Biennial Report on the Rare Diseases Research Activities at the National Institutes of Health

FY 2006

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Office of Rare Diseases

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Table of Contents

Executive Summary 5

Office of Rare Diseases (ORD) 7

National Institute on Aging (NIA) 26

National Institute on Alcohol Abuse and Alcoholism (NIAAA) 29

National Institute of Allergy and Infectious Diseases (NIAID) 36

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) 63

National Institute of Biomedical Imaging and Bioengineering (NIBIB) 78

National Cancer Institute (NCI) 80

National Institute of Child Health and Human Development (NICHD) 115

National Institute on Deafness and Other Communication Disorders (NIDCD) 120

National Institute of Dental and Craniofacial Research (NIDCR) 126

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) 138

National Institute on Drug Abuse (NIDA) 144

National Institute of Environmental Health Sciences (NIEHS) 159

National Eye Institute (NEI) 164

National Institute of General Medical Sciences (NIGMS) 166

National Heart, Lung, and Blood Institute (NHLBI) 169

National Human Genome Research Institute (NHGRI) 222

National Institute of Mental Health (NIMH) 227

National Institute of Neurological Disorders and Stroke (NINDS) 232

National Institute of Nursing Research (NINR) 239

National Center for Research Resources (NCRR).....240

National Library of Medicine (NLM).....245

National Center for Complementary and Alternative Medicine (NCCAM) 253

Office of Research on Women's Health (ORWH) 257

Office of Technology Transfer (OTT).....258

Office of Portfolio Analysis and Strategic Initiatives (OPASI)……..261

Acronyms…….....262

Index....…….270

Executive Summary[1]

The Rare Diseases Act of 2002, P.L. 107-280, instructs the Director of the Office of Rare Diseases, National Institutes of Health (NIH), to prepare the NIH Director's biennial report to Congress on rare disease research activities and future plans. The biennial report presents the contributions and research advances for fiscal year (FY) 2006 of the extramural and intramural research programs and of the Office of Rare Diseases (ORD) and other research offices.

Responses from the individual Institutes and Centers (ICs) provide an overview of ongoing rare diseases research activities, recent scientific advances in rare diseases research, new or planned rare diseases research initiatives, and rare disease-related activities such as scientific workshops and symposia, public and professional education and training, information dissemination, and other rare diseases research-related activities. The advances presented are the direct result of years of rare diseases research sponsored by NIH in the past. Patients with rare diseases continue to benefit from the treatment applications realized by the emphasis NIH places on both basic and clinical intramural and extramural research programs. Many of the rare diseases activities conducted at the NIH Clinical Center have been reported by the ICs in their respective sections of the report. For example, the Bench-to-Bedside research program at the Clinical Center was reported by the Office of Rare Diseases.

This report uses the definition of rare diseases as set forth in the Amendments to the Orphan Drug Act as a disease or condition with a prevalence of fewer than 200,000 people in the United States. Prevalence refers to the number of individuals alive with the disease within a geographic parameter. There are approximately 7,000 known rare diseases in the United States. Rare diseases are thought to affect approximately 25 million people in the United States. (Rare Diseases Act of 2002, Section 2, Findings.)

Activities undertaken in FY 2006 by the NIH ICs and the ORD included:

- Support of the Rare Diseases Clinical Research Network that includes 10 consortia and a data and technology coordination center;
- Support by the ORD of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Biliary Atresia Research Consortium, which contains ten pediatric liver disease centers;
- Continuation of the Collaboration, Education, Genetic Test Translation pilot project for rare diseases to make available to patients genetic tests through a network of Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories.
- Support of the ORD/National Human Genome Research Institute (NHGRI) rare diseases intramural research program that promotes fellowship training in the areas of clinical and biochemical genetics focusing on rare diseases; fosters protocol-based initiatives into rare

[1] In the text of this report, common diseases may be included when particular subpopulations are rare or treatments are under development that are not expected to be financially recoverable.

diseases not currently investigated in the intramural program; assists in the investigation of select, unique disorders of unknown etiology; and provides overall research support for diagnostics including genetic testing and therapeutics of rare diseases;
- Support of Bench-to-Bedside Grants in the NIH Clinical Center with matching support from the ICs;
- Cofunding by the ORD and NIH ICs of 71 scientific conferences in FY 2006 and to date in FY 2007, 55 scientific conferences.

The ORD scientific conferences program contributes to the establishment of research priorities; development of program announcements; establishment of diagnostic and monitoring criteria; initiation of the development of animal models; support of the development of patient and tissue registries, research protocols, and collaborative research arrangements; and dissemination of workshop results through publications and other means to encourage new collaborations.

- Support for the development of an inventory of human biospecimen repositories to facilitate the access by researchers to human biospecimens The inventory will be publicly accessible and Web based.

OFFICE OF RARE DISEASES (ORD)

Overview

The goals of ORD are to stimulate and coordinate research on rare diseases and to support research to respond to the needs of patients who have one of the approximately 7,000 rare diseases known today. ORD collaborates with the NIH ICs to stimulate rare diseases research activities, fosters collaboration with other entities nationally and internationally, and supported in FY 2006 the following activities:

- An extramural research program that includes a network of clinical research centers on rare diseases and the training of rare diseases researchers;
- An intramural research program for patients with specific rare conditions and programs to stimulate clinical research on rare diseases, including the training of researchers interested in rare diseases and in clinical and biochemical genetics;
- A scientific conferences program in response to scientific opportunities or to stimulate research where research progress may be slow or where little research exists;
- An information center to supply useful rare and genetic diseases information to the public, researchers, and health care providers;
- Activities to assist national patient advocacy groups in becoming research partners with the NIH by developing better understanding of the breadth and inclusiveness of NIH research programs;
- CETT, the ORD Collaboration, Education and Genetic Test Translation Pilot Program, translates genetic tests for rare diseases from the research laboratory to the clinic thereby making the tests available to the public;
- Development of a Web-based, publicly accessible inventory of repositories of human bio-specimens for research on rare and common diseases.

Scientific Advances

Extramural Research Program

- **The Rare Diseases Clinical Research Network (RDCRN)**

  Since FY 2003, ORD has collaborated with NIH ICs including National Center for Research Resources (NCRR), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Child Health and Human Development (NICHD), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and National Institute of Neurological Disorders and Stroke (NINDS) to support the Rare Diseases Clinical Research Network. The network consists of 10 consortia each of which focuses on a group of rare diseases. In addition, the network includes a data and technology coordinating center that serves all consortia.

At this time, 28 clinical protocols have been approved and 20 more are under development. The collaborating patient advocacy groups through a coordinating coalition participate on the network's steering committee. The network consists of more than 70 sites and more than 30 patient advocacy groups and conducts research on approximately 50 rare diseases. The vast distribution of research locations across the United States makes investigational studies and treatments more accessible to patients with rare diseases. The network, through the data and technology coordinating center, collects clinical information to develop biomarkers and new approaches to diagnosis, treatment, and prevention of rare diseases; provides training of new clinical research investigators; and supports demonstration projects in the following rare disease groups:

Table 1: The Rare Diseases Clinical Research Network, Diseases under Study.

Consortium	Principal Investigator	Primary Performance Site	Diseases
Urea Cycle Disorders Consortium	Batshaw, Mark L., M.D.	Children's National Medical Center, Washington, DC	• N-Acetylglutamate Synthase (NAGS) Deficiency • Carbamyl Phosphate Synthetase (CPS) Deficiency • Ornithine Transcarbamylase (OTC) Deficiency • Argininosuccinate Synthetase Deficiency (Citrullinemia I) • Citrin Deficiency (Citrullinemia II) • Argininosuccinate Lyase Deficiency (Argininosuccinic Aciduria) • Arginase Deficiency (Hyperargininemia) • Ornithine Translocase Deficiency (HHH) Syndrome
Angelman, Rett, and Prader-Willi Syndromes Consortium	Beaudet, Arthur L., M.D.	Baylor College of Medicine, Houston, TX	• Angelman Syndrome • Rett Syndrome • Prader-Willi Syndrome
CINCH - Consortium for Clinical Investigation of Neurological Channelopathies	Griggs, Robert C., M.D.	University of Rochester School of Medicine, Rochester, NY	• Andersen-Tawil Syndrome (Periodic paralysis) • Episodic Ataxias • Nondystrophic Myotonic Disorders
Bone Marrow Failure Disease Consortium	Maciejewski, Jaroslav P., M.D., Ph.D.	Cleveland Clinic Foundation, Cleveland, OH	• Aplastic Anemia • Myelodysplastic Syndromes • Paroxysmal Nocturnal Hemoglobinuria (PNH) • Large Granular Lymphocyte (LGL) Leukemia • Single Lineage Cytopenias: Pure Red Cell Aplasia, Amegakaryocytic

			Thrombocytopenic Purpura, Autoimmune Neutropenia
CLiC - Cholestatic Liver Disease Consortium	Sokol, Ronald J., M.D.	The Children's Hospital, Denver, CO	• PFIC (Progressive Familial Intrahepatic Cholestasis) • Bile Acid Synthesis Defects • Alagille Syndrome • Alpha One Antitrypsin Deficiency • Mitochondrial Hepatopathies
Vasculitis Clinical Research Consortium	Merkel, Peter A., M.D., Ph.D.	Boston University Medical Center, Boston, MA	• Wegener's Granulomatosis (WG) • Microscopic Polyangiitis (MPA) • Churg-Strauss Syndrome (CSS) • Polyarteritis Nodosa (PAN) • Takayasu's Arteritis (TAK) • Giant Cell (Temporal) Arteritis (GCA)
Rare Genetic Steroid Disorders Consortium	New, Maria I., M.D.	The Mount Sinai School of Medicine, New York, NY	• Congenital Adrenal Hyperplasia • Androgen Receptor Defects • Apparent Mineralocorticoid Excess (Low Renin Hypertension)
Rare Thrombotic Diseases Consortium	Ortel, Thomas L, M.D., Ph.D.	Duke University Medical Center Durham, NC	• Antiphospholipid Antibody Syndromes (APS) • Heparin-induced Thrombocytopenia (HIT) • Paroxysmal Nocturnal Hemoglobinuria (PNH) • Catastrophic Antiphospholipid Antibody Syndrome (Thrombotic Storm) • Thrombotic Thrombocytopenic Purpura (TTP)
Rare Lung Diseases Consortium	Trapnell, Bruce C., M.D.	Cincinnati Children's Hospital Medical Center, Cincinnati, OH	• Hereditary Interstitial Lung Disease (hILD) • Lymphangioleiomyomatosis (LAM) • Pulmonary Alveolar Proteinosis (PAP) • Alpha-1 Antitrypsin Deficiency (Alpha-1)
Genetic Diseases of Mucociliary Clearance Consortium	Knowles, Michael, R., M.D.	University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC	• Primary Ciliary Dyskinesia (PCD) • Cystic Fibrosis • Pseudohypoaldosteronism (PHA)
Rare Diseases Data and Technology	Krischer, Jeffrey P., Ph.D.	University of South Florida	

Coordinating Center		Tampa, FL	

- **Diagnostic Genetic Test Translation from the Research Laboratory to the Clinic**

  There are approximately 7,000 rare diseases, the majority of which are genetic disorders, thereby making genetic testing an essential part of the diagnosis and treatment continuum. Currently, genetic tests for rare diseases are available for only a small number of diseases. A significant number of potential genetic tests remain within research laboratories or a laboratory overseas. Developing and marketing tests for rare disorders is not considered profitable, given the small consumer base per test, so there are few incentives for translating research findings into clinical tests available to the public.

  People affected by rare inherited diseases need the reliable information that comes through quality genetic testing. ORD broadened a successful, limited NIH intramural genetic test translation project into the Collaboration, Education and Genetic Test Translation (CETT) for Rare Genetic Diseases pilot program to include genetic test translation to the clinic, thereby made available to the public. The CETT Program helps bring new tests to patients while encouraging clinical laboratory and research collaborations and stimulating dialogue with patient advocacy groups. Program goals include supporting the electronic collection of genetic and clinical data for use in public databases. This broader access is intended to improve the interpretation of the clinical testing as well as better the understanding of the rare disease.

  The CETT Program requires applicants to have a data-sharing plan for storing mutation and clinical data in public repositories, thus creating opportunities to identify genotype/phenotype associations that can lead to targeted treatments. The CETT Program partners with the National Center for Biotechnology Information (NCBI), the bioinformatics division of the National Library of Medicine, to meet emerging medical informatics needs by associating genomic data with phenotypes related to disease pathology. NCBI maintains and distributes public databases, creates analytic tools, and coordinates efforts to gather genomic information to aid in the understanding of fundamental molecular and genetic processes affecting human health. NCBI works directly with the CETT Program participants to create standard electronic formats and terminology so that genetic and clinical data from many laboratories can be compared, maximizing the value of the data generated by the CETT-sponsored genetic tests.

  The first applications were accepted in February/March 2006 and the first review board evaluation took place in April. Twenty-one tests have been reviewed, 19 have been approved, with resubmission of the remaining two likely. During its first year, the CETT Program has seen the successful development of ten clinical tests for:
  - Cornelia de Lange Syndrome at the University of Chicago;
  - Joubert Syndrome at Prevention Genetics;
  - Cherubism at Hospital for Sick Children, Canada;

- X-linked Chondrodysplasia Punctata at the University of Chicago;
- Kallmann Syndrome at GeneDX;
- Progressive Familial Intrahepatic Cholestasis at Baylor College of Medicine;
- Russell Silver Syndrome, MPS VI, and Niemann Pick Disease A/B at Emory University; and
- X-Linked Periventricular Nodular Heterotopia at Harvard University.

These tests include more than 18 conditions and 13 genes. Three other tests – Primary Ciliary Dyskinesia, Infantile Neuroaxonal Dystrophy and Arginase Deficiency – are expected to be released later this year. Another six tests are under development. Each of the collaborative groups has agreed to develop and/or update an entry in GeneReviews which is a Web-based data base that is used by genetic experts worldwide.

The CETT Program Staff, Review Board members and volunteer subject matter experts are working to improve clinical test reports to make them understandable both for clinicians and for patients and their families. In addition, they are developing templates that will help guide collaborative groups as they produce educational materials on the various disorders.

ORD has been providing updates on this pilot program to the Trans-NIH Rare Diseases Research Working Group. The working group has begun discussing means by which such an approach could be applied to NIH extramural programs in the future.

- **Amyloidosis**

Systemic Amyloidosis is a serious rare disease with various causes that affects multiple organ systems and therefore requires research attention by multiple NIH institutes. In fiscal years 2005 and 2006, NIH held several scientific conferences and workshops on various aspects of amyloidosis. In June 2006, ORD convened an expert focus group on systemic amyloidosis to identify the next steps to increase the understanding of amyloidosis and improve the prevention and treatment of this devastating disease. Participants at the "Systemic Amyloidosis Focus Group Workshop" consisted of American and international researchers and NIH scientific staff. Workshop members offered guidance to the NIH on research needs and future scientific opportunities. A workshop summary entitled, "Challenges and Opportunities for Systemic Amyloidosis Research" is to be published in the journal, Amyloid. Plans are also under way to issue a multi-Institute program announcement to inform the research community about the NIH interest in supporting research relevant to amyloidosis.

- **Inventory of Human Rare Diseases Tissue Repositories**

The issue of availability of high-grade biospecimen and clinical data for research constitutes a barrier to rare diseases research. ORD supported a demonstration project with the National Disease Research Interchange (NDRI) and brought this issue to the attention of the Trans-NIH Rare Diseases Research Working Group. The Genetic Alliance has established and maintains a "biobank" with support from participating Patient Advisory

Groups (PAGs). The Trans-NIH Rare Diseases Research Working Group suggested the development of a publicly accessible inventory of human tissue repositories which will invite repositories to enter information about their collections. The data base has been developed and pre-tested and will begin inviting participation and entry of data in the spring of 2007. Future plans include expanding the data base to international human tissue repositories and developing educational modules based on feedback from users of the site.

Other Extramural Research Opportunities in Rare Diseases

- ORD is collaborating with the NHLBI on demonstration/pilot projects, with the NINDS on improving treatment for lysosomal storage disorders, and with the NHGRI on patient-oriented research career development awards to stimulate approaches of genomics and proteomics to the study of rare diseases, and with NIH components clinical trial planning grants.

- ORD is also supporting with the NCRR a pilot program in human tissues for rare diseases research. NDRI has been providing customized procurements of fresh, fixed, and frozen human tissues to the biomedical research community. A range of normal and affected organs and tissues, cell lines, DNA and plasma are provided from rare diseases donors.

Table 2: 2003-2006 Progress Summary of Human Tissue Procurement

	2005	2006	2203-2007 Cum.
Rare Diseases Tissue Procured per year	366	1024	2063
Rare Diseases Tissues Banked in Online Biospecimen Catalog (cumulative)	508	1307	1427
Rare Diseases Tissues Placed with Researchers per year	128	192	541
Rare Diseases Researchers Served per year	20	22	72

	2005	2006
Online Biospecimen Catalog Tissues (cumulative)	508	1427
Blood, DNA and Cell Line Bank (cumulative)	11	37
Paraffin Blocks per year	144	848

Publications by Rare Diseases Researchers per year	13	13	45
Rare Diseases Researchers Data Base per Year	97	99	122

LAM[2] Tissue Repository/Supported by NHLBI (3/2007)	NA	15,000

[2] Lymphangioleiomyomatosis

Intramural Research Program Activities

- **Research Relating to Diagnosis, Evaluation, and Treatment**

The Rare Diseases intramural research activities are collaborative efforts between the ORD and the NHGRI at the NIH Clinical Center. The program includes evaluating gynecological aspects of rare diseases, evaluating undiagnosed inborn errors of metabolism, and initiating select clinical research protocols. In addition, a pilot program has been initiated to provide free patient travel to the NIH Clinical Center through Angel Flight/Mercy Medical Airlift. Recently, it has been expanded to include the extramural portion of ORD and now serves the NIH Clinical Center hospital and the Rare Diseases Clinical Research Network.

In the past year, researchers at the Intramural Research Program of the Office of Rare Diseases diagnosed, cared for, and treated a number of patients with rare diseases, including

- Chediak-Higashi disease (CHD)
- Hermansky-Pudlak syndrome (HPS)
- Gray platelet syndrome (GPS)
- Griscelli syndrome
- Jacobsen syndrome
- Oculocutaneous albinism associated with other systemic disorders
- Hutchinson-Gilford progeria syndrome (HGPS)
- Alkaptonuria
- Minocycline-induced ochronosis
- Hereditary inclusion body myopathy (HIBM)
- X-linked myopathy
- Autosomal recessive polycystic kidney disease with congenital hepatic fibrosis (ARPKD/CHF)
- Autosomal dominant polycystic kidney disease
- Cystinosis
- Glutathione synthase deficiency
- Homocystinuria
- Idiopathic nephrocalcinosis

Intramural staff evaluated gynecologic issues of patients with HPS, cystinosis, alkaptonuria, xeroderma pigmentosum, Smith-Magenis syndrome, and Smith-Lemli-Opitz syndrome. A member of the intramural program of the ORD provided gynecology consultations for rare disease patients throughout the NIH Clinical Center as she continued her fellowship in the field of clinical biochemical genetics.

Currently, the program is also supporting the conduct of clinical therapeutic trials of pirfenidone for the pulmonary fibrosis of HPS, nitisinone for the ochronotic joint disease of alkaptonuria, cysteamine for the renal and systemic disease of cystinosis, and intravenous

immune globulin for the muscle wasting of HIBM. Staff also collaborated on an NEI-sponsored treatment protocol for the use of cysteamine eye drops for the corneal crystals of cystinosis and on an National Institute of Allergy and Infectious Diseases (NIAID)-sponsored diagnostic protocol for the colitis associated with HPS.

Intramural staff—

- Performed fine mapping of the gene for GPS, bringing us closer to identifying the gene responsible for this disease.
- Mapped the gene for a new disease, White Platelet syndrome, to a 2 cM region, permitting the identification of a small number of candidate genes for this platelet disorder.
- Continued to enroll patients in a protocol entitled "Clinical Investigations into Autosomal Recessive Polycystic Kidney Disease (ARPKD) and Congenital Hepatic Fibrosis." Under this protocol, 60 patients have been examined and evaluated for the possibility of future treatment.
- Examined and investigated 15 patients with Hutchinson-Gilford Progeria Syndrome, a disorder of premature aging that is fatal in adolescence, under a new clinical protocol.
- Continued to follow patients with the rare disease Chediak-Higashi syndrome, investigating the clinical, molecular, and cell biological aspects of this disease.
- Completed enrollment of 40 patients in a randomized trial of nitisinone for the joint disease of alkaptonuria.
- Laid the groundwork for an aggressive treatment protocol for end-stage pulmonary fibrosis in Hermansky-Pudlak syndrome.

Other ORD-Supported Intramural Initiatives:

- Rare Diseases Research Initiative: The Office of the Clinical Director of NHGRI continued to admit patients with rare, undiagnosed disorders under a protocol entitled "Diagnosis and Treatment of Patients with Inborn Errors of Metabolism."
- Molecular Diagnostics of Rare Diseases: In collaboration with the NHGRI, the intramural program of the NHGRI previously conducted a program to contract with Clinical Laboratory Improvement Act (CLIA)-certified laboratories to establish molecular diagnostic tests for specific rare diseases research. Thereafter, these tests are made available on a fee-for-service, insurance-reimbursable basis to the general public. In the past year, this intramural initiative was transferred to include the extramural research program under the title of CETT.
- Research Training: One physician in the Intramural Research Program completed training in clinical biochemical genetics and another remains a clinical biochemical genetics fellow.
- Rare Disease Scientific Conference: Members of the intramural research ORD program conducted a workshop on the pulmonary fibrosis of Hermansky-Pudlak Syndrome (HPS), attended by experts in pulmonology as well as the cell biology of HPS. In addition, the intramural ORD published in the Journal of Pediatrics a statement concerning a previous workshop on Autosomal Recessive Polycystic Kidney

Intramural Research Plans for FY 2007-2008

The ORD/NHGRI intramural research collaboration will expand to study different types of renal tubular disorders, including the identification of genes causing familial autosomal recessive and autosomal dominant Fanconi syndrome. Staff will pursue the genes responsible for Gray Platelet syndrome and for White Platelet syndrome, and will investigate the megakaryocytes of rare disease patients. They continue to characterize the natural history of ARPKD and Congenital Hepatic Fibrosis in both cross sectional and longitudinal fashions, to determine appropriate clinical outcome parameters for a therapeutic trial. Staff will complete the nitisinone trial for the treatment of joint disease in alkaptonuria, and continues to enroll patients in the pirfenidone study of Hermansky-Pudlak syndrome (HPS) patients. Additional studies will include the continuation of the study of progeria and gynecologic disorders associated with other rare metabolic diseases.

<u>New Rare Disease Initiative</u>

- Expansion will occur through the protocol "Diagnosis and Treatment of Inborn Errors of Metabolism."

- Clinical Protocols: Intramural investigators plan to collaborate with extramural investigators in a study of the effects of early galactose restriction in individuals with one classical galactosemia mutation and one Duarte variant. The Section on Human Biochemical Genetics intends to initiate treatment protocols for ARPKD and to complete its clinical trials of nitisinone in alkaptonuria and pirfenidone in HPS. This intramural group of investigators supported by the ORD will pursue a pilot study of multidrug treatment of end-stage pulmonary fibrosis in HPS, and plans to see patients with platelet dysfunction due to the Jacobsen 11q deletion syndrome and with renal and hepatic complications of Joubert syndrome.

- Other Initiatives: In concert with the NHGRI Intramural Program, the ORD will initiate a new plan to foster clinical/translational research into rare diseases at the NIH. This involves linking a patient advocacy group with an intramural principal investigator (PI) who is an authority on a disease and who is clinically oriented. An advocacy group might support a 3-5 year fellowship to leverage a clinical protocol at the NIH Clinical Center thereby creating an expert in the disease of interest for the next generation. The fellow would acquire expertise in the disease of the particular advocacy group and would also learn other related diseases and work toward board certification. The PI would supervise, provide mentoring, serve as attending physician for the patients, and provide a laboratory/clinic environment. This initiative might be an initial collaboration between the NHGRI, Office of the Clinical Director and the ORD, and could be made available to clinical PIs throughout the NIH. This could foster an expansion to translational labs. Biotech companies might be invited to test their rare disease-specific drugs in a plan coordinated through the Intramural ORD office.

Bench-to-Bedside Intramural Research Awards

In FY 2006, ORD supported with NIH ICs eight, 2-year Bench-to-Bedside awards at the NIH Clinical Center. Intramural and extramurally supported scientists enter into basic science-clinical research collaboration with colleagues in other NIH or extramural laboratories with a focus on rare disease. The awards included:

Table 3: FY 2006-2007 Rare Diseases Bench-to-Bedside Awards

Institute(s)	Project	Investigators
NHLBI, NIH Clinical Center, Harvard, Georgetown, National Naval Medical Center	"Role of Cyclin D1 in Myelodysplasia"	PI: Neal S. Young, MD, NHLBI PI: Elaine M. Sloand, MD, NHLBI AIs: Roger Kurlander, MD, NIH Clinical Center; Jerome J. Groopman, MD, Harvard University; Jan Blancato, PhD, Georgetown University; Kenneth More, MD, NNMC
NHLBI, NIH Clinical Center (CC), Walter Reed Army Medical Center	"Exploring the Anti-Tumor Effects of In Vitro Expanded Natural Killer (NK) Cells Against Renal Cell Carcinoma Sensitized to NK-TRAIL Cytotoxicity with Bortezomib"	PI: Richard W. Childs, MD, NHLBI PI: Gauri Alvarez, DO., WRAMC PI: Andreas E. Lundqvist, PhD, NHLBI AIs: E.J. Read, MD, and Anthony Suffredini, MD, NIH Clinical Center; Edward Gorak, DO, WRAMC; Maria Berg, NHLBI; Ramaprasad Srinivasan, MD, PhD, and Shivani Srivasatava, MD, NCI
NHLBI, MD Anderson Cancer Center	"A New Global Function for a Rare Disease Gene: Clinical Significance of the Regulation of Mitochondrial Respiration by Tumor Suppressor p53 in Li-Fraumeni Syndrome"	PI: Paul M. Hwang, MD, PhD, NHLBI PI: Lousie Strong, MD, MD Anderson Cancer Center AIs: Ross Arena, PhD, Medical College of Virginia; Aarif Khakoo, MD Anderson Cancer Center; Robert Balaban, MD, Satoaki Matoba, Michael Sack, Myron Waclawiw, NHLBI; Oksana Gavrilova, NIDDK
NCI, NHLBI	""Therapeutic Approaches for Cancer Stem Cells in Small Cell Neuroendocrine Carcinomas"	PI: Curtis C. Harris, MD, NCI AIs: Lyuba Varticovski, MD, Phillip A. Dennis, MD, Susan Bates, MD, NCI; Cynthia Dunbar, MD, NHLBI; Ron McKay, PhD, NINDS; William D. Travis, MD, Memorial Sloan-Kettering Cancer Center
NCI (DCEG&CCR)	"High Density Genotyping in Diffuse Large B-cell Lymphoma (DLBCL) and Follicular Lymphoma – Translating Etiologic Clues into Prognostic Relevance Within the NCI-SEER NHL Case Control Study"	PI: Sophia S. Wang, PhD, NCI PI: Stephen Chanock, MD, CCR, NCI AIs: Patricia Hartge, Lou Staudr, Nathaniel Roghman, Lindsay Morton, Sholom Wacholder, NCI; Wendy Cozen, University of Southern California; Richard Severson, Karmanos

		Cancer Institute and Wayne State University; Scott Davis, Fred Hutchinson Cancer Research Center and the University of Washington; James R. Cerhan, Mayo Clinic College of Medicine
NIH CC, NCI, University of Toronto/Ontario Cancer Institute	"Novel Suicide Gene-Modified Donor Th2 Cells for GVHD Prevention"	PI: Daniel H. Fowler, MD, NCI PI: Jeffrey Medin, PhD, Ontario Cancer Institute and University of Toronto AIs: E.J. Reed, NIH Clinical Center; Aron Lavie, Ph.D, University of Illinois at Chicago
NIDDK, NHLBI, University of Maryland	"A Nutrigenomics Intervention for the Study of the Role of Dietary Sitosterol on Lipid, Glucose and Energy Metabolism"	PI: Francesco S. Celi, MD, NIDDK AIs: Vandana Sachdev, MD, NHLBI; Alan Shuldiner, MD, Richard Horenstein, MD, JD, Susan K. Fried, PhD, University of Maryland, Division of endocrinology, Diabetes and Nutrition
NHLBI, NIH CC	"Pilot Trial of Intravenous Nitrite for Sickle Cell Vaso-Occlusive Pain Crisis"	PI: Mark Gladwin, MD, NHLBI PI: Gregory Kato, MD, CC AIs: Lewis Hsu, MD, Drexel University and NIH Clinical Center; Kyle Mack, MD, NCI; Roberto Machado, MD, Sruti Shiva, PhD, James Taylor, MD, Xunde Wang, MD, NHLBI; Alan Schechter, MD, NIDDK

ORD also continued to support with NIH ICs ten Bench-to-Bedside awards in their second year.

Identifying Future Research Opportunities for Rare Diseases: Scientific Conferences

ORD collaborates with Institutes, Centers, and Offices at NIH and other Federal agencies to stimulate rare diseases research by supporting with the NIH ICs and other organizations scientific conferences where research is lagging or to take advantage of scientific opportunities. The outcomes of these scientific conferences have included the establishment of research priorities, development of collaborative research protocols, criteria for diagnosing and monitoring rare diseases, specific discoveries, publications, and new research endeavors. These scientific conferences have also contributed to the exchange of ideas and information among basic and clinical investigators, patient advocacy groups, NIH staff, and the pharmaceutical industry.

In FY 2006, ORD supported with NIH ICs and other organizations 71 national and international scientific conferences. Examples of the subjects of the scientific conferences in FY 2006 include childhood cancers, bone marrow failure, sickle cell disease, congenital heart disease, dystonias, pediatric stroke, neurofibromatosis, and primary lateral sclerosis. A list of the scientific conferences is provided in Tables 4 and 5. For FY 2007, ORD has already provided partial support for 55 conferences and expects to partially support another 41 for a total of 96.

Table 4: Scientific Conferences Partially Supported in FY 2006 (71)

Primary Sponsor	Titles of Scientific Conferences
National Institute on Aging (NIA)	• RecQ Helicases and Other Helicases in Telomere Maintenance and Related Pathways • Xeroderma Pigmentosum and Other Diseases of Human Premature Aging and DNA Repair: Molecules to Patients
NIAID	• Considerations in Allogeneic Hematopoietic Cell Transplantation (HCT) for Nonmalignant Disorders, Including Autoimmune Diseases • Gene Therapy for Primary Immune Deficiencies: Advances and Safety Issues • Gordon Research Conference on the Biology of Spirochetes • 20th Meeting of the American Society for Rickettsiology
NIAMS	• Gordon Research Conference on Intermediate Filaments • International Research Conference on Ankyloblepharon-Ectodermal Dysplasia-Cleft Lip/Palate AEC Syndrome • Multiple Hereditary Exostoses: Insights into Pathogenesis • New Research Strategies in Osteogenesis Imperfecta • Obstacles to Translating Basic Knowledge of Genetic Skin Diseases into Therapies • Paget's Disease of Bone/Fibrous Dysplasia: Advances and Challenges • Reaching Clinical Trials for Pachyonychia Congenita
National Institute of Biomedical Imaging and Bioengineering (NIBIB)	• Stem-Cell Based Tissue Engineering in Regenerative Medicine Conference: 24th Conference of the Society for Physical Regulation in Medicine and Biology
NCI	• ABC Transporters and Genetic Disease • Biology and Therapy for Malignant Salivary Gland Tumors • FASEB Summer Research Conference on Biological Methylation • Immunobiology and Immunotherapy for Cutaneous T- cell Lymphoma Workshop • Interagency Workshop on the Science and Practice of Informal Caregiving • Large Granular Lymphocyte (LGL) Leukemia: Pathogenesis, Pathobiology, and Treatment • Mechanisms and Consequences of c-MYC-deregulating Chromosal Translocations • Proline Metabolism and Human Diseases • Scanning and Risk for Childhood Cancer: International Collaborative Study • Testicular Cancer and Testicular Dysgenesis Syndrome: Current Perspectives and Future Directions • Translational Genomics of Neuroblastoma (TgiN) • 9th Meeting of the Society for Natural Immunity "NK Cells and Innate Immunity"
NICHD	• Critical Pertussis in U.S. Children • Defining the Metabolic Syndrome in Children and Adolescents • International Conference on Adrenal Cortex and Molecular Steroidogenesis • New Horizons in GnRH Research

	• New Therapies for Necrotizing Enterocolitis (NEC) • Preeclampsia: A Pressing Problem • Prenatal Imaging: Ultrasound and MRI • SDHB-related Pheochromocytoma: Recent Discoveries and Current Diagnostic and Therapeutic Approaches • The FMR1 Premutation and Premature Ovarian Failure: Worldwide Community Guideline Development
National Institute on Deafness and Other Communication Disorders (NIDCD)	• Workshop on Brain-Computer Interfaces for Speech Synthesis
National Institute of Dental and Craniofacial Research (NIDCR)	• Seventh Research Workshop on the Biology, Prevention, and Treatment of Head and Neck Cancer
NIDDK	• Alpha-1 Antitrypsin Deficiency and Other Liver Diseases Caused by Aggregated Protein • Nutrient Sensing, Insulin Signaling, and Harmatoma Syndromes • Screening and Outcomes in Biliary Atresia
NIEHS	• Environmental Mutagen Society 37th Annual Meeting • Molecular Mechanisms of Chemical Teratogenesis • Seventh International Conference on Lactoferrin: Structure, Function, and Applications
National Eye Institute (NEI)	• Autoimmune Retinopathies (AIR)
NHLBI	• Cardiofaciocutaneous Syndrome and Noonan Syndrome Scientific Meeting 2006 • Conference on Adult Sickle Cell Disease Care: Guidelines for Pain Management • Evolution of Pulmonary Hypertension: Emerging Diseases and Novel Therapeutics • Lung Surfactant: Cellular and Molecular Biology–FASEB Summer Research Conference • Neuroimaging of Sleep Disorders • Progeria Research Foundation: International Progeria Workshop • The Science and Medicine of Barth Syndrome: The Remaining Big Questions • Vascular Anomalies: 2005–Research Update and Current Controversies • Workshop on Recognition and Treatment of Rare Inherited Arrhythmias • 29th Annual Meeting of the National Sickle Cell Disease Program
NHGRI	• NIH Workshop–Hereditary Hemorrhagic Telangiectasia: Vascular Biology and Pathophysiology
NINDS	• American Society for Neurochemistry: Cellular and Molecular Mechanisms of Neural Development and Disease • Ataxia Telangiectasia Clinical Research Workshop • Conference on the Diagnosis of Multiple System Atrophy • Developing New Treatments for Tourette Syndrome: Clinical and Basic Science Dialogue • Gangliosides in Health and Disease • International Conference on Episodic Ataxias Syndromes

	• Lysosomal Disease Network–Third Annual WORLD Symposium • NIH Pain Consortium First Annual Symposium: Advances in Pain Research • Neurobiology of Disease in Children Conference (2006-2010), a Satellite Symposium of the Child Neurology Society Annual Meeting • Scientific Conference on Moebius Syndrome • Second New Directions in Biology and Disease of Skeletal Muscle • 5th International Conference on HHV-6 and 7, Including the Workshop on HHV-6 and 7 in Encephalitis, Status Epilepticus and Seizures • 11th International Symposium of Neural Regeneration
ORD	• Systemic Amyloidosis Focus Group Workshop
Genetic Alliance	• Genetic Alliance Annual Conference: Celebrating 20 Years of Excellence in Advocacy
National Organization for Rare Disorders	• NORD 2006 Conference: Roadmap for Rare Disease Research

Table 5: Scientific Conferences Partially Supported in FY 2007 (as of April 4, 2007) (54)

Primary Sponsor	Titles of Scientific Conferences
NIAID	• Bi-Annual Meeting of the IUIS Expert Committee on Primary Immunodeficiency (PID) • Development of a Multicenter International Collaborative Network for the Study of Rare Eosinophil-Mediated Disorders • Implementation of the NIH Consensus Criteria for Clinical Trials in Chronic Graft-versus-Host Disease (cGVHD) • Primary Immune Deficiency Consortium Conference
NIAMS	• Gordon Research Conference on Epithelial Cell Differentiation and Keratinization • Pigmentation and Diversity • 4th International Workshop on the Study of Itch
NCI	• A Multicenter Cohort Investigation of Chromosomal Translocations and Hyperdiploidy at Birth and Childhood Leukemia by the International Childhood Cancer Cohort Consortium • Barrett's Esophagus and Adenocarcinoma Consortium Meeting • Clinical Advisory Committee for the WHO Classification of Malignant Lymphomas • Genetic Toxicology Gordon Research Conference • International Study of Genetic and Other Risk Factors for Differentiated Thyroid Carcinoma • Synergizing Epidemiology Research on Rare Cancers Meeting • The 4th Annual North American Genetic Analysis of ABC Transporters Workshop • 10th International Workshop on Kaposi's Sarcoma Herpes Virus (KSHV) and Related Agents
NICHD	• Galactosemia and Primary Ovarian Insufficiency • International Clubfoot Symposium • Membrane Biophysics of Exocytosis, Endocytosis, and Viral Fusion Health

	• Newborn Screening for Rare Genetic Disorders in the Arab Populations–Local/State Government • Improving Child Health: The Role of Policy Makers in Prevention and Treatment of Birth Defects and Developmental Disabilities • Society of Inherited Metabolic Disorders (SIMD) Annual Meeting
NIDCD	• 11th International Conference on Cochlear Implants in Children
NIDDK	• Acute Liver Failure • Improving Long Term Outcomes in Pediatric Liver Transplantation • Inherited Bone Marrow Failure Syndromes: Definitions and Diagnostic Criteria • Lipodystrophy and the Metabolic Consequences of Altered Fat Deposition
NIEHS	• Genetic and Environmental Risk Factors for Major Birth Defects • Ion Channel Regulation, a FASEB Summer 2007 Conference • Mitochondrial Medicine 2007
NHLBI	• American Society of Gene Therapy Annual Meeting • Blood and Marrow Transplant State of the Science Symposium • Second International Role of Nitrite in Physiology, Pathophysiology, and Therapeutics Meeting • Update and Modification of Task Force Criteria for ARVD/C • Vascular Anomalies, 2007: Update and Controversies • 2007 Gordon Research Conference on Cilia, Mucus, and Mucociliary Interactions • 2007 LAM Foundation Lymphangioleiomyomatosis International Research Conference
NHLBI/NICHD	• Smith-Lemli-Opitz Syndrome and Inborn Errors of Cholesterol Synthesis
NHGRI	• Innovative Approaches to Social and Behavioral Research in Rare Genetic Diseases • Methylmalonic Acidemia: Clinical and Scientific Advances • The First International Chordoma Research Workshop
National Institute of Mental Health (NIMH)	• Childhood Onset Schizophrenia: Research Challenges and Opportunities on the Neurobiology, Developmental Trajectory, and Treatment
NINDS	• Angiogenesis in the Nervous System • International Conference on the Non-Dystrophic Myotonias • Joint 12th International NCL Congress and BDSRA Meeting: Therapeutic Approaches • Lysosomal Disease Network–3rd Annual WORLD Symposium • NINDS International Workshop on Wilson's Disease and Other Disorders of Copper Metabolism • The 5th International Conference on Unstable Micro Satellites and Human Disease • Translational and Clinical Progress in the Mucopolysaccharidoses • 2007 CAG Triplet Repeat Disorders Gordon Conference • 3rd International Friedreich's Ataxia Scientific Conference • 11th International Myasthenia Gravis Meeting
National Center for Complementary and Alternative Medicine (NCCAM)	• The Status and Future of Acupuncture Research: 10 Years Post-NIH Consensus Conference

ORD	• NIH Spinal Cord Tumor Workshop • Systemic Amyloidosis Workshop

Education and Public Information, Input and Facilitation

- **Genetic and Rare Diseases Information Center**

  The ORD supports with the NHGRI the Genetic and Rare Diseases Information Center (GARD). The information center provides information about rare diseases research and treatment to patients and their families, health professionals, researchers, and the public. Since FY 2004, the information center has become more accessible to minority and underserved populations through services in Spanish and a more user-friendly Web-based approach. Since its inception in September 2001, the Information Center has responded to approximately 18,000 inquiries for 4,400 rare diseases.

  Beginning in 2007, GARD is transitioning to a Web-based self service source of information. The service will utilize the extensive amount of information compiled in the past by preparing customized responses to inquiries, and make them available in a question and answer format as a part of the ORD Web site so that users can gain access instantly to information. GARD is also partnering with the National Library of Medicine (NLM) to direct inquiries that are better served by NLM services. Networking with NLM and other information providers to avoid duplication of effort will ensure continued cost-effectiveness.

  GARD will utilize the database of inquiry responses and other previously developed resources to provide broad and instantaneous access to the information via the Internet through the Rare Diseases Terms. The Web site will provide the public and health professionals with wider access to GARD health information resources by promoting access to NIH, NHGRI, ORD and GARD-developed information resources. The main objective of this approach is to provide wider dissemination and promotion of genetic and rare disease information while at the same time creating cost efficiencies for the service by using current and future information (collected during the preparation of customized responses to inquiries) to develop self-service features. While this approach will initially limit direct interaction of GARD staff with individual inquirers, it will maintain the personal interaction for new and complex requests that cannot be answered by the information on the Web site.

  The ultimate goal for the GARD Web site is to improve the user's ability to gain access to existing information more effectively and in a more cost-efficient manner while retaining access to Information Specialists where needed.

  To provide Web site users with the ability to offer ideas or suggestions for the GARD Web site and/or its content, the GARD Web site will also provide a feature that allows users to submit feedback. A "feedback box" will be offered on the main GARD Web page to gage user satisfaction.

- **Genetics Education for Healthcare Providers: National Coalition for Health Professional Education in Genetics (NCHPEG**)

  ORD also supported the National Coalition for Health Professional Education in Genetics (NCHPEG). Established in 1996 by the American Medical Association, the American Nurses Association, and the NHGRI, NCHPEG is a national effort to promote health professional education and access to information about advances in human genetics. NCHPEG members are an interdisciplinary group of leaders from approximately 120 diverse consumer and voluntary groups, medical societies, government agencies, private industry, managed care organizations, and genetics professional societies. By promoting frequent and open communication between stakeholders, NCHPEG seeks to capitalize on the collective expertise and experience of members and to reduce duplication of effort.

  As patients ask more questions about genetic tests and disease risk, more responsibility for the use and interpretation of genetic tests and information will fall to primary care physicians, nurses, physician assistants, advanced practice nurses, and other health professionals who may not be formally trained in genetics. This is of importance to ORD since it is estimated that 80 percent of rare diseases have a genetic basis. Core competency educational materials have been produced in English and in Spanish.

  NCHPEG is coordinating "Genetic Resources on the Web (GROW)" a source of information about human genetics for health professionals and the public. ORD cofounded GROW with other NIH components and Federal agencies.

ORD supports NCHPEG with the Health Resources and Services Administration (HRSA) and the National Human Genome Research Institute (NHGRI). The goal is to educate health care professionals about genetic concepts and genetic applications in practice because genetics, especially in the wake of the human genome project, are transforming and will continue to transform health care. Specific genetic education accomplishments in 2006 included:

- NCHPEG Annual Meeting on Pharmacogenetics
- Redesign of the NCHPEG Web site
- Review of Genetics Competencies that have helped guide the development of genetics curricula across many healthcare disciplines
- Reduction of the number of Genetics Competencies to 21 to be revised and released in 2007
- Development of the NCHPEG on-line newsletters: Genetics Application in Practice
- Targeted genetics education initiative for speech-language pathologists and audiologists
- Exhibiting at professional meetings
- Marketing Continuing Education Credits (CEUs) in Genetics through professional organizations, journal articles, and targeted blast e-mails

- Development of a Web-based targeted education program that addresses the relevance of genetics in infectious disease, oncology nursing, and common diseases
- Development of a Web-based targeted professional education program for physician assistants, targeting dieticians in 2007
- Continued development of the NCHPEG/GROW Web site and a GROW-Listserv with links to genetic articles of interest
- Development of the Clearinghouse of Genetics Education Resources
- A planned GeneFacts for 2007 that will involve the creation of a point-of-care genetics resource for primary care providers

- **Public Input**

  ORD continued to support the annual meetings of the Genetic Alliance and the National Organization for Rare Disorders (NORD). These two umbrella organizations represent collectively more than 600 rare diseases patient advocacy groups. ORD utilized these meetings to conduct focus group sessions to determine the needs of member organizations and to identify programs ORD should consider implementing. Also, NIH research scientists and ORD staff are active participants in all sessions of the annual meetings and disseminate information about NIH rare diseases research programs.

- **Angel Flight America at the NIH**

  This not-for-profit organization provides transportation free of charge to and from the Clinical Center and to the Rare Diseases Clinical Research Network for patients to be evaluated for enrollment or enrolled in research protocols and for family members. Since it began operations through the Office of the Clinical Director of the National Human Genome Research Institute (NHGRI) in January of 2004, Mercy Medical Airlift has flown more than 498 patient and family member in 293 missions to and from the NIH Clinical Center and to and from the rare Diseases Clinical Research network consortia for evaluation or treatment. The patients with a variety of diagnoses have been enrolled in protocols of the National Eye Institute (NEI), National Cancer Institute (NCI), NHGRI, and other Institutes. Rare diseases included alkaptonuria, ARPKD, cystinosis, DiGeorge syndrome, HPS, Pallister-Hall syndrome, Ehlers-Danlos syndrome and various types of rare cancers. This initiative has grown from being a pilot program for the intramural program to providing transportation for the NIH Clinical Center hospital as well as the Rare Diseases Clinical Research Network.

Collaborative Research Efforts

- International Congress on Rare Diseases and Orphan Drugs

  The ORD continues to play an active role in fostering global research collaborative efforts. The goal is to link the rare diseases research community together to address significant issues that remain problematic. Ongoing themes of the Conference sponsored by the

International Conference on Rare Diseases and Orphan Drugs (ICORD) include the following:

- Patient and family needs across the life span
- Product discovery and development: Linking the academic research community to the pharmaceutical and biotechnology industries
- Development of research assessment tools
- Recruitment of patients for clinical research studies
- Establishing and meeting requirements for regulatory approval
- Harmonization of genetic testing requirements
- Rare diseases research and orphan product development in developing nations

Future conferences are scheduled for Brussels on September 14-15, 2007, and in Washington, D.C., on May 19-21, 2008. Specific tasks will be identified from the thematic areas presented, and collaborative efforts will be supported by various offices in governments throughout world. Efforts are ongoing to merge information from GeneTests (USA) and EuroGen Test from the European Union (EU) data bases. The resulting data base will be an extensive collection of genetic tests available from clinical and research laboratories in the USA and the EU. A similar approach will be considered for a) an inventory of human biospecimen collections and b) research discoveries and technologies available for licensing.

- **The Orphan Drug Act (1983-2008): 25 Years of Advancement**

In 1983, President Reagan signed Public Law 97-414, the Orphan Drug Act leading to significant advances in the treatment of rare diseases. Several conferences are planned in 2008 to recognize these accomplishments and to focus on future research opportunities and directions for rare diseases. Collaborative Conferences will be sponsored by various organizations:

- Neglected Diseases – National Academy of Sciences (NAS)/Institute of Medicine (IOM) Forum on Drug Discovery Development, and Translation
- International Congress on Rare Diseases and Orphan Drugs (ICORD)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- Office of Orphan Products Development at the Food and Drug Administration
- National Organization for Rare Disorders
- The Genetic Alliance.

NATIONAL INSTITUTE ON AGING (NIA)

Overview

The National Institute on Aging (NIA) leads the federal effort in conducting and supporting research on aging and the medical, social, and behavioral issues of older people. Rare diseases and conditions that affect older people include some forms of neurodegenerative diseases such as early onset Alzheimer's disease, familial forms of Parkinson's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), and Rett syndrome. NIA also supports research on Bloom syndrome, Frontotemporal dementia, and progeroid syndromes such as Werner, Cockayne, and Hutchinson-Gilford that cause premature aging.

Recent Scientific Advances in Rare Diseases Research

Bloom syndrome (BS)

Bloom syndrome (BS) is a genetic disease characterized by dwarfism, immunodeficiency, genomic instability, and cancer susceptibility. The protein defective in BS, called BLM, is a component of at least 3 multiprotein complexes that play critical roles in guarding genome stability. NIA investigators previously identified a protein called BLAP75, which is present in all three BLM syndrome complexes. NIA investigators have now demonstrated that BLAP75 is essential for the stability and function of BLM complexes, and its depletion results in genomic instability similar to cells deplete of BLM. Identification of this molecular machine and its biochemical activity should provide new means to screen candidate drugs for the treatment of BS and could eventually contribute to the development of cancer therapies.

Frontotemporal dementia (FTD)

Frontotemporal dementia (FTD) is a set of rare brain disorders. While most cases are sporadic, an estimated 20 to 50 percent of people diagnosed with FTD have a family history of dementia, according to the Association for Frontotemporal Dementias. FTD affects the frontal and temporal lobes of the brain, and people with FTD may exhibit uninhibited and socially inappropriate behavior; changes in personality; and in late stages, loss of memory, motor skills and speech. NIA-supported investigators have discovered genetic mutations occurring in a single gene that scientists believe are responsible for a large component of inherited FTD. These clues to the underlying mechanism involved in this devastating disease may provide insight for future development of a treatment for FTD.

Progeroid syndromes

Progeroid syndromes are diseases and conditions that mimic selected features of normal aging processes. Life span in yeast is determined by the number of daughter cells a mother cell can produce. Daughter cells from old mother cells tend to have shorter life spans. A specific set of proteins known as SIR (silent information regulator) form an ordered compact structure that is restrictive to transcription and includes SIR2, a large family of closely related proteins that prolong longevity in yeast mother cells. NIA-supported investigators have demonstrated that a member of

the SIR2 family, SIRT6, plays a key role in DNA repair and maintenance of genomic stability in cells. In addition, SIRT6 is necessary to maintain an organism's health and to prevent the development of several progeroid pathologies in mice. Further studies of SIRT6-deficient mice hold promise for a better understanding of the molecular mechanisms that regulate the main DNA repair pathway that removes spontaneously occurring single-stranded DNA lesions as well as its role in the aging process.

Rett syndrome (RS)

Rett syndrome (RS) is a neurodevelopmental disorder seen almost exclusively in females that begins to show its effects in infancy or early childhood. Patients have a defect in MeCP2, a gene that provides instructions for making a protein that is essential for normal brain development. An earlier study suggested that the MeCP2 gene interacts with the Brahma (BRM) chromatin remodeling protein complex. This complex rearranges the structure of chromatin, the crucial DNA and protein assembly found inside the nuclei of an organism's cells involved in DNA replication and repair. A recent study by NIA investigators has shown that the MeCP2 gene may not function through BRM. This contradictory finding that the RS protein may not be a part of a multicomponent complex is an important finding that changes the view held by scientists in the field and stimulates the investigation of MeCP2 function from a different perspective.

Werner syndrome (WS)

Werner syndrome (WS) is a recessive genetic disease characterized by early onset of many characteristics of normal aging such as wrinkling of the skin, graying of the hair, cataracts, diabetes, and osteoporosis. The symptoms of WS begin to appear around puberty, and most patients die before age 50. Recently, NIA investigators conducted a study to better clarify the molecular mechanisms of the Werner syndrome protein (WRN) in DNA repair. These investigators demonstrated that WRN works in a coordinated manner with the early onset breast cancer gene (BRCA1) to facilitate DNA repair. When WRN protein activity is inhibited, abnormal processing of damaged DNA occurs, permitting the replication of damaged DNA. New advances in the understanding of the underlying molecular mechanisms of the human premature aging process will help scientists design new strategies for intervention against age-associated diseases like WS.

New/Planned Research Initiatives

NIA announced the following research initiatives in fiscal year 2006:

- PA-07-033, *Focal Cognitive Deficits in Central Nervous System (CNS) Disorders* (R01), to expand basic and translational research, including intervention research, on the types, nature, and functional consequences of focal or specific cognitive deficits experienced by persons with CNS disorders, particularly nondementing disorders such as the rare disease amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease, and certain forms of epilepsy and cerebral palsy. Nondementing CNS disorders may affect a range of functions, such as decision-making, psychosocial behaviors, participation in health-seeking and health-

maintaining behaviors, or occupational performance. Cosponsors are NINR, NICHD, NINDS, and OBSSR.

- RFA-NS-07-004, *Biomarkers for Neurodegeneration,* as part of the Neuroscience Blueprint effort for which NIA is a cosponsor. This initiative addresses a significant roadblock to the advancement of neuroprotective treatments by encouraging studies of biomarkers for neurodegenerative diseases, including rare forms of diseases such as Alzheimer's, Parkinson's, ALS, and Huntington's as well as disorders responsible for retinal degeneration and other damage to sensory systems.
- RFA-EY-07-001, *Therapeutics Delivery for Neurodegenerative Diseases* (R21), as part of the Neuroscience Blueprint effort for which NIA is a cosponsor. Challenges in the development and delivery of potential therapeutic agents for the treatment of neurological disorders of both the central nervous system (CNS) and peripheral nervous system (PNS) are significant. Major barriers include needed research in medicinal chemistry, pharmacodynamics, drug formulation, and development of approaches to overcome the challenge of delivering therapeutics across the blood brain barrier (BBB) or other barriers to specific cell populations in the CNS and the PNS.
- PA-06-533, *Functional Links between the Immune System, Brain Function, and Behavior* (R21), to identify research opportunities that may help to bridge the gap in understanding how immune cells and their mediators affect brain development, function, and behaviors related to cognition and mood. Neuroinflammation and neuroimmune activation have been shown to play a role in the etiology of a variety of neurological disorders, including rare forms of diseases such as Parkinson's and Alzheimer's, multiple sclerosis, and AIDS-associated dementia. NIA cosponsors this PA with NIMH, NIAMS, NIDA, NIBIB, NINDS, and NCI.

Rare-Disease Related Conferences and Workshops

NIA held an exploratory workshop titled, "Nuclear Receptors and Aging" on May 9-10, 2006, in Potomac, Maryland. Workshop presentations focused on the Nuclear Receptor Signaling Atlas (NURSA) project cofunded by NIA, NIDDK, and NCI and various topic areas that involve aging and age-related diseases, including (1) the role of the nuclear receptor (NR) homologue, daf-12, and its activating ligand in life span extension in *C. elegans*; (2) the roles of NRs in aging liver, kidney, prostate, and progeroid syndromes; (3) the role of NRs in caloric restriction and activation of NRs as caloric restriction mimetics; and (4) the role of steroid hormone receptors in aging. Information obtained in this workshop will be used in the development of an initiative to enhance our understanding of the roles of NRs in the aging process and in the initiation and progression of several age-related diseases, some of which are rare.

With recent NIA-supported research uncovering an important new gene and the identification of the protein present in the cellular and nuclear inclusions of a large subset of Frontotemporal dementia (FTD) cases, new avenues for research have opened up. A workshop to set the agenda for future research on FTD will be held in Miami on January 17-19, 2007, as a joint project between NIH and the Association for Frontotemporal Dementia. The workshop will be sponsored primarily by NINDS and will involve NIA and other Institutes.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

Overview

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) conducts and supports research on the causes, consequences, prevention, and treatment of problems and diseases that arise from alcohol misuse. In addition to alcohol use disorders such as alcoholism, medical consequences include digestive diseases (*alcoholic fibrosis*, alcoholic hepatitis, cirrhosis, and *alcoholic pancreatitis*), cardiomyopathy, hemorrhagic stroke, *Wernicke-Korsakoff syndrome*, and *fetal alcohol spectrum disorders*. Because alcohol exposure can adversely affect all organs and systems of the body, alcohol use is also associated with immune and reproductive dysfunction, and certain *cancers*. Several of the disorders resulting from alcohol abuse are rare diseases.

NIAAA intramural researchers are investigating the mechanistic basis of alcohol-related carcinogenesis (induction of cancer), which involves production of a specific type of mutagenic acetaldehyde DNA adduct. They are also deciphering the molecular basis of neurological disease in patients with rare diseases resulting from hereditary defects in DNA repair pathways. These diseases are *xeroderma pigmentosum, Cockayne syndrome, and ataxia telangiectasia.*

Recent Scientific Advances in Rare Diseases Research

Fetal alcohol syndrome and other alcohol-related birth defects

Fetal alcohol spectrum disorders (FASD) describes a spectrum of prenatal alcohol effects that arise from maternal alcohol consumption during pregnancy. The most serious disorder is fetal alcohol syndrome (FAS), a cluster of defects that includes mild craniofacial abnormalities, growth retardation, and central nervous system impairments manifested by deficits in executive function, memory and learning, and motor activity. FAS is the most common nonhereditary form of mental retardation. Alcohol-related neurodevelopmental disorder (ARND) is more variable in phenotype but can be equally debilitating. Various alcohol-related organ system birth defects have also been reported among children with FAS or ARND, including congenital heart defects, ocular abnormalities, and increased susceptibility to infections. The NIAAA is the lead Federal agency for funding research on FASD.

Alcohol causes apoptosis, or programmed cell death, of susceptible neurons at specific times throughout development. Neurons involved in the signaling of the neurotransmitter serotonin are among those vulnerable to alcohol's effects. NIAAA-supported researchers examined how agents that augment serotonin activity (serotonin agonists) protect against alcohol-induced cell death. They discovered that the protective effect involved activation of a specific pro-survival biochemical pathway that, when blocked by chemical inhibitors, abolished the protective effects of the serotonin agonists. The findings add to our understanding of how alcohol damages the fetal brain, and provide clues to drugs that might prevent or ameliorate the damage.

Alcohol exposure during early embryogenesis induces apoptosis within certain embryonic cell populations, leading to craniofacial and neurological defects. In cultured mouse embryos, which

are a tool for studies of early mammalian development, alcohol rapidly induced apoptosis in a time- and dose-dependent manner, suggesting induction by intracellular biochemical signals. Co-treatment with a naturally occurring growth factor prevented the alcohol-induced apoptosis. The results suggest that differences in expression of specific endogenous survival factors within individual embryos could be partly responsible for the variable FASD phenotypes among prenatally exposed offspring.

The mechanisms by which alcohol causes cognitive deficits are not fully understood, but one area of interest is its effects on neuronal plasticity, the ability of neurons to alter connections with other neurons. NIAAA-supported researchers found that a class of drugs called phosphodiesterase inhibitors, which is known to enhance neuronal plasticity in normal subjects, had the same effect in an animal model of FAS that exhibits a well characterized form of neuronal plasticity. Thus, this class of compounds may have potential as a treatment for the cognitive deficits associated with FAS.

Normal development of the brain requires ordered migration of immature neurons. One of the ways prenatal alcohol can harm the brain is by disrupting this process. In an animal model of FAS, scientists found that alcohol alters neuronal migration through its effects on the levels of specific signaling molecules in the cell (calcium ions and cyclic nucleotides). Treating cells in ways that reversed the effects of alcohol on these signaling processes also reversed its effects on neuronal migration, suggesting avenues for developing ways of preventing alcohol's harmful effects in early development.

Children with FASD exhibit altered behavioral responses to stressful or challenging situations. The body's response to stress is controlled by the hypothalamic-pituitary-adrenal axis. One laboratory has been using a rat model to investigate how prenatal alcohol exposure affects this system. On a task that measures anxiety, alcohol-exposed animals showed less anxiety-like behavior than controls. However, when animals were treated with the hypothalamic peptide hormone, corticotrophin-releasing factor (CRF), which increases anxiety, the alcohol-exposed animals were even more anxious than controls. Thus, increased sensitivity to CRF may mediate some of the aberrant behaviors associated with FASD.

Neonates, children, and adults with FASD may have disruptions in sleep patterns, which can contribute to reduced overall physiological functioning. Researchers using a rat model of FAS discovered that alcohol exposure during the period of rapid brain development produces biochemical alterations and structural damage in a brain structure that controls daily (circadian) rhythms such as sleep and hormone fluctuations. This damage caused permanent changes in rat circadian behaviors and in the ability to return to normal rhythms after disruption. The findings suggest a mechanistic basis for disrupted circadian rhythmicity.

Children with cognitive impairment benefit from multimodal presentation of information (i.e., employing vision, hearing, and motor skills), and computer instruction can fulfill this requirement. Enhancement of learning, retention and transference of information in alcohol-affected children through the use of computers was demonstrated. Two self-directed virtual world computer games were developed and tested with preschool and school-aged children with FAS or partial FAS to

teach fire safety and street safety skills. A majority of the children were able to learn the safety rules, perform correct responses on the computer, verbalize the rules after the computer training, and generalize the rules to appropriate real-world behavior.

Alcoholic pancreatitis

Long-term heavy alcohol consumption is associated with both acute and chronic pancreatitis, which is an inflammation of the pancreas. Acute pancreatitis occurs suddenly and lasts for a short period of time and usually resolves. Chronic pancreatitis does not resolve itself and results in a slow destruction of the pancreas. Either form can cause serious complications and may lead to multiple comorbidities including maldigestion, diabetes, and pancreatic cancer. NIAAA-funded researchers have made significant progress in understanding the underlying mechanisms by which alcohol intake leads to the development of pancreatitis.

Researchers studying mice have found that viral infection may be involved in the development of alcoholic pancreatitis. Exposure to alcohol alone or to an avirulent strain of coxsackie virus did not elicit pancreatic injury, but inflammation and fibrosis were evident when mice were exposed to alcohol and the virus at the same time. Exposure to a virulent strain of the virus induced pancreatic injury, which was exacerbated by exposure to alcohol.

Significant alterations in rat pancreatic gene expression were observed following long-term alcohol feeding. Activating transcription factor 3 (AFT3), heat shock protein 70 (hsp70), hsp27, and mesotrypsinogen were upregulated, whereas pancreatitis associated proteins (Pap), folate carrier, and metallothionein were downregulated. Based on the known functions of these genes, they likely contribute to sensitization of the pancreas to cellular stress and further injury. These changes in gene expression may help explain the relationship between long-term alcohol abuse and pancreatic disease.

Alcohol alone does not induce pancreatitis in animal models; however, alcohol sensitizes the pancreas to tissue injury due to cholecystokinin (CCK-8). Previously, researchers discovered that alcohol treatment of isolated pancreatic acinar cells augments CCK8-induced activation of nuclear factor kappa B (NF-kB), a key signaling molecule in the inflammatory response of pancreatitis. The recent work demonstrated that this enhancing effect of alcohol on NF-kB activation is partially mediated through activation of protein kinase C-epsilon (PKC-epsilon). Thus, selective inhibition of PKC-epsilon may represent a potential therapeutic approach to preventing or treating alcoholic pancreatitis.

An important feature of alcoholic pancreatitis is death of pancreatic acinar cells, which may occur through two pathways – apoptosis or necrosis. The severity of acute pancreatitis is directly correlated to the extent of necrosis and inversely associated with apoptosis. A study was undertaken in rats to determine the effects of alcohol on cell death pathways in the pancreas. Chronic alcohol administration resulted in significant decreases in the activities of caspase-8 and caspase-3 (markers of apoptotic cell death). In contrast, the activity of cathepsin B (a marker of necrotic cell death) was significantly increased. These results suggest that alcohol may promote pancreatic injury by preventing apoptosis and promoting necrosis. Understanding how alcohol

influences the pattern of death responses is important in investigations of the pathogenesis and treatment of pancreatitis.

Alcohol-induced hepatic fibrosis

Chronic heavy alcohol consumption is a major cause of liver cirrhosis, which ultimately results in death. Cirrhosis is a progression of fibrosis which results from excessive deposition of extracellular matrix components, especially collagen, in the liver. Although various hepatic cells are involved in the development of fibrosis, hepatic stellate cells (HSCs) are the primary source of extracellular matrix components. A major feature of fibrosis is the activation of HSCs, consisting of an early initiation phase followed by a perpetual phase. NIAAA-funded researchers have made significant progress in understanding the mechanisms of HSC activation, as detailed below.

NIAAA investigators previously showed that phagocytosis of apoptotic bodies by HSC results in their activation, and is associated with increased expression of transforming growth factor-beta (TGF-beta) and procollagen-alpha1. Using animal models of liver fibrosis and an immortalized HSC line, researchers have now shown that production of reactive oxygen species and NADPH activation play a role in upregulation of procollagen-alpha 1, but not TGF-beta. These results suggest that attenuation of oxidative stress may prevent liver fibrosis.

One of the key molecular changes that underlie activation of HSC is depletion of peroxisome proliferator-activated receptor gamma (PPARgamma). Treatment with PPAR gamma ligands or ectopic expression of the receptor suppressed HSC activation and decreased procollagen-alpha1 expression. Further studies have been undertaken to understand the molecular mechanism by which PPARgamma inhibits collagen production in HSCs. PPARgamma exerted its inhibitory effect on alpha1(I) procollagen promoter at a region proximal to -133bp. At this region, PPARgamma inhibits collagen promoter activity via inhibition of p300-facilitated NF-I binding to DNA in HSCs.

Several lines of evidence from one group of investigators have shown that adenosine and hepatic adenosine A(2A) receptors play an active role in the pathogenesis of hepatic fibrosis. Most notably, mutant adenosine A(2A) receptor-deficient mice were protected from hepatic fibrosis induced by hepatotoxins, and receptor antagonists diminished hepatic fibrosis in wild-type mice. The findings suggest a novel therapeutic target for the prevention of hepatic cirrhosis.

Research has established that the immune system plays an important role in disease-related liver damage, but the mechanisms are complex and not yet fully understood. NIAAA intramural researchers showed in a mouse model of liver fibrosis that natural killer cells (a class of immune cells) help to limit fibrosis by inducing apoptotic cell death of HSC. They also used mice with selective genetic deletions of key immune regulator molecules to trace the regulatory cascade involved in the process. This work helps clarify why suppression of the immune system by alcohol consumption can enhance progression of liver fibrosis.

Xeroderma pigmentosum (XP)

Patients with XP have a genetic defect in a specific DNA repair mechanism called nucleotide excision repair which is critical for repairing damage from ultraviolet radiation. A subset of patients develops a profound neurodegeneration condition, which is hypothesized to be caused by the inability to repair some form of internally generated DNA damage. Intramural researchers have identified a class of oxidative DNA lesions containing cyclopurines that may accumulate in the brain and prevent normal transcription, thus resulting in death of affected neurons.

Significant Ongoing Rare Diseases Research Initiatives

Intramural Research on Rare Genetic Diseases

Work is continuing on the mechanisms of neurological disease in *xeroderma pigmentosum (XP), ataxia telangiectasia (AT), and Cockayne syndrome (CS).* One focus is the mechanism by which cyclopurines in DNA block normal transcription and stimulate the production of unique mutant RNA transcripts, thus leading to brain cell death in XP patients. In AT, the focus is on the role of the ATM protein in dysfunctional DNA repair in cerebellar Purkinje cell neurons. With regard to CS, researchers are characterizing the different truncated polypeptides that occur at the gene locus for the human CSB protein, which is involved in DNA repair.

Prenatal Alcohol in Sudden Infant Death Syndrome (SIDS) and Stillbirth (PASS) Research Network

The PASS Network is a cooperative agreement mechanism established jointly with NICHD in 2003 to determine the underlying causes of *sudden infant death syndrome* and adverse pregnancy outcomes such as stillbirth and *fetal alcohol syndrome*, and the role of alcohol in their pathophysiology. Two comprehensive clinical sites in the Northern Plains States and Western Cape Province of South Africa, a developmental biology and pathology center, a physiology assessment center, and a data coordinating and analysis center comprise the network. Over a three-year period the PASS Network planned and piloted multidisciplinary investigations using common protocols within communities at high risk for maternal alcohol consumption during pregnancy. The protocols incorporate methodologies in epidemiology, physiology, pathology, and the neurosciences to decipher the complex relationship between prenatal alcohol exposure and other variables (such as compromised maternal nutrition during pregnancy) and their effects on the developing fetus and infant. In FY 2006 NICHD and NIAAA funded the next phase of the PASS Network, which will include a seven-year comprehensive longitudinal cohort study of 12,000 pregnant women and their infants up to one year of age. Enrollment is anticipated to begin in 2007. The long-term goals of this initiative are to decrease fetal and infant mortality and improve child health in the affected communities.

Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD)

Ongoing research within this cooperative agreement consortium exploits multiple international research sites with a high incidence of *fetal alcohol syndrome* (FAS) and fetal alcohol spectrum

disorders (FASD). Basic science and clinical projects within the consortium are aimed at refining the diagnosis of FAS, defining a specific neurobehavioral phenotype (or fingerprint) for FAS/FASD, exploring interventions to ameliorate the cognitive and behavioral aspects of the disorder in affected children, examining the effects of a nutritional intervention for alcohol-consuming mothers on offspring growth and development, and developing diagnostic tests for earlier detection of FAS and FASD in affected individuals. The NIAAA will issue an RFA in FY 2007 to continue and expand the CIFASD.

New/planned Extramural or Intramural Research Initiatives

The following new Funding Opportunity Announcements were issued by NIAAA or jointly with other ICs in FY 2006:

RFA-06-004, RFA-06-005, Alcohol Metabolism and Epigenetic Effects on Tissue Injury. One of the objectives of this RFA was to decipher the effects of prenatal alcohol exposure on epigenetic mechanisms, to identify imprinted genes that are permanently altered by alcohol exposure, and to determine the physiological and behavioral consequences of these alterations for the developing animal. Three grants addressing this objective were funded.

PA-06-413, PA-06-414, Diet, Epigenetic Events, and Cancer Prevention (with NCI, NIDDK, ODS). The NIAAA is seeking applications that investigate the interactions between alcohol and dietary supplements that contribute to epigenetic mechanisms leading to alcohol-related cancers such as *hepatocellular carcinoma*.

Rare Disease-specific Conferences, Symposia, or Workshops

Rare Diseases Resulting From Defects in DNA Repair Genes, symposium at the September 2006 Environmental Mutagen Society meeting, Vancouver, Canada, organized by an NIAAA intramural researcher.

Fetal Alcohol Spectrum Disorders Study Group annual meeting held as a satellite of the June 2006 Research Society on Alcoholism annual meeting in Baltimore, Maryland. NIAAA supports this meeting annually through a 5-year conference grant (R13). The meeting is designed to inform researchers, parents, and health care providers of the latest research findings on a variety of topics related to *fetal alcohol syndrome* and *alcohol-related neurodevelopmental disorder*.

International Symposium on Alcoholic Liver and Pancreatic Diseases and Cirrhosis, Marina Del Rey, California, May 18-19, 2006, cosponsored by NIAAA, USC-UCLA Research Center for Alcoholic Liver and Pancreatic Diseases, USC Cirrhosis Research Center, and University of Southern California School of Medicine. Among several topics, mechanisms of alcohol-induced *liver and pancreatic fibrosis* were discussed. Proceedings of the symposium were published in J. Gastroenterol. Hepatol. 21(Suppl 3):S1-S110.

In FY 2005 the NIAAA and ORD cosponsored a satellite symposium, "*Mechanisms of Alcohol-Induced Hepatic Fibrosis*," at the annual meeting of the Research Society on Alcoholism. A

summary of the symposium has now been published: Purohit V, Brenner DA. (2006) Mechanisms of Alcohol-Induced Hepatic Fibrosis: A Summary of the Ron Thurman Symposium. *Hepatology* 43:872-878.

Activities with Rare Diseases Patient Advocacy Groups to Stimulate Research

Patient Outreach on Xeroderma pigmentosum, Cockayne syndrome, and Ataxia Telangiectasia

One of NIAAA's intramural researchers works with patient organizations for these rare diseases and counsels parents and patients on how to arrange for tissue sample donations to the appropriate repositories.

Education Activities on Rare Diseases for the Researcher, Public, and the Health Care Provider Communities

Education Outreach on Fetal alcohol syndrome

The Communications and Public Liaison Branch of NIAAA is working with the National Organization on Fetal Alcohol Syndrome, a public advocacy group, to promote the Public Awareness Campaign for African American Women in the District of Columbia as a model universal FAS prevention program that can be implemented in other communities. A presentation on the success of the program was made at the School of Social Work, Catholic University.

NIAAA engaged in science education outreach by conducting a workshop for teachers at the National Science Teachers Association Southern Regional Conference in Nashville, Tennessee, to highlight the Institute's science education programs. Among the programs is a curriculum to teach students about *fetal alcohol syndrome*. Staff also gave presentations at four public high schools in Nashville. Travel for this outreach effort was sponsored by the Dana Foundation.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

Overview

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. Many of the disorders encompassed by the NIAID mission are rare diseases in the United States. Rare immune disorders affect, in aggregate, a large number of Americans, and understanding these disorders will provide important insights into how the healthy immune system functions. Some infectious agents that cause rare diseases are common worldwide, but are not prevalent in the United States. Others affect very few people at present, but have the potential to emerge among a much larger population—either naturally, which public health authorities fear may occur with H5N1 avian influenza infection in humans, or deliberately, such as might occur with anthrax or Ebola should these agents be used in a bioterror attack. For these reasons, the NIAID research portfolio has recently been expanded considerably to meet the challenges posed by newly emerging and re-emerging infectious diseases and bioterrorism.

For the purpose of reporting on NIAID rare diseases research activities, this report is divided into four areas: infectious diseases, primary immunodeficiency diseases, autoimmune diseases, and other immune system-mediated conditions. *Infectious diseases* are caused by bacteria, viruses, fungi, protozoans, and parasites. *Primary immunodeficiency diseases* are hereditary disorders caused by intrinsic defects in the cells of the immune system and are characterized by unusual susceptibility to infection. *Autoimmune diseases* result when the immune system in the body attacks its own organs, tissues, and cells. *Other immune system-mediated diseases*, such as asthma and allergic diseases, are caused by inappropriate or destructive immune responses. NIAID research seeks to understand the mechanisms by which these diseases harm people and how the immune system responds to them. The ultimate goal is to develop new and more effective strategies of disease diagnosis, treatment, and prevention.

Rare Infectious Diseases

Scientific Advances

Anthrax

The ability to develop new countermeasures for bioterror agents, such as anthrax and plague, is limited by the fact that human trials cannot be performed using these pathogens. In order to better evaluate treatment regimens, NIAID-funded researchers developed a method using animal models to mimic human responses to antibiotics. The researchers found that, compared with other ways to deliver the antibiotic, the new method more accurately simulates what happens in humans. This research enhances the confidence with which animal models may be used to reliably predict proposed antibiotic treatments in humans. In a separate study, NIAID researchers developed a simple, sensitive and noninvasive assay for high throughput screening of anthrax toxin inhibitors. The assay is now being used by the NIH Chemical Genomics Center for high throughput screening

of anthrax toxin inhibitors. Of the 10,000 compounds screened thus far, several potent anthrax toxin inhibitors have been identified.

Conventional prophylactic treatment against inhalational anthrax due to spore exposure involves a prolonged course of antibiotics. NIAID researchers showed that a short course of antibiotic treatment was an effective prophylactic treatment in vaccinated nonhuman primates challenged with a high-dose of *Bacillus anthracis* spores. Thus, vaccination after exposure can shorten the duration of antibiotic prophylaxis required to protect against inhalational anthrax. This finding may impact public health management of a bioterrorism event.

Avian influenza

Avian influenza viruses, which usually do not infect humans, are a significant global human health threat. The potential of a virus to infect and spread in humans who have not been previously exposed could result in a global influenza pandemic. NIAID-funded researchers conducted the first large scale sequencing of Avian Influenza Virus (AIV) isolates and doubled the amount of AIV sequence data in the public domain. This sequence data includes 2,196 AIV genes and 169 complete genomes from a diverse sample of birds. This large-scale sequence study provides valuable data to the public and was already used to identify a potential marker to predict which AIV strains will be more dangerous.

Other NIAID-funded researchers determined the structural features of the hemagglutinin (H) protein from a highly pathogenic H5N1 influenza virus (A/Vietnam/1203/2004; Vietnam 2004). The overall molecular topology was found to be similar to that of many other influenza H proteins and was closer to the structure of H1 hemagglutinin of the deadly 1918 strain than to other H5 proteins. This research provides clues that might help define which hemagglutinin properties confer increased virulence.

Current influenza vaccines elicit antibodies against a single specific strain of the virus, but new strategies are urgently needed for protection against many strains. While DNA vaccines have been shown to provide protection in animals against many different virus strains, they are not very potent. NIAID scientists tested in animals a DNA prime-recombinant adenovirus boost vaccine targeted at one of the influenza viral proteins, nucleoprotein (NP). This strategy was substantially more potent than DNA vaccination alone and more importantly, protected against a lethal challenge of the highly pathogenic H5N1 virus. Thus, gene-based vaccination with NP may be a way to provide protective immunity against diverse influenza viruses.

Botulinum toxin

Botulinum toxins rank among the most toxic substances known and are responsible for food poisoning cases with high morbidity and mortality. However, there is limited understanding of how the toxin recognizes and enters neurons. NIAID-funded researchers identified how the toxin "catches a ride" into the neural cell. The toxin binds to a synaptic vesicle protein SV2 (isoforms A, B, and C) and enters the neuron through these synaptic vesicles. Understanding how these

toxins enter neurons opens opportunities to develop new strategies for prophylaxis and therapeutics.

Congenital cytomegalovirus (CMV)

Congenital CMV is the most common intrauterine infection in the United States, with 3,000-4,000 infected newborn infants developing symptomatic CMV disease each year. However, it has not been known how an infected mother passes the infection to the fetus. NIAID researchers found that CMV can cross the placenta through a transport pathway for IgG antibodies. These findings provide new insight into the means by which CMV crosses the placenta to infect the fetus and may explain why treating with hyperimmune IgG for primary CMV infection during gestation works. This finding suggests that vaccination may be a preventive strategy.

Ebola

Ebola virus causes a hemorrhagic fever syndrome that is associated with high mortality in humans. Developing a vaccine is important because there are no effective therapies. Some vaccines using two Ebola proteins, glycoprotein (GP) and nucleoprotein (NP), have been tested but they have some side effects. Researchers at the NIAID Vaccine Research Center (VRC) found a mutated GP that could be used without NP to confer immune protection. This simplified vaccine is a potential human vaccine candidate. Other NIAID researchers explored a paramyxovirus-vectored vaccine. The researchers found a single intranasal inoculation could protect guinea pigs from a lethal-dose Ebola virus challenge. The highly effective immunity achieved with a single dose suggests that intranasal immunization with live vectored vaccines may be an approach to induce a protective response.

Other NIAID-funded researchers studied two glycoproteins of the virus envelope ($GP_{1,2}$) used by the virus to attach and enter cells. The researchers found Lake Victoria Marburg virus and Zaire Ebola virus bind filovirus-permissive cell lines with a specific portion of the GP_1 subunit. This finding that these two hemorrhagic fever viruses share a receptor may make it possible to develop drugs or vaccines that provide protection against both viruses at the same time.

Escherichia coli (Enterotoxigenic)

Two globally prevalent pathogens are enterotoxigenic *E. coli* (ETEC) and enteropathogenic *E. coli* (EPEC). ETEC typically causes travelers' diarrhea and EPEC most often causes diarrhea in children. Recently, scientists have shown that people are often infected with multiple strains of *E. coli* and that infection with more than one strain may increase the severity of the disease. NIAID-funded researchers studied cells infected with both of these pathogens. Toxins from ETEC increased the damage EPEC causes to epithelial cells, as well as components released from EPEC-damaged epithelial cells increased the severity of ETEC infection in cells. These data suggest that coinfection with these two pathogens may lead to increased disease severity in patients.

Leishmaniasis

Leishmania parasites are responsible for an array of disfiguring, fatal diseases worldwide, including sand fly disease, kala-azar, Dum-Dum fever, and "Baghdad boil." During infection with *Leishmania*, the pathogen resides in an organelle of the host cell called a phagosome. Phagosomes usually engulf and digest pathogens and present the resulting small protein fragments of the digested pathogen to CD8+ T cells (immune cells) to make antibodies in a process called cross-presentation. NIAID researchers found *Leishmania* is not digested by this mechanism; this may represent a strategy the parasite has evolved to delay the onset of host immunity. Researchers hope to disable these novel parasite proteins that protect the pathogen and to create *Leishmania* mutants that can generate vaccines.

