Roadmap for Drug Development for Niemann-Pick Disease

Kanagaraj Subramanian, Ph.D.
NNPDF Peter D. Pentchev Research Fellow
Sponsor: Dr. William. E Balch
Lay Summary for Progress Report #1 (October 2014 – March 2015)

Niemann-Pick Type C (NPC) disease is a neurodegenerative disorder characterized by the abnormal accumulation of cholesterol and other lipids in the endosomal/lysosomal (LE/LY) compartments. Defective function of either the NPC1 or NPC2 protein impairs the cholesterol efflux from LE/LY compartments. Over 300 disease-causing NPC1 mutations have been reported in the clinic. Among these mutations, I1061T is the most prevalent mutation. In our unpublished studies, we have found that >70% of NPC1 clinically relevant alleles (130 variants examined to date during previous funding period) exhibit folding and trafficking defects before proceeding to the LE/LY compartments. These will require correction by small molecule protein folding modulator(s) that impact the proteostasis system supporting NPC1 function.

To restore the folding, trafficking and functional defect of NPC1 variants, in the past year we have entered into a close collaboration with Dr. Jason Gestwicki (University of California San Francisco) to screen for small molecule proteostasis regulators that correct the misfolded NPC1 variants by modulating proteostasis networks maintaining the fold. In our initial screens, using novel folding modulators that inhibit or activate the Hsp70-40 chaperone axis, we have found two proteostasis regulators (designated NPC1-C1 and NPC1-C2) that substantially correct (up to 50% of WT levels) the folding, trafficking and function of the I1061T mutation (a lumenal cysteine-rich domain variant) and the cytoplasmic tail G1240R mutant- thereby leading to a striking reduction in cholesterol accumulation in LE/LY compartments. These results suggest to us unanticipated new folding principles that could accelerate global clinical management of NPC1 rare disease reflected in the highly divergent and heterogeneous allelic variant composition of the targeted clinical patient population.

To further extend our studies, we will be testing the impact of our current top hit Gestwicki proteostasis regulators by generation of a large number of additional analogs through application of structure-activity relationship (SAR) analyses using high throughput format assays in conjunction with our 130 NPC1 library of variants that cover 90% of the heterologous allelic composition found in the patient population. Specifically, the Gestwicki laboratory recently provided ~20 additional analogues of NPC1-C1/C2 series with the goal of enhancing their potency and brain penetrance. These, and up to an additional 500 proteostatic modulators, will be screened in the coming year using select NPC1 variants to optimize our success in identifying key scaffolds that could be used for clinical development. In our ongoing collaboration with Dr. Dan Ory (Washington School of Medicine, St. Louis), we will continue to test the ability of our most active and brain penetrant NPC1-C1/C2 series compounds to correct the folding, trafficking and function of the NPC1-I1061T variant in I1061T mouse embryonic fibroblasts (MEFs) obtained from Ory. These studies will serve as a prelude for testing in the Ory I1061T mouse model. Furthermore, in the coming months, we will address the molecular mechanism(s) of action (MOA) of active compounds in our NPC1-C1/C2 series. Here, we will apply tandem-mass-tag (TMT) mass spectrometry to quantitatively analyze the changes in the NPC1 variant interactome in response to correction by proteostasis regulators. These studies will accurately measure the degree of restoration of normal protein-protein interactions typically observed in wild-type NPC1. Such studies will be used to generate a comprehensive roadmap of correction pathways impacted by proteostasis regulators to further our efforts for clinical developmental of these series.