CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

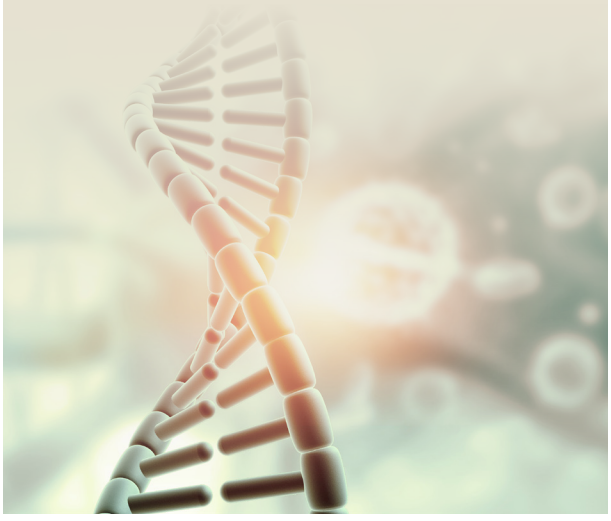
Neurofibromatosis Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. Programs managed by the CDMRP have formalized strategic plans that identify program-specific research priorities, how to best address these urgencies, short- and long-term goals, investment strategies, and ways to identify and evaluate program successes with respect to the priorities.

The current Neurofibromatosis Research Program Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. The NFRP formulated this plan to provide greater clarity regarding the program's goals over time to the public and other stakeholders. Congress appropriates funding to the NFRP annually, and there is no guarantee of future funding. The NFRP Strategic Plan is reviewed annually during the program's annual vision setting meeting and updated as necessary.



NFRP BACKGROUND AND OVERVIEW

Neurofibromatosis is a group of three genetically distinct disorders, called NF1, NF2, and schwannomatosis, that cause multiple tumors to develop in the central or peripheral nervous system.[1] The syndrome may 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. NF1 is most commonly diagnosed in children, and NF2 and schwannomatosis are typically diagnosed at the beginning of adulthood. Neurofibromatosis is often chronic and there is no cure yet. Fewer than 200,000 Americans receive a NF diagnosis each year, and these diagnoses happen across sexes, races and ethnic groups. Military personnel engage in activities that make them more prone to fractures, osteoarthritis and other bone-related conditions. This makes it critical for NF-supported research to aid the acceleration treatment and prevention options for military Service Members, Veterans, and their beneficiaries.

Efforts of the NF community led to $8 million in congressional appropriations to establish the NFRP in FY96. Since then, the programmatic panel shaped the program's vision, mission, priorities, and investment strategies. This panel is composed of leading scientists, clinicians and consumer advocates, including patients and caregivers, in the NF field who articulate the needs and/or challenges of those living with the disease. In evaluating proposals, the CDMRP uses a two-tier review process. The first tier is a scientific peer review of proposals measured against established criteria for determining their scientific merit. In the second tier, the programmatic panel compares applications and makes funding recommendations based on scientific merit, portfolio balance, and relevance to the overall program goals.

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 these disorders that impact Service members, Veterans, and the general public

FUNDING HISTORY

Between FY96 and FY23, Congress appropriated $427.85M to the DOD to conduct NF research that increases our understanding and creates novel therapies for NF disorders.

Total congressional appropriations FY96–FY23	Total compliant applications received through FY22:	Total awards issued through FY22:	FY23 anticipated number of awards:
$427.85M	1903	500	24

RESEARCH PORTFOLIO AND ACCOMPLISHMENTS

The program's research portfolio includes awards spanning basic, clinical, and population-based research. NFRP funding investments by scientific area of research are shown in **Figures 2a** and **2b below**. The NFRP fosters therapeutic development efforts to help patients with NF, as reflected in the portions of funding investments dedicated towards clinical trials and clinical and experimental therapeutics.

