

GOAL III

**DEVELOP CELL
REPLACEMENT THERAPY**



The *Special Statutory Funding Program for Type 1 Diabetes Research* has laid the foundation for, and contributed to, major advances toward developing cell replacement therapies for type 1 diabetes.

Collaborative research consortia supported by the *Special Diabetes Program* have played a central role in advancing pancreatic islet transplantation and other potential cell replacement therapies while opening a range of new scientific avenues. In addition to the significant research progress described in this chapter, information on the program evaluation related to Goal III can be found in Appendix A (Allocation of Funds), Appendix B (Assessment), and Appendix C (Evaluation of Major Research Consortia, Networks, and Resources).

Type 1 diabetes is characterized by the destruction of a person's beta cells by their own immune system. These insulin-producing cells of the pancreas are critical to the ability of the body to regulate uptake of dietary glucose (sugar) for energy into cells and tissues. Without insulin, the cells and tissues of people with type 1 diabetes are starved while blood glucose levels continue to rise. Patients are faced with requiring a lifetime of insulin replacement therapy, administered by injections or a pump, to control their blood glucose levels. While insulin helps people with type 1 diabetes control blood glucose levels, it is not a cure. Even the most diligent patients are at risk for sudden, acute episodes of dangerously low or high blood glucose levels, either of which can be life-threatening in extreme cases. Therefore, a major goal of research supported by the *Special Statutory Funding Program for Type 1 Diabetes Research* (*Special Diabetes Program* or *Program*) is to vigorously investigate methods to replace the destroyed beta cells—a potential cure for the disease.

One strategy for replacing beta cells is islet transplantation. As described in this chapter, at the

beginning of the *Special Diabetes Program* in 1998, the potential of islet transplantation as a treatment for type 1 diabetes was as yet unrealized. Now, due largely to support from the *Special Diabetes Program*, the potential of islet transplantation has grown and critical efforts are under way to improve this experimental procedure and its outcomes. Scientists are also exploring other strategies to replace beta cells, such as coaxing any remaining beta cells in the pancreas to generate additional beta cells, expanding islets in culture, or directing other pancreatic cell types to become beta cells. The development of strategies to successfully generate beta cells from human embryonic stem (ES) cells,²³ and other stem/progenitor cell populations, such as induced pluripotent stem (iPS) cells holds great promise. Huge strides have been made in these areas and in the basic understanding of pancreas development due to research supported by the *Special Diabetes Program*. As described in this chapter, the *Special Diabetes Program* has supported many accomplishments that are accelerating progress toward the development of cell-based therapies as a cure for type 1 diabetes.

²³ The NIH supports research using human embryonic stem cells within the NIH Guidelines for Human Stem Cell Research.

Graphic: Image of human islet. Islets in the pancreas produce and secrete insulin to aid in metabolism. In people with type 1 diabetes, the insulin-producing beta cells in islets are destroyed by a misguided immune system attack. Image credit: Steve Gschmeissner/Photo Researchers, Inc.

HIGHLIGHTS OF RECENT RESEARCH ADVANCES RELATED TO GOAL III

Conducted First Multicenter Trial of Islet Cell Transplantation: Building on the 2000 finding that insulin independence could be achieved with islet transplantation coupled with a steroid-free immunosuppressive regimen, nine sites participating in the Immune Tolerance Network (ITN) successfully replicated the “Edmonton protocol” for islet transplantation. While most people in the study experienced a gradual loss of transplanted islet function over a period of years, even those individuals who retained only partial islet function and did not remain “insulin free” benefited greatly from improved post-transplant glycemic control. The study played a critical role in defining the challenges, obstacles, and feasibility of moving islet transplantation into the therapeutic arena and demonstrated that islet transplantation holds promise as a treatment for type 1 diabetes.

Launched Clinical Trials To Improve Islet Transplantation: The Clinical Islet Transplantation (CIT) Consortium has seven ongoing trials testing new strategies to improve islet transplantation. These trials are testing U.S. Food and Drug Administration (FDA)-approved and experimental agents to improve islet survival and insulin independence after transplantation and to prevent rejection of the transplanted tissue. In addition, new approaches for islet isolation are also being studied. The Collaborative Islet Transplant Registry (CITR) is collecting and disseminating data from the CIT Consortium and other islet transplant programs to expedite progress and promote safety in this research field.

Contributed to Unprecedented Islet Transplant: Research supported by the *Special Diabetes Program* laid the foundation for an unprecedented islet transplant to an American airman who was wounded while serving in Afghanistan. The airman’s pancreas was damaged beyond repair by gunshot wounds, resulting in the need for removal of the entire pancreas. The pancreas was transported to researchers at the University of Miami who isolated and purified the islets and sent the purified islets back to Walter Reed Army Medical Center, where the cells were successfully infused into the patient’s liver, freeing him from the insulin-requiring diabetes that would have ensued from loss of the pancreas. This advance was built on research supported by the *Special Diabetes Program* on islet isolation, purification, and transplantation.

Fostered “Bench to Bedside” Research Toward Goal of Cell Replacement Therapy: Translating key findings in the laboratory to clinical trials is critical to capitalizing on knowledge resulting from successful basic research, but can be difficult for scientists to do on their own. Programs supported by the *Special Diabetes Program* aim to facilitate this translation and have been successful. For example, researchers using mouse models demonstrated that an anti-inflammatory drug called lisofylline can protect newly transplanted islets from recurrent destruction by the immune system. Building on these results, the CIT Consortium is now testing the drug in humans using lisofylline manufactured through the T1D-RAID program, which helps scientists ready agents for testing in clinical trials. Likewise, the T1D-RAID program is generating a mixture of medicines, demonstrated by researchers in the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) to promote long-term survival of islets

after transplantation into non-human primates, for use in an ITN clinical trial to test this therapy in people with newly diagnosed type 1 diabetes.

Identification of Progenitor Cells in the Adult Pancreas that Form Insulin-producing Beta Cells: To gain further understanding about pancreatic progenitor cells, scientists surgically induced a specific type of wound to the adult mouse pancreas, which caused the number of beta cells to double. The scientists took advantage of this doubling in number to test for the presence of a well-established marker of embryonic pancreatic progenitor cells, called *Ngn3*, and observed that levels of *Ngn3* not only increased in the pancreas in response to injury, but that *Ngn3* played a role in increased beta cell numbers following the injury. By further examining the *Ngn3*-expressing cells within the injured mouse pancreas, the scientists demonstrated that these cells showed many of the same characteristics as embryonic progenitor cells, suggesting that the adult mouse pancreas contains progenitor cells that are able to regenerate beta cells. If, with further research, these embryonic-like progenitor cells are identified in the human pancreas, then this discovery may foster the development of therapies for both type 1 and type 2 diabetes.

Adult Pancreas Cells Reprogrammed to Insulin-producing Beta Cells: In order to promote the formation of new beta cells, scientists in the Beta Cell Biology Consortium (BCBC) are determining when and how certain pancreatic progenitor cells become “committed” to developing into specific pancreatic cell types and discovering flexibility in these cells. In one study, scientists made an exciting discovery that a type of adult cell in the mouse pancreas, called an exocrine cell, can be reprogrammed to become an insulin-producing beta cell. Using a genetically engineered virus and a combination of just three transcription factors, the researchers were able to reprogram some of the exocrine cells into beta cells. The newly formed beta cells produced enough insulin to decrease high blood glucose levels in diabetic mice. If the same type of approach can be developed to work safely and effectively in humans, this discovery could have a dramatic impact on the ability to increase beta cell mass in people with diabetes.

