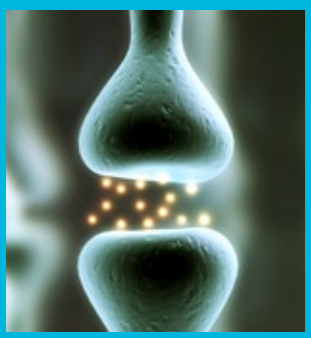
CDMRP

Department of Defense

Neurofibromatosis Research Program

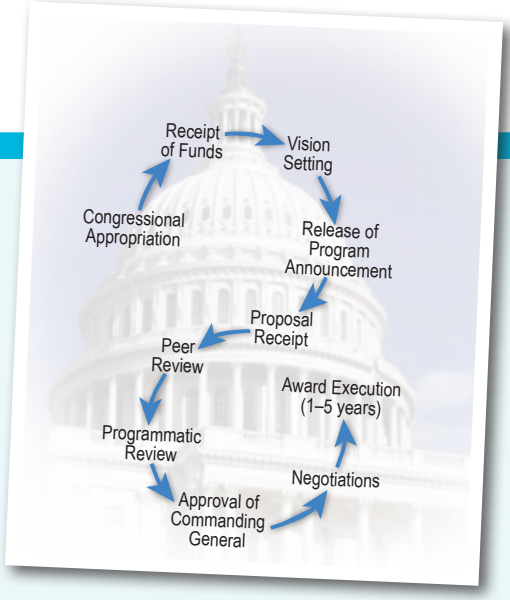


U.S. Army Medical Research and Materiel Command

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 1992 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 1992, the CDMRP has grown to encompass multiple targeted programs and has received $6 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

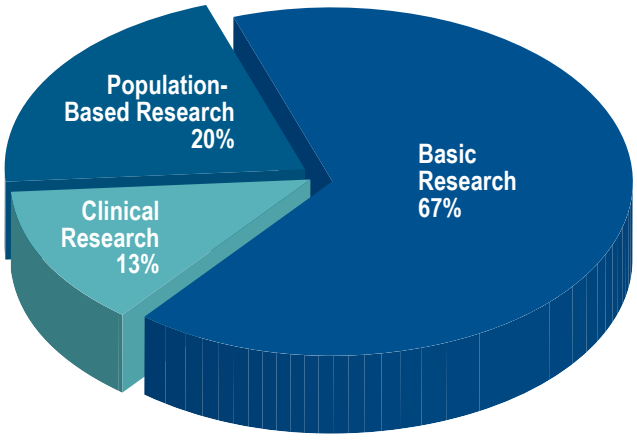
Find and fund the best research to eradicate the clinical impact of neurofibromatosis (NF).

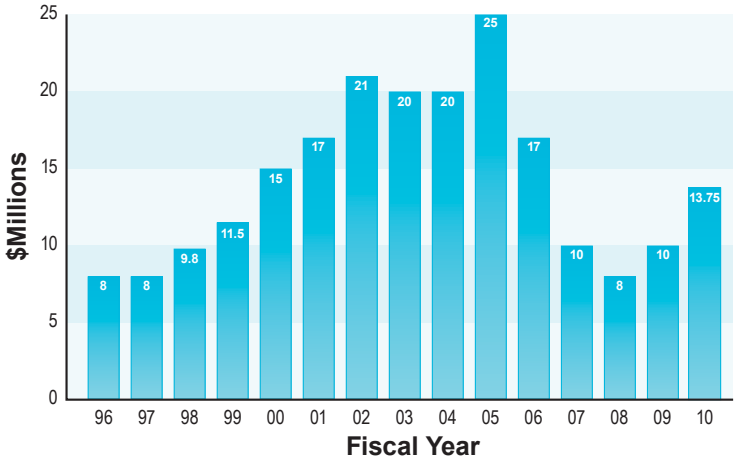
MISSION

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 $214M, including $13.75M for FY10 has been managed by the NFRP in an effort to decrease the clinical impact of NF. Over its 14-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 9 clinical sites that are currently conducting 3 clinical trials for the treatment of NF





Unique Features of the NFRP

Creating and Maintaining Partnerships Throughout the NF Community

The successes of the NFRP have been 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 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 neurofibromatosis type 1 (NF1), NF2, and schwannomatosis and their family members have an equal voice in the 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 panel members ensures that the NFRP's vision and investment strategy prioritize and focus on the needs of the NF community.

