

## NNPDF Peter G. Pentchev Research Fellowship

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

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### Lay Summary for Progress Report #2 (April 2013 – September 2013)

Niemann Pick type C disease is caused due to mutations in NPC1 or NPC2 protein resulting in an accumulation of cholesterol in the cells. We previously demonstrated that histone deacetylase inhibitors (SAHA and LBH589) can reduce cholesterol level in NPC patient fibroblast (skin) cells and increase NPC1 protein level. SAHA (also called Vorinostat), is an FDA-approved drug for treatment of a cancer, and we are seeking approval from the FDA for tests in NPC patients. Merck, the patent holder, has agreed to assist Lysomics LLC, a company formed to develop histone deacetylase inhibitors for the treatment of lysosomal disorders, in the application to the FDA and to provide the drug for approved clinical trials.

The fellowship proposal is to study the mechanism by which histone deacetylase inhibitors are reducing cholesterol levels in patient fibroblast cells. Determining how histone deacetylase inhibitors are correcting the NPC phenotype would lay the basis for targeted therapy based on genetic screening of NPC patients expressing unique mutations. We proposed that the mechanism by which SAHA is correcting cholesterol levels is by enhancing the expression of protein chaperones in the cells, which results in an increase in NPC1 protein. We had previously checked for expression level of different chaperones in SAHA-treated cells and found an increase in BiP, a chaperone that may assist in getting NPC1 protein to the correct cellular organelles. We are currently testing if BiP is involved in reduction of cholesterol by overexpressing BiP in NPC1 cells. We also found activation of another protein IRE1 $\alpha$  after SAHA treatment and we plan to investigate if this protein is involved in reducing cholesterol.

We are also currently testing more selective histone deacetylase inhibitors (with varying concentrations) for cholesterol reduction by high content screening process. This might lead to a more selective drug than SAHA for the treatment of NPC disease with reduced side-effects.