Lyme disease and other tick-borne pathogens

Lyme disease, caused by the bacterium *Borrelia burgdorferi,* is typically transmitted by ticks to mammals. The outer surface of *Borrelia burgdorferi,* changes dramatically as the pathogen moves from the tick vector to a mammalian host. One protein, called outer surface protein A (OspA), is abundant on the surface of bacteria present in the midguts of infected ticks before they feed. However, another protein, called OspC, replaces OspA on the bacterial surface after ticks begin to feed on a mammalian host. This switch in the outer surface of the Lyme disease spirochete was previously hypothesized to be required for transmission of *B. burgdorferi* from the tick to the mammalian host. NIAID researchers directly tested this hypothesis and found that the OspC protein is absolutely essential for initiating mammalian infection by the Lyme disease bacteria. This research identified a vulnerable time and target with which to block infection and ensuing disease.

It has long been known that immunizing mice with OspA protects against the transmission of *B. burgdorferi* infection and reduces feeding ticks from carrying this pathogen. Recently, NIAID-funded researchers developed a murine-targeted OspA vaccine using vaccinia virus and found a single dose oral vaccination could both protect the mice against infection by *B. burgdorferi* and more importantly reduce feeding ticks from carrying this pathogen. These findings indicate that such a vaccine is effective and may provide a means to lower the incidence of human disease in endemic areas.

The severity of Lyme disease varies due to many different types of outer surface protein C (OspC) associated with the illness. NIAID-funded researchers examined Lyme disease patients in Maryland and identified three additional types (C, D, and N) of OspC associated with invasive infections. Using this information, the researchers tested several different recombinant OspC proteins and protein fragments and identified new epitopes mice will make antibodies against. These findings suggest one possible reason why there is a variable response in making antibodies and in severity of the disease. Another group of NIAID-funded researchers found the differences in disease severity can be explained in part by genetic differences of innate immunity of the host. Using a mouse model of Lyme disease, the researchers found that when an effector molecule MyD88 of innate immune cells was absent, this enhanced the ability of the tick to acquire and transmit *B. burgdorferi.*

Another group of NIAID researchers studied the immune response of one immune cell, human monocyte, infected with *B. burgdorferi*. These researchers followed how toll-like receptors (TLR), receptors involved in immune response, changed during infection; two (TLR2 and TLR1) had higher levels, and one (TLR5) was down-regulated. Researchers suggest the down-regulation of TLR5 could be used by the pathogen to evade an immune response and alternatively, the host could down-regulate TLR5 where a strong and persistent innate immune response is not desirable—for example, the central nervous system or intestinal mucosa. These results indicate that TLR expression patterns may change in response to diverse environments and that they may be regulated differently at the site of inflammation.

Relapsing fever virus (Borrelia)

The spirochetes that cause tick-borne relapsing fever and Lyme disease are closely related human pathogens, yet they differ significantly in ecology and how they cause disease. Researchers at NIAID's Rocky Mountain Laboratories identified a protease in relapsing fever spirochetes *Borrelia hermsii* that is absent from Lyme disease spirochetes. This protease protects the relapsing fever spirochetes from oxidative stress and killing by the host's white blood cells. This enzyme may play an important role in protecting the bacteria from the host's innate immune response, allowing the relapsing fever spirochetes to achieve high cell densities in the blood during acute illness in humans and may provide clues on how to control infection.

Tick-borne encephalitis virus

Langat virus (LGT), the naturally attenuated member of the tick-borne encephalitis virus (TBEV) complex was previously tested in clinical trials as a live TBEV vaccine and was found to induce a protective, durable immune response; however, it retained the ability to invade the neurosystem in mice and humans. NIAID researchers were able to make temperature sensitive mutants of this virus and found that these mutants lacked the ability to invade the neurosystem in immunodeficient mice. In another study, NIAID researchers compared three antigenic chimeric live and inactivated tick-borne encephalitis virus vaccines for safety, immunogenicity and efficacy in rhesus monkeys. They found that two vaccines, TBEV/DEN4Delta30 and LGT/DEN4, are safe and efficacious in rhesus monkeys. A Phase I clinical trial testing LGT/DEN4 vaccine in healthy adult volunteers recently was conducted at Vanderbilt University Medical Center and the vaccine failed to provide sufficient immunity. Further development of other candidate vaccines is under way.

Plague

Yersinia pestis causes bubonic plague, characterized by an enlarged, painful lymph node, termed a bubo. In susceptible animals, the bacteria rapidly escape the lymph node, spread through the blood, and produce fatal sepsis. Previously, it was thought that *Y. pestis* is virulent because it avoids phagocytosis. NIAID-funded researchers examined the *Y. pestis* gene expression and found that the bacterium makes several proteins that protect it against the nitric oxide environment the host uses to kill the bacterium. Hmp flavohemoglobin, a hemoglobin-like protein, was found to detoxify the nitric oxide and decrease the virulence of the bacteria when the gene was mutated.

Yersinia pestis is transmitted by fleas and usually leads to bubonic plague, but it can also cause primary septicemic plague. The common way investigators mimic a flea bite is intradermal injection of *Y. pestis*, but this leads only to bubonic plague. NIAID-funded researchers found that a particular strain of *Y. pestis* could cause the fatal primary septicemic plague at low incidence when transmitted by fleas, but caused no disease if given by an intradermal or subcutaneous injection. This strain lacked the plasmid that carries the cell-surface plasminogen activator (Pla). The results clarify a long-standing uncertainty about the origin of primary septicemic plague, and support an evolutionary scenario in which plague first emerged as a flea-borne septicemic disease of limited transmissibility. Subsequent acquisition of the Pla gene by horizontal transfer enabled the bubonic form of disease and increased the potential for epidemic spread.

Schistosomiasis

Chronic S*chistosoma mansoni* infection can cause a life-threatening liver fibrosis. NIAID researchers infected interleukin-21 (IL-21) receptor-deficient mice with *Schistosoma mansoni.* They found that the IL-21 receptor promoted liver fibrosis by enhancing Th2 effector function. The results from this study suggest that antibodies or small molecule antagonists that disrupt interleukin-21 receptor signaling might be useful in the treatment of a wide variety of chronic fibrotic diseases, including liver fibrosis, idiopathic pulmonary fibrosis, and systemic sclerosis.

S*chistosoma japonicum* is a waterborne parasite, and the disease it causes, schistosomiasis japonica, is a major public health problem in southern and southwestern China among other places. Through an ongoing collaboration between the China Tropical Medicine Research Center, the Chinese Human Genome Center at Shanghai and international collaborators, the genome and proteome of *S. japonicum* is being analyzed. Approximately 100,000 transcript sequences have been determined, along with more than 3,000 protein sequences. It is anticipated the complete genome sequence for *S. japonicum* will be reported in the scientific literature soon. This will represent a landmark achievement in schistosomiasis research, enabling scientists to better understand the biology of the microbe and the host response, and develop improved diagnostics, vaccines and therapeutics.

Severe acute respiratory syndrome (SARS)

Severe acute respiratory syndrome (SARS) emerged in 2003, but has since disappeared from the human population. In August 2004, SARS coronavirus (SARS-CoV) was added to NIAID's list of Category C priority pathogens for biodefense. Concern that SARS-CoV could reemerge makes it imperative that effective means to prevent and treat the disease are developed. Two NIAID-funded research groups investigated structural components of SARS and other coronaviruses. The first group investigated the papain-like protease (PLpro), a protein used in the replication of SARS and other coronaviruses (CoV). From a bioinformatic analysis of multiple CoVs, NIAID-funded researchers identified several important structural sites of the SARS-CoV PLpro which may be critical to the development of antiviral drugs. A second group of NIAID-funded researchers provided two-dimensional images of the S, M, and N proteins of SARS-CoV and two other

coronaviruses using electron cryomicroscopy. This is the first detailed view of coronavirus ultrastructure and assists in the understanding of the coronavirus assembly pathway.

Smallpox

Smallpox is a highly lethal infectious disease caused by the *Variola major* virus and it is a Category A priority pathogen. After smallpox was eliminated from the human population in the late 1970s, immunization programs worldwide were discontinued. Very few people born since then have ever been vaccinated, and the protection for people vaccinated years ago has declined substantially. The possibility that smallpox might be used as a biological weapon has made the development of smallpox treatments that could help people with little or no immunity a high priority.

NIAID-funded researchers found that ST-246, an orally bioavailable antipoxvirus compound, protected mice from a lethal orthopoxvirus challenge. These results, coupled with its lack of toxicity, make ST-246 a superb candidate for further development and eventual licensure by the Food and Drug Administration (FDA) to prevent or treat smallpox infection in humans.

For example, if someone has the skin disease atopic dermatitis (AD), immunization can cause the potentially life-threatening complication eczema vaccinatum (EV). NIAID-funded researchers, building on their earlier work, learned more about why AD patients are at risk for EV. These researchers determined that inflammation-promoting molecules interleukin-4 (IL-4) and interleukin-13 (IL-13) control the production of a protein (LL-37) in skin. Skin cells from healthy individuals produce more LL-37, than do skin cells of patients with AD. These researchers turned off IL-4 and IL-13 with neutralizing antibodies and restore LL-37 and protection against vaccinia virus. Together, their findings suggest a strategy for new treatment approaches to EV, including development of drugs that mimic the action of LL-37, or neutralize IL-4 and IL-13.

Another group of NIAID researchers made the first candidate monoclonal antibody that could be used in place of the currently approved smallpox vaccine. These researchers used portions of chimpanzee antibodies (Fabs) against the B5 envelope glycoprotein of vaccinia virus and combined them with portions of human immunoglobulin to make chimpanzee/human anti-B5 monoclonal antibodies. These monoclonal antibodies protected mice from a virulent vaccinia virus challenge. These antibodies may be useful in developing therapeutics to prevent and treat smallpox.

Other NIAID researchers focused on understanding poxvirus biology and structure. One group of NIAID researchers defined the structure of the enzyme G4, an enzyme required for proper folding of the viral proteins which are critical for virus maturation and host cell infection. Their studies found several structural features such as a thioredoxin fold and a Cys-X-X-Cys active site which may serve as a target for drug design. Another group of NIAID researchers described the structural features of the protein D13, which makes a scaffold structure and forms the external lattice responsible for the spherical shape of immature vaccinia virions.

Another NIAID research team made important advances in understanding how poxviruses enter cells. These researchers described a complex of eight viral membrane proteins that are conserved in all members of the poxvirus family and showed that at least six of them are essential for fusion of viral and cellular membranes. If vaccinia virions lack any one of these six, the virus cannot enter cells and is noninfectious. In addition, the researchers identified two pathways by which the virus enters the cells. This finding may explain why the virus has such a wide host range.

Spongiform encephalopathies

Transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative diseases that may be caused by small proteinaceous infectious particles, or prions. They include scrapie of sheep, Creutzfeldt-Jakob disease of humans, bovine spongiform encephalopathy (BSE) or "mad cow" disease, and chronic wasting disease (CWD) of deer and elk. CWD is emerging in deer and elk in an increasingly wide geographic area. While there is no evidence CWD can spread to humans, a related spongiform causes a variant of Creutzfeldt-Jakob disease in humans. Meat consumption would be the most likely way humans could be exposed. NIAID-funded researchers tested to see if skeletal muscle of diseased deer contains infectious prions. The researchers used bioassays in transgenic mice to show the presence of infectious prions in skeletal muscles of CWD-infected deer. These results indicate that humans consuming or handling meat from CWD-infected deer might be at risk to prion exposure. The studies reinforce the need to develop testing that can detect CWD before the muscle becomes infectious.

Other NIAID-funded researchers investigated whether scrapie-infected mice exhibit signs of infection beyond the neural system. They found hearts of transgenic mice expressing a prion protein had amyloid deposits, myocardial stiffness and cardiac disease. This research identified heart infection as a new aspect of TSE diseases and also provides cardiologists an animal model in which to study heart amyloidosis, a family of heart diseases that also affect humans.

While there are some drugs that can delay disease after a peripheral scrapie inoculation, few compounds are effective against advanced disease. NIAID-funded researchers tested multiple related porphyrins and found that Fe(III)meso-tetra(4-sulfonatophenyl)porphine (FeTSP) injected into mouse brains after intracerebral scrapie inoculation could increase the survival. In a second study, these NIAID-funded researchers combined this newly discovered compound, FeTSP, with pentosan polysulfate PPS (Elmiron), a semisynthetic carbohydrate polymer approved by the FDA as an oral therapy for interstitial cystitis. Combination treatment with PPS and FeTSP in mice beginning 14 or 28 days after scrapie inoculation significantly increased survival times, these compounds may act cooperatively or synergistically *in vivo*. Combination therapy may therefore be more effective for treatment of TSE and related diseases.

Another group of NIAID researchers used spectroscopy to examine how various anti-TSE compounds interact with prion proteins. These studies led to a better understanding of the likely mechanism of action of several important classes of anti-TSE drugs. Two types, large polyanionic polymers and small molecules such as the porphyrins and phthalocyanines, interact with the amino-terminal half of normal prion protein. Many of the small molecule inhibitors bind to prion protein in an aggregated state, and thereby mimic the large polymeric inhibitors. These inhibitors

cluster the prion protein, which causes the prion protein to be taken into the cell prevented from converting to the pathological form. Improved understanding of these prion inhibitors may facilitate the development of anti-TSE treatments.

Streptococcal Group A Invasive Disease

Streptococcus pneumoniae is a major cause of pneumonia, meningitis, bacteremia, and swelling in the ear in young children and older adults. There are at least 90 serotypes, each with a unique polysaccharide capsule (chain of sugars on the outside of the bacteria). In order to determine which vaccines to use, identifying the geographic distribution of serotypes is important. There are several methods for typing *Streptococcus pneumonia*, but they are manual, slow and tedious to perform. Recently a semi-automated assay developed that was shown to be highly specific, using bacterial strains representing all 90 known serotypes present in the United States. NIAID-funded researchers validated the assay using 495 clinical isolates of *Streptococcus pneumonia* from three different countries: Brazil (345), Denmark (100), and Mexico (50). This new methodology will be useful for large epidemiologic studies because the assay is simple, reliable and fast.

Streptococcus Group B

Group B streptococci (GBS) are the major cause of bacterial infections in newborns. They can cause sepsis and meningitis. GBS has recently been reported as an increasingly important cause of invasive disease in the elderly, especially individuals with other diseases. Early efforts to prevent GBS disease focused on developing vaccines against the polysaccharides on the bacteria's capsule. There are nine different types of GBS capsule, however, and each vaccine only provides protection against one type. An alternative approach for GBS vaccine development is to identify conserved proteins that provide cross protection against all GBS strains. NIAID-funded researchers conducted a genomic analysis of eight different GBS strains and identified genes in each of the strains that encode pilus-like structures (long surface structures made of proteins that extend out from the cell wall and capsular polysaccharide of GBS). Protein components from these pilus-like structures were shown to be antigenic and induce protective immunity in mouse models. This research suggests that proteins from pilus-like structures may be promising potential vaccine candidates.

S*treptococcus pneumonia, drug-resistant invasive diseases*

Group A streptococci (GAS) cause a spectrum of illness that ranges from uncomplicated to life-threatening. GAS can be treated with penicillin, but some patients have adverse reactions to penicillin. Patients who react to penicillin are treated with macrolides, but macrolide-resistance has emerged in many parts of the world. NIAID-funded researchers studied the mechanisms of newly arising GAS macrolide-resistance by genotyping a total of 212 strains of macrolide-resistant GAS from 34 countries, including countries in all 6 major continents. By applying mathematical modeling, the researchers estimate that GAS acquired macrolide-resistance as a result of more than 49 independent genetic events. The findings suggest that acquisition of macrolide resistance followed by transfer to GAS with different genetic backgrounds and global distribution of

macrolide-resistant strains are mechanisms that contribute to the current GAS macrolide-resistance problem.

West Nile virus

West Nile virus (WNV) belongs to a group of disease-causing viruses known as flaviviruses, which are spread by mosquitoes and other insects. WNV was first isolated in Uganda in 1937 but emerged in 1999 for the first time in the Western Hemisphere in the New York City area. It has subsequently become endemic across North America. There are no drugs to treat the virus and no vaccines available to prevent infection in humans. Research on WNV and other arthropod-borne viruses is part of NIAID's comprehensive emerging infectious diseases program.

About 1 of approximately every 150 human WNV infections results in neuroinvasive disease. Immunosuppressed patients are at higher risk of developing this severe neuroinvasive disease. NIAID-funded researchers developed an immunosuppressed hamster model of WNV infection. By comparing WNV infection in immunosuppressed and immunocompetent hamsters, the researchers found that the immunosuppressed hamsters developed a much more severe disease and had a higher fatality rate than the immunocompetent hamsters. While WNV infection of the immunocompetent animals was confined to the brain and spinal cord, WNV infection in the immunosuppressed animals was much more extensive and involved the adrenal, kidney, heart and lung, as well as brain and spinal cord. As with immunosuppressed people, the immunosuppressed hamsters failed to develop antibodies against WNV and rid the body of infection. The results provide insights into the increased severity of WNV infection observed in immunosuppressed people.

Several groups of NIAID-funded researchers have developed high-throughput anti-WNV assays and used these assays to identify several classes of small molecule anti-WNV compounds as potential therapeutics. One small molecule anti-WNV compounds tested was RNA interference (RNAi), a recently discovered cellular mechanism in which small pieces of double-stranded RNA (small interfering RNAs or siRNAs) suppress the expression of genes. NIAID-funded researchers used RNAi to protect laboratory animals against lethal infection with WNV and Japanese encephalitis virus (JEV). In one study, the investigators demonstrated that a single siRNA, targeting a conserved sequence present in both WNV and JEV, protected mice infected with WNV or JEV from lethal encephalitis when administered before or after infection.

While several West Nile virus (WNV) vaccines are in development, none is yet available for humans. In two complementary papers, NIAID-funded researchers describe the production, purification and protection of a nonreplicating recombinant subunit WNV vaccine in mice and in a hamster model of WNV encephalitis. Nonreplicating vaccines may be safer than replicating vaccines, such as a chimeric vaccine or live attenuated vaccine, in populations at high risk for complications, such as the elderly and immunosuppressed individuals. These studies demonstrated that immunization of hamsters with the nonreplicating subunit WNV vaccines plus adjuvant protected them from severe WNV disease up to 12 months post-vaccination. These results are highly encouraging and warrant further vaccine development. NIAID researchers also tested a live attenuated West Nile vaccine candidate, WN/DEN4del30 virus, and found it to be safe in a variety

of experimental animals such as mice, geese and monkeys. A Phase I clinical trial of this vaccine candidate was initiated this year at the Johns Hopkins School of Public Health.

Clinical Trials Initiated in FY 2006

- Tick-borne encephalitis virus vaccine: A Phase I clinical trial of LGT/DEN4 vaccine in healthy adult volunteers was conducted at Vanderbilt University School of Medicine and the vaccine failed to provide sufficient immunity. Further development of other candidate vaccines is under way.
- Ebola vaccine: A Phase I adenovirus vaccine trial in humans began in September 2006.
- Cytomegalovirus vaccine: A trial began recruitment in April 2006 in transplant recipients.
- SARS vaccines: The VRC contracted with Vical, Inc., to manufacture a single closed, circular DNA plasmid-based vaccine encoding the S protein of SARS-CoV. A Phase I open-label clinical study to evaluate safety, tolerability, and immune response was completed in May 2006. The study enrolled ten healthy 18-50 year old subjects, and administered 4 mg DNA vaccinations at three one-month intervals. Interim study results indicate that the vaccine is well tolerated, and immunogenicity analysis of the stored samples is ongoing.
- *Streptococcus pneumoniae* vaccine: The Comprehensive International Program for Research on AIDS (CIPRA) project at the University of Witwatersrand is enrolling subjects into a Pediatric Vaccine Protocol to study antibody responses to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccines.
- West Nile Virus vaccine: NIAID intramural scientists, in collaboration with Vical, Inc., have developed a second generation DNA vaccine using an improved expression vector. A Phase I clinical trial commenced in March 2006.

Ongoing Clinical Trials

- Avian influenza vaccines**:** cGMP manufacture of H5N1 pandemic influenza vaccines for human clinical studies is under way, including a Phase I clinical trial of a DNA vaccine encoding H5N1 that is scheduled for the fourth quarter of 2006. Additional plans include influenza A subtype H7N7 and H5N1 (clade 1 and clade 2) vaccines.
- Cytomegalovirus vaccines: Phase I/II trials are ongoing for three different candidate vaccines for human CMV. One clinical trial is testing a vaccine's effectiveness to prevent infection for post-partum CMV-seronegative women.
- Cytomegalovirus antiviral: The Adult AIDS Clinical Trials Group is analyzing data from a Phase III clinical trial that examined valganciclovir's safety and effectiveness in preventing cytomegalovirus organ damage in HIV-infected subjects. A study of oral valganciclovir syrup in neonates and young infants with symptomatic congenital CMV disease to determine the pharmacokinetics/pharmacodynamics and safety and tolerability in this population has been recently completed. A new study is being planned to use the equivalent oral dose and extend the treatment period to six months.
- Eosinophilic gastroenteritis therapeutics: Omalizumab (therapeutic monoclonal anti-IgE) for eosinophilic gastroenteritis study is currently enrolling subjects.
- GBS vaccine: NIAID-supported scientists are conducting a Phase II randomized, double-blinded, comparative clinical trial for a group B streptococcal (GBS) type III polysaccharide-

tetanus toxoid vaccine in 18-40 year old women to evaluate prevention of vaginal acquisition of GBS type III. The clinical trial is expected to be complete by FY 2008.

- Influenza Antiviral: NIAID is supporting a study to help characterize the safety profile of oseltamivir in very young children and future studies are in the advanced planning stages.
- Shiga toxin-producing *Escherichia coli* antivirals: The NIAID-supported Vaccine and Treatment Evaluation Units (VTEUs) will continue Phase I testing of monoclonal antibodies against Shiga toxin of *E. coli* O157:H7 and other Shiga toxin-producing *Escherichia coli* strains as a way to prevent the development of hemolytic-uremic syndrome in infected children.
- Syphilis therapeutic: The NIAID-supported STD Clinical Trials Unit is conducting a randomized Phase III trial to evaluate if oral azithromycin is equivalent to injectable benzathine penicillin for treatment of primary syphilis.
- Typhi vaccine: The VTEUs began a clinical trial on the Safety and Immunogenicity of a Live, Attenuated *Salmonella typhi* vaccine (Ty800).
- West Nile virus natural history: The NIAID-funded Collaborative Antiviral Study Group (CASG) is conducting a Phase I/II clinical trial to assess the natural history of WNV encephalitis to characterize the serious disease patterns and evaluate potential prognostic indicators of disease progression. The CASG is also testing intravenous immunoglobulin G (Omr-IgG-am^{TM}) in an FDA-cleared Phase I/II randomized, placebo-controlled clinical trial.
- West Nile virus vaccines: Two Phase I clinical trials testing WNV vaccines were initiated in FY 2005. One is a chimeric WNV using a dengue virus as a backbone to carry West Nile virus genes and another is a DNA-based vaccine, developed in collaboration with Vical, Inc.

Planned Clinical Trials and IND applications

- Ebola vaccine: The NIAID VRC will continue to develop an accelerated adenoviral Ebola vaccination strategy to be used in an acute outbreak or occupational exposure. Scientists plan to demonstrate product efficacy, evaluate the vaccine in the presence of preexisting adenoviral immunity, and evaluate alternative strategies to overcome such immunity.
- Enteroaggregative *E. coli*: The VTEU will conduct a clinical trial in fall 2006/winter 2007 on the pathology of enteroaggregative *E. coli* in adult volunteers.
- SARS vaccines: NIAID plans to conduct Phase I clinical trials of two inactivated whole virus SARS vaccines and several recombinant SARS S glycoprotein vaccines.
- Smallpox antiviral: NIAID has supported development of an IND to support the use of cidofovir as primary treatment of smallpox. The VTEU has developed clinical protocols to assess activity of cidofovir as back-up therapy after vaccine immune globulin (VIG) for complications related to smallpox vaccine. Thus far, no one has needed to be enrolled in this protocol.
- Typhoid vaccine: The VTEU plans a clinical study for FY 2006 to evaluate the ability of licensed VI typhoid vaccine to boost the immune response to live attenuated vaccine strain CVD909.

New Activities

- Cooperative Research into Therapeutics and Diagnostics for Category B Bacteria, Viruses, and

Parasites supports preclinical product development projects relating to NIAID Category B pathogens, including WNV.

- Development of Therapeutic Agents for Selected Viral Diseases supports promising candidate therapeutics for specific NIAID Category A, B, and C priority viruses (i.e., smallpox, Ebola, Marburg, Rift Valley fever, Lassa fever, dengue hemorrhagic fever, West Nile virus, and influenza) through a well-defined product development path that includes completion of a Phase I clinical trial within the five year contract period.
- Services for Preclinical Development of Therapeutic Agents establishes a resource to facilitate preclinical development of therapeutic agents (drugs or biological products) including activities required for Investigational New Drug applications.
- Southeast Asia (SEA) Influenza Clinical Research Network supports a collaborative clinical research network to advance the scientific knowledge and management of human influenza. This network, established in March 2006, is a multilateral, collaborative partnership of hospitals and institutions in Indonesia, Thailand, United Kingdom, United States, and Viet Nam. The first clinical trials will include trials that investigate appropriate dosing regimens with antiviral agents for influenza and avian influenza.
- Tropical Medicine Research Centers support international centers located in disease endemic areas to conduct research in major tropical diseases. The 2006 RFA solicited applications in the areas of leishmaniasis, Chagas disease, and human African trypanosomiasis in order to facilitate translational research utilizing the recently published genomes of the trypanosomatids.

Ongoing Activities

- Bacteriology and Mycology Biostatistical and Operations Unit and the Bacteriology and Mycology Study Group initiatives support clinical trials against fungal and resistant bacterial infections. A reserve fund to support orphan drug studies that cannot be funded through industrial sponsors is available through the contract.
- Biodefense and Emerging Infectious Diseases Research Opportunities initiative supports research leading to the diagnosis, prevention, and treatment of diseases caused by emerging infectious diseases, including potential agents of bioterror.
- Biodefense and Emerging Infections Research Resources Program provides high quality resources for the research community, such as sets of West Nile peptides.
- Biodefense Proteomics Research Centers in FY 2006 identified more than 2,400 potential new pathogen targets for vaccines, therapeutics, and diagnostics and generated more than 5,700 new corresponding host targets.
- Collaborative Antiviral Testing Group has projects on Yellow Fever, Dengue, West Nile virus, Venezuelan Equine Encephalitis (VEE), Pichinde virus (a surrogate for arenaviruses), Punta Toro virus (a surrogate for Rift Valley Fever, Sandfly Fever, and hantavirus), prion disease, SARS-CoV, and smallpox. In FY 2006, over 110,000 compounds were tested *in vitro* and over 100 compounds were tested *in vivo*. Several compounds with efficacy against pathogens of rare diseases were identified, including compounds against smallpox, Punta Toro virus, Pichinde virus, prion disease, WNV, and SARS-CoV.
- Collaborative Antiviral Study Group (CASG) is a multi-Institute, collaborative network composed of 63 institutions under which clinical studies of therapies for viral infections are

conducted. The CASG has four pediatric clinical trials aimed at treating neonatal herpes simplex virus infections, sepsis caused by a group of viruses called enteroviruses, and cytomegalovirus (CMV) infections involving the central nervous system.

- Cooperative Research Partnerships for Biodefense supports the discovery/design and development of vaccines, therapeutics, adjuvants, and diagnostics for NIAID Category A, B and C priority pathogens and toxins.
- Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense and SARS in FY 2005 had 27 awards to support research on biodefense, including rare diseases such as hemorrhagic fever caused by Ebola virus, SARS, and tularemia.
- Cooperative Centers for Translational Research on Human Immunology and Biodefense supports eight research centers to conduct immunological studies on Category A, B and C pathogens and their vaccines in humans.
- Immune Epitope Database provides centralized information on immune epitopes of Category A, B and C pathogens to the scientific community.
- Immune Function and Biodefense in Children, Elderly, and Immunocompromised Populations funds ten contracts to define immunological parameters of vaccination or infection in immunocompromised human populations.
- Intramural Biocontainment Construction supports construction of three BSL–3/4 laboratories, one on the NIH campus, one in collaboration with U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) in Frederick, Maryland, and one at the Rocky Mountain Laboratories in Hamilton, Montana. These facilities will house research programs involving highly infectious agents.
- *In vitro* and Animal Models for Emerging Infectious Diseases and Biodefense Program provides a range of resources for preclinical testing of new therapies and vaccines, including nonhuman primate models for agents such as anthrax, plague, tularemia, smallpox, SARS, ricin, and Burkholderia. This project has supported development of four animal models including: monkeypox in African Dormice, Venezuelan Equine Encephalitis in mice, SARS Co-V in hamsters, and human metapneumovirus in cotton rats.
- Innate Immune Receptors and Adjuvant Discovery Program supports five contracts to identify and develop new adjuvant candidates that target the innate immune system.
- Large Scale Antibody and T Cell Epitope Discovery supports 14 contracts to identify novel immune epitopes of Category A, B and C pathogens.
- Microbial Sequencing Centers provide rapid and cost efficient resources for producing high quality genome sequences of pathogens. In FY 2006, NIAID supported approximately 40 large-scale genome sequencing projects for additional strains of viruses, bacteria, fungi, parasites, viruses, and invertebrate vectors. New projects include additional strains of *Borrelia, Clostridium, E.coli, Salmonella, Streptococcus pneumonia, Ureaplasma, Coccidioides, Penicillium marneffei, Talaromyces stipitatus, Lacazia loboi, Histoplasma capsulatum, Blastomyces dermatitidis, Cryptosporidium muris* and, Dengue viruses, and additional sequencing and annotation of *Aedes aegypti*.
- Modeling Immunity for Biodefense support interdisciplinary research development of user-friendly mathematical modeling tools to understand host immune responses to infection by, or vaccination against Category A, B or C priority pathogens, and to guide laboratory

experiments of host immune responses against infectious agents. Four awards were made in FY 2005.

- Mycology Research Units (MRUs) support interdisciplinary research to increase understanding of the biology and host-pathogen interactions of the medically important fungi.
- Neutralizing Monoclonal Antibodies for Type A Botulinum Neurotoxins initiative has the objective to develop novel methods for protecting or treating immunocompromised individuals at risk from bioterror threats. The research program covers the identification of biological mechanisms responsible for increased susceptibility to infection or decreased effectiveness of vaccines in these populations, as well as testing of treatments designed to increase safety or efficacy. Ten awards were made under this program in FY 2005.
- NIAID International Research in Infectious Diseases (IRID) R03 Program supports the development of local scientific expertise and increases collaborative research partnerships at NIAID international sites.
- Partnerships for Vaccines and Diagnostic Development Program cooperative agreement program focuses on the development of vaccines against GAS, GBS, and *Helicobacter pylori*. Epidemiological studies have been initiated to determine burden of GAS disease in Nicaragua (2005 and 2006), Fiji (2005 and 2006), and Mali (2006).
- Pathogen Functional Genomics Resource Center at the Institute for Genomic Research (TIGR) provides a wide range of genomic and related resources and technologies for the functional analysis of microbial pathogens and invertebrate vectors of infectious diseases.
- Population Genetics Analysis Program: Immunity to Vaccines/Infections has awarded six Centers. Studies include examining host response to immunization against smallpox, anthrax, typhoid fever, and cholera. In FY 2006, these Centers have focused on recruitment of the samples needed for genotyping. For example, more than 1,100 smallpox vaccinated individuals and controls have been recruited and blood and peripheral blood mononuclear cells samples obtained for whole genome association studies in FY 2007.
- Recombinant Type E Botulinum Neurotoxins Vaccine supports manufacture of a recombinant type E botulinum neurotoxin vaccine, using authorities provided by Project Bioshield. One award was made in FY 2005.
- Regional Biocontainment Laboratories Construction Program funded construction of Regional Biocontainment Laboratories (RBLs), for a total of two National Biocontainment Laboratories (NBLs) and 13 RBLs.
- Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs) supports centers that conduct research relevant to rare diseases including new approaches to blocking the action of anthrax, botulinum, and cholera toxins, and developing new vaccines against anthrax, plague, tularemia, smallpox, and hemorrhagic fevers.
- Respiratory Pathogens Reference Laboratory is a contract with the University of Alabama that supports a resource facility to provide reagents and assay development for measurement of the human immune response to targeted bacterial respiratory pathogens.
- The Schistosome Resource Center of the Biomedical Research Institute and the Filaria Resource Center of the University of Georgia are resources for helminth (parasitic worm) research.
- Therapeutics for Centers for Disease Control and Prevention (CDC) Category A Agents: Bioshield Accelerated Product Development supports research projects focused on the design

and/or preclinical development of therapeutics for CDC Category A agents. Twelve awards were made in FY 2005.

- Training and Career Development for Biodefense and Emerging Diseases supports awards to ensure that an adequate cadre of well-trained and motivated investigators is available to pursue research and development objectives in biodefense and emerging diseases.
- Tularemia Vaccine Development Teams support research to identify and evaluate new tularemia vaccine candidates. Two awards were made in FY 2005.
- NIAID has continued to actively test new candidate compounds for efficacy against infectious complications of AIDS in culture and in animals through its anti-infective drug development contracts. These contracts have been awarded for research on several rare diseases caused by these microorganisms: *Mycobacterium avium*, *Pneumocystis*, *Cryptosporidium*, *Cryptococcus*, and *Microsporidium*.
- Cooperative program with the USAMRIID conducts vaccines research for viral hemorrhagic fevers using Ebola virus and (in conjunction with FDA) evaluates the efficacy of antibiotic treatment in a model of pneumonic plague in African green monkeys. The F1–V Plague vaccine manufacturing process is being developed in conjunction with the National Cancer Institute (NCI).
- In collaboration with USAMRIID and CDC, NIAID supports the *in vitro* screening of candidate drugs against the SARS coronavirus.
- NIAID and FDA, through an inter-agency agreement, continued to support the screening of compounds that may be effective against biodefense-related and emerging viruses, including vaccinia, cowpox, West Nile, yellow fever, and SARS CoV.
- NIAID and the U.S. Department of Defense (DoD) are collaborating to provide for the coordinated development of a recombinant vaccine to protect against serotypes A and B of botulinum toxin. Through a Memorandum of Understanding (MOU) with DoD's Chemical/Biological Defense Program, NIAID is advancing the development of the Army's tularemia LVS vaccine by conducting toxicology testing and Phase I clinical trials. The MOU is being extended beyond its original 2004 agreement to continue this collaboration.

Planned Activities

- Advanced Development of Multivalent Filovirus (Ebola and Marburg) Hemorrhagic Fever Vaccines will conduct advanced product development activities for multivalent vaccines for filovirus hemorrhagic fever virus.
- Biodefense Vaccination Enhancement will conduct advanced product development to integrate novel product stabilization and antigen delivery technologies with biodefense vaccines to significantly improve both product stability and vaccination effectiveness.
- Clinical Proteomics Centers for Infectious Diseases and Biodefense will expand proteomics research resources, reagents, and technologies with potential clinical application for monitoring susceptibility and resistance to infection, early detection of infection, and therapeutic and vaccine response.
- Clinical Trial for Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections will focus and mobilize clinical capacity to test interventions on community acquired methicillin-resistant *S. aureus* (CA-MRSA) infection.

- Cooperative Research Partnerships for Influenza Product Development will develop potent new antiviral agents and diagnostics against influenza.
- Cooperative Research into Therapeutics and Diagnostics for Category B Bacteria, Viruses, and Parasites will support translational research and advanced product development, i.e., beyond basic research on identification of diagnostic or therapeutic targets and also the adaptation of technologies or products to Category B biodefense applications.
- Cooperative Research Partnerships into Therapeutics and Diagnostics for Biodefense Toxins will support cooperative translational research into developing therapeutics and diagnostics for certain biodefense toxins: Shiga toxins, ricin toxin, the Staphylococcus enterotoxin B (SEB), Clostridium perfringens epsilon toxin, and the botulinum neurotoxins.
- Development of Therapeutic Agents for Selected Biodefense Bacterial Diseases will support the development of novel small molecule and antibody therapeutic inhibitors against Category A, B and C bacterial agents.
- Development of Therapeutic Agents for Selected Biodefense Pathogens will support promising candidate therapeutics for select high priority biodefense viral and bacterial pathogens, with a special emphasis on therapeutics with broad spectrum activity or that address antimicrobial resistance (e.g., smallpox, filoviruses (Ebola and Marburg), anthrax, gram negative bacteria (broad spectrum), and influenza).
- Immune Mechanisms of Viral Control will support a synergistic network of research teams focused on basic immunological parameters of viral infection and vaccination leading to practical approaches to prevent and treat pandemic influenza outbreaks, including methods to (a) induce tissue-specific immunity and (b) control virus-induced inflammation and immunopathology.
- Innate Receptors and Adjuvant Development will advance the best candidate compounds that stimulate the innate immune response through Toll-Like Receptors and demonstrate strong adjuvant properties in animal models to Phase I clinical trials.
- Network on Antimicrobial Resistance in *Staphylococcus aureus* will support research on antimicrobial resistance (AR) in *Staphylococcus aureus* by facilitating communications within the research community and providing research resources to multidisciplinary investigators and clinicians studying and treating AR in *S. aureus*.
- NIAID Centers of Excellence for Influenza Research and Surveillance will support the surveillance and characterization of influenza viruses in Asia, natural history studies on the emergence of influenza viruses with pandemic potential and the generation of reagents.
- Nonantibiotic Selectable Markers for Biodefense supports research leading to development of nonantibiotic selectable genetic markers for Category A, B and C bacterial pathogens with priority for those Category A, B and C pathogens lacking readily available vaccines and/or subject to few selectable marker options (e.g., *Bacillus anthracis, Francisella tularensis, Yersinia pestis, Brucella* species, *Burkholderia* species, *Rickettsia* species, and *Coxiella burnetii*).
- Nonbiodefense Emerging Infectious Diseases Research Opportunities will support research to understand the natural history of microbial agents of human infectious diseases and events leading to the acquisition of pathogenic potential by non-biodefense pathogens.
- Partnerships to Improve Diagnosis and Treatment of Selected Drug-Resistant Healthcare-Associated Infections will support development of prophylactic and post-infection treatments and diagnostic clinical decision-making tools for the following healthcare-associated, drug-

resistant pathogens: C*lostridium difficile, Pseudomonas, Acinetobacter, Stenotrophomonas, Enterobacter, Proteus, Serratia* and *Klebsiella*.

- Pharmacological Approaches to Combating Antimicrobial Resistance will encourage partnerships between antimicrobial pharmacologists and infectious disease researchers to apply pharmacokinetic and pharmacodynamic principles to the development of *in vitro* and animal models that will enhance our understanding of the emergence of antimicrobial drug resistance.
- Phase I Clinical Trial Unit for Therapeutics Against Infectious Diseases will support a NIAID clinical resource with the capability and expertise to undertake Phase I clinical trials for drugs.
- Production of Monoclonal Antibody-Based Therapeutics for Botulism will support the development of monoclonal antibody-based therapeutics against the botulinum neurotoxins for evaluation in preclinical and early phase clinical studies.
- Statistical and Data Coordinating Center (SDCC) for Clinical Research in Infectious Diseases provides comprehensive statistical support, data management and analysis activities for clinical work sponsored by the NIAID Division of Microbiology and Infectious Diseases.
- Structural Genomics Centers for Infectious Diseases will support state-of-the-art structural genomics technologies to structurally characterize targeted proteins from NIAID Category A, B, and C pathogens and organisms causing emerging or re-emerging infectious diseases.
- Systems Approach to Immunity and Inflammation will support systems biology analyses of innate and/or adaptive immune responses to infection, vaccination, or immunotherapy, with a focus on NIAID Category A, B, and C priority pathogens.
- Systems Biology Approach to Infectious Diseases Research supports a systems biology approach to better understand infectious disease pathogens and their interactions with the host.
- Typhoid vaccine: The VTEU plans a clinical study for FY 2006 to evaluate the ability of licensed VI typhoid vaccine to boost the immune response to live attenuated vaccine strain CVD909.
- Vaccine and Treatment Evaluation Units (VTEU): Evaluation of Control Measures Against Diseases Other than AIDS will use contract resources for the evaluation of control measures for infectious diseases other than AIDS.

Scientific Conferences, Symposia, and Meetings

- Innate Immune Receptors and Adjuvant Discovery Meeting was held on March 8, 2006 in Bethesda, Maryland.
- Monoclonal Antibody Therapeutics for Biodefense and Emerging Infectious Diseases Workshop was held March 29, 2006 in Bethesda, Maryland.
- Cooperative Centers for Translational Research on Human Immunology and Biodefense Annual Meeting was held on April 4-5, 2006 in Bethesda, Maryland.
- Development of Broad Spectrum Therapeutics Workshop was held April 18, 2006 in Rockville, Maryland.
- Gordon Research Conference on the Biology of Spirochetes was held April 23-28, 2006 in Ciocco, Barga, Tuscany, Italy.
- Workshop on Patch-Clamp of Human Erythrocytes Infected with *P. falciparum* was held June 25-30, 2006 in Rockville, Maryland.

- Pulmonary Nontuberculous Mycobacterial Infections: Development of a Research Agenda was held summer 2006 in Bethesda, Maryland.
- 20th Meeting of the American Society for Rickettsiology and the 5th International Conference on Bartonella as Emerging Pathogens were held September 2-7, 2006 in Pacific Grove, California.
- DHHS BioShield Stakeholders Workshop was held September 25-26, 2006 in Arlington, VA
- Population Genetics Analysis Program: Immunity to Vaccines/Infection was held on October 14-15, 2005 in Washington, D.C.
- Immune Function and Biodefense in Children, Elderly, and Immunocompromised Populations was held on September 27-28, 2006 in Gaithersburg, Maryland.
- The second Annual Epitope Database and Discovery Workshop was held on November 1-3, 2005 in Bethesda, Maryland.
- Molecular Biology of Spirochetes was held December 5-8, 2005 in Prague, Czech Republic. Hands On Workshop Of Immune Epitope Tool Developers was held on November 4, 2005, in Bethesda, Maryland.
- Immune Modeling Centers Program held a kick-off meeting on December 5, 2005 in Bethesda Maryland.

Primary Immunodeficiency Diseases

Scientific Advances

Common variable immunodeficiency

Common variable immunodeficiency (CVID) patients can develop an inflammatory bowel disease resulting in chronic diarrhea and life-threatening inability to absorb nutrition. NIAID researchers characterized the nature of this inflammation and found that gastrointestinal symptoms in CVID arise from a combination of cytokines (excess IL-12 and interferon-beta, but lacking IL-23 and IL-17) that differs from other gut diseases such as Crohn's disease. These findings extend understanding of the cytokine-restricted mucosal responses and provide the rationale for a recently launched new treatment protocol.

CVID is characterized by low levels of serum immune globulins, lack of antibody response, and reduced numbers of memory B cells. Although defects in other immune cells such as T, B, and dendritic cells have been described, for the great majority of cases, genetic causes have not been identified. NIAID-funded researchers investigated activation of B cells and dendritic cells induced via TLR9, an intracellular recognition receptor that detects pieces of DNA from viruses and bacteria. The investigators demonstrated that, although there were no mutations or polymorphisms of TLR9, there were broad TLR9 activation defects in CVID; these defects may lead to impaired responses of dendritic cells and loss of B cell function.

In addition to gastrointestinal disorders, individuals with CVID are susceptible to pneumonia, recurring ear and sinus infections, and the development of B cell tumors. A study is under way to identify a genetic cause for a primary immunodeficiency with significant morbidity and mortality.

Through genetic testing, clinicians will be able to more quickly identify individuals who would benefit from immunoglobulin replacement therapy and preventive antibiotics.

Chronic granulomatous disease (CGD)

Chronic granulomatous disease (CGD) is a life-threatening, inherited disorder in which immune cells called phagocytes are unable to kill bacteria and fungi. NIAID researchers found two patients with CGD that also had sarcoidosis, an autoimmune disease generally not seen in CGD. This finding suggests that CGD immune dysregulation may trigger autoimmune diseases in a subset of individuals with a genetic predisposition. These findings also suggest that patients should be managed with specific therapies proven to be effective for the specific autoimmune disease triggered by CGD rather than only preventing infections and controlling inflammation.

Severe combined immunodeficiency disease (SCID)

X-linked severe combined immunodeficiency (XSCID) is characterized by profound immunodeficiency and early mortality. The only potential cures are hematopoietic stem cell (HSC) transplantation or gene therapy. Current clinical gene therapy protocols targeting HSCs are based upon *ex vivo* gene transfer, potentially limited by the adequacy of HSC harvest, transduction efficiencies of repopulating HSCs, and the potential loss of their engraftment potential during *ex vivo* culture. NIAID-funded researchers demonstrated an important proof of principle by showing that a durable immune reconstitution in XSCID dogs was achieved following intravenous injection of a retrovirus vector encoding the corrective gene (interleukin-2 receptor gamma chain (gamma c)). This is the first demonstration that *in vivo* gene therapy targeting HSCs can restore both cellular and humoral immunity in a large-animal model of a fatal immunodeficiency.

Other NIAID-funded researchers identified a novel genetic cause of SCID. Antigen stimulation of immune cells triggers calcium entry, cell activation, and subsequent immune response. Cells from patients with one form of SCID are defective in calcium entry. The genetic defect in these patients was identified as a protein called Orai1, which contains four putative transmembrane segments. The SCID patients are homozygous for a single missense mutation in Orai1, and expression of wild-type Orai1 in SCID T cells restored calcium influx, suggesting that Orai1 is an essential component or regulator of the calcium channel complex.

X-linked lymphoproliferative disease (XLP)

Individuals with X-linked lymphoproliferative disease (XLP) show defects in B cell differentiation *in vivo*. Specifically, XLP patients do not generate a normal number of memory B cells, and the few memory B cells that are present express immunoglobulin M (IgM). Recent studies have suggested that these cells protect against T cell-independent pathogens. NIAID-funded researchers showed that human XLP IgM memory B cells resemble normal memory B cells both morphologically and phenotypically, and exhibit functional characteristics of normal memory B cells. However, analysis of spleens from XLP patients revealed a paucity of germinal centers (GCs), and the rare GCs detected were poorly formed. The immunoglobulins present in XLP memory B cells had undergone genetic selection in the same manner as normal memory B cells.

These findings reveal a differential requirement for the generation of IgM and other memory B cells, with the latter only being able to generate fully formed GCs. High affinity, mature IgM from IgM-memory B cells may provide a defense against some pathogens in XLP patients.

Neutropenia

Cyclic neutropenia occurs in humans and gray collie dogs, and is characterized by recurring low counts of neutrophils which are immune cells. Current treatment is by daily injections of recombinant granulocyte colony-stimulating factor (G-CSF). NIAID-funded researchers administered a lentiviral vector encoding canine G-CSF cDNA into an affected dog and were able to elevate the dog's neutrophil production for nearly 18 months. The gray collie gained weight, showed no clinical signs of infection and fever, and no longer needed housing in a pathogen-free environment. These studies show that an adult animal can respond long-term to lentivirus-mediated G-CSF delivery, suggesting this approach may be applied for treatment of adult patients with cyclic and other neutropenias.

Other NIAID-funded researchers investigated cases of severe congenital neutropenia (SCN) after determining that the same sperm donor was used by four different families to impregnate mothers who subsequently bore children with the disorder. Because donor sperm was not available for analysis, DNA was isolated from leukocytes of the affected children and their mothers and the ELA2 gene was sequenced. None of the mothers had a mutation in ELA2, but all five affected children had the same mutation. Linkage mapping analysis confirmed that all affected children had the same paternal allele. These findings support an autosomal dominant inheritance of ELA2 mutation resulting in the expression of SCN.

X-Linked aggamaglobulinemia (XLA)

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency disease caused by mutations in the gene for Bruton tyrosine kinase (BTK) that lead to the deficient development of B lymphocytes and hypogammaglobulinemia or low levels of immunoglobulins in the blood. Because the disorder is uncommon, it has been difficult to study sufficient numbers of patients to develop a comprehensive clinical picture of the disorder. A NIAID-funded national registry of United States residents with XLA provided an updated clinical view of the disorder in a large cohort of patients, based on a total of 201 patients who were registered by 66 physicians. This registry is providing information on initial clinical presentations, the average age of diagnosis, common comorbidities, and causes of death. The information will be useful in extending the understanding of this disease.

Mendelian Susceptibility to Mycobacterial Diseases (MSMD)

Germline mutations in five autosomal genes cause Mendelian susceptibility to mycobacterial diseases (MSMD), but the molecular basis of X-linked recessive (XR)-MSMD remains unknown. NIAID-funded researchers found mutations in the leucine zipper (LZ) domain of the NF-kappaB essential modulator (NEMO) gene in three unrelated families with XR-MSMD. The mutant proteins were produced in normal amounts in blood and fibroblastic cells. However, the patients'

monocytes were unable to stimulate T cells to make IFN-gamma. These two mutations in the NEMO LZ domain provide the first genetic etiology of XR-MSMD. They also demonstrate the importance of monocyte-derived cells for protective immunity to mycobacteria in humans.

Clinical Trials Initiated in FY 2006

- Common variable immunodeficiency pilot trials will assess the safety and efficacy of the IL-12/23 inhibitor, STA-5326 Mesylate, for symptomatic gastrointestinal inflammation associated with common variable immunodeficiency.

Ongoing Activities

- Primary Immunodeficiency Diseases Consortium is cosponsored with the National Institute of Child Health and Human Development (NICHD). The Consortium: (l) provides leadership and mentoring; facilitates collaborations; enhances coordination of research efforts; solicits, reviews, recommends, and makes awards for pilot or small research projects; (2) maintains and expands a primary immunodeficiency diseases registry which provides data to the research community about the clinical characteristics and prevalence of these diseases; and (3) develops a repository of specimens from subjects with primary immunodeficiency diseases.
- Center for International Blood and Marrow Transplantation Research (CIBMTR) supported by NIAID, NCI, and the National Heart, Lung, and Blood, Institute (NHLBI) is a data resource for analysis of blood and marrow transplants. The CIBMTR Working Committee in Immune Deficiencies is conducting analyses of the clinical database to address issues relevant to hematopoietic stem cell transplantation for Chediak Higashi syndrome, Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis, severe combined immunodeficiency syndrome, Wiscott-Aldrich syndrome, and other inherited immune deficiencies.

Scientific Conferences, Symposia, and Meetings

- Meeting on Primary Immunodeficiency Diseases was held in conjunction with the 6th annual meeting of the Federation of Clinical Immunology Societies June 1-5, 2006 in San Francisco, California.
- Gene Therapy for Inherited Immune Deficiencies: Advances and Safety Issues was held September 18-19, 2006 in Bethesda, Maryland.

Autoimmune Diseases

Scientific Advances

Pemphigus vulgaris

Pemphigus vulgaris (PV) is a life-threatening autoimmune skin disease characterized by blistering and detachment of the skin cells keratinocytes (acantholysis). NIAID-funded researchers showed that pathogenic autoantibodies formed during PV trigger signaling cascades in keratinocytes that involved the enzyme p38 mitogen-activated protein kinase (p38MAPK). These researchers were

able to prevent the PV blistering in a mouse pemphigus model by inhibiting the enzyme p38MAPK. These results expand understanding of the disease mechanism and suggest that targeting this p38MAPK pathway may have therapeutic benefit.

Ongoing Clinical Trials

- Pemphigus Vulgaris therapeutic: A double-blind, placebo-controlled, randomized Phase II safety and efficacy study of infliximab (Remicade) as a treatment for Pemphigus Vulgaris.

Planned Clinical Trials and IND applications

- Allogeneic Hematopoietic Stem Cell Transplantation for Autoimmune Diseases: sponsored by NIAID, in cooperation with the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), NHLBI and NCI, these pilot clinical studies of allogeneic hematopoietic cell transplantation as a treatment for autoimmune diseases, including scleroderma.

New Activities

- Cooperative Study Group for Autoimmune Disease Prevention, cosponsored by NIAID, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Juvenile Diabetes Research Foundation International (JDRF), conducts research on the development of new targets and approaches to prevent autoimmune diseases and evaluate these approaches in pilot and clinical studies. In FY 2006, the Study Group was renewed with the award of six cooperative agreements.

Ongoing Activities

- Autoimmunity Centers of Excellence (ACEs), cosponsored by NIAID, NIDDK, and the Office of Research on Women's Health (ORWH) is a cooperative program that supports collaborative basic and clinical research on autoimmune diseases, including single-site or multisite pilot clinical trials of immunomodulatory therapies.
- HLA Region Genetics in Immune-Mediated Diseases has the objective to define the association between human leukocyte antigen (HLA) region genes or genetic markers and immune-mediated diseases, including risk and severity of disease, and organ and cell transplantation outcomes. In FY 2005, NIAID, with cosponsorship from the National Institute of Neurological Disorders and Stroke (NINDS), awarded five research cooperative agreements under the new program.
- Multiple Autoimmune Diseases Genetics Consortium (MADGC) 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. This repository provides well-characterized material for use in research aimed at identifying the genes involved in autoimmune diseases.
- Stem Cell Transplantation for Autoimmune Diseases Consortium supports clinical trials to assess the efficacy of hematopoietic stem cell transplantation to treat several severe autoimmune diseases, including multiple sclerosis, SLE, and scleroderma.

Scientific Conferences, Symposia, and Meetings

- Considerations in Allogeneic Hematopoietic Cell Transplantation (HCT) for Nonmalignant Disorders, Including Autoimmune Diseases, a State-of-the Art Workshop, sponsored by NIAID, NCI, and the Office of Rare Diseases, NIH, was held October 20-21, 2006 in Bethesda, Maryland.

Other Immune System-mediated Diseases

Scientific Advances

Eosinophilic esophagitis and gastroenteritis

Eosinophilic esophagitis (EE) is an inflammatory disease characterized by high numbers of immune cells called eosinophils in the esophagus. NIAID-funded researchers developed a genetic profile of this poorly understood disease and showed that eotaxin-3, an eosinophil-specific chemoattractant, is dramatically elevated in the esophageal biopsies of subjects with the disease. Further, researchers showed that mice lacking receptors for eotaxin-3 were protected against developing a mouse model of EE. This research suggests that a drug to target eotaxin-3 might have therapeutic value.

Transplant immunology

The role of T-regulatory cells (T-regs) in preventing transplant rejection and establishing immunologic tolerance has been an area of increasing interest and importance in transplantation research. NIAID-funded researchers have made important contributions to the understanding of T-regs.

All individuals who receive an organ transplant are at risk for organ rejection. Currently, rejection can be diagnosed only after there is evidence of organ injury. One of the goals of transplant immunology research is to be able to predict when an episode of rejection will occur, and also to predict what the outcome of an episode of rejection will be. NIAID-funded researchers have demonstrated that measurement of *FOXP3* (a gene associated with T-regs) mRNA level in urinary cells of human kidney transplant recipients predicts immunologic events in the setting of acute kidney rejection and its aftermath. Individuals with clinical or biopsy-proven acute rejection had significantly higher copy numbers of *FOXP3* mRNA as compared with those with chronic or no kidney dysfunction. In addition, among those with acute rejection, higher copy numbers of *FOXP3* mRNA were associated with complete resolution of the rejection episode, whereas those with lower copy numbers were significantly more likely to progress to failure of the transplanted kidney. These findings suggest that the presence of T-regs limits immunologic damage to the transplanted kidney, while their absence results in unrestrained activity of those cells that damage the graft. These findings may provide a cellular mechanism for the differences in outcome after an episode of allograft rejection, and have implications for the individualization of therapy in transplant recipients with acute rejection.

In another NIAID-funded study, investigators demonstrated for the first time, in a mouse model, a critical functional role for mast cells in the establishment of T-reg mediated immune tolerance to allografts. In addition, their study indicated that the production of IL-9 by T-regs leads to the recruitment and activation of mast cells, resulting in long-term allograft tolerance.

Clinical Trials Initiated in FY 2006

- Stem cell transplantation for autoimmune disease therapy: Two clinical trials are evaluating autologous hematopoietic stem cell transplantation for the treatment of scleroderma and SLE, two autoimmune diseases. These complex trials, opened in FY 2006, will also include studies of the underlying immune mechanisms of these diseases and treatments.

Ongoing Activities

- Center for International Blood and Marrow Transplantation Research (CIBMTR) supported by NIAID, NCI, and NHLBI, is a data resource for analysis of blood and marrow transplants. The C.W. Bill Young Cell Transplantation Program established by Congress in December 2005 requires collection of outcomes data on related and unrelated allogeneic hematopoietic cell transplants (HCT) done in the United States. Observational research including analysis of the clinical database to address important issues in the biology and clinical application of HCT is the core activity of the CIBMTR. CIBMTR Working Committees directly relevant for rare diseases and NIAID include Autoimmune Diseases, Immune Deficiencies, Graft-versus-Host Disease, Immunobiology/Histocompatibility, Infection and Immune Reconstitution, and Nonmalignant Marrow Disorders.
- Cooperative Clinical Trial in Pediatric Transplantation (CCPT) was established in 1994 to support multicenter clinical trials of novel approaches to prevent acute and chronic graft rejection in pediatric kidney transplantation; evaluate modifications of immunosuppressive drug regimens to mitigate unwanted side effects of immunosuppression; and assess pre-transplant immunotherapy to improve transplantation outcomes. The CCTPT also conducts mechanism-of-action studies to determine the effect of these interventional approaches on the immune system. This program will be expanded in 2007 and renamed Clinical Trials in Organ Transplantation in Children.
- Clinical Trials in Organ Transplantation (CTOT) is a cooperative multisite consortium cosponsored by NIAID, NHLBI, and NIDDK. Its purpose is to develop and implement interventional and observational clinical studies, accompanied by mechanistic studies, designed to enhance the understanding of and ultimately reduce the immune-mediated morbidity and mortality of organ transplantation. This group currently is enrolling subjects in three clinical trials, and has three others in development.
- Genomics of Transplantation Cooperative Research Program was developed to support large-scale, broad-scope genomic studies in clinical transplantation, including solid organ, tissue, and cell transplantation. This program was expanded in 2006, with two additional awards made. The long-term goal of the program is to understand the genetic basis of immune-mediated graft rejection and differences in transplant outcomes, and thereby provide a rational basis for the development of more effective treatment and prevention strategies to improve long-term graft survival and quality of life for transplant recipients.

- HLA Region Genetics in Immune-Mediated Diseases program, supported by NIAID with cosponsorship from NINDS, awarded five research cooperative agreements. The objectives of this program are to define the association between human leukocyte antigen (HLA) region genes or genetic markers and immune-mediated diseases, including risk and severity of disease, and organ and cell transplantation outcomes.
- Hyperaccelerated Awards for Mechanisms in Immunomodulation Trial cosponsored by NIAID, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIDDK, NINDS, supports immune-based mechanistic studies associated with clinical trials of infectious disease vaccines and immunotherapies for immune-mediated diseases.
- Immune Tolerance Network (ITN) cosponsored by NIAID, NIDDK, and JDRF is an international consortium of over 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases, asthma and allergic diseases, and rejection of transplanted organs, tissues, and cells. The ITN has established state-of-the art core laboratory facilities to conduct integrated mechanistic studies, and to develop and evaluate markers and assays to measure immunologic tolerance in humans.
- Immunobiology of Xenotransplanation Cooperative Group (IXCG) consists of five cooperative agreement research grants and is cosponsored by NIAID and NIDDK. The goals of this program are: (1) to delineate the cellular and molecular mechanisms of xenograft rejection and the induction of tolerance and accommodation; (2) to develop effective strategies to improve xenograft survival; and (3) to characterize the physiological compatibility/limitations of xenografts. Together, these goals will lead to the development of novel and efficacious strategies for the broad application of xenotransplantation in the clinic.
- National Center for Biotechnology Information cosponsored by NIAID and the National Library of Medicine is a centralized public database of results from clinical blood and marrow stem cell transplants involving unrelated donors.
- Pathogenesis of Polyomavirus Associated Nephropathy supports projects that are focused on basic, preclinical, clinical, and epidemiological research projects on polyomavirus-associated nephropathy (PVAN).
- Sex-based Differences in the Immune Response research initiative cosponsored by NIAID, NIAMS, NINDS, ORWH, and the National Multiple Sclerosis Society supports research to increase our understanding of the mechanisms underlying the differences in the immune response in males and females. Findings may allow more targeted approaches for the prevention and treatment of immune-mediated disease.
- Systems Approaches to Innate Immunity, Inflammation, and Sepsis supports a multidisciplinary team at Scripps Research Institute, which is 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.

Planned Activities

- Immune Tolerance Network will be recompeted in FY 2007.
- Non Human Primate Transplantation Tolerance Cooperative Study Group will be re-competed in 2007.
- Clinical Trials in Organ Transplantation in Children (CTOTC) is a new program that will be initiated in FY 2008. This is a renewal and expansion of Cooperative Clinical Trials in Pediatric Transplantation and will support a consortium of investigators and centers to conduct clinical trials with associated mechanistic and epidemiologic studies in pediatric organ transplantation.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES (NIAMS)

Overview

The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of basic and clinical scientists to carry out this research; and the dissemination of information on research progress in these diseases. NIAMS-supported researchers have made significant progress in broadening the base of knowledge related to many of the rare diseases within the Institute's scope.

Recent scientific advances in rare disease research

Epidermolysis bullosa

Epidermolysis bullosa acquisita (EBA) is a severe blistering skin disease that can be seen as an isolated clinical condition or is sometimes seen in association with systemic lupus erythematosus (SLE, also known as "lupus"). Antibodies are usually produced by the immune system to protect against foreign agents, but autoantibodies may emerge in disease states and attack one's own organs and tissues. Autoantibodies in EBA are directed against type VII collagen, which forms a structure in the skin that helps attach the outer layer (epidermis) to the deeper layer of skin (dermis). A recent study found that treating mice with these autoantibodies from human patients generated an identical condition to EBA, thus identifying these autoantibodies as the cause of the disease. This important finding pinpoints a therapeutic target: reducing or eliminating these autoantibodies should ameliorate disease.

Fibrodysplasia ossificans progressiva

Fibrodysplasia ossificans progressiva (FOP) is one of the rarest genetic diseases. But for the estimated 2,500 patients who have FOP, the result is nothing short of devastating. During early childhood, their bodies' muscles, tendons, ligaments, and other connective tissues undergo a metamorphosis to bone, forming a second skeleton that renders them permanently unable to move. In April 2006, after a 15-year quest, NIAMS-funded investigators located the disease-causing mutation in a gene that controls formation of cartilage and bone. The discovery immediately suggests two treatment approaches requiring further exploration: either block the defective protein's activity or prevent it from forming in the first place. The finding also offers potential applications for other problems associated with either too much bone (such as bone spurs that occur in osteoarthritis) or too little (such as osteoporosis). Research leading to this discovery was funded by the NIH, private donations from families and friends of FOP patients worldwide, and the International FOP Association.

Ichthyosis

Researchers have discovered that moderate or severe forms of ichthyosis vulgaris (IV), the most common inherited disorder of skin, hair, and nail formation, are cause by mutations to the filaggrin gene (FLG). Normally, filaggrin protein functions as a component of the skin barrier, protecting the body from water loss, allergens and infectious agents. It had not been directly associated with any human disease, however, until NIAMS-funded researchers analyzed blood and skin biopsy samples from families who had symptoms of IV and found two different mutations in FLG. Filaggrin is one of the proteins in the epidermal differentiations complex (EDC) on chromosome 1. Because the same region also contains many other genes involved in the skin's barrier function, researchers also hypothesize that mutations in other nearby genes might be involved in IV and other diseases in which skin structure is impaired.

Additionally, IV is frequently associated with atopic dermatitis, or eczema. The authors suggest that filaggrin may be a factor in atopic dermatitis and other skin disorders with a genetic component. More recent work, the authors say, has indeed shown that FLG mutations are common in atopic dermatitis and appear to be strong predisposing genetic factors for this disease. Thus, loss of filaggrin protein is also associated with eczema, probably because the skin barrier is compromised.

Malignant hyperthermia and central core disease

Malignant hyperthermia (MH) is an inherited disorder of muscle that often is not diagnosed until general anesthesia triggers metabolic changes that can cause serious, and sometimes deadly, muscle failure. It is caused by molecular defects in the type 1 ryanodine receptor (RYR1) gene, which is involved in regulating intracellular calcium concentrations. Mutations to RYR1 also are associated with central core disease, a childhood condition characterized by muscle weakness, atrophy, and an increased risk of MH. Recent findings from NIAMS-funded researchers studying central core disease have shown that small deletions in the RYR1 gene can have opposite effects on calcium channel function: one defect caused calcium to leak from intracellular stores, while another prevented calcium from being released when needed. In a separate study, researchers developed a mouse model in which the RYR1 calcium channel gene contained a mutation associated with MH. They are using the model to examine the mechanisms underlying temperature dysregulation and skeletal muscle contraction in MH and heat stroke. Better understanding of the molecular processes of central core disease and MH, and of the defects in calcium channel structure and function, may lead to treatments for these diseases or more effective screening methods to avoid MH crises. Furthermore, since calcium release and re-uptake are impaired as muscles fatigue and as body temperature rises, better understanding of the mechanisms of calcium cycling may lead to strategies to promote muscle recovery after strenuous exercise or to treat heat-induced illness.

Marfan syndrome

Marfan syndrome is an inherited disorder caused by a mutation in the fibrillin gene. This mutation causes the tendons, ligaments, and other connective tissues in the body to weaken. Marfan syndrome can affect the heart, skeletal system, eyes, and other organs in the body, and symptoms range from mild to severe. Premature death for Marfan patients is caused by heart failure or aortic rupture following development of an aortic aneurysm. Fibrillin-1 regulates the growth factor TGF-β and this growth factor is over-produced in Marfan syndrome patients. Losartan is a medication that lowers blood pressure and leads to inhibition of the effects of TGF-β. In a recent study, losartan was administered in drinking water to mice with aortic aneurysms. Aortic wall architecture was restored and the course towards aortic rupture was reversed.

Mutations in the genes encoding TGF-β receptors 1 and 2 have been found recently in association with the range of affected organ systems and clinical features. Progress has been made to identify the physical characteristics associated with this affliction in patients at highest risk of requiring vascular surgery or dying at a young age, which will help physicians treat Marfan syndrome.

Muscular dystrophies (including Duchenne and limb-girdle muscular dystrophies, sarcotubular myopathy, and myotonic dystrophy)

"Muscular dystrophy" is a broad term used to describe gene-related disorders that affect muscles throughout the body. More than 20 specific genetic disorders are considered to be muscular dystrophies. Most have the same result (a reduction in muscle strength due to weakening and deterioration), but these various conditions are specific to different muscles in the body and different rates of degeneration. The NIAMS funds considerable research to elucidate cellular and molecular mechanisms that underlie muscle degeneration associated with muscular dystrophies and to develop potential treatment strategies.

New findings from NIAMS-supported researchers reveal a possible mechanism by which a mutation, found in patients who have limb-girdle muscular dystrophy type 2H or an even more rare muscular dystrophy known as sarcotubular myopathy, interferes with normal muscle formation and degradation. Both diseases are associated with a mutation in a gene for tripartite motif-containing protein 32 (TRIM32). The scientists recently demonstrated that TRIM32 can interact with the two major muscle proteins, actin and myosin, and can specifically target actin for degradation. In other words, TRIM32 attaches a molecular flag (called ubiquitin) to actin molecules that need to be degraded. Although researchers still do not understand the disease-causing mutation's exact effect, they hypothesize that it disrupts normal muscle turnover.

The Institute also supports extensive research in other areas of muscle biology, which may point to targeted interventions for the treatment of muscular dystrophies and other disorders. As anyone who has ever had a limb in a cast knows, muscles rapidly lose mass and strength when they are not used. This process—known as muscle disuse atrophy—occurs not only when a limb is immobilized, but also in connection with certain diseases such as muscular dystrophy, nerve damage, weightlessness, and age-related inactivity. Recent mouse studies conducted by NIAMS-

funded researchers showed that muscle function may be preserved by a compound called Bowman-Birk inhibitor, which currently is being tested in clinical trials for other diseases.

Recent mouse experiments using another compound also have yielded promising results for muscular dystrophy patients. An international collaboration involving researchers from the NIAMS intramural research program demonstrated for the first time that a single drug, trichostatin A, can rebuild damaged muscle in strains of mice that develop diseases comparable to Duchenne muscular dystrophy and human limb-girdle muscular dystrophy. Trichostatin A is a member of a drug class called deacetylase inhibitors that currently are being tested in clinical trials for a variety of human diseases. Although the mice with muscular dystrophy could not run or swim before receiving the experimental therapy, they were virtually indistinguishable from healthy mice after two or three months of treatment. Although the report, published in the October 2006 issue of *Nature Medicine*, is the first example of using a therapeutic compound to counteract muscular dystrophy in mouse models, the drug only is promoting muscle regeneration—it is not curing the defect that causes muscle deterioration. Furthermore, additional studies are needed to determine whether the benefits of trichostatin A or related compounds can be sustained, and if the drugs work in larger animals with bigger muscles (such as dogs), before they can be tested in people.

Researchers also have made progress on understanding myotonic dystrophy, a subset of muscular dystrophies that—although rare—is the most common inherited degenerative muscle diseases in adults. A defect in a gene called DMPK causes the diseases by producing mRNA molecules that are thought to "clump" together and sequester proteins (such as muscleblind-like 1, (MBNL1)) that are required for transcribing other essential muscle genes. In fiscal year 2006, NIAMS-supported investigators published multiple papers describing results from animal studies that may lead to new therapeutic approaches for intervening in the causes of myotonic dystrophy. Researchers now know that over-expression of MBNL1 using a gene-therapy technique in a myotonic dystrophy mouse model improves muscle function, and that inhibiting production of malformed mRNA in a new mouse model of myotonic dystrophy type 1 can reverse skeletal muscle myotonia and cardiac defects. Taken together with earlier findings, these results suggest three potential treatment strategies for patients who have myotonic dystrophy: increasing production of MBNL1, releasing the trapped protein from mRNA clusters, or decreasing expression of the defective DMPK gene.

Osteoporosis-pseudoglioma syndrome

People who have an inactive version of a protein called LRP5 have a serious disease called osteoporosis-pseudoglioma syndrome, which is characterized by very low bone mass and a very great susceptibility to fractures. This year, researchers reported that LRP5-deficient mice make much less new bone than normal mice in response to mechanical stress such as weight bearing activities, but make new bones as well as normal mice do in response to parathyroid hormone (a current treatment for osteoporosis). Their findings suggest that the bone cells of people with osteoporosis-pseudoglioma syndrome may not be generally defective in bone formation, but only unable to respond to the specific stimulus of mechanical loading. In the short term, the findings indicate that parathyroid hormone therapy is more likely than weight bearing exercises to benefit these patients. Moreover, the results suggest that pharmacological modulation of LRP5 activity

may be a means of increasing bone mass with minimal deleterious side effects for the millions of people affected by more common forms of osteoporosis.

Neonatal-onset multisystem inflammatory disease (NOMID)

NIAMS intramural researchers recently found that a rheumatoid arthritis drug called anakinra brings marked improvement both in symptoms and the inflammation underlying a rare and debilitating disorder called neonatal-onset multisystem inflammatory disease (NOMID). NOMID, also known as chronic infantile neurologic cutaneous articular syndrome, is an inflammatory disorder that affects numerous organs and body systems, including the skin, joints, eyes and central nervous system. For most children, the first sign of the disease is a rash that develops within the first six weeks of life. Other problems, including fever, meningitis, joint damage, vision and hearing loss, and mental retardation, can follow. Despite treatment to control the inflammation—including high-dose corticosteroids, disease-modifying antirheumatic drugs such as methotrexate, and nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen—the disease is progressive and often fatal. Intramural researchers, building on their understanding of the molecular cause of the disease, tested anakinra, which works on the same molecular pathway that is defective in NOMID. Researchers treated anakinra in 18 NOMID patients, all of whom had an immediate clinical response to the drug. Rash and conjunctivitis (inflammation of the membrane lining the eyelids), both common in NOMID, disappeared within three days. By three months, laboratory measures of inflammation had improved, and by six months, 33 percent of the patients showed improved hearing and another half of the patients had no further hearing loss. Although disease flared in 11 patients when they were withdrawn from anakinra as part of the study, disease quickly responded again when anakinra therapy was restarted.

Smith-Lemli-Opitz syndrome

Each year, an estimated 1 in 50,000 babies in the United States is born with Smith-Lemli-Opitz syndrome (SLOS), a condition characterized by severe bone malformation, food intolerance, and susceptibility to infection. Children with SLOS have a defect in cholesterol metabolism that causes extremely low blood levels of cholesterol and high levels of a precursor to cholesterol called 7-dehydrocholesterol (DHC). Recently, intramural researchers from the NIAMS and National Institute of Child Health and Human Development (NICHD) determined that the buildup of DHC leads to immune hypersensitivity, a finding which may explain why SLOS patients have increased food allergies and inflammatory responses. The mutation responsible for SLOS causes the DCH to accumulate on the mast cell membranes and, since inflammation is regulated in part by cholesterol and its precursors on cell membranes, this causes the cells to be more easily activated. Thus, something innocuous to most people—food, for example—sets off an immune reaction in a child with SLOS. Traditionally, children were treated with high-cholesterol diets and supplements to increase blood levels of cholesterol. Interestingly, these findings suggest that the solution to this low-cholesterol disease could be statin drugs that are marketed now to lower cholesterol, as they block formation of cholesterol precursors.

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a rare, heritable, neurological disorder primarily characterized by seizures, mental retardation, and skin and eye lesions. Small benign tumors may grow on the face and eyes, as well as in the brain, kidneys, and other organs. Individuals with TSC may experience none, some, or all of the associated symptoms, with varying degrees or severity.

NIAMS-supported researchers are examining the mechanisms of development of TSC and associated angiogenesis (blood vessel development). TSC is caused by mutations in the genes TSC1 or TSC2 whose protein products, hamartin and tuberin, normally function as a complex that regulates many cellular processes, including cell growth. NIAMS-supported researchers have created a mouse model with mutations in the tuberin gene that develops unique skin and brain tumors similar to those in TSC patients. Investigators are exploring how molecular signals upstream and downstream of the hamartin/tuberin complex affect tumor development and growth. Knowledge of how these events impact the development of TSC may lead to therapies that can prevent or improve the skin manifestations of the disease in humans.

TSC1 and TSC2 are part of the mTOR signaling pathway which is involved in the regulation of protein translation and cell growth. Several NIAMS-funded researchers are studying signaling in the mTOR pathway and its involvement in normal cellular processes and abnormal conditions and diseases. A better understanding of the mTOR pathway will provide additional targets for drug intervention in TSC, as well as a better understanding of how mutations in TSC1 and TSC2 lead to abnormalities in multiple organ systems.

Significant ongoing rare disease research initiatives

Familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and other diseases

NIAMS intramural researchers are testing an experimental drug for patients who have familial cold autoinflammatory syndrome or Muckle-Wells syndrome, two diseases associated with a mutation to the CIAS1 gene (the same gene associated with NOMID, mentioned above). Begun in October 2004, the study examines the safety and effectiveness of a drug called IL-1 Trap, which works on the same molecular pathway as anakinra but can be injected once a week, instead of daily. People with similar autoinflammatory diseases like familial Mediterranean fever or adult Still's disease are also eligible for the study.

Juvenile idiopathic arthritis

NIAMS supports a state-of-the-art genomics project to uncover gene expression patterns that contribute to the development of pediatric arthritis. Researchers are using DNA microarrays (small silicon chips that contain tiny amounts of thousands of known genes) to analyze thousands of genes in blood, fluids, and tissues of children newly diagnosed with various types of pediatric rheumatic diseases including juvenile idiopathic arthritis. Identifying gene expression patterns,

groups of genes that are "turned on" for different types of childhood arthritis, will help to improve diagnosis and to predict disease severity for affected children.

The Institute is also supporting clinical trials to examine therapeutic interventions in children with juvenile idiopathic arthritis (JIA). One such trial is investigating osteopenia (reduced bone mass), a frequent complication of JIA. This clinical trial measures the effectiveness of daily oral calcium supplementation to increase total body bone mineral density. The long-term goal is to determine the safety and effectiveness of current and new biologic and pharmacologic treatments as alternative treatments to calcium in those JIA patients with osteopenia.

Juvenile lupus, scleroderma, and x-linked hypophosphatemic rickets research at NIAMS Centers of Research Translation

In FY 2006, NIAMS launched its Centers of Research Translation program to unite basic and clinical research in a way that translates basic discoveries into diagnostic approaches and treatments. Applicants were responsible for identifying diseases that their centers will address, and three of the four new grants focus on rare diseases:

- ***Center for Lupus Research.*** A team of immunologists and clinicians are addressing multiple aspects of lupus, with an emphasis on the juvenile form of the disease. Areas of investigation include development of markers of disease activity and severity, and identification of new treatment targets.
- ***Center for Research Translation in Scleroderma.*** This Center is using molecular genetics techniques (single nucleotide polymorphism genotyping and DNA microarrays) to elucidate the genetic processes causing scleroderma and identify predictors of the disease's course. Results from these studies will be applied to development of treatment improvements for scleroderma patients.
- ***Center for X-Linked Hypophosphatemic Rickets.*** Researchers are studying factors regulating death of cartilage cells (i.e., chondrocytes), mechanisms by which fibroblast growth factor receptors transmit signals, the influence of hyperparathyroidism on disease severity, and whether correcting hyperparathyroidism improves skeletal health.
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Juvenile systemic lupus erythematosus

In the area of childhood lupus, NIAMS-supported researchers are currently conducting a large, controlled study to assess the ability of statins (cholesterol-lowering agents) in preventing or delaying progression of cardiovascular disease in children with lupus. This research study involves 20 centers from the Pediatric Rheumatology Research Network in establishing the largest cohort of pediatric lupus patients ever prospectively studied. Approximately 15 percent of patients have been enrolled and baseline data analysis is currently under way.

Malignant hyperthermia and central core disease

In FY 2006, the NIAMS renewed a program project grant to investigators at the Brigham and Women's Hospital for studies of the molecular basis of malignant hyperthermia. This research

will elucidate how mutations in the gene for RYR1 (described above) differentially perturb intracellular concentrations of calcium ions and will characterize factors that influence the severity of clinical manifestations.

Marfan syndrome

NIAMS-supported researchers have developed a multisite translational research program in Marfan syndrome. The long-term goal of this program is to translate basic research in matrix biology into treatment strategies for individuals with Marfan syndrome and related disorders of connective tissue. The program is utilizing a comprehensive and multidisciplinary approach that integrates the scientific interest and expertise of four leading laboratories in this and related research fields. Researchers are studying genetically engineered mouse models of Marfan syndrome to uncover the abnormal cellular activities that contribute to this disorder and will translate this new knowledge into more effective therapies.

Muscular dystrophies (including Duchenne muscular dystrophy, facioscapulohumeral dystrophy, and myotonic dystrophy)

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers: NIAMS supports basic, translational, and clinical studies on the muscular dystrophies and other muscle diseases and disorders. A major component of the NIAMS muscular dystrophy research portfolio includes funding for two of the six NIH-supported Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. Each Wellstone center brings together expertise, infrastructure, and resources focused on major questions about muscular dystrophy. The Wellstone Centers promote side-by-side basic, translational, and clinical research, and provide resources that can be used by the national muscle biology and neuromuscular research communities. The first NIAMS-supported center is located at the University of Pittsburgh where researchers are examining the use of gene and stem cell therapies to treat Duchenne muscular dystrophy, the most common childhood form of muscular dystrophy. The second center is located at the University of Pennsylvania where researchers are investigating strategies to inhibit muscle degeneration and to promote muscle growth. These approaches could be applicable to a wide range of muscular dystrophies and other muscle diseases.