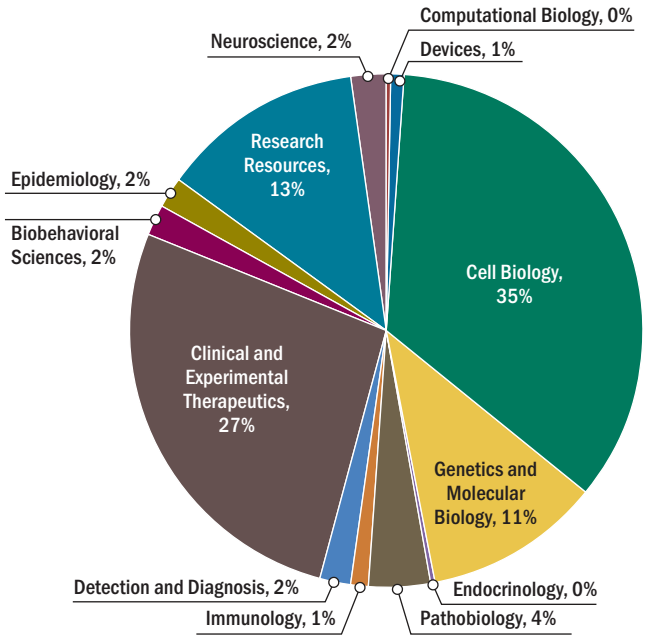


Figure 2a. NFRP FY96-FY16 Investments by Scientific Area of Research

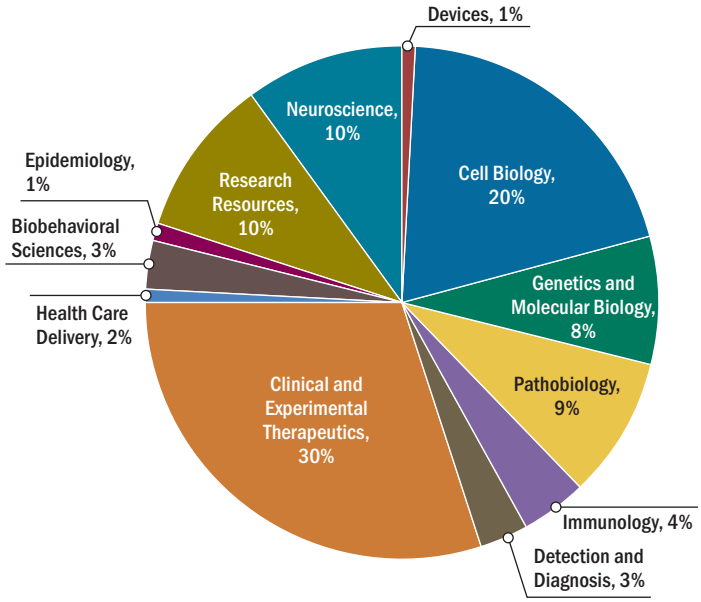


Figure 2b. NFRP FY17-FY22 Investments by Scientific Area of Research

The NFRP supports research in treatment of all three NF subtypes. Reflective of the state of the science and the number of applications submitted by investigators, NFRP investments support a majority of awards addressing treatments for NF1, followed by NF2. A few awards address a mix of NF subtypes.

