Juvenile Diabetes Cure Research Tax Check-Off Program Annual Report

Jan. 1, 2016 – March 31, 2017

pennsylvania
DEPARTMENT OF HEALTH

Tom Wolf, Governor

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Juvenile Diabetes Cure Research Tax Check-Off Program

Created in September 2004 with the passage of Act 133, Juvenile Diabetes Cure Research, the Juvenile Diabetes Cure Research Tax Check-Off Program provides a state income tax check-off option for individuals to contribute a portion of their state tax refund to support research for juvenile diabetes, more commonly known as type 1 diabetes. The program funds research grants focused on restoring normal blood levels, preventing and reversing complications of the disease, and prevention of juvenile diabetes.

Type 1 Diabetes Overview

Type 1 diabetes (T1D), previously known as insulin-dependent diabetes mellitus (IDDM), or juvenile-onset diabetes, is an auto-immune disease in which the immune system destroys the insulin-producing beta cells of the pancreas that regulate blood glucose. Thus, the pancreas no longer produces insulin, the hormone needed to convert sugar (glucose), starches and other foods into energy needed for living. This form of diabetes usually strikes children and young adults, although disease onset can occur at any age. Among people of all ages, type 1 diabetes accounts for approximately 5 percent of all diagnosed cases of diabetes.[1] Risk factors may be autoimmune, genetic or environmental, but the exact cause of type 1 diabetes is unknown, with no known way to prevent it. In addition, there is no cure.

Type 1 diabetes comes on suddenly, causes dependence on injected or pumped insulin for life, and carries the constant threat of devastating complications. While insulin injections or infusions allow a person with type 1 diabetes to stay alive, they do not cure diabetes, nor do they necessarily prevent the possibility of the disease's devastating effects, which may include kidney failure, blindness, nerve damage, heart attack, stroke and amputations. Research focused on type 1 diabetes provides hope to detect its causes and to find a cure.

The Scope of Diabetes: About 1.5 million people aged 18+ years were newly diagnosed with diabetes in 2015 in the United States.[1]

The Cost of Diabetes: The total cost of diabetes in the US in 2012 was $245 billion, comprising S176 billion in direct medical cost and $69 billion indirect cost (disability, work loss, premature death). [2]

The Harm Caused by Diabetes: Diabetes was the seventh leading cause of death in the United States in 2015, based on the 79,535 death certificates in which diabetes was listed as the underlying cause of death. In 2015, diabetes was mentioned as a cause of death in a total of 252,806 certificates. Diabetes may be underreported as a cause of death.[1]

Diabetes Statistics

In 2015, the World Health Organization reported that non-communicable diseases (NCDs) kill 40 million people each year. Cardiovascular diseases account for most NCD deaths, or 17.7 million people annually, followed by cancer (8.8 million), respiratory disease (4 million) and diabetes (1.6 million). These four groups of diseases account for about 81 percent of all NCD deaths and share four common risk factors: tobacco use, physical inactivity, the harmful use of alcohol and unhealthy diets.[3]

Researchers from the Institute for Health Metrics and Evaluation tracked the costs associated with 155 diseases for 18 years and found that diabetes is the most expensive condition in terms of total dollars spent nationwide, costing $101 billion in diagnosis and treatment in 2013 — 15 percent more than the next costliest condition, ischemic heart disease.[4]

- According to the Centers for Disease Control and Prevention (CDC), an estimated 30.3 million people of all ages—or 9.4 percent of the U.S. population—had diabetes in 2015.[1]

- After adjusting for population age and sex differences, average medical expenditures in 2015 among people with diagnosed diabetes were 2.3 times higher than expenditures would be in the absence of diabetes.[1]
- Overall, the prevalence of diabetes was higher in 2015 among American Indians/Alaska Natives (15.1 percent), non-Hispanic blacks (12.7 percent), and people of Hispanic ethnicity (12.1 percent) than among non-Hispanic whites (7.4 percent) and Asians (8.0 percent).[1]
- Diabetes and its complications are the sixth leading cause of death in Pennsylvania, responsible for 11,250 Pennsylvania deaths in 2014.[5]
- In 2015, 10 percent of Pennsylvanian adults (1,130,813) age 18+ were estimated to have ever been told they have diabetes.[6]
- Since diabetes can remain undetected for many years, it is believed that the percentage of Pennsylvania adults with diabetes was likely higher than 10 percent in 2015.