In another study, scientists uncovered plasticity in another pancreatic cell type—the alpha cell. Using genetic techniques in mice, the researchers increased the levels of a protein called *Pax4*, which is known to be involved in promoting cells to develop into a certain pancreatic cell type. They found that mice with high levels of *Pax4* had oversized clusters of beta cells, which resulted from alpha-beta precursor cells and established alpha cells being induced to form beta cells. In addition, in a mouse model of diabetes, the high levels of *Pax4* promoted generation of new beta cells and overcame the diabetic state. In a recent study, BCBC scientists observed spontaneous conversion in beta cell-depleted mice of alpha cells to insulin-producing cells. This discovery—that adult pancreatic cells have the potential to convert to beta cells—generates a fuller picture of pancreatic development and may pave the way toward new cell-based therapies for diabetes.

Mouse Model for Studying Beta Cell Regeneration: Scientists in the BCBC developed a mouse model useful for studying beta cell regeneration. When the genetically engineered mice are treated with a certain drug, a toxin is expressed in their beta cells. Expression of the toxin causes the beta cells to die, and the mice to develop diabetes.

Surprisingly, the researchers found that if they stopped the drug treatment after the mice developed diabetes, the animals recovered from the disease. The mice not only regained normal blood sugar levels, but also regenerated their beta cell mass. The scientists determined that the new beta cells came predominantly from preexisting beta cells, suggesting that beta cells have a significant capacity for regeneration. This research suggests that finding ways to promote regeneration of existing beta cells may be a therapeutic approach for treating diabetes. It also provides an important model system for testing the effect of therapeutic agents on beta cell regeneration.

Discovery of a New Indicator for Type 1 Diabetes Autoimmunity: To enhance understanding of the pathogenesis of type 1 diabetes and elucidate potential new therapeutic strategies, as well as to improve testing for autoimmunity, researchers in the BCBC sought to identify additional beta cell proteins that generate autoantibodies, factors that attack proteins within the body, rather than invading pathogens. By examining a set of proteins made exclusively or almost exclusively in beta cells, and testing with antibodies taken from people with new-onset diabetes, the scientists discovered that autoantibodies to a beta cell protein called ZnT8 are an excellent marker for type 1 diabetes autoimmunity. The scientists found that using ZnT8 autoantibodies can substantially improve prediction of diabetes when used in combination with the previously discovered autoantibodies commonly used to monitor for type 1 diabetes risk in research studies.

ISLET TRANSPLANTATION RESEARCH

Islet Transplantation Becomes a Reality: The field of islet transplantation was propelled forward by the success of a small clinical study in Edmonton, Canada. In 2000, seven consecutive patients achieved normal blood glucose levels following islet transplantation using a new protocol (referred to as the “Edmonton protocol”). This protocol did not use steroids to prevent rejection of the transplant; rather, a new combination of anti-rejection drugs was tested. Each patient received a large number of islets isolated from two to three donor pancreata as multiple transplants and infused into the recipient’s liver. Progress in methods for isolating and storing islets from donor pancreata prior to transplantation also added to the success of this trial. However, the success of the transplants brought on new questions and challenges. While patients maintained normal blood glucose levels for a period after the transplant,

the islets tended to lose their insulin-producing function over time, prompting study of what caused this loss of function and how it could be halted. In addition, it remained to be demonstrated whether Edmonton’s success could be replicated at other sites around the world in a standardized way. While the *Special Diabetes Program* did not support the original Edmonton trial, the *Program* has supported efforts to further progress in islet transplantation.

Replicating the Success at Edmonton in a Multicenter

Trial: The ITN (see Goal II) took on the challenge to replicate the “Edmonton protocol” in a multicenter trial. ITN is an international consortium that receives support from the *Special Diabetes Program* and is led by NIAID in collaboration with NIDDK and JDRF. In the first multicenter trial of islet cell transplantation, from 2001-2006, nine sites in North America and Europe successfully replicated the “Edmonton protocol.” One

year after transplant, 44 percent of the participants (16 out of 36) achieved insulin independence with good glycemic control; 14 percent achieved insulin independence with a single donor islet function. By helping people with type 1 diabetes achieve better glycemic control and prevent episodes of hyper- or hypoglycemia and associated complications, the study was heralded a success. Importantly, even among patients who still required insulin injections, the survival of functioning transplanted islets led to an absence of severe hypoglycemic events due to hypoglycemia unawareness. As of January 2008, 21 participants had reached the 5-year evaluation after their final transplant—six were judged to be insulin-independent, and 15 were insulin-dependent. Although insulin independence declined over time in study participants, this important study confirmed and extended the demonstration that islet transplantation may be an alternative to whole organ transplantation, a major surgical procedure with significant risks. The results also highlight the continued need for research to develop safer, more tolerable, and longer-lasting anti-rejection therapies, as well as alternative engraftment sites and other approaches to enhance islet viability.

Research Challenges to Developing Islet

Transplantation: While these results represent major clinical progress, several challenges remain before this technique can be implemented in a large-scale fashion. Researchers have now confirmed that many islet transplant recipients are able to maintain near normal blood glucose levels. They also have observed, however, that success of the transplantation process varies greatly and wanes over time, underscoring the need for more durable outcomes and further research. Moreover, patients are trading the need for insulin and

the dangers of hypoglycemia for the risks associated with drugs to prevent rejection. Thus, the procedure is only used in people with recurrent severe hypoglycemia or those who already require immunosuppression after kidney transplantation. The complexity of barriers associated with islet transplantation requires multiple avenues of research, many of which are supported by the *Special Diabetes Program*. Methods for acquisition and delivery of islets must be optimized, so that fewer donor organs are needed and islets are as healthy as possible prior to transplantation. An adequate supply of islets for all transplant patients must be created based on new understanding of how beta cells are formed and maintained. Better tolerated therapies to combat the body's tendency to destroy the transplanted islets need to be developed to avoid toxic side effects. Sometimes islets do not "take" and never produce insulin; efforts to identify the best graft site, and improve the survival and functionality of the transplanted islets are necessary. Finally, research to understand how to prevent the immune system destruction of transplanted islets and ideally to re-program the immune system so ongoing intervention is minimized will be critical to the success of this procedure.

Coordinating Studies To Advance Islet

Transplantation: The CIT Consortium, an international network of 11 centers, was created to study and refine islet transplantation technology. The CIT Consortium is led jointly by NIDDK and NIAID and is supported by the *Special Diabetes Program*. As knowledge of islet cell biology and the processes associated with transplantation and immune rejection increase, and pre-clinical studies evaluating new approaches to immunomodulation in conjunction with islet transplantation in animal models progress, a means is needed by which to rigorously

study these new approaches. Using a well-coordinated, collaborative approach, the CIT Consortium is conducting studies to find methods that have higher success rates and fewer risks. It also aims to validate standardized protocols for generation of islets of sufficient quality for FDA licensure as a biologic product. Since its inception, the CIT Consortium has developed and implemented a program of clinical and mechanistic studies to address the challenges in islet transplantation with or without an accompanying kidney transplant.

The CIT Consortium launched six single and multi-center trials, with associated immunologic, metabolic, and mechanistic studies, of islet transplantation in individuals with type 1 diabetes with severe hypoglycemic events despite intensive medical management. An additional trial, including Medicare beneficiaries as mandated by the Medicare Prescription Drug Improvement and Modernization Act of 2003 (Public Law 108-173), specifically consists of individuals with type 1 diabetes who have previously undergone kidney transplantation for diabetic nephropathy and are thus already receiving immunosuppressive therapy to prevent rejection of the donor kidney. These trials are testing FDA-approved and experimental agents to improve islet survival and insulin independence after transplantation and to prevent rejection of the transplanted tissue. In addition, new approaches are also being studied for islet isolation. These types of improvements can ultimately lead to more widespread use of this treatment strategy for individuals with type 1 diabetes.