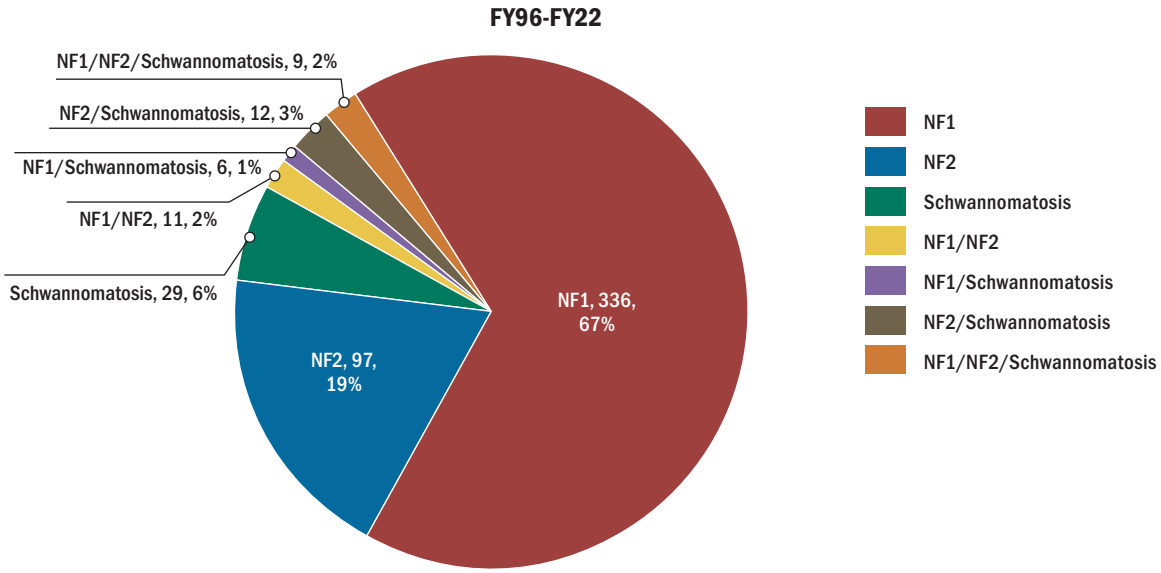


Figure 3. NFRP Number of Awards Funded by Disease Type

PROGRAM INVESTMENTS IN BASIC RESEARCH

Basic research continues to be an important part of what generates the fundamental knowledge base for understanding processes and mechanisms in the NF field. This knowledge base eventually leads to improved ways of preventing, identifying and treating diseases. The program's investment in this area will lead to improvements for prevention and effective therapeutic strategies that may include new drugs, devices and tools to improve quality of life. The research highlights shown below illustrate the impactful research supported by the NFRP.

Improving Hearing in NF2 Patient Who Use the Auditory Brainstem Implant

Daniel J. Lee, Ph.D., Massachusetts Eye and Ear

NF2 presents as a slow-growing tumor, and an estimated 90-95% of patients develop bilateral tumors on the balance nerves connected to the inner ear, called vestibular schwannomas. Most NF2 patients typically experience extreme hearing loss in one or both ears. Physicians use the auditory brainstem implant to treat NF2. Limitations currently exist because, when surgeons do not have an acceptable view of the ABI's target during surgery, they must rely on other indicators for precise positioning. In addition, the ABI is outdated and often results in less than desired outcomes.[2] Investigators experimented with CT imaging to test pitch perception in some patients. This method showed improved positioning and other features of the ABI for achieving better outcomes. Following these accomplishments, the investigators received a recent award to assemble a multidisciplinary team across several institutions to further develop the new, improved ABI for clinical applications. The team plans to improve on their previous research work with higher accuracy and apply artificial intelligence to test their predictive model of ABI performance in NF2 patients. They will also use mouse models of NF2 to improve understanding of the effect of ABI placement and tumor growth on speech recognition ability and quality. The ABI study holds great promise for prompt clinical translation.

