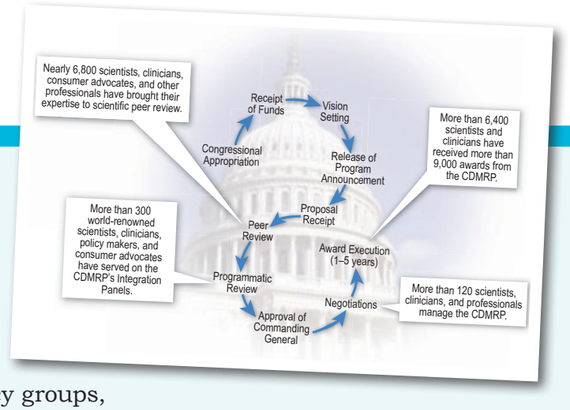
CDMRP
Department of Defense

Neurofibromatosis Research Program

U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

The Office of the Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the public, Congress, and the military. The CDMRP was established within the U.S. Army Medical Research and Materiel Command (USAMRMC) in 1993 when Congress, in response to grassroots advocacy efforts, tasked the Department of Defense (DOD) with developing and managing an innovative breast cancer research program. Since 1993, the CDMRP has grown to encompass multiple targeted programs and has received more than $5.4 billion in appropriations. Funds for the CDMRP are added to the DOD budget where support for individual programs, such as the Neurofibromatosis Research Program (NFRP), is allocated via specific guidance from Congress.



Two-Tier Proposal Review Process

The NFRP, like all CDMRP programs, is conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine; this model has received high praise from the scientific community, advocacy groups, and Congress. The first tier is a peer review of proposals against established criteria for determining scientific and technical merit. Proposals are evaluated by scientific discipline, specialty area, or award mechanism by both scientific and consumer peer reviewers. The second tier is a programmatic review, conducted by members of the program's Integration Panel (an advisory board of leading scientists, clinicians, and consumer advocates). Programmatic review compares proposals against each other and recommends submissions for funding based on scientific merit, relative innovation and impact, portfolio balance, and overall program goals. Scientifically sound proposals that most effectively address the unique focus and goals of the program are subsequently recommended to the Commanding General, USAMRMC, for funding.

Neurofibromatosis Research Program

VISION

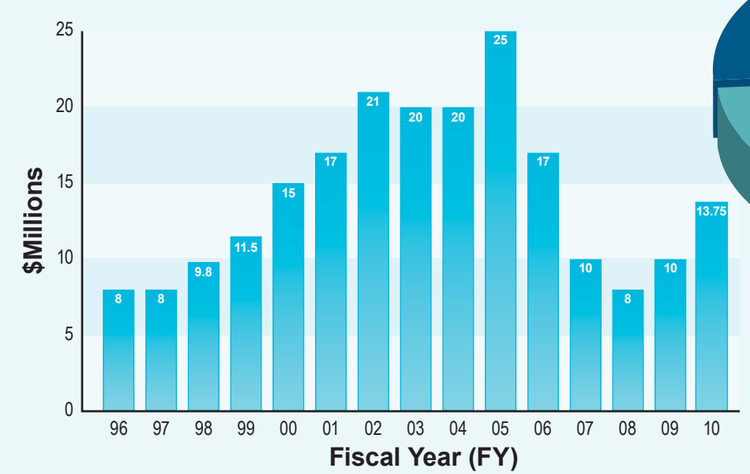
Find and fund the best research to eradicate the clinical impact of neurofibromatosis (NF).

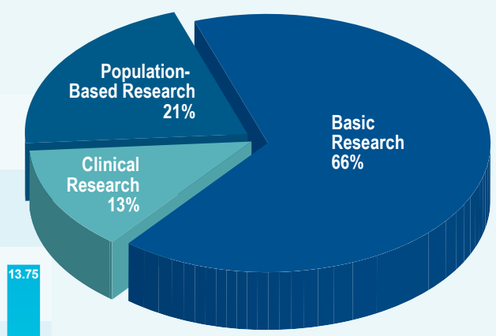
MISSION

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

The NFRP was established in fiscal year 1996 (FY96) when the efforts of neurofibromatosis advocates led to a congressional appropriation of $8 million (M). Since that time, more than $200M, including $10M for FY09, has been managed by the NFRP in an effort to decrease the clinical impact of NF. For FY2010, $13.75M has been appropriated to continue NF research. Over its 13-year history, the NFRP has invested in key initiatives to support the development of critical resources, sponsor multidisciplinary collaborations, bring talented investigators into the field, and promote the translation of promising ideas into the clinic. Exemplary advancements funded through the NFRP include:

