Section V.
NEUROFIBROMATOSIS RESEARCH PROGRAM

CONTENTS

CDMRP

Neurofibromatosis Research Program

Vision: Decrease the impact of neurofibromatosis

Mission: To promote research directed toward the understanding, diagnosis, and treatment of NF1 and NF2 as well as to enhance the quality of life for individuals with the disease.

Congressional Appropriations for Peer-Reviewed Research
$25.8M in FY96–98, $11.5M in FY99, and $15M in FY00

Award Summary
24 awards from the FY96–98 appropriations
21 awards from the FY99 appropriation
~20 awards anticipated from the FY00 appropriation

"There is no question in my mind that the U.S. Army's NFRP has moved us in less than a decade from basic science to the advent of clinical trials in NF. From a taxpayer's and consumer's perspective, I can also attest to the high degree of professionalism with which the U.S. Army's staff manages the peer review process on which the program's grant decisions are based. The future of all individuals in the world with NF1 and NF2 is considerably brighter because of the successes of the NFRP."

Peter Bellerman
Consumer, Integration Panel Member

The Disease

Neurofibromatosis (NF) includes two distinct genetic disorders of the nervous system, NF1 and NF2, in which tumors grow on or about nerves anywhere in the body. It can also affect non-nervous tissue, such as bone and skin. These tumors impact people's lives through disfigurement, loss of hearing, blindness, bone deformation, and, in some cases, death. NF1 and NF2 are both genetically autosomal dominant disorders; a parent with NF has a 50% chance that expression of the disease will occur in his/her child. NF can also arise from spontaneous mutations in genes; 30% to 50% of cases are due to spontaneous mutations. Surgical intervention can provide palliative relief; however, at this time there is no cure.

NF1 is the more common type, affecting about 1 in 4,000[1] individuals. The *Nf1* gene is located on chromosome 17. A characteristic of NF1 is the appearance of flat, pigmented markings on the skin called café-au-lait spots. NF1 is also characterized by neurofibromas, which are growths that develop on or just under the skin and are composed of tissue from the nervous system and fibrous tissue. Approximately 50% of people with NF1 have learning disabilities.

NF2 is rarer than NF1, only affecting about 1 in 40,000[1] individuals. The *Nf2* gene is located on chromosome 22. NF2 is characterized by the growth of tumors on nerves of the inner ear, among other complications. The inner ear neuromas in NF2 patients cause hearing loss and can eventually result in deafness.

[1] Report on Neurofibromatosis, Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Neurological Disorders and Stroke, 1993.

History of the Neurofibromatosis Research Program

——Program Background

The Congressionally Directed Medical Research Programs (CDMRP) began managing the Department of Defense (DOD) Neurofibromatosis Research Program (NFRP) in response to the fiscal year 1996 (FY96) Senate Appropriations Committee Report No. 104–124, which provided $8 million (M) for research in NF.[2] At that time, the U.S. Army Medical Research and Materiel Command convened a meeting of expert scientists, clinicians, and consumer advocates in the field of NF to define the goals and areas of emphasis of the program. The overall mission of the NFRP has been and continues to be funding basic and clinical research relevant to NF that will result in substantial improvements over today's approach to the understanding, diagnosis, and treatment of NF1 and NF2 as well as enhance the quality of life for individuals with the disease.

——Congressional Appropriation and Funding History

From FY96–00, Congress appropriated a total of $52.3M to fund peer review NF research through the NFRP. The investment strategy executed is consistent with the congressional language and reflects the program's vision to decrease the impact of NF. A total of 45 awards were made in the FY96–99 programs across the categories of research, training/recruitment, and infrastructure. Since 1996, emphasis has been placed on Investigator-Initiated Awards, which is a mechanism that supports basic and clinical research relevant to NF. A feature of Investigator-Initiated Awards was the option to include one or more Nested Postdoctoral Traineeships to encourage postdoctoral trainees to continue careers in NF research under the mentorship of a senior investigator. Appendix B, Table B–4, summarizes the directions from Congress for the NFRP appropriations, the program's withholds and management costs, and the investment strategy executed by the NFRP for FY99–00. Additional details of the FY96–98 programs appear in the DOD CDMRP Annual Report, September 1999.

"I would like to thank the NFRP for giving me the opportunity to train and work in the NF field as a postdoctoral fellow. Funding at this important juncture in my career has fostered my interest in and commitment to working on NF1. As a result, I am now starting my own laboratory, which will continue to focus on understanding the development of this disease."

Karen Cichowksi, Ph.D.
NFRP Award Recipient

[2] The USAMRMC, but not the CDMRP, was also responsible for managing congressional appropriations in FY92 for neurofibromatosis research.

