CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS

Neurofibromatosis Research Program

Decreasing the Clinical Impact of Neurofibromatosis

For more information, please visit
cdmrp.health.mil/nfrp

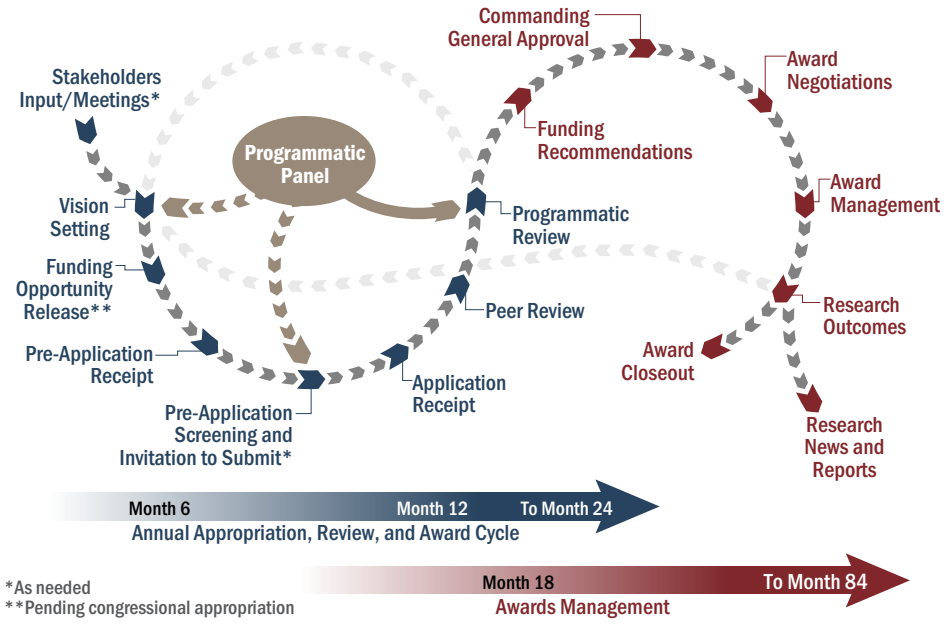
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

HISTORY

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 $19.4 billion in appropriations from its inception through fiscal year 2022 (FY22). 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. The goal of the two-tier process is to develop funding recommendations that balance the most meritorious science across many disciplines and offer the highest promise to fulfill the programmatic goals set forth in the relevant funding opportunity.



Review Process Cycle

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 serve as full voting members and 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. This helps to maintain the focus of the program on research that is relevant and has the potential to make a significant impact on the community affected.

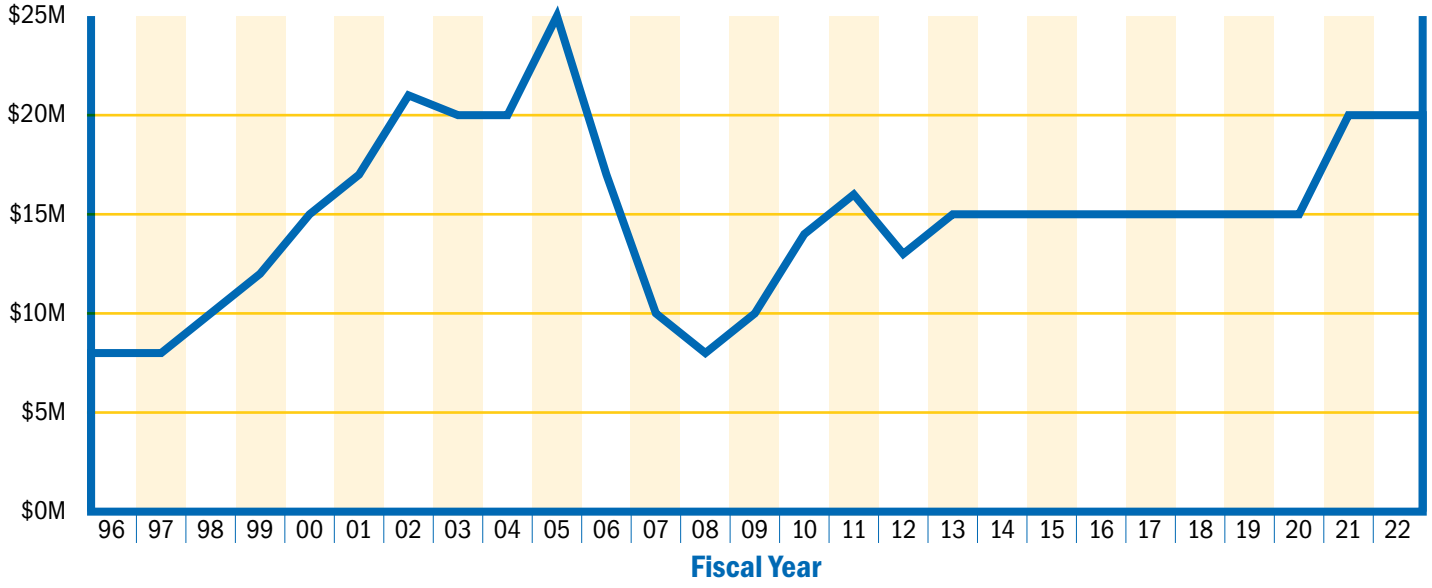
NEUROFIBROMATOSIS RESEARCH PROGRAM

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**. NF1 is most commonly diagnosed in children and NF2 and schwannomatosis are typically diagnosed at the beginning of adulthood. This condition is typically chronic and there is no cure yet. Fewer than **200,000** Americans are diagnosed every year, and it occurs in both sexes and in all races and ethnic groups.

VISION:

Decrease the clinical impact of neurofibromatosis

FY96–FY21 NFRP Appropriations



HISTORY

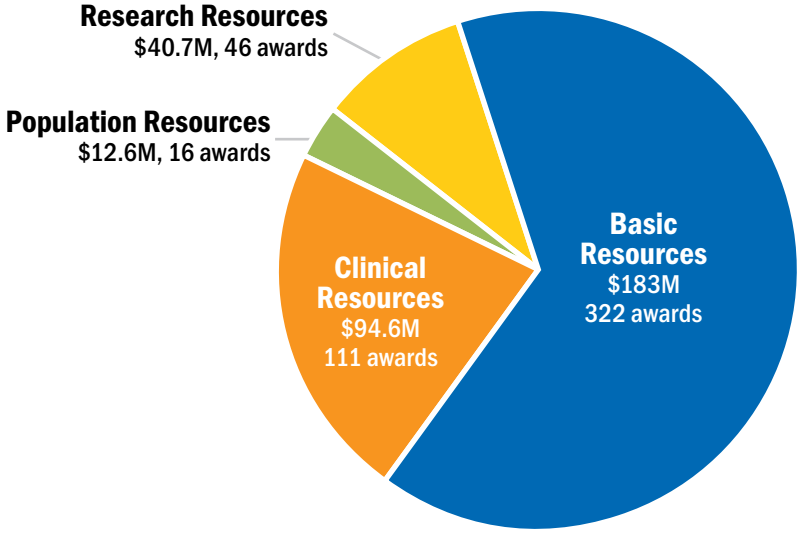
The NFRP was first funded in FY96 and has since been appropriated a total amount of **$447.85M**, including FY23.

