

## DoD Neurofibromatosis Research Program (NFRP)

*Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.*

Year	NFRP Research Contributions	Additional Information and Hyperlinks
1996	Dr. Margaret Wallace identified that the loss of neurofibromin is associated with tumorigenesis.	
1996	Dr. Mia MacCollin established associations between types of NF2 mutations and clinical features, and she also developed novel methods for detecting NF2 mutations.	
1996	Dr. Tyler Jacks developed the first mouse model of NF1-related MPNSTs.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> <li>• <a href="#">NFRP News Highlight</a></li> </ul>
1996	Dr. Luis Parada characterized loss of NF1 in various cell types and demonstrated that loss of NF1 in the Schwann cell lineage was sufficient to generate tumors.	
1996	Dr. J.M. Friedman determined clinical features of NF1 such as Lisch nodules, intertriginous freckles, and café-au-lait spots often cluster together in individual patients and within affected families.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
1996	Dr. Channing Der provided evidence that the Nf2 gene strongly inhibits Ras and Rac function in cultured cells, and inhibits Rac-induced formation of colonies in soft agar (a sign that cells have become cancerous).	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
1996	Dr. Camilynn Brannan generated mice lacking neurofibromin type II and finds that the adult mice show specific impairments in spatial learning, contextual discrimination, and motor coordination. The results from this novel mouse model suggest that learning deficits in NF1 patients could result from the disruption of neurofibromin type II function.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
1997	Dr. Bruce Korf studied the natural history of NF1 plexiform neurofibromas and established volumetric MRI as the standard approach for measuring these tumors in clinical trials.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
1997	Dr. William Slattery III established a consortium of nine international sites to study natural history of NF2 and developed standard operating procedures for MRIs and an NF2-specific database.	
1998	Dr. Andrea McClatchey provided insight into the function of the NF2 (merlin) protein, which acts as a tumor and metastasis suppressor by controlling cell–cell contact.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
1998	Dr. Andrea McClatchey provided insight into the function of the NF2 (merlin) protein, which acts as a tumor and metastasis suppressor by controlling cell–cell contact. Research results provided evidence to suggest that loss of merlin may result in the disruption of normal cellular junctions, cell-to-cell communication and, ultimately, contact-dependent growth inhibition leading to tumor growth and metastasis.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
1999	Dr. Kathryn North established that MRI T2 hyperintensities measured in children with NF1 are a good predictor of cognitive dysfunction in adulthood.	
1999	Dr. Karen Stephens used MRI to detect schwannomas in a transgenic mouse model of NF2.	

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1999	Dr. Klaus Scheffzek identified and solved the crystal structure of a novel bipartite molecule of neurofibromin, NF1-Sec-PH. Mutations in the NF1-Sec-PH domain have been identified in NF1 patients, indicating that this region may be critical for the maintenance of normal cellular and molecular function.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
1999	Dr. Raymond Mattingly identified an inhibitor of the MAP kinase pathway that decreases the ability of neurofibrosarcoma cells to grow.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
1999	Dr. Andreas Kurtz found mitochondrial DNA mutations present in normal tissues from NF1 patients and demonstrated that these mutations accumulate in neurofibromas. These findings suggest that mitochondrial aberrations may contribute to neurofibroma growth and development.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2000	Dr. William Slattery III characterized growth rates and clinical course of tumors associated with NF2.	
2000	Dr. Margaret Wallace demonstrated that steroid hormones can significantly affect the growth of NF1 tumor cells.	
2001	Dr. Kevin Shannon developed mouse models of MPNSTs, PNF, astrocytomas, and ependymomas for assessing the mutagenic potential of NF1 tumor therapies.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Video Highlight</a></li> <li>• <a href="#">NFRP News Highlight</a></li> </ul>
2001	Dr. Alcino Silva demonstrated that lovastatin treatment reverses learning deficits in an Nf1 mouse model.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2002	Dr. Raymond Mattingly demonstrated that a novel farnesyltransferase inhibitor combined with lovastatin reduces proliferation and induces apoptosis of MPNST cells, and is a potential treatment for NF1 MPNSTs.	
2002	Dr. Karen Cichowski demonstrated that neurofibromin regulates the mTOR pathway, through activated Ras.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Video Highlight</a></li> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2002	Dr. David Muir determined that angiogenesis (formation of new blood vessels), required for the growth of tumors, in response to low oxygen levels, is higher in the retinas of mice lacking the NF1 gene (Nf1+/- mice) than in normal mice. Additionally, he showed that a protein called fibroblast growth factor 2 enhances angiogenesis in the corneas of Nf1+/- mice compared to control mice.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2002	Dr. Cynthia Hingtgen investigated the underlying mechanism of neurofibromatosis-associated pain and demonstrated that NF1 neurons have enhanced excitability, firing with much less stimulation and firing more frequently from a single stimulation.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2002	Dr. Wallace Ip revealed that Merlin is attached to lipid rafts in the cell membrane and its activation is accompanied by the dissociation of merlin-containing lipid rafts from the cell's cytoskeleton. Merlin is the first tumor suppressor to be identified as localized to lipid rafts.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2002	Dr. David Gutmann provided results that suggest K-Ras is the primary target for neurofibromin in astrocytes, and that excessive activation of K-Ras plays a critical role in the formation of NF1 gliomas.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2003	Dr. Robert Martuza developed a herpes simplex virus vector therapy for NF2 that reduces schwannoma tumor volume in an NF2 mouse model.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2003	Dr. Nancy Ratner identified and validated a 159-gene signature that distinguishes MPNST cells from normal Schwann cells. Many of these genes have been implicated in other cancers, suggesting that therapeutics developed for other types of tumors may be useful for the treatment of MPNSTs.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>

