IV. Neurofibromatosis Research Program

"I have been involved with the NF community now for almost 15 years. I have watched the DOD program evolve during this time, to the point it is the single largest source of research funds for NF. The dedication of the DOD and the scientific community—the number of hours they devote to the process—is incredible. As a consumer advocate, to be able to see the incredible array of research concepts is inspiring. Being in the midst as a consumer advocate is a wonderful experience, and the respect of the scientists for my point of view as a parent of a son with NF2 is very much appreciated. As a parent knowing there is a group dedicated to accelerating the research to treatments and a cure helps me through the frightening times wrestling with this horrible disease."

Barbara Franklin
Children's Tumor Foundation
FY07 Peer Reviewer

"Being a part of the scientific review panel for the CDMRP-NFRP was a unique and inspiring experience. The interaction between the clinicians and basic scientists on the panel was excellent and demonstrated how much each of us can learn from those who have a different perspective on neurofibromatosis. It is easy to become excited about the latest technology, but having consumer representatives on the panel ensured that we stayed focused on research that can result in practical treatment options for those with neurofibromatosis. I came home to my clinic and laboratory driven by the inspiring and inciteful comments of the consumer panel members."

Cynthia M. Hingtgen, M.D., Ph.D.
Indiana University Melvin and Bren Simon Cancer Center
FY06-FY07 Peer Reviewer

Promoting Vital Research

Vision

To find and fund the best research to eradicate the clinical impact of NF.

Mission

To promote research directed toward the understanding, diagnosis, and treatment of NF1, NF2, and schwannomatosis to enhance the quality of life for individuals with those diseases.

"I am pleased to have been selected to serve on the [Integration] Panel… for neurofibromatosis…. This panel includes both basic scientists and clinicians representing a variety of disciplines as well as consumers who work together to promote research, new therapies, and clinical trials. The multidisciplinary panel provides expertise to support research and clinical activities…to give hope to improved therapy, understanding, and outcomes in patients with this challenging genetic abnormality."

Norman E. Leeds, M.D., FACR, FAHA
Mount Sinai Hospital and School of Medicine
FY08 Integration Panel Member

The Disease

Neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2) are distinct genetic disorders of the nervous system that usually result in tumors involving nerves anywhere in the body.

- Together, NF1 and NF2 affect more than 100,000 Americans of both genders and all ethnic groups.
- NF1 and NF2 usually are 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 to 50 percent of NF1 and NF2 cases arise as a result of a spontaneous genetic change.
- Tumors that develop in individuals with NF can cause disfigurement, deafness, blindness, bone deformation, learning disabilities, and in some cases death. These tumors can vary significantly, even among affected individuals in the same family.
- Schwannomatosis is a rare form of NF that has been discovered only recently.
- Schwannomatosis is characterized by the growth of multiple homogeneous tumors, called schwannomas, consisting of Schwann cells or nerve sheath cells. As with NF1 and NF2, the severity of schwannomatosis varies greatly among patients.
- While surgical intervention can provide palliative relief, at this time there is no cure for these diseases.

Signs and Symptoms

- Learning disabilities; large head (macrocephaly)
- Tumor on the optic nerve that may interfere with vision (optic glioma); pigmented bumps on the iris (Lisch nodules)
- Curvature of the spine (scoliosis)
- Freckling in the armpits or groin
- Pea-sized bumps or nerve tumors (neurofibromas), which may occur anywhere on or under the skin
- Six or more cafe-au-lait spots, light brown spots similar to birthmarks, which can occur on any area of the body
- Early (precocious) or delayed onset of puberty
- Large tumors affecting a bundle(s) of nerves (plexiform neurofibromas), which can occur anywhere
- Bowing or thinning of the shin bone (tibia)

Program Background

The CDMRP began managing the 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. The NFRP represents the second oldest program to the CDMRP and continues to be a major source of funding worldwide for research on NF1, NF2, and schwannomatosis. The NFRP has managed $190.3M in appropriations from FY96 to FY08 as depicted in Figure IV-1, NFRP Appropriations. A total of 209 awards were made through FY07 to promote vital research spanning basic research, clinical research, and research resources.

"I have found the experience of being a scientific peer reviewer for the CDMRP program in neurofibromatosis immensely valuable for two reasons. First, there is the professional satisfaction of seeing so many excellent and outstanding applications. Second, there is the recognition that this strong science is being proposed in the context of a syndrome that had not been adequately addressed prior to the DOD program."

