

## NIH

### National Institute of Allergy and Infectious Diseases

#### SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

FY 2006 House Appropriations Committee Report Language (H. Rpt. 109-143)

##### Item

***Asthma*** - The Committee is pleased with NIAID's leadership regarding asthma research and management. The Committee encourages NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also encourages NIAID to collaborate more aggressively with voluntary health organizations to support asthma prevention, treatment, and research activities. Additionally, recent studies suggest that a variety of viral and bacterial agents may play a role in the development of asthma. The Committee recommends that the Institute consider expanding research into the role that infections and vaccines may play in the development of asthma. (p. 76)

##### Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) continues to support research aimed at reducing the impact of asthma on the lives of children and adults through prevention, treatment, and management. For example, the Institute supports thirteen Asthma and Allergic Diseases Research Centers that conduct basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma.

To improve our asthma management efforts, especially related to children, the NIAID intramural program opened a pediatric allergy clinic at the NIH Clinical Center. In collaboration with NIAID intramural laboratories, the new clinic will conduct translational research and clinical trials of novel therapies. The NIAID also supports the Inner-City Asthma Consortium (ICAC) to evaluate the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. Current ICAC studies include investigations of markers for asthma severity and the immunologic causes of recurrent wheezing. The ICAC is also planning a study of the safety and efficacy of Xolair (omalizumab) in inner-city children with moderate to severe allergic asthma whose symptoms are inadequately controlled with inhaled steroid.

The NIAID works in high-risk communities to promote asthma prevention, treatment and research. Using results of the National Cooperative Inner-City Asthma Study (NCICAS), which was conducted in collaboration with the Centers for Disease Control and Prevention, NIAID-supported researchers developed the Child Asthma Risk Assessment Tool, or CARAT. With this tool, caregivers can develop an asthma intervention strategy

tailored to their child's asthma risk profile. In addition, the Institute supports Demonstration and Education research projects that target asthma in medically underserved, predominately inner-city Hispanic and African American populations. These projects include school-based studies to identify children with asthma and implement strategies to reduce asthma severity.

#### Item

***Bioterrorism*** - Respiratory pathogens that cause life-threatening pneumonia are commonly proposed agents of bioterrorism. The following are associated with acute pneumonia/lung injury: anthrax, smallpox, plague, and tularemia. The Committee encourages further research on the mechanisms of pneumonia by these respiratory pathogens and the development of new therapeutic interventions to reduce injury and death. (p. 78)

#### Action taken or to be taken

The NIAID is the lead Institute within NIH for research related to potential agents of bioterrorism. The NIAID's biodefense research agenda includes short- and long-term research targeted at the design, development, evaluation, and approval of diagnostics, therapies, and vaccines that would be needed to control a bioterrorist-caused infectious disease outbreak. Basic research on anthrax, smallpox, plague, and tularemia will increase knowledge of how these infections could lead to respiratory infections such as pneumonia. The NIAID supports a broad portfolio of such research. For example, NIAID-supported researchers have discovered critical host-defense mechanisms against tularemia in a mouse model.

The NIAID's Biodefense and Emerging Infectious Diseases Research Opportunities initiative encourages the submission of investigator-initiated research grant applications on research leading to the diagnosis, prevention and treatment of diseases caused by potential bioterrorism agents. Recent awards through this initiative include support for research on pulmonary responses to Category A pathogens, which include anthrax, smallpox, plague, and tularemia; research on the basis of anthrax-induced vascular damage, and evaluation of lung-targeted antivirals against the poxviruses.

In addition, the NIAID has developed several initiatives that are targeted to the development of therapeutics for biodefense. The initiative, Therapeutics for CDC Category A Agents: Bioshield Accelerated Product Development, supports research projects focused on the design and preclinical development of therapeutics for CDC Category A agents, including anthrax, smallpox, plague, and tularemia. Another initiative—Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense and SARS—supports discovery, design and development of vaccines, therapeutics, adjuvants, and diagnostics for biodefense. Through the program, *In vitro* and Animal Models for Emerging Infectious Diseases and Biodefense, the Institute is screening existing antimicrobials,

which are already approved by the Food and Drug Administration, for activity against pneumonic plague and inhalational anthrax.

In 2005, the NIAID completed a national network of ten Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs) to support research focused on countering threats from bioterror agents and emerging infectious diseases. Each Center is comprised of a consortium of universities and complementary research institutions serving a specific geographical region. The research being conducted within the RCEs spans a broad range of biodefense and emerging infectious disease topics.

#### Item

***Coinfection research*** – The Committee is concerned that there is growing evidence of liver toxicity resulting from HIV treatment protocols such as highly active antiretroviral therapy (HAART) in those with chronic viral hepatitis and those with decompensated liver disease awaiting liver transplantation. There also appears to be an emerging problem of liver cancer in co-infected patients. The Committee encourages NIAID to initiate research initiatives in both of these areas. (p. 77)

#### Action taken or to be taken

The NIAID maintains its commitment to the study of AIDS-associated opportunistic infections and co-infections, such as hepatitis B virus (HBV) and hepatitis C virus (HCV), that affect people with impaired immune systems who are unable to fight off pathogens. Despite the fact that potent highly active antiretroviral therapy (HAART) has prolonged survival and reduced the incidence of opportunistic infections and co-infections in HIV-infected individuals, complications and side-effects associated with HAART have become an increasing concern for the medical management of HIV-infected individuals. In particular, individuals co-infected with HIV and hepatitis are experiencing therapy-related liver complications now being addressed by the scientific research community.

NIAID-supported researchers at Johns Hopkins University are studying liver disease and HIV-HBV co-infection in patients on HAART through the Liver and Pancreatic Disease in HIV Infection research initiative. This initiative is intended to stimulate research on the pathogenesis and therapeutics of the liver and pancreatic diseases associated with HBV and HCV co-infections that occur in patients with HIV infection. The NIAID is also conducting the Solid Organ Transplant in HIV study on the outcome of kidney and liver transplants in HIV-positive subjects who achieved viral suppression with HAART, many of whom are co-infected with HCV or HBV.

In addition, NIAID's Adult AIDS Clinical Trials Group (AACTG) formed the Hepatitis Research Agenda Committee (HepRAC) which aims to develop clinical protocols to answer scientific questions in the areas of treatment and management, viral dynamics, immunology, and genomics of HIV/HCV and HIV/HBV co-infections as well as HCV

and HBV monoinfections. The emphasis of the HepRAC is on the development of strategies for the optimal timing and treatment of each viral infection and for the treatment of drug resistance and salvage therapy. The HepRAC will also be looking at non-hepatitis steatosis, hepatotoxicity, fatty liver disease, and drug interactions particularly with antiretrovirals or other drugs used in the treatment of AIDS. Currently, the AACTG is conducting a study to evaluate the safety and efficacy of interferon-based therapies such as PEG-interferon in persons co-infected with HIV and HCV.

