CDMRP

Department of Defense

Neurofibromatosis Research Program

U.S. Army Medical Research and Materiel 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 nearly $7 billion in appropriations from its inception through fiscal year 2012 (FY12). Funds for the CDMRP are added to the Department of Defense (DoD) budget in 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 Integration Panel, which compares applications to each other 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 NF (encompassing 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 the 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, caregivers, and clinicians who treat them.

Neurofibromatosis Research Program

HISTORY OF THE DOD NFRP

The NFRP began in FY96 when the efforts of NF advocates led to a congressional appropriation of $8 million (M). Since that time, $242.85M has been appropriated to the program, including $12.8M in FY12. Over its 16-year history, the NFRP has invested in key initiatives to support the development of critical resources, sponsor multidisciplinary collaborations, bring talented investigators into the field, and promote the translation of promising ideas into the clinic.

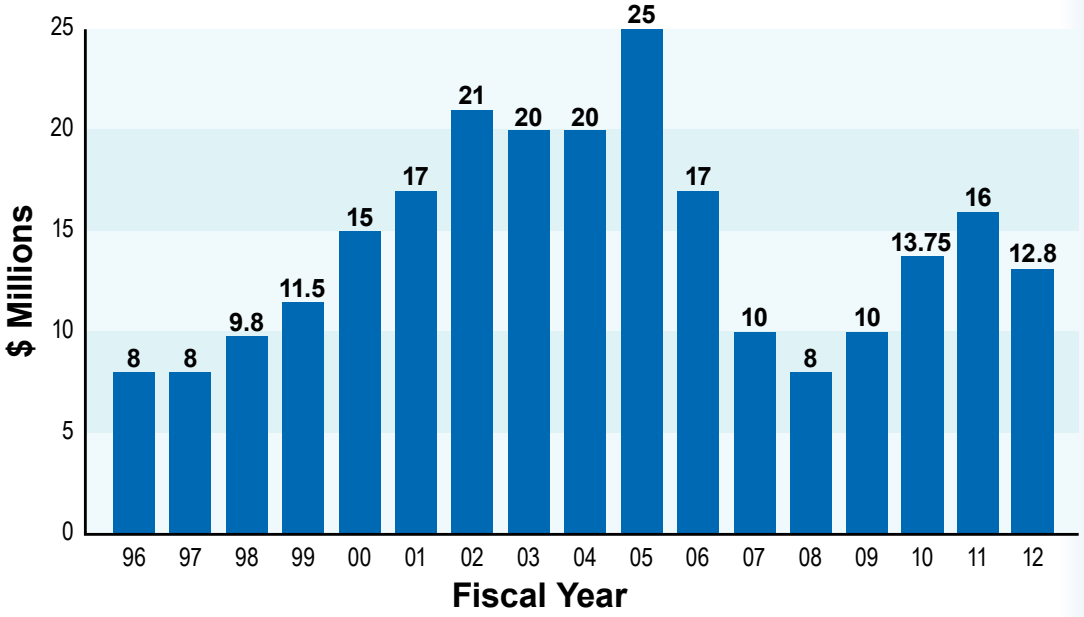
VISION

Decrease the clinical impact of neurofibromatosis.

MISSION

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

NFRP FY96–FY12 Appropriations



NFRP Portfolio

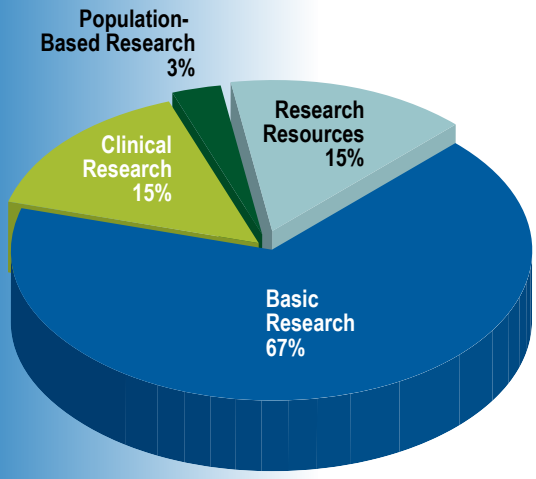
The NFRP's goal is to advance vital research to address the critical needs of the NF community by:

