CDMRP
Department of Defense

Neurofibromatosis Research Program

Decreasing the Clinical Impact of Neurofibromatosis

U.S. Army Medical Research and Development Command

Congressionally Directed Medical Research Programs

HISTORY OF THE CDMRP

The office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a Congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. The success in managing the initial Congressional appropriations in breast cancer research, combined with additional advocacy movements and the need for focused biomedical research, catapulted the CDMRP into a global funding organization for cancer research, military medical research, and other disease-specific research. The CDMRP has grown to encompass multiple targeted programs and has received over **$12 billion** in appropriations from its inception through fiscal year 2019 (FY19). Funds for the CDMRP are added to the Department of Defense (DoD) budget, from which support for individual programs, such as the Neurofibromatosis Research Program (NFRP), is allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for application evaluation, with both steps involving dynamic interaction between scientists and clinicians (subject matter experts) and consumers. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Programmatic Panel, which compares applications and makes funding recommendations based on scientific merit, portfolio composition, and relevance to program goals.

CONSUMER ADVOCACY PARTICIPATION

A unique aspect of the CDMRP is the active participation of consumer advocates or patient representatives throughout the program's annual cycle. Individuals with neurofibromatosis (NF) (encompassing NF type 1 [NF1], NF2, and schwannomatosis) and their family members have an equal voice in the research administration process of setting the NFRP's vision, reviewing applications, and making final funding recommendations. From their unique perspective gained through personal experience, consumers bring a sense of urgency and focus to each part of the program cycle. Consumers evaluate the impact of the research to individuals with NF, as well as the needs of their family members and caregivers and the clinicians who treat them.

Neurofibromatosis Research Program

NF is a group of three genetically distinct disorders that cause tumors to grow in the nervous system and also produce other abnormalities in the skin and bones. The tumors begin in the supporting cells that make up the nerve and the myelin sheath, and the type of tumor that develops depends on the type of supporting cells involved. There are three types of NF: **NF1**, **NF2**, and **schwannomatosis**. An estimated **100,000** Americans have an NF disorder, which occurs in both sexes and in all races and ethnic groups.

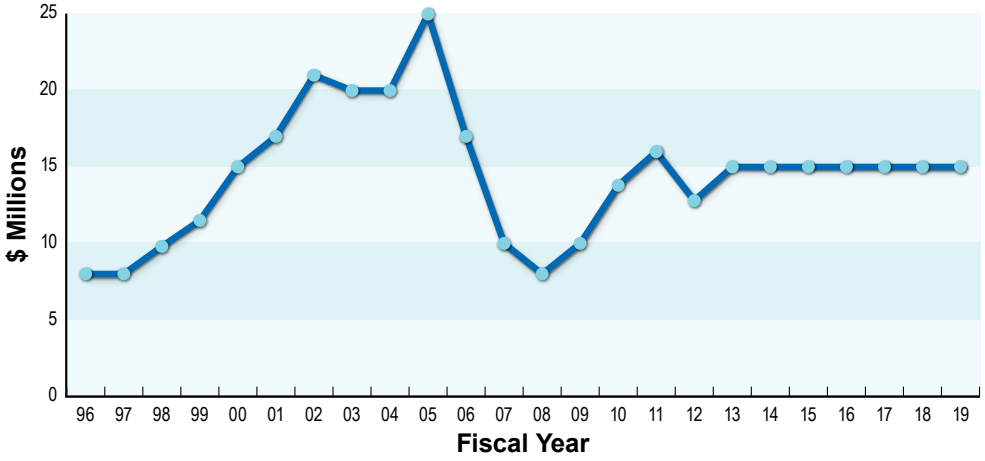
PROGRAM VISION

Decrease the clinical impact of neurofibromatosis

HISTORY OF THE DoD NFRP

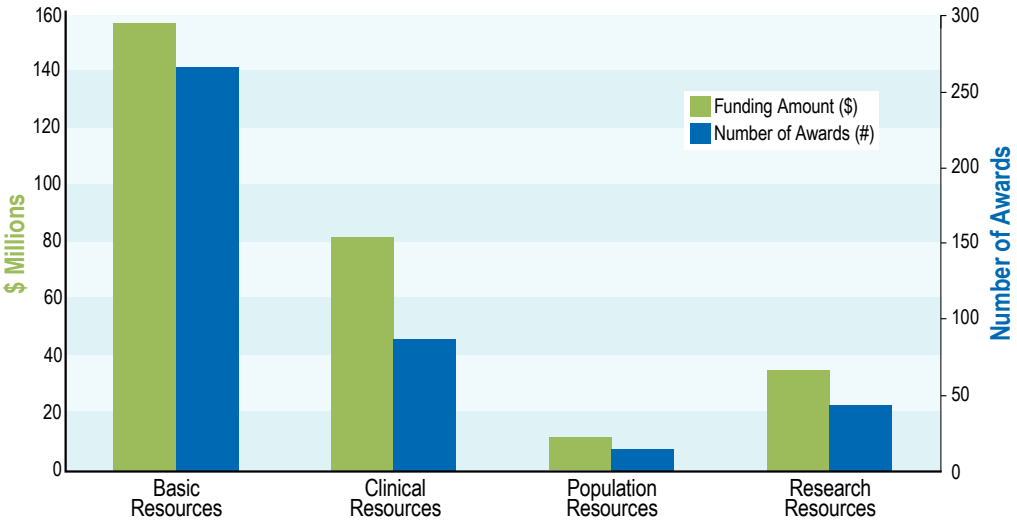
The NFRP was first funded in FY96, when the efforts of NF advocates led to a Congressional appropriation of $8 million (M). Since that time, **$347.85M** has been appropriated to the program, including **$15M in FY19**.

FY96–FY19 NFRP Appropriations



The NFRP has funded **409** basic, clinical, population-based, and resources research projects.

FY96–FY18 NFRP Portfolio



** Includes the FY06 and FY11 NFRP Consortium Awards, with funding for both infrastructure and research.*

PROGRAM OBJECTIVES

- **FOSTER** Basic Research
- **FACILITATE** Therapeutics Development
- **INCREASE** Research Capacity
- **ENCOURAGE** Critical Research

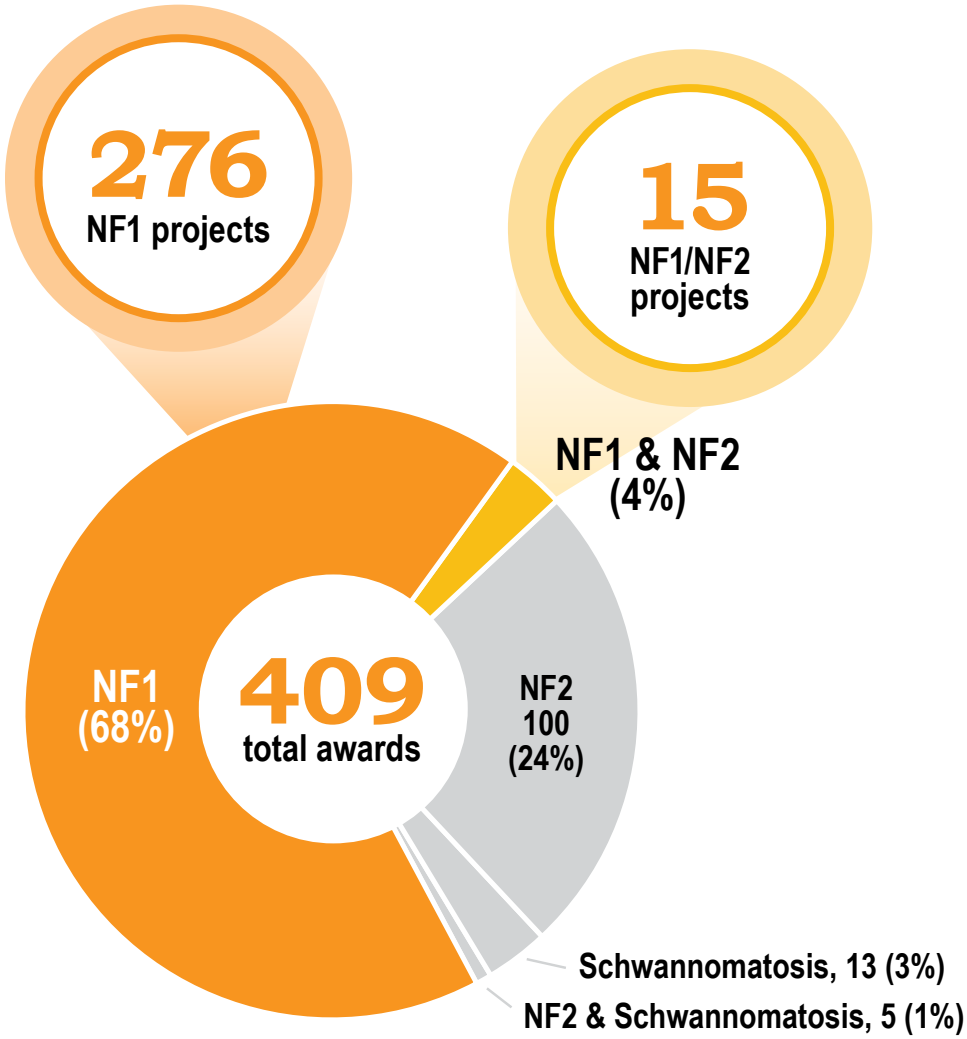
NF1

NF1, also known as von Recklinghausen NF or peripheral NF, is the most common subtype of NF. While between 30% and 50% of new cases result from a spontaneous genetic mutation of unknown cause, the remaining percentage are caused by both copies of the NF1 gene in Schwann cells (SC) losing their function to produce the protein neurofibromin. Neurofibromin regulates the Ras family of oncogenic proteins, which causes the Ras-MEK-ERK signaling pathway to become overactive. NF1 affects **1 in every 3,000–4,000** people, results in disruptions between SC and the neuron, and causes tumorigenesis. Manifestations include the growth of low-grade gliomas of the optic pathway, neurofibromas (benign tumors of the peripheral nerves), and issues with the musculoskeletal system, such as bone dysplasias, spinal malformations, failure to repair long bones after fracture, muscle weakness, and low muscle tone (hypotonia).