- Completion of natural history studies that formed the foundation for future clinical trials
- Development of nearly 100 animal models essential to understanding the underlying mechanisms of NF and crucial for preclinical testing of promising pharmaceuticals
- Support for the development of unique therapeutic agents such as Pak inhibitors and oncolytic viral vectors
- Establishment of the NF Consortium, a network of nine clinical sites that are currently conducting three clinical trials for the treatment of NF





NF FY96–FY08 by Research Area

Unique Features of the NFRP

Creating and Maintaining Partnerships Throughout the NF Community

The successes of the NFRP have and continue to be critically dependent on creating and maintaining strong partnerships. Consumer advocates, peer review panel members, Integration Panel members, and the scientific community have worked synergistically to achieve the goal of eradicating the clinical impact of NF. The combination of their diverse expertise has generated ideas that have accelerated NF research.

Consumer Advocate Participation: Understanding the Needs of the Community

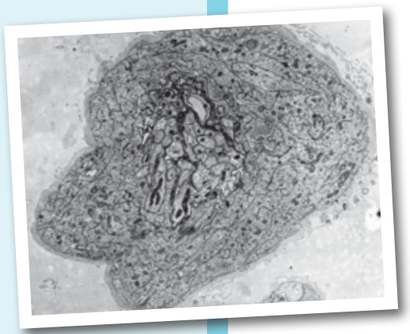
A unique feature of the NFRP is that consumer advocates are active participants in virtually all aspects of program execution. The efforts of the NF and schwannomatosis consumer advocacy communities have been vital to the establishment and continuing growth of the NFRP. Individuals with NF1, NF2, and schwannomatosis, and their family members, have an equal voice in the research administration process of proposing the program's vision, participating in the review of proposals, and making funding recommendations. The unique partnership between consumers, scientists, Integration Panel members, and peer review members ensures that the NFRP's vision and investment strategy prioritize and focus on the needs of the NF community.

Advocacy for the Cure

Advocure is an international grassroots advocacy group committed to raising the profile of NF2 and accelerating therapies to manage this disorder. Founded as a direct result of friendships and allegiances within this group, FY08 Consumer Peer Reviewer Rosemary Lee has served as the Chair of Advocure since its inception and believes that "We are on the brink of a very exciting time as NF research translates into clinical practice with far-reaching implications for many other cancers and disabilities." In 2000, Rosemary's son Louis was diagnosed with NF2 at age 7 after an MRI revealed two massive meningiomas. Although excised, subsequent MRIs revealed that Louis had an optic nerve sheath meningioma (ONSM) causing an almost complete loss of vision as a result of the surgery. Further testing indicated that Louis had another ONSM on his other eye and tiny vestibular schwannomas on each side. Rosemary reflects, "There are several factors that make the DOD programs truly outstanding and unique, but this mantra is at the core: Innovative research and science are given top priority in the assessment process—work that is truly going to take us forward and punch through the barriers. This is refreshing and very necessary in order to truly advance cures for many conditions and diseases."

Peer Review Panel Members

NFRP peer review panel members represent a renowned group of research scientists, clinicians, and consumer advocates from the NF community. Unbiased, expert advice on the scientific and technical merit of proposals is submitted to the program by individual peer review panel members. Scientific reviewers are selected for their subject matter expertise and experience with scientific peer review. Consumer reviewers are nominated by an advocacy or support organization and are chosen on the basis of their leadership skills; their commitment to advocacy, support, and outreach; and their interest in expanding their scientific knowledge.



Dr. Michael Stern, FY98, FY04, and FY05 Scientific Peer Reviewer, is a Professor of Biochemistry and Cell Biology at Rice University. His studies focusing on NF began in 1999 when he identified a regulatory pathway involving NF1 that controls growth of the glial layers in *Drosophila* peripheral nerves. Currently, Dr. Stern's laboratory is investigating the role of PI3 kinase (PI3K) on neuronal activity and on glial growth within peripheral nerves using the *Drosophila* peripheral nerve as a model. "I have participated in NFRP peer review several times over the past 10 years and always find it particularly rewarding taking part in selecting the most significant and scientifically excellent proposals for funding. I also find the presence of the consumer reviewers to be extremely valuable as these reviewers provide unique insights and their presence continuously reminds us of why we are all there."