Collecting Data on Islet Transplantation To Inform

Future Research: To advance this field as rapidly as possible, scientists need access to information on every islet transplant that takes place, not just those in their local facility. Patients considering the

procedure and their physicians also need information on success rates and risks. Therefore, the CITR, which is led by NIDDK and supported by the *Special Diabetes Program*, was created to collect data on islet transplantations for use by the entire research field and the public. It expedites progress and promotes safety in islet transplantation through collection, analysis, and communication of comprehensive and current data on all islet transplantations performed in North America. An annual report is widely disseminated throughout the islet transplant community, diabetes community, and general public with data on recipient and donor characteristics; pancreas procurement and islet processing; immunosuppressive medications; the function of the donated islets; lab results; and adverse events. Examples of progress made through CITR include reporting that 72 percent of islet transplant recipients achieved insulin independence at least once, and that 1 year after islet transplantation, individuals still requiring insulin injections had significant reduction in their insulin requirements. By collecting and analyzing these data, CITR is helping to define the overall risks and benefits of islet transplantation as a treatment option for people with type 1 diabetes, which is informing future research efforts.

Bridging Basic and Clinical Research To Propel Islet

Transplantation: Integral to successful and effective clinical therapies are programs that bridge the discoveries made in basic research and studies to test these advances in animal models and clinical trials. The *Special Diabetes Program* has supported critical programs aimed to promote the translation of scientific advances to treatments. For example, improvement in the processing and handling of islets has been essential for increasing success and reducing the risks and costs associated with

transplantation and extending the availability of islet transplant to a greater number of people with diabetes. Research to improve islet isolation techniques, islet quality, the shipping and storage of islets, and assays for characterizing viability of purified islets has been accelerated due to the efforts of the *Special Diabetes Program*-supported Islet Cell Resource Centers (ICRs) that made human islets available for research studies. A new program also supported by the *Special Diabetes Program*, the NIDDK-led Integrated Islet Distribution Program (IIDP), builds upon the experience obtained with the ICRs and provides human islets not suitable for islet transplantation to basic scientists as a critical resource to advance scientific discovery and translational medicine.

Investigating New Therapies in Transplantation in Large Animal Models: The NHPCSG was begun to move advances in transplantation toward human clinical trials. The NHPCSG, led by NIAID and supported, in part, by the *Special Diabetes Program*, is evaluating the safety and efficacy of novel therapies to induce immune tolerance in non-human primate models of islet, kidney, heart, and lung transplantation. In addition to establishing two species of non-human primate breeding colonies to derive specific pathogen-free animals and provide a shared resource of high-quality animals for these research studies, the NHPCSG has made several advances in islet transplantation. The NHPCSG was the first to demonstrate long-term and sustained beta cell function without continuous immunosuppressive therapy following islet transplantation in a drug-induced diabetic non-human primate model. In addition, studies of agents used to prolong transplanted islet cell survival in non-human primates have shown promise and have been moved into clinical trials, as described in this chapter.

Facilitating Success in “Bench to Bedside” Translation:

The *Special Diabetes Program* vigorously supports “bench to bedside” research toward the goal of replacing insulin-producing beta cells. For example, researchers demonstrated that, in a mouse model of type 1 diabetes, treatment after islet transplantation with an anti-inflammatory drug, called lisofylline, protected the cells from recurrent destruction by the immune system. Building on these results, the CIT Consortium is now testing this drug in humans. The lisofylline being used in the trial was manufactured through the *Special Diabetes Program*-supported Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program, which helps scientists ready agents for testing in clinical trials. In another example, researchers in the NHPCSG demonstrated long-term survival of islets after transplantation when the animals were given a novel mixture of factors that target the immune system. Based on these findings, the ITN approved a clinical trial to test this therapy in people with newly diagnosed type 1 diabetes, to determine if the agent can slow progression of the disease. The T1D-RAID program is undertaking production of the agent for these studies. These examples demonstrate how the *Special Diabetes Program* supports the discovery, manufacture, and testing of promising therapeutic agents, creating a robust pipeline of agents that have the potential to improve the health of people with type 1 diabetes.

DEVELOPING NOVEL STRATEGIES TO REPLACE ISLETS

Limitations in the islet supply create a major roadblock to developing islet transplantation as a cure because the number of donor pancreata does not meet the demand for islets nationwide. Therefore, a major focus has been

placed on the development of new methods to stimulate human beta cell growth in the laboratory setting prior to transplantation. In addition, scientists have begun to explore methods to replace the insulin-producing beta cells in a person with type 1 diabetes without the need for donor pancreata and toxic anti-rejection drugs. Just a few decades ago, little was known about pancreatic development and whether it would be possible to recapitulate the process of normal beta cell development in the laboratory setting. It was understood that beta cells develop from a pool of precursors, or stem cells, but these were poorly defined and many of the factors critical to this process remained to be identified. However, the stage was set for significant advances in this field as scientists had increased their understanding of mechanisms that allowed individual cell types to develop, the events involved in development and regeneration of the pancreas, and the factors required for normal function and development of the beta cells.

A Team-based Approach to Studies of Beta Cell

Biology: To accelerate research in the field of beta cell biology, a unique team-based and collaborative consortium was established—the BCBC. Led by NIDDK and supported in part by the *Special Diabetes Program*, the BCBC provides an infrastructure that is conducive to tackling critical issues that can revolutionize type 1 diabetes research and, ultimately, the treatment of people with type 1 diabetes. The BCBC is pursuing key challenges: (1) use cues from pancreatic development to directly differentiate beta cells from human stem/progenitor cells; (2) enhance functional beta cell mass; (3) reprogram progenitor or adult cells to beta cells; and (4) use patient-derived tissues and mouse models to generate and study human beta cells/islets in the context of a human autoimmune environment. Over

50 BCBC investigators and over 200 affiliates work collaboratively and regularly share data and information. In addition, research through the BCBC and the broader scientific community is accelerated by having BCBC core facilities that produce key laboratory reagents (e.g., mouse models, antibodies, microarrays), which allow the scientists to spend more time performing experiments, rather than generating and preparing reagents. The team-based approach of the BCBC has been a success and has promoted major advances in the field by synergizing the skills and ingenuity of many creative scientists and minimizing duplication in research efforts. To date, the BCBC has made significant contributions to the field of beta cell biology, as described below and in the Feature “The Beta Cell Biology Consortium: An Experiment in Team Science” found later in this chapter.

Increased Understanding of Pancreatic Development Leads to Generation of Insulin-producing Cells:

Today, in part due to advances from the BCBC, scientists understand a great deal more about the development of the pancreas. Many of the genes responsible for the establishment of different pancreatic lineages have been identified and much more is known about the integrated cascade of interactions that lead to the formation of the adult pancreas. Overall, these studies have led to a more detailed understanding of the factors that drive development of the pancreas and the islets. This knowledge has laid the foundation for the development of rational and informed strategies to successfully generate beta cells from human ES cells, and other stem/progenitor cell populations, such as iPS cells. Using a step-wise protocol to mimic how the pancreas forms during fetal development, scientists were able to direct human ES cells through stages resembling this process and obtain insulin-producing cells. Some

of these human ES cell-derived insulin-producing cells have insulin content approaching that of adult beta cells. However, unlike the adult beta cells they need to replace, the cells are not very responsive to glucose. Although these cells do not yet display regulated insulin secretion, nor is the process to produce them highly efficient, this major achievement provides proof-of-principle that it is possible to replicate, in the laboratory, the steps leading to the production of insulin-producing cells—a significant leap forward toward the goal of developing beta cell replacement therapies to cure type 1 diabetes or severe type 2 diabetes.