Each Wellstone Center has core facilities that are available to other investigators as a national resource. The Pittsburgh Wellstone Center supports core imaging capabilities, development of gene therapy approaches, and a muscular dystrophy dog colony. The Pennsylvania/Johns Hopkins University Wellstone Center has a physiological assessment core that assists with studies using mouse models of muscular dystrophy.

To enhance the ongoing activities of the NIH-supported Wellstone Centers, NIAMS recently joined several other NIH components in announcing the availability of administrative supplements to these Centers. One promotes collaborations by the Wellstone Centers, and increases opportunities for career development among junior investigators affiliated with these Centers. The other encourages the Directors of the Wellstone Centers, in collaboration with other muscular dystrophy researchers and representatives from voluntary health organizations, to conduct

workshops or conferences focused on specific topics in muscular dystrophy research. These workshops will fill a specific need in the muscular dystrophy field to bring investigators together to achieve a range of objectives, including developing collaborations, focusing efforts and resources, and reaching consensus on research and patient care strategies. Funding for the career development supplements and workshops will be available through FY 2009.

National Registry of Myotonic dystrophy and Facioscapulohumeral dystrophy Patients and Family Members: Since FY 2000, the NIAMS and National Institute of Neurological Disorders and Stroke (NINDS) have supported the National Registry of Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members, a resource for the collection and analysis of clinical information from patients and their families to accelerate research on these diseases. The long-term goal of the registry is to facilitate research in myotonic and facioscapulohumeral dystrophies by serving as a liaison between affected families who are eager to participate in research and investigators who are conducting specific projects relevant to these disorders.

Ongoing Program Announcements: The NIAMS, along with the NINDS, NICHD, and NIH Office of Dietary Supplements, is cosponsoring two program announcements to support training of scientists in muscle disease research. The first, Ruth L. Kirschstein National Research Service Awards for Postdoctoral Fellowships in Muscle Disease Research, encourages postdoctoral fellows with diverse scientific interests to apply their expertise to enhance our understanding of the pathogenesis and treatment of muscle diseases and disorders, including the muscular dystrophies. The second program announcement, Mentored Clinical Investigator Career Development Awards in Muscle Disease Research, was issued in recognition of a need for highly skilled researchers who are able to integrate various disciplines and successfully address the increasing challenges in the current research environment of muscular dystrophy and other muscle diseases. These career development programs are expected to increase the number of investigators in basic, translational, and clinical research on muscular dystrophy and other muscle diseases, and to improve the quality of their research and training.

Myositis

Dermatomyositis and polymyositis are two disorders within a group of inflammatory muscle diseases. Dermatomyositis is characterized by a rash preceding or accompanying muscle weakness. In polymyositis, weakness occurs in muscles close to the trunk of the body. NIAMS initiated a multisite clinical trial, testing rituximab in the treatment of adults and children with dermatomyositis or adult polymyositis which has been unresponsive to other treatment. Rituximab is a biological agent that depletes a cell population in the immune system and is effective in the treatment of some cancers (e.g, non-Hodgkin's lymphoma) and some autoimmune diseases (e.g., lupus and rheumatoid arthritis).

Neonatal lupus

The NIAMS recently renewed its commitment to the Research Registry for Neonatal Lupus for an additional 5 years. The registry collects patient information, sera, and DNA from women and

infants affected by neonatal lupus, as well as other family members who may be healthy. Currently, 412 children and 350 mothers have been registered. Through the registry, investigators will be able to obtain material for research on disease causes or improved diagnostic methods.

Neonatal-onset multisystem inflammatory disease (NOMID)

When NIAMS intramural researchers began studying the natural history and cause of NOMID in April 2003, they intended to examine and test children with NOMID to learn about the cause and course of the syndrome, with the hope of someday finding a therapy for these young patients. When the anakinra treatment described above proved successful, however, all patients enrolled in the natural history study began receiving anakinra. Now, the researchers' objective is to monitor the patients over time to evaluate anakinra's long-term effectiveness, and any risks associated with the drug.

Scleroderma

Scleroderma, often referred to as a single disease, is actually a symptom of a group of diseases that involves the abnormal growth of connective tissue that supports the skin and internal organs. In some forms of scleroderma, hard, tight skin is the extent of the disease. In other forms, however, the problem goes much deeper, affecting blood vessels and internal organs such as heart, lungs, and kidneys. A NIAMS-funded project is using a unique sample set—lung tissue from scleroderma patients undergoing lung transplant surgery and lung tissue from donor lungs—to facilitate investigation into the cellular changes that cause the hardening of the lungs. Other NIAMS-supported researchers are examining the cellular and molecular processes of scleroderma, cell transfer between mother and child, and the development of innovative therapies.

The NIAMS continues to support the Scleroderma Family Registry and DNA Repository at the University of Texas Health Sciences Center in Houston. Researchers are collecting and analyzing serum samples and health information from patients and their families to quantify associations between scleroderma and other autoimmune diseases (such as lupus) and to identify genes involved in scleroderma. The registry also serves as a resource for other investigators interested in scleroderma.

Vasculitis Clinical Research Consortium

The NIAMS continues to provide support for the Vasculitis Clinical Research Consortium, part of the Rare Diseases Clinical Research Network. The clinical and research expertise of four vasculitis centers and the resources of the NIH-supported General Clinical Research Centers at each site comprise the core of the consortium. The consortium has established a large longitudinal cohort of patients with at least one of the following diseases—Wegener's granulomatosis, microscopic polyangiitis, Churg Strauss vasculitis, polyarteritis nodosa, Takayasu's arteritis, and giant cell arteritis—and it provides an electronic Web site resource with information about these diseases for clinicians, researchers, and patients.

New/planned extramural or intramural research initiatives

In FY 2006, the NIAMS released several solicitations to encourage research on rare diseases. Many were issued in collaboration with other Institutes and patient advocacy groups, as indicated below.

Muscular dystrophies (including Emery-Dreifuss, facioscapulohumeral, limb-girdle, and oculopharyngeal muscular dystrophies)

NIH Translational Research Initiatives in Muscular Dystrophy: After evaluating the state-of-the science and holding numerous discussions with representatives from patient advocacy groups, the NIAMS, NINDS, and NICHD developed two targeted initiatives to encourage translational research in the muscular dystrophies: "Exploratory/Developmental Program for Translational Research in Muscular Dystrophy" and "Translational Research in Muscular Dystrophy."

Muscular Dystrophy: Pathogenesis and Therapies: The NIAMS, in collaboration with the NINDS, the NICHD, and the National Heart, Lung, and Blood Institute, cosponsored a set of program announcements, "Muscular Dystrophy: Pathogenesis and Therapies," to encourage research on basic, translational, or patient-oriented studies of the muscular dystrophies. This program announcement updated two previous solicitations entitled "Therapeutic and Pathogenic Approaches for the Muscular Dystrophies," which was released in January 2001, and "Pathogenesis and Therapy of the Muscular Dystrophies," released in March 1998.

Nuclear Structure-Function Defects in the Pathogenesis of Muscular Dystrophy: The NIAMS, together with the NINDS and the Muscular Dystrophy Association (MDA), cosponsored a Request for Applications (RFA) titled "Nuclear Structure-Function Defects in the Pathogenesis of Muscular Dystrophy." The RFA invites applications focused on determining the mechanisms underlying a subset of muscular dystrophies that may have their basis in defects in the structure/function of the cell's nucleus. Applications are specifically solicited for studies of Emery-Dreifuss, facioscapulohumeral, limb-girdle muscular dystrophy 1B, and oculopharyngeal muscular dystrophies. The partnership between the MDA and NIH on this initiative will expand the pool of potential applicants and the number of grants that can be funded. The NIH will review applications submitted for this RFA and consider meritorious applications for support. Applicants not funded by the NIH will be invited to submit their NIH applications and critiques to the MDA for a second level of consideration regarding funding.

Plans for Continuation of Funding of Wellstone Centers: The NIAMS will participate in a multi-Institute effort to solicit applications from institutions that are interested in participating in the program for FY 2008 and beyond.

Sarcoidosis

Sarcoidosis: Research into the Cause of Multi-Organ Disease and Clinical Strategies for Therapy: NIAMS and other NIH institutes have issued a funding opportunity announcement

to promote research into the cause of and care for sarcoidosis, an immune-mediated inflammatory disease affecting multiple organ systems, including the lungs, joints, skin, and liver. The announcement encourages exploration of factors leading to multiple organ involvement and mechanisms to mitigate the psychosocial burden of patients and their families.

Tuberous sclerosis complex

Understanding and Treating Tuberous Sclerosis Complex (TSC): The NIAMS and other NIH institutes have issued multiple program announcements to solicit grant applications that would elucidate cellular mechanisms that cause TSC and would lead to new therapies against this often devastating disorder. Grants funded under these initiatives are expected to build on existing knowledge about the genes that cause TSC (TSC1 and TSC2) and the pathways in which their corresponding proteins are involved, and studies with the potential to identify new therapeutic targets or that involve preclinical testing of candidate therapeutics are particularly encouraged.

Rare disease-specific conferences, symposia, or workshops with outcomes

Familial Mediterranean fever

Familial Mediterranean Fever and Beyond (November 2005): In November 2005, researchers participating in the *Fourth International Congress on Systemic Autoinflammatory Diseases* met to discuss clinical features, molecular genetics, and treatment of inherited disorders of inflammation. Topics addressed at the meeting, which was organized by the NIAMS—and cosponsored by the National Human Genome Research Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Deafness and Other Communication Disorders, the NIH Office of Rare Diseases, and the Foundation for the National Institutes of Health—included rare diseases such as:

- Adult-onset Still's disease.
- Behçet's disease.
- Familial Mediterranean fever.
- Hyperimmunoglobulinemia D with periodic fever syndrome.
- Juvenile idiopathic arthritis.
- Muckle-Wells syndrome.
- Neonatal-onset multisystem inflammatory disease.

Hereditary multiple exostoses

Hereditary Multiple Exostoses: Insights into Pathogenesis (November 2005): The NIAMS provided funding for a conference titled "Multiple Hereditary Exostoses: Insights into Pathogenesis," which was held in early November 2005 in Houston, Texas. Multiple hereditary exostoses is a genetic bone disorder in which benign cartilage-capped tumors (exostoses or osteochondromas) form from the growth plates of long bones or from the surface of flat bones throughout the body. Exostoses cause numerous problems, including compression of peripheral nerves or blood vessels, skeletal deformity, chronic pain and fatigue, early onset arthritis, and an

increased risk of developing chondrosarcoma. At the meeting, researchers, health care providers, and patients and family members attended presentations and workshops on topics including bone development, clinical care issues, disease genetics, tumor formation, orthopaedic research, and conditions related to multiple hereditary exostoses.

Muscular dystrophies

High-Throughput Drug Screening in Muscular Dystrophy (April 2006): In April 2006, the NIAMS cofunded a workshop at Children's National Medical Center, a Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center in Washington, D.C. The 2-day workshop was the first in a new series of conferences that are supported by administrative supplements to the Wellstone Centers (see "Significant ongoing rare disease research initiatives," above). It brought together leaders in the field of high-throughput screening to discuss possible strategies to identify small molecules that could have therapeutic potential for muscular dystrophy patients. Workshop participants concluded that—although substantial high-throughput screening resources are available, and several screens are focusing on a number of promising targets for therapy development in muscular dystrophy—additional robust and physiologically relevant assays still are needed.

Second New Directions in Biology and Disease of Skeletal Muscle (April 2006): The NIAMS, together with other NIH components and the Muscular Dystrophy Association, sponsored a conference on "Second New Directions in Biology and Disease of Skeletal Muscle" in April 2006. The purpose of this conference was to bring together researchers who study different aspects of muscle diseases, since the lack of a centrally focused meeting was an impediment in understanding and treating important muscle diseases. This was only the second national meeting to address functions and disorders of skeletal muscle. The conference attracted clinical and basic researchers and provided an excellent forum for them to interact and share ideas about muscular dystrophy and other muscle disease research. This conference is now scheduled to occur every two years, with the next meeting planned for April 2008. The conference will retain the focus on cellular and molecular aspects of skeletal muscle as they relate to health, disease and dysfunction.

Translational Research in Muscular Dystrophy (June 2007): The NIH is planning a Workshop on Translational Research in Muscular Dystrophy for June 2007. The meeting will be held in conjunction with the upcoming Muscular Dystrophy Coordinating Committee meeting, thereby encouraging member organizations to participate in the workshop and fostering better coordination of efforts of various agencies and groups. The meeting will serve as a forum to discuss and evaluate progress toward identifying opportunities for therapeutic development.

Osteogenesis imperfecta

New Research Strategies in Osteogenesis Imperfecta (April 2006): Osteogenesis imperfecta, or "brittle bone disease," leads to weak bones that fracture easily. The NIAMS awarded a grant to the Osteogenesis Imperfecta Foundation for partial support of a scientific meeting titled "New Research Strategies in Osteogenesis Imperfecta," which occurred in April 2006. Approximately 45 investigators attended the meeting, including the clinical directors from

the Foundation's Linked Clinical Research Centers project, a cooperative network of research and treatment facilities nationwide designed to increase opportunities for researchers and improve the standard of care for people who have osteogenesis imperfecta.

The Osteogenesis Imperfecta Foundation also participates in activities coordinated by the NIH Osteoporosis and Related Bone Diseases ~ National Resource Center, which is managed by the NIAMS. Most recently, the organization was represented at the resource center's Coordinating Panel Meeting, held on October 10, 2006.

Pachyonychia congenita

Reaching Clinical Trials for Pachyonychia Congenita (May 2006): The NIAMS awarded an R13 grant to the Pachyonychia Congenita Project for partial support of a symposium *Reaching Clinical Trials for Pachyonychia Congenita*. The meeting was held in Philadelphia, Pennsylvania, prior to the annual meeting of the Society of Investigative Dermatology so that scientists could easily attend both meetings. Approximately 35 physicians and researchers participated, sharing results from ongoing research and exchanging ideas and forming collaborations for future projects.

Activities with rare diseases patient advocacy groups to stimulate research

Muscular dystrophies

Muscular Dystrophy Coordinating Committee (MDCC): In accordance with the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Public Law 107-84), the NIAMS is one of the 10 government agencies that, along with 5 public representatives, comprise the MDCC. Public members including representatives from the MDA, Parent Project Muscular Dystrophy, and the Facioscapulohumeral Society regularly participate in the MDCC, which is chaired by the NIAMS Director Dr. Stephen Katz. The most recent committee meeting (held May 10, 2006) focused on implementation of the MDCC's *Action Plan for the Muscular Dystrophies*. The next meeting of the MDCC is scheduled for late spring in Washington, D.C. The agenda for this meeting will include updates on Action Plan-related activities at each agency and organization, and a discussion of the strategies for recruitment, training, and retention of basic and clinical researchers in the muscular dystrophies.

RFA: Nuclear Structure-Function Defects in the Pathogenesis of Muscular Dystrophy: The RFA "Nuclear Structure-Function Defects in the Pathogenesis of Muscular Dystrophy," cosponsored by the NIAMS, NINDS, and MDA, is described above in the section "New/planned extramural or intramural research initiatives."

Workshop: Second New Directions in Biology and Disease of Skeletal Muscle (April 2006): The workshop was sponsored by the NIAMS, other NIH components, and the MDA. It is described above in the section "Rare disease-specific conferences, symposia, or workshops with outcomes."

Education activities on rare diseases for the researcher, public, and health care provider communities

Publications for patients and the public

In FY 2006, the NIAMS expanded its collection of ***Fast Facts: An Easy-to-Read Series of Publications for the Public*** to include two additional rare diseases:

- lichen sclerosis, and
- Marfan syndrome.

The Institute also published an updated version of the ***Handout on Health: Scleroderma*** booklet, which it originally produced in 2001, and began revising other publications:

- ***Questions and Answers about Juvenile Idiopathic Arthritis.***
- ***Questions and Answers about Marfan syndrome.***
- ***Questions and Answers about Polymyalgia Rheumatica and Giant Cell Arteritis.***
- ***Questions and Answers about Heritable Disorders of Connective Tissue,*** which includes information about several rare diseases such as
    - Ehlers-Danlos syndrome,
    - epidermolysis bullosa,
    - Marfan syndrome, and
    - Osteogenesis imperfecta.

New materials for health care providers

Pediatric Rheumatic Diseases and Other Related Information for You and Your Patients CD-ROM: The NIAMS, in partnership with the Arthritis Foundation, launched the *Pediatric Rheumatic Diseases and Other Related Information for You and Your Patients CD-ROM*, a comprehensive and cost-effective educational and informational tool for doctors and other health professionals who treat children with pediatric rheumatic diseases and related conditions. The CD-ROM, which was released in November 2005, provides information about rare diseases such as

- juvenile idiopathic arthritis,
- osteogenesis imperfecta, and
- juvenile osteoporosis.

As of September 30, 2006, 9,430 copies of the CD-ROM had been distributed.

NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING (NIBIB)

Overview

The mission of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) is to improve human health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating the physical and engineering sciences with the life sciences to advance basic research and medical care. The Institute works to achieve this mission by supporting research that has broad applicability across disease or organ lines.

The NIBIB funds research on rare diseases through its extramural programs via grant solicitations, although the Institute's primary support of research is through unsolicited, investigator-initiated grant awards. Rare disease research funded in FY 2006 includes cancer of the esophagus, basal cell carcinoma, stress urinary incontinence, glaucoma, and copper metabolism disease. Highlighted below are some of NIBIB's activities related to treating and preventing rare diseases and conditions that fall within the purview of the Institute's mission.

Recent Scientific Advances in Rare Diseases Research

Cancer of the esophagus

Barrett's esophagus is a condition in which the esophagus changes so that some of its lining is replaced by a type of tissue similar to that normally found in the intestine. This process is called intestinal metaplasia. While Barrett's esophagus may cause no symptoms itself, a small number of people with this condition develop a relatively rare but often deadly type of cancer of the esophagus. Barrett's esophagus is estimated to affect about 700,000 adults in the United States. Currently doctors must perform biopsies at random to diagnose the cancer. NIBIB researchers are developing a tool that will enable doctors to quickly assess the region of Barrett's esophagus in a patient with this disease. This tool will be based on a technique of light imaging that will allow doctors to detect early precancerous changes. Doctors can then biopsy suspicious areas and verify diagnosis of this rare disease. The tool will reduce the time and costs associated with diagnosing cancer of the esophagus as well as reduce patient discomfort by requiring fewer biopsies.

Basal cell cancer

Basal cell cancer (BCC), or skin cancer, is the most common form of cancer in the United States, with more than 800,000 new cases estimated each year. Basal cells are cells that line the deepest layer of the epidermis, the top layer of skin. This type of cancer occurs most frequently on older people in vulnerable body parts such as the eyes, mouth, nose, and ears. Basal cell cancer can usually be diagnosed with a biopsy and is treated with precise microsurgery. NIBIB researchers are developing an improved imaging method that will provide surgeons with images of the basal cell cancers during surgery to enhance precision.

Glaucoma

Glaucoma is the leading cause of blindness in the United States. It is a disease of the optic nerve, the part of the eye that carries images to the brain. When damage to the optic nerve fibers occurs, blind spots develop. Blindness can occur if the blind spots go undetected and significant damage to optic nerve occurs. However, medical advances have made it easier to diagnose and treat glaucoma. NIBIB researchers have developed new high-frequency ultrasound systems that provide new opportunities to advance tissue evaluation in the anterior segment of the eye. This technique allows research to develop a three-dimensional representation of blood flow in the anterior segment of the eye, providing important information in the staging and diagnosis of glaucoma.

NATIONAL CANCER INSTITUTE (NCI)

Recent Scientific Advances

Natural Killer Cells Induced to Fight Liver Cancer in Mice

Two types of killer immune cells play divergent roles in fighting cancer located in the liver, according to a new study conducted by NCI. A team led by scientists from the Center for Cancer Research has shown that the activities of these cells can be manipulated by treating mice with interleukin—biological response chemicals that dial up or down the body's natural immune response—to simultaneously stimulate helpful natural killer cells and alter the sometimes detrimental effects of natural killer T cells to combat cancer in the liver. They showed that treating mice that had cancer with IL-18/IL-12 induced high levels of IFN- γ and greatly reduced the number of tumors in the liver. Surprisingly, the researchers also noticed that treatment with IL-18/IL-12 not only increased numbers of NK cells in the liver, but also decreased the number of NKT cells that could be detected. Rather than restricting the immune system's ability to fight cancer, altering or eliminating NKT cells further inhibited tumor growth. The researchers hope that enhancing NK cell function, while also eliminating or altering NKT cells, will improve cancer immunotherapy.

The liver is a target organ for the spread of many types of tumors, including kidney, colorectal, and breast cancer. All of these tumors can be lethal based, in part, on their spread to vital organs such as the liver. Thus, approaches that enhance immune responses against cancer in the liver might be beneficial for cancer patients with tumors that arise in, or metastasize to, the liver. *Cancer Research* 2006; Vol. 66, Issue 22.

Novel Protein Identified That Ties Disruption of a Critical Cellular Pathway to Birt-Hogg-Dubé syndrome

Researchers at the Center for Cancer Research, part of the National Cancer Institute, have linked specific genetic mutations to defects in cells that lead to a rare disease known as Birt-Hogg-Dubé syndrome. Building on previous clinical and genetic work spanning several years, the researchers discovered a novel protein that binds to the normal version, but not the mutant version, of the protein implicated in Birt-Hogg-Dubé syndrome. This new protein, which they named folliculin interacting protein 1 (or FNIP1), links Birt-Hogg-Dubé syndrome to disruptions in critical energy- and nutrient-sensing cellular pathways. These findings open new avenues of further research and therapeutic development for Birt-Hogg-Dubé syndrome, as well as other diseases and cancers related to the same pathways. *PNAS*, online edition, October 2, 2006.

A Unique Pattern of Gene Activity Can Predict Liver Cancer Spread

Researchers have found that a unique pattern of activity for genes in cells located in the tissue surrounding a liver tumor can accurately predict whether the cancer will spread to other parts of the liver or to other parts of the body. This preliminary research was led by a team of scientists from the National Cancer Institute's Center for Cancer Research. Researchers analyzed gene

expression signatures—patterns of gene activity—largely in immune cells within the liver microenvironment, which is the area immediately surrounding the tumor. The set of 17 genes included those that encode the messages for cytokines, which are small proteins produced by immune cells that are used to communicate messages between cells in the immune system to either turn up or down the immune response.

From the 17-gene set, researchers identified a unique pattern in the immune cells found in normal tissue of the liver microenvironment that could predict the potential for liver tumor metastasis. This metastasis-specific profile included gene activities responsible for increased production of certain cytokines that are associated with an anti-inflammatory response, as well as suppression of immune response. Increased levels of these cytokines are associated with a poor prognosis of cancer.

Using the gene signature of immune cells in the liver, researchers were able to predict tumors that would metastasize in 92 percent of the samples studied, allowing for the first time stratification of HCC patients to identify those who would benefit from certain post-surgical treatments to prevent metastases and recurrence. The tendency of hepatocellular carcinoma tumors to metastasize or recur following surgery contributes to the poor outcome associated with this disease. Accurately predicting this cancer's risk of spread will provide critical guidance on treatment choices. *Cancer Cell*. August 2006, Vol. 9, Issue 8.

Gene Expression Profiling Can Accurately Diagnose Burkitt's Lymphoma

Gene expression profiling, a molecular technique that analyzes many genes simultaneously, can accurately distinguish between two types of immune cell tumors—Burkitt's lymphoma and diffuse large B-cell lymphoma (DLBCL)—according to a team of researchers led by scientists from the Center for Cancer Research, part of the National Cancer Institute. Burkitt's lymphoma and DLBCL cells appear similar when viewed under a microscope but correct diagnosis is critical because each cancer requires very different treatments.

Burkitt's lymphoma and DLBCL are types of non-Hodgkin's lymphoma (NHL), a malignancy of B lymphocytes, a type of white blood cell. Because both lymphomas can occur in the same age group and patients present similar clinical symptoms, it is often difficult to distinguish these two types of NHL. Using gene expression profiling, researchers are able to take microscopically identical tumors from different patients and demonstrate that they are genetically distinct, in order to provide greater certainty about diagnosis and prognosis. Eventually, this type of analysis will help to understand the molecular mechanisms causing this disease and identify novel targets for therapeutic interventions. *New England Journal of Medicine*, June 8, 2006, Vol. 354, No. 23.

Tumor Stem Cells are Better Models for Glioblastoma Research

Researchers at the Center for Cancer Research, NCI, and the National Institute of Neurological Disorders and Stroke, have found that tumor stem cell lines derived directly from human glioblastoma brain tumors are a better model to study the biology and physiology of glioblastomas than are cancer cell lines that have been commonly used in cancer research laboratories. They also

discovered the conditions under which to preserve the biological integrity and genetic characteristics of these glioblastoma tumor stem cell lines.

Cells in traditional cancer cell lines often bear little resemblance to the cells found in the corresponding original tumor. Glioblastoma tumor stem cells, however, accurately reflect the biological mechanisms and genetic characteristics of the parent tumor. These tumor stem cells are capable of self-renewal—a characteristic that is essential for tumor growth—and of developing into glioblastomas when injected into mice with compromised immune systems. Thus, these tumor stem cell lines offer a powerful new tool to study the biology of glioblastomas and to test drugs for treatment of this disease. *Cancer Cell*. May 15, 2006, Vol.9, Issue 5.

Expression Profiling Identifies Altered Expression of Genes Involved in TGF-beta Signaling in Ovarian Cancer

Ovarian cancer is resistant to the antiproliferative effects of transforming growth factor-beta (TGF-beta); however, the mechanism of this resistance remains unclear. A team led by researchers from the Center for Cancer Research, NCI, used oligonucleotide arrays to profile early-stage papillary serous cancers to identify signaling pathways involved in ovarian cancer. A total of seven genes involved in TGF-beta signaling were identified that had altered expression in the ovarian cancer specimens compared with normal ovarian surface epithelium. The expression of these genes was coordinately altered: genes that inhibit TGF-beta signaling were up-regulated in advanced-stage ovarian cancers and, conversely, genes that enhance TGF-beta signaling were down-regulated compared with the normal samples. These results suggest that altered expression of these genes is responsible for disrupted TGF-beta signaling in ovarian cancer and they may be useful as new and novel therapeutic targets for ovarian cancer. *Cancer Res* 2006; 66(17):8404-12.

Detection and quantitation of serum mesothelin, a tumor marker for patients with mesothelioma and ovarian cancer

Scientists at the Center for Cancer Research, NCI have recently determined that mesothelin, a cell surface protein highly expressed in mesothelioma and ovarian cancer, is shed into serum and developed an assay to accurately measure it. The serum mesothelin assay shows that mesothelin is elevated in patients with mesothelioma and ovarian cancer. The rapid decrease in mesothelin levels after surgery in patients with peritoneal mesothelioma suggests that serum mesothelin may be a useful test to monitor treatment response in mesothelin-expressing cancers. They have also developed a blood test for mesothelioma and ovarian cancer by measuring the serum levels of mesothelin. It could be an important tool for the diagnosis and follow-up of patients with these cancers. *Clin. Cancer Res* 12:447-53, 2006.

MC1R Germline Variants Confer Risk for BRAF Mutant Melanoma

Germline variants in *MC1R*, the gene encoding the melanocortin-1 receptor, and sun exposure increase risk for melanoma in whites. Melanomas that occur on skin with little evidence of chronic sun-induced damage (non-CSD) frequently exhibit mutations in the *BRAF* oncogene, whereas this mutation is much less common in melanomas on skin with marked CSD. In two

independent white populations, the *MC1R* variants were shown to be strongly associated with *BRAF* mutations in non-CSD melanomas. In this tumor subtype, the risk for melanoma associated with *MC1R* is due to an increased risk of developing melanomas with *BRAF* mutations. *Science* 2006; 313:521-522.

Identifying Individuals at High Risk of Melanoma: A Practical Predictor of Absolute Risk

Cutaneous melanoma among the white population is a problem of increasing clinical and public health importance. In the United States, incidence rates have increased steadily for several years, and in 2006, the estimated number of new cases reached an all-time high of over 62,000. Because detection of melanoma at its earliest stages is critical for improved survival, a prediction model to identify individuals who are at high absolute risk would be an important tool for primary care providers. Such a model was developed to estimate the chance of a white man or woman between the ages of 20 and 70 years to develop a first primary melanoma over the next 5 years. The model is based on specified risk factors that can be easily ascertained during a routine physical exam by a health care provider. Assessment of risk factors requires a patient's response to two questions, depending on the patient's sex, and an examination of his or her back. A program to calculate estimated absolute risk using this model is now available online: (http://dceg.cancer.gov/melanomarisktool). The model can be used by primary care providers to identify individuals who are at high absolute risk for developing cutaneous melanoma. These individuals could then be referred for either screening or intervention protocols. The model may be widely generalizable for use with appropriate incidence and mortality rates to develop absolute risk estimates, not just for the U.S., but for other regions of the world with comparable UVB intensity levels and similar melanoma risk factors. *J Clin Oncol* 2006; 24:3590-3596.

Genetic Variation in TNF and IL10 and Risk of Non-Hodgkin Lymphoma

Evidence that genetic susceptibility plays a part in lymphomagenesis is provided by strong and consistent findings from registry and population-based epidemiologic studies that show an increased risk of non-Hodgkin lymphoma in individuals with a family history of this disease. A consortial approach was used to evaluate whether single-nucleotide polymorphisms in immune-related candidate genes are associated with risk of non-Hodgkin lymphoma by pooling data from eight European, Canadian, and U.S. case-control studies of the International Lymphoma Epidemiology Consortium (InterLymph). Twelve single-nucleotide polymorphisms located among nine genes were selected for analysis on the basis of previous functional or association data. Two polymorphisms, one from tumor necrosis factor (*TNF*) gene and the other in the interleukin 10 *(IL10)* gene, were associated with increased risk of non-Hodgkin lymphoma, particularly for diffuse large B-cell lymphoma. For individuals homozygous for the *TNF* –308A allele and carrying at least one *IL10* –3575A allele, the risk of diffuse large B-cell lymphoma doubled. These results underscore the importance of consortial collaborations for investigating the genetic basis of chronic diseases such as cancer. *Lancet Oncology* 2006; 7:27-38.

Acute Myeloid Leukemia Following Hodgkin Lymphoma: A Population-Based Study of 35511 Patients

Treatments for Hodgkin lymphoma are associated with large, increased relative risks of acute myeloid leukemia (AML), but there are few estimates of the excess absolute risk (EAR), a useful measure of disease burden in a population. This large, international, population-based study of one-year Hodgkin lymphoma survivors demonstrated an overall reduction in the burden of AML over time. Patients whose initial treatment included any chemotherapy, compared with radiotherapy alone, had a significantly larger EAR of AML. Excess absolute risks were higher for older patients (≥35 years versus <35 years) and for the earlier period (1970–1984 versus 1985–2001). The decline over calendar years, as measured by the difference in the EARs, was particularly apparent among patients who initially received any type of chemotherapy. Excess absolute risk for AML was highest during the first 10 years after Hodgkin lymphoma diagnosis and then steadily declined thereafter; however, risks were still significantly elevated compared to the general population. The excess risk of AML declined significantly after 1984, which may be associated with modifications in chemotherapeutic regimens. *J Natl Cancer Inst* 2006; 98:215-218.

Risk of Monoclonal Gammopathy of Undetermined Significance (MGUS) and Subsequent Multiple Myeloma Among African American and White Veterans in the United States

Multiple myeloma (MM) is a blood-borne malignancy characterized by uncontrolled proliferation of plasma cells in the bone marrow. Age-adjusted incidence and mortality rates are 2-fold higher in African Americans than in whites, but the basis for this race-related difference is unknown. Monoclonal gammopathy of undetermined significance (MGUS), a benign disorder with a strikingly elevated monoclonal immunoglobulin level, is a predisposing risk factor for MM. Etiologic factors for MGUS and determinants for transformation of MGUS to MM are unknown. This study quantified the prevalence of MGUS and subsequent risk of MM among 4 million African-American and white male veterans admitted to Veterans Affairs (VA) hospitals. The age-adjusted prevalence ratio of MGUS in African Americans compared with whites was 3.0 (2.7-3.3, 95 percent confidence interval). However, among the MGUS cases, the estimated cumulative risk of MM during the first 10 years of follow-up was similar (P=0.37) for African Americans (17 percent) and whites (15 percent). This finding suggests that the excess risk of MM in African Americans results from an increase in risk of MGUS and not an increased risk of progression from MGUS to MM. *Blood* 2006; 107:904-906.

Primary Thyroid Cancer After a First Tumor in Childhood (The Childhood Cancer Survivor Study): A Nested Case-Control Study

Survivors of childhood cancer who have had radiotherapy to the head, neck, or upper thorax have an increased risk of subsequent primary thyroid cancer, but the magnitude of risk over the therapeutic dose range has not been well established. This study quantified the long-term risk of thyroid cancer after patients received radiotherapy and/or chemotherapy for initial childhood cancer. The risk of subsequent primary thyroid cancer after a first tumor in childhood rose with increasing radiation dose (greatest risk 20–29 Gy), but decreased at doses of more than 30 Gy.

The drop in the radiation dose-response for a solid cancer after a first cancer in childhood was consistent with a cell-killing effect of radiation at high doses. The trend was more pronounced in those diagnosed with a first primary malignant disease before age 10 years than in those older than 10 years. Chemotherapy for the first cancer was not associated with thyroid-cancer risk, and did not modify the effect of radiotherapy. These data underscore the importance of yearly examination of the neck and thyroid gland in all cancer survivors previously given radiation to the thorax or head and neck region. *Lancet* 2005; 365:2014–2023.

Randomized Double-blind Factorial Trial of Three Treatments to Reduce the Prevalence of Precancerous Gastric Lesions

A randomized trial was conducted to test the effects of one-time *Helicobacter pylori* treatment and long-term vitamin or garlic supplements in reducing the prevalence of advanced precancerous gastric lesions among residents of Shandong Province, China, who had undergone baseline endoscopies in 1994. In 1995, 3,365 eligible subjects were randomly assigned to one of three interventions or placebo: 1) *H. pylori* treatment, amoxicillin and omeprazole for two weeks in 1995; 2) vitamin supplement, vitamin C, vitamin E, and selenium for 7.3 years; and 3) garlic supplement, aged garlic extract and steam-distilled garlic oil for 7.3 years. Subjects underwent endoscopies with biopsies in 1999 and 2003, and the prevalence of precancerous gastric lesions was determined by histopathologic examination of seven standard biopsy sites. *H. pylori* treatment resulted in statistically significant decreases in the combined prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer in 1999 (OR = 0.77; CI = 0.62–0.95) and in 2003 (OR = 0.60; CI = 0.47–0.75), and had favorable effects on the average histopathologic severity and on progression and regression of precancerous gastric lesions in 2003. *H. pylori* treatment did not reduce the combined prevalence of dysplasia or gastric cancer. However, fewer subjects receiving *H. pylori* treatment (19/1,130; 1.7 percent) than receiving placebos (27/1,128; 2.4 percent) developed gastric cancer (adjusted $p = 0.14$). No significant favorable preventive effects were seen for vitamin supplements or garlic. *J Natl Cancer Inst* 2006; 98:974–983.

Annual Report to the Nation on the Status of Cancer

First issued in 1998, the *Annual Report to the Nation* is a collaboration among the North American Association of Central Cancer Registries (NAACCR), the National Cancer Institute (NCI), the American Cancer Society (ACS), and the CDC. The current report is the first comprehensive compilation of cancer information dedicated solely to U.S. Latinos. It is the most comprehensive coverage of cancer information for this large and rapidly growing ethnic group and is based on 90 percent of the U.S. Latino population. The report finds that for 1999 to 2003, Latinos had lower incidence rates than non-Hispanic whites (NHW) for most cancers, but were less likely than the NHW population to be diagnosed with localized stage disease for cancers of the lung, colon and rectum, prostate, female breast, and cervix. However, Latino children have higher incidence rates of leukemia, retinoblastoma, osteosarcoma, and germ cell tumors than do non-Latino white children.
Annual Report to the Nation on the Status of Cancer, 1975-2003, Featuring Cancer among U.S. Hispanic/Latino Populations. Holly L. Howe, Ph.D. (NAACCR), Xiaocheng Wu, M.D.

(NAACCR), Lynn A.G. Ries, M.S. (NCI), Vilma Cokkinides (ACS), Faruque Ahmed, Ph.D. (CDC), Ahmedin Jemal, Ph.D. (ACS), Barry Miller, Ph.D. (NCI), and Melanie Williams, Ph.D. (NAACCR), Elizabeth Ward, Ph.D. (ACS), Phyllis A. Wingo, Ph.D. (CDC), Amelie Ramirez, Dr.PH. (Baylor), and Brenda K. Edwards, Ph.D. (NCI).

Chronic Stress Promotes Tumor Growth and Angiogenesis in a Mouse Model of Ovarian Carcinoma

Epidemiologic and experimental animal studies have shown that stress may alter tumor growth. However, the biological mechanisms underlying such effects are not well understood, and their clinical significance for human disease remains controversial as a result. Based on the authors' prior studies linking behavioral factors to circulating VEGF levels *in vivo* and showing catecholamine regulation of tumor cell VEGF production *in vitro*, the authors sought to determine whether sympathetic nervous system activity might mediate a causal effect of stress on the growth and metastasis of ovarian cancer *in vivo*. Researchers also sought to define the role of angiogenic cytokines in mediating those effects. This study showed that chronic behavioral stress results in higher levels of tissue catecholamines, greater tumor burden and more invasive growth of ovarian carcinoma cells in an orthotopic mouse model. These data also suggest that blocking ADRB-mediated angiogenesis could have therapeutic implications for the management of ovarian cancer. Thaker, P.H., Han, L.Y., Kamat, A.A., Arevalo, J.M., Takahashi, R., Lu, C., Jennings, N.B., Armaiz-Pena, G., Bankson, J.A., Ravoori, M., Merritt, W.M., Lin, Y.G., Mangala, L.S., Kim, T.J., Coleman, R.L., Landen, C.N., Li,Y., Felix, E., Sanguino, A.M., Newman, R.A., Lloyd, M., Gershenson, D.M., Kundra, V., Lopez-Berestein, G., Lutgendorf, S.K., Cole, S.W., and Sood, A.K. (2006). Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nature Medicine*, 12(8), 939-44.
http://www.nature.com/nm/journal/v12/n8/abs/nm1447.html

Meat and Fat Intake as Risk Factors for Pancreatic Cancer and A Ray of Hope for Pancreatic Cancer? Lots of Vitamin D Might Cut Risks Studies Show

Pancreatic cancer is the most fatal cancer in adults; it is generally diagnosed at a late stage and is poorly responsive to therapeutic modalities. It ranks fourth among U.S. cancer deaths, and the 5-year survival rate is less than 5 percent. Because of the poor prognosis and the minimal impact of conventional treatment methods, it is important to focus on prevention of this disease. Various dietary factors have been investigated as potential risk factors for pancreatic cancer, but no firm conclusions about the role of meat or fat in the etiology of pancreatic cancer can be drawn. The JNCI article presents the findings of 7-year prospective data from the Multiethnic Cohort Study on the relationship of meat, dairy product, and egg consumption and of fat, saturated fat, and cholesterol intake to pancreatic cancer risk.

Another study looked at the relationship between vitamin D and the risk of pancreatic cancer. One of the first of its kind, this epidemiology approach to investigate the association between the two factors was used for collection. Dietary intake was assessed using a quantitative food frequency questionnaire. The strongest association was with processed meat. Intakes of pork and of total red meat were both associated with 50 percent increases in risk. There were no associations of

pancreatic cancer risk with intake of poultry, fish, dairy products, eggs, total fat, saturated fat, or cholesterol. Intake of total and saturated fat from meat was associated with statistically significant increases in pancreatic cancer risk but that from dairy products was not.

From the vitamin D study investigators found a reduced risk of pancreatic cancer with higher levels (600 IU/d or more) of vitamin D. Participants consuming in the higher range experienced a 41 percent reduction in pancreatic cancer verses those individuals with less than 150 IU/d. Multivariable analyses that controlled for factors previously linked with pancreatic cancer such as retinol, calcium, and multivitamin supplement strengthened the association between total vitamin D intake (with higher doses) and the risk of pancreatic cancer.

The results raise the possibility that individuals might reduce their risk of pancreatic cancer by reducing consumption of red and processed meat. However, because the fat components of the meats did not seem to account for the findings, other compounds in these foods that are responsible for the association need to be identified. Future analyses of meat and pancreatic cancer risk should focus on meat preparation methods and related carcinogens.

Nöthlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. *J Natl Cancer Inst* 2005 Oct 5; 97(19):1458-65.

Skinner et al. Vitamin D intake and the Risk for Pancreatic Cancer in two cohort studies. *Cancer Epi Biomarkers Prevention* 2006 Sept.

Ethnic and Racial Differences in the Smoking Related Risk of Lung Cancer

The incidence of lung cancer is substantially higher among blacks, Native Hawaiians, and other Polynesians and lower among Japanese Americans and Hispanics than among whites in the United States. The vast majority (80 to 90 percent) of these cases are attributable to cigarette smoking. Previous studies have provided moderate support for the existence of ethnic and racial differences in the smoking-related risk of lung cancer, with black smokers and Native Hawaiian smokers having a greater risk than other populations. Among cigarette smokers, African Americans and Native Hawaiians are more susceptible to lung cancer than whites, Japanese Americans, and Latinos. This data provides further support for the existence of ethnic and racial differences in the smoking-associated risk of lung cancer. Studies assessing differences in the metabolism of nicotine and tobacco carcinogens may help explain differences between populations in the susceptibility to smoking-related lung cancer.

Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, Henderson BE, and Le Marchand L. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med* 2006 Jan 26; 354(4):333-42. http://content.nejm.org/cgi/content/abstract/354/4/333

Kaposi's sarcoma: Two Viruses, Same Doorway

Parent Grant: R01CA082053
"Cytotoxic T Cell Responses to HHV8"
Dr. Charles R. Rinaldo
University of Pittsburgh

A gamma herpesvirus, HHV8/KSHV (human herpesvirus 8 or Kaposi's sarcoma-associated herpes virus) is an essential causative agent present in all forms of Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and Multicentric Castleman's disease (MCD). Kaposi's sarcoma is also the most prevalent AIDS-associated malignancy. Understanding the interplay between HHV8/KSHVand HIV (human immunodeficiency virus) is essential for the development of effective therapeutics. Despite the reduction of circulating HIV obtained through therapy with highly active antiretroviral therapy (HAART), mutations in the HIV viral genome result in therapy failures, which are often followed by the development of an AIDS-associated malignancy. An NCI supported investigator at the University of Pittsburgh, Dr. Charles Rinaldo is studying DC-SIGN (dendritic cell specific, ICAM-3 grabbing, non integrin protein) a cell surface protein found on antigen presenting cells (dendritic cells, monocyte/macrophages, and B lymphocytes). DC-SIGN has a bridge-like structure that permits attachment of antigen presenting cells to molecules found on T lymphocytes recruited to an infection site. Dr. Rinaldo and colleagues examined myeloid dendritic calls and a sub-population of stimulated macrophages and found that when the HHV8/KSHVvirus was incubated in tissue culture with these cells the virus was quickly taken up. If the DC-SIGN receptor was blocked, infection by HHV8/KSHV was also blocked. In a second paper, the investigators found that when B lymphocytes from normal donors expressing DC-SIGN were mixed with HIV, the virus was quickly taken up. If the DC-SIGN receptor was blocked, no virus entered the B lymphocytes. The investigators subsequently determined that while no active replication of HIV was occurring, the infected B lymphocytes were able, through DC-SIGN, to attach to T lymphocytes and productively infect them with HIV. B lymphocytes are found in association with T lymphocytes in lymphoid organs of HIV positive patients. This finding suggests a role for B lymphocytes in HIV infection.

These results are significant, because the identification of a cellular receptor that allows the entry of both HHV8/KSHV and HIV is a molecular target for drug development. A drug that blocks DC-SIGN, when used in combination with highly active antiretroviral therapy (HAART) could knock out one route of infection of T cells by HIV, and might also be useful for treatment of Kaposi's sarcoma. At present there are no good therapies for treatment of KS, and particularly in AIDS-Associated KS, the disease is rapidly fatal once it progresses from skin lesions to body cavities.
Citations: http://www.jimmunol.org/cgi/reprint/176/3/1741,
http://pathogens.plosjournals.org/archive/1553-7374/2/7/pdf/10.1371_journal.ppat.0020070-S.pdf

Wilms Tumor: An X Chromosome Gene, *WTX*, is Commonly Inactivated in Wilms Tumor
Parent Grant: R37CA058596
"Functional Properties of the Wilms' Tumor Gene WT1"
Dr. Daniel A. Haber
Massachusetts General Hospital Cancer Center
Wilms tumor, also called nephroblastoma, accounts for about 90 percent of pediatric kidney cancers. Wilms tumor is a rare disease, developing in approximately one out of 10,000 children. It is generally treated with surgery and chemotherapy, with about 80 per cent of patients surviving. In 1990, scientists linked Wilms tumor with mutations in a gene called WT1, but inactivation of WT1 onlyis only associated with a small percentage of Wilms cases (5 – 10 percent). In order to identify additional genetic abnormalities linked with the disease, Dr. Daniel Haber and colleagues

at the Massachusetts General Hospital Cancer Center performed a detailed genome-wide scan for aberrations in DNA from 82 patient tumor samples.

They identified a novel gene, WTX, that is mutated in 30 percent of children with Wilms tumor. This gene resides on the sex-determining X-chromosome. Males carry only one copy of the X chromosome, while females carry two. In samples from female patients, WTX mutations were found only on the active X, indicating that only one mutated copy of the gene would be sufficient for cancer to develop. This is the first example of an X chromosome gene being implicated as a tumor suppressor and suggests that X chromosome genes may have a bigger role in cancer than previously believed.

Dr. Haber's team found that WTX is normally expressed in cells involved in the development of the embryonic kidney suggesting a potentially key role for this gene in organ development. Follow-up studies should lead to a better understanding of normal kidney development and tumorigenesis. The WTX gene may also prove to be an important clinical marker, helping physicians to guide treatment by identifying patients with more or less-aggressive disease.

Citation: "An X Chromosome Gene, WTX, is Commonly Inactivated in Wilms Tumor." Miguel N. Rivera, Woo Jae Kim, Julie Wells, David R. Driscoll, Brian W. Brannigan, Moonjoo Han, James C. Kim, Andrew P. Feinberg, William L. Gerald, Sara O. Vargas, Lynda Chin, A. John Iafrate, Daphne W. Bell, Daniel A. Haber. *Science*, January 4 2007. Epub ahead of print.

Deciphering the Heterogeneity of Chronic Myeloid Leukemia

The heterogeneity of leukemia is well known and evolving technology is translating laboratory findings to the clinical problems of progression, response, and relapse. Chronic myeloid leukemia (CML) may be sensitive to imatinib and respond rapidly, while those sensitive to interferon-alpha may take years to respond. New research shows the response difference is due to each drug's effect on various types of CML cells. CML cells resistant to imatinib may be sensitive to another similar drug, dasatinib; another class of drugs, including tipifarnib and ionafarib, are in Phase I trials for patients resistant to both imatinib and desatinib and a vaccine derived from proteinase 3 also shows promise. A recent study found 300 genes associated with CML progression; this set was reduced to 20 genes clearly differentiating between blast and chronic CML phases.

Improving Bone Marrow Transplant Treatments

Immunotherapy studies are focusing on making blood or bone marrow transplants a better treatment for leukemias and non-Hodgkin's lymphoma. For instance, new studies using T cells with artificial T-cell receptors targeting the cell surface of B-cell malignancies may be promising. Although targeted biological therapies hold promise for treating cancer, their use is limited by delivery constraints and effective tumor targeting. Recent studies show a synergistic potential when combining biotherapeutics for treating blood cancers.

Progress on Myeloproliferative Disorders

The myeloproliferative disorders (MPD) include several rare, understudied malignancies. An international research group to study new treatments and biomarkers for this disease group, the MPD Research Consortium, recently received new funding. Also, a nonconsortium study this year found that azacitidine provides complete remissions in 10 to 17 percent of treated patients.

NCI Focuses on Pediatric Brain Cancers

The Pediatric Brain Tumor Consortium (PBTC) is supported by NCI to rapidly conduct phase 1 and 2 clinical evaluations of new therapeutic drugs, biological therapies and radiation treatment strategies in children with brain tumors. The NCI also funds the New Approaches for Neuroblastoma Treatment (NANT) consortium of 12 institutions by a program project grant to conduct early phase drug and treatment regimen trials for children with high risk neuroblastoma.

The Chronic Lymphocytic Leukemia Research Consortium Established

The Chronic Lymphocytic Leukemia (CLL) Research Consortium, a multicenter collaboration of investigators, was funded by NCI in FY 2006 containing 6 projects and 4 cores. Some consortium project leaders were also successful in obtaining NCI funding for another grant on epigenetic regulation of CLL gene expression. The grant will focus on CLL treatment with certain classes of drugs that affect DNA.

NCI also supports CLL research activities through the Quick Trials mechanism, cooperative agreements, contracts, and through the intramural research program.

Imaging and Surgical Research for Gynecologic Cancer

The use of superparamagnetic iron oxide nanoparticles may improve the accuracy of lymphatic imaging. The NCI is sponsoring a study evaluating the diagnostic accuracy of 2 imaging techniques (FDG-PET/CT and ferumoxtran-10/MRI) in identifying metastases in patients with cervical carcinoma.

The NCI supported a randomized clinical trial in patients with vulvar cancer designed to study the safety and efficacy of a fibrin sealant applied to the inguinal wound after lymph node dissection as part of treatment for vulvar cancer.

Extramural Clinical Trials for Liver Cancer

Currently, 16 new agents in 22 NCI extramural phase I/II clinical trials are under development and studies with 3 investigational agents are being reviewed. NCI is also funding phase II trials evaluating radiofrequency ablation and chemoembolization for hepatocellular cancer.

New NCI Gastrointestinal Steering Committee Formed

In 2005, the Clinical Trials Working Group (CTWG) recommended restructuring of the national clinical trials enterprise to ensure its founding on the best science. This strategy preserves and strengthens all of the existing NCI clinical trials system components, but asks them to work together in fundamentally different ways. The restructuring created Disease-Site-Specific Scientific Steering Committees to address, design, and prioritize clinical treatment trials. The first committee to organize was the NCI Gastrointestinal Steering Committee (GISC) with members from all the Cooperative Groups, SPOREs, Cancer Centers, and R01/P01 investigators along with community oncologists, biostatisticians, patient advocates, and NCI staff. The GISC has six disease-site task forces, including one on Hepatobiliary/Hepatocellular Cancer, which will increase the efficiency of clinical trial collaboration in hepatocellular cancer.

Blood and Marrow Transplant Clinical Trials Network Focuses on Lymphoma

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was renewed in FY 2006 by NHLBI and NCI (NCI will contribute $3.2 million per annum for 5 years). A Phase III network trial is comparing two pre-transplant conditioning regimens to determine possible progression-free survival differences after autologous hematopoietic stem cell transplantation for chemotherapy-sensitive diffuse large B-cell lymphoma (DLBCL). The BMT CTN is designing a new transplant lymphoma trial with the NCI national clinical trials cooperative groups. New concepts for protocols are under review.

Childhood Cancer Survivor Study Includes Lymphoma Research

NCI funded the Childhood Cancer Survivor Study (CCSS) in FY 2006. Hodgkin's as well as non-Hodgkin's lymphoma (NHL) patients are well represented in the study.

Studying the Role of the Immune System in Lymphoma Progression and Treatment

The role of the immune system in lymphoma progression and treatment is being studied in a funded program project by Ronald Levy. Published earlier reports of signaling profiles in response to cytokine in AML are being extended to follicular lymphoma (FL) in which altered signaling mechanisms in response to IL-4 are being discovered in different FL patient biopsies, which suggest modulation of IL-4 signaling in immune effector cells may be important to tumor maintenance. In another project, the role of host immune status in tumor regression is being studied in mouse lymphoma models in which tumors regress after oncogene (specifically myc) inactivation. Finally, patients with B-cell lymphoma and cutaneous T-cell lymphoma are being treated in novel Phase I and Phase I/II vaccination trials with immune stimulant CPG both alone and in combination with other therapies, to induce an immune response by activation of endogenous dendritic cells.

Immunotherapeutic approaches are ongoing for this disease, taking advantage of antibody-directed targeting of antigens at the cell surface of the malignant B cells.

Rituximab is an anti-CD20 monoclonal antibody which targets the CD20 molecule on B cell lymphomas. This reagent, in combination with CHOP chemotherapy, has been studied in comparison to CHOP alone in diffuse large B cell lymphoma (DLBCL) in older patients. The results of the 3 year follow up show that rituximab administered as either induction or maintenance with CHOP significantly prolonged failure-free survival in these patients, consistent with an additive effect of rituximab. A phase III randomized intergroup trial for treatment of previously untreated advanced follicular lymphoma is currently under way comparing efficacy of the promising CHOP plus tositumobab/iodine I-131 tositumobab regimen with efficacy of CHOP + rituximab. The 5 year follow up of the phase II trial showed an overall response rate of 91 percent, including a 69 percent complete remission rate in the experimental arm; the overall and progression-free survival rates were each 23 percent better than the corresponding figures for patients treated on previous protocols with CHOP alone. In a multicenter Phase II study, efficacy and toxicity of humanized anti-CD22 antibody, epratuzumab, in combination with rituximab, for refractory or recurrent non-Hodgkin's lymphoma was examined. Objective responses were highest in follicular lymphoma and DLBCL, with response rates higher in patients with low prognostic index scores. The study showed that the combination therapy was well tolerated without toxicity greater than rituximab alone and the combination warrants further study.

In 2006, NCI also funded studies aimed at understanding the pathogenesis of infectious agents in the context of lymphomas in the immunocompromised.

Advances in gene expression profiling in lymphoma provide knowledge for both prognostic markers and molecular targets. The Lymphoma/Leukemia Molecular Profiling Project results show that gene expression profiling is an accurate, quantitative method for distinguishing Burkitt's lymphoma from DLBCL, and another study from this project that looked at BCL-2 expression as a prognostic marker in DBCL showed that there was no significant correlation between BCL2 expression and overall survival in the germinal center B-cell-like group, but expression of BCL2 had a significant adverse effect on overall survival in the activated B-cell subcategory of DBCL. In a separate funded study of Germinal center B cell lymphomas at the Dana Farber Cancer Center, the most important molecular events in the progression of B cell lymphomas are being studied to refine current prognostic assessments and credential rational targets for specific therapeutic intervention. For instance, a recent study showed that interferon-gamma induced expression of a transcription modulator contributes to the molecular signature of DLBCL's that are defined by a brisk response to host inflammatory responses, which highlight the interplay between inflammatory infiltrates and the malignant B cells in these tumors.

Studying Lymphomas Associated with AIDS

In 2006, NCI funded using supplemental awards, investigators in the field of AIDS associated lymphomas, specifically to support studies aimed at understanding the pathogenesis of infectious agents in the context of lymphomas in the immunocompromised.

In addition, the AIDS Malignancy Consortium (AMC) was successfully re-competed in FY06. AIDS-associated lymphoma will continue to be an important focus of the AMC. The AMC has recently completed a Phase II trial of infusional EPOCH chemotherapy given either concurrently

with or sequentially followed by Rituximab in HIV-associated lymphoma. The early data suggest that Rituximab plus infusional chemotherapy in HIV-associated lymphoma is effective and well tolerated. The AMC plans to determine the effectiveness of Rituximab-EPOCH compared with their previous trial using Rituximab-CHOP. The NCI supported AIDS Cancer Specimen Resource continues to provide biological specimens to investigators involved in studies assessing the viral infectious etiologies of cancers, including the role of viruses such as EBV and KSHV/HHV-8 and investigators exploring the role of other novel lymphomagenic infectious agents, including examining such cancers for the presence of novel agents.

Groundbreaking Melanoma Research Suggests Distinct Genetic Pathways for Cancer Resulting from Sun Damage

Malignant melanoma continues to increase rapidly in incidence in the U.S. and worldwide. In the U.S. alone, an estimated 62,190 new cases of melanoma will be diagnosed in 2006. Currently the diagnosis is made using established clinicopathological criteria. There is a need to improve accuracy of estimating prognosis in melanoma patients at the time of primary diagnosis using other strategies that can be implemented in routine clinical practice. Thus the major goals for the melanoma research and clinical communities are improved diagnosis and prognosis to predict which patients will develop metastasis and who would benefit from alternative therapy. In addition, there is a need to identify new therapeutic targets and to develop new therapies since the current treatments are not effective.

Recent studies from the University of California San Francisco from the group led by Boris Bastian and Daniel Pinkel generated groundbreaking discoveries for understanding melanoma etiology and developing improved tumor classification. Specifically, the investigators provided experimental evidence for the existence of distinct genetic pathways in development of melanoma depending on the anatomical site of origin and levels of sun exposure. The data demonstrated significant differences in the number of copies of DNA in particular chromosomal regions and in mutation frequencies in the BRAF oncogene between melanomas from skin with evidence of chronic sun-induced damage (CSD melanoma) and without chronic sun-induced damage (non-CSD melanoma). The majority of non-CSD melanomas carried mutations in BRAF or NRAS oncogenes, whereas these mutations were less frequent in CSD melanoma. Furthermore, the investigators showed that germline variants in MC1R, the gene encoding the melanocortin-1 receptor, are strongly associated with BRAF mutations in non-CSD melanomas and confer an increase in risk of developing melanoma.

These important studies showing significant differences in genetic changes provide the basis for developing a new molecular classification system for melanoma. Importantly, newly identified molecular alterations could be targeted for treatment in various subtypes of melanoma. Certain subtypes of this disease may respond to already available cancer drugs targeting BRAF kinase. Furthermore, germline mutation status of MC1R gene could help to identify individuals in the Caucasian population with an increased risk for melanoma.

Sentinel-Node Biopsy Shown of Value for Melanoma Surgery

The NCI also sponsored a melanoma study evaluating wide excision and postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred versus wide excision and sentinel-node biopsy with immediate lymphadenectomy if nodal micrometastases were detected on biopsy. This study showed sentinel-node biopsy provides important prognostic information and identifies patients whose survival can be prolonged by immediate lymphadenectomy.

Imaging Research Holds Promise for Mesothelioma

The National Cancer Institute recognizes the significant challenge that malignant mesothelioma represents, and has strong commitment to promote mesothelioma research in an effort to find better ways to prevent and treat this disease. NCI currently funds a broad research portfolio where several novel research areas that show promise for mesothelioma are being tested.

Mesothelioma is a disease in which malignant cells are found in the sac lining of the chest, the lining of the abdominal cavity, or the lining around the heart. Most commonly linked to exposure to asbestos, the disease usually remains asymptomatic for many years until reaching late stages that limit treatment options and result in poor rates of success.

The NCI is currently sponsoring a research project intended to develop a fully automated, computerized system to assist radiologists in the quantitative assessment of pleural-based diseases using helical computed tomography (CT) scans. Currently, assessment of mesothelioma severity is based on manual measurements of the pleural thickness at different locations in the lung. This is a tedious effort, suffering from subjectivity of the observer and variability among different observers.

Automated methods, such as those under research through the NCI, will bring a level of standardization to the diagnostic process. By delineating the chest wall, lung border, and other anatomical features, measurement of the pleural thickness, and therefore mesothelioma tumor, is facilitated. Eventually, this computerized method will aid in the monitoring of the progression of the disease and provide objective assessment of response to specific modes of treatment.

Clinical Trials for Mesothelioma

The Cancer Therapy Evaluation Program (CTEP) of DCTD currently supports three active Phase II clinical trials, with another trial recently approved and two more under review. Many novel targeted therapies for mesothelioma are being tested including antiangiogenic molecules, multikinase inhibitors, EGFR inhibitors and histone deacetylase inhibitors.

CTEP has recently committed approximately $6.5 million during the next 5 years to support a P01 Program Project from the University of Pennsylvania (2P01CA066726-10A2). This program will study novel immunogenetherapies for malignant pleural mesothelioma, and will also target the

tumor antigen mesothelin, highly expressed in mesothelioma, as well as in other tumors such as pancreatic cancer.

DCTD is also funding studies on molecular pathways of cell death in mesothelioma as potential therapeutic targets.

Ten Grants Are Investigating Gene and Protein Functions in Neurofibromatosis

Neurofibromatosis (NF), which encompasses type 1 (NF1) and type 2 (NF2), are distinct genetic disorders that affect the growth and development of nerve cells as well as cells in bone and skin. NF1 (the more common type) and NF2 patients are predisposed to dying from benign and malignant nerve sheath, myeloid, and other tumors. NCI is funding ten grants that are investigating NF1 and NF2 gene and protein functions and their deregulation in NF. These include: outlining the fine-tuned regulation by the NF1 protein of a key cell communication protein termed Ras, which is lost in NF1; examining bone marrow cell formation by the NF1 gene, which should help in understanding JMML; and generating unique NF animal models, such as mice and zebrafish, to analyze how mutations in growth control genes cause cancer.

In collaboration with NINDS, NCI also funds an annual NF international meeting of basic scientists and clinical investigators that helps to establish very effective research collaborations.

Children's Oncology Group Leads Extramural NCI Pediatric Cancer Clinical Trials

The National Cancer Institute funds clinical and translational research focused on improving the diagnosis, treatment outcome and treatment-related late effects of childhood cancer through a variety of cooperative research efforts. The Children's Oncology Group (COG) develops and conducts national, multi-institutional pilot, phase 2 and phase 3 clinical trials at over 200 pediatric oncology centers. COG is currently conducting ~50 clinical treatment trials including virtually all childhood cancers. The COG Phase 1 Consortia, a separately funded clinical research effort by 20 select pediatric oncology institutions, performs the first trials of experimental anti-cancer agents in children with relapsed cancer and is able to initiate 6-7 new clinical trials per year that introduce novel agents into the pediatric setting.

14,000 Survivors Focus of Late-Effects of Childhood Cancer Treatment Study

The Childhood Cancer Survivor Study (CCSS), the largest investigation of its kind, follows the late-effects of treatment for more than 14,000 survivors diagnosed and treated between 1970 and 1986 through 26 participating pediatric cancer centers. NCI additionally funds the Pediatric Preclinical Testing Program, a unique resource that provides preclinical information about the potential utility of novel anticancer agents in the treatment of childhood cancers. The childhood cancer clinical research programs described above all include tumor and normal tissue acquisition for banking and for biological research aimed at improving our understanding of childhood cancer biology, distinguishing the risk of cancer relapse at diagnosis to enable the use of risk-stratified treatment regimens, and identifying new potential molecular targets that can be the focus of novel therapeutic development.

Clinical Trials for Childhood Osteosarcoma Include Large International Phase III Study

The National Cancer Institute funds clinical and translational research focused on improving the diagnosis, treatment outcome and treatment-related late effects of childhood cancer. The Children's Oncology Group (COG) is part of the NCI-supported cancer clinical trials cooperative group program and COG develops and conducts national, multi-institutional pilot, phase 2 and phase 3 clinical trials at over 200 pediatric oncology centers. The COG Bone Tumor Committee is currently conducting a phase 3 randomized treatment trial for children and adolescents with newly diagnosed resectable osteosarcoma that incorporates a maintenance treatment of interferon alpha for patients demonstrating a good tumor response to initial chemotherapy and an intensified treatment regimen for patients demonstrating a poor tumor response to initial chemotherapy. This large trial is being conducted in coordination with multiple European pediatric cooperative groups. This year, COG completed a pilot study of herceptin antibody (anti-HER2) and chemotherapy combined treatment for newly diagnosed metastatic osteosarcoma patients as the expression of HER2 has been associated with a poorer outcome. Additionally, the COG has been conducting a phase 2 study of inhaled granulocyte-macrophage colony stimulating factor (GM-CSF) treatment for osteosarcoma patients with pulmonary recurrence. The National Cancer Institute additionally funds the Pediatric Preclinical Testing Program, a unique resource that provides preclinical information about the potential utility of novel anticancer agents in the treatment of childhood cancers, and there is a panel of osteosarcoma mouse model tumors included in the testing of all relevant promising agents. The COG clinical trials also include tumor and normal tissue acquisition for banking and for biological research aimed at improving our understanding of osteosarcoma biology, distinguishing the risk of osteosarcoma relapse at diagnosis to enable the use of risk-stratified treatment regimens, and identifying new potential molecular targets that can be the focus of novel osteosarcoma therapy development.

Significant New and Ongoing Initiatives

Genome-Wide Association Study for Pancreatic Cancer Consortium (PanScan)

Within the framework of the NCI-sponsored Cohort Consortium, NCI's Division of Cancer Epidemiology and Genetics (DCEG) is forming a Pancreatic Cancer Cohort Consortium to conduct a genome-wide association study (GWAS) of common genetic variants to identify genetic markers of susceptibility to pancreatic cancer. Pancreatic cancer is a high priority cancer site for which the Cohort and PanScan Consortia offer a unique and powerful potential for meaningful advancement in understanding the pancreatic cancer etiology and prevention. This cancer ranks fourth for cancer mortality in the United States. Since there is no effective screening test for the malignancy, it is often diagnosed at an advanced stage, which contributes to a dismal 5-year survival rate of 4.3 percent.

A dense set of the most common single nucleotide polymorphisms (SNPs) will be selected based on an analysis of data provided by the International HapMap Project. SNPs that are highly likely to be markers for genetic variants related to pancreatic cancer risk are expected to emerge from this analysis and lead to further studies of gene-gene, gene-environment, and gene-lifestyle interactions with pancreatic cancer risk factors, including known exposures and biomarkers. After

the scans are completed, results of the genome scan and the final joint analysis of the scan and validation studies will be made available to the research community. The genotyping data from the GWAS will also be posted on a controlled-access Web site, available to the biomedical research community.

HPV Vaccine Trial

NCI is conducting the HPV Vaccine Trial, a multiyear effort currently under way in Costa Rica, which is testing the ability of virus-like particle (VLP) vaccines, originally developed at NCI, to protect against HPV-16/18 infection. The pivotal Phase III trial, which involves investigators from the Division of Cancer Epidemiology and Genetics, the Center for Cancer Research, and the Division of Cancer Prevention, is being carried out in close collaboration with Costa Rican investigators. It represents the culmination of several decades of work by NCI investigators to demonstrate that HPV is causally linked to the development of cervical cancer and to develop prophylactic vaccines.

In this blinded study, either the experimental HPV vaccine or a hepatitis A vaccine has been given to all healthy young women enrolled in the trial. By the end of December 2005, more than 7,300 women were randomized, representing approximately 35 percent of eligible 18-25 year old women in the region. All vaccinations were completed by September 2006. The women will be followed for the development of HPV infection and cervical lesions, which will be treated according to state-of-the-art standard-of-care guidelines. Women in both arms of the study will benefit from excellent cervical cancer screening throughout the trial, and at the end of the study, cross-over vaccination and vaccination against hepatitis B will be offered to all participants.

It is anticipated that the results from the trial will support licensure of the GlaxoSmithKline-manufactured prophylactic vaccine as well as provide a wealth of information on the mechanisms of action of the vaccine and on the natural history of HPV infection and cervical neoplasia post-vaccination. The vaccine is likely to have its major impact on the prevention of cervical cancer in developing nations where medically underserved women are especially at risk for this devastating disease and in underserved areas within the U.S. The current vaccine targets HPV-16 and -18, which together account for about 60-70 percent of cervical cancer worldwide. If a vaccine is 90 percent effective against these HPV types, it will have the potential of reducing the incidence of cervical cancer by more than 60 percent. An effect of this magnitude could translate to a reduction of about 150,000 deaths per year worldwide from cervical cancer.

International Lymphoma Epidemiology Consortium

NCI intramural and extramural investigators have joined forces in a consortium of ongoing case-control studies focused on non-Hodgkin lymphoma (NHL). The NHL collaboration, known as InterLymph, represents a new generation of large-scale molecular epidemiology research, with investigators pooling data from North America, Europe, and Australia to identify reasons for the increasing incidence of this malignancy around the world. Each case-control study includes a detailed review of the pathological and genetic characteristics of the NHL cases. The investigators share data in order to test for genetic and environmental causes that cannot be addressed in

individual studies with smaller sample sizes. Because the Consortium involves essentially all major on-going epidemiologic studies of NHL, it represents a model for the study of many malignancies.

The first breakthrough findings from the consortium were published in early 2006, demonstrating that the TNF-alpha and IL10 genes play a key role in diffuse large B-cell lymphoma, and a number of analyses exploring additional genetic factors and environmental exposures are continuing. Several results are expected to be published in 2007. In addition, the InterLymph Fifth Annual Meeting took place in March 2006, where investigators participating in the Consortium discussed manuscripts, preliminary findings, and future work. The meeting preceded a half-day workshop on the Environment and Non-Hodgkin Lymphoma that most investigators attended.

Testicular Cancer Consortium

The Testicular Cancer Consortium (TCC) is an active collaboration of scientists conducting epidemiologic research to elucidate the etiology of testicular cancer. Formed in 2005, its intent is to pool data, biological specimens, and other resources across existing and planned studies of testicular cancer to examine etiologic hypotheses of shared interest. The Consortium held an inaugural meeting in April 2006, in conjunction with the annual meeting of the American Association of Cancer Research. Funding awarded by the Office of Rare Diseases of the National Institutes of Health (NIH) will support a workshop on testicular cancer in March 2007, during which TCC members will reconvene to set priorities, share ideas, and discuss ongoing and future activities in testicular cancer research.

Human Papillomavirus, HIV, and Penile Cancer Precursors in the Rakai Circumcision Trial

Human Papillomavirus (HPV) infection has been associated with penile cancers in men and is considered the direct cause of cervical cancer in women. Multiple putative factors have been suggested as possible precursors to penile neoplasia, including lack of circumcision, poor genital hygiene, and chronic inflammation due to conditions such as balanitis. Suspected precursors, including HPV infection, genital hygiene, and the interrelationships of these factors with penile inflammation and penile cancer (historically found at high rates in Uganda), are being evaluated within two trials of male circumcision to prevent HIV transmission in Uganda. The goals of this study are to determine whether genital hygiene practices influence foreskin inflammation, and whether hygiene, HIV status, and circumcision status influence HPV persistence and penile neoplasia. This work should lead to improved understanding of factors influencing penile neoplasia and potential approaches to genital cancer prevention, with significant public health implications for both men and women regarding risks of oncogenic HPV infection.

Cohort and Case-Control Consortia

Among NCI's top priorities is to understand how genes that make individuals susceptible to cancer are influenced by environmental factors such as chemicals, diet, and pharmacologic agents. NCI's Division of Cancer Control and Population Sciences (DCCPS) and the Division of Cancer Epidemiology and Genetics (DCEG) are collaborating to facilitate the development of consortia of

cohort and case-control studies in order to accelerate research on gene-gene and gene-environment interactions in the etiology of cancer. The creation of such consortia is part of the revolutionary shift to big science, where studies of the future will be conducted on a much larger scale by multidisciplinary teams of scientists who pool their resources.

NCI is also fostering development of case-control consortia. Investigators may come together informally at first to discuss shared interests, for example, as has already occurred for brain tumors. In time, a formal structure may evolve, as with the International Consortium of Investigators Working on Non-Hodgkin's Lymphoma Epidemiologic Studies (InterLymph Consortium). Another advantage of consortia arrangements is the potential for advancing study of less common cancers and highly lethal cancers, for which it is difficult, if not impossible, for individual investigators to recruit sufficient study participants.

Breast/Ovarian Cancer Family Registries

The Breast/Ovarian and Colon Cancer Family Registries (CFR) studies support research to identify genetic changes that predispose to breast, ovarian, and colon cancers, and to explore gene-gene and gene-environment interactions that may contribute to the development of cancer among families with these cancers. These registries provide the tools and resources needed to clarify gene-environment interactions in cancer risk. They have identified thousands of families at high risk for breast, ovarian, and colorectal cancers who have agreed to be part of this research. Of particular interest are potential collaborations aimed at identification and characterization of cancer susceptibility genes; definition of gene-gene and gene-environment interaction in cancer etiology; and cooperative research on the translational, preventive, and behavioral aspects of such findings. The outcome will be a clearer understanding of the genes that affect the development of cancer, and how environmental factors may modify these genes.

Trans-NCI Pancreatic Cancer Program Announcements

In April 2006, NCI released two program announcements for Pilot Studies in Pancreatic Cancer (PA-06-303 for R21s and PA-06-314 for R03s). Pancreatic cancer is a highly lethal disease marked by pain, anorexia, sleep problems and weight loss. It has the worst prognosis among all of the major malignancies. Despite efforts over the past century, conventional treatment approaches such as chemotherapy, radiation surgery, or combinations of these modalities have had little impact on the course of this disease. It is clear that a better understanding of the molecular biology and biochemistry of pancreatic cancer is urgently needed to effectively diagnose, prevent, and treat this malignancy. The Trans-NCI Pancreatic Cancer program announcement will support a variety of research areas across multiple disciplines.

Pancreatic Cancer Cohort Consortium (PanScan)

Within the framework of the NCI-sponsored Cohort Consortium, we are forming a Pancreatic Cancer Cohort Consortium (PanScan) to conduct a whole genome scan (WGS) of common genetic variants to identify genetic markers of susceptibility to pancreatic cancer. This study is designed to take advantage of the strengths of a two-stage design. We will conduct a nested-case-control

study of 1,200 incident pancreatic cancer cases and 1,200 controls from the 12 PanScan cohorts to perform the initial whole genome association study by assaying for 550,000 SNPs. In a subsequent validation study, we will genotype the top candidate SNPs in an additional 800 incident cases and 800 controls with at least 50 percent from the cohorts and 50 percent from the Mayo Clinic Molecular Epidemiology of Pancreatic Cancer Case-Control Study. We anticipate that SNPs highly likely to be markers for genetic variants related to pancreatic cancer risk will emerge from this analysis and lead to further studies of gene-gene, gene-environment, and gene-lifestyle interactions with pancreatic cancer risk factors, including known exposures and biomarkers collected on these individuals. In addition, our effort will provide a foundation for subsequent research, including potential application to familial pancreatic cancer. This first step should lead to future fine mapping, resequencing, and functional characterization of plausible causal variant(s). PanScan will offer a unique and powerful potential for meaningful advancement in understanding the cancer's etiology and prevention. NCI funded about $1M toward this initiative in FY06.

Trans NIH Working Group on Tuberous Sclerosis

The Division of Cancer Biology (DCB) represents the NCI on the Trans NIH Working Group on Tuberous sclerosis complex (TSC). In FY 2006, this group established a committee to develop a plan of attack for treatment of brain (subependymal giant cell) tumors in TSC patients. DCB is working with the NCI Division of Cancer Treatment and Diagnosis (DCTD), NINDS, the Tuberous Sclerosis Alliance and the extramural community in this effort to design clinical trials that could also assess the cognitive effects of candidate cancer therapies.

DCB is participating on the trans-NIH initiative, Understanding and Treating Tuberous Sclerosis Complex, PAS-05-085, and has used this mechanism to fund a new investigator to study the relationship between regulatory inhibitors of the TSC protein such as the kinase Akt and potential cancer therapies.

In May 2006, DCB sponsored, with NIDDK and the NIH Office of Rare Diseases, a workshop entitled, "Nutrient Sensing, Insulin Signaling and Hamartoma Syndromes" that brought together over 100 researchers to discuss new ideas about the regulation and function of the TSC proteins. In addition to TSC, the rare diseases Peutz Jeghers Syndrome and Cowden's Syndrome were discussed.

Screening and Development of Anticancer Agents

NCI continues to screen new synthetic and natural compounds for antitumor activity using the automated cancer cell line screen. Over 87,000 defined chemical structures have been evaluated since the screen became operational in April 1990. More than 9,200 compounds have demonstrated in vitro antitumor activity, of which more than 5,200 agents have been selected for in vivo evaluation for assessment of therapeutic activity.

Obviously, there are more compounds to test/develop than current resources would allow. The Drug Development Group (DDG) oversees the decision-making process regarding the

development of new drugs and relies on extramural review of proposed activities. A complete description of this process is available on the Developmental Therapeutics Program Web site (dtp.nci.nih.gov).

Including vaccines and other biologicals, as well as chemotherapeutic agents, 4 agents are in DDG level 1B (early preclinical testing), 14 are in DDG level 2A (GMP production and late preclinical testing), 5 agents are in DDG level 2B (IND-directed toxicology), and 17 are in DDG level 3 (ready for human testing subject to obtaining an IND). Table 1 lists the agents in the DDG process. As the agents move through the different levels of the decision process, the level of NCI's financial commitment increases.

The NCI cooperates on the development of novel anticancer therapies with commercial as well as institutional entities ranging from fresh startups to the multinational biopharmaceutical firms. NCI currently holds 39 Cooperative Research and Development Agreements (CRADAs), 57 Clinical Trials Agreements (CTAs), 19 Clinical Supply Agreements (CSAs), and 399 Material Transfer Agreements (MTAs) with its collaborators. These are shown in Table 2.

Table 3 shows the number of investigational new anticancer agents in early clinical trials. NCI's Cancer Therapy Evaluation Program (CTEP) is sponsoring trials of many novel agents, from "first-in-man" through large, randomized comparisons of these new therapies with standard treatments. With the emerging understanding of the importance of different signaling pathways in cancer, and the availability of therapeutic agents that target those pathways, CTEP has prioritized the exploration of rational combinations of these novel investigational agents. These agents include small molecule receptor tyrosine kinase inhibitors, signal transduction inhibitors, agents that target tubulin and the mitotic spindle, agents that modulate gene transcription, DNA-interactive agents, vaccines, monoclonal antibodies, antisense agents, and gene therapy. Increasingly, NCI's industry collaborators have recognized the importance of these combination studies, which may not have be carried out without NCI sponsorship.

To expedite the movement of academic discoveries from the laboratory to proof of principle clinical trials, NCI initiated the program Rapid Access to Intervention Development (RAID) in 1998. RAID makes resources available, on a competitive basis, to the academic research community that are necessary to convert a new molecule into a drug candidate suitable for clinical testing and are generally not available to academic investigators who lack a corporate partner. These resources include 1) GMP synthesis, formulation, range finding, and IND-directed toxicology and pharmacology; 2) clinical trial planning; and 3) regulatory assistance so that FDA requirements may be satisfied by any investigator who seeks to put a new molecule into the clinic. As of December 2006, 351 applications have been received, 116 of which were approved for NCI support. A description of the successful applicants and the projects can be found at dtp.nci.nih.gov/docs/raid/raid_index.html <<HTTP://dtp.nci.nih.gov/docs/raid/raid_index.html>>. Table 4 lists current RAID projects pertaining to rare diseases.

