

## Lay Summary

Niemann-Pick type C (NPC) disease is a fatal, pediatric neurodegenerative disease due to either lysosomal accumulation of cholesterol or sphingolipids. Currently, there is no effective therapy to treat NPC disease. Moreover, given the fatal pediatric nature of this disease, patients and families do not have time to wait for the ~10 years required for development and FDA approval of a novel drug. With great excitement, my postdoctoral research recently identified an already FDA-approved drug that can ameliorate the lipid accumulation that causes the neurodegeneration in NPC disease (1). Surprisingly, this drug [SAHA (aka Vorinostat, Zolinza®)] is approved to treat cutaneous T-cell lymphoma (a specific form of cancer), a disease that is not related to NPC disease. This drug is an inhibitor of histone deacetylase (HDAC) genes, and thus called an HDAC inhibitor. As my findings came from experiments conducted in NPC patient cells, these results cannot be automatically translated to whole body results in animals or human patients. In addition, the mechanisms underlying the rescue of lipid accumulation in NPC disease cells by HDAC inhibition have not been determined. Thus the major questions are now: Will HDAC inhibitors ameliorate the lipid accumulation and neurodegeneration in animal models of NPC disease? How does this therapy work and will there be side effects of HDAC inhibitors?

Prior to being prescribed off-label to human patients, the mouse and cat models of NPC disease will be evaluated for impact of HDAC inhibitors on neurodegeneration and other symptoms of NPC disease. The three aims of my research proposed herein for the NNPDF Peter Pentchev Research Fellowship will define the molecular basis for this candidate therapy as a treatment in mouse, cat and human models of NPC disease. There are as many as 11 HDAC genes to be inhibited by HDAC inhibitors. The ideal HDAC inhibitor to treat NPC disease would be one that inhibits only the HDAC genes that are upregulated in NPC disease; otherwise there is potential to have side effects by impacting pathways that are not defective in NPC disease.

As my first aim, I propose to determine if there are specific HDAC genes in specific tissues that can be targeted to specifically treat NPC disease in humans. I will measure gene expression of the 11 HDAC genes in the liver, different brain regions, and other organs in the mouse and cat models of NPC disease, each with mutations that resemble mutations in NPC patients. These results are critical to the design and interpretation of testing HDAC inhibitors as a therapy of NPC disease in the murine and feline models of NPC disease.

As my second aim, I propose to identify a precise mechanism for the amelioration of lipid accumulation by the HDAC inhibitor drug. I will measure gene expression of all genes in the human genome in the presence and absence of a HDAC inhibitor. Specifically, I will do this in fibroblasts that have identical different NPC1 mutations. I will identify the genes that respond to the HDAC inhibitor treatment. These results will identify a mechanism that explains the therapeutic effect of HDAC inhibitors to treat NPC disease.

As my third aim, I propose to determine if HDAC4 is a mechanism to explain the therapeutic treatment of HDAC inhibitors in NPC patient fibroblasts. In my recent publication, I demonstrated that HDAC4 is the most upregulated HDAC gene in NPC patient fibroblasts that is most inhibited by an HDAC inhibitor. In these same patient fibroblasts, I will knockdown expression of HDAC4 and determine if the knockdown of HDAC4 alone can ameliorate the NPC disease phenotype of cholesterol accumulation in these cells. These results will determine if there is one major HDAC gene responsible for the therapeutic efficacy of HDAC inhibitors.

In summary, I anticipate that these experiments will determine the tissues, genes, and pathways to be targeted by HDAC inhibitors in the treatment of NPC disease. The HDAC inhibitor SAHA is FDA-approved and crosses the blood-brain barrier, critical parameters to NPC patients who can ill afford to wait for development of a new drug. The dosage used to rescue the lipid accumulation in cells is also within the range approved by the FDA. It is this lipid accumulation that causes neurodegeneration. Intriguingly, SAHA has been used to ameliorate neurodegeneration in mouse models of Huntington's disease and Alzheimer's disease. Despite this promise, we should be skeptical until drugs such as SAHA have been tested in the animal models of NPC disease to assess therapeutic efficacy with respect to neurodegeneration. The research proposed herein will define the molecular basis for this promising treatment of HDAC inhibitors, and help design and interpret animal studies to determine efficacy in treating neurodegeneration in NPC patients.