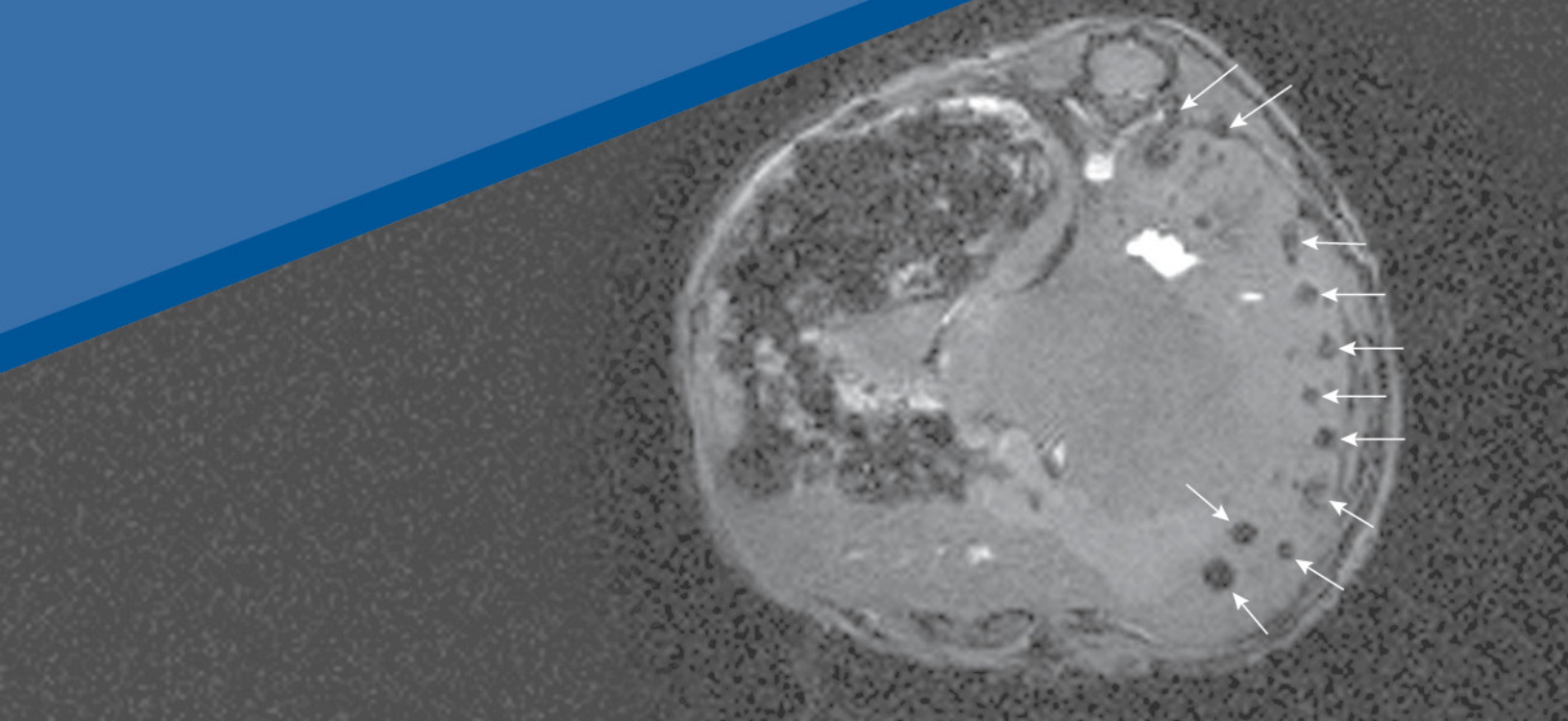
GOAL VI

ATTRACT NEW TALENT AND APPLY NEW TECHNOLOGIES TO RESEARCH ON TYPE 1 DIABETES



The *Special Statutory Funding Program for Type 1 Diabetes Research* has expanded the research opportunities in type 1 diabetes and its complications by harnessing cutting edge tools and technologies and attracting creative and skilled scientists with diverse background. This has resulted in significant scientific progress, which is described in this chapter and in other chapters throughout the report. Additional information on the program evaluation related to Goal VI 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 affects many organ systems and involves diverse areas of science. Thus, it is imperative to pursue a broad range of research to have the greatest impact on the health of people. Toward that end, it is important to recruit scientists with different areas of expertise and to promote collaboration to conduct research on type 1 diabetes. It is also imperative to capitalize on new and emerging technologies and fields of science to propel research progress. Research supported by the *Special Statutory Funding Program for Type 1 Diabetes Research* (*Special Diabetes Program* or *Program*) has led to major scientific advances by attracting new scientific talent with diverse backgrounds and applying new and emerging technologies to the study of this complex disease.