Advocacy for the Cure

Ms. Kim Bischoff

FY05 Consumer Peer Reviewer and Executive Director of Neurofibromatosis, Inc., **Kim Bischoff** recalls that her first experience with neurofibromatosis occurred 25 years ago when her oldest daughter, Jennifer, then 2½, was diagnosed with a growing optic glioma. Kim and her husband, Bob, sought treatment for Jennifer as the tumor progressed. After a nationwide search for a treatment option, they decided to have the optic glioma treated in Chicago using a new protocol of chemotherapy for optic gliomas. Although Jennifer lost the vision in her left eye, the treatment saved the vision in her right eye. Jennifer is now 27 years old and doing very well.

In her search for treatment options for Jennifer, Kim was referred to the local NF, Inc. organization. The Bischoffs asked the local board how much federal funding is spent on NF research, and to Kim's dismay, the answer was "None." The couple immediately became involved in raising funds for and awareness of NF. "The organization offered support for our family and allowed us to focus not just on finding help for our daughter, but also on finding help for millions of others." In addition to her 25-year involvement with NF, Inc., Kim and Bob have taken a very active interest in the Neurofibromatosis Research Program since its inception in 1996, noting, "It's been very exciting to see the research go from identifying the NF gene to clinical trials in a short period of time."

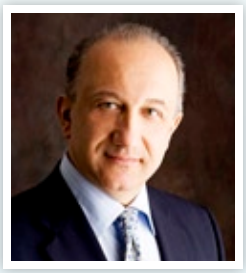
"The NFRP has created a very open, cooperative environment where information can be freely exchanged between scientists and consumers. I feel absolutely certain that consumer feedback impacts the way studies are conducted."

Reflecting on her service as an NFRP Consumer Peer Reviewer, Kim points to the genuine interest shown by scientists on the panel to hear about NF from the consumers' personal perspectives. She notes, "The NFRP has created a very open, cooperative environment where information can be freely exchanged between scientists and consumers. I feel absolutely certain that consumer feedback impacts the way studies are conducted." With recognition of "the passion that scientists on the panel put into their work" toward finding a treatment for NF, Kim gratefully acknowledges that, "It is because of their countless hours of dedication that we have hope that our daughter's condition will one day be stabilized and that millions of other children with NF will not have to endure the physical and psychological damage that this horrible disease causes."

Ms. Jennifer Bischoff

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. Marco Giovannini's career in NF research began in 1994 after joining the laboratory of Dr. Gilles Thomas as a postdoctoral fellow where "the team had just identified the NF2 gene and my goal was to generate mouse models of NF2 to assist in understanding the molecular pathogenesis of NF2 and provide tumor-bearing animals, which can then be used to develop and test potential treatments." As the NF2 field is at a critical juncture, Dr. Giovannini believes "we have now developed a broad set of tools and a collaborative network that are instrumental to efficiently tackle the challenges of NF2 translational research." Currently at the House Ear Institute, Dr. Giovannini is using his mouse models of NF2 to test the effects of individual drugs and combinations of drugs against schwannomas and meningiomas. Dr. Giovannini is hopeful that "we will come up with drug combinations that will have a significant effect on these tumors, many of which are essentially impervious to any current treatments." Dr. Giovannini further reflects that serving as a peer reviewer for the FY10 NFRP "offered me a fast track to a highly relevant and personally enriching experience that others have earned throughout their entire careers. While the time commitment is considerable, the professional rewards that result from the peer review experience are immeasurable."

Dr. David Viskochil, FY99–00, FY02–04, FY06–07, and FY10 Scientific Peer Reviewer, is a Professor of Pediatrics and the Director of Clinical Genetics Services at the University of Utah. Beginning his research investigations on NF in 1988, Dr. Viskochil's studies now focus on bone abnormalities associated with NF, NF clinical trials, and setting guidelines for clinical management. Of his experiences in serving on the NF peer review panel over the years, Dr. Viskochil notes that "this is a unique program that has been instrumental in bringing in new investigators and maintaining the highest integrity in NF-related research. It has also changed the way consumers help define the most concerning issues."

Barbara Franklin, of Advocure—an international grassroots advocacy group seeking treatment options and supporting the NF2 community—has served as a Consumer Peer Reviewer for the NFRP since FY07. When Barbara's son, Adam, was 10 years old, he was diagnosed with NF2, and since then, has undergone a number of brain surgeries that have left him with diminished hearing and vision. He is now 26 and, Barbara reports, doing well. He is still closely monitored for persistent brain and spinal tumors but lives life with a "joie de vivre that is unmatched—and a positive attitude that has helped him achieve great things." Of her experience in working with the NFRP over the years, Barbara reflects, "This program is one of the most important—if not the—most important aspect of NF2 research. As such, I have committed myself to being a part of it as often as I can. There's no doubt there's work to do, but it is so rewarding to see the incredible breakthrough concepts that researchers propose, as well as the amazing devotion that all participants—consumers and scientists alike—give to this program. I have watched it grow since its inception and it only gets better."