While at the Children's Hospital of Pittsburgh, FY05 Scientific Peer Reviewer **Dr. Vinodh Narayanan**, in collaboration with Dr. Dietrich Stephan at the Children's National Medical Center, initiated his first NF-related project. This project, which was supported by the DOD, applied gene expression profiling to the NF1 knock-out mouse. Currently, Dr. Narayanan's laboratory uses animal models of single gene disorders (NF1, TSC, and Rett Syndrome) to investigate the mechanisms by which these genetic defects disrupt brain development. Of his experience as a peer reviewer, Dr. Narayanan says, "Serving as a peer reviewer has been very educational for me and will help me be a better scientist."

Fifteen years ago, **Dr. Kristine Vogel** became involved in NF research as a postdoctoral fellow in Dr. Luis Parada's laboratory, focusing on the characterization of sensory and sympathetic neurons in Nf1 mutant mouse embryos. Her current research at the University of Texas Health Science Center at San Antonio, in collaboration with Dr. Olivia Smith and Dr. Kaoru Tominaga, focuses on how DNA repair capacity influences tumorigenesis and Schwann cell behavior in the context of mouse models for NF1. As an FY02–FY05 and an FY08 Scientific Peer Reviewer, Dr. Vogel remarks, "I take my responsibilities as a peer reviewer for NFRP very seriously, but nevertheless I always enjoy the review process and meetings and learn from both the other scientists and the consumer reviewers. I always return with numerous ideas and perspectives that I can use in my research and in teaching medical students."

Michael Kingsley, of Neurofibromatosis, Inc., served as an FY09 Consumer Peer Reviewer for the NFRP. At age 16, Michael's daughter Meghan underwent MRI testing that revealed numerous tumors on her cranial nerves and along her spine. Since being diagnosed with NF2, Meghan, now 24, has endured two major surgeries, has difficulty with balance and walking, is hearing impaired, and has had bouts with vision issues and elevated cranial pressure. Of his experience working with the NFRP, Michael notes, "The opportunity to serve as a consumer peer review panelist was rewarding beyond words. Scientists, consumers, and CDMRP-NFRP leaders vetted proposals in a constructive fashion searching for consensus on the viability and impact of each request. The researchers and doctors participating displayed genuine interest in the consumers' comments. Much work remains to be done in the search for answers, but the knowledge that a vast number of scientists and doctors are so dedicated to finding ways to enhance the lives of those afflicted with neurofibromatosis provided encouragement and inspiration."

Integration Panel Members

Serving on the Integration Panel are innovative, prominent members of the NF community. The Integration Panel refines the program focus and investment strategy and recommends a broad portfolio of proposals for funding that reflects the investment strategy for that particular program cycle. Thus, the recommendations of individual Integration Panel members enable the NFRP to find and fund cutting-edge research and set important program priorities aimed at eradicating the clinical impact of NF.

The FY09 NFRP Integration Panel is composed of eight prominent scientists, clinicians, and consumer advocates with varied expertise. Integration Panel members use their knowledge and expertise to develop and recommend an annual vision and investment strategy for the NFRP that focuses on innovative research aimed at understanding the pathogenesis of NF and to translate these findings to the care of individuals with NF. Additionally, Integration Panel members review proposals and suggest a broad-based research portfolio that best meets the program's vision and mission.

Elizabeth Petri Henske, M.D.
(Chair)
Brigham and Women's Hospital

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.
M.D. Anderson Cancer Center

Sandra Parker, J.D.
Neurofibromatosis, Inc.

John Risner
President, Children's Tumor Foundation

Dr. John Kyriakis has served on both the FY08 and FY09 NFRP Integration Panels. He has investigated the importance of mitogen-activated protein kinases (MAPKs) in signaling from the Ras proto-oncogene, including the role of neurofibromin and merlin in negatively regulating MAPKs. Dr. Kyriakis believes that the NFRP has a well-balanced portfolio, funding both basic and clinical research, and is addressing an unmet need for energetic, targeted NF research. He feels that a major area of focus for future research should be the development of cross-disciplinary investigations and an increased effort devoted to NF2 research contributing to an improved understanding of cellular processes and disease outcomes. With respect to his experience in serving on the NFRP Integration Panel, Dr. Kyriakis reflects, "I have enjoyed working with the panel and have been consistently impressed with their devotion and commitment to improving the lives of NF patients. This is true not only of the consumer advocates but of the investigators on the panel."

Decreasing the Impact of NF and Schwannomatosis Through Innovative Research

As a primary source of support for NF and schwannomatosis research worldwide, the NFRP funds innovative basic, clinical, and translational studies with the potential to improve the detection, diagnosis, treatment, or management of these disorders and the quality of life of affected individuals. The NFRP's flexible management strategy allows for the annual adaptation of the program's vision to meet the changing needs of the field and take advantage of emerging opportunities.

