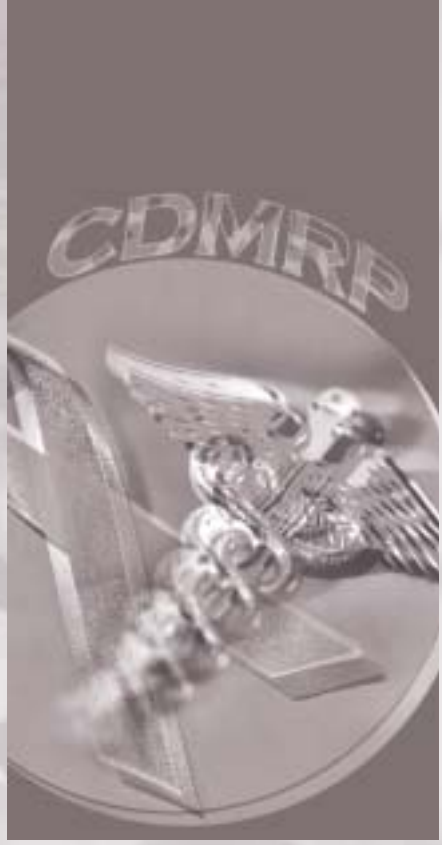


Section V Neurofibromatosis Research Program

Vision: To decrease the impact of neurofibromatosis.

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

Congressional Appropriations for Peer-Reviewed Research: $52.3 in FY96–00, $17M in FY01, and $21M in FY02

Funding Summary: 65 awards from the FY96–00 appropriations; 20 awards from the FY01 appropriation; ~20 awards anticipated from the FY02 appropriation

The Disease

Neurofibromatosis includes two distinct genetic disorders of the nervous system, NF1 and NF2. These disorders usually result in tumors involving nerves anywhere in the body; however, non-nervous tissue such as bone and skin can also be affected. Together, these two genetic disorders affect more than 100,000 Americans of both genders and all ethnic groups. NF1 and NF2 are usually inherited as autosomal dominant disorders. Therefore, a parent with NF has a 50% chance of passing on the disorder to his or her child. However, 30% to 50% of NF1 and NF2 cases arise as a result of a spontaneous genetic change.[1] Tumors that develop in individuals with NF can cause disfigurement, deafness, blindness, bone deformation, learning disabilities, and in some cases death. The tumors that appear in NF patients can vary significantly, even among affected individuals in the same family. 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, and is also known as Von Recklinghausen's Disease or Peripheral NF. A common 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. Symptoms of NF often appear at birth and usually by the age of 10. Approximately 50% of people with NF1 have learning disabilities.

NF2 is rarer than NF1, only affecting about 1 in 40,000[1] individuals, and is also known as bilateral acoustic NF. 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. Hearing loss in NF2 patients can appear in the teen years.

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 (USAMRMC) 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 in the understanding, diagnosis, and treatment of NF1 and NF2 and will enhance the quality of life for individuals with the disease. The NFRP's role in supporting an international effort to assemble clinical and research resources that can later be used to test potential NF1 treatment options is summarized in the box story on page V-3.

"The U.S. Army's CDMRP program is, to my mind, government at its best. Taxpayers are extraordinarily well served by this program since it has a low administrative overhead and involves highly competent U.S. Army personnel and subcontractors who are working with world class scientists and clinicians to address an underserved area of medicine with enormous potential for numerous other health issues affecting millions of patients and their families. The peer review system put in place by the U.S. Army for this program is second to none and thus assures the taxpayers that public funds are provided only to the most meritorious basic science and clinical research."