"Living with neurofibromatosis has taught me that one never knows what can come next for NF patients. Having undergone multiple surgeries and survived NF-related cancers, I am extremely appreciative of the work that is done at the peer review panel for the NFRP. Together, clinicians, scientists and patients/ patient representatives work collectively to fund the projects with highest impact to NF patients. We need to continue this important work that moves science forward and brings hope to patients and their families."

Andres Lessing

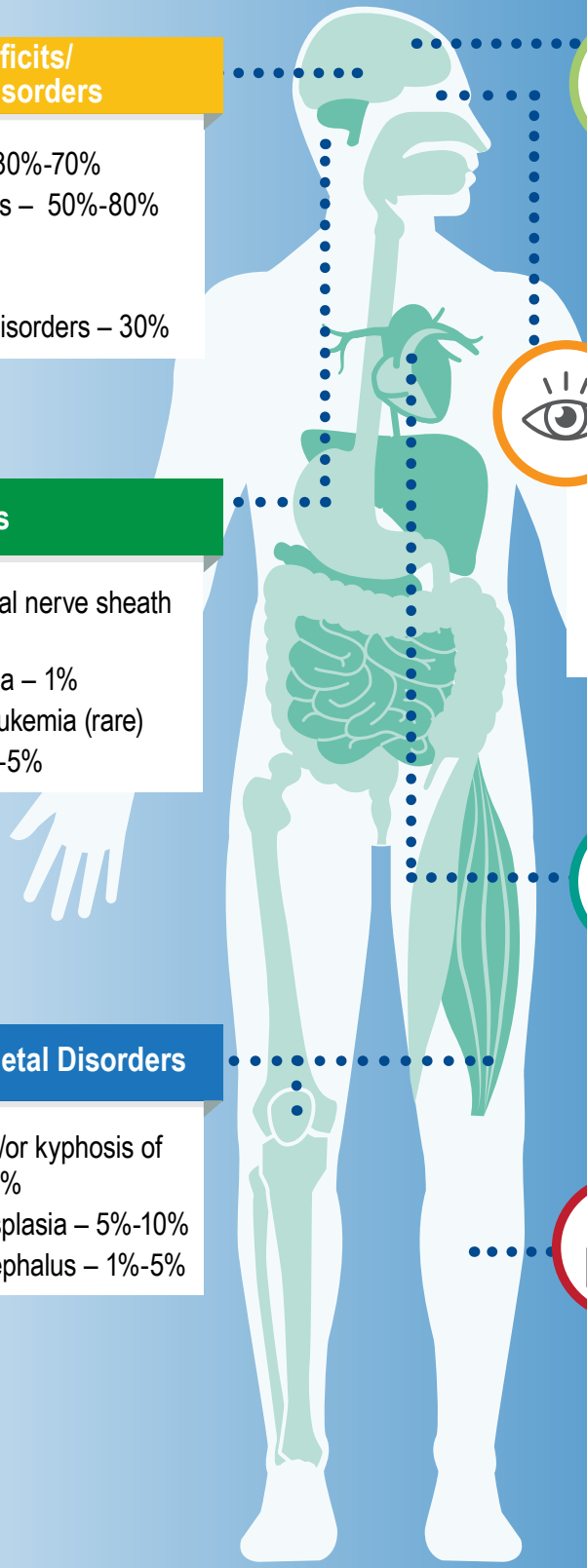
The NFRP has funded:



Together, NF1 accounts for 71% of the total number of projects funded by the NFRP.

Some of the most prevalent complications of NF1.

Clinical Manifestations



Learning Deficits/ Cognitive Disorders

- Attention deficit – 30%-70%
- Learning disabilities – 50%-80%
- Motor deficits
- Spatial deficits
- Autism spectrum disorders – 30%

Nervous System Disorders

- Neurofibromas – 30%-50%
- Seizures – 4%-7%
- Headaches – 47%

Visual Impairments

- Lisch nodules on the iris – 90%-100%
- Retinal hamartomas (small percent)
- Optic gliomas – 15%

Malignancies

- Malignant peripheral nerve sheath tumors – 10%
- Pheochromocytoma – 1%
- Chronic myeloid leukemia (rare)
- Brain tumors – 3%-5%

Vascular Disease

- Dysplasia of blood vessels – 2%
- Hypertension (frequent)

Musculoskeletal Disorders

- Focal scoliosis and/or kyphosis of the spine – 10%-15%
- Sphenoid bone dysplasia – 5%-10%
- Congenital hydrocephalus – 1%-5%

Skin Conditions

- Café-au-lait spots – >95%
- Dermal neurofibroma – 95%

For more details: https://cdmrp.army.mil/nfrp/default

Research Highlights

Identification of Novel Therapeutic Targets for NF1 Optic Pathway Glioma by Examining the Tumor as an Ecosystem

David H. Gutmann, M.D., Ph.D., Washington University in St. Louis

Children with NF1 are prone to develop low-grade gliomas of the optic pathway (OPGs). These tumors grow slowly, are heterogeneous, and can lead to vision loss. With an FY12 Investigator-Initiated Research Award, Dr. David Gutmann studied these tumors as "ecosystems" to discover novel therapeutic targets for treating these gliomas. The studies under this award have led to greater knowledge of the cellular components and the importance of their interactions in optic glioma development. In 2015, Dr. Gutmann's group published a report demonstrating the isolation and characterization of cancer stem cells from mouse Nf1 low-grade gliomas. In 2017, his group released another publication examining the cell of origin of optic gliomas in two different mouse models. Their findings suggested that the time to tumor formation may be due to the specific cell of origin. An additional study published in 2017 used RNA sequencing to characterize these tumors as cooperative cellular societies or ecosystems. In this study, the team found that histologically similar optic gliomas in mice had distinct molecular signatures. Further investigation revealed that the gene expression pattern observed in the tumor reflected the intercellular interactions within the tumor, not the individual cell types, highlighting the importance of considering the tumor as a whole. Dr. Gutmann's findings have laid the groundwork for future studies into potential biomarkers for NF1 patients, pointed to novel targets for optic glioma treatment, and provided mechanistic insights into drug resistance in currently-used treatments.

For more details:
https://cdmrp.army.mil/nfrp/research_highlights/18gutmann_highlight

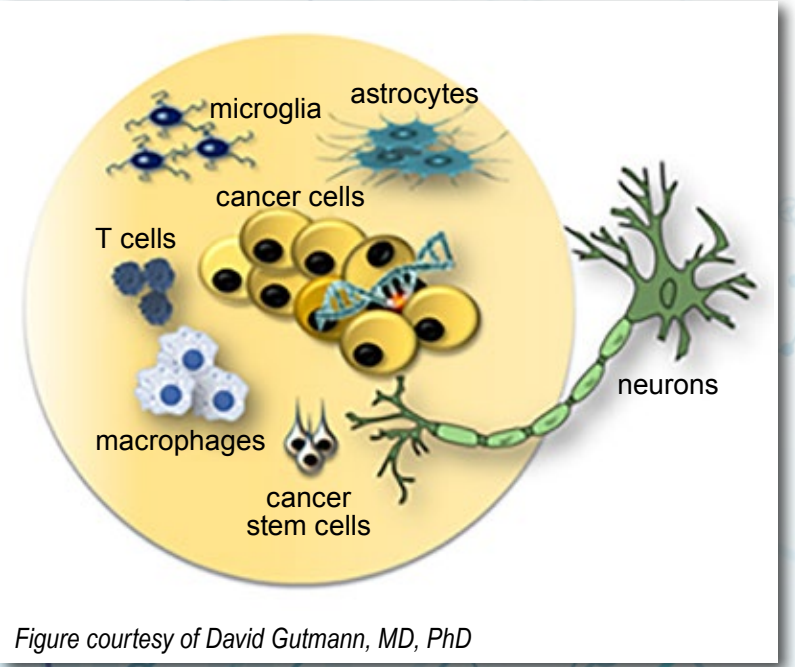


Figure courtesy of David Gutmann, MD, PhD

Pathophysiology and Treatment of Muscle Weakness in NF1

Aaron Schindeler, Ph.D., The Children's Hospital at Westmead

Current clinical trials are focused on using MEK inhibitors for tumor treatment; however, tumors are not the only manifestation of NF1. With an FY13 Exploration - Hypothesis Development Award, Dr. Aaron Schindeler investigated whether a MEK inhibitor or dietary changes may have therapeutic value for the muscular issues of conditional knockout Nf1-/- mice. Muscle specimens from a skeletal muscle knockout (Nf1MyoD-/-) and limb embryonic tissue knockout (Nf1Prx1-/-) mouse models were used. Dr. Schindeler's group focused on metabolism and intramyocellular lipids for possible dietary interventions. Muscle specimens from both versions of knockout Nf1-/- mice were found to be enriched with long-chain fatty acids (LCFA) containing neutral lipids, suggesting an impaired LCFA metabolism. A genetic profile of Nf1MyoD-/- muscle tissue extracts revealed alterations in genes associated with metabolism and cell signaling. Most recently, Dr. Schindeler's team used these mice models to test the capacity of PD0325901, an MEK inhibitor, to influence fat droplets stored in muscle cells. Their findings supports the idea that the MEK/ERK-dependent mechanism underlies NF1 muscle metabolism during development. However, the data does not support MEK inhibitor therapy for treating individuals with established NF1-associated muscle weakness. The collective evidence from this work provides strong proof of principle that treatments affecting lipid metabolism will be able to ameliorate the muscle symptoms of NF1. In 2019, Dr. Schindeler's team is commencing a clinical trial for L-carnitine supplementation in children with NF1 to determine whether this intervention improves quality of life and functional outcomes.

