Roadmap for Drug Development for Niemann-Pick Disease

Kanagaraj Subramanian, Ph.D.
NNPDF Peter D. Pentchev Research Fellow
Principal Investigator: Dr. William. E Balch

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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 exhibits folding, trafficking defects leading to aberrant cholesterol homeostasis. We have found that >70% of NPC1 clinically relevant alleles exhibit diverse defects in folding/trafficking and function at the LE/LY compartments. These will require correction by small molecule protein folding modulator(s) that impact the proteostasis system, the versatile system we now realize can be reprogrammed to restore most NPC1 variant function. In collaboration with Dr. Jason Gestwicki (University of California San Francisco), 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. Further, our studies show that the analogues of NPC1-C1/C2 series compounds enhance the folding, trafficking of I1061T in mouse embryonic fibroblasts (MEFs), providing strong evidence for analysis of these compounds in the NPC1 I1061T mouse model recently generated by the Ory laboratory. My current efforts will be used to develop a novel therapeutic drug to restore the function of NPC1 variants in patient clinical population. In the coming months we will be testing more than 500 proteostatic modulators (collaboration with Drs. Gestwicki, Morimoto, Kelly laboratories) using select NPC1 variants on a HTS system we have developed to optimize our success in identifying novel drugs that could be the basis for clinical development.