—Peter Bellerman, M.P.A., President, The National Neurofibromatosis Foundation, Inc., FY02 Integration Panel Chair

[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.*

[2] *The U.S. Army Medical Research and Materiel Command, but not the CDMRP, was also responsible for managing congressional appropriations in FY92 for NF research.*

From FY96–02, Congress appropriated a total of $90.3M to fund peer review NF research through the NFRP. A total of 85 awards have been made through FY01 across the categories of research, infrastructure, and training/recruitment. The NFRP has developed a multidisciplinary research portfolio that encompasses basic, clinical, and population-based research projects. Appendix B, Table B-3, summarizes the congressional appropriations, and the investment strategy executed by the NFRP for FY01–02. Additional details of the FY96–00 programs appear in the DOD CDMRP Annual Reports of September 1999, September 2000, and September 2001.

FY01 Program

Congress continued the DOD NFRP in FY01 with a $17M appropriation. The programmatic vision in FY01 called for five award mechanisms: Clinical Trial, Idea, Investigator-Initiated, New Investigator, and Therapeutic Development Awards. The last award mechanism was offered for the first time in FY01 and is intended to boost the number of NF clinical trials by sponsoring the development and evaluation of preclinical model systems for NF1 and NF2. Table V-1 provides a summary of the FY01 NFRP award categories and mechanisms in terms of proposals received, number of awards, and dollars invested. As illustrated in Figure V-1, the portfolio of research supported by the NFRP is diverse.

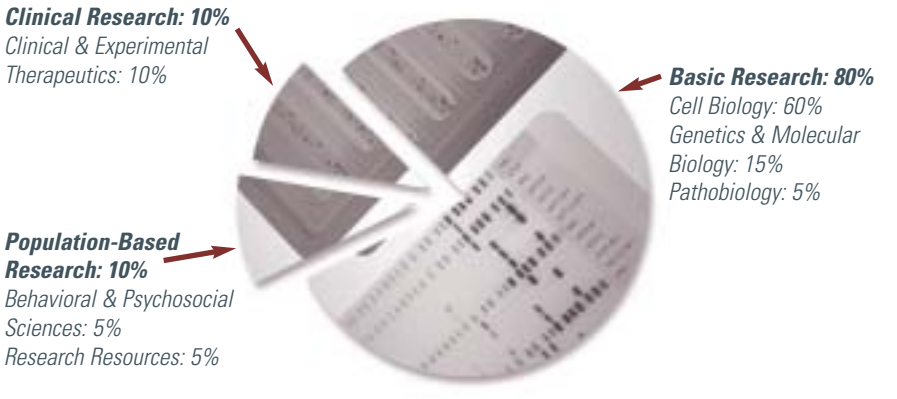
NFRP Supports an International Effort to Elucidate the Growth Patterns of NF1 Tumors

Individuals with neurofibromatosis 1 (NF1) are often plagued by neurofibromas (benign tumors that occur on nerves that run throughout the body). A plexiform neurofibroma is a specific type of neurofibroma that is associated with larger nerves and multiple nerve branches. The growth patterns of plexiform neurofibromas are quite unpredictable and factors that influence their growth are largely unknown. NFRP-funded researcher Bruce Korf, M.D., Ph.D., of the Harvard Partners Center for Genetics and Genomics is directing an international research study focused on determining the growth patterns of plexiform neurofibromas. Currently, 14 institutions are participating in the study, including hospitals/universities in the United States, Canada, England, Germany, and Australia. Dr. Korf and his colleagues have adapted a method of magnetic resonance imaging (MRI) to precisely measure the volumes of plexiform neurofibromas. They are collecting measurements every 6–24 months to document the rate of change in size of the plexiform neurofibroma. They have established a web site (http://healthcare.partners.org/nfstudies/) for the study to facilitate enrollment and aid in the dissemination of results. The web site contains information about the study, entry and exclusion criteria, the progress of patient recruitment, and internet links to each center involved in the study, among other features. Overall, this study is assembling clinical and research resources that can later be used to test potential treatments of plexiform neurofibromas.