New Knowledge Spurs Novel Strategies for Cell-based Therapies: The knowledge gained by studying basic pancreas development has also spawned studies of reprogramming, cell plasticity, and pancreatic beta cell regeneration. Scientists are studying the potential of many different non-insulin producing pancreatic cell types to be reprogrammed to insulin-producing cells. Research from the BCBC performed in diabetic mice has shown that introducing expression of just three genes is sufficient to reprogram non-insulin-producing adult pancreatic cells (and potentially other cell types) into beta cell-like insulin-producing cells. The reprogrammed cells lowered blood glucose in diabetic animals and represent important progress toward harnessing regenerative medicine to treat diabetes. This ability to reprogram other pancreatic cell types could be used in the laboratory to generate insulin-producing cells for islet transplants and/or could be used in the clinical setting to coax non-insulin-producing pancreatic cell types to insulin-producing cells within a patient. As a result of research supported by the *Special Diabetes Program*, both of these approaches hold significant potential to improve glycemic control in patients with type 1 diabetes.

Additional research is necessary, though, to develop the potential of these approaches into safe and effective cellular therapies.

Advances in Beta Cell Regeneration: In addition to studies to generate insulin-producing cells from other cell types, scientists are investigating the potential of beta cells to replicate and regenerate the beta cell mass. In people with type 1 diabetes, beta cell depletion is often not absolute, and scattered insulin-producing cells may often be observed even after many years of disease. Similarly, animal studies of how changes in beta cell mass are regulated during pregnancy to meet increased insulin demands have rendered new insights that the beta cell mass is dynamically regulated and beta cells can regenerate. One of the difficulties in studying beta cell regeneration has been the lack of a robust, animal system that would allow the controlled destruction of beta cells and study of subsequent cell proliferation in the adult pancreas. However, a mouse model developed by BCBC scientists now permits the study of the dynamics of beta cell regeneration from a diabetic state. Insights from the study of this new mouse model will aid in the evaluation of beta cell regeneration as a potential treatment for type 1 diabetes. Also, recent successes by BCBC investigators will allow scientists, for the first time, to study the regenerative capacity of human islets *in vivo*. The successful BCBC has advanced the field of pancreas development and beta cell biology, and will continue to propel this field toward the ultimate goal of curing type 1 diabetes.

SUMMARY

This chapter highlights some of the significant research progress that has been made possible by the *Special Diabetes Program* toward the goal of developing cell

replacement therapy. Without support from the *Special Diabetes Program*, it would not have been possible to establish large, collaborative networks, such as the BCBC, at an unprecedented scale. As new insights and opportunities emerge from the basic research of the BCBC and from animal studies of the NHPCSG, the CIT Consortium is poised to test new strategies for islet transplantation in people with type 1 diabetes.

Additionally, discoveries from the BCBC have illuminated the potential of other approaches to regenerate the beta cells that are destroyed in people with type 1 diabetes. Progress has already been achieved, and additional progress is expected in the future as islet transplantation is improved and new cell-based therapies are identified and tested in the people who could benefit from them.

RESEARCH CONSORTIA AND NETWORKS RELATED TO THE DEVELOPMENT OF CELL REPLACEMENT THERAPY

Evaluation of research consortia and networks supported by the *Special Diabetes Program* and related to Goal III is found in Appendix C. Highlights of these are summarized below.

Beta Cell Biology Consortium (BCBC): The BCBC is an international consortium of over 50 principal investigators and over 200 affiliates. The BCBC brings a team-based approach to studies of pancreas and beta cell biology and development, as well as the generation of new research tools, reagents, and technologies that are vital for developing new cellular therapies in diabetes. The BCBC's Antibody Core has generated and/or validated more than 110 antibodies and distributed more than 700 orders since its inception. The BCBC's Mouse ES Cell Core has generated over 50 new lines of genetically altered mice or mouse embryonic stem cell lines. The BCBC has made numerous scientific discoveries reported in over 290 publications, including progress in understanding the steps necessary to turn stem/progenitor cells into insulin-producing cells, and generated many research resources, including a mouse model in which to study beta cell regeneration.

Clinical Islet Transplantation (CIT) Consortium: The CIT Consortium is conducting studies to improve the safety and long-term success of methods for islet transplantation in people with type 1 diabetes. The CIT Consortium has seven ongoing trials, with associated immunologic, metabolic, and mechanistic studies, testing new strategies for islet transplantation, including a congressionally-mandated clinical trial of islet transplantation in Medicare recipients.

Collaborative Islet Transplantation Registry (CITR): The CITR expedites progress and promotes safety in islet transplantation through the collection, analysis, and communication of comprehensive and current data on all islet transplants performed in North America. The CITR has prepared six widely disseminated annual reports to define the overall risk and benefits of islet transplantation as a treatment option for people with type 1 diabetes. Information on characteristics of donors, recipients, islets, treatments, and outcomes allows comprehensive analysis of over 200 factors that may influence results of the procedure. CITR has reported that 72 percent of islet-alone recipients achieved insulin independence at least once and that, one year after islet infusion, individuals requiring insulin

injections had a significant reduction in their insulin requirements. CITR's current North American database includes information on 339 allogenic islet recipients, 658 allogenic infusion procedures, 722 donor pancreata, and 213 autograft recipients and their islets, from 28 centers that have performed islet transplantation since 1999.

Islet Cell Resource Centers (ICRs)/ Integrated Islet Distribution Program (IIDP): Formerly the ICRs provided a valuable resource by distributing islets to the scientific community for basic research studies and for clinical transplantation. They provided more than 92 million islet equivalents for transplantation and distributed more than 201 million islet equivalents to more than 270 investigators for research. In addition, the ICRs made progress to improve isolation techniques, islet quality, the shipping and storage of islets, and assays for characterizing purified islets. Now CIT supports production of islets for transplantation research protocols, and the need for human islets for fundamental research is met through the IIDP, a new program to process and distribute human islets. The IIDP builds on the experience of the ICRs for notification of islet availability to investigators and for optimized shipping conditions to ensure that precious human islets not needed for transplantation are efficiently distributed to approved researchers studying human beta cell biology to develop new approaches to therapy for all forms of diabetes.

Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG): The NHPCSG is a multi-institution Consortium collaboratively developing and evaluating the safety and efficacy of novel therapies to induce immune tolerance in non-human primate models of islet, kidney, heart, and lung transplantation. The NHPCSG has made many scientific contributions, including significantly enhancing the utility of the non-human primate as a model of human transplantation. One agent with promising results from NHPCSG studies is now in trials conducted by the CIT Consortium and ITN; a second agent has been approved for an ITN clinical trial upon completion of pre-clinical studies. These studies are being coordinated with the T1D-RAID program which is also undertaking production of the agent for these studies.

Feature: The Beta Cell Biology Consortium— An Experiment in Team Science

The Beta Cell Biology Consortium (BCBC), created by NIDDK and supported in part by the *Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program)*, brings team science to the acquisition of new knowledge and production of new resources necessary to develop novel cell-based therapies for insulin delivery. Cell-based therapies could increase the mass of insulin-producing beta cells in a person with type 1 diabetes, either by inducing new beta cell growth in the pancreas or by transplanting new beta cells or islets. Therefore, the BCBC has been guided by three main goals: (1) understanding how endogenous beta cells are made through the study of pancreatic development, with the hope of making pancreatic cells in the laboratory for transplantation; (2) exploring the potential of animal and/or human stem cells as a source of making pancreatic islets; and (3) determining the basic mechanisms underlying beta cell regeneration in the adult as a basis for producing new cellular therapies for diabetes.