FY99 Program

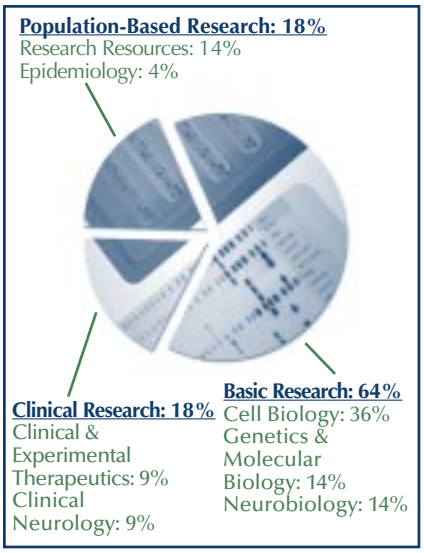


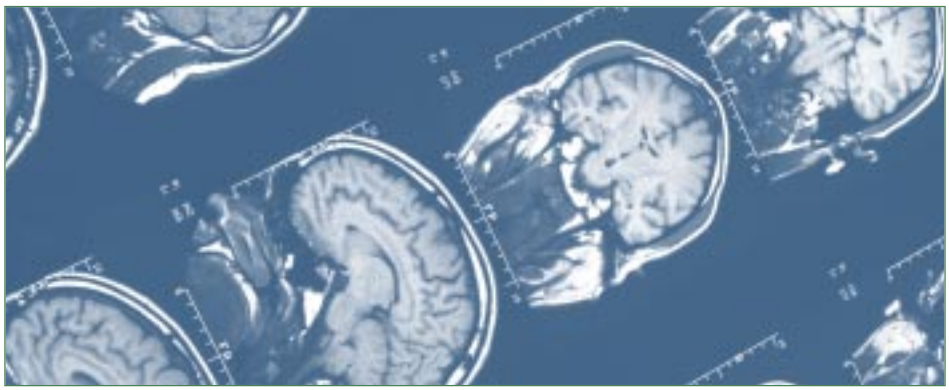
Figure V-1. FY99 NFRP Portfolio by Research Area

Congress appropriated $11.5M in FY99 to continue the DOD peer review NFRP. The programmatic vision for the FY99 NFRP was implemented by requesting proposals in four award mechanisms: Investigator-Initiated Awards (with or without Nested Postdoctoral Traineeships), New Investigator Awards, Idea Awards, and Clinical Trial Awards. Investigator-Initiated Awards offer support for basic research leading to clinical trials relevant to NF. New Investigator Awards were intended to support innovative NF research from investigators who are either (1) at the Assistant Professor or equivalent level or (2) more senior investigators who are new to the NF field. Idea Awards were intended to support research that represents new paradigms in the study of NF, challenges existing paradigms, or examines a problem from a new perspective. Clinical Trial Awards were intended to support clinical pharmacologic or gene therapy studies that examine the toxicity (Phase 1) or investigate the efficacy (Phase 2) of any novel therapeutic approach for NF1 or NF2. Table V–1 reflects the funding summary for the FY99 NFRP.

Table V–1. Funding Summary for the FY99 NFRP Awards

Award Mechanism	Number of Proposals Received	Number of Awards	Investment
Idea Awards	15	6	$1.5M
New Investigator Awards	15	7	$2.4M
Investigator-Initiated Awards	16	8	$5.6M
Clinical Trial Awards	2	0	$0M

Figure V–1 illustrates the diverse portfolio of research funded by the FY99 NFRP. The major investment is in basic research in the disciplines of cell biology (36%), genetics and molecular biology (14%), and neurobiology (14%). The NFRP also has a large investment in population-based research (18%).



FY00 Program

Due to the success of the program, Congress appropriated $15M to the DOD NFRP in FY00. The programmatic vision in FY00 was very similar to that of FY99, consisting of Idea Awards, New Investigator Awards, Investigator-Initiated Awards (with or without Nested Postdoctoral Traineeships), and Clinical Trial Awards. The Clinical Trial Award mechanism was continued in FY00 to encourage Phase 1 and Phase 2 NF clinical trials to develop technologies that could improve the ability to assess outcomes, improve diagnosis and predict prognosis, and develop new modalities for noninvasive diagnosis. The NFRP Program Announcement was released on April 7, 2000. A total of 41 proposals were received. Peer review will be November 15–16, 2000, and programmatic review will be completed on January 23–24, 2001. Award negotiations will be completed no later than September 30, 2001.

Scientific Achievements

Research funded by this program is already showing signs of productivity and promise. For example, investigators funded in the FY96–97 programs have published their findings in prestigious scientific journals (including *Science, Journal of Biological Chemistry*, and *Oncogene*) and have presented their data at national and international scientific conferences (including annual meetings of the American Society for Human Genetics, the National Neurofibromatosis Foundation, and the Society for Neuroscience). In addition, investigators funded in the FY96–97 programs have generated several important transgenic mouse models and cell lines that will aid in elucidating the molecular mechanisms underlying the cause and progression of NF. The outcomes of the 15 investigators funded in FY96–97, after approximately 2 years of research, are summarized in Table V–2.

