Summary of Research Activities by Disease Categories

Autoimmune Diseases

The immune system has always been considered the body’s protector against disease-causing organisms and foreign bodies. The idea that a person’s immune system could launch an attack against itself was so unthinkable that in 1900, bacteriologist and immunologist Paul Ehrlich coined the term horror autotoxicus to describe the body’s innate aversion to forming antibodies against itself. More than 40 years later, Mac Burnet postulated that a so-called “thymic censor” blocked the creation of autoantibodies—antibodies that attack the self rather than foreign bodies. Burnet suggested that these autoantibodies might be produced if the “thymic censor” malfunctioned. We now know that autoimmunity is the failure of the immune system to distinguish between self (the body’s own cells, tissues, and organs) and non-self (disease-causing organisms and other foreign substances). When this happens, the immune system reacts as though the body is nonself and acts accordingly—it attacks. Burnet went on to win the Nobel Prize for subsequent work in immunology. He and Peter Medawar won the prize by demonstrating that the body can learn to not attack a foreign presence (e.g., a transplanted organ). This concept, called immune tolerance, is central to many of today’s most important advances in immunology.

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 disease 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 a heightened susceptibility. Some of the more common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, multiple sclerosis, systemic lupus erythematosus, 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, non-organ-specific diseases, such as systemic lupus erythematosus, 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, because most autoimmune diseases are more common in women than in men, hormones are suspected of playing a role. For these and other reasons, the autoimmune diseases are best recognized as a family of related disorders that must be studied together as well as individually.

Most autoimmune diseases disproportionately affect women and, as a group, are among the leading causes of death for young and middle-aged women[38]. Although treatments are available for many 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, including NIAID, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIDDK, NCI, NIDCR, NINDS, the National Human Genome Research Institute (NHGRI), and NIEHS, collaborate with professional and patient advocacy organizations to support autoimmune disease research. The Autoimmune Diseases Coordinating Committee (ADCC) facilitates inter-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, and prevention interventions. However, NIH recognizes that more needs to be done to close the gaps in knowledge and achieve the overall goal of reducing the rising toll of autoimmune diseases. The major tasks facing researchers in autoimmune diseases are:

- Development of a mechanism-based, conceptual understanding of autoimmune diseases
- Translation of this knowledge into new, broadly applicable strategies for treatment and prevention of multiple diseases
- Development of sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals

NIH supports an array of programs to accomplish these tasks, including research and activities to:

- Advance understanding of the distribution of autoimmune diseases through epidemiological studies
- Apply the knowledge provided by the Human Genome Project toward elucidating the hereditary risks of autoimmune diseases
- Extend understanding of genetic and environmental factors contributing to autoimmune diseases and then develop effective prevention strategies that arrest the autoimmune process before it can irreversibly damage the body
- Enhance the translation of scientific advances in autoimmune disease to clinical practice 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

In autoimmune diseases, a major goal of contemporary research is to “re-educate” the immune system by using tolerance induction strategies that aim to selectively block or prevent deleterious immune responses while leaving protective immunity intact. Immune tolerance will be evaluated by integrating mechanistic studies of tolerance induction and suppression of disease into clinical research studies and by conducting clinical trials of a variety of agents and strategies through dedicated clinical networks.

Overarching priority areas that promise to accelerate autoimmune disease research include biomarker development, bioinformatics, and application of new technologies. The development of biomarkers holds great promise for earlier and more accurate diagnosis of autoimmune diseases, better prediction of disease flare-ups, susceptibility genes and to study gene and protein patterns in tissue samples. They also 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-Institute and multidisciplinary collaboration as a way to address complex challenges in biomedical research.