### Item

***Detection of disease and bioterror agents-*** The Committee recognizes the potential threat to national security posed by terror attacks involving biological, chemical, nuclear, and radiological weapons. One of the challenges facing public health officials responding to such an attack is the limited ability to diagnose exposure to these agents in the non-sick-appearing and early illness individuals. The Committee recognizes that disease outbreaks—such as SARS in Asia and Canada, avian influenza in East Asia, and Ebola and Marburg virus in Africa—demonstrate that the speed of diagnosis and implementation of public health measures can mean the difference between an isolated outbreak and a global pandemic. The Committee commends NIAID for its initiatives that provide comprehensive genomic, bioinformatics, functional genomics, and immune cell proteomic research resources to the scientific community conducting basic and applied research on infectious agents and the immune system. The Committee encourages NIAID to maintain its support of these programs, which provide a critical resource for the scientific community that could lead to the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics and immunotherapeutics. (p.79)

### Action taken or to be taken

To meet the needs for diagnostic tests, interventions, and treatments after exposure to biological, chemical, nuclear, and radiological weapon, the NIAID supports a number of initiatives that will lead to a deeper understanding of the many cellular components of the human immune system, how they interact with pathogens, and what changes they undergo in these interactions. For example, the NIAID supports the Systems Approach to Innate Immunity-Inflammation-Sepsis collaborative project. This multi-year, cooperative agreement supports a multidisciplinary team of researchers who are employing a systems biology approach to create a comprehensive picture of innate immunity, an essential first line of defense against bacterial, viral, and fungal diseases. The goals of this program include the identification of the proteins expressed and the biochemical pathways triggered by encounters between innate immune system cells and infectious agents. The Institute also supports the Biodefense Proteomics Collaboratory program to identify and quantify the differential expression of key proteins in immune system cells in response to potential bioterror pathogens. Understanding of these proteins may someday be useful in designing diagnostic tests.

NIAID's efforts in this area also include the development of searchable electronic databases. For example, the Institute supports the Bioinformatics Integration Support Contract (BISC) to develop a platform for the organization, analysis, and integration of basic and clinical immunological data, including proteomic data. The BISC will provide the means for scientists to easily access, generate, analyze, and exchange complex high-quality data sets. The NIAID Biodefense Proteomics Research Programs initiative will facilitate the identification of new targets for potential future diagnostics, therapeutics, and vaccines. A component of this program includes the development of a web-based platform for public distribution of all data and reagents generated in the research centers of the program.

### Item

**Food allergies** – The Committee is concerned about the high prevalence of food allergies, among children in particular, with up to eight percent affected. The Committee recognizes that 30,000 individuals require emergency room treatment for food allergies each year, that 100 to 200 individuals die each year from allergic reactions to food, and that there is currently no cure for food allergies. The Committee is encouraged by the March 2005 release of a report in *The Journal of Allergy & Clinical Immunology* containing guidelines for the definition of anaphylaxis, and hopes that these guidelines will improve the diagnosis, treatment, and understanding of food allergy and anaphylaxis. NIAID is encouraged to invest in research into the causes of food allergies and its potential treatments. (p.77)

### Action taken or to be taken

Allergic reactions in children and adults from food allergy vary in severity and can result in the need for emergency room medical care, or in more serious cases can result in death. Reducing the burden of food allergy through targeted research continues to be a priority for the NIAID.

In response to recommendations made by a panel of experts in 2003, in FY 2005, the NIAID established the Food Allergy Research Consortium to conduct basic, clinical and epidemiological studies, and to develop educational programs aimed at parents, children, and healthcare providers to develop new approaches to treat and prevent food allergy. An additional grant will fund a statistical center to support the Consortium. The Consortium's first project is a study to evaluate a potential therapy for peanut allergy.

Another example of research directed toward improving the diagnosis, treatment, and understanding of food allergy and anaphylaxis is a project of the NIAID-supported Immune Tolerance Network (ITN). The ITN is developing a clinical trial to determine whether feeding a peanut-containing snack to young children at risk of developing peanut allergy will prevent development of this allergy. Study participants will include children between four and ten months of age who have atopic dermatitis and/or are allergic to eggs.

Future plans for food allergy research include the NIH Food Allergy Expert Panel, which will be convened in March 2006. The panel will review current basic and clinical research efforts related to food allergies and make recommendations to the Secretary of Health and Human Services for enhancing and coordinating research activities related to food allergies. The panel's recommendations are expected in the fall of 2006. In FY 2007, the Institute plans to establish the Allergen and T-Cell Reagent Resources for the Study of Allergic Diseases program to identify novel allergens and reagents to facilitate the development of strategies to treat and prevent allergies. In addition, the NIAID plans to re-compete the ITN to continue support of clinical trials of tolerance induction to prevent or treat asthma and allergic diseases, including food allergy.

#### Item

***Genetic tools for infectious disease research*** - The Committee believes that, with regard to both biodefense and public health, the development by NIAID of multi-pathogen identification arrays that can be used to identify infectious agents through epidemiological outbreak surveillance is critically important. The use of whole genome expression, all exon transcription analysis and whole genome SNP analysis studies to identify and understand host biomarkers that may identify the type, severity and likely response to therapeutics of infectious agents holds great promise. The Committee encourages NIAID to pursue these lines of inquiry. (p. 79)

#### Action taken or to be taken

The NIAID has made a significant investment in large-scale sequencing projects that continue to generate DNA sequence information. The NIAID has launched initiatives, including the Microbial Sequencing Centers, the Pathogen Functional Genomics Research Center, and the Proteomics Centers, to provide comprehensive genomic and proteomic resources to the scientific research community. The Institute has completed genome sequencing of over 50 pathogens and continues to support pathogen sequencing projects. In addition, microbial genomics is being used together with the human genome sequence to better understand the host immune response and an individual's genetic susceptibility to pathogens.

The NIAID supports a number of projects to develop multi-pathogen identification microarrays. Examples include a DNA microarray diagnostic chip that will detect 18 bacterial pathogens and 25 viruses and will also be able to detect genetic changes in these organisms; polymerase chain reaction (PCR) assays that distinguish up to 60 different species-specific DNA sequences in a single assay well; and an integrated microarray detection platform combined with sample preparation technology on a CD-type format.