For more details:
https://cdmrp.army.mil/nfrp/research_highlights/19schindeler_highlight

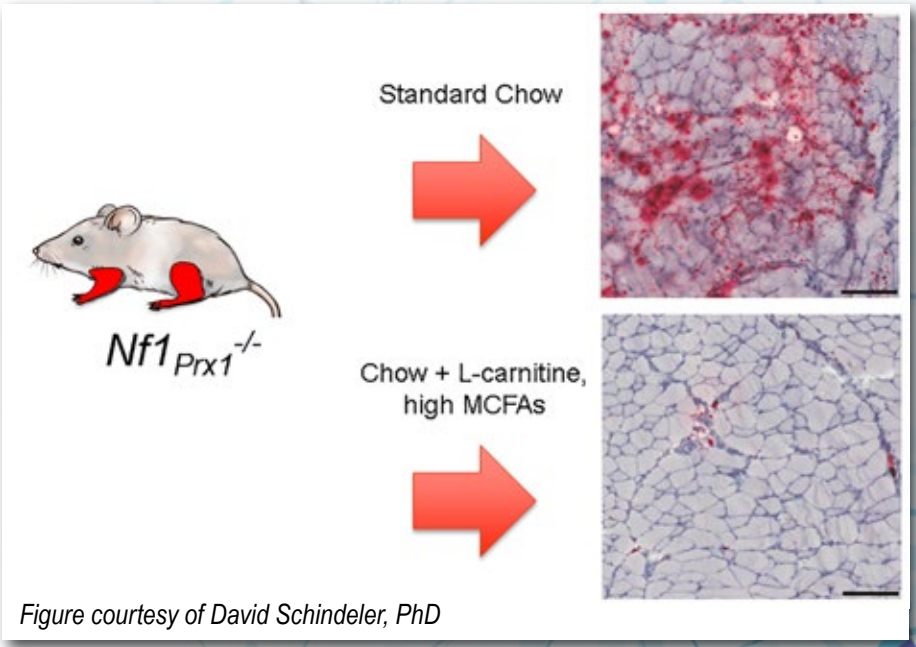


Figure courtesy of David Schindeler, PhD

Identification of Molecular and Cellular Contributions to Neurofibroma Formation and Growth

Nancy Ratner, Ph.D., Jianqiang Wu, M.D., M.S., Carlos Prada, M.D., Kwangmin Choi, Ph.D., Children's Hospital, Cincinnati

Dr. Nancy Ratner

Dr. Jianqiang Wu

Dr. Carlos Prada

Dr. Kwangmin Choi

Neurofibromas are benign tumors of the peripheral nerves that are strongly associated with the NF1 syndrome. Neurofibromas are characterized by disruptions between Schwann cells (SC) and their attached neurons. Dr. Ratner and her team learned that Pexidartinib (PLX3397), a drug that blocks infiltration by a type of white blood cells called macrophages, was more effective in established tumors of mice 7 to 9 months of age, compared to mice 1 to 4 months of age who had much smaller tumors. As a tumor becomes more established, macrophages are recruited as a part of the immune response, releasing cytokines and chemokines, which stimulate blood vessel growth (increasing tumor volume), and have other effects. This stage-dependent role of macrophages indicates that macrophage inhibitors could represent a therapeutic strategy for established neurofibromas. Dr. Ratner's team

A neurofibroma is a type of non-cancerous tumor that develops from cells and tissues that cover the nerves. Neurofibromas form soft bumps on or under the skin, and are most commonly associated with NF1.

For more details:
https://cdmrp.army.mil/nfrp/research_highlights/18ratner_highlight

also demonstrated significant differences in neurofibroma SC and macrophage cytokine gene expression compared to cells from normal nerves. Computational reconstruction of molecular networks and signaling predicted the changes of cytokines, chemokines, and growth factors and verified the presence of a macrophage chemo-attractant, colony stimulation factor 1, by SC, and predicted a decrease in type-1 interferon (IFN), a cytokine upstream in immune response signaling. Experiments confirmed the computational prediction of reduced type-1 IFN expression in neurofibromas and showed that treatment of neurofibroma-bearing mice with polyethylene glycolyated type-1 IFN-alpha-2b reduced overexpression of many other cytokines, which is consistent with observed reduction of neurofibroma growth in a Phase II trial of PEGylated IFN-alpha-2b (NCT00678951). Findings from Dr. Ratner's group under this award have improved understanding of neurofibroma formation and provides a platform for numerous future investigations to target neurofibroma therapy, including examination of the genetic makeup of macrophages and SC and the signals influencing potential cross-talk for Ras and interferon pathways.

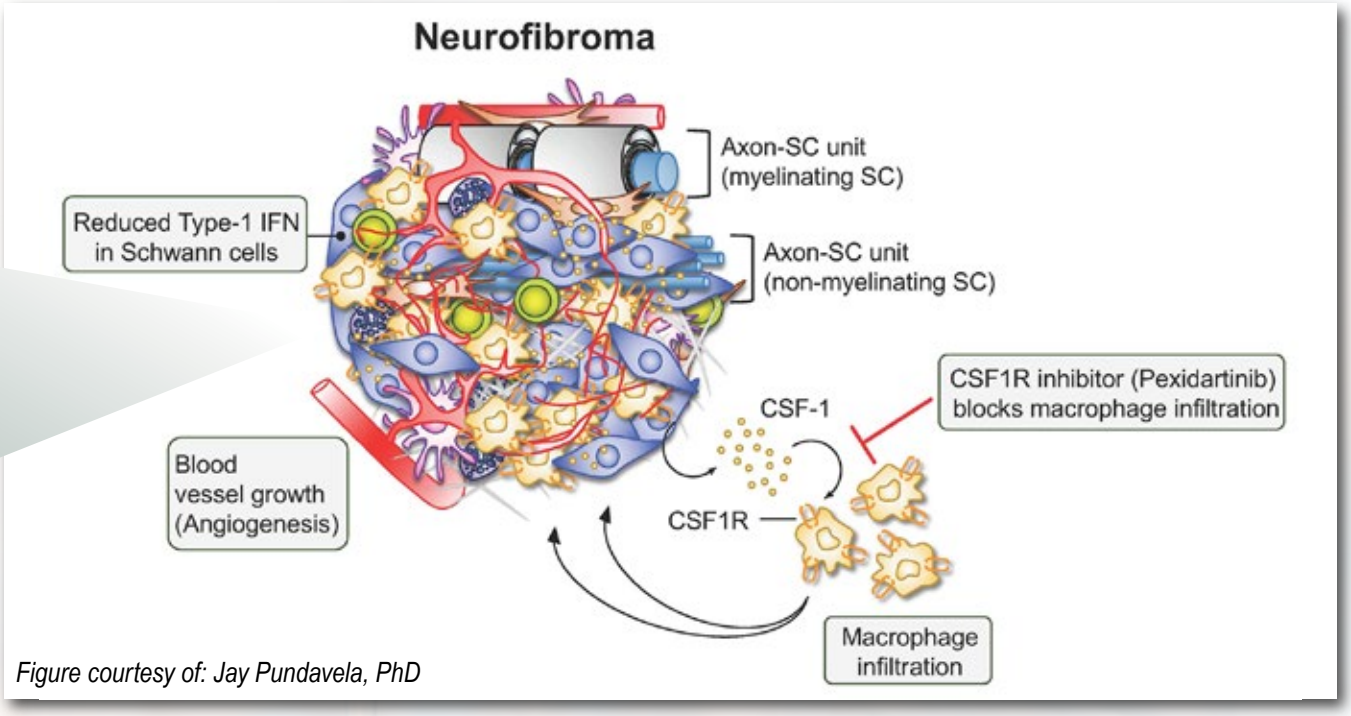
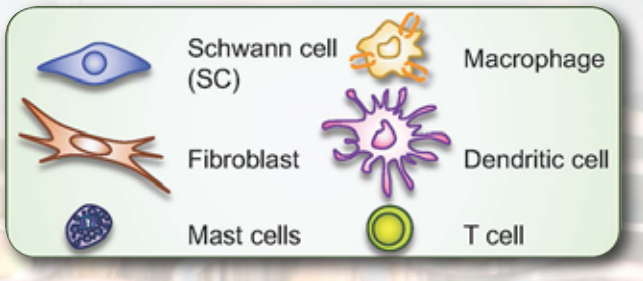