**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 prevalence is rising. Examples of prevalence and incidence statistics for some autoimmune diseases are:

- An estimated 2.1 million people in the United States (about 1 percent of the population), including about 30,000 to 50,000 children, have rheumatoid arthritis 39.
- About 730,000 to 1.5 million people have type 1 diabetes (National Diabetes Fact Sheet, 2005). About 15,000 people younger than age 20 are diagnosed annually with type 1 diabetes 40.
- An estimated 250,000 to 350,000 people in the United States have been diagnosed with multiple sclerosis 41.
- In the United States, 239,000 people have been diagnosed with or are suspected to have systemic lupus erythematosus 42.
- As many as 1.4 million people in the United States have inflammatory bowel disease 43.

For more information, see [http://www3.niaid.nih.gov/topics/autoimmune/PDF/ADCCFinal.pdf](http://www3.niaid.nih.gov/topics/autoimmune/PDF/ADCCFinal.pdf)

**NIH Funding for Autoimmune Disease Research**

In FYs 2006 and 2007, NIH funding for autoimmune diseases research was $598 million and $587 million respectively. The table at the end of this chapter indicates some of the research areas supported by this investment (see “Estimates of Funding for Various Diseases, Conditions, and Research Areas”).

**Summary of NIH Activities**

NIH seeks to understand the onset and progression of autoimmune diseases and to use that knowledge to develop better interventions 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 means that research on one autoimmune disease often advances our understanding of others.

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40 For more information, see [http://jama.ama-assn.org/cgi/content/abstract/297/24/2716](http://jama.ama-assn.org/cgi/content/abstract/297/24/2716)


43 Loftus EV Jr. *Gastroenterology* 2004;126:1504-17, PMID: 15168363
Providing Research Resources and Infrastructure

Disease Registries
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 these research efforts. For example, disease registries provide an important epidemiological resource for tracing the natural history of autoimmune diseases, assessing its burden in different populations, and identifying and tracking trends in incidence and prevalence. NIH supports patient registries for numerous autoimmune diseases, including alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, epidermolysis bullosa acquisita, juvenile and adult-onset rheumatoid arthritis, lupus, neonatal lupus, and scleroderma. Some of these registries also contain relevant clinical data linked to tissue samples.

Other Research Resources
NIH-supported research resources also include programs for the preclinical development of therapeutic agents, such as the Type 1 Diabetes-Rapid Access to Intervention Development Program; biological specimen repositories; animal models; provision of genetic, genomic, and other molecular assays for specific projects; clinical trials infrastructure; and assistance in identifying collaborators. Some of these resources are mentioned in more detail in the “Notable Examples” later in this section.

Identifying Environmental Triggers of Autoimmune Diseases

Two large-scale projects that are searching for environmental triggers of autoimmune diseases are the Carolina Lupus Study and The Environmental Determinants of Diabetes in the Young (TEDDY) study. The Carolina Lupus Study, initiated in 1997, was the first population-based epidemiological study to examine the influence of hormonal and occupational exposures on lupus. The investigators found a striking association between occupational exposure to silica dust and lupus in individuals living in North and South Carolina. They also found that, compared with people who did not have lupus, patients with lupus were more likely to self-report occupational exposure to mercury, agricultural work that involved mixing pesticides, or work in a dental office or laboratory.

These and similar findings are expected to lead to improved prevention strategies for lupus and other autoimmune diseases and suggest possibilities for studies of the molecular development of lupus.

TEDDY is pinpointing environmental factors—such as infectious agents or diet—that can trigger type 1 diabetes in genetically susceptible individuals. This international consortium is following individuals who are at high genetic risk for type 1 diabetes from birth until age 15 to discover how environmental factors after birth contribute to the development of prediabetic autoimmunity and type 1 diabetes. Because type 1 diabetes and celiac disease share similar genetic predispositions, 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.

Understanding the Genetics of Autoimmune Diseases

NIH-supported scientists are identifying the genetic underpinnings of autoimmune disorders, research that can elucidate molecular pathways of disease and possible therapeutic targets. For example, investigators recently showed that a gene called PSORS1 plays a role in determining who gets psoriasis. Individuals with a particular form of this gene (the HLA-Cw6 allele) are more likely to develop early-onset psoriasis. Scientists hope that further

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research will lead to a treatment that interferes with the disease by targeting the PSORS1 gene. Researchers also have discovered genes that variously appear to play roles in lupus, rheumatoid arthritis, inflammatory bowel disease, and alopecia areata, bringing us a step closer to understanding the mechanisms of these diseases 46.

