2023 Drug Discovery Initiative (DDI) Awardees

The Children's Tumor Foundation is pleased to announce the 2023 Drug Discovery Initiative (DDI) award recipients, an investment of nearly $300,000 through the CTF Discovery Fund. The DDI stimulates NF drug discovery by funding researchers proposing to investigate novel or repurposed therapies for NF or to develop tools that support such research.

Sherif Ahmed
Massachusetts General Hospital

Development of Nanobody-decorated Bacterial Outer Membrane Vesicles for Schwannoma Immunotherapy

This research group recently showed that injecting attenuated *Salmonella typhimurium* alone or in combination with systemic checkpoint inhibitor directly into tumors in a schwannoma mouse model showed an anti-tumor effect. The present work, instead of using live bacteria, will utilize bacterial outer membrane vesicles (OMVs) for schwannoma therapy. OMVs are nanosized vesicles released by bacteria and possess the same immunostimulatory molecules, and preferentially accumulate in tumor tissues. Preliminary data showed that a single systemic injection of attenuated *S. typhimurium* OMVs, loaded with novel bispecific nanobody against CD74 and PDL-1 receptors, resulted in rapid tumor cell death and synergistic tumor regression in schwannoma mouse models, without any noticeable adverse effects. This study will further evaluate the effect of this novel therapy and investigate its long-term effects.

Dominique Lallemand
INSERM, France

Development of cell-penetrating peptides targeting the Yap/Tead complex in the context of NF 2

NF2-related schwannomatosis (*NF2*-SWN), characterized by the development of intracranial tumors, is caused by the inactivation of the *NF2* gene. The absence of merlin, the *NF2* gene product, inactivates the Hippo signaling pathway, resulting in the accumulation of YAP and TEAD proteins in the nucleus of affected cells. YAP and TEAD bind to each other and activate mechanisms that lead to tumor development. Thus, preventing the association of YAP with TEAD is a possible strategy to prevent tumor development. Previous work by the Lallemand group identified a candidate peptide that can enter cells and disrupt the binding of YAP to TEAD. The current study aims to improve this peptide to make it more stable and efficient at dissociating the YAP/TEAD complex. The study will also create new models of schwannomas that better replicate the proliferation of tumor cells and the growth of schwannomas.

Eduard Serra-Arenas
Health Sciences Research Institute of the Germans Trias i Pujol Foundation, Spain

Identification of Drugs Targeting Epigenetic Regulators in an iPSC-Based 3D MPNST Model

The Serra-Arenas group has developed a new cell-based model system for NF1 using induced pluripotent stem cells (iPSCs), cells that have the capacity to differentiate into any cell type. Using this system, they generated iPSCs with variants in multiple genes like in malignant peripheral nerve sheath tumors (MPNSTs). These cells can be grown in 3D spheres and exhibit the genetics and biological characteristics of MPNSTs. In this study, they propose to use this new 3D MPNST model system to rapidly screen ~600 compounds. Based on the results, a selected group of compounds will be tested further as single agents or in combination with other known drugs to identify new therapies for MPNST.

Lawrence Sherman
Oregon Health and Science University

Developing a Thrombopoietin Inhibitor to Treat NF2 Hearing Loss and Schwannoma Growth

Patients with *NF2*-SWN often suffer hearing loss, balance problems, and facial paralysis due to schwannomas on their acoustic nerves. The Sherman group previously found that a drug called losartan could prevent hearing loss in a mouse model of *NF2*-SWN. Although losartan is generally safe, it is unclear if it will be effective in *NF2*-SWN patients and sometimes has severe side effects. The proposed study will use a different drug, a thrombopoietin antisense oligonucleotide (TPO-ASO) that is being tested in clinical trials for other diseases and which also regulates platelets but does not have side effects linked to losartan. This study will test if TPO-ASO could be a drug candidate to protect or improve hearing and reduce tumor growth in *NF2*-SWN patients.