Figure courtesy of: Jay Pundavela, PhD

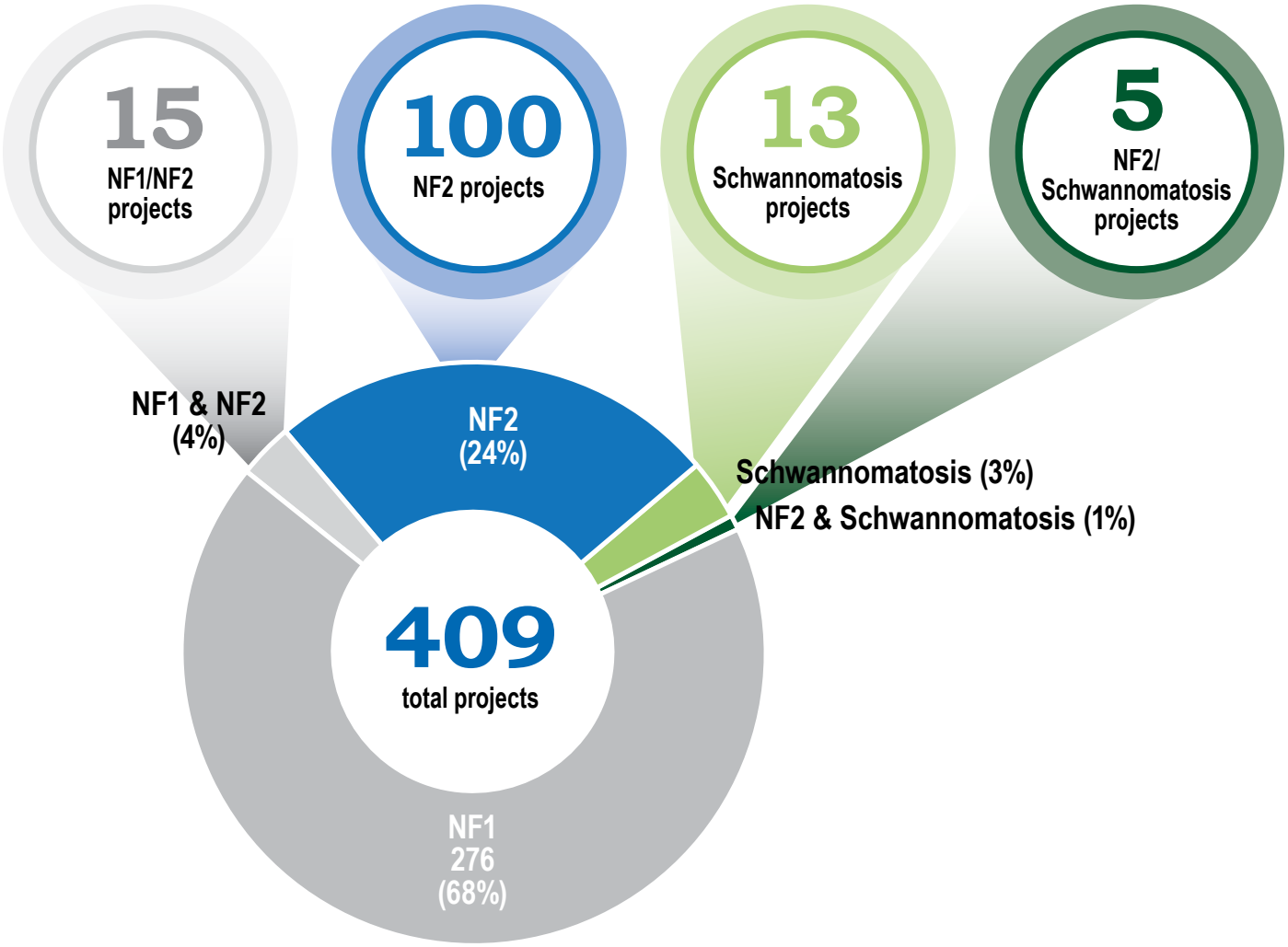


NF2 & Schwannomatosis

NF2 is a genetic syndrome caused by loss of function of the NF2 gene that encodes the Merlin tumor suppressor protein. NF2, also known as bilateral acoustic NF, is a rare disorder affecting about **1 in 25,000** people that is caused when SC form noncancerous tumors called schwannomas on cranial, spinal, and peripheral nerves. Complications of tumor growth may cause hearing loss, balance dysfunction, vision problems, weakness in arms and legs, and fluid buildup in the brain and can be fatal. Approximately 50% of those with NF2 inherit the disorder, while in others the syndrome is caused by a spontaneous genetic mutation of unknown cause.

Schwannomatosis is a much rarer disorder, affecting an estimated **1 in 40,000** people. The inherited form accounts for 15% of all cases, and while not completely understood, studies suggest that the mutation of one of the tumor suppressor genes, SMARCB1 or LZTR1, may be involved in familial schwannomatosis. Recent data also suggest that inactivation of the NF2 gene may play a role in SMARCB1-initiated schwannoma development. Patients with schwannomatosis develop extremely painful spinal, peripheral, and cranial nerve schwannomas and frequently suffer from additional neurological symptoms, including numbness and weakness in the extremities.

The NFRP has funded:



Together, NF2 accounts for 29%
of the total number of projects funded by the NFRP.

Some of the most prevalent complications of NF2 & Schwannomatosis.

Clinical Manifestations

NF2

Non-Malignant Tumors

Vestibular schwannomas – 98%
Spinal cord tumors – 66%

Headaches

Malignant Brain Tumors

Visual Defects

Blindness – 1%
Decreased acuity – 33%
Cataracts – 81%

Hearing Loss - 9%-35%

Schwannomatosis

Non-Malignant Tumors

Schwannomas (non-vestibular) – 8%-89% (depending on location)

Headaches - 20%

Neurological Symptoms

Numbness – 10%
Tingling
Weakness in fingers/toes – 10%

Chronic Pain - 68%

"I think the consumer reviewers add empathy and a critical piece to the NFRP review panels - they add the 'so what?' factor, challenging scientists to come up with research that will actually translate into tangible solutions that will improve the everyday lives of NF patients. Additionally, the consumer reviewers can carry back to their advocacy organizations how passionately the scientists are working on the diseases and how the scientific process and translation from bench to bedside works."

Catriona Miller, Ph.D., Neurofibromatosis Network

For more details: https://cdmrp.army.mil/nfrp/default

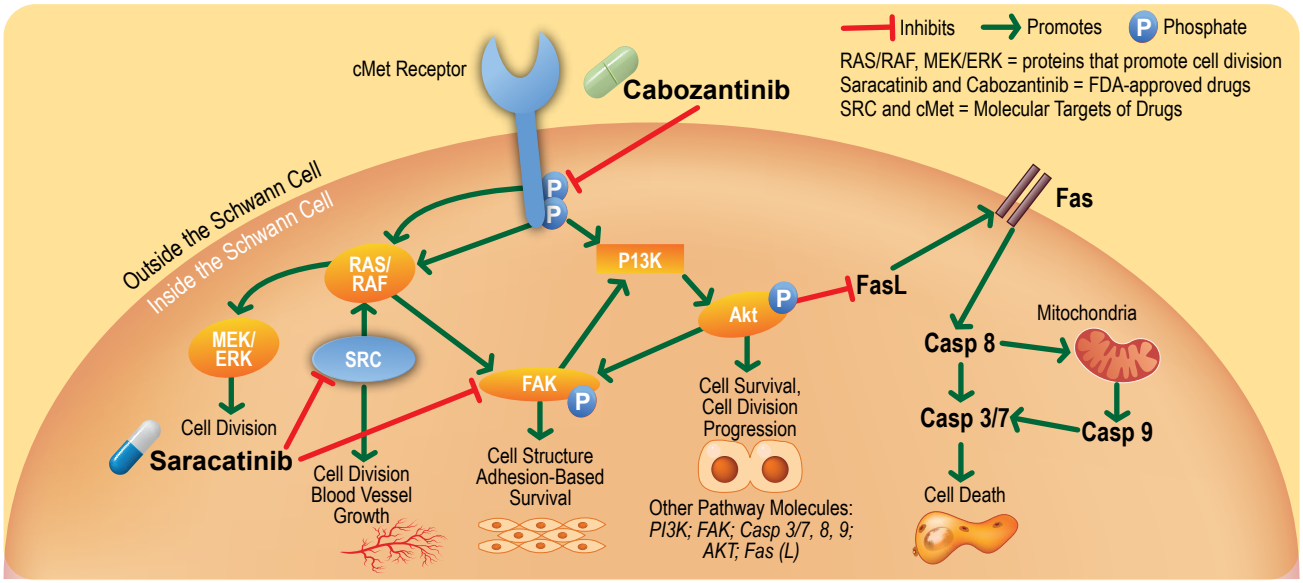
Research Highlights

Potential Therapeutics for Neurofibromatosis Type 2-Associated Schwannoma Tumors

Cristina Fernandez-Valle, Ph.D., University of Central Florida

The loss of Merlin protein causes Schwann cells to form noncancerous tumors called schwannomas on cranial, spinal, and peripheral nerves. Complications of tumor growth may cause hearing loss, balance dysfunction, vision problems, weakness in arms and legs, fluid buildup in the brain, and death. To date there are no US Food and Drug Administration (FDA)-approved therapies that target schwannoma cells in order to reduce the complications associated with NF2. With support from an FY14 NFRP Investigator-Initiated Research Award, Dr. Cristina Fernandez-Valle and her colleagues investigate FDA-approved drugs targeting Src and c-Met alone and in combination treatments to determine if they could be repurposed for schwannoma treatment. When Merlin-deficient mouse Schwann cells were treated singularly with the c-Met inhibitor, cabozantinib, or with one of the Src inhibitors, ponatinib, dasatinib or saracatinib, they displayed reduced viability. The molecular targets of the drugs were proteins related to the cell cycle, as a robust arrest at the G1 phase of the cell cycle in Merlin-deficient Schwann cells was detected. When the cells were treated with a combination therapy of cabozantinib and saracatinib, apoptosis (cell death) was selectively induced in Merlin-deficient Schwann cells but not in wildtype (normal) Schwann cells. The combination treatment also reduced growth of Merlin-deficient mouse Schwann cells in a mouse model by 80% compared to vehicle treatment. Human schwannoma cells with NF2 mutations displayed a 40% decrease in cell viability with the combination treatment when compared to control treatment. The success of these repurposed drugs in inhibiting Merlin-deficient Schwann and schwannoma cell proliferation warrants future studies in mouse models of NF2 to further address the possible use of these drugs as effective therapies for NF2 patients. Also, these results indicate that the combined inhibition of Src and c-Met can trigger Schwann cell death, which suggests a vulnerability in schwannomas that could potentially be targeted for the development of much needed NF2 therapies.

For more details:
https://cdmrp.army.mil/nfrp/research_highlights/18fernandez-valle_highlight



Original figure courtesy of Cristina Fernandez-Valle, Ph.D., modified from Fig 6F in Fuse et al. (2017).

Cerebellopontine Angle (CPA) Model: A Novel Tool for Investigating Tumor Biology and Developing Novel Therapeutic Strategies in Neurofibromatosis Type 2 Vestibular Schwannomas

Lei Xu, M.D., Ph.D., Massachusetts General Hospital

NF2 is characterized by benign tumors made of neoplastic Schwann cells within the nervous system called bilateral vestibular schwannomas (VSs) that are capable of causing multiple complications, including progressive hearing loss, facial paralysis, neuropathies of the cranium, and even mortality. With support from a Fiscal Year 2015 New Investigator Award (NIA) through the NFRP, Dr. Lei Xu and her team are utilizing animal models to evaluate the potential of immunotherapy in controlling tumor progression for enhanced survival. Preliminary data from Dr. Xu's group confirms the presence of immune checkpoint molecules in NF2 schwannomas and demonstrates that NF2 patients are in an immune suppressive state. The group has also previously shown that anti-VEGF treatment, via normalizing the abnormal schwannoma vasculature, improves perfusion, reduces tumor hypoxia and significantly enhances radiation efficacy. Dr. Xu's team recently published a protocol on their newly developed cerebellopontine angle (CPA) model for the in vivo study of NF2-related VSs pathophysiology and neurological function. The protocol describes a technique for delivering schwannoma cells into the mouse brain CPA region. This technique opens several avenues for investigating tumor biology, hearing, and neurological function in VSs. The group describes applications of state-of-the-art intravital imaging and hearing assessment techniques for the study of tumor growth and hearing loss. This animal model is a powerful tool in facilitating the study of VS pathobiology through several perspectives, including tumor progression, hearing and neurological function, and facilitates testing the efficacy of novel therapeutics. Through the NIA, Dr. Xu has developed new techniques, which could be utilized in elucidating the complex biology of NF2 and VS-associated hearing loss. Dr. Xu's CPA model can also be applied in the study of metastatic lesions, meningiomas, lipomas, and various other CPA disorders. If successful, Dr. Xu's work will fill the current knowledge gap in the biology of the immune component of VSs, inform on the immune status of NF2 patients, and provide knowledge on the potential efficacy of immunotherapy for NF2-related schwannomas. The findings from this group will also determine the rationale and directly inform the design of future clinical trials for combined immunotherapy with anti-VEGF treatment. This effort has the potential to improve treatment of patients with NF2 VSs through rapid translation to the clinic.

