Summary of Research Activities by Disease Category

Autoimmune Diseases

Just a few decades ago, 30 percent of people died within 25 years after being diagnosed with type 1 diabetes, an autoimmune disease. One in 4 people developed kidney failure, and diabetic retinopathy was responsible for 12 percent of new cases of adult blindness. Now, the outlook for people with longstanding type 1 diabetes has greatly improved, largely due to long-term NIH-supported research.

The concept of controlling blood glucose tightly to prevent diabetes-related complications was untested. To address this gap in knowledge, in 1983, NIH launched the Diabetes Control and Complications Trial (DCCT), which enrolled 1,441 people with type 1 diabetes. In 1993, the trial showed that intensive control of blood glucose reduced the risk for eye, kidney, and nerve complications by a dramatic 50 percent to 75 percent. Upon completion of the original landmark study, intensive therapy rapidly became the standard of care nationwide.

Nearly all participants in the original trial continue to be followed in an ongoing successor study, the Epidemiology of Diabetes Intervention and Complications (EDIC). EDIC has found that participants show not only continued dramatic reductions in eye, kidney, and nerve complications, but also more than 50 percent reductions in heart disease and stroke. These landmark discoveries—along with advances in insulin formulations, insulin delivery, glucose monitoring, and the treatment of heart disease risk factors—now have translated into greatly improved health outcomes for people with type 1 diabetes. In 2009, DCCT/EDIC researchers reported that 30 years after their initial diagnosis, fewer than 1 percent of the intensively controlled participants have become blind, required kidney replacement, or had an amputation. These exciting findings reinforce the message that people with type 1 diabetes should begin intensive glucose control as soon as possible after diagnosis to greatly improve their long-term health.

Introduction

Autoimmune diseases are a group of more than 80 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues, and cells. The causes of autoimmune diseases remain unknown, although genetic factors play major roles in susceptibility. Some of these diseases may be triggered by an infectious agent or an environmental exposure, especially in individuals who have inherited susceptibility.

Emerging data indicate that the incidence and prevalence of some autoimmune diseases, such as type 1 diabetes and celiac disease, are increasing. This trend has serious implications including the future physical, psychosocial, and financial toll of these illnesses. NIH recognizes that more needs to be done to close the gaps in knowledge and reduce the rising impact of autoimmune diseases. NIH is committed to advancing the understanding of how autoimmune diseases develop and to applying results of basic research to improve the health and quality of life of patients affected with these diseases.

Some of the more common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, multiple sclerosis, celiac disease, and inflammatory bowel disease. Organ-specific autoimmune diseases are characterized by immune-mediated injury localized to a single organ or tissue, for example, the pancreas in type 1 diabetes and the central nervous system in multiple sclerosis. In

contrast, nonorgan-specific diseases, such as systemic lupus erythematosus (lupus), are characterized by immune reactions against many different organs and tissues, which may result in widespread injury.

Autoimmune diseases can affect any part of the body and have myriad clinical manifestations that can be difficult to diagnose. At the same time, autoimmune diseases share some features related to their onset and progression. In addition, overlapping genetic traits enhance susceptibility to many of these diseases, so that a patient may suffer from more than one autoimmune disorder, or multiple autoimmune diseases may occur in the same family. Furthermore, scientists suspect that hormones may play a role in the development of at least some autoimmune disorders. For these and other reasons, autoimmune diseases are best recognized as a family of related disorders that must be studied together as well as individually.

Many autoimmune diseases disproportionately affect women, and this group of diseases is among the leading causes of death for young and middle-aged women.[79] Although treatments are available for numerous autoimmune diseases, cures have yet to be discovered and patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, and hospitalization. The social and financial burden of these diseases is immense and includes poor quality of life, high health care costs, and substantial loss of productivity.

NIH supports research and promotes progress toward conquering autoimmune diseases through a wide range of research projects and programs. Because autoimmune diseases span many organ systems and clinical disciplines, multiple NIH Institutes conduct and support autoimmune disease research, often in collaboration with professional and patient advocacy organizations. The congressionally mandated Autoimmune Diseases Coordinating Committee (ADCC) facilitates trans-Institute collaboration and coordination in the development, review, award, and post-award monitoring of solicited autoimmune diseases research programs.

Several decades of intensive research have produced a wealth of information that has transformed conceptual understanding of autoimmune diseases. This research has helped set the stage for major advances in diagnosis, treatment interventions, and prevention. In particular, scientists are studying the causes of these diseases through epidemiologic and mechanistic studies, discovering the genetic and environmental factors that make people susceptible to autoimmune diseases, and conducting broad investigations into basic immunology. NIH supports research to translate knowledge about autoimmune diseases into broadly applicable prevention strategies that arrest the inflammatory and immune processes before they can irreversibly damage the body. Other research focuses on the development and testing of effective therapies and sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals. NIH enhances this translational research through the conduct of training and education activities for researchers and clinicians in collaboration with nonprofit and advocacy organizations and through effective information dissemination to patients, their families, and the public.

A major goal of autoimmune disease research is to “re-educate” the immune system by using tolerance induction strategies that selectively block or prevent deleterious immune responses while leaving protective immunity intact.

A major goal of autoimmune disease research is to “re-educate” the immune system by using tolerance induction strategies that selectively block or prevent deleterious immune responses while leaving protective immunity intact. NIH-supported research integrates mechanistic studies of tolerance induction and suppression of disease into clinical research studies and conducts trials of a variety of agents and strategies through dedicated clinical networks.

Overarching priority areas that promise to accelerate autoimmune disease research include biomarker identification, bioinformatics, and application of new technologies. Biomarkers hold great promise for earlier and more accurate diagnosis of autoimmune diseases, better prediction of disease flare-ups, and improved monitoring of disease progression and response to treatment. New technologies, such as genome-wide association studies (GWAS), provide scientists with improved means to identify susceptibility genes and molecular pathways that may be targeted in the development of therapies. Other genomic and proteomic technologies make it possible to characterize antibodies in serum, which may provide vital insights into the mechanisms of onset and progression of autoimmune disease. Bioinformatics tools, which help scientists to assemble and analyze large amounts of data, will be particularly important. Many of these research areas intersect with initiatives planned under the NIH Roadmap, which fosters trans-NIH and multidisciplinary collaboration as a way to address complex challenges in biomedical research.

