IV. Neurofibromatosis Research Program

VISIONARY APPROACHES

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.

NFRP Making Headlines

- **Tracing the Pathways of Neurofibromatosis: Researchers Find Genetic Flaw Starts Biochemical Domino Effect**
  Science Daily, January 19, 2007
- **$10 Million Awarded for NF Research**
  Children's Tumor Foundation, February 22, 2007
- **Brain Tumors Coax Important Support from Nearby Immune System Cells**
  Science Daily, April 12, 2007
- **Research Round Up: Neurofibromatosis Center Expands Clinical Services Following Neurofibromatosis Funding**
  St. Louis Children's Hospital, May 2007
- **Washington University Neurofibromatosis Center Receives Department of Defense Grant to Participate in NF Clinical Trials Consortium**
  Washington University of St. Louis News Release, July 1, 2007

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 percent 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, 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) may occur anywhere on or under the skin
- Six or more cafe-au-lait spots, light brown spots similar to birthmarks, 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 [PNs]) can occur anywhere
- Bowing or thinning of the shin bone (tibia)

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. The NFRP represents the second oldest CDMRP program and a major source of funding worldwide for research on NF1, NF2, and schwannomatosis. To date, the program has managed **$182.3M in appropriations** from FY96 to FY07 (see Figure IV-1, NFRP Funding History). **A total of 198 awards** has been made through FY06 spanning basic research, translational research, and clinical research.

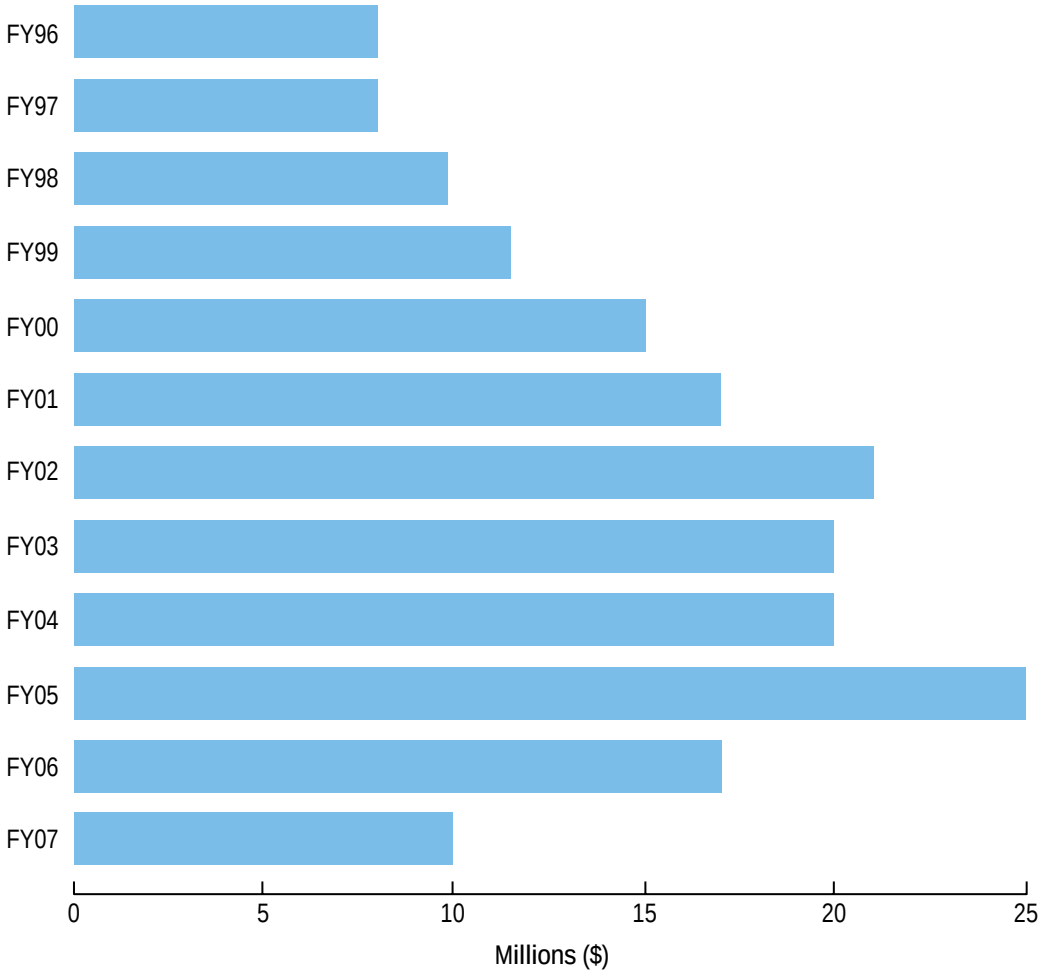


Figure IV-1. NFRP Funding History

The Visionaries

Consumer Advocates

Consumer advocates bring the voice and vision of over 100,000 men, women, and children in the United States living with NF to the NFRP. Their dedication has played a vital role in the establishment and continuing growth of the program for the past decade. Over **40 consumer advocates** have worked side by side with scientists to set 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. The NFRP values and applauds the efforts of consumer advocates who are essential to the success of the program. Section I (Overview) of this report contains additional information regarding consumer advocate participation.