HIGHLIGHTS OF RECENT RESEARCH ADVANCES RELATED TO GOAL VI

Attracted New Talent to Research on Type 1 Diabetes: Evaluation of research supported by the *Special Diabetes Program* showed that approximately 38 percent of scientists who received R01, R21, or DP2 grants were new investigators, and that number is likely an underestimation. In addition, the *Program* supported a training and career development program for a cadre of pediatricians specializing in childhood diabetes. An evaluation of the K12 (Physician Scientist Award) component of this training program showed that 28 pediatric endocrinologists received training, and 27 of them (96 percent) remain in academic medicine. Thus, the *Special Diabetes Program* has attracted new researchers to the study of type 1 diabetes and has also trained a new generation of pediatric endocrinologists to conduct diabetes research.

Positron Emission Tomography (PET) Imaging Agents Target the Pancreatic Beta Cell: ^{11}C-DTBZ (^{11}C-dihydrotetrabenazine) is an imaging agent developed for PET imaging of the dopaminergic neurons of the brain. Its target, the Vesicular Monoamine Transporter 2 (VMAT2) protein, was identified in gene array screens of islet cells. The imaging agent binds specifically to beta and pancreatic polypeptide-producing cells of the islet and has been used to visualize these cells in the human pancreas in healthy people and in people with diabetes. Currently, researchers are working to modify the molecule in order to improve its imaging and binding characteristics to the point where it can be reliably used to monitor beta cell mass in people. Other research is ongoing to determine the

Graphic: Noninvasive in vivo magnetic resonance imaging (MRI) of transplanted human islets, designated by white arrows, in the livers of healthy mice. Islets were labeled with a magnetically "visible" contrast agent for imaging. Image credit: Dr. Anna Moore.

specific location and expression of its molecular target in the pancreas. Additional highly promising imaging agents are being developed that target markers enriched in the beta cell, such as the glucagon-like protein (GLP)-1 receptor. Development of the imaging agent ^{11}C-DTBZ has thus spurred noninvasive studies of beta cells.

Magnetic Resonance Imaging (MRI) Agents Hold Promise for Imaging Transplanted Islets: The current practice of transplanting islets into the livers of people with diabetes presents both challenges and opportunities for imaging. The liver takes up many of the molecular imaging agents in a non-specific way, and therefore tends to have a high background signal in most experiments. Considerable progress has been made by labeling either the islets themselves with iron-based contrast agents prior to transplantation, or by encapsulating the isolated islets in immunoprotective coatings that contain iron- or gadolinium-based contrast agents. Signals persist long after transplantation in rodent, porcine, and primate models, and correlate very well with islet survival. Human trials are under way using this approach.

Ability To Image Islet Inflammation *In Vivo*: The presence of islet autoantibodies, and perhaps metabolic changes as detected in the circulation, are the current standards to measure islet autoimmunity, but are an indirect measure. In preliminary experiments, the specific T cell populations that cause insulitis have been directly visualized using molecular imaging approaches, but the most promising and least invasive approach is to take advantage of the vasculature 'leakiness' that develops during inflammation. Large, iron-based MRI contrast agents tend to remain in the bloodstream except in sites of compromised vasculature, and a persistent signal in the pancreas due to islet inflammation has been successfully monitored in type 1 diabetes mouse models and in people recently diagnosed with type 1 diabetes.

Attracting New Talent to Type 1 Diabetes Research

A major goal of the *Special Diabetes Program* is to attract new talent to the study of type 1 diabetes and its complications. Encouraging new researchers to study type 1 diabetes brings fresh talent to the field and promotes the careers of young scientists poised to make a difference in public health. From the *Program*'s inception in Fiscal Year (FY) 1998 through FY 2009, approximately 38 percent[28] of scientists who received R01, R21, or DP2 grants were new investigators, and this number is likely an underestimation. In addition to attracting new scientists, the *Special Diabetes Program* has also facilitated novel collaborations among scientists with diverse interests to study type 1 diabetes and its complications.

Type 1 Diabetes Pathfinder Awards: Through support from the *Special Diabetes Program*, the NIDDK employed a novel strategy to attract new scientists to type 1 diabetes research. Ten scientists who had not previously received an NIH grant successfully competed for Type 1 Diabetes Pathfinder Awards for highly innovative research studies. Some of the scientists supported by the Pathfinder Awards were new to type 1

[28] Data collected through the NIAID electronic Scientific Portfolio Assistant (e-SPA). More information on data and methodology related to new investigators is found in Appendix B.

diabetes research, demonstrating how this innovative strategy attracted scientists to apply their expertise to a new research field. Profiles of two scientists who received Type 1 Diabetes Pathfinder Awards are found later in this chapter.

Supporting the Next Generation of Scientists: Management of diabetes in children is particularly arduous and requires an exceptional level of effort from the children, their families, and their health care providers. These extraordinary clinical care demands make it challenging for pediatric endocrinologists involved in diabetes care to also pursue research careers. Furthermore, there is a long process of training and career development before a new independent investigator is ready to obtain grant support and lead a research laboratory. Through support from the *Special Diabetes Program*, a cadre of pediatricians specializing in childhood diabetes received such research training and career development. A recent evaluation of the K12 training program showed that 28 pediatric endocrinologists received training under the program, and 27 of them (96 percent) remain in academic science. Many of them have also successfully competed for independent funding to conduct research. As just one example of the success of this training program, one of the trainees, Dr. Stuart Weinzimer, attained a faculty position at Yale University and is making significant contributions to research on continuous glucose monitoring technology and the development of an artificial pancreas (see Dr. Weinzimer's Investigator Profile later in this chapter).