[79] Walsh SJ, Rau LM. *Am J Public Health* 2000;90(9):1463-6. PMID: 10983209. PMCID: PMC1447637.

Burden of Illness and Related Health Statistics

Although many individual autoimmune diseases are rare, collectively they affect millions of Americans, and for unknown reasons, their incidence and prevalence are rising. Since cures are not yet available for most autoimmune diseases, patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, reduced productivity at work, and high medical expenses. Some examples of current statistics on the incidence and prevalence of autoimmune diseases in the United States include:

- An estimated 1.3 million adults ages 18 and older (about 0.6 percent of the population) have rheumatoid arthritis and about 294,000 children have juvenile arthritis.[80]
- About 895,000 to 1.8 million people have type 1 diabetes. About 15,000 people younger than age 20 are diagnosed annually with type 1 diabetes.[81,82]
- In the general U.S. population, prevalence of multiple sclerosis is 0.9 per 1,000.[83]
- About 322,000 people have definite or probable lupus. Of this number, 161,000 people have received a definite diagnosis.[84]
- As many as 1.4 million people have inflammatory bowel disease.[85]
- More than 2 million Americans have celiac disease.[86]

[80] Helmick CG, et al. *Arthritis Rheum* 2008;58(1):15-25. PMID: 18163481.
[81] National Diabetes Fact Sheet, 2007. Available at: www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf.
[82] The Writing Group for the SEARCH for Diabetes in Youth Study Group. *JAMA* 2007;297(24):2716-24. Available at: http://jama.ama-assn.org/cgi/content/abstract/297/24/2716. PMID: 17595272.
[83] Hirtz D, et al. *Neurology* 2007;68(5):326-37. PMID: 17261678.
[84] Helmick CG, et al. *Arthritis Rheum* 2008;58(1):15-25. PMID: 18163481.
[85] Loftus EV Jr. *Gastroenterology* 2004;126(6):1504-17. PMID: 15168363.
[86] Rubio-Tapia A, et al. *Gastroenterology* 2009;137(1):88-93. PMID: 19362553. PMCID: PMC2704247.

NIH Funding for Autoimmune Disease Research

Actual NIH funding support levels for autoimmune diseases research were $762 million in FY 2008, and $879 million and $138 million in FY 2009, respectively, for non-ARRA (regular appropriations) and

ARRA (Recovery Act appropriations). Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in this investment (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

NIH seeks to understand the onset and progression of autoimmune diseases and to use that knowledge to develop better strategies for disease prevention, diagnosis, and treatment. With more than 80 distinct autoimmune diseases, this may seem to be a daunting task. However, the many commonalities in the mechanisms that cause autoimmune disorders mean that research on one autoimmune disease often advances our understanding of others.

Providing Research Resources and Infrastructure

Many autoimmune diseases are rare, and researchers often must engage in national and international collaborative research to ensure access to sufficient numbers of patients and tissue samples to conduct their studies. NIH provides resources to facilitate this collaboration. For example, NIH supports patient registries for numerous autoimmune diseases, including alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, epidermolysis bullosa acquisita, juvenile and adult rheumatoid arthritis, systemic lupus erythematosus (lupus), pediatric lupus, psoriasis, Sjogren's syndrome, and scleroderma. Some disease registries also contain relevant clinical data linked to tissue samples.

Disease registries provide an important epidemiological resource for tracing the natural history of an autoimmune disease, assessing its burden in different populations, and identifying and tracking trends in incidence and prevalence. NIH-supported disease registries, as well as biological sample repositories, also have been instrumental in the successful application of genome-wide association studies (GWAS) to the study of autoimmune diseases (see *Understanding the Genetics of Autoimmune Diseases* in this section for more details).

NIH-supported research resources also include programs for the preclinical development of therapeutic agents; biological specimen repositories; animal models; antibodies and other research reagents; national data systems; provision of genetic, genomic, proteomic, high-throughput, and other emerging technologies and assays for specific projects; and research training programs. NIH supports infrastructure for clinical trials and preclinical, transdisciplinary, and translational research. Many of these resources and infrastructure elements are mentioned in more detail throughout this section.

Understanding the Genetic, Environmental, and Immunologic Factors Contributing to Autoimmune Disease

Genetic Factors

NIH-supported scientists are identifying the genetic underpinnings of autoimmune diseases. Their findings may elucidate molecular pathways of disease and identify possible therapeutic targets. GWAS are bringing new insights to this research by comparing the genomes of groups of people with an illness to groups of people who do not have the illness. This comparison improves the identification of even subtle genetic differences between affected and unaffected people. GWAS have yielded important information about disease risk, molecular pathways of disease development, and potential

therapeutic targets in several autoimmune diseases, such as type 1 diabetes, multiple sclerosis, inflammatory bowel disease, psoriasis, rheumatoid arthritis, lupus, and ankylosing spondylitis. NIH supports follow-up studies to evaluate the likelihood that a person with a newly discovered genetic variation associated with disease susceptibility will develop the disease. Integration of GWAS, environmental, demographic, and other genetic data will yield a better understanding of the mechanisms leading to disease and the development of tools for disease prevention and treatment.

Genome-wide Association Studies have yielded important information about disease risk, molecular pathways of disease development, and potential therapeutic targets in several autoimmune diseases, such as type 1 diabetes, multiple sclerosis, inflammatory bowel disease, psoriasis, rheumatoid arthritis, lupus, and ankylosing spondylitis.

