CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS: PARTNERING FOR A CURE

IV. Neurofibromatosis Research Program

Collaboration

Vision

To decrease the impact of neurofibromatosis and schwannomatosis.

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.

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) 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. As the second-oldest CDMRP program and a major source of funding for NF1, NF2, and schwannomatosis investigators worldwide, the NFRP has managed $172.3M from FY96 to FY06 (see Figure IV-1 – NFRP History). A total of 181 awards have been made through FY05 across the categories of research, research resources, and training/recruitment. While the NFRP funds innovative basic, clinical, and translational studies, the program has placed emphasis on building collaborations and interaction among the NF community. Highlights of selected NFRP collaborations and other achievements can be found later in this chapter on pages 10–11.

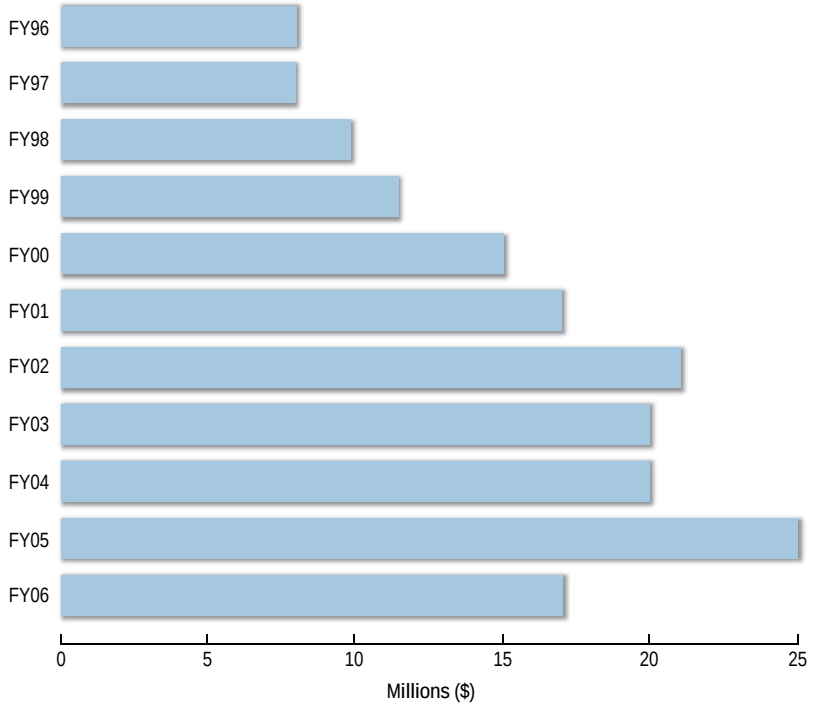


Figure IV-1. NFRP History

The Program Today

Fiscal Year 2005

The NFRP was continued in FY05 with a congressional appropriation of $25M, marking the largest congressional appropriation to the NFRP since its inception. The emphasis for the FY05 program was placed on innovation, clinical research, and collaboration. Table IV-1 provides a summary of the FY05 NFRP award categories and mechanisms in terms of number of proposals received, number of awards made, and dollars invested. As illustrated in Figure IV-2, the FY05 NFRP has developed a diverse research portfolio that encompasses basic, clinical, and population-based research.

Fiscal Year 2005

155 Proposals Received

$25M in Appropriations

41 Awards

Table IV-1. Funding Summary for the FY05 NFRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Clinical Research			
Clinical Trial	2	1	$931,923
Therapeutic Development	7	4	$3,175,688
Innovative Research			
Concept	63	14	$1,249,708
Investigator-Initiated Research	53	10	$13,545,655
New Investigator	14	3	$2,184,707
Research Resources			
NF Consortium Development Operations Center*	2	n/a	$1,034,765
NF Consortium Development Site	14	9	$239,958
TOTAL	155	41	$22,362,404

* NF Consortium Development Operations Award totals $2,999,828 of which $1,965,063 is from FY04 funds and $1,034,765 is from FY05 funds.