Raymond R. Mattingly, Ph.D.
Wayne State University
FY05-FY07 Peer Reviewer

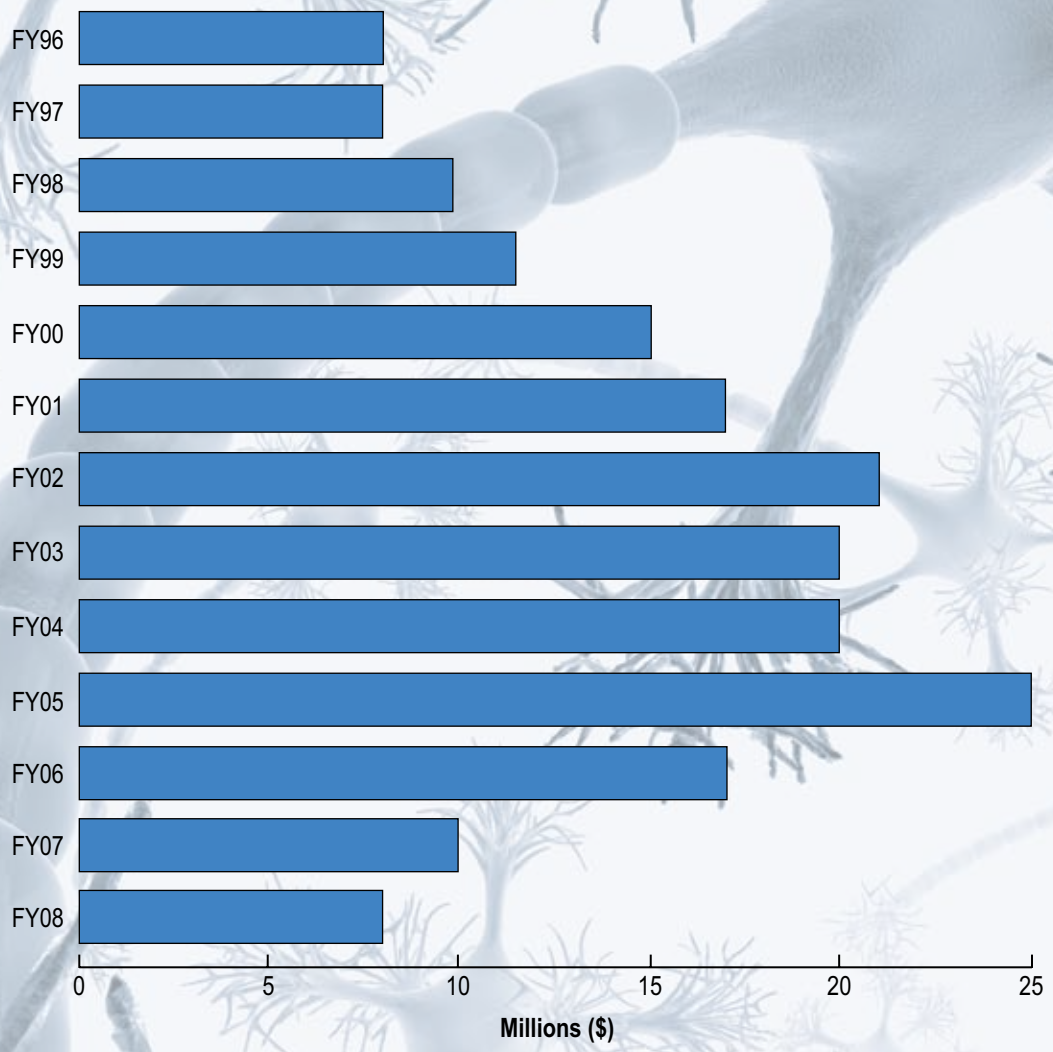

Figure IV-1. NFRP Appropriations

Extraordinary People

The unwavering commitment of extraordinary people—consumer advocates, peer reviewers, Integration Panel (IP) members, and the scientific community—has made meaningful differences in the success of the NFRP.

Consumer Advocates

Representing the voice and vision of more than 100,000 men, women, and children in the United States living with NF, consumer advocates play a vital role in the continuing success of the NFRP. Consumer advocates for the NFRP are individuals living with NF, or they are family members of individuals affected by the disease who are also active participants in consumer advocacy organizations. Consumer advocates participate as equal voices in the research administration process in which they propose the program's vision, participate in the review of proposals, and make funding recommendations. This unique partnership ensures that the program's vision and investment strategy prioritize and focus on the needs of the NF community. Additional information regarding consumer advocate participation can be found in Section I, Overview.

Peer Review Panel Members

NFRP peer review panels are composed of esteemed, NF-focused scientists and clinicians and dedicated consumer advocates who provide unbiased, expert advice on the scientific and technical merit of the proposals. Peer reviewers also evaluate the overall relevance of the proposals based on the review criteria published for each award mechanism. Approximately 250 scientists, clinicians, and consumer advocates have participated in the peer review process for the NFRP. For additional details about peer review, refer to Section I, Overview.

