GOAL VI

ATTRACT NEW TALENT TO RESEARCH ON TYPE 1 DIABETES

Type 1 diabetes research spans an extraordinarily broad range of scientific disciplines: endocrinology and metabolism; immunology; genetics and the influence of environmental factors; the physiology of the heart, eyes, kidneys and urologic tract, and the central and peripheral nervous systems; and the special medical and behavioral issues of a disease diagnosed primarily in children and adolescents. Moreover, research efforts in these fields extend from basic laboratory studies to preclinical testing with animal models and clinical trials in human patients. Understanding the molecular basis of type 1 diabetes and developing new strategies for prevention and cure of this disease and its complications will require a cadre of scientists who can bring diverse research training and experience to bear on the problems of type 1 diabetes.

In the early years of the Special Statutory Funding Program for Type 1 Diabetes Research, RFAs for pilot and feasibility studies helped to attract newly-independent investigators or scientists who had not previously applied their expertise to the study of type 1 diabetes to pursue research opportunities related to diabetes. The increased funding in FY 2001 spurred the development of initiatives that were specifically designed to recruit new basic and clinical science investigators and to support innovative, cross-disciplinary ideas for research on type 1 diabetes and its complications. These awards were open to grant applications from researchers in all relevant scientific disciplines.

Photo
Public Health Service
grant application.

(Photo Credit: Richard Nowitz for NIDDK)

RESEARCH TRAINING PROGRAM AND COLLABORATIONS

With the marked increase in special statutory funds that became available in FY 2001, solicitations for collaborative research to increase the number of investigators working in the diabetes field were launched in FY 2001 and FY 2002. Brief descriptions of the research efforts and expected outcomes of initiatives supported in whole or in part by the special funds are presented below. More detailed scientific plans are available in Appendix 3. It is premature to assess accomplishments of the newly formed training programs or investigator-initiated research grants awarded in FY 2002.

Training Programs in Diabetes Research for Pediatric Endocrinologists (RFA DK02-024)

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. The NIDDK, ADA, and JDRF solicited applications for programs of research training and career development in pediatric endocrinology at institutions with environments, mentors, and programs that will make them particularly effective in enhancing the number of independent investigators contributing to research in pediatric endocrinology. Five combined research training/career development programs were established in FY 2002 for periods up to 5 years. Two additional programs were launched in FY 2003.

Investigator-Initiated Research Collaborations (RFA DK02-022 and DK02-023)

A "bench-to-bedside" research initiative fosters interactions between basic and clinical scientists to move discoveries from a laboratory setting to preclinical or clinical testing of new therapies that could improve the health of individuals with type 1 diabetes. In a related program, type 1 diabetes researchers are encouraged to act as "talent scouts" to recruit and partner with investigators with scientific expertise or technologies that had not previously been applied to research on diabetes or its complications. In FY 2002, a total of 26 collaborative, multidisciplinary partnerships were awarded for developing and testing innovative methods to prevent, cure, or improve treatment of type 1 diabetes and its complications.

Highlights of accomplishments by investigators who were new to diabetes research or in multidisciplinary collaborations are included in the preceding chapters within the context of the relevant goals.

"Bench-to-bedside" research project grants are designed to bring promising discoveries in basic science to a stage in which novel therapies can be developed and tested. These grants foster collaborations between basic and clinical investigators to ensure the effective and timely translation of laboratory discoveries into new treatments that will improve the health of those with diabetes.

(Photo Credit: Richard Nowitz for NIDDK)

EXTERNAL EVALUATION

This section provides commentary from leading scientific experts within the diabetes research community who assessed the accomplishments of the special statutory funding program and from researchers who participated in the use of the special funds. A complete description of the evaluation process and the use of evaluative data regarding the special funding program is available in the Assessment chapter and Appendix 2.