Type 1 Diabetes Statistics

- The rate of T1D incidence among children under age 15 is estimated to increase by 3 percent annually worldwide.[7]
- As many as 1.25 million Americans currently have T1D; 40,000 people are diagnosed yearly in the U.S., with 5 million people expected to have T1D by 2050.[8]
- T1D accounts for $14 billion in annual health care costs in the U.S.[8]
- Forty thousand Americans are diagnosed yearly with T1D.[8]
- About 84 percent of people living with T1D in the US are adults, while about 16 percent of people living with T1D in the U.S. are children.[8]
- The prevalence of T1D in Americans under age 20 rose by 21 percent between 2001 and 2009.[9]
- An estimated 10 percent (95% confidence interval: 9-11) of Pennsylvania adults age 18+ that were ever told they have had diabetes have type 1 diabetes.[10]
- Age-adjusted incidence rate of T1D in Philadelphia children younger than 5 years increased by 70 percent between 2000 and 2004.[11]

Diabetes Costs Overview

Diabetes is one of the costliest chronic diseases. Medical expenses for people diagnosed with diabetes are more than two times higher than for people without diabetes.[1]

- National estimated diabetes costs for 2012[2]
  - ✓ Total (direct and indirect): $245 billion
  - ✓ Direct medical costs: $176 billion
  - ✓ Indirect costs: $69 billion (disability, work loss, premature death)

- Pennsylvania estimated diabetes costs[12]
  - ✓ Pennsylvania estimated total diabetes cost in 2012 were $13.4 billion, comprising $10.2 billion in direct medical costs and $3.2 billion indirect costs due to loss of productivity.
  - ✓ In 2015, the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health invested $111,205,293 in diabetes-related research projects in Pennsylvania.
  - ✓ The Division of Diabetes Translation at the CDC spent $2,409,984 on diabetes prevention and educational programs in Pennsylvania in 2016.

Administration of the Program

The Pennsylvania Department of Health Diabetes Prevention and Control Program is responsible for the administration of the Juvenile Diabetes Cure Research Tax Check-Off Program. A two-year grant for $100,000 was awarded to The Pennsylvania State University (PSU), College of Medicine, to conduct research to understand the molecular basis for vision impairment in diabetic retinopathy for patients with type 1 diabetes. Research began Jan. 1, 2009, and ended on Dec. 31, 2010. A second two-year grant for $150,000 was awarded to the Pennsylvania State University, Department of Pharmacology, to conduct vision impairment diabetic retinopathy research. Research began July 1, 2012, and ended on June 30, 2014. A third two-year grant for $200,000 was awarded to the Pennsylvania State University, College of Medicine, to study the role and mechanism of microRNA-34an (a gene) in curing and preventing type 1 diabetes; this research began in January 2015.

Significant progress has been made using these funds, and the eventual significance of this research on public health outcomes could be enormous. The results of these studies have led to published manuscripts that describe roles for altered lipids and enzyme inhibition in diabetic retinopathy and complications. A list of these manuscripts starts on page 9.

In the first grant, the Pennsylvania State University, College of Medicine, has leveraged its findings for additional extramural funding as a bridge to national research funding from the National Institutes of Health (NIH) and American Diabetes Association (ADA):

1) National Institutes of Health National Eye Institute – The Role of Glycosphingolipids in Diabetic Retinopathy
2) American Diabetes Association – Therapeutically modulating glycosphingolipid metabolism in a model of type 1 diabetes

In the second grant, Pennsylvania State University, Department of Pharmacology, has incorporated further exploration of the role of diminished caveolin-1 in ocular inflammation and vascular leakage and leveraged these funds.

The findings of the third grant awarded to PSU, College of Medicine, to research the role and mechanism of microRNA-34a in curing and preventing type 1 diabetes will significantly strengthen a future research application for national funding and improve its chances to be funded at a higher level by something such as an NIH Research Project Grant Program (RO1) grant.

