

Resource and Infrastructural Needs



Photo: Richard T. Nowitz, for NIDDK.

The DRWG's Strategic Plan recognized that the efficient conduct of research requires a supportive infrastructure. This infrastructure includes not only the appropriate facilities in which to perform research studies, both basic and clinical, but also a cadre of talented and trained researchers; research programs to train and support investigators; mechanisms to harness new technologies; and the development of appropriate animal models to study diabetes and its complications. Some examples of newly initiated programs are outlined below. Please note that many of these are also described in the sections of this report that address "Extraordinary Opportunities" and "Special Needs for Special Problems."

Strengthening Research Talent

The DRWG realized that solving the puzzle of diabetes will require a cadre of exceptionally talented and dedicated researchers. To enhance the development of diabetes investigators and to recruit and train scientists with interest in diabetes, the NIH provides a number of different mechanisms tailored to the needs of investigators at various stages of their scientific development.

Mechanisms include awards to support training in biomedical research at the predoctoral and postdoctoral levels, career development awards given to newly trained or independent scientists in the early and formative periods of their careers, and fellowships that provide the opportunity for experienced scientists to make major changes in the direction of their research careers to broaden their research capabilities or to enlarge their command of an allied research field. Since 1999, both predoctoral and postdoctoral National Research Service Award fellowship stipends have increased approximately 20 percent. Moreover,

career development award support (both salary and research-related costs) has increased at the vast majority of the NIH Institutes. The NIH is reaching out to new diabetes investigators through improvements in Internet-based dissemination of information on research and training opportunities, presentations at national meetings, and invitations to conferences and meetings at the NIH tailored to enhance their career development. In response to the DRWG recommendations, a number of specific new initiatives were developed to recruit, train, and support new diabetes research talent.

▶ ATTRACTING NEW TALENT TO DIABETES RESEARCH

An innovative partnership program is promoting collaboration among diabetes researchers and those in areas other than diabetes who have expertise or technology that could advance diabetes research projects. This program was initiated with the special type 1 diabetes funding, using the diabetes centers as a catalyst to bring researchers together from disparate components of institutions for collaborative, multi-disciplinary research relevant to problems associated with type 1 diabetes. Subsequently, the program was expanded to investigators at all institutions. The goal is to encourage diabetes researchers to act as “talent scouts” to identify other researchers who could contribute to research breakthroughs in diabetes.

▶ HELPING NEW INVESTIGATORS GET STARTED IN DIABETES RESEARCH

Many NIH initiatives to stimulate research in the promising areas identified by the DRWG have solicited pilot and feasibility (R21) grants, as well as the standard (R01) research grant. The pilot and feasibility mechanism is particularly well suited to newly independent investigators and/or investigators new to diabetes research in that it supports development of preliminary data and evidence of feasibility that can be used in subsequent applications for more substantial grant support. These solicitations have targeted new investigators and provided an entree into diabetes research for those new to the field. The significant number of pilot project grants that have been awarded recently is expected to increase the flow of new investigators into diabetes research.

▶ BRINGING TOGETHER BASIC AND CLINICAL RESEARCHERS

An innovative program supports collaboration between basic research scientists, whose findings have potential direct applicability to development of new treatments or diagnostic tests, and clinical scientists, who can help to translate these basic discoveries into pre-clinical or clinical trials. The special type 1 diabetes funding allowed this program to be initiated with a focus on type 1 diabetes and diabetes complications. If successful, this bench-to-bedside research program will be expanded to all forms of diabetes.

▶ DEVELOPING CLINICAL RESEARCHERS FOR CHILDHOOD DIABETES

In collaboration with the ADA and the JDRF, the NIH is intensifying efforts to expand the cadre of pediatric endocrinologists pursuing research careers. A new program addresses a critical shortage of clinical researchers in the important field of childhood diabetes. This effort will support a combination of complementary programs at institutions with particular strength in pediatric diabetes research. These combined programs will support development of new researchers by providing research training during pediatric endocrinology fellowships followed by a special career development award framed to provide research support for individuals who have completed their research training and have dedicated themselves to becoming independent clinical researchers.