- Accelerating discoveries that support high-impact, innovative research
- Encouraging new investigators to pursue NF research
- Delivering research resources and tools to the NF research community
- Fostering collaborations between basic and clinical researchers
- Accelerating promising therapeutics through the NF Clinical Consortium
- Promoting translational and clinical studies to move promising ideas from bench to bedside

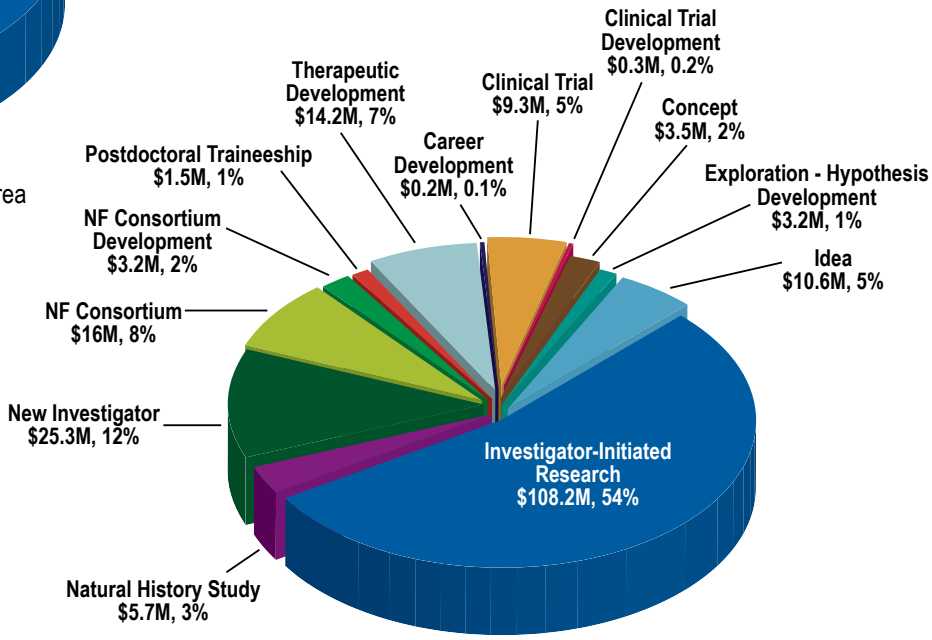
The NFRP's current portfolio includes 282 basic, clinical, and population-based research awards over 15 years and 13 different award mechanisms.

"The CDMRP Neurofibromatosis Research Program continues to be one of the most fruitful programs that supports basic and clinical research. I have been involved in the NFRP for over 12 years as a grant reviewer, serving as IP Chair, and now head of the Integration Panel, and I truly believe that it is a model for how to translate basic science into clinical applications. I am proud to be a part of this program and look forward to promoting the discoveries that NFRP will support in the coming years."

Larry Sherman, Ph.D., Oregon Health & Science University, IP Chair



NFRP FY96–FY11 Portfolio by Research Area



NFRP FY96–FY11 Portfolio by Award Mechanism

NF Clinical Trials Consortium

Primary Consortium Sites

Children's Hospital of Los Angeles/University of Southern California – Tena Rosser, M.D.

Children's Hospital of Philadelphia/University of Pennsylvania – Michael Fisher, M.D.

Children's Hospital of Westmead – Kathryn North, M.D.

Children's National Medical Center – Roger Packer, M.D.

Cincinnati Children's Hospital – Elizabeth Schorry, M.D.

Harvard Medical School Center of NF and Allied Disorders – Nicole Ullrich, M.D., Ph.D.

National Cancer Institute – Brigitte Widemann, M.D.

New York University Langone Medical Center – Jeffrey Allen, M.D.