Table 1. Compounds That Passed Drug Development Group (as of December 2005)

Drug Development Group 1B

NSC Number

735210 JPM free acid
726850 PIA5
726852 PIA23
624244 Discreet

Drug Development Group 2A

NSC Number
703939 RN321
680410 Adaphostin
711516 Chimeric antiamyloidosis MAb
724910 Discreet
721782 1-methyltryptophan
722134 Discreet
736512 Discreet
737186 Discreet
729280 Discreet
740281 Discreet
740282 Discreet
740283 Discreet
740480 Discreet
740481 Discreet
740482 Discreet

Drug Development Group 2B

NSC Number

281612 Dimethane sulfonate
729746 HA22
740377 ^{111}In-CHX-A-Herceptin™
678515 FAU and ^{18}F-FAU
678516 ^{18}F-FMAU

Drug Development Group 3

NSC Number

716976 BNP7787
724770 VEGF-Trap
711193 CDDO
731636 SGN-30
737664 ABT-888
735464 AZD0530
737754 VEGFR 034
729968 Reolysin
732084 PCLUS 6.1-18MN and E1M184V HIV peptides
729280 GX-015-070
720735 PPI-2458 Fumagillin Analog
740102 2C4-pertuzumab
320846 Batracylin
740377 Herceptin Scan
678515 & 678516 19F-FAU & 18FMAU
741078 AZD6244
736511 Sutent (Sunitinib Malate, SU11248)

Table 2: Active Research and Development Agreements (as of January 9, 2006)

Agent	Company	Type
17-AAG (NSC#330507)	Kosan Biosciences Inc	CRADA
17-DMAG (NSC#707545)	Kosan Biosciences Inc	CRADA
280-446	Novartis Pharmaceuticals Corporation	CTA
2-Methoxy Estradiol (NSC#659853)	Entremed Inc	CRADA
506U78 (NSC#686673)	GlaxoSmithKline	CTA
ABT-888 (NSC#737664)	Abbott Laboratories	CTA
Adeno-p53 (Ad5CMV-p53); Advexin (NSC#683550)	Introgen Therapeutics Inc	CTA
AE-941 (Aeterna Shark Cartilage Extract) (NSC#706456)	Aeterna Laboratoires	CTA
Alemtuzumab (Campath) (NSC#715969)	Berlex Inc	CTA
ALL-TRANS RETINOIC ACID	F Hoffmann-La Roche Ltd	CTA

ANTI-CTLA4 ANTIBODY	Medarex Inc	CTA
Arsenic trioxide (Trisenox) (NSC#706363)	Cephalon Inc	CTA
ARTEMISININ	Elsohly Laboratories, Inc.	M-CRADA
Azacitidine (NSC#102816)	Pharmion Corporation	CTA
AZD0530	AstraZeneca Pharmaceuticals LP	CRADA
AZD2171 (NSC#732208)	AstraZeneca Pharmaceuticals LP	CRADA
AZD6244	AstraZeneca Pharmaceuticals LP	CRADA
BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) (NSC#724772)	Bayer Corporation	CTA
Bevacizumab (rhuMAb VEGF) (NSC#704865)	Genentech Inc	CRADA
BMS 214662 (NSC#710086)	Bristol-Myers Squibb	CTA
BMS 275291 (MMPI) (NSC#713763)	Bristol-Myers Squibb	CTA
BMS-354825 (NSC#732517)	Bristol-Myers Squibb	CTA
BNP7787 (NSC#716976)	BioNumerik Pharmaceuticals Inc	CTA
BPU (Benzoylphenylurea) (NSC#639829)	Ishihara Sangyo Kaisha Ltd	CTA
Carboxypeptidase G2 (CAMR) (NSC#641273)	Protherics, Inc.	CTA
CC-5013 (lenalidomide, Revlimid) (NSC#703813)	Celgene Corporation	CTA
CCI-779 (rapamycin analog, temsirolimus) (NSC#683864)	Wyeth Pharmaceuticals	CRADA
CDDO (NSC#711193)	Reata Pharmaceuticals Inc	CRADA
Clodronate (Bonefos) (NSC#713466)	Schering OY	M-CRADA
Cytochlor (NSC#371331); THU	Halogenetics Inc	CTA
Decitabine (5-aza-2'-deoxycytidine) (NSC#127716)	MGI Pharma Inc	CRADA
E7389 (Halichondrin B Analog) (NSC#707389)	Eisai Inc	CRADA

EMD 121974 (Cilengitide) (NSC#707544)	Merck KgaA	CRADA
Epothilone-B BMS 247550 (NSC#710428)	Bristol-Myers Squibb	CTA
Exemestane (Aromasin) (NSC#713563)	Pfizer Inc	M-CRADA
FK228 (Depsipeptide) (NSC#630176)	Gloucester Pharmaceuticals Inc	CRADA
Flavopiridol (alvocidib) (NSC#649890)	Sanofi Aventis	CRADA
Fumagillin analog (PPI-2458) (NSC#720735)	Praecis Pharmaceuticals	CTA
G3139 (oblimersen; Genasense) (NSC#683428)	Genta Inc	CRADA
GM-CSF	Berlex Inc	CTA
gp100 cDNA/gold (Plasmid Vector pWRG1644) (NSC#708477)	Powderject	CTA
GTI-2040 (NSC#722929)	Lorus Therapeutics Inc	CTA
GW572016 (lapatinib) (NSC#727989)	GlaxoSmithKline	CTA
GW786034 (NSC#737754)	GlaxoSmithKline	CTA
GX015-070 (NSC#729280)	Geminx Biotechnologies	CTA
HALOFUGINONE I.V.	Collgard Biopharmaceuticals Ltd	CRADA
Hu 14.18/IL-2 Fusion Protein (EMD 273063) (NSC#721298)	EMD Pharmaceuticals	M-CRADA
In2B8/Y2B8 Radiolabeling Kit (Ibritumomab tiuxetan, Zevalin) (NSC#710085)	Biogen Idec	CTA
IPI-609	Infinity Pharmaceuticals	CRADA-LOI
Irinotecan (CPT-11, Camptosar) (NSC#616348)	Pfizer Inc	CTA
Irofulven (MGI-114) (NSC#683863)	MGI Pharma Inc	CTA
KRN5500 (NSC#650426)	Kirin Brewery	CTA
Lymphoma IG vaccine-KLH (NSC#659770)	BioVest International Inc	CRADA
Medi 522 (Vitaxin) (NSC#719850)	MedImmune Inc	CRADA
MLN 518 (NSC#726292)	Millennium Pharmaceuticals Inc	CRADA

Motexafin gadolinium (Xcytrin) (NSC#695238)	Pharmacyclics Inc	CRADA
Motexafin lutetium (NSC#695239)	Pharmacyclics Inc	CRADA
MS-275 (NSC#706995)	Schering AG	CRADA
O-6-Benzylguanine (NSC#637037)	AOI Pharmaceuticals	CRADA
OSI-774 (erlotinib; Tarceva) (NSC#718781)	OSI Pharmaceutical Inc	CTA
OXALIplatin (Eloxatin) (NSC#266046)	Sanofi Aventis	CRADA
Perifosine (NSC#639966)	AOI Pharmaceuticals	CRADA
PROSTVAC-F/TRICOM [Recombinant Fowlpox-PSA(L155)/TRICOM] (NSC#717171); PROSTVAC-V/TRICOM [Recombinant Vaccinia-PSA(L155)/TRICOM] (NSC#717170)	Therion Biologics Corporation	CTA
Proteinase 3:PR1 Peptide (NSC#698102)	Vaccine Company	CTA
PS-341 (bortezomib; Velcade) (NSC#681239)	Millennium Pharmaceuticals Inc	CRADA
PSC-833 (NSC#648265)	Novartis Pharmaceuticals Corporation	CTA
PXD 101 (NSC#726630)	TopoTarget	CRADA
PXD 101 (NSC#726630)	Curagen	CTA
R115777 (tipifarnib, Zarnestra) (NSC#702818)	Johnson & Johnson	CTA
Reolysin (NSC#729968)	Oncolytics Biotech Inc	CTA
rF-B7.1 (Recombinant Fowlpox-B7.1) (NSC#679008)	Therion Biologics Corporation	CRADA
RF-TRICOM; rF-TRICOM (Recombinant Fowlpox-TRICOM) (NSC#710658)	Therion Biologics Corporation	CRADA
Rituximab (MoAb C2B8 anti CD20, chimeric) (NSC#687451)	Biogen Idec	CRADA
SB-715992 (NSC#727990)	GlaxoSmithKline	CTA
SC-55494	Searle	CTA
SGN-30 (NSC#731636)	Seattle Genetics	CTA
SJG-136 (NSC#694501)	Ipsen	CRADA
SMART 1D10 (HU1D10)	Protein Design Labs	CTA

STI571 (imatinib, Gleevec) (NSC#716051)	Novartis Pharmaceuticals Corporation	CRADA
Sunitinib malate (SU011248 L-malate; Sutent) (NSC#736511)	Pfizer Inc	CTA
Thalidomide (Thalomid) (NSC#66847)	Celgene Corporation	CTA
Tirapazamine (NSC#130181)	Sanofi Aventis	CTA
Topotecan (NSC#609699)	GlaxoSmithKline	CTA
Trastuzumab (Herceptin) (NSC#688097)	Genentech Inc	CRADA
Triapine (NSC#663249)	Vion Pharmaceuticals Inc	CTA
Tumor Necrosis Factor (TNF-alpha) (Boehringer Ingelheim/R&D Systems) (NSC#697068)	Boehringer Ingelheim Pharmaceuticals Inc	CTA
UCN-01 (NSC#638850)	Kyowa Pharmaceuticals Inc	CTA
VEGF-Trap (NSC#724770)	Sanofi Aventis	CTA
Vorinostat (suberoylanilide hydroxamic acid; SAHA) (NSC#701852)	Merck and Company Inc	CTA
XK469	Bristol-Myers Squibb	CTA
XL119 (becatecarin, rebeccamycin analog) (NSC#655649)	Exelixis Inc	CTA
ZD1839 (gefitinib, Iressa) (NSC#715055)	AstraZeneca Pharmaceuticals LP	CTA

Table 3: Investigational New Anticancer Agents in Early Clinical Trials (as of January 2006)

Phase I	Phase II
Biologic Agents	
Adenovirus p53 (Advexin)	Adenovirus p53 (Advexin)
Anti-idiotype-KLH Myeloma Vaccine	Anti-idiotype-KLH Myeloma Vaccine
Antisense GTI-2040	Antisense GTI-2040
Apolizumab + Rituxan	Avastin® (bevacizumab, MoAb: anti-VEGF)
Avastin™ (bevacizumab, MoAb: anti-VEGF)	Avastin® PAP-pulsed Dendritic Cells
G3139	Avastin® + Erbitux™
Gp100-reactive autologous cells + rFgp100P209	FGF-5 peptides
Herceptin® (trastuzumab; MoAb: humanized Her2)	G3139
IL-12	gp100 Peptides A,C,F Vaccine

IL-12 + IL-2	Gp100-reactive autologous cells + rFgp100P209
LBM 2 Immunotoxin	Gp100 retroviral vector-transduced CD8 cells + IL-2
MART-1 retroviral vector-transduced cells + IL-2 + MART-1 peptide	Herceptin® (trastuzumab; MoAb: humanized Her2)
MDX-010 (Human Anti-CTLA4 MoAb)	IL-12 + IL-2
MEDI-522	LMB-2 Immunotoxin
MoAb: CAMPATH-1H (Anti-CD52)	MDX-010 (Human Anti-CTLA4 mAb)
MoAb: HeFi-1 (Anti-CD30)	MoAb: CAMPATH-1H (Anti-CD52)
MS275	Mutated VHL Peptides Vaccine
PANVAC-VF®	PANVAC-VF®
PR-1 Peptide Vaccine	PR-1 Peptide Vaccine
PSA Tricom Vaccine	PSA Tricom Vaccine
ras/p53 Vaccine	ras/p53 Vaccine
Recombinant Fowlpox GM-CSF Vaccine	Recombinant Fowlpox- CEA(6D)/TRICOM + Vaccinia- CEA(6D)/TRICOM Vaccine
Recombinant Fowlpox- CEA(6D)/TRICOM + Vaccinia- CEA(6D)/TRICOM Vaccine	Recombinant Fowlpox-gp100:ES209-217(210M) Vaccine
Recombinant Fowlpox-TRICOM and Vaccinia-TRICOM Vaccine	Recombinant Fowlpox-PSA Vaccine
Rituxan® (rituximab, MoAb: IDEC-C2B8)/Chemotherapy	Recombinant Fowlpox-TRICOM and Vaccinia-TRICOM Vaccine
SAHA	Rituxan® (rituximab, MoAb: IDEC-C2B8)/Chemotherapy
SB-IL2 + autologous T cells	SAHA
	SB-IL2 + autologous T cells
Sodium Phenylbutyrate (IV)	SGN-00101 (HspE7) Vaccine
SS1(dsFv) PE38	Thalidomide
Zevalin®(MoAb: Y2B8)	Zevalin®(MoAb: Y2B8)

Chemotherapeutic Agents

Phase I	Phase II
17-AAG	17-AAG
17-DMAG	Arsenic Trioxide
2-ME	AZD2171
Arsenic Trioxide	BAY 43-9006
BAY 43-9006	BMS 247550 (Epothilone B Analog)
BMS 247550 (Epothilone B Analog))	Bryostatin 1
BPU	CAI
Bryostatin 1	CCI-779 (Rapamycin Analog)
CAI	COL-3

Camptosar® (Irinotecan, CPT-11)	Compound 506U78
CCI-779 (Rapamycin Analog)	Decitabine
Cytochlor + Tetrahydrouridine	Depsipeptide
Decitabine	EF5
Depsipeptide	EMD 121974
E7389 (Halichondrin B Analog)	Fenretinide
EMD 121974	Flavopiridol
Flavopiridol	Gleevec® (Imatinib Mesylate, STI571)
Gleevec® (Imatinib Mesylate, STI571)	GW572016
GW572016	Halofuginone (Topical)
Iressa (ZD1839)	Iressa (ZD1839)
O^6-BG	Irofulven (MGI-114)
OSI-774	O^6-BG
Oxaliplatin	OSI-774
Pyrazoloacridine	Oxaliplatin
R115777	Perifosine
Rebeccamycin Analog	R115777
SB-715992	Rebeccamycin Analog
SJG-136	SB-715992
Suramin	Suramin
Tirapazamine	Tirapazamine
Triapine®	Topotecan (Hycamtin®)
UCN-01	Triapine
Velcade™ (Bortezomib, PS341)	UCN-01
XK469	Velcade® (Bortezomib, PS341

Table 4. Current RAID Projects for the Treatment of Rare Diseases (As of 12/05)

Compound NSC	Name	Disease	Investigator	Pediatric Use
715816	Tropism-Modified Adenoviral Vector	Ovary	Glenn Peters; U. of Alabama Comprehensive Cancer Center	
717205	Eukaryotic EF-2 Kinase	Glioblastoma	William Hait; Cancer Institute of New Jersey	
718877	Psuedomonas Exotoxin Construct	Glioblastoma Multiforme, Neoplastic Meningitis	Darrell Bigner; Duke University Comprehensive Cancer Center	Yes

719277	Nonpathogenic Oncolytic Poliovirus Chimeras	Glioma	Matthias Gromeier; Duke University Medical Center	Yes
720836	IL-6 plus Interferon	Multiple Myeloma	Richard Jones; Johns Hopkins University	
721769	Wolinella-derived L-asparaginase	ALL	Donald Durden; Emory University	
723256	d-24-RGD oncolytic virus	Chronic lymphocytic leukemia	Alfred Yung; University of Texas, M.D. Anderson Cancer Center	
729138	Secondary Lymphoid Tissue Chemokine (SLC)	Melanoma	James Mulé; Moffitt Cancer Research Institute	
731413	Ad5/3-delta24	Ovary	Akseli Hemminki; Helsinki University Hospital	
731442	KSR antisense oligonucleotide	Pancreatic	Richard Kolesnick; MSK Cancer Center	
736285	hsp110-gp100/hsp110-TRP-2 Vaccine	Melanoma	John Kane; Roswell Park Cancer Center	
740833	Adenovirus GM-CSF-CA-IX	Renal Cell	Arie Belldegrun; UCLA	
741763	STAT3 Decoy	SCCHN	Jennifer Grandis; U. Pittsburgh	
741764	AQX-016A	Myeloma	Gerald Krystal; BC Cancer Research Centre	
736285	hsp110-gp100/hsp110-TRP-2 Vaccine	Melanoma	John Kane; Roswell Park Cancer Center	
740833	Adenovirus GM-CSF-CA-IX	Renal Cell	Arie Belldegrun; UCLA	
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741763	STAT3 Decoy	SCCHN	Jennifer Grandis; U. Pittsburgh
741764	AQX-016A	Myeloma	Gerald Krystal; BC Cancer Research Centre

Rare Disease-Specific Conferences, Symposia, or Workshops with Outcomes

The ALARA (As-Low-as-Reasonably-Achievable) Concept in Pediatric Interventional and Fluoroscopic Imaging Workshop
February 11-12, 2006 – Ms. Ruth Kleinerman

The Society for Pediatric Radiology identified a critical issue for practitioners in the field—minimizing the dose to pediatric patients undergoing interventional radiologic procedures. The goal of the workshop was to promote greater awareness and discussion of improving pediatric medical care through radiation imaging while limiting radiation doses to children. Experts in the field of radiation epidemiology, pediatric radiology, and clinical imaging from hospitals, universities, government, and industry participated in a scientific exchange on radiation dose reduction to children. Speakers addressed the role of NCI/NIH in radiation exposure research, equipment strategies to reduce pediatric radiation doses, and radiation management in interventional cardiology, radiology, and general fluoroscopy. Interventional imaging equipment acquisition was also discussed.

Proceedings of the workshop were published in a special issue of Pediatric Radiology, available in print (*Pediatr Radiol* 2006; 36, Supplement 14:107-239.) or online at: http://www.springerlink.com/content/l32l3g6817u8/.

Kidney Cancer-Current Perspectives, Future Directions
April 5-6, 2006 – Dr. Lee Moore

This workshop was held to discuss preliminary results from two NCI-supported studies, the Central and Eastern European Kidney Cancer (RCC) Study, and the U.S. Kidney Cancer Study, and to stimulate ideas for future collaborative research among epidemiologists, clinical, and laboratory scientists. Conference attendees included DCEG investigators and collaborators from these two studies in addition to other kidney cancer researchers from Australia, the Netherlands, and the University of California Cancer Center in San Francisco.

The meeting began with presentations highlighting questionnaire, genetic susceptibility, and tumor marker research from the Central and Eastern European RCC Study. Participants spent the remainder of the meeting discussing future research ideas for genotyping, pooling biological samples across studies, and piloting studies to identify the determinants of survival. Specific plans for future work include finalizing pilot work necessary to conduct a survival study in Eastern

Europe; planning future tumor marker studies with identified PIs and collaborators; and planning future genotyping studies. The group plans to meet again in October 2006.

Relationship Between Pediatric CT Exposure and Cancer Risk
June 1-2, 2006 – Dr. Elaine Ron

The use of computed tomography (CT) scans has increased rapidly over the past two decades. Radiation doses from these scans are substantially greater than from conventional X-rays and are in the range for which increased cancer risks have been shown. Pediatric CT scans are of particular concern because in comparison with adults, children are exposed to higher doses, they are generally more sensitive to the carcinogenic effects of radiation, and they have a longer life-span to express radiation-related cancer. Because empirical data are lacking, we propose conducting a retrospective cohort study to determine whether the risk of developing cancer is increased in children undergoing CT scans, paired with a nested case-control study of leukemia in which bone marrow doses will be estimated to evaluate dose response. Our findings will help public health authorities address the important issue of proper use of CT scans in children. Goals of the meeting were to discuss the potential for a large, international collaborative study between several independent CT scan studies; discuss study methods; set up eligibility criteria for participation; evaluate the feasibility of biological repository collection; discuss potential funding sources; and discuss issues of data protection and study ethics. A timeline was constructed for the assembly of necessary study data and components for the development of a unified collaborative study protocol.

Hereditary leiomyomatosis and renal cell cancer (HLRCC)
July 26, 2006 – Dr. Jorge Toro

Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) is a recently- identified, rare condition characterized by skin leiomyomas, uterine leiomyomas, and renal cell cancer in individuals with aberrations in the *HLRCC* gene on chromosome 1q. Much remains to be discovered about the cause of HLRCC and its natural history, and to date, no consistent diagnostic criteria have been established. At this meeting, researchers from NCI and their collaborators described advances in existing research, and developed a provisional set of diagnostic guidelines based on clinical experience and research data from the family studies currently being conducted in several countries. Further, recommendations for screening and surveillance activities for families at risk were discussed, as well as opportunities for conducting pooled analyses.

Participants considered ways to move research on this rare disease forward through a consortial approach. Thus, investigators explored the development of a collaborative effort, identified specific scientific questions that could be answered by pooled data, and defined a common approach to analyze epidemiologic and mutation data.

Participants included researchers from Columbia University, Finland, and the United Kingdom, who represent the largest studies of HLRCC available, and other attendees from across NIH and Transgenomics, Inc. These attendees joined researchers from the NCI HLRCC Group, which is comprised of investigators from the Genetic Epidemiology Branch, Diagnostic Pathology, the

Laboratory of Pathology, Urologic Oncology Branch, and the Intramural Research Support Program at SAIC-Frederick, Inc. In a discussion of future research directions, investigators agreed to collaborate and pool their data to conduct joint analyses on phenotype-genotype relationships, the risk of uterine leiomyosarcomas, and possible modifiers of renal cell carcinoma risk. A summary of the proceedings is being developed for publication.

Agricultural Cohort Consortium Meeting
September 25-26, 2006 – Dr. Aaron Blair

This meeting brought together investigators leading major agricultural cohort studies to discuss available data from each study and to explore opportunities for developing a consortium as an efficient means to pool data, conduct collaborative research projects, evaluate rare diseases, and replicate findings from individual studies. Thirty-nine individuals attended the meeting from Canada, Korea, New Zealand, France, Norway, and from several states in the United States (California, Wisconsin, Iowa, North Carolina, Ohio, and Maryland). Information available from thirteen agricultural cohorts was presented and discussed. Additional presentations focused on various diseases and outcomes associated with agriculture exposures and the rural lifestyle, including allergic disorders, injuries, autoimmune conditions, cardiovascular disease, cancer, respiratory disease, infectious disease, neurological outcomes, and reproductive outcomes. Discussions following these presentations focused on research needs and opportunities that a cohort consortium might provide to fill research gaps associated with these outcomes. Specific attention focused on rare diseases where the number of events might be insufficient for analysis in individual cohorts. The pooling of data from several cohorts would be useful for studies of several cancers (e.g., ovary, testicular, and thyroid), idiopathic pulmonary fibrosis, Parkinson's disease, stillbirths, injuries to farm children, and lupus. Pooled cohorts would also provide opportunities to evaluate interactions between exposures and genes/exposures for rare and moderately common diseases. Participants of this workshop expressed interest in a follow-up meeting in one year to further discuss the logistics of maintaining a consortium infrastructure, the inclusion of additional cohorts, and to plan specific collaborative and/or pooling projects.

A paper describing the meeting is planned for publication in the literature to inform the scientific community of this effort and to identify additional agricultural cohorts that may be suitable for inclusion. A poster describing the Consortium will be prepared for an appropriate scientific meeting during the next year.

Mechanisms and Consequences of c-MYC-Deregulating Chromosomal Translocations
October 22-24, 2006—Dr. Charles Rabkin

A workshop was held on chromosomal translocations and the need for cross-disciplinary exchange regarding the mechanisms, genetics, molecular evolution, and biological consequences of chromosomal translocations relevant to human cancer. Thirty-seven international experts participated in this two-day conference, which was held at the Arlie Conference Center in Warrenton, Virginia. The first half of the workshop was devoted to recent findings on the molecular mechanisms of chromosomal translocations with a particular focus on MYC-IGH, the best elucidated model system. The second half covered pathologic consequences and associations

with risks of hematopoietic and other malignancies. To share the proceedings with others interested in this important disease process, the invited papers will be published as a monograph by the Journal of the National Cancer Institute.

Rare Disease-Specific Conferences, Symposia, or workshops with outcomes

In FY06, NCI's Division of Cancer Control and Population Sciences (DCCPS) received funds from the Office of Rare Diseases for an Interagency Workshop on the Science and Practice of Informal Caregiving. Several NIH Institutes are working together and with the Veterans Administration (VA) to identify gaps in the science and practice of informal caregiving. This workshop held in early 2006 was an opportunity for NIH and the VA to engage in a dialogue in which science and practice are joined. The goal for the Workshop was to identify areas of research that will advance both the science and the practice of informal caregiving. The results will be used to inform the revision of a Program Announcement on informal caregiving for chronic conditions. Multiple NIH Institutes are expected to support this Program Announcement.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

Overview

The mission of the National Institute of Child Health and Human Development (NICHD) is to ensure that children are born wanted, timely, and healthy, and that they develop their full physical, emotional, and cognitive potential. The Institute achieves its mission in part by conducting and supporting a broad range of innovative research, outreach, and education activities, including those that address rare diseases and conditions in human reproduction and in infants and children. Below are examples of these activities.

Recent Scientific Advances

Clinical Trial of Two Interventions for Severe Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a potentially fatal inflammatory disorder of the intestine that occurs in premature infants and that affects one in 2,000 to 4,000 births each year. The NEC process leads to infection which can result in necrosis (death) of intestinal tissue and intestinal perforation. At that severe stage, mortality is 30 to 50 percent. Surgical resection of the affected tissue has become the standard approach to treating tiny NEC patients with necrotic or perforated intestines. In recent decades, however, a less invasive, alternative approach has come into widespread use, especially in very premature infants. In this approach, a surgeon makes a tiny incision to place a small drainage tube into an infant's peritoneal cavity to drain the infection. Originally developed as a temporary measure to enable the most fragile infants to improve before surgery, this approach came into wider use after clinicians observed that a substantial number of infants treated this way survived without needing further surgery. This alternative remained controversial, however, and relatively small trials have not resolved questions of how to determine which infants should have this procedure.

In general, randomized, controlled trials of surgical procedures are not common, and especially not in children, because most pediatric disorders are relatively rare. To compare the outcomes of the two NEC interventions, the NICHD supported a randomized, controlled clinical trial at 15 tertiary care centers in the U.S. and Canada. Outcomes measured were survival, length of hospitalization, and reliance on total parenteral nutrition. Investigators found no significant differences in outcomes between infants assigned to the two treatment groups. The trial results, however, provide important evidence to help guide treatment decisions of clinicians treating these infants. The study is also considered to have set a new standard for future studies of other controversial questions in pediatric surgery.

Gene discovered for rare form of osteogenesis imperfecta

Researchers from the NICHD have discovered that a previously unexplained fatal form of Osteogenesis Imperfecta (OI), a disorder that weakens bones and that may cause frequent fractures, results from a genetic defect in a protein involved in the production of collagen. Their discovery could ultimately enable couples who have lost a child to this form of OI to be advised of

the risk that they may conceive another child with the disorder. Siblings could also be counseled about their likelihood of carrying the gene. There are several known forms of OI, which vary in severity. In the most severe forms, infants may die at or shortly after birth. In other forms, individuals may lead a relatively normal life, but have bones that fracture easily. In still other cases, affected individuals may have only a slightly increased risk for bone fracture.

The affected gene contains the information for CRTAP (cartilage associated protein). Although the function of CRTAP is not well understood, it is known to be part of a complex of proteins involved in the chemical transformation of collagen from simple protein "chains" into its final form. The well-known forms of OI result from a defect in the genes for type I collagen, which serves as a kind of molecular scaffolding that holds together bone, tendons, skin, and other tissues. The collagen defects result from dominant mutations, requiring only one copy of a mutant gene to cause the bone disease. The NICHD researchers discovered that mutations in the CRTAP gene accounted for a recessive form of the disorder, requiring two copies of the affected gene to show a particular trait. This finding may enable OI experts to offer families who have lost a child to OI a test for the presence of the recessive CRTAP gene that is associated with this fatal form of the disorder.

Significant Ongoing Rare Diseases Initiatives

Pediatric drug trials

As directed by the 2002 Best Pharmaceuticals for Children Act (BPCA), the NICHD developed and continues to coordinate an annual cycle for identifying and prioritizing drugs in need of pediatric studies. Such studies would provide data, now lacking, on the safety and efficacy of the drugs in children, and appropriate pediatric doses. In the prioritizing process, the NICHD works closely with other Institutes, the FDA, and outside experts to select drugs on the basis of: 1) frequency of use in the pediatric population; 2) severity of the condition to be treated by a drug; and 3) the potential for providing a health benefit to the pediatric population. These criteria allow drugs for rare as well as common conditions, and drugs that would not otherwise be within the NICHD's research mission, to be selected as priority drugs for research. Coordination includes data gathering, expert consultation and critical analysis with NICHD experts in pediatrics as well as consultation with pediatric experts at other ICs and at the FDA to identify drugs to be studied. Within the NIH, the prioritization process begins with the identification of off-patent drug candidates for studies, determination of relevant indications for those drugs in pediatric populations, review of data available at FDA concerning best use of those drugs in children, investigation of the use/utility of those drugs in treating children, and identification of gaps in knowledge that, if addressed, would improve pediatric public health. In FY 2006, NICHD continued to cofund, with the National Cancer Institute, trials of two priority drugs for Wilms tumor and for rhabdomyosarcoma, rare forms of pediatric cancer. Data from the trials of the drugs, Dactinomycin (also known as Actinomycin-D) and Vincristine may contribute to an increased understanding of how to use these drugs in children of different ages. The NICHD also continued cofunding, with the National Heart, Lung, and Blood Institute, Preclinical, Phase I, Phase II and Phase III clinical studies of Hydroxyurea to improve treatment of children with sickle cell disease.

New/Planned Extramural or Intramural Research Initiatives

Newborn screening initiative

The NICHD leads a major, multi-Institute initiative to greatly expand the number of rare genetic conditions that can be identified at birth and to develop treatments for such conditions. Expanding knowledge of the genetic and molecular bases of various disorders and advances in testing technologies have paved the way for expansion of current state newborn screening programs, but also heightened the need for new treatments for potentially screenable conditions. In the past year, NICHD has issued two sets of initiatives relevant to newborn screening. The purpose of the first, "Innovative Therapies and Clinical Studies for Screenable Disorders," is to improve the understanding and/or development of therapeutic interventions for currently screened conditions and "high priority" genetic conditions for which investigators could potentially develop screening tests in the near future. The second, "Novel Technologies in Newborn Screening" seeks to develop a multiplexed screening technology prototype for newborn screening, particularly for disorders with current or promising therapeutic interventions, like Duchenne Muscular Dystrophy. To date, the NIH has received 30 applications in response to these initiatives, and currently has plans to fund four research projects. Also participating in these funding initiatives are the National Institute on Deafness and Other Communication Disorders and the National Institute of Diabetes and Digestive and Kidney Diseases.

As a next step in this initiative, the NICHD recently decided to support a new research infrastructure in which important questions that face state newborn screening programs can be investigated. When implemented, this Newborn Screening Translational Research Network (NBSTRN) will link states' newborn screening programs and enable the NICHD and other Institutes and Agencies to pursue research questions that are immediately relevant to these programs. NBSTRN will be able to support a variety of studies with clear and easily defined outcome measures, and draw on the experience and insight of practicing clinicians and geneticists to help identify and frame research questions. Moreover, because NBSTRN can use the existing personnel and infrastructure of established newborn screening laboratories and clinics, certain types of studies can be conducted in a cost-effective manner. The NBSTRN would build on the two funding opportunities released in 2006 to create a system which could potentially translate the outcomes from these initiatives into clinical practice. The network could potentially offer sufficient statistical power for the validation of technologies and therapeutic interventions for multiple rare conditions.

Rare disease-specific conferences, symposia, or workshops

New Therapies for Necrotizing Enterocolitis

The NICHD hosted a conference to discuss new anti-inflammatory therapies and new approaches for preventing necrotizing enterocolitis (NEC) in newborn infants at high risk for the disease. Conference participants discussed promising data on new therapies generated by animal models and focused on current theories of the origins and development of NEC in order to develop targets for novel anti-inflammatory therapy. Also discussed were logistical models that would permit the

identification of infants at highest risk of NEC in order to design interventions that could be used to prevent or mitigate the onset of the disorder in these newborns. Recent experiments in animal models of NEC have indicated that epidermal growth factor decreases the severity of NEC and improves survival rates. Other animal studies have shown that polyclonal antibodies to the receptor for platelet activating factor also act to diminish the severity of the inflammatory condition. Given the availability of new monoclonal and polyclonal antibodies to tumor necrosis factor alpha (TNF-alpha) and to other inflammatory cytokines that may play a role in the pathogenesis of NEC, experts consider that the time has come to design clinical trials to test the efficacy of these new agents in infants with NEC.

Cushing's syndrome

The NICHD participated in two conferences that are related to the rare disorder Cushing's syndrome, which is caused by overexposure of the body's tissues to the hormone cortisol. One conference, a symposium entitled "Cortisol Secretion Abnormalities," was organized by the NICHD's Developmental Endocrinology Branch. Cortisol secretion abnormalities and related disorders of the hypothalamic-pituitary-adrenal axis are rare disorders that had not been addressed in any NIH-held meeting over the last decade. Symposium participants reviewed the current status of the investigation of these diseases. The NICHD also participated in the International Conference on the Adrenal Cortex and Molecular Steroidogenesis, which was a combination of the Adrenal Cortex Conference and the Congress on Molecular Steroidogenesis. This conference provided a forum for both new and established investigators to highlight recent discoveries and present state-of-the-art research relevant to adrenal and gonadal physiology, biochemistry, and molecular steroidogenesis. It also provided a framework for understanding the functions of the steroidogenic glands and their importance in health and disease. One topic that was on the conference agenda was adrenocortical tumors, which are associated with disorders such as Cushing's syndrome.

Activities with Rare Diseases Patient Advocacy Groups to Stimulate Research

Newborn screening research network

In planning and developing its newborn screening translational research network, described above, the NICHD will work closely with nongovernmental groups such as the Muscular Dystrophy Association, as well as other NIH institutes and government agencies. The research network will facilitate and encourage collaborative research on screenable conditions, such as rare neuromuscular diseases, that will be able to produce findings that are immediately relevant to newborn screening programs and clinical practice.

Trans-NIH Neurofibromatosis Working Group

The NICHD participates on the trans-NIH Neurofibromatosis Working Group, chaired by the National Institute of Neurological Disorders and Stroke, and attends the group's annual meetings. In addition to staff from other NIH institutes, representatives of the neurofibromatosis research community and patient advocacy groups also attend the annual meeting.

Education Activities

The NICHD completely revised its Web site in 2006, to make information on rare diseases within the Institute's scientific mission more easily accessible to families of individuals with these disorders, clinicians, investigators, the media, and the general public. For example, the Web site offers "plain language" information on Asperger Syndrome, Congenital Adrenal Hyperplasia, Fragile X, Osteogenesis Imperfecta, and Rett Syndrome, among many others. Also in 2006, the NICHD updated its fact sheet on Rett Syndrome and translated it into Spanish. These fact sheets are both available to the public through the NICHD information resource center and the NICHD Web site.

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS (NIDCD)

Overview

NIDCD conducts and supports research and research training on normal mechanisms and diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. This mission is achieved through a wide range of research performed in its own laboratories, a program of research grants, individual and institutional research training awards, career development awards, center grants, cooperative clinical trials, and contracts to public and private research institutions and organizations. The Institute also conducts and supports research and research training that is related to disease prevention and health promotion. NIDCD addresses special biomedical and behavioral problems associated with individuals who have communication impairments or disorders. NIDCD also supports efforts to create devices that substitute for lost and impaired sensory and communication functions.

Recent Scientific Advances in Rare Diseases Research

Acoustic neuroma

Neurofibromatosis type 2 (NF2) is an autosomal dominant genetic disorder that occurs in about one out of every 40,000 Americans. This mutation on chromosome 22 is strongly associated with the development of bilateral nerve tumors, called acoustic neuromas or vestibular schwannomas. These grow specifically in the auditory-vestibular nerve that runs from the ear to the brain, and can cause hearing and balance disorders as well as life-threatening compression of the brainstem. NIDCD supports a research project on how regulation of gene transcription is involved in vestibular schwannoma tumorigenesis and how specific biochemical signaling pathways for growth are deregulated in vestibular schwannomas. Treatment of these bilateral acoustic neuromas often requires removal of these important sensory nerves on both sides, which renders the individual deaf and suffering a significant loss of balance. Electrical stimulation of the residual neural pathways within the cochlear nucleus can provide a sense of hearing after this surgery. NIDCD-supported scientists are working to optimize the design of a neural implant used for electrical stimulation of the cochlear nucleus in these individuals, with the goal of providing a device equal in performance to the cochlear implant used in individuals that have an intact nerve but profound peripheral hearing loss.

Auditory neuropathy

A small but substantial number of individuals with bilateral hearing loss have normal cochlear function. These individuals have severely abnormal central neural processing of auditory sensory input as evidenced by poor or absent auditory brainstem responses. Standard treatment strategies for bilateral hearing loss, such as hearing aids, are of little use to these individuals. When this disorder strikes young children or infants, it can cause severe disruption of normal language and speech development. The most likely cause of hearing loss is a disorder of the auditory nerve or central auditory pathway, hence the term “auditory neuropathy.” This disorder is rare but more

common than previously estimated. Investigation of the physiologic mechanisms, the genetic basis, and possible treatments for this disorder is ongoing.

Enlarged vestibular aqueduct (EVA) and Pendred syndrome (PS)

EVA is characterized by progressive childhood sensorineural hearing loss in association with enlarged vestibular aqueducts. NIDCD intramural scientists have determined that these cases can be clinically and genetically classified into one of the three groups. Approximately one third of individuals have PS, which causes hearing loss in combination with, in some cases, enlargement (goiter) of the thyroid gland (due to a defect in the ability of the thyroid gland to organify iodine in the synthesis of thyroid hormone), and two mutations of the PS gene (*PDS*). Another one-third of individuals have a single *PDS* mutation, but do not have a thyroid organification abnormality and do not have PS (their EVA is nonsyndromic). NIDCD intramural scientists are working to identify the genetic basis of EVA, including several cases where it is clearly not caused by mutations in *PDS*. Family studies indicate that there must be one or more other etiologic cofactors that cause EVA, which is inherited as a complex trait, in these individuals. Congenital cytomegalovirus (CMV) infection was shown not to be an etiologic cofactor in these cases. The other one third of EVA individuals have no *PDS* mutations, normal thyroid glands (i.e., nonsyndromic), and these cases are sporadic. Current and future studies are oriented toward identifying the causes of EVA in these latter two groups of individuals, as well as generating a mouse model for this condition.

Fanconi anemia (FA) and Squamous cell carcinoma (SCC)

Fanconi anemia (FA) is a genetically heterogeneous bone marrow failure syndrome associated limb malformations and hearing loss. NIDCD intramural scientists have prospectively studied a large group of individuals with FA to characterize the clinical presentation and manifestations of hearing loss in this disorder. This study has identified a distinctive middle ear malformation which is visible upon direct visual examination. The hearing loss of these individuals is being analyzed for diagnostically or prognostically useful features and for correlation with underlying genotype and other phenotypic features. Fanconi anemia also predisposes affected individuals to squamous cell carcinomas (SCC) of the head and neck, cervix and vulva. NIDCD and NCI intramural scientists have collaborated in studies to ascertain genotypes associated with development of head and neck SCC; and determine whether FA pathway related gene expression is altered in sporadic head and neck SCC.

Hereditary cerebellar ataxia syndrome of early onset

Several abnormal genes that are associated with inherited cerebellar syndromes and cause disorders of balance and coordination have been identified. Relatively little is known about how different mutations lead to specific types of the disorder. There are typically great differences in the clinical signs and symptoms within families that segregate the same mutation, and across families with mutations in the same gene. NIDCD-supported scientists have previously identified a suggestive linkage to chromosome 19p in four families with episodic vertigo and the inability to coordinate muscle movement (ataxia). The scientists have identified a missense mutation in the calcium channel gene on chromosome 19p in a family with severe progressive cerebellar ataxia of

early onset involving the trunk, the limbs, and speech function. High-resolution genome scan genotyping from 20 multigenerational families with familial benign recurrent vertigo (BRV) also has defined 2 loci with suggestive evidence of genetic linkage.

Hutchinson-Gilford progeria syndrome

Hutchinson-Gilford Progeria syndrome is a distinctive disorder characterized by rapid aging and death by the second decade of life. It is caused by mutations in the *lamin A* gene. NIDCD-supported scientists are studying a group of these individuals to document the effects of this disorder in the auditory system.

Kallmann syndrome

Kallmann syndrome is a rare genetic disorder with two main symptoms: an absence of the ability to smell and failure of the gonads to mature. There is a five- to seven-fold increased chance that this syndrome occurs in males when compared to females, suggesting that the X-linked form of the disease is the most frequent. NIDCD-supported research has led to the identification of a common developmental defect in neuronal migration, which links the two major disease symptoms. A unique family of proteins and their receptors that regulate neuronal migration and direction during development are under investigation by NIDCD-supported scientists. Additional research is focused on isolating and cloning an X-linked gene responsible for Kallmann syndrome.

Laryngeal (Respiratory) Papillomas (Recurrent, Juvenile)

Respiratory Recurrent Papillomas (RRP) is a rare viral disease characterized by multiple benign growths (papillomas) in the middle and lower respiratory tract. Symptoms usually begin with hoarseness and/or a change in voice. They are the most common benign tumor occurring in children, usually under five years of age; although adults represent about one-third of all documented cases. The growths may be surgically removed, but frequently recur and may require additional surgery. Affected individuals may experience long periods without recurrence (remission), and/or the disease may disappear completely. NIDCD-supported scientists have examined the efficacy and safety of a microvascular targeting technique (MVT) for RRP treatment. This novel approach provides a less traumatic alternative to surgery, and will provide a potentially "voice-preserving" therapy for RRP that will deliver long-term efficacy in managing RRP.

Mitochondrial genes and deafness

Mitochondria are specialized structures within cells that play a crucial role in metabolism and energy production. Mitochondria contain their circular genome, which replicate during cell division. All of the mitochondria present in individuals are inherited from the mother. Therefore, diseases that appear to be passed exclusively through the maternal lineage are often linked to defective mitochondrial genes.

NIDCD-supported scientists have identified several specific mitochondrial mutations that predispose an individual to hearing damage resulting from toxicity from the aminoglycoside class of antibiotics to the inner ear hair cells. These investigators have determined that genetic loci in the nucleus of the cell act to modify the effects of the mitochondrial mutations. Most recently, a specific gene was identified in mice, which modulates the severity of mitochondrial deafness, which is implicated in age-related hearing loss. This mouse model will be extremely valuable for detailed studies of the molecular mechanisms by which mitochondrial mutations contribute to deafness. These findings could be used to develop genetic tests to determine whether an individual has an increased risk for aminoglycoside-induced hearing damage.

Muenke syndrome

The clinical hallmark of Muenke syndrome is Craniosynostosis, a condition in which the sutures (soft spots) in the skull of an infant close too early that causes problems with normal brain and skull growth. Muenke syndrome is caused by the P250R mutation of the *FGFR3* gene. A variety of other clinical abnormalities have also been reported for Muenke syndrome, including hearing loss. NIDCD intramural scientists have shown that hearing loss as a highly penetrant feature of Muenke syndrome. It is manifest as a mild to moderate low frequency sensorineural hearing loss that may occur with or without conductive hearing loss, the latter of which is secondary to otitis media.

Olfactory function

NIDCD-supported scientists are investigating relationships between decreased olfactory function and a number of rare diseases. Studies have shown that olfactory loss appears to be among the first signs of such common neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Recent psychophysical studies have evaluated the prevalence and magnitude of olfactory loss in subtypes of Parkinson's disease, Down syndrome, schizophrenia, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and the rare amyotrophic lateral sclerosis/Parkinsonism/dementia complex of Guam. Better understanding of the associations between olfactory function and rare diseases may lead to earlier diagnosis and improvement in monitoring of these rare diseases.

Pallister-Hall syndrome

Pallister-Hall syndrome is associated with a variety of malformations including polydactyly (more than 5 fingers or toes) and bifid epiglottis (the right and left sides of the epiglottis are not joined). It is caused by truncating, gain-of-function, mutations of the *GLI3* gene. NIDCD intramural scientists have now identified sensorineural hearing loss as an incompletely penetrant feature of Pallister-Hall syndrome. The hearing loss is highly variable in severity and primarily affects low frequencies. Molecular and cellular studies of *GLI3* in wild type and mutant mice have elucidated the role of this gene in morphogenesis of the cochlea and patterning of hair cells in the auditory neurosensory epithelium.

Spasmodic dysphonia

Spasmodic dysphonia (SD), a focal form of dystonia, is a neurological voice disorder caused by involuntary movements of one or more muscles of the larynx or voice box. Individuals who have spasmodic dysphonia may have occasional difficulty saying a word or two or they may experience sufficient difficulty to interfere with communication. Spasmodic dysphonia causes the voice to break or to have a tight, strained, or strangled quality. The first signs of this disorder are found most often in individuals between 30 and 50 years of age. More women appear to be affected by spasmodic dysphonia than are men. NIDCD-supported scientists have been examining the parts of the brain that are associated with SD and how they play a role in causing the involuntary movements associated with SD. Once characterized, these brain pathways can be targeted for further study with functional imaging studies or development of novel medical and surgical therapies.

Turner syndrome

Turner syndrome is characterized by short stature, ovarian failure, and partial or complete deletion of the X chromosome in affected females. Hearing loss is frequent but the phenotype is widely variable in terms of severity, type, and audiometric configuration. NIDCD intramural scientists have prospectively ascertained more than 200 individuals with Turner syndrome with a wide range of karyotypes and mosaicism to better define the phenotype and correlate it with karyotype, other phenotypic features, and exogenous factors such as growth hormone treatment.

Usher syndrome

Usher syndrome (USH) is recessively inherited and characterized by hearing loss, retinitis pigmentosa (RP) and, in some cases, a vestibular disorder. About 5 percent of individuals who are deaf have USH, and more than half of the deaf and blind individuals (>10,000) in the United States have USH. The severity of the hearing loss and the presence of vestibular dysfunction distinguish two major clinical subtypes of USH, types 1 and 2. Individuals who have USH type 1 are congenitally deaf, and have a balance deficiency at birth, while RP has an onset at about the time of puberty. Individuals with USH type 2 are distinguished from USH type 1 in having a less severe hearing loss. A third form of USH (type 3) is characterized by progressive loss of hearing and retinal function. Mutations can cause USH in more than eleven different genes. NIDCD intramural scientists have identified and characterized some of the genes responsible for USH and two common recessive mutations that cause USH in the Ashkenazi Jewish population. They have discovered that the genes for Usher syndrome type 1D and type 1F, both encode cell adhesion proteins cadherin 23 and protocadherin 15, respectively. In addition, several NIDCD-supported scientists reported cloning the gene for Usher syndrome type 2A. The *USH2A* gene encodes a protein, Usherin, that has structures similar to other proteins involved in assembling cells and tissues into functional organs. NIDCD-supported scientists also have identified the genes responsible for Usher type 1C. These advances are critical steps towards developing strategies to treat this devastating disease that causes deafness and blindness.

Waardenburg syndrome (WS)

WS is an autosomal dominant disorder, which is characterized by pigmentary disturbances and deafness. NIDCD-supported scientists are seeking to determine the loci for WS type 2 by utilizing a high-density genome scan coupled with linkage analysis to identify candidate genes mutations that could be the cause of this disorder in three large, multigenerational families and several smaller families with WS2. Other scientists are studying the Dalmatian breed of dog as an animal model for understanding the genetics of pigment-associated deafness in the dog and human. The relationship between pigmentation and deafness is not unique in Dalmatians and this model offers a unique opportunity to conduct genetic analysis of hereditary deafness.

Conferences, Symposia, Meetings

The NIDCD and the NIH Office of Rare Diseases jointly sponsored a workshop in May 2006 to evaluate the potential for brain-computer interfaces (BCI) to provide a means for speech synthesis and control of other forms of assistive technology that support communication. Sixteen scientists and clinicians discussed topics ranging from brain computer interface data acquisition and analysis, cortex neurophysiology, speech synthesis, augmentative and alternative communication, and individual care needs.

The NIDCD, the National Institute on Neurological Disorders and Stroke, and other NIH Institutes cosponsored the June 2006 meeting of the Neurofibromatosis (NF) Consortium for NF1, NF2 and Schwannomatosis, on "Progress: From Bench to Bedside" with five sessions covering molecular mechanisms of NF through translational models to clinical therapies.

NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH (NIDCR)

Overview

The mission of the National Institute of Dental and Craniofacial Research is to improve oral, dental, and craniofacial health through research, research training, and the dissemination of health information. NIDCR's programs encompass basic, translational, and clinical studies of the broad range of diseases, disorders, conditions and syndromes involving the oral cavity and craniofacial structures. NIDCR's section of this report highlights scientific advances within the Institute's intramural and extramural programs and related program activities relevant to rare diseases.

Recent Scientific Advances in Rare Diseases Research

Amelogenesis imperfecta

Amelogenesis imperfecta (AI) is the most common of a rare group of inherited disorders that affect the formation of dental enamel and that result in thin, malformed, easily abraded enamel. As a normal tooth develops from its bud, an organic matrix forms that gradually crystallizes into tooth enamel. This process destroys nearly all traces of the matrix, along with clues to key aspects of tooth formation.

- A team of NIDCR grantees has identified several novel gene mutations in two different genes that are responsible for various aspects of enamel formation. They have identified genetic changes in another enamel gene, ameloblastin, which is thought to be responsible for AI.
- Last year NIDCR researchers created a line of mice that lack the protein amelogenin, causing them to display typical X-linked AI. The availability of the new mouse model made possible investigations yielding a number of discoveries concerning the role of amelogenin in tooth formation and AI development. Crossing these mice with other mouse lines demonstrated the importance of functional differences in amelogenin splice variants. In addition to their enamel-specific roles, amelogenins were also implicated in the formation of root cementum, as well as additional roles in tooth formation. In order to determine the precise role of amelogenins, researchers analyzed tooth roots of aging amelogenin-null mice, which unexpectedly revealed progressive cementum defects in the null mice. Current work aims to characterize the functions of different forms of amelogenin.
- Research continues with analysis of tooth proteins in amelogenin-ameloblastin double knockout mice. The research team has found that amelogenins inhibit normal bone resorption. Current work is aimed at clarifying the mechanism underlying this inhibition. So far the investigators have identified about 60 potential candidate genes that bind to amelogenin. Contrary to expectations, none of the proteins identified is predominantly expressed in tooth roots. Work is ongoing to test some of these binding proteins for cellular functions and modulation by amelogenins.

Cleft lip/Cleft palate

- Work continues on a multicenter epidemiological study of oral clefts. The study is being conducted in four sites: Baltimore, Taiwan, Singapore, and Beijing. Recruitment of families has begun in each center and DNA collection has begun. Preliminary analysis between Asian and US populations will define the range of genetic diversity among the participating sites, increasing our understanding of the role of genetics in the development of cleft lip and/or palate. A recent publication reported on a comprehensive analysis of 104 candidate genes on chromosome 2, and identified a novel candidate gene (ZNF533) that consistently provided evidence of linkage and association with both cleft lip with and without cleft palate.
- NIDCR is sponsoring a clinical trial to determine the effect of 4 mg and 0.4 mg doses of folic acid, taken daily during preconception and the first trimester of pregnancy, on the incidence of oral clefts in children borne to women at high risk for having a child with an oral cleft. Women enrolled in the study must have an oral cleft or previously have had a child with this condition. All clinical sites are in Brazil, and the total sample will include 6,000 women.
- Human genetic linkage and association studies support one or more genes for nonsyndromic cleft lip with or without cleft palate on chromosome 4 at or near the PDGF-C gene locus. The PDGF-C gene is necessary for palate formation in mice, and its absence is associated with a complete cleft of the secondary palate. At the Chinese study site, the PDGF-C gene was sequenced in cases and controls to evaluate its role in human cleft lip/palate. One form, the 986T SNP allele, was found to be significantly associated with the condition.

Dentinogenesis imperfecta

Dentinogenesis imperfecta (DI) is an inherited disorder resulting from mutations of three genes that primarily affect dentin mineralization. DI is classified into three subtypes: type I is the least severe, and type III is the most severe. Type I is also associated with osteogenesis imperfecta, while the more severe forms are restricted to dentin. Several mutations have been identified in the dentin sialophosphoprotein (DSPP) gene in patients with DI. DSPP is expressed predominantly in dentin-producing odontoblasts, and transiently in enamel-producing ameloblasts. Low levels have also been detected in several other tissues like bone, inner ear, salivary glands, kidney, etc.

- NIDCR researchers have identified the genetic mutation in DSPP responsible for DI in the Brandywine population from Maryland. After researching multiple forms of DI, it was found that the mutation responsible for most of these forms of DI results from an endoplasmic reticulum storage type disease. Researchers have previously determined that molecular chaperones can increase release of the mutant protein from the endoplasmic reticulum. The researchers are in the process of evaluating biocompatible chaperones that may permit treatment of DI.
- Continued work will focus on treatment of DI. Working with the NIH Animal Core, NIDCR researchers are putting human normal and mutant forms of DSPP into mice lacking the protein to see if 1) normal function can be restored, and 2) if human type DSPP mutations can be introduced into the animals and treatments evaluated.

Dyssegmental dysplasia, Silverman-Handmaker type (DSSH

DDSH is a rare inherited skeletal disorder characterized by short limbs and abnormal vertebral bodies. Individuals with DDSH also have craniofacial abnormalities including a flat face, small jaws, cleft palate, and reduced joint mobility due to joint cartilage defects. NIDCR scientists previously identified mutations of the perlecan gene (HSPG2) in three patients with DDSH. These results indicate that perlecan is essential for cartilage development and has biological functions in other diseases and in tissue homeostasis. Mutations of the perlecan genes have also been identified in another human disease called Schwartz-Jampel syndrome (SJS), also characterized by cartilage defects.

- NIDCR researchers have created a knockout mouse strain in which recombinant perlecan acted specifically on cartilage but not other tissues. Using the mutant mice, the researchers found that in the absence of perlecan, tumor growth and angiogenesis were increased, and that skin wound healing was significantly accelerated. In cell cultures, fibroblasts from mutant mice migrated faster than wild-type fibroblasts. Results suggest that perlecan plays important roles in cellular processes in various adult tissues and repair processes.

Fabry disease

Fabry disease is a familial sex-linked disorder of lipid metabolism in which glycolipid accumulates in many tissues. It is caused by a deficiency of the lysosomal enzyme α-galactosidase A (AGA). Major disease manifestations include pain in the extremities, abnormalities of the skin and eyes, oral and dental abnormalities, and vascular disease of the heart, kidney, and brain, leading to premature death. In collaboration with NINDS investigators, NIDCR scientists reported a high prevalence of oral and dental abnormalities in Fabry patients, including malocclusion, diastemas, and developmental anomalies.

- Researchers have generated and characterized a line of AGA-deficient mice which show similarities to patients with Fabry disease. By studying these Fabry mice and investigating methods to replace the defective gene using viral gene transfer methods, there is potential for developing treatments for people who are born with this devastating disease.

Growth hormone deficiency (Adult)

Growth hormone deficiency (GHD) is a disorder most commonly caused by pituitary disease, often due to the presence of nonfunctional pituitary adenomas or as a result of surgery or radiotherapy to treat pituitary adenomas. NIDCR scientists previously demonstrated the considerable value of salivary glands as gene transfer target sites for the treatment of rare systemic single protein deficiency disorders, including growth hormone (GH) deficiency in adults, a disorder with a prevalence of about 1/10,000.

Salivary glands secrete proteins in both exocrine (saliva) and endocrine (bloodstream) directions. Growth hormone (GH), an endocrine protein normally secreted into the bloodstream via the regulated secretory pathway (RSP), is also secreted via the RSP from rodent salivary glands into saliva. Conversely, erythropoietin (EPO), normally secreted by kidney cells, is similarly secreted

from rodent salivary cells to the bloodstream. This is not useful for those proteins such as GH, whose therapeutic function is required systemically. It is important for developing clinical applications to understand the sorting signals and cellular machinery responsible for protein sorting, so that specific proteins can be delivered to either the bloodstream or upper GI tract (via saliva).

- NIDCR researchers are comparing the basal level of secretion of mutant GH with that achieved on stimulation. Although a mutation that can dramatically alter GH's sorting behavior still has not been identified, progress has been made and evidence with different experimental techniques suggests that this approach will eventually bear fruit.
- Studies are examining the secretion of hGH and hEPO fusion products. In mice, two clear populations of animals have been found that sort the fusion protein product differently. Work continues to understand the genetic basis for these sorting differences.
- To date, *in vivo* studies have been conducted in mice and rats, but it is unknown whether protein sorting behaviors in larger animals and humans are similar to those observed in rodents. As part of efforts to move salivary gland gene transfer into clinical application, NIDCR scientists have initiated *in vivo* secretory protein studies in two large animal models: the miniature pig and rhesus monkey. Studies in parotid glands of miniature pigs have shown similar results as those in rodents, with the exception that hEPO from these glands is not secreted mainly into the bloodstream. Studies of hGH secretion from rhesus parotid glands are ongoing.

Hypoparathyroidism

Hypoparathyroidism is caused by loss of parathyroid hormone (PTH), due either to surgical removal of the parathyroid glands, autoimmune destruction of the glands, or various molecular defects related to parathyroid gland function or formation. The result is profound mineral metabolism abnormalities and unexpectedly high bone mass.

- Investigators are furthering the understanding of the roles of PTH and $G_s\alpha$ signaling in bone. Because PTH, like FGF-23, a newly-identified hormone that regulates mineral metabolism, is also involved in mineral metabolism, patients with hypoparathyroidism are good models for the study of physiologic regulation and role of FGF-23. Two new clinical studies are under way to study the regulation of FGF-23 and the bone and mineral metabolism in hypoparathyroidism patients with.

Kaposi's sarcoma

Kaposi's sarcoma (KS) is the most common cancer arising in HIV-infected and other immunosuppressed patients. KS has also emerged as one of the most prevalent cancers among children and adult men in the developing world, accounting for up to 25 percent of pediatric cancers in parts of Africa. The Kaposi's sarcoma-associated herpes virus (KSHV; HHV-8) has been recently identified as the infectious cause of Kaposi's sarcoma. Compelling evidence now supports a critical role for the oral cavity as the primary source of infectious HHV-8 in both immunocompetent and immunosuppressed patients. As the most frequent oral neoplasm in AIDS

patients, KS is an infectious disease of paramount concern for oral health. The sequencing of the full KSHV genome revealed a candidate gene known as vGPCR, which promoted the development of visible dermal and internal vascular tumors that resemble KS lesions. The results implicated vGPCR in both the initiation and promotion of Kaposi's sarcoma.

- As only a fraction of cells in advanced KS lesions express vGPCR, its contribution to KS progression is still unclear. Thus, NIDCR researchers explored whether the few cells that express vGPCR in established tumors represent an appropriate therapeutic target for the treatment of patients with pre-existing KS. Cell lines were produced that rendered vGPCR expressing cells sensitive to the antiviral drug ganciclovir. Mixed cell populations were created with genetic characteristics similar to gene-expressing cells in KS. When mice containing these cell lines were treated with ganciclovir, they exhibited tumor regression despite the latent KSHV. These findings indicate that vGPCR may play a key role in KS maintenance and progression and thus provides experimental justification for developing molecular-based therapies targeting vGPCR.
- Investigation continues to determine which mitogenic and survival pathways are utilized by vGPCR to cause tumors. Currently available evidence indicates that vGPCR stimulates an enzyme found to be a hallmark of human KS. Recently, effort was focused on another enzyme that controls the synthesis of proteins required for cell proliferation. Pharmacologic inhibition of this enzyme with rapamycin seems to prevent tumor formation, while over-activation of this pathway was sufficient to render endothelial cells cancerous. These findings identified this pathway as a therapeutic target for KS, and provide the rationale for the clinical evaluation of rapamycin and its analogs for its treatment.
- Investigators developed a tissue cell culture model using keratinocytes from human tonsils to test whether KSHV utilizes the differentiation of oral epithelium as a mechanism for the activation of virus replication and production. They found that KSHV activation occurs as epithelium differentiates and matures, and it may be responsible for the presence of infectious KSHV in saliva. The results illustrate an *in vitro* model of a natural cellular process causing the switch from latent to lytic replication, which will be of value in unraveling the cellular and viral mechanisms involved in activation of latent KSHV.

Sjögren's syndrome and Systemic lupus erythematosus

Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE) are both systemic autoimmune diseases that are characterized by the presence of antibodies to proteins made in our bodies (autoantibodies). The origin and development of autoantibodies to these intracellular proteins is not clear. The cause of SS remains largely unknown and therapy is empirical and mainly symptomatic. Many drugs that are effective in treating other autoimmune disorders are not effective for the treatment of SS. NIDCR investigators participate in several clinical studies in SLE, including a protocol using autologous hematopoetic stem cell transplantation for patients with severe treatment resistant lupus.

- To provide information regarding the local lesions found in SS, NIDCR researchers have begun to explore immune cell infiltrates as well as their products that are fundamental to evolution of glandular dysfunction. In recent years, clinical studies done at NIDCR with

immunomodulatory drugs, such as thalidomide and Etanercept (anti-TNFα), suggested that TNFα is not an effective target.

- In an effort to address the role of immune-mediated destruction of salivary gland function observed in SS, NIDCR researchers initiated a new clinical pilot study with a monoclonal antibody against an adhesion molecule required for the migration of inflammatory cells. In addition to evaluating clinical response, participants will have a salivary gland biopsy and various immunologic tests done to assess treatment-related immunologic changes in the peripheral blood and the target organ simultaneously.
- ID3 is an immediate early-response gene in growth regulation. It has been reported that ID3 knockout mice develop many disease symptoms found in primary SS patients. NIDCR researchers have successfully established such a colony, and some of the aged mice have begun to develop the disease, displaying inflammation in salivary glands, liver, and skin, that closely resembles patients with SS. The specific immunological mechanisms leading to SS in the affected mice have been identified as a deficiency in a particular type of T regulatory cells. An unexpected finding was that affected mice more than one year old exhibit a severe enlargement of the spleen that has never been described, indicating additional functions of the ID3 gene.

McCune-Albright syndrome and Fibrous dysplasia of bone

The McCune-Albright Syndrome (MAS) is defined by the triad of fibrous dysplasia of bone (FD), café-au-lait skin spots, and endocrine gland hyperfunction. It is caused by activating mutations of the signaling protein $G_s\alpha$. Some patients may have only a single focus of bone affected, and others may have severe disease affecting multiple endocrine glands and virtually the entire skeleton. Craniofacial bones are among the tissues most profoundly affected. Overgrowth can lead to macrocephaly, deafness, and blindness. NIDCR intramural scientists and clinicians have studied MAS and FD for the last 10 years, performing a number of clinical studies examining various aspects of the disease.

Studies of the natural history of MAS/FD have revealed:

- The craniofacial morbidity is directly linked to the subgroup of patients with growth hormone excess. This led to the recommendation of early screening and aggressive treatment.
- The involvement of the spine with FD as a common and major problem, contributing to the development of a progressive and lethal form of scoliosis. This too led to the recommendation for early and ongoing screening and surgical intervention, when necessary.
- Fractures, disability, and associated malignancies were defined, leading to evidence-based algorithms for evaluation and treatment.
- Treatment studies: Clinical trials for the treatment of FD, precocious puberty, and growth hormone excess are either completed or in progress. This will lead to better care and improved quality of life for patients with MAS and FD.

Mucolipidosis-IV (ML-IV)

ML-IV is a rare inherited metabolic disorder that leads to abnormal accumulation of certain fatty substances and complex carbohydrates in the cells of many tissues. It is generally characterized by mental retardation, impaired coordination of muscular and mental activities, and corneal opacity.

- Currently, there is no animal model available to develop effective therapies to treat this fatal disorder. However, in collaboration with NINDS investigators, NIDCR scientists have generated a mouse model with an altered ML-IV locus. These mice are currently being studied to identify whether they mimic ML-IV disease. If so, the mice will provide new opportunities to study mechanisms and possible treatments.

Paget's disease/Osteopetrosis

Normal bone remodeling is essential for a healthy skeleton; however, in Paget's disease, the rates of bone resorption and bone formation at affected sites are so rapid that the new bone is both over-abundant and of poor quality. A key feature of the disease is excessive numbers and activity of the cells, called osteoclasts, which resorb bone. The large number of active osteoclasts, in turn, stimulates excessive bone formation by other cells. Osteoclasts arise from precursor cells that are present in bone marrow.

- Osteoclasts differentiate from hematopoietic precursors under systemic and local controls. Chemokines and receptors direct leukocyte traffic throughout the body and may help regulate site-specific bone resorption. NIDCR-funded researchers investigated bone gene expression in vivo during rapid osteoclast differentiation induced by colony-stimulating factor 1 (CSF-1) in Csf1-null toothless (tl/tl) rats. The toothless (tl/tl) rat is an autosomal recessive mutation in which a frameshift in the CSF-1 gene causes severe osteopetrosis due a virtually complete lack of osteoclasts. While various chemokines have been implicated in osteoclastogenesis in vitro, this first systematic analysis of chemokines and receptors during osteoclast differentiation in vivo highlights the key role of the chemokine CCL9 in this process.

Papillon Lefevre syndrome

Papillon Lefevre syndrome (PLS) is an inherited disorder characterized by hyperkeratosis of the palms and the soles of the feet, along with aggressive early onset periodontitis that typically results in the premature loss of most teeth. The skin lesions are variable, but can be very painful.

- NIDCR scientists played a lead role in the initial identification of the underlying mutation that causes PLS. The scientists are continuing to study the mutations to better understand the underlying pathophysiology and develop new treatment strategies. Recent studies suggest that the severe periodontal tissue destruction in Papillon-Lefevre syndrome may be related to excess accumulation of inflammatory proteins in the periodontium.

Schwartz-Jampel syndrome

Schwartz-Jampel syndrome (SJS) is a rare inherited skeletal disorder characterized by short stature, muscle stiffness, a characteristic "fixed" facial expression, pursed lips, and sometimes low-set ears and myopia. The electromyography shows persistent spontaneous activity, particularly in the face and thigh muscles, which tends to diminish at rest.

- NIDCR scientists and others have recently identified mutations of the perlecan gene of patients with SJS. The SJS phenotype appears to encompass a wide spectrum of disorders that may mimic or might have been misdiagnosed as other genetic diseases.
- A mouse model has been devised. This perlecan knockout genotype is normally lethal, but researchers created lethality-rescued perlecan KO mice by expressing recombinant perlecan to cartilage but not other tissues. With electromyelographic symptoms of SJS blocked by treatment with curare, the rescued mice are useful to study the mechanism of myotonia and to identify the role of perlecan in adult tissue functions and diseases.

Squamous cell carcinomas of the head and neck

Although relatively rare (incidence is estimated at 38,500 annually in the U.S.), squamous cell carcinomas of the head and neck (SCCHN) are among the most fatal and morbid of cancers at any anatomic site. Most patients with head and neck cancers are treated with surgery and irradiation (IR). Head and neck cancer patients frequently fail to respond to standard therapies, and their 5-year survival rate is less than 50 percent, a number that has improved only marginally over the past three decades. Those who survive often suffer from poor quality of life, due to extensive disfigurement and destruction of structures critical to speaking, breathing, salivation, and swallowing. In 2006 these cancers resulted in approximately 8,300 deaths in the U.S.

A number of scientific advances were realized in this field during the past year:

- Radiotherapy is used to treat the majority of patients with head and neck cancers. Salivary glands in the radiation field are significantly damaged by this procedure. Currently there is no generally useful means to prevent this irreversible damage. The condition leads to considerable morbidity, including difficulty in eating and swallowing, chronic oral infections such as candidiasis and dental caries, and decreased mucosal wound healing. NIDCR scientists and colleagues at NCI showed that a stable nitroxide compound known as Tempol, when administered intraperitoneally shortly before radiation, was able to provide radioprotection of salivary glands in mice. These and other clinical findings strongly suggest that Tempol is a promising candidate to protect salivary glands in patients undergoing radiotherapy for head and neck cancers. Additionally, it was determined that Tempol treatment can protect normal tissue, but not tumor tissue, from the effects of irradiation. These preclinical studies support the use of nitroxide radioprotectors in conjunction with functional nitroxide/MRI as a completely novel approach of selective normal tissue radioprotection worthy of clinical evaluation.
- Currently, thousands of cancer patients suffer from dry mouth secondary to IR. Previously, NIDCR researchers have reported the restoration of salivary gland function in rats and pigs

using a viral vector to transfer the human aquaporin-1 gene. Following the approval of a human clinical protocol by all required oversight groups in the NIDCR, NIH, and FDA, the investigators are now poised to being a clinical trial.

- Researchers are attempting to generate immunotoxins with high selectivity for oral cancer. To that effect, a series of recombinant diphtheria toxins that are fused to growth factor fusion toxins have been generated, thus taking advantage of the high level expression of these components on oral squamous carcinoma cells. The recombinant toxins are currently being screened for cytotoxic activity towards a series of oral squamous carcinoma cell lines.
- NIDCR-funded scientists have developed the first mouse model of human head and neck cancer. This animal model mimics human head and neck cancer at both the pathological and molecular levels, including many of the molecular alterations found in head and neck cancer patients. This animal model provides a valuable tool to identify key molecular pathways and networks involved in head and neck carcinogenesis. In addition, it serves as a screen for novel therapeutic and preventive approaches for this devastating disease.
- The malignant progression and metastatic spread of oral cancers requires angiogenesis (the growth and remodeling of new blood vessels from a pre-existing vascular network) to ensure the delivery of oxygen and nutrients to rapidly dividing transformed cells. Emerging evidence suggests that molecules involved in transmitting axonal guidance cues during embryogenesis may also play a role in blood vessel guidance during development. NIDCR researchers have found that a family of axon guiding molecules may represent a new therapeutic target for the treatment of many highly prevalent human malignancies, including oral cancer.
- Vascular endothelial growth factor (VEGF) plays a central role in both vasculogenesis and angiogenesis (initiation and growth of veins and arteries) for endothelial cells. Unregulated VEGF expression also contributes to the aberrant growth of most solid tumors. A recent NIDCR study found that activation of VEGF receptors leads to a chain of events that may open new therapeutic opportunities for the treatment of many human diseases that involve pathological vessels.
- Another area of study is mitogenic signaling from G protein coupled receptors (GPCRs), as a simple model for identifying critical molecules that regulate normal cell proliferation and tumor development. GPCRs have been linked to tissue specific, fully differentiated cell functions such as exocytosis, chemotaxis, hemostasis, photoreception, chemoreception, homeostasis, neurotransmission, and immune response, as well as smell and taste. GPCRs are also expressed in proliferating cells, and they have been implicated in embryogenesis, tissue repair and remodeling, inflammation, angiogenesis, and cancer.
- Emerging clinical and experimental evidence now indicates that nonsteroidal anti-inflammatory drugs can reduce cancer incidence due to the inhibition of COX-2 and one of its pro-inflammatory metabolites, prostaglandin E2 (PGE2). However, how COX-2 and PGE2 promote the aberrant growth of cancer cells remains poorly understood. As part as an ongoing effort to investigate this aspect of cancer biology, NIDCR? researchers investigated the molecular mechanism underlying the potent mitogenic effect of PGE2, using colon cancer cells as a model system. Their findings may provide a molecular framework for the future clinical evaluation of new chemopreventive strategies for many highly prevalent human cancers.
- Recently the details of the *ras* oncogene were described in salivary glands of adult mice. The expression of a mutated form of this gene leads to the development of a complex array of pre-cancerous skin lesions and carcinomas in 100 percent of the animals, in as little as one week.

This NIDCR-funded study provided evidence that the *ras* oncogene, when targeted to a specifically sensitive cell compartment within the salivary glands, can trigger a series of event that are sufficient for full carcinogenesis.

- The small molecular weight proteosome inhibitor, PS-341 (Velcade ™ (Bortezomib)), has been used for human cancer therapy, including solid tumors of head and neck. Its mechanism leads to programmed cell death (apoptosis) of tumor cells that seems to be different from the apoptosis induced by other chemotherapeutic agents.
- The last decade has seen significant effort to define the molecular pathways involved in tumor formation. In a large number of studies relevant to SCCHN, research has focused on the loss of tumor suppressor genes such as p53. Developing specific therapeutic strategies to restore the function of p53 has been challenging, with limited clinical success. However recent research has delineated a functional chain of molecules that interact with p53.

Temporomandibular joint disorders

Temporomandibular joint disorders (TMJDs) are a group of conditions causing pain and dysfunction in the temporomandibular joint and surrounding muscles. While there are no firm data on how many people are affected by TMJDs, orofacial pain is a major cause of poor quality of life. Examination of several mouse models in which specific matrix molecules have been eliminated revealed degenerative changes in the articular surfaces of the temporomandibular joint (TMJ). Such changes have been implicated in the development of TMJDs; current studies are focused on characterizing how these matrix molecules are involved in maintaining integrity of the TMJ.

- Results from a randomized clinical trial show that TMD pain patients receiving four sessions of individual cognitive behavior therapy (CBT), combined with brief "home-work" exercises, showed significantly better outcomes at one year as compared with comparable patients randomized to an education/attention control condition. Patients were thoroughly evaluated with clinical examinations and psychometric and self-report instruments.
- Treatments for patients seeking care for painful temporomandibular disorders (TMJDs) range from conservative treatments such as physiotherapy to aggressive, irreversible treatments such as tooth grinding, occlusal modifications, or jaw surgery. Intraoral hard splints are commonly prescribed, based on the rationale that splints may alleviate jaw muscle strain associated with tooth grinding or occlusal disharmonies. NIDCR-supported investigators randomized 200 patients diagnosed with TMD into three groups. The first group received usual conservative dentist-prescribed self-care treatment (UT) without any intraoral splint appliance, the second group received UT plus a conventional custom-fitted hard acrylic splint, and the third group received UT plus a soft vinyl athletic mouth guard. The investigators found comparable improvement over time in all groups, and that the hard acrylic splint offered no benefit over the soft splint. Moreover, neither splint therapy offered greater benefit than did self-care treatment without splint therapy.
- Molecular studies on TMJD have identified a number of proteins and neurotransmitters that play an important role in the normal functioning of the temporomandibular joint (TMJ) and the development of the disorder. An NIDCR-funded study examined the effects of blocking integrin (a type of cell surface protein) function in the TMJ of male and female rats on

activation of trigeminal neuronal pain pathways. The results suggest that integrins contribute to nerve activation by jaw movement only under very particular circumstances, the details of which yield important information about TMJ pain.

- The role of genetics in the wide variation in responses to pain and analgesic therapies and in the development and chronicity of TMJD is being examined in a number of laboratories. NIDCR-funded researchers have examined common haplotypes in the beta-2-adrenergic receptor ADRB2 in order to study the relationship between genetic markers and painful musculoskeletal temporomandibular joint disorder. They found that the haplotypes influence receptor expression levels and efficiency after stimulation by agonists. The presence of haplotypes associated with the most positive psychological traits and higher resting blood pressure were also associated with a ten-fold reduction in the risk for developing TMJD.
- This team also has expanded on studies of single nucleotide polymorphisms (SNP) in the catechol-O-methyltransferase (COMT) gene and association with pain experience to now include haplotype mapping of this gene and responses to specific pain-evoking stimuli. They have identified three common haplotypes in the COMT gene and their associations with threshold and tolerance to thermal, ischemic, and mechanical stimuli, and temporal summation to heat pain in their female study population. Haplotype associations were strongest for measures of thermal pain and there was no association of haplotypes and summation of heat pain. Interestingly, one particular SNP was associated with differences in the summation of heat pain but not with other pain measures.

Tricho-dento-osseous syndrome

Tricho-dento-osseous syndrome (TDO) is an autosomal dominant genetic condition that typically affects the hair, teeth, and bones of affected individuals. The bones of affected individuals get thicker and denser with age.

- NIDCR scientists have successfully generated mice which carry the same mutation responsible for TDO in humans. The mice have phenotypic features including atypical molar teeth, enhanced bone density and thickness. Preliminary data have demonstrated that these mice show defects in tooth-forming cells known as odontoblasts and cementoblasts, resulting in markedly reduced dentin formation. Bone destruction is reduced compared to those of control mice.

Tumor-induced osteomalacia

Tumor-induced osteomalacia (TIO) is a disease caused by sporadic, benign mesenchymal tumors that hyper-secrete FGF-23, a newly-identified hormone that regulated mineral metabolism.

- An ongoing clinical study is under way to investigate the best way to diagnose and treat patients with TIO, and associated bench studies are investigating the cell and molecular biology of FGF-23.

Education Activities on Rare Diseases

The NIDCR Web site contains information, order forms for educational materials, and references, including pertinent news releases and links to advocacy groups. A number of rare conditions are addressed under the heading "Genetics." Salivary gland disorders, temporomandibular joint disorders, and oral cancers are listed individually. To learn more, please see: www.nidcr.nih.gov/HealthInformation/DiseasesandConditions/

Other outreach activities: This year researchers from NIDCR's Gene Therapy and Therapeutics Branch participated in a round table discussion sponsored by the National Organization for Rare Diseases entitled *"The New Medical Breakthroughs: Real Progress or False Promises?"* Panelists discussed recent advances in enzyme replacement therapy, small molecule research, bone marrow transplantation, gene therapy, and stem cell research for the treatment of rare diseases.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK)

Overview

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports basic and clinical research on many rare diseases. For example, although diseases such as type 1 diabetes, type 2 diabetes, and obesity are not rare, there are rare single gene defects that cause these conditions such as Maturity Onset Diabetes of the Young (MODY), neonatal diabetes and lipodystrophy. In addition, the NIDDK supports research on both common and rare causes of kidney, liver and gastrointestinal diseases. The Institute also supports research on genetic metabolic diseases such as cystic fibrosis; lysosomal storage diseases including Krabbe disease and Mucopolysaccharidoses; disorders of amino acid metabolism such as tyrosinemia and maple syrup urine disease; disorders of copper transport including Menkes and Wilson disease; and hematologic diseases such as Cooley's anemia and sickle cell disease. Many times research on rare diseases leads to insights into cellular processes relevant to the more common diseases.

Recent Scientific Advances in Rare Disease Research

Neonatal diabetes

Novel heterozygous mutations in a component of an ion channel in insulin-producing beta cells have been found to contribute to the development of neonatal diabetes. This form of diabetes appears in the first months of life, and may either be permanent, or transient—with the possibility of relapse later in life. Researchers studying families with neonatal diabetes screened their DNA for mutations in a gene, *ABCC8*, which encodes one subunit of a transmembrane ion channel in the pancreatic beta cells. Mutations in the gene for the other subunit of this channel, *KCNJ11*, have also been shown to cause neonatal diabetes. Investigators found mutations in the *ABCC8* gene in 9 of 34 patients with neonatal diabetes—in whom no other genetic defect had been previously identified. The mutations are thought to upset the careful regulation of potassium and calcium ions inside and outside of the beta cells. Disrupting this balance inhibits the release of insulin from the beta cells, leading to a dangerous rise in overall blood glucose levels. Fortunately, patients with mutations in either *ABCC8* or *KCNJ11* responded favorably to treatment with a class of orally-administered drugs known as sulfonylureas, simplifying their treatment. These drugs act by binding to the complex of proteins that make up the ion channel, increasing their surface expression, and inhibiting the release of potassium ions from the beta cell. These actions allow insulin release in response to elevated blood glucose. These studies identify a novel mechanism for the development of a significant fraction of permanent and transient neonatal diabetes in a particularly vulnerable group of individuals, and shed light on the biochemical mechanism of action of the drugs used to treat it.

Johanson-Blizzard syndrome (JBS)

Johanson-Blizzard syndrome is a rare autosomal recessive genetic disorder with an incidence of about 1 in 250,000. The abnormalities frequently seen include exocrine pancreatic insufficiency,

mental retardation, facial and dental abnormalities, imperforate anus and deafness. To identify the genetic defect in JBS, researchers conducted a genome-wide linkage scan on seven families. They were able to identify a region on chromosome 15q that was homozygous in affected individuals. The researchers were able to identify one gene, *UBR1*, which contained changes that coded for either amino acid substitutions or splicing changes in each individual. The gene, *UBR1* encodes an E3 ubiquitin (Ub) ligase that is part of the N-end rule pathway. This pathway controls the degradation of many intracellular proteins through the ubiquitin proteasome pathway. Studies in both patients and in a knockout mouse model showed that *UBR1* was required for maintenance of the pancreatic acinar cells. The identification of the gene responsible for this syndrome should allow for new diagnostic tests for this disease and provide new insights into the pathophysiology.