For more details:
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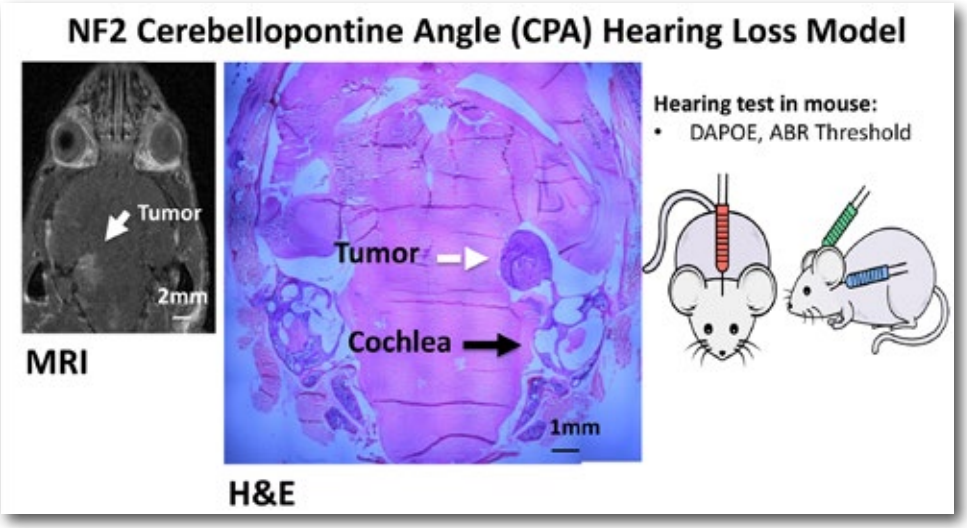


Figure: Establishment of a novel schwannoma cerebellopontine model for evaluation of hearing function in mice. Left and middle: Representative brain MRI and H&E images of the brain of a mouse bearing NF2-/- tumors (white arrow) implanted at the root entry zone of the 8th cranial nerve, located in close proximity to the cochlea (black arrow). Right: representation of the hearing test in mice. Figure courtesy of Lei Xu, Ph.D. and Grace Lee.

NF Clinical Trials Consortium

History

The Neurofibromatosis Clinical Trials Consortium (NFCTC) (http:/www.uab.edu/nfconsortium) was established by the DoD NFRP to develop and perform clinical trials for the treatment of NF complications in children and adults. The consortium is composed of 15 clinical sites, 9 collaborating sites, and an Operations Center at the University of Alabama at Birmingham under the direction of Dr. Bruce Korf. The purpose of the Operations Center is to provide administrative, data management, and statistical support to the NFCTC. Each of the clinical and collaborating sites has expertise in the treatment and management of NF and an established patient population available for clinical trials.

Planning — 2004

- Meeting of Programmatic Panel, National Institutes of Health directors, and subject matter experts to address clinical trial issues in NF
- Consensus recommendation that consortium was needed to move NF trials forward

Development — 2005

- Initial Request for Proposals released for applicants
- Selection of operations center
- Selection of 9 clinical sites
- Proposal and protocol development
- Funding $3M to operations center and $30K to each site

Initiation — 2006

- Initiated 4 trials, including one in collaboration with the Sarcoma Alliance for Research through Collaboration (SARC)
- Included one ancillary study
- 1st study opened 2007
- Funding $9M

Second Award — 2011

- Expanded to 20 sites, increased operations and statistical center
- Initiated 6 trials, one in collaboration with SARC
- Collaboration with non-consortium sites
- Collaboration with industry and other consortia
- Leveraged funding (Philanthropy, CTF, Pharma)
- Strong involvement with CTF/NTAP*
- Funding $9M

Third Award — 2016

- Expanded to 24 sites
- Initiated 3 trials thus far, one in collaboration with SARC
- Several potential trials in planning stages
- Continued collaboration with industry and other consortia
- Close ties to DHART SPORE**
- Continued leveraging of funding
- Funding $9M

* *Close ties to Children's Tumor Foundation (CTF)/Neurofibromatosis Therapeutic Acceleration Program (NTAP) Preclinical Consortium*

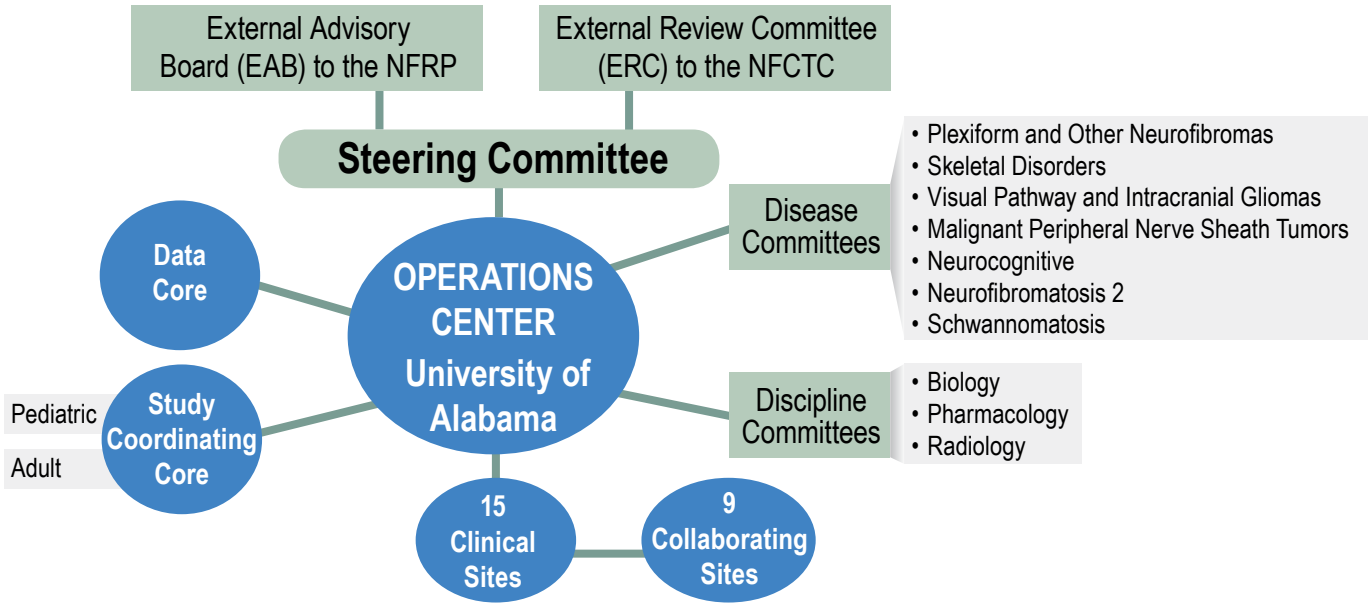
** *Developmental and Hyperactive RAS Tumor (DHART) Specialized Programs of Research Excellence (SPORE)*