DEVELOPING THE TEAM

In 1999, the congressionally-established Diabetes Research Working Group recommended that NIH increase research on beta cell biology and development. This recommendation, in conjunction with the inception of the *Special Diabetes Program*, provided the opportunity to ignite research in this field with a new approach. Rather than solely supporting individual investigators pursuing projects independently, NIDDK

launched an experiment in team science which would be continually propelled by a translatable clinical goal. In 2001, the BCBC (the first funding cycle of which is referred to as BCBC 1.0) was launched with the announcement of six collaborative agreement awards. As with other NIH grants, these awards were time limited, meaning that the investigators would be required to “recompete” to continue to participate in the BCBC. In 2005, the second round of BCBC investigators received their awards and the BCBC 2.0 was launched. In this round, 10 collaborative agreement awards were funded. As expected, the groups of investigators funded in the first and second rounds were similar, but not identical. The third round of the BCBC (BCBC 3.0) was launched in summer 2010 with the funding of 16 collaborative agreement awards. These awards bring nearly 50 multidisciplinary principal investigators and over 200 affiliates into the BCBC team. BCBC members are at different stages in their careers and are located at multiple institutions around the world.

A STUDY IN TEAM SCIENCE

Team science is not a concept unique to the BCBC; the past decades have been witness to a number of large-scale team science efforts. Some have been considered successes, while others have been less successful. This bloom of team science efforts may reflect the complexity of human disease and the urgency of developing therapies and strategies to combat increasing prevalences of diseases; solving complex problems may benefit from an integration of perspectives and disciplines. The rationale for team science is simple in concept. Collaboration can be a powerful driver for innovation and progress, and a team approach can both stimulate and facilitate the rapid development and

translation of new discoveries. Meaningful advances can require the skills, often interdisciplinary, and ingenuity of many people. Synergies can be obtained and duplication can be minimized with coordinated efforts. Early results from the emerging field of the science of team science suggest that teams are, in general, more scientifically productive than individuals.¹

Barriers and Challenges to Team Science: Team science, however, is not without significant barriers and challenges that impact its success. In the effort to establish and conduct the BCBC, many of these barriers and challenges have come to light and these examples are likely applicable to other team science efforts. For example, in the current institutional system, scientists are rewarded for their individual accomplishments, which often can be easily determined. Contributions to a team effort are difficult to measure and therefore may not be as valued. Understandably then, investigators have their own interests, scientific and professional, that must be considered when working in a team. These individual interests can lead to competition among members of a team. For the BCBC, managing rapidly evolving priorities—individual and otherwise—that were sometimes in conflict was a key challenge. Similar to investigators, institutions have their own priorities, and these may not align with the priorities of the team. Institutional regulations can sometimes make it difficult to transfer funds. Therefore getting research money to where it is needed is not trivial and can be a barrier to team science. For the BCBC, an additional challenge is integration of the large quantity of data being generated; highly functional informatics was, and still is to some extent, a challenge. Finally, with any team effort, individual personalities and abilities are an important factor in the success of the team. Studies in team science

indicate that individuals who value collaboration, a culture of sharing, and openness to diverse disciplinary perspectives are well-suited for team efforts.²

Lessons Learned—Build Trust: The BCBC, therefore, is an ongoing experiment in team science; NIDDK has closely monitored the group's challenges and successes and provided enhancements to the program where possible to overcome obstacles. As the BCBC matured, the Consortium identified themes that mirror those resulting from studies of team science. These themes led to the generation of "lessons learned" by the BCBC. Many of these lessons were realized during the early years and were used to guide the BCBC 2.0. They continue to be important themes for the BCBC and team science in general. First, the BCBC found that building trust among members of the team is essential, but also takes time. Studies of team science suggest that building and sustaining trust is critical to the success of a team, especially when the team is not in close physical proximity.³ As the Consortium evolved and appreciated the importance of building trust, participants were particularly oriented to team goals, which enabled them to accept differences more readily and led to an environment of openness. This environment was one of the factors that increased and maintained trust within the BCBC.

This lesson was implemented from the beginning of BCBC 2.0. In August 2005, a kickoff meeting established the importance of trust and set a tone of high expectations among members. This provided an opportunity for members to meet in person and generate familiarity. Interactions among members were stimulated at this meeting, allowing new collaborations to be built and contacts to be made. Again, studies of

team science echo more broadly what the BCBC has observed. Initial face-to-face contact seems to increase the level of trust among team members, facilitate the formation of team atmosphere and operating procedures, and aid the establishment of group identity. Face-to-face contact early in the formation of a team has been suggested to be a prerequisite for successful remote collaboration.⁴ The BCBC kickoff meeting also provided an opportunity for participatory, team goal setting. Priorities were discussed and defined at the meeting. Studies note that group goal setting generates structure, connection, and shared goals and builds feelings of trust and inclusiveness.⁵ A kickoff meeting for BCBC 3.0 is scheduled for October 3-5, 2010 and will focus on key aspects of how the BCBC will operate, including instruction of new functionalities for information exchange via the Web site, an enhanced Sharing Policy, and general discussion of timelines and deliverables. In addition, the leaders of all collaborative agreement awards will introduce their research plans to the group at large, and strategic discussions to identify new scientific opportunities that could become trans-BCBC projects will take place.

Lesson Learned—Have Frequent Communication:

Another piece to building trust and a successful team is frequent communication. In general, it has been reported that teams with high levels of trust initiate communication more often to request clarification, to garner consensus, or to provide timely and substantive feedback.⁶ Teams like the BCBC are now exploring how social networking can increase communication among team members and add value to team science. In addition to an initial meeting, retreats have also been shown to promote communication, reduce friction, and stimulate integration.⁷ The BCBC holds semi-annual

meetings: a planning meeting for investigators in the fall and a scientific retreat for all participants in the spring. These meetings provide another opportunity for investigators to interact in person, form contacts, discuss pressing issues, and establish new collaborations. Monthly teleconferences of the Executive Committee and newly established Workgroups enable attentive oversight; these discussions are crucial to exchange information and build consensus in order to quickly and effectively resolve operational issues.

Lesson Learned—Promote Open Sharing of Scientific Information:

Another key to the BCBC and its success is that open sharing of information stimulates progress within the team and with the broader scientific community. Greater emphasis was placed on the timely sharing of unpublished information as the Consortium developed. To this end, the BCBC Web site is a vital resource that provides a forum for sharing research information throughout the BCBC. Data sharing is critical to the success of the BCBC, however significant issues to protect the confidentiality of unpublished results and to avoid conflict of interest issues generated a barrier to this activity. To ensure confidentiality and promote the sharing of preliminary research information and reagents, access to resource information on the BCBC Web site was restructured to enable a high degree of access control. This assures that BCBC investigators can access all information that they have privileges to see, while maintaining confidentiality of unpublished results and avoiding conflict of interest issues. Again, studies in team science indicate that “cyber-infrastructure” is essential to the success of distance collaboration.⁸ Many reagents are described on and publicly accessible via the BCBC Web site. To enable this, the BCBC established a sharing policy in which all BCBC investigators agreed

to the timely sharing of data and reagents. Sanctions are possible for individuals who do not comply, and new reagents must be distributed to academic investigators without regard to the requestor's identity or experimental plans. This promotes overall progress in the beta cell biology field. To date, the BCBC Web site has received over 65,000 unique visits from 152 countries, demonstrating its utility.

Lesson Learned—Need for Organization and

Leadership: An important difference between the first and second funding cycles of the BCBC is the increase in organization as time progressed. It took time to build the resource cores, assemble the coordinating center, establish the cyber-infrastructure, and stimulate fruitful collaborations. Patience and time are required for establishing a productive team. The importance of thoughtful planning and goal-oriented results cannot be underestimated and require good leadership to achieve. Leadership in the BCBC does not rest on one person, ensuring that no single person is dominant and underscoring that every member has an important role and contributes to the goals of the BCBC. The BCBC found, however, that it was helpful to define these roles and monitor them to assist progress. For example, several committees with clearly defined responsibilities and which include BCBC investigators, scientists outside the BCBC, and NIDDK staff, are involved in guiding the Consortium. Communication and cooperation between BCBC scientists and NIDDK staff have been essential to establishing leadership in the BCBC and have led to a stimulating and collegial environment.