"This program is one of the most important—if not the—most important aspect of NF2 research. As such, I have committed myself to being a part of it as often as I can"

As an FY05–06 and FY10 NFRP Scientific Peer Reviewer, **Dr. Steven Carroll's** interests in NF research began approximately 7 years ago following the generation of a transgenic mouse overexpressing a class II neuregulin-1 isoform in Schwann cells. Interestingly, these animals were developing tumors very similar to malignant peripheral nerve sheath tumors (MPNSTs) and subsequent investigations revealed that signaling by neuregulin-1 and its erbB receptors promoted the growth of human neurofibromas and MPNSTs. Currently, Dr. Carroll's research focuses on the pathogenesis of peripheral nerve sheath tumors in NF, with a particular emphasis on understanding the role aberrant growth factor signaling plays in this process, and using that information to develop new therapeutic approaches. Of his experiences in serving on the NFRP peer review panel, Dr. Carroll notes that "the NFRP peer review process is unique for two reasons: it is focused on a specific disease and it includes input from consumer reviewers. These two features greatly strengthen the process as it keeps the scientist reviewers focused on the impact the work under consideration will have on the lives of NF patients and their families."

FY10 NFRP Scientific Peer Reviewer **Dr. Athar Chishti** has been working with the NF2 tumor suppressor protein, merlin, for approximately 12 years and received a Career Development Award from the NFRP in 2003. Currently, Dr. Chishti's research focuses on membrane-cytoskeletal interactions and specifically on the FERM domain interactions of merlin and other family members. Of his first experience on the NFRP peer review panel, Dr. Chishti notes that "one of the greatest strengths of the NF review process was the professionalism of the peer review staff including the efficiency and knowledge of the peer review section Chair in ensuring a rigorous and fair review process."

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 FY10 NFRP Integration Panel is composed of nine 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 recommend proposals for funding that comprise a broad-based research portfolio that best meets the program's vision and mission.

John Risner (Chair)
President, Children's Tumor Foundation

John Carey, M.D.
University of Utah

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

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

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

Norman Leeds, M.D.
M.D. Anderson Cancer Center

Sandra Parker, J.D.
Neurofibromatosis, Inc.

Vincent Riccardi, M.D.
The Neurofibromatosis Institute

Larry Sherman, Ph.D.
Oregon Health and Science University

A Dedication to Improvement and Innovation: Strategic Planning for the Cure

John Risner, Chair of the FY10 NFRP Integration Panel, has been working with the Children's Tumor Foundation (CTF) for nearly 20 years and has served as President of CTF since 2005. John's son, now 21 years old, was born with a number of café au lait spots and was subsequently diagnosed with NF1. With respect to the impact of the CTF on the field of NF research, John has indicated the importance of attracting new investigators to the field with funding mechanisms implemented by the CTF, including the Young Investigator Award, "which have been instrumental in funding many of the key advances, including the discovery of the genes that cause NF, identifying signaling pathways, and mouse model development." In addition, John notes that the CTF's strategic plan in 2006 identified 5 keys areas of potential impact including "increasing preclinical screening of candidate drugs, establishing a national NF Clinic Network, funding pilot clinical trials, establishing an NF patient registry and tissue bank, and identifying new NF biomarkers."

"It is impossible to overstate the importance of the NFRP."

In serving as a member of the NFRP Integration Panel since 2006, and as its Chair in FY10, John notes that the NFRP "has been critical to the advances in NF. The CTF could not have established the Clinical Trials Consortium in 2005, or funded the current trials under way." He says that he is "not given to hype, but it is impossible to overstate the importance of the NFRP." John believes that the areas of NF research that have been most influenced by NFRP funding include those focusing "on late stage translational and early stage clinical research with the promise of actually getting FDA approval for NF treatments." John sees the future of NF being the FDA approval of drugs treating all of the complications associated with NF. Although he realizes that it will take a long time to address all of the complications of NF, John remains confident that there will be a breakthrough in at least 1 or 2 areas within the next 2 to 4 years. Thus, John notes that the NFRP should "continue to focus on clinical and therapeutic areas, and [he is] particularly excited that NFRP is funding pain research, as this is a very under-researched area. In addition to NF, this has application to the health of our warfighters and the general population." In addition to pain research, John feels that future research initiatives should also focus on bone complications associated with NF as well as potential phenotypic relationships between NF and other disorders including tuberous sclerosis complex and autism. Further, John believes that although there is good balance in the current funding of the research pipeline, the cost/benefit of each award mechanism offered by the NFRP should continue to be weighed at Vision Setting meetings held each fiscal year.

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 (IIRA), the New Investigator Award (NIA), the Clinical Trial Award (CTA), and the NF Consortium Award.