Since its inception, the NFRP has been committed to the implementation of research award mechanisms aimed at filling important research gaps and minimizing the impact of NF and schwannomatosis, such as the Investigator-Initiated Research Award, the New Investigator Award, and the NF Consortium Award.

Supporting Efforts for Improvements in Diagnosis and Treatment: By supporting basic and clinically oriented research that provides insight into the development of NF and related diseases, the Investigator-Initiated Research Award (IIRA) focuses on improving today's approach to the diagnosis and treatment of NF and schwannomatosis, and to enhance the quality of life of persons with those diseases. The IIRA also supports collaboration between basic scientists, clinical researchers, academic scientists, and biotechnology/pharmaceutical industry scientists. The NFRP IIRA mechanism was first offered in FY96. Since that time, 321 IIRA proposals have been received, and 92 have been recommended for funding.

Funding the Next Generation of Innovation: By assisting in the career transition and development of promising independent investigators in the field, the New Investigator Award (NIA) supports investigators at or below the Assistant Professor level. The NIA encourages scientists to broaden the research field and fosters new approaches to answering NF research needs such as refinement and standardization of imaging techniques, quality of life metrics, and treatment options for NF complications, including neoplasms, cerebrovascular abnormalities, skeletal maladies, learning deficits, and pain. The NFRP NIA mechanism was first offered in FY99. Since that time, 179 NIA proposals have been received, and 38 have been recommended for funding.

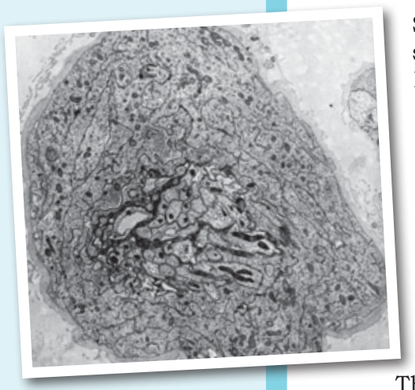
Impacting Patients' Lives: The Clinical Trial Award (CTA) supports clinical research with the potential to have a major impact on the treatment or management of NF and/or schwannomatosis, including Phase 0, I, or II clinical trials. The NFRP CTA mechanism was first offered in FY99. Since that time, 23 CTA proposals have been received, and 6 have been recommended for funding.

Partnerships for a Cure: With a strong commitment to promoting translational research, the NFRP developed the NF Consortium Award in FY06 to establish a network of clinical centers devoted to accelerating basic NF1 research into the clinic. The NF Consortium Award supports a major goal/product-driven consortium to accelerate the clinical translation of basic NF1 research and ultimately decrease the overall impact of the disease. The consortium conceives, develops, and conducts collaborative pilot and Phase I and II clinical evaluations of promising therapeutic agents or approaches for the management or treatment of NF1. The consortium was designed around a central operations center with clinical sites participating in both patient accrual and the clinical trials.

Supporting Efforts for Improvements in Diagnosis and Treatment

Control of Growth Within *Drosophila* Peripheral Nerves by Ras and Protein Kinase A

Michael Stern, Ph.D., Rice University, Houston, Texas
Investigator-Initiated Research Award, FY03



Serendipity has long been a part of scientific discovery. And so it was for Eric Howlett, a Ph.D. student working in the laboratory of DOD NFRP-funded researcher Dr. Michael Stern. While engaged in NF research in which he was studying the control of growth within *Drosophila* peripheral nerves by Ras and Protein Kinase A, Howlett and colleagues identified a novel mechanism for negative feedback control of excitability in the *Drosophila* larval motor neuron. Negative feedback processes can maintain neuronal homeostasis and are widely observed in neuronal systems. Disruption of this homeostasis can lead to neurological disorders, such as epilepsy, NF, autism, and schizophrenia.

The mechanism identified by the researchers involved phosphatidylinositol 3-kinase (PI3K) and the *Drosophila* metabotropic glutamate receptor (DmGluRA) located at motor nerve terminals. Several laboratories have demonstrated a significant role for the PI3K pathway in mediating the effects of Nf1 on growth in neurons, glia, and other cells. mGluRs are a family of G protein coupled receptors for which the excitatory amino acid glutamate (a major neurotransmitter in both the mammalian central nervous system and glia, as well as at the *Drosophila* neuromuscular junction) acts as ligand. Howlett found that PI3K regulates motor axon diameter in the larval peripheral nerve. When activated, the PI3K pathway increased axon diameter while suppression of the pathway had the opposite effect. The researchers also found that the effects of PI3K on neuronal activity seem to be mediated by the transcription factor FOXO, which negatively regulates PI3K-induced transcription, and is inhibited by Akt-dependent phosphorylation. In addition they observed that alterations in the *Drosophila* DmGluRA effect both neuronal excitability and synaptogenesis were similar to what they observed with PI3K. In this mechanism, activation of mGluRs by glutamate decreases excitability by activating PI3K, which in turn causes the phosphorylation and inhibition of Foxo. Foxo inhibition consequently decreases neuronal excitability.

