Adrenomyeloneuropathy (AMN) is the most common phenotype of X-linked adrenoleukodystrophy, a debilitating neurological disorder caused by mutations in the ABCD1 gene that encodes a peroxisomal ATP binding cassette transporter (ABCD1) responsible for transport of CoA-activated very long-chain fatty acids into the peroxisome for degradation. Using an AAV9 mediated approach of the normal human ABCD1 gene we demonstrated in vitro and in vivo biochemical correction in a mouse model of this disorder (Gong, Mol Ther 2015).

In the current project we plan to (1) confirm target engagement through lipidomic analysis of key structures of the central and peripheral nervous system, (2) determine the biodistribution of intrathecal AAV9-hABCD1 in the AMN mouse model and compare to known AAV9-GFP distribution in larger mammals to optimize dosing, and (3) compare potential cardiac toxicity after intrathecal AAV9-hABCD1 delivery and assess mechanisms underlying toxicity in a cell culture system of primary cardiomyocytes following ABCD1 overexpression. We hypothesize that intrathecal AAV9-mediated ABCD1 gene transfer (AAV9-ABCD1) is effective and safe in AMN. We further hypothesize that determining the biodistribution of intrathecal AAV9-hABCD1 in target tissues will accelerate trial development for AMN. The goal of the proposal is to translate measurable benefits of gene correction in a rodent model of AMN to trial design in humans thereby enabling a submission of an FDA IND application.

In this project we aim to translate measurable benefits of gene correction in a rodent model of AMN to trial design in humans. We believe that this gene therapy can improve the quality of life of patients with AMN that currently have no treatment options. This project provides a path towards a treatment, including first biodistribution and toxicity studies needed to guide next steps with industry collaborators. Results from experiments proposed in the grant are essential for the submission of an FDA IND application supporting AAV9-mediated gene therapy.