Dr. Deepti Gadi, Weill College of Cornell University –

Understanding the cellular mechanism of HDAC inhibitors for the treatment of NPC disease.

Layman Summary –

The goal of this research is to understand the mechanism by which histone deacetylase inhibitors (HDACi) are enhancing NPC1 expression. We propose to test whether HDACi work by boosting endoplasmic reticulum (ER) chaperone function thereby assisting NPC1 mutant proteins to bypass the ER degradation pathway resulting in an increase in the expression level of NPC1. We would like to test this hypothesis by first establishing if HDACi treatment of NPC is mutant-specific or non-specific. AS NPC disease can be caused by any one of over 100 mutations in the NPC1 protein, it is important to establish which NPC1 mutants can be treated successfully by HDACi. If we see an increase in chaperone expression levels upon HDACi treatment of these different NPC1 mutations, then we will test for overexpression and knockdown of ER chaperones and check for corresponding effects to confirm our hypothesis. Determining how HDACi are rectifying the NPC phenotype would lay the basis for targeted therapy based on genetic screening of NPC patients expressing unique mutations.