Promoting Research Collaborations: The *Special Diabetes Program* has promoted successful collaborations among scientists with diverse interests to combat type 1 diabetes. The *Special Diabetes Program* has facilitated the creation of multiple research consortia to tackle specific challenges that will impact the health of people with type 1 diabetes. Collaboration has been a key component to the success of these efforts. For example, the Beta Cell Biology Consortium (BCBC; see Goal III) has brought together experts in diverse fields such as developmental biology, bioinformatics, animal model development, immunology, and other areas, to work collaboratively toward the goal of developing cell replacement therapy for type 1 diabetes. The BCBC has been extremely successful, has resulted in major scientific advances, and is now being used a model for other new collaborative research programs being established by NIH. In another example, researchers in DirecNet (experts in continuous glucose monitoring technology) and Type 1 Diabetes TrialNet (experts in clinical trials focused on type 1 diabetes prevention and early treatment) forged a collaboration to test whether a closed-loop system could preserve beta cell function in newly diagnosed patients. (For more information about the collaboration on this trial, please see the Investigator Profile of Dr. Bruce Buckingham in Goal IV.) Collaboration between these two groups of scientists was crucial to undertake this type of study and such coordination and collaboration continues to be essential as type 1 diabetes research evolves.

Pilot and Feasibility Projects: Pilot and Feasibility (P&F) projects have been used successfully to attract new talent to type 1 diabetes research. Several of the consortia supported by the *Special Diabetes Program*, such as the BCBC, the Animal Models of Diabetic Complications Consortium, and the Cooperative Study Group for Autoimmune Disease Prevention, support P&F projects to attract new talent. These programs give new researchers the opportunity to test novel hypotheses that have

conceptual promise, established investigators a chance to explore a new application or direction for their research, or scientists not studying type 1 diabetes an opportunity to apply their talents to a completely new research field. Thus, this mechanism has provided a means to attract new talent to research on type 1 diabetes and its complications.

Applying New Technologies to Type 1 Diabetes Research

The tools of biomedical research have changed rapidly due to the biotechnology revolution. Many methods that were used as recently as 10 or 20 years ago have been replaced by technologies that permit scientists to conduct research more efficiently and to ask and answer new research questions.

Capitalizing on New Genetics Tools and Technologies: Recent advances in the genetics of type 1 diabetes are a prime example of progress that has been achieved due to the development of new technologies. Technological developments in the 1980s sped up the ability to sequence genes, which in turn enabled NIH to launch the Human Genome Project in 1990. Completed in 2003, the Human Genome Project mapped all the genes in the human genome. The elucidation of the entire human genome made possible another effort, called the International HapMap Project, to develop a "haplotype" map of the human genome. The haplotype map, or "HapMap," is a tool that allows researchers to find genes and genetic variations that affect health and disease.

The new research tools that emerged from the Human Genome Project and the International HapMap Project laid the foundation for new "genome wide association studies" (GWAS) to identify even subtle genetic differences between people with specific illnesses and unaffected individuals. As recently as 2003, just three type 1 diabetes genes were known. Now, through GWAS and other genetics studies, scientists supported by the *Special Diabetes Program* and others have identified over 40 genes or genetic regions associated with type 1 diabetes. This remarkable progress demonstrates how researchers supported by the *Program* capitalized on new tools and technologies to make major strides in understanding the genetic underpinnings of type 1 diabetes. Researchers supported by the *Special Diabetes Program* are now building on these scientific discoveries to pinpoint the exact genes that influence type 1 diabetes susceptibility and to understand their role in health and disease. This knowledge can lead to the development of new prevention and treatment strategies, and possibly personalized therapies. For more information on the genetics of type 1 diabetes, please see Goal I.

Supporting Research in a New Era of "Omics" Technologies: Historically, scientists have looked at individual genes or proteins to understand how they influence disease. This has been a useful strategy and has led to revolutionary progress and new treatment approaches, but could be limiting—much like looking at one piece of a puzzle. The era of "omics" technologies is providing researchers an opportunity to understand how networks of cellular components work together to produce a state of health and to identify key players that go awry in disease. Toward that goal, researchers supported by the *Special Diabetes Program* are using "omics" technologies to generate a system-wide picture of all of the molecules in a cell and how they are affected by type 1 diabetes. This research includes determining the sequences and expression of all genes in a certain

cellular context (genomics), mapping out all interactions of different proteins and how they are modulated in disease (proteomics), and following the path of all metabolic intermediates (metabolomics).