University of Alabama, Birmingham – Bruce Korf, M.D., Ph.D.

University of Chicago – James Tonsgard, M.D.

University of Indiana – D. Wade Clapp, M.D.

University of Utah – David Viskochil, M.D., Ph.D.

Washington University – David Gutmann, M.D., Ph.D.

Collaborating Sites

House Research Institute/University of California, Los Angeles – Marco Giovannini, M.D., Ph.D. and Alcino Silva, Ph.D.

Johns Hopkins Hospital – Jaishri Blakeley, M.D.

Northwestern University Hospital – Robert Listernick, M.D.

Ohio State University Hospital – D. Bradley Welling, M.D., Ph.D.

Bruce Korf, M.D., Ph.D., University of Alabama at Birmingham

Individuals suffering from NF1 may develop neurofibromas, malignant peripheral nerve sheath tumors (MPNSTs), skeletal dysplasia, cognitive disorders, or low-grade gliomas. Individuals with NF2 develop vestibular schwannomas, often resulting in deafness, and other tumors such as meningiomas and ependymomas. Those with schwannomatosis develop multiple schwannomas and severe pain. The severity of NF-related complications in affected individuals is extremely variable, and current therapies are unable to eradicate symptoms. Therefore, the identification of effective NF therapies is greatly needed. The Neurofibromatosis Clinical Trials Consortium (NFCTC) was established in 2006 to accelerate clinical trials for children and adults with significant complications of NF. Over the past 5 years, with funding from the NFRP, the NFCTC has conducted clinical trials investigating treatments for NF1 and its complications, including plexiform neurofibromas, cognitive disorders, low-grade gliomas, and MPNSTs. With support from the NFRP in FY11, the NFCTC will continue its mission. The consortium has expanded to include 13 member sites as well as 4 additional collaborating sites to improve geographical coverage and inclusion of adults and children with all forms of NF. In addition, the NFCTC will broaden its focus to include NF2 and schwannomatosis alongside NF1 in performing clinical trials.

Research Highlights

Modeling Brain Defects in NF1

Nancy Ratner, Ph.D., Children's Hospital, Cincinnati

NF1 is a genetic disorder resulting in the development of peripheral nerve sheath tumors, pigmentation defects, enlarged brain size, brain tumors, learning difficulties, and delayed acquisition of motor skills. The majority of children with NF1 have T2 hyperintense lesions visible by magnetic resonance imaging. One pathologic study of T2 hyperintensities suggests that these lesions are areas of myelination failure. Additionally, recent data suggest that thalamus T2 hyperintensities are correlated with low IQ scores and learning deficiencies. Dr. Nancy Ratner hypothesized that oligodendrocytes, the central nervous system's myelin-producing cells, are aberrant in NF1 patients, resulting in T2 hyperintensities and myelination defects that contribute to NF1-associated brain abnormalities and learning difficulties. Dr. Ratner's research team, with funding from an FY09 NFRP Investigator-Initiated Research Award, is utilizing a mouse model with a deletion of the Nf1 gene exclusively in oligodendrocytes to investigate this hypothesis. Interestingly, preliminary data suggest that loss of Nf1 in oligodendrocytes results in myelination defects. Studies are currently under way to determine if these myelination abnormalities contribute to cognitive defects and tumor development.