"As a past Chair of the Tuberous Sclerosis Research Program Integration Panel and current Chair of the Neurofibromatosis Research Program, and as a former member of both Integration Panels and a former reviewer of proposals for the TSCRP, I have had a broad range of opportunities to see the impact of DOD-supported research. The DOD encourages innovation and creativity, thereby fast-tracking outstanding, world-class research. It is truly an honor to serve in the CDMRP."

Elizabeth Petri Henske, M.D.
Fox Chase Cancer Center
FY08 Integration Panel Chair

Integration Panel Members

The NFRP IP is composed of notable scientists, clinicians, and consumer advocates. They work to serve the interests of the NF and schwannomatosis communities by recommending annual investment strategies, cutting-edge research priorities, and multidisciplinary research portfolios (for more information about the functions of the IP, see Section I, Overview). The visionary approaches and active input of the IP members enable the NFRP to find and fund the best research and set important program priorities aimed at eradicating the clinical impact of NF.

Scientific Community

The NFRP has funded more than 140 researchers and clinicians worldwide to conduct vital research on the detection, diagnosis, treatment, management, and quality of care of persons affected with NF and schwannomatosis. The remainder of this section showcases a sample of the NFRP-supported portfolio.

FY08 NFRP IP Members

Elizabeth Petri Henske, M.D.
(Chair)
Fox Chase Cancer Center

D. Wade Clapp, M.D.
Indiana University School of Medicine

Channing Der, Ph.D.
University of North Carolina at Chapel Hill

Jane Fountain, Ph.D.
National Institute of Neurological Disorders and Stroke

John Kyriakis, Ph.D.
Tufts New England Medical Center

Norman Leeds, M.D.
Mount Sinai School of Medicine

Michael Morin, Ph.D.
Oncovia

Sandra Parker, J.D.
Neurofibromatosis, Inc.

John Risner
Children's Tumor Foundation

"The CDMRP neurofibromatosis program has been instrumental in helping scientists to unravel the disease mechanisms. Now, with the organization of the NF consortium to conduct clinical trials, the bench-to-bedside pipeline is open and multicenter clinical trials are under way. The hope that this program has provided to patients cannot be underestimated."

Bruce Korf, M.D., Ph.D.
University of Alabama at Birmingham
NF Consortium Operations Center Principal Investigator

Promoting Vital Research

Clinical Consortium

Integral Collaboration

The NFRP is strongly committed to promoting translational research. In FY06, the NFRP developed the Consortium Award to establish a network of clinical centers devoted to accelerating basic NF1 research into the clinic. The consortium was designed around a central operations center with clinical sites participating in both patient accrual and the clinical trials. Drs. Jeannette Lee and Bruce Korf of the University of Alabama at Birmingham are the Principal Investigators at the central operations center. The extensive experience of both Drs. Lee and Korf in conducting multicenter clinical trials has led to the development of two clinical trials through the consortium.

The first clinical trial examines rapamycin for the treatment of plexiform neurofibromas (PNs). This tumor type commonly occurs in patients with NF1. PNs can result in debilitating pain, paralysis, or even death due to their potential for malignancy. This Phase II clinical trial will specifically investigate the potential of rapamycin to slow tumor growth and decrease tumor volume in NF1 patients ages 3 and older with inoperable PNs. Accrual to this trial is anticipated to open soon.

The second clinical trial is intended to address the severity and frequency of cognitive deficits in children with NF1. Currently, there is a crucial need to investigate interventions that can improve cognitive functioning in children with NF1. This trial will investigate whether the cholesterol-lowering drug lovastatin can significantly improve the visual spatial learning, memory, and/or attentional impairments associated with NF1 in a Phase II clinical study. The design and implementation of this second trial have recently started. All nine clinical sites are expected to participate. This Phase II study is expected to accrue 142 patients.