Their findings are of interest because altered PI3K activity and group II mGluRs are associated with a number of neurological disorders, such as autism, NF, epilepsy, anxiety disorders, and schizophrenia. Their results provide a previously uncharacterized role for PI3K in regulating the relative excitability of neurons in vivo and suggest that some of the deficits in the aforementioned neurological disorders may result from disruption of glutamate-mediated homeostasis. Finally, their results suggest that the PI3K pathway may be a vital mediator of signaling by these mGluRs and that a similar negative feedback process functioning in the mammalian central nervous system may be implicated in neuronal disorders involving the group II mGluRs or PI3K.

Functional Analysis of Protein 4.1 Tumor Suppressors

David H. Gutmann, M.D., Ph.D., Washington University School of Medicine, St. Louis, Missouri
Investigator-Initiated Research Award, FY03

Tumor formation in neurofibromatosis type 2 (NF2) results from mutational inactivation of the NF2 tumor suppressor gene, which encodes a protein called merlin or schwannomin. Merlin plays an active role in the regulation of cell growth and motility in many different types of cells. However, the exact mechanism underlying NF2 gene function in central nervous system cells remains unclear. This is particularly important since individuals affected with NF2 develop central nervous system glial cell tumors. Dr. David Gutmann of Washington University in St. Louis has been examining the role of merlin in the growth of primary brain glial cells (astrocytes) lacking NF2 expression. Dr. Gutmann's studies have demonstrated, for the first time, that astrocyte growth is regulated by merlin through activation of the sarcoma (Src) proto-oncogene pathway. In NF2-deficient cells, merlin is absent, which leads to activation of another important player in carcinogenesis, epidermal growth factor receptor B2 (ErbB2). Active ErbB2 initiates a downstream signaling cascade that results in uncontrolled glial cell growth. In normal cells, merlin is present and controls cell growth by competing with Src for direct binding to ErbB2 thereby preventing ErbB2 activation and increased cell growth. Dr. Gutmann's team showed that pharmacologic or genetic inhibition of Src or ErbB2 activation reduces the excessive glial cell growth seen in NF2-deficient astrocytes to the levels seen in normal cells. These studies have identified novel regulators of glial cell growth that represent potential therapeutic targets for the treatment of NF2-associated glial tumors.

A New Therapy for Plexiform Neurofibromas

D. Wade Clapp, M.D., Indiana University School of Medicine, Indianapolis, Indiana
Luis Parada, M.D., University of Texas Southwestern Medical Center, Dallas, Texas
Investigator-Initiated Research Award, FY02

Dr. D. Wade Clapp and Dr. Luis Parada have recently collaborated to identify a mechanism and potential drug treatment for growth of neurofibromatosis type 1 (NF1)-associated plexiform neurofibromas (PNs). These tumors are complex, composed of many different cell types, making them difficult to remove surgically and resulting in significant morbidity for those affected.