Defining Quality of Life in NF2

Maura Cosetti, M.D., New York University School of Medicine

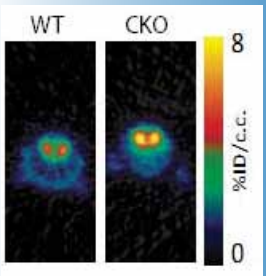
NF2 is a genetic disorder characterized by the development of bilateral vestibular schwannomas, benign tumors of the nerve that transmit sensory information from the inner ear to the brain. NF2 patients are also at risk for developing other types of nervous system tumors, cataracts, and skin tumors. While these tumors are nonmalignant, tumor growth may result in loss of hearing and balance, ringing in the ears, headache, abnormal sensation and vision, as well as more life-threatening symptoms based on the location of tumor. The clinical management of NF2 is complex and controversial as therapeutic interventions may also lead to significant nerve damage and dysfunction. NF2 experts agree that patient quality of life (QoL) is an important consideration in clinical decision making; however, no NF2-specific QoL scales are available. Dr. Maura Cosetti received an FY10 Postdoctoral Traineeship Award from the NFRP to address this need. During this traineeship, Dr. Cosetti will develop, refine, and validate a multidimensional metric to evaluate QoL in NF2 patients. Beginning with a literature review of existing QoL metrics and structured interviews with NF2 clinicians and patients, Dr. Cosetti will develop a QoL questionnaire that will address the unique concerns of the NF2 population. This questionnaire will be refined and further validated in a larger cohort of NF2 patients, and results will be compared to clinical outcome measures and other QoL measurements. Dr. Cosetti's disease-specific, validated QoL metric will be used to inform NF2 patient treatment, evaluate treatment outcomes, and standardize results across clinical trials.

Improving Cognitive and Behavioral Function in NF1 Genetically Engineered Mice

David Gutmann, M.D., Ph.D., Washington University

NF1, which results from a mutation of the NF1 gene, predisposes individuals to tumor growth along nerves resulting in pain, loss of function in the area of the affected nerve, or difficulty with movement. Approximately two-thirds of children affected with NF1 experience learning disabilities and attention deficit disorder (ADD), limiting their performance in school. Additionally, NF1 children may experience further cognitive disability resulting from the cancer treatments used to treat optic gliomas, a type of brain tumor that is common in NF1. Dr. David Gutmann, recipient of an FY09 Investigator-Initiated Research Award from the NFRP, is hoping to expand the understanding of NF1-associated learning disorders using a genetically engineered mouse model of NF1 in which the mice develop optic gliomas.

Characterization of the NF1 mouse model revealed behavior and attention deficits similar to those observed in children with NF1. In addition, Dr. Gutmann confirmed that NF1 mutant mice had reduced levels of the neurotransmitter dopamine, which has a variety of functions including roles in cognition, attention, learning, and memory. With funding from the NFRP, he demonstrated that the deficit in dopamine in NF1 mutant mice can be reliably detected using positron emission tomography (PET), establishing a noninvasive method to monitor dopamine in live animals. To demonstrate that the NF1 mutant mouse model can be used as a therapeutic drug testing platform, Dr. Gutmann measured NF1 mouse behavior and dopamine levels using PET following administration of the ADD medication methylphenidate or l-deprenyl, which increases dopamine levels in the brain. Treatment with either of these agents corrected the attention deficit seen in NF1 mutant mice and returned dopamine levels, measured by PET, to those of normal mice. Dr. Gutmann's work suggests that there may be a subset of children with NF1-associated learning disabilities that may respond more favorably to dopamine-targeted therapies, and these children could be identified using noninvasive PET imaging techniques.



PET scan of wild-type (WT) and Nf1 mutant mice. Shown is a representative 1-hour PET scan of WT and Nf1 mutant (CKO) mice at baseline. CKO mice have increased raclopride binding in the striatum indicative of reduced dopamine levels in the brain.

NFRP Integration Panel

FY13 Members

Larry Sherman, Ph.D. (Chair)
Oregon Health & Science University

Kim Bischoff
Neurofibromatosis Network

Douglas Miller, M.D., Ph.D.
University of Missouri

Jill Morris, Ph.D.
National Institute of Neurological Disorders and Stroke

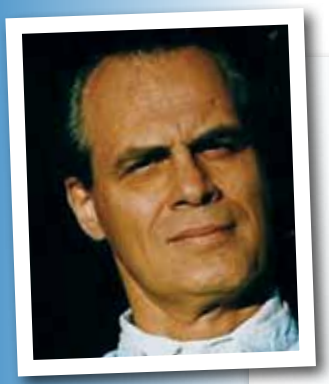
John Mulvihill, M.D.
University of Oklahoma Health Sciences Center

