

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: \$69.3M in FY96–01, \$21M in FY02, and \$20M in FY03

Funding Summary: 85 awards from the FY96–01 appropriations; 18 awards from the FY02 appropriation; ~19 awards anticipated from the FY03 appropriation

...shaping the future of health care to prevent, control, and cure diseases.



"It is my privilege to be a consumer representative for the NFRP, which truly represents the consumer viewpoint at all stages. NFRP is the leader in including scientists, clinicians, and consumers in a process that funds research towards a treatment for NF1 and NF2. It continues to provide hope for those who are affected."

Brenda Duffy
Neurofibromatosis, Inc.;
FY03 Integration Panel Member

The Disease

Neurofibromatosis (NF) 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, nonnervous 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 percent chance of passing on the disorder to his or her child. However, 30 percent to 50 percent 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 4,000² 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 percent of people with NF1 have learning disabilities.

NF2 is rarer than NF1, only affecting about 1 in 40,000³ individuals, and is also known as bilateral acoustic NF (BAN). 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 as early as 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)

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 Ibid.

³ Ibid.

Senate Appropriations Committee Report No. 104-124, which provided \$8 million (M) for research in NF.⁴ As a leader in the support of extramural NF research, the NFRP has managed \$110.3M from FY96 to FY03 to fund peer reviewed NF research. A total of 103 awards have been made through FY02 across the categories of research, research resources, and training/recruitment. The NFRP has developed a multidisciplinary research portfolio that encompasses basic, clinical, and population-based research projects.

The Fiscal Year 2002 Program

Congress continued the DOD NFRP in FY02 with a \$21M appropriation. The FY02 NFRP strove to advance basic NF research and bring laboratory research to the clinic. (See related box story on page V-6.)

Six award mechanisms were offered: Career Development, Clinical Trial, Idea, Investigator-Initiated, New Investigator, and Therapeutic Development Awards. The Career Development Awards (CDAs) represented a new feature in FY02 to encourage established scientists or research clinicians currently working in areas other than NF to shift their focus to NF research. (See related box story on page V-7.) In response to the FY02 Program Announcements, 76 proposals were received and 18 were funded. Table V-1 provides a summary of the FY02 NFRP award categories and mechanisms in terms of proposals received, number of awards, and dollars invested. The portfolio of research supported by the FY02 NFRP is illustrated in Figure V-1.

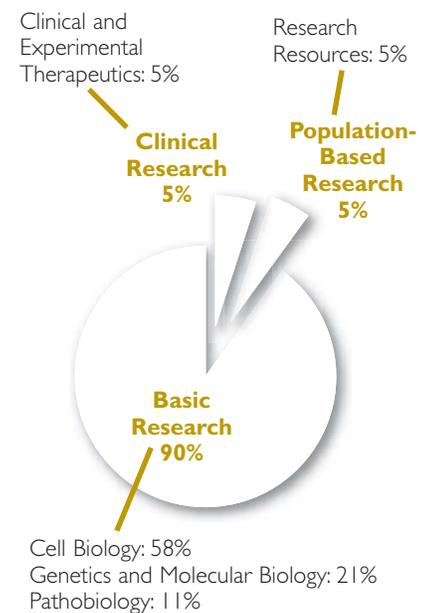


Figure V-1. FY02 NFRP Portfolio by Research Area

Table V-1. Funding Summary for the FY02 NFRP

Category and Award Mechanism	Number of Proposals Received	Number of Awards	Investment
Research			
Clinical Trial	2	0	0.0
Idea	25	4	\$2.4M
Investigator-Initiated	24	8	\$13.0M
New Investigator	18	4	\$2.8M
Therapeutic Development	6	1	\$0.6M
Training/Recruitment			
Career Development	1	1	\$0.2M
Total	76	18	\$19.0M

⁴ 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.



The Vision for the Fiscal Year 2003 Program

Congress appropriated \$20M to continue the NFRP in FY03. Six award mechanisms were offered: five of which were previously established by the NFRP (Clinical Trial, Idea, Investigator-Initiated, New Investigator, and Therapeutic Development Awards) and one that is new to the NFRP in FY03 (Clinical Trial Development Awards). The goal of the Clinical Trial Development Award is to support communication among multiple centers and the development of a formal protocol for a clinical trial. This new award mechanism is intended to fund the development of a plan for communication, real-time data transfer, the handling and distribution of specimens and imaging products, and a plan for statistical analysis among the participating institutions. For the FY03 program, 63 proposals were received, as detailed in Table V-2, and approximately 19 awards are anticipated. Appendix B, Table B-3, summarizes the congressional appropriations and the investment strategy executed by the NFRP for FY02–03.