Research Results from the Program

PSU College of Medicine 2009-2010 Grant:

Results from this grant indicated that too much of a type of glycolipid in the type 1 diabetic retinas of both rat and mouse models causes failure of insulin to be processed properly and detrimental effects of inflammation, vascular dysfunction and neuronal cell death. An enzyme called glucosylceramide synthase (GCS) catalyzes the reaction that creates glucosylceramide in the retina. Juvenile Diabetes Cure Research Tax Check-Off Program grant funds were successfully used to identify and validate GCS as a target in reducing or eliminating diabetic complications.

PSU Department of Pharmacology 2012-2014 Grant:

The title of this grant was "Studies to Verify Dysfunctional Toll-like Receptor Signaling and Diabetic Retinopathy." Studies were initiated in July 2012 to quantify the expression, cell-type and lipid microdomain localization of toll-like receptors (TLRs) in the diabetic retina. The grantee reported significant progress on all tasks towards addressing the major goals of this proposal, which were to

identify the major alterations of inflammatory TLRs in the diabetic retina and to test the hypothesis that TLRs contribute to diabetic retinopathy.

Diabetic retinopathy is the leading cause of vision loss among working age adults. The ability of the microbiome to contribute to retinal health was the focus of the research. Changes in the "microbiome" (i.e., the bacteria in the gut) have received much attention in recent years in terms of the ability to control the health of an individual. The "microbiome" consists of microorganisms, such as bacteria, that live inside the human body. This population of microorganisms can be beneficial as well as detrimental. The grantee investigated how this microbiome may contribute to complications of diabetes with an emphasis on diabetic retinopathy. One mechanism by which the human body recognizes microorganism is a group of proteins called toll-like receptors. Upon binding of microorganism components to these TLRs, several signaling events can occur that may contribute to pathology of diabetic retinopathy.

The researchers at PSU Department of Pharmacology found that, within models of type 1 diabetes, there is an elevation in endotoxins. Endotoxins are a component of certain types of bacteria and can initiate inflammation through the binding and subsequent activation of TLR4. Researchers further investigated how endotoxins may contribute to retinal pathology in diabetes through increasing white blood cell (leukocyte) adhesion to the retina vasculature, and, more specifically, what underlying changes to lipids endotoxins have on the retina. They noted significant alterations of retinal lipids comprised of the omega-3 polyunsaturated fatty acid, docosahexaenoic acid (DHA). DHA is very abundant in the retina and is very important for visual function. The researchers observed changes in lipids comprised of arachidonic acid, an omega-6 fatty acid that can have inflammatory properties. An investigational drug was used to inhibit retinal inflammation, and in vitro work has shown this inhibitor to suppress inflammation-induced leukocyte adhesion molecules.

Though the researchers did not see a rescue in retina function as assessed by electrophysiology due to the complexity of diabetic retinopathy, this absence may not be surprising. Research data suggest a minimal effect on neuronal pathology but a significant effect on the retinal vasculature. Thus, future researchers may need to focus in vivo studies on the vasculature and at a longer duration of diabetes when vascular changes are typically more pronounced.

Researchers also became interested in investigating the contributions of inflammation to the lipid changes that they have observed, specifically to determine if endotoxin-induced inflammation contributes to retinal lipid changes in diabetes. As previously stated, changes in the "microbiome" (i.e., the bacteria in the gut) have received much attention in recent years. The ability of the microbiome to contribute to retinal health will be of great interest going forward.

The major goal of this research grant was to help focus data for submission of a NIH proposal that will tentatively focus on endotoxin-TLR4 regulation of retina lipid composition and microvascular complications of the retina in diabetes.

<u>PSU College of Medicine 2015-2016 Grant</u>:
During the first 180 days, the researchers made substantial progress towards objective 1 of this grant, which was to characterize peripheral B cell populations in type 1 diabetes. B cells are lymphocytes that produce antibodies and stimulate other lymphocytes like T cells, which mediate T1D.

Studies prior to the mid-term report showed that T1D-protected mice had significantly fewer B cells with impaired functional responses compared to T1D susceptible mice. These important results indicate that B cells from T1D-protected mice may have impaired ability to stimulate T1D-mediating T cells. Therefore, for the next task of this project, it was critical to determine the ability of B cells to stimulate diabetogenic T cells and their capacity to mediate T1D in mice, which was proposed in the grant (task 2). These findings were selected to be presented at the Bio 2015 Conference in Philadelphia, the largest international biotechnology conference in the world. In addition, a publication reporting data in T1D-protected and T1D-susceptible mice was published (Berry G et al. Genomics Data, Volume 5, September 2015, pages 184–188).