STRATEGIC GOALS ARE:

- Foster Basic and Exploratory Research
- Facilitate Rapid Testing of Potential Therapeutics
- Increase Research Capacity
- Encourage Research in Areas of Critical Interest to NF Patients

The NFRP has funded **471** basic, clinical, population-based, and resources research projects.

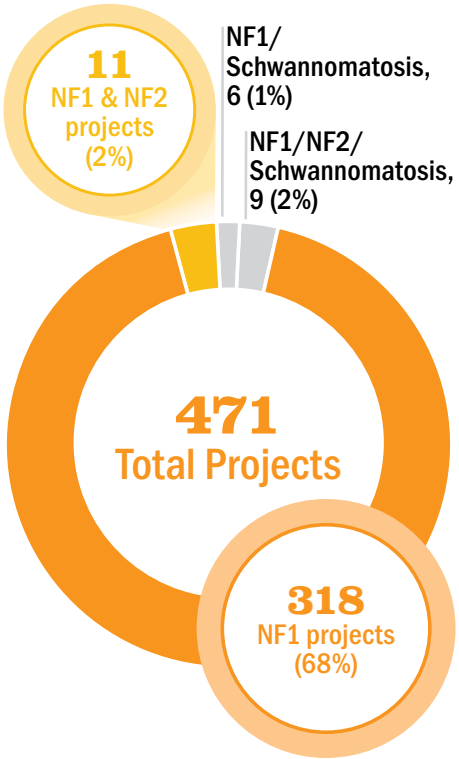
FY96-21 NFRP-Funded Awards by Strategic Goals



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 rest 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 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).

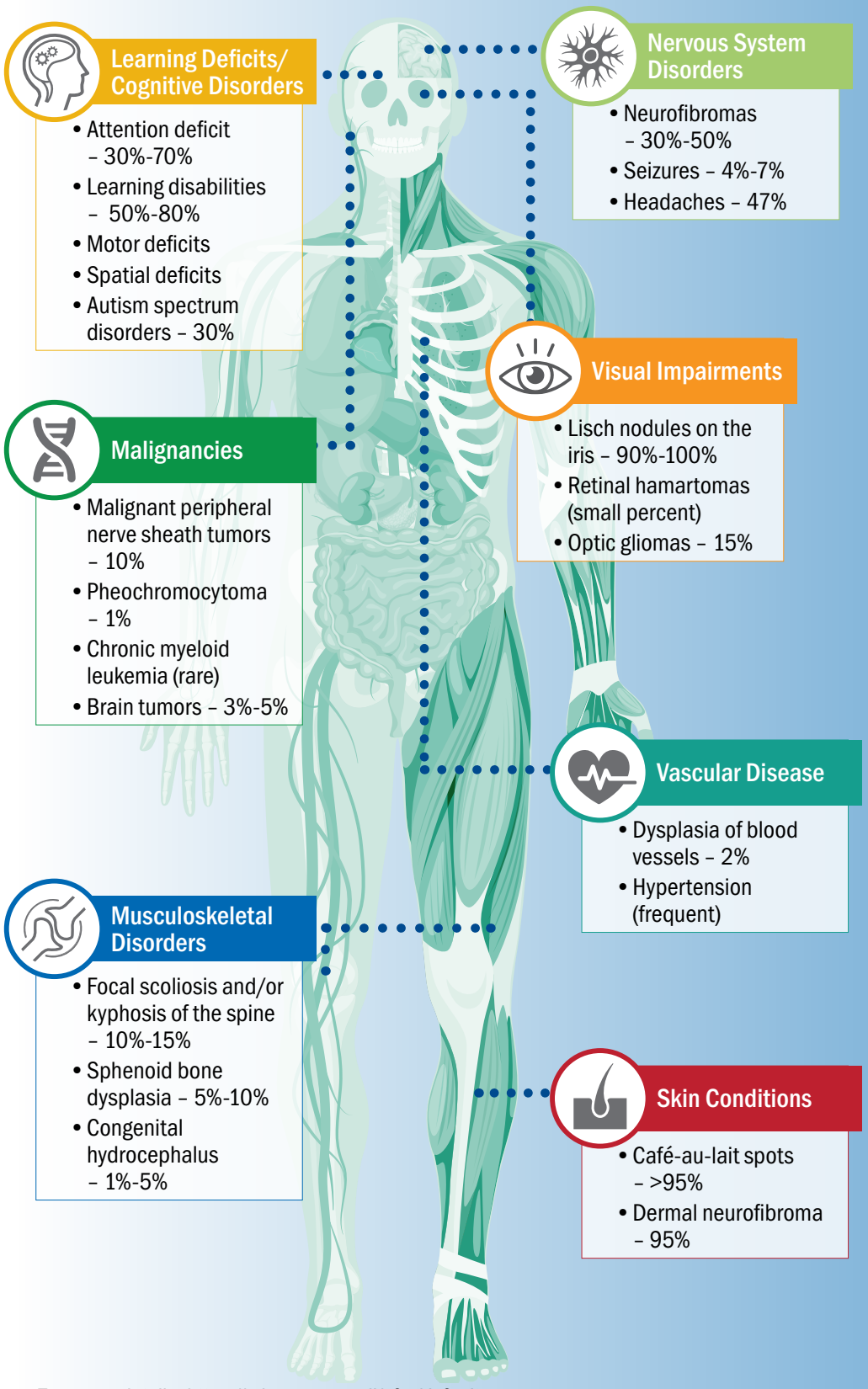
The NFRP has funded:



NF1 accounts for **73%** 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

Pharmacological Alk Inhibition Impacts Behavior and Cognition in Adult NF1 Mutant Mice

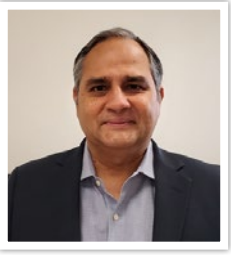
Dr. Jacob Raber, Oregon Health and Science University

NF1 is a negative regulator of Ras, a proto-oncogene and activator of the mitogen activated protein kinase (MAP kinase) cascade that is often activated by receptor tyrosine kinases. Previous research in drosophila and mouse studies support a genetic interaction between NF1 and Alk, a receptor tyrosine kinase and activator of the Ras-MAP kinase cascade. Orally active Alk inhibitors have been developed for human tumors and have been shown to rescue cognitive impairments in NF1 mutant drosophila and improve spatial memory retention in NF1 mutant mice. Further study has been necessary to assess the effects of prolonged pharmacologic Alk inhibition on sleep, hippocampal neurogenesis, and depressive and anxiety-like behaviors.