Scientific Outcomes and Advances

The DOD NFRP-supported research is producing advances in basic NF research and bringing laboratory research into clinical trials. The following projects represent some of the most exciting advances that are being supported by the NFRP.



Table V-2. Award Mechanisms Offered and Proposals Received for the FY03 NFRP

Category and Award Mechanism	Number of Proposals Received
Research	
Clinical Trial	2
Idea	23
Investigator-Initiated	16
New Investigator	16
Therapeutic Development	4
Research Resources	
Clinical Trial Development	2
Total	63

Merlin Unmasked: Identifying a Key Role of the Neurofibromatosis 2 Suppressor Gene

Andrea McClatchey, Ph.D., Massachusetts General Hospital

Neurofibromatosis 2 (NF2) is a familial cancer syndrome characterized by the development of multiple brain tumors, including acoustic neuromas (tumors of the otic nerve), meningiomas, and ependymomas (tumors of the linings of the brain). The NF2 gene encodes a tumor suppressor known as merlin (or NF2), which is mutated in most patients with the disease. Studies in mice with this mutated gene have shown that merlin is involved in regulating cell proliferation. Its loss results in both tumor development and metastasis in mice. The molecular function of merlin is not currently understood; however, researchers at Massachusetts General Hospital have looked at fibroblasts (connective tissue cells) derived from merlin-deficient mice and compared them to normal mouse fibroblasts. They have shown that while normal cells stop growing when they come into contact with each other, the NF2-deficient cells do not. This suggests that these cells cannot sense when they are touching other cells. Furthermore, the NF2-deficient cells lacked structures called adherens junctions, which connect and are involved in communication between adjacent cells. They have also found that by adding merlin back into the NF2-deficient cells, they could restore the formation of these junctions and subsequently, normal contact-dependent growth inhibition between cells. Therefore, loss of merlin may result in the disruption of normal cellular junctions, cell-to-cell communication, and ultimately, contact-dependent growth inhibition leading to tumor growth and metastasis.

For additional reading about this research, please refer to the following publications:

- ◆ Lallemand D, Curto M, Saotome I, et al. 2003. NF2 deficiency promotes tumorigenesis and metastasis by destabilizing adherens junctions. *Genes & Dev.* 17:1090–1100.

"The CDMRP program for neurofibromatosis has been critical for the rapid acceleration of research leading to the identification of novel mechanisms of action for the NF1 and NF2 genes. The NF Mouse Models Consortium has developed and is sharing with other investigators a number of mouse models, which develop tumors representative of the tumors found in NF1 and NF2. Future studies on therapeutic development and preclinical and clinical testing will be possible much more quickly thanks to the commitment of the CDMRP to funding high-quality NF research. As a scientist, and a parent of a child with NF1, I appreciate the efforts that have brought the NF research field to this critical point."

Judy A. Small, Ph.D.
Director, Clinical Trials and
Technology Transfer,
The National Neurofibromatosis
Foundation, Inc.;
FY03 Integration Panel Chair

Advancing Basic NF Research into the Clinic

Since FY99, the NFRP has been encouraging clinical trials in NF. A Clinical Trial Award made in FY01 to Dr. Roger Packer at the Children's Hospital in Washington, DC is demonstrating the safety and effectiveness of a novel agent for the treatment of plexiform neurofibromas. These tumors arise from the coverings of multiple nerves and are a common manifestation in patients afflicted with NF1. Plexiform neurofibromas often cause disfigurement and neurological impairment, and other than surgery, there is no effective treatment for this problem. Dr. Packer is conducting two sequential clinical studies to determine whether Pirfenidone, an antifibrotic agent that targets certain growth factors elevated in plexiform neurofibromas, can be used in the management of children with NF1 and progressive plexiform neurofibromas. A Phase I study is under way demonstrating the safety of Pirfenidone in pediatric patients with progressive plexiform neurofibromas, and a Phase 2 study will begin to determine its efficacy. Preliminary results indicate that Pirfenidone is well tolerated in children at the doses tested. The NFRP is dedicated to improving and enhancing patient quality of life and believes that Dr. Packer's studies have the potential to offer a new approach to the management of this disease.

Developing Improved Mouse Models of NF1 and NF2 for Preclinical Testing

Kevin Shannon, M.D., University of California, San Francisco

Animal models of human disorders provide a powerful means for researchers to study disease mechanisms and test the effectiveness and safety of novel treatments prior to human clinical trials. The lack of appropriate models has impeded progress in NF research. To address this critical need, Dr. Kevin Shannon is leading a consortium of investigators that aims to develop, characterize, and validate mouse models of NF1 and NF2 for preclinical research. The team, part of the National Cancer Institute's Mouse Models of Human Cancer Consortium, generated models of common NF1- and NF2-associated tumors, including plexiform neurofibromas, malignant peripheral nerve sheath tumors, astrocytomas, meningiomas, and schwannomas. They also developed techniques to image tumors in living mice, which will aid in the evaluation of therapeutic responses. These mouse models are being used to identify novel therapeutic targets and study the effectiveness of experimental agents, with the ultimate goal of translating these data into improved treatments for NF1 and NF2 patients.