During the second half of 2015, experiments performed in tissue-culture dishes (in-vitro) or in mouse models (in-vivo), were designed to determine the functions of diabetogenic T cells in T1D-prone and T1D-protected mice. The ability of B cells from T1D protected mice or T1D-prone mice to stimulate diabetogenic T cells was compared. It was observed that B cells from T1D-protected mice were unable to cause diabetogenic T cell expansion and activation both in-vitro and in-vivo, compared to B cells from T1D-prone mice. These findings proved the hypothesis that, in T1D-protected mice, inefficient T cell activation by peripheral B cells, combined with B cell deficiency, impairs the proliferation and functions of T cells that can damage the pancreatic tissue. In the absence of diabetogenic T cells, the pancreatic islets are protected, as observed in these mice. This study highlighted the important role of B cell-mediated T cell functions in the pathology of T1D, suggesting that B cells should be the therapeutic targets for T1D.

There are 19 genes in the Idd9.3 genetic region of the T1D protected mice, including the microRNA 34a (miR-34a) gene. The miR-34a was recently shown to play an important role in B cell development and expression of this microRNA. The hypothesis proposed for the remaining period of the research was that altered expression of the miR-34a leads to reduced B cell numbers and subsequent T cell activation in T1D-protected mice. To test this hypothesis, the principal investigator originally proposed to overexpress miR-34a gene in T1D-prone mice and determine whether the development of T1D can be prevented (proposed objective 2 of the project) by targeting this gene. This was objective 2 of this research grant. While performing these experiments, the initial principal investigator left PSU, and the research project was interrupted and delayed until an appropriate replacement was found. This caused additional delays, since the new project investigator encountered two obstacles: (1) the mice had to be replaced and a new breeding colony to be established because they became too old to breed, and (2) it took longer time than initially planned to acquire the miR-34a expressing retroviral construct to overexpress the miR-34a gene. The preliminary experiments in mice overexpressing the miR-34a gene indicate promising therapeutic implications for miR-34a. However, the researcher concluded that additional time and funding would be needed to definitively determine whether targeting miR-34a gene in T1D-prone mice can be a potential therapeutic strategy to attenuate the development of T1D.

In summary, through this research, it was found that B cells play an important role in T1D pathogenesis and that the T1D protected mice have a lower number of B cells and impaired B cell-mediated activation of T cells that cause T1D pathogenesis. These impaired B cell functions appeared to be due to altered functions of miR-34a gene. Therefore, B cells and miR-34a are attractive therapeutic targets for T1D.

Fiscal Year 2016-2017

Due to the delays caused by the change in principal investigator at PSU College of Medicine in the summer of 2015, the grant to research the role and mechanism of microRNA-34a in curing and preventing type 1 diabetes was renewed for three more months, and it ended on March 31, 2017.

Plans for Fiscal Year 2017-2018

The Diabetes Prevention and Control Program (DPCP) has decided to not fund a research project during this period. An adequate balance was not available in the fund account, due to a considerable reduction in contributions for the past several years. Efforts have been made to increase contributions to the fund by posting information on the department's website and through messages included in the Make A Choice media campaign that will be officially launched in August 2017. DPCP will issue a new RFA with the effective start date July 1, 2018. Proposed projects must have been subject to an established peer and scientific review process identical or similar to the National Institutes of Health review system. The purpose of the resulting grant will be to conduct research that focuses on juvenile diabetes as it relates to restoring normal blood levels, preventing and reversing complications from the disease, and/or preventing juvenile diabetes. Research funds from the program are restricted to institutions of higher education and independent research institutes of the Commonwealth of Pennsylvania.

Tax Check-Off/Private Contributions

Tax Year 2016 (Calendar Year 2017) was the 11th year in which contributions were collected for this fund. Contributions to the fund in 2016 totaled $18,819.00. These annual contributions are displayed below in Figure 1. Total revenue through Dec. 31, 2016, was $569,926.86, and the cumulative balance was $123,996.86.

