Application Title: Effect of the c-Abl inhibitor Nilotinib on cholesterol accumulation in Niemann-Pick C disease

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Our project is centered in c-Abl kinase. c-Abl activity is induced in NPC neurons and its inhibition, using the classic inhibitor Imatinib, prevents neuronal death and improves motor skills and survival of NPC mice. Interestingly, our recent results show that inhibition of c-Abl also induces a decrease in cholesterol accumulation NPC cells.

Altogether, our results show that c-Abl inhibition by Imatinib has several positive effects decreasing cholesterol accumulation and neuronal death in NPC cells. Unfortunately, the limited brain penetration of Imatinib is the main limitation for its therapeutic use in NPC disease. Therefore, new c-Abl inhibitors such as Nilotinib, which shows greater effectiveness in brain pathologies, are good drug candidates for NPC disease. Our overall goal is to demonstrate that the c-Abl inhibitor Nilotinib decreases cholesterol accumulation in NPC cells and to study the mechanism involved. In addition, we will test Nilotinib effects decreasing cholesterol accumulation and cellular damage in the Npc1 null mouse model.