YOUNG INVESTIGATOR AWARDS 2023

The Children's Tumor Foundation is pleased to announce the 2023 Young Investigator Award recipients of this latest round of funding, an investment of nearly $1.2 million through the CTF Discovery Fund. These exciting new projects span all types of NF, including NF1, *NF2*-SWN, and SWN. The YIA is the Foundation's oldest grant-giving mechanism, given to early-career researchers. CTF's seeding of the NF field with new talent has been hailed as one of the key reasons for rapid advancements in NF research in recent years.

JADWIGA BILCHAK

University of Pennsylvania

Investigating the Link Between Sensory and Social Deficits in a Drosophila Model of Neurofibromatosis Type I

NF1 is characterized primarily by tumors of the nervous system, but in addition, up to 50% of patients experience learning and social communication deficits. The present study will investigate the molecular mechanisms in sensory neurons affected by *NF1* variants and how disrupted sensory messages are transformed in the brain to shape behavior. The results from this study will shed light on how *NF1* affects behavioral circuits in the brain and how this relates to differences in social interactions.

SRIRUPA BHATTACHARYA

Massachusetts General Hospital

To Understand the Role of Apelin-Mediated Angiogenesis in NF2-Associated Tumors

NF2-associated tumors have shown inconsistent response to treatment with the antiangiogenic drug bevacizumab (Avastin), which targets vascular endothelial growth factor (VEGF). Avastin can cause severe side effects like bleeding and high blood pressure. Previous work from the Ramesh lab showed increased expression of the angiogenic peptide apelin (APLN) in *NF2*-negative tumor cells. This study aims to understand the role of apelin in NF2 tumors and will explore if targeting apelin disrupts angiogenesis and tumor growth.

ROOPE KALLIONPÄÄ

University of Turku, Finland

Risk Factors and Characteristics of NF1-Associated Cancer

NF1 increases the risk for various cancers, such as MPNST and breast cancer, and such cancers are a major cause of premature deaths among individuals with NF1. The three main objectives of this study are determining the risk for multiple cancers in individuals with NF1, determining the role of family history in cancer risk in NF1 and correlating it with NF1 gene variants, and identifying breast cancer characteristics unique to NF1. The study will analyze a Finnish cohort of over 1800 NF1 patients, for whom data are also available through other comprehensive Finnish population and disease registers. Results from this analysis can lead to improved personalized care strategies for NF1 patients.

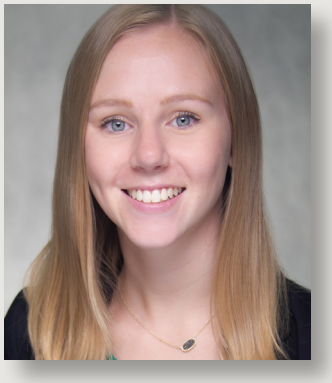
CLARA NOGUE I ANSON

IDIBELL Spain

Dissecting DGCR8 Syndrome and the Molecular Mechanisms Driving DGCR8-Associated Schwannomatosis

The Rivera group recently identified a variant in the *DGCR8* gene, also located on chromosome 22, responsible for a familial form of multinodular goiter that manifests together with peripheral schwannomas. This proposal will investigate the characteristics of *DGCR8*-mutated schwannomas and identify the mechanisms that lead to their formation. Given the global role of *DGCR8* in cellular processes, knowledge of key dysregulated events in *DGCR8*-schwannoma formation can also apply to other schwannomas with alterations on chromosome 22.

ALEXA SHEEHAN
The University of Iowa



Mechanisms of MPNST Metastasis

Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive tumors with high metastasis rate and poor clinical prognosis in NF1 patients. The present study will test newer formulations of Lox inhibitors, which are more specific and less toxic, to decrease MPNST metastasis. Since PRC2 loss also changes global gene expression in MPNSTs, this study will also test a second category of drugs called epigenetic modulators for their effect on metastasis. Overall, this study will determine if targeting Lox proteins induced by PRC2 loss is a viable treatment option for patients with metastatic MPNST.

ADITYA SHETH
Indiana University

CENPF as a Biomarker and Therapeutic Target for NF1-Associated MPNST

Preliminary data shows that the *CENPF* gene, which codes for the Centromere Protein F (CENPF), is activated when plexiform neurofibromas (PNFs) progress into MPNSTs. Higher levels of CENPF are detected in MPNSTs compared to PNFs, suggesting that this gene may promote the progression of PNFs into cancerous MPNSTs. This study will evaluate whether increased CENPF correlates with PNF progression and whether CENPF loss prevents MPNST formation.

JUN SUN
Weill Medical College of Cornell University

A Skeletal Stem Cell Basis and Novel Therapeutic Approaches for Fracture Healing Defects in NF1

Pseudarthroses or non-healing fractures are major skeletal manifestations of NF1 that contribute to overall pain and disability. MEK inhibitors, which are effective against NF1 tumors, are not clearly known to treat skeletal problems in NF1. This study will investigate the mechanism by which *NF1* loss in skeletal stem cells contributes to impaired fracture healing, MEKK2's role in this process, and the effect of MEKK2 inhibitors in reversing this effect. It will also develop a method to selectively deliver drugs to the non-healing fractures, avoiding unwanted side effects in other organs.

SARA VEIGA
Massachusetts General Hospital

Tumor: Macrophage Interactions in Schwannoma

Schwannomas are made of different cell types, including Schwann cells, axons (part of a nerve cell), blood vessels, immune cells, and an extracellular matrix. This complex microenvironment makes tumors very heterogeneous and is also suspected to contribute to the diverse clinical response of these tumors to drugs. Macrophages, a type of immune cells, are found in developing schwannomas and influence the presence or absence of pain. However, how these immune cells are recruited to the tumor is poorly understood. The goal of this proposal is to study how macrophages are recruited to schwannomas and to understand how they interact with schwannoma tumor cells to help the tumor grow. This understanding will be valuable for developing new therapies to fight tumor growth and alleviate symptoms such as pain.

ZHENZHEN YIN
Massachusetts General Hospital

Co-Targeting HMGB1 and EGF Signaling for the Treatment of NF2 and Associated Hearing Loss

Preliminary studies have shown that a protein called HMGB1, a potent inflammation initiator and amplifier is released by schwannomas and can cause inflammation in the ears, leading to hearing loss. The aim of this study is to test if blocking HMGB1 can prevent hearing loss in mice. Since the HMGB1 blockade activates epidermal growth factor (EGF) signaling, which may compensate for tumor growth, this study will also explore how combined HMGB1 and EGF receptor (EGFR) blockade can prevent hearing loss and delay tumor growth in mice with schwannomas. The study will help us understand how HMGB1 causes inflammation in the ears and how we can stop the tumors from growing, which can be useful in designing future treatments for patients with vestibular schwannoma.