Recent technological advances have led to the development of genome-wide association studies that compare the genomes of people with an illness to those of people without the illness. Through this comparison, it becomes possible to identify even subtle genetic differences between affected and unaffected people (see the Genomics section in Chapter 3 for more information about genome-wide association studies). Genome-wide analysis is beginning to yield important results in the study of autoimmune diseases. For example, recent studies have led to the identification of key genes involved in type 1 diabetes 47 and inflammatory bowel disease 48. Recent technological advances have led to the development of genome-wide association studies that compare the genomes of people with an illness to those of people without the illness. Through this comparison, it becomes possible to identify even subtle genetic differences between affected and unaffected people (see the Genomics section for more information about genome-wide association studies). Genome-wide analysis is beginning to yield important results in the study of autoimmune diseases, including the identification of key genes involved in type 1 diabetes and IBD. In other research, investigators using a large familial dataset found the first new genes linked to MS in more than 20 years. These genes code for proteins that influence the way T cells patrol the body for pathogens, shedding light on a possible mechanism of MS onset and progression 49. In a similar quest to identify disease genes, the Type 1 Diabetes Genetics Consortium is studying families with two or more siblings with type 1 diabetes. In addition, NIH supports the Genetic Association Information Network (GAIN), which provides genotyping services, including genome-wide association studies to enhance and extend the utility of existing of research efforts. Through GAIN, NIH supports a long-term collaboration in which investigators are seeking to identify new genetic susceptibility factors for the development of psoriasis."

Understanding the Mechanisms of Autoimmune Disease Onset and Progression

NIH sponsors research to illuminate the causes of autoimmune diseases and the regulatory mechanisms that control autoantibody production and function. For example, researchers recently used a mouse model to show that toll-like receptors, a set of immune receptors involved in the earliest immune responses to infection and long thought to play a key role in autoimmune responses, are indeed implicated. They showed that even minor mutations in toll-like receptors can spark autoimmunity, suggesting that this family of proteins could be an important therapeutic target for lupus or other autoimmune diseases 50. Related research showed that a recently identified joint protein, cadherin 11, plays a role in rheumatoid arthritis in a mouse model of the disease. The investigators showed that a treatment that targets this protein prevents the abnormal adhesion and cartilage destruction typical of rheumatoid arthritis in mice, revealing a potential new therapeutic target in humans 51.


NIH supports a range of initiatives such as the following to better understand the mechanisms of autoimmune disease onset and progression and to develop effective interventions.

The Cooperative Study Group for Autoimmune Disease Prevention, established in 2001, is a collaborative network of investigators devoted to understanding the functioning of the immune system in both health and autoimmune disease. The Study Group works to develop the knowledge base necessary to design safe and effective interventions for the prevention of autoimmune disorders. Participating centers support preclinical research, innovative pilot projects, and noninterventional clinical studies, with an emphasis on type 1 diabetes. The Study Group, renewed recently for another 5 years, includes six cooperative agreements among researchers across the Nation.

The Beta Cell Biology Consortium (BCBC) is a team science initiative established in 2001 and competitively continued in 2005. This program facilitates interdisciplinary approaches to advance the understanding of insulin-producing pancreatic beta cell development and function. Currently, BCBC consists of 29 scientists, the majority of whom participate as investigators on 10 cooperative agreements. Scientists from two intramural NIH laboratories also are involved. In addition to conducting research, the Consortium develops research resources, such as antibodies, mouse models, and gene arrays, for use by the scientific community.