Table V–2. Outcomes of 15 FY96–97 NFRP Grantees

Publications (including manuscripts in press)	19
Abstracts/Presentations	25
Cell Lines/Animal Models Developed	6

Investigators funded by the NFRP have been making great advances in both basic and clinically oriented research. The following projects represent some of the most exciting advances in NF research that are being supported by the NFRP.

"The DOD NRFP has widened the scope of NF research by providing a greater flexibility of funding for this disorder, permitting world-class researchers to pursue not only fundamental mechanisms of disease, but also to amass the difficult to obtain clinical information essential for translating findings at the lab bench to treatments in the clinic. I have no doubt that the DOD NRFP has contributed immensely to hastening the day when successful treatments will be available for both NF1 and NF2."

James Gusella, M.D., Ph.D.
Chair Emeritis, Integration Panel

Building Infrastructure

In FY97, the NFRP seized an opportunity to build an infrastructure in which future NF research could be developed by offering Natural History/Consortia Awards. The overall goal of these NF natural history studies is to establish large, multidisciplinary consortia of clinical centers to generate quantitative data on tumor growth rates that can be readily translated into clinical trials. Two awards were made, one focusing on NF1 and the other on NF2. The first award was made to Children's Hospital in Boston, where investigators are studying plexiform neurofibromas (i.e., tumors that grow along the length of nerves and often involve multiple branches of a nerve) in NF1 patients. This study uses volumetric magnetic resonance imaging to measure plexiform neurofibromas and gather data on their growth. The second award was made to the House Ear Institute in Los Angeles, where investigators are studying the growth rates and clinical course of vestibular schwannomas (i.e., tumors affecting the nerves of the ear) in NF2 patients. In this study, image and volumetric tumor data are being collected to assess audiological function and to analyze the molecular, pathological, and clinical characteristics of NF2. ❖

"The NF community—patients, families, and researchers—are deeply grateful to the NFRP for its significant funding of NF research over the past several years. NFRP funding in my lab allowed us to build and begin to characterize animal models of NF1 and NF2, which have already proven to be useful in investigating basic mechanisms of disease development. In the coming years, we expect these models to be critical in evaluating potential therapies for the treatment and prevention of these diseases."

Tyler Jacks
NFRP Award Recipient

Identifying a Gene Involved in the Development of Leukemia in NF1: Children with NF1 are at risk for developing certain types of leukemias (i.e., cancer of the white blood cells and bone marrow). Researchers at the University of Florida College of Medicine in Gainesville are looking for genes involved in *Nf1*-induced leukemias. The researchers have shown that the *c-myb* gene is likely to cooperate with the loss of the *Nf1* gene, which is a characteristic of NF1, and appears to cause the development of a specific type of leukemia known as acute myeloid leukemia. This research may lead to improved prevention, diagnosis, and treatment for other malignancies that affect NF1 patients.

Developing New Agents that Inhibit Cells from becoming Cancerous in NF2: The *Nf1* and *Nf2* genes are mutated in individuals with NF1 and NF2, respectively. The mutated *Nf1* and *Nf2* genes no longer effectively control other genes in patients' cells, which can lead to these cells becoming cancerous. Researchers at the University of North Carolina at Chapel Hill are studying the effect that mutations in the *Nf2* gene have on functions of the *ras* gene, an important regulator in normal cell growth. Several agents have been developed that inhibit the *ras* gene, and these investigators are testing their abilities to stop cells with a mutated *Nf2* gene from becoming cancerous. This study holds significant promise for developing drugs to treat NF2-associated malignancies.

Identifying Factors Leading to the Excessive Growth of Schwann Cells in NF1: Schwann cells, which surround the nerves of the body, promote the growth of nerves. The abnormally excessive growth of Schwann cells in NF1 patients can lead to the formation of two types of tumors: the relatively benign neurofibromas and the malignant neurofibrosarcomas. Researchers at the Chicago Association for Research and Education in Science are studying the molecular mechanisms underlying the excessive growth of Schwann cells that occurs in NF1 patients. The researchers obtained cells from neurofibromas and neurofibrosarcomas and examined factors that bind to these cells and cause their abnormal growth.

Several types of receptors for these growth-promoting factors were found to be more abundant in these cells. Ultimately, this research may represent a critical step in developing a method to control the abnormally excessive growth of Schwann cells that is observed in NF1 patients.