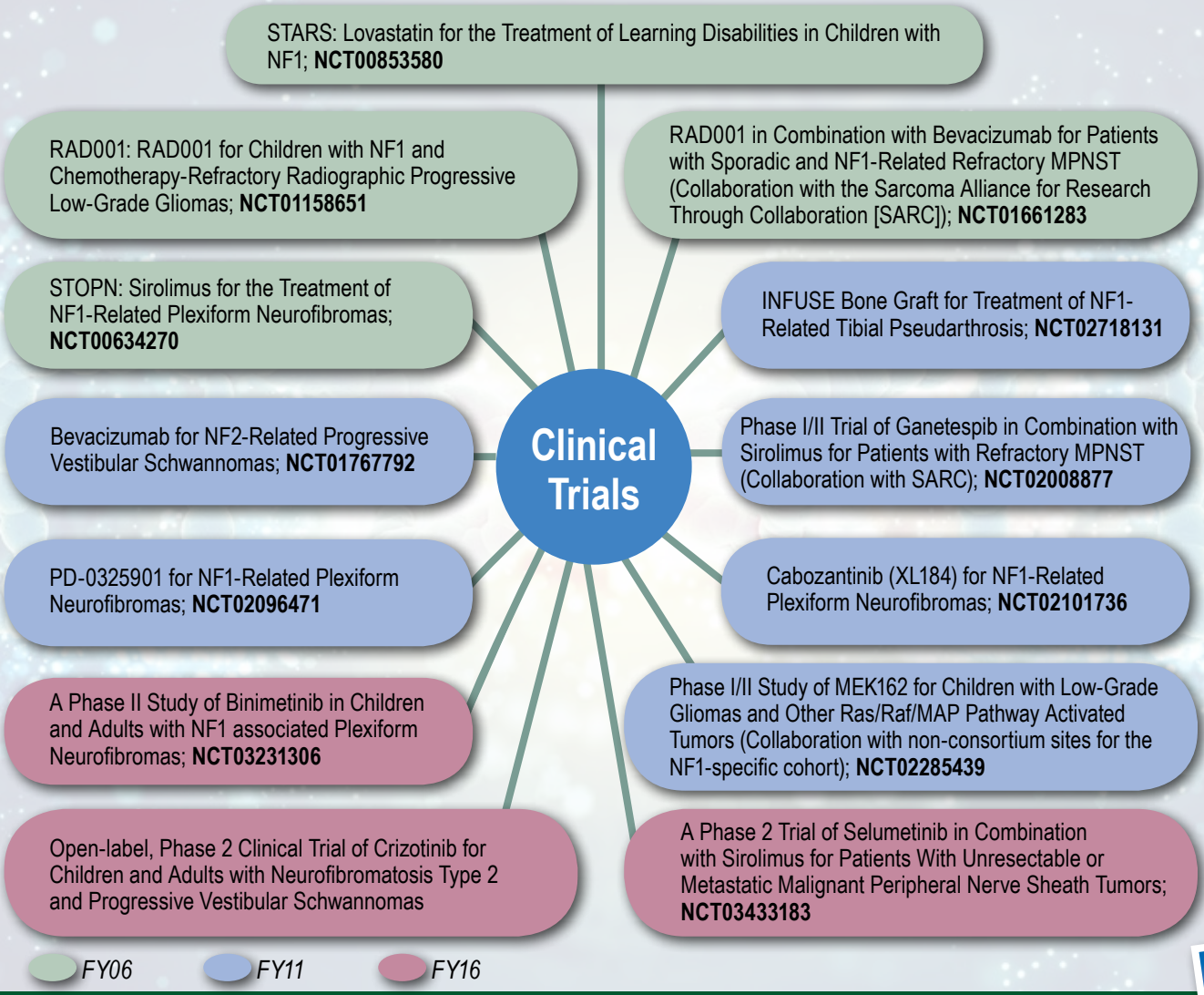
"The NF Clinical Trials Consortium is one of the most important advances for the NF field in the past several decades. This unparalleled group of world class NF clinicians, clinical trialists, lab researchers, and hospitals works seamlessly together to rapidly evaluate potential new therapies for all complications of NF1, NF2, and schwannomatosis. The close collaboration between the clinical and laboratory scientists remains crucial to the Consortium's success. As the Consortium has matured, the number of involved NF centers has expanded as has the number of clinical trials launched each year. These trials not only evaluate potential new therapies, but provide treatment opportunities to patients with few other options. Importantly, the Consortium is not exclusive, and collaborates with anyone with exciting and compelling new ideas for treatment. The NF Clinical Trials Consortium has become a true vehicle of change and hope for the NF community."

Dr. Michael Fisher

For more details: http://cdmrp.army.mil/nfrp/consortium/nfrpctc and *http://www.uab.edu/nfconsortium/*

Structure


External Advisory Board (EAB) to the NFRP
External Review Committee (ERC) to the NFCTC
Steering Committee
Data Core
OPERATIONS CENTER
University of Alabama
Disease Committees
• Plexiform and Other Neurofibromas
• Skeletal Disorders
• Visual Pathway and Intracranial Gliomas
• Malignant Peripheral Nerve Sheath Tumors
• Neurocognitive
• Neurofibromatosis 2
• Schwannomatosis
Pediatric
Study Coordinating Core
Adult
Discipline Committees
• Biology
• Pharmacology
• Radiology
15 Clinical Sites
9 Collaborating Sites


STARS: Lovastatin for the Treatment of Learning Disabilities in Children with NF1; NCT00853580
RAD001: RAD001 for Children with NF1 and Chemotherapy-Refractory Radiographic Progressive Low-Grade Gliomas; NCT01158651
RAD001 in Combination with Bevacizumab for Patients with Sporadic and NF1-Related Refractory MPNST (Collaboration with the Sarcoma Alliance for Research Through Collaboration [SARC]); NCT01661283
STOPN: Sirolimus for the Treatment of NF1-Related Plexiform Neurofibromas; NCT00634270
INFUSE Bone Graft for Treatment of NF1-Related Tibial Pseudarthrosis; NCT02718131
Clinical Trials
Bevacizumab for NF2-Related Progressive Vestibular Schwannomas; NCT01767792
Phase I/II Trial of Ganetespib in Combination with Sirolimus for Patients with Refractory MPNST (Collaboration with SARC); NCT02008877
PD-0325901 for NF1-Related Plexiform Neurofibromas; NCT02096471
Cabozantinib (XL184) for NF1-Related Plexiform Neurofibromas; NCT02101736
A Phase II Study of Binimetinib in Children and Adults with NF1 associated Plexiform Neurofibromas; NCT03231306
Phase I/II Study of MEK162 for Children with Low-Grade Gliomas and Other Ras/Raf/MAP Pathway Activated Tumors (Collaboration with non-consortium sites for the NF1-specific cohort); NCT02285439
Open-label, Phase 2 Clinical Trial of Crizotinib for Children and Adults with Neurofibromatosis Type 2 and Progressive Vestibular Schwannomas
A Phase 2 Trial of Selumetinib in Combination with Sirolimus for Patients With Unresectable or Metastatic Malignant Peripheral Nerve Sheath Tumors; NCT03433183
FY06
FY11
FY16

NF Clinical Trials Consortium

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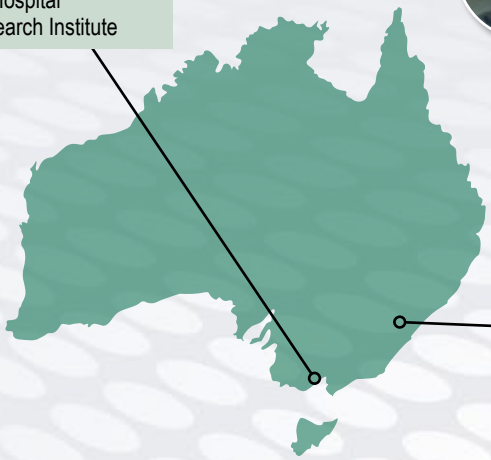
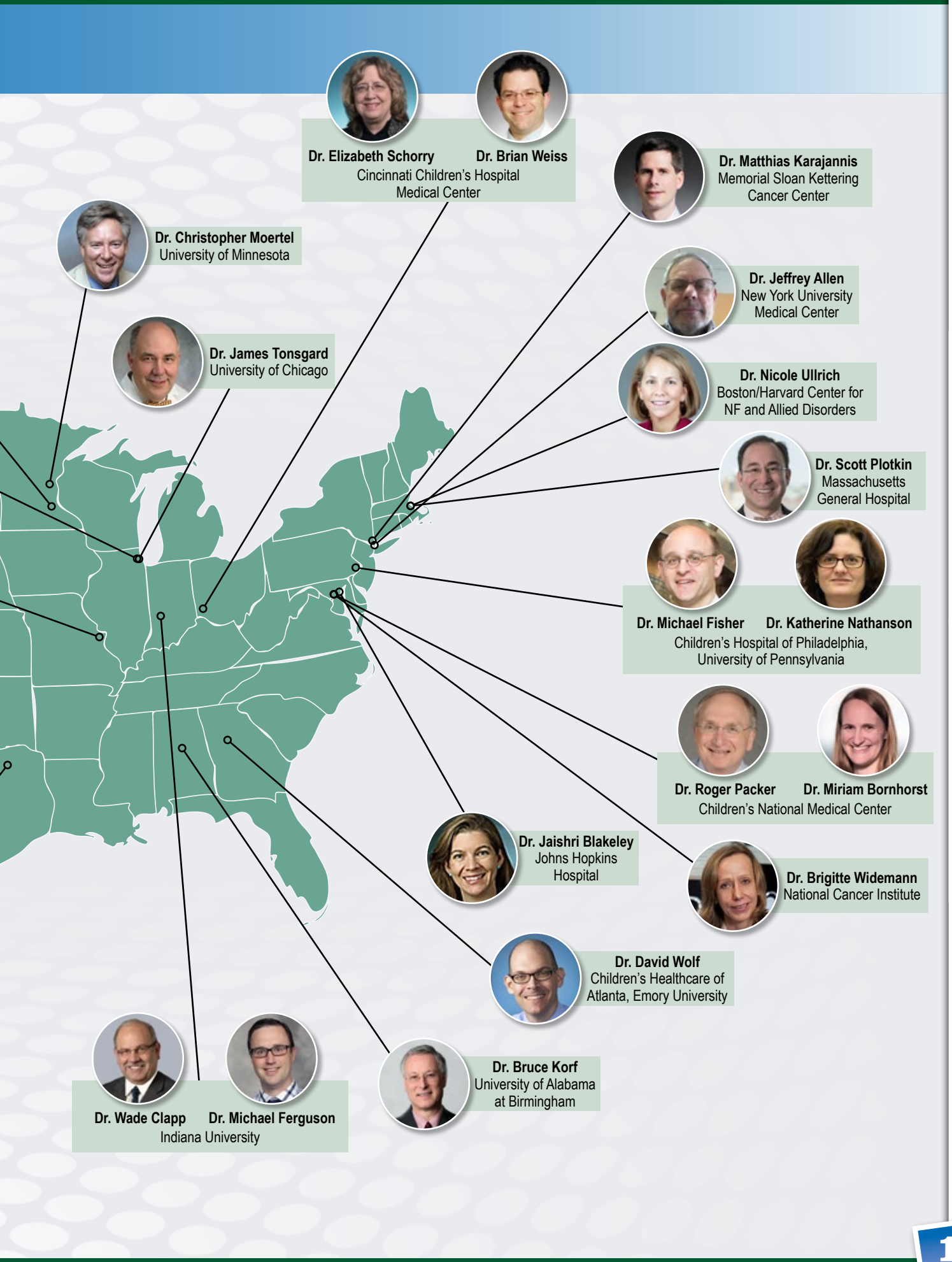
University of Texas
Southwestern



