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Dextran-Modified Poly(allylamine) Nanoparticles as Nanocarriers for the Delivery of Enzymes involved in Lysosomal Storage Diseases

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Lysosomal storage diseases (LSDs) are rare inherited disorders caused by defects in lysosomal enzymes, resulting in the accumulation of undegraded macromolecules and progressive tissue damage.[1] Enzyme replacement therapy (ERT) has emerged as a standard treatment for several LSDs, such as the Hunter's syndrome for which the recombinant human enzyme idursulfase (Elaprase®) is given by intravenous infusion.[2] However, the delivery of these therapeutic enzymes remains challenging due to poor stability, rapid degradation, and limited cellular uptake. To overcome these challenges, smart nanosystems offer a promising solution by protecting enzymes and facilitating their targeted delivery to lysosomes. Poly(allylamine) hydrochloride (PAH) are polymers that self-assemble into nanoparticles in phosphate buffer (PB) and have been investigated for their pH-responsive properties.[3] However, their positive charge can cause toxicity at high concentrations, requiring modifications for improved biocompatibility. In this study, dextran (DEX) with two different molecular weights (6 KDa and 9-11 KDa) was conjugated into the PAH backbone resulting in the formation of glyconanoparticles (glyco-NPs) in PB. In addition to improve the biocompatibility of the NPs, DEX should guarantee efficient intracellular uptake, and thus cargo delivery to cells. After physico-chemical characterization (NMR, DLS, cryo-EM), the potential of these glyco-NPs as delivery systems was evaluated using bovine serum albumin (BSA) as a model protein. The pH-dependent BSA encapsulation and release was demonstrated with different complementary methods (FCS, CD, DLS, BCA). The encapsulation and delivery of idursulfase (provided by Prof. Amelia Morrone from Meyer Children's Hospital IRCCS, Firenze) is currently under investigation. These studies focus on optimizing the release profile of idursulfase and assessing the efficacy of smart glyco-NPs compared to non-encapsulated idursulfase, towards a new delivery system for the potential treatment of Hunter's disease.

[1] F. M. Platt et al., *Nat Rev Dis Primers.* **2018**, *4*, 27.
[2] M. Stapleton et al., *Expert Opin Orphan Drugs*. **2017**, *5*, 295-307.
[3] P. Andreozzi et al., *Appl. Mater. Interfaces*. **2017**, *9*, 38242-38254.

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