Adam Kanack
Peter G. Pentchev Fellowship Update

Lay Summary:

Niemann-Pick disease type C (NPC) is most commonly caused by mutations in the NPC1 protein. Frequently these mutations cause NPC1 to be prematurely targeted for destruction. The C-terminus of HSC70-interacting protein (CHIP) is primarily responsible for targeting NPC1 for destruction. Here, I have set out to find small molecules that block CHIP's ability to target NPC1 for destruction. By preventing the degradation of NPC1, the total amount of functional NPC1 would be increased at any given time. Increasing NPC1 levels would be therapeutic for individuals with NPC as it would alleviate cholesterol accumulation, a primary hallmark of the disease. In the first six months of my fellowship, I developed methods to screen for small molecules that inhibited CHIP. Thus far, I have found several lead compounds that have demonstrated an ability to inhibit CHIP. In the most recent six months I have performed assays with closely related compounds to screen for additional small molecules that can increase NPC1 levels and decrease cholesterol accumulation. Thus far, I have identified a small number of related compounds that in preliminary experiments, are able to modestly improve NPC1 protein levels and decrease cholesterol accumulation in cells.