Cystic fibrosis (CF)

Cystic fibrosis is the most common fatal genetic disease in Caucasians, affecting approximately one in 3,000 newborns. Patients are diagnosed in early childhood with symptoms such as failure to thrive. With management of the nutritional problems and infections, the life expectancy for people with CF has increased to over 30 years. CF is caused by mutations in the gene encoding the CFTR protein, which resides in the outer surface of cells lining the lung and intestine, where it regulates the movement of chloride. The lungs of CF patients contain thick mucus that contributes to the development of chronic bacterial infections. Infection by *Pseudomonas aeruginosa* causes much of the morbidity and mortality in CF patients. Researchers have studied serial isolates of *P. aeruginosa* from a CF patient and have identified numerous genetic adaptations over 8 years of infection. These changes were confirmed in serial isolates from other CF patients. These studies show that *P. aeruginosa* adapts in the CF lung through a series of mutations. Several genes are frequently mutated including multidrug-efflux pumps and virulence factor genes. Understanding these changes can identify new vulnerabilities that can be used to develop more effective treatments.

Polycystic kidney disease (PKD)

Polycystic kidney disease (PKD) is an inherited disease characterized by fluid-filled cysts in the kidneys. These cysts, ranging in size from a pinhead to a grapefruit, over time can destroy functioning kidney tissue. This destructive process may result in irreversible kidney failure (end-stage renal disease), for which the only treatments are dialysis or kidney transplantation. There are two forms of inherited PKD. Autosomal dominant PKD (ADPKD) is one of the most common genetic disorders and seems to affect people regardless of sex or ethnic origin. Autosomal recessive PKD is relatively rare and often causes significant mortality in the first month of life.

The NIDDK supported a clinical study, the Consortium for Radiologic Imaging Studies of PKD (CRISP), to test whether magnetic resonance imaging (MRI) of kidney and cyst volumes is a reliable early marker for monitoring disease progression. CRISP investigators used innovative imaging techniques and analyses to follow disease progression in 241 PKD patients over three years. This study showed that magnetic resonance imaging could accurately track structural changes and will likely enable an earlier prediction of functional changes than is

possible with standard blood and urine tests in people with ADPKD. The CRISP study found that the cysts grew at a continuous, steady rate specific to each patient and that this enlargement was associated with a decline in kidney function. The CRISP study results suggest that changes in cyst and overall kidney size over time may be a reliable method of monitoring disease progression. With these new insights, researchers may be able to study agents that act earlier in the disease process, before massive enlargement of the kidneys has occurred, and thus find ways to prevent the progression of PKD patients to end stage renal disease.

Previous research showed that two mutated genes, either *PKD1* or *PKD2,* are responsible for most cases of the major form of ADPKD. However, the respective roles of these genes in disease progression, as indicated by ultrasound analysis, have remained unclear. The CRISP investigators, using a more sensitive MRI imaging method, reported that patients with the *PKD1* gene have more cysts and significantly larger kidneys than those with the *PKD2* gene. Data from the CRISP study suggest that this difference results from earlier development of cysts, not from a faster growth of cysts, in patients with *PKD1* mutations. These clinically important results will inform the development of targeted therapies for patients with the most prevalent form of this disease.

Alagille syndrome (AGS)

Alagille syndrome is a dominant disorder which shows liver, cardiac, skeletal and ophthalmologic manifestations. In about 94 percent of patients, this syndrome is caused by mutations in the gene for Jagged 1 *(JAG1*) which is a ligand in the Notch signaling pathway. Investigators have screened patients that did not have mutations in *JAG1* and found that two of these patients have mutations in another member of the Notch signaling pathway, the Notch 2 receptor (*NOTCH2*). In addition to the abnormalities normally seen in AGS, these patients both had severe renal disease. *NOTCH2* expression is important for kidney development so mutations in *NOTCH2* may define a subset of AGS patients with kidney abnormalities.

Joubert syndrome

Joubert syndrome is a recessive disorder associated with nephronophthisis, retinal degeneration, and defects in central nervous system development. Six genes have been identified which contribute to nephronophthisis alone or in combination with retinal degeneration in Senior-Loken syndrome. However, there are still families in which no mutation has been found in any of the known genes. Researchers analyzed these kindreds and identified a region on chromosome 12q that was homozygous in some of these families. Further analysis identified mutations in the gene, *CEP290* in families with Joubert Syndrome. The gene, *CEP290*, encodes a centrosomal protein, nephrocystin-6 which binds to the transcription factor, ATF4 and activates it. When *CEP290* is mutated in zebrafish , they show a similar renal, retinal and cerebellar phenotype confirming the role of this protein in the development of these organs. These studies have identified a new pathway that is important for kidney development.

Rare Diseases Research Initiatives

The NIDDK has joined NINDS and NIA in cosponsoring a Program Announcement entitled, "Targeting Diseases Caused by Protein Misfolding or Misprocessing." The purpose of this initiative is to invite applications to identify and optimize small molecule reagents of any kind that specifically ameliorate a protein folding or processing defect in inherited diseases. Because so many mutant proteins, once folded and exported to their normal location, retain some functional activity, "chemical chaperones" have potential to rescue mutant phenotypes in many diseases, including many which are rare. Agents which selectively upregulate or modulate the cell's endogenous chaperone and quality control activities may also prove useful. The initiative solicits applications for research efforts at all stages in the therapeutic continuum. The first set of applications were reviewed and funded in 2006. These included applications on CF, Gaucher disease, Niemann-Pick C, and Krabbe disease. This Program Announcement has been reissued and we anticipate funding additional applications in 2007.

The NIDDK has funded the second phase of the Consortium for Radiologic Imaging Studies of PKD (CRISP) in 2006 which will continue until 2010. The initiative includes 4 primary awards (3 Clinical Site awards and 1 Data Imaging and Coordinating Center award).

The NIDDK has joined the NINDS, NIMH, NCI, NIAMS, and the Tuberous Sclerosis Alliance in cosponsoring a Program Announcement entitled, "Understanding and Treating Tuberous Sclerosis Complex." The purpose of this initiative is to encourage research to understanding or treat Tuberous Sclerosis Complex (TSC). The genes that cause TSC, *TSC1* and *TSC2* are known, understanding of the pathways in which they act is increasing, and animal models now exist that mimic certain features of the disease. As a result, there is a remarkable opportunity to increase knowledge about the mechanisms that cause TSC and translate this knowledge into therapies for this often devastating disorder. This Program Announcement continues to solicite applications in 2006.

The NIDDK sought to encourage translational research in cystic fibrosis (CF) by reissuing an RFA, entitled "Cystic Fibrosis Research and Translational Core Centers," to support both basic and clinical studies. These applications have been received and we anticipate funding two additional Centers in 2007.

Rare Diseases-Specific Conferences

The meeting "Alpha-1 Antitrypsin Deficiency and Other Liver Diseases Caused by Aggregated Protein" was held on January 26-28, 2006 at the Emory University Conference Center in Atlanta, Georgia cosponsored by the NIDDK, the Office of Rare Diseases, the American Association for the Study of Liver Diseases (AASLD), the American Liver Foundation (ALF), and the Alpha-1 Foundation. A total of 23 talks along with extensive discussion sessions occurred over two and a half days. Additionally, an evening poster session and late-breaking oral poster sessions were incorporated into the meeting agenda. The speakers were all internationally recognized leaders and the meeting was well attended. The major aims accomplished by this conference included several talks on the state of the science of alpha-1 antitrypsin deficiency disease pathophysiology,

particularly in relation to liver disease. New insights into the cellular injury mechanisms and pathways of accumulated mutant alpha-1 antitrypsin protein now invoke downstream pathways of protein degradation. The conference also highlighted a variety of other rare disease conditions that shared similar pathophysiological mechanisms. This included presentations on tyrosinemia, Hepatitis B, hemochromatosis, Wilson disease, cystic fibrosis, and lysosomal storage diseases. The final session of the conference focused on new therapeutic approaches including small molecule chaperones, pharmacologic chaperones, hepatocyte transplantation and gene therapy. The conference also included oral presentations of abstracts and a poster session. This allowed participation by young investigators. The chairmen of the conference plan to submit a meeting summary manuscript to the ***Journal of Hepatology*** for publication.

In 2006, the NIDDK Hematology Program re-established an Interagency Coordinating Committee (IACC) for Hematology and organized a one-day Hematology IACC meeting entitled, "Workshop on Inherited Marrow Failure Disorders" which took place on Friday, March 10, at the NIH. Inherited marrow failure disorder encompass a number of rare diseases including Diamond Blackfan Anemia (DBA), Fanconi Anemia (FA), Dyskeratosis Congenita (DC), Schwachman Diamond Syndrome (SDS), Severe Congenital Neutropenia (SCN), Amegakaryocytic Thrombocytopenia, Thrombocytopenia Absent Radii and Congenital Dyserythropoietic Anemias (CDAs). The meeting began with a symposium that reviewed current insights into the etiology and clinical presentation of inherited bone marrow failure syndromes (IBMFS) and then focused on challenges and opportunities for the development and use of IBMFS disease-specific patient registries for translational research. Progress in translational clinical research that will advance the understanding, diagnosis and treatment of IBMFS depends on effective patient registries, and the development of such registries will benefit substantially from interagency cooperation and coordination. This IACC meeting was attended by representatives from 6 NIH IC's and the CDC. This meeting has led to a follow-up workshop organized by the NIDDK Hematology Program and cosponsored by the ORD (Inherited Bone Marrow Failure Syndromes (IBMFS): Definitions and Diagnostic Criteria to be held at NIH on January 26, 2007). The objective of this follow-up workshop is to establish common definitions and diagnostic criteria for IBMFS disorders in order to promote coordination of IBMFS patient registries and to facilitate the development of clinical research consortia, an issue identified in the March IACC meeting.

The National Cancer Institute (NCI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIH Office of Rare Diseases (ORD) held a meeting entitled, "Nutrient Sensing, Insulin Signaling, and Hamartoma Syndromes" on May 11th and 12th, 2006. The meeting focused on nutrient sensing and insulin signaling pathways, particularly as they relate to the hamartoma syndromes: Tuberous Sclerosis, Peutz-Jeghers Syndrome, and Cowden's syndrome. Sessions included clinical and basic studies on hamartoma syndromes, insulin signaling and mammalian Target of Rapamycin (mTOR), and nutrient sensing. Plenary talks, selected short talks, and a poster session provided a forum for interactions among investigators working across these areas. The overall goal for the meeting was to encourage investigators in the fields of insulin signaling and nutrient sensing to consider the applicability of their work to hamartoma syndromes and to have an increased focus on these diseases. We see increasing evidence of this in our investigator-initiated application portfolio, indicating that awareness of these diseases has increased.

On June 20, 2006, the Amyloidosis Sub-committee of the Trans-NIH Rare Diseases Working Group sponsored the "Advisory Focus Group Workshop on Systemic Amyloidosis" in Bethesda, Maryland. This workshop, sponsored by the ORD, was prompted by discussions at meetings of the Amyloidosis Sub-committee. Dr. Daniel Wright, Director of the NIDDK Hematology Program and member of the subcommittee served as a principal organizer of this workshop which was convened to identify opportunities, challenges, and priorities for systemic amyloidosis research and was attended by 13 amyloidosis research experts drawn from both the U.S. and other counties. Dr. Wright subsequently served as primary author of a workshop proceedings summary entitled ***Challenges and Opportunities for Systemic Amyloidosis Research*** which will be published in ***Amyloid***, an international journal focused on protein folding disorders.

The meeting on "Screening and Outcomes in Biliary Atresia," was held in Bethesda, Maryland on September 11 and 12, 2006 cosponsored by the NIDDK, the Health Research Services Administration, the NIH Office of Rare Diseases, the Children's Liver Association for Support Services, and the American Liver Foundation. The purpose of this meeting was to assess current knowledge of the pathogenesis, natural history, surgery and outcomes of biliary atresia in the U.S. and internationally. A major focus of the meeting was to determine the role of newborn screening and means of early detection in biliary atresia, as well as to consider the effectiveness and medical outcomes associated with available screening methods. Participation in this meeting was high and broad, with speakers and attendees including American investigators, some associated with the NIH's Biliary Atresia Research Consortium (BARC); health care providers; and patient advocates, as well as international investigators and practitioners from countries in which pilot or full-scale national screening programs have been implemented to rapidly diagnose and treat infants born with biliary atresia. Discussions addressed such important issues as optimal diagnostic tests and public health approaches to screening for biliary atresia; improving outcomes of treatments such as surgery (the "Kasai procedure") or liver transplantation; and approaches to patients' unique nutritional and developmental needs. The participants' diverse perspectives enabled the experts assembled to determine the current state of knowledge concerning biliary atresia and to reach some conclusions about ways to approach screening and optimize outcomes for affected infants in the U.S. The meeting sponsors and participants plan to work together in order to crystallize discussions at this meeting into recommendations for future research. A summary of the meeting and its recommendations will be submitted for publication, in order to share them with the wider research/health care community.

Activities with Rare Diseases Patient Advocacy Groups

On October 26-27, 2006, NIDDK sponsored an international symposium on **Frontiers in Painful Bladder Syndrome and Interstitial Cystitis.** Meeting cosponsors included the American Urogynecologic Society, Associatiazione Italiana Cisite Interstiziale (Italy), the Comfortable Urology Network (Japan), International Painful Bladder Foundation, Interstitial Cystitis Association of America, Interstitial Cystitis Association Deutschland (Germany), Interstitial Cystitis Association Österreich (Austria).

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

Overview

The National Institute on Drug Abuse (NIDA) provides national leadership on the prevention and treatment of drug addiction by conducting and supporting biomedical and behavioral research, health services research, research training, and health information dissemination. NIDA plans, conducts, fosters, and supports a comprehensive program of research and research training relating to the causes, prevention, treatment, patterns, and consequences of drug abuse and addiction. Research is performed in NIDA's own laboratories and through contracts and grants made to scientific institutions and individuals. Training relevant to fundamental sciences and clinical disciplines of drug addiction is performed via institutional and individual research training awards, and through collaborations with other research institutes and federal health agencies. NIDA collects and disseminates research findings and related educational materials for health professionals, educators, and the public. In addition, NIDA coordinates with institutions, professional associations, and agencies both domestically and abroad that specialize in the treatment and research of drug addiction. Specifically, NIDA coordinates with the Substance Abuse and Mental Health Services Administration (SAMHSA) on services research issues as well as on other programmatic issues.

Size of Drug Addicted Population

In the United States (U.S.), opiates such as heroin and other narcotics are abused by more than 1 million persons, and stimulants such as cocaine and “crack cocaine” by more than 2 million (National Survey on Drug Use and Health, 2004). However, even the lowest estimates from any source put addiction levels for these substances at figures well above the 200,000 threshold generally used for defining orphan diseases. Incidence and prevalence figures for addiction to controlled substances are difficult to estimate, as they vary from type of drug, community, and supply availability (generally a function of supply interdiction/law enforcement). Some addiction indications affect less than 200,000 persons in the U.S. The total cost to society of drug abuse and addiction in the U.S. has been estimated to exceed $500 billion per year (including alcohol and tobacco).

Drug Addiction as an Orphan Disease

Although drug addiction is a serious public health concern, historically, it has been treated as an orphan disease because the pharmaceutical industry rarely profits from marketing drugs for the treatment of addiction, and there is little incentive for pharmaceutical companies to pursue research and development of new treatment medications for this population. Although total numbers of persons afflicted may seem sufficient in the aggregate, unlike other disease states, many of these persons are not treatment-seeking upon diagnosis. Therefore, the actual patient population is less than the total number of persons afflicted. Additionally, many of these persons will be treated in publicly funded clinics where companies perceive reimbursement as modest or inadequate and perhaps subject to artificial cost controls. Finally, much of the U.S. treatment system is based on nonpharmacological treatment modalities.

A further complication is that some treatment agents may themselves be abusable and will be strictly controlled. For example, methadone is classified as a Schedule II controlled substance for use in opiate maintenance therapy. Some 900 U.S. clinics licensed to dispense methadone serve approximately 254,000 persons per year, with a pharmaceutical market value of only about $40 million per year. When compared to other treatment indications, most manufacturers view the drug addiction treatment market as unattractive based on low projected return on investment. Each of these points is well documented in the Institute of Medicine Report on *the Development of Medications for the Treatment of Opiate and Cocaine Addiction, 1995,* and is well known to the pharmaceutical and market research industries. Therefore, while opiate and cocaine addiction do not strictly fit the definition of orphan products, in practice, they certainly are treated as such. An example was the development and approval of levomethadyl acetate hydrochloride (trade name ORLAAM), an alternative to methadone for the treatment of opiate addiction. Despite the facts that human data on 6,000 subjects from government-sponsored studies was available for ORLAAM and the government had a large supply of the compound available for anyone interested in obtaining a New Drug Application (NDA), no private sector entity was interested in completing the development of this compound. Ultimately, NIDA contracted with a company to complete the work. Similarly, the development of the narcotic antagonist naltrexone was largely a NIDA-funded effort. Therefore, these products should be viewed as entirely "orphan-like" insofar as their ability to attract private sector sponsors.

History of NIDA Rare Diseases Research

Currently, there are four medications for the treatment of opiate addiction that have received orphan product designation. These drugs are ORLAAM, naltrexone, buprenorphine, and buprenorphine combined with naloxone. NIDA was substantially involved in the development of these products. ORLAAM received NDA approval in 1993. Naltrexone, an opiate antagonist for use in detoxified patients, was approved in 1985. Currently, orphan exclusivity for ORLAAM and naltrexone has expired. Additionally, ORLAAM's distributor notified physicians that distribution of the product would be discontinued in 2004, due to poor sales in the U.S. and its withdrawal from European markets. ORLAAM's orphan product designation expired in 2000, and thus there is no legal requirement for a manufacturer to maintain the product in the U.S. market.

The opiate partial agonist buprenorphine and a combination of buprenorphine plus naloxone have also received orphan designation (see details below) and were approved for marketing in the U.S. on October 8, 2002. These products represent a major success, as the FDA designated them both as orphan products. Buprenorphine became the first product to receive an orphan designation based on economic rather than population based rationale (i.e., the product would not recoup its developmental expenses in 7 years of exclusivity in the U.S. market).

Recent Scientific Advances in Rare Diseases Research

The discovery of opiate receptors by NIDA-funded scientists in the 1970s opened a new era of neurobiological research that is ongoing. Scientists continue to map brain receptor system types and subtypes, continuously gaining understanding of their structure and function. This information

could help design interventions (behavioral, chemical, and genetic) that could be used to treat brain disorders.

A generation of research has shown that drug addiction is a complex biomedical and behavioral disease that affects parts of the brain that underlie and mediate human emotions. Hence, drug addiction is a brain disease that can and often should be treated with medicine.

Medications reestablish normality to brain function and behavior so that the addicted patient has the *opportunity* for rehabilitation through counseling, psychotherapy, vocational training, and other therapeutic services. While the mechanisms of many central nervous system disorders are still to be elucidated, scientists working in the field of drug abuse have now identified and cloned the putative site of action in the brain for every major drug of abuse. In addition, recent application of microarray technology to characterize drug effects on gene expression has identified intracellular proteins that are altered by drugs of abuse after their initial receptor interactions. Thus, the potential to develop new treatments is enormous.

Rare Diseases Research Initiatives

As described in the history section above, NIDA considers medications for the treatment of drug addiction to be de facto orphans. Thus, the development of medications for the treatment of drug addiction could be considered rare diseases research occurring within the context of an urgent public health need and a wholly inadequate private sector response. Therefore, NIDA's Medications Development Program effort can be considered as part of a rare diseases research initiative.

Functions of the Division of Pharmacotherapies and Medical Consequences of Drug Abuse

In 1990, the Medications Development Division (MDD) was established in NIDA. In 1999, the MDD became the Division of Treatment Research and Development (DTR&D). In 2004, DTR&D became part of the Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA). The functions of MDD within the new division remained the same; namely, DPMCDA conducts studies necessary to identify, develop, and obtain FDA marketing approval for new medications for the treatment of drug addiction and other brain and behavior disorders; develops and administers a national program of basic and clinical pharmacological research designed to develop innovative biological and pharmacological treatment approaches; supports training in fundamental sciences and clinical disciplines related to the pharmacotherapeutic treatment of drug addiction; collaborates with (a) the pharmaceutical and chemical industry in the U.S. and other nations, and (b) other federal medications development programs; (c) academia, and works closely with the FDA to assure that research designed to show the clinical efficacy of new compounds is evaluated and approved expeditiously. In addition, the DPMCDA operates within the larger context of a NIDA-wide Medications Development Program that incorporates basic research discoveries from both the intramural and extramural communities in the quest to develop new pharmacological treatments. This enables DPMCDA to access the latest research findings and test them in controlled clinical settings.

NIDA's current efforts are placing more emphasis on discovery and development of medications for treating cannabis and stimulant addiction, since there are no FDA-approved products for the treatment of these indications. Clinical trials for stimulant dependence primarily test medications marketed for other indications in collaboration with pharmaceutical companies. Efforts are also directed toward supporting, through grants and contracts, synthesis of novel compounds for screening and pharmacological testing.

Significant areas of research and development are summarized below:

1. Opiate Addiction Treatment

Buprenorphine/Buprenorphine-Naloxone Combination: A major milestone and achievement for NIDA's Medications Development Program and for Reckitt Benckiser Pharmaceuticals, Inc. (NIDA's collaborator in a Cooperative Research and Development Agreement) was the October 8, 2002, FDA approval for the marketing of two new products for the treatment of opiate addiction. These two new products, known under the trade names Subutex and Suboxone, represent new tools in the arsenal of anti-addiction medications. Both have been designated as orphans, based on the expectation that these products will not recoup their developmental expense during their period of U.S. marketing exclusivity. Marketing of these products began in January 2003, but is subject to certain restrictions imposed by U.S. law and regulations. Nevertheless, these products may, under the conditions specified in law and regulations, be prescribed in a variety of settings, including physicians' offices. These medications offer additional treatment options to physicians and patients, and should expand treatment availability.

Subutex and Suboxone now join methadone as medications for the treatment of heroin and opiate addiction. Their availability represents the culmination of several years of research and development between NIDA and Reckitt Benckiser Pharmaceuticals, Incorporated. The unique pharmacology of Subutex (buprenorphine) and Suboxone (buprenorphine combined with naloxone) and the statutory changes enacted by the Drug Addiction Treatment Act of 2000, as contained in P.L. 107-273, "The Children's Health Act of 2000," authorizes appropriately trained physicians to prescribe these products in settings other than the existing, but limited, Opiate Treatment Programs (OTPs). In addition to increasing treatment availability across the U.S., these new medications provide another option for patients without access to OTP programs. As of the date of this report, SAMHSA reports that 9,808 physicians have taken the training required by law to prescribe these two medications, and 6,767 have registered as providers.

Depot Naltrexone: Naltrexone, a marketed long-acting, orally effective opioid antagonist, was approved in 1984 for blocking the pharmacological effects of exogenously administered opiates. It is an adjunct to the maintenance of the opioid-free state in detoxified, formerly opioid-addicted individuals.

One of the major obstacles to the success of naltrexone has been patient compliance with therapy. Naltrexone must be taken at least three times per week and has no effect other than to block the effects of heroin. Because of this, many patients forget to take or choose to stop taking their

medication. Therefore, the greatest success with naltrexone has been in a limited population of highly motivated, formerly opiate-addicted patients.

During 1999, NIDA completed, via a Small Business Innovative Research (SBIR) grant to Biotek, Inc., the production and preclinical testing of a batch of 120 doses of a sustained release form (depot) naltrexone. These doses produced a blood level of about 2 ng/ml, which remains relatively constant over a 30-day period when administered subcutaneously in humans. Depot naltrexone, in an inpatient clinical study, blocked the subjective response to 25 mg IV heroin challenges for at least 4 weeks in most subjects. This study was completed in 2000. A two-site outpatient double-blind study was subsequently carried out to test the product in a real-world setting. This outpatient study began in November 2000 and was completed in 2003. The results of the trial, which were reported at a scientific meeting in June 2004 and subsequently published, indicate that the depot preparation has a significant ability to limit relapse to heroin. (Comer et al., 2006)

Additionally, the NIDA Intramural Research Program conducted clinical trials to test another investigational sustained release formulation of naltrexone supplied by Alkermes, Inc. This study provided safety and duration of effect information on this potential treatment product.

The oral form of naltrexone was approved in 1984. Alkermes reports that their dosage form of depot naltrexone reduces heavy drinking behavior in males (but not females). The FDA approved the depot formulation in April 2006. The depot preparation is currently being marketed for the treatment of alcohol dependence.

2. Cocaine Addiction Treatment

Several small studies of potential cocaine addiction treatment agents have been completed and are in various stages of data analysis. Significant findings will be followed up in larger clinical trials as warranted. In addition, NIDA continues to work toward the discovery and development of new molecular entities, such as kappa opioid antagonists, for cocaine addiction treatment.

Ondansetron: A receptor 5HT3 antagonist that can block dopamine release and increase GABA tone and has shown efficacy in reducing cocaine use at a dose of 8 mg/day in a recently completed NIDA study. A follow-up Phase IIb study to explore and confirm the results of the Phase IIa study with two doses of Ondansetron at 8 mg and 16 mg and placebo is being considered.

Modafinil: A nondopaminergic stimulant that has shown reduction in cocaine use in a pilot study (Dackis 2003). A multisite trial for confirmation of efficacy was completed in 2006. Two NIDA grant projects are also pursuing a variation on this protocol independently.

Atomoxetine: A selective norepinephrine reuptake inhibitor approved for ADHD, currently in Phase I trials for safety in cocaine-abusing subjects. A Phase II study in comorbid cocaine subjects with ADHD is planned, pending the outcome of the safety study.

Baclofen: A GABA-B transaminase inhibitor that has been shown in a pilot trial to reduce cocaine use in heavy users. The multisite clinical trial failed to replicate the initial findings.

Disulfiram: Antabuse, marketed as aversive therapy for treating alcoholism; shows promise in the treatment of cocaine addiction.

Three efficacy trials conducted with different populations of cocaine-addicted individuals suggest that disulfiram, in combination with each of three different therapeutic interventions (cognitive behavioral treatment, 12-step facilitation, and clinical management), might be effective in treating cocaine addiction. In cocaine-alcohol abusers, disulfiram treatment showed sustained effect on reduced cocaine and alcohol use 1 year after cessation of the therapy. Disulfiram treatment of cocaine abusing, opioid-addicted patients maintained on methadone resulted in significant decrease of the amount and frequency of cocaine use. A preliminary study showed that disulfiram also decreases cocaine use in cocaine-opioid addicts maintained on buprenorphine.

NIDA is currently sponsoring two large outpatient clinical trials with disulfiram, a treatment for cocaine addiction: (1) a study on 160 opioid-cocaine-addicted patients maintained on methadone, conducted at the University of Arkansas; and (2) a study on 150 opioid-cocaine-addicted patients maintained on buprenorphine, conducted at Yale University.

A study conducted at the University of Pennsylvania evaluating disulfiram and naltrexone alone and in combination treatment of 208 alcohol-cocaine addicted individuals was completed in October 2004. The combination of medications was more likely to be associated with 3 weeks of continuous abstinence than either medication alone or placebo.

Finally, NIDA has completed a Phase I clinical pharmacology/safety study examining the interactions between disulfiram and intravenous administered cocaine. Data analysis is in process.

Topiramate: A small pilot double blind study showed a significant effect for topiramate in reducing cocaine use and decrease craving in a subgroup of patients with mild withdrawal symptoms. Further larger studies are being pursued by the same investigator at the University of Pennsylvania.

Vigabatrin: A GABA transaminase inhibitor that has been shown in animal models to decrease self-administration of cocaine and to block dopamine release following cocaine administration in PET imaging studies. A Phase II trial for cocaine dependence is planned as a proof-of-concept study of Vigabatrin against placebo to assess efficacy in reducing cocaine use.

Talampanel: An AMPA antagonist that blocks stress-induced reinstatement in preclinical studies. This mechanism may make it a candidate for Phase II testing in a relapse prevention paradigm. Prior to the Phase II study, a Phase I cocaine safety interaction study will be conducted.

Dopamine Agonists: The activation of the dopaminergic reward system in the brain appears to be the principal neurochemical mechanism involved in the addiction to stimulants such as cocaine and amphetamine. Chronic abuse of these drugs results in dopamine deficiency in the brain, which has been hypothesized to lead to stimulants craving, depression, anhedonia, and dysphoria.

Most recently, studies in rodents, and to a lesser extent in monkeys, have differentiated the roles of D1 and D3 receptors with regard to cocaine. The D1 system may inhibit the effects of cocaine, while the D3 system may block conditioned cues. Compounds that affect both systems are under study.

Kappa Opioid Antagonists: While the discovery of a selective kappa opioid antagonist for potential use in preventing relapse to opiates has been a goal of NIDA for several years, the recent discovery and evaluation of JDTic – a highly selective kappa antagonist synthesized by a NIDA grantee – has provided a rationale for effectiveness in preventing relapse to cocaine. Interestingly, JDTic has been shown to prevent stress-induced reinstatement of response for cocaine in a rat model of cocaine relapse. The compound is currently undergoing initial preclinical safety testing to determine its development potential as a medication.

Glucocorticoid and Corticotropin Releasing Factor (CRF) Antagonists: Studies have shown that cocaine causes the release of stress hormones known as glucocorticoids in both rats and humans. Evidence from rat studies suggests that glucocorticoid antagonists and CRF antagonists reduce cocaine self-administration in a dose-related manner. NIDA will follow up on these basic research findings with additional studies aimed at developing a potential treatment for cocaine addiction. DPMCDA is attempting to obtain CRF antagonist compounds from pharmaceutical company sources.

Cocaine "Receptor" Imaging Studies: In addition to the categories of compounds being tested as described above, a new imaging technology is being investigated for its value in predicting efficacy of potential cocaine treatment medications. Research in the field of structure-activity relationships has revealed highly selective and potent binding ligands for the dopamine transporter. NIDA intramural researchers have developed three “generations” of such compounds, with each succeeding generation being more selective and potent than the previous one. RTI-55, the first potent compound, was shown to be an effective in vivo labeling agent in animal studies and was subsequently examined in human imaging studies by SPECT. A second compound, RTI-121, was found to be more selective for the dopamine transporter but had a higher apparent lipid solubility and exhibited a lower specific-to-nonspecific binding in vivo. NIDA researchers are testing new compounds and are also utilizing some older compounds (e.g., WIN-35,428) in brain imaging studies. Procedures have been developed for estimating the occupancy of transporter sites in vivo. Dopamine transporter imaging studies of cocaine abusers have been completed. This technology may make it possible to estimate the effectiveness of a potential treatment compound or regimen by correlating receptor occupancy (as shown in imaging studies) with actual clinical results. NIDA will continue to follow this line of research.

Additionally, NIDA is participating in an effort with NIMH, NINDS, and NIAAA to develop appropriate imaging ligands to significantly advance the study of many brain and CNS conditions, as well as the effects of various treatments.

Immunology: DPMCDA presently supports an immunotherapy program for the treatment and prevention of drug abuse. This program has led to the clinical development of vaccines for cocaine and nicotine addiction. Although these vaccines are being developed as therapeutic

vaccines, their potential as prophylactic vaccines could be explored once efficacy is established in patient populations. This program has also led to the preclinical development of monoclonal antibodies, which have been designed to rapidly reverse the effects of methamphetamine, MDMA, and phencyclidine overdose. If successful in humans, monoclonal antibody treatment will not only provide a rapid reversal of drug effects in an emergency room setting, but could also reduce or prevent the long-term medical problems (neurotoxicity and addiction) associated with stimulant drugs of abuse.

Cocaine Vaccine: There is presently no established pharmacotherapy for cocaine abuse, but active immunotherapy with a cocaine vaccine has potential as a therapeutic intervention. The cocaine vaccine TA-CD (owned by Celtic Pharma/Xenova) was developed through a NIDA-funded grant. Evaluation of safety, efficacy, and immunogenicity of the vaccine at Yale University in an open-label, 14-week dose-escalation study in 18-cocaine dependent subjects showed that the vaccine was well tolerated, that subjects reported attenuation of cocaine's euphoric effects, and that cocaine specific antibodies persisted at least 6 months (Martell BA, et al., 2005). Dr. Tom Kosten at Yale University presently has completed the Phase II efficacy testing of the vaccine in 132 methadone-maintained cocaine abusing subjects.

Treatment of PCP Abuse and Overdose: NIDA has been funding a project, currently in its 12th year, to Dr. Michael Owens at the University of Arkansas to develop a new generation of monoclonal antibody-based medications for treating PCP overdose. These medications function as pharmacokinetic antagonists, and are designed to provide a rapid reversal of drug effects in an emergency room setting, as well as reduce or prevent the long-term medical problems associated with their use. In rats, a single dose of a mouse anti-PCP mAb reduced the locomotor effects and brain concentrations of PCP in overdose studies (Hardin JS, et al., 2002). The antibody has also proven effective in preventing the adverse health effects of PCP in rats in chronic dosing studies (Laurenzana EM, et al., 2003). A chimeric (mouse/human) form of the mAb has been reported (Lacy and Owens, in press).

NIDA is funding a Phase I study of an STTR Fast Track grant to Inflexion Therapeutics (in collaboration with Dr. Owens) for the large-scale agricultural production of the chimeric anti-PCP monoclonal antibody in tobacco plants, as well as the advanced preclinical development needed for Investigational New Drug filing (IND). If the IND is approved, a Phase II collaboration with Dr. Tom Kosten is planned to test the effects of the PCP antibody in PCP users in outpatient treatment. Thus, the initial efficacy testing will be done on outpatients before possible testing of PCP overdose in emergency room settings.

Treatment of Methamphetamine Abuse and Overdose: NIDA is presently funding research by Dr. Michael Owens for the development of a new generation of monoclonal antibody-based medications for treating the abuse and overdose of methamphetamine, amphetamine, and ecstasy (MDMA). These medications would function as pharmacokinetic antagonists, and are designed to provide a rapid reversal of drug effects in an emergency room setting, as well as reduce or prevent the long-term medical problems associated with their use. The components of the project are focused on the production of highly selective and potent fully human anti-methamphetamine, anti-amphetamine, and anti-MDMA monoclonal antibodies; behavioral pharmacology studies to test

the effectiveness of the medications in reducing the addictive properties of these drugs in animal models; pharmacokinetic and pharmacodynamic studies for evaluating the fundamental medical consequences of rapid input of these drugs into the central nervous system and the protective effects of these medications in overdose situations; and the large-scale production of these antibodies in tobacco plants. The team has been successful in producing fully human anti-methamphetamine and anti-amphetamine monoclonal antibodies that block self-administration (in rats) of methamphetamine and amphetamine, respectively, at specific dose levels (Byrnes-Blake KA, et al., 2003). They have also assessed the dose levels that are necessary to reverse drug effects in animal models, and have made advances in developing the technology for large-scale production of monoclonal antibodies in plants. This technical innovation makes the monoclonal antibody approach commercially feasible.

3. Methamphetamine Addiction Treatment

Methamphetamine is a potent psychomotor stimulant that has gone through episodic periods of widespread use and abuse in the U.S. Cocaine abuse and addiction surpassed use of methamphetamine in the 1970s and 1980s, but methamphetamine abuse and addiction has been re-appearing in many regions of the U.S. and is widespread in western U.S. cities such as San Francisco, San Diego, Los Angeles, Denver, and Phoenix. According to the 2005 National Survey on Drug Use and Health, approximately 12 million persons (aged 12 and older) had used methamphetamine at least once in their lifetimes, 1.4 million had used it in the past year, and 600,000 had used it in the past month.

There are no accepted treatment medications for methamphetamine addiction or abuse. As a result, NIDA has developed a Medications Discovery Program for methamphetamine and is funding a number of extramural and intramural studies to develop medications to treat methamphetamine abuse.

Ondansetron: There is evidence that selective serotonin 5-HT_3 receptor antagonists attenuate behavioral responses to d-amphetamine and methamphetamine, suggesting that 5-HT_3 receptors modulate brain dopamine in animals. This action of 5-HT_3 receptor antagonists may therefore reduce the rewarding effects of abused substances. Ondansetron is a selective 5-HT_3 receptor antagonist that decreases stimulated dopamine release and has been shown to reduce the development of behavioral tolerance and sensitization to cocaine following a period of acute and chronic withdrawal. Furthermore, suggestions that 5-HT_3 antagonists may also reduce discomfort or post-cessation anxiety following psychostimulant withdrawal prompted NIDA to test whether Ondansetron might have these effects following cocaine use cessation. NIDA, through a Methamphetamine Clinical Trials Group (MCTG) established with UCLA, conducted a Phase II double-blind, placebo-controlled, dose-response trial with Ondansetron. The study, completed in 2003, showed no significant effects for any Ondansetron dose compared to placebo. No further development is planned for this indication for Ondansetron.

Aripiprazole: This is an atypical neuroleptic drug that has been approved by the FDA to treat schizophrenia and bipolar mania. It is a functional antagonist at the dopamine D_2 receptor level in a hyperdopaminergic environment, a functional agonist at the same level in a hypodopaminergic

environment, a serotonin antagonist with serotonin 5-HT_{2A} receptors, and a partial agonist with serotonin 5-HT_{1A} receptors. It has moderate affinity for $alpha_1$-adrenergic and histamine (H_1) receptors. Long-term methamphetamine abuse results in schizophrenia-like symptoms. By extension, aripiprazole may have potential as a methamphetamine abuse therapeutic. NIDA has recently completed a Phase I safety interaction study with aripiprazole and methamphetamine and data analysis is under way.

Lobeline: This medication is a derivative from Indian tobacco plants. Because it stimulates a subclass of nicotine receptors, it was tested in the clinic for its potential as a smoking cessation therapeutic. Additionally, lobeline redistributes dopamine in nerve terminals by preventing dopamine uptake into synaptic vesicles without inhibiting MAO-B. In contrast, methamphetamine enters synaptic vesicles and inhibits MAO-B. Studies in rats revealed that lobeline decreases methamphetamine self-administration without affecting the rats' ability to self-administer sugar water. These data suggest that lobeline may reduce the acute rewarding effects of methamphetamine and its corresponding abuse liability. NIDA is collaborating with a pharmaceutical company and has completed Phase 1 single dose and multiple dose studies. Planning for a Phase 1 interaction study with lobeline and methamphetamine is under way.

Bupropion: This medication has been approved to treat depression and promote smoking cessation. It is a dopamine uptake inhibitor that is well-tolerated and has a good safety record. NIDA is testing bupropion for its ability to alleviate the dysphoria seen in early abstinence and reduce methamphetamine craving and relapse to drug using. A Phase II, double-blind, placebo-controlled study with bupropion is now complete. Analysis of the primary outcome showed a trend for significance ($p=0.09$) for the total sample ($n=150$ patients). However, when the group was split according to baseline use into high and low/moderate users, bupropion was significantly efficacious in reducing methamphetamine use for the low/moderate users ($p=0.03$). No effect was seen for the high users. A follow-up Phase II study is under consideration to examine bupropion's efficacy in the low/moderate use population.

Modafinil: This is a nondopaminergic stimulant used to treat narcolepsy through modulation of the glutamate/GABA system. Recently, it has been shown that modafinil blunts cocaine euphoria under controlled conditions and improves clinical outcomes in cocaine-addicted patients receiving standardized psychosocial treatment. Because methamphetamine is a stimulant like cocaine, NIDA is endeavoring to evaluate modafinil's potential as a methamphetamine abuse therapeutic. NIDA completed a Phase I safety trial, as requested by FDA, prior to conducting a Phase II trial which is projected to start in May 2007.

Topiramate: This medication is a fructopyranose derivative approved for treating seizure disorders. In a clinical trial, it was found to be superior to placebo in improving drinking outcomes in alcohol-addicted individuals. Data from a pilot proof of concept study suggest that topiramate may be a useful medication for preventing relapse to cocaine use. Shared stimulant properties of cocaine and methamphetamine may mean that topiramate could also help prevent relapse to methamphetamine use. To that end, NIDA provided grant support to conduct a Phase I safety interaction study between topiramate and methamphetamine. This study was completed with no safety concerns. NIDA, in collaboration with OrthoMcNeil pharmaceuticals, launched a

Phase II outpatient study testing topiramate for the potential treatment of methamphetamine dependence in 2006.

4. Medications Development for Cannabis-Related Disorders

The treatment of cannabis-related disorders (CRDs) is an issue of great public health concern. Currently, marijuana is the most commonly used illicit drug in the U.S., recent estimates from SAMHSA reporting 14.6 million past-month users. In 2004, marijuana was used by 76.4 percent of current illicit drug users. An estimated 56.8 percent of current illicit drug users used only marijuana, and 19.7 percent used marijuana and another illicit drug. Among persons aged 12 or older, the overall rate of past-month marijuana use was about the same in 2004 (6.1 percent) as it was in 2003 (6.2 percent) and 2002 (6.2 percent). In 2004, 3.2 million persons were using marijuana on a daily or almost daily basis over a 12-month period, similar to the estimates in 2002 and 2003.

Sufficient research has been carried out to confirm that the use of cannabis can produce serious physical and psychological consequences. The consequences of cannabis use may be due to the acute effects of the drug or to the chronic exposure that may ultimately produce addiction. The use of a large amount in a short period of time may induce hallucinations, delirium, and other perceptual manifestations similar to a psychotic episode. Chronic users of cannabis may experience difficulty in stopping or controlling drug use, develop tolerance to its subjective and cardiovascular effects, and eventually present withdrawal symptoms after sudden discontinuation of use.

Unfortunately, there is currently no effective pharmacological treatment for CRDs and limited research focused on identifying and developing medications to treat these disorders. Several factors support the timeliness of an accelerated program to develop medications to treat CRDs. First, newly marketed medications are available whose mechanisms of action may have potential therapeutic effects on the clinical manifestations of CRDs. Second is the recent discovery of an endogenous cannabinoid system with specific receptors and endogenous ligands. Third, the availability of genetically engineered knockout mice that lack functional cannabinoid receptors make it possible to study genetic predispositions to the effects of cannabinoids. Fourth, the subsequent development of reliable preclinical models to study the rewarding and addiction-producing effects of THC, combined with the preceding, enable understanding of basic therapeutic mechanisms. Finally, the discovery and development of new chemical entities—some of them already being investigated at the clinical level—target the cannabinoid system and have beneficial therapeutic potential. All of these factors are setting the stage for the development of medications to treat CRDs.

a. New Research Projects for Medications Development for Cannabis-Related Disorders

Based on the needs described above, NIDA funded several new research grants through RFAs, the goal of which was the development of safe and effective medications for the treatment of CRDs. Preclinical and clinical studies are focusing on the treatment of marijuana, hashish, or other cannabis derivatives use disorders. Medications studied under this RFA are aiming to treat CRDs,

such as abuse and addiction, intoxication, delirium, psychosis, and anxiety. They are also focusing on the specific symptoms of the disorder, such as withdrawal, craving or relapse, complications, (e.g., cognitive impairment), sleep disorders/disruption of normal rhythms, or the clinical surrogates of use, such as depression and other mood disorders.

The rationale for choosing the medication(s) to be investigated is based on a top-down approach, a bottom-up approach, or both approaches combined. The top-down approach tests marketed medications available for other indications that may also be promising candidates for the treatment of CRDs. The bottom-up approach involves the identification and testing of new chemical entities that, because of their chemical characteristics and mechanisms of action, are being developed specifically for CRDs.

NIDA is currently funding research to evaluate the safety and efficacy of cannabinoid antagonists, anticonvulsants (valproic acid), antidepressants (e.g., fluoxetine, bupropion, selegiline), and antipsychotic medications (e.g., clozapine, olanzapine) for the treatment of cannabis dependence.

5. Consequences of Drug Addiction

As a result of the reorganization that created DPMCDA, the program of research on medical consequences of drug abuse and co-occurring infections now resides within this division. As described below, these studies involve marketed medications and would not typically be performed by the public sector. Under this program, the supported studies may be categorized into four major programs of research that are in various stages of development and progress:

1. Metabolic and endocrine disorders of HIV/AIDS and drug abuse;
2. Pharmacokinetic/pharmacodynamic drug-drug interactions between medications used in the treatment of drug addiction (e.g., methadone, newly FDA-approved buprenorphine), Infections (e.g., HIV, HCV, TB), and mental health disorders;
3. Medical and health consequences of chronic use/abuse of licit and illicit drugs of abuse and co-occurring infections (e.g., HIV, HCV, TB, STDs); and
4. Oro-maxillary complications (e.g., facial and dental injuries) associated with drug abuse and co-occurring infections.

New avenues of research are planned that fit within these major themes:

- Metabolic and endocrine disorders of HIV/AIDS among drug abusers;
- Directly observed therapy (DOT) (a technique used to treat HIV-infected drug abusers, which requires a staff person observing the patient to ensure that the entire course of medication is taken in the correct dose, at the correct time and for the complete period);
- Hepatitis C;
- Issues in the medical management of HIV/HCV coinfections among drug abusers;
- Mini-symposium on TB among drug abusers; and
- Role of hormones and nutrition in drug abusers coinfected with HIV and HCV.

Injection drug use and sexual contact among users is a highly correlated vector in the spread of HIV, hepatitis, and tuberculosis, creating a public health problem of enormous magnitude. Medical consequences may range from drug addiction-based brain disease to effects on almost every organ system, including the central and peripheral nervous, cardiovascular, endocrine/hormonal, pulmonary/respiratory, renal, hepatic/metabolic, reproductive, immune, and other systems. For example, stimulants such as cocaine and methamphetamine increase the heart rate while constricting the blood vessels; in susceptible individuals, these two actions together set the stage for cardiac arrhythmias and strokes. Cocaine use decreases blood flow to the brain, increases heart rate, and elevates blood components that promote clotting effects, which can lead to stroke or heart attack even in those not otherwise at risk for these serious cardiovascular events. NIDA-funded research also shows that chronic cocaine use is associated with left ventricular dysfunction and increased calcium deposits in the coronaries of HIV-infected African-Americans, and that its use may also facilitate the entry of HIV into brain cells, leading to cognitive and memory impairment. The club drug methylene-dioxy-methamphetamine (MDMA), also known as "ecstasy," which many users mistakenly believe to be safe, has caused on rare occasions malignant hyperthermia, permanent kidney damage, and death. MDMA also damages serotonin nerve fibers in the brain. Heroin can cause a life-threatening kidney condition called focal glomerulosclerosis and PCP (phencyclidine) decreases heart rate and blood pressure, triggers violent aggression, and may cause muscle contractions strong enough to break a bone. Marijuana, often perceived by many as innocuous, is also associated with consequences ranging from memory to cognitive and motor problems in youths and adults (Khalsa, et al., 2002).

Injecting drug use further promotes blood clots, severe skin infections, and blood-borne infections, including life-threatening endocarditis, viral hepatitis, and HIV/AIDS. Abuse of some drugs is associated with impulsive sexual activity that elevates individuals' risks for acquiring and transmitting HIV/AIDS and other STDs.

In a relatively new area of research at NIDA, data show that nutrition may play an important role in HIV disease progression. Preliminary research shows that drug abusers with inadequate nutrition, particularly those with sub-optimal levels of anti-oxidant micronutrients like selenium and zinc, are at high risk of mortality if they are coinfected with HIV/AIDS. Clinical trials are under way to determine if supplementing with selenium, zinc, and other anti-oxidant micronutrients would slow the progression of HIV/AIDS. This research would have worldwide implications, such that people in underdeveloped countries who cannot afford expensive antiretroviral therapy would benefit from an inexpensive treatment modality to slow disease progression and improve quality of life.

Research also shows that HCV is another blood-borne pathogen easily transmitted through contaminated drug injection paraphernalia. Furthermore, both viruses—HCV and HIV—frequently coexist because of common routes of transmission. Liver injury seems to occur in HIV/HCV coinfection through the induction of a novel signaling pathway that is cooperatively activated by specialized protein molecules known as HCV E2 and HIV gp120, providing a rationale for therapeutic interventions. NIDA continues to support a wide spectrum of research on epidemiology, natural history, underlying pathogenesis, prevention, and treatment of HIV/HCV coinfections among drug abusers.

6. Drug-Drug Interactions

Research shows that some illicit drugs and drug abuse medications can interact with medications used for treating other diseases, resulting in possible adverse effects and loss of efficacy. For example, an interaction can occur between methadone and the protease-inhibiting drugs that are currently the most effective treatments for HIV infection. This interaction can make the treatment ineffective and increase the toxic side effects from one or both drugs. In some cases, the presence of a protease inhibitor increases the metabolism (processing) of methadone sufficiently to cause patients to go into withdrawal. The most current research shows that interaction between a protease inhibitor and the newly approved addiction treatment medication buprenorphine does not result in withdrawal, allowing clinicians to use buprenorphine for the treatment of drug addicts coinfected with HIV. Identifying such interactions and developing alternative regimens remain high NIDA priorities under a new program of Research on Drug-Drug Interactions within the Branch of Medical Consequences of Drug Abuse and Co-occurring Infections.

Due to the lack of pharmaceutical industry interest in developing new medications to treat addiction to controlled substances, NIDA has been substantially involved in the development of nearly all such medications since the Institute's inception in 1974. NIDA works with several government agencies, pharmaceutical companies, and academic institutions to develop pharmacological treatments for the treatment of drug addiction. Historically, drug addiction has been treated as an orphan disease because the pharmaceutical industry rarely profits from marketing drugs for the treatment of drug addiction, and little or no incentive exists for pharmaceutical companies to pursue research and development of new treatment medications for this population (currently, there are four medications for the treatment of opiate addiction have received orphan product designation—ORLAAM, naltrexone, buprenorphine, and buprenorphine combined with naloxone).

Since there are no FDA-approved products for the treatment of cannabis and stimulant dependence, NIDA's efforts are currently shifting toward a greater emphasis on discovery and development of medications for these disorders. Clinical trials for stimulant dependence have primarily tested marketed medications as part of attempts to collaborate with pharmaceutical companies. Efforts are also directed toward supporting, through grants and contracts, the synthesis of novel compounds for screening and pharmacological testing. NIDA is currently sponsoring several clinical trials for the treatment of cocaine, methamphetamine, and nicotine dependence, and NIDA continues to progress research and development in an area that has truly been treated as an orphan disease.

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NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)

Overview

NIEHS supports research into the fundamental mechanisms of how environmental exposures interact with the human body to produce disease and dysfunction. This research on molecular pathways and environmental interaction has also yielded insights into the basic mechanisms involved in the pathogenesis of rare diseases and conditions. Diseases for which this research has yielded important clues in 2006 include autoimmune diseases, mitochondrial diseases, Amyotrophic Lateral Sclerosis (ALS), and birth defects.

Recent Scientific Advances in Rare Diseases Research

Autoimmune Diseases

Myositis

Autoimmune diseases are an increasingly frequent group of disorders that disproportionately affect women and minorities and are thought to be the result of environmental exposures in genetically susceptible individuals. A group of poorly-understood, life-threatening autoimmune muscle diseases called the myositis syndromes are defined by chronic muscle inflammation and weakness associated with specific autoantibodies. There appear to be many different types of these muscle diseases based on the particular problems and the specific autoantibodies that persons develop. Investigators at NIEHS asked whether these different types of myositis were the result of different genetics and if some genes could increase risk while others might actually decrease risk for the development of disease. By performing careful molecular genetic investigations on the largest population of myositis patients ever studied along with a large number of normal controls, researchers showed that although some genes that regulate the immune system are risk factors for all types of myositis, other immune-modifying genes are risk factors for only certain forms. Additionally, in some of the subgroups, selected immune genes appear to protect persons from the development of myositis. Caucasian and African-American myositis patients also differ in their risk and protective genes. Taken together with information from other studies, these findings suggest that genes regulating the immune system are important in the development of myositis and that different combinations of risk and protective genes, along with particular environmental exposures, result in the wide variety of disorders known as the myositis syndromes. These findings may have important diagnostic implications and could allow for a better understanding of the mechanisms that lead to chronic autoimmune-mediated muscle destruction. Additional studies to define the responsible environmental exposures in genetically-defined subgroups are under way.

Autoimmune Toxicity of Chlorinated Compounds

Autoimmune disorders effect upwards of 10 million Americans, and it is clear that for most of these disorders both genetic and environmental factors contribute to the development and progression of disease. NIEHS supported researchers have shown that three chlorinated pesticides have estrogenic effects in vivo—o,p'-DDT, chlordecone, and methoxychlor—and that these

significantly accelerate the development of autoimmune disease in lupus model mice. The hypothesis that the development and progression of autoimmune disease is due to estrogen activity is also being tested in mice. Additional experiments were conducted to test the hypothesis that chlordecone might influence autoimmunity by affecting B- and T-cell programmed cell death (apoptosis). After six weeks of treatment, both chlordecone and estradiol seemed to reduce the percentage of apoptic B cell populations compared to the control group, while there was little effect on the apoptic T cell populations. The delayed apoptosis of B cells might partially explain why both chlordecone and estrogen increase titers of antibody to double-stranded DNA, which correlates with development of the lupus-like syndrome in mice.

Mitochondrial Diseases

Progressive external ophthalmoplegia

Progressive external ophthalmoplegia (PEO) is a disease characterized by late onset (between 18 and 40 years of age) bilateral ptosis and progressive weakening of the external eye muscle, resulting in blepharoptosis and ophthalmoparesis, proximal muscle weakness and wasting as well as exercise intolerance. The disease is often accompanied by cataract, hypogonadism, dysphagia, hearing loss and may, within several years, lead to development of neuromuscular problems. Neurological problems may include depression or avoidant personality. Skeletal muscles of PEO patients present red ragged fibers and lowered activity of respiratory chain enzymes. PEO is a mitochondrial disorder associated with mitochondrial DNA (mtDNA) deletions and point mutations. The disorder can be inherited in an autosomal dominant or recessive manner. NIEHS investigators identified a new genetic locus in progressive external ophthalmoplegia and biochemically characterized the defect. They found that a heterozygous dominant mutation in POLG2, the gene encoding the p55 accessory subunit of polymerase gamma, causes PEO with multiple mtDNA deletions and cytochrome c oxidase (COX)–deficient muscle fibers. Biochemical characterization of the purified, recombinant mutant protein in vitro revealed incomplete stimulation of the catalytic subunit due to compromised subunit interaction. In vivo, the disease most likely arises through haplotype insufficiency or heterodimerization of the mutated and wild-type proteins, which promote mtDNA deletions by stalling the DNA replication fork. The progressive accumulation of mtDNA deletions causes COX deficiency in muscle fibers and results in the clinical phenotype. This study enhances our understanding of causes of this disease.

Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) is a rare motor disorder characterized by degeneration primarily of motor neurons, atrophy and paralysis of skeletal muscles, and rapid progression to death. The mechanism underlying ALS remains poorly understood although in recent years transgenic animal models for SOD1-induced ALS have played a significant role in advancing the understanding and treatment of ALS. One NIEHS grantee has generated transgenic flies that show many features associated with ALS in humans. Researchers want to establish a fruit fly model for ALS that can be used to screen for potential drugs and environmental factors. Also, NIEHS supports research using a transgenic mouse line, testing the hypothesis that exposure of neurons to methylmercury (MeHg) predisposes them to excitotoxic damage. Another NIEHS-supported study investigates the role that mutation in SOD1 plays in the development of ALS and

shows that there is decreased stability, decreased binding of zinc or copper, gain of a deleterious oxidative activity, binding of heat shock proteins, and aggregation likely resulting in oxidative stress. These researchers have developed manganese porphyrin derivatives that dramatically delayed paralysis and death. Gene-environment interactions are being studied in clusters of high-risk clusters in the Western Pacific Islands, as well as the increased incidence of the disease that has been reported in deployed compared to nondeployed Gulf War veterans. Another NIEHS-supported study is collecting data on ALS Registry patients and controls to ascertain genetic and environmental effects on disease progression. Two other studies are looking for biomarkers of ALS in cerebral spinal fluid using proteomics and in plasma using metabolomics that will facilitate identifying the pathogenesis and diagnosis of the disease and potentially serve as surrogate markers in ALS therapeutic trials.

Birth Defects

Sensitive Genotypes to Arsenic as a Model Environmental Teratogen

A NIEHS-supported project explores the genetic basis of sensitivity to environmentally induced birth defects. There is now a growing and compelling experimental body of evidence that *in utero* exposure to inorganic arsenic disrupts normal embryonic development resulting in significant congenital anomalies, including neural tube defects (NTDs) and craniofacial malformations, and that folate supplements in the prospective mother before conception reduces the risk for NTDs and cleft lip and palate. This research attempts to enhance understanding underlying genetic and environmental interactions. In support of the genetic microarray analyses of neuroepithelial and neural crest cells obtained from the developing neural tube and craniofacial tissues, the investigators are applying an intensive bioinformatics analysis of the expression profiles in these model systems, to enable them to track the molecular fingerprint of neural tube and craniofacial development, and learn how folate regulates these events. They are also examining epigenetic factors that are compromised by teratogen exposure in these same model systems.

The scope of the studies is such that the investigators are obtaining a comprehensive understanding of genetic and epigenetic factors that regulate sensitivity to environmentally-induced birth defects.

Conferences

Chemically Induced Congenital Anomalies: Is Oxidative Stress a Common Pathway? Cosponsored by the NIH Office of Rare Diseases, was held June 28, 2006 in conjunction with the 46th Annual Meeting of the Teratology Society, in Tucson, Arizona.

The Symposium identified critical common molecular pathways that were modified by chemical teratogens and that could lead to chemically-disrupted developmental outcomes. This symposium included a detailed discussion of these response pathways as potential underlying mechanisms for developmental disorders and highlighted their relevance to teratogenesis. Emphasis was placed upon the integration of research findings from embryo culture and animal studies. The major topics included in this symposium were (1) how xenobiotics, including therapeutic drugs, social drugs like alcohol, and environmental chemicals can enhance oxidative stress and the formation of

embryopathic reactive oxygen species (ROS), (2) how similar ROS-related embryopathic processes can occur in diseases like diabetes, and (3) how ROS may exert their embryopathic effects via oxidative damage to cellular macromolecules or via altered signal transduction.

Environmental Mutagen Society 37th Annual Meeting, Rare Diseases Resulting from DNA Repair Defects Symposium: The Symposium was offered at the annual meeting September 16-20, 2006, in Vancouver, British Columbia, Canada, and included presentations on molecular mechanisms of neurological disease in hereditary DNA repair disorders; xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy; and catalytic properties of tryosyl DNA phosphodiesterase, the protein mutated in spinocerebellar ataxia with neuropathy. Presentations also offered were: BRCA1-Associated Helicase BACH1 is Critical for Homologous Recombination and Appears to be the Faconi Anemia Gene Product FANCJ, and DNA Repair Activities of the Mre11/Rad50/Nbs1 Complex: Implications for Ataxia Telangiectasia-Like Disorder and Nijmegen Breakage Syndrome.

7th International Conference on Lactoferrin: Structure, Function and Applications: The Conference at Waikiki Beach, Hawaii, October 16-19, 2005, reviewed the state-of-the-science and prioritized future objectives with regard to production and characterization of lactoferrin for use in mechanistic and efficiency studies; the structure function relationships of lactoferrin with regard to the transferring family and its role in regulation of iron homeostasis; physiological and environmental factors regulating the expression of the lactoferrin gene; molecular mechanisms of interaction of lactoferrin with both bacteria and mammalian cells; antibacterial and antiviral activities of lactorferrin; and the role and molecular mechanisms of growth inhibition of tumor cells by lactoferrin.

Future conferences

Ion Channel Regulation, a FASEB Summer 2007 Conference: This Conference in Snowmass Village, Snowmass, CO, June 9-14, will be the third biennial FASEB summer conference on Ion Channel Regulation, unique in focusing on signaling in ion channel function and dysfunction. The conference will highlight significant recent developments in the field and highlight the multidisciplinary and integrated approaches currently used to study ion channel function.

Mitochondrial Medicine 2007: An international symposium presented by the United Mitochondrial Disease Foundation, San Diego, California, June 13-17, 2007. Subjects will include mitochondrial mechanisms and disease; the role of mitochondria in diseases of aging; current options for treatment; and future treatment prospects. Potential cosponsors include NIA, Edith Trees Foundation, Tischon, Blessings Fund, Mitochondrial Research Guild, and Freedom Fund.

Genetic and Environmental Risk Factors for Major Birth Defects: Genetic and environmental risk factors may play a role in such rare diseases as renal agenesis, polydactyly, hypospadias, Townes-Brocks syndrome (imperforate anus, triphalangeal and supernumerary thumbs, dysplastic ears, and sensorineural hearing loss) due to mutations in the SALL1 gene. This conference in Pittsburgh, Pennsylvania, June 27, 2007, will use these disorders to illustrate ways in which the environment can interact with genetic endowment to produce rare but important malformations.

The symposium will present the epidemiologic and clinical features of the disorders and the underlying molecular mechanisms of the gene-environment interaction.

NATIONAL EYE INSTITUTE (NEI)

Overview

The National Eye Institute was created on August 16, 1968, by Public Law 90-489 for the purpose of supporting and conducting research for improving the prevention, diagnosis, and treatment of diseases that affect the eye and vision. Eye diseases and blindness cost the Nation an estimated $38.4 billion per year. More than 12 million people in the United States suffer some significant impairment of vision. Over the years, vision researchers supported by the NEI have conducted many pioneering studies that have greatly advanced our understanding of eye diseases, including those classified as rare, and provided eye care professionals with new tools and methods to prevent or cure many sight-threatening conditions. In October of 2003, the NEI released its strategic plan for vision research National Plan for Eye and Vision Research. This plan is the seventh in the series that dates back to the publication of Vision Research Program Planning in 1975. The development and publication of the aforementioned plans address the visual health needs, including rare diseases of the eye and visual pathways, of the Nation.

Recent Scientific Advances in Rare Disease Research

Retinitis pigmentosa and related disorders

Retinitis pigmentosa (RP) is a group of blinding hereditary retinal degenerative diseases that are characterized by a progressive loss of vision due to the degeneration of photoreceptor cells. RP patients frequently report night blindness and loss of mid-peripheral vision during adolescence, and are usually legally blind by the age of 40. Photoreceptor cells of the retina (the rods and cones) are responsible for the capture of light and the initiation of an electrical signal to the brain in the process of vision. The study of signaling in photoreceptor cells, termed the visual phototransduction cascade, has provided a detailed molecular description of this pathway.

Neurotrophic Therapy: Neurotrophic factors are naturally occurring proteins that have shown promise in slowing the progression of neurodegenerative diseases. Animal model studies have found that ciliary neurotrophic factor (CNTF) can slow the progression of RP. Although CNTF is a potential therapeutic candidate, translational efforts to begin clinical trials have been hampered by the lack of a drug delivery vehicle that can chronically administer this agent to the retina. To overcome this hurdle, the NEI is evaluating a novel drug delivery device called Encapsulated Cell Technology (ECT). The implantable device contains cells transfected with the gene encoding CNTF in a semi-permeable membrane that allows the protein to diffuse out to the retina. Results from an NEI-sponsored phase I clinical trial published in 2006 found that the implantable device was safe and well-tolerated. Ten participants received CNTF implants in one eye. When the implants were removed after 6 months, they still contained viable cells with minimal cell loss and produced CNTF at levels previously shown to be therapeutic in animal model studies. With safety now established, the therapeutic value of this highly novel approach to delivering therapeutic proteins to the retina will be further evaluated in phase II clinical trials.

Gene Transfer Therapy: NEI-supported researchers have been evaluating a promising gene therapy treatment that has restored vision in dogs with a retinal disease similar to a human disease known as Leber congenital amaurosis (LCA). Children with LCA are born with severe visual impairment that often leads to complete blindness at an early age. A gene causing LCA, named RPE65, was identified by NEI researchers in 1997. That same year, mutations in the RPE65 gene were also identified as the cause of retinal disease in Briard dogs. Leveraging these findings, researchers developed a gene transfer therapy to provide a functional copy of the RPE 65 gene. Almost all treated dogs have retained their vision, making this a candidate treatment for clinical trial evaluation. To gain regulatory approval, NEI-sponsored investigators conducted a series of studies to test for the presence of the viral vector used to transfer the RPE65 gene in tissues and organs of treated Briard dogs. The safety studies revealed no presence of the vector in the optic nerve or visual processing centers of the brain. These results suggest that the vector stays safely confined to the targeted retinal tissue and does not travel to the brain. This study was an important step in gaining final regulatory approval to begin a phase I clinical trial slated for early 2007.

Autoimmune diseases

Sjögren's syndrome is a rare autoimmune disease that attacks moisture producing glands in the body. Sjögren's syndrome limits the production of saliva in the mouth and tear film in the eye. It can also affect skin, joints, lungs, kidneys, blood vessels, digestive organs, and nerves. Symptoms can include dry skin, joint and muscle pain, pneumonia, vaginal dryness, and fatigue. The syndrome mostly affects women over age 40.

Sjögren's syndrome Conference: In fiscal year 2006, NEI cofunded a conference grant to support an international symposium entitled "The IXth International Symposium on Sjögren's Syndrome." The symposium, held in Washington, D.C. on April 27-29, 2006, is the pre-eminent research meeting on Sjögren's syndrome and brings together a distinguished group of international authorities. The symposium represents a unique opportunity for interactions between groups that typically do not meet scientifically and fosters cross-cutting collaborations.

Sjögren's syndrome Research Registry: In addition, NEI continues to support the International Research Registry Network for Sjögren's Syndrome. The registry has the goal of promoting cutting-edge research in the area of Sjögren's syndrome with emphasis on diagnosis, epidemiology, causes, prevention and treatment.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES (NIGMS)

Overview

The National Institute of General Medical Sciences (NIGMS) supports broad-based fundamental research that is targeted toward understanding the general biological mechanisms that operate in the functioning of all biological system rather than being relevant to any specific organ system or disease. Examples include basic studies on the structure and function of organelles and membranes at the cellular and molecular level; investigations into the replication, organization, and function of the genome in organisms ranging from bacteria to man; development of improved instrumentation and technology for the investigation of biological problems; studies on bio-related organic chemistry for the elucidation of biosynthetic pathways and the development of new synthetic strategies for molecules of biological interest; and investigations of pharmacologic mechanisms at the molecular level. In general, investigations related to specific diseases are supported only if the mechanisms under investigation are widely applicable across disease or organ system lines.

Human Genetic Cell Repository

The NIGMS Human Genetic Cell Repository provides a valuable resource for investigators studying genetic disorders. The Repository, located at the Coriell Institute for Medical Research in Camden, NJ, collects, characterizes, maintains, and distributes cell lines and DNA samples from patients and families with a wide variety of genetic disorders and from normal persons whose tissues serve as controls. Over 10,000 unique cell lines, representing 511 different inherited human disorders (diagnoses with OMIM numbers), and more than 4,850 DNA samples are available to qualified investigators. The Repository stimulates research on rare diseases by providing access to these cell lines, both fibroblasts and transformed lymphoblasts, and DNA samples derived from these cell lines, that otherwise are not readily available. The cell lines requested most frequently in the last year were those from patients with rare diseases such as xeroderma pigmentosum, Ataxia Telangiectasia, fragile X-linked mental retardation, Huntington disease, Seckel syndrome, trisomy 21, Myotonic Dystrophy, Niemann-Pick disease, Friedreich ataxia, and spinal muscular atrophy. The most requested DNA samples over the year have been for cystic fibrosis, fragile X-linked mental retardation, coagulation factor II, and the hemoglobinopathies. Recent acquisitions to the collection include samples from patients with the following rare disorders: congenital disorder of glycosylation (Types 1a through 1j), hemoglobin-delta, holocarboxylase synthetase deficiency, inclusion body myopathy, Kawasaki disease, L-2-hydroxyglutaric aciduria, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, Peters-plus syndrome, and thrombophilia. Cell lines with verified biochemical deficiencies have been established from newborn screening samples for 26 of the most commonly tested conditions. All of the cell lines in the repository collection are available for biochemical, cellular, and molecular studies to help elucidate the causes of genetic defects. The disease-related mutation has been characterized at the molecular level in over 1800 of the genetic cell lines. The molecular defect is known for most all of the newly acquired cell lines that are accepted into the Repository. The Repository also houses an expanding collection of chromosomally aberrant human cell lines; some of these have been evaluated with array comparative genomic hybridization (aCGH). DNA is

available from isolated chromosome-specific somatic cell hybrid panels for nearly every human chromosome. Sets of cell lines (and DNAs derived from them) that represent the CEPH family collection and other extended families, the National Human Genome Research Institute's DNA Polymorphism Discovery Resource and other identified populations that represent the genetic diversity of humans across the globe are available from the Repository. These samples will help researchers map and identify genes that are involved in the etiology of complex genetic diseases.

Recent Scientific Advances in Rare Diseases Research

Cockayne syndrome: a disease of transcriptional deregulation

Cockayne syndrome (CS) is a recessively inherited developmental disease characterized by severe growth failure (dwarfism), abnormal sensitivity to sunlight, and the appearance of signs of premature aging, such as retinal degeneration, cataracts, and sensorineural hearing loss. In the classical form of the syndrome the symptoms are progressive and typically become apparent only after the age of one year. An early onset form is apparent at birth, while a third form is late onset and presents with only a few of the characteristic symptoms. While it has been known for awhile that genetic defects in any of five identified genes can cause CS and it appears that the proteins encoded by each of these genes may play some role in repair of oxidative or ultraviolet DNA damage, the mechanisms by which the molecular defects produce the CS phenotypes have remained obscure.

Researchers supported by NIGMS have now used gene expression microarrays to define the defect in cultured fibroblast cells from CS patients lacking a functional CS group B protein (CSB); CSB defects are responsible for most cases of CS. The protein is a DNA-dependent ATPase that can wind DNA and remodel chromatin *in vitro* and is required for translocation of the CS group A (CSA) protein to the nuclear matrix after chromosomal DNA damage has occurred. The observation that CSB physically interacts with chromatin components suggested that it plays a direct role in facilitating chromatin modifications involved in regulating transcription. Microarray analysis demonstrated altered patterns of gene expression in CSB-null cells resembling those induced by agents that modify protein structural components. Loss of CSB leads to a gene expression profile with aberrant transcription patterns in growth suppressive, inflammatory, and pro-apoptotic pathways. This pattern is consistent as a link between CSB dysfunction and the CS phenotype. The ‘‘inflammatory" transcription phenotype’’ may be responsible for the neurodegenerative and wasting symptoms of this progeroid disease.

Barth syndrome: misplaced mitochondrial proteins

Barth syndrome (BTHS) is an X-linked, metabolic and neuromuscular disorder that primarily affects boys. Cardio-skeletal myopathy, neutropenia, and growth retardation typically become apparent during infancy, but age of onset, severity of symptoms and disease course can vary considerably, even among affected members of the same family. Without prompt attention and appropriate treatment, heart failure resulting from a dilated cardiomyopathy and bacterial infections can be life-threatening complications. Although it has been known since 1996 that mutations in the tafazzin (TAZ) gene are present in the X-chromosome of all patients with BTHS,

a biochemical mechanism for the condition had not been established. Defective mitochondria seemed to be involved, as in many other inherited muscle diseases, but it took experiments by NIGMS-funded researchers using newly developed antibodies to definitively show that the tafazzin (Taz1p) protein specifically functions in a highly localized section of mitochondria in cells from normal subjects. Mutant Taz1p, however, was also found to be present in mitochondria from BTHS fibroblasts. It required the use of a laboratory yeast model system to perform the complex genetic manipulations that were necessary to prove that the mutated human Taz1p proteins do not become positioned in the correct intermembrane space. The normal and mutated versions can both perform the enzymatic, acyltransferase function necessary to provide cardiolipin to mitochondrial membranes, but this is not useful unless the protein does it in the correct place.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

Overview

The NHLBI provides leadership for a national program in the causes, diagnosis, treatment, and prevention of diseases of the heart, blood vessels, lungs, and blood; in sleep disorders; and in the uses of blood and the management of blood resources. Through research in its own intramural laboratories and through extramural research grants and contracts, it conducts and supports an integrated program that includes basic research, clinical trials, epidemiological studies, and demonstration and education projects.

Although much of the research supported by the NHLBI addresses common conditions such as hypertension, coronary heart disease, and chronic obstructive pulmonary disease, a significant amount of research is devoted to rare diseases in children and adults. NHLBI activities related to rare disease research in fiscal year (FY) 2006 are described below.

Recent Scientific Advances in Rare Diseases Research

Cardiovascular Diseases Programs

Abetalipoproteinemia

Abetalipoproteinemia is a disorder of lipid metabolism characterized by the absence of apoprotein B-containing lipoproteins from the plasma. Symptoms include diarrhea, severe fat malabsorption, and acanthocytosis, a rare condition in which the majority of red blood cells have multiple spiny cytoplasmic projections. Other symptoms, including blindness and neurologic defects, all appear to be secondary to defects in the transport of vitamins A and E in the blood. Recent research suggests that the disease is the result of abnormal processing of apolipoprotein B (apoB) caused by an absence of microsomal triglyceride transfer protein (MTP). Through its extramural program, the NHLBI funds research grants to study the genetic, biochemical, and metabolic aspects of abetalipoproteinemia. Researchers in the NHLBI intramural program are investigating the molecular, cellular, and metabolic defect of MTP and its role in abetalipoproteinemia. Patients with abetalipoproteinemia are followed to develop a better understanding of the natural history of the disorder and to seek more effective treatments. Metabolic studies are performed in abetalipoproteinemia patients to determine the role of MTP in triglyceride (fat), apoB, and fat soluble vitamin absorption. Collaborative studies are conducted with the National Eye Institute and the National Institute for Neurological Disorders and Stroke. Intramural scientists also continue to investigate the role of MTP in the formation of triglyceride containing- and fat soluble vitamins (vitamins E, A, and K) in the intestine and liver.

The defining characteristic of MTP is its ability to transfer lipids between small unilamellar vesicles *in vitro*. Recently, NHLBI-funded researchers developed new methods to measure the lipid transfer activity of MTP, using simple fluorescence assays to measure transfer of triacylglycerol (TAG), phospholipids (PLs), and cholesteryl esters (CEs) by MTP. Because the new assays are easy to perform, the investigators recommend their use for routine MTP activity

measurements. The new assays should facilitate studies of MTP and may help researchers to identify specific inhibitors for individual lipid transfer activities, characterize different domains involved in transfer, and isolate mutants that bind to, but cannot transfer lipids. More recently, investigators using human MTP, reported that the phospholipid transfer activity of MTP is sufficient for the assembly and secretion of primordial apoB-lipoproteins, and thus could represent MTP's earliest function, which may have evolved for the mobilization of lipid in invertebrates.

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD or ARVC)

ARVD/C is a complex arrhythmogenic disorder characterized by gradual loss of myocytes (heart muscle cells) and their replacement by fatty and fibrous tissue. It leads to dilation of the right ventricle (RV) and impaired cardiac function. The clinical course is characterized by ventricular arrhythmias (ventricular tachycardia), heart failure, and sudden death. Although relatively uncommon, ARVD/C has devastating consequences in otherwise healthy, young, individuals, accounting for approximately five percent of sudden deaths in people under the age of 65.

In familial cases of ARVD/C, which are believed to account for at least half of ARDV/C cases, autosomal dominant inheritance with variable penetrance has been reported. Sporadic cases are thought to be acquired via an unknown mechanism or to be due to inheritance of genes that have yet to be identified. Recent evidence suggests that typical ARVD/C is a disease of, specialized cadherin-based cell-cell adhesion structures called cardiac desmosomes that are abundant in cardiac muscle and skin epidermis. NHLBI-supported investigators have identified a number of new variants in desmosomal genes including those encoding desmoglein-2 (*DSG2*), desmoplakin (*DSP*), desmocollin-2 (*DSC2*), junctional plakoglobin (*JUP*), plakophilin-2 (*PKP2*), and plakophilin-4 (*PKP4*) among ARVD/C patients enrolled in the North American ARVD Registry. Genetic heterozygosity or compound heterozygosity exists in a number of probands, supporting the hypothesis that reduced penetrance is observed in many cases because ARVD/C may actually be an autosomal recessive disease with common genetic variants or modifiers, giving the appearance of a dominant disease.

The NHLBI supports the five-year Multidisciplinary Study of Right Ventricular Dysplasia, an integrated network of three separate research groups, to investigate genotype-phenotype relationships in familial forms of ARVD. The program is investigating and characterizing the cardiac, clinical, and genetic aspects of arrhythmogenic right ventricular dysplasia (ARVD). It will determine the influence of genotype on the clinical course of ARVD, explore phenotype-genotype associations that could contribute to improved therapy, and develop quantitative methods to assess right ventricular function to enhance the specificity and sensitivity of ARVD diagnosis. In addition, a North American ARVD Registry has been established by enrolling patients and their family members.

In FY 2006, investigators made several advances in ARVD research. For example, investigators identified a number of genes and gene mutations that contribute to ARVD along with their associated clinical features. Investigators also used new technologies to identify and quantify cardiac abnormalities in individuals with ARVD. Finally, investigators identified a role for implantable cardioverter-defibrillators to prevent sudden cardiac death in individuals with ARVD.

Bartter's syndrome

Bartter's Syndrome is characterized by salt imbalance and low blood pressure. Research on Bartter's Syndrome is currently being pursued as a part of the NHLBI Specialized Centers of Research on the Molecular Genetics of Hypertension. Researchers have discovered a mutation in a potassium channel that can lead to Bartter's Syndrome and have demonstrated that the channel is an important regulator of blood pressure and ion and fluid balance. Mutations in chloride channels have also been identified and implicated in the development of Bartter's Syndrome. Researchers think that additional Bartter's Syndrome genes may exist. The hypotensive state caused by Bartter's Syndrome suggests that the mutated genes may protect against the development of high blood pressure.

Brugada's syndrome

Brugada's Syndrome is a rare inherited disorder characterized by cardiac electrophysiological abnormalities in the absence of structural heart disease. The syndrome is associated with a high occurrence of sudden cardiac death. The NHLBI supports research on Brugada's syndrome through two program project grants and a small portfolio of individual research project grants studying the molecular, clinical, and genetic bases of the condition.

Recent research advances in this area include three new reports on SCN5A, the only gene known to be associated with Brugada's syndrome. In the first report, NHLBI-funded researchers found that locoregional anesthesia with bupivacaine could induce the electrocardiographic and arrhythmic manifestations of the Brugada's syndrome in silent carriers of SCN5A mutations. In the second report, six common DNA variants found in the SCN5A promoter in Asian subjects were shown to modulate susceptibility to ventricular fibrillation in response to challenges. The mutations may contribute to the higher prevalence of Brugada's syndrome in Asia. In the third report, researchers found that dimethyl lithospermate B, an extract of a Chinese herbal remedy, eliminates the arrhythmogenic substrate responsible for Brugada's syndrome.

Carney complex

Carney complex is a multiple neoplasia (abnormal and uncontrolled cell growth) syndrome that includes recurrent cardiac myxoma, a benign tumor of the heart, as one of its main manifestations. The NHLBI intramural program is using cardiac magnetic resonance to characterize the cardiac manifestations of Carney Complex, including myxomas and subclinical myocardial infarction. Studies are being conducted in collaboration with the National Institute of Child Health and Human Development.

Cholesteryl ester storage disease

Cholesteryl ester storage disease (CESD) is a rare syndrome characterized by an enlarged liver and spleen and abnormal liver enzymes. The disorder is known by a variety of names including lysosomal acid lipase deficiency, acid cholesteryl ester hydrolase deficiency, and Wolman disease. The severe infantile-onset Wolman disease and the milder late-onset cholesteryl ester storage

disease (CESD) are believed to be caused by mutations in different parts of the acid lysosomal lipase gene. The mutations affect acid lysosomal lipase, an enzyme that removes lipids (cholesteryl esters and triglycerides) from lipoproteins. Acid lysosomal lipase deficiency causes a massive accumulation of lipids in tissues. The hypercholesterolemia that is common in individuals with CESD predisposes them to atherosclerosis. Researchers in the NHLBI intramural program are conducting studies to determine the role of acid lysosomal lipase in the removal of lipids from the plasma and from tissues.