Lupus research advanced appreciably in FY 2008 and FY 2009 thanks to the study of the genetics of autoimmune diseases. NIH-supported investigators identified genetic variations in lupus patients that may lead to a prognostic test to detect disease flare-ups or transient increases in disease severity. Furthermore, the discovery of some genetic factors on the X chromosome yields an important clue to the preponderance of this disease in females.[87]

[87] Jacob CO, et al. *Proc Natl Acad Sci U S A* 2009;106(15):6256-61. PMID: 19329491. PMCID: PMC2669395

Environmental Factors

Research suggests that infectious agents, dietary factors, toxic agents, or psychosocial factors, such as stress, may contribute to the development of autoimmune diseases. However, the sometimes long delay between environmental exposure and the onset of clinical disease, as well as the interaction of multiple genes or environmental factors, makes it difficult to determine which environmental factors are important to disease development.

NIH supports research to determine how environmental exposures influence the development of autoimmune diseases. For example, The Environmental Determinants of Diabetes in the Young (TEDDY) is a large-scale study focused on pinpointing environmental factors that can trigger type 1 diabetes in genetically susceptible individuals. This international consortium follows individuals from birth until age 15 to identify factors that lead some but not all genetically predisposed children to develop the disease. Because type 1 diabetes and celiac disease share many risk genes, TEDDY investigators also are examining environmental triggers of celiac disease. The dataset and biologic samples amassed in TEDDY will provide a valuable resource for future studies. NIH-supported researchers also are studying environmental risk factors for multiple sclerosis to identify environmental triggers in patients known to have genetic susceptibility to the disease. The study of environmental triggers in a clinically and ethnically homogeneous study sample from the same geographic region (Wisconsin) will help identify these triggers—an important step toward disease control and prevention.

NIH-supported animal model research and other basic research efforts are helping to decipher the role of various environmental exposures in the development of autoimmunity. For example, investigators are using mouse models to study how mercury affects the onset and progression of systemic autoimmunity, autoimmune heart disease, neuropsychiatric lupus, and the neuroimmune system.

Immunologic Factors

NIH sponsors research to illuminate the causes of autoimmune diseases and the regulatory

mechanisms that control autoantibody production and function. For example, researchers are studying the possible involvement of various types of immune cells, such as T cells, B cells, and "natural killer cells," in autoimmune diseases. In one study, investigators recently reported that individuals with lupus who have high levels of the protein CD19 in their B cells appear to have poorer clinical outcomes than lupus patients not displaying high levels of CD19.[88] Other research has shed light on the role of one type of T cell, T-helper cells, in autoimmune disease. Studies indicate that altered levels of IL-17, a protein that stimulates a particular subset of T-helper cells to release molecules that cause inflammation, are associated with the development of two autoimmune diseases: psoriasis and Job's syndrome.[89] Studies of this nature extend understanding of how autoimmune diseases develop and will enhance efforts to identify effective therapies. In another area of research, investigators are attempting to learn whether regions called "lipid rafts," which are found in the membranes of cells, may play a role in the development of autoimmune diseases.[90]

NIH supports a range of initiatives to better understand the mechanisms of autoimmune disease onset and progression and to develop effective interventions. The Somatic Hypermutation Group is using mouse models to study the onset and progression of lupus. One project is examining the possible role of a protein called "activation-induced deaminase" (AID), which triggers a process called somatic hypermutation. This process generates more specific antibodies to a wide variety of infectious agents or, in the case of autoimmunity, self proteins. The investigators found that decreased levels of AID resulted in a dramatic drop in the levels of a type of antibody associated with lupus and led to a decrease in the severity of lupus-induced inflammation of the kidney.[91]

The Cooperative Study Group for Autoimmune Disease Prevention (CSGADP), established in 2001, is a collaborative network of investigators seeking to understand how immune system dysfunctions may contribute to the development of autoimmune diseases, especially type 1 diabetes. Investigators at the six participating centers work to create and validate models of disease pathogenesis and therapy, use these models as validation platforms to test new tools for human studies, and encourage core expertise and collaborative projects for rapid translation from animal to human studies. Investigators recently reported that the development and progression of type 1 diabetes in mice may be characterized by differences in the expression of specific genes. Researchers also discovered specific patterns of gene expression that may prove useful as biomarkers of disease onset or progression.[92]

The NIH Centers of Research Translation (CORTs) are designed to bring together basic and clinical researchers to translate basic discoveries into new drugs, treatments, and diagnostics. Each center encompasses at least three projects, including one clinical and one basic research study. Several CORTs are investigating autoimmune diseases:

- The Center for Lupus Research investigates the role of different cell types in the origin and development of lupus, markers of disease activity and severity, and new targets for treatment.
- The Center for Genetic Dissection of Systemic Lupus Erythematosus studies mouse models of lupus to identify the genetic background of developmental stages of the disease. The research is based on previous studies that identified two major steps leading to lupus in mice, and aims to identify similar stages in the development of lupus in humans. The work also may uncover early markers and key molecular mediators of the disease, which could pave the way for new treatment opportunities.
- The Center for Research Translation in Scleroderma is studying the molecular basis of scleroderma to understand its underlying causes.

Clinical studies supported by the Environmental Autoimmunity Group (EAG) seek to understand the mechanisms for the development of autoimmune disease and reduce the burden of illness. The EAG focuses on the roles of genetic and environmental risk factors in the development of rheumatoid arthritis, lupus, systemic sclerosis (scleroderma), and idiopathic inflammatory myopathies. EAG studies include epidemiologic surveys, molecular genetic studies, and clinical investigations in disease

pathogenesis, as well as the development of clinical tools for assessment of innovative therapies.

The Center for Human Immunology, Autoimmunity, and Inflammation is a new trans-NIH intramural initiative designed to study the human immune system. The center organizes integrated teams of physicians and basic scientists to perform research on immune pathophysiologies, the role of inflammation in a wide variety of common disorders, and the translation of new knowledge into improvements in disease diagnosis and treatment.

