NanoMedicines Research Group

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DHSM as helper lipids to improve circulation and potency of liposomal LNPs

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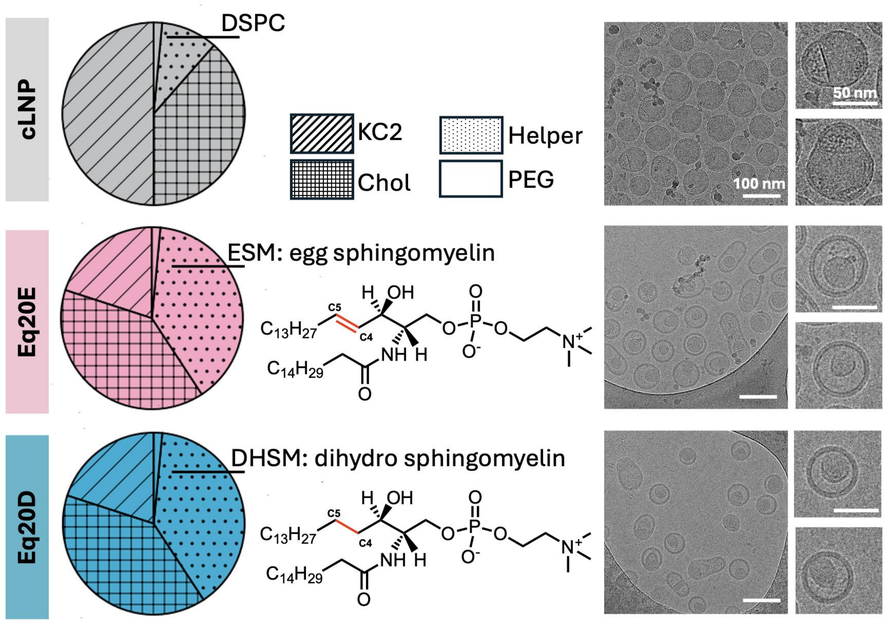
Background

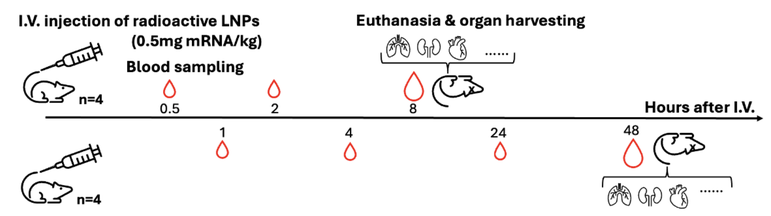
Lipid nanoparticles (LNP) are currently the most advanced delivery platform for mRNA therapeutics. To reach extrahepatic tissues, it is beneficial to engineer mRNA-LNP systems with improved stability and prolonged blood circulation lifetimes. Here we investigate the effects of employing dihydrosphingomyelin (DHSM) as the helper lipid on liposomal LNP performance. We show that inclusion of DHSM substantially extends the blood circulation half-life, thus improving the extrahepatic distribution of LNPs. Further, the presence of DHSM leads to a substantial improvement in transfection of hepatic and extra-hepatic tissues as compared to liposomal LNP systems containing ESM.