Essential Research
Year in Review

Functional Role of Merlin in Meningioma Cells

Anita Lal, Ph.D.
University of California, San Francisco

Dr. Anita Lal at the University of California researches NF2, a cancer predisposition syndrome phenotypically characterized by the presence of multiple benign brain tumors, primarily schwannomas and meningiomas. Unfortunately, most studies evaluating the mechanism of action of merlin, the NF2 gene product, have used cell lines unrelated to NF2 target cells. With funding from an FY05 New Investigator Award, Dr. Lal isolated and immortalized human meningioma cell lines, and with these, engineered merlin-deficient or merlin-expressing meningioma cells. Dr. Lal used these cells to characterize the phenotypic effects of merlin loss in this more accurate NF2 environment. Dr. Lal determined that the loss of merlin in meningioma cells caused those cells to neglect to undergo the normal contact inhibition of growth. With the loss of merlin, those cells also exhibited enhanced anchorage-independent growth in soft agar. Merlin loss was found to alter the cell growth cycle, causing an increase in S-phase entry and a concomitant decrease in G0-G1 and G2 populations. Dr. Lal determined that merlin loss in this cell population was associated with an increase in transcript and protein levels of cyclin E1, a regulator of the G0-G1 to S transition and a potential downstream target of merlin. Merlin loss was also found to affect the apoptotic rates in these meningioma cell lines, causing a decrease in spontaneous apoptotic rates and increasing resistance to Stsp(staurosporine)-mediated apoptosis.

Dr. Lal intends to investigate these results further, along with exploring for other downstream transcriptional effectors of meningiomas. This more accurate NF2 model will be useful in the future to test potential novel therapeutics against NF2.

Understanding the Pathogenesis of Skeletal Manifestations of NF1 Patients

Feng-Chun Yang, M.D., Ph.D.
Indiana University School of Medicine

NF1 is a common, autosomal dominant disorder caused by mutations in the NF1 tumor suppressor gene. At least 50 percent of NF1 patients have one or more skeletal abnormalities, including kyphoscoliosis, pseudoarthrosis, and osteoporosis, but only limited efforts have been focused on understanding the underlying molecular mechanisms. Dr. Feng-Chun Yang received an FY07 New Investigator Award to identify the mechanisms underlying the skeletal manifestations of NF1 in murine and human systems. Dr. Yang plans first to evaluate the skeletal phenotype in a murine model of NF1. In collaboration with a skeletal biologist who has experience in the use of biomechanical engineering and bioimaging methods, Dr. Yang will perform detailed structural studies of bone and examine the role of NF1 in bone repair and remodeling. Dr. Yang will also begin to dissect the intracellular signaling cascades that control the alterations in osteoblast differentiation while collaborating with a clinical geneticist who is focusing on the diagnosis and treatment of the skeletal dysplasias in NF1.

New Hope from a Glimmer: Photodynamic Therapy for the Treatment of Plexiform Neurofibromas (PNs)

Michael J. Fisher, M.D.
Children's Hospital of Philadelphia

PNs occur with great frequency in patients with NF1. These tumors can result in disfiguration and functional impairment, and they can even be life threatening. While surgical intervention is sometimes effective, in most cases it is not a viable option. In addition, current therapeutics may arrest PN growth, but they are not likely to shrink large PNs. Through funding from an FY07 New Investigator Award, Dr. Michael Fisher of the Children's Hospital of Philadelphia is investigating the feasibility of a new type of therapy in children suffering from PNs. His study will use photodynamic therapy, or light therapy, which employs a photosensitizer that, upon interacting with a particular wavelength of light, can kill nearby cells through the production of reactive oxygen species. This study will test the safety and effectiveness of using the photosensitizer LS11 to treat PNs in children and young adults. The small implantable light source being used in the study is designed to limit the activation of LS11 to the confines of the tumor. It is anticipated that this treatment will induce tumor shrinkage and subsequently reduce the morbidities associated with PNs.

Molecular Mechanism of NF1 Vasculopathy

David Ingram, M.D.
Indiana University

Neurofibromatosis often results from mutations within the NF1 tumor suppressor gene, which encodes the protein neurofibromin. Vasculopathies are an acceleration of blood vessel degeneration, constituting a major source of morbidity for NF1 patients. Under the most serious of circumstances, this condition can even result in death. The role of neurofibromin in regulating blood vessel cell function is understood only at a fundamental level. Advances in understanding the biology of adult endothelial cell and vascular smooth muscle cell function are necessary to effectively treat the morbidity associated with vasculopathies in NF1 patients. Through an FY07 Investigator-Initiated Research Award, Dr. David Ingram will investigate the molecular mechanisms behind the role of NF1 in vascular smooth muscle and endothelial cell functions in vivo. Based on existing preliminary data in the field, Dr. Ingram has carefully designed a plan to genetically engineer several animal models. Each model will simulate the pathobiology of this condition in NF1-deficient mice. These experiments will provide critical clues regarding the molecular pathways that initiate the formation of vasculopathies. Furthermore, the data will elucidate the nature of each pathway's relationship to neurofibromin. This project will provide the necessary tools through which the molecular pathogenesis of vasculopathies can be better understood and may pave the way for promising therapeutics or diagnostic agents.