With support from an NFRP FY16 Investigator-Initiated Research Award, Dr. Jacob Raber aimed to test the hypothesis that the pharmacologic inhibition of Alk has short- and long-term effects on behavioral performance, including measures of anxiety, depressive-like behaviors, circadian activity, cognitive performance, and neurogenesis in heterozygous NF1 mutant mice treated in adulthood. Specifically, they tested the optimal timing and dose of pharmacologic Alk inhibition to achieve maximal cognitive performance, the potential benefit of Alk inhibition on altered circadian activity levels, and potential adverse behavioral and cognitive effects of Alk inhibition in wild-type and NF1 heterozygous mice. To test these questions, the Alk inhibitor CH5424802 (Alectinib) was provided to NF1+/- mice in a variety of doses. Findings revealed that short-term treatment (starting 10 days prior to behavioral testing) with Alectinib improved spatial learning of the male mice in the 3.6 mg/kg treatment group, especially during the second and third hidden platform sessions in the water maze test. Long-term treatment (24 weeks) with Alectinib rescued impairments in object recognition and cognitive performance in the water maze. Additionally, their findings determined the effect of the parental gene carrier on the behavioral phenotype of the offspring. Specifically, (1) it appears to matter whether the mother or father were the NF1 HET carrier and (2) mice that received the NF1 gene from their father (paternal carrier) showed increased activity during the dark period (active period) and improved cognitive flexibility with the Alk inhibitor. Furthermore, the Alk inhibitor increased baseline activity during the fear-conditioning test when the mice received the NF1 gene from their mother (maternal carrier).

Taken together, these results indicate that the Alk inhibitor affects behavioral and cognitive phenotypes and that responsiveness to Alk inhibition in heterozygous NF1 offspring may depend on whether the parental carrier is maternal or paternal. Overall, these data and interesting findings support the therapeutic potential of pharmacological Alk inhibition in NF1+/- mice and ultimately may benefit NF patients.

References:
Krenik D, Weiss JB, Raber J. 2021. Role of the parental NF1 carrier in effects of pharmacological inhibition of anaplastic lymphoma kinase in Neurofibromatosis 1 mutant mice. Brain Research. 1769:147594. doi:10.1016/j.brainres.2021.147594.



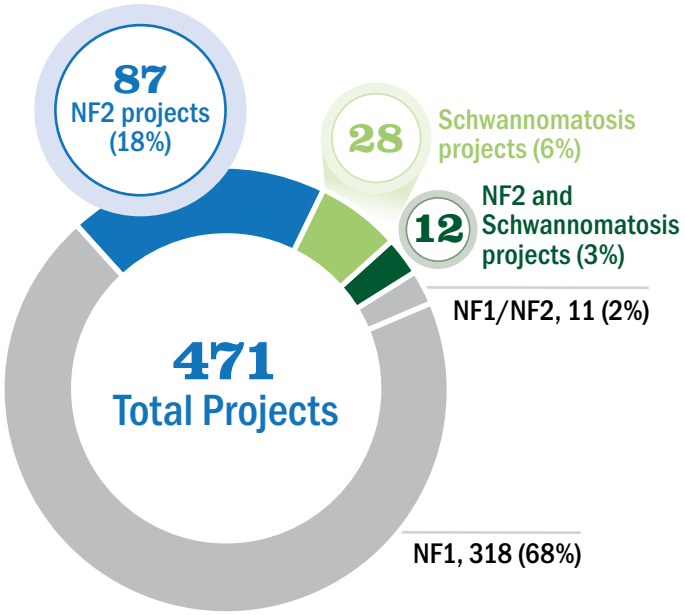
"All panel members, many of whom are leaders in neurofibromatosis and schwannomatosis research and advocacy, take the mission of the NFRP very seriously. Our commitment to reducing the burden for families affected with these conditions is paramount. The panel serves a key role in setting the vision for future research, which we do by debating the areas of research that are under developed, and naming these as priority areas for funding. Recognizing that modern scientific research is heavily dependent on "team science," which takes advantage of the expertise of a multidisciplinary group of investigators, we recently added a new mechanism of funding designed to promote such research in neurofibromatosis and schwannomatosis. As a result of robust advocacy, we were fortunate to see a recent expansion in the congressionally approved budget of the NFRP, which allowed us to allocate much needed funds towards development of potential therapies for neurofibromatosis and schwannomatosis."

Sanjay Bidichandani,
FY16-Present Programmatic Panel Member,
FY20-22 Panel Chair

NF2 AND 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.



Together, NF2 accounts for **25%** and schwannomatosis accounts for **6%** of the total number of projects funded by the NFRP.

Some of the most prevalent complications of NF2 and 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%

Reprogramming the Tumor Microenvironment to Improve Hearing and Treatment Efficacy in NF2 Vestibular Schwannoma

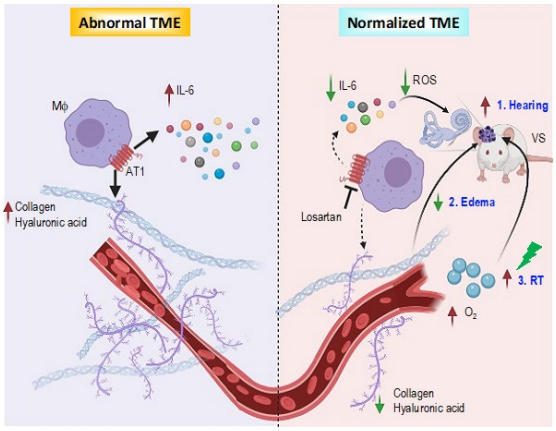
Lei Xu, M.D., Ph.D., Massachusetts General Hospital

Konstantina Stankovic, M.D., Ph.D., Massachusetts Eye and Ear Infirmary

NF2 is a genetic disorder characterized by vestibular schwannomas (VSs), an overproduction of Schwann cells developing into tumors.[3] As the VSs grows, pressure increases on the balance and hearing nerves, which can lead to hearing loss, tinnitus, and loss of balance.[1] Unfortunately, the current NF2 treatment of radiation therapy (RT) can exacerbate hearing loss as well. Dr. Lei Xu has received two NFRP awards, an FY15 New Investigator Award and an FY19 Investigator-Initiated Research Award, to support research aimed to mitigate VS-related hearing loss while minimizing the toxicity of radiation therapy (RT). Dr. Xu proposed using lower doses of RT with losartan, an antihypertensive drug designed to inhibit fibrotic and inflammatory signals and shown to reduce VS-related hearing loss. Her collaborator who co-led the study is Dr. Konstantina Stankovic of Stanford University. Results were published in 2021 in the journal, *Science Translational Medicine*.[5]

First, Dr. Xu's team used NF2 mouse models to confirm that losartan normalized the tumor microenvironment (TME). The TME propels the progression of malignant cancer growth and the resistance to treatments.[2] Losartan reduced schwannoma extracellular matrix (ECM), normalized tumor vasculature, and increased oxygen delivery. The team performed histological analysis that showed that schwannoma ECM reduction led to decreased pressure on the blood vessels and increased perfusion, which decreased nerve edema. Additionally, losartan is known to affect the IL-6/STAT3 signaling pathway involved in immune regulation, inflammation, and cancer growth, by promoting tumor immune cell growth in the TME.[2,4] In collaboration with Dr. Stankovic, while using patient samples, the team demonstrated that increased tumor-derived IL-6 was linked to a reduction in cochlear cell viability, which can affect hearing. They found that losartan treatment reduced neuroinflammation by decreasing tumor-associated macrophages (TAMs), corroborating their finding that RNA-sequence analysis of patient samples indicated patients with poor hearing had higher levels of TAMs.