▶ **EDUCATIONAL ENRICHMENT AS A MECHANISM OF ATTRACTING NEW TALENT TO DIABETES RESEARCH**

This curriculum-driven program is aimed at creating educational opportunities that will attract undergraduate and graduate students and postdoctoral fellows to careers in particular areas of biomedical research, including diabetes. Curricula will be developed at research institutions to enhance basic scientists' understanding of clinical medicine using particular diseases, such as diabetes, as models. A particular goal is to attract students and postdoctoral fellows from scientific disciplines underrepresented in disease-oriented biomedical research, such as engineering, informatics, computer science, and computational sciences, and encourage them to apply their expertise to research relevant to diabetes.

▶ **FOSTERING PARTICIPATION OF NURSE INVESTIGATORS IN DIABETES RESEARCH**

Expansion of the clinical trials networks has created new opportunities for nurse investigators to contribute to diabetes research.

▶ **LOAN REPAYMENT**

New NIH-wide loan repayment programs will address physician indebtedness, a major obstacle to recruiting physician scientists, pediatric researchers, and under-represented racial/ethnic minority researchers to diabetes research. These programs repay a fixed amount of educational loans in exchange for dedicated research commitments in the areas of pediatric and/or clinical research.

Enhancing Resources and Harnessing New Technology for Diabetes Research

The tremendous acceleration in the pace of scientific discovery over the last decade, coupled with the development of many new technologies, has created an era of unparalleled opportunity to uncover the causes of disease and identify effective therapies.

The DRWG urged the identification, improvement, and modification of existing technology for use in diabetes research and the development of totally new technologies essential to advance diabetes research. Specific opportunities for harnessing new technology for diabetes research have been discussed in each of

the earlier sections focused on high priority areas of research. Summarized here are some key measures, undertaken in response to the DRWG recommendations, to enhance application of new technologies to the diabetes research effort and to expand specific elements of the diabetes research infrastructure.

▶ ENHANCEMENT OF DIABETES RESEARCH CENTERS

Since the DRWG urged expansion of the existing diabetes centers program, the number of Diabetes Endocrinology Research Centers (DERCs) has increased from six to eight and the cap on annual costs at each center has increased by one third. Additional expansion of the DERCs is anticipated in fiscal years 2002 and 2003. In addition, a new program of Diabetes Prevention and Control Project (R18) grants has been established as a means of expanding translational diabetes projects that were previously subject to budgetary limits on the Diabetes Research and Training Centers (DRTC) in which they were administratively housed, thus freeing DRTC funds to be used for expanded research infrastructure and pilot research project support. Substantial new funding for equipment is also now available through the centers' grants, outside their annual operating budgets. In addition, a new centers of excellence program, "Excellence in Partnerships in Community Outreach, Research on Health Disparities and Training" (also called Project EXPORT), has been launched to provide a research infrastructure with multidisciplinary approaches to address disparities in health status. Many of these centers will focus on identifying methods to reduce the burden of diabetes in minority communities.

▶ BIOTECHNOLOGY CENTERS

The recent development of gene expression profiling using technologies such as chips, microarrays, or serial analysis of gene expression (SAGE) is facilitating comprehensive high-throughput screening of gene expression. These genetic profile technologies are used to compare gene expression between individuals who have a disease and those who do not, to study animals that have been treated with potential therapeutics, or to identify changes in gene patterns associated with experimental mutagenesis. Analysis of changes in gene expression differences can direct researchers toward understanding the underlying causes of disease and mechanisms by which therapies exert their effects. New biotechnology centers are making genomic profiling resources and comprehensive gene expression technologies widely available to investigators working in diabetes.

