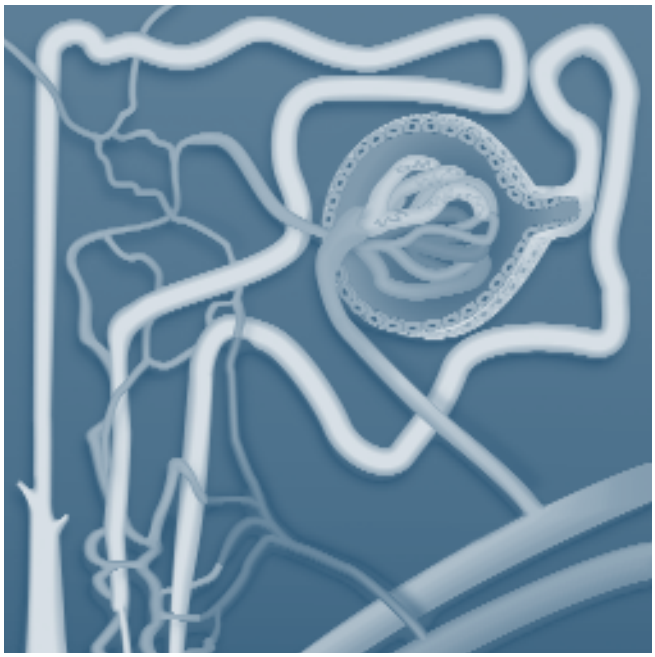
- Uncover the role of inflammation in vascular complications of diabetes, particularly with respect to the functional interactions between monocytes and endothelial cells;
- Expand clinical studies of the role of aspirin, statin therapy, blood pressure control, and other factors, which are effective in preventing cardiovascular disease in type 2 diabetes, to type 1 diabetes;
- Develop improved animal models of diabetes complications.

Applying New Methodologies

- Use monocytes for assessing the effects of interventions that affect inflammatory pathways relevant to vascular complications;
- Develop microarrays for research on gene expression patterns in tissues and organs affected by diabetic complications;
- Use congenic technology to develop rat and mouse models that combine diabetic susceptibility with the propensity to develop long-term complications.

Resources and Infrastructure

- Form consortia of investigators studying individual complications to promote tissue sharing and examination of multiple complications—particularly in studies of new therapeutic agents in humans and animals—to enhance the cost effectiveness of research;



Kidney nephron diagram.

(Credit: Maryetta Lancaster, for NIH Medical Arts and Photography Branch).

- Establish consortia of endothelial cell biologists, immunologists, and investigators studying inflammation to study cardiovascular disease in type 1 diabetes;
- Encourage partnerships between industry and academia to spur drug development and testing;
- Develop mechanisms to bring discoveries with therapeutic applications that originate in academic laboratories through preclinical development;
- Create a resource for distributing animals with prolonged, sustained hyperglycemia for use in testing new therapeutics;
- Publish a central knowledge base of complications-related initiatives supported across the NIH.

GOAL VI Attract New Talent to Type 1 Diabetes Research

Important Questions and Research Goals

- Attract new basic and clinical researchers to research on type 1 diabetes;
- Ensure that new technologies and insights from a variety of fields are rapidly applied to research on type 1 diabetes.

Resources and Infrastructure

- Extend opportunities for research training and pilot and feasibility studies beyond the life span of a single solicitation;
- Issue flexible solicitations that allow investigators to identify promising projects from a breadth of research areas.

Public Health Service grant application.

(Photo Credit: Richard Nowitz for NIDDK)