[88] Nicholas MW, et al. *Clin Immunol* 2008;126(2):189-201. PMID: 18077220. PMCID: PMC2812414.
[89] Milner JD, et al. *Nature* 2008;452(188):773-6. PMID: 18337720.
[90] Kim W, et al. *J Immunol* 2008;181(9):6236-43. PMID: 18941214. PMCID: PMC2597670.
[91] Jiang C, et al. *Immunology* 2009;126(1):102-13. PMID: 18624728. PMCID: PMC2632700.
[92] Kodama K, et al. RoadMap of NOD TD1. Available at: http://fathmanlab.stanford.edu/roadmap_study_design.html.

Improving the Diagnosis and Prognosis of Autoimmune Diseases

Autoimmune diseases can affect any part of the body and have myriad clinical manifestations that can be difficult to diagnose. Research on biomarkers—clinical signs that correlate with the onset or progression of disease—may lead to better techniques for diagnosing autoimmune disorders. Improvements in technologies that enable clinicians to more quickly identify and test biomarkers hold great promise for earlier and more accurate autoimmune disease diagnosis, better prediction of disease flares, and improved monitoring of disease progression and response to treatment.

Recent progress in identifying biomarkers for lupus provides an example of NIH's work in this area. Researchers have uncovered numerous genes involved in the expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene is associated specifically with severe forms of lupus that include kidney disease, but not skin manifestations. Researchers also have developed tests, based on gene expression analysis of blood samples, to predict episodes of lupus activity and guide individualized treatment.

NIH-supported researchers also have identified two biomarkers detectable through blood tests that can predict the occurrence of a flare of lupus disease activity. They also showed that moderate doses of prednisone can prevent flares in people who have these biomarkers.[93]

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[93] Tseng CE, et al. *Arthritis Rheum* 2006;54(11):3623-32. PMID: 17075807.

Developing Evidence-Based Treatment and Prevention Interventions

NIH supports the development of effective strategies to prevent and treat autoimmune diseases and to translate successful strategies for use in patients. Furthermore, scientists are applying research discoveries made in cancer and other diseases to advance autoimmune disease research. For

example, evidence-based cancer therapies that target the protein mTOR may be effective against several autoimmune diseases known as lymphoproliferative disorders, which are associated with an excess production of lymphocytes.

The Immune Tolerance Network (ITN) is a collaborative research effort to study and test new drugs and therapies that induce immune tolerance for the treatment and prevention of autoimmune diseases and other immune-related disorders, while, at the same time, maintaining the body's ability to fight infection. Scientists hope that immune tolerance strategies one day will replace the use of immunosuppressive agents, which broadly reduce the body's immune response and place patients at increased risk for infection. ITN studies related to autoimmunity focus on pancreatic islet transplantation for type 1 diabetes and approaches to slow or reverse progression of autoimmune diseases. Each ITN clinical trial includes a coordinated set of laboratory studies of the genetic, cellular, and immunological mechanisms behind the experimental treatment. These studies build an understanding of how the body reacts to treatment and may lead to better ways to measure immune tolerance in the immune system.

The NIH focus on treatments for type 1 diabetes extends to a variety of other programs and initiatives. For example, NIH leads an international clinical trials network, the Type 1 Diabetes TrialNet, that tests promising new strategies for prevention in those at elevated risk and early treatment to slow or reverse the course of disease in those newly diagnosed. TrialNet researchers recently found that rituximab, a therapeutic agent currently in use for non-Hodgkin's lymphoma and rheumatoid arthritis, can delay progression of type 1 diabetes in newly diagnosed patients. Several other trials are ongoing through TrialNet, including a trial testing whether oral insulin administration can prevent or delay type 1 diabetes in a group of people who have high levels of antibodies targeted against insulin. These antibodies are markers of preclinical type 1 diabetes.[94]

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Other research focuses on devising new means to provide insulin to people with type 1 diabetes, who by definition are unable to produce insulin. For example, NIH extramural investigators are working toward the creation of an artificial pancreas. The Clinical Islet Transplantation Consortium is conducting research on transplanting islet cells, the cells from the pancreas that produce insulin, into people whose own islet cells have been destroyed by the autoimmune process that characterizes type 1 diabetes. The consortium focuses on improving the safety and long-term success of methods for islet transplantation.

The NIH Beta Cell Biology Consortium (BCBC)[95] collaboratively pursues research relevant to the development of cell-based therapies for type 1 diabetes, including studies of pancreatic development, the potential of stem cells as a source for making islets, and mechanisms underlying beta cell regeneration. The BCBC has generated research resources, such as animal models and antibodies, which are available to the scientific community.

CombiRx, a double-blind, placebo-controlled Phase III trial, is investigating multiple sclerosis treatment strategies. This study is comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting multiple sclerosis. Investigators are identifying biomarkers that may predict which treatment most likely will benefit a particular patient.

Through the Autoimmunity Centers of Excellence (ACEs), NIH fosters collaboration in prevention and treatment research across scientific disciplines and medical specialties and between basic and clinical scientists. Nine ACEs focus on strategies that induce immune tolerance or regulate the immune

system. Researchers also explore the molecular mechanisms underlying the agents evaluated in ACE trials. The enhanced interactions between basic and clinical researchers help to accelerate the translation of research findings into medical applications. ACEs currently support 10 active clinical trials studying treatments for lupus, multiple sclerosis, pemphigus vulgaris, rheumatoid arthritis, and Sjogren's syndrome.

Other NIH-supported initiatives seek to identify and advance novel therapies for autoimmune diseases. For example, the Center for Psoriasis Research Translation pursues research on novel photodynamic therapy for psoriasis. The Sjogren's Syndrome Clinic conducts research on gene therapy and bioengineering that holds promise for the repair or even replacement of salivary glands ravaged by Sjogren's Syndrome.

[94] Pescovitz MD, et al. *N Engl J Med* 2009;361(22):2143-52. PMID: 19940299.
[95] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-04-018.html

Addressing the Comorbidities of Autoimmune Diseases

Research to understand, prevent, diagnose, and treat comorbidities that affect many patients with autoimmune diseases can contribute toward reducing the burden of disease. Comorbidities range from the presence of more than one autoimmune disease to conditions arising from immune attacks on various body tissues or from adverse side effects of autoimmune therapies. For example, the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial tests whether statins—lipid-lowering drugs that reduce serum cholesterol levels—can delay the progression of arterial thickening from atherosclerosis in children diagnosed with lupus.

