DEVELOPMENT OF A NANOPARTICLE PLATFORM FOR ENCAPSULATION OF CATIONIC AMPHIPHILIC DRUGS AND RNA THERAPEUTICS

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Small nucleic acid (NA) therapeutics, such as small interfering RNA (siRNA) and messenger RNA (mRNA), are generally formulated in nanoparticles (NPs) to overcome the multiple extra- and intracellular barriers upon in vivo administration. Unfortunately, for most state- of-the-art NPs, endosomal escape is largely inefficient. Opposed to this paradigm, we recently reported that a selection of cationic amphiphilic drugs (CADs) could strongly promote functional siRNA delivery from the endolysosomal compartment via transient induction of lysosomal membrane permeabilization (Joris et al. 2018)(Van De Vyver et al. 2020). Here, our major objective is to co-encapsulate both CADs and RNA into a single NP formulation. It is anticipated that such a co-delivery strategy could contribute to in vivo translation of this concept by (1) conferring improved control over extra- and intracellular biodistribution, (2) lowering the required CAD dose to observe an adjuvant effect and (3) reducing toxicity (Joris et al. 2018)(Van De Vyver et al. 2020). A series of distinct NPs was constructed, efficiently co-encapsulating RNA therapeutics and CADs with diverging pharmacology. Detailed physicochemical characterization revealed that the NPs had an average hydrodynamic diameter of ˜200 nm and a zeta-potential of ˜25 mV, as measured via dynamic light scattering (DLS). Transmission electron microscopy (TEM) was additionally performed to shed light on the morphology of the obtained formulations. Selected NPs demonstrated functional delivery of distinct RNA therapeutics in various cell models, including easy-to-transfect cancer cells (e.g. human cervical carcinoma HeLa cell line) as well as hard-to-transfect primary cells (e.g. primary bovine epithelial cells).
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