Vincent Riccardi, M.D.
The Neurofibromatosis Institute

John Risner
Children's Tumor Foundation

Kristine Vogel, Ph.D.
University of Texas Health Science Center at San Antonio

Robert Zimmerman, M.D.
The Children's Hospital of Philadelphia



"My years of involvement with the CDMRP have convinced me that our armed forces will benefit greatly from research focused on the neurofibromatoses. For example, one of the neurofibromatoses, NF1, is not just a matter of concern for the girls and boys, women and men with the disorder itself. Respecting the role of trauma in the origin of NF1 nerve tumors (neurofibromas), understanding their origin directly and indirectly contributes to understanding how to treat nerve damage in general—a matter of great importance to the U.S. military."

Vincent Riccardi, Ph.D., The Neurofibromatoisis Institute, IP Member

"Participating in the NFRP peer review and Integration Panel meetings is always a highlight of my year, as it gives me a chance to become informed about the most recent developments in neurofibromatosis and schwannomatosis research, and to interact with a wonderful group of dedicated scientists, clinicians, and consumer reviewers. One of my personal goals as an educator in the anatomical disciplines is to inform the medical and dental students about NF and the associated complications, in the contexts of their neuroscience, embryology, and cancer genetics coursework. I've lost count of the number of former students who have told me that they were grateful for this introduction later, when they treated individuals with NF in their medical or dental practices, because they were able to provide informed and compassionate care for these patients."

Kristine Vogel, Ph.D., University of Texas Health Science Center at San Antonio, IP Member

"My observation as a Consumer Reviewer is the scientists on the NFRP panel are genuinely interested in listening to consumers' viewpoints about NF. It is an amazing opportunity for a consumer to have significant input in the direction of NF research and to have that input valued by the scientific team. The extraordinary work of these scientists is replacing fear with hope for those personally affected by this devastating disease."

Kim Bischoff, Executive Director, Neurofibromatosis Network, IP Member

"The CDMRP is an example of federal funding at its best. By focusing on clinical research, the work of this program builds on the basic research done by NIH, academic labs and the Children's Tumor Foundation. In 2005 there were 7 clinical trials for NF and today there are over 30. The CDMRP is a huge part of making these happen, not just through direct funding, but fostering collaboration and encouraging innovation throughout the research community."

John Risner, President, Children's Tumor Foundation, IP Member

Please visit the NFRP Research Resources page for the most up-to-date listing of research tools and databases from NFRP-funded investigators.

http://cdmrp.army.mil/nfrp/resources/nfrpresources

NFRP Perspectives

Jerry Patterson

Jerry Patterson's first experience with NF occurred approximately 3 years ago when his granddaughter Leah, then 7 years old, was diagnosed with NF2. Since being diagnosed, Leah has endured three major surgeries, including one surgery to remove a large tumor impinging on her spinal cord, a second surgery to fuse her cervical vertebrae, and a third surgery to remove one of her six existing brain tumors.

After Leah's initial diagnosis, Jerry attended a symposium to learn more about NF2 and to evaluate the current available treatment options. At the symposium, Jerry became familiar with Neurofibromatosis Network, Northeast. Following discussions with members of the group, he dedicated himself to actively support their goal of finding a cure for NF. Currently, Jerry's family and friends are committed to becoming more knowledgeable about NF2, raising money to support NF research, and increasing the public awareness of this disorder.

From left: Jerry Patterson, Kathleen Patterson, Linda (Patterson) Manth, and John Manth. Front row: Leah Manth.
Photo taken by Catherine Mooney and used with the permission of Jerry Patterson and family.

