mRNA Delivery to Cardiac Fibrosis via Fibroblast Activation Protein-Targeted Lipid Nanoparticles

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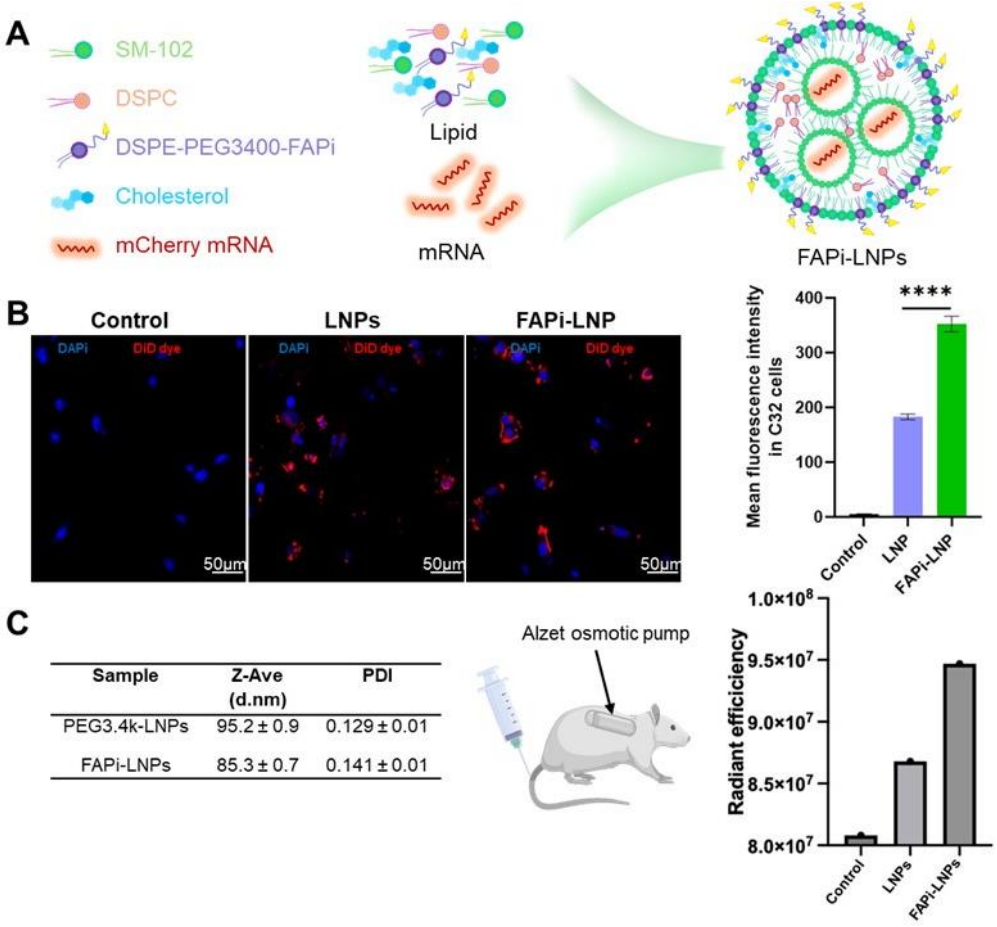
Following the successful approval of the first two mRNA-vaccines for COVID-19 and their resounding success, Lipid nanoparticles (LNPs) are now a well-established mRNA-delivery system.[1] However, the precise and efficient delivery of mRNA therapeutics to specific pathological sites remains a major challenge,[2] limiting the broader clinical translation of this breakthrough technology beyond infectious diseases. One such critical area is heart failure (HF), a global health burden doomed to further increase in our ageing population. To date, no treatment can satisfactorily restore impaired cardiac function in HF. To harness the full potential of mRNA therapeutics in HF, we investigated the delivery of mRNA-LNPs to fibrotic regions of the heart. Our innovative strategy involves engineering LNPs with small molecule ligands/inhibitors, selectively bind to the Fibroblast Activation Protein (FAP), a key biomarker of fibrosis. Importantly, FAP is minimally expressed in healthy cardiac tissue but significantly upregulated in pathological conditions such as hypertrophic and dilated cardiomyopathy.[3] The highly potent and selective inhibitor of FAP UAMC-1110 was functionalized on LNPs using a custom-made microfluidic nanoprecipitation device. The C32 FAP+ve cell line was used to assess binding affinity and specificity in vitro. A mice model of HF was used to test in vivo performance. Cardiac fibrosis was induced via Alzet Osmotic pump delivering angiotensin II and phenylephrine. Physicochemical characterization of targeted and non-targeted LNPs showed excellent size of 95±0.9nm and 85±0.7nm respectively. In vitro studies confirmed that the FAP-conjugated LNPs exhibited significantly higher binding and mRNA expression potential in FAP+ve C-32 cells. Moreover, in vivo biodistribution analysis revealed increased LNPs accumulation and expression of mCherry in damaged regions of the heart, further confirming the enhanced targeting capability of the FAP LNPs. This proof-of-concept study establishes a promising foundation for advancing mRNA-based therapies for cardiac tissue regeneration and cardiac reprogramming.



Sample	Z-Ave (d.nm)	PDI
PEG3.4k-LNPs	95.2 ± 0.9	0.129 ± 0.01
FAPi-LNPs	85.3 ± 0.7	0.141 ± 0.01

Figure: Preparation of FAPi conjugated lipid nanoparticles (A). In vitro cell binding in FAP+ve C-32 cells (B). In vivo mCherry expression in the heart for FAPi conjugated and non-conjugated LNPs in a mice model of HF (C).

References:

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[3] He, X, et al. Signal transduction and targeted therapy, 2022. 7(1): 134.