Patients with type 1 diabetes are at increased risk for many comorbidities related to elevated levels of blood glucose, including eye disorders, nerve and kidney damage, and heart disease. The landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study has shown that intensive control of blood glucose levels reduces the development of these long-term and often life-threatening diabetes complications. This research has revolutionized disease management and led to the recommendation that patients begin intensive therapy as early as possible. These findings also emphasize the importance of investigating new technologies for glucose control and insulin delivery, such as artificial pancreas technologies. [96]

[96] Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, et al. *Arch Intern Med* 2009;169(14):1307-16. PMID: 19636033.

Conclusion

NIH-sponsored research in autoimmune diseases is producing a wealth of knowledge while enhancing collaboration among basic scientists, clinical investigators, and individuals from a host of technical disciplines. Advances in our ability to generate and share genome-wide genotyping data and clinical information from varied cohorts are making it possible for new segments of the general research community to engage in and contribute to research in autoimmune diseases. Over the next several years, NIH will exploit every opportunity to build on its progress in autoimmune disease research, and

eagerly looks forward to continuing successes that will yield new knowledge and interventions to improve the lives of all Americans affected by autoimmune diseases.

Notable Examples of NIH Activity

Key
E = Supported through **E**xtramural research I = Supported through **I**ntramural research O = **O**ther (e.g., policy, planning, or communication) COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct IC acronyms in **bold** face indicate lead IC(s).

Basic Immunology

New Program to Focus on Better Defining Human Immune Profiles: In 2009, NIH requested applications for a new research program designed to build on recent advances in immune profiling to measure the diversity of human immune responses to infection or vaccination. Grantees will use a variety of modern analytical tools that will define molecular signatures of specific infections, vaccines, or immune adjuvants, as well as describe steady-state human immune status by a number of parameters. This program is a critical component of the NIH immunology research portfolio. This initiative supports studies that characterize human immune cells and their products isolated from diverse subsets of the population after vaccination, infection, or treatment with adjuvants. NIH will create a grantee consortium that will develop and manage a comprehensive database that consolidates and disseminates information for the scientific community and develop new assays and bioinformatics tools to facilitate productivity. This program, originally intended as an FY 2011 initiative, began 1 year early with ARRA funding.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-040.html
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIAID**) (ARRA)

Progress Toward Immune Tolerance: Since 1999, NIH, with its cosponsor the Juvenile Diabetes Research Foundation International, has supported the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN is pioneering novel strategies for studying and testing new drugs and therapies against autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based upon principles of immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to "reeducate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. To understand the underlying mechanisms of action of the candidate therapies and to monitor tolerance, the ITN has established state-of-the art core laboratory facilities to conduct integrated mechanistic studies, and to develop and evaluate markers

and assays to measure the induction, maintenance, and loss of tolerance in humans. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse progression of autoimmune diseases such as type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus and other rheumatologic disorders; approaches to treat and prevent asthma and allergic disorders, including food allergy; and therapies to prevent liver and kidney transplant rejection without using lifelong immunosuppressive drugs.

- For more information, see http://www.immunetolerance.org/
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIAID**, NIDDK)

Providing Research Resources and Infrastructure

Centers of Research Translation (CORT): The NIH CORTs are designed to bring together basic and clinical research to translate basic discoveries into new drugs, treatments, and diagnostics. Each CORT encompasses at least three projects, including one clinical and one basic research study. The centers are:

- The Center for Translating Molecular Signal Pathways to Orthopaedic Trauma Care studies the biological basis of fracture healing and the efficacy of a potential new treatment, teriparatide, an injectable form of human parathyroid hormone that stimulates new bone formation.
- The Center for Lupus Research investigates the role of different cell types in the origin and development of lupus, markers of disease activity and severity, and new targets for treatment.
- The Center for X-Linked Hypophosphatemic Rickets Research focuses on the various molecular contributors to this genetic form of rickets, and works toward developing new treatments.
- The Center for Research Translation in Scleroderma is studying the molecular basis of scleroderma to understand its underlying causes, using functional genomics and gene networks.
- The Center for Genetic Dissection of Systemic Lupus Erythematosus (lupus) studies mouse models of lupus to identify the genetic background of developmental stages of the disease.
- The Center for New Approaches to Assess and Forestall Osteoarthritis in Injured Joints is developing new methods of forestalling post-traumatic osteoarthritis (PTOA).
- The Center for Psoriasis Research Translation uses a Phase I mechanistic, safety, and preliminary efficacy study to test a novel photodynamic therapy for psoriasis.

    - For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/11_08.asp
    - For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2007/corts.asp
    - This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
    - (E) (**NIAMS**)

Center for Human Immunology, Autoimmunity, and Inflammation: The Center for Human Immunology, Autoimmunity, and Inflammation (CHI) is a new trans-NIH intramural initiative designed to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiologies, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease. The Center provides unique specific technologies often unavailable to individual laboratories

because of cost, complexity, and novelty. The core of CHI is made up of three technology centers. The first center features assays of immune cells and their products, based mainly on a technique known as flow cytometry and similar emerging techniques. The second center contains high-throughput systems technologies, involving the use of new methods for large-scale examination of genes, proteins, enzymes, and/or lipids. It also features advanced biostatical and computer modeling methods for mining these diverse data sets, thereby providing for a deeper understanding of immune function and pathology. The third center is based in protocol development, with staff dedicated to producing methods that efficiently translate to the clinic while considering all of the ethical and regulatory requirements for human research.