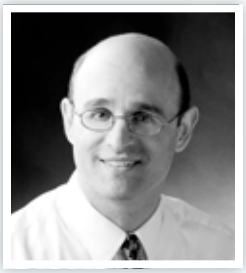
Supporting Efforts for Improvements in Diagnosis and Treatment: By supporting basic and clinically oriented research, the IIRA focuses on improving today's approach to the diagnosis and treatment of NF and schwannomatosis. The IIRA also supports collaboration between basic scientists, clinical researchers, academic scientists, and biotechnology/pharmaceutical industry scientists. The NFRP IIRA mechanism was first offered in FY96. Since that time, 341 IIRA applications have been received, and 96 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 NIA supports investigators at or below the level of Assistant Professor. The NFRP NIA mechanism was first offered in FY99. Since that time, 196 NIA applications have been received, and 43 have been recommended for funding.

Impacting Patients' Lives: The CTA supports clinical research with the potential to have a major impact on the treatment or management of neurofibromatosis and/or schwannomatosis, including Phase 0, I, or II clinical trials. The NFRP CTA mechanism was first offered in FY99. Since that time, 28 CTA proposals have been received, and 7 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 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



Phase I Study of Intratumoral Photodynamic Therapy in Children with NF1 and Plexiform Neurofibromas
Michael Fisher, M.D., Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
New Investigator Award, FY07

Plexiform neurofibromas (PNs) are tumors of the peripheral nerves that occur with great frequency in patients with NF1. These tumors can cause serious morbidity characterized by pain, functional impairment, and disfigurement, and may even be life-threatening. Complete surgical removal is the only current successful treatment option, but this approach can be difficult because the tumors are often very large and infiltrate or surround normal structures. In addition, radiotherapy and chemotherapy approaches have not been effective for PNs. Previous preclinical and clinical studies of photodynamic therapy (PDT), or light therapy, using a photosensitizer (a drug) and a particular type of light, in adults with different types of cancer have demonstrated that this approach is well tolerated and results in tumor reduction in many patients. Dr. Michael Fisher, recipient of an NIA through the FY07 NFRP, is presently evaluating the safety of the photosensitizer LS11 combined with an implantable light source in a Phase I study treating children with PNs. Dr. Fisher's unique PDT approach could potentially result in tumor reduction in children and young adult patients with PNs, which could drastically improve their quality of life.

With respect to his interests and career in NF research, Dr. Fisher notes, "My main research interests are new imaging modalities and treatments for children with tumors of NF. I became interested in NF research through my work with patients as a neuro-oncologist. The unique difficulties of managing low-grade tumors such as plexiform neurofibromas and optic pathway gliomas were apparent. My NF research career got started when I was awarded a Young Investigator Award from the Children's Tumor Foundation in 2001."

Induced Pluripotent Stem Cells as Potential Therapeutic Agents in NF1
Jonathan Chernoff, M.D., Ph.D., Fox Chase Cancer Center, Philadelphia, Pennsylvania
Exploration – Hypothesis Development Award, FY09

Although previous investigations have revealed signaling pathways regulated by the neurofibromatosis type 1 (NF1) protein, there are currently no effective medical therapies for the treatment of NF1. Individuals with NF1 may experience a variety of clinical manifestations including the development of neurofibromas, optic gliomas, skeletal abnormalities, and learning disabilities. NF1 tumors are composed of a mixture of Schwann cells, fibroblasts, perineural cells, and mast cells. In humans who inherit a mutant Nf1 allele, the second copy of the gene is lost in tumors (homozygous loss), whereas the surrounding tissues have only lost one copy (heterozygous loss). In mouse models of NF1, researchers have shown that this heterozygous background is essential for the development of disease. In particular, Nf1-heterozygous mast cells appear to play a vital role. Such mast cells are prone to migrate to the tumor site and secrete substances that facilitate Schwann cell growth. Thus, a potential therapeutic strategy is to repair the damaged Nf1 allele in mast cells. With funding from an FY09 Exploration – Hypothesis Development Award, Dr. Jonathan Chernoff, at the Fox Chase Cancer Center, will repair the defective Nf1 allele in induced pluripotent stem cells derived from murine Nf1 heterozygote skin cells and will then transplant these cells into irradiated NF1 mice. By normalizing mast cells, it is anticipated that the outcomes of this research will demonstrate a reduction in the development of neurofibromas in NF1 mice and may provide a new method for the treatment of NF1.