Advisory Panel

A panel of scientific and lay experts on type 1 diabetes research convened at the NIH in May 2002 to review the use of the special statutory funds. Comments from the advisory panel regarding recruitment initiatives established by the special funding program include:

- The efforts to recruit new investigators to type 1 diabetes research were considered by the advisory panel to be among the most important initiatives undertaken through the special funding program.
- The panel was greatly impressed by the number of applications received in response to these initiatives. Moreover, the advisors supported the use of the R21 (pilot and feasibility) mechanism in the short term as a way to generate new ideas in diabetes research.
- The NIH was commended for its development and support of the pediatric endocrinology research training and career development program, which was deemed a creative means of bolstering entry into this under-represented, but vital, clinical specialty.

Extramural Grantees

Principal investigators who received grants or grant supplements awarded with the special statutory funds between FY 1998-2000 responded to a survey asking, in part, about the impact of this grant on their careers. Multiple investigators cited their type 1 diabetes grant support as a key element in establishing themselves as independent investigators and providing the research track record necessary for gaining academic tenure.

In addition, many researchers reported that graduate students and postdoctoral fellows, whose work was supported by these grants, have continued to pursue careers in diabetes research. Representative remarks from the principal investigators include:

- "This was my first funding support related to type 1 diabetes. As I attend meetings to discuss my findings, and when I discuss my work with members of the public, I have been impressed with the continuous struggle faced by those with type 1 diabetes. They walk the razor's edge, always striving to avoid both hypoglycemia and hyperglycemia. This struggle significantly detracts from the quality-of-life that they and their loved ones experience. I plan to continue to pursue diabetes-related research, now that I am aware of the many complications and problems resulting from this disease."
- "This funding launched my career. Since receiving this funding, I have been awarded funding for numerous other projects for which this study provided the preliminary results. Additionally, two of my collaborators have received diabetes related funding as a result of this work and one now devotes a significant amount of her research efforts to diabetes related work. Neither worked in the area of diabetes previously. I have been fortunate to be invited to give a number of presentations over the past few years. Based on conversations and questions following these talks, I believe that my findings (thanks to this funding) have stimulated other investigators to consider the relationship of their own work to diabetes and to apply their systems to diabetes related questions."

- "I have been an active research scientist for more than 30 years, but had only one previous publication relevant to diabetes. This grant has focused a significant portion of my research efforts on diabetes."

- "As a result of this funding, I am now doing 90 percent diabetes research, while previously I was mainly focused on the pancreatic acinar exocytosis, and was doing only 20 percent diabetes research. Also, I have extended my collaboration with key scientists in the exocytosis field and membrane ion channel field, who were not at all interested in diabetes. This allowed me to tap the best talents in these fields to the study of islet function."

- "This grant was very important to my career as it provided data to support my major scientific conviction that glucose causes nerve cells to die. Data from this grant are allowing my laboratory to investigate specifically how the cells are dying, which has never been examined. I will continue to pursue type 1 diabetes research until there is a cure."

- "This was the first grant of mine in diabetes research. As a result of the support of this grant, I have established all the animal models [and] techniques [needed for my] diabetes studies. This grant also enabled me to train two graduate students and two postdoctoral fellows in diabetes studies. These young researchers are all determined to continue diabetes-related research in their careers."

- "As a new investigator, this grant was instrumental in establishing this line of research in my lab. I have other NIH grants to study neurotrophins and nerve injury, but I had great interest in moving into the field of diabetic neuropathy...Now, the majority of research in my lab is devoted to diabetic neuropathy."

- "The grant directed my efforts on understanding type 1 diabetes and working towards a cure, where previously I have worked primarily in other areas of immunology and immunological tolerance. Over half my laboratory is now working on type 1 diabetes."

Innovative partnership grants pair diabetes researchers with scientists who have a needed technology or expertise that can be applied to type 1 diabetes research. These grants help to bring new ideas and state-of-the-art technology to the study of diabetes.

(Photo Credit: Richard Nowitz for NIDDK)

- "This grant allowed me to pursue a project developed on my own ideas and gave me the independence to fully explore these ideas. Awarding of this grant earned me considerable respect among peers and other workers. This allowed interactions and collaborations that may not otherwise have developed. I have continued to pursue research on type 1 diabetes."