Regarding his service as an FY10 NFRP Consumer Peer Reviewer, Jerry reflects that "it was truly a privilege to sit on a panel with such a distinguished group of scientists and dedicated advocates. Serving on the panel as a consumer advocate was truly rewarding and enriching. I learned so much about NF and the dedicated researchers working so diligently to find a treatment or cure for NF. To have the opportunity to preview the future areas of research was personally enlightening, and very rewarding to do so, on behalf of all NF patients and their families. The NFRP is such a unique program, bringing together NF families, scientific reviewers, and the front-line researchers, all united in the quest to find a cure for neurofibromatosis."

Beverly Oberlander

As the middle generation of a multigenerational NF1 family, I have dealt with NF from every conceivable angle—patient, parent, daughter, and family member. Not only have I been diagnosed with NF, but my brother, son, and niece were diagnosed with NF, and I have lost my father to the disease. NF has been a part of my life for as long as I can remember. I have seen firsthand the devastation this disorder can bring to a single family.

My father had numerous surgeries to remove tumors, many of them malignant and some the size of footballs. He lost his lifelong battle with NF after the tumors grew in his lungs. I had a pheochromocytoma, a rare type of adrenal tumor, during my pregnancy and was confined to the hospital for several months and later had a major portion of my stomach removed due to a massive neurofibroma in my stomach wall. My son, Eli, had a craniotomy when he was 8 years old to remove a tumor that had eroded the bone of his eye socket. He has had two subsequent surgeries to remove two tumors near the eyelid nerves, has been diagnosed with learning disabilities, has an NF-related aneurysm, and has tumors up and down the nerve roots of his spine. Despite this, his attitude is "I am not my disease." Having graduated from college with a B+ average, he now teaches elementary school full-time in Las Vegas. Eli has also worked as a professional actor and model, refusing to let NF stop him from doing anything he wants to do.

I have chosen to fight NF by becoming involved in NF organizations for the past 25 years. For many years I was an active board member and president of the Midwest Chapter of Neurofibromatosis, Inc., a chapter in Chicago that my parents helped establish. As a board member, parent, and someone with NF, sharing my experiences helps both medical professionals and newly diagnosed families understand that having NF does not mean the end of a normal life and brings hope and knowledge to both groups. After moving to the west coast, I took on the same role with NF California, Inc. As part of the NF, Inc. network, I have traveled to Washington, DC, to advocate for more research funding for NF to help advance the progress that is being made against this disease.

I have had the honor and privilege of serving as a consumer peer reviewer for the NFRP. Serving as a consumer reviewer is one of the most exciting, exhilarating, and awe-inspiring experiences I have had as an NF advocate. To see the progress that has been made as a result of the NFRP is mind-boggling. Twenty-five years ago, NF was thought to be a skin condition by many doctors, consisting of lumps and bumps, if you will. Our family was told that it could only be passed from father to son and that females do not develop NF. Through research supported by the NFRP we now have not only a better understanding of the NF1 and NF2 genes, but clinical trials have been initiated to mitigate and one day cure the more deadly and devastating manifestations of NF.

Words cannot express my awe and gratitude to the scientists who serve on the peer review panels. They treat consumer reviewers with the utmost respect, listen to our concerns, and invest countless hours studying the applications before the review. As fellow reviewers sitting side by side on the panels, we encourage each other to return to our communities determined to work a little harder for each other—the scientists to find a cure, the consumers to raise more NF awareness and support for these researchers.

The NFRP is truly one of the best, if not the best, NF research programs—funding-focused, innovative, and stringently reviewed research. Not only am I honoring my father, my brother, and the many friends who have lost their lifelong battles with NF, I am also shaping a brighter future for those living with NF by sharing my story, advocating for NF research, and participating as a consumer for the NFRP.

"Serving as a consumer reviewer has been a tremendously rewarding experience. It empowers me to think I am making a contribution that might lead to better treatment options and understanding of neurofibromatosis. My faith in the science and in the scientists who pour so much passion into their work has been renewed as I see the tremendous amount of work that is under way. My input on the panels has been valued and while I can't take away my granddaughter's NF, by serving as a reviewer I can try to make her life better."

Peggy Burke, Ed.D., Children's Tumor Foundation
Consumer Peer Reviewer

For more information, visit
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