Identification of a New Target and Treatment Compound for NF1-Associated Cancer

David H. Gutmann, M.D., Ph.D., Neurofibromatosis Center, Washington University School of Medicine, St. Louis, Missouri
Investigator-Initiated Research Award, FY05

Tumors in the inherited cancer syndrome, NF1, are characterized by the loss of function of the NF1 gene product, neurofibromin. Neurofibromin functions primarily as a negative regulator of the Ras proto-oncogene with further evidence identifying the mammalian target of rapamycin (mTOR) as being a critical downstream effector of neurofibromin/Ras-induced cell proliferation and tumorigenesis. Previous studies from Dr. David Gutmann's laboratory at the Washington University School of Medicine have identified that Rac1 activation is required for mTOR-dependent growth control.

As there are currently very few Rac1-specific inhibitors for preclinical/clinical study, Dr. Gutmann, with support from an FY05 IIRA through the NFRP, explored an alternative approach to identifying new, potent anticancer compounds suitable for the treatment of NF1-associated brain tumors. Using an unbiased high-throughput chemical library screen of NF1-deficient MPNST cells, a novel compound, cucurbitacin-I, has been selected for its cell growth inhibitory and pro-apoptotic effect. Since cucurbitacin-I is known to inhibit signal transducer and activator of transcription-3 (STAT3) function in other cell types, Dr. Gutmann examined whether STAT3 could play a role in the growth of NF1-associated tumors and Nf1-deficient primary brain cells. Dr. Gutmann identified that neurofibromin negatively regulated STAT3 activity in vitro and in vivo, leading to STAT3 hyperactivation in NF1-deficient cells. Based on their findings, a model for neurofibromin cell growth regulation involving the mTOR/Rac1/STAT3 signaling pathway and the role of STAT3 in controlling transcription, apoptosis, and proliferation were also established. Excitingly, cucurbitacin-I, via STAT3 inhibition, decreased NF1-deficient MPNST cell and tumor growth in vivo. These novel discoveries may ultimately lead to improved therapeutic approaches for the management of NF1-associated brain tumors.

Characterizing KEN: A Novel NF2/Merlin Protein Complex Modulating Growth Control

Duojia Pan, Ph.D., Johns Hopkins University School of Medicine and Howard Hughes Medical Institute, Baltimore, Maryland
Investigator-Initiated Research Award, FY09

A critical aspect of NF2 research is the identification of downstream effector pathways regulated by the NF2/merlin tumor suppressor protein. Previous investigations by Dr. Duojia Pan of Johns Hopkins University have identified Kibra, a novel tumor suppressor gene in Drosophila. Dr. Pan has also shown that Kibra, NF2/merlin, and the related FERM domain protein Expanded (Ex) form a protein complex. The resulting Kibra, Ex, NF2/merlin (KEN) complex regulates the Hippo pathway, a conserved signaling pathway involved in tissue homeostasis. Hippo signaling is modulated by several tumor suppressors, ultimately resulting in the phosphorylation and inactivation of the oncoprotein Yki (Drosophila)/YAP (mammals). Thus, the functional link between the KEN complex and the Hippo pathway may provide a potential mechanism by which NF2/merlin functions as a tumor suppressor. With funding from an FY09 NFRP IIRA, Dr. Pan proposes to further elucidate the molecular mechanism by which the NF2/merlin tumor suppressor functions together with Ex and Kibra in the context of the Hippo signaling pathway, using Drosophila and mammalian cells as experimental models. This research could offer insight into how NF2/merlin functions as a tumor suppressor protein, therefore leading, potentially, to better prevention and treatment of NF2.

Dr. D. Bradley Welling (left) and Dr. Long-Sheng Chang (right).

Generation of a Mouse Model for Schwannomatosis

Long-Sheng Chang, Ph.D., The Research Institute at Nationwide Children's Hospital, Columbus, Ohio

Exploration–Hypothesis Development Award, FY08

Although sharing many features of the NF, the causes of schwannomatosis are unknown and there are currently no effective medical treatments for the disease. Schwannomatosis is a genetic disorder characterized by the formation of multiple tumors (schwannomas) on peripheral, cranial, and spinal nerves. Previous investigations have hypothesized that the formation of schwannomatosis-associated tumors may involve the inactivation of INI1/SNF5 and NF2 genes. With funding from an FY08 Exploration–Hypothesis Development Award, Dr. Long-Sheng Chang, of The Research Institute at Nationwide Children's Hospital, is generating a mouse model of schwannomatosis to assess whether simultaneous inactivation of the Snf5 and Nf2 genes in specific tissues will result in multiple schwannoma formation. To date, Dr. Chang has produced five lines of transgenic NF2-CreER mice carrying a tamoxifen-inducible Cre recombinase for gene inactivation. Also, he and his collaborators, Dr. D. Bradley Welling at The Ohio State University and Dr. Alex Kuan at Cincinnati Children's Hospital Medical Center, have demonstrated in mice that inactivation of Nf2 in neuroprogenitor cells during mid-to-late gestation results in the development of schwannomas and lymphomas at a high frequency. Currently, Dr. Chang is assessing the effects of Snf5 inactivation in NF2-expressing tissues. He is in the process of establishing a collaboration with Dr. Marco Giovannini at House Ear Institute to generate mice with simultaneous inactivation of Snf5 and Nf2. Ultimately, these studies may lead to the production of the first mouse model of schwannomatosis aiding in preclinical drug testing and assisting in the understanding of the synergistic role of Snf5 and Nf2 in schwannomatosis-associated tumors.