Table V-1. Funding Summary for the FY01 NFRP

Category and Award Mechanism	Number of Proposals Received	Number of Awards	Investment
Research			
Clinical Trial	2	1	$1.5M
Idea	18	8	$3.5M
Investigator-Initiated Research*	12	5	$3.3M
New Investigator	11	4	$1.9M
Therapeutic Development	5	2	$4.9M
Total	**48**	**20**	**$15.1M**

**Includes optional nested postdoctoral traineeship(s).*



Note: Percentages based on number of awards.

Figure V-1. FY01 NFRP Portfolio by Research Area

A new feature of the FY01 NFRP was electronic proposal submission. The electronic format was well received by the research community and resulted in reduced administrative costs. The success of this feature for the FY01 NFRP catapulted electronic proposal submission for the programs managed by the CDMRP in FY02. For more information on electronic innovations, see Section II of this report.

The Vision for the FY02 Program

Congress appropriated $21M to continue the NFRP in FY02. The FY02 NFRP continues to place emphasis on encouraging established scientists in the field, attracting new scientific expertise, fostering the collection of preclinical data, and conducting clinical trials. Six award mechanisms were offered in an effort to advance basic NF research and bring laboratory research to the clinic, including Career Development, Clinical Trial, Idea, Investigator-Initiated, New Investigator, and Therapeutic Development Awards. The Career Development Awards represent a new feature in FY02 and are aimed at encouraging established scientists or research clinicians currently working in areas other than NF to shift their focus to NF research. Read about the NFRP's effort to bring therapeutic agents to patients in the box story on page V-5.

A total of 76 proposals were received electronically, as detailed in Table V-2. Scientific peer review is scheduled for November 2002, and programmatic review is scheduled for January 2003. Approximately 20 awards are anticipated.

Scientific Outcomes and Advances

The DOD NFRP-supported research is producing advances in basic NF research and bringing laboratory research into clinical trials. The success NFRP-funded research can be gauged, in part, by the number of resultant publications, abstracts/presentations, and patents/licensures reported by awardees. This information is summarized in Table V-3.

The following projects represent some of the most exciting advances that are being supported by the NFRP.

Many Types of NF1 Mutations Can Lead to the Development of Tumors in NF1 Patients.
Bruce Korf, M.D., Ph.D., Harvard Partners Center for Genetics and Genomics; and Lin Kluwe, Ph.D., University Hospital Hamburg-Eppendorf, Germany:
Neurofibromatosis 1 is a genetic disease caused by mutations in the NF1 gene. Nearly one-third of NF1 patients develop tumors called plexiform neurofibromas. These tumors occur in a variety of shapes

Table V-2. Award Mechanisms Offered and Proposals Received for the FY02 NFRP

Category and Award Mechanism	Number of Proposals Received
Research	
Clinical Trial	*2*
Idea	*25*
Investigator-Initiated	*24*
New Investigator	*18*
Therapeutic Development	*6*
Training/Recruitment	
Career Development	*1*
Total	***76***

Table V-3. FY96-99 NFRP Award Outcomes

Number of Awards	*45*
Publications in Scientific Journals	*>55*
Abstracts/Presentations at Professional Meetings	*133*
Patents/Licensures (including applications)	*6*

and sizes and can become very large. Dr. Korf at the Harvard Partners Center for Genetics and Genomics, in collaboration with researchers at several other universities, screened 42 NF1 patients from 41 families with plexiform neurofibromas for mutations in the NF1 gene. Mutations in genes come in a number of types: nonsense, frameshift, splicing, and missense. Dr. Korf and his colleagues found the aforementioned types of mutations in the NF1 gene in the patients they examined. They found that there was no correlation between the type of NF1 mutation and the size, location, or feature of plexiform neurofibromas. This finding suggests that there is no specific type of NF1 mutation that leads to the development of plexiform neurofibromas.

Elucidating the Relationship between Learning Deficits and the NF1 Gene.

