SUMMARY AND RECOMMENDATIONS

The Strategic Plan will serve as a scientific guidepost to the National Institutes of Health (NIH) and to the investigative and lay communities by identifying compelling research opportunities that will inform future type 1 diabetes research efforts and propel research progress on the understanding, prevention, treatment, and cure of type 1 diabetes and its complications for the next decade.

OVERVIEW OF TYPE 1 DIABETES

Type 1 diabetes is a devastating disease in which the body's immune system attacks and destroys insulin-producing beta cells, which are found in clusters in the pancreas called islets. Without this vital hormone, the cells and tissues cannot absorb glucose (sugar), and patients' cells can starve to death, despite high levels of glucose in the bloodstream. Therefore, patients require daily insulin administration for survival. Type 1 diabetes, as patients and parents say, "never takes a day off." Patients or caregivers must constantly monitor glucose levels. If they are too high, patients must take insulin. If too low, they must eat food to boost their glucose levels. The constant burden of this disease greatly affects the quality of life of patients and family members.

Although life-saving, insulin therapy is not a cure. Despite the vigilant efforts of patients to keep their glucose levels as close to normal as possible, chronically high glucose levels (hyperglycemia) damage their organs. This damage, in turn, can result in the development of life-threatening disease complications, such as blindness, kidney failure, nerve damage, lower limb amputation, heart disease, and stroke. These complications can reduce average life span by many years. Given the unremitting demands of diabetes, it is not surprising that it heightens the risks for various psychiatric disorders, such as depression. On the flip side, when patients aggressively manage their glucose levels with insulin therapy to try to prevent these devastating complications, they are at risk for dangerous episodes of low blood glucose (hypoglycemia). Patients may not even be aware that they are experiencing these episodes (hypoglycemia unawareness). If left untreated, hypoglycemia can result in coma and even death. Patients with type 1 diabetes must constantly walk a tightrope to balance the risks of the immediate danger of hypoglycemia and the long-term danger of complications from high blood glucose levels.

Type 1 diabetes differs from type 2 diabetes, which is more commonly diagnosed in adulthood, is strongly associated with overweight and obesity, and disproportionately affects minority populations. However, both forms of the disease share the same complications. Treating diabetes and its complications places an enormous public health burden on the United States.

RESEARCH OBJECTIVES

This Strategic Plan identifies key research objectives that will guide future NIH efforts to achieve six overarching Goals of type 1 diabetes research. The objectives outlined in this Plan build upon recent scientific advances and represent scientific opportunities for overcoming current barriers and achieving progress in type 1 diabetes research over the next 10 years.

Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes

Type 1 diabetes results from an interplay of genetic and environmental factors. Several key genes involved in the disease have been identified, but many more remain unknown. Environmental factors have also been found to play a role, but no single trigger has been conclusively identified. Research

on genetic and environmental factors could help predict who will develop type 1 diabetes, and could also lead to the identification of novel prevention strategies. Key research objectives in this area are:

Genetic Causes

- Create Resources for the Study of Type 1 Diabetes Genetics
- Identify Human Genes Causing Type 1 Diabetes
- Use Knowledge About the Genetic Underpinnings of Type 1 Diabetes To Prevent and Treat the Disease

Environmental Causes

- Monitor Rates of Type 1 Diabetes
- Assess Environmental Causes of Type 1 Diabetes

Goal II: Prevent or Reverse Type 1 Diabetes

Preventing type 1 diabetes onset would obviate the need for daily insulin administration and the serious disease complications. Research to explore the defects in the immune system that are associated with autoimmunity could lead to new methods to predict, diagnose, treat, and ultimately prevent the disease. In addition, research is required to halt or reverse beta cell destruction after disease onset, to preserve patients' insulin producing capacity. Key research objectives in this area are:

Risk Assessment

- Identify and Optimize the Detection of Immunologic, Genetic, and Metabolic Markers of Type 1 Diabetes

Immunopathogenesis

- Understand the Interplay Between Early Environmental Encounters and the Immunoregulatory Defects That Results in Beta Cell Destruction in Human Type 1 Diabetes
- Advance Basic Understanding of Facets of the Human Immune Response (e.g., Regulatory T Cells, Innate Immunity) That Have Recently Been Appreciated as Key Mediators of Beta Cell Destruction

Clinical Trials

- Identify an Intervention Capable of Long-term Reversal of Recent Onset Type 1 Diabetes Without Concomitant Short- or Long-term Adverse Effects
- Develop a Safe and Universal Means for the Primary Prevention of Type 1 Diabetes