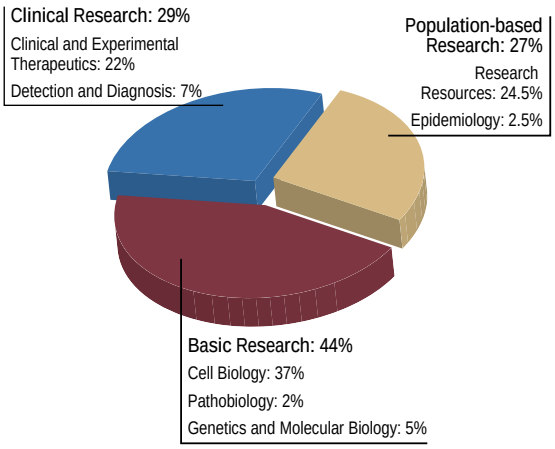


Figure IV-2. FY05 NFRP Portfolio by Research Area

Fiscal Year 2006

The DOD NFRP was continued through an FY06 congressional appropriation of $17M. A total of 93 proposals were received across six award mechanisms, and approximately 26 awards are anticipated. As shown in Figure IV-3, the FY06 award mechanisms span innovative basic research, clinical and translational research, development of resources, and collaborations to advance clinical care. Appendix B, Table B-3, summarizes the congressional appropriations and the investment strategy executed by the NFRP for FY05 through FY06.

Fiscal Year 2006

93 Proposals Received

$17M in Appropriations

~26 Awards

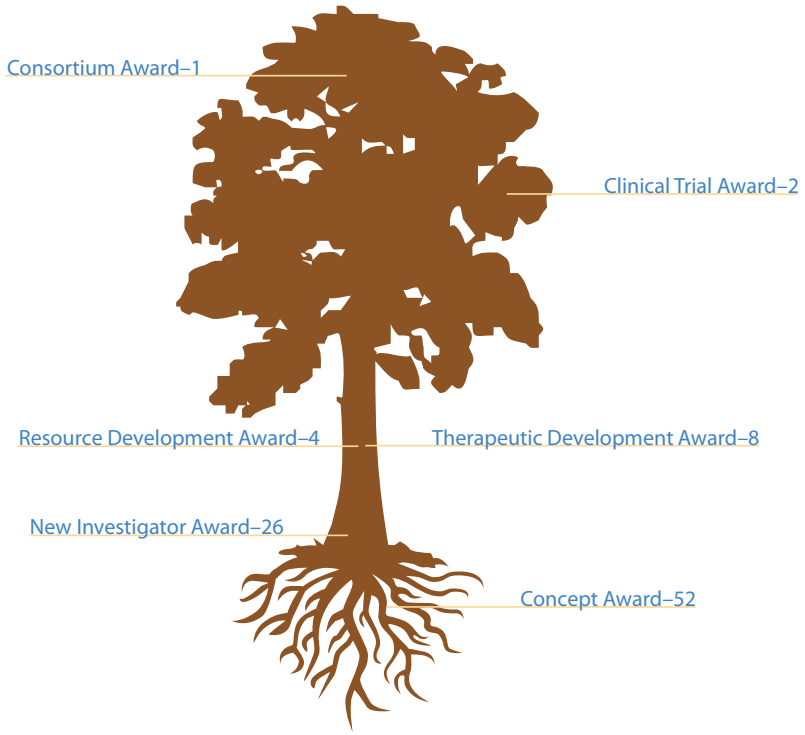


Figure IV-3. Award Mechanisms Offered and Proposals Received for the FY06 NFRP

Collaborative Connections with the Best People

Simply stated, the NFRP believes in collaboration and recognizes the collective efforts of the best people—from scientists, clinicians, and research managers, to those ultimately affected by the disease—in decreasing the impact of NF and schwannomatosis.

JOHN RISNER, M.B.A., C.F.A.,
FY06 CONSUMER INTEGRATION PANEL MEMBER

"The CDMRP Neurofibromatosis Research Program has created an outstanding model for research and has funded many critical advances. I am particularly impressed with the program's effort to translate basic research into effective therapies for NF through the Clinical Trials Consortium. This cannot come too soon for the 100,000 people with NF in the US."

Consumer Advocate Participation

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 played vital roles in the establishment and continuing growth of the NFRP. Individuals with NF1, NF2, and schwannomatosis and their family members work in collaborative partnership with leading scientists and clinicians to contribute their unique perspectives and ensure that program priorities and funding decisions reflect the concerns and meet the needs of their communities. By serving as liaisons between their constituencies and the scientific community, consumer advocates also enhance awareness of the importance of research and strengthen consumer–scientist relationships. More information about consumer advocate participation can be found in Chapter I.