Doreen Stolzenberg Feldman, J.D.
Neurofibromatosis, Inc.
FY06–07 Consumer Member, Integration Panel Member
NF Patient

Doreen Stolzenberg Feldman was diagnosed with NF at a young age, when very little was known about the disorder. She is a founding member of the Mid-Atlantic Chapter of NF, Inc., served on its Board of Directors, and was active for many years in education, fundraising, and promoting awareness of NF. Doreen is an Assistant General Counsel at the U.S. Government Accountability Office. She lives in Falls Church, Virginia, with her husband, Mitch, and enjoys yoga, travel, hiking, and golf. "I feel privileged to have the opportunity to serve as a consumer reviewer for the Neurofibromatosis Research Program. It has been exciting and rewarding to read the wide range of research proposals, participate in funding decisions, and experience firsthand the dedication of the physicians and scientists who are seeking to find a treatment and cure for neurofibromatosis."

Peer Review Panel Members

Scientific peer review is conducted by a panel of expert scientists and clinicians who represent a scientific discipline or specialty area. The primary responsibility of the peer review panel is to provide unbiased, expert advice on the scientific and technical merit of proposals submitted to the NFRP. To date, over **250 prominent scientists, clinicians, and consumer advocates** have brought their expertise to the NFRP scientific peer review process. Scientific peer review is described in greater detail in Section I.

Scientific Community

Over **167 NFRP-supported researchers** from around the world are exploring the cutting edge of science and medicine to improve the detection, diagnosis, treatment, management, and high quality of care of persons affected with NF and schwannomatosis. A glimpse of progress in these areas made by NFRP-supported investigators is highlighted throughout the remainder of this section.

Larry Sherman, Ph.D.
Oregon National Primate Research Center
FY07 Scientific Peer Reviewer

"The DOD neurofibromatosis program has consistently impressed me at every level. The review process is outstanding and thorough. I have served on many different panels and this one is by far the best in terms of the intellectual process and the level of discussion that goes into reviewing every grant. I am also highly impressed by the immense amount of progress this program has generated in converting basic science into clinical studies. It is amazing that so many of the early studies funded by this program are at the levels of preclinical and even early clinical trials. This would not have been possible without the focus of this outstanding program."

Integration Panel Members

The NFRP Integration Panel (IP) comprises distinguished scientists, clinicians, and consumer advocates. They work to serve the interest of the NF and schwannomatosis communities by recommending effective investment strategies, cutting-edge research priorities, and multidisciplinary research portfolios (for more information about the functions of the IP, see Section I). 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.

Nancy Ratner, Ph.D.
Cincinnati Children's Hospital Medical Center
FY07 Integration Panel Chair

"The DOD program on neurofibromatosis has raised the profile of NF1, NF2, and schwannomatosis by facilitating the expansion of research in existing NF labs and by attracting many new investigators into the NF community. The DOD program on neurofibromatosis has f exibility to inspire the research community to chart novel courses each year. RFAs have been written that encourage investigators to temper basic scientific agendas with goals of the patient community. This year the NF research community was challenged to meld basic science and translational goals by integrating basic scientists with scientists in other disciplines, clinicians, and/or partners in industry."

FY07 NFRP IP Members

Nancy Ratner, Ph.D. (Chair), Cincinnati Children's Hospital Medical Center

William Johnson, M.D. (Chair Emeritus), UMDNJ, Robert Wood Johnson Medical School

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

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

Doreen Stolzenberg Feldman, J.D., Neurofibromatosis, Inc.

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

Elizabeth Henske, M.D., Fox Chase Cancer Center

Michael Morin, Ph.D., Pfizer Global Research & Development

Sandra Parker, J.D., Neurofibromatosis, Inc.

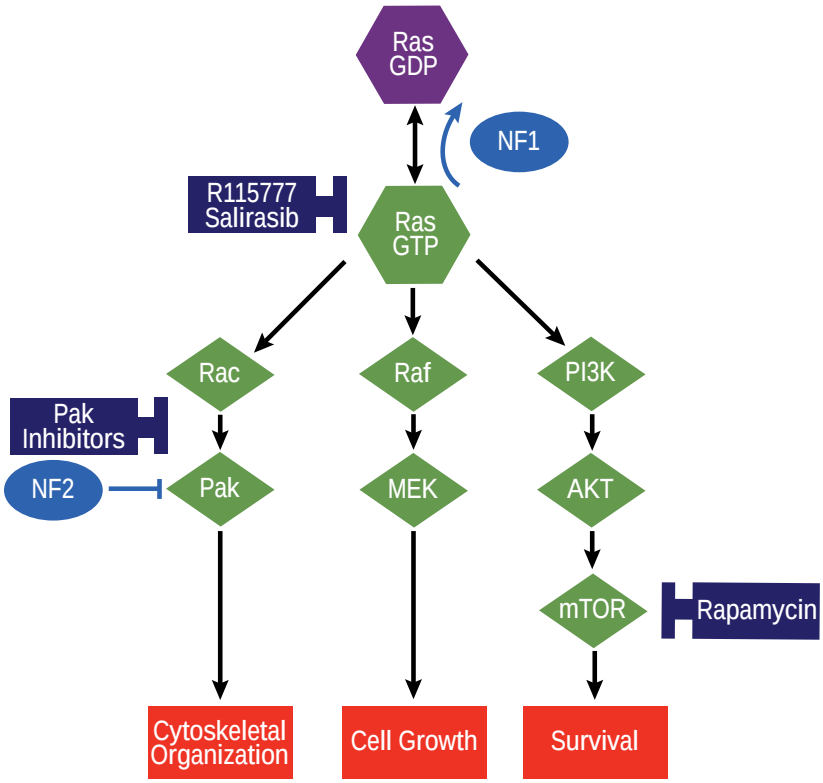
Tina Young Poussaint, M.D., Children's Hospital Boston