Microbial genomics is being used together with the human genome sequence to better understand the host immune response and an individual's genetic susceptibility to pathogens. The NIAID supports an initiative that will provide a better understanding of

immune responses to infection and vaccination, which may lead to identification of novel immunotherapeutic targets for vaccines and drugs to prevent and treat infections.

The NIAID is also supporting host biomarker studies, including utilization advanced technologies to determine which proteins are present in the body of as a result of infection with various microbes, including monkeypox virus.

NIAID's Microarray Research Facility (MRF) provides expertise and resources for all phases of microarray-based research projects. In addition to mouse and human arrays, MRF has produced custom microarrays to address a variety of research needs. These include microarrays for *Mycobacterium tuberculosis* (tuberculosis), *Plasmodium falciparum* (malaria), and *Cryptococcus neoformans* (fungal infections).

#### Item

***Hemophilia*** – The Committee encourages NIAID to continue its efforts with voluntary organizations in developing and advancing research initiatives for addressing hepatitis C (HCV) within the bleeding disorders community. The Committee understands that HCV continues to have a devastating impact on this community, with nearly half of all persons with hemophilia having contracted HCV from blood clotting factor products. (p. 76)

#### Action taken or to be taken

The NIAID remains committed to the support of research targeted to the HIV-infected hemophiliac population. The current scientific needs of the HIV-infected hemophiliac population are focused on the impact of hepatitis C virus (HCV) infection. To meet the research needs in this area, the Institute is supporting a University of Cincinnati study of liver disease progression and HCV genomic variability in HIV-infected hemophiliacs. The NIAID will continue to support this study in FY 2006, through a no-cost extension.

In addition, NIAID extramural program staff recently met with the leadership of the National Hemophilia Foundation to discuss ways in which the Foundation's constituency, in which there is a prevalence of HCV infection, might participate in NIAID-supported clinical trials.

#### Item

***Hepatitis C virus (HCV) vaccine development***--The Committee is encouraged to learn that a small hepatitis C vaccine human trial has been successfully completed. The Committee urges NIAID to begin to implement the results of the recent workshop that was held to discuss and evaluate efforts toward development of HCV vaccines with the goal of spurring their development and testing. The Committee also encourages NIAID to proceed with phase two of the human clinical trial as soon as it is scientifically practicable. Additionally, NIAID is urged to foster the development of an in vitro culture

system for HCV as well as new animal models for basic research. The Committee continues to be concerned about the prevalence of hepatitis and urges NIAID to work with public health organizations to promote liver wellness, education, and prevention of hepatitis. (p.77)

#### Action to be taken

Progress toward the development of a vaccine against hepatitis C virus (HCV) and reduction in the prevalence of this disease continues to be a priority for the NIAID. The NIAID plays a key role in hepatitis C research efforts across the NIH. These trans-NIH efforts include a broad range of research activities in support of vaccine development, including basic research on HCV that guides vaccine development, studies that define potential population groups in which vaccines could be evaluated, the development of both preventive and therapeutic vaccines, and preclinical evaluation and clinical trials of vaccine candidates.

In 2004, the Institute launched a Phase I trial to evaluate the safety, tolerability, and immunogenicity of a candidate HCV vaccine. This trial is being conducted in the NIAID's Vaccine and Treatment Evaluation Units (VTEU) and is ongoing. The NIAID is currently working with two companies to develop two additional Phase I trials of HCV vaccine candidates; these trials will also be conducted at VTEU sites.

In February 2005, the NIAID held a workshop on HCV vaccines which provided a forum for the comprehensive review of progress towards the development of vaccines for HCV. Scientists from academic institutions, pharmaceutical companies, biotechnology companies, and Federal government agencies participated. In response to the suggestions stemming from this workshop, the NIAID developed the initiative Partnerships for Hepatitis C Vaccine Development, which will be supported in FY 2006.

The NIAID has helped support a collaborative effort involving Rockefeller University, the Massachusetts Institute of Technology and the Scripps Research Institute to produce a tissue culture cell line in which the entire HCV replicates. This development will allow further investigation into the life cycle of the virus and provides a tool for screening new therapies and testing vaccine candidates.

The NIAID is also supporting research toward new animal models for HCV through the initiative Animal Models for the Prevention and Treatment of Hepatitis B and Hepatitis C. In addition, NIAID investigators are studying infection of the tamarin with GB virus B, a close relative of HCV, as a model for hepatitis C infection in humans.

#### Item

***Inflammatory Bowel Disease*** –The Committee continues to note with interest a scientific research agenda for Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel disease) entitled "Challenges to Inflammatory Bowel Disease." This



report identifies strong linkages between the functions of the immune system and IBD. The Committee encourages the Institute to enhance its support of research focused on the immunology of IBD, as well as the interaction of genetics and environmental factors in the development of the disease. (p. 76)

#### Action taken or to be taken

The NIAID continues its long standing commitment to research directed toward understanding and reducing the burden of inflammatory bowel disease (IBD). Since 1998, when the NIAID sponsored a workshop on Crohn's disease, the Institute has initiated cross-disciplinary research including studies that investigate the genetic and environmental factors that contribute to IBD. The NIAID plans to sponsor a follow-on workshop to the 1998 workshop, titled "Discoveries in Microbial Etiology of Crohn's Disease," in the summer of 2006.

The NIAID intramural program has expanded laboratory research on the immunology of IBD and is conducting clinical trials of promising new therapies. The intramural program in translational medicine for IBD has developed a number of clinical trials of novel drugs at the NIH Clinical Center. For example, NIAID scientists completed a Phase II trial of a novel immune-based therapy for Crohn's disease. In this trial, researchers evaluated the safety and efficacy of monoclonal anti-IL-12 antibody, which has shown promise as an effective treatment of active disease.

NIAID's extramural initiatives and programs such as the Autoimmunity Centers of Excellence, the Immune Tolerance Network and the Autoimmune Disease Prevention Centers provide opportunities for trans-NIH collaboration on IBD. For example, the NIAID participates in the Digestive Diseases Interagency Coordinating Committee led by the National Institute of Diabetes and Digestive and Kidney Diseases. The Committee facilitates research on digestive diseases including the immunology, genetics and role of the environment in IBD pathogenesis.

One of the recently-established units of the NIAID Food and Waterborne Diseases Integrated Research Network has recently begun to explore the feasibility of developing an animal model of human Crohn's disease. Such an animal model could prove valuable in research on the associations between bacterial agents and Crohn's disease. In addition, the NIAID supports research projects under the FY 2002 initiative, Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection, co-sponsored by the National Cancer Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and the NIH Office of Research on Women's Health. The purpose of research grants supported through this initiative is to identify and validate the role of pathogens in chronic diseases, including Crohn's disease.