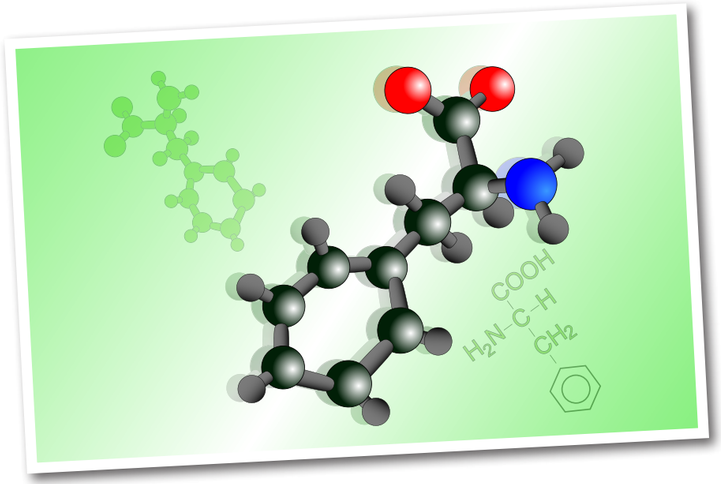
The scientists used several mouse models to dissect out the role of the various cells in the tumor ecosystem, including mast cells. While these mast cells have been observed infiltrating PNs, their role has remained unclear until now. The research team has uncovered a complex mechanism of tumor formation that involves cross-talk between Schwann cells and mast cells. Previous findings had determined that tumor growth required two distinct steps: loss of both copies of the Nf1 gene (NF1 -/-) in Schwann cells, the primary culprits in tumor formation, and loss of one copy of the Nf1 gene (Nf1 +/-) in the infiltrating mast cells. To determine the mechanism of tumorigenesis, the investigators used an NF-1 mouse model to show that Nf1 +/- mast cells derived from bone marrow migrate to developing PNs and are necessary for their growth. These mast cells were dependent on c-kit receptor tyrosine kinase (c-kit) activity. As c-kit is known to promote mast cell migration, proliferation, and survival, it also was found to be required for neurofibroma formation. Given that the mast cells were c-kit-dependent, the investigators treated neurofibromas with imatinib mesylate (Gleevec), an effective c-kit inhibitor. Gleevec is currently used to treat chronic myelogenous leukemia, gastrointestinal stromal tumors, and several other malignancies. In this study, the investigators found that Gleevec decreased the size of PNs in the NF-1 mouse models. As these studies were nearing completion, the investigators were told of a 3-year-old NF1 patient with a life-threatening PN compressing her airway. Unable to remove the PN surgically, she was treated with Gleevec for 6 months. A 70% decrease in tumor volume was observed. Based on these promising results, a Phase II clinical trial to determine the efficacy of Gleevec treatment for PNs is under way.

Bevacizumab: An Anti-VEGF Therapy to Improve Hearing of NF2 Patients with Progressive Vestibular Schwannomas

Scott Plotkin, M.D. Ph.D., Harvard Medical School, and Massachusetts General Hospital, Boston, Massachusetts
Investigator-Initiated Research Award, FY05

NF2 is an autosomal dominant genetic disorder that is associated with the development of benign tumors or schwannomas composed of neoplastic Schwann cells, a variety of non-neuronal cells that normally provide support and protection for neurons. Bilateral vestibular schwannomas may result in profound hearing loss and, currently, there is no effective treatment for these tumors. Vascular endothelial growth factor (VEGF) and its receptor are expressed in schwannomas, and their increased expression correlates with a greater rate of tumor growth. Although schwannomas are not traditionally considered vascular tumors, the association between VEGF expression and tumor growth provided a rationale for evaluating the anti-VEGF drug bevacizumab (Avastin) in NF2 patients.

Dr. Scott Plotkin evaluated the efficacy of bevacizumab in a retrospective study of 10 patients with NF2—marked by the presence of progressive vestibular schwannomas—who were poor candidates for the standard treatment with radiation or surgery. As a result of bevacizumab treatment, tumors shrank in 9 of 10 patients. Additionally, improvements in hearing (at about 8 weeks since initiating the therapy) were observed in four of seven eligible patients. All four patients have continued to respond to therapy for 11 to 16 months. These exciting results were published in the *New England Journal of Medicine* in July 2009 and warrant a larger trial of bevacizumab to determine the optimal drug regimen and duration for long-term therapy.



Funding the Next Generation of Innovation:

Neurofibromin Function in Chondrocytes

Florent Elefteriou, Ph.D., Vanderbilt University Medical Center, Nashville, Tennessee
New Investigator Award, FY08

Dr. Florent Elefteriou of Vanderbilt University received an FY08 NFRP New Investigator Award to elucidate the etiopathology of NF1 skeletal defects. There are three main cell types in the bone whose function is critical: chondrocytes for growth, osteoblasts for bone formation, and osteoclasts for bone resorption. Chondrocytes and osteoblasts derive from a common progenitor, that is, mesenchymal stem cells (MSCs). Dr. Elefteriou hypothesizes that loss of NF1 in MSCs cause NF1-related skeletal defects. In his proposed studies, he will use a novel mouse model lacking NF1 in MSCs, chondrocytes, and osteoblasts that manifests many skeletal defects seen in NF1 patients. First he will characterize the mechanism by which NF1 loss disrupts bone development and healing. These studies will provide crucial evidence to understanding the underlying cause of the defects and may identify targets for treatments. In the second phase of his studies, he will determine whether inhibition of Ras by lovastatin treatment during development will prevent the NF1 skeletal phenotypes of the mice. If successful, this study will provide preclinical evidence for the design of the first nonsurgical therapy for NF1-mediated skeletal abnormalities.