John Risner, Children's Tumor Foundation

Anat Stemmer-Rachamimov, M.D., Massachussets General Hospital

Visionary Approaches to Eradicate the Clinical Impact of NF

Groundbreaking studies by the nation's and world's finest NF researchers are highlighted throughout the remainder of this section. While many different approaches are converging to make the NFRP vision a reality, a snapshot of some of the key approaches taken by NFRP-supported researchers is depicted in the following cell-signaling diagram. Illustrated in this graphic are a few of the candidate therapeutic targets including Ras, mTOR, and Pak along with several therapeutic agents under study for the treatment of NF1 and NF2.



Adapted from Figure 1, Schubbert et al. *Nature Reviews Cancer*, April 2007.

This figure illustrates the Ras signaling pathway that normally functions to regulate cell proliferation and death by controlling outcomes including cytoskeletal organization, survival, and proliferation. Ras activation plays a critical role in both NF1 and NF2. In response to external growth factors, the exchange of guanosine di-phosphate (Ras-GDP) for guanosine tri-phosphate (Ras-GTP) results in the activation of Ras. This process ultimately affects downstream signaling molecules associated with cell proliferation, cytoskeletal organization, and cell survival. The neurofibromin (NF1) protein normally attenuates the response to growth factor stimulation and yields inactive Ras-GDP. Increased Ras activation is observed in patients with dysfunctional NF1.

The NF2 protein (Merlin) regulates processes associated with cytoskeletal organization by exerting its action on the p21-activated kinases (Paks). Dysfunctional NF2 cannot properly regulate Pak signaling, resulting in the formation of tumors.

Researchers have targeted the Ras signaling pathway at several critical junctions to treat both NF1 and NF2. Notable examples include Rapamycin, Salirasib, and the Pak inhibitors.

Visionary Approaches to the Development and Testing of Therapeutics for NF1—Ras Inhibitors

Neurofibromin, the protein product of the NF1 gene, normally acts as a brake to negatively regulate levels of the Ras protein in cells. The function of Ras is a switch to stimulate cell growth and division. However, in NF patients, the NF1 protein is mutated disrupting this careful balance of key mediators within the cell. Consequently, levels of Ras go unchecked and rise uncontrollably leading to excessive cell growth that can ultimately lead to tumor development. Researchers believe that by inhibiting these high levels of Ras they may be able to inhibit growth of tumors. This same paradigm is seen in approximately 30 percent of human cancers where Ras is mutated and is permanently switched on, telling the cell to grow. Therefore, targeting Ras has great potential as a therapy to benefit those with NF1 as well as those with other cancers.

Brigitte Widemann, M.D.
National Cancer Institute

Determining the Impact of Ras Inhibitors in Patients with NF1

Dr. Brigitte Widemann of the National Cancer Institute (NCI) has been conducting a multi-institutional Phase II clinical trial of the farnesyltransferase inhibitor, R115777 (tipifarnib), in children and young adults with NF1-associated PNs. Farnesylation is a process necessary to the function of Ras, which provides the rationale for the evaluation of farnesyltransferase inhibitors in children with NF1. Given the unknown natural history of PNs, this trial used a randomized, placebo-controlled, double-blinded cross-over design to define the effect of this novel drug on the rate of PN growth. Accrual on the trial is close to completion, and results regarding the activity of R115777 for PN will become available when all patients are evaluated for time to disease progression, the primary trial endpoint. However, during the course of this study and others conducted at the NCI, standard imaging techniques and three-dimensional volumetric magnetic resonance imaging (MRI) were compared. Results decisively showed the advantage of the volumetric method that could capture and quantify smaller changes in tumor size than could be detected by the standard methods and was not affected by differences in body position between scans. Volumetric MRI analysis is therefore used on this and other trials to determine time to disease progression. Using volumetric MRI analysis of PNs, Dr. Widemann also determined that PNs from younger children show more rapid growth compared to the same tumors in older children, and that body growth alone did not account for the more rapid growth of PNs in children with NF1. This information is extremely valuable for the design of future clinical trials for children with NF1. While this design is complex, it allows for collection of natural history data from the placebo arm; the progression data generated on the placebo arm of this trial will serve as historical control for future treatment trials, which aim at decreasing time to disease progression.

