YOUNG INVESTIGATOR AWARDS 2024

The Children's Tumor Foundation is excited to announce a substantial commitment of over $888,000 in research focused on NF1, *NF2*-SWN, and *LZTR1*-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.

ISAM NABER, MD

University of California, Los Angeles

Proteome Analysis of Inner Ear Fluids in NF2 Mouse Models with Hearing Loss

NF2-related schwannomatosis (*NF2*-SWN) 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 hearing loss associated with vestibular schwannoma. Examining the proteins detected in the two mouse models could identify potential biomarkers linked to and the mechanism behind hearing loss in *NF2*-SWN vestibular schwannoma patients.

PERNELLE PULH, PhD

INSERM, France

Identification and Functional Validations of Actionable Targets for Prevention or Treatment of Cutaneous Neurofibromas and Characterization of NF1 Healthy-Looking Skin

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 the 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 understand better the cNFs-related heterogeneity seen in NF1 patients.

GEORGIA DARAKI

Leibniz Institute on Aging, Germany

Exploring the Interplay Between Lipid Metabolism and LZTR1 in Peripheral Nerve Pathologies

Patients with *LZTR1*-related schwannomatosis (*LZTR1*-SWN) 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, affecting 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.

ALEXIS STILLWELL

Pennington Biomedical Research Center

Developmental Analyses of Skeletal Manifestations in "Mild" NF1 Patient Mutation p.M992del in Knock-In Mouse Model

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 this deletion (p.M992del) are clinically described as having 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 to more thoroughly understand how skeletal defects happen in NF1 patients.

ANNA NAGEL, PhD
University of Central Florida

Deciphering Crucial Cell Death Pathways in NF2-SWN

Histone deacetylase (HDAC) inhibitors are being investigated as therapeutic agents for *NF2*-related schwannomas. This study aims to understand how 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.

ALEX DYSON, PhD
Massachusetts General Hospital

Genetic and Molecular Investigation of the Neuronal Functions of NF1

Neurofibromatosis type 1 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 how these changes can be improved by administering small-molecule drugs.

RAMYA RAVINDRAN
Cincinnati Children's Hospital Medical Center

Pathways that Drive Inflammation and EMT in Schwann Cells after NF1 Loss

The development of plexiform neurofibromas in NF1 is marked by the activation of inflammation-associated pathways in Schwann cells and by the 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 activates the NF-kB inflammation pathway to cause EMT, which promotes plexiform neurofibroma development. This study will also test if inhibiting the NF-kB pathway affects plexiform neurofibroma formation in vivo.

SARAH MORROW
Indiana University

Investigating the Role of ZNF423 in NF1-Related MPNST

The leading 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 (PNs). When tumors progress from PN 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, this study aims to analyze further how ZNF423 contributes to the growth and survival of MPNST to uncover novel, druggable targets or therapeutic strategies.