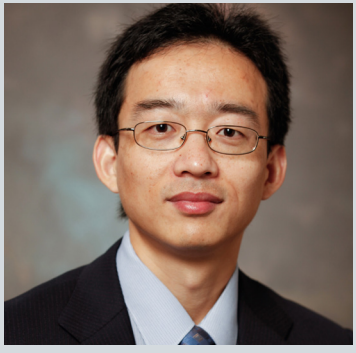
2023 NF1 Gene Therapy Awardees

The Children's Tumor Foundation is pleased to announce the funding of three 2023 awards as part of the NF1 Gene Therapy Initiative, a research program focused on gene-based therapeutic approaches for the treatment of NF1.



Jiangbing Zhou, PhD
Yale University

Targeted Delivery of Gene Replacement Therapy for NF1 Plexiform Neurofibromas

Award amount: $323,375.00 for a duration of two years

The goal of this project is to develop next-generation nanoparticles designed for targeted delivery of full-length human *NF1* cDNA preferentially to plexiform neurofibromas (pNF). This study will also characterize the therapy in animal models and target specific human pNF-relevant pathogenic variants. Successful completion of the study will result in novel therapeutic regimens for improved treatment of pNFs.

Harish Vasudevan, MD, PhD
University of California, San Francisco

Too Much of a GAP: Full-length NF1 Reconstitution in Neurofibroma and MPNST

Award amount: $329,445.00 for a duration of two years

This project aims to define the mechanistic effects, functional requirement, and anti-tumor efficacy of NF1 gene therapy in the peripheral nervous system. The researcher will study how full-length neurofibromin restoration differs from that of GAP-related domain (GRD) alone or an arginine finger mutant (R1276P) incapable of inactivating Ras. This study will be critical to define the parts of the *NF1* gene required for successful gene therapy for NF1.

Nicholas Boulis, MD
Emory University

Patient-derived Plexiform Neurofibromas Organoid Model for Drug Repositioning in Precision Medicine

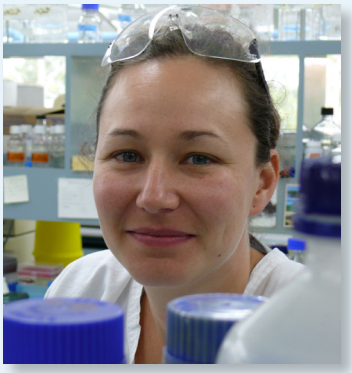
Award amount: $164,817.00 for a duration of one year

This study aims to develop a patient-derived pNF and MPNST organoid system that preserves tumor heterogeneity and microenvironmental features and can be used for both high-throughput pharmacological screening (HTS) as well as transplantation in patient-derived xenograft (PDX) models. Using a peripheral nerve tumor bank and an existing FDA-approved compound library, the study will identify candidates for translational therapy and demonstrate the proof of concept of this methodology in pNF and MPNST.

NF1 GENE THERAPY INITIATIVE

The Children's Tumor Foundation is pleased to announce the funding of two awards as part of the CTF NF1 Gene Therapy Initiative. Each award is for $240,000 for a total duration of two years. Peggy Wallace, PhD, a longtime associate of the Foundation, is the chief consultant for this initiative.

SAMANTHA GINN, PHD
Senior Research Officer, Children's Medical Research Institute, Australia
"A mutation-independent genome editing approach for the treatment of neurofibromatosis type 1 (NF1) using novel AAV vectors"



Dr. Ginn and her team propose to use a clustered regularly interspaced short palindromic repeat/Cas9 (CRISPR/Cas9) based homology-independent targeted integration (HITI) approach to replace large sections of mutated NF1 gene. In contrast to methods targeting individual patient-specific mutations, this approach has the advantage of targeting multiple mutations with a single gene editing vector, and thus will be applicable to many NF1 patients. To ensure clinical applicability, they will optimize the recombinant adenoassociated virus (rAAV) vector by screening and directed evolution, and test the approach in primary human Schwann cells. The ultimate goal of this study is to combine optimal gene editing tools with the most functional rAAV vectors to create reagents for in vivo NF1 editing.

JAMES WALKER, PHD
Assistant Professor, Harvard Medical School
"Development of NF1 therapeutics with CRISPR-based technologies"

Dr. Walker and his team aim to investigate the feasibility of using genome editing (both CRISPR-based homology-directed repair and base editing) as a therapeutic approach to correct three pathogenic NF1 mutations in cultured human Schwann cells. They will capitalize on recently developed CRISPR/Cas9 and -Cas12a variants, which increase the targeting range, activity, and fidelity (reducing off-targets) of gene editing. With a view to developing the most promising strategies into potential therapies for NF1 tumors, they will also initiate a screen to optimize viral vehicles for Schwann cells that will be essential for in vivo delivery of CRISPR genome engineering tools.