Development of Therapeutic Strategies for NF1-Associated Optic Pathway Glioma

Yuan Zhu, Ph.D., Children's National Hospital

The NF1 gene is a tumor-suppressor gene, and every person's genetic code contains two copies of this gene. Inactivation or genetic mutation of one copy of the NF1 gene usually results in the NF1 subtype of NF. This subtype is characterized by growth of benign tumors along the visual pathway, ultimately leading to development of optic pathway gliomas, or OPG, vision loss or blindness. The location of OPG in the optic nerve makes conventional treatment options like surgery and chemotherapy unsuitable, so preventative treatment techniques are required. Zhu's previous research investigated the cell of origin of NF1-OPG and evaluated early-stage drug testing. Building on this previous work, Zhu's team sought to determine the cellular and molecular drivers of OPG development with the goal of identifying a preventative treatment target. Working to characterize cell growth within the optic nerve, they discovered that glial progenitor cells drive OPG evolution.[3] They also discovered from previous research work that a chemical called MEK helps control growth and survival of optic nerve cells and that MEK inhibition is associated with the prevention of brain defects that result from NF1 loss. The team confirmed the role of MEK in preventing brain defects in a sample of NF1 patients. After establishing the mechanisms involved in OPG development, the team investigated MEK inhibition as a potential preventative treatment for OPG. They administered a low-dose MEK inhibitor to nursing female mice, and through feeding their neonatal pups, successfully prevented the developmental defects and OPG formation associated with NF1. This study offers possibilities for different treatment approaches that are more suitable and beneficial for children living with NF1.

CLINICAL TRIALS

Since FY96, the NFRP invested over $50M in 29 clinical trials focused on treatment of the different forms of NF manifestations. The NFRP funded the clinical trials through 2 Clinical Trial Development Awards, 23 Clinical Trial Award (23 trials), 2 Clinical Consortium Awards, 1 Clinical Trial Consortium Award and 1 New Investigator Award mechanisms. **Figures 4a and 4b** show the investment percentages in trials by NF type and by characteristic manifestation.