For example, scientists are using proteomics to elucidate beta cell function and to identify new proteins on the beta cell that may be targets of the immune system's attack. In addition, research supported by the *Special Diabetes Program* demonstrated that, in mice, the trillions of bacteria that live in the gut may protect against the immune system attack that causes type 1 diabetes. Thus, knowledge stemming from the NIH Human Microbiome Project, which is identifying and characterizing the microorganisms found in the body, can be utilized to explore this fascinating insight into type 1 diabetes. In fact, the samples that are being collected by TEDDY (see Goal I) could be analyzed with new technologies emerging from the Human Microbiome Project, to uncover potential environmental triggers of type 1 diabetes. Also, because celiac disease shares the same genetic risk factors as type 1 diabetes, TEDDY will also study the environmental triggers for celiac disease. Therefore, application of "omics" technologies to type 1 diabetes provides a chance to see the entire puzzle, facilitating a greater understanding of the disease process than ever before possible, which can lead to the identification of new targets or strategies for prevention and therapy.

Development of New Continuous Glucose Monitoring Technology and Research Toward an Artificial Pancreas: While there has been remarkable progress due to involvement of bioengineers in developing current continuous glucose monitoring technology, a next generation of sensors, algorithms, and insulin formulations are needed. Recent research supported by the *Special Diabetes Program* is intended to build on earlier success and develop even more accurate devices. More information on continuous glucose monitoring and artificial pancreas technologies is found in Goal IV.

Applying New Technologies To Improve Detection of Diabetic Eye Disease: Scientists supported by the *Special Diabetes Program* are developing new tools and technologies that can be used for increasing patient access to eye exams for detecting diabetic retinopathy, a complication of diabetes that can lead to blindness. Many people with diabetes live in communities without ophthalmologists trained in examining the retina for signs of diabetic damage. New tools combined with telemedicine can address this problem and overcome a barrier to regular eye exams that can lead to prompt vision-sparing therapy. For example, researchers are seeking to develop a low-cost, handheld camera that is capable of assessing the human retina. This type of device could be used by non-eye specialists, such as primary care physicians, to acquire and transmit retinal images to a remote processing site for interpretation and diagnosis by retinal specialists. This technology could help improve detection of diabetic retinopathy because patients would not necessarily have to make a trip to an eye specialist for an exam. Early detection could lead to early treatment to prevent blindness.

Imaging the Pancreatic Beta Cell: Another research area that has been fostered by the *Special Diabetes Program* is imaging the pancreatic beta cell. The NIDDK, through support from the *Program*, spearheaded a series of targeted research solicitations and scientific workshops to accelerate research progress in this area. At the first workshop, in 1999, only a handful of scientists were in attendance. At the most recent workshop, in April 2009, a few hundred scientists and trainees were in attendance

to discuss research progress and future directions. The overall intended goal of the research is to develop clinically useful imaging approaches for monitoring the mass, function, and inflammation of naturally occurring or transplanted beta cells in the body, in people with type 1 or type 2 diabetes, or people who are at risk for these diseases. Imaging the beta cell holds promise as a means to allow scientists to visualize the extent of pancreatic damage and, potentially, to see directly if a therapy is effective. This ability could lead to smaller, shorter, and less expensive clinical trials for both type 1 and type 2 diabetes. It could also allow physicians to see damage to the pancreas before onset of symptoms, thus possibly allowing for earlier intervention. Furthermore, imaging could help physicians monitor islets after transplantation, which could permit them to intervene when necessary to prevent the islets' destruction.

Applying Other New and Emerging Technologies to Research on Type 1 Diabetes: In addition to the examples given above, the *Special Diabetes Program* has supported research on a wide range of scientific areas using new and emerging technologies. For example, research supported by the *Special Diabetes Program* suggests that manipulating dendritic cells of the immune system is a promising strategy to prevent, delay, or reverse type 1 diabetes (see Goal II). Scientists are also using small interfering RNA (siRNA) technology to identify target genes that promote type 1 diabetes, and developing strategies for therapeutic application of siRNA to turn off genes of interest. Bioengineers are studying ways to protect transplanted islets for immune system attack, such as by encasing cells in a protective barrier.

Summary

The diabetes research enterprise requires a diversely-trained, multidisciplinary, and interactive workforce to fully address the complexity of disease etiology and treatment. The *Special Diabetes Program* has augmented such a workforce to combat complex problems related to diabetes prevention, treatment, and cure. Scientists with expertise in areas not historically associated with type 1 diabetes, such as bioengineers, are now applying their talents to type 1 diabetes research. As scientists from diverse fields continue to study type 1 diabetes and its complications, additional progress will be achieved.

The highlights of scientific accomplishments described in this chapter showcase how the *Special Diabetes Program* is capitalizing on new and emerging technologies toward the goal of improving health and quality of life of people with type 1 diabetes. Research that was not possible at the inception of the *Program* is now possible because of these new technologies. New technologies applied to type 1 diabetes research have resulted in major scientific advances, such as the identification of numerous genes associated with the disease and its complications. In many cases, such as in the development of continuous glucose monitoring technology and imaging inflammation, the *Special Diabetes Program* supported the development of the new technologies themselves, which is having a far-reaching impact.