RT promotes fibrogenic signaling, which increases the volume of tumor ECM leading to a common side effect of hearing loss. Dr. Xu's team combined RT with losartan, using low-dose RT (5 Gy), and found the combination to be just as effective as a higher dose (10 Gy) of RT alone in treating NF2 mouse model. Furthermore, mice receiving the combined treatment lived 50% longer than those receiving only RT. Immunohistochemistry staining of the treated NF2 mouse model and MTT assay of in vitro NF2 schwannoma cell model (evaluating tumor cell presence and viability) confirmed the normalizing effects of losartan on the TME and reduction of tumor growth cells by RT treatment. For more representative translatability, Dr. Xu's and Dr. Stankovic's team developed a patient-derived xenograft mouse model and confirmed that losartan and RT combination therapy inhibit tumor growth more than RT treatment alone.



Dr. Xu's and Dr. Stankovic's research has improved the understanding of how losartan affects sensorineural hearing loss as a therapeutic for VS. This research provides an opportunity for future investigations into VS therapy, including possibly expanding losartan uses to treat other neurological symptoms.

References:

1. https://www.nidcd.nih.gov/health/vestibular-schwannoma-acoustic-neuroma-and-neurofibromatosis

2. Jia H, El Sayed MME, Smail M, Mosnier I, et al. 2018. Neurofibromatosis type 2: Hearing preservation and rehabilitation. Neurochirurgie. Nov;64(5):348-354. doi: 10.1016/j.neuchi.2018.09.003. Epub 2018, Oct 9. PMID: 30314805.

3. Wu L, Vasilijic S, Sun Y, et al. 2021. Losartan prevents tumor-induced hearing loss and augments radiation efficacy in NF2 schwannoma rodent models. Science Translational Medicine. Jul 14;13(602):eabd4816. doi: 10.1126/scitranslmed.abd4816. PMID: 34261799 PMCID: PMC8409338.

4. Johnson DE, O'Keefe RA, Grandis JR. 2018. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nature Reviews Clinical Oncology. Apr;15(4):234-248. doi: 10.1038/nrclinonc.2018.8. Epub 2018, Feb 6. PMID: 29405201; PMCID: PMC5858971.

5. Manhiani MM, Seth DM, Banes-Berceli AK, et al. 2015. The role of IL-6 in the physiologic versus hypertensive blood pressure actions of angiotensin II. Physiological Reports. Oct;3(10):e12595. doi: 10.14814/phy2.12595. PMID: 26486161; PMCID: PMC4632961.

NF THERAPEUTIC DEVELOPMENT RESEARCH EFFORTS

CLINICAL TRIALS

Resiliency Training in Adolescents with NF1 and NF2: A Randomized Controlled Trial via Secure Live Video to Improve Emotional, Social, and Physical Health

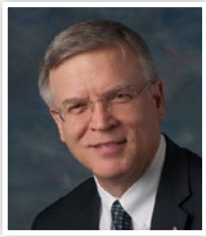
Ana-Maria Vranceanu, Ph.D., Massachusetts General Hospital, Boston, Massachusetts

An increasing number of adolescents have received early diagnoses of NF1 and NF2 due to advances in genetic research. The challenge of managing certain adolescence-related issues, such as development of social relationships, sense of self, and emotional balance, can prove more challenging for NF adolescent patients, who also must manage NF-related concerns. Adolescents with NF1 and NF2 frequently report that they experience distress or psychosocial difficulties due to their NF1/2 symptoms, which impacts their physical, psychological, social, or environmental quality of life. To provide an intervention mechanism to meet the needs of NF1/2 adolescent patients and help manage these difficulties, Dr. Ana-Maria Vranceanu and her team have developed a clinical protocol called Resilient Youth for NF (RY-NF). With support of an FY18 Clinical Trial Award, Dr. Vranceanu will test the efficacy of the RY-NF intervention plan compared to previously established intervention plans, which are not specific to the adolescent population.

RY-NF is thought to be the first intervention plan catered exclusively to the adolescent population and would be delivered adjunct to medical care. With a previously funded FY16 Clinical Trial Award, Dr. Vranceanu and her team provided a similar intervention and training plan for adults. As a result of this research, they recognized the need to develop a plan specifically for adolescents that focuses on more adolescent-appropriate issues (such as school sports involvement, doing homework, dealing with bullying, and making friends). The hypothesis is that the RY-NF intervention plan will increase the likelihood of an improvement in quality of life, depression, anxiety, and pain management over the current Health Education for NF plan. The goal of this study is to teach adolescents coping mechanisms for the NF symptoms, effectively called NF resiliency skills, which would allow adolescents to ultimately allot less stress toward NF and adolescent-related issues and improve their quality of life in these areas. The team plans to enroll 200 adolescents to participate in their clinical trial, who will take part through video conferencing in a group intervention structure and provide feedback on their ability to integrate these NF resiliency skills over the course of a year. Dr. Vranceanu and her team aim to promote and spread this intervention option, if successful, to better serve the adolescent population, while working with providers, NF organizations, and the Children's Tumor Foundation.

"Serving as a reviewer on the NFRP panel has definitely further stimulated my interest and passion for medicine and science. I was excited to be nominated last year by the Littlest Tumor Foundation to be a consumer reviewer. I really enjoyed reading and reviewing the applications. I also felt a strong responsibility because I was representing the NF community and wanted to ensure I represented their needs well. I think the NFRP community is not afraid to take risks (high-risk), so that they can make the largest impact in the communities. I look forward to seeing new treatment options coming from the funded NF awards a few years from now."

Hannah Kim,
FY21 Consumer Peer Reviewer



Prospective, Randomized, Placebo-Controlled Phase 2 Trial of Aspirin for Vestibular Schwannomas

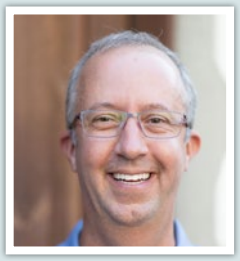
Bradley Welling, M.D., Ph.D., Massachusetts Eye and Ear Infirmary

Although a less common NF condition, NF2 generates noncancerous tumors that are beset with significant pain and paralyzing effects and can lead to early loss of life. A very distinct indicator of NF2 is the presence of VSs, which give rise to hearing loss and tinnitus. Current therapies are very costly and carry great probability of further injuries. Therefore, research for alternative and effective treatments with little to no negative side effects is required.

Aspirin, the most common type of salicylates, otherwise known as non-steroidal anti-inflammatory drugs (NSAIDs), presents as a suitable option because it has been shown to treat pain and inflammation and also possesses chemoprevention properties. Dr. Welling and his team generated preclinical and retrospective clinical data on salicylates that support this premise and, through an FY16 Clinical Trial Award, they propose to investigate two research aims: (1) to ascertain whether aspirin medication inhibits the development of VS and (2) to investigate and determine the amounts of aspirin and other inflammatory cytokines and/or mediators present in the blood correlate with treatment response (VS tumor volume changes, hearing improvement).

Individuals aged 12 years and older with no known aspirin allergy will be recruited in a randomized controlled trial of 325 mg of aspirin or placebo twice daily. Pediatric patients weighing less than 50 kg will be given a reduced dose of 81 mg of aspirin or placebo twice daily. The study (NCT03079999) experienced some administrative delays that have been resolved, and participants are currently being recruited.

Potentially positive impacts could accrue if the drug becomes the first Food and Drug Administration (FDA)-approved medication for NF2. It would provide a safe(r), effective, affordable, and readily available over-the-counter NSAID for patients. It could also translate to use in other diseases, especially schwannomatosis, that sometimes present with VSs and could also be deployed in combination with other therapies.



