mRNA delivery to the heart using lipid nanoparticles

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Background

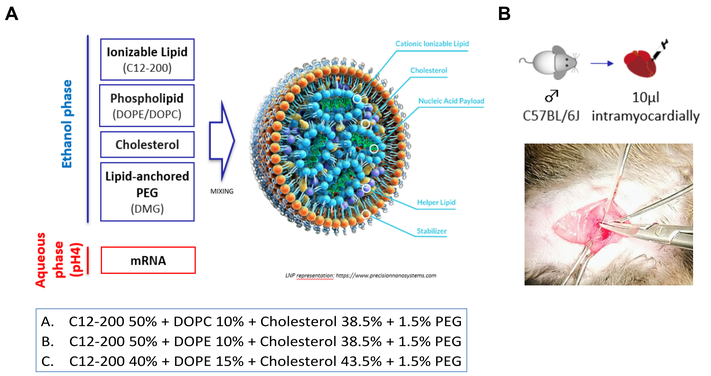
Myocardial infarction is a global health burden for which there is no treatment available that aims to recover the damaged tissue after the ischemic event. After myocardial infarction, endogenous mechanisms that enable repair of the functional damaged tissue can be triggered by modified mRNA (modRNA) delivery, locally in the infarcted area. Lipid nanoparticles (LNPs) represent a well characterized class of mRNA delivery systems, which were recently approved for clinical usage in their application for mRNA-based covid-19 vaccines.

Aim

- Deliver mRNA to the heart applying LNPs as delivery systems.

- Determine which of the tested LNP formulations transfects the heart most efficientlly.

LNP formulation & intramyocardial delivery



A. C12-200 50% + DOPC 10% + Cholesterol 38.5% + 1.5% PEG
B. C12-200 50% + DOPE 10% + Cholesterol 38.5% + 1.5% PEG
C. C12-200 40% + DOPE 15% + Cholesterol 43.5% + 1.5% PEG

Figure 1. (A) LNPs were formed after mixing of an ethanol phase which contained the lipids and an aqueous phase which contained the mRNA. Three LNP formulations (A,B and C) were tested in vivo. (B) Mice received one single injection into the left ventricular wall of 10µl of one of the corresponding treatments.

In-Vivo LNP transfection

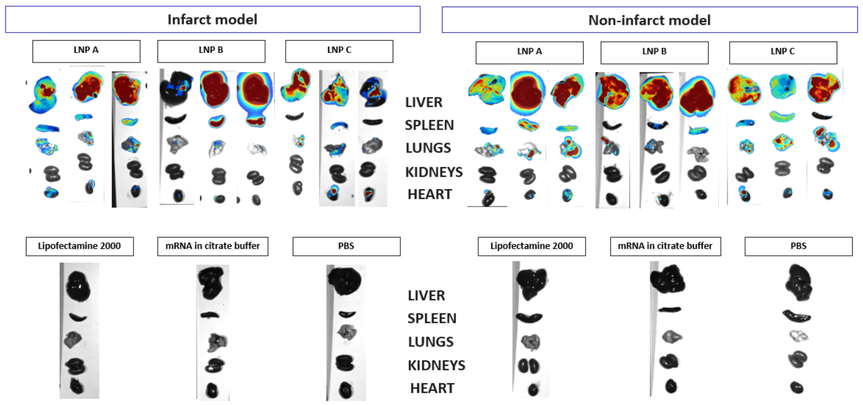


Figure 2. LNPs outperform naked mRNA in citrate buffer in terms of overall transfection efficacy in vivo. The liver was the main targeted organ by LNPs. Bioluminescence imaging 24h after intramyocardial administration of luciferase encoded by mRNA-LNPs. Luminescence is detected after i.p. administration of luciferin.

Tissue lysates analysis

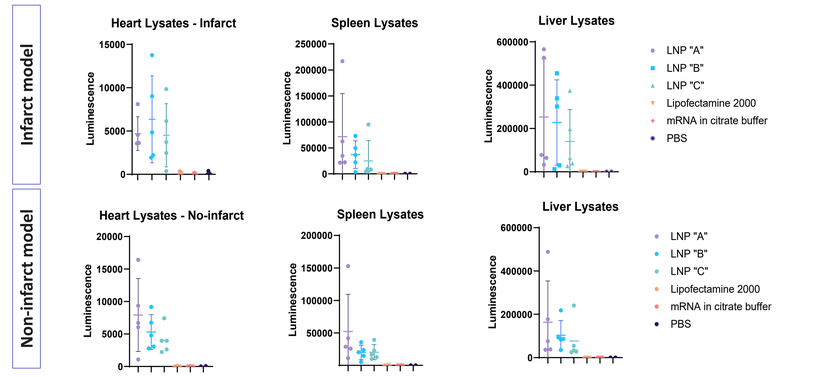


Figure 3. No significant differences in heart transfection efficacy between the three tested LNP formulations, shown by the tissue - lysates luminescence quantification 24 h after intramyocardial administration of luciferase mRNA -LNPs in an infarct model and a non-infarct model.

LNP biodistribution after 24 h

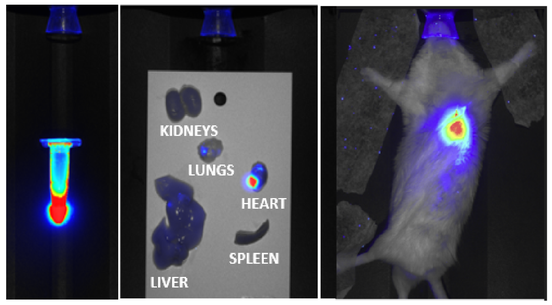


Figure 4. The injected LNPs mainly remain at the injection site (left ventricular wall) 24h after local injection. Fluorescence imaging 24h after intramyocardial administration of LNPs labeled with cy5.5 fluorophore.

Histology

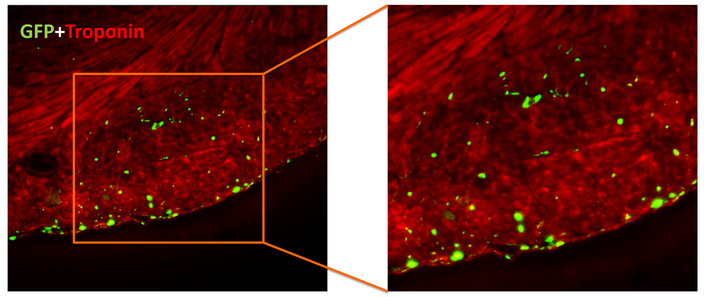


Figure 5. Epicardial cells as well as cardiac interstitial cells are targeted by LNP formulation B. Left ventricular histology sections showing GFP-mRNA transfection 24h after intramyocardial administration of GFP-mRNA LNP formulation B. Staining with GFP in green +Troponin in red.

Conclusion & Future Plans

- LNPs may serve as mRNA delivery systems to target the heart.
- We found no significant difference among the tested LNP formulations in terms of transfection efficacy.
- mRNA-LNPs seem to be more efficient than naked mRNA in transfecting the heart.
- Forward plans: based on the targeted cell types, to set mRNA therapeutic targets.

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