MS. SANDRA PARKER
FY06 CONSUMER INTEGRATION PANEL (IP) MEMBER
MOTHER OF 10-YEAR-OLD EMILY PARKER, NF1 PATIENT

"I am honored, excited, and humbled to be a part of the CDMRP process for NF. The program is absolutely top notch and attracts researchers and scientists of the highest caliber; therefore, I believe the CDMRP represents our best hope for treatment and a cure for NF. The CDMRP gives the gift of hope to those of us who deal with the devastating disease of NF on a daily basis, in a way that cannot be overstated. It has been said 'Hope is the companion of power, and mother of success; for who so hopes strongly has within him the gift of miracles' (Samuel Smiles). I have seen within the participants in the CDMRP hope for treatment and a cure for NF and the potential for the gift of miracles. Hope is alive and well in the hearts of patients, families, researchers, and program workers. As long as hope continues to live, we can look forward to the day when treatment and a cure will be here! A heart-felt thanks to our Congressmen, the American taxpayers, scientists, researchers, and all others responsible for making the CDMRP possible! "

Collaboration

Scientific Community

Renowned researchers from around the world are exploring the cutting-edge of science and developing collaborative efforts to improve the detection, diagnosis, treatment, and management of NF and schwannomatosis and the quality of life of affected individuals. Selected NFRP-supported investigators and their accomplishments are highlighted.

NF1 MICROARRAY CONSORTIUM

Drs. Nancy Ratner, Shyra Miller, Bruce Aronow (Cincinnati Children's Hospital), Margaret Wallace (University of Florida), Conxi Lazaro (Cancer Research Institute, Spain), Marco Giovannini (INSERM, France), Grier Page (University of Alabama), and Anat Stemmer-Rachamimiov (Massachusetts General Hospital) have formed an NF1 microarray consortium utilizing funds received through an FY03 Investigator-Initiated Research Award. The microarray consortium aims to assemble and facilitate a multiexperiment, integrated dataset to conduct cross-species gene expression analysis using microarray profiling. The investigators hypothesize that the transformation of NF1-related neurofibromas to malignant peripheral nerve sheath tumors (MPNSTs) is marked by distinct changes in gene expression. These studies will define these changes across a spectrum of human and animal models, validate how accurately mouse models replicate human pathogenesis, and potentially identify possible therapeutic targets involved in tumor progression. The group recently identified a 159-gene molecular signature that distinguishes MPNST cells derived from patients with NF1 from normal Schwann cells. One of the genes upregulated in MPNSTs and identified as a possible therapeutic target was TWIST1, which has been implicated in apoptosis inhibition, resistance to chemotherapy, and metastasis. The investigators found that reduction of TWIST1 expression in MPNST cells did not affect apoptosis or chemoresistance but did inhibit cell chemotaxis. These promising results highlight the utility of gene expression profiling in the identification of biomarkers and therapeutic targets for the treatment of MPNSTs in patients with NF1.

Members of Dr. Nancy Ratner's Research Group

STATINS AS THERAPEUTIC DRUGS FOR THE TREATMENT OF NF1-RELATED LEARNING DISABILITIES

Cognitive impairments associated with NF1 include multiple learning and attention problems. Genetically engineered Nf1 mutant mice show similar learning impairments to those seen in patients with NF1. Dr. Alcino Silva (University of California, Los Angeles [UCLA]) was awarded an FY01 Investigator-Initiated Research Award to examine the parallels between the learning deficits associated with Nf1 mutations in mice and humans. Working with co-principal investigator Dr. D. Wade Clapp (Indiana University) and members of his laboratory (Dr. Weidong Li and Dr. Steven Kushner), Dr. Silva demonstrated a deficit in Ras/MAPK signaling in brain regions such as the hippocampus, which is important for learning and memory. Furthermore, he demonstrated that Nf1 mutant mice have impairments in long-term potentiation, a process thought to underlie learning and memory. The team hypothesized that agents that decrease Ras/MAPK signaling, such as statins, may reverse the learning deficits in these mice. While working at UCLA, Dr. Silva, now director of the intramural research program at the National Institute of Mental Health, published the finding that Lovastatin, a potent inhibitor of Ras activity in the brain and commonly used for the treatment for hypercholesterolemia, rescued the long-term potentiation deficits, resulting in a reversal of spatial learning and attention impairments in Nf1 mutant mice. These results suggest that Lovastatin may be a useful drug in the treatment of NF1-related learning disabilities. (Dr. Li and Dr. Kushner, pictured)