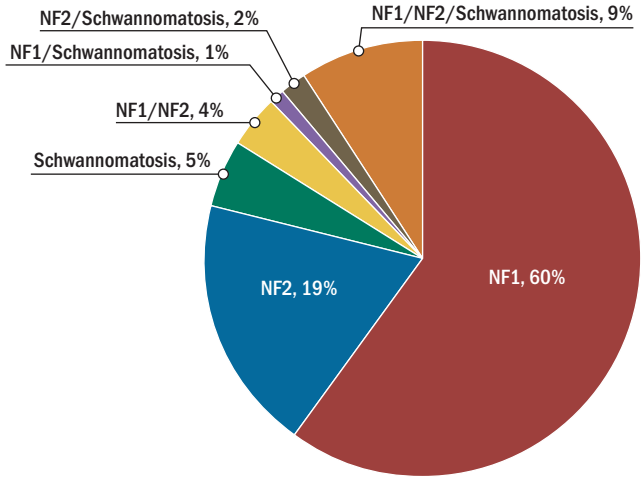


Figure 4a. NFRP FY96 – FY22 Investments in Clinical Trials by NF Type

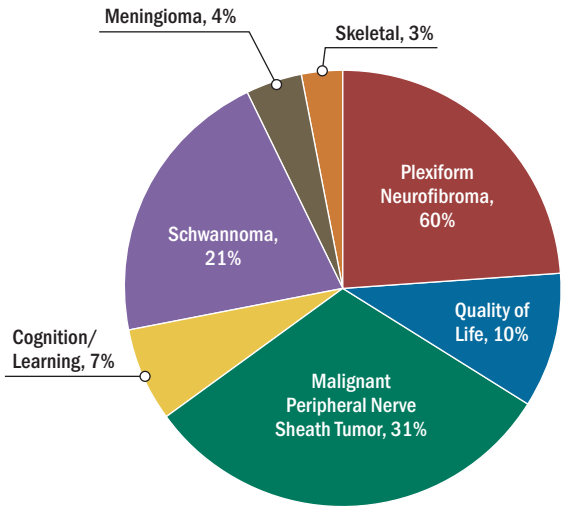


Figure 4b. NFRP FY96 – FY22 Investments in Clinical Trials by NF Manifestation

OTHER CLINICAL TRIAL INVESTMENTS – THE NEUROFIBROMATOSIS CLINICAL TRIAL CONSORTIUM

NEUROFIBROMATOSIS
CLINICAL TRIALS CONSORTIUM

In FY06, the NFRP established the Neurofibromatosis Clinical Trials Consortium to support and ensure continuous drug development and testing for treatment of children and adults. The program funded subsequent NFCTC awards in FY11, FY16 and FY21, facilitating more collaboration and sustaining efforts to increase diversity in trial populations. The continued growth of the consortium resulted in the development of additional clinical trials to focus on specific NF populations, expanded the NFRP's focus on disease complication, and led to the development of a registry/umbrella study, a type of trial where multiple targeted therapies are evaluated across NF subtypes. Currently, there are 25 clinical sites in the consortium. An operations center at the University of Alabama at Birmingham provides administrative, data management and statistical support to the NFCTC. The consortium launched 18 clinical studies, and an additional five are currently in development. The team published 18 peer-reviewed journal articles, with another five in preparation or recently submitted. NFRP-funded researchers presented at least 36 abstracts at various meetings and honored 44 presentation invitations.

In 2019, the NFCTC published the results of a trial evaluating whether a higher initial dose, known as the induction dose, of bevacizumab every two weeks improved NF2 disease outcomes over the standard lower dose administered at the same time interval.4 Results of this trial showed that the higher dose of bevacizumab did not yield better outcomes than standard doses. In a newly released publication, an NFTCT-funded research team reported the results of a trial evaluating different doses of bevacizumab administered every three weeks for 18 months as extended maintenance therapy for NF2.[5] The team demonstrated that maintenance therapy with standard lower doses of bevacizumab were safe for patients and resulted in higher rates of hearing preservation and tumor stability over higher maintenance doses. Importantly, they also showed that extended bevacizumab treatment reduced distress related to tinnitus and maintained NF2-related quality of life. The most recent NFCTC-supported clinical trial, NCT01767792, evaluated maintenance dosing of bevacizumab for children and adults with NF2-related schwannomatosis and progressive vestibular schwannoma. This study enrolled 22 participants to identify the safety, tolerance and effectiveness of bevacizumab when given as both induction therapy followed by maintenance therapy.

RESEARCH AND FUNDING ENVIRONMENT

STATE OF THE SCIENCE

NF currently has no known cure. The variability of this disorder makes it a challenging condition to tackle.

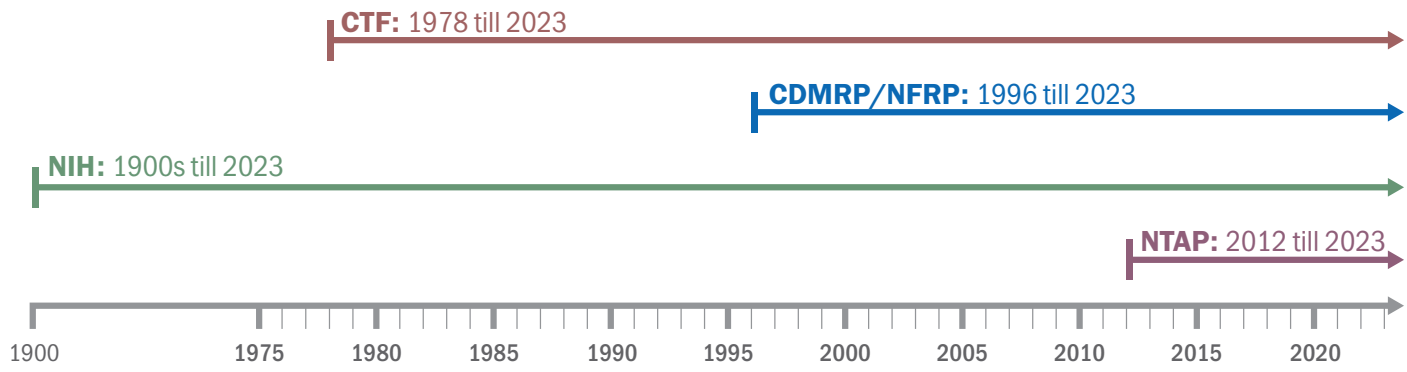
Ongoing research involves understanding the genetic origins of the disease and using clinical trials to advance diagnosis and treatment. Conventional treatment plans include medication to alleviate pain, and surgery or radiation when possible to eradicate growths. Since FY96, the NFRP serves as a critical funding source for NF researchers. In recent years, collaborative efforts among the NFRP and other NF-focused research organizations propelled NF research and led to the NF Open Science Initiative, a joint enterprise of the Children's Tumor Foundation, CTF, the Neurofibromatosis Therapeutic Acceleration Program, NTAP, at Johns Hopkins University, and the NFRP. These collaborations aimed to foster scientific data sharing with the general research community.[6]