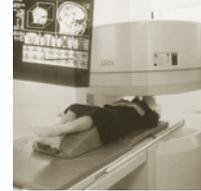
Below is a list of selected publications about this research.

- ◆ Weiss B and Shannon K. 2003. Mouse cancer models as a platform for performing preclinical therapeutic trials. *Current Opinion in Genetics and Development* 13:84–89.
- ◆ Zhu Y, Ghosh P, Charnay P, et al. 2002. Neurofibromas in NF1: Schwann cell origin and role of tumor environment. *Science* 296:920–922.
- ◆ Gutmann DH and Giovannini M. 2002. Mouse models of neurofibromatosis 1 and 2. *Neoplasia* 4:279–290.
- ◆ Messerli SM, Tang Y, Giovannini M, et al. 2002. Detection of spontaneous schwannomas by MRI in a transgenic murine model of neurofibromatosis type 2. *Neoplasia* 4:501–509.

Mitochondrial Aberrations in NF1 Tumors — A Potential Explanation for Disease Variability?

Andreas Kurtz, Ph.D., Massachusetts General Hospital, Boston

Neurofibromatosis type 1 is an inherited disorder affecting approximately 1 in 4,000 people. All individuals with mutations in the NF1 gene develop disease symptoms, but the severity of those symptoms varies greatly between patients and even between family members. Alterations in mitochondria, the energy-producing structures of the cell, cause several diseases that exhibit heterogeneous expression. Importantly, mitochondria interact with neurofibromin, the product of the NF1 gene. Dr. Andreas Kurtz and colleagues at Massachusetts General Hospital are examining mitochondrial DNA (mtDNA) mutations in NF1 tumors. Dr. Kurtz's team found that mtDNA mutations are present in normal tissues from NF1 patients and that those mutations accumulate in neurofibromas. These findings suggest that mitochondrial aberrations may contribute to neurofibroma development and growth. Studies are in progress to examine the correlation between mtDNA mutations and neurofibroma tumor burden. Elucidation of the role of mitochondria in NF1 tumor development may aid in the prediction of disease severity and eventually lead to new preventive treatments for high-risk patients.



FY02 CDA Recipient

Dr. Athar Chishti, Chief, Section of Hematology and Oncology Research at St. Elizabeth's Medical Center in Boston, Massachusetts, was the first recipient of the Career Development Award offered by the NFRP. This award mechanism was launched in FY02 to encourage established scientists currently working in areas other than NF to shift their research focus to NF. And, this mechanism did just that. Dr. Chishti has invested over 20 years studying the erythrocyte (red blood cell) plasma membrane, with emphasis on erythrocyte membrane protein 4.1 and its role in malaria parasite-infected red blood cells. Importantly, the classification of schwannomin (the protein product of the NF2 gene) as a member of the family of proteins to which protein 4.1 belongs motivated Dr. Chishti to turn his attention to the study of schwannomin. As the recipient of the NFRP CDA, Dr. Chishti plans to study the biochemical basis of schwannomin using the red cell plasma membrane as a model. Thus, Dr. Chishti brings his expertise in the field of red cells to unravel the biochemical basis of schwannomin and validate his entry into the field of NF. Dr. Chishti is now a Professor in the Department of Pharmacology at the University of Illinois College of Medicine Cancer Center in Chicago, Illinois.

"To see significant accomplishments made in understanding and lessening the impact of neurofibromatosis is very fulfilling. To serve as Program Manager affords me an opportunity to facilitate these advances."

Richard Kenyon, Ph.D.,
NFRP Program Manager

Summary

Since 1996, the DOD NFRP has been responsible for managing \$110.3M in congressional appropriations, which has resulted in 103 awards for FY96–02. These awards have 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 will improve the understanding, diagnosis, and treatment of NF1 and NF2 as well as enhance the quality of life for individuals with this disease. Research highlights, award data, and abstracts of funded NFRP proposals can be viewed on the CDMRP website (<http://cdmrp.army.mil>).

Fiscal Year 2003 Integration Panel Members

Judy Small, Ph.D. (Chair)

The National Neurofibromatosis Foundation, Inc.

Peter Bellermand, M.P.A. (Chair Emeritus)

The National Neurofibromatosis Foundation, Inc. and International Neurofibromatosis Association

Bruce Korf, M.D., Ph.D. (Chair Elect)

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