# 8 Bold Minds, $888K to Fuel the Future of NF Research



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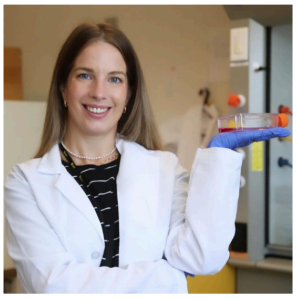
Children's Tumor Foundation invests in Young Investigators with research projects focused on hearing loss, *NF2*-SWN drug therapy, pain, learning difficulties, cutaneous neurofibromas, skeletal defects, and MPNSTs

The Children's Tumor Foundation (CTF) is excited to announce a significant investment of over $888,000 in research focused on neurofibromatosis type 1 (NF1) and all forms of schwannomatosis (SWN), including *NF2*-related schwannomatosis (*NF2*-SWN). These funds will be distributed through CTF's Young Investigator Awards (YIA), a grant program designed to support pioneering research by early-career scientists and clinicians.

**Proteome analysis of inner ear fluids in *NF2* mouse models with hearing loss**
Isam Naber, University of California, Los Angeles
*NF2*-related schwannomatosis often leads to gradual, irreversible hearing loss but the degree of hearing loss does not always correlate with vestibular schwannoma growth. Also, vestibular schwannoma patients have a buildup of precipitated protein in their inner ear but its significance is not understood. Using two different mouse models, both of which experience hearing loss but show differences in inner ear protein buildup and schwannoma development, this study will investigate the mechanism of hearing loss associated with vestibular schwannoma. Examining the proteins detected in the two mouse models could lead to identifying potential biomarkers linked to and the mechanism behind hearing loss in *NF2*-SWN vestibular schwannoma patients.



**Deciphering crucial cell death pathways in *NF2*-related schwannomatosis**
Anna Nagel, University of Central Florida
Histone deacetylase (HDAC) inhibitors are being investigated as therapeutic agents for *NF2*-related schwannomas. This study aims to understand the mechanism by which a dual HDAC/PI3K inhibitor, CUDC-907, induces apoptosis of *NF2*-related schwannomas. Because HDAC inhibition affects many cell processes that can lead to adverse drug effects, understanding the mechanistic details can help identify novel targets or safer drug combinations for *NF2*-related schwannoma therapy.

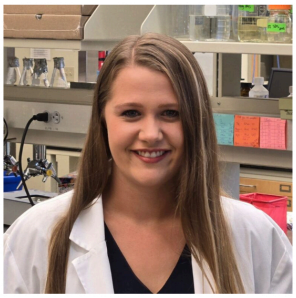
**Exploring the Interplay between Lipid Metabolism and LZTR1 in Peripheral Nerve Pathologies**
Georgia Daraki, Leibniz Institute on Aging, Germany
Patients with LZTR1-related schwannomatosis experience higher levels of pain compared to schwannomatosis patients with other pathogenic variants, but the association between LZTR1 gene and neuropathic pain is poorly understood. Preliminary studies indicate a role for LZTR1 in lipid metabolism, with the deficiency leading to problems with fatty acid metabolism and composition, which in turn affects the protective myelin sheath around nerves. This research will investigate the mechanism of pain development due to LZTR1 loss, the role of LZTR1 in lipid metabolism, and the effects of LZTR1 deficiency in peripheral nerve disease.

**Genetic and molecular investigation of the neuronal functions of NF1**

Alex Dyson, Massachusetts General Hospital
Neurofibromatosis type 1 (NF1) is often associated with neurological complications like learning difficulties, ADHD, and autism. However, precisely how NF1 gene variations affect brain development and activity to cause these issues is poorly understood. Using a Drosophila (fruit fly) model of NF1, this study aims to identify the regions of neurofibromin required for its interaction with other proteins involved in brain cell function, how disrupting these interactions results in behavioral changes, and these changes can be improved by administering small-molecule drugs.

**Identification and Functional Validations of Actionable Targets for Prevention or Treatment of Cutaneous Neurofibromas and Characterization of NF1 Healthy-Looking Skin**
Pernelle Pulh, INSERM, France
Almost all NF1 patients develop non-cancerous tumors called cutaneous neurofibromas (cNFs) in the skin. These tumors cause significant cosmetic burden, and currently there is no treatment to prevent or reverse their development. This study will identify the proteins overexpressed in growing and mature cNFs, and validate them as targets for prevention or treatment of cNFs. The project's secondary goal is to analyze the impact of a double mutation of NF1 that occurs during embryonic development long before the development of cNFs. This will help to better understand the cNFs-related heterogeneity seen in NF1 patients.

**Pathways that drive inflammation and EMT in Schwann cells after NF1 loss**
Ramya Ravindran, Cincinnati Children's Hospital Medical Center
The development of plexiform neurofibromas in NF1 is marked by the activation of inflammation associated pathways in Schwann cells and by increased presence of markers of a cellular differentiation process called Epithelial to Mesenchymal Transition (EMT). This study will test the hypothesis that NF1 loss in Schwann cells specifically activates the NF-kB inflammation pathway to cause EMT, which in turn promotes plexiform neurofibroma development. This study will also test if inhibiting the NF-kB pathway affects plexiform neurofibroma formation in vivo.



**Developmental Analyses of Skeletal Manifestations in "Mild" Neurofibromatosis Type I Patient Mutation p.M992del in Knock-In Mouse Model**
Alexis Stillwell, Pennington Biomedical Research Center
NF1 is characterized by a wide range of clinical manifestations, some of which are very severe complications while some others may be mild. One such mild manifestation is due to a single amino acid deletion at position 992 in the neurofibromin protein. Patients with p.M992del are clinically described as Noonan-like phenotype due to short stature, scoliosis, heart defects, and abnormal chest wall development, along with learning disabilities and cognitive impairment. Using a novel mouse model recapitulating the "mild" p.M992del NF1 gene variation, this study will study how bone cells and their precursors are affected due to this variation and will tease out the pathways disrupted disrupted to more thoroughly understand how skeletal defects happen in NF1 patients.

**Investigating the role of ZNF423 in NF1-related MPNST**
Sarah Morrow, Indiana University
The main cause of death in NF1)patients is the development of malignant peripheral nerve sheath tumors (MPNST). These tumors are rare and highly aggressive and can arise from non-cancerous growths called plexiform neurofibromas (PNF). When tumors progress from PNF to MPNST, levels of a protein known as ZNF423 markedly increase, indicating that ZNF423 may be vital for MPNST survival. Experimentally reducing the levels of ZNF423 in MPNST cells significantly reduced their growth. Hence, the aim of this study is to further analyze how ZNF423 contributes to the growth and survival of MPNST to uncover novel, druggable targets or therapeutic strategies.

Click here to learn more about the Young Investigator Awards and other opportunities for funding.

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