

Smart delivery of actives by polyrotaxanes providing new options for the treatment of Niemann-Pick type C disease

Kerstin Egele¹, Shayak Samaddar², David H Thompson and Gerhard Wenz¹

¹Saarland University, Germany

²Purdue University, USA

Niemann–Pick type C disease (NPC) is a lysosomal storage disease that is characterized by a progressive accumulation of unesterified cholesterol in the lysosomes leading to organ damage from cell dysfunction. Hydroxypropyl- β -cyclodextrin (HP- β -CD) is an attractive drug candidate for treating NPC, as it diminishes cholesterol accumulation in NPC cells. Systemic HP- β -CD treatment, however, is limited by rapid renal clearance.

Polymeric delivery vehicles have been employed to improve both the solubility and the bioavailability of drugs to improve their efficacy and/or diminish their toxicity. Besides various polymeric carriers, polyrotaxanes are interesting alternative carrier entities that can act as supramolecular prodrugs and can improve the bioavailability of drugs and the retention of the drug in the human body due to reduced renal clearance because of their higher mass. Polyrotaxanes are molecules where many macrocyclic rings are strung onto a polymer chain.⁷ We designed a new anionic HP- β -CD polyrotaxane to act as a slow release formulation based on a polyalkylene phosphate core. The polyalkylene phosphate comprises hydrophobic decamethylene spacers linked by biodegradable anionic phosphodiester bonds. HP-

β -CD was threaded onto this polymer first and α -CD afterward to prevent burst release of the threaded HP- β -CD. Our findings show that HP- β -CD was slowly released from the polyrotaxane over a 30 days period. The polyrotaxane provided persistently diminished cholesterol levels in NPC1 cells by 20% relative to untreated cells. These results demonstrate the therapeutic potential of these polyrotaxane constructs as supramolecular drug delivery system.

Biography

Kerstin Egele studied chemistry at Saarland University, Germany and graduated with honors in 2016. After two research internships in France (Universit copy; de Lorraine and Strasbourg University) and an internship in a medical analysis laboratory in Germany, she joined the Institute of Organic Macromolecular Chemistry at Saarland University as Ph.D. student. In her doctoral thesis, she is now dealing with cyclodextrins and polyrotaxanes for pharmaceutical applications.

kerstin.egele@uni-saarland.de