Investigator Profile

Stuart Weinzimer, M.D.

Nurturing Research Careers in Pediatric Endocrinology

Stuart Weinzimer, M.D.

Stuart Weinzimer, M.D. is an Associate Professor in the Department of Pediatrics at the Yale University School of Medicine. He was a recipient of an NIH Clinical Scientist Career Development Program (K12) award, which was supported by the Special Statutory Funding Program for Type 1 Diabetes Research *to cultivate clinical researchers in pediatric endocrinology. Now he is an independent investigator pursuing cutting-edge research on new technologies in diabetes management for children, including research toward the development of an artificial pancreas. This profile describes Dr. Weinzimer's research, the impact of the K12 award on his career, and the importance of fellowship awards to recruit pediatric endocrinologists to research.*

A Marriage of Technologies: The Artificial Pancreas

"We need to improve the lives of people now," says Dr. Weinzimer passionately when describing the objective of his research. Toward this goal, his research focuses on the use of technology to improve diabetes care for children. This has included studies on technological advancements such as insulin pumps and continuous glucose monitors through the *Special Diabetes Program*-supported Diabetes Research in Children Network (DirecNet). Dr. Weinzimer is now working on a "marriage of those two technologies," an artificial pancreas that "closes the loop" between the insulin pump and continuous glucose monitors. "Closed loop is really nothing more than insulin delivery that's automated so that a person with diabetes or a caretaker doesn't have to manually do it," describes Dr. Weinzimer.

This technology has the potential to significantly improve the quality of life of people with type 1 diabetes by automatically measuring glucose levels in real time and administering the proper amount of insulin. By replicating what the body does naturally, it is hoped that the artificial pancreas will help people with type 1 diabetes achieve tighter control of their blood glucose levels, reduce risks of long-term complications from chronic hyperglycemia (high blood glucose), and eliminate dangerous episodes of hypoglycemia when blood glucose levels drop too low. Research from the landmark NIDDK-supported Diabetes Control and Complications Trial and the follow-on Epidemiology of Diabetes Interventions and Complications study has demonstrated that intensive control of blood glucose levels can have long-lasting effects toward reducing

the onset and progression of diabetes complications involving the kidneys, eyes, nerves, and heart. "With closed loop technologies, it will be the first time we've ever been able to offer people a new tool for diabetes that's associated with less burden of care rather than more burden of care," explains Dr. Weinzimer.

"It's humbling," he says, describing what it is like to work with patients with type 1 diabetes. "I went into pediatric endocrinology because it was very logical and rational and all the metabolic pathways were beautiful and elegant. And the reason I went into diabetes is because it's completely irrational and makes no sense," he explains. In addition to his research, Dr. Weinzimer is the Medical Director of Yale's Type 1 Diabetes clinic, seeing children with diabetes every week. While that may seem like a lot to juggle, it's the right balance for Dr. Weinzimer. "I need to have different facets—where I'm seeing patients and working on research protocols and I can very easily pick up what I'm doing in my research and apply it to the clinic. It allows me a lot of variety, but [they are] similar enough where one informs the other." For example, after performing basic pharmacology studies looking at the rate of insulin absorption, he was able to immediately apply the results to how his patients were being treated with insulin pumps. Conducting type 1 diabetes research and seeing patients in the clinic is a perfect combination for him.

Enticing Pediatric Endocrinologists to Research

When Dr. Weinzimer started his training in pediatric endocrinology (diabetes is an endocrine disease), he worked in a laboratory studying the molecular determinants of growth and growth factors. Although he found the research interesting, he decided to pursue another facet of pediatric endocrinology—diabetes. "I always had a clinical interest in diabetes management," notes Dr. Weinzimer, "and I wanted a change in my career trajectory." He began speaking with clinical diabetes researchers, in search of a program that would be a good fit for his interests in diabetes research, and met with Dr. William Tamborlane, a renowned type 1 diabetes researcher at Yale University. Yale had received funding from NIH to recruit pediatric endocrinology fellows into research and had dedicated and committed senior investigators with the mentoring qualities for which Dr. Weinzimer was looking.

To enlarge the pool of pediatric endocrinologists conducting diabetes research, NIH, in partnership with the American Diabetes Association (ADA) and the Juvenile Diabetes Research Foundation International (JDRF) and with support from the *Special Diabetes Program*, awarded institution-wide research training and career development grants to seven medical centers with strong research programs in childhood diabetes. Dr. Weinzimer's award, the Clinical Scientist Career Development Program (K12) grant mechanism of the NIH, was designed to provide 2-3 years of support for junior clinical investigators. The funding supported up to five positions at each medical center; each center was free to decide how many of the five slots were to be reserved for pediatric endocrinology fellows or investigators who were transitioning from fellow to independent scientist.