Dr. Elefteriou began his career as a postdoctoral fellow characterizing the bone phenotype of mice lacking Nf1 in osteoblasts in collaboration with Dr. Luis Parada. This New Investigator Award is his first award since establishing his laboratory at Vanderbilt University. His previous awards, such as the Children's Tumor Foundation's Young Investigator Fellowship and his NIH R21 grant, allowed him to connect with the NF research community, as well as the patients. This passion, plus his desire to create a better preclinical model, helped him obtain this award and has allowed his laboratory to dedicate half of its time to NF1 research.

Paks: Potential Therapeutic Targets for the Treatment of NF2

Joseph L. Kissil, Ph.D., The Wistar Institute, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
New Investigator Award, FY05

Despite progress made in the study of NF2, the tumor-suppressive function of the NF2 gene and its product, merlin, remains unclear. Previous investigations have shown that phosphorylation of merlin at serine 518 suppresses its growth inhibitory activity, an effect that is mediated by p21-activated kinases (Paks), which bind to activated Rac/Cdc42. Increasing evidence indicates that merlin is not only regulated by the Rac-Pak axis but also acts to negatively regulate Rac1 signaling via inhibition of Pak. As Paks have been implicated in cell growth regulation and tumorigenesis, Dr. Joseph Kissil, of The Wistar Institute, hypothesized that merlin functions as a tumor suppressor, at least in part, via inhibition of Paks and that Pak inhibition may be a useful treatment modality for NF2. With funding from an FY05 New Investigator Award, Dr. Kissil first assessed Pak1 activity in primary schwannoma tumor samples isolated from NF2 patients. Data from this study revealed that Pak1 activity is elevated in primary tumors from NF2 patients, suggesting that merlin functions as a tumor suppressor by blocking Pak1 activation. Utilizing animal and cellular models, Dr. Kissil also found that simultaneous depletion of Pak1, Pak2, and Pak3 partially inhibits tumor formation and prevents hyperproliferation induced by Nf2BBA (a dominant-negative form of merlin). Taken together, these studies have identified Paks as potential therapeutic targets in NF2. As a next step, Dr. Kissil is currently working with collaborators in the structural biology and organic chemistry fields to develop and test novel Pak inhibitors for the treatment of NF2.

Dr. Kissil began his career studying NF2 as a postdoctoral fellow at the Massachusetts Institute of Technology in the laboratory of Dr. Tyler Jacks. He was interested in pursuing NF2, in particular, because it was an understudied and rare disease. Dr. Kissil credits his NFRP New Investigator Award, the first large federal grant he received, as having had a major impact on his career. It was invaluable in putting him in a position to obtain follow-up funding and remain in NF research. Dr. Kissil is now an Assistant Professor at The Wistar Institute and recently had the honor of co-chairing the 2009 NF Conference, the premier annual meeting for NF scientists and clinicians.

Impacting Patients' Lives

Moving from Bench to Bedside: A Phase II Trial for the Treatment of NF2-Related Vestibular Schwannomas

Langdon Miller, M.D., PTC Therapeutics, South Plainfield, New Jersey
Clinical Trial Award, FY05

NF2 is characterized by the development of vestibular schwannomas (VS). These tumors can lead to deafness, tinnitus (ringing in the ears), imbalance, and pain, causing diminished quality of life for those affected. Currently, surgery is the primary treatment option for those affected; however, not all VS can be removed. Dr. Langdon Miller of PTC Therapeutics has just been awarded an FY08 Clinical Trial Award to conduct a Phase II trial of a novel PTC299 in NF2 patients with bilateral VS who are not good surgical candidates and have either progressive tumors or hearing impairment. To grow and spread, all tumors require the development of blood vessels to capture nutrients. Production of VEGF by tumor is critical to this process. Blocking VEGF-mediated growth is known to slow tumor growth in some tumor types. PTC299 is a novel drug developed by PTC Therapeutics that may offer several advantages over existing drugs. Unlike currently available VEGF blockers, this drug uses an innovative small-molecule approach to halt the production of VEGF within tumor cells, which may result in greater efficacy. Because the action of PTC299 is primarily in tumors, it may offer greater safety. An additional advantage is that PTC299 can be administered orally, offering convenience to patients. Patient treatment and evaluation for this study will be conducted by Dr. Scott Plotkin, Director of the NF Clinic at the Massachusetts General Hospital Cancer Center. Tumor size, hearing, tinnitus, tumor blood flow, and VEGF levels in the blood will all be carefully monitored. Scientists are hopeful that PTC299 has the potential to safely reduce tumor volume and improve hearing for patients with NF2.