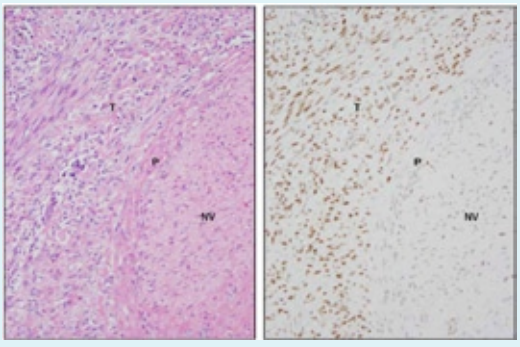
Funding the Next Generation of Innovation:

Somatostatin and CD26: A New Approach for the Treatment of NF1 Tumors
Slawomir Antoszczyk, Ph.D., Massachusetts General Hospital, Massachusetts
Postdoctoral Traineeship, FY09

NF1 is characterized by developmental changes in the nervous system. A distinctive feature of NF1 is the development of PN, which are benign nerve sheath tumors that can progress to MPNSTs. Currently, there are no effective pharmacologic methods for the treatment of PNs and MPNSTs, thus further investigation of alternative treatment strategies are warranted. One potential strategy is the use of oncolytic herpes simplex virus (oHSV) vectors, which are cytotoxic alone and are promising carriers for anticancer transgenes. With funding from an FY09 Postdoctoral Traineeship Award, Dr. Slawomir Antoszczyk of Massachusetts General Hospital will use oHSV vectors expressing the neuropeptide somatostatin or soluble CD26/DPP-IV (dipeptidyl-peptidase IV) to assess the efficacy of these vectors in treating NF1 tumors via inhibition of the chemokine receptor CXCR4 and modulation of its ligand, stromal cell-derived factor-1 (SDF-1). This represents a novel approach as previous studies demonstrate that SDF-1 is upregulated in tumor fibroblasts, therefore stimulating tumor cell proliferation and metastasis via interaction with the CXCR4 receptor. Yet, the role of SDF-1/CXCR4 signaling in NF1 peripheral tumors is unknown. The outcomes of this research may indicate whether SDF-1/CXCR4 signaling is critical in NF1 tumor growth and identify strategies to enhance oHSV efficacy for the treatment of NF1 tumors.

Heat Shock Factor 1 (HSF1) as a Modifier of NF1-Associated Tumorigenesis and a Potential Therapeutic Target
Susan Lindquist, Ph.D., Whitehead Institute for Biomedical Research, Cambridge, Massachusetts
New Investigator Award, FY07

Patients with NF1 frequently develop multiple benign and malignant peripheral nerve sheath tumors but are also predisposed to developing other neoplastic disorders, including leukemia. Tumor predisposition results from inherited and postnatally acquired mutations of the NF1 gene, which encodes the tumor suppressor protein neurofibromin. To date, it has been difficult to improve tumor-associated morbidity and mortality in patients with NF1 due to a lack of understanding of the genetic and environmental factors interacting with NF1 mutations resulting in clinical manifestations. Previous evidence in the laboratory of Dr. Susan Lindquist indicates that inhibition of the major regulator of heat shock response, heat shock factor 1 (HSF1), markedly inhibits the growth of human NF1-associated neural tumor cells. Thus, Dr. Lindquist, recipient of an FY07 NFRP NIA, is exploring the use of HSF1 as a potential therapeutic target in the treatment of NF1-associated MPNSTs. Working with colleagues Luke Whitesell and Sandro Santagata, Dr. Lindquist has used various genetic techniques to alter HSF1 functionality as a modifier of NF1 mutated proteins. They have already demonstrated that reducing HSF1 function dramatically reduces tumor formation in a mouse model of NF1 and, most importantly, have shown this to be well tolerated in both normal cells and in animals. Dr. Lindquist will continue to validate this therapeutic strategy in NF1 in addition to focusing on the identification of promising candidates for clinical development.



