Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

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Neurofibromatosis Research Program

Neurofibromatosis and its impact on U.S. Service members, Veterans and their Beneficiaries: The underlying causes of neurofibromatosis (NF) have a direct relationship to tumor formation in many non-cancer sarcomas and malignant cancers. Furthermore, NF research holds clinical relevance for a multitude of significant medical issues including chronic pain, mechanisms of bone and peripheral nerve repair, vision and hearing loss, attention deficit disorder and cognitive disability.

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

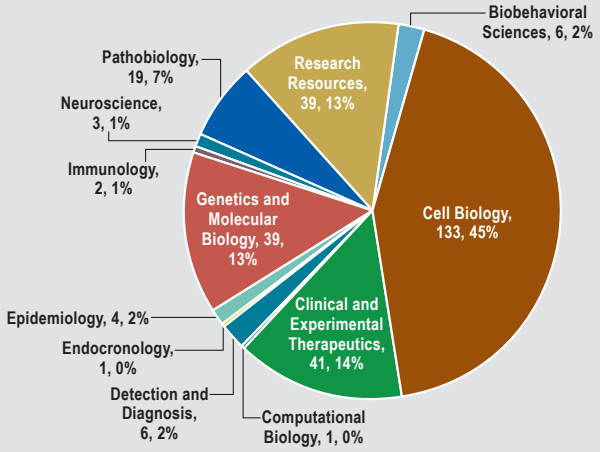
PROGRAM HISTORY

The Department of Defense Neurofibromatosis Research Program (NFRP) was established in fiscal year 1996 (FY96), when the efforts of NF advocates led to a Congressional appropriation of $8 million (M). Since that time, $332.9M has been appropriated to the program, including $15M in FY18. Over its 22-year history, the NFRP has invested in key initiatives to support development of critical resources, sponsor multidisciplinary collaborations, bring talented investigators into the field, and promote the translation of promising ideas into the clinic. The program's research portfolio includes 385 awards spanning basic, translational, and clinical research through FY17.

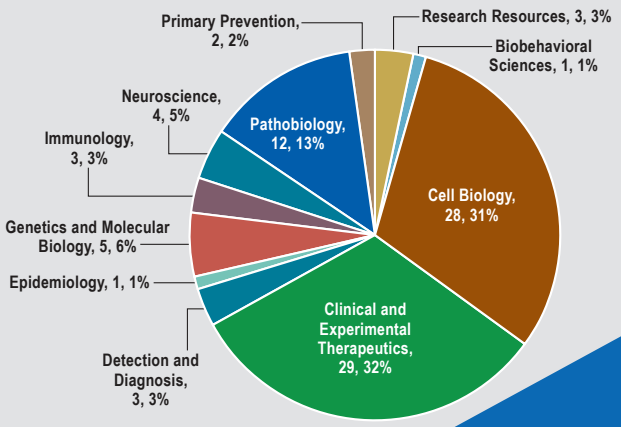
PORTFOLIO OF RESEARCH INVESTMENTS

The NFRP's research portfolio encompasses the range of research spanning, from basic research to advance understanding of the biological basis of NF to preclinical testing of promising therapeutics to clinical trials.