Elucidating the Clinical Features of NF1: NF1 is highly variable among patients of the same age, affected members of a single family, and even within individual patients at different times in their lives. Researchers at the University of British Columbia are using a combination of clinical, epidemiological, molecular genetic, and statistical methods to study a number of clinical features of NF1. They are utilizing the resources of several large NF databases to obtain the information needed for this study. Using standard statistical methods, the investigators determined that certain clinical features are often grouped together in particular patients and within affected families. This study is helping to define subgroups of NF1 patients who are especially likely to develop serious complications, which will allow screening efforts to be focused on those at greatest risk. In addition, the insight gained on the clinical variability of NF1 may lead to the development of new treatment approaches for this devastating disease. The outcomes of this research will have a significant impact on the lives of NF1 patients and their families by giving them more definitive information about their potential diagnosis.

Determining Genes that Cooperate with NF1 to Form Malignant Tumors: One of the hallmarks of NF1 is the development of benign neurofibromas, which sometimes progress to aggressive, malignant tumors. Researchers at the Massachusetts Institute of Technology have created a new mouse model that can be used to elucidate the genetic events underlying the conversion of benign tumors into malignant tumors. The investigators of this study are examining the effect that the *p53* gene may have on the *NF1* gene. The *p53* gene is being examined because other studies have shown it to be involved in the formation of malignant tumors. The researchers found that mutations in *NF1* and *p53* cooperate in the development of malignant tumors. This mouse model will provide valuable insights into the fundamental aspects of disease development and may be a potential model for testing therapeutic strategies for NF1.

"The NFRP is a milestone marking the changes in history that are affecting the entire NF community and leading the way toward treatments that will give hope to all generations, including my son and grandson."

Mary Ann Wilson
Consumer, Integration Panel Member

Summary

The DOD NFRP is supporting basic and clinical research that will decrease the impact of NF. Since 1996, this program has made important contributions to understanding the molecular mechanisms, natural history, and treatment of NF1 and NF2. Projects funded by the NFRP are yielding results that can be tested in the clinic, thus providing hope for all individuals affected by this devastating disease. The DOD NFRP will be continued in FY01 with a congressional appropriation of $17M.

"NF1 is the most common dominantly inherited disease affecting the nervous system. The human costs of this disease are enormous. The targeted research of the NFRP is bringing us closer to the day when effective treatments for NF1 will be available."

David Pleasure, M.D.
Chair, Integration Panel

FY00 Integration Panel Members

***Chair*, David Pleasure, M.D.:** Professor of Neurology, Pediatrics, and Orthopaedic Surgery at the University of Pennsylvania. Director of the Joseph Stokes, Jr. Research Institute at Children's Hospital of Philadelphia.

***Chair Elect*, Allan Rubenstein, M.D.:** Director, Mount Sinai Neurofibromatosis Research and Treatment Center, Department of Neurology at Mount Sinai Hospital. Helped co-found the National Neurofibromatosis Foundation and currently serves as its Medical Director.

***Chair Emeritus*, James Gusella, Ph.D.:** Director, Molecular Neurogenetics Unit at Massachusetts General Hospital. Bullard Professor of Neurogenetics at Harvard Medical School. Member of the Scientific Advisory Board of the National Neurofibromatosis Foundation.

Peter Adamson, M.D.: Chief, Division of Clinical Pharmacology and Therapeutics at Children's Hospital of Philadelphia.

Peter Bellermann: President, National Neurofibromatosis Foundation. Chairman, International Neurofibromatosis Association. Advisor to the World Health Organization on ethical, social, economic, and political issues in genetics.

Neal Copeland, Ph.D.: Director of the Mouse Cancer Genetics Program at the National Cancer Institute, Frederick Cancer Research and Development Center.

Kurt Fischbeck, M.D.: Chief, Neurogenetics Branch at the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Zach Hall, Ph.D.: Executive Vice Chancellor of Research at the University of California, San Francisco.

Robert Murray, Jr., M.D., Ph.D.: Professor and Chairman, Graduate Department of Genetics and Human Genetics at Howard University. Professor of Pediatrics and Medicine, and Chief of the Division of Medical Genetics, Department of Pediatrics and Child Health in the College of Medicine at Howard University. Member of National Academy of Sciences' Institute of Medicine.

Louis-Gilbert Vézina, M.D.: Director of Neuroradiology in the Department of Diagnostic Imaging and Radiology at Children's National Medical Center in Washington, DC. Associate Professor of Radiology and Pediatrics at George Washington University.

Mary Ann Wilson: Chair, Education Committee of Neurofibromatosis, Incorporated. Consumer Staff Representative for the Alliance of Genetic Support Groups. Founded a neurofibromatosis support group in the Metropolitan Washington, DC, area.

For more information about the NFRP and other programs managed by the CDMRP, visit **http://cdmrp.army.mil**