NF2 NATURAL HISTORY CONSORTIUM

Dr. William Slattery (House Ear Institute, Los Angeles, California) was awarded an FY00 Investigator-Initiated Research Award to expand upon an international NF2 natural history consortium formed through the funding of an FY97 Natural History Study Award. The NF2 natural history consortium consists of clinical centers across the globe including the University of Texas, Massachusetts General Hospital, Royal Victorian Eye and Ear Hospital in Australia, Ohio State University, Universitatsklinikum Hamburg-Eppendorf in Germany, and Hôpital Beaujon in France. The consortium has developed and utilizes standardized methods for the volumetric analysis of tumors in patients with NF2 who are being followed over 4 years. These data are stored in a centralized database and are used to define the growth rates, molecular features, and clinical course of tumors associated with NF2 that may help predict tumor behavior. These data are fundamental in determining the effectiveness of future medical or surgical therapies for NF2. The framework of clinical centers and data management provides a core for use in future therapeutic treatment trials.

Integration Panel Members

The NFRP IP is composed of extraordinary scientists, clinicians, and consumer advocates who use their expertise to create successful investment strategies, craft innovative research priorities, and develop multidisciplinary research portfolios (for more information about the functions of the IP see Chapter I). The active input of the IP enables the NFRP to find and fund the best research and set important program priorities aimed at decreasing the impact of NF and schwannomatosis.

Fiscal Year 2006 IP Members

WILLIAM JOHNSON, M.D. (CHAIR), UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY, ROBERT WOOD JOHNSON MEDICAL SCHOOL

JACKSON GIBBS, PH.D. (CHAIR EMERITUS), ASTRA ZENECA

NANCY RATNER, PH.D. (CHAIR-ELECT), CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

JEFFREY ALLEN, M.D., NEW YORK UNIVERSITY MEDICAL CENTER

CHERYL COFFIN, M.D., UNIVERSITY OF UTAH

SANDRA DABORA, M.D., PH.D., BRIGHAM AND WOMEN'S HOSPITAL

DOREEN FELDMAN, J.D., NEUROFIBROMATOSIS, INC.

ROBERT FINKELSTEIN, PH.D., NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

ELIZABETH HENSKE, M.D., FOX CHASE CANCER CENTER

ANDREA MCCLATCHEY, PH.D., MASSACHUSETTS GENERAL HOSPITAL

SANDRA PARKER, J.D., NEUROFIBROMATOSIS, INC.

TINA YOUNG POUSSAINT, M.D., CHILDREN'S HOSPITAL BOSTON

JOHN RISNER, THE CHILDREN'S TUMOR FOUNDATION

Collaborative Connections to Advance Clinical Care

The NFRP recognized that basic scientific knowledge of the underlying mechanisms of NF has been slow to be translated into the development and deployment of therapies urgently needed by individuals living with the disease. Therefore, in September 2004, leading NF clinicians and scientists from around the world convened to discuss and prioritize the barriers to the clinical translation of basic NF research and to determine strategies to overcome those barriers. Attendees agreed that groundbreaking advances in the clinical management and treatment of NF would be made by assembling a multidisciplinary team to focus on pivotal questions in NF research. The NFRP responded by supporting the development of an NF Consortium: a multi-institutional, interdisciplinary alliance of clinical research sites focused on accelerating treatments for NF from bench to bedside. While this NFRP-supported initiative is open to any group of institutions, FY05 NFRP Consortium Development Operations Center Awardees and NFRP Consortium Development Site Awardees must compete jointly for the FY06 NF Consortium Award with fully developed clinical trials. The FY05 recipients of these prestigious awards are:

