Roadmap for Drug Development for Niemann-Pick Disease

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Niemann-Pick type C (NPC) disease is a rare, 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 affect 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 and exhibits folding and trafficking defects leading to aberrant cholesterol homeostasis in the cell. 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 (PRs)" to manage the folding pathways of NPC1 variant function in maintaining cholesterol homeostasis at the LE/LY compartments. In collaboration with Dr. Jason Gestwicki (University of California San Francisco (UCSF)), we have found two PRs (designated NPC1-C1 and NPC1-C2) 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, the treatment of NPC1-C1 corrects the folding and trafficking defects of a large fraction of NPC1 variants expressed transiently in U2OS-shNPC1 (npc1-null) cells (collaboration with Fred Maxfield (Weill Cornell Medical School). Furthermore, the analogues of NPC1-C1/C2 series compounds enhanced the folding, trafficking of the I1061T variant 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. We have initiated a study to understand the NPC1-C1 drug response to potential protein and lipid biomarkers for NPC disease in NPC1 I1061T fibroblasts. These efforts will considerably expand our understanding of disease progression and pathology, and potentially enable the development of novel drug candidates to improve the health span of the NPC1 patient clinical population.