Goal III: Develop Cell Replacement Therapy

Islet transplantation has engendered tremendous hope as a possible cure for type 1 diabetes. This therapeutic strategy replaces the insulin-producing beta cells destroyed by the immune system, thereby eliminating or reducing the need for insulin administration. However, to make this strategy a viable option for most patients, it is imperative to overcome the numerous obstacles that still exist, such as the shortage of available islets and the need for less toxic methods to prevent islet rejection and the recurrence of autoimmunity. Research on both beta cell biology and clinical islet transplantation can help to overcome these and other barriers. Key research objectives in this area are:

Islet Transplantation

- Develop Novel Strategies and Infrastructure That Support Advancing Pancreas Procurement and Islet Processing
- Develop Improved Methods To Assess Islet Beta Cell Viability and Function That Predict Early Islet Function After Transplant
- Investigate the Use of Porcine Islets as an Alternate Source of Islets for Transplantation
- Improve Islet Transplant Procedures
- Develop Novel Methods To Accurately Assess the Post-Transplant Islet Mass
- Harness New Understanding of the Immune System To Develop Improved Clinical Monitoring and Immunotherapies

Pancreatic Development, Stem Cells, and Regeneration

- Grow a Renewable Supply of Pancreatic Beta Cells That Can Be Transplanted into Patients
- Understand How Mature Beta Cells Are Maintained and Replenished in the Adult Pancreas
- Develop Strategies To Regenerate Beta Cells Through Replication or Neogenesis

Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes

Hypoglycemia is a distressing, acute complication of type 1 diabetes. Low blood glucose impairs brain and other bodily functions, including defenses against future hypoglycemia episodes, causing a vicious cycle of recurrent events. Understanding how the brain and body work together to sense and

adjust glucose levels, as well as research to improve and link glucose monitoring and insulin delivery, could help scientists develop strategies to prevent hypoglycemic episodes and improve patients' quality of life. Key research objectives in this area are:

Brain and Peripheral Nervous System Mechanisms of Hypoglycemia

- Define the Mechanisms and Modulators of Metabolic Sensing
- Elucidate Brain Alterations in Response to Hypoglycemia
- Develop New Strategies To Prevent or Reverse Hypoglycemia-Associated Autonomic Failure

Clinical Interventions To Prevent or Reduce Hypoglycemia

- Control Hypoglycemia Through Behavioral Therapies
- Close the Loop: Develop the Tools Required for an Artificial Pancreas

Goal V: Prevent or Reduce the Complications of Type 1 Diabetes

Persistent elevation of blood glucose can lead to life-threatening disease complications. Research has dramatically demonstrated that intensive control of blood glucose levels can prevent or delay the development of these complications. However, because of the limitations and difficulties of current therapies for achieving good glucose control, as well as the threat of hypoglycemia associated with intensive control, patients rarely achieve recommended glucose levels. Future research strategies will build upon the existing approaches to control diabetes, as well as develop novel approaches to break the link between high glucose and chronic complications. Key research objectives in this area are:

Molecular Mechanisms of Common Pathways in Diabetic Complications

- Identify Molecular Pathways of Hyperglycemia Damage
- Clarify Mechanisms Linking Fuel Utilization and Heart Disease
- Understand the Systems Biology of Diabetic Complications

Metabolic Memory

- Discover the Molecular Mechanisms of Metabolic Memory

Genetic Factors

- Identify Genes Conferring Susceptibility and Resistance to Diabetic Complications

Animal Models

- Develop More Human-like Animal Models of Diabetic Complications

Biomarkers and Surrogate Endpoints To Facilitate Clinical Trials

- Identify Biomarkers or a Combination of Biomarkers for Earlier Detection of Cell and Tissue Damage
- Validate Surrogate Endpoints for Assessing the Progression of Complications in Clinical Trials

Therapies To Improve Patient Health

- Identify Therapeutics That Prevent or Reverse the Development and Progression of Diabetic Complications
- Mitigate Psychosocial Complications and Comorbidities of Diabetes To Improve Quality of Life
- Combine New Technology for Diabetes Management with Behavioral and Translational Research

Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes

Continued research progress depends on attracting and training a workforce of scientists with diverse expertise to conduct research on type 1 diabetes and its complications. In addition, the harnessing of new and emerging technologies sets the stage for innovative discoveries that can bring tremendous benefits to patients. Key research objectives in this area are:

Engaging Talented Scientists

- Recruit Expertise from Diverse Fields
- Design Incentives That Reward Research Innovation
- Train New Scientists in Clinical Type 1 Diabetes Research