Congenital heart defects

Congenital heart defects encompass a constellation of abnormalities in the heart that occur during embryonic development. Abnormalities of the heart are the most common of birth defects, occurring in up to one percent of live births, and are an important cause of infant mortality, pediatric and adult morbidity, and shortened adult life expectancy. About one-third of affected infants and children require open heart surgery or interventional cardiac catheterization to repair or ameliorate their defects. Approximately the same proportion has associated extracardiac anomalies, such as chromosomal abnormalities and syndromes involving other organ systems. The NHLBI has supported research in pediatric cardiovascular medicine since it first funded heart research grants in 1949. NHLBI-supported researchers have been instrumental in developing diagnostic fetal imaging techniques; surgical techniques, including various operations and refinements in cardiopulmonary bypass; and medical therapies now used to ensure healthy survival for most affected children. They also have made significant contributions to research on the epidemiology of congenital heart defects and to understanding the molecular and genetic basis of normal and abnormal heart development.

In FY 2006, the NHLBI-supported Pediatric Heart Network released results of two studies; one showing that cardiac rehabilitation can improve the exercise performance of children with congenital heart disease, and a second showing that children and adolescents who survive surgeries for single ventricle defects have deficits in physical and psychosocial functioning compared to the U.S. population sample. The results have the potential to change medical practice by identifying the need for cardiac rehabilitation and by incorporating effective detection, prevention, and management of psychosocial issues for patients with congenital heart disease. Basic research investigating the underlying causes of congenital heart disease also has been a focus of NHLBI-supported research. Research funded during FY 2006 includes studies characterizing multipotential progenitor cells in the embryonic heart, studies in animals to identify the variety of genes that, when defective, produce heart defects, and human studies to determine whether the genes that cause defects in animals are also responsible for defects observed in patients.

DiGeorge syndrome

DiGeorge Syndrome, which occurs in about 1 in 4,000 live births, causes many abnormalities, including cardiac outflow tract anomalies, hypoplasia of the thymus and parathyroid glands, cleft palate, facial dysmorphogenesis, learning difficulties, and other neurodevelopmental deficits. It is usually sporadic, but may be inherited, and is caused by deletion of a segment of chromosome 22 that is known to contain numerous genes. The NHLBI supports both human and animal studies of

DiGeorge Syndrome through several individual research grants, program project grants, and a Specialized Center of Clinically Oriented Research (SCCOR) in Pediatric Heart Development and Disease. Much of the NHLBI-supported basic research on congenital heart defects also enhances understanding of DiGeorge Syndrome because several of the most frequent cardiac malformations occur in conjunction with it. The recent identification of a gene associated with DiGeorge Syndrome has enabled further research on how the gene is regulated and how it affects embryonic development through regulation of downstream genes. For example, in FY 2006, NHLBI-funded researchers used transgenic mice to continue a systematic study of the spatial and temporal requirements for the gene during embryonic development. Other researchers within the SCCOR are continuing to investigate the genetics of DiGeorge Syndrome in human patients, and have developed a new rapid method to test for the chromosome deletion that causes DiGeorge Syndrome.

Dysbetalipoproteinemia

Dysbetalipoproteinemia, or type III hyperlipidemia, is a disorder with a strong heritable component characterized by the presence of beta-migrating very-low-density lipoprotein. It leads to the formation of characteristic yellow skin plaques (xanthomas) on the palmar creases and predisposes to premature ischemic heart disease and peripheral vascular disease. The defect occurs in people with mutated forms of a protein, apoprotein E (apoE). A mutant form of apoE, apoE2, has been identified as the chief molecular defect. The NHLBI intramural program is investigating the molecular, cellular, and metabolic defect of the apoE2 and its role in dysbetalipoproteinemia. Patients with dysbetalipoproteinemia are followed by intramural researchers in an effort to define the natural history and to find better treatments. Metabolic studies are performed in patients with dysbetalipoproteinemia to clarify the role of the apolipoprotein E particles in the development of atherosclerosis. The intramural research has shown that apolipoprotein E greatly influences the metabolic fate of different lipoproteins and likely influences the development of atherosclerosis.

Familial hypobetalipoproteinemia

Familial hypobetalipoproteinemia (FHBL) is a disorder of lipid metabolism characterized by greatly reduced levels of apoprotein B (apoB)-containing lipoprotein cholesterol. At least three different types of FHBL exist, each resulting from a different genetic mutation. The three genetic forms of FHBL that have been reported: are (a) FHBL caused by mutations that lead to the truncation of apoB, (b) FHBL linked to chromosome 3p21, and (c) FHBL not linked either to the mutations that cause apoB truncation or to the mutations on chromosome 3p21. Fatty livers (i.e., livers with a five-fold increase in fat compared to normal livers) may be present in up to 80 percent of people with the form of FHBL that results from apoB truncation. In the most severe form, patients develop defects in the transport of vitamin A and E in the blood resulting in blindness and neurologic defects. The NHLBI intramural program is investigating the molecular, cellular, and metabolic defect of apoB and its role in FHBL as well as investigating other potential causes of FHBL. Patients with FHBL are being followed to characterize the natural history of the disorder and to look for more effective treatments. Metabolic studies are performed in patients with FHBL to clarify the role of apoB and other factors that cause defects in triglyceride (fat) and fat soluble

vitamin (vitamins E, A, and K) absorption. The role of apoB in the formation of triglyceride containing and fat soluble vitamins in the intestine and liver continues to be investigated.

Homozygous familial hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disorder characterized by elevated concentrations of low-density lipoproteins (LDL). The homozygous form of FH is rare (one in a million) but people who have it are very prone to premature coronary heart disease. Cholesterol derived from LDL, when deposited in arteries, leads to heart attacks and, when deposited in tendons and skin, causes yellow skin plaques (xanthomas). FH is caused by a mutation in a gene specifying the receptor for plasma LDL. Because LDL receptors facilitate the removal of LDL, the deficiency or lack of the receptors due to FH reduces the rate of LDL removal, thereby causing the level of LDL in the plasma to rise. Although patients with FH have elevations in LDL cholesterol levels, plasma triglyceride levels are generally normal, suggesting that other mechanisms are responsible for clearing the majority of triglyceride-rich very-low-density lipoprotein (VLDL) and VLDL remnants. The NHLBI supports studies of the biochemistry, genetics, and potential treatment of FH; the regulation of LDL receptors; and blood cholesterol levels. The NHLBI intramural program is investigating the molecular, cellular, and metabolic defect of the LDL receptor and its role in FH. Patients with FH are followed by intramural investigators and are eligible to undergo serial testing that includes noninvasive cardiac monitoring and the measurement of biomarkers to obtain a better understanding of the natural history of the disorder and the development of atherosclerosis. Intramural researchers also are exploring the great promise of magnetic resonance imaging (MRI) for the noninvasive evaluation of the development of aortic root atherosclerosis in patients with FH. In FY 2006, NHLBI-supported extramural investigators continued to characterize a newly discovered family of proteins that regulate cholesterol and lipid levels. Their discovery is an important step towards better clinical management of hypercholesterolemic patients who are susceptible to statins and may eventually lead to the discovery of key steps suitable for targeted interventions.

Hypereosinophilic syndrome

Hypereosinophilic syndromes (HES) are a rare group of heterogeneous disorders that may be complicated by cardiac manifestations, including fatal endomyocardial fibrosis. The NHLBI intramural program is using cardiac magnetic resonance to characterize patients with hypereosinophilia. Studies are being conducted in collaboration with the National Institute of Allergy and Infectious Diseases.

Progeria (Hutchinson-Gilford progeria syndrome)

Progeria (premature aging) is caused by a mutation in a gene called LMNA that produces the lamin A protein (the structural scaffolding that holds the nucleus of a cell together). Scientists believe that the defective lamin A protein makes the nucleus unstable, thereby causing premature aging. Although children with progeria are born looking healthy, they begin to show many characteristics of accelerated aging at around 18-24 months of age, such as growth failure, loss of body fat and hair, aged-looking skin, stiffness of joints, hip dislocation, and generalized

atherosclerosis. Such children have a remarkably similar appearance, despite differing ethnic backgrounds. They die at an average age of thirteen years from either a stroke or heart attack. Progeria is extremely rare, affecting 1 in 8 million newborns worldwide. About 200 cases have been reported in the scientific literature since the condition was first described in 1886. In FY 2006, the NHLBI supported four grants on progeria. Scientists tested the hypothesis that blocking farnesylation of lamin would ameliorate the nuclear shape abnormalities characteristic of progeria. They treated affected fibroblasts with a farnesyltransferase inhibitor, which significantly improved nuclear shape in two fibroblast cell lines from progeria patients. When the studies were extended to a transgenic animal model for progeria, clinical improvement was shown. The findings suggest a potential strategy for treating the disease.

Klippel-Trenaunay-Weber syndrome (KTWS)

KTWS is a very rare, vascular deformation disease of unknown incidence, involving capillary, lymphatic, and venous channels. It usually manifests as three symptoms: cutaneous port-wine capillary malformations, varicose veins, and enlargement of soft tissues and bone in one limb. KTWS symptoms are usually present at birth, with 75 percent of patients having symptoms before the age of ten. The NHLBI supports molecular research on characterizing the gene(s) responsible for KTWS.

Lecithin Cholesterol Acyltransferase Deficiency

Lecithin cholesterol acyltransferase (LCAT) deficiency is a rare syndrome characterized by cloudy cornea, kidney failure, and extremely low levels of high-density lipoprotein (HDL). The disorder is inherited on chromosome 16 and is caused by a lack of the enzyme, LCAT, which aids in the formation of normal HDL. Researchers in the NHLBI intramural program are investigating the molecular, cellular, and metabolic defect of human LCAT and its role in LCAT deficiency. Patients with LCAT deficiency are being followed in an effort to clarify the natural history of the disorder. Metabolic studies are performed in patients with LCAT deficiency to define the role of LCAT in HDL formation. Cellular and molecular studies are focusing on the role of LCAT in the development of atherosclerosis and investigating better treatments.

Recently, human metabolic studies conducted by intramural researchers in patients with LCAT deficiency showed an upregulation in low-density lipoprotein (LDL) receptors as well as a change in LDL particle properties that resulted in faster clearance of LDL in LCAT deficient individuals than in normal individuals. The increased LDL particle clearance likely accounts for the absence of atherosclerosis in the patients despite extremely low HDL levels. Treatments directed at the mechanism involved in the rapid clearance of LDL might offer a new approach for treatment of atherosclerosis.

Liddle's syndrome

Liddle's syndrome is a disorder of severe hypertension, characterized by increased renal reabsorption of sodium resulting in hyperaldosteronism, or overproduction of the hormone aldosterone from the outer portion (cortex) of the adrenal gland. The hyperaldosteronism of

Liddle's Syndrome results in low potassium levels (hypokalemia), reduced acidity of the body (alkalosis), muscle weakness, excessive thirst (polydipsia), increased urination (polyuria), and hypertension. Genetic mutations associated with Liddle's syndrome increase the number of sodium channels at the cell surface and therefore increase the amount of sodium reabsorbed. The NHLBI currently funds an investigator-initiated project focusing on Liddle's Syndrome.

In FY 2006, NHLBI-funded researchers found that the genetic mutations associated with Liddle's syndrome increase not only the number of sodium channels at the cell surface, but also the fraction of channels cleaved (shortened) by enzymes. They found that cleavage produces channels with a high probability of being open, or active. The increase in cleavage may be caused by fewer channels being bound to a protein that targets the sodium channels for degradation. The result of the cleavage is increased reabsorption of sodium and higher blood pressure.

Li-Fraumeni syndrome

Li-Fraumeni Syndrome is a heritable mutation in one copy of the tumor suppressor gene p53, which results in the premature development of various cancers. Researchers in the NHLBI intramural program recently discovered that p53 regulates mitochondrial respiration and energy generation. Though no metabolic defects have been reported in subjects with the p53 mutation, intramural researchers plan to examine various metabolic parameters that may be altered in individuals with Li-Fraumeni syndrome. The changes may affect cardiovascular functions such as exercise capacity and may also play a role in tumorigenesis.

Lipoprotein lipase deficiency

Lipoprotein lipase deficiency (LPL) is a rare genetic lipid disorder characterized by extremely elevated triglyceride (fat) levels. It is caused by a genetic defect that affects an enzyme involved in breaking down triglyceride and removing it from the blood. The specific gene defect, which is found on chromosome 8, is in the gene encoding the LPL enzyme. The excess triglycerides characteristic of the disorder are often deposited in the skin (eruptive xanthomas), back of the eye (lipemia retinalis), liver, and spleen and cause abdominal pain or pancreatitis in children. Researchers in the NHLBI intramural research program are conducting metabolic studies in patients with LPL deficiency to determine the role of the lipases in the metabolism of triglyceride lipoproteins and in the development of atherosclerosis and pancreatitis. Intramural researchers also are investigating the molecular, cellular, and metabolic defect of human LPL and its role in LPL deficiency. Patients with LPL are being followed in an effort to clarify the natural history of the disorder and to look for more effective treatments. Recently, intramural researchers found that LPL greatly influences the metabolic fate of triglyceride lipoproteins and has an important role in the development of pancreatitis and atherosclerosis.

Long QT syndrome (LQTS)

LQTS is a heart disease syndrome characterized by a prolonged QT segment on an electrocardiograph. It is associated with fainting (i.e., syncope), ventricular arrhythmias, and, frequently, sudden cardiac death. About 70 percent of diagnosed cases are in women. LQTS

comprises a family of related diseases that are often inherited and that are associated with alterations in cellular cardiac action potential repolarization caused by cardiac ion channel defects and derangements in the regulation of intracellular ion activities. The defects are directly associated with mutations in cardiac ion channel genes or indirectly with mutations in a gene encoding a protein that anchors ion channels to the cell membrane. In some forms of LQTS, affected individuals may inherit other abnormalities, such as deafness, and have varied clinical outcomes depending on their specific mutational patterns. Intense emotional states that affect the electrical stability of the heart may influence the likelihood of clinical events in LQTS patients. Researchers have identified mutations in eight specific genes that are associated with eight forms of LQTS (LQT1-LQT8). Three of them have been show to be ion channel gene mutations (KvLQT1, hERG, and SCN5A), which are associated with three forms of LQTS (LQT1, LQT2, and LQT3).

The NHLBI currently supports research on LQTS through two program project grants and a small portfolio of individual research project grants that address the molecular, clinical, and genetic bases of the condition. An investigator-initiated grant supports an international LQTS Registry with over 1200 families. The registry includes 3,010 affected individuals, 1,731 family members with borderline LQTS, and 3,068 unaffected family members. Investigators continue to study known genetic variants in registry members and identify new variants and mutations. LQTS researchers also are evaluating factors that may trigger malignant ventricular arrhythmias and assessing genotype-phenotype correlations to determine the long-term course of the disease, improve risk stratification, and aid in patient management.

Recent analyses of data from the international LQTS registry have yielded two important findings. First, researchers found that considerable variability exists in measurements of electrocardiogram QTc interval duration in LQTS patients during childhood. However, the maximum QTc duration measured at any time before age 10 was shown to be the most powerful predictor of cardiac events during adolescence, regardless of baseline, mean, or most recent QTc values, suggesting that patient risk stratification should include repeated follow-up electrocardiograms. Second, a study of 2,772 participants from the registry led to identification of three important factors for estimating risk of life-threatening events in adolescent patients with suspected LQTS: timing and frequency of recent syncope, the duration of the QTc interval on electrocardiograph, and sex. They also found that, among patients with recent fainting episodes, beta blocker treatment could reduce risk.

Several advances in LQTS research were reported in FY 2006. One report focused on mutations in the KCNQ1 ion channel, which cause the first type of LQTS (LQT1). The researchers found that mutations in KCNQ1 that disrupt the interaction between calmodulin and the KCNQ1 ion channel prevent functional assembly of the ion channels, leading to cardiac arrhythmias. Another study reported that twenty-eight out of 34 missense mutations of hERG, the gene that causes the second type of LQTS (LQT2), resulted in deficient trafficking of ion channels to the cell membrane, a step needed for normal ion channel function. The trafficking defects of many of these mutant channels could be corrected and therefore represent a potential new focus for developing therapeutic strategies. A third recent study focused on mutations in the SCN5A sodium channel gene, which are known to cause the third type of LQTS (LQT3). Ranolazine, a new antianginal drug, was found to block the negative effects of some types of SCN5A mutants

and may play a role in treating LQT3 patients. Also in FY 2006, investigators found that three novel KCNJ2 mutations associated with Anderson syndrome (also known as LQT-7) caused loss of channel function, but did not prevent ions from trafficking properly to the plasma membrane. Finally, another report described an analysis of data from 186 patients with the Jervell and Lange-Nielsen syndrome (J-LN), an autosomal recessive form of LQTS. The analysis showed that J-LN syndrome is a severe variant with a very early onset. Subgroups at relatively lower risk for cardiac arrest and sudden death could also be identified.

Marfan syndrome

Marfan syndrome is an inherited connective tissue disorder associated with potentially severe cardiovascular complications such as aortic aneurysms and mitral valve prolapse, as well as noncardiac complications such as dislocation of the eye lens. The disease occurs in about 1 per 10,000 persons and in all races. The NHLBI supports animal research on the assembly of microfibrils and the contribution of dysregulated transforming growth factor beta (TGF beta) activity to the pathogenesis of cardiovascular disease. In addition, the NHLBI supports a significant research portfolio on aortic aneurysm development and its treatment in the atherosclerotic population, which may have implications for treating aneurysms in people with Marfan syndrome and other types of genetic disorders that cause aortic aneurysms. In September 2006, the NHLBI awarded a contract to Research Triangle Institute (RTI) International to establish a national registry of patients with Marfan syndrome and other genetically triggered aortic aneurysms. In FY 2006, investigators found that multisystemic manifestations of Marfan syndrome are due to dysregulation of the cytokine TGF beta in a murine model. The findings are consistent with other findings of mutations in genes encoding TGF beta receptor units in patients with physical symptoms similar to the symptoms seen in Marfan syndrome. In January 2007, a randomized trial was initiated to compare the effect of losartan versus atenolol on the rate of aortic root enlargement in 604 Marfan patients aged 6 months to 25 years old.

Myocarditis

Myocarditis is an acute inflammatory condition of the myocardium that may cause cardiomyopathy. Researchers in the NHLBI intramural program are using cardiac magnetic resonance to characterize patients with both community acquired myocarditis and interleukin-2 associated myocarditis.

Niemann-Pick Type C disease (NPC)

NPC disease is a lipid storage disorder usually characterized by excessive accumulation of cholesterol in the liver, spleen, and other vital organs. Several types of Niemann-Pick disease exist, including types A (NPA), B (NPB), C (NPC), and D (NPD). Animal and basic studies show that the mutation that causes NPC interferes with lipid metabolism, cholesterol homeostasis, and intracellular cholesterol trafficking. The defects cause severe damage to the nervous system, bone marrow, and other tissues and organs in patients with NPC. Affected individuals have cardiovascular disease, enlargement of the liver and spleen (hepatosplenomegaly), and severe progressive neurological dysfunction. The gene deficiency in NP disease types A and B affects

sphingomyelinase, an enzyme that breaks down the lipid sphingomyelin. The gene deficiency in NP disease types C and D affects the NPC-1 protein whose function remains obscure. Several NHLBI-supported grants fund research on the regulation of intracellular cholesterol movement as it relates to cholesterol accumulation in NPC disease.

Recently, NHLBI-supported investigators obtained data supporting the hypothesis that acid sphingomylinase activity is activated intracellularly. In individuals with Niemann-Pick disease, the activation step appears to be inhibited by excess cholesterol accumulation causing further perturbation of cholesterol trafficking in cells. Thus, a cycle seems to exist in which cholesterol accumulation inhibits acid sphingomylinase, which, in turn, increases the accumulation of excess cholesterol. In addition to the possible relevance of the finding to the development of atherosclerosis, the result may explain why people with the cholesterol trafficking defect in Niemann-Pick C (NPC) disease have low acid sphingomylinase activity in their cells even though their gene for acid sphingomylinase is normal. Moreover, the cycle proposed above may explain why Niemann-Pick C patients progressively accumulate intracellular cholesterol, with worsening of symptoms, as they age.

Primary lymphedema

The lymphatic system is important in the absorption of fat from the gut, the trafficking of lymphocytes, and the regulation of extracellular body fluids. Lymphedema occurs when the lymphatic system becomes compromised genetically or as a result of surgical intervention. The two major types of lymphedema are primary (inherited) lymphedema and secondary lymphedema (caused by tissue injury, scarring, cancer, lymph node removal, or infection). Primary lymphedema is a rare disease. People with the condition are born lacking a complete lymphatic system. Lymphatic fluid builds up in the soft tissues of the body, usually in an arm or leg; causing swelling that usually appears during adolescence. There is no cure for lymphedema. Treatment usually involves massage to move fluid as well as special exercises while wearing compression stockings or bandages. In FY 2006, the NHLBI supported 13 research project grants that address lymphatic research.

Also in FY 2006, NHLBI-supported research led to two significant advances in primary lymphedema research. First, using the Chy mouse model for primary lymphedema, researchers found that primary lymphedema does not induce an interstitial inflammatory reaction, suggesting that inflammation does not have a major pathogenic role in the development of lymphedema. Second, researchers developed a well-characterized mouse model that develops lymphedema in its tail. The mouse model is expected to provide insight into the pathophysiologic differences that exist between primary and secondary lymphedema.

Sitosterolemia

Sitosterolemia is a rare inborn error of metabolism characterized by increased absorption of dietary cholesterol and sterols from plants and shellfish. The distinguishing feature of the disorder, a 50- to 100-fold elevation in plasma plant sterol levels, reflects both an increase in absorption of sterols from the intestine and a decrease in excretion of sterols into bile. Patients with sitosterolemia

accumulate plant sterols (sitosterol) throughout the body and have a markedly increased risk of premature cardiovascular disease. Two members of the ATP-binding cassette (ABC) transporter family (human ABCG5 and ABCG8) located on chromosome 2 have been identified as the defects in sitosterolemia. ABCG5 and ABCG8 are thought to prevent the absorption of plant sterols into the bloodstream by pumping them back into the intestine.

The NHLBI intramural program is investigating the molecular, cellular, and metabolic defect of human ABCG5 and ABCG8 and its role in sitosterolemia. Patients with sitosterolemia are followed in an effort to clarify the natural history of the disorder and to investigate better treatments. Metabolic studies are performed in patients with sitosterolemia to determine the role of the plant sterols in the development of atherosclerosis. Animal studies are looking at the role of ABCG5 and ABCG8 overexpression in the intestine and liver to see whether it may offer a new treatment of atherosclerosis. Thus far, cellular and animal studies have shown an important role for ABCG5 and ABCG8 in the absorption and hepatic removal of plant sterols in bile. Recently, NHLBI intramural researchers found that the intestinal cholesterol absorption inhibitor, ezetimibe, can reduce plasma sitosterol levels over the long-term. The inhibitor may offer an effective treatment for patients with sitosterolemia.

Smith-Lemli-Opitz syndrome (SLOS)

SLOS is an inherited disorder caused by a defect in an enzyme active in the last step of cholesterol biosynthesis. As a result of the defect, synthesis of endogenous cholesterol is inadequate to meet biological demands for functions such as cell membrane production and bile acid synthesis. Newborns with SLOS have a distinctive facial dysmorphism; suffer from multiple congenital anomalies including cleft palate, congenital heart disease, genitourinary abnormalities, and malformed limbs; and exhibit digestive difficulties, severe developmental delays, and behavioral problems. Scientists now think that SLOS may be the cause of many previously unexplained cases of mental retardation. The NHLBI funds various individual projects for research on sterol balance and lipid metabolism in infants with SLOS, on the effectiveness of cholesterol-supplemented baby formula for ameliorating some of the behavioral and digestive symptoms of SLOS, and on the effectiveness of simvastatin therapy in lowering the plasma concentrations of toxic forms of abnormal cholesterol precursor compounds.

In FY 2006, NHLBI-supported researchers published a study describing how ingestion of dietary cholesterol affects the pattern of abnormal sterol intermediates in urine; results indicate that multiple metabolic pathways regulate the processing of exogenous (externally derived) cholesterol. In another report by NHLBI-funded researchers, membrane lipid defects observed in SLOS were characterized at the physicochemical level, including impaired fluidity and decreased sterol content. The findings could explain the multiple system abnormalities observed in SLOS. Finally, a 2006 publication by NHLBI grantees described autism spectrum disorders in virtually all of the SLOS patients studied, indicating that SLOS has a highly consistent relationship with autism, more so than any other single gene disorder. Biological relationships may exist between cholesterol metabolism and autism. Further study may help improve understanding of the biological basis of autism.

Supravalvular Aortic Stenosis (SVAS)

SVAS is a vascular proliferative obstructive disease that affects the aorta and the coronary, carotid, and peripheral arteries. The incidence of SVAS is thought to be less than five percent of all congenital heart defects. SVAS is associated with a mutation in the gene for elastin, an extracellular matrix protein accounting for about 50 percent of the dry weight of the vascular wall. The NHLBI supports grants focused on SVAS. Research shows that SVAS is associated with decreased elastin and altered arterial mechanics.

Tangier disease

Tangier Disease is a rare syndrome characterized by a deficiency of high-density lipoprotein (HDL), mild hypertriglyceridemia, neurologic abnormalities, and massive cholesterol ester deposits in various tissues such as the tonsils. The disorder is inherited and is due to excessive breakdown of HDL rather than to a fault in HDL synthesis. Tangier Disease patients have defective intracellular lipid trafficking that prevents removal of cholesterol from cells. The disorder is caused by mutation in the gene for human ABCA1, a member of the ATP-binding cassette (ABC) transporter family located on chromosome 9. The NHLBI funds extramural research grants to investigate the cell biology and biochemistry of human ABCA1 and its role in Tangier Disease. Researchers in the NHLBI intramural program are investigating the molecular, cellular, and metabolic defect in human ABCA1 and its role in Tangier disease. Patients with Tangier disease are being followed in an effort to clarify the natural history of the disorder. Recently, intramural researchers reported that ABCA1 is involved in the formation of HDL particles in the liver in mice. Cellular studies have shown an intracellular role of ABCA1 in the removal of cholesterol from peripheral cells. Small peptides that mimic apolipoprotein A-I on HDL are being developed that may stimulate the efflux of cholesterol by ABCA1 from macrophages and other cells involved in the development of atherosclerosis.

Lung Diseases Programs

Advanced Sleep Phase Syndrome (ASPS)

ASPS is a rare, genetically-based sleep disorder characterized by an early evening onset of sleep, normal sleep duration, and spontaneous early awakening. The disorder leads to insomnia, excessive daytime sleepiness, and impairment of daily functioning and quality of life. The NHLBI supports basic research to elucidate the neural pathways through which the biological clock mechanism regulates sleep, clinical research to elucidate genetic risk factors, and applied research to determine the role of the biological clock in disturbed sleep and alertness of shift workers, school-age children, and drowsy drivers. Recently, a human gene mutation has been discovered that causes ASPS in some families. The mutation decreases the enzymatic activity of casein kinase I and lengthens the duration of the biological clock cycle.

Alpha-1 Antitrypsin Deficiency (AAT)

Alpha-1-antitrypsin (AAT) deficiency is an inherited deficiency of circulating AAT, a proteinase inhibitor that is manufactured primarily in the liver. The decrease in AAT is associated with emphysema, presumably due to inadequate protection of lung elastic fibers from enzymatic destruction by neutrophil elastase. Fifteen percent of the AAT-deficient population also develops liver disease. The NHLBI funds clinical and basic research on AAT deficiency, including studies of the molecular mechanisms that impair AAT secretion, methods of gene therapy delivery, and methods to increase the availability of defective, but partially active, AAT. NHLBI-supported investigators are defining abnormalities and degradation pathways associated with AAT, characterizing the inflammation that leads to disease in various AAT deficiency states, developing alternative sources of AAT for augmentation therapy, and searching for small molecule therapeutic agents that enhance AAT secretion. A genetic study of families is looking for genes that may modify the nature and severity of the disease. Two gene therapy clinical trials are testing whether the AAT protein is produced in skeletal muscle cells after injection of a viral vector construct that includes the AAT gene. In addition to research that specifically focuses on AAT, the NHLBI supports related studies addressing lung transplantation; the general causation of emphysema; the function, synthesis, secretion, and interaction of the enzymes that are inhibited by AAT; animal models of other enzyme inhibitor deficiencies; gene regulation; cellular signaling, injury, and repair; and protein processing. The NHLBI COPD Clinical Research Network is measuring AAT blood levels in subjects enrolled in its clinical trials. The Network study is expected to clarify the prevalence of AAT among patients with COPD and test the efficacy of putative therapeutic agents.

Asbestosis

Asbestosis is an occupational lung disease that is characterized by interstitial pneumonitis and fibrosis resulting from exposure to inhaled asbestos fibers. In response to the deposition of asbestos fibers, macrophages and lymphocytes accumulate, type II alveolar epithelial cells and smooth muscle cells proliferate, fibrosis appears in the adjacent walls of respiratory airways, and the alveolar septa thicken. Asbestos fibers also can be associated with cell transformation and proliferation related to lung cancers. NHLBI-supported researchers are investigating the molecular and cellular events that trigger cellular proliferation in and regulate remodeling of lung tissue, which results in fibrotic lesions and perhaps, in malignant cell changes in response to asbestos.

Bronchopulmonary dysplasia (BPD)

BPD is a chronic lung disease characterized by disordered lung growth, changes in lung cell size and shape, and a reduction in the number of alveoli available for gas exchange. The NHLBI program in developmental lung biology and pediatric pulmonary disease supports basic and clinical research focused on closing the gaps in our understanding of BPD and on identifying treatment opportunities. The Collaborative Program for Research in BPD provides a well-characterized primate model of BPD for a multidisciplinary exploration of the molecular mechanisms involved in its etiology. One of the participating Centers of the SCOR Program in Pathobiology of Lung Development had identified nitric oxide as an important regulator of the lung circulation during development. Two clinical trials on the role of nitric oxide in preventing

and treating chronic lung disease in premature infants reported their findings in 2006. Together, they are yielding definitive information about the utility and "window of therapeutic opportunity" for prevention of chronic lung disease with inhaled nitric oxide in very-low-birth-weight premature infants. Other NHLBI funded research focuses on identifying opportunities for optimizing lung growth and function and for reversing the incomplete vascularization of dysplasic alveoli observed in premature neonates with BPD. The NHLBI has entered into a funding collaboration with the National Institute of Child Health and Human Development Neonatal Research Network to conduct a prospective, randomized study to test the individual factors of lower oxygen levels and volutrauma reduction via nasal Continuous Positive Airway Pressure (nCPAP) oxygen delivery in a population of very-low-birth-weight (1300-1400 gram) premature infants. The results of the study are expected to exert broad influence on the clinical management of such infants.

Results of two NHLBI-supported, randomized, placebo-controlled, clinical trials on the use of inhaled nitric oxide therapy in high risk premature infants were published in 2006. One study enrolled 793 newborns that were 34 weeks of gestation or less and required mechanical ventilation. Low dose inhaled nitric oxide did not reduce the overall incidence of BPD, except among infants with a birth weight of at least 1,000g, but it did reduce the overall risk of brain injury. The second trial administered nitric oxide to 582 infants who required mechanical ventilation between 7 and 21 days of age. Results showed that nitric oxide improves outcome for premature infants when started between 7 and 21 days of age. Infants receiving nitric oxide were discharged sooner and received supplemental oxygen for a shorter time. Further work is needed to determine the status of enrolled infants in follow up studies at 2 years of age, and to determine the therapeutic window of opportunity that will assist clinicians in optimizing therapy for these fragile infants.

A report from the Collaborative Program in BPD highlighted the effects of different ventilation strategies (either early continuous positive airway pressure or delayed continuous positive airway pressure preceded by positive pressure ventilation) on the extent of brain injury and altered development in a primate model of prematurity. The results suggested that premature delivery in the absence of potential factors, such as hypoxia or infection, is associated with a decrease in brain growth and the presence of subtle brain injury, which seems to be modified by respiratory therapies with early continuous positive airway pressure being associated with less overall cerebral injury.

Congenital Central Hypoventilation syndrome (CCHS)

CCHS is a rare disorder characterized by normal breathing while awake, but shallow breathing during sleep (hypopnea) that is not effective in moving fresh air into the lungs. In severe cases, breathing is also ineffective in affected individuals who are awake. The NHLBI supports a basic research program to elucidate the anatomical and physiological factors responsible for generating neural rhythm and translating it into breathing. Research is focused on understanding how breathing is regulated and identifying the conditions under which reflexive generation of respiratory rhythm is suppressed. Identification of the neuronal pathways producing respiratory rhythm and pattern is a prerequisite for a full understanding of a variety of respiratory sleep disorders such as CCHS. Genetic and pathology studies of CCHS patients are now leading to

identification of candidate genes and of specific areas of the brain stem involved in autonomic regulation including respiration. Recently, brain lesions have been discovered in patients with CCHS that may be responsible for their difficulty in breathing during sleep. Using magnetic resonance imaging, researchers found that the CCHS brain is characterized by underdeveloped neural pathways (diminished myelination) that weaken the connection between brain regions that regulate breathing.

Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) is a developmental disorder that occurs once in every 2,400 births. Often CDH occurs in isolated fashion, i.e., not associated with other life-threatening anomalies or chromosomal aberrations. Without surgical intervention, neonates, with livers extending into the thoracic cavity and small lung/head ratios, die soon after birth because their lung tissue, compressed by their herniated viscera, is inadequately developed and hypoplasia of the lung and its vascular bed leads to pulmonary hypertension or persistent fetal circulation syndrome. Some investigators hypothesize that this constellation of defects results from genetic or environmental triggers that disrupt mesenchymal cell function not only in the primordial diaphragm but also in the thoracic organs. An alternative hypothesis is that the displacement of the abdominal viscera in the chest secondarily perturbs the development of the heart and lungs. Recently, loss-of-function mutations in the gene encoding FOG-2, a transcriptional coregulator, have been linked to CDH and pulmonary hypoplasia in humans and mice.

The NHLBI supports basic research projects on CDH and lung development. One project is exploring the role of the gene Fog 2 in lung hypoplasia and will sequence the human genes FOG2 and GATA 4/5/6/ in patients with CDH and lung hypoplasia. The NHLBI also supports a randomized clinical trial to evaluate the effect of chronic treatment with sildenafil on pulmonary vascular function and reactivity in infants with CDH. In addition, results from studies funded under the RFA: "Coordination of Vascularization and Lung Development" may reveal the mechanisms underlying the hypertensive pulmonary disorders of the newborn and the hypoplastic lung development associated with CDH. A new RFA "Collaborative Studies on Lung Stem Cell Biology and Cell Based Therapy" was announced in April 2006. Research supported under it will explore mechanisms of lung growth and regeneration and the potential of stem cells to promote the functions.

A recent paper reported findings from a small study on cardiac catheterization and response to chronic therapy in infants and children with lung hypoplasia and chronic pulmonary hypertension due to severe CDH. All patients had elevated pulmonary artery pressures at initial catheterization and all had significant vasodilation during treatment with inhaled nitric oxide. The study found that chronic lung disease following pulmonary hypoplasia from CDH is associated with chronic pulmonary hypertension. The authors concluded that chronic vasodilator therapy may improve pulmonary vascular function and enhance lung growth in infants and children who are treated during a period of potential rapid lung growth. Another recent study examined the effect of CDH on lung airspace fluid adsorption in rats. The study demonstrated that CDH delays lung maturation and causes impaired absorption of fluid secondary to inadequate sodium ion uptake by

the lung epithelium, which results in fluid filled lungs at birth and a reduced capacity to establish postnatal breathing.

Another area of progress relates to findings that mutagenesis of the gene for GATA-4, a transcription factor known to interact functionally with FOG-2, predisposes inbred mice to a set of birth defects similar to those seen in CDH. Analysis of wild-type mouse embryos demonstrated co-expression of *Gata4* and *Fog2* in mesenchymal cells of the developing diaphragm, lungs, and heart. A significant proportion of mice heterozygous for a *Gata4* deletion mutation died within 1 day of birth. Developmental defects in the heterozygotes included midline diaphragmatic hernias, dilated distal airways, and cardiac malformations. The investigators concluded that GATA-4, like its coregulator FOG-2, is required for proper mesenchymal cell function in the developing diaphragm, lungs, and heart.

Cystic fibrosis

Cystic fibrosis (CF) is a multisystem disease affecting a variety of epithelial tissues that is characterized by defective transport of chloride and sodium across the cell membrane. More than 25,000 Americans have CF, which has an incidence of about 1 in 3,300 among Caucasians making it the nation's number one genetic cause of death for children and young adults. Lung disease is the major cause of morbidity and mortality in people with CF. Defects in a single gene, the CF transmembrane conductance regulator (CFTR) gene, give rise to the disorder. The defects lead to abnormal secretions, recurrent infection and inflammation, bronchiectasis (chronic dilatation of the bronchial tubes), and premature death. Increasing evidence suggests that defects in the CFTR gene do not function alone in determining disease outcome. The severity of pulmonary disease can vary greatly among individuals, even in those with identical CFTR mutations. Researchers hypothesize that the variation is due to the interaction of the defects in the CFTR gene with other genes that can affect the final disease presentation.

The NHLBI supports a program of basic, clinical, and behavioral research in CF focused on causes, pathophysiology, and treatment, specifically as related to pulmonary manifestations. In FY 2005, the NHLBI began an initiative to establish Specialized Clinical Centers of Research in Host Factors in Chronic Lung Disease to foster multidisciplinary basic and clinical research related to the pathogenesis of chronic lung diseases and speed progress in their diagnosis, prevention, and treatment. In FY 2006, a grant in the area of CF was awarded as part of this initiative. The goal of the research funded by the grant is to test the hypothesis that mucociliary clearance, a central innate defense mechanism of the airways, fails in diseases such as CF and chronic obstructive pulmonary disease, leading to recurrent infections and inflammation and contributing to disease pathogenesis. Insights into underlying mechanisms are expected to spur development of new therapies to transform treatment of major chronic lung diseases. In response to an FY 2004 program announcement to establish bioengineering research grants, a virtual lung project in CF was initiated in 2006. The long term goal of the project is to develop a comprehensive computational model of the hydrodynamics and biochemistry of airway mucus in close coordination with experiments in human bronchial epithelial cell cultures. Such experiments should enable an integrated view of the biophysics of the mucus clearance system and help identify and evaluate new therapeutic strategies. Development of a sophisticated physics-based

model of polymer dynamics and viscoelastic hydrodynamics needed to build a virtual lung is being undertaken by a multidisciplinary team of researchers. Another grant is continuing efforts to identify most of the major genetic modifiers in CF. The work has identified transforming growth factor beta 1 (TGF-B1) as an important modifier of the severity of CF lung disease. Another grant is identifying proteins that are required for regulating biofilm formation and may represent targets for anti-biofilm drug discovery. Scientific findings indicate that colonization of the CF lung by Pseudomonas aeruginosa involves a biofilm mode of growth, which leads to recurrent, chronic, bacterial infections that are antibiotic-resistant and difficult to eradicate.

Experts have long debated the cause of the mucus accumulation that makes CF patients vulnerable to infection. Disparate theories and scientific findings lead to opposite treatment strategies. For example, according to the theory that CF patients have too little water on the surface of their airways, an appropriate therapeutic option would be to add salt, which would draw water, to the volume-depleted airway surfaces. Alternatively, according to the theory that the ion composition is abnormal, e.g., high salt, therapy should be directed at removing salt, but not water, from the CF airway surfaces. Recent findings from two independent clinical trials conducted in the U.S. and Australia provide clinical proof that rehydration of the airways of CF patients by inhaling a concentrated salt water solution improves the ability of the lungs to clear mucus, reduces infections, and improves lung function. This fundamental discovery in the clinical arena is fueling new therapies to prevent the complications of CF. The success of the concentrated salt water treatment points to a promising and previously unexplored therapeutic role for rehydrating the airways in CF. Measures of sustained mucus clearance may serve as useful surrogate outcomes for related future drug development. If effective when administered to infants and young children with CF early in the course of their disease, the new therapeutic approach might prevent or slow the destructive chronic infections that lead to premature death.

In another breakthrough, NHLBI-funded researchers have identified a modifier gene, TGF-B1 that may help explain the variable presentation of disease among patients homozygous for the same mutation. The findings that genetic variants of the TGF-B1 gene are associated with worse disease using two different study designs, different populations, and large numbers of patients open the possibility for discovering other such modifier genes that could serve as specific therapeutic targets and prognostic indicators. The genetic profiles of patients may help to predict more precisely how the clinical manifestations of disease are modulated and inform the choice of the best strategies for therapeutic intervention targeted to specific cellular pathways (such as inflammation versus mucus versus growth and metabolism) involved in the course of disease. Although the identification of modifier genes has just begun, the era of genome-wide association studies and high-throughput genotyping technologies should enable efficient screening of most genetic variants across the genome in large, well-characterized populations of CF patients. Based on other studies demonstrating an association of genetic variants in TGF-B1 with asthma and COPD, genetic modifiers discovered in CF may have important implications for other diseases as well.

Lymphangioleiomyomatosis (LAM)

Lymphangioleiomyomatosis (LAM**)** is a rare lung disease that affects women, usually during their reproductive years. Symptoms develop as the result of proliferation of atypical, smooth muscle-like cells and the formation of cysts in the lungs. Although the cells have histologic features that make them appear nonmalignant and the etiology of LAM remains unknown, clinical and genetic evidence provides support for the neoplastic nature of LAM. Diagnosis is usually made by lung biopsy. Common symptoms include shortness of breath, cough, and sometimes coughing up blood. Patients often develop spontaneous pneumothorax or chylous pleural effusion (collapse of the lung or collection of milky looking fluid around the lung). The clinical course of LAM is quite variable, but is usually slowly progressive, eventually resulting in death from respiratory failure. Although no treatment has been proven effective in halting or reversing LAM, lung transplantation is a valuable treatment for patients with end-stage lung disease. Some patients with Tuberous sclerosis complex (TSC), a genetic rare disease, develop lung lesions identical to those seen in LAM. However, LAM-related lung dysfunction appears to be milder in the TSC-LAM cases than in women who have LAM alone. In some cases, the clinical distinction between TSC and LAM is difficult. The underlying genetic mechanisms leading to smooth muscle proliferation in LAM and TSC are controlled by abnormalities in the same genes, but TSC is inherited and LAM is a disease that occurs sporadically (i.e., does not appear to run in families). Pulmonary LAM is caused by mutations in the tuberous sclerosis complex gene TSC2. The same types of mutations occur in the cells taken from LAM lesions in the lungs and cells taken from benign kidney tumors, known as angiomyolipomas. The cells in the lung and the kidney are thought to have a common genetic origin.

The NHLBI supports research on LAM in both its intramural and extramural programs. As part of the intramural program, the Institute has established a research laboratory at the NIH Clinical Center to study the cause and progression of LAM at the molecular, cellular, and clinical levels. Researchers are determining the characteristics of the unusual smooth muscle cells that damage the lungs of LAM patients. An important aspect of the research is learning how their growth is regulated. The intramural investigators also manage one of the clinical sites participating in the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) Trial (Sirolimus is also called rapamycin). The MILES study, which has begun recruiting patients, is part of the Rare Diseases Clinical Research Network supported the National Center for Research Resources and the Office of Rare Diseases. NHLBI extramural staff assists in the management of the study.

The NHLBI LAM Registry enrolled patients from the summer of 1998 through September 2001 with 243 eligible patients recruited. Although the program ended in 2005, intramural investigators continued to attend transplants and the LAM Registry program continued to help manage the collection, processing, and distribution of LAM tissue. Because the registry grant is no longer active, the functions are in the process of being consolidated and relocated.

Narcolepsy

Narcolepsy is a disabling sleep disorder affecting over 100,000 people in the United States. It causes excessive daytime sleepiness and rapid onset of deep (REM) sleep. Other symptoms include abnormalities of dreaming sleep, such as dream-like hallucinations and transient periods of physical weakness or paralysis (cataplexy). Low cerebrospinal fluid levels of hypocretin, a neurochemical messenger linking sleep with the regulation of muscle tone and alertness, are highly specific to narcolepsy. The NHLBI supports basic and clinical research to identify abnormalities in regulation of sleep associated with narcolepsy that contribute to symptoms such as excessive daytime sleepiness, sleep disturbance, and physical weakness.

Persistent pulmonary hypertension of the newborn (PPHN)

PPHN affects approximately 1 in 500 newborns. Due to inappropriate muscularization of fetal pulmonary vessels, the lung arteries of affected newborns fail to dilate after birth to allow normal blood flow through the lung. Infants with PPHN are poorly oxygenated and require costly and prolonged medical care including: intubation of the airway, inhalation of oxygen, mechanical ventilation and, often, heart/lung bypass (extracorporeal membrane oxygenation). Recent clinical studies point to a critical role for endogenous nitric oxide as a modulator of levels of the vasoactive mediators whose net balance determines pulmonary vascular tone and reactivity. The NHLBI supports a spectrum of basic and clinical research grants concerned with achieving a mechanistic understanding of structural and functional defects of the pulmonary circulation in order to create new opportunities for correcting them. An NHLBI-funded Specialized Center of Research on the Pathobiology of Lung Development is studying several aspects of the unique vascular response of the neonate to injurious stimuli to identify basic molecular mechanisms involved in the development of hypertensive pulmonary disorders such as PPHN.

An NHLBI supported study recently reported that impairment of systemic oxygenation in an animal model of PPHN can be improved significantly (up to threefold) with intratracheal delivery of an antioxidant compound, recombinant superoxide dismutase, given with or without inhaled nitric oxide. Oxygenation improved more rapidly with the combination of superoxide dismutase and inhaled nitric oxide compared with either intervention alone. The investigators concluded that intratracheal recombinant superoxide dismutase alone or in combination with inhaled nitric oxide rapidly increases oxygenation and reduces vasoconstriction and oxidative injury in newborn lambs with PPHN. The work has important implications for clinical trials of superoxide dismutase and inhaled nitric oxide in newborn infants with PPHN.

PPHN is associated with decreased nitric oxide release and impaired pulmonary vasodilation. NHLBI-supported investigators recently investigated the hypothesis that increased oxidant (superoxide ion) release contributes to impaired pulmonary vasodilation in PPHN. The results of studies conducted in an animal model of PPHN suggested that nitric oxide synthase, a key enzyme in nitric oxide pathways, malfunctions in PPHN and is, at least in part, a source of oxidative stress in PPHN. The oxidative stress in turn, contributes to impaired pulmonary vasodilation in PPHN during transition of the fetus to postnatal life. The mechanisms responsible for disrupted nitric oxide synthase function in PPHN require further investigation.

Primary ciliary dyskinesia (PCD)

PCD, also known as Kartegener's syndrome or immobile ciliary syndrome, is an inherited disease characterized by defects in the cilia lining the respiratory tract. The result of the defects is impaired ciliary function, reduced or absent mucous clearance, and susceptibility to chronic, recurrent, respiratory infections, including sinusitis, bronchitis, pneumonia, and otitis media. The disease typically affects children through the age of 18, but the defect associated with it has a variable clinical effect on disease progression in adults as well. Many patients experience hearing loss and, in males, infertility is common. Another symptom, situs inversus (having organs on the opposite side from usual), occurs in approximately 50 percent of PCD patients. Clinical progression of the disease is variable with lung transplantation required in severe cases. For most patients, aggressive measures to enhance clearance of mucus, prevent respiratory infections, and treat bacterial superinfections are recommended. Although the true incidence of the disease is unknown, it is estimated to be no more than 1 in 32,000.

The NHLBI has a small, but growing portfolio of grants related to PCD. In response to an FY 2004 program announcement to establish bioengineering research grants, a virtual lung project in CF was awarded in 2006. The complex defenses that protect the airways and cause disease when they become dysfunctional are relevant not only to CF, but also to PCD. Therefore, the computational models of CF are expected to provide important insights into the pathophysiology of PCD as well. Another grant awarded in 2006 is focused on overcoming the epithelial defenses breached in PCD by delivering "targeted" antiproteases to the lung to reduce the bacterial burden and prevent the escalation of the excessive inflammatory response that leads to progressive airway obstruction and bronchiectasis. An additional grant is building on insights into the genetics of PCD to create a murine model of the disease. The animal model will enable in depth study of key questions relating to the pathogenesis and treatment of PCD that were previously unanswerable due to the lack of a suitable model system.

A recent study showed that defects of the outer dynein arms of cilia, which are composed of several light, intermediate, and heavy dynein chains, are among the most common abnormalities seen in PCD. The defects result in immotile or dysmotile cilia. Greater than 90 percent of PCD patients show defects in cilia. The studies reveal that most of the mutations are more common in patients with Caucasian ethnicity. The findings are useful for establishing clinical molecular genetic tests for PCD to improve diagnosis and counseling. Another study focusing on the genetics of PCD has identified a high frequency of mutations in the gene encoding the human heavy-chain dynein (DNAH5) in patients with PCD exhibiting outer dynein arm defects. Mutations were identified in almost half of the patients with PCD with outer dynein arm defects. Moreover, the mutations clustered mostly in five exons (regions of genes used to make mRNA). Hence, the DNAH5 dysfunction appears to be major cause of PCD cases with outer dynein arm defects. The result provides some of the strongest evidence to date to support the feasibility of genetic testing for PCD.

Primary pulmonary hypertension (PPH)

PPH is a rare, progressive, and fatal form of pulmonary arterial hypertension (PAH) that predominantly affects women, regardless of age or race. It causes deadly deterioration of the heart and lungs. The two basic types of PAH are 1) primary or idiopathic, which includes PAH of unknown cause and inherited PAH; and 2) secondary PAH, which is caused by other serious disorders such as scleroderma and lupus or by use of anorexigens.

In FY 2006, the NHLBI supported a portfolio of more than 80 projects on PH. The projects include: basic cell and molecular biology of PH; identification of the gene(s) and gene mutations that predispose to development of PH; and multidisciplinary program projects combining basic and patient-based research. One project is gathering genetic information on patients with PH to determine whether PH might be caused by interactions between genes and environment. In FY 2006, the NHLBI also began funding a clinical trial to determine the effects of aspirin and simvistatin in the treatment of PH. Two Specialized Centers of Clinically Oriented Research (SCCORs) will begin in 2007. Both SCCORs will contain basic science projects focusing on mechanisms underlying PAH and clinical trials for adult and pediatric PH. The NHLBI extramural program continues to encourage the submission of new applications in both basic and clinical research for PH as well as career development applications. In addition, the NHLBI intramural program supports two ongoing clinical trials to examine the underlying mechanisms of PH, secondary to sickle cell anemia.

Recent PH research advances include two basic research studies that examined new therapies for PH. Both used rat models in which the disease is induced. One study examined the effects of simvastatin, a cholesterol lowering drug that has been shown to reduce the proliferation of some cells. When rats with PH were treated with simvastatin, the disease process was reversed. Pulmonary artery pressure and the size of the right heart were greatly reduced in rats with PH treated with simvastatin as compared to untreated rats. The other evaluated the use of stem cells to treat PH. Stem cells were isolated from rat bone marrow and then injected into the trachea of rats with PH. Stem cell therapy reduced both pulmonary artery pressure and right ventricle size. The mechanism by which stem cells attenuate PH is not yet clear.

Pulmonary alveolar proteinosis (PAP)

PAP is a rare disorder in which accumulation of surfactant, a fluid secreted by the cells of the alveoli (the air sacs in the lungs), results in respiratory insufficiency due to impaired gas exchange. The clinical course is variable, ranging from spontaneous resolution to respiratory failure, and can be complicated by serious secondary infections. Although the disorder occurs in three distinct clinical forms, primary (idiopathic), secondary, and congenital, over 90 percent of PAP cases are primary. The NHLBI supports a modest basic research program on the causes and pathogenetic mechanisms underlying PAP. Results of a clinical trial examining the efficacy of Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) for the treatment of PAP were published in 2006. The trial included 25 patients given daily subcutaneous injections of GM-CSF over a period of 12 months. Patients treated with GM-CSF showed an improvement in oxygenation of the blood, decreased dyspnea and improvement in the six minute walk test.

Although the study was supported by industry, some NHLBI grantees with basic research grants on PAP participated in the research.

Pulmonary fibrosis

Pulmonary fibrosis (PF) is a chronic diffuse lung injury of unknown cause that is characterized by inflammation and fibrosis (scar formation) of the lung's supporting tissue (intersititium) and air sacs (alveoli). A prototype of this group of lung diseases is idiopathic pulmonary fibrosis (IPF), which has a prevalence of approximately 100,000 persons and an incidence of about 30-50,000 new cases per year in the United States. IPF has an especially severe course with a 5 year mortality of about 50 percent and no predictably effective treatment. Lung transplantation, often of a single lung, is only an option for a few patients (approximately 300/year), and the complications from an allograft are significant. Treatment of established IPF disease has relied on the use of corticosteroids in conjunction with immunosuppressive drugs, such as cyclophosphamide, along with the use of other supportive measures. More recently interferon gamma has been used to inhibit transforming growth factor beta. Although pirfenidone, an antifibrotic compound, and antioxidant therapy with acetylcysteine, have been tested as therapies, neither seems to impede the disease process. As yet, neither an effective management strategy nor a standard of care treatment regimen has been developed.

Among patients presenting with diffuse PF, approximately 10 percent will be found to have an acute form of hypersensitive pneumonitis (HP), also called extrinsic allergic alveolitis, which often progresses to a chronic hypersensitivity pneumonitis (CHP). HP is one of many environmental exposure diseases, often caused by the inhalation of thermophilic bacteria or fungi encountered in work situations, especially in agriculture or the home (bird fancier's disease). Although the prevalence of HP in the U.S. is considered to be about 200,000 cases/year, it is greatly under-diagnosed because a large number of workers or hobbyists exposed to harmful environmental agents have few symptoms. Chronicity from continued environmental exposure is frequent. Incapacity from severely compromised lung function, rather than death, is the usual outcome. The best therapy is avoidance of antigen exposure, if possible, when the causative agent has been identified. Recognition of the cause and making an early diagnosis are important medical issues.

The NHLBI has supported an active research program in basic and clinical studies of PF, including IPF and HP or CHP, since the 1970s. A recent assessment of research in IPF has resulted in several new programs. Research needs in lung transplantation, a definitive therapy for IPF, have been formulated. Researchers recently reported on new results on PF. PF occurs when lung fibrous cells turn into myofibroblasts and cause a scar to form. The researchers, using rats as a research model, showed that the change in the myofibroblasts was caused by an enzyme, telomerase, which breaks off small end parts of chromosomes causing cells to replicate. Inhibiting the enzyme may be a method to treat fibrosis. Another study in a rat model showed that keeping a donor lung in a low oxygen environment prior to transplantation causes injury and fluid leakiness that impairs lung function. Exposure of the lung to carbon monoxide provides cell protection from ischemia/reperfusion injury, with less fibrin material accumulation and less clogging of white blood cells.

Sarcoidosis

Sarcoidosis is a disease involving multiple organ systems in which normal tissue is invaded by pockets of inflammatory cells called granuloma. Most sarcoidosis patients have granuloma in their lungs. The disease can occur in a mild form that disappears spontaneously or in a severe form that results in a life-long condition. Estimates of the number of Americans with sarcoidosis range from 13,000 to 134,000, with between 2,600 and 27,000 new cases appearing each year. Up to 5 percent of individuals with pulmonary sarcoidosis die of causes directly related to the disease. The morbidity associated with sarcoidosis can be severe, entailing significant loss of function and decrease in quality of life. The causes of sarcoidosis are presently unknown, but disease development is thought to involve both a genetic predisposition and the immune system. Treatments often include anti-inflammatory drugs, especially corticosteroids, and other immunosuppressant drugs. Therapy is neither standardized nor predictable.

The NHLBI has supported research on sarcoidosis in its extramural and intramural programs since the 1970s. The Institute funds laboratory-based research to investigate granuloma formation and to obtain a better understanding of initiating events, disease processes, and the contribution of susceptibility genes. Investigators in the NHLBI supported A Case Control Etiologic Study of Sarcoidosis (ACCESS) created a repository of DNA specimens collected from more than 700 sarcoidosis patients and paired controls. ACCESS data have contributed to our understanding of the disease. Another NHLBI-supported study of sarcoidosis, the Sarcoidosis Genetic Analysis Consortium (SAGA), ended in 2005. SAGA collected environmental, phenotypic, and genotypic data on 360 African American families with two or more affected siblings to identify sarcoidosis susceptible genes and to determine how these genes and environmental risk factors act together to cause sarcoidosis. Data from SAGA are now being analyzed. In addition, intramural investigators have initiated a clinical trial to evaluate atorvastatin as a treatment for pulmonary sarcoidosis. Atorvastatin may reduce inflammation and reduce the requirement for prednisone.

Recent research has focused on the variable severity and course in sarcoidosis patients. For example, in Scandinavia, patients with a special white blood cell antigen, termed HLA-DRB1*0301, were found to have a milder course of disease than patients without it. The antigen correlated with cell factors and Th1 cytokines measured in fluid used to wash the patients' lungs (bronchoalveolar lavage.) The finding may provide a new method to monitor the course of the disease.

Scleroderma lung disease

Scleroderma (SSc) is an automoimmune connective tissue disorder of unknown cause characterized by microvascular injury, excessive fibrosis of the skin, and distinctive visceral involvement including the heart, lung, kidneys and gastrointestinal tract. It affects between 5,000-10,000 new persons annually and is associated with a high morbidity and a poor prognosis. A high proportion of SSc patients (80 percent) develop lung involvement, either interstitial lung disease and/or pulmonary hypertension, which are the leading causes of death due to SSc. Forty percent of all SSc patients develop at least moderate restrictive lung disease. The mortality rate in SSc patients with severe restrictive lung disease is about 30 percent within 10 years of onset. The

statistics underscore the need for effective treatment, preferably at an early stage in the illness during which the greatest decline in FVC occurs, to prevent progression to severe interstitial lung disease.

The Scleroderma Lung Study (SLS) was supported by NHLBI and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. It was designed as a randomized trial of placebo versus cyclophosphamide to access benefit in lung function, dyspnea, cough, and skin thickness for cyclophosphamide treated patients. The SLS was designed to evaluate treatment with, and safety of, oral cyclophosphamide, an immunosuppressant, versus oral placebo for 1 year in patients with active, symptomatic alveolitis due to SSc. A 13-center, randomized, parallel-group, double-blind, placebo-controlled clinical trial design was used that involved treatment with oral cyclophosphamide. Patients were followed for an additional year. One hundred and sixty-two patients (70.4 percent female), ages 21 to 86 yrs, were enrolled from September 27, 2000, until January 23, 2004. Of 158 patients randomized to receive either placebo or cyclophosphamide, 72 and 73 patients, respectively, were evaluated for the primary outcome. Results of the clinical trial indicate that cyclophosphamide treatment preserves lung function modestly in SSc patients with interstitial lung disease (alveolitis) and favorably affects other endpoints such as dyspnea, cough, and skin problems. Side effects were predictable from cyclophosphamide but were well controlled and not life threatening. Cyclophosphamide therapy is therefore likely to become the standard of medical care for patients with SSc lung disease.

Blood Diseases and Resources Programs

Acquired aplastic anemia

Acquired aplastic anemia is disease in which the bone marrow fails to produce red cells, white cells, and platelets resulting in severe anemia, low white blood cell counts, and low platelet counts. The NHLBI extramural program, as part of the Bone Marrow Transplantation Clinical Trials Network, is supporting a Phase I "dose finding" and Phase II "dose selection refining" multicenter trial entitled "Fludarabine-based Conditioning for Allogeneic Marrow Transplantation from HLA-compatible Unrelated Donors in Severe Aplastic Anemia." The trial, which is jointly sponsored by the NHLBI and the NCI, opened for patient accrual in December 2005. Its primary objective is to determine the feasibility of using fludarabine-based conditioning to reduce transplant-related toxicity while maintaining (or ideally improving) engraftment in allogeneic donor marrow transplantation from matched (and mismatched) unrelated donors in patients with severe aplastic anemia. The combination of reduced transplant-related toxicity and preserved engraftment is expected to translate into improvement in long-term survival.

The NHLBI intramural research program conducts clinical and laboratory research on bone marrow failure syndromes, including aplastic anemia. Intramural researchers have conducted multiple laboratory experiments directed at understanding the pathophysiology of aplastic anemia as well as clinical programs dedicated to treating the disease using immunosuppression and stem cell transplantation. The NHLBI intramural program also provides sibling donor, nonmyeloablative peripheral blood stem cell transplant as investigational treatment for eligible patients with aplastic anemia. Two advances in aplastic anemia research recently have been

reported by intramural researchers. First, researchers described a new method to overcome graft rejection in heavily transfused and alloimmunised patients with bone marrow failure syndromes using fludarabine-based haematopoietic cell transplantation. Second, researchers have demonstrated the efficacy of a monoclonal antibody, daclizumab, in treating patients with moderate aplastic anemia.

Antiphospholipid syndrome (APS)

Antiphospholipid syndrome (APS) is an autoimmune disorder caused by antibodies that attack healthy body tissues and organs. APS is characterized by the presence of circulating antibodies to phospholipids, mainly cardiolipin, as well as to the SLE anticoagulants. The antibodies promote thrombosis in veins and arteries and may lead to recurrent miscarriage. Many patients with APS also have systemic lupus erythematosus (SLE).

The NHLBI supports research to identify genetic factors that might predispose individuals to APS, to develop reliable assays for the antibodies in APS, and to investigate the role of the antibodies in atherogenesis and thrombosis. In 2006, the NHLBI awarded a Specialized Center of Clinically Oriented Research in Thrombosis and Hemostasis that includes research on APS. The goal of the study is to investigate the role of circulating microparticles in the pathophysiology of APS and their potential usefulness as surrogate markers of disease activity and in monitoring the efficacy of new therapies. The Institute continues to support studies on rare thrombotic disorders through the Rare Diseases Clinical Research Network. A protocol entitled “Genetics of Antiphospholipid Antibody Syndrome” has begun patient recruitment. The goal of the study is to determine the genetic and environmental factors that contribute to the development of the antibodies and subsequent thrombosis in APS.

Several advances in APS research were reported in FY 2006. A recent NHLBI-supported study showed that development of autoantibodies and subsequent thrombosis in patients with APS depends on both genetic and environmental factors. Another ongoing NHLBI-funded study showed that the antibodies in APS recognize domain I of beta-2 glycoprotein I and compete with annexin 5 for anionic phospholipids. Anionic phospholipids promote blood clot formation and, in normal individuals, are shielded with annexin 5 thereby protecting against thrombosis. The competition for the phospholipids by the antibodies in APS leaves them exposed to blood and thrombus formation. The finding may explain the placental thrombosis and fetal loss observed in APS.

Cooley’s anemia

Cooley’s anemia (also called beta-thalassemia, thalassemia major, or Mediterranean anemia) is a genetic blood disease that results in inadequate production of hemoglobin. Individuals affected with Cooley's anemia require frequent, lifelong blood transfusions. Because the body has no natural means to eliminate iron, the iron contained in transfused red blood cells builds up over many years and eventually becomes toxic to tissues and organs. In addition, many children with Cooley’s anemia have acquired other diseases such as hepatitis through years of transfusion exposure. The NHLBI continues to support research identifying mutations in the globin gene

cluster that lead to Cooley's anemia, determining the mechanism by which naturally occurring mutations significantly increase levels of fetal hemoglobin in adult red blood cells, developing therapeutic applications related to naturally occurring mutations, studying iron chelation, identifying clinically useful therapies and drugs for the disorder, and developing gene therapy to reduce morbidity and mortality associated with Cooley's anemia.

Until recently, the only iron chelator licensed in the U.S. for patients with Cooley's anemia was deferroxamine, an agent that must be administered slowly and intravenously over many hours several times a week or, in some cases, every day. The oral iron chelator deferasirox was licensed this year and may have advantages for many patients in managing their iron overload and improving their quality of life. L1-deferiprone is another iron chelator used widely in Europe and the Middle East. The Thalassemia Clinical Research Network is currently studying the drug in patients with heart dysfunction.

Several highlights in Cooley's anemia research have been reported. Recent research reveals that the incidence of thalassemia is changing in the United States and worldwide. In particular, more people from Southeast Asia are now immigrating to the United States, many of whom have Hemoglobin E beta thalassemia. The changing profile of thalassemia in the U.S. will require physicians to consider not only the traditional beta thalassemia major, but also the Hemoglobin E form. Another recent study underscores the importance of quality of life issues among patients with thalassemia since considerable variability exists in the severity of disease depending on genotype and environmental factors. Additional research focuses on curative therapies for Cooley's anemia and other hemoglobinopathies, an area of great interest to the NHLBI. Transplant procedures using cord blood and bone marrow have been improving in the last several years and the procedures now allow some patients an opportunity for a cure. Unfortunately, some risk is still associated with the procedures and many patients cannot find a suitable histocompatible match. Progress is being made in the area of gene therapy for hemoglobinopathies, which could offer an alternative to cord blood and bone marrow transplantation. Vector construction, transduction, and gene expression are addressed by recent research. Although safety issues still need to be resolved, phase I studies should help to address those issues.

Creutzfeldt-Jakob disease (CJD)

CJD is a slow degenerative disease of the central nervous system that is characterized by motor dysfunction, progressive dementia, and vacuolar degeneration of the brain. The disease is rare, but invariably fatal, and is associated with a transmissible agent. A protease-resistant protein or prion is the hallmark of all transmissible spongiform encephalopathies (TSE) including CJD. Therefore, the term prion diseases is applied to this group of neurodegenerative illnesses, which includes bovine spongiform encephalopathy (BSE) or "mad cow disease," scrapie in sheep, and chronic wasting disease in deer and elk. Prion diseases may cross the species barrier, the most notable example being the recent cases of variant CJD in humans caused by consumption of beef contaminated with BSE. Classical CJD occurs worldwide at a rate of 1-2 cases per million people per year.

A major goal of several NHLBI programs is to develop blood tests that would be suitable for screening the U.S. blood supply to detect TSE in asymptomatic individuals. The lack of a rapid, sensitive, and specific test for TSE infectivity has slowed progress in the study and control of CJD and other prion diseases. Because TSE agents are at very low concentrations in the blood of laboratory animals, investigators are developing methods to concentrate the agents so that they can be detected using currently available assays. For the past several years, the NHLBI has supported extramural grant and contract programs to develop tests for TSE diseases. Considerable progress has been made and tests have recently been developed with excellent sensitivity to detect TSE agents. However, the tests are still not sensitive enough to detect the agents in blood. The NHLBI continues to encourage research on the development of an assay capable of detecting low levels of TSE agents in blood.

The NHLBI is supporting a Phase II SBIR grant entitled, "A Catalytic Conformational Prion Sensor" to develop a blood based screening assay for the misfolded prion protein implicated in CJD. The investigators have developed an assay based on the observation that abnormal prion proteins catalyze the formation of additional abnormal prion proteins by converting the normal cellular prion protein to the abnormal form. The investigators have synthesized special peptides labeled with pyrene fluorophores. When the peptides are added to samples of abnormal prions, they also assume an abnormal configuration and line up so as to cause fluorescence of the pyrene peptides, signaling the presence of abnormal prions. The assay appears to be very sensitive. The investigators have been able to distinguish consistently between plasma samples from TSE-infected and noninfected laboratory animals. Further, the test is able to distinguish a small number of human CJD plasma samples from controls. A number of studies have been conducted using blinded specimens.

Fanconi anemia (FA)

Fanconi anemia (FA**)** is a rare, genetic, inherited anemia that leads to bone marrow failure (aplastic anemia). It is a chromosome instability syndrome characterized by childhood-onset aplastic anemia, cancer, or leukemia susceptibility, and cellular hypersensitivity to DNA crosslinking agents. Many FA patients can be identified at birth because of congenital anomalies, although approximately 25 percent do not have birth defects. FA is a clinically heterogeneous disorder that currently can be divided into at least twelve complementation groups (A, B, C, D1, D2, E, F, G, I, J, L, M). Currently, the genes and proteins associated with the 12 FA complementation groups have been identified; and most of them have been extensively characterized. Two of the most recently discovered FA genes, FANCB and FANCL, appear to have a significant role in the assembly of the FA core complex.

The NHLBI supports studies to identify and clone the remaining FA genes. An ongoing NHLBI program project has taken a multidisciplinary approach to identify causes of FA at the molecular and cellular level. The scientific areas represented in the program include molecular hematology, molecular genetics, mouse genetics, gene therapy, stem cell biology, and DNA repair. Continued efforts to develop protocols for the efficient identification and targeting of hematopoietic stem cells, to obtain information on how *ex vivo* manipulation of stem cells alters their biologic properties, and to improve vectors are expected to make significant contributions to enhancing the

potential for a cure for FA. Recently the NHLBI funded a new study, "Novel Molecular and Cellular Therapies in Fanconi Anemia," with a clinical component that is using gene therapy to treat Fanconi patients.

Clinical trials are under way to determine whether a sufficient number of CD34+ stem cells can be collected for gene modification and to evaluate the safety and efficacy of hematopoetic stem cell-corrective gene transfer in FA genotype A (FANCA) patients. Gene discovery research continues; with genes for 11 of the 12 complementation groups and 10 independent genes already cloned and characterized. Although two FA genes FANCA and FANCC account for an estimated 75 percent of all FA patients, the new FA complementation group FANCL, is thought to play a critical role in gene repair. A number of studies are currently under way to determine the causes of developmental abnormalities in FA. Ongoing studies are expected to provide new insight into the potential function of the abnormal proteins of Fanconi syndromes.

The only current therapy for FA is allogeneic bone marrow transplantation. Rejection after allogeneic bone marrow transplantation for FA is an important research area since rejection remains a complication with a high risk of mortality. Recently, treatment with antilymphocyte globulin has shown promise for preventing rejection. In one study, rejection of a second allogeneic graft in a child with FA was reversed by antilymphocyte globulin and donor lymphocyte infusion. Because the molecular defects responsible for the many forms of FA have been characterized, FA is a good candidate for using gene therapy with genetically-manipulated, autologous hematopoietic stem cells as an alternative to allogeneic bone marrow transplantation. Reports of leukemia following retroviral-mediated gene transfer have raised interest in the development of nonviral vectors for gene therapy to avoid risks associated with retroviruses. The NHLBI recently awarded a Phase I SBIR grant to develop further the new nonviral Sleeping Beauty transposon system for gene delivery to correct the defect present in FA. The Sleeping Beauty system offers a new means to achieve permanent gene insertion into a large number of predictable points within the genome.

The FA pathway has emerged as a model for several processes. Because of its role in genomic stability and tumorigenesis, FA has become a model for understanding cancer. The interaction of the FA proteins with a breast cancer susceptibility gene (BRCA1) in a common pathway is another area of intense study. A recent review of FA research summed up the general model that has emerged for the FA pathway. It is currently thought that the FA pathway is an arm of the DNA-damage response following exposure to DNA damaging agents. One recent review article summarizes current understanding of the FA core complex and proposes a model for its activity. Another one describes the 12 genetic subtypes of FA and notes that all of them except FANCI have been linked to a distinct gene. A recent study dissected the functional relationship between the classical FA pathway and BRCA2 more precisely, looking at MMC-induced Rad51chromatin loading and foci formation in cells with or without a functional FA pathway or BRCA2. Finally, two new FA genes, FANCB and FANCL, were recently identified and their discovery has allowed a more detailed study into the molecular architecture of the FA pathway. The interaction between FANCA and FANCL is dependent on other FA proteins, FANCB, FANCG, and FANCM, but independent of FANCC, FANCE, and FANCF. The findings provide a framework for the protein

interactions that occur “upstream” in the FA pathway and suggest that besides the FA core complex other sub-complexes exist that may have specific functions.

Hemophilia

Hemophilia is a hereditary bleeding disorder that is caused by a deficiency in either blood coagulation factor VIII or factor IX. The approximately 20,000 individuals in the United States with hemophilia are dependent on lifelong treatment to control periodic bleeding episodes. The NHLBI supports a broad spectrum of activities on blood coagulation and its disorders. Hemophilia research topics include viral and nonviral approaches for gene therapy, mechanisms of antibody inhibitor formation, modification of factors for improved therapeutics, safety of plasma derived products, and blood product-associated infections. In addition, basic genetic, molecular biology, and protein biochemistry studies of factors VIII and IX are supported to improve understanding of their mechanisms of action and their regulation. The NHBLI supports two program project grants related to hemophilia. One of them funds multiple approaches to develop gene-based therapies for hemophilia A and B. The other investigates immune responses to adeno-associated viral-mediated gene transfer of factor IX. Five new individual research project grants were awarded in response to the Request for Applications, “Improved Therapies for Hemophilia and Hereditary Bleeding Disorders.” In August 2006, under the Transfusion Medicine/Hemostasis Clinical Trials Network, the Institute initiated the RICH trial (Rituximab for the Treatment of Inhibitors in Congenital Hemophilia A.) The study is evaluating the safety and effectiveness of rituximab (humanized mouse monoclonal antibody to human CD 20) as an approach to block the production of antibodies to factor VIII in patients with severe congenital hemophilia A and high titer antibody inhibitors.

Several research advances in hemophilia were reported in FY 2006. NHLBI-supported investigators tested a strategy that would protect factor VIII from inactivating antibodies in the circulation while still allowing it to be available when needed to achieve hemostasis. They found that expression of factor VIII in platelets, which secrete their contents when activated at an injury site, can correct the bleeding phenotype of hemophilia mice with high titer factor VIII inactivating antibodies. Other investigators reported that liver-specific gene transfer of human factor VIII DNA into hemophilia mice results in production of high levels of functional factor VIII, followed by rapid loss of activity due to inhibition by anti-factor VIII antibodies. Short-term immunosuppression therapy was found to suppress the immune response allowing long term expression of factor VIII in hemophilia mice. A clinical study of Adeno-associated viral (AAV)-factor IX delivered to the liver in individuals with severe hemophilia B showed that the procedure was well tolerated but expression of therapeutic levels of factor IX were transient. Follow-up experiments suggest that a T cell-mediated immune response to the AAV vector leads to the destruction of the AAV-infected liver cells expressing factor IX. Finally, AAV vector-mediated hepatic gene transfer was used to induce tolerance to human factor IX in mice. The investigators found that gene transfer to the liver could prevent the immune response to both the vector and factor IX through a suppression mechanism mediated by regulatory T cells. The findings suggest that augmentation of regulatory T cells may prevent destructive immune responses after gene transfer.

Hereditary hemorrhagic telangiectasia (HHT)

Hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu disease) is a bleeding disorder caused by weakness of the vascular support structure. Its most common manifestations are red spots on the lips and bleeding from mucosal membranes such as in the nose. In an advanced stage, arterio-venous malformations often develop in the lung, brain, gut, and liver. Two gene defects associated with the transforming growth factor (TGF) complex have been identified in patients with HHT. The NHLBI supports a broad spectrum of research in vascular biology and in hemostasis and thrombosis that are expected to enhance understanding of HHT. The research focuses on understanding the biology of endothelial cells, platelet activation, the mechanism of clotting, and the interaction of blood with the vascular surface. Progress has been made in determining the underlying molecular basis of HHT, which appears to be a mutation in the genes of two TGF beta receptor family members present on endothelial cells. The TGF beta signaling pathway regulates several biological processes including cellular proliferation, apoptosis, and migration. Disruption of the pathway causes malformations of the skeletal, muscular, and cardiovascular systems and enhances the risk for cancer. Several small molecule inhibitors have been developed and initial studies show that they are effective in reducing tumor metastasis.

Mantle cell lymphoma (MCL)

MCL is a rare, B-cell, NonHodgkin lymphoma (NHL) that has only recently been recognized as a distinct biologic entity. MCL, which comprises approximately 6 percent of all NHLs, usually occurs in the elderly, has a male predominance, and typically presents at an advanced stage. Bortezomib, a proteasome inhibitor, is a new active agent that can induce a good clinical response in about half of MCL patients. However, its effect on tumor cells is incompletely understood. To determine the mechanisms underlying bortezomib responsiveness and the tumor features that influence clinical response, intramural researchers are analyzing tumor cells obtained from patients during bortezomib treatment to look for resultant changes in gene expression. The researchers have been able to show that bortezomib induces a distinct cellular stress response in tumor cells that may serve as a predictor of treatment success and that can guide the development of rational combination therapy regimens. The researchers also showed that the mechanisms conferring resistance to bortezomib in tumor cell lines differ from classic mechanisms conferring resistance to other types of chemotherapy. The findings provide a foundation for the development of improved combination therapies.

Paroxysmal nocturnal hemoglobinuria (PHN)

PNH is an acquired genetic disease in which a mutation in a specific gene, called PIG-A, results in deficient presentation of a large number of different proteins affecting hematopoietic stem cells and their progeny white blood cells, red blood cells, and platelets. Clinically, the disease can produce intravascular destruction of circulating red blood cells, bone marrow failure, and clotting in veins. The NHLBI intramural research program conducts clinical and laboratory research on bone marrow failure syndromes, including PNH. It also provides sibling donor, nonmyeloablative, peripheral blood stem cell transplant as an investigational treatment for eligible patients with PNH. Both clinical and laboratory studies have been performed in the intramural program. In the

laboratory, the PNH cell clone has been described both functionally and at the level of RNA production using microarray technology. Research results suggest that PNH clones "escape" from the toxic immunological environment of the failed bone marrow. NHLBI intramural investigators have collaborated with others to test a new monoclonal antibody directed against a late component of complement. The antibody, eculizumab, blocks complement activation and therefore red blood cell lysis. Administration of the antibody improves hemoglobin levels and diminishes transfusion dependence in the large proportion of PHN patients. Eculizumab has been shown to be an effective agent in controlling hemolysis in PNH, improving quality of life regardless of effects on anemia, and reducing the risk of venous thrombosis. Other recent experiments by intramural investigators have helped to overcome graft rejection in heavily transfused and alloimmunised patients with bone marrow failure syndromes by using fludarabine-based haematopoietic cell transplantation.

Renal cell carcinoma

Renal cell carcinoma is a cancer originating in the kidney. The NHLBI provides sibling donor, nonmyeloablative peripheral blood stem cell transplant as an investigational treatment for eligible patients with renal cell carcinoma.

Sickle cell disease

Sickle cell disease (SCD) is an inherited blood disorder that is most common among people whose ancestors come from Africa, the Middle East, the Mediterranean basin, or India. In the United States, approximately 50,000 individuals, primarily African Americans, have SCD (SS hemoglobin). SCD occurs when an infant inherits the gene for sickle hemoglobin from both parents or the gene for sickle hemoglobin from one parent and the gene for another abnormal hemoglobin from the other parent. Each year, approximately 2,000 babies with SCD are born in the U.S. SCD is characterized morphologically by the presence of abnormally-shaped red blood cells (often sickle shaped) caused by hemoglobin polymerization. Persons with sickle cell disease experience acute painful episodes that are the hallmark of the disease, as well as acute lung syndrome, stroke, renal failure, splenic sequestration, and liver damage. Chronic organ injury occurs with age. Hospital data from the U.S. show that 113,098 hospitalizations occurred among patients with SCD in 2004, with average length of stay of 5 days and an average cost of $6,223 per hospitalization. Two-thirds of the hospitalizations occurred among patients aged 18-44 and one-quarter among 1-17 year olds.

The NHLBI extramural research program supports SCD-related basic and translational research to improve understanding of the gene expression of beta and gamma globins, discover compounds and gene products that regulate fetal hemoglobin, elucidate the complex mechanisms of cell adhesion and vaso-occlusion, describe the genetic factors that are responsible for the wide spectrum of clinical severity of SCD, and develop a prospective program for gene therapy. The new intramural Vascular Medicine Branch (VMB) of the NHLBI was formed in FY 2005 from the former Vascular Therapeutics Section of the Cardiovascular Branch. The VMB divides its closely allied translational research efforts between basic science and clinical investigation, focusing on pulmonary hypertension in patients with sickle cell disease. The basic science component of the

VMB investigates the disruption of normal nitric oxide chemistry in SCD patients. Its clinical research component studies the epidemiology, pathophysiology, proteomics, genetics, and gene expression patterns in sickle cell pulmonary hypertension. The VMB clinical research team also performs pilot studies of new therapeutics, particularly those related to the nitric oxide pathway, and collaborates with extramural sites in multicenter clinical trials. It also investigates genetic modifiers of sickle cell disease, especially those related to pulmonary hypertension and other vascular complications and collaborates with investigators from the National Institute for Diabetes and Digestive and Kidney Diseases and the Clinical Center to characterize cardiac and hepatic organ dysfunction in SCD patients. Several research protocols are currently under way in the VMB.