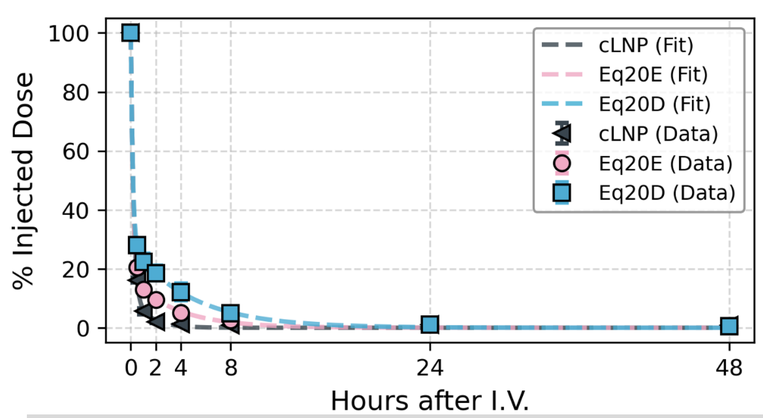
LNP formulation & structure

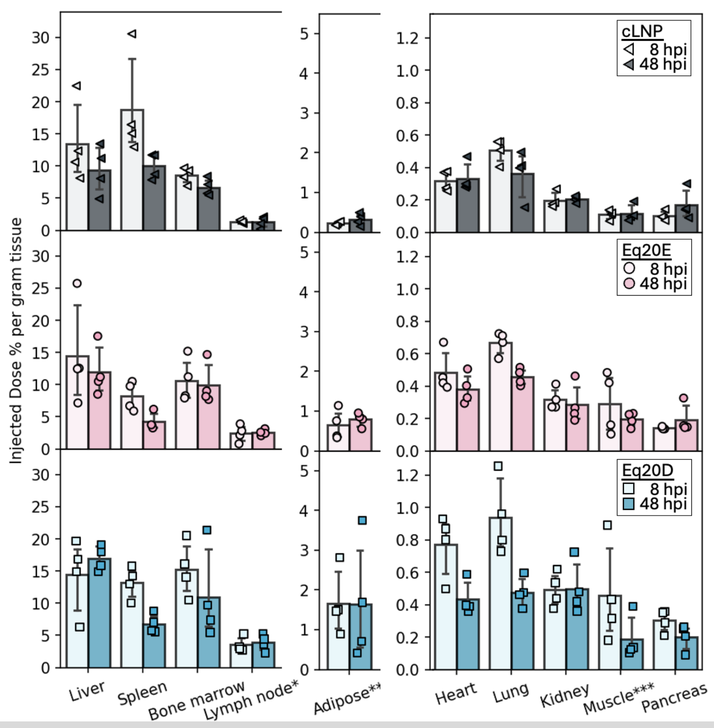


Saturating the double bonds in ESM leads to DHSM with more structural flexibility to allow for H-bonding and tighter packing. This was proven to increase the retention of vincristine by Johnston et al. (*Biochimica et Biophysica Acta (BBA)-Biomembranes 1768.5 (2007): 1121-1127.*)