Using Modified Oncolytic Herpes Simplex Virus (HSV) to Treat NF2 Tumors

Robert L. Martuza, M.D. (pictured)
Xandra Breakefield, Ph.D.
Samuel Rabkin, Ph.D.
Massachusetts General Hospital

Schwannomas and meningiomas are tumors that form in NF2 patients by overgrowth of cells that support neurons in the nervous system. Such tumors can cause pain, paralysis, seizures, hearing loss, and death. Through his FY03 Therapeutic Development Award, Dr. Robert L. Martuza and his colleagues Drs. Xandra Breakefield and Samuel Rabkin sought to develop safe, targeted gene delivery methods to treat and evaluate responses in schwannomas and meningiomas. Dr. Martuza and colleagues tested the use of oncolytic HSV type 1 vectors as a new treatment for NF2-associated tumors. Oncolytic viruses (viruses that can infect and kill cancer cells while leaving normal cells alone) are not 100 percent efficient when used in therapies. Dr. Martuza and colleagues attempted to improve efficiency by arming the oncolytic viruses with therapeutic transgenes to allow the vector to attack the tumor in multiple ways. They found that the oncolytic HSV vector G47 delta decreased cell viability of a human schwannoma cell line 2.5-fold. Dr. Martuza and colleagues tested G47 in a spontaneous NF2 schwannoma mouse model and found that all tumors treated with G47 delta decreased in size by more than 60 percent. They then added a transgene to an HSV vector that would specifically kill schwannoma cells. In a schwannoma model, three injections of this vector led to almost complete regression of tumors during treatment. The tumors only resumed growth 7 days after the third and final vector treatment.

Neurofibromin Ubiquitin Ligase: Regulation and Function

Karen Cichowski, Ph.D.
Brigham and Women's Hospital

Very little is currently known about how the NF1 protein neurofibromin normally functions to control cell growth. Interestingly, Dr. Karen Cichowski and colleagues have shown that neurofibromin is regulated by a specific ubiquitin ligase. This ligase facilitates the rapid degradation of neurofibromin, resulting in the activation of cell growth mediated by Ras. The molecular activation of Ras by ligase-mediated neurofibromin degradation represents a landmark discovery in understanding the underpinnings of this disease and its progression. Using this key observation, Dr. Cichowski plans to research ways to block this process. Through funding from an FY07 Investigator-Initiated Research Award, Dr. Cichowski will study and identify other proteins that regulate the function of neurofibromin and the associated ubiquitin ligase. In researching this fundamental process, Dr. Cichowski hopes to find pharmacologic targets to slow or even halt the degradation of neurofibromin. These findings may serve as a platform by which future therapeutics can be rapidly tested for efficacy ahead of clinical trials, an additional benefit to the NF1 community.

Providing Access to Fundamental Resources

The NFRP began a research resource initiative in 2008 to facilitate and speed vital research on the disease by publicizing newly available resources supported by the NFRP. A reference guide was developed on the NFRP website that displays available resources such as animal models, cell lines, and antibodies, as well as contact information for each resource. The goal of this initiative is to encourage collaboration among the NF research community and promote resource sharing by making the information publically available. The reference table can be found at (http://cdmrp.army.mil/nfrp/nfrpresources.htm).

Although animal models may not be derived from NF patients, they provide important model systems for studying the disease. The NF genes are highly conserved in mice. For example, there is over 90 percent similarity between human and mouse NF1 or NF2 proteins. This suggests that NF1 and NF2 have very similar functions in different species. These models can be used to learn about basic molecular and cellular functions of NF1 and NF2, thereby providing the foundation for the development of new therapies. The models can also be used to test the potential efficacy and toxicity of candidate therapeutics so that the best drugs can be given to NF patients. The NF1 protein, neurofibromin, is an inhibitor of the Ras signaling pathway while the NF2 protein, merlin, inhibits the activity of PAK1, a downstream protein in the Ras pathway. Proteins in this signaling pathway play central roles in regulating growth and/or apoptosis.

"What a thrill it has been to participate as a consumer on the peer review panel for the Neurofibromatosis Research Program! These panels are a unique opportunity to ensure that the NF community's voice is heard. It's a credit to the foresight and compassion of the CDMRP that consumers are invited to weigh in on research priorities. Everyone affected by NF should be reassured to know that the research community is listening. It is our job to speak up."

Rosemary Anderson
Neurofibromatosis, Inc.
FY06-FY07 Peer Reviewer

http://cdmrp.army.mil/nfrp/animalmodels.htm

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Search Site: GO

New Research Resources Initiative by the NFRP

The NFRP now offers a service on our website featuring a listing of available NF research resources!! Our goal is to facilitate and speed NF research by publicizing new resources and aiding collaborations. The list displays available resources and repository or PI contact information. Please contact the repository or PI directly for information and requests.