Yoel Kloog, Ph.D.
Tel Aviv University

Studying a Novel Class of Ras Inhibitors

Dr. Yoel Kloog of the Tel Aviv University in Israel has been working to show the therapeutic potential of a novel Ras inhibitor salirasib using funds from an **FY03 Therapeutic Development Award**. Salirasib (or FTS) is a potent Ras inhibitor that differs from farnesyltransferase inhibitors in its ability to act on all three active forms of Ras. Dr. Kloog conducted studies using malignant peripheral nerve sheath tumor (MPNST) cells to examine the effects of salirasib on the characteristics of these NF1-deficient cells. Salirasib treatment effectively inhibited Ras in these cells that was accompanied by downregulation of three major Ras-associated signaling pathways: ERK, Ral A, and Akt. Furthermore, salirasib inhibited abnormal growth of NF1-deficient cells and inhibited tumor growth in an NF1 mouse model by 58 percent. Dr. Kloog extended these findings by using gene expression profiling to dissect the gene expression alterations that resulted from salirasib treatment in a variety of cancer cell lines. Analysis identified a distinctive core transcriptional response to salirasib that was common to all cancer cell lines tested involving the transcription factor FOS, survivin (which blocks apoptosis), and Bach2-regulated genes (involved in translation and stress responses). Results of an ongoing Phase I study of FTS in patients with relapsed hematologic malignancies were recently published showing that FTS had promising activity in these malignancies with minimal toxicity. Based on these impressive results, salirasib appears to be a strong candidate for the treatment of patients with NF1 as well as those suffering from Ras cancers such as lung, pancreatic, hematologic, and colon.

Designing the Next Generation of Ras Inhibitors

Raymond Mattingly, Ph.D.
Wayne State University

Dr. Raymond Mattingly of Wayne State University, working in collaboration with Dr. Richard Gibbs of Purdue University, has used support from an **FY02 Idea Award** to design and validate a new class of Ras inhibitors for the treatment of NF1-associated cancers with a focus on MPNST. An initial study of cell lines derived from NF1 patients showed that the predominant Ras isoform being activated was N-Ras. However, currently available compounds are most effective against H-Ras. The investigators hypothesized that tumorigenesis in NF1 patients may be specifically driven by aberrant activation of N-Ras. Therefore, Drs. Mattingly and Gibbs developed several innovative compounds that blocked cellular processing of N-Ras and subsequently blocked their downstream effectors including ERK. Several of these prodrugs were found to block cell proliferation and impair cell survival in three MPNST cell lines. Investigators are optimistic that these compounds may point the way toward a new treatment option for malignancies in NF1 patients.

Nicolas Nassar, Ph.D.
State University of New York, Stony Brook

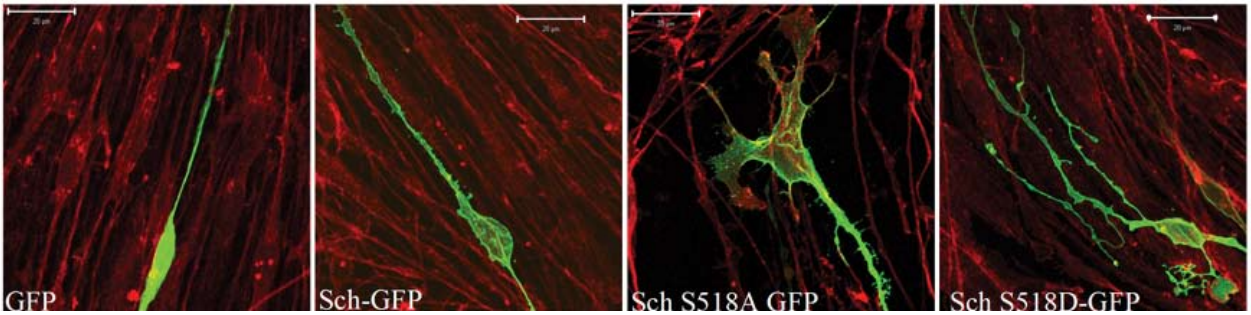
Dr. Nicolas Nassar of the State University of New York, Stony Brook received an **FY06 New Investigator Award** to search for improved Ras inhibitors. In preliminary work, Dr. Nassar screened the NCI's library of small molecules searching for inhibitors of a nonsignaling conformation of Ras that was recently stabilized and characterized. Because this form of Ras is not able to interact with downstream signaling partners, it is an ideal target for drug design. Dr. Nassar aims to test the top candidates for their ability to inhibit cell growth in NF1-deficient cells and block tumor development in NF1 mouse models. Hopefully, these molecules will be developed into therapies to benefit those with NF and other Ras cancers.

Visionary Approaches to Identifying Targets for NF2 Therapeutics

Schwannomin, the protein product of the NF2 gene, normally acts as a brake on cell growth and division. In patients with NF2, the loss of schwannomin function leads to uncontrolled cell growth and the development of tumors such as schwannomas and meningiomas around nerves. Although these tumors are rarely malignant, they can result in pain, loss of hearing or sight, seizures, and paralysis. Despite extensive study, the exact molecular mechanism by which schwannomin functions within the cell remains unclear. Researchers continue to investigate how schwannomin functions and search for key mediators that interact with schwannomin. Identifying key schwannomin binding partners may lead to targets for future therapeutic development and testing. Dedicated scientists are striving to envision a brighter future for those living with NF2.