FY05 NF CONSORTIUM DEVELOPMENT OPERATIONS CENTER AWARDEE:
Jeannette Lee, Ph.D., University of Alabama at Birmingham; Birmingham, Alabama

FY05 NF CONSORTIUM DEVELOPMENT SITE AWARDEES:
David Gutmann, M.D., Ph.D., Washington University; St. Louis, Missouri
Mira Irons, M.D., Children's Hospital Boston; Boston, Massachusetts
Bruce Korf, M.D., Ph.D., University of Alabama at Birmingham; Birmingham, Alabama
Roger Packer, M.D., Children's National Medical Center; Washington, DC
Peter Phillips, M.D., Children's Hospital of Philadelphia; Philadelphia, Pennsylvania
Elizabeth Schorry, M.D., Cincinnati Children's Hospital Medical Center; Cincinnati, Ohio
James Tonsgard, M.D., University of Chicago; Chicago, Illinois
David Viskochil, M.D., Ph.D., University of Utah; Salt Lake City, Utah
Brigitte Widemann, M.D., National Cancer Institute; Bethesda, Maryland

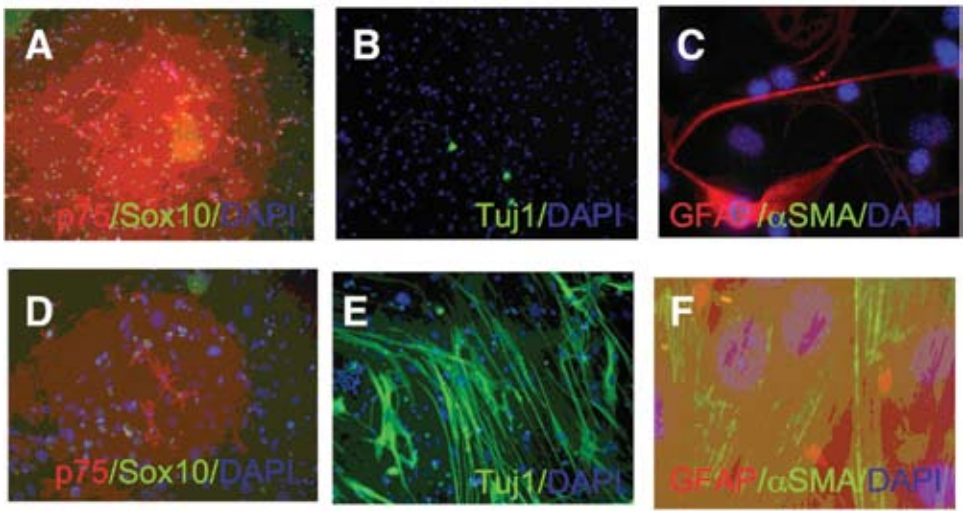
Collaboration

Clinical Trials

Individuals with NF1 have a 10 percent lifetime risk of developing MPNSTs (malignant peripheral nerve sheath tumors). Under current treatment regimens, the prognosis of incompletely resected or metastatic MPNSTs is poor and may be worse for individuals with NF1 than for those with sporadic MPNSTs. Dr. Bridgette Widemann of the National Cancer Institute was awarded an FY05 Clinical Trial Award to conduct a multicenter Phase II trial in collaboration with the Sarcoma Alliance for Research through Collaboration. The trial will assess whether chemotherapy administered prior to surgery for rapidly growing, unresectable MPNSTs can induce tumor shrinkage. The study also aims to assess the disparity in prognosis reported in patients with and without NF1. A number of new imaging techniques will be utilized in the study with the goal of measuring changes in tumor size more sensitively, which may result in better predictors for response to therapy and outcome in patients. Molecular studies of tumor tissue samples will be used to possibly identify novel treatment targets, and blood samples will be obtained with the goal of identifying a serum biomarker of MPNST in patients that could lead to earlier diagnosis. Infrastructure of this collaborative effort will serve as a platform to conduct future clinical studies together. The outcome of these studies decidedly will influence the treatment of MPNSTs in patients with NF1.