Camilynn Brannan, Ph.D., University of Florida, Gainesville: Neurofibromatosis 1 is a commonly inherited genetic disorder caused by mutations in the NF1 gene. Symptoms include the presence of neurofibromas (benign tumors that can become malignant), café-au-lait spots (pigmented lesions on the skin), Lisch nodules of the iris, and a wide range of learning disabilities. Dr. Brannan and her colleagues at the University of Florida, Gainesville, are studying neurofibromin, which is the protein produced by the NF1 gene. The NF1 gene encodes two distinct forms of neurofibromin: types I and II. Dr. Brannan and her colleagues generated mice lacking neurofibromin type II and demonstrated that the mice developed normally and did not have an increased predisposition to tumor formation. However, they found that these mice as adults (between the ages of 4 and 13 months) had specific impairments in spatial learning, contextual discrimination, and motor coordination. The results from this novel mouse model suggest that the learning deficits in NF1 patients could result from the disruption of neurofibromin type II function. Ultimately, this study may lead to the development of a treatment for the learning disabilities associated with NF1.

Targeting Cellular Signaling Pathways to Inhibit the Growth of NF1 Tumors.

Raymond Mattingly, Ph.D., Wayne State University, Detroit, Michigan: In NF, a protein called Ras becomes activated because of the lack of neurofibromin. Ras activation leads to uncontrolled cell growth and tumor formation by activating a cascade of proteins, called the mitogen-activated protein kinase (MAPK) pathway. By using specific inhibitors of the Ras protein, as well as inhibitors of the MAPK pathway, NFRP-funded researcher Dr. Mattingly has been able to inhibit the growth of neurofibrosarcomas, malignant tumors that occur frequently in

Accelerating Research from Bench to Bedside

There are presently only a small number of clinical trials of drugs to treat NF. The NFRP hopes to change this using a multifaceted approach. Beginning in FY97, the NFRP supported the development of future clinical trials by offering Natural History/Consortia Awards. The goal of these awards was to establish large, multidisciplinary consortia of clinical centers to generate quantitative data on tumor growth rates that can be readily translated into clinical trials for NF. Next, in FY01–02, the NFRP offered Therapeutic Development Awards to encourage the development and evaluation of preclinical model systems for NF. Finally, the NFRP offered Clinical Trial Awards in FY00–FY02 to test new agents for the treatment of NF. Using this comprehensive, multiyear approach, the NFRP hopes to greatly accelerate the progression of therapeutic agents and procedures from bench to bedside.

"It is a great honor to work with consumers, scientists, and clinicians as a team geared to fund research offering hope to individuals and their families dealing with neurofibromatosis."

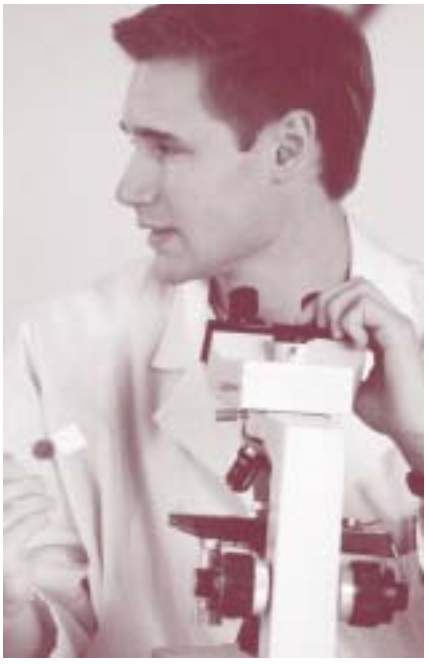
—Richard Kenyon, Ph.D., NFRP Program Manager

people with NF1. These inhibitors may be developed into drugs that are less toxic and more specific for NF1 related tumors, and could thus be used in clinical trials to prevent tumor formation or to treat existing tumors.