Discovering Novel NF2 Binding Partners

Dr. Olli Carpen at the University of Helsinki, Finland is using an **FY04 Investigator-Initiated Research Award** from the NFRP to examine whether schwannomin suppresses tumorigenesis by regulating the cell cycle in schwann cells. Dr. Carpen's research team has identified a novel cell cycle regulator HEI10 as a molecule that specifically partners with schwannomin. Studies showed that the two molecules move concurrently between the nucleus and the cytoplasm depending on the phase of the cell cycle. This co-localization and nuclear-cytoplasmic shuttling may indicate a means to affect cell growth, suggesting that schwannomin may act to target HEI10 to the appropriate location during cell division. Subsequently, cells deficient in schwannomin, such as those found in patients with NF2, can no longer target HEI10 properly, possibly contributing to tumorigenesis. Though the complete mechanism of this action is not yet known, it may involve cyclin B, an important cell cycle regulator implicated in the development of many other cancers. Dr. Carpen and his colleagues have also been investigating a link between schwannomin and microtubules, which are composed of tubulin. Microtubules form the structural network of a cell working to coordinate processes such as cell growth and division. Schwannomin and tubulin are co-localized during mitosis at the mitotic spindles and during cytokinesis at the midbody where the cells separate. These studies determined that loss of schwannomin in schwann cells caused drastic changes in microtubule organization, suggesting a mechanism by which a loss of schwannomin may lead to the cytoskeletal defects observed in human schwannomas.



The Phosphorylation State of Schwannomin Alters the Polarity of Primary Rat Schwann Cells.
Schwann cells expressing GFP (green fluorescent protein)-tagged Sch-S518A that mimics the unphosphorylated protein at serine 518 become unipolar whereas those expressing Sch-S18D that mimics the phosphorylated protein become multipolar. Those expressing wild-type schwannomin remain bipolar and extend long processes. GFP is shown in green, and F-actin stained with phalloidan is shown in red.

A team of scientists at the University of Central Florida led by Dr. Cristina Fernandez-Valle is working to identify how schwannomin functions to regulate Schwann cell growth using funding from an **FY02 Investigator-Initiated Research Award**. Dr. Fernandez-Valle's team has shown that the protein paxillin plays a role in the phosphorylation of schwannomin localized to the plasma membrane. It was shown that paxillin binding of schwannomin was required for phosphorylation by p21-activated kinase (Pak), a therapeutic target in NF2 research currently under intense study. This phosphorylated form of schwannomin was found at the most peripheral aspects of the Schwann cell in the lamellipodia and distal tips. Beyond this, Dr. Fernandez-Valle's team looked at how schwannomin phosphorylation at these localized areas affected Schwann cell morphology, as this would illustrate the effect of the loss of schwannomin in NF2. Studies showed that phosphorylated schwannomin localized at the cell membrane enabled Schwann cells to keep their elongated, bipolar shape. In contrast, when phosphorylation was inhibited, many cells adopted a unipolar shape that was not elongated, as well as increased surface area and excessive membrane ruff ing. The disruption of the actin cytoskeleton in this aberrant morphology could reasonably lead to problems with axonal development. Further work to elucidate schwannomin's binding partners such as paxillin will help researchers identify therapeutic targets necessary for the development of treatments for NF2.

Jeffrey Peterson, Ph.D.
Fox Chase Cancer Center

Developing Innovative Targeted Therapies for NF2

There has been great interest recently in the potential of Pak1 inhibitors for the treatment of both NF1 and NF2. Pak is believed to execute a biochemical signal that results in the cancerous transformation of cells. It is widely held that Pak inhibitors could be an effective therapeutic target for neurofibromatosis, as well as other cancers including breast, ovarian, pancreatic, and colon. Dr. Jeffrey Peterson of the Fox Chase Cancer Center has taken an innovative approach to developing inhibitors of Pak, targeting not the catalytic site, as the vast majority of currently available kinase inhibitors do, but rather targeting the autoinhibitory domain of Pak1. This variation results in significantly greater specificity for Pak1 than typical active site-directed kinase inhibitors. Future work will then be focused on establishing the therapeutic utility of these allosteric inhibitors in the treatment of neurofibromatosis. Dr. Peterson developed a high-throughput screening method to screen over 30,000 small molecules for Pak1 inhibitors. A total of 343 active compounds identified by the screen were further winnowed down to 8 compounds that were effective in the presence of high concentrations of ATP and failed to inhibit Pak1 after activation (indicating that they did not target the ATP-binding pocket). From these, Dr. Peterson zeroed in on 2 compounds, IPA-3 and IPA-5, which effectively inhibited Pak1 activity, and expanded testing to other Pak isoforms. Inhibition of Pak activity has also been applied in other diseases such as Fragile X syndrome (FXS), a cause of mental retardation and autism involving abnormal neurons in the brain. When Pak activity was inhibited in mice with FXS, abnormal features in the neurons, as well as behavior abnormalities, were actually reversed. Researchers in other disciplines including pancreatic and colon cancer are investigating Pak inhibitors in mouse models of cancer. Pak inhibitors hold exciting potential as therapeutic agents for neurofibromatosis and an array of cancers, and researchers are hopeful this can be translated into an effective treatment.