"I had experienced back pain in 2004 and was diagnosed with a degenerative disc. I ignored growing pain for 10 years before my GP said the lump on my lower back causing pain was not related to a degenerative disc. Delayed and misdiagnosis is common with rare diseases. I was honored to be selected to participate in the 2021 CDMRP NF grant funding review as a patient reviewer. It was a well-organized process that allowed time to prepare my feedback in a thoughtful and timely manner. I was well prepared for our online session with a variety of experts and I was one of the 'experts.' I would urge patients and caregivers to take advantage of an opportunity to help guide the future of NF research, as I believe our participation is vital and respected throughout the process. My participation as a patient representative will hopefully translate into shorter diagnosis period for patients in the future."

Dale Berg,
FY21 Consumer Peer Reviewer

Using Selumetinib to Prevent Future Plexiform Neurofibroma Growth and Morbidity in Children with Neurofibromatosis type 1

Andrea Gross, M.D., National Cancer Institute (NCI), National Institutes of Health (NIH)

Laura Metrock, M.D., University of Alabama at Birmingham

Plexiform neurofibromas (PN) are tumors that grow along the nerve linings and are found in 30-50% of individuals with NF1.[6] Despite being benign, these growths can occur on any nerve of the body and can potentially cause a variety of serious symptoms such as pain and airway obstruction, depending on where they arise. Selumetnib (KoselugoTM), a recently FDA-approved drug, demonstrated in a phase 2 clinical trial that it can shrink most of the PN in children with NF and additionally relieves additional PN-related symptoms; however, some types of PN-related comorbidities, including blindness and nerve damage, are not likely to reverse as the PN decrease in size. With an FY20 NFRP Clinical Trial Award, Drs. Andrea Gross and Laura Metrock, in collaboration with the Neurofibromatosis Clinical Trials Consortium, aim to identify and treat patients with NF1 and asymptomatic PN in high-risk locations to prevent tumor growth and development of PN-related pain and co-morbidities. They hypothesize that treating patients with PN with selumetnib in childhood before developing any co-morbidities will prevent PN growth and related issues.

The team's clinical trial will consist of three parts. In part one, the team will conduct a single-arm observational study using whole-body magnetic resonance imaging (WBMRI) to evaluate the PN frequency and location in children with NF aged 1 to 8 years of age. The team will determine a subset of these children who have asymptomatic PN with the potential to cause future morbidity. In part 2, the team will determine whether these identified children will benefit from selumetinib treatment using a randomized control trial and observation. In part 3, any patients from part 2 that developed PN progression or related symptoms will participate in a single-arm selumetinib treatment plan. The aim will be to determine whether patients who achieve a tumor response with the standard dose of selumetinib will be able to maintain the same level of response after transitioning to a lower-dose maintenance treatment schedule.

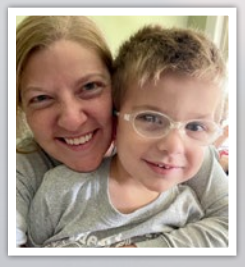
This clinical trial is just getting started; however, the team's research has the potential to guide the future of clinical management of children with NF1. If Dr. Gross and Dr. Metrock's hypothesis is correct, early treatment of PN will help prevent the development of serious PN complications such as disfiguration and blindness. These potential results may suggest the need to perform routine WBMRI in all children diagnosed with NF1. On the other hand, if early treatment does not benefit the patients, the data will still inform future clinical guidelines.

References:

6. Radke H, Rosser T, Ullrich N. 2020. Plexiform Neurofibromas in Neurofibromatosis Type I [Brochure]. Children's Tumor Foundation. https://www.ctf.org/images/uploads/documents/Plexiform_Neurofibromas_NF1.pdf.

Links:

Public and Technical Abstracts: Selumentinib for the Prevention of Plexiform Neurofibroma Growth and Morbidity in Young Children with Neurofibromatosis Type 1 (NF1)



"Neurofibromatosis has had our family on a roller coaster ride for over 4 years. Our son Jay has had a variety of medical complications big and small. The one constant is an overwhelming uncertainty of what will come next. Having the opportunity to be a peer reviewer with the NFRP has helped to soothe some of the anxiety this uncertainty has given me as a mother. Seeing first-hand how hard medical professionals, researchers, and scientists are working to find a cure and better treatments is truly encouraging."

Laura Haslam,
FY21 Consumer Peer Reviewer

Multimodal Intervention Trial for Cognitive Deficits in Neurofibromatosis Type 1: Efficacy of Computerized Cognitive Training and Stimulant Medication

Kristina Hardy, Ph.D., Children's National Hospital

In individuals diagnosed with NF1, the most prevalent effects of long-term dysfunction are difficulties with memory and attention. More specifically, there is a high incidence of children with NF1 demonstrating working memory (WM) difficulties that impact cognitive, social, and academic functioning. Previous research has found that dopamine, a chemical in the brain that influences mood, movement, and pleasurable senses, also plays a key role in memory function and ability, making it a potential therapeutic target for cognitive deficiencies associated with NF1. Methylphenidate (MPH), a pharmacological intervention that influences dopamine levels and improves attention, awareness, and thinking skills, is currently administered to children with NF1. Although effective, many still experience deficits, indicating a need to look into alternative interventions that act on the dopaminergic system.

Cognitive training (CT) programs are computerized behavioral interventions that have recently been shown to be associated with changes in dopamine receptor concentration and effective in improving WM. Since CT programs also affect dopaminergic systems, the intervention is promising for individuals living with NF1. With support from the CDMRP's NFRP Clinical Trial Award, Dr. Hardy specifically aimed to evaluate the efficacy of a home-based computerized CT program designed for children with NF1, called Cogmed[RM]. In a phase 2 randomized parallel group controlled clinical trial, Dr. Hardy and her team tested the hypothesis that children randomized to the Cogmed[RM] intervention will have improved memory capabilities compared to children receiving a control version (a computerized reading intervention). Participants aged 8–16 years took part in 25 sessions of CT for up to 11 weeks and were assigned a training coach to help with strategy and motivation each week via phone. The research team administered two versions of Cogmed[RM] to participants. In the first version, CT exercises increased in difficulty with participant improvement; in the second version, the level of difficulty remained constant throughout the control intervention.

Although results indicated that the children showed some cognitive improvements while participating in the Cogmed[RM] program compared to the control, the parents did not observe any behavioral changes. Specifically, the children receiving Cogmed[RM] showed more progress in digit and spatial spans, two performance-based tests that measure short-term WM. Digit span testing involves verbal recall of numbers, while spatial span, a nonverbal analogue of digital span, measures the capacity of visuospatial memory. Improved performance in these two measures indicated that CT may help children make gains in certain aspects of WM. Generally, the children found the interventions to be accessible, enjoyable, and feasible. Lack of access to resources such as specialized psychological services in clinical settings due to socioeconomic difficulties and location in remote areas can be a challenge; however, the increased access to technology via Cogmed[RM] proved to be beneficial for the participants. Overall, the study increased knowledge of the efficacy and acceptability of CT in children living with NF1.

