2024 **Drug Discovery Inititative** (DDI) **Awardees**

The Children's Tumor Foundation is pleased to announce a significant investment of more than $995,000 in Drug Discovery Initiative (DDI) Awards focused on drug discovery for the most challenging NF manifestations.

LJUBICA CALDOVIC, PhD
Children's Research Institute (CNMC)

Targeting PRMT5 in MTAP-Deleted NF1 High Grade Gliomas

NF1 is characterized by mutations in the *NF1* gene, which drive tumor growth by increasing Ras/MAPK pathway activity. While low-grade gliomas (LGGs) are common in children with NF1, these can transform into high-grade gliomas (HGGs) during adolescence, leading to poor survival outcomes. One frequent genetic mutation in NF1 HGGs is the deletion of the *MTAP* gene, found in 90% of cases. *MTAP* loss results in vulnerability to protein methyltransferase 5 (PRMT5) inhibitors. This project aims to test the efficacy of PRMT5 inhibitors, both alone and in combination with MEK inhibitors, in treating *MTAP*-deleted NF1 HGG cells. Initial studies suggest that PRMT5 inhibitors are more effective in *MTAP*-deleted cells and work synergistically with MEK inhibitors.

KIMBERLY OSTROW, PhD
Johns Hopkins University School of Medicine

GsMTtx-4 as a Novel Inhibitor to Block Non-NF2-SWN Pain

SWN frequently causes multiple painful tumors along major nerves, with limited treatment options available. Surgical removal is often impractical, and current pain management relies on trial-and-error medication approaches. This project seeks to investigate the use of GsMTx-4, a protein that has shown promise in blocking pressure-sensitive ion channels that trigger pain. Preliminary research has demonstrated that GsMTx-4 can reduce pain sensitivity in animal models, and this project aims to explore its efficacy in treating SWN-related pain. The research will evaluate whether GsMTx-4 can block the resulting pain sensitivity by using tumor-secreted products from painful schwannomas.

DAOCHUN SUN, PhD
The Medical College of Wisconsin

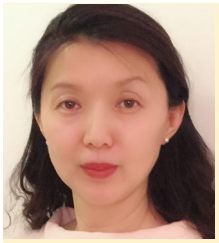
Repurposing Montelukast to Treat Plexiform Neurofibromas in Combination with Selumetinib

Selumetinib is the only FDA-approved drug for treating pediatric plexiform neurofibromas (PN), but its side effects and long-term safety raise concerns. This study proposes repurposing montelukast, an FDA-approved asthma drug, to reduce the required dose of selumetinib and enhance efficacy. Montelukast affects immune cells, specifically macrophages, which are abundant in the tumor microenvironment of NF1. Preliminary data indicate that montelukast can inhibit tumor-promoting macrophages while also reducing tumor cell growth. The study aims to test the combination of montelukast and selumetinib in cell lines and mouse models, exploring the impact on tumor growth and macrophage activity.

KEILA TORRES, MD, PhD
University of Texas M.D. Anderson Cancer Center

In Vivo Assessment of BET Blockade Combined with PARP Inhibition to Sensitize MPNST to Radiation Therapy

Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive, highly lethal tumors that affect up to 15% of NF1 patients. These tumors are resistant to chemotherapy and radiation, leaving few effective treatment options. This project explores a combination approach using BET inhibitors, which reduce DNA repair gene expression, and PARP inhibitors, which block DNA repair signaling. Both drugs have shown some efficacy in slowing tumor growth in MPNST models, but neither fully stops progression. The hypothesis is that combining these inhibitors with radiation therapy will enhance tumor cell death by impairing the tumor's ability to repair DNA damage.



LEI XU, MD
Massachusetts General Hospital

Targeting HIF-2 for the Treatment of NF2-SWN Vestibular Schwannoma

Patients with *NF2*-related schwannomatosis (*NF2*-SWN) often develop vestibular schwannomas, which can lead to hearing loss and significant tumor growth. Bevacizumab, an anti-VEGF therapy, has been a primary treatment, but some patients either cannot tolerate its side effects or experience tumor progression despite its use. This project investigates the use of belzutifan, an FDA-approved HIF-2 inhibitor, as a potential treatment for *NF2*-SWN. Since vestibular schwannomas exhibit abnormal blood vessel growth and low oxygen levels, belzutifan may help inhibit these processes. The research will test belzutifan in a mouse model of schwannomas, comparing its effectiveness to bevacizumab and evaluating its ability to rescue tumors that are resistant to anti-VEGF therapy. The ultimate goal is to identify new combination therapies that could prevent tumor growth and hearing loss in *NF2*-SWN patients.