In the area of clinical research, the NHLBI is committed to finding improved treatments for SCD and other hemoglobinopathies. Institute-initiated studies have begun to yield new therapies to alleviate the symptoms of sickle cell anemia and procedures that may ultimately provide a cure. Current clinical research includes:

- The Multicenter Study of Hydroxyurea (MSH) Patients' Follow-up to assess the toxicity of long-term hydroxyurea use in patients who participated in the adult hydroxyurea clinical trial that ended successfully in 1995. A significant finding of the study was that patients who took hydroxyurea for 9 years experienced a 40 percent reduction in deaths.
- The BABY HUG study to assess the effectiveness of hydroxyurea in preventing onset of chronic organ damage in young children with sickle cell anemia. At baseline, the trial demonstrated that the spleen and kidneys already suffer some damage by 1 year of age.
- The SWiTCH study to determine whether hydroxyurea and phlebotomy can maintain an acceptable stroke recurrence rate and significantly reduce hepatic iron burden in comparison to transfusion plus chelation in children who have had prior overt stroke.
- The Multicenter Neurocognitive and Neuroimaging Study in Adult Sickle Cell Disease to assess baseline neurocognitive function and neuroimaging abnormalities in adults with SCD and to randomize patients with subnormal neurocognitive scores to receive 6 months of transfusion versus standard care, followed by reassessment of baseline neurocognitive function.
- The Comprehensive Sickle Cell Centers (CSCC) to support basic research, training, and patient service activities, multicenter Phase II trials, neurocognitive and neuroimaging studies, development of a collaborative database, and a study of the epidemiology of priapism among sickle cell patients. Several additional studies will be initiated in the near future.
- The Sickle Cell Disease Clinical Research Network, which consists of eight clinical sites, a data coordinating center and two patient outcome cores. Its mandate is to conduct multiple Phase III randomized, controlled clinical trials to test the efficacy and effectiveness of new therapies to treat and prevent complications of SCD and, when appropriate, thalassemia. The Network will conduct Phase II and III clinical trials. In addition, the Network is designed to create data sets to enable better characterization of patients and their clinical course; apply genomic and proteomic techniques for improved diagnostic and therapeutic approaches; expand the clinical application of multimodal therapies, and examine patient outcomes.

- The Pulmonary Complications in Sickle Cell Disease program to integrate clinical and basic scientific research on the pulmonary effects of sickle cell disease and encourage collaborative research between investigators in hematology and pulmonary science. Its objectives are to stimulate translational research on the pulmonary complications of sickle cell disease, elucidate the mechanisms underlying the complications, and develop new treatments. Current protocols focus on pulmonary hypertension, asthma and nocturnal hypoxemia, and acute chest syndrome.
- The Sildenafil for Pulmonary Hypertension in Adult Patients with Sickle Cell Disease - Phase II Clinical Trial. The trial is designed to test the effects of 16 weeks of chronic sildenafil therapy on exercise endurance and pulmonary artery pressure in patients age 14 or older with pulmonary hypertension and sickle cell disease. The NHLBI intramural VMB will participate as one of the nine clinical centers in this trial.

The development of a safe and effective antisickling agent could reduce the negative effects of SCD, reduce medical costs, and increase the life expectancy of SCD patients. A new Phase I SBIR grant was recently awarded to a company to pursue preclinical, *in vivo* animal efficacy and toxicology studies of a promising new antisickling agent (5-hydroxymethyl furfural). In addition, in 2006 the Institute supported an NIH Rapid Access for Intervention Development (RAID) project to support chemical synthesis, formulation, and toxicology work for the same agent.

Another approach to treating sickle cell disease involves elevating fetal hemoglobin (HbF) expression in patients. HbF production aids in preventing red cell polymerization, thereby decreasing the tendency of the cell to sickle. It also increases red cell lifespan, further mitigating anemia. The Institute recently awarded a Phase II SBIR grant to develop new small molecule therapeutics (prolyl hydroxylase inhibitors) to up-regulate the expression of HbF in adult red blood cells. Also in 2006, the Institute cosupported with the National Institute for Diabetes and Digestive and Kidney Diseases an NIH RAID project to support chemical synthesis and preclinical toxicology work for a different type of HbF-inducing agent (a short chain fatty acid known as ST20).

The NHLBI has expanded the sickle cell program to include initiatives in outcomes research, including psychosocial issues, quality of life, and health services research. In addition, the NHLBI has supported working groups and meetings to develop an understanding of the health and quality of life challenges faced by adults with sickle cell disease. The effort is ongoing, and in 2006 the Institute supported several activities that address the needs of the adult SCD patient community, including patient outcome cores in the Sickle Cell Disease Clinical Research Network, the Sickle Cell Disease Health-Related Quality of Life Questionnaire Project, and an effort to develop and validate an instrument to measure health-related quality of life (HRQOL) among adults with sickle cell disease.

Highlights of basic research advances reported in FY 2006 include two studies that demonstrated proof of principle in rodent models that genetic modification of embryonic stem cells (ES) can be used to correct disease causing mutations and that the corrected ES cells can give rise to animals cured of sickle cell disease. In addition, researchers have developed an improved gene therapy method for sickle cell disease in rodents that involves simultaneous delivery of a normal

hemoglobin gene and a separate RNA interference gene that reduces expression of sickle hemoglobin. Finally, a study in SCD patients demonstrated that biologically active CD40 ligand is elevated in patients with sickle cell anemia. The work offers new insights into the processes that contribute to inflammation and coagulation in the disease and suggests a previously unrecognized role for platelets in SCD pathophysiology.

Recent highlights of clinical research advances include reports on the prevention and treatment of stroke in children with sickle cell disease, which has been the focus of two NHLBI-sponsored multicenter clinical trials. The first trial, the Stroke Prevention Trial in Sickle Cell Anemia (STOP), identified children at high risk for stroke and then assigned them to transfusion therapy or observation. The trial was terminated early because of a 90 percent lower incidence of strokes in the transfusion group. Because transfusion therapy can lead to the accumulation of toxic amounts of iron in the body, possibly leading to liver and heart disease, the NHLBI organized the Optimizing Primary Stroke Prevention in Sickle Cell Anemia Study (STOP 2) to determine whether the risk of stroke recurs if transfusions are discontinued. Children at high risk for stroke, who had been on chronic transfusion therapy for at least 30 months, were randomized to either continued transfusions or no transfusions. The endpoints were either reversion to an abnormal transcranial Doppler study, or a stroke. The trial was stopped by the NHLBI because of safety concerns after 79 children had been enrolled because 14 of 41 children in the group that was not being transfused developed an abnormal transcranial Doppler study and 2 had strokes. In contrast, none of the 38 children who continued to receive transfusions developed either an abnormal Doppler or a stroke. The striking result confirmed the necessity of keeping children at high risk of stroke on transfusions indefinitely. An ongoing NHLBI sponsored study, the SWiTCH Trial (Stroke With Transfusions Changing to Hydroxyurea) is examining a nontransfusion medical regimen in this population of children.

The NHLBI intramural program published several research advances in FY 2006. One major article was published on pulmonary hypertension, a consequence of increased pressures in the blood vessels of the lungs that has recently been recognized as an independent predictor of death in patients with SCD. The investigators demonstrated that an elevated level of a hormone produced by the heart, the N-terminal pro-BNP (brain natriuretic peptide), was highly predictive for the development of pulmonary hypertension and mortality. If the utility of the test is confirmed, it could enable identification of patients who would benefit from therapies for pulmonary hypertension. In another report on a pilot clinical investigation, NHLBI intramural researchers found that erythropoietin shows promise as a clinically useful adjunct to hydroxyurea therapy in patients with SCD, particularly in patients with impaired erythropoietin secretion due to renal insufficiency. Intramural researchers also reported that, in patients with SCD, several known complications cluster together epidemiologically, constituting a hemolysis-endothelial dysfunction syndrome characterized by pulmonary hypertension, cutaneous leg ulceration, priapism, and possibly stroke. The finding suggests that the vasculopathic complications may have a shared pathophysiology related to nitric oxide scavenging by cell-free plasma hemoglobin released during intravascular hemolysis. Another study by NHLBI intramural scientists showed that impaired nitric oxide bioavailability induced by intravascular hemolysis and leading to pulmonary hypertension in sickle cell disease is also seen in thalassemia and in a canine model of hemolysis. The finding suggests that the mechanism is likely to operate generally in all human diseases

involving severe intravascular hemolysis, such as malaria, paroxysmal nocturnal hemoglobinuria, and thrombotic thrombocytopenic purpura. Finally, a growing body of data indicates that pulmonary hypertension is closely correlated to early mortality in SCD. Preliminary clinical experience indicates that pulmonary hypertension can be diagnosed and treated, with favorable effects on morbidity and possibly mortality. A review of the encouraging data demonstrates the need for larger scale clinical trials.

Advances in patient outcomes and health services research in 2006 include a study of children and adults with SCD in Tennessee that compared race- and age-specific death rates of SCD patients with those of the nonsickle cell population. Results showed that the death rate in adolescents and young adults with SCD continues to be much higher than population-specific rates. Within all age groups, SCD patients had significantly higher rates of hospitalization and emergency room (ED) use than nonsickle cell patients. Another study, the Project in Sickle Cell Epidemiology Study (PiSCES) also reported new results in FY 2006. PiSCES developed and validated a biopsychosocial model of SCD pain, pain response, and healthcare use in a large, multisite adult cohort. PiSCES participants completed a baseline survey and six months of daily pain diaries in which they recorded levels of SCD-related pain and related disability and distress as well as responses to pain (e.g., medication use, hospital visits). The most recent publication shows that men and women had similar pain experiences, but that men reported a higher percentage of days with a crisis and health care use than women.

Small lymphocytic lymphoma/Chronic lymphocytic leukemia (SLL/CLL)

SLL/CLL is a neoplasm of small, round B-lymphocytes in the peripheral blood, bone marrow, and lymph nodes. SLL/CLL is a rare disease comprising about 7 percent of Non-Hodgkin lymphoma cases and is currently incurable. Treatment options for symptomatic disease include combination chemotherapy, monoclonal antibody therapy, and, for aggressive disease, bone marrow transplantation. The NHLBI intramural program is studying the signals that enable the leukemic cells to survive and improving treatment options for patients with CLL. To test the role of survival and growth signals that normal cells provide to leukemia cells, intramural scientists are using Affymetrix microarrays to measure gene expression in CLL cells from different sites in the body such as blood, lymph nodes, and bone marrow. The researchers also are applying the same approach to characterize the molecular changes induced in the CLL cells by anti-leukemic therapy. Intramural researchers recently found that CLL leukemia cells exhibit different gene expression in the bone marrow than in the peripheral blood. The differentially expressed genes indicate that the cells grow better in the bone marrow and point to specific pathways that could mediate the effect. The differentially expressed genes could potentially be used as targets for new therapies.

Systemic lupus erythematosus (SLE)

SLE is an autoimmune disorder in which the body produces antibodies that harm its own cells and tissues. Typical symptoms include fatigue, arthritis, kidney problems, spontaneous fetal loss, and increased risk of thrombosis and heart disease. SLE affects more women than men. Although the cause remains unknown and no cure is currently available, most SLE patients may lead an active life with appropriate treatment. The NHLBI supports research on blood coagulation and vascular

biology in order to obtain a better understanding of the pathophysiology of increased thrombosis and coronary artery disease in patients with SLE. Biomarkers to predict and identify clinical events in patients with SLE are urgently needed; and biomarker development represents an important area of study for the disease. Recently, an NHLBI grantee reported that the blood protein C4d is deposited on platelets and this deposition is specific for patients with SLE. Since platelets play an important role in thrombosis, platelet C4d may serve as a biomarker to identify the subset of SLE patients with an increased risk of thrombosis and pregnancy loss.

Thrombotic thrombocytopenic purpura (TTP)

TTP is a potentially fatal disease characterized by low blood platelet levels and widespread platelet thrombi in arterioles and capillaries. It has a sudden onset and individuals with TTP often exhibit hemolysis, high fever, and neurological abnormalities. Management of patients with TTP is difficult due to the lack of specific diagnostic criteria and rapid progression of disease. The standard therapy for TTP is plasma exchange. Relapse after the acute phase is common. The clinical course differs significantly for patients with idiopathic TTP compared to patients with TTP provoked by predisposing conditions. A congenital or acquired deficiency of a plasma metalloprotease, ADAMTS 13, which cleaves large polymers of von Willebrand factor (vWF), has been linked to the disease. Despite advances in basic research on TTP, treatment options are limited and mortality remains high. The NHLBI supports a broad spectrum of research in hemostasis and thrombosis that includes research on platelet biology, blood coagulation, thrombolysis, and the interaction of blood with vascular and artificial surfaces. Investigator-initiated grants on TTP have led to the development of improved assays for ADAMTS 13, recombinant variants of ADAMTS 13, and a mouse model of the disease. Efforts are under way to develop large scale production of recombinant ADAMTS 13 and its variants.

Several advances in TTP research have been reported. First, patients with chronic TTP develop antibodies to ADAMTS 13 that inhibit its activity and may cause relapse. Using molecular techniques, variants of ADAMTS 13 have been produced that retain their ability to cleave VWF but are not recognized by patient autoantibodies. These ADAMTS variants may be useful in the treatment of patients with TTP and would eliminate the need for plasma exchange. Second, clopidogrel, a thienopyridine derivative widely used for the treatment of patients with cardiovascular diseases, can cause some patients to develop TTP. According to a recent report, patients treated with clopidogrel who develop early onset TTP are deficient in ADAMTS 13. Finally, a mouse model deficient in ADAMTS 13 has been developed that shows some of the TTP disease phenotypes when exposed to shigatoxin. The animal model should be useful in investigating the pathophysiology of TTP and developing new therapies.

Rare Disease Research Initiatives

Ongoing Initiatives

- Animal Models of Antigen-Specific Tolerance for Heart and Lung Transplantation
- Blood and Marrow Transplant Clinical Research Network

- Blood and Marrow Transplant Clinical Trials Network
- Cell-Based Therapies for Heart, Lung, Blood, and Sleep Disorders and Diseases
- Chronic Fatigue Syndrome: Pathophysiology and Treatment
- Clinical Hematology Research Career Development Program
- Clinical Networks for the Treatment of Adult Respiratory Distress Syndrome (ARDS)
- Clinical Research Network for the Treatment of Acute Lung Injury (ALI) and Acute
- Respiratory Distress Syndrome (ARDSnet)
- Comprehensive Sickle Cell Centers
- Coordination of Vascularization and Lung Development
- Developmental Processes in Differential Expression of Globin Genes
- Diagnostic Laboratories for Diseases of Red Cells and White Cells
- Diamond-Blackfan Anemia and Other Congenital Bone Marrow Failure Syndromes: Underlying Molecular Mechanisms
- Functional Heterogeneity of the Peripheral, Pulmonary and Lymphatic Vessels
- Genelink
- Genetic Aspects of Tuberculosis in the Lung
- Genetic Modifiers of Single Gene Defect Diseases
- Genetically Triggered Thoracic Aortic Aneurysms and Other Cardiovascular Conditions
- Conditions (GENTAC): National Registry
- Granulomatous Lung Inflammation in Sarcoidosis
- Hemophilia and Hereditary Bleeding Disorders: Improved Therapy
- Heritable Disorders of Connective Tissue
- Hutchinson-Gilford Progeria Syndrome: Exploratory/Developmental Grants
- Idiopathic Pulmonary Fibrosis Clinical Research Network
- International Cooperative Biodiversity Groups (ICBG)
- Liver Disease: New Technologies
- Lung Response to Inhaled Highly Toxic Chemicals
- Mechanisms of Fetal Hemoglobin Gene Silencing for Treatment of Sickle Cell Disease and Cooley's Anemia
- Mesenchymal Stem Cell Biology

- Molecular Mechanisms of Mucous Metaplasia and Excess Mucin Secretion in Human Airway Diseases
- Multicenter Study of Hydroxyurea in Sickle Cell Disease: Patient Follow-Up Extension I
- Muscular Dystrophy: Pathogenesis and Therapies
- Myelodysplastic Syndromes (MDS): Pathogenesis and Disease Progression
- Myeloproliferative Disorders (MPD): Pathogenesis and Disease Progression
- NHLBI Clinical Proteomics Programs
- NHLBI Lung Tissue Resource
- Novel Approaches to Enhance Animal Stem Cell Research
- Organ Transplantation: Clinical Trials
- Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases
- Pathogenesis of SARS Lung Disease: In Vitro Studies and Animal Models
- Pediatric Heart Disease Clinical Research Network
- Pediatric Heart Disease Network
- Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG)
- Pediatric Mechanical Circulatory Support
- Plasticity of Human Stem Cells in the Nervous System
- Programs for Genomic Applications (PGAs) for Heart, Lung, and Blood Research
- Programs of Excellence in Gene Therapy (PEGT) for Heart, Lung, and Blood Diseases
- Protein Interactions Governing Membrane Transport in Pulmonary Health and Disease
- Proteomic Studies of Platelet Functions
- Pulmonary Complications of Sickle Cell Disease
- Pulmonary Fibrosis: Molecular Targets and Interventions
- Rare Diseases: Exploratory and Developmental Research Grants
- RNA Interference (RNAi) Biology: Stability, Delivery, and Processing by Tissues
- Sickle Cell Disease Clinical Research Network
- Somatic Cell Therapy Processing Facilities
- Specialized Centers of Clinically Oriented Research in Vascular Injury
- Specialized Centers of Research (SCOR) in (a) Neurobiology of Sleep and Sleep Apnea and (b) Airway Biology and Pathogenesis of Cystic Fibrosis
- Thalassemia Clinical Research Network

- Transfusion Medicine/Hemostasis Clinical Research Network
- Tuberculosis Curriculum Coordinating Center
- Zebrafish Research Tools

Initiatives Started in 2006

Blood and Marrow Transplant Clinical Trials Network

A renewal in FY 2006 of an NHLBI-initiated Request for Applications (RFA), supported in collaboration with the National Cancer Institute (NCI), funds a network to accelerate research on the management of hematopoietic stem cell transplantation. The objective of the program is to standardize existing treatments and evaluate new ones. The network of 15 interactive clinical centers and a data coordinating center provides a coordinated, flexible mechanism to accept ideas and build consensus from the transplant community. Network investigators develop protocols, perform multicenter Phase II and Phase III clinical trials, and provide information to physicians, scientists, and the public with the ultimate goal of improving stem cell transplantation therapy for diseases such as leukemia, sickle cell disease, thalassemia, and Fanconi anemia. The renewal will include a new collaborative arrangement with the Pediatric Blood and Marrow Transplant Consortium to conduct trials in children.

Clinical Hematology Research Career Development Program (K12)

A new RFA, initiated by the NHLBI in FY 2006, establishes multidisciplinary career development programs in nonmalignant clinical hematology research to equip new academic researchers with the knowledge and skills necessary to address complex problems in blood disease, transfusion medicine, and cellular therapies. Five K12 awards are available for established clinical hematology investigators to recruit and mentor four to six young physicians during the five-year award period,. Alternatively, one slot at any one time may be dedicated to a nonphysician health professional with doctoral preparation. Each scholar receives two to three years of training in research design and methodology, clinical management of patients with rare hematologic diseases, and research opportunities in the diseases. Programs include a core curriculum, didactics, and a short-term research project for each scholar. At the end of their training, candidates will be expected to submit a K23 grant application to allow them to continue their research as a faculty member at an academic institution.

Diagnostic Laboratories for Diseases of Red Cells and White Cells

A new NHLBI Program Announcement (PA) begun in FY 2006 supports laboratories developing new DNA chip analyses to diagnose, in red and white cells, heritable diseases that are difficult to diagnose using current methods. Studies in red cells may focus on disorders associated with hemoglobin mutations, surface antigen abnormalities, membrane defects, or enzymopathies. In white cells, analyses may focus on disorders associated with phagocytosis, adhesion, chemotaxis, opsonization, ingestion, degranulation, and oxidative metabolism. The creation of one or more gene chip diagnostic laboratories through the Small Business Innovation Research (SBIR) program

would facilitate diagnosis of red cell and white cell diseases and thereby effect better treatment and ultimately better health care for individuals with these rare diseases.

Genetically Triggered Thoracic Aortic Aneurysms and Other Cardiovascular Conditions (GENTAC): National Registry

A new NHLBI-initiated Request for Proposals (RFP) establishes a national registry to facilitate research on best medical practices for the clinical management of genetic thoracic aortic aneurysms and other cardiovascular complications associated with connective tissue diseases such as Marfan syndrome. The registry will: 1) develop standard methods to collect data and specimens which will be used for research to characterize patients at risk for aortic rupture and development of heart failure; 2) record the demographics of patients undergoing surgical repair of aneurysms and their clinical outcomes including related costs; 3) process tissue/blood specimens; 4) analyze data collected; 5) provide access to registry resources to researchers who are interested in advancing the fundamental understanding of genetic aortic aneurysms and management of afflicted patients; and 6) publish and disseminate results. The NHLBI will collaborate with the National Institute of Arthritis and Musculoskeletal and Skin Diseases on the initiative.

Liver Disease: New Technologies

In FY 2006, the NHLBI is funding a new PA, initiated by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), to develop, through the small business research community, resources, research tools, instrumentation, biomarkers, devices, drugs, and innovative approaches for the diagnosis, monitoring, management, treatment, and prevention of chronic liver diseases. The PA summarizes the opportunities for transactional research appropriate for small businesses that are described in the February 2005 Trans-NIH Action Plan for Liver Disease Research. The NHLBI is especially interested in developing effective treatments to reduce or eliminate the progression of liver damage caused by the Hepatitis C virus (HCV) to end-stage liver disease in hemophiliacs.

Lung Response to Inhaled Highly Toxic Chemicals

A new FY 2006 PA, initiated by the NHLBI and funded in collaboration with the National Institute of Environmental Health Sciences (NIEHS), supports research to investigate acute mucosal irritation in the upper and lower respiratory tract occurring after aerosol exposure to toxic chemicals. The goals of the research will be to develop methods for: (1) minimizing initial injury promptly, (2) retarding and ameliorating progressive mucosal irritation or inflammation, and (3) offering prophylaxis against pulmonary edema.

Pediatric Heart Disease Network

In FY 2006, the NHLBI renewed an RFA to operate, for a second five-year period, a network of interactive pediatric clinical research centers to promote the evaluation of new treatments and management strategies that may benefit children with structural congenital heart disease, inflammatory heart disease, heart muscle disease, and arrhythmias. Therapeutic trials and studies

involve investigational drugs, drugs already approved but not currently used, devices, interventional procedures, and surgical techniques. The network, which comprises seven clinical centers and a data coordinating center, provides an effective, flexible framework in which to study adequate numbers of patients with rare diseases such as congenital cardiovascular malformations. Efficiencies are achieved through standardizing procedures to recruit, characterize, monitor, and follow patients. Approximately 2,000 patients are expected to participate in 6-12 different protocols over the 5-year project period. The network also serves as a platform to train junior investigators in pediatric clinical research and as a vehicle for rapid and wide-spread dissemination of findings.

Protein Interactions Governing Membrane Transport in Pulmonary Health and Disease

A new, FY 2006, NHLBI-initiated PA encourages research to delineate the global protein interactions governing membrane trafficking pathways operative in pulmonary disease and develop new therapeutic interventions. Completion of the human genome project and technological advances such as mass spectometry, genomics, and new protein purification methods, now make it possible to probe the molecular pathology of pulmonary diseases associated with misfolded proteins destined for delivery to the cell surface and subsequent secretion. Therapeutic approaches directed toward augmenting the processing and trafficking pathways offer promise for promoting selective stimulation of protein transport to the cell surface to mitigate or prevent lung disease.

Proteomic Studies of Platelet Functions

The NHLBI issued a new RFA in FY 2006 to support the use of proteomic tools to identify platelet disorders. Although platelets play an important role in cardiovascular diseases and stroke, current tests cannot predict platelet function or guide clinical therapy. Furthermore, diagnosis of platelet disorders that increase the risk of bleeding remains difficult. Aggregation of platelets and secretion of platelet components have been studied for many years, but they are complex processes, and platelets may be activated by different agonists through multiple pathways. The RFA encourages proteomic studies of platelets and the application of new technologies to the study of platelets from patients with defective platelet function. The studies are expected to enable the development of proteomic approaches and provide new markers of platelet function.

RNA Interference (RNAi) Biology: Stability, Delivery, and Processing by Tissues

A new FY 2006 RFA, initiated by the NHLBI and supported by several other NIH Institutes, will increase understanding of the biology of RNAi, an effective post-transcriptional strategy for silencing genes. RNAi potentially can be applied to develop new therapies for a wide range of heart, lung, and blood diseases. The initiative is expected to provide insight into the uptake and processing of RNAi by target tissues; assess RNAi stability, half-life, and off-target effects; and determine optimal delivery methods for RNAi uptake.

Sickle Cell Disease Clinical Research Network

A new RFA, initiated by the NHLBI in FY 2006, establishes a clinical research network to conduct multiple Phase III randomized, controlled clinical trials to test the efficacy of new therapies to treat and prevent complications of sickle cell disease and, when appropriate, thalassemia. The interventions are based on results from basic studies and Phase I and Phase II clinical trials conducted in programs such as the NHLBI Comprehensive Sickle Cell Centers Program. The network will comprise a data coordinating center and up to 15 clinical centers that are expected to enroll 50 or more patients per center per year into multiple trials using common protocols. In addition, the network is designed to generate data sets that can be used to characterize patients and their clinical course, apply genomic and proteomic techniques for improved diagnostic and therapeutic approaches, expand clinical application of multimodal therapies, and examine patient-centered outcomes.

Zebrafish Research Tools

In FY 2006, the NHLBI, along with several other Institutes, is funding the renewal of a PA to develop new tools and genetic and genomic resources of high priority to the zebrafish community. The goal is to use the new tools to advance the detection and characterization of genes, pathways, and phenotypes of interest in development and aging, organ formation, behavior, sensory processing, physiological processes, and disease processes. Areas of interest to the NHLBI in which zebrafish are likely to be a useful model include: (1) cellular and molecular functions of zebrafish genes that have the potential to model human cardiovascular, blood, and pulmonary, or sleep disorders; (2) the genetic bases of disorders of cardiovascular development and function; (3) the effect of mutations on subsequent organ development leading to such disorders as arrhythmia, cardiac hypertrophy, dilated cardiomyopathy, and heart failure; (4) developmental aspects of endothelial dysfunction as the basis for vascular disorders; (5) developmental defects in hematopoiesis and the relationship to disorders of the hematopoietic system; (6) the genetic basis of angiogenesis, and vasculogenesis; and (7) the genetic basis, regulation, and role of biological clock mechanisms in development and circadian behavior.

Initiatives Planned for the Future

Ataxia Telangiectasia: Understanding and Treating

A new PA, to be issued in FY 2007 and sponsored by several Institutes including the NHLBI, will conduct basic and translational studies to determine how the symptoms of Ataxia Telangiectasia (A-T) develop, generate resources to further A-T research, accelerate research into promising therapeutic approaches for A-T, and facilitate interdisciplinary research on A-T.

Blood and Marrow Transplant Clinical Research Resource

In FY 2008, the NIH will renew an RFA, via a limited competition, to continue collection and analysis of outcome data from recipients of hematopoietic stem cell transplants (HSCT). The Center for International Blood and Marrow Transplantation Research (CIBMTR) Statistical Center

database is a valuable resource containing information on autologous, related donor, and unrelated donor transplantations of blood, bone marrow, and umbilical cord blood. Clinical data has been collected on more than 200,000 recipients of allogeneic and autologous HSCT treated in more than 600 transplant centers in 47 countries. Data from the resource, which was established at the Medical College of Wisconsin in 1997, have been used extensively by the transplant community to determine transplant results in specific clinical situations; identify prognostic factors; compare transplant regimens; compare transplant with nontransplant therapy; assess inter-center variability in diagnosis, practice and outcome; plan clinical trials or treatment protocols; and develop approaches to evaluate transplant outcomes—including quality of life of long-term transplant survivors. The initiative is sponsored by the National Heart, Lung, and Blood Institute, the National Cancer Institute, the National Institute of Allergy and Infections Diseases.

Comprehensive Sickle Cell Centers

In FY 2008, the NHLB will renew an RFA to continue operations of a nationwide network of interactive, state-of-the-art, comprehensive centers in basic and translational research focused on the development of cures or significantly improved treatments for sickle cell disease. The network of ten centers and a statistics and data management core conducts basic research, inter-center collaborative Phase II clinical trials, and local Phase I clinical studies focused on the most promising biomedical and behavioral therapeutic modalities. The centers also support the career development of young investigators in sickle cell disease research and patient support services including education, counseling, and community outreach. This will be the ninth re-competition of the program, which was established by a Presidential initiative and Congressional mandate in 1972. New components required for the funding cycle beginning in FY 2008 include translational research, health services research, and high-risk, short-term basic research.

Hypersensitivity Pneumonitis: Early Identification and Mechanisms of Disease

A new PA, initiated by the NHLBI in FY 2007, will investigate the basic mechanisms and early clinical identification of hypersensitivity pneumonitis (HP) interstitial lung disease to determine how the disease progresses, and sometimes evolves into interstitial fibrosis or airway obstructive disease. Improved understanding of basic mechanisms of HP and methods for early diagnosis should help improve the outlook for HP patients.

Network for Cardiothoracic Surgical Investigations in Cardiovascular Medicine

The NHLBI will issue a new RFA in FY 2007 to conduct multiple, collaborative, proof-of-concept, clinical protocols to evaluate surgical and minimally invasive interventions to improve treatment of cardiovascular disease in adults. The program will establish a cooperative network of academic centers with clinically active cardiothoracic surgeons and their colleagues in allied specialties interested in promulgating the use of evidence-based medicine in surgical practice. The Network will foster a culture of rigorous scientific comparisons and promote the evaluation of newer surgical techniques, technologies, devices, and innovative pharmaceutical and bioengineered products directed at cardiovascular disease. The Network will comprise seven clinical centers and a data coordinating center and will enhance the capacity to disseminate study

results and translate findings to large-scale trials or practice. Other sponsors of the Initiative include the National Institute of Neurological Disorders and Stroke and the Institute of Circulatory and Respiratory Health of the Canadian Institutes of Health Research.

Sarcoidosis: Etiology of Multi-Organ Disease and Clinical Strategies

In FY 2007, the NHLBI will initiate a new PA in collaboration with several other Institutes to support innovative, multidisciplinary basic and clinical research on the etiology of sarcoidosis and on related host factors that might enhance susceptibility to sarcoidosis. The initiative focuses on symptomatic, multi-organ disease that involves critical organs (e.g., lungs, heart, eyes, central/peripheral nervous system, kidneys, and abdominal viscera) and that creates serious illness and problems in disease management.

Specialized Centers of Clinically Oriented Research (SCCOR) in Pulmonary Vascular Disease

In FY 2007, the NHLBI will initiate a new RFA to conduct multidisciplinary research on clinical questions related to the diagnosis, prevention, and treatment of pulmonary vascular disease. The program will address primary (idiopathic) and secondary pulmonary arterial hypertension, acute and chronic pulmonary thromboembolism, right ventricular dysfunction, and pulmonary vascular disorders of infants and children. Centers will carry out a minimum of three research projects directly related to a unifying theme. At least half of the projects in each center will be clinically-oriented to assure that basic science findings are rapidly applied to clinical problems. Applicants may propose inclusion of a Clinical Research Skills Development Core to enhance the research skills of new clinical investigators.

Transfusion Medicine/Hemostasis Clinical Trials Network Renewal

In FY 2007, the NHLBI will renew an RFA to continue, for a second five-year period, a network of interactive clinical research groups to promote the efficient comparison of new management strategies of potential benefit for children and adults with hemostatic disorders and also to evaluate novel as well as existing blood products and cytokines for the treatment of hematologic disorders. Hemostatic abnormalities may be congenital; immune-mediated—such as idiopathic thrombocytopenia (ITP) and thrombotic thrombocytopenic purpura (TTP); or due to coagulopathies resulting from chemotherapy, surgery, or trauma and can lead to excessive bleeding or thrombosis. The network will consist of 17 core clinical centers and a Data Coordinating Center.

Rare-Disease Related Program Activities

Alpha-1 antitrypsin deficiency (AAT)

The NHLBI recently initiated a COPD Awareness and Education Program that will implement a nationwide campaign for education of the public and physicians regarding obstructive lung diseases, including AAT deficiency.

Acquired aplastic anemia

In August 2006, the Aplastic Anemia & Myelodysplastic Syndromes (MDS) International Foundation held its annual Patient and Family Conference in Nashville, Tennessee.

The Aplastic Anemia & MDS International Foundation held a Bone Marrow Failure Scientific Symposium in Washington, D.C. on October 17, 2005.

The NHLBI intramural program collaborates with the Aplastic Anemia & MDS International Foundation in organizing conferences, research projects, and patient referrals. A new collaboration is planned to organize an international conference on bone marrow failure syndromes in Asia.

A Webcast on aplastic anemia, sponsored by the Aplastic Anemia & MDS International Foundation, is currently in preparation.

Arrhythmogenic Right Ventricular Dysplasia (ARVD)

In FY 2006, one of the principal investigators of the Multidisciplinary Study of Right Ventricular Dysplasia received an R13 award from the NHLBI to enable a two-day symposium to discuss and develop consensus on updating and modifying the current ARVD Task Force criteria for diagnosis of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. The meeting will be held May 12-14, 2007. The symposium will bring together several members from the original Task Force on ARVD, and experts in imaging modalities, electrocardiography, and pathology who have had experience with diagnosis of ARVD/C. The update will establish normal values for standardizing measurements of the right ventricle to establish mild, moderate, and severe disease standards for each quantitative approach. Histomorphic analysis standards will also be set to delineate the amount of fat and fiber found in biopsy samples. Newer diagnostic testing modalities such as voltage mapping, T-wave alternans, and 3D echocardiography will also be presented and considered for possible inclusion in the revised ARVD criteria and standardization.

Although ARVD has no formal advocacy group, investigators maintain a relationship with an active online ARVD/C support group. They have worked with this group to disseminate information about the ARVD Registry, including its eligibility requirements and importance in furthering understanding of the disease. The ARVD investigators share published results with the support group leaders and help prepare information for posting.

Each year, the Johns Hopkins ARVD Program hosts a conference for those affected with ARVD/C, their family members, physicians, and other interested parties. In 2006, the conference was cosponsored by the device company, St. Jude. A principal investigator from the Multidisciplinary Study of Right Ventricular Dysplasia and a psychologist with expertise in the psychosocial implications of implantable cardioverter-defibrillators, were guest speakers. A summary of the seminar is posted on the Johns Hopkins ARVD Web site.

The ARVD programs at Johns Hopkins and the University of Arizona have Web sites (www.arvd.com; www.arvd.org) that provide clinical information about ARVD/C, identify useful resources for patients and families, describe opportunities for research participation including the NIH-sponsored Registry, and give updates on new developments in ARVD/C research. Much of the information is for patients, but test protocols and lists of publications are also provided for health professionals. The site also allows individuals to request a free brochure on ARVD/C and to email questions to a genetic counselor regarding ARVD/C. The Web site is visited by 1,500-2,000 unique visitors per month.

Genetic counselors, including the Johns Hopkins Study Coordinator for the Registry, published a booklet in coordination with the Children's Cardiomyopathy Foundation and the National Society of Genetic Counselors entitled "Cardio What? A Kid's Guide to Cardiomyopathy." It explains familial cardiomyopathy, including ARVD/C in age- appropriate language for young adolescents.

Bronchopulmonary dysplasia (BPD)

The NHLBI and Office of Rare Diseases provided funding for a conference on "Lung Surfactant Molecular and Cell Biology," which addressed basic cell mechanisms of lung cell regeneration, surfactant proteins and the immune system, and lung development. All of the topics are relevant to understanding pathogenesis and future treatments of BPD.

The annual meeting of the Collaborative Program for Research in BPD took place in September 2006 in Bethesda, Maryland.

Brugada's syndrome

A keystone symposium entitled "Cardiac Arrhythmias-Linking Structure Biology to Gene Defects" was held January 29 – February 3, 2006.

On September 14-15, 2006, the NHLBI and ORD held a workshop on the recognition and treatment of rare inherited arrhythmias.

Congenital Heart Disease

In FY 2006, the NHLBI provided funds to support a number of scientific conferences dedicated to adult congenital heart disease, cardiovascular development, development of mechanical devices used in treatment of pediatric cardiac patients, and rare diseases associated with cardiac defects, such as Noonan Syndrome and Barth's Syndrome.

The Pediatric Heart Network sponsors a Web site that provides information for parents and health care providers about completed, current, and future network studies and about how they can participate: http://www.pediatricheartnetwork.org/.

Cooley's anemia

The NHLBI currently holds an investigational new drug approval from the FDA for the study of L1-deferiprone, an oral iron chelator. Studies of the drug are currently under way in the U.S. and abroad.

A major Symposium on Cooley's anemia was held in May 2005. Information presented at the symposium was published in the Annals of the New York Academy of Sciences in November 2005.

The National Executive Director of the Cooley's anemia Foundation attended the Steering Committee Meeting of the Thalassemia Clinical Research Network held on October 17, 2006 in Arlington, VA.

Representatives from the NHLBI attended the medical advisory board of the Cooley's anemia Foundation held in Orlando, FL on December 9, 2006.

The development of gene therapy is of high importance to the Institute. An educational program on this topic was presented to physicians at the American Society of Hematology meeting.

A symposium sponsored by the Iron Disorders Institute, the NHLBI, and the CDC provided an educational program on managing iron in the body in patients with hemochromatosis. However, the information from the symposium was also pertinent to thalassemia patients who have iron overload.

Cystic fibrosis

A joint U.S.-Ireland workshop entitled "Inflammation and Infection in Cystic Fibrosis and Therapeutic Implications" was held on June 23, 2006. The workshop was sponsored by the NHLBI, the National Institute of Diabetes and Digestive and Kidney Diseases, the Cystic Fibrosis Foundation, the Research and Development Office (Northern Ireland), the Department of Enterprise, Trade, and Employment, Health Research Board, Science Foundation Ireland, and InterTradeIreland. The overarching goal was to develop recommendations for new research directions in common areas of basic and clinical research interest to U.S./Ireland investigators in the area of CF, particularly focused on the infectious/inflammatory cycle, genetic modifiers of disease, animal models of CF lung disease, novel therapeutics in CF, and neonatal screening for CF.

Fanconi anemia (FA)

The eighteenth Annual Fanconi Anemia Research Symposium, cofunded by the NHLBI and the NCI, was held on October 22, 2006. The symposium provided information to research and medical personnel new to Fanconi anemia research and clinical care. Major sessions covered gene discovery and regulation, functions of FA proteins, hematopoiesis, stem cell transplantation, carcinogenesis and cancer prevention, leukemia, model organisms and cell-free systems, and

therapeutics. The sessions presented an overview of unanswered questions and new research directions.

Hemophilia

The RFA, Improved Therapies for Hemophilia and Hereditary Bleeding Disorders, was cosponsored by the National Hemophilia Foundation (NHF). This collaborative effort resulted in the NHLBI funding five new grants in FY 2005 and the NHF funding three additional projects in 2006.

A recombinant porcine Factor VIII is being developed by Octagen Corporation, with SBIR support, as a treatment option for hemophilia A patients who develop antibody inhibitors that neutralize the activity of currently available types of replacement Factor VIII. In FY 2005, Octagen received a competing continuation of their Phase II SBIR grant to conduct clinical trials to support FDA licensure of the product.

Hereditary hemorrhagic telangiectasia (HHT)

The second NIH workshop on Hereditary Hemmorrhagic Telangiectasia was held in May 2006 in Bethesda, Maryland. The workshop was cosponsored by the NHLBI and the National Human Genome Research Institute (NHGRI). The primary recommendation of the workshop was to stimulate basic research on HHT. A complete workshop summary and recommendations will be published on the NHGRI Web site.

The NHLBI staff met with members of the HHT Foundation and investigators in the field to discuss promoting research and overcoming research barriers. The participants recommended a patient registry, sample bank, and database to advance research and treatment development in HHT.

The staff of the NHLBI and the Center for Scientific Review conducted an afternoon session in conjunction with the NIH HHT Workshop on opportunities in training and career development and research grant writing.

Li-Fraumeni syndrome

Researchers in the NHLBI intramural program plan to recruit Li-Fraumeni subjects from a cohort being followed at the MD Anderson Cancer Center. The intramural program also is recruiting patients via the NIH clinicaltrials.gov Web site.

Long QT syndrome (LQTS)

A keystone symposium entitled “Cardiac Arrhythmias-Linking Structure Biology to Gene Defects” was held January 29 to February 3, 2006.

On September 14-15, 2006, the NHLBI and the NIH Office of Rare Diseases held a workshop on the Recognition and Treatment of Rare Inherited Arrhythmias.

Lymphangioleiomyomatosis (LAM)

The NHLBI and the LAM Foundation cosponsored the 2006 Lymphangioleiomyomatosis Research Conference, March 31-April 2, 2006 in Cincinnati, Ohio. The meeting included keynote talks as well as concurrent clinical, patient oriented and basic science sessions. The basic research session focused on the molecular mechanisms of smooth muscle proliferation and cystic lung destruction.

NHLBI participates in the Trans NIH TSC Coordinating Committee meetings led by the National Institute of Neurological Disorders and Stroke.

The LAM fact sheet was updated and revised in the Diseases and Conditions Index format. It is available on the NHLBI public Web site.

Marfan syndrome

The National Marfan Foundation is providing funds to conduct three ancillary studies in the Marfan Trial of losartan versus atenolol.

Paroxysmal nocturnal hemoglobinuria (PHN)

In August 2006, the Aplastic Anemia & Myelodysplastic Syndromes (MDS) International Foundation held its annual Patient and Family Conference in Nashville, Tennessee.

The Aplastic Anemia & MDS International Foundation held a Bone Marrow Failure Scientific Symposium in Washington, D.C., on October 17, 2005.

Persistent pulmonary hypertension of the newborn (PPHN)

A scientific meeting for investigators participating in an NHLBI Request for Applications program took place in October 2005 to discuss progress in integrative development of the lung vasculature and lung structure.

Primary lymphedema

A Gordon Research Conference on Molecular Mechanisms in Lymphatic Function and Disease, supported by the NHLBI and the NIH Office of Rare Diseases, was held September 3-8, 2006.

NHLBI staff members meet frequently with the Lymphatic Research Foundation to discuss methods to promote lymphatic-related research within the extramural community. In addition, many of the discussions involve the Trans-NIH Coordination Committee for Lymphatic Research,

which meets almost monthly. A trans-NIH working group meeting is also being developed for late summer (2007).

A clinical cardiologist from the Stanford University School of Medicine was recently recruited by the NHLBI, under the Intergovernmental Personnel Act (IPA), to initiate and promote a clinical intramural program in lymphatic disease and assist in the preparation of an initiative.

Primary pulmonary hypertension (PPH)

In FY 2006, the NHLBI provided partial funding for the 7th International Conference of the Pulmonary Hypertension Association, held June 23-25, 2006 in Minneapolis, Minnesota. The meeting consisted of scientific presentations, discussions of current knowledge and therapies for patients and clinicians, and patient support networking. The importance and usefulness of magnetic resonance imaging (MRI) and echocardiograms as diagnostic tools was discussed. Other presentations focused on the central role of inflammation and immunobiology in the development of severe PH and the identification of genes linked to both familial and sporadic PH.

The Pulmonary Hypertension Association continues to cofund, with the NHLBI, one K08 or K23 award each year to enable a young clinical investigator to pursue a research career in PH.

Progeria (Hutchinson-Gilford progeria syndrome)

A workshop on progeria was held November 3-5, 2005 to promote scientific discussions within formal and informal settings (including a poster session), and to provide an opportunity for scientists to meet with children and families living with progeria. Collaborations were formed, data were shared on a variety of topics, and new ideas were discussed. The round-table discussion by parents of children with progeria was particularly powerful. The meeting was supported, in part, by the NIH Office of Rare Diseases.

The Progeria Research Foundation has been instrumental from the beginning in promoting progeria research. As a result of their efforts, the molecular underpinnings of the disease were described in 2003.

Pulmonary fibrosis

The Coalition for Pulmonary Fibrosis held a meeting in Washington, D.C., on September 27, 2006, to discuss the NHLBI research program on IPF with Coalition members.

Sickle cell disease

The intramural program has a CRADA entitled “Nitric Oxide for Inhalation in the Treatment of Secondary Pulmonary Hypertension in Patients with Sickle Cell Anemia” in partnership with INO Therapeutics, Inc. An intramural researcher also holds investigational new drug approvals for several agents relevant to the treatment of SCD.

The NHLBI sponsors a Sickle Cell Disease Advisory Committee meeting twice a year (recent meetings were held on November 5, 2005, and June 6, 2006). The advisory committee is always attended by representatives from the SCDAA. In addition to the SCDAA, government agencies, including the Centers for Disease Control and Prevention, the Veterans' Administration, and the Health Services and Research Administration, attend.

The NHLBI convened a Working Group to develop health objectives for people with sickle cell disease. Although Healthy People 2010 includes an objective for prevention of pneumonia among children, the Working Group sought to address additional areas not included in the objective. The Working Group included consumers, health care providers, and researchers. It is the beginning of an effort to help the SCD community catch up with national efforts by specifying health objectives for people with SCD throughout the lifespan, and identifying existing, or if need be, creating new data systems for monitoring improvements in health.

Complementary to these efforts, the NHLBI also supported a conference grant in 2006 to address the problem of sickle cell pain management. The grant includes future plans to establish, over the next several years, a panel of SCD experts—appropriate specialists, primary care providers, SCD patients, and members of the SCD community—to create evidence-based guidelines covering the main areas of clinical concern in SCD, which are chronic and acute pain, renal disease, pulmonary disease, transfusion and stem cell transplantation, routine health care maintenance, women's and men's health, and psychosocial issues.

The 29th Annual Meeting of the National Sickle Cell Disease Program was held in Memphis, Tennessee, April 8-12, 2006. The meeting was cofunded by the NHLBI and the NIH Office of Rare Diseases. It included approximately 300 abstracts on basic research, clinical research, and outcomes research related to sickle cell disease. Participants included all staff from the NHLBI Comprehensive Sickle Cell Center (CSCC) program, and non-CSCC investigators from the U.S. and overseas.

An NHLBI intramural researcher presented an educational talk on sickle cell pulmonary hypertension pathophysiology, diagnosis, and treatment for hematologists at the American Society of Hematology 47th Annual Meeting and Exposition in Atlanta, Georgia on December 10-13, 2005. Hematologists were urged to look for pulmonary hypertension in patients with sickle cell disease and suggested guidelines for management were provided.

An NHLBI intramural researcher gave a presentation to European hematologists at the Advanced Workshop on Sickle Cell Disease and Related Disorders at the King's College London School of Medicine on February 9-10, 2006.

The Annual Sickle Cell Disease Clinical Research Meeting was held August 27-31, 2006, at the Natcher Conference Center, NIH campus, Bethesda, Maryland. The meeting was attended by more that 200 basic scientists, physicians, study coordinators, nurses and statisticians from across the United States. The meeting provides an opportunity for all interested investigators to discuss the progress and issues related to the NHLBI sponsored clinical trials. A program book including the agenda, roster of participants, and abstracts associated with the meeting is available.

NHLBI staff members attended the recent national meeting of the Sickle Cell Disease Association of America (SCDAA) held September 25-29, 2006, in Dallas, Texas. The meeting includes members of sickle cell community organizations from across the United States as well as patients and parents of patients with this disease. An NHLBI intramural scientist was invited to give a talk entitled "New Uses for Old Drugs In Sickle Cell Disease." Patients and their families were given encouraging news about therapeutic advances in sickle cell disease and were urged to participate in clinical trials to speed up these advances.

A Best Practices Development Conference for the Management of Acute And Chronic Pain in Adults with Sickle Cell Disease was held September 25-27, 2006, in conjunction with the Sickle Cell Disease Association of America (SCDAA) Annual National Meeting in Dallas, Texas. A panel of experts in sickle cell disease, emergency medicine, pain medicine, psychology, and nutrition, along with primary care providers, sickle cell disease patients, and members of the community reviewed available pain management recommendations, experiences, and observations. Over the 2-day meeting, they established the groundwork for best practice which could be utilized as the basis for institution-specific acute and chronic pain management in various care settings, including the emergency department, inpatient hospital services, especially on general medical service, and in outpatient settings, especially by primary care providers. Strategies were identified for the successful dissemination and implementation of best practices in collaboration with representative partners, including professional societies (specialty, emergency medicine, primary care), agencies (health care services, governmental), and patient advocacy groups. A summary of the conference was presented on September 27 to the "Adult Perspectives: Meeting Unmet Needs" public session of the Sickle Cell Disease Association of American National Meeting, after which public commentary was invited. There were an estimated 200 attendees to this session. Feedback and commentary from this forum was noted and will be incorporated into the final proceedings, which will be completed by end of February 2007. Participants in the Best Practices Conference also served on a panel for the Lonzie Lee Jones Patient Advocacy Forum on September 27, answering questions and addressing concerns raised by members of the community affected by sickle cell disease as well as their family members and advocates.

Thrombotic thrombocytopenic purpura (TTP)

TTP and processing of VWF by ADAMTS 13 are now major topics of discussion in national and international meetings, e.g., the American Society of Hematology and the Gordon Conference on hemostasis.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE (NHGRI)

Overview

The National Human Genome Research Institute (NHGRI) led the National Institutes of Health's (NIH) contribution to the International Human Genome Project (HGP). With the achievement of its final goal, the finished sequence of the human genome in April 2003, this project was successfully completed ahead of schedule and under budget, and has already begun to change the way we address rare diseases.

In October 2005, a different international consortium of dedicated scientists from six countries, again led by the NHGRI, announced the production of a very different map of the human genome, one that may prove even more powerful, because of its medical applications. This is the "HapMap," and once again all of the data has been placed in the public domain. The Genome Project spelled out the letters of the DNA code that we all share. The HapMap provides detailed knowledge of the variation in the genome. The HapMap investigates those spelling differences in the human instruction book that predispose some people to diabetes, others to heart disease, and others to cancer. In December 2006, NHGRI awarded a contract to continue the HapMap Project to make it an even more powerful tool for reveal the way in which this genetic variation is organized into chromosomal neighborhoods. The HapMap provides insight not only into the causes of common disease, but provides an important genomic tool for the understanding of the genetics of rare disease

Hereditary hemorrhagic telangiectasia

Hereditary Hemorrhagic Telangiectasia (HHT): Vascular Biology and Pahthophysiology Workshop. Almost 100 scientists and disease advocates from North America and Europe attended the meeting, which was held in June 2006. During this two-day meeting, each attendee participated in workshops focused in the following areas: the transforming growth factor-β pathway, vascular biology, endothelial biology, and organ pathophysiology. On the second day of the meeting attendees divided into workshop subgroups to discuss the future direction of HHT research. Each subgroup was asked to focus on three topics the most promising opportunities, current major obstacles, and the best ways to advance the area of research. The discussions from these workshops were then shared with, and refined by, the larger group. Although each topic had different obstacles, there was a consensus that all four subject areas would benefit from sharing of resources and tools.

Multiple endocrine neoplasia type I

Multiple Endocrine Neoplasia Type I (MEN1) is characterized the development of tumors in the parathyroid, anterior pituitary, and enteropancreatic endocrine cells. Other associations occasionally found in MEN1 patients include foregut carcinoids, facial angiofibromas, lipomas, collagenomas, meningiomas, and smooth muscle tumors. MEN1 patients typically inherit loss of function mutations in the *MEN1* gene, and tumors arise following loss of the remaining wild-type allele. The absence of the protein menin, which is produced by this mechanism, is poorly

understood. Using state of the art genome-wide chromatin immunoprecipitation coupled with microarray analysis technology, researchers set out to investigate menin's role as a transcriptional regulator and enlarge our understanding of the role of menin. Researcher found that menin not only targets specific classes of genes like *HOX* and *CDK* inhibitors, but also targets a very broad range of promoters in multiple tissues, which expands the realm of menin-targeted genes several hundred-fold. Menin is expressed in nearly all tissues, so to answer why MEN1-associated tumors arise primarily in endocrine organs researchers have proposed a model for tumor suppression by menin in pancreatic islets, which opens the door to more research into Multiple Endocrine Neoplasia Type I.

Scacheri PC, Davis S, Odom DT, Crawford GE, Perkins S, et al. Genome-Wide Analysis of Menin Binding Provides Insights to MEN1 Tumorigenesis. *PLoS Genet*, 2(4)e51. 2006. http://genetics.plosjournals.org/perlserv/?request=getdocument&doi=10.1371/journal.pgen.0020051.

Methylmalonic acidemia

Methylmalonic Acidemia (MMA) is heterogeneous, clinically and biochemically. Several different complementation groups exist. The isolated methylmalonyl-CoA mutase deficiency disorders, defined by the cblA, cblB, cblH, and mutase complementation classes, share a common defect in the activity of the adenosylcobalamin-dependent enzyme, methylmalonyl-CoA mutase. Affected patients exhibit extreme elevations of methylmalonic acid in all tissues and body fluids and are metabolically fragile. People with MMA may also have problems with learning and development and kidney functioning. NHGRI is currently conducting a study to evaluate patients with MMA to learn more about the genetic causes of the various types of this inherited metabolic disorder and the medical complications associated with them.

Charcot-Marie Tooth

Charcot-Marie Tooth hereditary neuropathies are a group of disorders in which the motor and sensory peripheral nerves are affected, resulting in muscle weakness and atrophy, primarily in the legs and sometimes in the hands. This disorder affects the nerves that control many muscles in the body. The nerve cells in individuals with this disorder are not able to send electrical signals properly because of abnormalities in the nerve axon or abnormalities in the insulation (myelin) around the axon. Researchers at NHGRI have identified the gene associated Charcot-Marie-Tooth disease, the discovery has provided the opportunity to study the function of protein it encodes. This information opens the door to further research to define the pathological consequences of disease-associated mutations, and to generate animal models of these disorders.

Chediak-Higashi syndrome

Chediak-Higashi Syndrome (CHS) is a rare autosomal recessive disorder characterized by oculocutaneous albinism, a bleeding diathesis, recurrent infection due to abnormal neutrophil and natural killer cell function, and eventual progression to a lymphohistiocytic infiltration known as the "accelerated phase." Death often occurs within the first decade because of bleeding, infection, or development of the accelerated phase; bone marrow transplantation is curative except for the

late occurrence of neurological deterioration. NHGRI researchers are continuing the study the LYST gene - the gene responsible for classic CHS-and investigate other genes that may cause milder forms of the syndrome.

Progeria syndrome

Progeria syndrome is an extremely rare genetic disease of childhood characterized by dramatic, premature aging. The most severe form of the disease is Hutchinson-Gilford progeria syndrome HGPS. As newborns, children with progeria usually appear normal. However, within a year, their growth rate slows and they soon are much shorter and weigh much less than others their age. Death occurs on average at age 13, usually from heart attack or stroke. In 2003, NHGRI researchers, together with colleagues at the Progeria Research Foundation, the New York State Institute for Basic Research in Developmental Disabilities, and the University of Michigan, discovered that Hutchinson-Gilford progeria is caused by a tiny, point mutation in a single gene, known as lamin A (*LMNA*). The spectrum of effects of this gene defect on cellular function, and how these effects culminate in the HGPS disease phenotype, are yet to be determined. Research at NHGRI has shown that anti-cancer drugs show promise when used by progeria patients. NHGRI continues to conduct studies to better understand variations in phenotypes of HGPS, and stimulate new research into HGPS and the aging diseases associated with HGPS, such as atherosclerosis. These studies will also allow us to evaluate new clinical outcome parameters and to design other appropriate therapeutic interventions.
Varga R et al. Progressive vascular smooth muscle cell defects in a mouse model of Hutchinson-Gilford Progeria syndrome. *Proc Natl Acad Sci USA*, 103(9) 3250-3255, 2006.

Gray Platelet syndrome

Gray Platelet Syndrome (GPS) is a condition that causes patients with GPS to bleed longer than others due to a lack of some of the protein carrying sacs that help form blood clots after an injury. Researchers at NHGRI are studying patients with GPS and their unaffected family members to identify the gene(s) involved in GPS using linkage analysis and gene mapping strategies. Characterization of gene(s) involved in GPS could provide important insight into the mechanisms of vesicle formation and protein sorting in human cells.

Hermansky-Pudlak syndrome

Hermansky-Pudlak Syndrome (HPS) is a rare inherited disorder that has been identified in about 400 people worldwide. Affected individuals are characterized by decreased pigmentation (ocular or cutaneous albinism), a lack of platelet dense bodies (causing bleeding problems), and their storage of an abnormal fat-protein compound, called ceroid, which leads to dysfunction in some organs. The disease can cause prolonged bleeding and poor function of the lungs and intestine; fatal pulmonary fibrosis also is a possible complication. An ongoing clinical trial at NHGRI is testing the drug pirfenidone as a potential HPS treatment. The purpose of the trial is to find out whether pirfenidone can relieve symptoms associated with pulmonary fibrosis.

NHGRI research also continues to focus on the clinical and molecular delineation of human malformation syndromes. The investigation is into two classes of disorders: classic multiple congenital anomaly syndromes and segmental overgrowth disorders. Classic congenital anomaly syndromes include disorders that exhibit various combinations of central nervous system malformations, visceral malformations, and polydactyly (extra fingers and toes), such as Pallister-Hall syndrome, Greig cephalopolysyndactyly syndrome, McKusick-Kaufman syndrome, Bardet-Biedl syndrome, and Lenz microphthalmia syndrome. Segmental overgrowth is a group of disorders, such as Proteus Syndrome, which cause highly variable overgrowth of parts of the body, such as excessive postnatal growth of bones, organs, and fatty tissue. Continued research focuses on the diagnosis and management of these disorders to one day improve the medical care of patients affected by the disorders, provide generalized knowledge about the broad field of birth defects, and better understand basic mechanisms of normal and abnormal human development.

Autoimmune lymphoproliferative syndrome

Autoimmune Lymphoproliferative Syndrome (ALPS) is a rare syndrome in which lymphocytes fail to die once they have finished doing their job, and as a result, the spleen and lymph nodes grow large, and immune cells may attack the body's own tissues, a condition known as autoimmunity. As researchers at NHGRI continue to study mutations associated ALPS, their findings are entered in to the ALPSbase, a database prepared by ALPS investigators NHGRI and NIAID. ALPSbase is available online as research resource of mutations that cause ALPS.

Holoprosencephaly

Holoprosencephaly (HPE) covers a nearly continuous spectrum of midline abnormalities ranging from unmistakable cyclopia with absence of forebrain separation to mild microforms, such a single central incisor. NHGRI is currently conducting studies aimed to identify genetic factors that contribute to the pathogenesis HPE or related brain malformations; by studying the range of defects analyses chromosomal rearrangements, uses positional cloning and gene isolation, and mutational analysis of candidate genes.

Severe combined immunodeficiency

Severe Combined Immunodeficiency (SCID) is a term applied to a group of inherited immune system disorders characterized by defects in both T and B cell responses. Caused by defects in any of several possible genes, SCID makes those affected highly susceptible to life-threatening infections by viruses, bacteria and fungi. NHGRI researchers continue to investigate the roles of genes that control the reproduction and differentiation of blood-forming stem cells in order to significantly increase the supplies of these life-saving cells for clinical use. Although NHGRI's leading intramural primary immunodeficiency investigator left the NIH in 2006, the NHGRI continues to work in this important area of applied research. NHGRI researchers have an ongoing Clinical Research Protocol that allows them to receive immunodeficient patients' samples and study them with an X-linked SCID screening assay. Since this protocol is not limited to recruiting only X-linked SCID patients, once the system is fully tested for X-linked SCID, samples from patients affected with other forms of SCID (e.g., ADA-SCID, JAK3-SCID) and other T-cell

immunodeficiencies (e.g., Wiskott-Aldrich syndrome) will extend the study to these other diseases, potentially in partnership with the public sector.

Genetic and Rare Diseases Information Center (GARD)

In order to respond to the public's need for information on genetic and rare disorders, NHGRI and the Office of Rare Diseases, NIH, maintains and supports the NHGRI/ORD Genetic and Rare Diseases Information Center. The Information Center focuses on meeting the information needs of the general public, including patients and their families, health care professionals, and biomedical researchers. The purposes of the Information Center are to: 1) serve as a central, national repository of information materials and resources on genetic and rare diseases, conditions, and disorders; 2) collect, produce, update, and disseminate information on the diagnosis, treatment, and prevention of genetic and rare disorders; and 3) coordinate with organizations and associations interested in genetic and rare disorders to explore networking capabilities, avoid duplication of effort, and identify information gaps.

See: http://rarediseases.info.nih.gov/html/resources/info_cntr.html.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

Overview

The mission of the National Institute of Mental Health (NIMH) is to reduce the public health burden of mental and behavioral disorders through research on mind, brain and behavior. A landmark NIMH-funded study known as the National Comorbidity Survey Replication (NCS-R) revealed that half of all lifetime cases of mental illness begin by age 14. In addition, the NCS-R demonstrated the severity and chronicity of the mental health problem. Seriously disabling mental illnesses such as schizophrenia, depression, bipolar disorder, anxiety disorders, and autism are the major foci of research that NIMH supports and conducts. Additional research areas of importance to NIMH can be categorized as rare diseases and include pediatric bipolar disorder, childhood-onset schizophrenia, Fragile X syndrome, suicide, and aging and HIV/AIDS.

Pediatric bipolar disorder

Reflecting a paradigm shift in clinical neuroscience, many chronic psychiatric illnesses are now hypothesized to result from perturbed neural development. However, most work in this area focuses on schizophrenia. NIMH investigators applied this paradigm to pediatric bipolar disorder (BD), studying brain structures implicated in BD, such as the amygdala, from the developmental psychobiology perspective. Research in adult patients and in animals specifically implicates the amygdala, striatum, and ventral prefrontal cortex in the pathophysiology of BD; this circuit has considerable developmental plasticity. To study potential dysfunction in this circuit, researchers have examined neural mechanisms mediating face processing in 22 youths (mean age 14.21 ± 3.11 yr) with BD and 21 controls of comparable age, gender, and IQ. Event-related functional magnetic resonance imaging (fMRI) compared neural activation when attention was directed to emotional aspects of faces (hostility, subjects' fearfulness) vs. nonemotional aspects (nose width). Compared with controls, patients perceived greater hostility in neutral faces and reported more fear when viewing them. Also, compared with controls, patients had greater activation in the left amygdala, accumbens, putamen, and ventral prefrontal cortex when rating face hostility, and greater activation in the left amygdala and bilateral accumbens when rating their fear of the face. There were no between-group behavioral or neural differences in the nonemotional conditions. Results implicate deficient emotion–attention interactions in the pathophysiology of BD in youth and suggest that developmental psychobiology approaches to chronic mental illness have broad applicability, potentially with specific circuits implicated in specific conditions.

Childhood onset-schizophrenia

Structural changes in the brain's memory centers associated with COS

Childhood onset schizophrenia (COS), defined with onset of psychotic symptoms before the 13th birthday is a rare and severe form of the illness that is continuous with its adult counterpart. Prior cross-sectional anatomic brain imaging studies of the hippocampus in schizophrenia have generally shown loss in total hippocampal volume although the progressive course of these changes remains unknown. In this study, NIMH investigators provide the first prospective sub-

regional maps of hippocampal development in COS, reconstructed from serial brain MRI scans of 29 children with COS scanned every 2 years (87 scans) and compared to 31 controls matched for age, sex, and scan interval (94 scans). As expected, the COS subjects showed significant bilateral deficits (9-10 percent) in total hippocampal volume that remained consistent between ages 9 and 26. However, sub-regional maps showed heterogeneous changes with loss of hippocampal volume in both anterior as well as posterior ends while the body of the hippocampus gained in volume. This finding suggests that hippocampal subunits are differentially affected in schizophrenia.

Genetic influences on brain development in COS

Evidence is building for a genetic influence on brain development in COS patients. Variation in the gene neuregulin 1 (NRG1) has been shown to be associated with schizophrenia in adults. In a recent study, NIMH investigators found that the gene variant is found in COS patients as well. Furthermore, the genetic variation of NRG1 is also associated with an adverse affect on brain development prior to the onset of psychotic symptoms. The researchers genotyped 56 markers spanning the NRG1 locus on 78 COS patients and their parents. Most subjects also underwent brain MRI scans at 2-year intervals. Further, the investigators genotyped a sample of 165 healthy controls to examine genetic risk effects on normal brain development. Investigators were able to identify an association between the genetic variant and poorer social functioning, a hallmark of schizophrenia. Further, the genetic variant was associated with different trajectories of change in brain volume. In the COS group, carriers of the variant had greater total gray and white matter volume in childhood. In addition, a normal part of brain development during adolescence, the loss of gray matter, was exaggerated in the COS group, with even steeper rate of loss demonstrated in those with both COS and the genetic variant. By contrast, in healthy children, possession of the gene variant was associated with different trajectories in gray matter only and was confined to specific regions of the cortex, indicating that variations in other additional genes may be necessary to induce illness.

Evaluation of available treatment options for COS

Clinicians rely on a limited evidence base to guide treatment for childhood onset schizophrenia (COS), particularly as there are no rigorous trials in children examining atypical antipsychotics, the mainstay of current treatment. In a recent study, NIMH investigators aimed to compare the efficacy and safety of olanzapine and clozapine, two atypical antipsychotic medications, hypothesizing that clozapine would be more efficacious. To address this question, the investigators initiated a double-blind randomized 8-week controlled trial, with a 2-year open-label follow-up. They found that clozapine was associated with a significant reduction in all outcome measures, whereas olanzapine showed a less consistent profile of clinical improvement. While there were moderate to large differential treatment effects in favor of clozapine, these reached significance only in the alleviation of negative symptoms (e.g., lack of facial expression, inability to initiate and maintain planned activities, lack of pleasure in daily life) from an antipsychotic-free baseline. Clozapine was associated with more overall adverse events. At 2-year follow-up, 15 patients were receiving clozapine with evidence of sustained clinical improvement, but additional adverse events emerged, including lipid anomalies (n = 6) and seizures (n = 1). While not demonstrating definitively the superiority of clozapine compared with olanzapine in treatment-refractory COS, the

study suggests that clozapine has a more favorable profile of clinical response, which is balanced against more associated adverse events.

Fragile X syndrome

Fragile X is a genetic disorder characterized by cognitive impairment ranging from learning disabilities to severe mental retardation, behavioral dysfunction and subtle physical abnormalities. In patients with Fragile X, a specific protein, the fragile X mental retardation protein (FMRP), has been found to be defective. Research has indicated that FMRP plays an important role in the synthesis of a number of other proteins in the cerebral cortex. NIMH continues to invest in this area of research and has recently reissued a Program Announcement (PA) entitled "Shared Neurobiology of Fragile X Syndrome and Autism" to stimulate research that explores the links between etiological and pathophysiological mechanisms in Fragile X and autism.

Suicide

While a number of NIMH researchers continue to work on a range of biological and psychosocial clues that may predict susceptibility to suicide risk, other researchers have developed treatments to help those who have already attempted suicide. Since a prior suicide attempt is one of the most potent predictors of later death by suicide, determining effective interventions among persons already known to have been suicidal is an important area of interest to NIMH. NIMH-funded researchers recently reported that cognitive therapy reduced the rate of repeated suicide attempts by 50 percent during a year of follow-up, regardless of the person's diagnoses (depression, substance abuse, personality disorder, etc.). Other research has also found that specific kinds of psychotherapy may be helpful for specific groups of people. For example, an NIMH-funded study reported in 2006, showed that a treatment called dialectical behavior therapy reduced suicide attempts by half, compared with other kinds of therapy, in people with borderline personality disorder (a serious disorder of emotion regulation).

FY 2006 Rare Disease-Specific Request for Applications

Aging and HIV/AIDS

Following a meeting supported by the Office of Rare Diseases (ORD) in 2002 on Mental Health Research Issues in HIV Infection and Aging, NIMH released a Request for Applications (RFA) entitled "HIV/AIDS and Aging: Basic and Clinical Research." Significant findings emerged from Institute support of neurocognitive and biological research studies in this area. NIMH-funded research in the neurocognitive area has shown that older age is associated with an increased risk for HIV-associated dementia as well as an increased risk for minor cognitive motor disorder. Early identification of neurocognitive impairment in older HIV-1-infected persons should be considered a high research priority in that such screening could be used to forestall the eventual development of the neurocognitive disorders. Two ongoing areas of research regarding neurocognitive disturbance in older HIV-infected adults are neuroimaging research of underlying brain substrates and neurobehavioral research of the functional importance/expression of cognitive deficits. In spite of escalating HIV and AIDS prevalence rates in older adults and the expectation

of longer survival periods due to highly active antiretroviral therapy, few studies have conceptualized and developed interventions for HIV-infected older persons. Future initiatives need to address HIV intervention. In addition, future work should address service delivery and comorbidity for the aged HIV infected population because research indicates that older adults living with HIV/AIDS are in need of age-appropriate mental health support services and experience more comorbid health conditions and neuropsychiatric disorders than younger HIV-infected persons.

Suicide

In 2006, NIMH supported five grants funded in response to an RFA entitled "Antidepressant Treatment and Suicidality." The studies address populations of children, youth, adults and older adults. The projects range in approach and scope. They include the examination of large, multiple data bases of persons treated with antidepressants in defined treatment systems (e.g., Medicaid, Veterans Affairs) and their outcomes, as well as smaller, focused studies on more specific patterns of responses to antidepressants (possible prodrome behaviors to suicidality; more frequent computerized self-assessments).

Significant Ongoing Rare Diseases Research Initiatives

Suicide

NIMH supports numerous projects in suicide prevention across multiple populations that address multiple risk and protective factors. NIMH continues to facilitate collaboration across three developing centers on suicide prevention (cofunded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA)) and several Veterans hospital and research centers. The American Foundation for Suicide Prevention, as a private, nonprofit partner among these centers, plans to support a collaborative project that will test the feasibility of a suicide attempt registry across several of these sites. Measurement of suicide risk developed and tested by these centers will have implications for the implementation of a new patient safety goal of identifying clients at risk for suicide by the Joint Commission on Accreditation of Healthcare Organizations.

Rare Disease-Specific Conferences, Symposia, and Meetings

Suicide

In February 2006, a conference entitled "Indigenous Suicide Prevention Research and Programs in Canada and the United States: Setting a Collaborative Agenda" was convened in Albuquerque, New Mexico to bring together representatives from research, service organizations, youth, community programs, and governments (across a range of countries, tribes, and villages). Participants were asked to share the most current information on indigenous suicide, find ways to foster communication and collaboration, and form workgroups to bring substantive research and prevention efforts to under-served indigenous communities. The conference hosted participants from the United States, U.S. Territories, and Canada. In addition to ORD support, meeting

cosponsors included NIMH, the Indian Health Service (IHS), the Division of Behavioral Health of Health Canada, Canadian Institutes of Health, the Institute of Aboriginal Peoples' Health, NIH Office of Research on Women's Health (ORWH), NIH Office of Behavioral and Social Sciences Research (OBSSR), NIDA, NIAAA, NLM, and the Substance Abuse and Mental Health Services Administration. The goals of this bi-national effort were to: foster knowledge exchange regarding what works to prevent suicide in indigenous communities, including best practices and promising strategies; increase the number of indigenous researchers and research projects that utilize community-based participatory research methods; and, promote collaborative action for suicide prevention initiatives across borders. Follow-up activities are taking place with regard to all of these goals. A complete summary of this meeting is available at http://www.nimh.nih.gov/scientificmeetings/2006/indigenous-suicides.cfm.

In FY 2005, ORD provided support for the workshop "Assessing Suicidality During Antidepressant Treatment." A full summary of this meeting is available on the NIMH Web site. This workshop has been an important source of technical assistance for NIMH staff in helping scientists, as well as the media and the public, understand the remaining questions around the possible link between suicidality and antidepressant use.
http://www.nimh.nih.gov/scientificmeetings/ssrisummary.cfm

Education Activities on Rare Diseases for The Researcher, Public, and The Health Care Providers Communities

Suicide

Educational materials on suicide for the public:

NIMH maintains information on suicide and suicide prevention on its Web site at http://www.nimh.nih.gov/suicideprevention/index.cfm.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS)

Overview

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disease—a burden borne by every age group and every segment of society worldwide. The brain, spinal cord, and nerves are vulnerable to hundreds of disorders, most of which are rare. The NINDS supports research to uncover the causes of, and develop treatments for rare disorders, while also promoting cross-cutting research on topics such as stem cells, gene therapy, and neuroimaging that will impact multiple rare neurological disorders.

The NINDS supports basic, clinical, and translational research on rare diseases through both its extramural and intramural programs. The NINDS also collaborates with the NIH Office of Rare Diseases (ORD) and rare disease patient voluntary organizations to stimulate specific research areas via workshops, grant solicitations, and strategic planning efforts. The Institute's primary support of research is through unsolicited, investigator-initiated grant awards, as investigators often have the greatest insight into the critical questions facing a particular field of research. Of the new grants funded by the NINDS in FY 2006 many focused on rare diseases. Examples include hereditary spastic paraplegia, Friedreich's ataxia, Batten disease, amyotrophic lateral sclerosis, transmissible spongiform encephalopathies, Huntington's disease, Klinefelter syndrome, spinal muscular atrophy, spinobulbar muscular atrophy, Niemann-Pick disease, and Rett syndrome.

Examples of Recent Scientific Advances Funded by NINDS

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) selectively destroys motor neurons, the nerve cells in the brain and spinal cord that activate muscles, leading to paralysis and ultimately death usually within a few years of diagnosis. Mutations in the SOD1 gene cause an inherited form of ALS that closely resembles the more common noninherited type, whose cause is unknown. Scientists have demonstrated that the mutant SOD1 gene is toxic to cells, but it is not clear whether the harmful effects are within the motor neurons themselves, or within other cell types that influence the survival of motor neurons. By selectively activating the mutant SOD1 gene in different cell types of mouse brain and spinal cord, NINDS-funded researchers have now demonstrated that while the gene acts within motor neurons at the onset and early phase of ALS, the progression of the disease is dependent on SOD1 activity within other non-neuronal cells called microglia. Microglia are the resident immune cells and the primary mediators of inflammation in the brain and spinal cord. These findings provide crucial guidance in the development and cellular targeting of therapies for ALS.

Charcot-Marie-Tooth disorder

Charcot-Marie-Tooth (CMT) is a class of slowly progressive inherited disorders affecting the peripheral nerves that connect the brain and spinal cord to the muscles, sensory organs in the limbs

and other organs in the body. CMT causes mild loss of sensation in the limbs, progressive loss of movement of the legs and arms, and in some cases pain. There are many types of CMT, classified in part depending on whether the disease targets the myelin sheath, a covering of proteins and fatty substances that insulates nerve fibers (axons) and prevents dissipation of electrical signals (the "demyelinating" forms), or the axon itself (the "axonal" forms). An NIH funded facility that screens mutations in mice to identify new genes and animal models recently identified a mouse with a mutation in a gene, GARS, implicated in CMT2D, one of the axonal forms of the disease. Researchers characterized the physiological and cellular defects in this mouse strain and found them to be very similar to human cases of CMT2D. Interestingly, the mouse mutation did not prevent expression of the GARS enzyme, nor did it affect its enzymatic activity. These data, in combination with the fact that genetically altered mice which do not produce any GARS protein do not show CMT2D cellular defects, established that in CMT2D, the mutant GARS protein has a toxic activity in addition to its normal function. The fortuitous finding of a mouse mutation in GARS has provided CMT researchers with an animal model in which to study the mechanisms of disease development and progression, and to aid in the development of potential therapies.

Down syndrome

In addition to mental retardation and cardiac problems, people with Down syndrome experience cognitive decline similar to Alzheimer's disease. Scientists have long known that an extra copy of chromosome 21 is responsible for Down syndrome. However, researchers have been unable to determine which of the hundreds of extra genes on this chromosome contribute to the symptoms. Scientists have now identified a single gene that makes a major contribution to the abnormalities associated with Down syndrome. To isolate the contributions of this gene, called App, NINDS-funded researchers used genetically engineered mice that mimicked the extra chromosome of Down syndrome, and also manipulated the level of the App gene in these mice. The studies showed that the neurodegeneration seen in mice with an extra App gene is caused by a decrease in nerve cells' ability to take up and respond to natural nerve cell survival factors called neurotrophins. Mutations in the human version of App are also known to cause an early-onset type of Alzheimer's disease. These findings suggest that enhancing the sensitivity of neurons to neurotrophins may be an effective strategy for Down syndrome, Alzheimer's disease, and perhaps other neurodegenerative diseases as well.

Muscular dystrophies

A recent study from NINDS-funded investigators uncovered the molecular mechanisms responsible for myotonic dystrophy, the most common adult form of muscular dystrophy. Myotonic dystrophy is marked by myotonia (an inability to relax muscles following contraction) as well as muscle wasting and weakness. It is known that the disease results from the expansion of a short repeat in the DNA sequence (CTG in one gene or CCTG in another gene), and it has been hypothesized that these repeat expansions result in the accumulation of abnormal RNA (the template for the translation of genes into proteins) structures. The investigators have now shown that these mutant RNAs interfere with the activities of the muscleblind gene family, a family of proteins important for regulating other skeletal muscle genes. The researchers showed, using mouse models, that interactions between muscleblind and the mutant RNAs prevented the proper

processing and expression of several skeletal muscle genes, thereby compromising function. Overexpressing the muscleblind gene in skeletal muscle rescued the myotonia in a mouse model of myotonic dystrophy. This paper provides proof of concept that restoration of muscleblind protein expression, including developing a drug to block its binding to the DNA repeat sequence, is a viable therapeutic strategy for myotonic dystrophy patients.

Rett syndrome

Rett syndrome is a developmental disorder linked to mutations in a gene on the X chromosome called MECP2. Because boys with MECP2 mutations die early in life, before they can develop Rett, girls are exclusively affected by the disease, typically beginning around the first year of life. Severe motor and language deficits, mental retardation, and physical disabilities are a common consequence of the syndrome. In the last few years, NINDS-funded researchers have made great strides in understanding how MECP2 causes disease. MECP2 is a gene repressor, meaning that it prevents the expression of certain genes. One of the genes turned off by MECP2 is BDNF, a factor important for the survival and growth for nerve cells. Mutations in MECP2 cause excess BDNF and resulting neurological problems. A recent study by NINDS-funded scientists reveals some of the underlying mechanisms of the MECP2-BDNF interaction. They found that neural activity triggers a chemical change in MECP2, which is sufficient to release the inhibition on BDNF, turning on production of this factor. During infancy, both neural activity and the expression of genes like BNDF at precise times are critical for proper development, growth of neurons, and modification of connections between nerve cells. These results show that MECP2 plays an important role in regulating these development processes and offers clues as to how mutations in the gene cause the developmental defects seen in Rett syndrome.

Spinal and bulbar muscular atrophy

Motor neurons, the specialized nerve cells which control muscle movement, are affected in spinal and bulbar muscular atrophy (SBMA), a disease which affects mostly males and is characterized by progressive weakness and wasting of the throat, facial, and limb muscles. SBMA is caused by a mutation which expands a region of the gene which codes for the androgen receptor, a protein required for the effects of testosterone on the body. The mutation produces an abnormal receptor protein which is progressively toxic to some cells. Investigators funded by NINDS have found that the expanded androgen receptor activates an enzyme known as JNK. JNK plays a role in fast axonal transport, the process by which certain cellular structures and factors necessary for growth and nerve cell function are shuttled from the cell body along the nerve cell's process (axon) to the nerve terminals that contact muscles. Because axons of motor neurons are extremely long, these cells rely on fast axonal transport for survival and are extremely sensitive to defects in this process. The researchers showed that drugs that inhibit the activity of JNK were able to restore the transport of proteins and the growth of motor neurons. The results provide a new avenue of therapeutic exploration to limit or delay the effects of SBMA.