## Item

***Islet transplantation*** – The Committee commends NIDDK and NIAID for the establishment of the Clinical Islet Transplantation Consortium and the islet transplantation clinical trial that will include Medicare-eligible individuals whose transplant and related costs will be covered by Medicare. The Committee urges cooperation between NIDDK and NIAID and members of the Consortium to ensure the timely launch of these clinical trials. (p. 77-78)

## Action taken or to be taken

The Clinical Islet Transplantation Consortium (CITC), which is co-sponsored by the NIAID and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), was established in 2004, to design and perform studies of islet transplantation in patients with type 1 diabetes.

The CITC has developed and implemented a program of single- and multi-center clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. The studies will focus 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 and kidney failure, a common complication of diabetes.

The Consortium will conduct clinical trials at seventeen sites, including five international centers. Currently, the CITC has five Phase II and two Phase III clinical trials in development to: (1) provide data to support licensure of an islet product for treatment of type 1 diabetes in patients with normal kidney function; (2) provide data to support licensure of an islet product for treatment of Medicare beneficiaries who have type 1 diabetes and have undergone a kidney transplant; and (3) investigate innovative approaches to improve upon current outcomes in islet transplantation. The NIAID anticipates that the CITC clinical studies will begin enrolling study participants in FY 2006.

## Item

***Meningococcal disease/Serogroup B immunization research*** – Although meningococcal disease is vaccine-preventable in most cases, approximately 30 percent of the deaths and disabilities from this bacterial infection are attributed to serogroup B which is not vaccine-preventable. The Committee encourages NIAID to increase research efforts to develop an effective, low-cost vaccine against serogroup B that will help protect infants and adolescents in the near term.

### Action taken or to be taken

A major goal of the NIAID Respiratory Diseases Program is to stimulate and support research that may lead to more effective and accepted approaches for the prevention and control of respiratory infections, including the development of a vaccine against serogroup B meningococcus.

In October 2004, the NIAID and the National Vaccine Program Office of the Department of Health and Human Services co-sponsored a workshop entitled “Carbohydrate Moieties as Vaccine Candidates.” This workshop brought together research scientists, clinicians, and representatives from industry to identify research needs and scientific gaps in an effort to promote vaccine development for meningococcal disease. The workshop examined the mechanisms involved in the generation of an appropriate host immune response to selected antigens, highlighted recent advances, and discussed how this information could be used to advance the development of effective vaccines. This workshop included a discussion of the obstacles involved with the development of a vaccine against serogroup B meningococcus; the results of the workshop were published in *Clinical Infectious Disease* in September 2005.

The Institute continues to support pre-clinical and clinical studies to control selected human respiratory pathogens through its Respiratory Pathogen Research Units (RPRUs). Respiratory pathogens studied at the RPRUs include meningococci, the bacteria that cause meningitis.

The NIAID will continue to pursue research in support of the development and licensure of vaccines and therapeutic agents for respiratory pathogens. Among the Institute’s goals are to further the understanding of the etiology and long-term health impact of acute respiratory infections and to stimulate basic research that may provide additional information on the pathogenesis, immunity, and functional components of respiratory pathogens.

### Item

***Nasal aerosol and spray vaccine delivery systems*** - The prevention of infectious diseases through the effective use of vaccines has saved mankind untold suffering and death. Recent developments exploring new routes of immunization such as delivery of measles vaccine via the aerosol route and nasal spray give great hope for achieving this goal, generating significant savings, and resulting in fewer side effects than immunization by injection. The Committee encourages NIAID to support research in developing and testing these new approaches and translating this research into public benefits. The Committee recommends that NIAID build upon the testing already completed in older children by investigating this delivery method in younger children. The Committee believes that NIAID and other institutes should collaborate with physicians and researchers working with these newer and possibly superior methods of vaccine delivery in the hopes of developing safer, more effective, and less expensive vaccine delivery modes. (p. 78)

### Action taken or to be taken

Research leading to new and improved vaccines, including innovative vaccine delivery systems, is a high priority for the NIAID. The NIAID has a long history of development of vaccines against childhood diseases and of research in the nasal delivery of vaccines. The work of NIAID scientists was critical to the development of FluMist, the influenza vaccine made for nasal delivery. NIAID researchers are currently developing several candidate vaccines that are specifically designed for nasal delivery. A live, attenuated, intranasal vaccine candidate against respiratory syncytial virus (RSV) was recently evaluated in infants and shown to be well-tolerated and produced an immune response. NIAID scientists also are developing other vaccine candidates for nasal administration.

NIAID-supported researchers recently evaluated an aerosol measles vaccine in 9-month-old infants. The results suggest that a low-dose measles vaccine given by aerosol is safe and effective in inducing immunity to measles in most children. The research team is now developing a study protocol to evaluate, in infants, the safety and efficacy of an aerosol measles-rubella vaccine.

In addition, NIAID scientists have developed vaccines for two strains of avian influenza, H9N2 and H5N1, designed to be administered directly to the respiratory tract. Such live, attenuated vaccines generally induce broadly cross-reactive protection, which may be a useful feature in the event of a pandemic in which a vaccine generated from the actual pandemic strain is not available. A clinical trial of the H9N2 vaccine is underway.

The NIAID is also supporting the development of several other non-injection vaccines, including an inactivated intranasal influenza vaccine; an intranasal SARS vaccine; an adenovirus-vectored nasal anthrax vaccine; and a skin patch anthrax vaccine. In addition, the NIAID is supporting development of a nasal vaccine delivery vehicle that is suitable for delivering a number of different types of bacterial and viral antigens.

### Item

***Nontuberculous Mycobacteria (NTM)*** - Mycobacteria are environmental organisms found in both water and soil that can cause significant respiratory damage. The Committee is aware of the increasing incidence of nontuberculous mycobacteria (NTM) pulmonary infections in women, particularly involving rapidly growing mycobacteria, an inherently resistant subspecies. The Committee encourages NIAID to advance diagnostic and treatment protocols for patients suffering from NTM diseases. Further, the Committee recommends additional focus on research leading to a better understanding of NTM by establishment of an inter-institute coordinating committee to facilitate cooperation between NIAID, NHLBI, and other institutes. (p. 78-79)

### Action taken or to be taken

The NIAID continues to pursue research towards the improvement of the detection, diagnosis and treatment of patients suffering from nontuberculous mycobacteria (NTM) infection.

