

Polyrotaxane Variants and Their Effects on the Cholesterol Efflux in Patients Suffering from Niemann Pick type C

Sydney Smith, Zachary Struzik, David Thompson
Department of Chemistry, Purdue University

ABSTRACT

Niemann Pick type C disease (NPC) is a rare lysosomal storage disorder characterized by a progressive accumulation of cholesterol in the late endosomal/lysosomes compartment leading to cellular dysfunction and organ failure. Symptoms include ataxia, dysarthria, cognitive dysfunction, and seizures. Although average life expectancy is below 20, there are no FDA approved treatment available making it a serious unmet medical need. Clinical trials with 2-hydroxypropyl-beta-cyclodextrin (HP-beta-CD) has shown promise in cholesterol normalization within NPC cells. However, HP-beta-CD treatment has been shown to cause ototoxicity in NPC patients at high dosages. Supramolecular complexes known as polyrotaxanes have been synthesized in hopes of decreasing the amount of free HP-beta-CD in the body that will lead to hearing loss. The solubility of rotaxanes threaded with only HP-beta-CD in aqueous systems is low, but has seen an increase with the addition of sulfobutyl-beta-cyclodextrin (SBE-beta-CD). In this study, polyrotaxanes with varying amounts of HP-beta-CD and SBE-beta-CD were synthesized and used to treat NPC1 fibroblasts. Filipin staining and fluorescent imaging were performed on these fibroblasts to assess the levels of cholesterol after treatment thus finding the optimum ratio of HP-beta-CD to SBE-beta-CD.

KEYWORDS

Niemann Pick type C, lysosomal storage disorder, polyrotaxane