- "I did work on type 1 diabetes research prior to receiving this funding and will continue to do so in the future. However, this grant has had a significant impact on my career. I have been able to recruit two postdoctoral researchers and a Ph.D. student to investigate specifically autonomic neuropathy in type 1 diabetes with the funding. The support has also placed me in a strong position to form new collaborations, extend my research group, and have access to resources within the Institution."

- "This was very important to establishing a clinical translation to basic science research. It has allowed our center to form a translational research team, which can implement intervention trials for both new-onset and prediabetes, that has complemented the funding we have subsequently received *via* TrialNet. It has allowed me to continue my transition from animal models of type 1 diabetes to studying the human disease which is ultimately where our insights need to be put to the test. I have continued to pursue the causes and cure of type 1 diabetes and this grant has been important in allowing me to pursue this goal."

BENCH-TO-BEDSIDE RESEARCH: PREVENTING PROGRESSION OF DIABETES COMPLICATIONS

The Special Statutory Funding Program for Type 1 Diabetes Research has helped to propel studies of the devastating eye, kidney, nerve, and cardiovascular diseases associated with diabetes. These complications are caused by blood vessel (vascular) damage that results from elevated glucose levels and perhaps also lipid and other abnormalities. Intensive control of glucose levels can significantly reduce the development and progression of diabetes complications, as demonstrated by the landmark NIH-sponsored Diabetes Complications and Control Trial (DCCT). Yet, such strict control over blood glucose levels is difficult to maintain over the long term and carries with it an increased risk of dangerously low blood glucose levels (hypoglycemia). In order to treat or prevent complications of diabetes even when glucose control is imperfect, scientists are studying the molecular events that lead to the development of complications with the goal of elucidating new targets for therapy and biomarkers of therapeutic success.

A Potential New Strategy To Treat Diabetic Eye and Nerve Disease

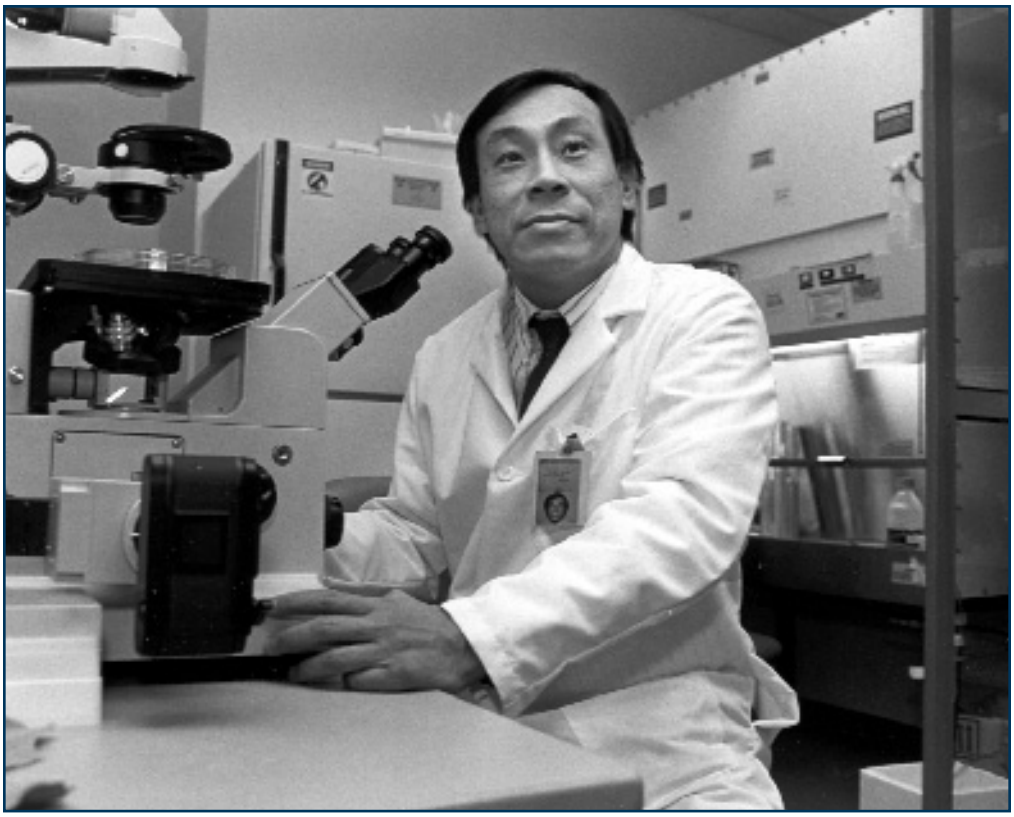
A promising new candidate drug for diabetes complications emerged from studies elucidating the mechanism of blood vessel damage is now in clinical trials. Known as a PKC beta inhibitor, the drug originated from basic research designed to understand what happens in cells as a result of high glucose levels. The research was a collaborative effort between Dr. George King's laboratory at the Joslin Diabetes Center (an affiliate of Harvard Medical School in Boston) and the pharmaceutical industry. "The focus of our laboratory," explains Dr. King, "has been to identify the molecular mechanisms by which high glucose levels are causing eye, kidney, and heart diseases in diabetic patients. Using cultured cells from the eye, kidney, or the heart, we found 10 years ago that high glucose levels will activate a protein called protein kinase C (PKC) in the vascular cells."