Spinocerebellar ataxia

Spinocerebellar ataxia type 1 is a disease characterized by progressive loss of motor coordination resulting from the degeneration of neurons in the cerebellum, a region of the brain that coordinates movement. While the disease shows an adult onset, a new study by NINDS-funded researchers shows that a crucial component of the adult pathology is set-up during development of the brain. Spinocerebellar ataxia type 1 is caused by an expansion mutation in the gene SCA1 which leads to expression of an aberrantly long protein, ATXN1. Recently, NINDS funded researchers found that neurodegeneration in this disease is dependent on the expression of the mutant ATXN1 during a critical early window of brain development. Expression of mutant ATXN1 during the period when the cerebellum is forming, but not after, leads to neurodegeneration and ataxia during adulthood. These results suggest that for spinocerebellar ataxia type 1, derailing the transcription program early in life may exert broad yet subtle changes in the molecular make-up of neurons which may lead to neurodegeneration years later.

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) results from genetic defects in tumor suppressor proteins TSC1 or TSC2 and is associated with a wide variety of symptoms and disorders, from benign tumors in a variety of organs, to epilepsy, autism, and cognitive disabilities. Mutations in just one copy of TSC1 or TSC2 are sufficient to cause some of the neurological symptoms. Recently, NINDS-funded scientists made progress in understanding the molecular pathways responsible for some of the neurological defects in TSC. Mice genetically altered to abolish expression of TSC1 or TSC2 in neurons showed enlargement of nerve cell bodies, fewer and oddly-shaped nerve cell outgrowths, and altered neuronal functional properties. Mice which only expressed one copy of TSC1 or TSC2 showed similar defects in nerve cell outgrowths and cell shape. These structural defects were dependent on an enzyme that regulates elements of the cytoskeleton (the network of proteins that form the molecular scaffold of the cell) and on mTOR, a protein involved in cell growth previously implicated in TSC pathology. The results point to changes in neuronal architecture and implicate these changes in the neurological symptoms of TSC.

Recent and Planned Research Activities

The NINDS released the following grant solicitations in FY 2006 to help encourage research on rare diseases. Some of these were issued in collaboration with other Institutes and patient voluntary organizations, as indicated below.

- Therapeutics Delivery for Neurodegenerative Diseases (with other ICs from the NIH Blueprint for Neuroscience Research)
- Nuclear Structure-Function Defects in the Pathogenesis of Muscular Dystrophy (with NIAMS and the Muscular Dystrophy Association)
- Targeting Diseases Caused by Protein Misfolding or Misprocessing (with NIDDK and NIA)
- Translational Research in Muscular Dystrophy (with NIAMS)

- Functional Links between the Immune System, Brain Function and Behavior (with NIMH, NIA, NIAMS, NIBIB, and NIDA)

FY 2007 solicitations include:

- Understanding and Treating Ataxia Telangiectasia (with NCI, NHLBI, NIA, NICHD, NIDCD, NIEHS, the A-T Children's Project, and the A-T Ease Foundation)

The NINDS also funds a number of clinical trials for rare diseases. In FY 2006, recruitment began for a clinical trial of long term ceftriaxone treatment in subjects with amyotrophic lateral sclerosis (ALS). This trial is the culmination of a drug screening program that was a collaboration of the NINDS, the ALS Association, and other organizations of 1040 FDA approved drugs in 29 assays relevant to various neurodegenerative disorders. Several cephalosporins (a class of antibiotics), including ceftriaxone, showed hits in ALS relevant assays. The investigators are currently enrolling subjects for the initial stage of the trial, which is designed to determine the pharmacokinetics, safety and tolerability profile of the drug in ALS patients. If the drug is well-tolerated, the trial is expected to move directly into Phase III efficacy testing.

In addition, in FY 2006, NINDS funded a clinical trial to address one of the most common quality of life issues for children with neurofibromatosis—reading disabilities. The trial will test whether children with neurofibromatosis and reading disabilities respond to interventions known to be effective for children with reading disabilities in the general population. The study will also investigate which specific interventional method is most effective.

New NINDS intramural clinical studies begun in FY 2006 include: a study to evaluate the safety and efficacy of dutasteride (a compound which blocks the action of enzymes that convert testosterone into dihydrotestosterone (DHT)) in patients with Kennedy's disease (spinal and bulbar muscular atrophy); a study investigating how the sensitivity to touch and smell in patients with Tourette syndrome differs from that of people without the disorder; a study testing whether primary lateral sclerosis and amyotrophic lateral sclerosis affects parts of the brain responsible for thinking, planning, memory, and emotion; and a number of studies aimed at a better understanding of the mechanisms underlying motor learning in patients with focal hand dystonia.

Significant Ongoing Rare Disease Activities

The NINDS, together with NIAMS, and NICHD, has been actively implementing the provisions of the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84). NIH currently funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, as well as supplements for research fellowships and workshops and conferences to enhance activities at the Centers. NIH plans to reissue the Request for Applications for Wellstone Centers in 2007, and anticipates awarding these Wellstone Center grants in 2008. The existing Wellstone Centers will be competing with new applications for selection for the new funding period. The NIH, together with its partners in other federal agencies, and the patient voluntary community, is also actively involved in the implementation of the Muscular Dystrophy Coordinating Committee's Action Plan for the

Muscular Dystrophy. This Plan includes over 70 specific goals to accelerate progress toward the effective detection, diagnosis, treatment, and prevention of all types of muscular dystrophies. NIH has also been working to advance translational research in muscular dystrophy, for example, through the Wellstone Centers Program, as well as grants to individual investigators, some of which have been funded through program announcements specifically targeted to translational research in the muscular dystrophies.

The SMA Project is making encouraging progress towards its ambitious goal of having a drug for spinal muscular atrophy (SMA) ready for clinical testing by the end of 2007. The project has tested more than 600 chemically modified versions of one of the "lead compounds," indoprofen with improvements of more than 100 fold in efficiency of delivery to the brain and spinal cord, more than 200 fold in potency, and 2.5 fold in maximum effectiveness, as well as elimination of the major unwanted effect of the indoprofen molecule. Not all of these desirable attributes are yet combined in one drug, but progress toward that goal is moving forward. The NINDS has applied for provisional patents to cover the newly discovered compounds. This will allow the NINDS to grant a license that would enable a company to invest in the extensive clinical testing that will be necessary to bring a drug to market. In 2007 and 2008, the project will continue drug development, identifying additional lead compounds, and moving the most promising candidate drugs through efficacy testing in a mouse model of SMA, as well as additional safety studies. The NINDS is also applying lessons learned from the SMA Project in a 2007 initiative to provide medicinal chemistry resources for the development of drugs for other neurological disorders. The SMA Project highlighted the lack of access to medicinal chemistry as a major roadblock to drug development and demonstrated that these resources can be provided efficiently and effectively via a contract approach.

The NINDS, NHBLI, NIEHS, NCI, NEI, NIGMS, NHGRI, NIA, NIAID, NICHD, NCRR, and ORD formed the Trans-NIH Ataxia Telangiectasia Working Group in FY 2005. This group was instrumental in the development of the A-T Research Plan which was finalized and sent to Congress in February 2006. The plan addresses basic through clinical research, includes short and long term goals, and serves the entire research community, including scientists supported by the NIH, patient voluntary groups, and industry. The NIH has already taken several steps to implement the plan. One of the goals is to develop a multisite, international clinical trial for testing promising A-T therapies. In March 2006, the NINDS held a workshop to define clinical measures that eventually could be used in such a trial. In January 2007, NIH released a program announcement to encourage new grant applications that address goals in the A-T plan (see "2007 Solicitations" above).

NINDS also oversees and cofunds one consortium—Clinical Investigations of Neurologic Channelopathies (CINCH)—that is part of the Rare Diseases Clinical Research Network. This network was established by the Office of Rare Diseases and the National Center for Research Resources to facilitate clinical research in rare diseases, and consists of a Data Technology Coordinating Center serving ten clinical consortia (http://www.rarediseasesnetwork.org/). The CINCH consortium serves patients with Andersen-Tawil Syndrome (a Periodic Paralysis), Episodic Ataxia 1 and 2 and the Nondystrophic Myotonias. Another aspect of the network is the involvement of patient voluntary groups associated with each of these diseases. The CINCH

consortium currently has two Data Safety and Monitoring Board-approved clinical research protocols—in Nondystrophic Myotonia and Episodic Ataxia (EA) Syndrome—and recruitment of patients is under way. The third protocol on Andersen-Tawil Syndrome should open in early February 2007.

Workshops, Symposia, and Meetings

In FY 2006 the NINDS led or participated in a number of workshops relevant to rare diseases, including:

- Ataxia Telangiectasia Clinical Research Workshop
- Metabolomic Approaches to Neurological Disorders
- Third International Friedreich's Ataxia (FRDA) Scientific Conference
- Advances in the Molecular Pathogenesis and Treatment of Myasthenia and Myasthenic Syndromes: An NINDS Symposium in Honor of Dr. Audrey Penn
- Neurological Sarcoidosis Workshop
- Second DMRF-NINDS Workshop on Dystonia: Recent Advances and Future Directions
- Developing New Treatments for Tourette Syndrome: Clinical and Basic Science Dialogue
- Glycosphingolipids in Health and Disease
- NIH Workshop on the Peripheral Neuropathies

For FY 2007 NINDS is organizing several meetings on rare diseases, including:

- Conference on the Diagnosis of Multiple System Atrophy (MSA)
- NINDS International Workshop on Wilson's Disease and Other Disorders of Copper Metabolism
- Translational and Clinical Progress in the Mucopolysaccharidoses
- Translational Research in Muscular Dystrophy
- Therapeutic Development for Spinocerebellar Ataxias
- NIH Workshop on Spinal Cord Tumors

NATIONAL INSTITUTE OF NURSING RESEARCH (NINR)

Overview

NINR supports clinical and basic research to establish a scientific basis for the care of individuals across the life span: from management of patients during illness and recovery to the reduction of risks for disease and disability, the promotion of healthy lifestyles, promoting quality of life in those with chronic illness, and care for individuals at the end of life. NINR's rare diseases research investigators, using an interdisciplinary approach, examine strategies to control, manage, and prevent complications.

Recent Scientific Advances in Rare Disease Research

Ovarian cancer

Investigators have explored dimensions of family communication and decision-making in seeking information about genetic risk factors for certain types of cancer. Through focus groups of family dyads, consisting of a breast or ovarian cancer patient and a close female relative, investigators identified a range of characteristics relating to how family members shared information and made decisions on their health, gained knowledge about genetic risk, and addressed barriers to the sharing of information. Together, these findings support the inclusion of family members and the consideration of family-related factors related to genetic cancer risk information-sharing among high-risk families.

Sickle cell disease

Pain is a common and troublesome complication of sickle cell vaso-occlusive episodes. A study of children with sickle cell disease who were hospitalized for acute pain found that, in addition to high levels of pain, the children experienced disrupted sleep-and-wake patterns, as well as decreased food intake and activity levels. These complications may pose added challenges to maintaining health during hospitalizations and may have long-term health consequences. The study’s results indicate that clinicians working with children with sickle cell disease need to assess these children for sleep patterns, eating, and activity to help them maintain an adequate functional status.

NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR)

Overview

The National Center for Research Resources (NCRR) provides laboratory scientists and clinical researchers with environments and tools that they can use to prevent, detect, and treat a wide range of diseases. This support enables discoveries that begin at the molecular and cellular level, move to preclinical and animal-based studies, and then are translated to clinical research, resulting in cures and treatments for both common and rare diseases. NCRR connects researchers with patients and communities across the nation to bring the power of shared resources and research to improve human health.

Through its support of multidisciplinary research resources, NCRR is uniquely positioned to provide resource support in partnership with other Institutes or Centers to address emerging clinical and basic research needs, such as for the study of rare diseases. Expansion of NCRR's efforts in new biomedical technologies and instrumentation, development of animal models, and clinical research resources will foster interdisciplinary collaborations and advance NIH's efforts to study rare diseases.

Recent Science Advances in Rare Diseases Research

Von Willebrand disease

Von Willebrand disease is a rare, inherited disease associated with abnormally prolonged bleeding, especially gastrointestinal, urinary, and uterine, and aggravated by surgery, trauma, and obstetrical events. It is now recognized that there are a variety of forms of the disorder: Type 1, an autosomal dominant disease is associated with a quantitative reduction in von Willebrand Factor (vWF), Type 2 is usually an autosomal dominant disease associated with various qualitative abnormalities of vWF, and Type 3, an autosomal recessive disease has severely reduced or undetectable levels of vWF. Individuals may have various levels of expression of the disease but no systematic method has been developed for assessing the phenotypes of individuals with von Willebrand Disease. At the Rockefeller University, a Clinical and Translational Science Award (CTSA) institution, clinical investigators and specialists in informatics are defining the phenotypes of individuals with von Willebrand Disease in order to more clearly relate clinical characteristics with genotypes of this disease. These phenotypes will also be useful in developing tools for predicting risks of hemorrhage and to determine optimal therapy.

Adrenoleukodystrophy (ALD)

Adrenoleukodystrophy (ALD) is a rare, X-linked disorder which begins with weakness and spasticity in early childhood and progresses to dementia, blindness, and quadriparesis. The incidence in males is 1 per 17,000. If diagnosed early, ALD can be treated effectively with hematopoietic stem cell transplantation (HCT). Early changes include asymptomatic brain lesions that are detectable using selected metabolites. At the General Clinical Research Center (GCRC) at the University of Minnesota, investigators are testing the potential for high field (4 Tesla and

higher) magnetic resonance imaging (MRI) to detect early manifestations of ALD at a more treatable stage than standard MRI which is 2 Tesla. Investigators have identified several metabolites which are easily detectable in the high field MRI.

Alveolar rhabdomyosarcoma (ARMS)

Rhabdomyosarcoma is a fast-growing, highly malignant tumor which accounts for over half of the soft tissue sarcomas in children. ARMS is characterized by a chromosomal translocation that results in the fusion of two transcription factors—proteins required for the transfer of genetic information from DNA into RNA—important for muscle development, Pax3 and FKHR. Investigators at the Tulane University Cancer Genetics Center of Biomedical Research Excellence (COBRE) discovered that the oncogenic fusion protein Pax3-FKHR, when expressed within differentiated tumor cells, is more stable than is the normal Pax3 protein, which may help explain the fusion protein's tumorigenic activity in differentiated cells.

Neuroblastoma

Neuroblastoma: Neuroblastoma (NB) is a form of cancer that arises in immature nerve cells and affects mostly infants and children. About 50 percent of the children diagnosed with NB die from the disease, emphasizing the need for identification of the critical genetic and molecular changes involved in NB. The cell surface protease, dipeptidyl peptidase IV (DPPIV) is a differentiation antigen that regulates the activities of many growth factors by proteolytic cleavage. Regulated expression of DPPIV is essential for sustaining normal neural development and maintenance. Investigators at the University of Vermont, Center for Neuroscience Excellence, have shown that DPPIV is expressed in normal mammalian neurons, but its expression is lost in NB. Importantly, DPPIV abrogates the survival and tumorigenic potential of melanoma cells. The long-term goal is to further elucidate the role of cell surface proteases in regulating the molecular mechanisms involved in peripheral neural and NB development, which may open up new directions for developing novel therapeutic approaches for NB.

Usher syndrome

Usher syndrome, is the most common genetic condition that involves both hearing and vision problems. The major symptoms of Usher syndrome are hearing impairment and retinitis pigmentosa, an eye disorder that causes a person’s vision to worsen over time. Some people with Usher syndrome also have balance problems.
Investigators in the Center of Biomedical Research Excellence (COBRE) for Mentoring Vision Research at the Oklahoma University Health Sciences Center are defining the mechanisms and downstream events that occur in response to a particular mutation leading to photoreceptor cell death, translating genetic and biochemical information into effective treatments. Investigators have examined the morphological, biochemical, and functional alteration in the retinas and cochleas of mice. Their data will provide insights into the mechanisms underlying photoreceptor and cochlear hair cell degeneration and protection. Novel therapeutic strategies developed through this project might also be applicable to a multitude of hereditary neurodegenerative diseases in other systems.

Significant ongoing Rare Diseases Research Initiatives

The Rare Diseases Clinical Research Network (RDCRN

RDCRN, a collaboration between NCRR, the NIH Office of Rare Diseases, and several other NIH institutes, includes 10 Rare Diseases Clinical Research Consortia (RDCRC) and a Data and Technology Coordinating Center (DTCC). Each RDCRC is focused on a subset of rare diseases with the mission to perform, in partnership with patient advocacy groups, longitudinal studies, clinical studies and trials, train new rare diseases clinical investigators, and educate patients and physicians. This year, the RDCRN opened twenty clinical studies with at least 10 more to open soon. These studies are providing information about over 35 rare disorders. The DTCC has enabled and trained site staff on a Web-based remote data entry system that incorporates RDCRN approved standards and Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT). In addition, they have developed and implemented an electronic adverse event reporting system that includes a standard reporting structure and automatic alerts and notifications. Other innovations include a sample tracking system for samples within studies, remote direct laboratory transfer, integrated vocabulary and laboratory standards, statistical support, and Web site development and maintenance. The RDCRN vocabulary unit continues its national collaborations with incorporation of unique concepts and terms necessary for rare diseases in national vocabularies, including SNOMED CT, Health Level Seven, and the National Library of Medicine ULMS.

The RDCRN Web site (http://www.rarediseasesnetwork.org) is a source of information for the public, physicians, patients, and investigators about rare diseases. The Web site includes information about current protocols at each of the participating sites and informative links. The RDCRN has implemented a unique Web-based contact registry for patients who wish to learn about clinical studies. Telephone and paper based registration are also possible. Each Consortium provides newsletters to their contact registry participants concerning open studies and advances in their diseases. The RDCRN Coalition of Patient Advocacy Groups (CPAG), which includes all of the patient support groups affiliated with each of the consortia, has been active in supporting each other in their outreach efforts to patients afflicted with rare diseases, their families and the public.

National Gene Vector Laboratories

Established by NCRR in 1993, the National Gene Vector Laboratories (NGVLs) have two primary goals. The first is to provide gene vectors to eligible investigators for use in clinical gene transfer protocols. The second goal is to support the development of toxicology data for the applicant's Investigational New Drug (IND) submission to the Food and Drug Administration (FDA). NCRR supports the infrastructure of three NGVL vector production centers and two NGVL toxicology centers while NHLBI, NINDS, NIEHS, NIAID, NIDDK, NCI, NIAMS, NICHD, NIDCR and the Office of Rare Diseases provide supplemental funding to the NGVLs for specific vector production and toxicology studies that address their missions. The NGVLs provide retrovirus, adenovirus, adeno-associated virus (AAV), DNA plasmid, herpes virus and lentivirus vectors at a substantially reduced charge (compared to commercial services) to clinical researchers who are

studying common disorders and rare diseases such as muscular dystrophy, alpha-1-antitrypsin deficiency, Fanconi's anemia, thalassemias, hemophilias, cystic fibrosis, and leukocyte adherence deficiency.

Rare Disease Research at General Clinical Research Centers (GCRCs) and Clinical and Translational Science Awards (CTSAs) Institutions

The NCRR-supported GCRCs and CTSAs host much of the research focused on rare diseases, as there are few large clinics available specifically for these unusual disorders. A trans-CTSA work group focused on rare diseases research is addressing national best practices and activities that will facilitate rare diseases research at CTSA institutions and across CTSA institutions. While most of these studies are investigator initiated, there are industry-sponsored phase 1, 2, and 3 trials of new interventions. Since the number of affected individuals is small, the expected market is also small, limiting the interests of many pharmaceutical companies. Recognizing the need to advance the development of new agents for these diseases, the Orphan Drug Act provides incentives for companies to develop and license agents for rare diseases. The NCRR, also recognizing the need and benefit of the support of new agents for rare disease, actively encourages collaborations with industry in the CTSA program. In addition, GCRC guidelines for industry-initiated studies and trials allow GCRCs to approve use of GCRC resources without charge. Normally, companies that wish to utilize the resources of the GCRCs in the performance of their studies must pay for those resources. The CTSAs have no requirements for cost recovery on support of industry studies.

Activities with Non-Profit Organizations

The Cystic Fibrosis Foundation (CFF)

In partnership with the CFF, NCRR supports a novel approach to develop new therapeutics for cystic fibrosis, a rare genetic disease. NCRR-supported General Clinical Research Centers, which provide personnel, resources, and space for the conduct of clinical research, are utilized by many cystic fibrosis investigators. In addition, NCRR supports a coordinating center, which provides informatics support for the management, conduct, and analysis of the studies. This biomedical informatics component includes a secure, interactive Web environment for network communication and data entry, as well as a biostatistical unit. These resources facilitate transfer of new discoveries from bench to bedside.

The National Disease Research Interchange (NDRI)

The NDRI founded in 1980, is a not-for-profit organization in Philadelphia. NCRR provides support for approximately one-third of their activities via a cooperative agreement. NDRI personnel obtain commitments from academic pathologists to provide human tissues for basic research and statements of need. These two lists, with very specific clinical details (but without patient identifiers), are kept in NDRI databases. When a tissue becomes available, a researcher is contacted by NDRI staff and asked if he/she can accept it. Upon positive reply, the pathologist is notified, prepares the tissue according to the researcher's protocol and sends it, anonymized, to the researcher. The researcher pays a relatively small fee. Through this cooperative agreement, NDRI

facilitates laboratory research on a broad variety of rare and common diseases by providing tissues obtained from individuals afflicted with such disorders to laboratory researchers engaged in studying those specific diseases.

The agreement is currently cofunded by NCRR, the Office of Rare Diseases, and five other NIH ICs.

NATIONAL LIBRARY OF MEDICINE (NLM)

Overview

The National Library of Medicine provides information resources useful to rare disease research and to those seeking information about conditions that affect them or their families.

Database resources

- Citations to articles on rare diseases have long been available in the MEDLINE database, now accessible to researchers, health professionals, and the public through NLM's free Web-based PubMed system, and also in the TOXNET system. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi and http://toxnet.nlm.nih.gov/
- MedlinePlus, NLM's consumer health information service, has a general rare diseases page, which has been effective in referring members of the public to the NIH Office of Rare Diseases at http://www.nlm.nih.gov/medlineplus/rarediseases.htmll and was accessed 17,672 times during FY 2006. MedlinePlus also incorporates links on health topic pages to Genetics Home Reference, a new NLM database which includes many rare diseases. Currently there are 221 links from MedlinePlus to Genetics Home Reference topics such as amyotrophic lateral sclerosis, Gaucher disease, and Marfan syndrome. In addition, MedlinePlus has continued to add topics on specific rare diseases requested by consumers; examples during FY 2006 included Friedreich's Ataxia, Hidradenitis Suppurativa, Rett Syndrome, Rickets, Thalassemia, Usher Syndrome, and Von Hippel-Lindau Disease. MedlinePlus also acquired a new interactive health tutorial about newborn screening for rare diseases. The suite of MedlinePlus Go Local Web sites, which direct users of MedlinePlus pages to services for their diseases and conditions, includes links to genetic counselors, clinical trials, and research centers.
- The Genetics Home Reference (GHR) is the NLM's Web site for consumer information about genetic conditions and the genes and chromosomes responsible for those conditions. GHR's integrated Web-based approach provides brief, consumer-friendly summaries of genetic conditions and related genes and chromosomes. Understanding is enhanced by direct links to glossary definitions and a handbook called "Help Me Understand Genetics" that explains fundamental genetic concepts. Additional links to consumer information from MedlinePlus, applicable clinical trials, and relevant patient support groups are provided. Each summary also includes links to advanced information from the NLM and other authoritative sources. GHR currently offers summaries for more than 210 genetic conditions, including numerous rare diseases and disorders; 357 genes related to these conditions; and each of the 23 pairs of human chromosomes. GHR's content includes information for all the rare metabolic disorders listed in the Health Resources and Services Administration's recommended core testing panel for newborn screening. New content is added and updated on a regular basis, and reviewed by experts in human genetics. http://ghr.nlm.nih.gov/

- ClinicalTrials.gov, the NLM consumer health information system for linking patients to medical research, currently includes over 36,800 studies. Of these, about 12,907 represent approximately 1051 rare disease conditions. Also, since FY 2003, study records in ClinicalTrials.gov, including those investigating rare diseases, were linked to relevant genetic

condition summaries in Genetic Home Reference. Such links provide consumers seeking information about clinical trials with additional background about the conditions and the genes responsible for the conditions. http://clinicaltrials.gov/ and http://ghr.nlm.nih.gov/

Research support

- NLM, working in partnership with organizations in Africa, the United States, the United Kingdom and Europe, has created MIMCom.Net, the first electronic malaria research network in the world. Using satellite technology, the network provides full access to the Internet and the resources of the World Wide Web, as well as access to current medical literature, for scientists working in Africa. The African research sites are of recognized high quality, require improved communications to accomplish ongoing research, and have the necessary resources to purchase equipment and sustain the system. http://www.mimcom.net/

- NLM is assisting NCRR in establishing the NIH-funded Rare Disease Clinical Research Network as an early test-bed for the use of standard clinical vocabularies to improve the efficiency of clinical research.

Grants

- Several recent publications (including those of the PI) have sought to recount and analyze the arrival of bubonic plague in San Francisco during the year 1900. The outbreak -the first in North America-generated radical and conflicting responses from federal, state, and local authorities, merchants and medical elites. According to the existing sources, this outbreak was restricted to Chinatown, leading to dramatic public health measures such as several quarantines of the entire district and repeated sanitary campaigns inside its perimeter that culminated in the demolition of houses and threats to permanently expel all inhabitants. Most of the information about the plague and its impact has come from official municipal, state and national authorities, as well as accounts published in local newspapers. They reflected the new medical concepts of disease based on bacteriology as well as the old prejudices of class and race aimed at the afflicted Chinese community. However, the available historical works share a common shortcoming: they never view the events through the eyes of the Chinese. Therefore, it is time to balance these reconstructions by including the contemporary ideas, feelings, and reactions of the community directly affected by the plague: the people of Chinatown. This project proposes to remedy the omission by systematically examining both the news and editorials dealing with plague, public health, and medicine, printed in the leading San Francisco Chinese language publication of the day, the daily newspaper Chung Sai Yat Po ((China West Daily). Preliminary investigations suggest that during the plague this widely circulated newspaper became an influential voice in the community, breaking ethnocentric barriers and encouraging the community to organize and fight discrimination. Combining this important source with additional Chinese and English -language sources, the proposed project aims to produce a monograph that integrates both the Western and Chinese narratives of the bubonic plague outbreak from 1900 to 1904 within a genuine transcultural framework. Moreover, a Web site containing the data obtained from this study will further facilitate the dissemination of this information. The conclusions may offer valuable lessons for understanding the contemporary

management of public health campaigns for global epidemic outbreaks such as AIDS, SARS and avian influenza as well as the health consequences of natural and terrorist disasters.

- Though most chronic diseases/conditions in childhood are very uncommon (<1/3000), together they affect about 13 percent of children in the United States. A busy pediatrician or family physician will care for many such patients, though few, if any, of her/his other patients will share the same diagnoses. Providing optimal care for Children with Special Health Care Needs (CSHCN) is challenging, requiring up-to-date knowledge, ready access to specialized health care resources, and considerable time to manage and coordinate care. Families and educators are also key providers of care and CSHCN will benefit when all the providers are enabled with information and when they work together as partners. These are key components of a "Medical Home". This project seeks to support primary care physicians, as well as families and educators, in meeting these challenges by providing a Web-based information and resource access system. The Utah Collaborative Medical Home Project (UCMHP) has developed the MedHome Portal (http://www.medhomeportal.org) to accomplish this goal. This proposal will further development of the site's infrastructure, enhance its utility and usability, and its offerings and its impact through the following specific aims: (1) Convert to an XML data structure and complete authoring and content management tools, integrating UMLS indexing. Use of XML will provide a robust and flexible structure for data and documents. UMLS indexing will allow optimal searching and navigation. Site and content management processes/tools will enable rigorous development and review of content and maintenance of current information on services. (2) Expand and optimize utility and usability of the MedHome Portal: Usability testing will drive ongoing improvement in presentation, navigation, and personalized features. Accessibility will be optimized. (3) Work with partners to expand content and impact of the Portal. Regional and national partnerships will expand content development and peer review, offer MedHome Portal resources through clinical information systems, and enable other locales to access customized versions of the Portal with local service listings. Promotion and training will be integrated for physicians, families, educators, and others. With increased registered user base, enhanced evaluation will be possible. Health system and public health partnerships will support long-term sustainability.

Rare Disease Research Initiatives

The National Center for Biotechnology Information (NCBI), a division of the NLM, serves as a national public resource for molecular biology information. In this capacity, NCBI establishes and maintains various genomic databases and develops software tools for mining and analyzing this data, all of which is freely available to the biomedical community to support research into the processes affecting human health and disease.

The human genetic map

NCBI is responsible for collecting, managing, and analyzing the growing body of data being generated from the sequencing and mapping initiative of the Human Genome Project. NCBI makes the sequence of the entire human genome, with its complement of over 26,000 known and predicted genes, available without restriction to the research community and to the general public. This unrestricted access has expedited the decoding by the scientific community of important

human genes, and as a result, scientists are beginning to understand the causes of many rare diseases. Access to the complete human genome and the related genetic data at NCBI helps scientists determine the organization of the genes on a chromosome, study how these genes produce their protein products, investigate how changes in a gene's DNA sequence give rise to a disease-causing mutation, and study how chromosomes are duplicated and inherited. Scientists have used these strategies to study gene defects on chromosomes 21 and 22 that lead to a variety of rare diseases, including Downs syndrome, Usher syndrome, DiGeorge syndrome, and Ewing's sarcoma. NCBI investigators have also played an instrumental role in the identification and analysis of other disease genes and genetic loci, and have analyzed genetic data leading to scientific advances in the understanding of several rare diseases and disorders, such as the identification and analysis of the genes for Kallmann syndrome and neurofibromatosis (NF1). Examples of the many rare diseases currently being studied by NCBI investigators include ataxia telangiectasia, breast cancer, hyper-IgE syndrome, nemaline myopathy, obesity, Fukuyama's muscular dystrophy, type II xanthinuria, xeroderma pigmentosum, kyphoscoliosis, sporadic hyperekplexia, autosomal-recessive polycystic kidney and hepatic disease, Imerslud-Grasbeck syndrome, amish microcephaly, common variable immudeficiency (CVID), nasopharyngeal carcinoma, and autoimmune lymphoproliferative syndrome (ALPS).

Genetic analysis software

NCBI investigators are working to develop, implement, and disseminate high performance computational tools and application software packages for the analysis of genetic data and its linkage to disease. Several of these software packages are described below.

FASTLINK is a computer program designed to analyze the associations between genes and genetic markers that lie near each other on a chromosome, a process called "genetic linkage analysis". Genes and other genetic markers that are linked are often inherited together and, therefore, can be used to map the location of a disease gene. NCBI scientists have used FASTLINK to study hyper-IgE syndrome, a rare immunodeficiency characterized by recurrent skin abscesses, pneumonia, and highly elevated levels of serum IgE. Using FASTLINK, researchers were able to find evidence linking this syndrome to chromosome 4. FASTLINK has been cited in over 400 other published genetic studies, including studies of macular dystrophy, type 1 hereditary sensory neuropathy, and Alstrom's syndrome.

CASPAR (Computerized Affected Sibling Pair Analyzer and Reporter) is a computer program designed at NCBI to study the genetics of complex diseases, or diseases involving the interaction of multiple genes. It allows a scientist to explore various hypotheses about how different factors may be involved in disease susceptibility. NCBI investigators have used CASPAR to study linkage analysis in patients with a form of diabetes.

The PedHunter computer program was developed to query genealogical databases to uncover connections between relatives that are afflicted with the same disease and to construct a pedigree suitable for genetic linkage analysis. NCBI scientists are using PedHunter to query the Amish Genealogy database to collect information on various genetic diseases, including nemaline myopathy, a rare genetic neuromuscular disorder that is usually apparent at birth and is

characterized by extreme muscle weakness. Using PedHunter, in combination with other genetic analysis software, NCBI investigators have demonstrated that, in the Amish, this disorder is caused by a mutation in the gene for the sarcomeric thin-filament protein, slow skeletal muscle troponin T (TNNT1). TNNT1 maps to chromosome 19 and has been previously sequenced. Further analysis resulted in the identification of a stop codon that segregated with the disease. Researchers concluded that Amish nemaline myopathy is a distinct, heritable, myopathic disorder caused by a mutation in TNNT1.

The Comparative Genomic Hybridization (CGH) analysis software package is being used by NCBI investigators for modeling the process of tumor formation in various forms of cancer. The function of the software is to develop models that relate genetic aberrations with tumor progression. Investigators have used CGH as part of a larger project to search for and identify possible susceptibility loci involved in both breast and bladder cancer. Investigators have also published the results of a case study in which CGH was used to analyze chromosomal abnormalities in a large collection of ovarian cancer samples.

Three-dimensional structure database

NCBI's Structure Research Group maintains a database of experimentally determined three-dimensional biomolecular structures, as well as tools for structural visualization and comparison. Studies of three-dimensional structures provide insight into the biological function of a macromolecule, its evolutionary history, and its interaction with other macromolecules. These insights greatly enhance our understanding of the causes of rare diseases, and can lead to better diagnostic tools and therapies.

Important insights provided by structural analysis can be illustrated in the case of leptin, a protein encoded by a gene linked to obesity and to some forms of diabetes. After the discovery of leptin, researchers analyzed the protein's sequence and were surprised to find that it was unlike that of any other known protein. In 1995, NCBI investigators hypothesized that, although the sequence of leptin could provide no direct clues to the identities of its molecular relatives, its three-dimensional structure might. Investigators conducted a search of the NCBI Structure database to determine whether this protein might adopt a folding pattern, or structure, similar to that of a protein already in the database. They predicted that leptin's sequence could indeed adopt a structure characteristic of a family of important regulators of cell growth that includes interleukin-2 and growth hormone. Subsequently, in 1997, this early prediction was confirmed by direct X-ray structure determination. Since 1997, many other members of this family of growth regulators have been shown to have three-dimensional structures similar to that of leptin. These include prolactin, a regulator of lactation; oncostatin, a regulator of both tumor and normal cell growth; thrombopoietin, erythropoietin, and stem cell factor, regulators of the growth of a variety of cell types including blood cells. Future studies of leptin, other leptin-regulated genes, and other members of leptin's structural family, may reveal the mechanisms by which leptin exerts its effect on the body.

Malaria genetics and genomics

Human malaria is caused by four Plasmodium parasites, P. falciparum, P. vivax, P. ovale, and P. malariae. Although P. vivax is widespread, P. falciparum is the most severe and lethal tropical parasite, leading to an estimated 1-2 million deaths each year, mostly of children in Africa. The resurgence of malaria in recent years is mainly attributed to the emergence and spread of multiple-drug-resistant parasites and insecticide-resistant mosquito vectors, presenting a serious problem for travelers and the military in malaria-endemic regions as well as for the resident populations. Accordingly, much research at the NIH focuses on the treatment and prevention of malaria, which is a curable disease if promptly diagnosed and adequately treated.

The NCBI, in collaboration with the NIAID, has supported the efforts to sequence and analyze the complete genome of P. falciparum and related parasites, thereby providing researchers with access to information relating to all of the genes found in these parasites. Moreover, a collaborative team of NIH investigators, including researchers from the NCBI, have constructed a genome-wide, high-resolution genetic linkage map of P. falciparum. The computer analyses based on these genetic parameters and markers have facilitated genome sequence assembly and are continuing to characterize the genes involved in parasite resistance to multiple drugs. Computations are also being used to trace the evolution and spread of these genes in parasite field populations in Africa, Asia and the Americas.

The NCBI, in collaboration with the WHO's Special Programme for Research and Training in Tropical Diseases (TDR) and other international partners, has continued to support the international outreach efforts to train scientists in developing countries to use current bioinformatics tools and genomic data, such as the mosquito and malaria genome, for their own research. NCBI staff have provided coordination and instruction at several international bioinformatics training courses and centers in Africa, Asia, and South America, including the WHO/TDR sponsored Regional Training Course in Bioinformatics Applied to Tropical Diseases.

Toxoplasma genetics and genomics

NCBI researchers have also been instrumental in developing genetic and genomic computational resources of the Apicomplexan parasite, Toxoplasma, which serves as an experimental biological model for malaria and other related parasites and is itself a significant cause of such diseases as mother-to-fetus transmitted congenital encephalitis, ocular chorioretinitis, and AIDS-related neurological conditions including dementia. In collaboration with extramural laboratories and genome centers, NCBI researchers have helped to construct the genome-wide genetic map and recombination parameters of the three predominant lineages found in human Toxoplasma infections and have used genetic linkage to identify a major parasite protein kinase gene that determines acute virulence. Such genetic and genomic resources and computational analyses are helping to develop a detailed molecular understanding of these relatively intractable persistent parasitic diseases.

Database of the major histocompatibility complex

The NCBI dbMHC database provides an open, publicly accessible platform for DNA and clinical data related to the human Major Histocompatibility Complex (MHC). MHC research and clinical data generated at meetings such as the International HLA Workshop and Congress has proven valuable to the international research community. NCBI makes these data available along with tools for submission and analysis of research data linked to the MHC. The dbMHC contains reagent data used for tracing DNA typing and a section with anonymous clinical data from MHC-related research projects related to diseases such as celiac disease, narcolepsy, ankylosing spondylitis, and hemochromatosis.

Additional human genome resources

NCBI makes available a number of other resources to facilitate the widespread use of human sequence data. The Human Genome Resources Web page serves as a focal point for biomedical investigators from around the world enabling them to use this data in their research. From the Human Genome Resources Web page, researchers can access the NCBI Map Viewer, which presents a graphical view of the available human sequence data in conjunction with cytogenetic, genetic, and physical maps. Researchers may quickly search for a gene or a gene marker of interest by querying against the entire human genome. Query results link to a graphical display of the gene or gene marker within the context of additional data. The coupling of the human genome sequence with genetic and physical maps bearing markers associated with disease helps researchers to identify candidate genes for further research. The NCBI Map Viewer also allows the maps and genomic sequences of organisms used in models of human disease, such as mouse and rat, to be viewed alongside the human maps. The ability to compare sets of genomes in this manner allows researchers to use the results obtained in their laboratories with these model organisms to better understand the roots of human disease.

NCBI's Genes and Disease Web page is designed to introduce visitors to the relationship between genetic factors and human disease. Genes and Disease provides information for more than 80 genetic diseases, including many rare diseases. A resource for both researchers and the general public, the Online Mendelian Inheritance in Man database, (OMIM), is a continuously updated catalog of inherited human disorders and associated sequence mutations, authored and edited by Dr. Victor A. McKusick and colleagues and developed for the Web by NCBI. OMIM now contains over 17,000 entries for diseases linked to over 11,000 locations on the human genome. Over 2500 records in OMIM are linked to GeneTests, a portal to information on genetic testing and its use in disease diagnosis, disease management, and in genetic counseling. Screens for a wide array of rare diseases are detailed in GeneTests. A few of interest include tests for Cystic Fibrosis, Marfan syndrome, Spinal Muscular Atrophy, Hereditary Nonpolyposis Colon Cancer, and Neurofibromatosis.

One of the primary reasons for sequencing the human genome was to gain an understanding of the role of genes in human disease. By studying the gene sequences associated with a human or model organism disease, researchers can gain important insights into the genetic and environmental basis of disease. The advances outlined here demonstrate the importance and utility of NCBI's

computer databases, data analysis tools, and software algorithms in identifying and understanding human disease genes; they will pave the way for the development of novel strategies to diagnose, treat, and ultimately, prevent, disease.

Partnerships

NCBI partners with ORD in their Collaboration, Education and Test Translation (CETT) program, a Federal effort to promote development of genetic tests for rare diseases. An important component of this project involves collecting de-identified information about the phenotypic traits associated with specific mutations. These data will allow a greater capability to identify genotype-phenotype associations and test result interpretation with the goal of further the understanding of diseases leading to improved diagnostics and treatments. NCBI is a member of the CETT staff, counseling and supporting CETT awardees on clinical and genotype data collection and management for future use in the GaP database.

Working with the Genetic Alliance, a consortium of patient advocates representing 575 organizations, NCBI is creating a portal page to facilitate understanding and use of scientific information by those living with rare genetic disorders. The portal features pre-filtered, disorder-specific introductory materials prepared by the NIH, including MedlinePlus, Genetics Home Reference and educational materials from the NHGRI. It offers direct links to GeneTests and Gene Reviews, as well as PubMed searches into patient-oriented categories, targeted display of the NCBI Bookshelf to encourage exploration by nonscientists, and annotation of some Entrez databases to enhance their value to lay users. The portal will be active in early 2007 through the Genetic Alliance Web-site. Dr. Jim Ostell and Dr. Lisa Forman, NCBI staff members, have given presentations at the Genetic Alliance's annual conference. Dr. Ostell spoke on the role of information technology in identifying promising treatment strategies and Dr. Forman hosted a hands-on workshop on PubMed searching.

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE (NCCAM)

Overview

Congress established NCCAM to lead the Federal Government's activities in research on Complementary and Alternative Medicine (CAM). NCCAM conducts and funds research, disseminates information and trains CAM researchers. In fulfilling its Congressional mandate, NCCAM is continuing to support a broad research portfolio of basic and clinical research addressing the efficacy, safety and mechanisms of action of CAM therapies in a number of rare disease areas.

Ongoing and Planned Rare Disease Research

Cancer

Childhood Cancers

NCCAM researchers are conducting a clinical trial to establish if electroacupuncture will assist in reducing nausea and vomiting in pediatric patients after chemotherapy for solid tumors. They have been successful in recruiting and treating patients with solid tumors such as Ewing's Sarcoma, Osteosarcoma and Synovial Sarcoma. They are also assessing the effects of electroacupuncture on biomarkers for stress. If the final analyses warrant further investigation, the researchers plan to design a larger trial with longer intervention periods, and utilize brain imaging techniques to assess the neurological effects of electroacupuncture.

Neurological Disorders

Alzheimer's disease

Two separate groups of NCCAM supported scientists are investigating naturally occurring compounds and their effects on Alzheimer's disease (AD). One group is investigating an extract from pine cones, Pinitol, and its effects on inhibiting the formation of beta-amyloid peptides in an AD animal model. A second group is examining if diets containing omega 3 fatty acids can aid in slowing the progression of AD in animal models. Both projects will also add to knowledge about the pathogenesis of AD.

Parkinson's disease

After 3-5 years of conventional medical treatment, Parkinson's disease (PD) patients begin to show debilitating side effects of their medication. NCCAM supported researchers are investigating whether an Ayurvedic treatment for PD (mucuna pruriens) can prevent the involuntary movements or dyskinesias suffered by PD patients.

Another group of NCCAM funded researchers are investigating whether consuming blueberry extract will assist in the viability of neuronal tissue which was transplanted in elderly subjects. The research, still in its infancy, if shown to be effective, could compliment conventional treatment for Alzheimer's and Parkinson's disease by assisting the survivability of transplanted neuronal tissue.

Epilepsy

NCCAM is supporting two separate studies addressing whether two specific dietary supplements could be complementary treatments for epilepsy. In one project, the investigator is studying the anticonvulsant properties of compounds extracted from the Passionflower. The extract will first be tested in an animal model of epilepsy. If promising results are obtained, the investigator plans to conduct pilot clinical trials using the selected compound as an augmentation to conventional treatment to reduce seizures and anxiety in epileptics.

In the second study investigators are determining if a popular creatine dietary supplement might have metabolic protective properties for epileptics. If successful, the investigators hope to demonstrate that creatine could complement conventional therapy. This research also contributes basic understanding about the metabolic pathology and physiology of epilepsy.

Multiple sclerosis

NCCAM funded researchers are investigating the potential value of an antioxidant, Lipoic Acid (LA) as an experimental treatment for Multiple Sclerosis (MS). The investigators will assess the safety and immunological effects of LA in a randomized placebo controlled trial involving patients with relapsing MS.

Amyotrophic lateral sclerosis

Investigators at one NCCAM Center of Excellence for Research on Complementary and Alternative Medicine are studying how an antioxidant can be used to treat Amyotrophic Lateral Sclerosis (ALS). They are studying the molecular and cellular mechanisms of Uric Acid in cell cultures and animal models of ALS. This work highlights NCCAM's commitment to pursue the mechanisms by which CAM therapies affect the cellular and molecular.

Other Rare Diseases

Cystic fibrosis

Antibiotic resistant bacteria are a public health threat of heightened concern among populations with compromised lung function. One group of NCCAM supported scientists is investigating whether a probiotic, *Lactobacillus*, could be utilized as a treatment to prevent bacterial infections, primarily *S. areus* and *P. aeruginosa*, in children suffering from Cystic Fibrosis. The investigators are planning to conduct a pilot study to determine the appropriate methodology and to determine if the hypothesis warrants testing in a larger population.

P. aeruginosa infection in patients suffering from Cystic fibrosis (CF) is a common cause of morbidity and mortality. NCCAM supported investigators are studying if ginseng can cause an enhanced immune response thus assisting the body in clearing bacterial infections. The researchers are determining if a specific extract of ginseng is more potent than others in providing the desired response. The results of this research would provide a complementary therapy to assist in treating or preventing bacterial infections in CF patients.

Liver disease

A naturally occurring compound, S-adenosylmethionine (SAMe), is vital to normal cellular function. NCCAM supported investigators are examining how SAMe affects various compounds which are responsible for regulating cell cycles in both normal liver cells and liver cancer cells. They are also attempting to determine which genes are regulated and which proteins are manufactured as a result of SAMe exposure to cell cultures, and the effects of chronic hepatic SAMe deficiency on liver fibrosis.

Crohn's disease

An NCCAM funded research team is expanding on their earlier preliminary observations to determine whether dietary modifications can assist in the management of Crohn's Disease (CD). A clinical study will address the idea that dietary intervention or a fructooligosaccharide supplement can prevent flare-up in patients with inactive CD and if the same modifications result in a change in the microflora of the colon. The clinical manifestations associated with any observed changes in colonic microflora will be investigated further. The study could provide information to suggest diet as a safe therapy for inflammatory bowel disease.

OFFICE OF RESEARCH ON WOMEN'S HEALTH (ORWH)

Overview

The Office of Research on Women's Health (ORWH) serves as the focal point for women's health research for the Office of the Director, NIH, to ensure that research on women's health is appropriately addressed and supported across the NIH ICs, to ensure that women are appropriately represented in biomedical and bio-behavioral research studies supported by the NIH, and to develop and support opportunities for biomedical careers for women or investigators interested in women's health research.

The report, *An Agenda for Research on Women's Health for the 21st Centur*y, provides the basis for ORWH to collaborate with the scientific and advocacy communities to address scientific initiatives about women's health and sex and gender factors in health and disease. Research priorities for women's health emphasize the importance of interdisciplinary collaboration. Some rare diseases are identified in this research agenda as areas of priority for which there are gaps in knowledge that need to be addressed. ORWH continues to successfully partner with ICs to fund or cofund new and innovative research, both basic and clinical, related to women's health or sex and gender factors. Because the ORWH does not have direct funding authority, ORWH support for research initiatives is always in conjunction with the primary institute or centers.

Research funded during FY 2006 by the Office of Research on Women's Health (ORWH)

During fiscal year 2006, the ORWH supported 9 grants classified as "rare diseases" by the NIH for a total of $917,955. Studies that will expand knowledge about multiple sclerosis (MS) were funded in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Allergy and Infectious Diseases (NIAID); whereas studies of Temporomandibular Joint Dysfunction (TMJD) were funded in collaboration with the National Institute of Dental and Cranial Disorders (NIDCR) and the National Institute on Aging (NIA).

FY 2006 Scientific Activities in Rare Diseases Research

Multiple sclerosis

The study funded with NINDS utilizes an animal model, experimental autoimmune encephalomyelitis (EAE), for multiple sclerosis (MS) found that treatment with 17estradiol (E2) can prevent clinical and histological signs of EAE and has narrowed the candidates that contribute to this preventive effect. The study promises to elucidate the mechanisms through which this effect occurs and establishing these pathways may have direct relevance for future clinical trials in MS patients. Three (3) Autoimmune Centers of Excellence support large translational studies that bridge basic science with clinical research are funded with NIAID. Within these large center grants, MS-specific studies are being undertaken along with a variety of studies focused on other autoimmune disorders such as Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and autoimmune diabetes (IDDM).

Temporomandibular joint dysfunction

A study funded with NIDCR tests the efficacy and elucidates the mechanisms of action of a brief behavioral intervention that promises to reduce pain and improve function in persons with temporomandibular joint dysfunction (TMJD). Another study with NIDCR aims to study the relationship between the levels of TMJD pain and phases of the menstrual cycle and to test the effects of pharmacological and nonpharmacological treatments alleviating this pain. A genetic project seeks to identify and characterize genes through which steroidal hormones affect the onset and/or the severity of human disease. In addition ORWH and NIDCR have established a TMJD implant registry and repository that will allow collection of clinical information and biological specimens in patients with TMJ implants across the United States. A study funded with NIA promises to elucidate the mechanisms by which of follicle stimulating hormone (FSH) may inhibit the shedding of receptors for and stimulate the cytokines that contribute to post menopausal skeletal health by examining leukocytes isolated from the blood of pre- and perimenopausal women was begun in 2006. An understanding of these mechanisms may lead to new therapies aimed at modulating FSH to eliminate health problems associated with depleted estrogen levels in menopause.

Future plans

ORWH cosponsored a workshop with NIAID on the importance of sex differences in *The Regulation of the Inflammatory Response*. This very successful meeting is summarized in full at http://orwh.od.nih.gov/ and should lend impetus to innovative studies or research projects in the future.

OFFICE OF TECHNOLOGY TRANSFER (OTT)

Overview

The NIH Office of Technology Transfer evaluates, protects, monitors, and manages the wide range of NIH and FDA discoveries, inventions, and other intellectual property as mandated by the Federal Technology Transfer Act and related legislation.

To accomplish its mission, OTT oversees patent prosecution and negotiates and monitors licensing agreements. OTT performs similar functions for patenting and licensing activities for the Food and Drug Administration (FDA), another component of the Department of Health and Human Services (HHS).

Other major functions within OTT include the development of technology transfer policies for NIH and with the other two major research components of HHS (the FDA and the CDC) and the implementation of decisions by the Technology Transfer Policy Board.

Employee Invention Reports submitted by the ICs to OTT during FY06 that relate to rare diseases or conditions

OTT Reference	Institute	Lead Inventor	Invention Title
E-003-2006	NCI	Dr. Ira H. Pastan	Recombinant Immunotoxin Isolated By Antibody Phage Display And Invitro Affinity Maturation Target Human Glycoprotein NMB (GPNMB) And Exhibit Anti-gloima, Anti-melanoma, Or Any Other GPNMB-expressing Tumor Cytotoxic Activity
E-025-2006	NCI	Dr. Barry R. O'Keefe	Antiviral Activity Of Griffithsin Against SARS And HCV
E-027-2006	NICHD	Dr. Constantine A. Stratakis	Identification Of Inactivating Mutations Of The PDE11A Gene In A Form Of Micronodular Adrenocortical Hperplasis, An Inherited Form Of Cushing Syndrome
E-075-2006	NIAID	Dr. Alan G. Barbour	Monoclonal Antibody To The Major Flagellin Protein (FLaB) Of Species Of The Bacterial Genus Borrelia. (Mab H9724)
E-083-2006	NIAID	Dr. Steven M. Holland	A Newly Discovered Bacterium In The Family

			Acetobacteraceae
E-086-2006	NCI	Dr. Richard A. Morgan	Construction Of Improved T Cell Receptors
E-090-2006	NCI	Dr. Maria R. Parkhurst	Immunotherapy With Natural Killer Cells Expanded Ex Vivo After Nonmyeloablative Lymphodepleting Chemotherapy
E-136-2006	NHLBI	Dr. J. Joseph Melenhorst	The Use Of Transfected, Activated T Cells For The Expansion Of Antigen-specific CD4+ And CD8+ T Cells For Adoptive Immunotherapy
E-180-2006	NIAID	Dr. Zhaochun Chen	Neutralizing Mabs To Botulinum Neurotoxin A
E-196-2006	NINDS	Dr. Raphael Schiffmann	Over-expression In Peripheral Blood White Cells From Patients With Fabry Disease Of The Neuronal Apoptosis Inhibitor Protein (NAIP) Gene, Also Known As Baculaoviral Inhibitor Apoptosis Protein (IAP) Repeat-containing (Birc1)

For further information, or to license any of the above technologies, please email nihott@mail.nih.gov or visit the OTT Web site at www.ott.nih.gov.

OFFICE OF PORTFOLIO ANALYSIS AND STRATEGIC INITIATIVES (OPASI)

Overview

The NIH Roadmap for Medical Research was established in 2003. Roadmap Programs funded via the NIH Common Fund are intended to benefit the spectrum of health research. While each broad Program is not targeted toward a specific disease, individual awards made through these programs are often relevant to specific diseases. Basic research in which biological pathways are explored are also relevant to many diseases, including rare diseases. Examples of rare diseases that are being addressed specifically by Roadmap awards include the following:

Huntington's Disease

Huntington's Disease is an inherited neurodegenerative disease that occurs when additional Glutamine amino acids have been inserted into a portion of the DNA. The majority of Huntington's patients have one incorrect and one correct copy of the corresponding messenger RNA. Researchers are developing small molecule inhibitors that would bind to only the incorrect copy of the messenger RNA, thereby potentially eliminating the disease while leaving intact the correct copy of the messenger RNA to carry out its normal biological function.

Bartter's syndrome

Bartter's syndrome is a genetically inherited disease in which the kidneys are unable to absorb potassium. Additionally, it is characterized by electrolyte imbalances and pH changes in the blood. It is a disease that usually occurs in childhood. The Roadmap Program involves the development of a test that will monitor a key protein that modulates the amount of potassium that enters the kidney. The researchers will then use the test to find conditions under which the kidneys are better able to absorb potassium. In addition to alleviating Bartter's syndrome, this test may lead to improved clinical management of other kidney disorders.

Acronyms

a-1	alpha-one
AA	aplastic anemia
AAMDSIF	Aplastic Anemia & MDS International Foundation
AAT	a1-antitrypsin,
AATD	a1-antitrypsin deficiency
ABPA	allergic bronchopulmonary aspergillosis
ACCESS	A Case Control Etiologic Study of Sarcoidosis (NHLBI)
ACMG	American College of Medical Genetics
ADCC	Autoimmune Diseases Coordinating Committee
ADHD	attention deficit hyperactivity disorder
AFSP	American Foundation for Suicide Prevention
AGS	Alagille syndrome
ALD	adrenoleukodystrophy (NLM)
ALL	(childhood) acute lymphoblastic leukemia
ALPS	autoimmune lymphoproliferative syndrome
ALS	amyotrophic lateral sclerosis
A/M	anophthalmia/microphthalmia
APS	antiphospholipid syndrome
ARDS	acute respiratory distress syndrome
ARND	alcohol-related neurodevelopmental disorder
ARVD	arrhythmogenic right ventricular dysplasia
AS	Angelman syndrome
ASCUS	atypical squamous cells of undetermined significance
ASF	Angelman Syndrome Foundation
ASPS	advanced sleep phase syndrome
AT	ataxia telangiectasia
BAA	broad agency announcement (NHLBI)
BBS	Bardet-Biedl syndrome
BDNF	brain-derived neurotrophic factor
BE	Barrett’s esophagus
BH4	tetrahydrobiopterin
BIBIN	bilirubin-induced brain injury in the newborn
BLM	human gene encoding Bloom syndrome
BN	bulimia nervosa
BPD	bronchopulmonary dysplasia
BS	Bloom syndrome
BSE	bovine spongiform encephalopathy
CAG (triplet repeat)	nucleotides (CAG) consecutively repeated within a region of DNA

CAM	complementary and alternative medicine
CASG	Collaborative Antiviral Study Group
CASPAR	computerized affected sibling pair analyzer and reporter
CBV	coxsackie virus B
CC	Warren Grant Magnuson Clinical Center, NIH
CCHS	congenital central hypoventilation syndrome
CDC	Centers for Disease Control and Prevention
CDG	congenital disorders of glycosylation
CDH	congenital diaphragmatic hernia
CF	cystic fibrosis
CFS	chronic fatigue syndrome
CFTR	cystic fibrosis (CF) transmembrane conductance regulator
CGD	chronic granulomatous disease
CHD	coronary heart disease
CHID	Combined Health Information Database
CHOP	Children's Hospital of Philadelphia
CIN	cervical intraepithelial neoplasia
CJD	Creutzfeldt-Jakob disease
CLL	chronic lymphocytic leukemia
CL/P	cleft lip and cleft palate
CMV	congenital cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRADA	cooperative research and development agreement
CRC	clinical research center
CRD	cannabis-related disorder
CRF	corticotropin-releasing factor
CS	Cockayne syndrome
CVB3	Cocksackie virus B3
CWD	chronic wasting disease
DCIPS	Developing Centers on Interventions for the Prevention of Suicide (NIMH)
DDG	Drug Development Group (NIH)
DeNOVO	delivery of NO for vaso-occlusion (clinical trial title)
DHHS	Department of Health and Human Services
DMAC	disseminated infection with mycobacterium avium complex
DNA	deoxyribonucleic acid
DOE	Department of Energy
DSRCT	desmoplastic small round-cell tumor
DTCC	Data and Technology Coordinating Center
EB	epidermolysis bullosa, severe blistering skin diseases

EBV	Epstein-Barr virus
ECMO	extracorporeal membrane oxygenation
EDS	Ehlers-Danlos syndrome
ES	Ewing’s sarcoma
FA	Fanconi anemia
FAS	fetal alcohol syndrome
FASD	fetal alcohol spectrum disorders
FBN1	fibrillin 1
FDA	Food and Drug Administration
FENIB	familial encephalopathy with neuronal inclusion bodies
FGFR3	fibroblast growth factor receptor 3
FH	familial hypercholesterolemia
FHBL	familial hypobetalipoproteinemia
FMR1	fragile X mental retardation gene
FRDA	Friedreich ataxia
FRX	fragile X syndrome
FSHD	facio-scapulo-humeral dystrophy
GCPS	Greig cephalopolysyndactyly syndrome
GCRC	General Clinical Research Center (NCRR)
GHR	Genetics Home Reference (NLM)
GLP	good laboratory practice
GMP	good manufacturing practice
GPS	Gray platelet syndrome
HAART	highly active anti-retroviral therapy
HbF	fetal hemoglobin
HD	Huntington disease
HDL	high-density lipoprotein
HEV	hepatitis E virus
HGP	human genome project
HGPS	Hutchinson-Gilford progeria syndrome
Hh	hedgehog (signaling pathway)
HHT	hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
HHV-8	human herpesvirus 8
HIBM	hereditary inclusion body myopathy
hIPF	hereditary idiopathic pulmonary fibrosis
HIV/AIDS	human immunodeficiency virus/acquired immune deficiency syndrome
HPP	health partnership program (NIAMS)
HPT-JT	hyperparathyroidism-jaw tumor (syndrome)
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HTLV	human T cell leukemia virus

IBMFS&C	idiopathic bone marrow failure states and cytopenias
IBS	irritable bowel syndrome
ICBG	International Cooperative Biodiversity Groups (NHLBI)
ICs	(NIH) Institutes and Centers
IDDM	insulin-dependent diabetes mellitus
IFN	interferon
IGFs	insulin-like growth factors
IL	interleukin
IND	investigational new drug
IPF	idiopathic pulmonary fibrosis
IRSA	International Rett Syndrome Association
ISIS	Imaging Science and Information Systems Center (NLM)
JDRF	Juvenile Diabetes Research Foundation International
JRA	juvenile rheumatoid arthritis
KTWS	Klippel-Trenaunay-Weber syndrome
LAM	lymphangioleiomyomatosis
LDL	low-density lipoprotein
LMNA	lamin A (gene)
LQTS	long QT syndrome
LVAD	left ventricular assist device
mAB	monoclonal antibodies
MADGC	Multiple Autoimmune Diseases Genetics Consortium
MALD	mapping by admixture linkage disequilibrium
MATT	Methamphetamine Addiction Treatment Think Tank (NIDA)
MCA/MR	multiple congenital anomaly/mental retardation
MD-CARE	P.L. 107-84, Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001
MDCC	Muscular Dystrophy Coordinating Committee
MDS	myelodysplastic syndrome
MDA	Muscular Dystrophy Association
MDD	Medications Development Division (NIDA)
MDMA	Methylene-dioxy-meth-amphetamine (ecstasy)
MEN1	multiple endocrine neoplasia type 1
MHC	major histocompatibility complex
MKS	McKusick-Kaufman syndrome
MMP	matrix metalloproteinase
MOU	Memorandum of Understanding
MPD	myeloproliferative disease
MR4	Malaria Research and Reference Reagent Resource (Center)
MS	multiple sclerosis
MSC	mesenchymal stem cell

MSH	Multicenter Study of Hydroxyurea
MTA	material transfer agreement
NBLs	National Biocontainment Laboratories
NBN	National Biospecimen Network
NBTT	New Approaches to Brain Tumor Therapy Consortium (NCI)
NCBI	National Center for Biotechnology Information
NCCAM	National Center for Complementary and Alternative Medicine
NCI	National Cancer Institute
NCL	neuronal ceroid lipofuscinosis (Batten disease)
NCMHD	National Center on Minority Health and Health Disparities
NCRR	National Center for Research Resources
NCS	National Children's Study
NDA	new drug application
ND-BD	nondementing brain disorders
NEI	National Eye Institute
NF1	neurofibromatosis type 1
NF-kappaB	nuclear factor kappaB
NGI	next generation Internet
NHGRI	National Human Genome Research Institute
NHL	non-Hodgkin lymphoma
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Disease
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute of Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
NNFF	National Neurofibromatosis Foundation
NO	nitric oxide
NOMID	neonatal onset multisystem inflammatory disease
NPA	Niemann-Pick type A disease
NPB	Niemann-Pick type B disease

NPC	Niemann-Pick type C disease
NPD	Niemann-Pick type D disease
OA	Osteoarthritis
OCRL	oculo-cerebro-renal syndrome (Lowe syndrome, LS)
ODS	Office of Dietary Supplements (Office of the Director, NIH)
OI	osteogenesis imperfecta
OPASI	**Office of Portfolio Analysis and Strategic Initiatives**
ORD	Office of Rare Diseases (Office of the Director, NIH)
ORWH	Office of Research on Women's Health (Office of the Director, NIH)
OTP	opiate treatment program (NIDA)
PA	program announcement
PACT-G	Pediatric AIDS Clinical Trial Group
PAP	pulmonary alveolar proteinosis
PCD	primary ciliary dyskinesia
PCP	phencyclidine
PCP	pneumocystis carinii pneumonia
PEGT	Programs of Excellence in Gene Therapy (NHLBI)
PGA	Programs for Genomic Applications (NHLBI)
PHS	Pallister-Hall syndrome
PKC	protein kinase C
PKU	Phenylketonuria
PML	progressive multifocal leuceoencephalopathy
POF	premature ovarian failure
PPH	primary pulmonary hypertension
PPHN	persistent pulmonary hypertension of the newborn
PTLD	post-transplant lymphoproliferative disease
PTS	post-traumatic stress syndrome
PWS	Prader-Willi syndrome
PXE	pseudoxanthoma elasticum
RA	rheumatoid arthritis
RAID	Rapid Access to Intervention Development Program (NCI)
RBLs	regional biocontainment laboratories
RDCRC	Rare Disease Clinical Research Consortium
RDCRN	Rare Diseases Clinical Research Center Network
REM	rapid eye movement (characteristic of deep sleep)
RFA	request for applications
RFP	request for proposals
RLGS	restriction landmark genome scanning
RNA	ribonucleic acid
RS	Rett syndrome
RTH	resistance to thyroid hormone

RTOG	Radiation Therapy Oncology Group
RTS	Rothmund-Thompson syndrome
SADDAN	severe achondroplasia with developmental delay and acanthosis nigricans
SAMHSA	Substance Abuse and Mental Health Services Administration
SAGA	Sarcoidosis Genetic Analysis Consortium
SARS	severe acute respiratory syndrome
SBIR	small business innovative research
SCD	sickle cell disease
SCD	sudden cardiac death
SCID	severe combined immunodeficiency disorder
SCOR	specialized center of research
SGBS	Simpson Golabi Behmel syndrome
SIDS	sudden infant death syndrome
SLE	systemic lupus erythematosus
SLOS	Smith-Lemli-Opitz syndrome
SMA	spinal muscular atrophy
SPORE	Specialized Program of Research Excellence
SUD	substance use disorder
SS	sickle cell
SS	Sjögren syndrome
SVAS	supravalvular aortic stenosis
TB	Tuberculosis
TCR	transcription-coupled repair
TIGR	The Institute for Genomic Research
TMAU	Trimethylaminuria
TMD	temporo-mandibular disorders
TMJ	temporomandibular joint
TSC	tuberous sclerosis complex
TSEs	transmissible spongiform encephalopathies
TTP	thrombotic thrombocytopenic purpura
UCD	urea cycle disorder
UIP	usual interstitial pneumonitis
UPD	uniparental disomy
UV	ultraviolet
VA	(Department of)Veterans Affairs
vCFD	variant Creutzfeldt-Jakob disease
VCFS	velo-cardio-facial syndrome
VCRN	Vasculitis Clinical Research Network
VEG5Q	vascular endothelial gene on chromosome 5q
VEGF	vascular endothelial growth factor
VLBW	very low birth weight

VLDL	very low-density lipoprotein
VTUs	vaccine treatment and evaluation units
VWD	von Willebrand disease
VWF	von Willebrand factor
WAS	Wiscott-Aldrich syndrome
WNV	West Nile virus
WRN	defective gene for Werner syndrome
WS	Waardenburg Syndrome (NIDCD)
WS	Werner syndrome (NIA)
WS1	Wilm’s tumor suppressor
XPD	a human DNA repair protein

Index

Abetalipoproteinemia 169
Acoustic neuroma 120
Acquired aplastic anemia 193, 214
Acute Myeloid Leukemia 84
Adrenoleukodystrophy 240
Advanced Sleep Phase Syndrome 181
AIDS 28, 46, 51, 53, 88, 92, 93, 129, 155, 156, 227, 229, 230, 247, 250
Alagille syndrome 9, 140
Alcoholic pancreatitis 29, 31
Alcohol-induced hepatic fibrosis 32, 34, 25
Alpha-1 Antitrypsin Deficiency 9, 19, 141, 182, 213
Alstrom's syndrome 248
Alveolar rhabdomyosarcoma 241
Alzheimer's disease 26, 123, 233, 253
Amelogenesis imperfecta 126
Amyloidosis 11, 20, 22, 43, 143
Amyotrophic lateral sclerosis 26, 27, 123, 159, 160, 232, 236, 245, 254
Angel Flight America at the NIH 24
Anthrax 36, 37, 49, 50, 52
Anticancer Agents 95, 96, 100, 101, 107
Antiphospholipid syndrome 194
Arrhythmogenic Right Ventricular Dysplasia 170, 214
Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy 170
Asbestosis 182
Ataxia Telangiectasia 19, 29, 33, 35, 162, 166, 211, 236, 237, 238, 248
Auditory neuropathy 120
Autoimmune diseases 18, 36, 55, 57, 58, 59, 60, 61, 71, 72, 130, 159, 165
Autoimmune lymphoproliferative syndrome 225 248
Autoimmune Toxicity of Chlorinated Compounds 159
Avian influenza 36, 37, 46, 48, 247
Barth syndrome 19, 167
Bartter's syndrome 171, 260
Basal cell cancer 78
Bench-to-Bedside Intramural Research Awards 16
Birth Defects 21, 29, 159, 161, 162, 172, 185, 196, 225
Birt-Hogg-Dubé syndrome 80
Blood and Marrow Transplant 21, 57, 58, 60, 91, 205, 206, 208, 211
Blood and Marrow Transplant Clinical Trials Network 58, 91, 206, 208
Bloom syndrome 26
Bone Marrow Transplant 89
Bone marrow transplantation 37, 193, 195, 197, 204, 223
BRAF Mutant Melanoma 82

Breast/Ovarian Cancer Family Registries 99
Bronchopulmonary dysplasia 182, 215
Brugada's syndrome 171, 215
Burkitt's Lymphoma 81, 92
Cancer of the esophagus 78
Cannabis-Related Disorders 154
Carney complex 171
Charcot-Marie-Tooth disorder 232
Chediak-Higashi syndrome 14, 223
Childhood Cancers 17, 95, 96, 253
Childhood onset-schizophrenia 227
Childhood Osteosarcoma 96
Cholesteryl ester storage disease 171, 172
Chronic granulomatous disease 55
Chronic lymphocytic leukemia 90, 110, 204
Cleft lip/Cleft palate 127
Clinical Hematology Research Career Development Program 206, 208
Cocaine Addiction Treatment 148
Cockayne syndrome 29, 33, 35, 162, 167
Cohort and Case-Control Consortia 98
Common variable immunodeficiency 54, 57
Comprehensive Sickle Cell Centers 201, 206, 211, 212
Congenital Central Hypoventilation syndrome 183
Congenital cytomegalovirus 38, 121
Congenital diaphragmatic hernia 184
Congenital heart defects 29, 172, 173, 181
Congenital Heart Disease 17, 172, 180, 209, 215
Consequences of Drug Addiction 155
Cooley's anemia 138, 194, 195, 206, 216
Creutzfeldt-Jakob disease 43, 195
Crohn's disease 54, 255
Cushing's syndrome 118
Cystic fibrosis 9, 138, 139, 141, 142, 166, 185, 207, 216, 243, 251, 254, 255
Cystic Fibrosis Foundation 216, 243
Database of the major histocompatibility complex 251
Dentinogenesis imperfecta 127
Diagnostic Laboratories for Diseases of Red Cells and White Cells 206, 208
DiGeorge syndrome 24, 172, 173, 248
Down syndrome 123, 233
Drug Addiction as an Orphan Disease 144
Drug-Drug Interactions 155, 157
Duchenne muscular dystrophy 66, 70, 117
Dysbetalipoproteinemia 173
Dyssegmental dysplasia, Silverman-Handmaker type 128
Ebola 36, 38, 46, 47, 48, 49, 51, 52

Enlarged vestibular aqueduct 121
Eosinophilic esophagitis and gastroenteritis 59
Epidermolysis bullosa 63, 77
Epilepsy 27, 235, 254
Escherichia coli 38, 47
EVA 121
Fabry disease 128, 259
Facioscapulohumeral dystrophy 70, 71
Familial cold autoinflammatory syndrome 68
Familial hypobetalipoproteinemia 173
Familial Mediterranean fever 68, 74
Fanconi anemia 121, 142, 196, 197, 208, 216
Fetal Alcohol Spectrum Disorders 29, 33, 34
Fetal alcohol syndrome 29, 33, 34, 35
Fibrodysplasia ossificans progressiva 63
Fibrous dysplasia of bone 131
Fragile X syndrome 227, 229
Frontotemporal dementia 26, 28
General Clinical Research Centers 72, 243
Genetic Alliance 11, 20, 24, 25, 252
Genetic analysis software 248, 249
Genetic and Rare Diseases Information Center 22, 226
Genetically Triggered Thoracic Aortic Aneurysms and Other Cardiovascular Conditions 206, 209
Glaucoma 78, 79
Gray Platelet syndrome 13, 15, 224
Growth hormone deficiency (Adult) 128
Gynecologic Cancer 90
Hemophilia 198, 206, 217, 243
Hereditary cerebellar ataxia syndrome of early onset 121
Hereditary hemorrhagic telangiectasia 19, 199, 217, 222
Hereditary idiopathic pulmonary fibrosis 263
Hereditary leiomyomatosis 112
Hereditary multiple exostoses 74
Hermansky-Pudlak syndrome 13, 14, 15, 224
HIV 46, 88, 93, 98, 103, 129, 155, 156, 157, 227, 229, 230
Hodgkin Lymphoma 84
Holoprosencephaly 225
Homozygous familial hypercholesterolemia 174
HPV Vaccine Trial 97
Human Genetic Cell Repository 166
Human Papillomavirus 98
Human Rare Diseases Tissue Repositories 11
Hutchinson-Gilford progeria syndrome 13, 14, 122, 174, 206, 219, 224
Hypereosinophilic syndrome 174
Hypersensitivity Pneumonitis 191, 212

Hypoparathyroidism....129
Ichthyosis....64
Johanson-Blizzard syndrome....138
Joubert syndrome....10, 15, 140
Juvenile idiopathic arthritis....68, 69, 74, 77
Juvenile systemic lupus erythematosus....69
Kallmann syndrome....11, 122, 248
Kaposi's sarcoma....20, 87, 88, 129, 130
Klippel-Trenaunay-Weber syndrome....175
Laryngeal (Respiratory) Papillomas (Recurrent, Juvenile)....122
Lecithin Cholesterol Acyltransferase Deficiency....175
Leishmaniasis....39, 48
Liddle's syndrome....176
Li-Fraumeni syndrome....16, 176, 217
Limb-girdle muscular dystrophies....65, 66, 73
Lipoprotein lipase deficiency....176
Liver Cancer....80, 90, 255
Liver Disease....5, 9, 19, 141, 142, 182, 206, 209, 255
Long QT syndrome....176, 217
Lung Cancer....87, 182
Lyme disease....39, 40
Lymphangioleiomyomatosis....9, 12, 21, 187, 218
Lymphocytic Leukemia....90, 110, 204
Lymphocytic Leukemia Research Consortium....90
Lymphoma....16, 18, 20, 71, 81, 83, 84, 88, 89, 91, 92, 93, 97, 98, 99, 105, 199, 204
Malaria....204, 246, 250
Malignant hyperthermia and central core disease....64, 69
Mantle cell lymphoma....199
Marfan syndrome....65, 70, 77, 178, 209, 218, 245, 251
McCune-Albright syndrome....131
Melanoma....82, 83, 93, 94, 110, 241, 258
Mendelian Susceptibility to Mycobacterial Diseases....56
mesothelioma....82, 94, 95
Methamphetamine Addiction Treatment....152
Methylmalonic acidemia....21, 223
Mitochondrial genes and deafness....122
Muckle-Wells syndrome....68, 74
Mucolipidosis-IV....132
Muenke syndrome....123
Multiple endocrine neoplasia typeI....222, 223
Multiple Myeloma....84, 110
Multiple sclerosis....28, 58, 61, 123, 254, 256
Muscular dystrophies....65, 66, 70, 71, 73, 75, 76, 233, 237
Myeloproliferative Disorders....90, 207
Myocarditis....178

Myositis 71, 159
myotonic dystrophy 65, 66, 70, 71, 166, 233, 234
Narcolepsy 153, 188, 251
National Coalition for Health Professional Education in Genetics 23
National Disease Research Interchange 11, 243
National Gene Vector Laboratories 242
National Organization for Rare Disorders 20, 24, 25
Necrotizing Enterocolitis 19, 115, 117
Neonatal diabetes 138
Neonatal lupus 71, 72
Neonatal-onset multisystem inflammatory disease 67, 72, 74
Network for Cardiothoracic Surgical Investigations in Cardiovascular Medicine 212
Neuroblastoma 18, 90, 241
Neurofibromatosis 17, 95, 118, 120, 125, 236, 248, 251
Neutropenia 9, 56, 142, 167
Newborn screening initiative 117
Newborn screening research network 118
Niemann-Pick Type C disease 178
Non-Hodgkin Lymphoma 83, 97, 98, 204
Olfactory function 123
Opiate Addiction Treatment 147
Orphan Drug Act 5, 25, 243
Osteogenesis imperfecta 18, 75, 76, 77, 115, 119, 127
Osteopetrosis 132
Osteoporosis-pseudoglioma syndrome 66
Ovarian cancer 82, 86, 99, 239, 249
Ovarian carcinoma 86
Pachyonychia congenita 18, 76
Paget's disease 18, 132
Pallister-Hall syndrome 24, 123, 225
Pancreatic cancer 31, 86, 87, 95, 96, 99, 100
Papillon Lefevre syndrome 132
Parkinson's disease 26, 113, 123, 253, 254
Paroxysmal nocturnal hemoglobinuria 8, 9, 199, 204, 218
Pediatric bipolar disorder 227
Pediatric brain cancers 90
Pediatric drug trials 116
Pediatric Heart Disease Network 207, 209
Pemphigus vulgaris 57, 58
Pendred syndrome 121
Penile cancer 98
Persistent pulmonary hypertension of the newborn 188, 218
Plague 26, 40, 41, 49, 50, 51, 246
Polycystic kidney disease 13, 14, 139
Prenatal Alcohol in Sudden Infant Death Syndrome 33

Primary ciliary dyskinesia 9, 11, 189
Primary lymphedema 179, 218
Primary pulmonary hypertension 190, 219
Primary Thyroid Cancer 84
Progeria 13, 14, 15, 19, 122, 174, 175, 206, 219, 224
Progeroid syndromes 26, 28
Progressive external ophthalmoplegia 160
Proteomic Studies of Platelet Functions 207, 210
Pulmonary alveolar proteinosis 9, 190
Pulmonary fibrosis 13, 14, 15, 41, 113, 191, 206, 207, 219, 224
Pulmonary Vascular Disease 213
Rare Diseases Clinical Research Network 5, 7, 8, 13, 24, 72, 187, 194, 237, 242
Relapsing fever virus 40
Renal cell cancer 112
Renal cell carcinoma 16, 113, 200
Retinitis pigmentosa and related disorders 164
Rett syndrome 8, 26, 27, 119, 232, 234, 245
Sarcoidosis 55, 73, 74, 192, 206, 213, 238
sarcotubular myopathy 65
Schistosomiasis 41
Schwartz-Jampel syndrome 128, 133
Scientific Conferences 6, 7, 11, 17, 18, 20, 53, 57, 59, 215
Scleroderma 58, 60, 69, 72, 77, 190, 192, 193
Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers 70, 75, 236
Severe acute respiratory syndrome 41
Severe combined immunodeficiency 55, 57, 225
Severe Necrotizing Enterocolitis 115
Sickle cell disease 17, 19, 116, 138, 200-203, 206-208, 211, 212, 219-221, 239
Sickle Cell Disease Clinical Research Network 201, 202, 207, 211
Sitosterolemia 179, 180
Sjögren's syndrome 130, 165
Small lymphocytic lymphoma 204
Smallpox 42, 47, 48, 49, 50, 52
Smith-Lemli-Opitz syndrome 13, 21, 67, 180
Spasmodic dysphonia 124
Spinal and bulbar muscular atrophy 234, 236
Spinocerebellar ataxia 162, 235, 238
Spongiform encephalopathies 43, 195, 232
Squamous cell carcinoma 121, 133
Stillbirth (PASS) Research Network 33
Streptococcal Group A Invasive Disease 44
Streptococcus Group B 44
Streptococcus pneumonia 44, 46, 49
Suicide 17, 227, 229, 230, 231
Supravalvular Aortic Stenosis 181

Systemic lupus erythematosus....63, 69, 130, 194, 204, 256
Tangier disease....181
Temporomandibular joint disorders....135, 136, 137
Temporomandibular joint dysfunction....256, 257
Testicular Cancer Consortium....98
The human genetic map....247
Three-dimensional structure database....249
Thrombotic thrombocytopenic purpura....9, 204, 205, 213, 221
Tick-borne encephalitis virus....40, 46
Toxoplasma....250
Trans NIH Working Group on Tuberous Sclerosis....100
Transplant immunology....59
Tricho-dento-osseous syndrome....136
Tuberous Sclerosis Alliance....100, 141
Tuberous sclerosis complex....68, 74, 100, 141, 187, 235
Tumor-induced osteomalacia....136
Turner syndrome....124
Usher syndrome....124, 241, 245, 248
Vasculitis Clinical Research Consortium....9, 72
Von Willebrand disease....240
Waardenburg syndrome....125
Werner syndrome....27
West Nile virus....45, 46, 47, 48
Wilms Tumor....88, 89, 116
Xeroderma pigmentosum....13, 18, 29, 33, 35, 162, 166, 248
X-Linked aggamaglobulinemia....56
X-linked lymphoproliferative disease....55
Zebrafish Research Tools....208, 211