Scientists studying autoimmune diseases are excited about the emerging research approach known as systems biology that seeks to understand the overall behavior of biological systems. Systems biology uses computational methods to analyze data or simulate the system of interest and requires collaboration among researchers from bioinformatics, computer science, molecular biology, genomics, and other disciplines. NIH-supported researchers are applying a systems biology approach to better understand Sjögren’s syndrome, an autoimmune disorder in which immune cells attack and destroy the glands that produce tears and saliva, and other salivary gland disorders. Salivary gland biology is conducive to systems biology because researchers already have extensively catalogued the genes and proteins expressed in salivary glands. The scientific opportunity is to create an integrative, quantitative, and dynamic model encompassing every known aspect of the molecular and cellular biology of salivary glands and to translate this model into precise and practical ways to treat Sjögren’s syndrome.

**Improving the Diagnosis and Prognosis of Autoimmune Diseases**

Biomarker research is one area of investigation that may lead to better techniques for diagnosing autoimmune disorders. Biomarkers, clinical signs that correlate with the onset or progression of disease, already are commonly used to help diagnose some diseases, including prostate cancer and certain types of heart disease. With the rise of technologies to identify and test biomarkers more quickly, this area of research holds great promise for earlier and more accurate autoimmune disease diagnosis, better prediction of disease flare-ups, 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. For example, researchers have identified biomarkers that can be detected in the urine of patients with kidney disease and that provide information about the type and severity of disease. If validated with further research, these biomarkers may provide the basis for a noninvasive test to replace repeated kidney biopsies in patients with lupus, who are at increased risk for potentially severe kidney disease.

The Biomarkers Consortium, of which NIH is a founding partner, recently approved the concept for a systemic lupus erythematosus Biomarkers Working Group. The Consortium is a public-private partnership that endeavors to

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discover, develop, and qualify biomarkers to identify risk for disease, make a diagnosis, and guide treatment. The systemic lupus erythematosus Biomarkers Working Group will focus on identifying and validating biomarkers for prognosis and assessment of lupus disease activity, with the goal of speeding drug discovery and evaluation of new therapies in a disease that has not had a new drug approved in 40 years. This work also may lead to the identification of common biomarkers for other autoimmune diseases.

**Developing Evidence-Based Treatment and Prevention Interventions**

NIH supports the development of effective clinical strategies to prevent and treat autoimmune diseases and the translation of successful strategies to clinical application. The following programs and initiatives highlight NIH’s work in this area.

**The Autoimmunity Centers of Excellence (ACEs)** encourage and enable collaborative research—across scientific disciplines and medical specialties, and between basic and clinical scientists—to test prevention and treatment interventions. 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. ACE currently is supporting 10 active clinical trials studying treatments for lupus, multiple sclerosis, pemphigus vulgaris, rheumatoid arthritis, and Sjögren’s syndrome.

**The Clinical Islet Transplantation Consortium** develops and implements a program of single- and multicenter clinical studies, with accompanying mechanistic studies, in islet transplantation for the treatment of type 1 diabetes. The Consortium is focused on improving the safety and long-term success of methods for transplanting islets, the insulin-producing cells of the pancreas, in people whose own islets have been destroyed by the autoimmune process that characterizes type 1 diabetes. Some studies will focus on improving combined islet and kidney transplants in patients with type 1 diabetes who have kidney failure, a common diabetes complication.

**The Immune Tolerance Network (ITN)** is a collaborative research effort to study and test new drugs and therapies for autoimmune diseases and other immune-related disorders. ITN studies are based on stimulating immunological tolerance, the mechanism by which the immune system naturally avoids damage to self.

Today, autoimmune diseases are commonly managed with immunosuppressive agents. Because these agents broadly reduce the immune response, they place patients at increased risk for infection. The ITN supports four clinical studies with the goal of identifying and developing interventions that selectively target harmful autoimmune responses, avoiding the burdensome and dangerous side effects of global immunosuppression. For example, researchers are evaluating agents that suppress the activity of proteins known to be involved in the pathology of many autoimmune diseases. These proteins include the major histocompatibility complex, large protein clusters that are heavily involved in immune function; T cell receptors, which help lymphocytes (a type of immune cell) recognize foreign material; and autoantigens, normal proteins or other molecules that are mistakenly recognized by the immune system.

