Dr. Gulam Abbas Manji

“This Orphan Drug Grant application is for a phase 2 clinical trial of combination therapy with a novel receptor tyrosine kinase (RTK) inhibitor and mammalian target of rapamycin inhibitor against malignant peripheral nerve sheath tumors (MPNSTs). No efficacious treatment options currently exist in this chemotherapy-resistant fatal disease. This is an investigator-initiated, multicenter, first in man study with preclinical data spanning over seven years which identified MPNST as a specific disease indication for PLX3397 (PLX), a potent and specific RTK inhibitor that inhibits five kinases of the over 200 tested. PLX specifically inhibits CSF1R, c-KIT, and PDGFRβ in vitro and in an MPNST xenograft model. We have shown that combination therapy with PLX and sirolimus resulted in sustained tumor growth inhibition and a marked depletion of tumor-associated macrophages and a shift from M2 (tumor promoting) to M1 (tumor inhibiting) macrophages. Therefore, this drug combination, by potently blocking RTKs and by altering tumor macrophage infiltration, represents a novel drug combination for MPNSTs.

The phase 1 portion of the phase 1/2 study has been approved by the FDA (IND #125719) and CUMC IRB (#AAAO6059) and has to date enrolled four patients using an adaptive design to identify the recommended phase 2 dose (RP2D).

The phase 2 portion of the study, and the focus of this application, will require pre-treatment, on-treatment, and on-progression biopsies in patients treated with the RP2D in hopes to demonstrate efficacy. The goal of the study is to (1) demonstrate a progression free survival benefit, (2) determine the response rate and overall survival, (3) correlate inhibition of target pathways and macrophage infiltration with efficacy, and (4) identify pathways of resistance by determining RTK phosphorylation status and level of macrophage infiltration in tumor samples from patients at time of progression compared to that on-treatment. Proof of efficacy of combination therapy with PLX and sirolimus in MPNST would be invaluable in the treatment of patients with MPNST and lead to improved medical management of this incurable and highly fatal disease.”