▶ METABOLIC AND FUNCTIONAL IMAGING TECHNOLOGIES

To foster the development of technology that the DRWG identified as critical for progress in diabetes research, a new initiative will develop techniques to image or otherwise non-invasively detect pancreatic islet beta cells in intact organisms; to measure their mass, function, or evidence of inflammation; and/or to monitor engraftment of transplanted isolated pancreatic islets. Another initiative supports centers for metabolic characterization of mouse models of diabetes. These will facilitate development and application of many technologies cited by the DRWG, including nuclear magnetic resonance (NMR), positron emission tomography (PET) scanning, and miniaturization techniques for metabolic studies.

▶ CENTERS FOR ANIMAL MODELS OF DIABETES

Creation of knockout and transgenic mice, in which specific genes relevant to diabetes or its complications are altered, has greatly enhanced our understanding of the pathophysiology underlying diabetes. New mouse phenotyping centers now provide a range of standardized procedures to efficiently characterize metabolism, body composition, feeding behavior, activity, tissue pathology, and other physiologic, anatomic, or pathologic alterations that may occur in these mice. In addition to the targeted mutagenesis being pursued in many individual laboratories, the NIH has created centers for large-scale mutagenesis studies involving the entire genome, including genes not currently known to be involved in diabetes. Ultimately, characterization of the mutant mice produced is expected to help elucidate the molecular pathways involved in the mechanisms of multiple human diseases, including diabetes. The DRWG called for establishment of centers for the maintenance and distribution of important mouse models of diabetes. Such a program has been created for mouse models of type 1 diabetes utilizing the special type 1 diabetes funds. Expanded support for diabetes centers is also being used for maintenance, shared access, and creation of mouse models of diabetes.

▶ NONHUMAN PRIMATE MODELS

Efforts have been made to expand the availability of nonhuman primate models because they are genetically, physiologically, and behaviorally more similar to humans than other laboratory animals and thus represent an extremely valuable research resource. Like humans, primates are outbred species, with significant intra-species genetic

variation. An initiative is under way to establish baboon colonies to make this large animal model available to the diabetes research community. Although diabetes has not been studied to a great extent in the baboon, approximately five percent of the baboon population appears to develop diabetes spontaneously. Some animals may be predisposed to diabetes and diabetes can be experimentally induced with drugs. The baboon animal model could be used to study the link between atherosclerosis, hypertension, and type 2 diabetes. In addition, a newly created consortium of investigators is using nonhuman primate models for study of pancreatic islet and kidney transplantation; the colony of primates available for this effort has been substantially expanded.

▶ ENHANCING ACCESS TO HUMAN BIOLOGICAL MATERIALS

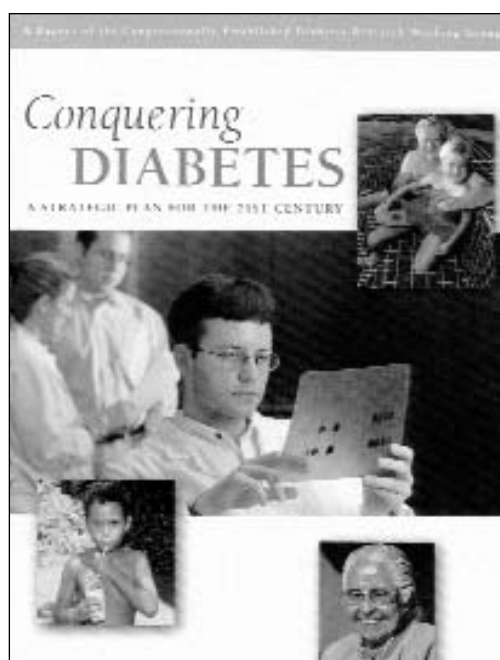
The NIH has substantially expanded access to human tissue for studies of islet transplantation and for basic research on the pancreatic beta cell through the establishment of human islet isolation centers. Pancreas and other human tissues are also available through expanded support of the National Disease Research Interchange. Many collections of human biologic samples arise from large clinical trials or epidemiologic studies and the phenotypic data associated with these samples greatly enhances their value. Creation of central repositories for biosamples and data collected in large, multi-site studies will expand their usefulness by providing access to the biosamples and data to a wider research community.