Generally, researchers want a therapeutic target to be as specific as possible so as not to interfere with other bodily functions. There are many different types ("isoforms") of PKCs found throughout the body. Dr. King and his laboratory postulated that persistent activation of one isoform, known as PKC beta, could cause the vascular problems that lead to some of the complications of diabetes. In order to test this hypothesis, Dr. King explained, "we had to find a drug to specifically inhibit the activation of PKC beta protein." The only compounds known at the time to inhibit PKC, however, were non-specific: they inhibited multiple isoforms of protein kinase C. Not only would these non-specific effects confound experiments to study PKC beta, but such widespread inhibition of different PKCs could be toxic and preclude the use of any such compound therapeutically. To solve this problem, Dr. King's laboratory collaborated with the pharmaceutical industry, which designed and synthesized a molecule that specifically inhibits PKC beta. The scientists tested their new PKC beta inhibitor, ruboxistaurin, in a rat model of type 1 diabetes. From these and other experiments, they discovered that the inhibitor could prevent and stop many blood vessel abnormalities in the eyes, kidneys, and other organs of diabetic animals.

With such encouraging results from the laboratory "bench" (a table on which experiments are performed), scientists moved quickly to begin clinical trials, with the hope that the PKC beta inhibitor could eventually be used to treat patients at the "bedside." The pharmaceutical industry is supporting trials to test the inhibitor as a treatment for both diabetic retinopathy (eye disease) and diabetic neuropathy

Dr. George King's research at the Joslin Diabetes Center in Boston has focused on identifying the molecular mechanisms by which high glucose levels cause eye, kidney, and heart diseases in patients with diabetes. His research, which has been supported in part by the Special Statutory Funding Program for Type 1 Diabetes Research, has led to the development of a new medication which is in clinical trials for prevention of diabetic complications.

(Photo Credit: Jerry Berndt courtesy of the Joslin Diabetes Center)



(nerve disease, which in diabetics causes loss of sensation and pain in the hands, feet, and legs, as well as impairment of sexual function). The Joslin Diabetes Center is one of the many trial sites around the world.

The results from Phase 1 and Phase 2 clinical trials were very exciting, suggesting that "several early blood vessel abnormalities and symptoms in the eye and nerve of both type 1 and type 2 diabetic patients can be improved," explains Dr. King. "If the results are positive for the Phase 3 trials, then this PKC beta inhibitor will be submitted to the FDA for approval as a new treatment for diabetic complications." Phase 3 clinical trials are ongoing as of the writing of this report.