Lesson Learned—Employ Flexible Funding

Mechanisms: The ability to distribute support in versatile and creative ways has helped to ensure rapid progress in the development and translation of new discoveries.

The BCBC utilizes Collaborative Bridging Projects (CBPs) which were created to support collaboration between various BCBC members and between the BCBC and other scientists; Pilot and Feasibility Projects (P&Fs) which attract new talent to beta cell biology; and the Seeding Collaborative Research Program that permits investigators outside the BCBC to collect preliminary data and form collaborative research teams prior to applying for full-scale funding during the BCBC re-competition. The CBP program, which supports projects that bridge two or more teams, has stimulated many productive interactions among investigators including higher impact and potentially riskier projects by providing the "glue" to bring BCBC investigators together in ways that are scientifically productive. These programs also bring non-BCBC investigators with relevant skills and talents into the Consortium. Many investigators who were brought into the BCBC through these programs went on to compete successfully to join subsequent funding cycles of the Consortium. These programs have allowed the BCBC to remain flexible, open, and responsive to new scientific developments and brought new skills and knowledge into the BCBC.

A HIGHLY-COLLABORATIVE AND PRODUCTIVE TEAM

The two completed funding cycles enable an evaluation of the Consortium's progress as the lessons learned were implemented and the program evolved. By comparing outcomes from the first and second cycles, it is possible to ascertain whether collaboration and productivity have been enhanced. Scientific interactions by BCBC investigators, as demonstrated in Figure 3, are tracked by the BCBC Coordinating Center and have increased as the Consortium matured. For 2001-2005 there was an average of 1-1.2 collaborations per investigator, while in 2005-2009 there was an average of 3 collaborations

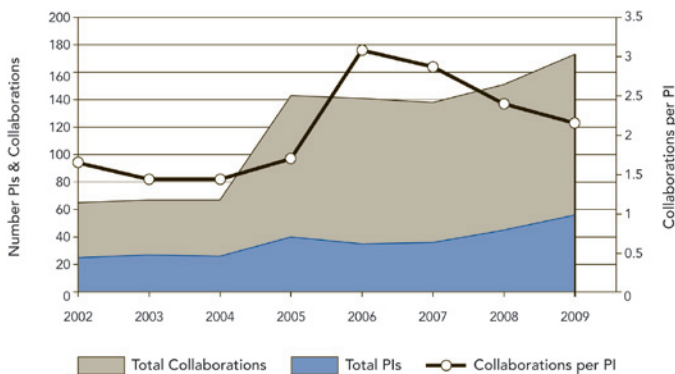


Figure 3: Collaborations in the BCBC
Total collaborations by the Consortium, as well as the number of collaborations per investigator, increased as the Consortium matured. Graph courtesy of Dr. Jean-Phillipe Cartailier, Vanderbilt University.

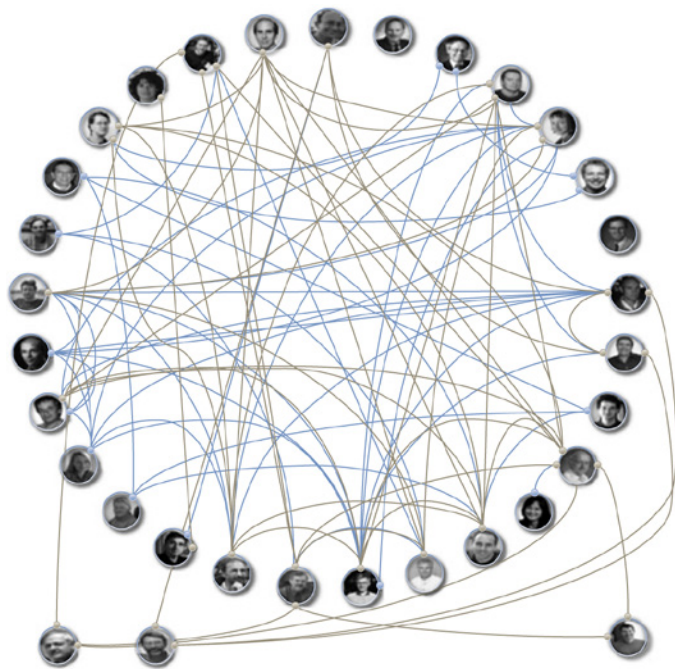


Figure 4: Scientific Interactions by BCBC Investigators
Scientific interactions by BCBC investigators. Collaborations are illustrated by a line between investigators. Collaborations have been stimulated by cooperative agreement awards (grey lines) or by the Collaborative Bridging Projects (blue lines). Many BCBC investigators participate in multiple collaborations. Image courtesy of Dr. Jean-Phillipe Cartailier, Vanderbilt University.

per investigator, suggesting that efforts by the BCBC to enhance collaboration were successful. These collaborations, illustrated in Figure 4, were complicated with dynamic interactions and multiple ties for the majority of investigators. Enhancements to the BCBC, guided by the lessons learned, have likely contributed to the increased collaborations.

Generation of Publications and Resources: In science, one measure of productivity is publications, as these are a manner in which results of studies are transmitted to the scientific community. Over the past 8 years, the BCBC has published more than 290 articles, as determined by the BCBC Coordinating Center’s query of PubMed for BCBC investigators. Over 200 of these publications occurred in BCBC 2.0, suggesting that improvements implemented as the Consortium progressed, in part, led to increased productivity.

Another goal of the BCBC, and measure of the Consortium’s productivity, is the generation of tangible resources. The BCBC is responsible for collaboratively generating necessary reagents, such as mouse strains, antibodies, assays, protocols, datasets, and other technologies that are beyond the scope of any single research effort and that would facilitate research on the development of novel cellular therapies for diabetes (see Figure 5). In addition to resource generation, the BCBC lists resources, of which more than 70 percent are publically available, on its Web site (www.betacell.org). These resources are distributed to BCBC and non-BCBC investigators. As illustrated in Figure 5, generation of resources accelerated as the Consortium progressed: fewer than 100 resources had been produced by 2005 while over 400 have now been produced. These new tools, strategies, and reagents will have lasting value in beta cell biology research. In addition, these reagents

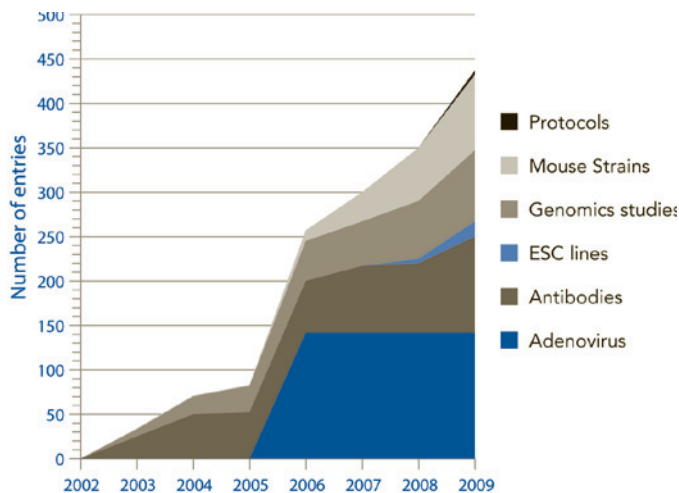


Figure 5: Expansion of BCBC Reagent Resources

Types and numbers of formal BCBC resources collected and made available by the Web site are illustrated. Graph courtesy of Dr. Jean-Phillipe Cartailier, Vanderbilt University.

are being more broadly used for research by the scientific community, for example in pancreatic cancer research.