Strategic Planning for Diabetes Research

As noted by the DRWG, strategic planning is an ongoing process that requires regular re-evaluation and assessment of research programs, opportunities, needs, and initiatives.

Since issuance of the DRWG report, the NIH has revitalized the Diabetes Mellitus Interagency Coordinating Committee (DMICC) as a vehicle for communication and coordination of the diabetes research effort across the NIH and with other agencies. The DMICC has orchestrated a series of meetings focused on special populations affected by diabetes, including children, the elderly, and minority populations, such as Native Americans. An ongoing series of DMICC meetings is focusing on translation of clinical trials research into clinical practice in the areas of diabetes prevention and prevention of macro- and microvascular complications. In addition, the NIH has convened numerous scientific conferences focused on specific opportunities identified by the DRWG and charged participants with presenting the current state-of-the-art research in those areas and identifying new opportunities and initiatives that could facilitate progress. Many of the initiatives reported previously, while emanating from the DRWG strategic plan, have been critically refined through interaction of NIH staff with external advisors at such meetings. To develop this update as requested by the Congress, the NIH has enlisted the participation of the many leading scientists listed in the appendix to identify progress and opportunities emerging since the 1999 DRWG Strategic Plan. Advice has been obtained from these investigators at advisory sessions focused on specific aspects of the DRWG recommendations.

The NIH will continue to be nimble and flexible in utilizing new communications technology for obtaining external advice on emerging opportunities and for the development of collaborative, cutting-edge initiatives. The NIH will also rely on the established structure of the DMICC to ensure needed coordination as we move forward toward conquering diabetes.

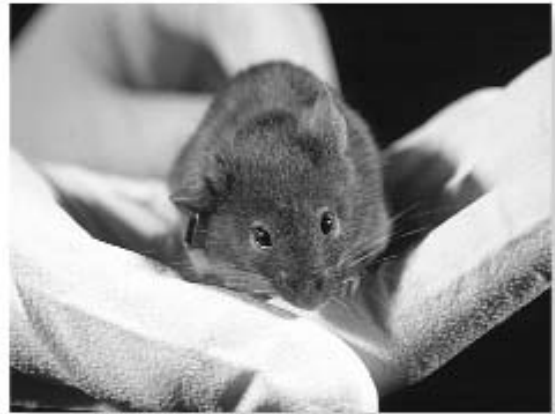


The 1999 DRWG Strategic Plan has been an important scientific guidepost for developing diabetes research initiatives.

Mouse Models of Diabetes

Although a mouse in the house may be viewed as a pest, mice are highly regarded as tools for solving a number of medical mysteries. Mice and humans share virtually the same set of genes and the DNA sequence of the mouse genome is therefore an essential tool to identify and study the function of human genes. In fact, the recently-obtained draft sequences of the human and mouse genomes indicate that the two are approximately the same size and are about 85 percent identical—and that the differences involve only a few hundred of the 35,000 or so genes in both organisms. Because of this high degree of similarity, it is believed that much research into mouse models of human disease has application to humans.

Genes serve as a set of instructions for the proper assembly of proteins that form the basis for the development of the organism. The DNA sequences in mice and humans that encode proteins are shared to a high degree. During evolution, sequences important for the development of the organism have been conserved. Thus, by comparing human and mouse genome sequences, scientists can gain important clues as to which regions encode proteins and which might be involved in regulation of gene expression by looking for conserved regions. Knowledge about the mouse genome sequence will facilitate the identification of genes when mouse models are used to study and understand human disease.