In 2005, NIAID researchers initiated the creation of the Nontuberculous Mycobacteria Consortium (NTMC) in an effort to advance diagnostic and treatment protocols for NTM and to promote collaborative efforts to increase the understanding of NTM. The Consortium is a nationwide network of research centers that are working to identify and understand the epidemiology, pathophysiology, diagnosis, therapy, and outcomes of NTM. The network includes seven centers with research or clinical programs focused on NTM and two centers with programs in NTM related to their focal area of cystic fibrosis. These two centers link to a network of other clinical cystic fibrosis centers in North Carolina and New York. The NTMC is currently developing a clinical protocol to compare the efficacy and toxicity of several treatment regimens in patients with pulmonary mycobacterium avium complex infection.

NIAID researchers have long standing collaborations across the NIH with colleagues who are also investigating NTM. A four-year, NIAID collaboration with the National Heart, Lung, and Blood Institute's (NHLBI) Pulmonary Branch is examining cystic fibrosis genetics in patients with NTM infections. This collaboration has resulted in a major study on the frequency of certain gene mutations in patients with pulmonary NTM disease. This and other collaborations will be enhanced by the addition of a pulmonologist at the NIAID who will serve as a liaison to NHLBI and the NIH Critical Care Medicine Department on pulmonary diseases.

Studies planned for the future include a multi-year study to identify and characterize the clinical, microbiologic, immunological, and genetic aspects of NTM infection; a protocol to study the use of immune adjuvants in patients with NTM infection, and a study of the use of mefloquine for treating pulmonary *Mycobacteria abscessus* infection.

### Item

**Primary immunodeficiency diseases** – NIAID is the lead agency for research into this class of diseases that is known to afflict about 500,000 Americans and may affect an equal amount that have not yet been diagnosed. To address the complex research needs of this group of about 140 separate diseases, the NIAID has created a research consortium comprised of the leading experts in primary immunodeficiency diseases. The Committee requests that NIAID report by February 28, 2006 on the management of the consortium, as well as its plans for future research in the field. (p. 76)

### Action taken or to be taken

The NIAID is deeply committed to supporting research efforts aimed at understanding the causes and immune mechanisms leading to the development of primary immunodeficiency diseases. To this end, in FY 2003 the NIAID, with support from the National Institute of Child Health and Human Development, established the U.S. Immunodeficiency Network (USIDNET), an international coalition of the most prominent researchers in the field of primary immunodeficiency diseases. Since its inception, the consortium has helped to prioritize and coordinate research directions in the area of primary immunodeficiency diseases and develop new resources for the study of these comparatively rare disorders. The mission of USIDNET is to form a cooperative network of primary immunodeficiency disease investigators; establish an award mechanism for peer-reviewed small, short-term projects for innovative studies; provide leadership and mentoring for clinical and basic investigators new to the field; enhance the primary immunodeficiency diseases registries currently supported by the NIH; and establish a repository for samples from individuals affected by primary immunodeficiency diseases.

The USIDNET is governed by a ten-member Steering Committee. The Steering Committee enhances the coordination of primary immunodeficiency diseases research effort by identifying research gaps and opportunities, mechanisms by which to foster more research on primary immunodeficiency diseases, and methods to encourage new investigators to enter this field. As of October 2005, 45 full applications have been submitted to the USIDNET and, of these, 16 grant awards have been made.

The USIDNET established a repository for samples from individuals affected by primary immunodeficiency diseases as well as a related patient data registry; diseases currently included in the repository are X-linked Agammaglobulinemia, Severe Combined Immunodeficiency Disease, Common Variable Immunodeficiency, Wiskott-Aldrich Syndrome, X-Linked Hyper IgM Syndrome, Chronic Granulomatous Disease, DiGeorge Anomaly, and Leukocyte Adhesion Defect. Approximately 1,500 patients with these disorders have been registered to date. Each disorder has a Scientific Advisory Subcommittee that provides oversight and has the authority to approve the use of registry information for scientifically meritorious reasons.

### Item

***Psoriasis*** - The Committee encourages NIAID to support research on psoriasis, a chronic, immune-related disease that affects between 5.8 and 7.5 million Americans. Safe and effective treatments for women of child-bearing age and for children are particularly lacking, and new research indicates mothers with psoriasis have a 50% increased risk of bearing a child with autism. The Committee asks NIAID to investigate the possible causes of this troubling finding, as well as related research on causes of and treatments for psoriasis. (p. 76)

### Action taken or to be taken

The NIAID supports the Immune Tolerance Network (ITN) to evaluate novel, tolerance-inducing therapies in autoimmune diseases, asthma, and allergic diseases; and to prevent rejection of transplanted organs, tissues, and cells. Through the ITN, the NIAID has recently initiated enrollment of patients in a clinical trial, "Treatment of Psoriatic Arthritis (PSa) with hOKT3λ1 (Ala-Ala)." The primary clinical objective of the study is to determine the safety and clinical efficacy of hOKT3γ1 (Ala-Ala) in combination with methotrexate or azathioprine in the treatment of psoriatic arthritis.

In addition, the NIAID supports a cooperative research group, "HLA Region Genetics in Immune-Mediated Diseases," to define the association between human leukocyte antigen region genes or genetic markers and immune-mediated diseases such as psoriasis.

In FY 2007, the NIAID plans to re-compete the Immune Tolerance Network. Autoimmune diseases, including psoriasis, will remain an important component of NIAID's research portfolio. The Institute will continue to support research into psoriasis, its possible causes and complications, and potential treatment and prevention strategies.

NIAID research focuses on the immunology of psoriasis and does not include investigations into the possible links between maternal psoriasis and autism. The National Institute of Mental Health, another component of the NIH, supports research into the association of pregnancy and birth complications with autism and other severe mental disorders, which could provide evidence of associations between maternal health during pregnancy and autism. The autism research matrix produced by the Interagency Autism Coordinating Committee in 2004 calls for research that will identify environmental factors, including maternal health, contributing to autism. The NIH will continue to pursue such research.

### Item

***Transplantation Research*** –The Committee is aware that while one-year organ transplantation survival has improved remarkably over the last fifteen years, there has been little success in reversing the decline in long-term graft and patient survival. The Committee suggests that NIAID convene an expert conference, in collaboration with NIDDK and NHLBI, to develop a five-year Transplantation Research Action Plan identifying the most urgently needed research to facilitate an increase in the success of organ transplantation. The expert conference should also focus on promising new technologies in pre-transplant organ care and post-transplant patient therapies. The Committee also suggests the initiation of a cohort study to assess the health outcomes of living donors, not only for the period immediately following the donation, but for the quality of life implications in the decades post-donation. (p. 75-76)

### Action taken or to be taken

The NIAID continues to pursue research initiatives to advance scientific understanding of the immunology of transplantation, to understand the critical role of immune tolerance in organ graft survival, and to improve long-term outcomes for transplant patients.