Dr. King has received support for his research from both the regularly-appropriated NIH funds and from the Special Statutory Funding Program for Type 1 Diabetes Research. One of Dr. King's colleagues at the Joslin Diabetes Center, Dr. Lloyd Aiello, chairs a multicenter clinical trial that has been testing the PKC beta inhibitor. Dr. Aiello has also received support from the Special Funds for Type 1 Diabetes Research for research on diabetic eye disease.

BENCH-TO-BEDSIDE RESEARCH: PREVENTING PROGRESSION OF DIABETES COMPLICATIONS (CONTINUED)

A Strategy To Ameliorate the Effects of Diabetes on Kidney Function

An earlier example of bench-to-bedside research on diabetes complications was the introduction of ACE inhibitors into clinical practice to slow the progression of diabetic nephropathy (kidney disease). Based on evidence that diabetic kidney disease may be linked to hypertension (high blood pressure), scientists in the 1980s studied the effects of anti-hypertensive drugs, including an ACE inhibitor (angiotensin-converting enzyme inhibitor), in a rat model of type 1 diabetes. They discovered that the ACE inhibitor was superior to the other anti-hypertensive drugs in protecting against kidney disease. In 1993, a large clinical trial supported by the NIH and industry studied the effects of ACE inhibitors in patients with type 1 diabetes. This critical study demonstrated that an ACE inhibitor can preserve kidney function in people with diabetes; it also showed that the effects of ACE inhibitors are due to factors other than simply controlling blood pressure. Clinical research on the use of ACE inhibitors for diabetic kidney disease has continued and more recently a related class of drugs (angiotensin receptor blockers) were shown to be effective in preventing diabetic kidney disease. Now these drugs are being studied in combination.

Ongoing Efforts To Further Understand and Develop New Treatments for Complications of Diabetes

Scientists are vigorously pursuing multiple avenues of research on complications of diabetes. Major initiatives supported by the Special Statutory Funding Program for Type 1 Diabetes Research span the bench-to-bedside continuum. To build upon our fundamental understanding of the molecular mechanisms underlying diabetic complications, NIH has established an Animal Models of Diabetic Complications Consortium to develop innovative animal models that mimic human complications. Animal models not only facilitate research on the progression of complications and potential underlying genetic influences, but such models are also valuable for preliminary testing of candidate drugs. Diabetic animal models facilitated the testing of the PKC beta inhibitor and ACE inhibitors. Scientists are also searching for biomarkers, which can detect the onset of complications earlier and are useful for determining whether new therapies are likely to be beneficial. Another major research goal is to identify genes that affect complications. Such genes might provide additional targets for therapeutic development. The Genetics of Kidneys in Diabetes (GoKinD) Study, sponsored by the Centers for Disease Control and Prevention (CDC) and the Juvenile Diabetes Research Foundation International, seeks to determine genetic risk factors for diabetic kidney disease. A complementary NIH effort is the Family Investigation of Nephropathy and Diabetes (FIND). Because kidney disease is thought to have a significant genetic component, the discovery of genetic risk factors may allow earlier diagnosis and medical intervention.

To spur new clinical trials, several major efforts are being launched. A Diabetic Macular Edema Clinical Trials Network is being established to conduct clinical trials of new potential treatments for the eye disease macular edema, which affects people with diabetes. Additionally, a program of pilot trials to prevent or slow progression of diabetic nephropathy is being developed to foster trials using novel agents or drug combinations to prevent or treat diabetic kidney disease. With these and other efforts, dedicated scientists are continuing to pursue the goal of conquering type 1 diabetes and preventing and curing its devastating complications.

HELP WANTED: PEDIATRIC ENDOCRINOLOGISTS

Funding Will Help Train Researchers in Childhood Diabetes

To enlarge the pool of pediatric endocrinologists conducting diabetes research, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) recently awarded research training and career development grants to seven medical centers with strong research programs in childhood diabetes.

"With this funding, we hope to create a pipeline of new and talented investigators whose focus is pediatric diabetes research," said Dr. Judith Fradkin, director of NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases. "These awards support not only research fellowships but also a longer period of research career development until a junior researcher is ready to begin an independent career."