Determining How Merlin/ Schwannomin Contributes to NF2 Tumor Formation.
Olli Carpen, Ph.D., University of Helsinki; Vijaya Ramesh, Ph.D., Massachusetts General Hospital; and Daniel Scoles, Ph.D., Cedars Sinai Medical Center: NF2 results from a mutation in the NF2 gene that encodes a protein called merlin (also known as schwannomin). Lack of merlin/schwannomin production leads to uncontrolled cell growth, which suggests that merlin/schwannomin normally acts as an inhibitor of cell growth. Several studies funded by the NFRP are trying to determine how merlin/schwannomin works by looking for other proteins that interact with merlin/schwannomin. For example, Dr. Carpen of the University of Helsinki, is studying the interactions between merlin/schwannomin and a protein called actin, which is part of the cytoskeleton. By comparing merlin/schwannomin interactions to those of the related protein ezrin, which is known to stimulate cell growth, they hope to better understand how merlin/schwannomin contributes to tumor formation. In a related study, Dr. Ramesh at Massachusetts General Hospital has also found that merlin/schwannomin interacts with actin, but also interacts with an ion exchange protein (NHERF) in the cell membrane, thus linking proteins that sense the outside environment to structural components of the cell. When merlin/schwannomin is missing, as in NF2, these proteins are no longer connected, which may explain the cytoskeletal disruption and tumorigenesis seen in this disease. Another important insight into the function of merlin/schwannomin has come from Dr. Scoles at Cedars Sinai Medical Center, who has found that merlin/schwannomin interacts with a subunit of a protein complex called eukaryotic initiation factor 3 (eIF3) that is involved in protein translation. This interaction suggests that the ability of merlin/schwannomin to inhibit cell growth could come from its ability to regulate protein translation. Once the function of merlin/schwannomin is determined, we will better understand how it contributes to tumor formation and the other symptoms associated with NF2. With that information, it will be easier to design drugs and improve treatments for this disease.

"CDMRP support of research on neurofibromatosis has energized the field. Emerging understanding of the basic mechanisms of neurofibromatosis and the availability of increasingly powerful animal models are providing the tools needed to develop effective therapies. As a clinical investigator, I have appreciated the forward thinking approach that the CDMRP has taken to stimulating the NF research effort."

—Bruce Korf, M.D., Ph.D., Medical Director, Harvard-Partners Center for Genetics and Genomics, FY02 Integration Panel Member



Summary

Since 1996, the DOD NFRP has been responsible for managing $90.3M in congressional appropriations, which has resulted in 85 awards for FY96–01. These awards have made important contributions to understanding the molecular mechanisms, natural history, and treatment of NF1 and NF2. The NFRP has developed a multidisciplinary portfolio that encompasses basic, clinical, and population-based research projects. Projects funded by the NFRP are yielding results that will improve the understanding, diagnosis, and treatment of NF1 and NF2 as well as enhance the quality of life for individuals with this disease.

FY02 Integration Panel Members

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

Chair Elect, Judy Small, Ph.D.: Director, Clinical Trials and Technology Transfer, The National Neurofibromatosis Foundation, Inc.

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

Peter Adamson, M.D.: Chief, Division of Clinical Pharmacology and Therapeutics at the Children's Hospital of Philadelphia. Associate Professor of Pediatrics at the University of Pennsylvania School of Medicine.

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

Brenda Duffy, M.A.: Consumer; President, Neurofibromatosis, Inc.

Nancy Fisher, M.D., M.P.H.: Medical Director, Regence BlueShield Clinical Associate Professor, University of Washington, Seattle.

Jackson Gibbs, Ph.D.: Senior Director, Merck Research Laboratories.

Bruce Korf, M.D., Ph.D.: Medical Director, Harvard-Partners Center for Genetics and Genomics. Associate Professor, Harvard Medical School.

John Mulvihill, M.D.: Kimberly V. Talley Chair of Genetics, Professor of Pediatrics, Director of the Program in Human Genetics, and Professor of Biostatistics and Epidemiology at the University of Oklahoma Health Sciences Center.

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.