Visionary Approaches to NF-Associated Learning Disabilities

Learning disabilities affect approximately 50 percent to 60 percent of patients with NF, making it a major source of morbidity for patients and a priority/focus for the NFRP. The NFRP is funding a spectrum of work in this area from studies designed to uncover the basis of NF-associated neurocognitive deficits to studies directed at improving the treatment and management of these issues in children and adults who are affected every day.

The North Research Team at Children's Hospital at Westmead in Australia (left to right): Coco Kang, Belinda Barton, Ph.D., Kathryn North, M.D., Jonathan Payne, Ph.D., Jennifer Lorenzo, M.S., and Sharon Watt, M.S.

Improving the Lives of Patients with Learning Disabilities

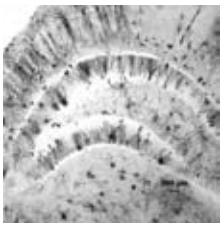
Dr. Kathryn North of the Children's Hospital at Westmead and the University of Sydney in Australia in collaboration with Drs. Maria Acosta and Roger Packer at the Children's National Medical Centre in Washington have been conducting studies to more thoroughly define the nature of cognitive deficits and the natural history of learning disabilities in young children with NF1. In the process of conducting the study, Dr. North hopes to identify early predictors of developmental delay in young children and create guidelines for the psychological assessment and interpretation of testing specifically for children with NF1. Early interventions may then be developed to improve the long-term outcome for patients. In addition, a better understanding of how NF1 impacts learning in preschool children and the natural history of their learning disabilities as they progress into primary school and high school will provide important data that can then be used to determine the optimal timing of specific therapies that may improve cognitive function in NF1, such as lovastatin. Thus far in her studies, current neuropsychological tests only identified a limited number of functional skills that were impaired in NF1 patients. This demonstrates the importance of combining neuropsychological assessment with functional assessment for the development of effective treatment strategies for those with NF1. Preliminary data suggest that more severe deficits in cognitive performance can be detected as early as 2 years of age while children at risk of attention problems and reading difficulties can be reliably identified as early as 5 years of age.

The Narayanan research lab at the Barrow Neurological Institute at St. Joseph's Hospital and Medical Center (left to right): Shannon Snyder, M.S., Vinodh Narayanan, M.D., Garilyn Jentarra, Ph.D., Gabe Rice, M.S., and Johana Vallejo, Ph.D.

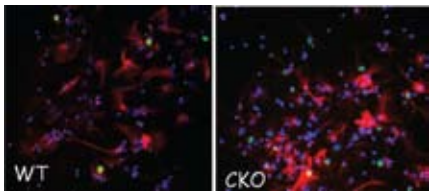
Determining the Underlying Basis of NF-Related Neurocognitive Deficits

Dr. Vinodh Narayanan of St. Joseph's Hospital and Medical Center hypothesizes that defects in neuronal axonal and dendritic transport may underlie the cognitive impairments seen in patients with NF1. Support through an **FY06 Concept Award** will be used to follow up on the finding that the NF1 gene product, neurofibromin, interacts with kinesin-1 and microtubules, proteins involved in the transport of vesicles up and down neuronal processes, called axons and dendrites. Coordinated regulation of this transport process is critical to proper nerve functioning and therefore may underlie the cognitive characteristics of NF1. Cutting-edge techniques involving live imaging of neurons derived from the brains of NF1 mice will be used to explore cellular transport processes in these cells. These studies will provide the first investigation of transport defects in NF1 mice and could provide a novel mechanism for the underlying cause of learning deficits.

As an alternative hypothesis, Dr. Laura Dugan of University of California, San Diego will be exploring the theory that NF1 dysfunction leads to increased levels of reactive oxygen species (ROS) in the brain. ROS form as a byproduct of normal cell metabolism and have important roles in cell signaling. However, high levels of ROS in other systems have been shown to result in significant damage to cell structures and alterations in neurotransmission, processes that could ultimately lead to learning and memory impairments. Dr. Dugan and her collaborator, Dr. David Gutmann of Washington University, hypothesize that Nf1-deficient cells may have abnormally high levels of ROS. Dr. Dugan will first determine if an Nf1 mouse model shows increased ROS levels in the brain using confocal imaging and electron paramagnetic resonance spectroscopy. Mice will then receive an antioxidant treatment to reduce ROS levels and determine if the treatment improves cognitive deficits seen in these mice. These studies could open new avenues for the treatment of learning deficits in NF1 children.



