Roadmap for Drug Development for Niemann-Pick Disease

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Niemann-Pick type C (NPC) disease is an inherited, progressive neurodegenerative disorder mainly caused by the abnormal accumulation of cholesterol and other lipids in the endosomal/lysosomal (LE/LY) compartments. Mutations in either the *NPC1* or *NPC2* gene impair 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. To restore the NPC1 variant function, we have used small molecule protein modulator(s) referred as 'proteostasis regulators' able to manage the folding pathways of NPC1 variant and function in maintaining cholesterol homeostasis at the LE/LY compartments. In collaboration with Dr. Jason Gestwicki (University of California San Francisco), we have found two proteostasis regulators (designated NPC1-C1 and NPC1-C2) that impact the heat shock protein 70 (Hsp70) pathway that substantially correct (up to 50% of WT levels) the folding, trafficking and function of the I1061T mutation, thereby leading to a striking reduction in cholesterol accumulation in LE/LY compartments. Further, our studies show that analogues of NPC1-C1/C2 series compounds enhance the folding, trafficking of I1061T in mouse embryonic fibroblasts (MEFs), providing evidence for analysis of the role of these compounds in the NPC1 I1061T mouse model recently generated by the Ory laboratory. Ongoing efforts now focus on understanding structure-activity relationships for our initial hit compounds, and to expand our survey of small molecule correctors to now include heat shock factor 1 (HSF1) regulators (the master regulator of proteostasis), and the Unfolded Protein Response (UPR) regulators involved in the folding of the newly synthesize protein in the ER. These efforts will considerably expand the repertoire of pathways that may impact the healthspan of the NPC1 patient clinical population.