Lipid Nanoparticles Using Alternative Polymer for mRNA Delivery

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Recent advances in messenger RNA (mRNA) COVID-19 vaccines reveal mRNA as an emerging class of therapeutics for a range of diseases. However, instability and innate immunogenicity of mRNA restrict broad performance of mRNA therapeutics. A robust carrier is essential to protect mRNA degradation and afford targeted delivery, and lipid nanoparticles (LNPs) have been utilized as the most common clinical nanocarriers with four standard components including ionizable lipids, structural phospholipids, cholesterol and polyethylene glycol (PEG)-lipids.[1] Although PEG-lipids play vital roles in LNP formulations to enhance the *in vivo* stability and retention of mRNA delivery system, rising concerns on PEG immunogenicity in general populations and low mRNA translational efficiency at the targeted site remain the key barriers to general mRNA therapeutical efficacy.[2]

To overcome these limitations, we developed a new polymer-lipid conjugate with an alternative hydrophilic polymer, poly(2-(methylsulfinyl)ethyl acrylate) (PMSEA), to be incorporated into a standard LNP formulation for mRNA delivery in the place of PEG. The aim of this work is to achieve a higher shielding effect and minimize the immunogenicity of the delivery system to reduce *in vivo* off-targeting effects of mRNA therapeutics, hence, enhance the accumulation of mRNA-LNPs at the targeted site. Here, we preliminarily demonstrate synthesis of PMSEA-lipid conjugates and LNP assembly (Fig 1(a)). We then compare the shielding effect of PMSEA LNPs (Fig 1(b)), and the encapsulation and transfection of mRNA with the use of this new LNP formulation (Fig 1(c)), revealing that this delivery system could be potentially applied for cancer immunotherapy.

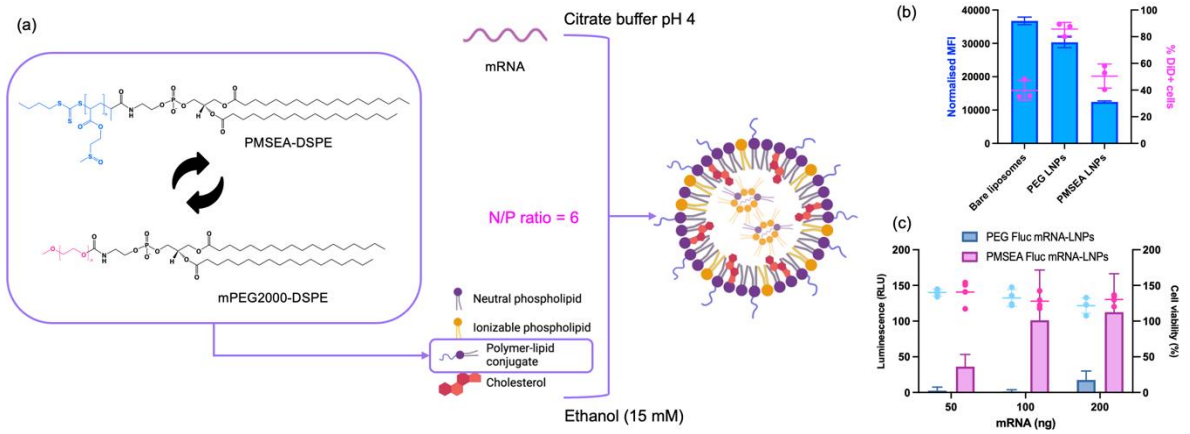

Figure 1: (a) Scheme of LNP assembly with different polymer-lipid conjugates. (b) Cellular association of DiD-loaded LNPs with CHO-K1 cells using flow cytometry. (c) Luminescence intensity for luciferase transfection of Fluc mRNA-LNPs with cell viability monitoring for 24 h.

References:

[1] Hou, X.; et al. *Nature Reviews Materials* **2021**, 6, 1078-1094.
[2] Rohner, E.; et al. *Nature Biotechnology* **2022**, 40, 1586-1600.