- For more information, see http://www.nhlbi.nih.gov/resources/chi/index.htm
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
- (I) (**NIAMS**, NCI, NHLBI, NIAID, NICHD, NIDDK, NINDS)

Seeking Solutions for People with Sjogren's Syndrome: Sjogren's syndrome is one of the most prevalent autoimmune disorders, affecting as many as 4 million people in the United States. Nine out of 10 patients affected are female. It is an autoimmune disease that progressively destroys salivary and lachrymal glands. The most common symptoms include dry eyes, dry mouth, fatigue, and musculoskeletal pain. A significant roadblock for moving discoveries ahead in the field of Sjogren's syndrome is the lack of data and biospecimens available for research. Recognizing the problem, NIH spearheaded an effort to establish Sjogren's patient registries at two extramural institutions as well as through its own intramural program. These groups are working together to generate and share with the general research community the genome-wide genotyping data and clinical information from the cohorts enrolled through these efforts. This resource should jumpstart efforts to understand genetic contributions to Sjogren's syndrome and the etiologic overlap with related autoimmune conditions such as lupus and rheumatoid arthritis. In addition to participating in the patient registry and genotyping efforts described above, the Sjogren's Syndrome Clinic, located in the NIH CC, collects systematic clinical and laboratory data on the Sjogren's syndrome (and salivary dysfunction) population. Gene therapy and bioengineering hold promise for the repair or even replacement of salivary glands ravaged by Sjogren's syndrome. More than 300 patient visits occur annually, and the clinic is expanding its patient recruitment to accelerate the conduct of clinical trials that might shed light on this disorder.

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  Roescher N, et al. *Oral Dis* 2009;15(8):519-26. PMID: 19519622. PMCID: PMC2762015.
  Nikolov NP, Illei GG. *Curr Opin Rheumatol* 2009;21(5):465-70. PMID: 19568172. PMCID: PMC2766246.
- For more information, see http://www.sjogrens.org/
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (**NIDCR**, CC, ORWH)

Understanding the Genetic, Environmental, and Immunologic Factors Contributing to Autoimmune Disease

Genome-Wide Association Studies of Autoimmune Disease Risk: In recent years, genome-wide association studies (GWAS) have transformed the identification of gene regions related

to disease risk, through an unbiased analysis of patients with a disease, in comparison with people who don't have it. These GWAS require large numbers of patients and individuals without the disease to obtain statistically significant results. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects, in addition to productive, multisite collaborations across the United States, including international researchers and contributions from the NIH Intramural Research Program. GWAS have yielded important information about disease risk, as well as understanding of disease pathways and potential therapeutic targets, in several autoimmune diseases in the past 2 years. Diseases studied include psoriasis, rheumatoid arthritis, systemic lupus erythematosus (or lupus), ankylosing spondylitis, and type 1 diabetes. Initial results from GWAS require confirmation by replication in additional groups of patients. More detailed localization of disease risk genes can be achieved through comprehensive DNA sequencing of candidate gene regions. New NIH initiatives are supporting these follow-up studies, which are critical to validating GWAS findings.

- Plenge RM, et al. *Nat Genet* 2007;39(12):1477-82. PMID: 17982456. PMCID: PMC2652744.
  Wellcome Trust Case Control Consortium, et al. *Nat Genet* 2007;39(11):1329-37. PMID: 17952073. PMCID: PMC2680141.
  Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
  Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
  Liu Y, et al. *PLoS Genet* 2008;4(3):e1000041. PMID: 18369459. PMCID: PMC2274885.
  Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
  Barrett JC, et al. *Nat Genet* 2009;41:703-707. PMID: 19430480. PMCID: PMC2889014.
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/10_04.asp
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-09-135.html
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2008/Ankyl_Spond_gene.asp
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-123.html
- For more information, see http://www.nature.com/ng/journal/v41/n6/abs/ng.381.html
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (**NIAMS**, NCRR, NHGRI, NHLBI, NIAID, NICHD, NIDA, NIDCR, NIDDK)

Lupus: There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group

disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

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  Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
  Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
  International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), et al. *Nat Genet* 2008;40(2):204-10. PMID: 18204446.
  Taylor KE, et al. *PLoS Genet* 2008;4(5):e1000084. PMID: 18516230.
  PMCID: PMC2377340.
  Chaussabel D, et al. *Immunity* 2008;29(1):150-64. PMID: 18631455.
  PMCID: PMC2727981.
  Smith-Bouvier DL, et al. *J Exp Med* 2008;205(5):1099-108. PMID: 18443225.
  PMCID: PMC2373842.
  Scofield RH, et al. *Arthritis Rheum* 2008;58(8):2511-7. PMID: 18668569.
  Jacob CO, et al. *Proc Natl Acad Sci U S A* 2009;106(15):6256-61. PMID: 19329491.
  PMCID: PMC2669395.
- This example also appears in Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAMS**, NCI, NCRR, NHLBI, NIAID, NIDCR, NINDS)

Immunological Factors in Autoimmune Disease: T Helper Cells: T helper cells are a category of immune cells that orchestrate many complex mechanisms in the immune system by receiving molecular signals and, in return, releasing other molecules that control activities of other cells. As a result, these recipient cells are stimulated, or inhibited, from damaging tissues or destroying pathogenic invaders. Studies in recent years have identified a number of T helper cell (Th) subsets that have fairly specific responses to immune system molecules, and are pivotal to attacks against pathogens, as well as autoimmune reactions—when the immune system aberrantly attacks the body it is supposed to protect. NIH-supported researchers have found that one Th subset (Th17) releases molecules that start a cascade of inflammatory events. The effects of Th17 and other pro-inflammatory cells are balanced by another Th subset, T regulatory cells (Tregs), which dampen inflammation. Job's syndrome is a rare immune disorder, characterized by recurrent and often severe bacterial and fungal infections. Due to a genetic mutation affecting a complex biochemical pathway, patients with Job's syndrome lack interleukin 17 (IL17), the molecule that stimulates Th17 cells. As a result, their immune systems fail to protect them from infections, which have the potential to become life-threatening. On the other hand, patients with psoriasis, an autoimmune skin disease, have high levels of IL17 and very active Th17 cells, which drive inflammation in the skin, leading to scaly, damaged tissue. Additional studies have revealed ways that the body might inactivate Tregs. By understanding the details of failures in biochemical pathways in disease states, scientists may begin to identify ways to correct them therapeutically.

