Understanding the Mechanism of Nanoparticle-Mediated Protein Delivery

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Introduction

Protein therapeutics are powerful medical treatments, but they generally cannot enter cells and maintain functional stability (Li et al., 2018). Lipidoid nanoparticles (LNPs) can deliver proteins into cells, thereby opening new intracellular therapeutic targets. Lipidoids are combinatorially synthesized in libraries and self-assemble to form nanoparticles with diverse delivery efficiencies. This study will investigate why certain lipidoids within a library are more successful in protein delivery than others. A representative chalcogen-containing LNP library will be screened at each step of the delivery mechanism. The variations at each step will be related to delivery efficiency and lipidoid structures. The findings will be used to propose novel LNP design strategies for optimized protein delivery.

Model LNPs and Protein Cargo

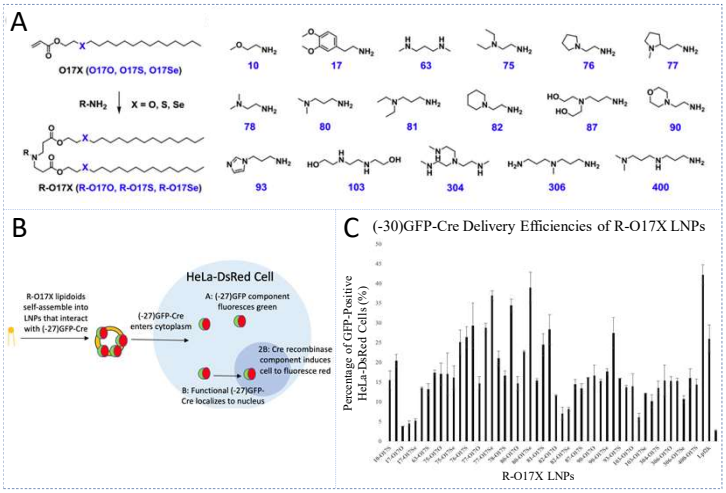

Figure 1: (A) A chalcogen-containing combinatorial library of lipidoids was studied. (B) (-27)GFP fused to Cre recombinase was used as the model protein due to its dual reporter capability. (C) Previous (-30)GFP-Cre delivery data (Li et al., 2018; n=4-6, error bars are standard deviations).

Experimental Strategy

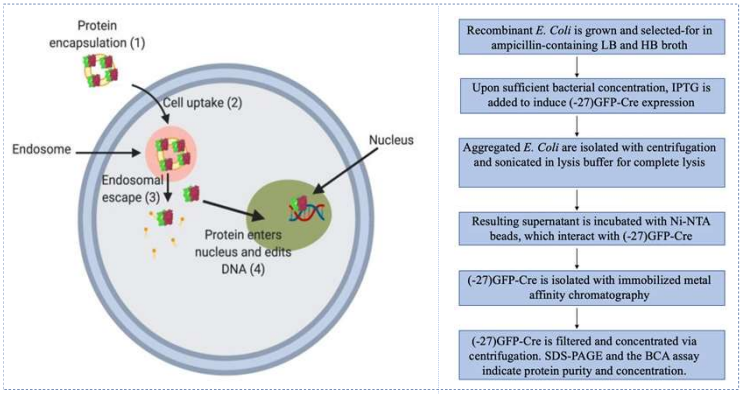

Figure 2: (A) Steps 1-3 from the proposed nanoparticle-mediated delivery mechanism will be studied (created with Biorender.com). (B) Strategy for (-27)GFP-Cre expression.

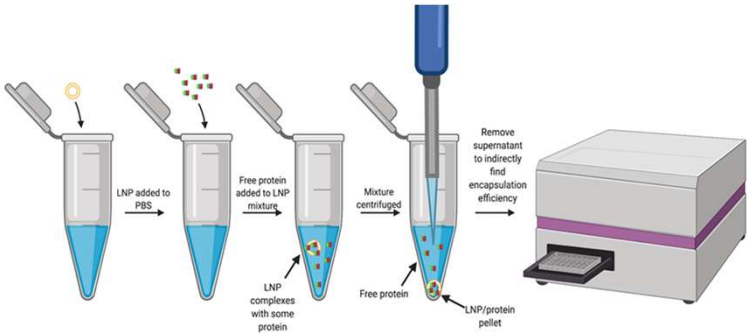

Figure 3: Screening strategy for LNP encapsulation of (-27)GFP-Cre in Step 1 (created with Biorender.com). Encapsulation efficiency will be correlated to delivery efficiency (Fig. 1C).

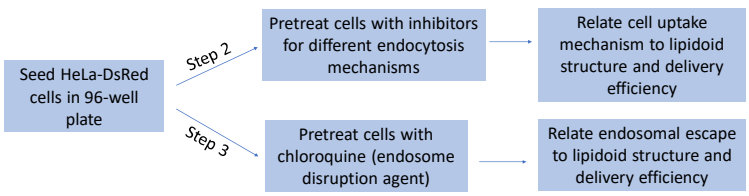

Figure 4: Screening strategy for LNP uptake and endosomal escape in Steps 2 and 3. Results will be correlated to delivery efficiency (Fig. 1C).

Preliminary Results

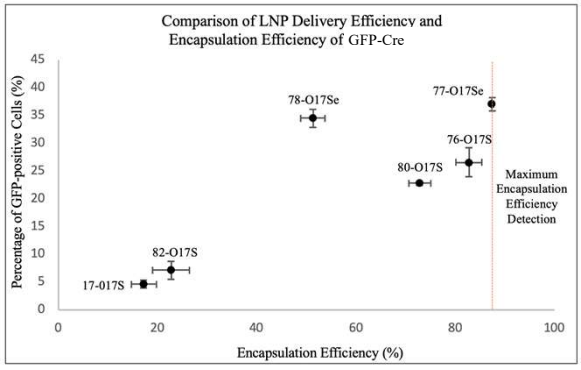

Figure 5: Initial findings qualitatively suggest association between encapsulation efficiency (n=2) and previously characterized delivery efficiency (Fig. 1C). Error bars are standard deviations.

Example of Long-Term Project Impact

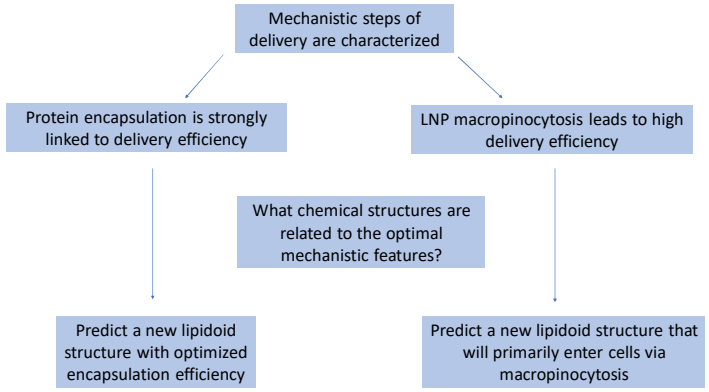

Figure 6: Hypothetical flow chart illustrating rational LNP design strategies derived from mechanistic characterization of protein delivery.

References

1. Li, Yamin, Tao Yang, Yingjie Yu, Nicola Shi, Liu Yang, Zachary Glass, Justin Bolinger, Isaac James Finkel, Wenhan Li, and Qiaobing Xu. 2018. "Combinatorial Library of Chalcogen-Containing Lipidoids for Intracellular Delivery of Genome-Editing Proteins." *Biomaterials* 178 (September): 652–62. https://doi.org/10.1016/j.biomaterials.2018.03.011.