Mice serve as important models for studying diabetes and obesity. They are essential for the testing of new drug treatments prior to clinical trials in human patients. They can also provide fundamental insights into the relationships between genes and disease.
Photo: Richard T. Nowitz for NIDDK.

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Another benefit of mouse models is that potential new therapies and treatments for a given condition can also be tested in mouse models before being tried in humans. Treatments that are found to control or cure the disease in the mouse could therefore lead to the development of a therapy that works in humans with a similar disease. Finally, on a practical level, mice are relatively inexpensive and easy to maintain and study in a laboratory setting, and so it is not surprising that mice—together with rats—are used in 90 percent of all research involving animals.

Mouse Models of Diabetes

ENGINEERED AND NATURALLY OCCURRING MOUSE MODELS OF DISEASE

Mice are relatively easy to modify genetically, either through direct genetic engineering or through selective breeding. Mouse embryonic stem cells can be manipulated in culture and then implanted in female mice to produce animals that lack a specific gene entirely—a traditional gene “knockout”—or that lack the gene only in certain tissues or only under certain conditions—a so-called “conditional knockout.” Both approaches contribute valuable information about the normal function of a gene by allowing scientists to observe the consequences of its absence.

A complementary approach to gene knockouts is the generation of “transgenic” mice through injection of foreign DNA into developing mouse embryos. This technique produces mice that possess a gene that they normally would not possess or that turn on a gene at times or in tissues where it normally would be silent. Researchers can then study the impact of a gene where it is normally not present as a way to gain insight into the gene’s function. Genes suitable for this kind of study are not limited to mouse genes, as genes isolated from a wide range of organisms are functional in mice.

Once derived, such knockout and transgenic animals may be simply interbred to produce mice with multiple genetic alterations. To date, literally hundreds of knockout and transgenic mouse lines have been derived, many possessing multiple genetic alterations. Such mouse models have provided important insights into the development and treatment of many diseases, including diabetes.

MOUSE MODELS OF TYPE 1 AND TYPE 2 DIABETES AND DIABETIC COMPLICATIONS

Mouse models of type 1 diabetes may be used to study the relationship between the insulin-producing beta cells of the pancreas and the immune system in order to more fully understand why the normally protective immune system goes awry and attacks the body’s own tissue, what genes are involved and how they interact, and what types of interventions are likely to be successful. Perhaps the most valuable and informative mouse model of type 1 diabetes is the non-obese diabetic (NOD) mouse. Studies of type 1 diabetes in NOD mice have uncovered evidence for up to twenty chromosomal regions contributing to the development of diabetes. Studies in NOD mice have also pointed out the critical role played by the various components of the immune system—including T cells and the major histocompatibility complex (MHC) of proteins—in the destruction of pancreatic beta cells. The animals have also been used to test possible novel preventative, therapeutic, and potentially curative approaches to type 1 diabetes.

To help facilitate research on type 1 diabetes, the NIH has funded a Type 1 Diabetes Repository at the Jackson Laboratory in Bar Harbor, Maine. This repository will house mouse models of type 1 diabetes that include mice with spontaneous and induced mutations as well as standard inbred and hybrid mice. The Repository will maintain, distribute, and preserve approximately 150 mouse stocks that are important to research in type 1 diabetes. Such models include not only NOD mice but also variations of this strain that have been genetically manipulated, including NOD-based transgenic and knockout mice. Important “congenic” strains of mice

have been developed which contain only portions of the NOD chromosome; these will be helpful for identifying the genes involved in diabetes. A coordinated database will facilitate the use of information about these various models. Through its support of such efforts, the NIH is attempting to make these valuable mouse models available to a wide range of investigators for research on type 1 diabetes.