- Lowes MA, et al. *J Invest Dermatol* 2008;128(5):1207-11. PMID: 18200064.
  Milner JD, et al. *Nature* 2008;452(7188):773-6. PMID: 18337720.
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2008/job_ma.htm
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2008/08_13b.asp
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*

- (E/I) (**NIAMS**, NCRR)

Cooperative Study Group for Autoimmune Disease Prevention: The Cooperative Study Group for Autoimmune Disease Prevention was established in 2001 by NIH and its cosponsor the Juvenile Diabetes Research Foundation International as a collaborative network of investigators who focus on understanding immune system dysfunctions that contribute to the development of autoimmune disease, with an emphasis on type 1 diabetes. NIH renewed the Study Group in 2006. It consists of six participating centers that support preclinical research, innovative pilot projects, and clinical studies. Of note, the centers initiated and supported the "Roadmap to Inflammation in the NOD (nonobese diabetic) Mouse" project to identify and characterize genes and proteins involved in the development of diabetes, and study the mechanisms by which diabetes develops. One notable finding suggested by this study is that the development of type 1 diabetes can be characterized by specific differences in how normal genes and gene variants are turned on and off during disease progression. In addition, researchers found patterns of coordinated gene expression that may prove useful as biomarkers of disease onset or progression. Another study, in press, identifies an unusual form of a gene whose expression in specific immune system tissues is associated with type 1 diabetes in both mice and humans.

- Kodama K, et al. *Clin Immunol* 2008;129(2):195-201. PMID: 18801706. PMCID: PMC2592195.
- For more information, see http://fathmanlab.stanford.edu/roadmap_study_design.html
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIAID**, NIDDK)

Mercury and Autoimmunity: The causes of autoimmune diseases remain unknown although genetic and environmental factors are believed to play major roles in susceptibility. NIH supports research projects investigating heavy metal-induced autoimmune diseases. The Mercury Induced Autoimmunity Project is working on the role that interferon-gamma plays in the development of induced murine systemic autoimmunity. Another NIH-supported project is investigating links between mercury (Hg) exposure and autoimmune heart disease. This project will assess programming changes that occur during the innate immune response to infection following exposure to Hg, with an overall effect on the progression of Coxsackievirus-induced autoimmune heart disease in mice, and apply the biomarkers from the studies in animals to a Hg-exposed human population in Amazonian Brazil. Another project is investigating the effect of Hg on the neuroimmune system. Studies will investigate the effects of Hg on production of autoantibodies to brain antigens. Antibodies to brain antigens have been demonstrated in patients with different neurological diseases, including neuropsychiatric lupus, Parkinson's disease, schizophrenia, and autism spectrum disorders. An ongoing project is working on development and uses mouse models to understand the relationships between immune system dysfunction and perinatal exposure to environmental toxicants in the development of neurobehavioral disorders such as autism. Mice from this project will be used to assess the effects of perinatal exposure to low levels of methyl mercury (MeHg) on abnormal brain development and behavior mediated by the immune system. These studies should allow insight into the mechanism of induction of immune dysfunction and point to a possible means of therapeutic intervention.

- Havarinasab S, et al. *Clin Exp Immunol* 2009;155(3):567-76. PMID: 19077085. PMCID: PMC2669534.
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*

- (E) (**NIEHS**)

Psoriasis: Early studies of families of psoriasis patients indicated a genetic susceptibility for the disease. Genome-wide association studies (GWAS) have revealed genetic variations in psoriasis patients for previously identified immune system proteins. New disease risk genes, which are associated with inflammation and immune function, also have been found. Some of these variations occur in or near gene regions associated with other autoimmune diseases, such as rheumatoid arthritis, lupus, and Crohn's disease, although in distinctly independent genes. In addition to variations in genes associated with immune function, GWAS have uncovered differences among psoriasis patients in genes involved with skin differentiation and regulation of inflammation.

- Liu Y, et al. *PLoS Genet* 2008;4(3):e1000041. PMID: 18369459. PMCID: PMC2274885. Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
- This example also appears in Chapter 3: *Genomics*
- (E) (**NIAMS**, NIDA)

Developing Evidence-Based Treatment and Prevention Intervention

Multiple Sclerosis Research: Although the exact cause of multiple sclerosis (MS) is unknown, recent research supported by NIH has begun to identify genetic variations associated with increased risk for developing the disease. In 2007, a genome-wide association study with NIH support reported the first new genetic risk factors for MS to be identified in more than 20 years, and in 2009, meta-analyses and replication studies revealed additional new susceptibility genes. NIH also funds and conducts basic, translational, and clinical research on disease mechanisms, biomarkers, and treatments for MS. For example, NIH supports a randomized, double-blind, placebo-controlled Phase III trial (CombiRx) comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting MS. The trial will determine whether combination therapy offers an improvement over the partial efficacy of either single treatment; it is the only direct comparison of these commonly used medications that is fully blinded and not supported by a commercial entity. NIH's Intramural Neuroimmunology Branch is collaborating with this trial to identify biomarkers associated with different clinical and treatment response profiles (BioMS). Such biomarkers may inform predictions about which treatment will most likely benefit a given patient, making this ancillary study an exciting addition to comparative effectiveness research in MS. Intramural investigators also will collaborate with the Swiss pharmaceutical company Santhera in a Phase I/II clinical trial to test the safety and efficacy of idebenone, which may protect against tissue damage, as a potential treatment for primary progressive MS.

- De Jager PL, et al. *Nat Genet* 2009;41(7):776-82. PMID: 19525953. PMCID: PMC2757648.
- For more information, see http://clinicaltrials.gov/ct2/show/NCT00211887
- For more information, see http://clinicaltrials.gov/ct2/show/NCT00325988
- For more information, see http://clinicaltrials.gov/ct2/show/study/NCT00950248
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E, I) (**NINDS**)

Basic Research on Type 1 Diabetes: NIH vigorously supports basic research on type 1 diabetes.