Development and Application of New Technologies

- Develop Noninvasive Imaging Technologies To Monitor Type 1 Diabetes
- Promote Application of Advances in Bioengineering to Type 1 Diabetes
- Foster Application of Gene Delivery and Gene Silencing Technology To Develop New Therapies for Type 1 Diabetes and Its Complications
- Apply New and Emerging Technologies in Functional Genomics, Proteomics, and Metabolomics to Type 1 Diabetes Research
- Improve the Power of Diabetes Research by Utilizing Computational Biology and Bioinformatics
- Apply New Technology to the Development of Improved Animal Models for the Study of Type 1 Diabetes

NIH SUPPORT FOR TYPE 1 DIABETES RESEARCH

Research toward achieving the six overarching Goals has been accelerated by the *Special Statutory Funding Program for Type 1 Diabetes Research*. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) administers this special appropriation on behalf of the Secretary of the Department of Health and Human Services (HHS), in collaboration with multiple other NIH Institutes and Centers, and the Centers for Disease Control and Prevention (CDC). The *Special Funding Program* has allowed the creation of unique, collaborative, and innovative research consortia and clinical trials networks to increase understanding about the prevention, treatment, and cure of type 1 diabetes. Initiatives supported by the program are different in size, scope, duration, and nature from other type 1 diabetes efforts supported through regular NIH appropriations. The *Special Funding Program* enabled the initiation of most of these large-scale, high-impact efforts, at a scientifically optimal scale of operation. Importantly, the research efforts that have been supported to date have spurred numerous future opportunities that could dramatically improve the lives of patients with type 1 diabetes. Type 1 diabetes research is also supported by regularly appropriated funds to HHS.

IMPLEMENTATION: GUIDING FUTURE RESEARCH EFFORTS

This Strategic Plan reflects a dynamic planning process that involves collaboration among numerous stakeholders to ensure that research progress is regularly assessed and that new and emerging opportunities are identified. The statutory Diabetes Mellitus Interagency Coordinating Committee will continue to play a key role by assessing progress toward attaining the goals and objectives described in this Plan, which was developed under its auspices. The NIH will also continue to solicit broad external input from the scientific, lay, and patient advocacy communities to inform its planning efforts. The NIH will use the research objectives described in this Strategic Plan as a scientific guidepost to improve current treatment strategies and to identify ways to prevent or cure type 1 diabetes and its complications.

Process for the Development of the Type 1 Diabetes Research Strategic Plan

Origin

One of the recommendations emanating from a January 2005 *ad hoc* planning and evaluation meeting focused on large scale efforts made possible by the *Special Statutory Funding Program for Type 1 Diabetes Research* was that the NIH should initiate a broad review of the entire state-of-the-science with respect to type 1 diabetes and its complications. In response to this recommendation, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) launched a new strategic planning effort for type 1 diabetes research.

Collaborative Planning Process

This Strategic Plan was developed through an open and inclusive planning process, with oversight by the statutory Diabetes Mellitus Interagency Coordinating Committee, and leadership by the NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases. The Committee, chaired by the NIDDK, includes representation from NIH components involved in diabetes research, as well as from other relevant federal agencies.

To develop the scientific chapters of the Strategic Plan, Working Groups were convened to identify recent scientific advances and research objectives for Goals I-V. Goal VI, "Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes," was addressed by all Working Groups because it is an interdisciplinary goal that applies across type 1 diabetes research. The Working Groups were composed of a diverse and talented group of individuals who are committed to propelling progress in type 1 diabetes research. They were chaired by scientists external to the NIH, with membership that included extramural scientists, NIH representatives, patients, and representatives from patient advocacy groups.

Public comment was solicited prior to publication by the posting of the draft plan on a Web site created for the planning effort (www.T1Diabetes.nih.gov/plan).

Organization of the Strategic Plan

The Strategic Plan was framed around the six overarching scientific goals of type 1 diabetes research. One version of the Plan was developed for patients with type 1 diabetes, their family members, and the public. It contains a description of how research addressing each goal could benefit people living with type 1 diabetes and their family members, as well as profiles of patients and scientists. Another version of the Plan was developed for the scientific research community. While tailored to different readers, both versions highlight key recent scientific advances that have accelerated research and/or benefited patients' health, and identify the most compelling opportunities and objectives for research.

Both versions of the Plan contain a summary of major research objectives. Research objectives are specific research directions that can be pursued over the next decade, within available NIH resources, to realize the goal of each chapter. In some cases, these objectives intersect with one another and may be dependent upon one another for progress. For example, identifying environmental triggers of type 1 diabetes (Goal I) will help to inform future disease prevention strategies (Goal II). Also, "Attract New Talent and Apply New Technologies" (Goal VI) is important for every area of type 1 diabetes research. The Strategic Plan describes a coordinated, multifaceted approach for significantly advancing research to combat type 1 diabetes.