The development of therapeutic vaccines is a promising approach being taken by ITN scientists. One therapeutic vaccine in development, called the “universal” major histocompatibility complex (MHC) class II peptide vaccine, might be used to treat a wide variety of autoimmune disorders. The vaccine’s target peptide—a short portion of a protein—is present in many of the molecules known to be associated with the pathology of rheumatoid arthritis. Because of this “universality,” one vaccine can be used to simultaneously disrupt multiple molecular pathways of rheumatoid arthritis, increasing the likelihood of treatment success.
One clinical trial of special note is the Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial. The SCOT trial will compare the potential benefits of stem cell transplant and high-dose monthly cyclophosphamide (Cytoxan) in the treatment of scleroderma. This approach differs from current organ-specific treatments by seeking to treat the immune system as a whole.

**Addressing the Comorbidities of Autoimmune Diseases**

Another strategy for reducing the burden of disease is to support research to understand, prevent, diagnose, and treat comorbidities that affect many patients with autoimmune diseases. Comorbidities range from the presence of more than one autoimmune disease to conditions arising from immune attack on various body tissues or the interventions necessary to treat autoimmune disease. For example, a study of families with vitiligo, a pigmentation disorder in which white patches of skin appear on different parts of the body, found that family members of patients with vitiligo are predisposed to other, potentially more serious, autoimmune diseases. This finding may increase the ability to diagnose autoimmune diseases earlier, which could lead to better treatment.

Patients with type 1 diabetes are at increased risk for 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. In other research, investigators have identified potential molecular targets for prevention or treatment of chronic periodontitis, which can be a complication of diabetes.

**Notable Examples of NIH Activity**

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<thead>
<tr>
<th>Key for Bulleted Items:</th>
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<tbody>
<tr>
<td>E = Supported through Extramural research</td>
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<td>I = Supported through Intramural research</td>
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<tr>
<td>O = Other (e.g., policy, planning, or communication)</td>
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<tr>
<td>COE = Supported through a congressionally mandated Center of Excellence program</td>
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<tr>
<td>GPRA Goal = Concerns progress tracked under the Government Performance and Results Act</td>
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**Providing Research Resource and Infrastructure**

**Type 1 Diabetes–Rapid Access to Intervention Development (T1D-RAID):** Many investigators who have discovered promising therapeutic agents in the laboratory do not have the resources to ready the agents for use in human

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For more information, see [http://diabetes.niddk.nih.gov/dm/pubs/control/#study](http://diabetes.niddk.nih.gov/dm/pubs/control/#study)

Identifying Environmental Triggers of Autoimmune Diseases

**Carolina Lupus Study:** Since 1997, NIH has supported the Carolina Lupus Study, the first population-based epidemiological study to examine the influence of hormonal and occupational exposures, as well as the genetic factors that affect immune function and metabolism, on systemic lupus erythematosus. Lupus is a severe, disabling autoimmune disease that can lead to morbidity and mortality from renal and cardiovascular disease. African Americans are two to three times more likely than Whites to develop the disease, for unknown reasons. The study included 265 patients and 355 people without lupus living in 60 counties in North and South Carolina. The results of analysis of occupational exposure to silica dust in relation to risk for systemic lupus erythematosus were striking. Other associations were seen with self-reported occupational exposure to mercury, in mixing pesticides for agricultural work, and among dental workers. Weaker associations were seen between systemic lupus erythematosus and shift work and among health care workers with patient contact.