An image of the Golgi-Cox impregnation staining of Nf heterozygous mouse hippocampus from Dr. Narayanan's laboratory

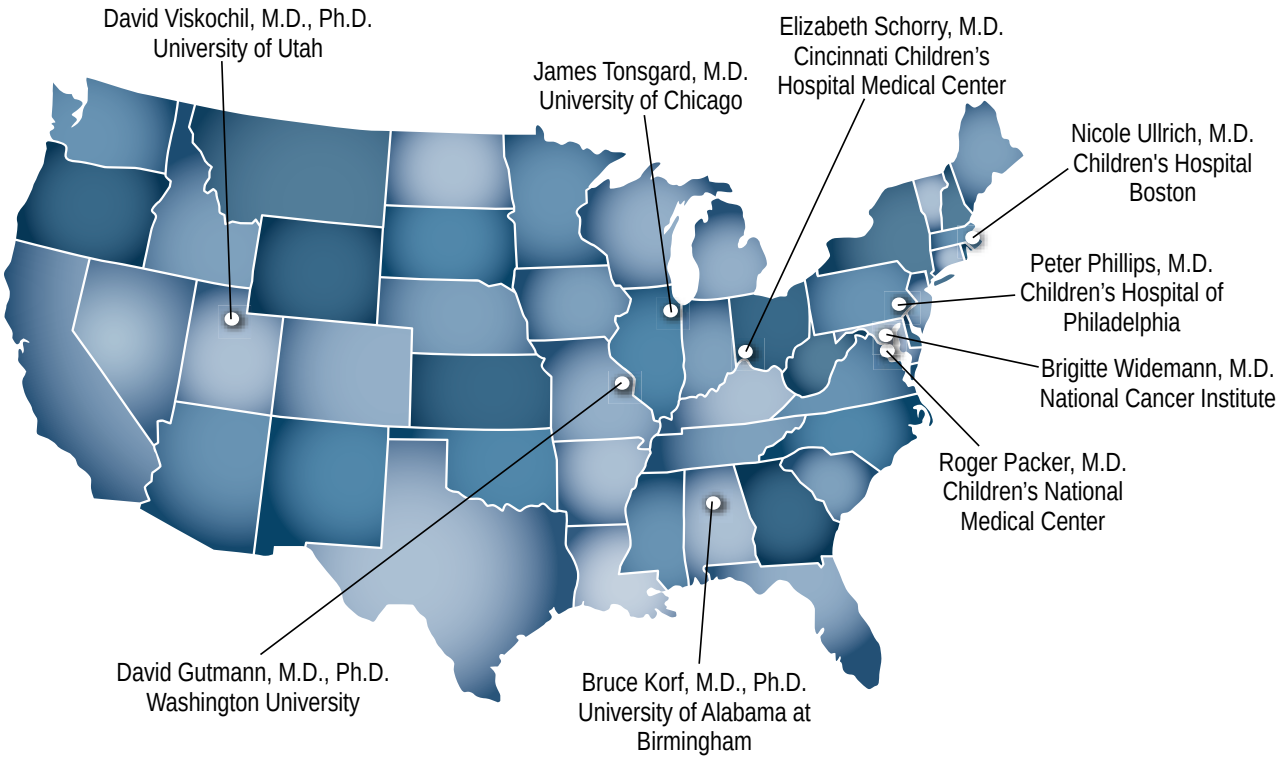


Dr. Laura Dugan's research on proliferating (BrdU+: blue) astrocytes (GFAP: red) from wild-type and Nf1 conditional knockout mice

Visionary Approaches to Accelerating Cutting-Edge Clinical Treatments for NF

The FY06 NF Consortium Award established a network of exceptional clinical centers across the United States that will focus on the rapid implementation of clinical trials for the treatment and management of NF. The formation of this alliance is a major step toward positively changing the lives of those living with NF.

This groundbreaking initiative is being led by the University of Alabama at Birmingham that serves as the operations center with Dr. Jeannette Lee as the principal investigator. The current participating clinical sites and lead investigators are shown below:



Roger J. Packer, M.D., Group Chair
Neurofibromatosis Clinical Trials Consortium
Children's National Medical Center

"The Neurofibromatosis Consortium is a great opportunity to expedite the development of new therapies for children and adults with neurofibromatosis and to make these therapies available to patients across the United States. It brings together a group of nine strong institutions and multiple key scientists, clinicians, and researchers with a proven track record in caring for patients with neurofibromatosis and performing well-conceived, important clinical trials. The consortium will develop therapies for neurofibromatosis-related disabilities important to the patients and their families including progressive neurofibromas, intracranial gliomas, and the learning/cognitive challenges these patients face. It will strive to rapidly bring discoveries from the laboratory to the patient with a focus on biologically based translational clinical research."

The first clinical trial to be conducted by the consortium will be a Phase II trial of rapamycin for the treatment of PNs. PNs occur in approximately 25 percent to 30 percent of those affected by NF1 and are among the most debilitating of NF1-associated tumors causing a range of problems from minor discomfort to extreme pain or even paralysis. Currently, surgery is the only available treatment. However, due to the nature of these tumors, surgical removal is often not an option, and the tumors can become malignant.