"This kind of funding mechanism really made this whole thing possible," says Dr. Weinzimer, referring to his transition to a new field and advancement to an independent investigator. "He [Dr. Tamborlane] was able to bring me to Yale from my previous institution, without my own hard funding, and I was basically able to train in a whole new area. By having the K12 I was able to learn

techniques, develop a whole new research expertise, and have the 'protected time' to do it." The award meant that Dr. Weinzimer could be trained in type 1 diabetes clinical research and conduct research, rather than having to spend the majority of his time in the clinic. He learned how to carry out clinical diabetes research studies in children and started studying how the body uses and responds to insulin delivered by an insulin pump.

Transition to an Independent Researcher

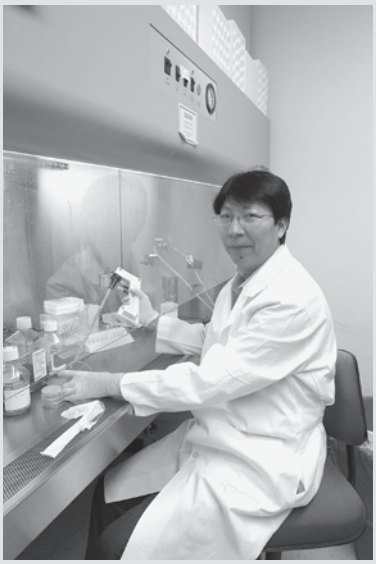
At the end of his fellowship, Dr. Weinzimer would transition from being a fellow to a faculty member, at which time he would be expected to find his own source of funding to support his research program. The K12 award allowed him to begin to develop his own research program as an independent investigator. "We were able to do some of our earliest closed loop studies under the K12 as well," Dr. Weinzimer notes. "That led very directly to both JDRF funding and my current R01 [an NIH Research Project Grant] funding." Dr. Weinzimer decided to continue his research at Yale where he is now an Associate Professor.

When asked if training awards like the K12 are a good mechanism to attract pediatric endocrinologists to diabetes, Dr. Weinzimer responds, "I will say that it's necessary, it's not just good. Pediatric endocrinology is a small field, and we have to be able to offer something to young investigators to help them either become interested or stay interested in pediatric diabetes research." Now as the fellowship director for Yale's pediatric endocrinology program, Dr. Weinzimer has an even broader perspective of the importance of awards like the K12: "It's really great for me to take a person who's interested in diabetes, be able to protect his or her time, and say 'Go off and do this, learn this' at a place such as Yale where we have the resources to do that. And I'll know at the end of the 3 to 4 years that we can develop an investigator who can go out and do great things. It's a tremendous investment and is incredibly important." Dr. Weinzimer himself fits this description well, as he continues to do great things through research and clinical practice to improve the lives of children with diabetes.

Pathfinder Investigator Profile

Deyu Fang, Ph.D.

Insight from Traditional Chinese Medicine Paves a Path to a Career in Type 1 Diabetes Research



Deyu Fang, Ph.D.

Deyu Fang, Ph.D., is an Associate Professor of Pathology at Northwestern University. He is a recipient of the Type 1 Diabetes Pathfinder Award, which is supported by the Special Statutory Funding Program for Type 1 Diabetes Research *and provides funding for new investigators pursuing innovative research on type 1 diabetes. Dr. Fang is conducting research to uncover how a specific protein ensures that potentially harmful cells of the immune system are kept inactive. This profile describes how he came to be involved in type 1 diabetes research, his research that is supported by the Pathfinder Award, and how this award has impacted his career as an independent investigator.*

"The overall goal for my research," begins Dr. Fang, "is to understand how type 1 diabetes develops. Why does a person with type 1 diabetes have immune cells that attack insulin-producing cells, but other people do not?"

The question is simple in its presentation, but finding the answer is complicated. Normally the immune system protects from foreign invaders—bacteria or viruses—that have entered the body. To be effective, the immune system needs to be able to distinguish cells in the body (self) from foreign invaders (non-self). "Tolerance" is the normal process that prevents the immune system from attacking self. When the body produces an immune system cell that may pose a threat to it, the body can delete the cell or ensure it stays inactive. Autoimmune diseases like type 1 diabetes develop from a defect in tolerance. In people with type 1 diabetes, the defect results in the fact that the aberrant immune cells are not destroyed or inactivated, so they target and destroy the insulin-producing beta cells in the pancreas. How tolerance works, and why and how it is altered in people with type 1 diabetes, are critical research questions that innovative researchers like Dr. Fang are trying to answer.

Demonstrating a Role for SIRT1 in Tolerance

Dr. Fang is investigating the function of a specific protein—known as SIRT1—in tolerance. He became interested in the role of SIRT1 in the immune system from an observation he made while in medical school in China. Says Dr. Fang, "The Chinese herbal medicine *Hu Zhang* has been used to treat autoimmune disease, particularly lupus, for thousands of years and no one thought about why." When it was discovered that this particular herbal medicine contained a small molecule called resveratrol, Dr. Fang saw a connection. Resveratrol is being studied for potential metabolic benefits, including enhancing insulin signaling and protecting tissues from damage

caused by reactive oxygen. Thus, Dr. Fang thought that the resveratrol in *Hu Zhang* might have protective effects in type 1 diabetes. He was prompted to study the role of SIRT1—a key enzyme which resveratrol is thought to influence—on tolerance, and hypothesized that "SIRT1 was likely to be a critical regulator for the immune response." If SIRT1 is important in the immune system, he thought that "dysregulated or misregulated SIRT1 function could be critically involved in the development of type 1 diabetes."