For example, the Beta Cell Biology Consortium (BCBC) collaboratively pursues research relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development, exploring the potential of stem cells as a source for making islets, and determining mechanisms underlying beta cell regeneration (cells that are the source of insulin production). The BCBC has generated research resources, such as animal models and antibodies, which are available to the scientific community. NIH also has launched initiatives to develop artificial pancreas technology for people with type 1 diabetes. One initiative solicited proposals from the small business community on the development of new technologies to advance progress toward an artificial pancreas. NIH also launched the Type 1 Diabetes Pathfinder Awards, to fund new investigators pursing innovative research on type 1 diabetes and its complications. Research supported through this program focused on areas such as cell replacement therapy, islet encapsulation, and diabetic wound healing.

- For more information, see http://www.betacell.org
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-001.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-08-012.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-08-013.html
- For more information, see http://www2.niddk.nih.gov/Funding/FundingOpportunities/RFA/RFA_T1D_Pathfinder_Announcement.htm
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIDDK**, NIBIB, NICHD)

Preclinical and Clinical Research on Type 1 Diabetes: NIH's Type 1 Diabetes TrialNet is an international network that tests strategies for prevention and early treatment of type 1 diabetes. TrialNet recently found that the drug rituximab delayed progression of type 1 diabetes in newly diagnosed patients. To identify environmental triggers of type 1 diabetes, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. TEDDY is enrolling newborns at high genetic risk and following them until age 15 to identify environmental triggers. NIH's landmark Diabetes Control and Complications Trial (DCCT) demonstrated that intensive control of blood glucose levels reduced complications of the eyes, nerves, and kidneys in type 1 diabetes patients. Long-term findings from the follow-on Epidemiology of Diabetes Interventions and Complications (EDIC) study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients begin intensive therapy as early as possible. To help patients achieve good glucose control, new initiatives focus on clinical and behavioral research related to new technologies for glucose control and insulin delivery (e.g., artificial pancreas technologies). NIH also supports research on islet transplantation through the Clinical Islet Transplantation Consortium. To provide resources for preclinical development of agents to test in clinical trials, NIH established the Type 1 Diabetes—Rapid Access to Intervention Development program.

- Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, et al. *Arch Intern Med* 2009;169(14):1307-16. PMID: 19636033. PMCID: PMC2866072.
  Pescovitz MD, et al. *N Engl J Med* 2009;361(22):2143-52. PMID: 19940299.
- For more information, see http://www.diabetestrialnet.org
- For more information, see http://www.teddystudy.org
- For more information, see http://diabetes.niddk.nih.gov/dm/pubs/control/
- For more information, see http://www.citisletstudy.org/
- For more information, see http://www.t1diabetes.nih.gov/T1D-RAID/
- This example also appears in Chapter 3: *Clinical and Translational Research*

- (E) (**NIDDK**, NCCAM, NCI, NIAID, NICHD)

Addressing the Comorbidities of Autoimmune Diseases

Pediatric Rheumatic Diseases: A rare, genetically inherited, inflammatory condition recently was discovered by researchers from NIH and other institutions. DIRA ("deficiency of the interleukin-1 receptor antagonist") patients often are misdiagnosed and do not receive appropriate treatment because their disease is characterized by symptoms seen in many illnesses: recurring episodes of systemic inflammation in multiple tissues, such as skin, bones, and joints. Inflammation is crucial in fighting infections, but uncontrolled, chronic inflammation can cause organ and tissue damage. It was found that DIRA symptoms are caused by a defective gene for a protein (IL-1Ra) that normally inhibits molecular signals for inflammation. Understanding DIRA symptoms and pathogenesis can guide better treatment for the disease, and may help clarify the IL-1Ra gene's role in promoting inflammation in more common diseases. On another front, children with lupus have a significantly increased risk for cardiovascular complications related to premature atherosclerosis, which is a potential source of long-term morbidity and mortality. Statins are drugs that lower cholesterol in blood and decrease the risk for atherosclerosis and cardiovascular disease. Statins also have intrinsic anti-inflammatory properties. The Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial has been testing whether statins can delay the progression of arterial thickening from atherosclerosis in children diagnosed with lupus. Another prospective study of adult and pediatric lupus patients confirmed previous observations, that children have more active disease than adults at the time of diagnosis. Over time, pediatric lupus patients also have more aggressive and severe disease than adult lupus patients.

- Aksentijevich I, et al. *N Engl J Med* 2009;360(23):2426-37. PMID: 19494218. PMCID: PMC2876877.
  Brunner HI, et al. *Arthritis Rheum* 2008;58(2):556-62. PMID: 18240232.
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2009/06_03.asp
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAMS**)

NIH Strategic Plans Pertaining to Autoimmune Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

- *NIAMS Long-Range Plan: Fiscal Years 2006-2009*
- *NIAMS Long-Range Plan: Fiscal Years 2010-2014*
- *The Future Directions of Lupus Research*

National Institute of Dental and Craniofacial Research (NIDCR)

- *NIDCR Strategic Plan*
- *NIDCR Implementation Plan*

National Institute of Allergy and Infectious Diseases (NIAID)

- *NIAID: Planning for the 21st Century — 2008 Update*

- *NIAID Plan for Research on Immune Tolerance (1998)*
- *Women's Health in the U.S.: Research on Health Issues Affecting Women (2004)*

National Center for Complementary and Alternative Medicine (NCCAM)

- *Expanding Horizons of Health Care: Strategic Plan 2005-2009*

Trans-NIH Plans

- *NIH Autoimmune Diseases Coordinating Committee: Autoimmune Diseases Research Plan*
  (CSR, FIC, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, ORD, ORWH)
- *NIH Action Plan for Transplantation Research (2007)*
  (NCI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NIDA, NIDCR, NIDDK, NIMH, NINDS)
- *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*
  (CC, CSR, NCCAM , NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)
- *Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases*
  (NINR, ORWH, NIA, NICHD, **NIDDK**, NIBIB, NIDA, NCCAM, NIEHS, NCI, NIGMS, NIAID, NCMHD, NIAAA)