Achievements of the BCBC: As a result of the BCBC’s efforts, new scientific insights have emerged and efforts toward cell-based therapies are progressing. Significant new knowledge has been gained of the genes involved in and events that occur during development that lead to the formation of pancreatic beta cells. This knowledge is being used in the development of strategies to generate beta cells from embryonic stem cells⁹ and/or other stem/progenitor cell populations, such as induced pluripotent stem cells, and may pave the way for new cell-based therapies for type 1 diabetes. Specific highlights of BCBC accomplishments include:

- Scientists in the BCBC identified progenitor cells in the adult mouse pancreas that form insulin-producing beta cells.
- Results from BCBC studies provided insight about the regenerative potential, or virtual lack thereof, of beta cells.

- BCBC investigators have also made significant strides toward being able to make beta cells from other cell types. For example, they reprogrammed adult mouse exocrine cells into beta cells and demonstrated spontaneous conversion of adult alpha cells into insulin-producing cells in beta cell-depleted mice.
- In addition to producing scientific knowledge that advances progress toward specific goals of the BCBC, such as the ability to coax cells along a pathway to make beta cells, the BCBC has also generated advances toward other goals. For example, researchers in the BCBC discovered that autoantibodies to a specific beta cell protein are an excellent marker for type 1 diabetes autoimmunity. They found that these autoantibodies can substantially improve prediction of diabetes when used in combination with other previously discovered autoantibodies commonly used to monitor for type 1 diabetes autoimmunity in research studies.

THE NEXT PHASE OF THE BCBC

The ever evolving nature of science and of team science provides new and continuing challenges for the BCBC. Transparency and sharing of data and results prior to publication are critical to accelerating progress and conducting team science. These features, however, must be balanced with the confidentiality of this information. As achievement in science is measured by publications and by being the first to report new information, BCBC investigators need to be able to pursue their results and publish their studies without risk of their results reaching a competitor. The BCBC also continues to balance its two efforts: resource generation and scientific performance. Both are critical to advancing progress in beta cell biology and to the success of the BCBC, and both interests require resources that are limited—time

and funding. As the BCBC enters its second decade, the Consortium is reviewing its overall goals in order to assure that it continues to stimulate progress in this important field. By maintaining a fresh approach and responding to cutting edge discoveries and technologies, the BCBC aims to continue its success and enhance progress. This flexibility and responsiveness to the changing nature of science, technology, and the team itself will allow the BCBC to remain timely and composed of the top scientists in the field. As the science of team science and evaluation of scientific progress further develop, the BCBC will have more tools to realistically assess progress and impact and enhance the Consortium further.

In response to the needs of and feedback from members of the BCBC, as well as external evaluation committees, the BCBC continues to evolve. As BCBC 3.0 begins, the focus will be enhanced toward more translational outcomes. Results from BCBC investigators and the field have enabled this evolution and paved the path toward these outcomes. Therefore, the time is right for the BCBC to capitalize on this knowledge and take advantage of recent developments in cell reprogramming, induced pluripotent stem cell technology, and mouse models with greater fidelity to human disease. The BCBC will focus on the issues that stand in the way of developing cell-based and regenerative therapies, and will increase studies of the

human islet to assist translation of this new knowledge to therapies.

SUMMARY

The BCBC has been a highly collaborative, productive, and successful consortium, and is now being used as a model for other team science efforts at NIH. Implementation of program enhancements, guided by the lessons learned from the BCBC, promoted increased collaboration and productivity as the Consortium matured. This group has demonstrated that the challenges of team science can be mitigated with planning, patience, time, flexibility, and leadership. Critically, investigators pursue their personal scientific interests with collaborations in line with the goals of BCBC, providing a balance between personal interests and independence, and team needs. The team-based approach and activities of the BCBC maximize the scientific productivity of participating scientists and accelerate progress toward the development of effective cell-based therapies for type 1 diabetes. As a result of BCBC research, these therapies are one step closer to becoming a reality for patients with the disease.

Notes:

- ¹ Wuchty S, Jones BF, and Uzzi B: The Increasing Dominance of Teams in Production of Knowledge. *Science* 316: 1036-1039, 2007.
- ^{2,8} Stokols D, Misra S, Moser RP, et al: The Ecology of Team Science. *Am J Prev Med* 35: S96-S115, 2008.
- ⁹ The NIH supports research using human embryonic stem cells within the NIH Guidelines for Human Stem Cell Research.

Feature:

Investigator Comments on the Value of the Beta Cell Biology Consortium (BCBC) Team-science Approach



BCBC scientists at the 2010 BCBC Investigator Retreat; Bethesda, MD.

Photo courtesy of Dr. Mark Magnuson, Vanderbilt University.

“The team-based approach of the BCBC has benefited our research in two ways. First, it has enabled us to gain the expertise of diverse individuals working together to understand previously unappreciated signaling pathways that promote the development of the pancreatic beta cell. Second, by sharing our discoveries within the larger group of the Consortium, prior to publication, it allows certain findings to be confirmed more rapidly by others and new twists to be revealed as early as possible.”

—Ken Zaret, Ph.D., University of Pennsylvania

“The team-based approach of the BCBC has transformed how I do research. We are now able to bring our knowledge and skills to bear on projects that were impossible for us to do before. By bringing leading scientists together, and then providing support for collaborative research, the BCBC accelerates the pace of discovery necessary for the development of novel, new therapies for both type 1 and type 2 diabetes.”

—Mark Magnuson, M.D., Vanderbilt University

“The BCBC is, to me, the best example of how to partner a truly scientifically excited and expert NIH staff with a large cluster of first-tier research labs, working globally and in an integrated, rapid fashion. An interactive and flexible leadership group has generated an incredibly trusting and enabling infrastructure not only to innervate BCBC member labs, but also to reach out, via completely novel concepts and tools, to help tons of other basic and translational researchers who are tackling diabetes. A focused and milestone-oriented approach within the BCBC has shaved years off the time involved in drawing up a precise molecular-genetic blueprint for the production of our body’s normal insulin-secreting beta cells. Personally, I am proud of my membership in the BCBC.”

—*Christopher Wright, D.Phil., Vanderbilt University*

“Having the BCBC, and having different people develop and share reagents and technologies, has moved the [beta cell biology] field so much faster. The way that the BCBC as a whole has advanced the field is much more than the sum of the parts. As part of the BCBC, I have been able to probe deeper into the questions that I wanted to ask and to do the research in a much shorter time span. The BCBC has also allowed my lab to branch out into new areas. Having access to unique reagents through the BCBC has allowed us to ask questions that we simply would not have been able to ask otherwise.”

—*Maïke Sander, M.D., University of California, San Diego*

The BCBC is an international Consortium of investigators using a team-science approach to studies of pancreas and beta cell biology and development toward a cell-based therapy for type 1 diabetes. BCBC researchers from around the world work collaboratively and are encouraged to share data and information on a regular basis. For more information about the BCBC, please see “The Beta Cell Biology Consortium: An Experiment in Team Science” feature in this chapter and Appendix C.

Patient Profile

Charlotte Cunningham

*With Type 1 Diabetes,
“Time is of the Essence”*

Late in the summer of 2005, Lilo Cunningham noticed that her then 10 year-old daughter, Charlotte, was beginning to drink copious amounts of water. This seemed unusual to Lilo because Charlotte was not fond of drinking water. “But no matter where we went, she was always looking for a water fountain,” says Lilo. Lilo also noticed that Charlotte was using the bathroom more frequently.

Lilo recognized these changes in Charlotte’s behavior as potential symptoms of diabetes. As two of Lilo’s sisters have sons with the type 1 form of the disease, Lilo decided not to take a chance. Within days of her observations, Lilo made an appointment with Charlotte’s pediatrician and, sure enough, learned that Charlotte’s blood sugar level was 680—about seven times above normal.

Charlotte was diagnosed with type 1 diabetes—previously known as juvenile diabetes—a devastating illness that often strikes in infancy, childhood, or young adulthood.