The long-term clinical impact of the study could enable more children to be treated at an earlier age before experiencing effects on learning and social functioning in school, with friends, and at home. Dr. Hardy's ultimate goal is to prevent long-term obstacles for high-risk patients with NF1 and to mitigate socio-cognitive deficits to provide a more enjoyable way of life for the NF1 community. Benefits of CT programs include no known side effects, treatment affordability, and ease of administration in a comfortable environment such as in the home, and they can be expanded for use by individuals living with NF1 in a variety of socioeconomic settings. Given this support for the acceptability and efficacy of Cogmed[RM], translation of this intervention into clinical practice may be warranted, but further study of how training gains can be better translated into real-world improvements is also needed.

Links:

Public and Technical Abstracts: Multimodal Intervention Trial for Cognitive Deficits in Neurofibromatosis Type 1: Efficacy of Computerized Cognitive Training and Stimulant Medication

THE NEUROFIBROMATOSIS CLINIC

NEUROFIBROMATOSIS CLINICAL TRIALS CONSORTIUM

Recognizing the importance of leveraging partnerships that work towards accomplishing shared goals, the NFRP NFCTC was initiated in FY05 to develop and perform phase 1 and 2 clinical trials for the management and treatment of NF complications in children and adults. The NFCTC currently consists of 15 primary sites and has 10 additional affiliate sites. 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. An operations center also exists for the purpose of providing administrative, data management, and statistical support.

Planning — 2004

- Meeting of the NFRP Programmatic Panel, NIH directors, and subject matter experts to address clinical trial issues in NF
- Consensus recommendation that a consortium was needed to move NF trials forward

Development — 2005

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

Initiation — 2006

- Initiated four trials, including one in collaboration with the Sarcoma Alliance for Research through Collaboration (SARC)
- Included one ancillary study
- First study opened in 2007
- 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)

CAL TRIALS CONSORTIUM (NFCTC)

Second Award

2011

- Expanded to 20 sites, increased operations and statistical center
- Initiated six 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

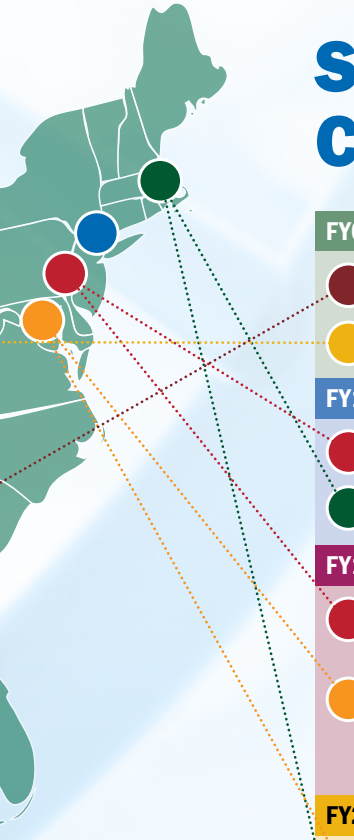
2016

- Expanded to 24 sites
- Initiated three 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

Fourth Award

2021

- New award through an Other Transaction Agreement
- Collaborative consortium efforts for rapid execution of clinical trials
- Provides more government involvement and flexibility in management
- Promoting resource sharing, best business practices and strengthened relationships in varying sectors
- Funding $25M over a 10-year period of performance



STATUS OF SOME CLINICAL TRIALS

FY06 (Completed)

- STARS: Lovastatin for the Treatment of Learning Disabilities in Children with NF1
- STOPN: Sirolimus for the Treatment of NF1-Related Plexiform Neurofibromas

FY11 (Completed)

- Cabozantinib (XL184) for NF1-Related Plexiform Neurofibromas
- Bevacizumab for NF2-Related Progressive Vestibular Schwannomas

FY16 (In progress)

- A phase 2 Study of Binimetinib in Children and Adults with NF1 associated Plexiform Neurofibromas
- A phase 1/2 Trial of the MEK Inhibitor Selumetinib and Bromodomain Inhibitor AZD5153 with Durvalumab (MEDI4736), a PD-L1 Antibody for Sarcomas Including Malignant Peripheral Nerve Sheath Tumors

FY21 (Planned)

- A Randomized, Placebo-Controlled Crossover Trial of Extended Release Guanfacine for the Treatment of ADHD and Cognitive Deficits in Children and Adolescents with NF1
- Losartan for Vestibular Schwannomas

INVESTIGATORS CHART

Dr. Christopher Moertel
University of Minnesota

Dr. Dusica Babovic-Vuksanovic
Mayo Clinic

Dr. Robert Listernick
Dr. Stewart Goldman
Ann & Robert H. Lurie Children's Hospital of Chicago

Dr. James Tonsgard
University of Chicago

Dr. Elizabeth Schorry
Dr. Brian Weiss
Cincinnati Children's Hospital Medical Center

Dr. Matthias Karajannis
Memorial Sloan Kettering Cancer Center

Dr. Jeffrey Allen
New York University Medical Center

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. Jaishri Blakeley
Johns Hopkins Hospital

Dr. Miriam Bornhorst
Children's National Medical Center

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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

Dr. Laura Klesse
University of Texas Southwestern

Dr. Steve Richards
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Dr. Tena Rosser
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Dr. David Viskochil
University of Utah

Dr. David Gutmann
Washington University

Dr. Kathryn North
Dr. Jonathan Payne
Royal Children's Hospital Murdoch Children's Research Institute

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

NFCTC-SUPPORTED TRIALS

Everolimus Therapy for NF1-Optic Gliomas in Children: A Clinical Trial

Nicole Ullrich, M.D., Ph.D., Boston Children's Hospital

Low-grade gliomas (LGGs) are a common type of brain tumor in children with with NF1. When LGGs occur along the optic pathway, they can affect visual acuity. The mammalian target of the rapamycin (mTOR) pathway is activated in NF1-associated LGGs and can lead to abnormal cell growth, cell proliferation, and angiogenesis. While previous studies have assessed chemotherapy for NF1-associated LGGs, targeted treatment with mTOR inhibitors has not been extensively studied in the NF1 population.

Based on preclinical observations, Dr. Nicole Ullrich and her team launched a clinical trial in the NFCTC in FY06 that studied the efficacy of the oral mTOR inhibitor everolimus in NF1-associated pediatric LGGs and its impact on visual acuity in NF1- associated optic pathway gliomas. Children with radiologic-progressive, NF1-associated LGG and prior treatment with chemotherapy were enrolled to receive daily oral everolimus. The team analyzed whole blood prior to, during, and after treatment for everolimus levels, as well as markers of PI3K/mTOR pathway inhibition. Serial magnetic resonance images (MRIs) were obtained during the course of treatment. The primary endpoint was progression-free survival at 48 weeks. They observed that 68% of participants demonstrated either shrinkage or arrest of tumor growth. Of these, 10/15 remained free of progression, and all remaining participants were alive at completion of therapy. To study the impact of everolimus on visual acuity, Dr. Ullrich and her team collected visual acuity data before and after treatment. They observed that everolimus treatment was able to stabilize (76%) visual acuity in a majority of children with optic pathway glioma, and some children even saw an improvement (16%).

These two studies demonstrated that everolimus can impact both LGG growth as well as visual acuity related to optic pathway gliomas. Specifically, patients with recurrent/progressive NF1-associated LGGs demonstrated tumor stability/shrinkage during everolimus treatment with a well-tolerated toxicity profile. Importantly, this treatment was associated with functional stabilization and/or improvement of visual acuity in children with optic pathway gliomas. Taken together, these findings indicate everolimus as an effective agent in this patient population.