Product or Resource	PI	Source	Link	Award Number	References
Animal Models developed through the CDMRP					
ROSA CreER	Dr. Kevin Shannon, Dr. Tyler Jacks	MMHCC	http://mouse.ncifcrf.gov/available_details.asp?ID=01XAB (external link)	NF010093	McLaughlin ME, Kruger GM, Slocum KL, Crowley D, Michaud NA, Huang J, Magendantz M, and Jacks T. 2007. The Nf2 tumor suppressor regulates cell-cell adhesion during tissue fusion. PNAS,104(9):3261-3266.
Nf1 conditional mutant: NF1 flox	Dr. Kevin Shannon, Dr. Luis	MMHCC	http://mouse.ncifcrf.gov/available_details.asp?ID=01XM4 (external link)	NF010018	Zhu Y; Romero MI; Ghosh P; Ye Z; Charnay P; Rushing EJ; Marth JD; Parada LF. Ablation of NF1 function in neuronal lineages leads to abnormal development of cerebral cortical and nigrostriatal dopaminergic systems and hyperactive ras signaling. Genes Dev. 15, 1858-1875. 2001. PMID: 11297510.
Nf2 KO3	Shannon, Jacks		http://mouse.ncifcrf.gov/available_details.asp?ID=01XM6&sid=&dna=&cdna=&cdna=&cdna= (external link)		Giovanni A, Wintzerith M, Vigne E, Dreyer C, Gerber U, Rubin JR, Hofstetter W, Lathy DR, Lecanet JP, Mornon JP, Spencer ML, Lindholm D, Thomas G, Kiss JZ. Expression of a chimeric protein in the spinal cord of mice with a severe form of spinal muscular atrophy. J Comp Neurol. 395, 267-280. 1998. PMID: 9596527.
Nf2 KO iso	Shannon, Jacks		http://mouse.ncifcrf.gov/available_details.asp?ID=01XM7&sid=&dna=&cdna=&cdna=&cdna= (external link)		Giovanni A, Wintzerith M, Vigne E, Dreyer C, Gerber U, Rubin JR, Hofstetter W, Lathy DR, Lecanet JP, Mornon JP, Spencer ML, Lindholm D, Thomas G, Kiss JZ. Expression of a chimeric protein in the spinal cord of mice with a severe form of spinal muscular atrophy. J Comp Neurol. 395, 267-280. 1998. PMID: 9596527.
Nf2 KO iso	Shannon, Jacks		http://mouse.ncifcrf.gov/available_details.asp?ID=01XM8&sid=&dna=&cdna=&cdna=&cdna= (external link)		Giovanni A, Wintzerith M, Vigne E, Dreyer C, Gerber U, Rubin JR, Hofstetter W, Lathy DR, Lecanet JP, Mornon JP, Spencer ML, Lindholm D, Thomas G, Kiss JZ. Expression of a chimeric protein in the spinal cord of mice with a severe form of spinal muscular atrophy. J Comp Neurol. 395, 267-280. 1998. PMID: 9596527.

"Eight years ago, the CDMRP neurofibromatosis program invested substantial resources in a consortium of five investigators who proposed to generate and characterize genetically engineered mouse models of NF1- and NF2-associated tumors and to make these strains broadly available to the research community. The results of this effort have been exceptionally successful by any measure. Our NF Mouse Models Consortium generated accurate models of many NF1- and NF2-associated tumors including plexiform neurofibroma, malignant peripheral nerve sheath tumor, glioma, meningioma, and myeloid leukemia and have provided these mice to over 50 laboratories worldwide. Studies performed in these models by us and by other investigators have contributed fundamental insights into mechanisms of tumor formation and maintenance, elucidated the effects of NF1 and NF2 loss on cell growth and signaling networks, and provided preclinical data that have led to novel therapeutic trials. The strains produced through this effort are the backbone of a new preclinical Drug Discovery Initiative developed by the Children's Tumor Foundation that has the goal of testing novel treatment strategies to benefit NF1 and NF2 patients. This visionary series of competitive awards by the CDMRP has not only advanced our knowledge of NF1 and NF2 disease pathogenesis but has enabled our consortium to generate novel reagents that will help to advance the field for years to come."