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2003	Dr. Andre Bernards provided evidence in <i>Drosophila</i> that suggests the cAMP/PKA-induced restoration of growth involves a function downstream in the Ras signaling pathway, as opposed to a separate, Ras-independent signaling event.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2003	Dr. Jan Dumanski used array-comparative genomic hybridization (CGH), a cutting-edge genetic analysis technology, and found no correlations between specific deletions in the NF2 gene (also called merlin or schwannomin) and disease severity, suggesting that the observed variability may be caused by other genes that affect NF2 symptom development.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2003	Dr. Michael Stern identified an uncharacterized role for PI3K in regulating the relative excitability of neurons in vivo and suggested that some of the deficits in certain neurological disorders might result from disruption of glutamate-mediated homeostasis.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2004	Dr. Karen Cichowski identified a negative feedback signaling pathway that protects benign lesions from becoming malignant in patients with NF.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Video Highlight</a></li> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2004	Dr. Feng-Chun Yang demonstrated that the growth factor TGF-beta secreted from mast cells plays a critical role in the initiation and progression of neurofibromas.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2005	Dr. Allan Belzberg developed the tibial neuroma transposition animal model of neuroma pain and hyperalgesia associated with neuropathic pain that allows researchers to test pain in response to mechanical stimulation of the neuroma rather than mechanically increased sensitivity to pain.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2005	Dr. Victor-Felix Mautner demonstrated that imatinib mesylate (Gleevec®) inhibits Schwann cell viability and reduces the size of PNF in a xenograft model, and reduces tumor volume of PNF fragments obtained from NF1 patients.	
2005	Dr. David Gutmann developed a non-invasive technique to detect optic glioma in a mouse model of NF1. In further studies exploring alternative approaches for the treatment of NF1-associated brain tumors, Dr. David Gutmann demonstrated that neurofibromin negatively regulated STAT3 activity, leading to STAT3 hyperactivation in NF1-deficient cells. He also showed that Curcubitacin-I, a known inhibitor of STAT3, was able to decrease NF1-deficient MPNST cell and tumor growth in vivo.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight, 2005</a></li> <li>• <a href="#">NFRP Research Highlight, 2010</a></li> </ul>
2005	Dr. Marlan Hansen demonstrated the ErbB2 signaling pathway is essential for vestibular schwannoma growth and an attractive therapeutic target.	
2005	Dr. Anita Lal engineered merlin-deficient and merlin-expressing human meningioma cells to characterize the phenotypic effects of merlin loss in an NF2 environment.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2005	Dr. Marlan Hansen demonstrated the ErbB2 signaling pathway is essential for vestibular schwannoma growth and an attractive therapeutic target.	
2006	Dr. Bruce Korf and colleagues established the NF Clinical Trials Consortium.	<ul style="list-style-type: none"> <li>• <a href="#">Neurofibromatosis Clinical Trials Consortium</a></li> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2006	Dr. Samuel Rabkin developed a strategy to treat MPNSTs in mice models by injecting oncolytic herpes simplex virus (oHSV) to grow within tumor cells in order to kill them while sparing normal cells.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>

