

Apolipoprotein-Mimetics for the Treatment of Niemann-Pick Diseases
Troy Halseth (Advisor: Anna Schwendeman)
Medicinal Chemistry 3rd Year Seminar
Thursday, January 28th at 4:00PM

Niemann-Pick Diseases (NPD) are extremely rare disorders of cholesterol (in the case of NPD Type C) or sphingomyelin (in the case of NPD Types A and B) storage and metabolism with no FDA-approved treatment options available to patients. Types A (NPA) and B (NPB) (together referred to as acid sphingomyelinase deficiency (ASMD)) result from loss of function mutations in the SMPD1 gene, which encodes for acid sphingomyelinase, an enzyme responsible for breaking down sphingomyelin in late endosomes/lysosomes. The clinical manifestations of ASMD can be quite severe, as patients with NPA experience hepatosplenomegaly, impaired liver and lung function, and neurological deterioration, resulting in death in early childhood. Patients with NPB retain slightly higher levels of enzyme activity (10% vs. 1-2%) than NPA, preventing neurological effects but still leading to hepatosplenomegaly and reduced pulmonary function. Unlike ASMD, Niemann-Pick Disease Type C results from mutations in either the NPC1 (95% of cases) or NPC2 (5% of cases) protein, which results in impaired cholesterol transport and metabolism. This can ultimately result in many of the complications seen in ASMD including hepatosplenomegaly, interstitial lung disease, cognitive impairment, and death.

Interestingly, patients with NPD have significantly lower levels of high-density lipoprotein (HDL) in circulation compared to healthy individuals. HDLs play a pivotal role in the mobilization and metabolism of cholesterol and phospholipids. HDLs are 8-12nm particles composed of a lipid membrane stabilized by Apolipoprotein A-I (ApoA-I), and they are formed when ApoA-I interacts with lipid microdomains formed by the ABCA1 transporter. Synthetic high-density lipoproteins (sHDLs) composed of phospholipids in complex with either the full-length ApoA-I protein or smaller peptides possessing the same properties as ApoA-1 have been extensively investigated in clinical trials for atherosclerosis due to their ability to function as scavengers for excess cholesterol and phospholipids. Because of this, we have been investigating different sHDLs and apolipoprotein-mimetic peptides to determine their ability to treat the different NPD.

Our previous work in NPC demonstrated that sHDLs are able to remove excess cholesterol from NPC patient fibroblasts as well as increase serum cholesterol levels, correct changes in body weight, and improve liver function in NPC mice. Ongoing studies in NPC now focus using sHDLs in combination with small molecules capable of increasing expression of the ABCA1 transporter to improve cholesterol removal. Our ongoing work in ASMD has highlighted several apolipoprotein-mimetic peptides capable of removing excess sphingomyelin from ASMD patient fibroblasts in addition to increasing serum sphingomyelin levels in ASMD mice following a single injection of sHDL. Further *in vivo* evaluation of sHDLs in ASMD to monitor changes in lipid accumulation in different organs and corrections in motor impairment will be conducted going forward. Together, the completion of these studies will provide insight into how apolipoprotein-based therapies can be used to help treat Niemann-Pick Diseases.