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Lay Summary:

The accumulation of misfolded proteins is a hallmark of many neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and the polyglutamine diseases. To prevent the accumulation of misfolded proteins, cells have numerous protective pathways, including the selective removal of misfolded proteins. One protein, the C-terminus of Hsc70-interacting protein (CHIP), is responsible for targeting misfolded proteins for removal. In the majority of Niemann Pick Type C (NPC) cases, a mutation in the NPC intracellular cholesterol transporter 1 (NPC1) causes it to fold more slowly. As a result, CHIP recognizes NPC1 as a misfolded protein and targets it for removal. Because increasing levels of NPC1 protein would be therapeutic in NPC patients, my goal is to devise strategies to prevent CHIP from targeting NPC1 for removal. In the first six months of my fellowship, I have begun preparing reagents to investigate the molecular details of how CHIP targets NPC1 for clearance. In addition, I have performed a small-scale drug screen and have identified first in class small molecules that inhibit CHIP activity. The long-term goal of these studies are to identify compounds that inhibit CHIP function. My hope is that these compounds will prevent removal of NPC1 and may someday be useful for treating the majority of cases of NPC disease.