The NFCTC was established through FY05 NFRP funding to develop and perform phase 1 and 2 clinical trials for the management and treatment of NF complications in children and adults. Over the years, the NFCTC has expanded from 9 to 15 primary sites with an additional 10 affiliate sites. The operations center is housed at the University of Alabama at Birmingham under the direction of Dr. Bruce Korf, and the NFCTC Steering Committee is led by Dr. Michael Fisher at the Children's Hospital of Philadelphia/University of Pennsylvania. Since the development awards offered in FY05, the NFCTC has been supported by additional awards from the NFRP in FY06, FY11, FY16, and FY21.

Cabozantinib for Neurofibromatosis Type 1-Related Plexiform Neurofibromas: A Phase 2 Trial

Neurofibromatosis Clinical Trials Consortium

Children and adults diagnosed with NF1 can develop a type of tumor called a PN that develops from cells and tissues that cover the nerves. PNs can be disfiguring and painful, impact function, and are life-threatening when they compress vital structures. Standard treatment approaches such as chemotherapy and radiation are not effective, and surgery is often not feasible given the tumor's involvement of the nerve and location near vital body structures such as blood vessels, the spinal cord, and the airway. Cabozantinib, an oral FDA-approved multi-receptor tyrosine kinase inhibitor, was tested in an animal model of PN in the laboratory of consortium member Dr. Wade Clapp (Riley Hospital for Children). After finding significant reduction of tumor number and size in Cabozantinib-treated animals, investigators sought to translate these findings to a phase 2 human study.

Based on preclinical observations, the NFCTC launched a clinical trial (NFCTC FY11) to determine the response rate (by MRI) of NF1 patients with plexiform neurofibromas treated with Cabozantinib. They performed a multicenter, nonrandomized phase 2 trial (NCT02101736) of Cabozantinib in participants 16 years and older with NF1 and either progressive or clinically significant inoperable PN. Participants took the drug daily for up to 2 years. No participant experienced disease progression while taking Cabozantinib, and 42% of the participants had a partial response (defined as 20% or greater reduction in tumor volume), demonstrating that this drug has considerable clinical activity against PN. Additional analyses revealed that inhibition of DDR1, DDR2, AXL, MERTK, and MET might underpin the therapeutic responses seen in these patients. The drug was reasonably well tolerated, with rare severe side effects. However, the low-grade side effects experienced led several participants to stop the treatment. Lower doses of Cabozantinib may be optimal for the NF1 population and still lead to therapeutic response. This trial is now enrolling a pediatric cohort of children aged 3 to 15 years.

This work was also supported by NIH/NCI funding (U54-CA196519-04) and Exelixis.

FUNDING FOR CONCEPT AND EXPLORATION-HYPOTHESIS DEVELOPMENT AWARDS

These are innovation-based awards in anticipation of quick results expected to serve as a foundation for additional scientific research.

Initial NFRP investment
$11,912,656
(FY04-FY19, 94 awards)

Total amount of follow-on funding
$16,237,079
(FY04–FY19)

THE NEW INVESTIGATOR AWARD (NIA)

The NIA has supported promising new independent investigators or established investigators transitioning from other career fields to bring new ideas, techniques, or expertise into the field of NF research.

EVALUATION (FY06-FY15)

FUNDING OBTAINED
NIA Original Funding: $7,277,700.58
CDMRP Additional Funding: $14,993,639.44
NIH Funding: $43,594,576
CTF Funding: $465,000
Other Funding: $50,000

65 Follow-on Awards Received

109 Publications

22 Research Resources

7 Patents

New Investigator Award Recipients Bring New Ideas to the Neurofibromatosis Research Program for Fiscal Year 2020

Each year, the NFRP aims to bring the next generation of investigators and their ideas to the NF research community through the NIA. This award mechanism supports the development of promising new independent investigators or established investigators transitioning into the NF research community from other career fields. The NIA aims to bring investigators who can bring new techniques or expertise into the field of NF research. Since 1999, when the first NFRP NIA was awarded, 374 NIA applications have been received, of which 85 were recommended for funding. In FY20, five NIAs were awarded. The research planned by these investigators addresses different NF research topic areas of interest, and all NIA researchers are bringing novel concepts to the NF research community.

Dr. Yang Hou of the University of Kentucky is studying the neurobehavioral phenotype of NF-1 using a large combined dataset and advanced data modeling. Specifically, Dr. Hou will analyze how neurobehavioral functioning develops across ages (i.e., neurobehavioral trajectories) and identify subpopulations of NF1 children with different profiles of various neurobehavioral problems (i.e., neurobehavioral profiles). She will also study biological/demographic predictors of neurobehavioral trajectories and neurobehavioral profiles in children with NF1. Additionally, she will examine how cognitive function relates to academic, behavioral, and socioemotional functioning in children with NF1.

Dr. Steve Angus of Indiana University is studying the modulation of a protein complex function (PRC2) and its relationship to NF1-related malignant peripheral nerve sheath tumor (MPNST) growth. He will elucidate protein kinome signatures in NF1 MPNSTs using a mouse model and observe how MPNST tumor growth responds to mitogen-activated protein kinase (MEK) inhibition. Dr. Angus will further identify genetic signatures using a knockout screening process within the context of MEK inhibition.

Dr. Daniel Vogt of Michigan State University proposes to study how sleep disruptions are elevated in NF1 patients and how the transcription factor, Lhx6, is related to cognitive manifestations. Specifically, his team will define the relationships between MEK, Lhx6, and underlying social and memory behaviors. They will also use a knockout mouse model to study how different brain regions contribute to sleep issues related to the RAS molecular pathway.

Dr. Ina Ly of Massachusetts General Hospital will develop clinically deployable models for predicting neurofibroma growth based on MRI features using deep learning. These models will be developed using a shared data repository from multiple centers and will be tested and compared in an independent patient cohort to determine how best to predict tumor growth in NF patients.

Dr. Miriam Bornhorst of Children's Research Institute at Children's National Medical Center will determine how NF1 affects lipid oxidation and how MEK inhibitor treatment influences metabolism and weight gain in the NF1 patient. Her team will begin by studying how MEK inhibitor treatment alters clinical metabolic factors using a mouse model and then further study these changes in an NF1 patient population by studying human blood and microbiome profiles.

