Cover Page

• Proposal Title:

A novel therapeutic strategy in Niemann-Pick Type C disease

• Lead PI:

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• Massachusetts-based Co-PIs if applicable: not applicable

• SNUH/SNUCM PI: presently not known

• Estimated Total Amount to be Requested: $250,000/year for two years

Proposal Overview

• Disease area: rare genetic diseases

• Brief description of proposed research

Niemann-Pick Type C disease (NPC) is a fatal neurodegenerative disorder affecting between 1 in 20,000 and 1 in 100,000 people. It is caused by the loss-of-function of NPC1 (in ~95% of cases) or NPC2 (in ~5% of cases), two proteins localized to lysosomes, organelles that hydrolyze various biological molecules. For lysosomes to function properly, the breakdown products must be efficiently evacuated; if evacuation is compromised, the affected product accumulates in lysosomes, causing lysosome dysfunction and consequent disease. NPC1 and NPC2 are part of a lysosomal pathway for the evacuation of cholesterol generated by the breakdown of lipoproteins taken up by endocytosis (Fig.1A). If the pathway is impaired by mutations in either NPC1 or NPC2, cholesterol accumulates in lysosomes, causing NPC. There is currently no effective treatment for NPC.

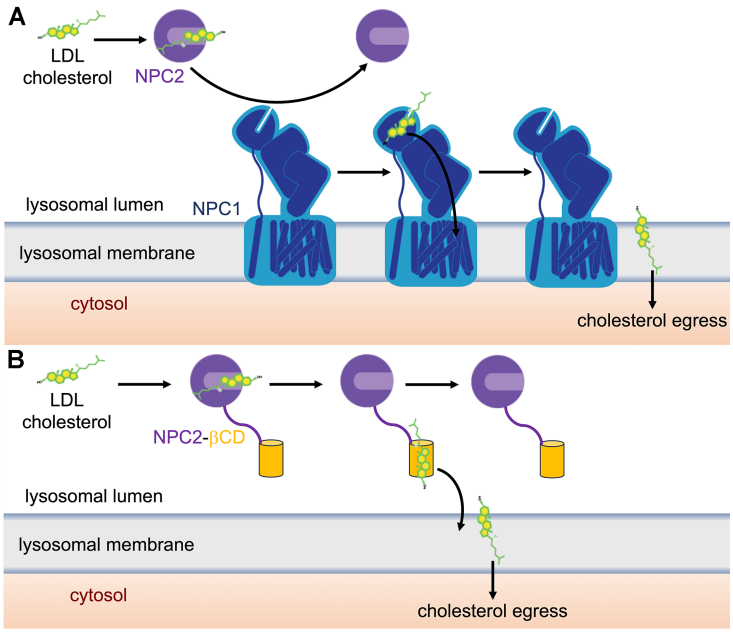

Fig.1: Treating Nieman-Pick Type C disease (NPC). **A)** Normal pathway for lysosomal cholesterol egress. Cholesterol from low-density lipoproteins (LDL) is transferred to the soluble luminal protein NPC2, which hands it off to the membrane cholesterol transporter NPC1 (related to two cholesterol transporters that my lab investigates, Dispatched and Patched). NPC1 inserts cholesterol into the lysosomal membrane, from where it is transferred to other organelles. NPC1 cannot bind cholesterol without NPC2, and NPC2 cannot donate cholesterol directly to the membrane in the absence of NPC1. **B)** Strategy for rescuing cholesterol accumulation in NPC based on NPC2-βCD conjugate. Since NPC2 rapidly donates cholesterol to βCD in solution, cholesterol should easily move from NPC2 to the βCD moiety within the NPC2-βCD conjugate. Then, the βCD moiety will readily donate cholesterol to the lysosomal membrane, bypassing NPC1 and reversing pathological lysosomal cholesterol accumulation.

I propose a simple but novel approach for NPC therapeutics, based on lysosome-targeted fusions that bypass the NPC1/2 pathway (Fig.1B). Briefly, NPC2 is easy to express and purify in large amounts, and is efficiently targeted to lysosomes when added to cells. By conjugating NPC2 to a non-toxic cholesterol-binding cyclic oligosaccharide such as beta-cyclodextrin (βCD), we will generate a fusion that, unlike NPC2 alone, can directly donate cholesterol to the lysosomal membrane, thus correcting the lysosomal storage defect (Fig.1B).

With two years of funding, I propose to accomplish the following aims: **1)** To generate a set of NPC2-βCD conjugates, varying in their βCD moieties and the connecting linker between NPC2 and βCD; **2)** To confirm targeting of NPC2-βCD conjugates to lysosomes; and **3)** To test the effect of the NPC2-βCD conjugates on lysosomal cholesterol accumulation in fibroblasts from NPC patients, to determine if and how they promote cholesterol egress.