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2007	Dr. Feng-Chun Yang developed a mouse model of NF1 that displays similar skeletal manifestations as humans with NF1.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight, 2008</a></li> <li>• <a href="#">NFRP Research Highlight, 2009</a></li> <li>• <a href="#">NFRP Research Highlight, 2010</a></li> <li>• <a href="#">NFRP Research Highlight, 2014</a></li> </ul>
2007	Dr. Karen Cichowski established that different mechanisms of NF1 inactivation occur in different tumors, which may result in changes in the tumor response to specific therapies.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Video Highlight</a></li> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2008	Dr. Nancy Ratner compared and contrasted gene expression patterns associated with NF1 neurofibroma development and progression to malignant tumors. These experiments and others with the MEK inhibitor PD0325901, demonstrated that deregulated Ras/ERK signaling is critical for the growth of NF1 peripheral nerve tumors.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight, 2006</a></li> <li>• <a href="#">NFRP Research Highlight, 2013</a></li> </ul>
2009	Dr. Duoqia Pan revealed multiple layers of evidence linking Merlin to the Hippo genetic signaling pathway, an important signaling pathway in cancer development.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight, 2010</a></li> <li>• <a href="#">NFRP Research Highlight, 2015</a></li> </ul>
2009	Dr. David Gutmann discovered that reduced brain dopamine levels are responsible for cognitive impairments in an NF mouse model which displays cognitive impairments that mirror those seen in children with NF1, including abnormal exploratory behaviors and spatial learning and memory deficits. He also provided preclinical evidence to suggest that there may be a subset of children with NF1-associated learning disabilities that may respond more favorably to dopamine-targeted therapies, and that these children could be identified using non-invasive PET imaging techniques.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight, 2012</a></li> <li>• <a href="#">NFRP Research Highlight, 2014</a></li> </ul>
2009	Dr. Elizabeth Schorry examined copy number variants (CNVs), genetic changes that may occur after conception, in identical twins with differing NF1 symptom severity, to better enable clinicians to identify patients that pose a higher risk of complications from the disorder.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2009	Dr. Jeremie Vitte developed a preclinical animal model to analyze the role of Snf5 in Schwann cell tumor development and schwannomatosis-related neurological pain.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2010	Dr. Wei Mo showed that CXCR4/CXCL12 mediates the cell-cycle progression in NF1-associated malignant peripheral nerve sheath tumor (MPNST).	
2010	Dr. Yuan Zhu demonstrated that deregulated ERK signaling is critical for the development of some of the brain abnormalities associated with Nf1 gene inactivation, identified a potential therapeutic agent (PD0325901), and highlighted a window of opportunity for treating children with NF1-associated brain abnormalities.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2010	Dr. Feng-Chun Yang demonstrated that dysregulated TGF- $\beta$ 1 signaling is a primary factor underlying the pathogenesis of NF1-associated osteoporosis and non-union fracture.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2011	Dr. Bruce Korf expanded the NF Clinical Trials Consortium to include clinical trials for NF2.	<ul style="list-style-type: none"> <li>• <a href="#">Neurofibromatosis Clinical Trials Consortium</a></li> </ul>
2011	Dr. D. Wade Clapp developed an NF2 mouse model that forms intracranial vestibular schwannomas and meningiomas, the most common brain tumors found in patients with NF2, and develops progressive hearing loss as well.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>
2012	Dr. Lu Le developed a novel 3D cell culture model of a neurofibroma and a novel MPNST mouse model, both from skin-derived precursors (SKPs), to study the evolution of neurofibromas and to identify pharmacological inhibitors that target these tumors.	<ul style="list-style-type: none"> <li>• <a href="#">NFRP Research Highlight</a></li> </ul>