Efforts are also under way to elucidate the genes responsible for the development of type 2 diabetes. Type 2 diabetes arises from a decreasing sensitivity of the body to insulin, which can lead to over production of insulin and ultimately, the failure of beta cells. Much of the research into the origins and development of this form of the disease has therefore focused on the central role of the insulin receptor (IR) and its cellular targets. The IR is a protein that spans the cellular membrane of insulin responsive cells and transduces signals generated by insulin to the intracellular machinery responsible for the metabolism and storage of the sugar glucose. The ability to modify or delete specific genes in mice has allowed researchers to generate animal models to assess the role of IR-mediated signaling. Simple IR knockout mice—in which the gene is completely functionally absent—die four to five days after birth. This early lethality obviously precludes the use of such animals to study development of type 2 diabetes. However, by applying new technologies, it is possible to generate viable mice that lack IRs only in specific tissues. It is also possible to develop mice that have one mutated copy of the IR gene combined with mutations in other genes in the IR signal transduction pathway, such as IRS-1 (insulin receptor substrate-1). Many of these tissue-specific knockouts display metabolic alterations often seen in

patients with type 2 diabetes and may therefore become important models of type 2 diabetes in the future.

For example, animals that lack IRs in their muscle exhibit elevated circulating triglycerides and free fatty acids without displaying glucose intolerance. Mice with a liver-specific IR knockout develop elevated blood glucose levels at a young age and also have changes in liver growth and function. Mice carrying a tissue-specific inactivation of IRs in brown fat—a specialized type of fat tissue—have diminished brown fat mass and show a progressive decrease in glucose tolerance due to a defect in the secretion of insulin. While muscle, liver, and fat are three tissues that are classically thought of as being insulin-responsive, interesting results have also been seen in tissue-specific knockouts of IR in other tissues. Mice with a tissue-specific knockout of the IR in insulin-producing pancreatic beta cells exhibit a defect in the secretion of insulin that is similar to that observed in people with type 2 diabetes; the result of this defect is a progressive impairment of glucose tolerance. Furthermore, mice who lack IRs in the brain eat more than normal mice, become obese, and show signs of type 2 diabetes, including insulin resistance and high blood sugar. All of these results suggest that insulin signaling is complex, spans a wide range of tissues, and involves frequent cross-talk between different target tissues.

The lack of good mouse models for diabetic complications has hindered the development of effective strategies to prevent and treat the often devastating and life-threatening complications of diabetes. To address this issue, the NIH has recently launched an initiative to bring together a number of projects representing a diverse set of disciplines and technologies into a Mouse Models of Diabetic

Mouse Models of Diabetes

Complications (MMDC) Consortium. This Consortium will promote the generation of mouse models that will be useful for studying the development, prevention, and treatment of diabetic complications. The MMDC will also test the role of candidate genes or chromosomal regions that emerge from genetic studies of human diabetic complications, particularly diabetic kidney disease and accelerated cardiovascular diseases. These efforts are particularly important in light of the fact that mouse models will be needed to test potential new therapies to address diabetic complications.

The use of animal models to study the causes of diabetes and its complications should help to identify important molecular and genetic factors and may lead to improvements in prevention and treatments for this disease and its devastating consequences. While the complexity of the disease may seem daunting from the point of view of researchers, an appreciation of the many factors involved also opens the door to multiple novel potential targets for therapy.

THE USE OF ANIMALS IN BIOMEDICAL RESEARCH

To ensure the appropriate care and use of animals involved in scientific research, the U.S. Government requires that individuals and institutions utilizing live animals adhere to a set of rules designed to ensure the safe and humane treatment of animals and to minimize discomfort, distress, and pain during experimental procedures. The NIH maintains an Office of Laboratory Animal Welfare within the Office of the Director to ensure compliance with the rules and regulations regarding animal research.

Type 1 Diabetes Repository

at The Jackson Laboratory



The National Center for Research Resources (NCRR) at NIH has funded a Type 1 Diabetes Repository (T1DR) at The Jackson Laboratory (TJL). The purpose of this repository is to collect and cryopreserve ~150 mouse stocks important to research in type 1 diabetes.