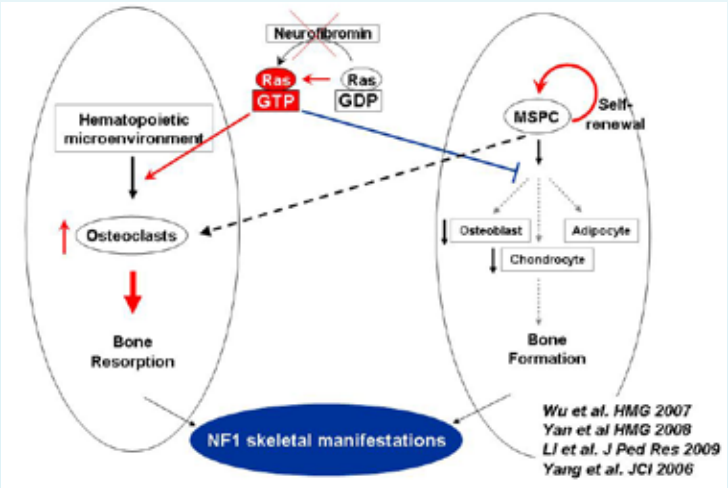
Increased level and nuclear localization of HSF1 in human MPNST samples. Immunohistochemical staining of human NF1-associated MPNST specimens demonstrates HSF1 over-expression and nuclear localization consistent with its activation. Left: Hematoxylin-Eosin staining, Right: HSF-1 immunohistochemistry. T, tumor; P, perineurium, NV, nerve.

Identification of the Cellular and Molecular Mechanisms Underlying the Skeletal Manifestations of NF1 in Murine and Human Systems

Feng-Chun Yang, M.D./Ph.D., Indiana University, Indianapolis, Indiana
New Investigator Award, FY07

NF1 is an autosomal dominant genetic disorder that is caused by mutations in the NF1 tumor suppressor gene. Approximately 50% of NF1 patients experience skeletal abnormalities/osseous manifestations (osteoporosis, kyphoscoliosis, pseudoarthrosis). The most prevalent of these skeletal abnormalities is kyphoscoliois (curvature of the spine), which often requires expensive multiple surgeries to avoid long-term complications such as restrictive lung disease, pain, and disfigurement. Although NF1 patients demonstrate a high incidence of skeletal abnormalities, the molecular mechanisms underlying the pathogenesis of skeletal abnormalities is unknown. As skeletal remodeling is controlled by interactions between osteoclasts and osteoblasts, Dr. Feng-Chun Yang, recipient of an FY07 NFRP NIA, has developed genetic intercrosses using Nf1flox/flox mice and osteoblast specific promoter(s) to model the different skeletal manifestations of NF1 patients including the reduction in body size, osteoporosis, scoliosis, and kyphoscoliosis. With funding from this award, Dr. Yang is using this mouse model to assess how Nf1 modifies the cell-cell interactions between bone resorptive osteoclasts and bone generative osteoblasts, to identify osteoclast-osteoblast interactions, to identify potential molecular targets influencing these interactions and to determine the role of Nf1 in altering mesenchymal stem cell fate and investigating the impact of hematopoietic lineage on the skeletal deficits.

Data generated thus far reveal that mice expressing an osteoblast-specific promoter (Nf1flox/-Col2.3Cre mice) have increased osteoclast activity and reduced bone mineral density, calcium ossification, and bone turnover. Dr. Yang's group has also found that the mice with deficiency of Nf1 in osteoblasts and haploinsufficiency of hematopoietic lineage develop multiple skeletal defects, including short stature, osteoporosis, delayed fracture healing, and kyphoscoliosis. This mouse model closely recapitulates the human NF1 osseous manifestations. Further investigation with this mouse model may provide a platform to understanding the molecular and cellular mechanisms that underlie the osseous manifestations of NF1 patients.



With respect to her research interests and goals, Dr. Yang notes "our study aims to test whether targeting specific signaling pathway(s) increase bone mass and improves fracture healing in our established NF1 murine models by utilizing both genetic and pharmacologic approaches. Our long-term goal is to move these preclinical studies to Phase I–II clinical trials to improve the fracture healing in NF1 patients who suffer from pseudoarthrosis."

Critical role of cell-cell interactions between osteoclasts-osteoblasts in the pathogenesis of skeletal manifestations in NF1. Deletion of Nf1, the tumor suppressor gene, results in hyperactivation of Ras-GTP activity, which leads to (1) increased osteoclast functions to resorb the bone, (2) inhibited osteoblast differentiation from its progenitors—mesenchymal stem/progenitor cells (MSPCs), and (3) Nf1-deficient MSPCs/osteoblasts, in turn, promote osteoclast development via paracrine effects. Together, the imbalanced osteoclast and osteoblast functions lead to pathological skeletal development.

