Andrew Munkacsi, Ph.D.
NNPDF Peter Pentchev Research Fellow
Progress Report #1 (October 2011-April 2012)

Lay Summary

We have established an "exacerbate-reverse" approach to identify genetic modifiers of NPC disease using unbiased, genome-wide analyses of the yeast model of NPC disease (Munkacsi *et al.*, J. Biol. Chem., 2011). We identified 12 pathways that exacerbate lethality in yeast that can potentially be reversed in human cells as a novel therapeutic strategy. One novel target is a pathway that regulates gene expression; this is the homeostasis between histone acetylation (HAT) and histone deacetylation (HDAC). We demonstrated that this HAT-HDAC pendulum is dysregulated in NPC disease with an excess of HDAC activity. Therefore, we used a clinically approved HDAC inhibitor (suberoylanilide hydroxamic acid, SAHA, Vorinostat, Zolinza®) to treat human NPC patient fibroblasts and reversed the major diagnostic criteria of NP-C disease: lysosomal accumulation of both cholesterol and sphingolipids and defective esterification of LDL-derived cholesterol. SAHA exhibits great potential as a therapy for NPC patients since it is already approved by the FDA to treat cutaneous T-cell lymphoma and is readily available as oral tablets. As an NNPDF Peter Pentchev Fellow, I am determining the therapeutic efficacy of SAHA by translating our *in vitro* results in fibroblasts to *in vivo* results in animal models. I have optimized dosage and delivery of SAHA in the *Npc1*^{nmf164} mouse model of NPC disease and critically determined that SAHA crosses the blood-brain barrier in P21 mice, an age that is comparable to a juvenile NPC patient where the blood-brain barrier is not readily permeable. This treatment regime resulted in micromolar concentrations in the plasma and brain of mice that were previously used to rescue lipid accumulation in NPC patient fibroblasts. This result predicts that SAHA treatment will rescue lipid accumulation in the brain and liver of the mice. Experiments are now in progress to determine if SAHA can ameliorate cholesterol and sphingolipid accumulation in the liver and brain at pediatric, adolescent and adult stages of the *Npc1*^{nmf164} mouse model of NPC disease. In the next few months, comparable experiments will be conducted in the feline model of NPC disease using a dosage that is calibrated for the weight of a cat. These studies testing the therapeutic efficacy of SAHA in a mouse model and a feline model will determine the potential of SAHA as a therapy to treat children affected with NPC disease.