Collaborative Connections through Research Resources

NFRP-supported investigators at the Massachusetts Institute of Technology and the University of California, San Francisco, were asked to join the Mouse Models of Human Cancers Consortium (MMHCC) Repository sponsored by the National Cancer Institute. The MMHCC was established in 1999 to support the formation of consortia to develop and validate mouse models of cancer. With NFRP funding, Dr. Kevin M. Shannon (University of California, San Francisco), and top investigators around the world have collaborated to develop and characterize numerous NF mouse models that are now available to the entire scientific community through the MMHCC Repository. These mouse models offer the means to test new approaches for the detection, diagnosis, imaging, and treatment of NF. Through collaborative efforts and sharing of valuable resources, NFRP-funded and National Cancer Institute-funded researchers are working together toward the common goal of decreasing the impact of NF and schwannomatosis.



Collaboration

International Collaborative Connections

Drs. Samuel Rabkin (Massachusetts General Hospital) and Andreas Kurtz (Robert Koch Institute, Germany) were awarded an FY01 Therapeutic Development Award to develop and characterize a novel combinational therapy for the treatment of MPNSTs (malignant peripheral nerve sheath tumors) associated with NF1. Researchers developed an oncolytic herpes simplex virus vector that can destroy the vasculature necessary for tumor growth through the expression of antiangiogenic factors. NF1- and MPNST-derived cell lines and mouse models were developed in collaboration with Drs. V. F. Mautner and S. Frahn (University of Hamburg, Germany) and Dr. Louis Parada (University of Texas Southwestern) to examine the efficacy of the proposed therapy. Antiangiogenic factors were developed in collaboration with Dr. Andreas Bikfavi (INSERM, France). The oncolytic vectors were shown to inhibit tumor growth and angiogenesis in human glioma and mouse MPNST models. This powerful new strategy targets both the tumor and tumor vasculature and shows great promise for clinical translation.

Collaborations in Basic Research

With support from an NFRP FY01 Investigator-Initiated Research Award, Dr. Long-Sheng Chang (Columbus Children's Hospital and Ohio State University) in collaboration with Dr. D. Bradley Welling (Ohio State University) began examining the posttranscriptional regulation of the NF2 gene and found that vestibular schwannomas express a distinct pattern of alternatively spliced NF2 transcripts lacking specific exons. This finding suggested that these alternatively spliced exons may be important for NF2 function. Additionally, Dr. Chang found that there is a specific regulation of NF2 promoter expression pattern during embryogenesis within the neural crest during cell migration, suggesting a specific regulation of the NF2 gene during this critical time in the development of the nervous system. This finding further supported the role of merlin, the NF2 gene product, in cell adhesion, motility, and proliferation during development. Dr. Chang is pursuing this finding in collaboration with Dr. Leonid Omelyanchuk and investigators at the Russian Academy of Sciences with an NFRP FY03 Idea Award. In this ongoing investigation, it has been found that a mutation in merlin leads to a prolonged proliferation during the cell cycle. This and other developmental findings indicate that merlin plays an important role in the completion of cell division. Future investigation of the signaling pathways that link merlin to intracellular signals regulating cell division may enable designs for novel therapeutic regimens to cure NF2 schwannomas and associated tumors.

Members of Dr. Long-Sheng Chang's Research Group

Collaborative Connections with Industry

Dr. Ruihong Chen at NexGenix Pharmaceuticals, a biotechnology company focused on drug development for NF, was awarded an FY05 Therapeutic Development Award to develop a potent and selective small-molecule Pak inhibitor as an NF2 therapeutic agent. Pak is a kinase activated in cells lacking merlin, the gene product mutated in patients with NF2. Researchers hypothesize that the inappropriate activation of Pak in NF2-deficient cells may lead to the aberrant cell growth and resulting tumors in patients with NF2, making Pak an excellent target for NF2 drug development. Dr. Chen's work builds on studies performed by past NFRP award recipients Dr. Tyler Jacks and Dr. Joseph Kissil (Massachusetts Institute of Technology Cancer Center), Dr. Jeffrey Peterson (Fox Chase Cancer Center), and Dr. Jonathan Chernoff (Fox Chase Cancer Center). Dr. Chen worked with the High-Throughput Screening Center at Stanford University to identify potential Pak inhibitors and with Dr. Ling Jong at SRI International to improve the potency and selectivity of the inhibitory compounds for testing in NF2 models. It is hoped that the proposed work will identify a new therapeutic agent for the treatment of NF2.