Design and Screening of Ionizable Lipids for Precision mRNA Delivery to Extrahepatic Organs

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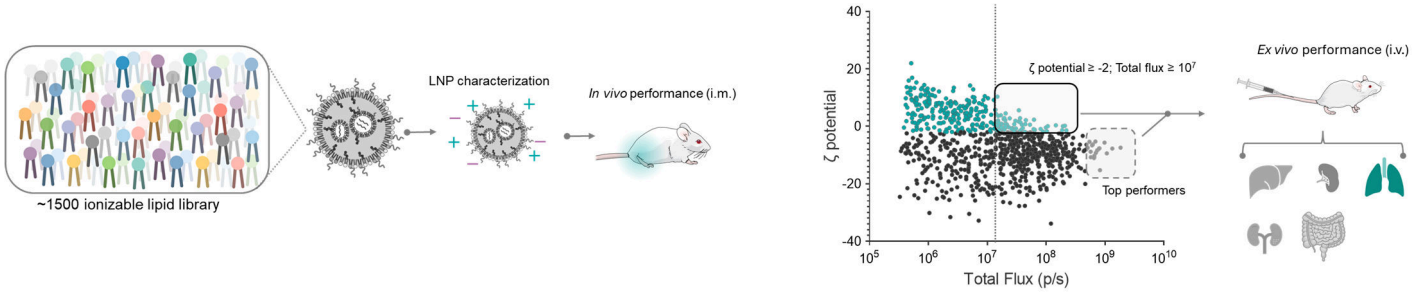
Introduction

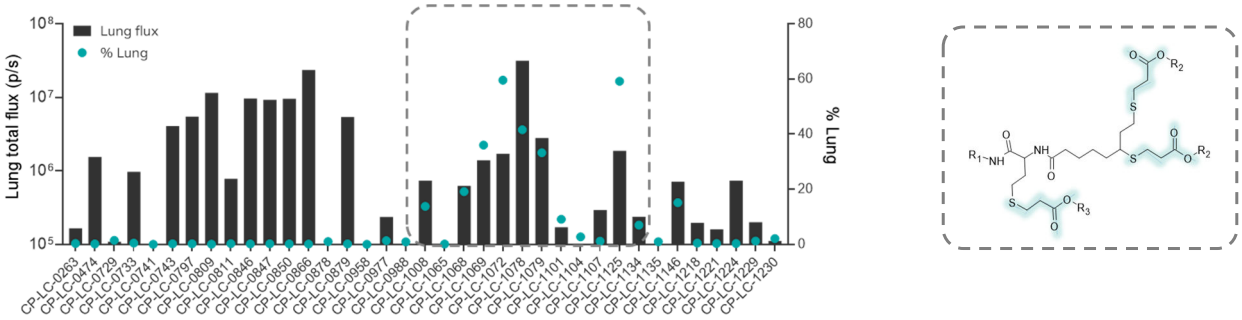
The current study explores how structural modifications in ionizable lipids (ILs) influence protein corona formation and organ-specific targeting, aiming to develop LNPs capable of selective delivery to the lungs and spleen.

Leveraging from our initial intramuscular screening of more than 1500 ionizable lipids, we carried out an intravenous screening of candidates which showed specific characteristics, both in zeta potential and performance. The hypothesis behind this experiment was that these characteristics might alter the protein corona of these LNPs, directing their targeting to other organs beyond the liver.



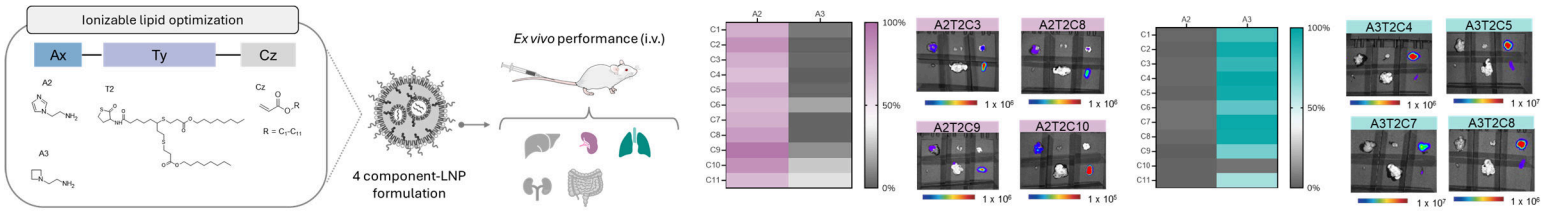
IV screening of selected lipids

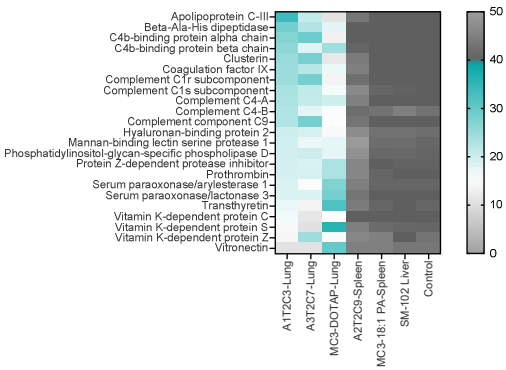
This intravenous screening in BALB/c mice of selected lipids resulted in the identification of a sub-family within our library that showed potential **selectivity towards extrahepatic organs, specifically lungs,** with high protein expression levels.

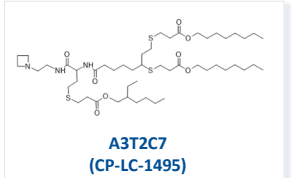


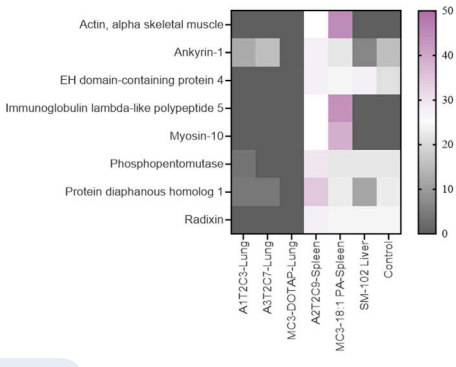
Optimization of lipid structure

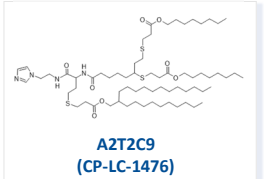
The further structural exploration of this sub-library led to lipids with high selectivity and protein expression in extrahepatic tissues. Interestingly, the polar head played a pivotal role, as it directed this selectivity towards lungs or spleen. Protein corona of best candidates were explored, showing interesting differences between LNPs with different targets.











Conclusions

We demonstrated that structural tuning of ionizable lipids enables precise extrahepatic mRNA delivery, with polar headgroup modifications driving lung or spleen selectivity. Top-performing LNPs achieved >90% organ selectivity and high protein expression, with A3T2C7 (CP-LC-1495) and A2T2C9 (CP-LC-1476) showing exceptional organ targeting towards lungs and spleen, respectively.

Protein corona profiling confirmed lipid-dependent tissue tropism, supporting the rational design of LNPs for targeted mRNA therapeutics.

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