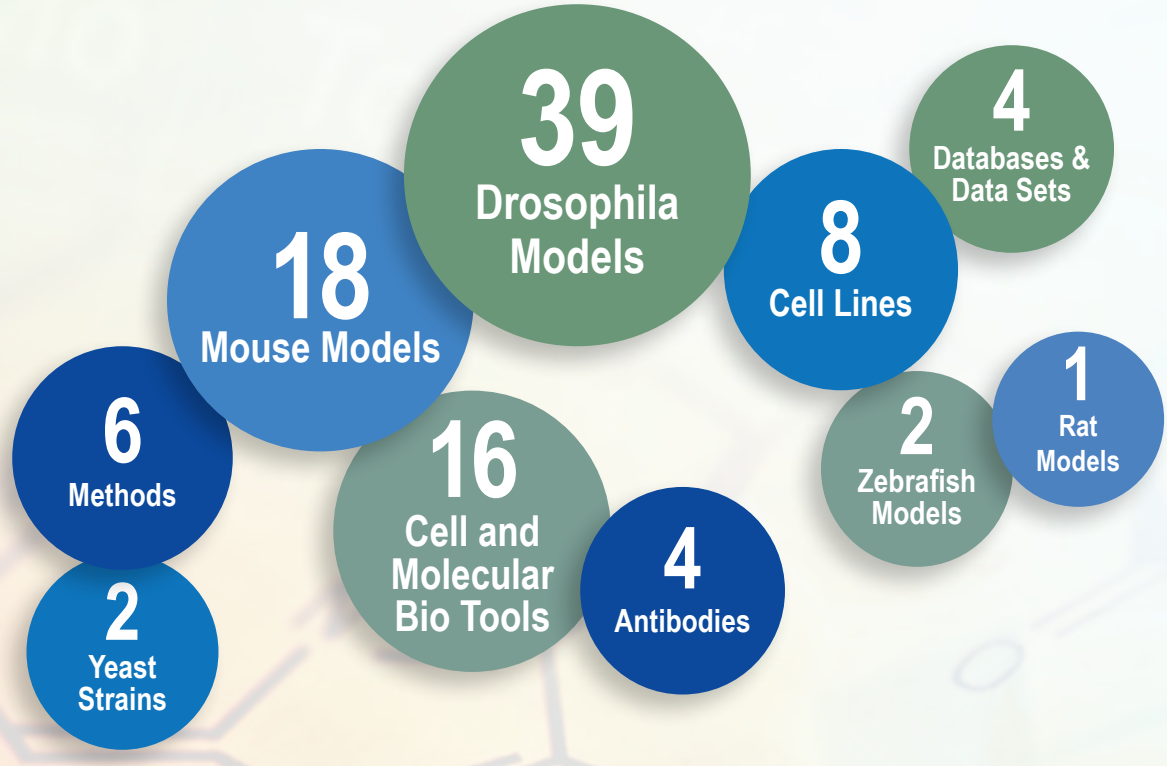
Dr. Belinda Barton
Children's Hospital at Westmead,
University of Sydney


Dr. Elizabeth Schorry
Dr. Brian Weiss
Cincinnati Children's Hospital Medical Center
Dr. Matthias Karajannis
Memorial Sloan Kettering Cancer Center
Dr. Christopher Moertel
University of Minnesota
Dr. Jeffrey Allen
New York University Medical Center
Dr. James Tonsgard
University of Chicago
Dr. Nicole Ullrich
Boston/Harvard Center for NF and Allied Disorders
Dr. Scott Plotkin
Massachusetts General Hospital
Dr. Michael Fisher
Dr. Katherine Nathanson
Children's Hospital of Philadelphia, University of Pennsylvania
Dr. Roger Packer
Dr. Miriam Bornhorst
Children's National Medical Center
Dr. Jaishri Blakeley
Johns Hopkins Hospital
Dr. Brigitte Widemann
National Cancer Institute
Dr. David Wolf
Children's Healthcare of Atlanta, Emory University
Dr. Bruce Korf
University of Alabama at Birmingham
Dr. Wade Clapp
Dr. Michael Ferguson
Indiana University

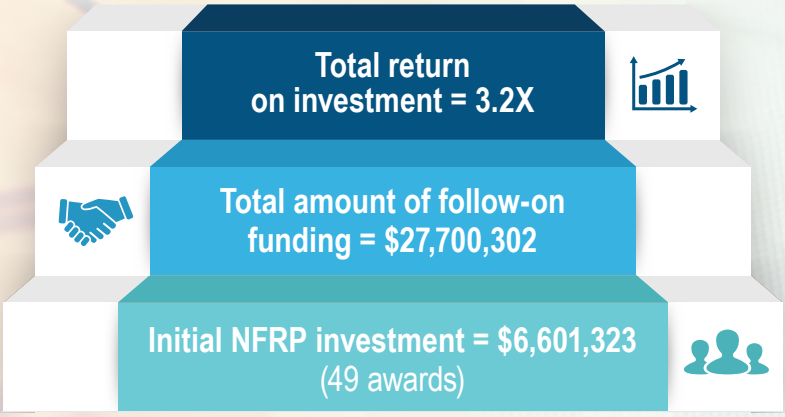
Accomplishments

Research Resources

The NFRP now offers a service on our website featuring a list of available NF research resources. In addition to providing access to resources developed through our program, Principal Investigators (PIs) can contact other sites. Our goal is to facilitate and speed NF research by publicizing new resources and aiding collaborations. The list displays available resources, as well as repository or PI contact information. Please contact the repository or PI directly for information and requests.



Exploration – Hypothesis Development Award



Data includes awards from 2004-2016

New Investigator Award (NIA)

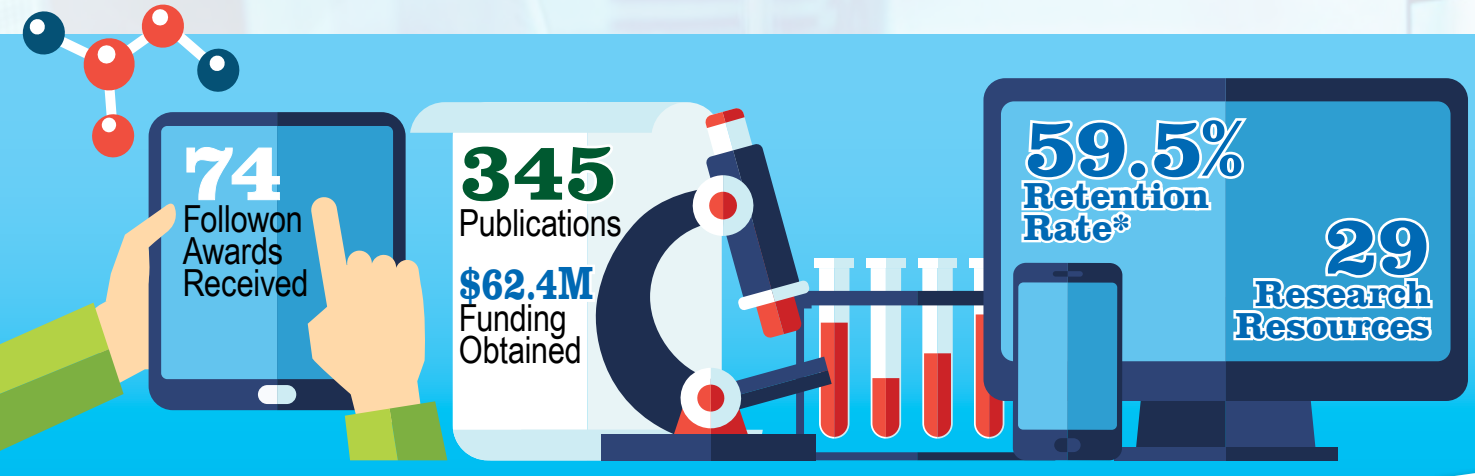
The NFRP has utilized the NIA to invest in research conducted by promising new independent investigators or established investigators transitioning from other career fields that can bring new research ideas, techniques, or expertise into the field of NF research.

KEY FACTS

- **The NFRP has supported 73 new investigators from 1999 to 2018, with over $42M in awards.**
- **According to survey results, 59.5% of NIA recipients remained in the field of NF research at least 5 years after their initial award ended.**
- **New investigators have published over 345 scientific articles, of which 140 were directly related to their NIA projects.**
- **More than 74 follow-on awards valued at millions of dollars of additional funding have been obtained by NFRP NIA recipients.**
- **Notable NIA recipients:**
  - Michael Fisher, M.D. in 2016 became the Chair of the NF Clinical Trials Consortium Steering Committee.
  - Karen Cichowski, Ph.D. was named the 2017 Friedrich von Recklinghausen Award Recipient by the Children's Tumor Foundation.
  - Fernando Camargo, Ph.D. and Marius Wernig, M.D., Ph.D. were named Howard Hughes Medical Institute Faculty Scholars in 2016.

"The impact of the New Investigator Awards from the NFRP cannot be overstated. My NIA allowed my laboratory to start a research direction that we would have otherwise not been able to pursue, and we gained detailed mechanistic insights at the atomic level of NF2. It also allowed me to obtain further funding to continue this important and significant research program, which resulted in major discoveries on the structure and function of the protein responsible for NF2. We were able to publish these discoveries in collaboration with leaders in the field of NF2 research. I was invited to present our discoveries as a speaker at the Joint Global Neurofibromatosis Conference in Paris in 2018. The NIA provided the foundation which has allowed me to train and excite a new generation of scientists on the importance that NF2 research has on the lives of patients. I am excited about the discoveries we will make in the next few decades, and their potential impact to enhance the quality of life for neurofibromatosis patients."

Tina Izard, Ph.D., The Scripps Research Institute



*includes all recipients who are 5 years past the end of their award's period of performance

Fostering Talent in NF Research

In FY16, two NIAs were awarded.

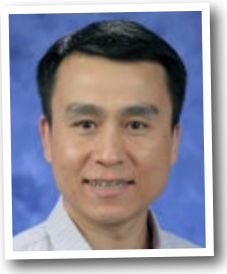
Dr. Maria Clara Franco, initially an Assistant Scientist at the University of Central Florida, is now an Assistant Professor in the Department of Biochemistry and Biophysics at Oregon State University. Dr. Franco aims to apply her expertise in redox biology and cell metabolism to the field of NF2. She was introduced to the field by Dr. Cristina Fernandez-Valle, an expert in NF2 and Schwann cell biology and a close collaborator and mentor. Dr. Franco was the first to demonstrate that tyrosine nitration, an oxidative modification to proteins that occurs in pathological and inflammatory conditions, regulates key processes of tumor cell metabolism. Using human and mouse cell culture models of NF2 in combination with intracellular cell signaling arrays and metabolic profiling, she proposes to determine the metabolic phenotype of NF2-associated SC, then identify the signaling pathways that are regulated by tyrosine nitration and how they promote schwannoma cell proliferation and survival. If successful, Dr. Franco's work would potentially identify key oxidized proteins and their relationship to NF2 tumorigenesis, resulting in novel therapeutic targets for NF2.