Partnerships for a Cure

In an effort to foster clinical advances in the treatment of NF, the NFRP has supported the development of the NF Consortium, a network of nine clinical centers focused on the rapid execution of clinical trials of therapeutics or approaches for the treatment of NF1. The consortium is currently implementing three clinical trials under the leadership of Dr. Bruce Korf at the University of Alabama at Birmingham.

All nine consortium sites are currently conducting a Phase II trial of rapamycin for the treatment of PNs in patients with NF1. PNs develop in approximately 25% of individuals with NF1 and may undergo transformation into malignant peripheral nerve sheath tumors. PNs can cause pain, paralysis, and disfigurement. Other than surgery, there are no treatment options for these complex tumors. Accrual on the trial opened in April 2008, and expected recruitment is already ahead of schedule. Investigators anticipate having preliminary efficacy data within 1 year.

Enrollment has just opened on a Phase II study of lovastatin for the treatment of NF1-associated learning and memory impairments. Cognitive deficits are the most common complication of NF1 in childhood so there is a crucial need to investigate interventions to help these patients. This study has brought on an international partner with the addition of a site at Children's Hospital West Mead, Sydney, Australia, under Dr. Kathryn North, the study's chair. Cognitive function will be evaluated in patients using the Cambridge Neuropsychological Test Automated Battery (CANTAB), a test designed to measure hippocampal-based learning and memory. The study expects to recruit 142 patients over the next 2 years. Investigators hope to find a treatment that will improve the long-term outcome and quality of life for NF1 patients.

The third trial being conducted by the consortium is "Phase II Study of RAD001 for Children with NF1 and Chemotherapy-Refractory, Progressive Low-Grade Gliomas (LGGs)." Approximately 25% of children with NF1 have evidence of an LGG. They may occur in the optic pathway, the brainstem, and/or the cerebellum. These tumors often run an unpredictable course but may lead to significant visual loss, blindness, and loss of motor function. Radiation therapy in these patients is associated with serious long-term risks including permanent neurocognitive deficits and an increased risk of secondary malignancy. Additionally, these approaches rarely result in recovery of vision or motor function. Observations in preclinical systems have implicated the mTOR signaling pathway in NF1 tumor progression. This study will evaluate the potential clinical benefit of the mTOR inhibitor RAD001 in children with progressive LGGs. The U.S. Food and Drug Administration has just approved RAD001 for the treatment of advanced kidney cancer following a successful Phase III trial of the drug in more than 400 patients. Pharmacokinetic and pharmacogenomic studies are also proposed to evaluate targeted inhibition of the mTOR signaling pathway by RAD001. The study is expected to accrue 20 patients beginning fall 2009.

The Vision for FY09

In FY09, Congress appropriated $10M to the NFRP for research. The vision of the NFRP is to find and fund the best research to decrease the clinical impact of NF. Toward this goal, the NFRP seeks to:

- Support innovative, high-impact research that will foster new directions for and address neglected issues in NF research
- Sponsor multidisciplinary and multi-institutional collaborations that will bring new perspectives to the field
- Foster the next generation of NF investigators
- Promote translational and clinical studies to move promising ideas from bench to bedside
- Develop a balanced portfolio of meritorious research related to all aspects of NF1, NF2, and schwannomatosis

Five award mechanisms encompassing these goals were offered in FY09 to address critical needs in NF research. The program encouraged proposals in the following areas:

- Complications of NF with high mortality such as neoplasms and cerebrovascular abnormalities
- Complications of NF with high morbidity such as skeletal maladies, learning deficits, hormone-associated effects, and pain
- Refinement and standardization of imaging techniques, molecular and cellular markers, and quality of life metrics for use in future clinical trials
- Translational research such as the development or preclinical testing of therapeutic agents for the treatment of NF

Focus	Award Mechanism
Clinical Research	Clinical Trial Award: Supports clinical research with the potential to have a major impact on the treatment and/or management of NF.
Innovative Research	Exploration–Hypothesis Development Award: Supports the initial exploration of innovative, untested, high-risk, high-gain, and potentially groundbreaking concepts in NF research. Multidisciplinary collaborations are encouraged to bring in new perspectives from other disciplines or bring new investigators into the field. Investigator-Initiated Research Award: Supports basic and clinically oriented research in NF.
Training/Career Development	New Investigator Award: Supports the career transition and/or continued development of promising independent investigators in the field of NF research. Postdoctoral Traineeship Award (New): Supports postdoctoral training of individuals who are interested in pursuing a career in NF research.

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