Understanding the Genetics of Autoimmune Diseases

**Multiple Sclerosis:** While the exact cause of multiple sclerosis is unknown, research suggests a strong genetic component. NIH funds a number of studies to determine the underlying genetic causes of multiple sclerosis, including a project to identify regions of the genome containing multiple sclerosis susceptibility genes by using a large familial dataset and genomic analysis tools. NIH also funds clinical trials to test therapies for multiple sclerosis, including the CombiRx trial, a randomized, controlled clinical trial comparing the efficacy of treatment combining interferon-beta and glatiramer acetate versus treatment with a single agent for relapsing forms of multiple sclerosis. A study conducted in conjunction with CombiRx by NIH intramural researchers (BioMS) is assessing multiple sclerosis biomarkers by using genomic and proteomic technology and relating the information obtained back to clinical and MRI data generated by the CombiRx clinical trial.

**Autoimmune Diseases and Genetics:** With the advancement of genomic science, more information has been gained about the genetic component of autoimmune diseases. Susceptibility genes have been identified for rheumatoid arthritis, lupus, psoriasis, and alopecia areata. Understanding the genetic influence of these diseases provides essential information for the design of new therapies.
• For more information, see
• For more information, see
• For more information, see
• For more information, see
• For more information, see
• This example also appears in Chapter 3: Disease Registries, Databases, and Biomedical Information Systems.
• (E) (NIAMS, NCRR, NHLBI, NIAID, NIMH)

**Genetic Susceptibility for Alopecia Areata:** Scientists supported by NIH have identified loci on four chromosomes that appear to play a role in the development of alopecia areata, an autoimmune disease characterized by hair loss that can affect the whole scalp or, in rarer cases, the entire body. Many U.S. families recruited for the study were identified through the Alopecia Areata Registry.

• For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/alopecia_areata.asp
• This example also appears in Chapter 3: Disease Registries, Databases, and Biomedical Information Systems.
• (E) (NIAMS, NIMH)

**Understanding the Mechanisms of Autoimmune Disease Onset and Progression**

The Cooperative Study Group for Autoimmune Disease Prevention: In 2006, NIH renewed the Cooperative Study Group for Autoimmune Disease Prevention, which was established in 2001. This collaborative network is devoted to understanding immune homeostasis in both health and autoimmune diseases and to developing interventions to prevent autoimmune disease. The six participating Centers support preclinical research, innovative pilot projects, and noninterventional clinical studies, with an emphasis on type 1 diabetes. By the end of 2006, grantees had published 109 original research papers, and 5 of 48 pilot projects had matured into investigator-initiated grants. Of note, the Centers are collaborating on the “Roadmap to Inflammation in the NOD [non-obese diabetic] Mouse” project, which will identify and characterize genes and proteins involved in the development of diabetes and study the mechanisms by which diabetes develops.

• For more information, see http://fathmanlab.stanford.edu/roadmap_study_design.html
• This example also appears in Chapter 3: Disease Registries, Databases, and Biomedical Information Systems.
• (E) (NIAMS, NIDDK)

**Systems Biology Approach to Salivary Gland Physiology:** Previous research has catalogued the genes and proteins expressed in the salivary glands. This initiative puts those catalogues into context by defining when and where genes and proteins are expressed and how they function as parts of a fully integrated biological system. The initiative combines the power of mathematics, biology, genomics, computer science, and other disciplines to translate this highly detailed information into more precise and practical leads to treat Sjögren’s syndrome, a debilitating autoimmune disorder that affects millions of Americans. The initiative also will help in learning to use saliva as a diagnostic fluid for a variety of conditions, from AIDS to cancer to diabetes.
• For more information, see http://www.nidcr.nih.gov/GrantsAndFunding/See_Funding_Opportunities_Sorted_By/ConceptClearance/CurrentCC/SysAppySal.htm
• For more information, see http://grants2.nih.gov/grants/guide/rfa-files/RFA-DE-08-001.html
• This example also appears in Chapter 2: Chronic Diseases and Organ Systems and Chapter 3: Genomics.
• (E) (NIDCR)

**Beta Cell Biology Consortium (BCBC):** The BCBC is collaboratively pursuing key challenges relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development to understand how insulin-producing beta cells are made, exploring the potential of stem cells as a source for making islets, and determining the mechanisms underlying beta cell regeneration. The BCBC has generated key research resources, such as animal models, microarrays, and antibodies, which are available to the scientific community.