Recognizing the need for engaging and promoting new and/or young investigators in the field, the NFRP recently introduced a new academy award mechanism, the NF Research Academy. This academy award mechanism brings together established investigators as mentors to early-career independent investigators, with the intent to develop successful, highly productive NF researchers and to lessen the clinical impact of NF1, NF2, and schwannomatosis.

Collaborative and coordinated efforts are crucial for the research of rare diseases, including NF. In 2006, the major federal funding programs coordinated their funding commitment to focus resources either on basic research through the NIH or on clinical trials through the NFRP. While both agencies funded critical projects from basic discovery through clinical trial endpoints, the NIH devoted their efforts to basic and translational research, while the NFRP committed to fund the NFCTC. This coordinated and synergistic approach across federal funders created a clear discovery pipeline for investigators. The NIH and NFRP continue to coordinate their funding through regular communication to avoid overlap. An analysis by these organizations determined how contributions over a decade led to leveraging efforts to increase available research resources and the strides of research gains.

RESEARCH FUNDING LANDSCAPE

Neurological disease research funding, part of which includes NF, spans over a century, as shown in the figure below[5]:



Other NF funders over this period of time include The Neurofibromatosis Network, Cupid's Charity, National Organization for Rare Diseases, Neurofibromatosis Northwest, Neurofibromatosis Midwest, Neurofibromatosis Forward, National Natural Science Foundation of China, Japan Society for the Promotion of Science, and The Japanese Neuroscience Society.

Figure 5. NF Funding Timeline by Major Organizations

The NFRP Programmatic Panel recommended funding strategies over the years to address gaps in research while complementing funding by other organizations. The NIH is the largest funder of research on neurological diseases. Other funding organizations include public and private partners such as the CTF and the NTAP. A five-year snapshot of funding distribution by organization is shown in Figure 5. The NFRP continues to collaborate with NIH, CTF and NTAP. Member representatives of these organizations participate on the programmatic panel to maintain strategic alliance and determine funding priorities.