Impacting Patients' Lives

Pilot Study of Gleevec/Imatinib Mesylate in Neurofibromatosis Type 1 Patients with Plexiform Neurofibromas

Kent Robertson, M.D., Ph.D., Indiana University, Indianapolis, Indiana

Clinical Trial Award, FY08

PNs are NF1-associated tumors that are often painful or disfiguring and can be life-threatening depending on their location. PNs are composed of Schwann cells, fibroblasts, endothelial cells, and mast cells and are refractory to therapeutic approaches such as chemotherapy, radiation, and surgery because of their slow growth and location near nerves, vessels, and the airway. Recent research has shown that the drug Gleevec, a c-kit inhibitor currently used to treat chronic myelogenous leukemia and several other malignancies, decreased the size of PNs in an NF1 mouse model. Based on these observations, a Phase II study of Gleevec in NF1 patients with serious PNs was initiated to assess efficacy and gather toxicity data. Although clinical improvements such as improved airway performance and reductions in spinal cord compression symptoms were observed, conventional magnetic resonance imaging (MRI) was determined to be inadequate to precisely evaluate the therapeutic response, due to the irregular shape of PNs. To determine the most sensitive method of evaluating the response of PNs to Gleevec treatment, Dr. Kent Robertson at Indiana University has been awarded an FY08 NFRP CTA. Imaging techniques that will be explored with this award include volumetric MRI scans and positron emission tomography scans that will be compared to standard MRI. Molecular and cellular markers will also be monitored to identify meaningful secondary end points that may correspond to treatment response. Additionally, a health-related quality-of-life tool will be developed and used to assess the functional impact on patients' lives over the course of Gleevec treatment. Ultimately, the results of this study have the potential to make a considerable impact on the NF field by identifying a more effective method to measure/quantify the response of PNs in NF1 patients to treatment.

Partnerships for a Cure

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 that are initially dedicated to 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.

The first study to be conducted by the Consortium is a Phase II trial of the mTOR inhibitor, Sirolimus (rapamycin), for the treatment of plexiform neurofibromas in patients with NF1. Accrual on the trial opened in April 2008 in this two strata study. Stratum 1 is designed as a time-to-progression study for the enrollment of patients with radiographically progressive plexiform neurofibromas, whereas Stratum 2 is designed as a radiographic response to treatment study for patients with nonprogressive tumors. The consortium has collectively enrolled 49 patients in both strata to date. Interim analysis in May 2009 determined no radiographic response in the first 12 Stratum 2 patients; therefore, Stratum 2 was officially closed. A recent protocol revision increased the Stratum 1 recruitment goal from 33 patients (for 29 evaluable) to a goal of 52 patients (for 46 evaluable). Currently, sites are actively recruiting under the revised protocol.

Enrollment for the Phase II study of lovastatin for the treatment of NF1-associated learning and memory impairments opened in 2009, with 29 participants having been enrolled to date. 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, a test designed to measure hippocampal-based learning and memory. 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 a Phase II study of the mTOR inhibitor, Everolimus (RAD001), for children with NF1 and chemotherapy-refractory, progressive low-grade gliomas. To date, the study protocol has been approved by the DoD, and each site is undergoing local institutional review board and Army approvals, with enrollment scheduled to begin by the end of 2010.

Recently, the NF Consortium began a collaborative effort with the Sarcoma Consortium (SARC), an existing clinical trials consortium focusing on sarcomas. The study was funded separately by the CDMRP through the Clinical Trial Award mechanism to Dr. Brigitte Widemann. This collaborative trial, entitled "A Pilot Study of Bevacizumab Combined with Irinotecan-Based Chemotherapy for Children with Neurofibromatosis Type-1 and Recurrent/Refractory Malignant Peripheral Nerve Sheath Tumor (MPNST)," is advantageous in that it allows for cost sharing and access to a larger patient population. The NF Consortium and SARC are currently collaborating to determine the implementation of procedures and time lines.

The Vision for FY10

In FY10, Congress appropriated $13.75M to the NFRP for research. The vision of the NFRP is to find and fund the best research to eradicate 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

Six award mechanisms encompassing these goals were offered in FY10 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
- Research focus areas such as wound repair, nerve regeneration, stress and inflammation, cognitive dysfunction, health-related quality of life, and neurofibromin protein

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. **Investigator-Initiated Focused Research Award (NEW):** Supports basic and clinically oriented research in NF addressing one or more of the following research focus areas: Pain, wound repair, nerve regeneration, stress and inflammation, cognitive dysfunction, health-related quality of life, and/or neurofibromin protein.
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:** Supports postdoctoral training of individuals who are interested in pursuing a career in NF research.

For more information, visit
http://cdmrp.army.mil
or contact us at:
CDMRP.PublicAffairs@amedd.army.mil
(301) 619-7071

12-2010