For example, current immunosuppressive medications necessary for the survival of transplanted organs or tissues can often result in systemic hypertension, diabetes mellitus, kidney problems, and malignancy in solid organ transplant recipients. Through initiatives such as the NIAID-supported Immune Tolerance Network (ITN), researchers are evaluating novel, tolerance-induction strategies and how the induction of tolerance can prevent rejection of transplanted organs, tissues, and cells.

In September 2005, the NIAID convened a panel of experts in transplant surgery and immunology to review current research in the field of transplantation and to develop recommendations for future research needed to improve graft acceptance and post-transplant quality of life. The recommendations of the expert panel will be published in a five-year action plan, which is anticipated to be completed in late spring 2006.

The NIAID also supports basic and clinical research in organ transplantation. For example, the Clinical Trials in Organ Transplant Consortium, initiated in FY 2004, is a 5-year program to define a scientific agenda for clinical research in organ transplantation and implement collaborative, multi-center clinical trials with associated basic studies in the immune system mechanisms involved in organ transplantation. This initiative is co-sponsored by the NIDDK and the National Heart, Lung and Blood Institute.

In FY 2006, the Institute will support a program, Outcomes of Live Organ Donors, which conduct epidemiologic research on the outcomes and health needs of live organ donors.

### Item

***Tuberculosis*** - The WHO estimates that nearly 1 billion people will become infected with TB, 200 million will become sick, and 70 million will die worldwide between now and 2020 of this disease. The Committee is pleased with NIAID's efforts to develop an effective TB vaccine. The Committee encourages the Institute to continue its TB vaccine development and to strengthen efforts to develop new drugs to treat TB. (p. 76)

### Action taken or to be taken

The NIAID supports research on *Mycobacterium tuberculosis* (Mtb), the causative agent of TB, and how the body responds to this pathogen, and conducts clinical trials to translate this research into improved health care interventions. The focus of this research is to develop drugs that will shorten and simplify TB therapy and to develop vaccines that will protect against all forms of TB.



The currently-available TB vaccine provides some protection against complications of TB in children but does not reliably prevent the development of contagious pulmonary TB in adults. Studies to improve upon this vaccine are being conducted at the NIAID's Vaccine Treatment and Evaluation Unit (VTEU) in St. Louis, Missouri. The VTEU will conduct a Phase I trial of primary and secondary BCG vaccination in healthy adults.

A key component of the NIAID's successful contribution to TB vaccine development is its TB Research Materials and Vaccine Testing contract. This contract provides exploratory and preclinical evaluation of promising new TB vaccine candidates in animal models, providing an interface between basic and applied science. Over 150 vaccine candidates have been tested under this contract; one recently entered human trials.

NIAID-supported scientists have also developed many promising new anti-TB drug candidates. The NIAID partnered with the Global Alliance for TB Drug Development for the advanced development of a novel antibiotic, PA-824. This drug, which may shorten the time needed to treat both drug-sensitive and multi-drug-resistant TB, has begun testing in humans. In addition, the NIAID's Challenge Grant Programs have supported the pre-clinical development of SQ109, a derivative of the known anti-TB drug ethambutol. SQ109 may enter Phase I human clinical trials in 2006.

The NIAID-supported Tuberculosis Research Unit (TBRU) recently completed data analysis from a Phase II study in Uganda of a therapeutic, Proleukin<sup>®</sup>, in non-HIV-infected adults with pulmonary TB. The TBRU is currently enrolling subjects for a number of additional clinical trials to evaluate improved TB drug regimens.

The Institute's Tuberculosis Animal Research and Gene Evaluation Taskforce contract supports research to evaluate, in animal models, the biological function of Mtb RNA and proteins for their utility as drug, vaccine or diagnostic targets. A collection of mutant Mtb strains that were developed under the contract are provided to the research community upon request; 81 mutants were distributed through FY 2005.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

Item

***Asthma*** - The Committee is very pleased with NIAID's leadership regarding asthma research and management. The Committee urges NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also urges the NIAID to collaborate more aggressively with voluntary health organizations to support asthma prevention, treatment, and research activities. Additionally, recent studies suggest that a variety of viral and bacterial agents, including agents used for immunization may play a role in the development of asthma. The Committee urges the Institute to expand research into the role that infections and vaccines play in the development of asthma. (p.117)

Action taken or to be taken

Please refer to page 35 of this document for NIAID's response to this significant item regarding asthma.

Item

***Atopic Dermatitis*** - The Committee was pleased to learn about NIAID research efforts related to atopic dermatitis undertaken through projects such as the Immune Tolerance Network and the Atopic Dermatitis and Vaccinia Immunization Network. Last year, the Committee encouraged NIAID to complement these efforts by working with NIAMS to spearhead a multidisciplinary, multi-institute initiative to encourage investigator-initiated research projects on AD as it relates to smallpox vaccination as well as the progression to asthma and other allergic diseases. The Committee requests an update in the FY 2007 appropriations justification on efforts that have been made to foster investigator-initiated research in this area. (p. 117)

Action taken or to be taken

Atopic dermatitis is one of the most common skin diseases and is frequently associated with other allergic diseases and asthma. The NIAID and other NIH Institutes and Centers support a broad range of investigator-initiated research on skin and skin diseases, including atopic dermatitis.

For example, the NIAID supports an investigator-initiated mechanistic study associated with a clinical trial to determine if the non-steroidal immunomodulatory drug pimecrolimus will prevent progression to asthma in young children with atopic dermatitis.

In addition, the NIAID-supported Immune Tolerance Network (ITN) is developing clinical trials to determine if oral administration of cat, grass, and house dust mite allergens will prevent the development of allergic diseases and asthma in children with atopic dermatitis and food allergy. The ITN is also developing a trial to investigate whether feeding a peanut-containing snack to young children at risk of developing peanut allergy will prevent development of this allergy; all patients enrolled in this trial will have atopic dermatitis or allergy to eggs.

Persons with atopic dermatitis are at risk of a severe skin rash, called eczema vaccinatum, in response to the currently-available Dryvax<sup>®</sup> smallpox vaccine. In FY 2004, the NIAID, with expert advice and support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), established the Atopic Dermatitis and Vaccinia Immunization Network to develop short- and long-term approaches to reduce the incidence and severity of eczema vaccinatum and to protect individuals with atopic dermatitis from the adverse consequences of smallpox vaccine exposure. In addition, the NIAID supports research to develop a vaccine with fewer side effects. In FY 2004, the NIAID continued its support of advanced development and manufacture of modified vaccinia Ankara (MVA) vaccine for smallpox by awarding two new contracts. These contracts specify that contractors conduct Phase I and II trials to determine the safety and immunogenicity of MVA in participants with diagnosed atopic disorders.