Dr. Erin Marcotte of the University of Minnesota, Twin Cities, is an Assistant Professor of pediatric epidemiology and clinical studies. She is interested in how maternal health and early childhood nutrition affect children's cancer. Dr. Marcotte proposes to investigate the correlation between maternal folic acid during the perigestational period and its effect upon NF1 cancer in their offspring. Initial studies will be conducted in a murine NF1 flox model in which varying dosages of dietary folic acid will be administered. She also proposes to conduct a pilot epidemiologic clinical study in which environmental, genetic, and nutritional information will be collected from NF1 families to understand how these factors modify risk for NF1-related tumors. Dr. Marcotte is one of the first in the field of NF research to investigate whether maternal intake of folic acid affects risk of NF1-related tumors in offspring. As such, findings from this study have the potential to lead to a better understanding of NF1 etiology and the advancement of new therapies or tumor prevention.

In FY17, three NIAs were awarded.

Dr. Renyuan Bai, while at the Technical University of Munich, focused on the nucleophosmin-anaplastic lymphoma kinase oncoprotein in leukemia and lymphoma. During this time, he identified and characterized several key cellular pathways, which assisted in the development of therapeutics. Later, when he took a lead position in protein engineering at Roche Vitamins, Ltd./DSM, he successfully engineered mevalonate kinase. Dr. Bai took his knowledge and skills to Johns Hopkins University's neurosurgical department, where he focused on therapies for neurological tumors and began work with Dr. Verena Staedtke, the Director of Pediatric Neurofibromatosis. Through this collaboration, Dr. Bai's interest in NF1-related tumors began, specifically in gene replacement therapies for the NF1 driver mutation. Dr. Bai and Dr. Staedtke propose to optimize a virus-based gene therapy for use in NF1-caused malignant peripheral nerve sheath tumors (MPNSTs). Gene therapy is presently an unexplored area of treatment for MPNSTs. This preclinical research, which includes developing an engineered adeno-associated virus vector and a humanized mouse model with MPNST and immunity traits, could lead to future clinical trials to move this treatment to the clinic. If successful, this work will be the first treatment for NF1 patients that corrects the molecular cause of MPNSTs.

Dr. Rebecca Dodd developed genetically engineered mouse models at Duke University to study multiple different variables concerning NF1-associated MPNSTs. The models she developed are used in multiple laboratories, and for her work on these NF1-deficient models, she received the Young Investigator Fellowship Award from the Childrens Tumor Foundation (CTF) in 2012. Dr. Dodd is currently an Assistant Professor at the University of Iowa, where she continues to design mouse models to improve oncology research and address critical questions in NF1 tumor biology. With the FY17 NFRP NIA, Dr. Dodd proposes to gain a better understanding of the cellular biology in MPNSTs by using CRISPR-Cas9 technology to model tumor biology in mice, specifically the role of mast cells and monocytes. To conduct this research, Dr. Dodd plans to collaborate with the Sarcoma Multidisciplinary Oncology Group at the University of Iowa, directed by Drs. Benjamin Miller and Munir Tanas of the Holden Comprehensive Cancer Center. If successful, this research will demonstrate that inhibiting specific immune cells could slow the growth of MPNSTs and therefore validate new cellular targets for treatment, such as myeloid cells or their cytokines.



Dr. Wei Li conducted his post-doctoral research with Dr. Filippo Giancotti at Memorial Sloan Kettering Cancer Center and focused on deciphering the function and regulation of the Merlin/NF2-Hippo pathway. For this research, he used mammalian cell culture and mouse tumor models, furthering his graduate work at Albert Einstein College of Medicine, where he used Drosophila to study cell biology relevant to tumorigenesis. Dr. Li's research in both areas led to publications in *Cell*, and in 2009, he received the Young Investigator Award from the CTF. Currently, Dr. Li is an Assistant Professor at Pennsylvania State University's Hershey Medical Center in the Department of Pediatrics, where he plans to continue developing his expertise in NF2 and calcium signaling in cancer. With the FY17 NFRP NIA, he proposes to investigate the recently discovered link between calcium and Merlin post-translational modification by the protein, ubiquitin. Examining the modification of Merlin, a multifunctional protein, could demonstrate the mechanism of Hippo pathway regulation and tumor suppression. If successful, this study will open avenues for the development of more effective therapies by providing a better understanding how Merlin is dysfunctional in NF2 individuals.

Consumer Perspectives

Michelle Hirsch Donovan: Taking Control of Neurofibromatosis Through Consumer Action

Riley Donovan was born prematurely, but seemingly healthy, at 36 weeks. She had low muscle tone, called hypotonia, but the reason for this was unknown. Riley received physical and occupational therapy from 3 months to 3 years of age to improve her muscle tone. Riley's mother, Michelle, still remembers the first day that Riley walked; she was 20 months of age, and it was if she had just finished a marathon! However, between Riley's 4th and 5th birthdays, Michelle started to notice some concerning traits. Riley started to show structural abnormalities within her right lip and cheek, and she had several light brown pigmentation spots, known as café au lait spots, which can be indicative of NF1. As a pathologist, Michelle had learned about NF in medical school and was worried, but hoped that she was wrong. Michelle presented these symptoms to Riley's pediatrician, who agreed with her fears. After clinical testing, Riley was diagnosed with the genetic disorder NF1, which, in hindsight, explained her low muscle tone at such a young age. One of the hallmarks of NF1 is the presence of benign but infiltrative tumors that are difficult to treat, called plexiform neurofibromas. Riley had her first magnetic resonance imaging test at 5 years of age and was found to have three of these tumors in her head and neck.

Riley is now 12 years old and receives annual screening by NF specialists. Thankfully, her tumors are slow-growing, and she has undergone only one minor NF-related surgery. Michelle and her family are waiting until Riley is a little older before considering any major surgeries. In addition to the challenges of NF1 tumors, Riley wears a brace for scoliosis, which is NF-related, and takes medication for attention deficit hyperactivity disorder. But Riley has persevered; she loves to play softball and spend time with her friends and, in many ways, is a normal pre-teen girl.

Michelle has found that the hardest part of dealing with an NF1 diagnosis is the fear, worry, and uncertainty that accompanies it. However, the unknowns in her daughter's future are what drive her family's approach to daily life. They refuse to allow NF1 to control their lives; instead, they focus on what they can control. Michelle is very active in the NF community through NF, Northeast (NFNE), an advocacy organization where she works with support groups and raises awareness for NF. She has completed seven Coast to the Cure NF Bike Rides and has personally raised nearly $112,000 for NFNE. In addition to her advocacy roles, Michelle is a consumer reviewer for the DoD's NFRP. Through the NFRP, Michelle is working to ensure that the NF consumer voice is heard and is positively impacting the review of NF research proposals to ensure wise investment in the research community to best fight NF and improve the lives of patients and families. Michelle feels that her participation in the NFRP is one of the most important things she does for her daughter and others affected by NF.

Chad Leathers: A Story of Persistence in the Fight Against NF

Schwannomatosis is not a word that is on most people's radar. However, for Chad Leathers, the disease described by this word has profoundly changed his life. His youngest brother, Drew, suffered with schwannomatosis, a rare form of NF, for nearly 15 years before losing his battle. For Chad, there was the feeling that not enough was being done to combat NF. So he closed the doors to his small business, completely changed his career path, and moved to New York City to fund-raise full time for the CTF.

Chad is now the Founder and Executive Director of Cupid Charities, as well as a CTF board member. Cupid Charities started the Cupid's Undie Run as a fundraising platform for specific research efforts, and they have provided the CTF with nearly $8M in the last 6 years. When he looks back over the last 10 years, Chad says that tremendous strides have been made, but he believes that there is still a monumental hill to climb in fighting NF. "Persistence is the only way to the top; there are no shortcuts," he says.

Chad heard of the NFRP early during his fundraising career and recognized it as a tremendous funding source that is important to the success of finding treatments for NF. He was pleased to learn that it is managed by the DoD and believes that its methodology and consistency provides a great system for funding management and accountability. While serving as a Consumer Reviewer during NFRP peer review, he was astounded at the complexity of the proposals that were submitted, but equally astonished at the elegance and smoothness of the management of the program. He feels that the scientific community behind NF research and the NFRP experience is a stellar representation of the persistence needed to succeed in treating NF.

Chad considers his consumer advocate role as vital to the success of the NFRP. He served as a team member in the review process to assist in addressing both endpoint applications and prioritizing patient needs. While the experience shed light on the vastness of the research landscape and the incredible knowledge and intelligence within the scientific community, he stated that there were numerous times when his input provided a new insight that may have otherwise been missed, stressing the importance of the consumer advocate voice. To those in the consumer advocate community, he would highly recommend serving on a review panel with the NFRP.

"When I was nominated to participate on the NFRP peer review panel, I was anxious. My college degree is in economics, so reviewing grant proposals involving cellular molecular biology was entirely foreign to me. I had previously advocated for the allocation of funds to this program, but now was tasked with helping to assess the scientific merit of each research application and their impact on the NF community. I felt an enormous sense of responsibility—not only to my son, but to all those affected by NF. My anxiety was eased by the incredibly talented researchers and clinicians in the room. As a peer reviewer, I soon realized that my frontline voice matters. I believe the NFRP is so efficiently run because it is managed by the DoD. It is a results-oriented program with a real return on investment that gives hope to NF patients and their families. I am inspired by the brilliant minds of the scientific community who are working to decrease the clinical impact of NF."

Gregg Erickson, Consumer Advocate Peer Reviewer

Promoting research directed toward the understanding, diagnosis, and treatment of NF1, NF2, and schwannomatosis to enhance the quality of life for persons with those disorders that impact Service members, Veterans, and the general public.

For more information, visit
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or contact us at:
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(301) 619-7071

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