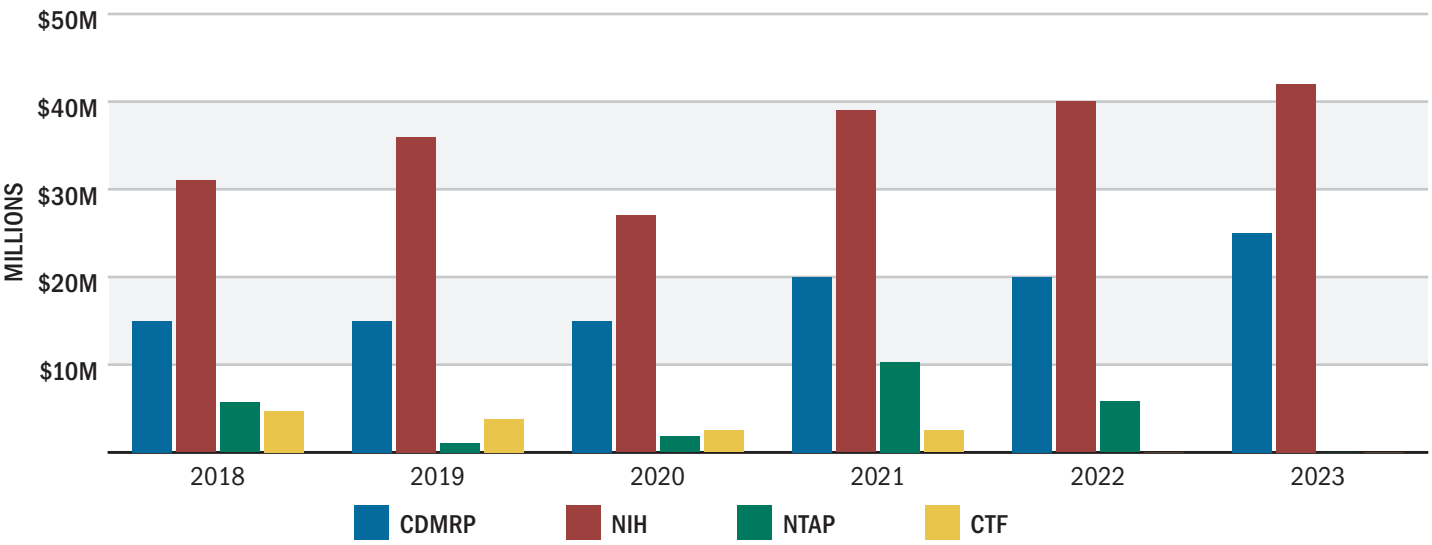


Figure 6. F18 – FY22 Investments by NFRP and Other NF-funding organizations

RESEARCH GAPS

Members of the NF Programmatic Panel include consumers, researchers, and clinicians, each representing the communities that they serve. Together, the programmatic panel recommends a strategy to address the varying needs of the NF community, while leveraging knowledge gathered through collaborations. This is done by guiding targeted research to address gaps and research areas of particular importance to the program which are termed as areas of emphasis. Programs annually revisit and revise areas of emphasis so that these program priorities always reflect current research trends. Currently, these are:

- NF2 and schwannomatosis-related areas, e.g., hearing, balance, schwannoma, ependymoma, meningioma, LZTR1, SMARCB1)*
- Endpoint validation, biomarker discovery, and technological innovation for assessments *
- Application of data science*
- Non-tumor manifestations not limited to:
  - o Pain
  - o Cognitive manifestations
  - o Sleep
- Heterogeneity of NF-related phenotypes
- Genetics, genomics, epigenetics, systems biology, metabolomics, or similar approaches*
- Preclinical efficacy studies
- Target identification and drug discovery
- Nutritional, environmental, and other modifiers of NF
- Health services research

*New or modified in FY22 and FY23

Figure 7 below shows the distribution by applicable areas of emphasis between FY17 and FY21. The largest funding investment areas and award counts aligned to the target identification and drug discovery category, followed by non-tumor manifestations and heterogeneity of neurofibromas. The "Other" category constitutes Clinical Trials Consortium Awards, which comprise both clinical trials and consortium infrastructure.