#### Item

***Autoimmune Diseases*** - The Committee applauds the formation of two cooperative research groups, the Autoimmune Centers of Excellence and the Cooperative Study Group for Autoimmune Disease Prevention, which support multidisciplinary research to understand and treat autoimmune diseases. The Committee urges NIAID to continue its support for the prevention centers and to encourage the participation of the wider research community in this initiative. (p. 117)

#### Action taken or to be taken

The NIAID continues to support and foster multidisciplinary research to better understand and treat autoimmune diseases. The NIAID, along with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIH Office of Research on Women's Health (ORWH), supports the Autoimmunity Centers of Excellence to conduct collaborative basic and clinical research on autoimmune diseases, including clinical trials and mechanistic studies of immunomodulatory therapies.

The NIAID also supports the Autoimmune Diseases Prevention Centers, which conduct research on the development of new targets and approaches to prevent autoimmune diseases and evaluate these approaches in pilot and clinical studies. In FY 2005, the Prevention Centers supported 22 pilot projects that may lead to the development of novel targets for disease prevention or assays for biomarkers of disease progression. The Prevention Centers are co-sponsored by NIDDK, the National Institute of Child Health

and Human Development (NICHD), ORWH, and the Juvenile Diabetes Research Foundation International (JDRF). The Institute will renew the Autoimmune Diseases Prevention Centers in FY 2006.

In addition, the NIAID supports other collaborations and consortia that conduct research into autoimmune diseases. The Immune Tolerance Network, co-sponsored by the NIDDK and JDRF, evaluates novel, tolerance-induction strategies and their mechanisms of action in autoimmune diseases. The Multiple Autoimmune Diseases Genetics Consortium is a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. The repository provides material to qualified researchers for use in research to identify genes involved in autoimmune diseases.

#### Item

***Bioterrorism*** - Respiratory pathogens that cause life-threatening pneumonia are commonly proposed agents of bioterrorism. The following are associated with acute pneumonia/lung injury: anthrax, smallpox, plague, and tularemia. The Committee encourages further research on the mechanisms of pneumonia by these respiratory pathogens and the development of new therapeutic interventions to reduce injury and death. (p. 117)

#### Action taken or to be taken

Please refer to page 36 of this document for NIAID's response to this significant item regarding bioterrorism.

#### Item

***Coinfection Research*** – The Committee is concerned that there is growing evidence of liver toxicity of highly active antiretroviral therapy (HAART) in those with chronic viral hepatitis and in particular those with decompensated liver disease awaiting liver transplantation. There also appears to be an emerging problem of liver cancer in co-infected patients (HCV and/or HBV with HIV). The Committee encourages NIAID to initiate significant research initiatives in both of these areas. (p. 117)

#### Action taken or to be taken

Please refer to page 37 of this document for NIAID's response to this significant item regarding coinfection research.

### Item

***Hemophilia*** – The Committee urges NIAID to continue its efforts to develop and advance research initiatives for addressing HCV within the bleeding disorders community. The Committee understands that HCV continues to have a devastating impact on this community, with nearly half of all persons with hemophilia having contracted HCV from blood clotting factor products. (p. 118)

### Action taken or to be taken

Please refer to page 41 of this document for NIAID's response to this significant item regarding hemophilia.

### Item

***Hepatitis*** – The Committee continues to be concerned about the prevalence of hepatitis and urges NIAID to work with public health organizations to promote liver wellness, education, and prevention of hepatitis. (p. 118)

### Action to be taken

The NIAID remains committed to the reduction of the burden of disease caused by hepatitis. The NIAID continues to promote awareness of hepatitis by organizing and participating in conferences on hepatitis and by providing easily accessible information on hepatitis.

The NIAID has supported two NIH Consensus Development Conferences focused on the management of hepatitis C disease. Held in 1997 and 2002, the purpose of these conferences was to evaluate the available scientific information on hepatitis and to develop a consensus statement that advances the understanding of hepatitis among health professionals and the public. In addition, NIAID investigators and program staff frequently participate in scientific workshops and meetings to discuss critical issues in basic hepatitis research and disease management. For example, NIAID extramural program staff recently met with representatives of the National Hemophilia Foundation to discuss ways in which the Foundation's constituency, in which there is a prevalence of infection with hepatitis C virus, might participate in NIAID-supported clinical trials.

NIAID also provides information on publications, research breakthroughs and disease management resources on the Institute's web site. This information includes links to resources on hepatitis disease management available through NIAID and other NIH Institutes. For example, information on hepatitis which is available through the National Institute of Diabetes and Digestive and Kidney Diseases is accessible through the NIAID web site.

The NIAID will continue to promote prevention of hepatitis through these efforts and through continued support of investigator-initiated research on hepatitis; applied research and development efforts through partnerships with academic and corporate scientists; clinical trials and ancillary research using NIAID-supported cooperative agreements and contracts.

Item

***Hepatitis C Vaccine Development*** - The Committee is encouraged to learn that a small hepatitis C vaccine human trial has been successfully completed. The Committee urges NIAID to implement the results of the recent workshop that was held to discuss and evaluate efforts toward development of HCV vaccines with the goal of spurring their development and testing. The Committee also urges NIAID to proceed with phase two of the human clinical trial as soon as it is scientifically practicable. Additionally, NIAID is urged to foster the development of an in vitro culture system for HCV as well as new animal models for basic research and for adequately testing vaccine candidates and antiviral drugs. (p. 118)

Action to be taken

Please refer to page 41 of this document for NIAID's response regarding hepatitis C vaccine development.

Item

***Infectious Disease Research***- The Committee believes that, with regard to both biodefense and public health, the development by NIAID of multi-pathogen identification arrays that can be used to identify infectious agents through epidemiological outbreak surveillance is critically important. The use of whole genome expression, all exon transcription analysis and whole genome SNP analysis studies to identify and understand host biomarkers that may identify the type, severity and likely response to therapeutics of infectious agents hold great promise for the most immediate results. The Committee encourages NIAID to pursue these lines of inquiry. (p. 119)

Action taken or to be taken

Please refer to page 40 of this document for NIAID's response to this significant item regarding genetic tools for infectious disease research.