• For more information, see http://www.betacell.org
• This example also appears in Chapter 2: Chronic Diseases and Organ Systems and Chapter 3: Molecular Biology and Basic Sciences
• (E) (NIDDK)

**Promising New Route to Rheumatoid Arthritis Therapy:** Rheumatoid arthritis is a debilitating autoimmune disease that is characterized by joint inflammation and affects approximately 2.1 million Americans. In this disease, a thin membrane of the joint, the synovium, overgrows and attaches abnormally to cartilage, leading to its erosion. A recently identified joint protein, cadherin 11, mediates the disease in a mouse model. Blocking synovium attachment to cadherin 11 prevents this abnormal adhesion and cartilage destruction in mice and reveals a potential new therapeutic target for the disease in humans.

• Lee et al. *Science* 2007;315:1006-10, PMID: 17255475
• For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cad_11.asp
• (E) (NIAMS)

**New Molecular Targets to Halt Periodontal Bone Loss:** Approximately 80 percent of American adults have some form of periodontal disease. Chronic periodontitis erodes supporting structures of the tooth, leading to tooth loss. The risk of periodontal diseases is higher in smokers and individuals with diabetes; 18 million Americans suffer from diabetes and related complications, including increased incidence and severity of periodontitis. This higher incidence and severity are associated with increased cell death in bone- and tissue-forming cells called osteoblasts and fibroblasts. The loss of these cells results in decreased capacity to repair tissue and bone. NIH-supported investigators published two separate papers describing the mechanisms by which the diabetic state enhances cell death. The papers suggest that diabetes-induced cell death and compromised tissue repair are mediated by the TNF-a pro-apoptotic pathway, and the major effector is caspase-3. Inhibition of TNF-a or caspase-3 activity reduces cell death and restores repair capacity. Discrimination between harmful microbes and commensal species is a critical property of the mucosal immune system, which is essential for maintaining health. Host immune cells have surface receptors that recognize bacterial species such as those known to be associated with periodontitis. Host immune cells can selectively learn to respond strongly or to tolerate endotoxin produced by recognized bacteria. NIH-supported scientists found that patients with chronic periodontitis overproduce a molecule known as SHIP, which plays an important regulatory role in signaling immune cells to tolerate endotoxin. The data from these studies suggest possible targets for developing new ways to treat or prevent chronic periodontitis.

Trans-NIH Initiative for Translational Research in Immunology, Autoimmunity, and Inflammation: A new, trans-NIH initiative is being developed by the intramural research program to facilitate the translation of advances in basic immunology to improved therapies and clinical care for immune-mediated diseases. The translation of basic immunology to the clinic has been impeded by separations between basic immunologists, physicians, and epidemiologists and by barriers among clinicians who address diseases that share pathophysiologic mechanisms but are historically separated in different specialty practices. The new program will integrate research efforts not only across the basic, clinical, and population sciences but also across conventional medical subspecialties. Research will focus on a variety of autoimmune diseases, congenital and acquired immunodeficiency syndromes, processes in which inflammation or altered immunity has a pathogenic role, and malignant diseases influenced by the immune system. Studies will address the underlying role of the immune system and the similarities and differences of the inflammatory response in many seemingly unrelated immune-mediated diseases. The initiative is expected to advance understanding of the causes of the diseases and to promote the development of new therapies. It also is expected to serve as a model for future trans-NIH translational research efforts to facilitate more rapid development and testing of new therapies and enhance interdisciplinary training.