Links:

Abstract for Dr. Hou
Public and Technical Abstracts: Using Big Data to Comprehensively Delineate the Neurobehavioral Phenotype of Children with Neurofibromatosis Type 1

Abstract for Dr. Angus
Public and Technical Abstracts: PRC2 Impact on the Functional Kinome in NF1-Related MPNST

Abstract for Dr. Vogt
Public and Technical Abstracts: Uncovering Mechanisms Underlying Cognitive Changes and Sleep in NF1

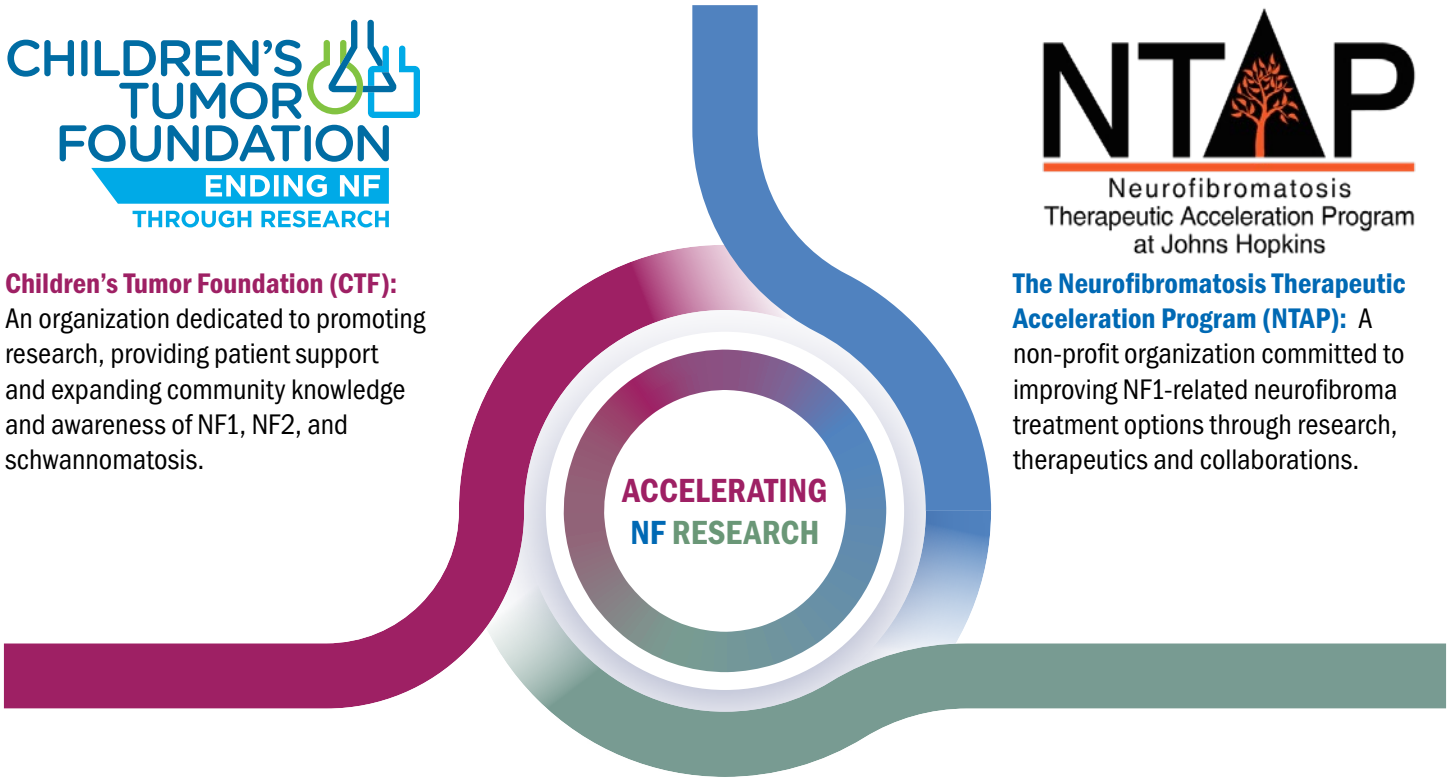
Abstract for Dr. Ly
Public and Technical Abstracts: Clinical and MRI Predictors of Internal Neurofibroma Growth in Neurofibromatosis Type 1

Abstract for Dr. Bornhorst
Public and Technical Abstracts: The Effect of MEK Inhibitor Treatment on Metabolism in Neurofibromatosis Type 1

STRATEGIC PARTNERSHIPS

The NFRP is engaged in collaborative efforts with organizations that can accelerate NF research:

Children's Tumor Foundation (CTF): An organization dedicated to promoting research, providing patient support and expanding community knowledge and awareness of NF1, NF2, and schwannomatosis.



The Neurofibromatosis Therapeutic Acceleration Program (NTAP): A non-profit organization committed to improving NF1-related neurofibroma treatment options through research, therapeutics and collaborations.

NF Open Science Initiative: A collaborative enterprise of CTF, NTAP, and Sage Bionetworks engaged in sharing data and analysis results with the general scientific community. A distinct option for research collaboration exists under the Investigator-Initiated Research Award mechanism, and applicants are highly encouraged to consider such if submitting applications to that mechanism.

PRODUCTS FROM RECENTLY FUNDED RESEARCH

FY18

- **1** Potential Therapeutic/ Vaccine
- **1** Cell Line
- **1** Clinical Care Tool

FY19

- **2** Potential Therapeutic/ Vaccines
- **1** Drug
- **1** Mechanistic Study

FY20

- **2** Potential Therapeutic/ Vaccines
- **1** Mechanistic Study

RESEARCH RESOURCES

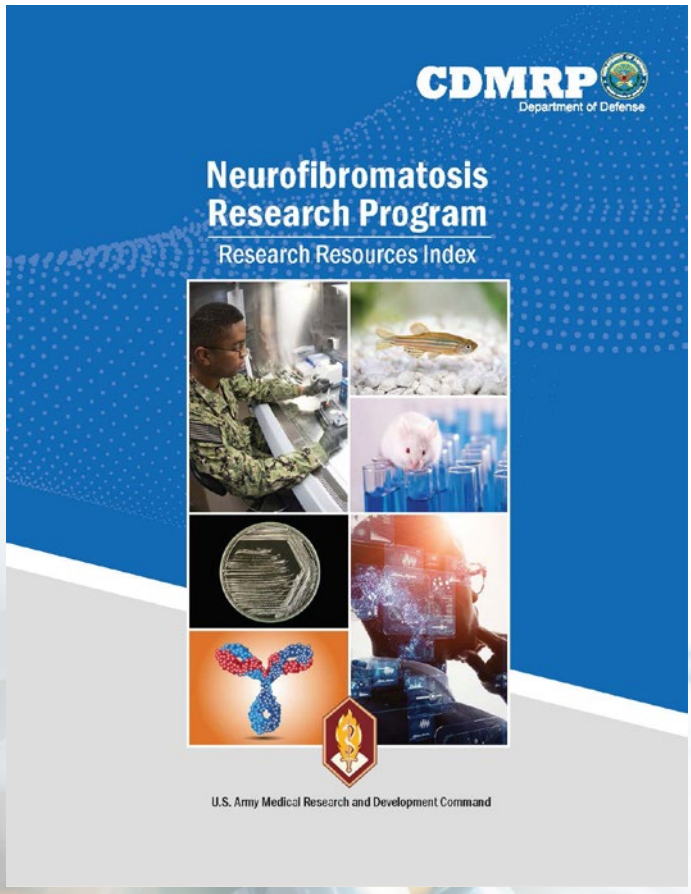
The recently updated NFRP Research Resources Book is available at. https://cdmrp.army.mil/nfrp/resources/nfrpresources. This resource exists to promote and accelerate NF research by providing resources developed by the program for information and to enable further collaboration among investigators.

Rat Models

Zebrafish Models

Antibodies

Drosophila Models



Cell and Molecular Bio-Tools

Mouse Models

Cell Lines

Yeast Strains

Databases & Data Sets

Methods

For more information, please visit
https://cdmrp.health.mil
or contact us at:
usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@health.mil
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