The NIDDK awards went to Baylor College of Medicine in Houston, TX; University of Colorado Health Sciences Center in Denver, CO; Washington University School of Medicine in St. Louis, MO; Joslin Diabetes Center in Boston, MA; Children's Hospital of Pittsburgh, PA; The Children's Hospital of Philadelphia, PA; and Yale University in New Haven, CT.

"Now is a wonderful time to consider a research career in childhood diabetes," said Dr. Georgeanna Klingensmith, who heads the Division of Pediatrics at the Barbara Davis Center, University of Colorado Health Sciences Center. "Diabetes research has progressed dramatically in the last 5 years, and many developments on the horizon can make a big difference. We need young people with energy and enthusiasm to take these new findings in molecular biology, genetics, and immunology and put them together to move the field ahead."

Dr. Georgeanna Klingensmith (right) reviews blood glucose values with a young diabetes patient. Dr. Klingensmith of the University of Colorado Health Sciences Center participates in a research training program, which permits fellows, who have already completed a pediatric residency, to merge their clinical expertise in pediatric treatment with studies of diabetes.

(Photo Credit: kentmeireisphotography.com)

HELP WANTED: PEDIATRIC ENDOCRINOLOGISTS

Funding Will Help Train Researchers in Childhood Diabetes (CONTINUED)

The scarcity of pediatric endocrinologists, reflected in the many unfilled vacancies for these specialists in medical centers around the country, has impeded clinical research in pediatric diabetes. Specifically, a shortage of clinical investigators has hindered research at a time when the momentum of basic research discoveries has rapidly accelerated. Physician scientists are needed to speed the flow of new information from the bench to bedside.

"We have a number of open faculty positions. We could hire two or three today, but we can't find individuals with in-depth training to fill them," noted Dr. Morey Haymond, chief of Pediatric Endocrinology and Metabolism at Baylor College of Medicine, one of the centers receiving the NIDDK awards. "I get letters almost weekly from institutions looking for pediatric endocrinologists at any level—assistant, associate, or full professor—to get their programs going. However, very few physicians are entering our training programs. And in the last decade, many of our colleagues have left—gone to industry or retired early."

Pediatric endocrinologists begin their careers as pediatricians. To be eligible for pediatric endocrinology training, a medical school graduate must first complete a 3-year pediatric residency. A fellowship in pediatric endocrinology normally takes an additional 3 years. The burden of debt and the length of training discourage many potential candidates from pursuing subspecialty and clinical research careers.

The awards, through the T32 (institutional research training) and K12 (clinical scientist career development program) grant mechanisms of the NIH, provide for 2-3 years of fellowship training as well 2-3 additional years of support for a junior clinical investigator in diabetes, for a total of 5 years. The funding supports up to five positions at each medical center. The center is free to decide how many of the five slots will be reserved for pediatric endocrinology fellows or investigators who are transitioning from fellowship to independent scientists.

The NIDDK, with support from the American Diabetes Association and the Juvenile Diabetes Research Foundation International, has been working to expand the cadre of pediatric endocrinologists pursuing careers in diabetes research. Support for the new training programs, which totals $17 million over 5 years, comes from special statutory funding for type 1 diabetes research, which was recently extended.

To attract physicians to clinical and pediatric research, the NIH, a component of the U.S. Department of Health and Human Services, has introduced a loan repayment program that offsets some of the educational debt incurred by many graduates in the health professions. Qualified candidates who agree to conduct pediatric research 50 percent of time, or not less than 20 hours per week, for a 2-year consecutive period may apply for the program. For more information, see <http://www.lrp.nih.gov/>.

Dr. Morey Haymond (center) instructs two pediatric endocrinology fellows in his laboratory at Baylor College of Medicine. Pediatric endocrinology research training opportunities such as this one provide clinically-trained pediatricians with a strong foundation in diabetes-related research that will assist the fellows in establishing themselves as independent researchers.

(Photo Credit: Marina Blum, Baylor College of Medicine)