Kevin Shannon, M.D.
University of California
FY96, FY99, FY01, and FY04 NFRP Awardee

The Program Today

FY07 Summary

The NFRP received a congressional appropriation of $10M in FY07 to continue the program. The emphasis of the FY07 program emerged from an NFRP-launched request for information from the NF scientific and consumer advocacy communities. Funding gaps and obstacles were identified, including additional emphasis on translational research, complications of NF with high morbidity, complications of NF with high mortality, and refinement and standardization of imaging techniques for use in future clinical trials. Three award mechanisms were offered to address these critical issues: Concept, Investigator-Initiated Research, and New Investigator Awards. Both the Investigator-Initiated and New Investigator Awards encouraged applicants to collaborate with another investigator. A total of 94 proposals were received across award mechanisms, and 11 awards were made, as summarized in Table IV-1. The FY07 portfolio by research area is illustrated in Figure IV-2.

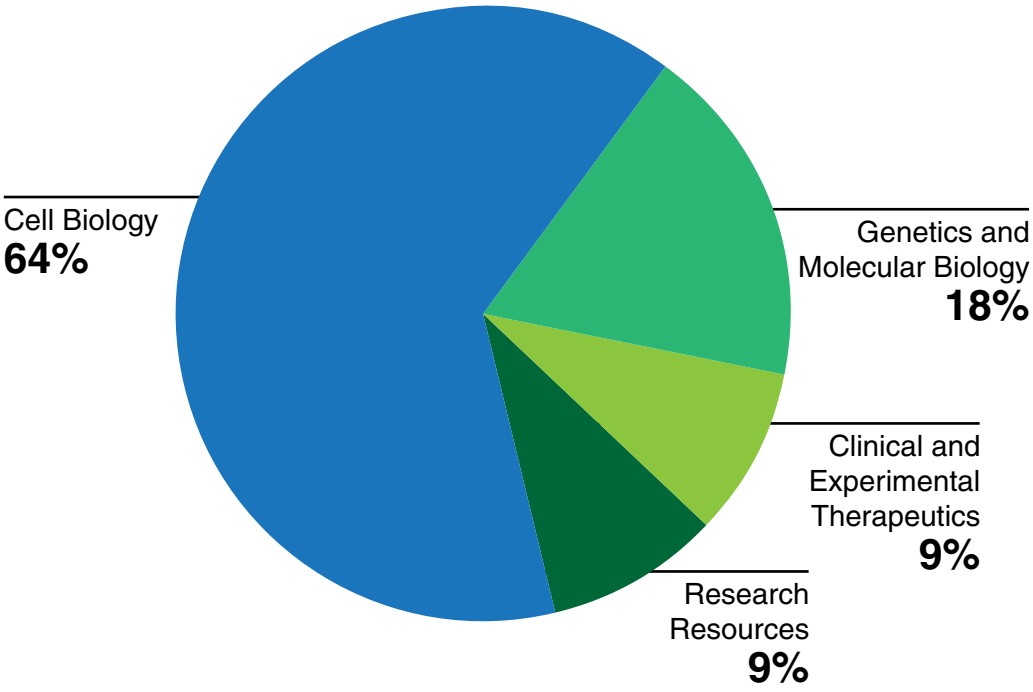


Figure IV-2. FY07 NFRP Portfolio by Research Area

Table IV-1. Funding Summary for the FY07 NFRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Concept	41	4	$0.41M
New Investigator	29	3	$1.76M
Investigator-Initiated Research	24	4	$3.75M
TOTAL	**94**	**11**	**$5.92M**

Note: Additionally, $3.2M was allocated to the clinical consortium protocol.

The Vision for FY08

Congress appropriated $8M in FY08 to continue the peer-reviewed NFRP. Four award mechanisms were offered: Clinical Trial, Exploration-Hypothesis Development, Investigator-Initiated Research, and New Investigator Awards. As shown in Figure IV-3, 72 proposals were received across the 4 award mechanisms. Approximately 14 awards are predicted. Appendix B, Table B-3, summarizes the congressional appropriations and the investment strategy executed by the NFRP for FY07 through FY08.