With funding from the Pathfinder Award, Dr. Fang and his colleagues have already made significant progress in testing this hypothesis. Results from his laboratory demonstrated that SIRT1 inhibits activation of T cells, a type of immune cell involved in autoimmunity, and is required for tolerance in mice. Mice genetically engineered to lack SIRT1 developed spontaneous autoimmunity in Dr. Fang's studies, suggesting that SIRT1 plays an important role in suppressing the autoimmune response.

With these exciting observations, Dr. Fang returned to his initial observation. If loss of SIRT1 can lead to the development of type 1 diabetes in mice, can treatment with resveratrol prevent the disease? In a pilot study, Dr. Fang and his colleagues tested the effects of resveratrol on mice that spontaneously develop type 1 diabetes. He summarized the result simply: "If we feed mice this small compound, then they won't develop diabetes." Dr. Fang is currently conducting a more-detailed study to conclusively demonstrate the preventative effects of resveratrol on type 1 diabetes in mice. If effective in mice, further studies would then be needed to determine if the compound is also effective in people.

Implications for Type 1 Diabetes and Beyond

Resveratrol has significant promise as a therapy for type 1 diabetes, but much remains to be understood about this compound and the role of SIRT1 in tolerance and autoimmunity. Dr. Fang will continue his research with the Pathfinder Award to address how SIRT1 regulates T cell activation and tolerance, and to determine the effects of resveratrol on type 1 diabetes development. Dr. Fang sees potential with this compound and aims to see his studies move beyond the laboratory bench: "My goal is to push this research toward a clinical trial."

Dr. Fang's research also has implications beyond type 1 diabetes. Because impaired tolerance is critical to the development of autoimmunity, his research may provide insights into other autoimmune diseases as well. "This Pathfinder Award allows us to figure out the common mechanism behind other types of autoimmune disease," explains Dr. Fang, "and whether we can find some small molecules to treat those diseases." Additionally, there is evidence to suggest that resveratrol may be effective in treating type 2 diabetes. With support from the Pathfinder Award, Dr. Fang has been able to establish collaborations with scientists studying type 2 diabetes to investigate the potential of resveratrol in treatment of both forms of the disease.

The Importance of the Pathfinder Award

Obtaining support through a Pathfinder Award has been critical in Dr. Fang's opinion. "Essentially, this award established my career and made this research project possible," he says. Before receiving the award, his laboratory studied rheumatoid arthritis, another type of autoimmune disease. The Pathfinder Award allowed

Dr. Fang to extend his research specifically to type 1 diabetes. In addition, the award has enabled him to recruit new graduate students to the laboratory and to type 1 diabetes research. "I think this award is extremely important, not only to develop a new generation of new investigators, but to develop the next generation. For example, because of this award, I was able to recruit several graduate students—very bright, smart, and highly motivated students—and train them to do research to combat type 1 diabetes," he says. Thus, like the potential of Dr. Fang's research to alter the treatment of type 1 diabetes and extend to other autoimmune diseases and perhaps even type 2 diabetes, the influence of the Pathfinder Award in Dr. Fang's laboratory will extend as well. As new graduate students are recruited to studying type 1 diabetes and trained to do research in this field because of Dr. Fang's Pathfinder Award, the impact of this award will continue long after its conclusion.

Pathfinder Investigator Profile

Bridget K. Wagner, Ph.D.

Bringing Small Molecules to a Career in Type 1 Diabetes Research

Bridget K. Wagner, Ph.D.
Photo credit: Maria Nemchuk, Broad Institute

Bridget K. Wagner, Ph.D., is a Group Leader in the Chemical Biology Program at the Broad Institute of MIT and Harvard. She is a recipient of the Type 1 Diabetes Pathfinder Award, which is supported by the Special Statutory Funding Program for Type 1 Diabetes Research *and provides funding for new investigators pursuing innovative research on type 1 diabetes. With the Pathfinder Award, Dr. Wagner is pioneering the use of small molecules to affect the biology of type 1 diabetes. This profile describes Dr. Wagner's research and the impact of the Pathfinder Award on her career in type 1 diabetes research.*

With a fiery enthusiasm for chemical biology and a burning spirit of discovery, Dr. Wagner is using the "spark of a grant," as she refers to the Type 1 Diabetes Pathfinder Award, "to ignite a career path towards type 1 diabetes research."

Finding Small Molecules To Affect Biological Processes

In line with the goals of the Pathfinder Award, Dr. Wagner is developing highly innovative new approaches to address problems in type 1 diabetes. "We are trying to bring small-molecule science to beta cell biology," Dr. Wagner says in explaining her overall goal of using small molecules to preserve the function of beta cells—the insulin-producing cells of the pancreas—during the course of development of type 1 diabetes.

