Soat1/Acat1 **blockade to ameliorate lipid storage defects in a mouse model of Niemann-Pick Type C disease**

Junghoon Lee, Adrianna De La Torre, Catherine C. Chang, Ta Yuan Chang

Department of Biochemistry and Cellular Biology, Dartmouth College, Hanover, NH, USA 03755

Niemann-Pick type C1 (NPC1) disease is a rare autosomal recessive neurodegenerative disease. Loss of function mutations in NPC1 causes neurovisceral lysosomal storage disorder, which is represented by abnormal accumulations of cholesterol and sphingolipids in late endosomal/lysosomal cellular compartment. These impairments result in neurodegeneration disorder and progressive dementia including Purkinje cell loss in the cerebellum, as well as liver dysfunction and splenomegaly. Although a couple of potential therapeutic interventions for NPC disease have been recently developed, it remains a critical need to develop new therapeutic approaches. Cholesterol homeostasis in the cells is tightly regulated in part by the ER-resident enzyme, acyl-coenzyme A:cholesterol acyltransferase 1 (ACAT1), also called sterol O-acyltransferase 1 (SOAT1). ACAT1 enzymatically converts cholesterol to cholesteryl esters for storage and affects overall free cholesterol contents in the cells. We recently reported the finding that genetic ablation of *Acat1* increased the life span of *Npc1*$^{nmf/nmf}$ mutant mice, and ameliorated pathologies in liver and spleen, and reduced the loss of Purkinje cells in the cerebellum at postnatal stage 80 (P80) (Rogers, Chang et al., 2022). Here, we examine further therapeutic applications of ACAT inhibition for NPC1 disease with pharmacological and genetic blockade of *Acat1* in *Npc1*$^{nmf/nmf}$ mice. F12511 is a small molecule potent ACAT inhibitor and had been tested clinically safe for anti-atherosclerosis studies. We established a new liposome procedure to encapsulate F12511 in high concentration (designated as nanoparticle F) (De La Torre et al, 2022). In WT (C57BL/6) mice, treatment of nanoparticle F at 46 mg/kg with a single IV injection strongly inhibited ACAT enzyme activity in different tissues, including forebrain, cerebellum, liver, and adrenal glands for up to 12 hrs. IV injections of nanoparticle F to WT mice for 7 days produced no overt toxicities in both systemic tissues and the CNS. In *Npc1*$^{nmf/nmf}$ mice, we demonstrated that two weeks of intravenous daily injections of nanoparticle F did not prevent or rescue the loss of Purkinje cells in *Npc1*$^{nmf/nmf}$ mice from P60 to P75. In addition, administrating nanoparticle from P40 to P55, where the loss of Purkinje cells become obvious, show no significant improvement in their pathology. This suggests that in order to prevent neurodegeneration of Purkinje cells, it is important to apply ACAT inhibition at early postnatal stage Therefore, we are currently expanding our approaches to apply AAV-anti-*Acat*1 mediated gene knockdown therapy to treat *Npc1*$^{nmf/nmf}$ mice at early postnatal stage. Our hope is that a single administration of AAV-mediated gene therapy expressing *Acat1* targeting miRNA, in combination of nanoparticle F delivered by continuous IV and IP injections may provide prolonged ACAT inhibition, and would help to extend lifespan, ameliorate neurodegeneration, and reduce biochemical pathology.

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References

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