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Lay Summary

We previously demonstrated that the homeostasis between histone acetylation (HAT) and histone deacetylation (HDAC), a process that regulates gene expression, is dysregulated in NPC disease with an excess of HDAC activity, and thus used the clinically approved HDAC inhibitor (suberoylanilide hydroxamic acid, SAHA, Vorinostat, Zolinza®) to reverse the major diagnostic criteria of NP-C disease in NPC patient cells (Munkacsi *et al.*, J. Biol. Chem., 2011). These hallmarks are the lysosomal accumulation of both cholesterol and sphingolipids as well as the defective esterification of LDL-derived cholesterol. As an NNPDF Peter Pentchev Fellow, I am determining the therapeutic efficacy of Vorinostat by translating our *in vitro* (cells in a dish) results to *in vivo* (whole body) results in animal models of NPC disease.

Vorinostat 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. To reformulate a drug used in adults for use in children, we optimized dosage and delivery of Vorinostat in mice at an age analogous to children (21 days old, the first day off mother's milk). We determined the maximum dose that is not toxic in the *Npc1*^{nmf164} mouse model of NPC disease. This treatment resulted in concentrations of Vorinostat in the mouse that we previously used to rescue lipid accumulation in NPC patient cells. Of particular importance to adapting a cancer drug to the neurodegenerative NPC disease, we critically determined that Vorinostat crosses the blood-brain barrier. These results predict that this Vorinostat treatment will rescue lipid accumulation in the brain and liver of the mice. We now have preliminary evidence that Vorinostat is a viable therapeutic option in the liver of the *Npc1*^{nmf164} mouse and are now in the process of testing if it is also a therapeutic in the brain extending the lifespan of the mouse. Comparable experiments will also 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 Vorinostat in animal models of NPC disease will determine the potential of Vorinostat as a therapy to treat children and adults affected with NPC disease.