Figure IV-3. Award Mechanisms Offered and Proposals Received for the FY08 NFRP

The NFRP Team

Naba Bora, Ph.D.
Program Manager

Hin Lee, Ph.D.
Grants Manager

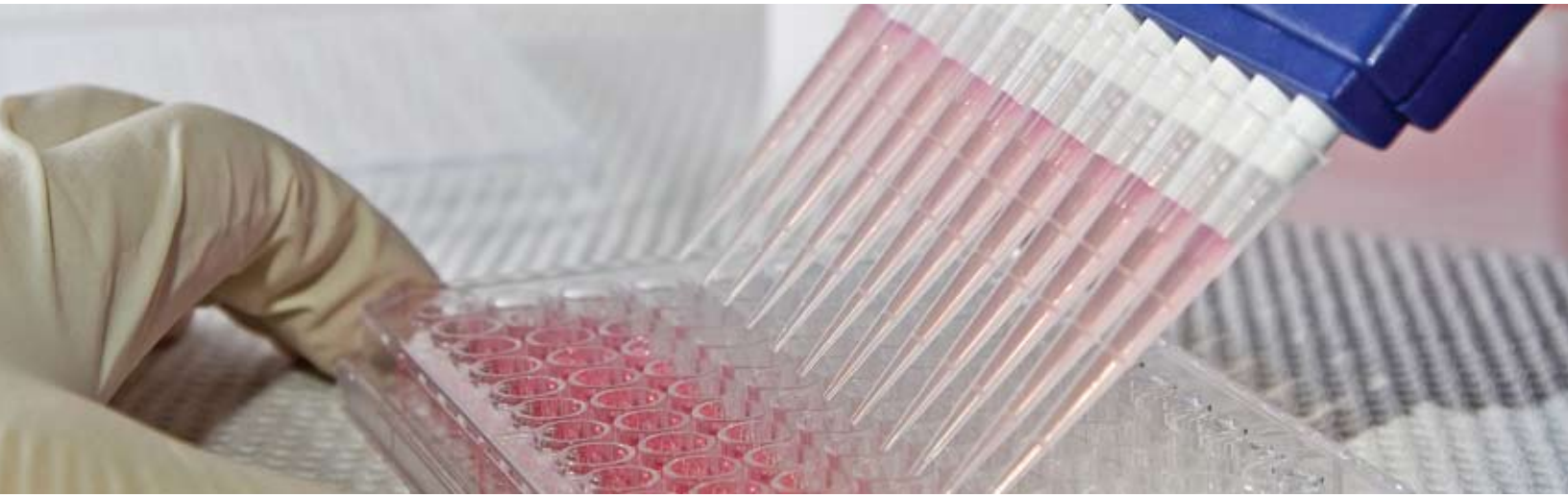
Patricia Roth, M.S.
Program Specialist, Azimuth

Bethany Orlando
Program Coordinator, SAIC

Michelle Sharp, M.S.
Biomedical Scientist, SAIC

Doug White, Ph.D.
Biomedical Scientist, SAIC

Dettrick Stith, Ph.D.
Peer Review Coordinator
SRA International



The NFRP— 11 Years of Funding Vital Research

Since the program's inception in 1996, the NFRP has strived to find and fund cutting-edge research to achieve the ultimate goal of discovering effective treatments for those with NF1, NF2, and schwannomatosis. The IP, consisting of scientists and consumer advocates, recommends an elite group of proposals with the potential of contributing to this goal. As the scientific field progresses toward this goal, the NFRP shifts the focus yearly along with the objective to fill the gaps in research and advance NF research to the forefront, ensuring that the most vital research is promoted and funded.

The following time line highlights some of the exemplary awards made to NF investigators who have contributed to the NFRP legacy over the past 11 years.

1996
- Genotype/phenotype analysis in NF1 (Friedman) and NF2 (MacCollin)
- Development of mouse models of NF1 and NF2 (Parada and Jacks)

1997
- Natural history studies of NF1 (Korf) and NF2 (Slattery)

1998
- Genetic evaluation of NF1 tumors (Viskochil)

1999
- Natural history of psychological aspects of NF1 (North)
- Preclinical evaluation of gene therapy for NF2 (Breakefield)
- Mouse models of MPNSTs and plexiform neurofibromas (Shannon)

2000
- NF2 natural history consortium (Slattery)
- Phase II trial of R115777 for NF1 (Widemann)
- Gene expression profiling of NF1 (Ratner) and NF2 (Pulst) cells

2001
- Phase I/II trial of pirfenidone for NF1 (Packer)
- Development of oncolytic virus therapies for NF1 (Rabkin)

2002
- Identification of the schwannomatosis locus (MacCollin)
- Studies of NF1 modifier genes (Bernards)

2003
- Generation of a new class of Ras inhibitors for NF1 (Kloog)
- Development of an HSV vector therapy for NF2 (Martuza)
- NF1 microarray consortium (Ratner)

2004
- Identifying Pak1 inhibitors as a treatment for NF2 (Peterson)
- Mouse models of astrocytomas and ependyomas (Shannon)

2005
- Phase II clinical trial of neoadjuvant chemotherapy for NF1 (Widemann)
- Statins for the treatment of NF1 cognitive deficits (Silva)
- Whole body MRI evaluation of NF1, NF2, and schwannomatosis patients (Plotkin)

2006
- NF clinical trials consortium
- Preclinical testing of oncolytic viral therapy combined with tyrosine kinase inhibitors (Rabkin)

2007
- Photodynamic therapy for the treatment of plexiform neurofibromas (Fisher)
- Oncolytic viral vectors for the treatment of NF2-related schwannomas (Martuza)