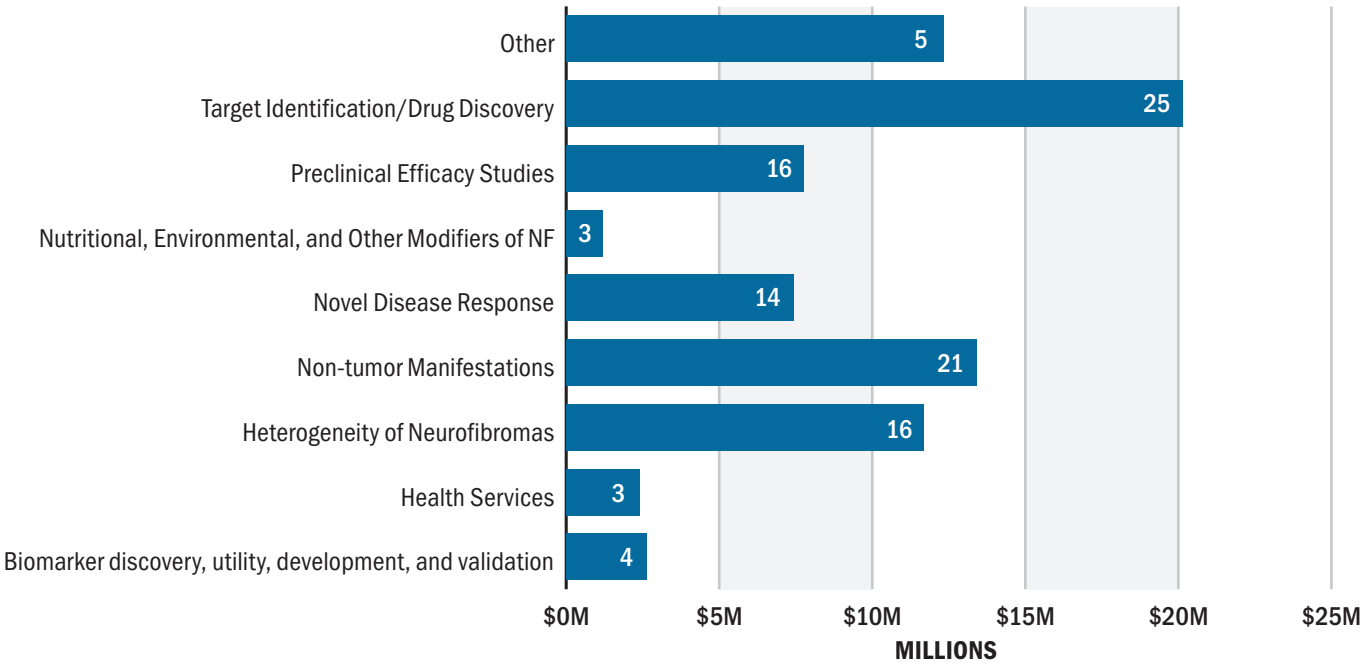


Figure 7. FY17 – FY21 Areas of Emphasis by Funding Amount and Number of Awards

STRATEGIC DIRECTION

The strategic direction for the NFRP is based on current research gaps in the NF community. The NFRP and NF community identified the most pressing research priorities, and needs as:

- Gaps in basic research
  - o Lack of support for the development of new concepts and ideas
  - o Lack of preclinical studies
  - o Lack of drug testing
  - o Lack of preclinical testing models mimicking the human condition
- Gaps in clinical trials infrastructure
- Small research community
- Lack of adequate support from biopharmaceutical companies
- Lack of basic/translational research in schwannomatosis

STRATEGIC GOALS

To better provide an overall perspective to the stakeholders, the NFRP identified four strategic goals to address the near- and long-term gaps and needs for the NF community of researchers, clinicians, and consumers. Funding opportunities and awards as they align with these goals are below.

STRATEGIC GOALS	Support Basic and Exploratory Research	Facilitate Therapeutic Development	Increase Research Capacity	Encourage Critical Research/Fill Gaps *All Mechanisms support Goal 4*
FUNDING OPPORTUNITIES	• Exploratory Hypothesis Development (EHDA) • Synergistic Idea Awards (SIA)	• Clinical Trial Award (CTA) • Investigator Initiated Research Award (IIRA)	• Early Investigator (EIRA) • IIRA with collaborators • New Investigator Award (NIA) • SIA	• EHDA • CTA • IIRA • NIA • EIRA • CTCA
NUMBER OF AWARDS	41 awards	20 awards	69 awards	101 awards
FUNDING AMOUNT	$18,370,112	$18,605,441	$49,391,073	$62,914,606

Figure 8. FY18 – FY22 Portfolio Investment by Strategic Goals

INVESTMENT STRATEGY

NEAR- TO LONG-TERM

- Fund innovation, new ideas, and generate preliminary data
- Support the transition of findings through preclinical and clinical testing of promising interventions
- Increase the number of NF investigators and resources
- Develop areas of emphasis

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