LNP pharmacokinetics & biodistribution

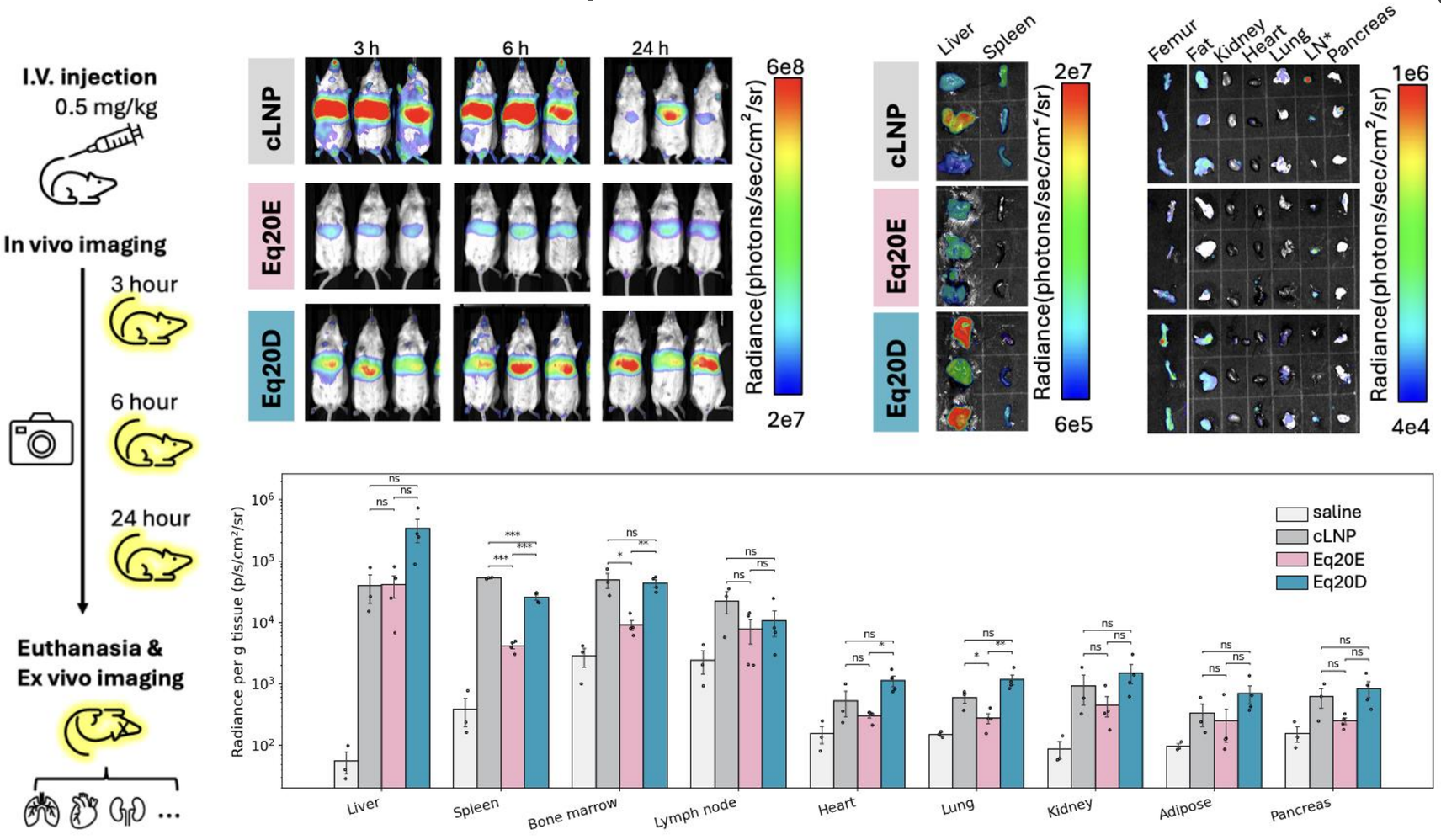






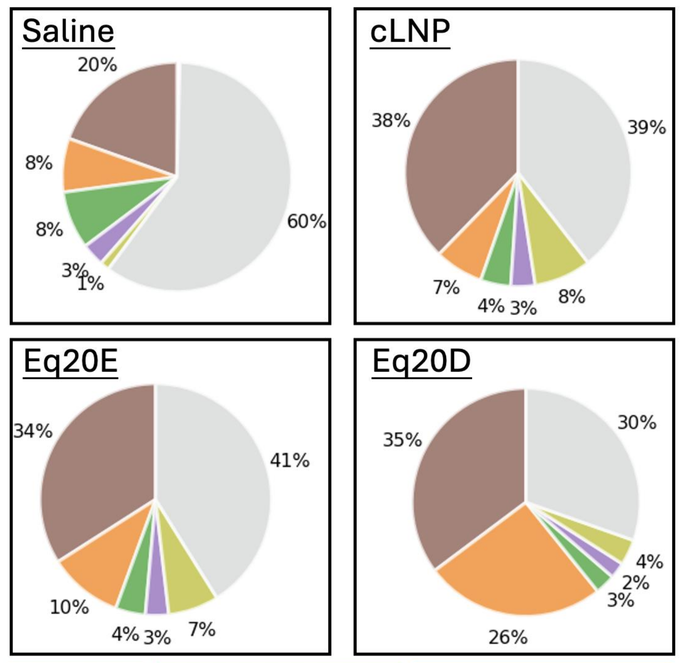
Eq20D exhibit extended circulation lifetimes and improved extrahepatic distribution. The pharmacokinetics and biodistribution of LNPs was assayed by ^{3}H-CHE labelling**.** The scatter plot indicating LNP clearance from the blood compartment 0~24 hours after injection; Bar charts showing biodistribution of LNPs

mRNA expression



Eq20D extend mRNA expression in vivo. Mice were injected with LNP formulations encapsulating firefly luciferase mRNA (mFluc), and expression was tracked over time by bioluminescence imaging. Whole-animal IVIS imaging and quantification of total radiance showed that Eq20D (blue) produced more sustained luciferase expression compared to the conventional LNP control (cLNP, grey) and the Eq20E formulation (pink). Ex vivo imaging of harvested tissues at 24 hours post-injection, together with radiance measurements from homogenized tissues, revealed the biodistribution of expression across organs including the lymph nodes.

Protein corona



Protein corona was isolated via size exclusion chromatography and Eq20D adsorb elevated levels of apolipoproteins.

The full story

Funding

NMIN
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AVENGER
D2R DNA TO RNA DE L'ADN À L'ARN
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