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.

**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.

**Jiangbing Zhou, PhD**
Yale University

**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.

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

**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.

**Nicholas Boulis, MD**
Emory University

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**CTF and American Academy of Pain Medicine Partner to Expand Field of Pain Studies in NF**

The Children’s Tumor Foundation and the American Academy of Pain Medicine (AAPM), a leader in pain study, prevention and care, have partnered to expand the number of investigators dedicated to the study of pain affecting the 2.5 million patients worldwide living with NF. The partnership announcement was made at the AAPM’s Annual Meeting this March.

Driven by the critical need to attract more researchers into the study of NF pain, CTF announced a request for applications that will provide up to $200,000 over 2 years to investigators new to NF, while also matching the researchers with CTF’s experts for collaboration and mentorship. Learn more at [ctf.org/aapm](http://ctf.org/aapm)
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.

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DRUG DISCOVERY INITIATIVE REGISTERED REPORTS

Two Drug Discovery Initiative Registered Reports Awards were granted for work on therapy resistance in NF2 and DNA damage in malignant peripheral nerve sheath tumors (MPNST).

KEILA E. TORRES, MD, PHD
MD Anderson Cancer Center

“Targeting DNA damage signaling and epigenetic deregulation as a combination therapy for malignant peripheral nerve sheath tumors”

People with neurofibromatosis 1 (NF1) are at risk of developing malignant peripheral nerve sheath tumors (MPNSTs) over the course of their lifetime. MPNSTs are aggressive tumors for which the only effective treatment is surgery. Often, though, the tumors grow back in the same location; thus, surgery to remove the MPNST may not always be an effective long-term treatment. The goal of this study is to address the lack of non-surgical treatments for MPNST by developing a therapy that combines two anti-cancer drugs to target pathways in the cell that are altered in MPNSTs. This research will measure how effective these anti-cancer drugs are when used together and will provide the preliminary results to help researchers decide whether this combination works well enough to be tested in people with MPNST.

CHUNLING YI, PHD
Georgetown University

“Evaluate Novel Hippo-Yap/Taz Inhibitors in Overcoming Therapy Resistance in NF2”

Hippo-Yap/Taz signaling pathway was identified as a major mechanism showed that NF2 tumor cells might be eradicated by combining a novel class of direct Hippo-Yap/Taz inhibitors with MEK inhibitors. Moreover, several other classes of drugs (including drugs that are FDA-approved and/or in clinical trials for NF2) synergize with Yap/Taz blockade in selective killing of NF2 schwannoma cells. This project will perform high throughput combination studies of four classes of drugs predicted by preliminary studies to be synergistic with clinical Hippo-Yap/Taz inhibitors developed by industry partner Vivace Therapeutics, and select the most efficacious combinations for testing in mice.