Item

***Immune Surveillance Cell Proteomes***- The Committee recognizes the potential threat to national security posed by terror attacks involving biological, chemical, nuclear, and

radiological weapons. One of the challenges facing public health officials responding to such an attack is their limited ability to diagnose individuals who have been exposed to these agents and do not show illness. Recent disease outbreaks—such as SARS in Asia and Canada, avian influenza in East Asia, and Ebola and Marburg virus in Africa—demonstrate that the speed of diagnosis and implementation of public health measures can mean the difference between an isolated outbreak and a global pandemic. Therefore, the Committee strongly supports research on immune surveillance cell proteomes (e.g. monocytes, neutrophils, dendritic cells, B cells and NK cells) and their response to chemical and biological pathogens. The Committee also urges the NIAID to fund the development of a searchable electronic database for biological proteomes, the proteomics of immune surveillance cell interaction with pathogens (biological and chemical), and proteins derived from the immune surveillance cells themselves, as well as their interaction with pathogens. (p. 118)

Action taken or to be taken

Please refer to page 38 of this document for NIAID's response to this significant item regarding detection of disease and bioterror agents.

Item

***Immune Tolerance*** – The Committee is encouraged by the progress of the Immune Tolerance Network in launching clinical trials of protocols to induce immune tolerance in patients with Type 1 diabetes. These trials have the potential to prevent the recurrence of autoimmunity in patients with long-standing diabetes who have undergone islet transplantation and halt the autoimmune attack in recently diagnosed Type 1 diabetes patients. The Committee encourages the NIAID to continue its strong support of this clinical network and to expand its clinical studies promoting the translation of promising basic discoveries. (p. 118)

Action taken or to be taken

The NIAID recognizes that advances in immune tolerance induction will provide valuable therapeutic strategies while eliminating the need for life-long, systemic immunosuppressive therapy with its deleterious side effects. Thus, the NIAID supports a broad range of basic, translational, and clinical research on the underlying mechanisms of immune tolerance and the evaluation of tolerance induction strategies in animal models and clinical trials.

An example of the Institute's research efforts in this area is the Immune Tolerance Network (ITN), an international, collaborative research consortium co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International. Researchers of the ITN evaluate novel tolerance induction strategies and their mechanisms of action in the treatment of autoimmune diseases, including Type 1 diabetes.

In addition, the NIAID supports the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) to develop novel approaches to tolerance induction and to evaluate the safety and efficacy of tolerogenic regimens in non-human primate models of kidney and islet transplantation. These models may lead to discoveries that help treat Type 1 diabetes.

In FY 2006, the NIAID will renew the Innovative Grants on Immune Tolerance program. In FY 2007, NIAID will renew the NHPCSG program and re-compete the ITN. Through continuing support of these programs, the NIAID will maintain its commitment to basic research on immune tolerance and the translational and clinical research that bring basic discoveries to the patient care arena.

#### Item

***Inflammatory Bowel Disease*** –The Committee continues to note with interest a scientific research agenda for Crohn’s disease and ulcerative colitis (collectively known as inflammatory bowel disease) titled “Challenges in Inflammatory Bowel Disease (IBD).” This report identifies strong linkages between the functions of the immune system and IBD. The Committee encourages the Institute to expand its research partnerships with the IBD community in FY 2006 and increase funding for research focused on: (1) the immunology of IBD and (2) the interaction of genetics and environmental factors in the development of the disease. (p. 119)

#### Action taken or to be taken

Please refer to page 42 of this document for NIAID’s response to this significant item regarding inflammatory bowel disease.

#### Item

***Lupus*** - The Committee recognizes that Lupus is a serious, complex, debilitating chronic autoimmune disease that causes inflammation and tissue damage to virtually any organ system in the body and impacts between 1.5 and 2 million individuals. The Committee strongly urges the National Institute of Allergy and Infectious Diseases to expand and intensify research and related activities with respect to Lupus. (p. 119)

#### Action taken or to be taken

Through the Immune Tolerance Network (ITN), the NIAID is currently evaluating a new potential treatment for lupus. The ITN is conducting a Phase II clinical trial of a two-drug combination consisting of a compound that may turn off the body’s inappropriate autoimmune response and a second drug known to have chemotherapeutic effects. The ITN also conducts other studies to evaluate novel, tolerance-inducing therapies in autoimmune diseases. The ITN program will be re-competed in FY 2007.



The nine Autoimmunity Centers of Excellence (ACE), which are co-sponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the NIH Office of Research on Women's Health (ORWH), conduct collaborative basic and clinical research on autoimmune diseases. Examples of ACEs-supported clinical trials include a Phase I/II clinical trial of anti-CD20 for treatment for lupus and a Phase I clinical trial of anti-TNF for treatment of lupus nephritis that is in development.

The NIAID, along with the NIDDK, the National Institute of Child Health and Human Development, the ORWH, and the Juvenile Diabetes Research Foundation International (JDRF), supports the Autoimmune Disease Prevention Centers to conduct research on the development of new targets and approaches to prevent autoimmune diseases, including lupus. This program will be renewed in FY 2006.

The NIAID also supports to the Multiple Autoimmune Diseases Genetics Consortium, a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more autoimmune diseases. This repository provides specimens and data to scientists who identify genes involved in autoimmune diseases.

In FY 2007, the NIAID plans to support a new initiative, "Allogeneic Hematopoietic Stem Cell Transplantation for Autoimmune Diseases," to evaluate the effectiveness of transplantation of hematopoietic stem cells – which can become blood and immune cells- to halt progression or even cure patients with autoimmune diseases, such as lupus. The initiative will also provide valuable data on the biological mechanisms that lead to autoimmune diseases.

The NIAID coordinates its lupus research activities with other NIH Institutes and Centers and with other Federal agencies through participation in the Lupus Federal Working Group and the Autoimmune Diseases Coordinating Committee (ADCC). The NIAID chairs the ADCC, which submitted its most recent report to Congress in March 2005.

#### Item

***Psoriasis*** - Psoriasis is a common, chronic, immune-mediated skin disease. The Committee urges NIAID to support additional research on psoriasis and psoriatic arthritis pathogenesis, research to develop diagnostic tests for psoriatic arthritis and clinical research to identify new safe and effective therapies for these diseases. (p. 119)

#### Action taken or to be taken

Please refer to page 48 of this document for NIAID's response to this significant item regarding psoriasis.

Item

***Tuberculosis*** - The World Health Organization (WHO) estimates that nearly one-third of the world's population will become infected with tuberculosis (TB); and by 2020, 70 million people will die worldwide of this disease. The Committee is pleased with NIAID's efforts to develop an effective TB vaccine. The Committee encourages the Institute to continue its TB vaccine development work and expand efforts to develop new drugs, including multi-drug resistant drugs to treat TB. (p. 120)

Action taken or to be taken

Please refer to page 50 of this document for NIAID's response to this significant item regarding tuberculosis.