FY96-FY12



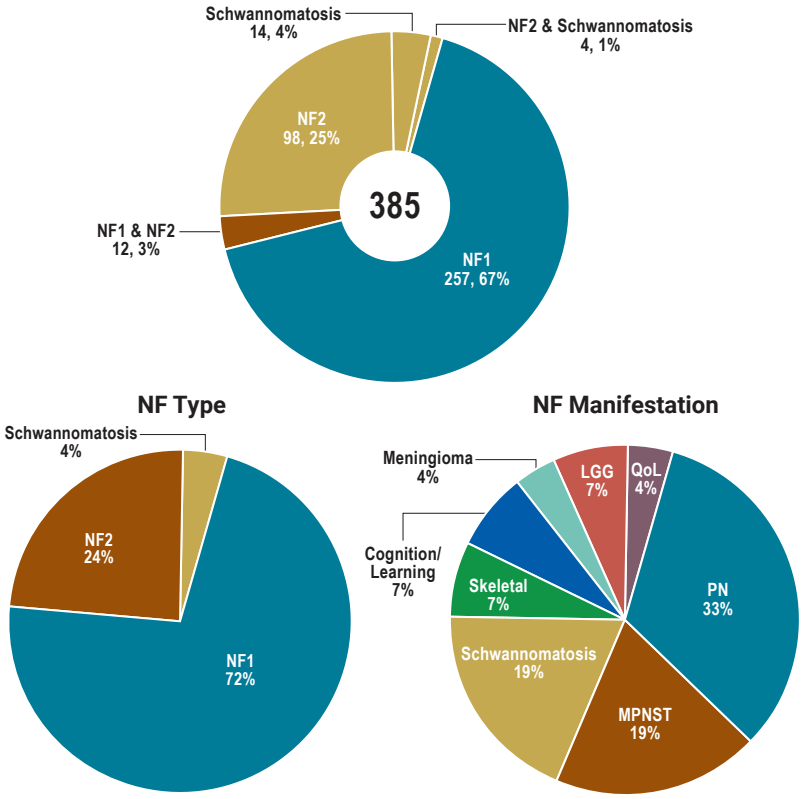
FY10-FY17



NFRP investments also span the three different types of NF that impact those affected.

ADVANCING AND TESTING OF PROMISING THERAPEUTICS

- A major focus of the NFRP has been testing promising therapeutics through clinical trials for treatment of several NF manifestations. Over $42M has been invested in 27 clinical trials to date.
- In 2004 the NFRP Clinical Trials Consortium (NFCTC) was established to develop and execute biologically based therapies for NF. Consisting of an Operations Center and 22 Clinical Centers, the NFCTC represents an investment of $30M, resulting in support for 14 trials.
- A portfolio of research focused on Mitogen-Activated Protein Kinase (MEK) inhibitors as a potential therapeutic has resulted in advances in basic science that led to several clinical trials.
- Funded projects test Food and Drug Administration-approved drugs used for other conditions that may have therapeutic potential for NF manifestations, including learning disabilities, schwannomas, and meningiomas.



LGG = low-grade gliomas; PN = plexiform neurofibroma; QoL = quality of life.

NFRP Investments in Clinical Trials for Treatment of NF1, NF2, and Schwannomatosis by Percentage

INCREASING RESEARCH CAPACITY

- To support the research community, the NFRP has invested in future NF researchers who have the potential to make important contributions to the field. Since 1999, $39M has been invested in 68 new investigators.
- Since inception of the NFRP, over $37M has been invested in research producing over 100 resources that are vital to conducting basic and translational research, including cell lines and mouse models. Resources are readily shared among researchers to build collaborations.

RECENT RESEARCH HIGHLIGHT

IDENTIFICATION OF MOLECULAR AND CELLULAR CONTRIBUTIONS TO NEUROFIBROMA FORMATION AND GROWTH

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

In NF1, both copies of the NF1 gene in Schwann cells (SC) lose their function to regulate the Ras family of oncogenic proteins. With an FY11 NFRP Investigator-Initiated Focused Research Award - Optional Qualified Collaborator, Dr. Ratner's team sought to study neuron-SC disruption and tumorigenesis, as well as identify cellular and molecular steps in neurofibroma formation. Dr. Ratner's team discovered that Pexidartinib (PLX3397), a drug that blocks macrophage infiltration, was more effective in established tumors, compared to early-stage small tumors. This connects to evidence that, as a tumor becomes more established, macrophages are recruited as a part of the immune response, indicating that macrophage inhibitors could represent a therapeutic strategy for established neurofibromas. SC and macrophage gene expression data from mouse neurons with functional *Nf1* genes (*Nf1*+/+) or *Nf1* mutant (*Nf1*-/-) neurons revealed that *Nf1*-/- SC and macrophages did not significantly differ from their normal counterparts, but there were significant differences in neurofibroma cytokine gene expression. In addition, computational reconstruction of molecular networks and signaling predicted the changes in cytokines, chemokines, and growth factors. These predictions verified the presence of a macrophage chemo-attractant and predicted a role for type-1 interferon (IFN). This work confirmed the computational prediction of type-1 IFN expression in neurofibromas and showed that treatment of neurofibroma-bearing mice with polyethylene glycolyated type-1 IFN-alpha-2b reduced overexpression of cytokines. These results are consistent with the observed reduction of neurofibroma growth in a Phase II trial of PEGylated IFN-alpha-2b (NCT00678951). Findings from Dr. Ratner's group under this award have improved understanding of neurofibroma formation through identification of several potential interactions between *NF1*-/- SCs and macrophages.

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