Small molecules are, as their name implies, small—usually a few hundred or even a thousand times smaller in terms of mass than a typical protein molecule that carries out a biological function in a cell. Despite their diminutive size, small molecules are extremely important for studying and affecting the function of genes, cells, and biological pathways. Small molecules have proven valuable for treating diseases, and they often can be administered orally and can be less costly to produce than protein-based therapies. A key challenge, however, is to identify small molecules that can modulate a given biological process or disease state. To do this, researchers like Dr. Wagner are developing high-throughput screening approaches that can systematically test, or screen, tens or hundreds of thousands of small molecules to find one or a few compounds that produce the desired effect.

Novel Application to Beta Cell Biology

While there has been a lot of effort to understand type 1 diabetes using traditional aspects of basic biology, immunology, and animal models, Dr. Wagner points out that "there haven't been many efforts to systematically perturb beta cell biology with small molecules." Under the Pathfinder Award, Dr. Wagner is applying her expertise in chemical biology and high-throughput screening to find small molecules that affect beta cell function.

In one project, her team is screening libraries of small molecules to identify compounds that preserve beta cell viability. In type 1 diabetes, beta cells are attacked and destroyed by the immune system. Dr. Wagner and her research team can mimic this process in the lab by growing beta cells from rodents in culture and treating them with inflammatory molecules. "If you treat the cells with particular inflammatory molecules, you can induce them to start to die in a programmed way. We use this as a mimic of what goes on during type 1 diabetes when beta cells are attacked by the immune system," says Dr. Wagner. Her team converted this simple assay to a high-throughput format, and, she explains, "We are looking for compounds that in the presence of the inflammatory molecules can allow beta cells to survive."

Using this system, Dr. Wagner has screened some 400,000 compounds available through the Broad Institute and the NIH Molecular Libraries Program. In preliminary studies, Dr. Wagner already has found a few promising compounds. "These compounds are very good at preserving beta cell viability not only in our primary screen, but they also improve various aspects of beta cell function," Dr. Wagner exclaims.

Pushing Forward Promising Compounds

But the problem does not end at just finding compounds that seem to affect the cells. "We are pursuing these compounds very eagerly now to figure out what they do in cells," says Dr. Wagner. "This is one of the key challenges in screening. The challenge is always figuring out, now what? What do they do, how are they accomplishing what you are detecting in cells?" Answering these questions can provide fundamental insights to the cellular processes that lead to the development of type 1 diabetes.

With many of the cellular processes that lead to type 1 diabetes still unknown, Dr. Wagner is excited to think about the answers her research might uncover. "This is one of the things I like best about a screening project—that we don't know ahead of time what's going to happen," she says. "The Pathfinder Award program is unique in that it has really allowed me to do experiments towards discovery—it's hypothesis-generating as opposed to hypothesis-driven science." While recognizing the inherent risks of this approach, Dr. Wagner feels her research will pay off with discoveries that lead to the development of clinically relevant compounds and fundamental understanding of disease processes in type 1 diabetes.

"This is very mission-oriented research," Dr. Wagner says. "We are trying to find compounds that we can really push forward as leads." While she acknowledges the challenges in going from finding "something that is interesting in a mouse to something that can be given to a human," Dr. Wagner's goal is to move promising compounds forward to eventual clinical trials. "That is definitely something that would just be terrific to get to that point," she says.

A Career in Type 1 Diabetes Research

Dr. Wagner brings to type 1 diabetes research more than a decade of success in developing and applying high-throughput screening to address problems in biology. Although some of her earlier work focused on aspects of muscle biology, Dr. Wagner points out that "it was still in the spirit of metabolic disease" as she was trying to understand "how small molecules can be brought to bear on metabolic processes."

With her experience in chemical screening and the recent expansion of type 1 diabetes research in the Chemical Biology Program at the Broad Institute, the timing was perfect for Dr. Wagner to pursue the Pathfinder Award. "I had enough of a background in small-molecule science," she recalls, "and I was starting to get more of a background in beta cell biology to have some interesting ideas towards perturbing beta cells with compounds."

The Pathfinder Award allows Dr. Wagner to pursue these ideas with a "new level of independence," she says. "I have been able to build a small team of researchers towards my overall goal. That really helps the research progress at a much faster rate."

This progress is already being realized. Having identified some promising compounds that affect beta cell biology in preliminary screens, Dr. Wagner is making discoveries that are spurring new ideas for future directions. As her research supported by the Pathfinder Award continues to move forward, Dr. Wagner is optimistic about the opportunities that lie ahead. With the data and interesting leads her current work is generating, Dr. Wagner believes that her Pathfinder Award—her spark of a grant—is setting a foundation for her to build upon with ongoing research to impact type 1 diabetes.

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 new and emerging technologies and attracting new research talent, are outlined in Appendix F.