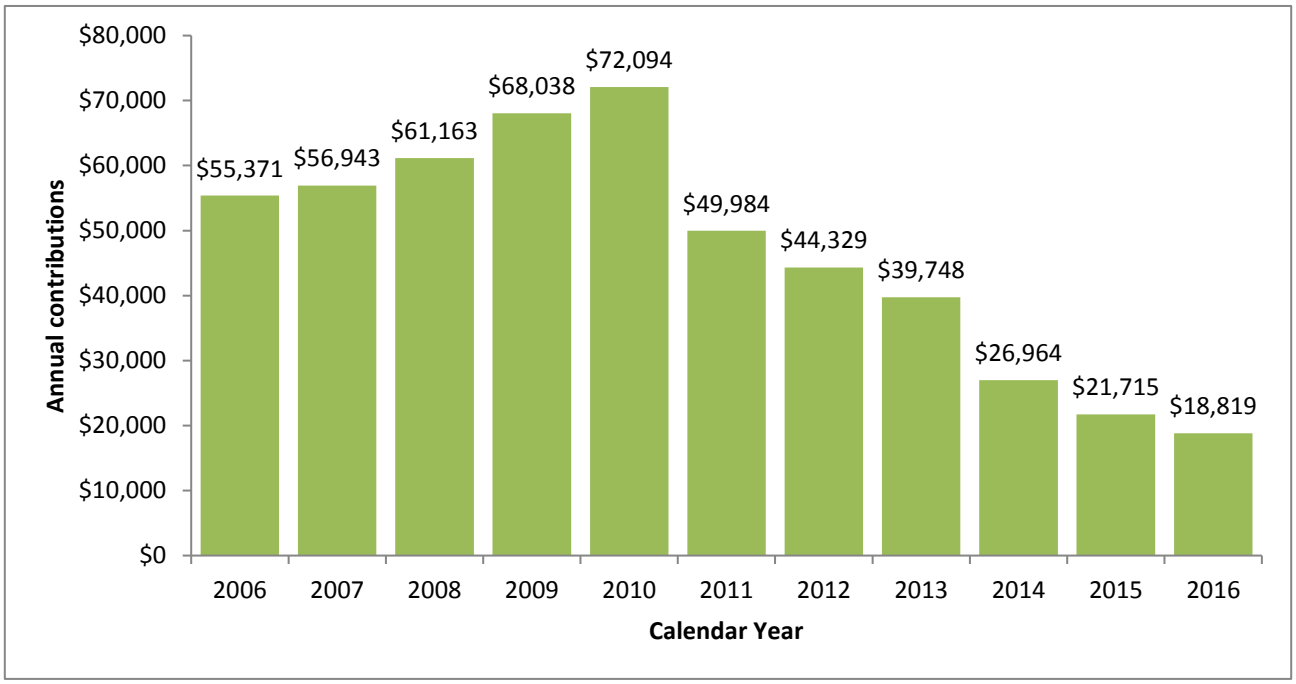

Figure 1: Annual Contributions Made in Calendar Years 2006-2016

How to Contribute to the Program Fund

Individuals may indicate the amount of their state tax refund they wish to contribute to the Juvenile (type 1) Diabetes Cure Research Fund. Contributions may be made payable to the Juvenile Diabetes Cure Research Fund and sent to:

Pennsylvania Department of Health
Bureau of Administrative and Financial Services
Division of Budget
625 Forster St.
Health and Welfare Building
Harrisburg, PA 17120

For Additional Information

This report was prepared by the Diabetes Prevention and Control Program, Division of Nutrition and Physical Activity, Bureau of Health Promotion and Risk Reduction, Pennsylvania Department of Health. For additional information, contact:

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For additional information regarding type 1 diabetes, including managing the disease and current research being conducted, please visit the following:

- Centers for Disease Control and Prevention, http://www.cdc.gov/diabetes;
- American Diabetes Association, http://www.diabetes.org;
- Juvenile Diabetes Research Foundation, http://www.jdrf.org; and
- SEARCH for Diabetes in Youth, http://www.searchfordiabetes.org.

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2. Fox TE, Bewley MC, Unrath KA, Pedersen MM, Anderson RE, Kim JK, Bronson SK, Flanagan JM, Kester M. "Circulating sphingolipid biomarkers in models of Type 1 diabetes" (The Journal of Lipid Research) March 2011 52(3):509-17.

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