Rapamycin is a promising therapeutic drug that specifically inhibits mTOR, a key cellular intermediary that plays a central role in the development and growth of NF-associated tumors as well as other cancerous tumors. Drugs that target mTOR are also currently being studied in breast, rectum, kidney, and pancreatic cancers. This study will evaluate the ability of rapamycin to slow tumor growth and decrease tumor volume in NF1 patients ages 3 and older with inoperable PNs. The measurement of tumors will be completed using innovative three-dimensional volumetric MRI technology that can noninvasively monitor PNs in patients. Researchers are hopeful that rapamycin has the potential to reduce morbidity and significantly improve the quality of life for those affected by PNs.

Future studies under development by the consortium include therapeutic interventions for NF-related neurocognitive problems, optic gliomas, and MPNSTs.

The Program Today

Fiscal Year 2006 Summary

A congressional appropriation of $17M was made to the NFRP in FY06. The emphasis of the FY06 program was placed on clinical research, innovation, and research resources. A total of **93 proposals** were received across **7 award mechanisms,** and **17 awards** were made, as summarized in Table IV-1. The FY06 NFRP supported a broad portfolio to understand the causes and mechanisms that underlie the development of NF1, NF2, and schwannomatosis; improve the detection and diagnosis of these diseases; develop effective treatment approaches; and improve high quality of care. The FY06 portfolio by research area is illustrated in Figure IV-2.

Table IV-1. Funding Summary for the FY06 NFRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Clinical Trial	2	0	0
Concept	52	10	$1.03M
New Investigator	26	2	$1.65M
Therapeutic Development	8	1	$2.19M
Investigator-Initiated Research[a] (FY05)	N/A	3	$4.03M
NF Consortium	1	1	$5.77M
Research Development	4	0	0
TOTAL	93	17	$14.67M

[a] These proposals had been placed on a prioritized alternate list in FY05 and were then funded with FY06 funds.

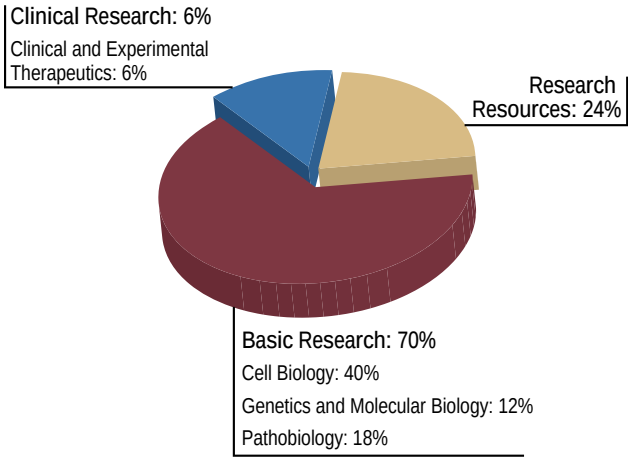


Figure IV-2. FY06 NFRP Portfolio by Research Area

Fiscal Year 2006

93 Proposals Received

$17M in Appropriations

17 Awards

The Vision for Fiscal Year 2007

The FY07 NFRP received a **congressional appropriation of $10M** to continue the peer-reviewed program. Three award mechanisms were offered, Concept, Investigator-Initiated Research, and New Investigator Awards. The program encouraged proposals across all three mechanisms that specifically addressed critical areas within the NF community, including:

- translational research
- complications of neurofibromatosis with high mortality
- complications of neurofibromatosis with high morbidity
- refinement and standardization of imaging techniques for use in future clinical trials

These focus areas emerged from an NFRP-launched request for information that was distributed to hundreds of NF scientists and consumers in 2006. The survey was initiated to gather fresh ideas about how the NFRP could respond to the current funding gaps and obstacles to facilitate progress.

In addition, for the first time the NFRP inspired collaborations within a single award by encouraging applicants of the Investigator-Initiated Research and New Investigator Awards to submit grants with a collaborator. As shown in Figure IV-3, **94 proposals** were received across the **3 award mechanisms**. Approximately 10 awards are anticipated. Appendix B, Table B-3, summarizes the congressional appropriations and the investment strategy executed by the NFRP for FY06 through FY07.

Figure IV-3. Award Mechanisms Offered and Proposals Received for the FY07 NFRP

The NFRP—A Decade of Funding Visionary Approaches

Since the NFRP's inception in 1996, the program 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. Each year the scientists and consumer advisors constituting the IP recommend an elite group of proposals with the potential to contribute to this goal. As the scientific field moves forward, the NFRP shifts its focus each year with the objective to fill gaps in the research and advance NF research to the forefront. Highlighted in the following time line are some of the exemplary awards made to NF investigators that have contributed to the NFRP legacy. Over the past 10 years, the NFRP has funded projects to develop new and improved models of NF for preclinical testing, sponsored clinical trials to test the most promising therapies, and developed a pipeline of the next generation of new drugs. All along, the program continued to support a stronghold of basic science research that is necessary to uncover the underlying mechanisms of disease and identify new targets for drug development.

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 NF (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 (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 microrarray consortium (Ratner)

2004

- Identifying Pak1 inhibitors as a treatment for NF2 (Peterson)
- Mouse models of NF (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
- Oncolytic viral vectors for the treatment of NF1 (Rabkin)