The diagnosis was frightening, but Lilo was able to turn to her sisters for advice. In addition to offering many practical suggestions for dealing with diabetes on a day-to-day basis, one of Lilo’s sisters, who is very active in the Juvenile Diabetes Research Foundation International (JDRF), informed her that several diabetes research trials



Charlotte Cunningham

were under way. She suggested that the Cunninghams might want to investigate these trials for Charlotte.

Because the Cunninghams were informed of several clinical trials shortly after Charlotte’s diagnosis, she was eligible to participate in a clinical trial specifically designed for newly diagnosed patients. The therapy being tested in this trial may slow down the progression of the disease, which could reap long-term benefits for patients and make it easier for them to control their blood sugar levels.

Controlling blood sugar levels is critical. The NIDDK’s landmark Diabetes Control and Complications Trial (DCCT) demonstrated that intensive blood sugar control offers remarkable long-term benefits when it comes to preventing or delaying complications frequently associated with type 1 diabetes, including eye, nerve, kidney, and cardiovascular disease.

At the time this profile was written, Charlotte was 13 years old and 3½ years post-diagnosis, and showed no signs of complications from diabetes. “Time is of the essence,” says Lilo, “the more we can slow the progression of this disease and keep Charlotte healthy, the better chance she has of leading a longer, healthier life.”

“The longer we can slow the progression of this disease and keep Charlotte healthy, the better chance she has of leading a longer, healthier life.”

About the Study

Type 1 diabetes occurs when a person’s immune system mounts a misguided attack and destroys the insulin-producing beta cells found in the pancreas. Insulin is critical for the body to absorb glucose from the blood and to use it for energy. Those with type 1 diabetes need daily administration of externally supplied insulin, either by injection or with a pump, and must monitor their blood sugar levels vigilantly. Researchers have discovered, however, that many individuals diagnosed with type 1 diabetes still make detectable amounts of insulin, even many years after they are diagnosed. The DCCT also showed that people with type 1 diabetes who still made some of their own insulin had fewer long-term disease complications, as well as reduced incidents of dangerously low blood sugar (hypoglycemia) from administration of too much insulin. These observations suggest that preserving patients’ remaining beta cell function, so that they still produce some of their own insulin, could have dramatic, long-term health benefits.

The trial in which Charlotte is participating is trying to do just that. A previous NIDDK-supported clinical trial indicated that an antibody, called hOKT3gamma1(Ala-ala)

or “anti-CD3”, halted the destruction of insulin-producing beta cells in a small number of newly diagnosed patients. Anti-CD3 alters the signal that triggers the disease-causing immune cells to attack the insulin-secreting cells. Charlotte is participating in a trial where researchers are determining if an additional treatment of anti-CD3 will provide further benefit, beyond that of the single treatment. This trial is being conducted by the Immune Tolerance Network, which is led by the National Institute of Allergy and Infectious Diseases, in collaboration with the NIDDK’s Type 1 Diabetes TrialNet. Both networks also receive funding from the *Special Statutory Funding Program for Type 1 Diabetes Research*. Because one of the requirements for participation in this particular trial was that patients enroll within 8 weeks of their diagnosis, the Cunninghams are very grateful that a family member counseled them to act quickly after Charlotte’s diagnosis.

“We were fortunate that Charlotte was diagnosed so early and was able to participate in this trial,” says Lilo. “As a result, she’s perhaps making more insulin than the average person in the early stages of diabetes and is doing very well.”

The trial requires Charlotte to be infused daily over a 14-day period with the anti-CD3 antibody. Each daily infusion takes between 15 to 30 minutes, and is administered into Charlotte’s upper arm. Charlotte received this 14-day set of infusions two times; the second treatment followed 19 months after the first. Charlotte returned to the trial site every 3 months in between the treatments and for 12 months following the second treatment. These visits were to monitor her response to the treatment and included a physical examination, a blood test, and a test to measure her insulin response. Except for a rash between her fingers,

which lasted only 1 day, Charlotte has experienced no side effects from the treatment.

When asked about her overall experience in the trial study, Charlotte responded, “It was very cool.” Not the typical response one would expect from an adolescent, but Charlotte has handled her diabetes extremely well from the beginning.

“We had an incredibly positive experience with Charlotte’s study. We were exposed to so many people who know so much about this disease—we learned so much!”

Lilo & Charlotte’s Message:

Don’t hesitate. Act quickly.

When it comes to diabetes, Lilo and Charlotte’s message to others is clear and simple: At the first sign of symptoms, do not hesitate; act quickly.

“If you have any suspicions or notice anything wrong with your child, go for a blood test [at your pediatrician’s office] and follow up immediately,” says Lilo. “If this study succeeds in allowing Charlotte to retain the ability to produce some of her own insulin, even for a little while longer than she might have otherwise, it will help to delay, reduce, and possibly even prevent the secondary complications that often accompany type 1 diabetes.” “And make sure you check your blood sugar level regularly,” adds Charlotte.

Lilo has not observed symptoms in other family members, but that does not mean she was going to take chances. The Cunninghams enrolled their two other children, Charlotte’s 16 year-old brother and 19 year-old sister, in a study as well—the TrialNet Natural History Study.

This study is screening relatives of people with type 1 diabetes to determine what level of risk these family members have for developing the disease. These studies are being conducted to learn more about the causes and indicators of risk for the development of type 1 diabetes. So far neither one of Charlotte’s siblings appears to be at increased risk. “But if either of them should show signs of the disease, I would enroll them in a clinical trial in a heartbeat,” Lilo says. “We had an incredibly positive experience with Charlotte’s study. We were exposed to so many people who know so much about this disease—we learned so much!” When asked her thoughts on participating in the trial, Charlotte proudly says “I’m an example of how diabetes research is helping people.”

“Having diabetes hasn’t really affected me much when I’m doing sports...my coaches are very understanding and let me do what I need to do to take care of myself.”

About Charlotte

Since February 2008, Charlotte’s need for injected insulin has increased dramatically. According to Lilo, it is hard to say exactly what is going on. “Charlotte is in the midst of puberty, which could mean her body is requiring more insulin because of hormonal changes,” she says. Nineteen months after her first treatment, Charlotte received her second and final 14-day infusion as part of the trial. The good news is that, even though Charlotte needs more external insulin, tests performed in July 2010 (nearly 5 years after her initial diagnosis) indicate that she is still producing a clinically significant amount of insulin. Because her need for external insulin has increased, Charlotte started using an insulin pump, a portable device that injects insulin at programmed intervals.

If anything, Charlotte's life has become more active, rather than less, since being diagnosed with diabetes. Prior to her diagnosis, Charlotte played tennis and basketball. Now she has added surf boarding, lacrosse, and softball to her repertoire of physical activities. "Having diabetes hasn't really affected me much when I'm doing sports," she says. "I need to make sure my blood sugar count is okay both before and while I'm playing, but my coaches are very understanding and let me do what I need to do to take care of myself."

In the meantime, at the time this story was written, Charlotte was preparing to go to summer camp with 70 of her peers, all of whom have diabetes. She has been to the camp twice before and says she likes it a lot. "We meet with meal planners and check our blood sugar regularly, but mostly it's a regular, fun camp," Charlotte explained. Like any 13-year-old, Charlotte simply wants to lead as active and normal a life as possible.

EMERGING RESEARCH OPPORTUNITIES RESULTING FROM THE *SPECIAL DIABETES PROGRAM*

The *Special Statutory Funding Program for Type 1 Diabetes Research* has fueled the emergence of a wide range of research opportunities. These opportunities were identified in a strategic planning process as being critically important for overcoming current barriers and achieving progress in diabetes research. Key questions and research opportunities relevant to type 1 diabetes, including those related to the development of cell-based replacement therapy, are outlined in Appendix F.