Improving the Diagnosis and Prognosis of Autoimmune Diseases

Monitoring Organ Rejection Using MRI: Organ transplants give patients a new lease on life. However, preventing the immune systems from rejecting the transplanted organ sometimes presents a challenge. Physicians must strike a balance between suppressing the immune system so that it does not reject the organ and maintaining enough immune activity to ward off infections. Tracking how the body accepts the new organ is critical to this process. The current “gold standard” for monitoring organ rejection is tissue biopsy, an invasive procedure in which a physician removes a small sample of the transplanted organ for testing. Biopsy has two drawbacks: patient discomfort (the physician must perform the procedure multiple times) and poor selectivity (biopsy removes tissue from only a limited number of sites and can miss rejection starting elsewhere in the organ). To overcome these limitations, NIH-supported researchers are developing a new method to monitor organ rejection with MRI. They label macrophages (immune cells) with polymer-coated, micron-sized iron oxide particles. These magnetic particles allow the migration of the macrophages to rejection sites in the transplanted organ to be clearly tracked by MRI. At present, this work is being performed on rats, but the investigators are extending it to large animals and humans. If successful, the approach could be used to optimize the administration of immunosuppressant drugs in clinical situations.

Developing Evidence-Based Treatment and Prevention Intervention

The Immune Tolerance Network: In 2007, NIH renewed support for the Immune Tolerance Network (ITN), a consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN studies and

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I) (NHLBI, NIAID, NIAMS, NIDDK)

- For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/25Sep06
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIBIB)

- The Immune Tolerance Network: In 2007, NIH renewed support for the Immune Tolerance Network (ITN), a consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN studies and
tests new drugs and therapies for autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based on stimulating immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to “re-educate” the immune system to eliminate harmful immune responses and graft rejection while preserving protective immunity against infectious agents. The ITN has established state-of-the-art core laboratory facilities to study the underlying mechanisms of candidate therapies and to monitor tolerance. In 2006, the ITN reported that a novel DNA-based ragweed allergy therapy could achieve long-lasting symptom reduction after only 6 weeks of therapy, compared with current methods that require years of biweekly injections. Current ITN studies include pancreatic islet transplantation for type 1 diabetes, approaches to slow or reverse the progression of autoimmune diseases, approaches to treat and prevent asthma and allergic disorders such as food allergy, and therapies to prevent liver and kidney transplant rejection without causing harmful suppression of immunity.

- For more information, see [http://www.immunetolerance.org/](http://www.immunetolerance.org/)
- For more information, see [http://content.nejm.org/cgi/content/abstract/355/14/1445](http://content.nejm.org/cgi/content/abstract/355/14/1445)
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAID)

**Addressing the Comorbidities of Autoimmune Diseases**

**Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC):** The 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 EDIC study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients should begin intensive therapy as early as possible. EDIC recently found that recurrent hypoglycemia associated with intensive control does not affect patients’ long-term cognitive function. After more than 20 years of studying this patient cohort, crucial insights continue to emerge.

- For more information, see [http://www.bsc.gwu.edu/bsc/studies/edic.html](http://www.bsc.gwu.edu/bsc/studies/edic.html)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK)

**Comorbidities:** Many autoimmune diseases affect multiple organ systems. Recent studies have identified the basis of concurrent diseases at a molecular level, as well as clinically. A biomarker for lupus-related kidney disease has led to a noninvasive diagnostic breakthrough. Patients with the skin pigmentation disease vitiligo are at increased risk for other autoimmune diseases. In addition, recent studies document an increased risk for cardiovascular disease among patients with rheumatoid arthritis.

- For more information, see [http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/journal_special_text.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/journal_special_text.asp)
- (E) (NIAMS, NCRR, NHLBI, NIAID)
Vitiligo: Vitiligo is a skin disease characterized by a loss of pigment in all people who are affected. The psychological and social consequences can be particularly profound in affected people of color. A study of 133 families with vitiligo found that family members—even those who do not have vitiligo—are also predisposed to other, potentially more serious autoimmune diseases.

- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/04_10.asp
- This example also appears in Chapter 2: Minority Health and Health Disparities.
- (E) (NIAMS, NIAID, NIDDK)

**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*
- *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)**


**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
  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 , NCMDH, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM