Cardiac-tropic Lipid Nanoparticles For Selective Vascularization After Myocardial Infarction

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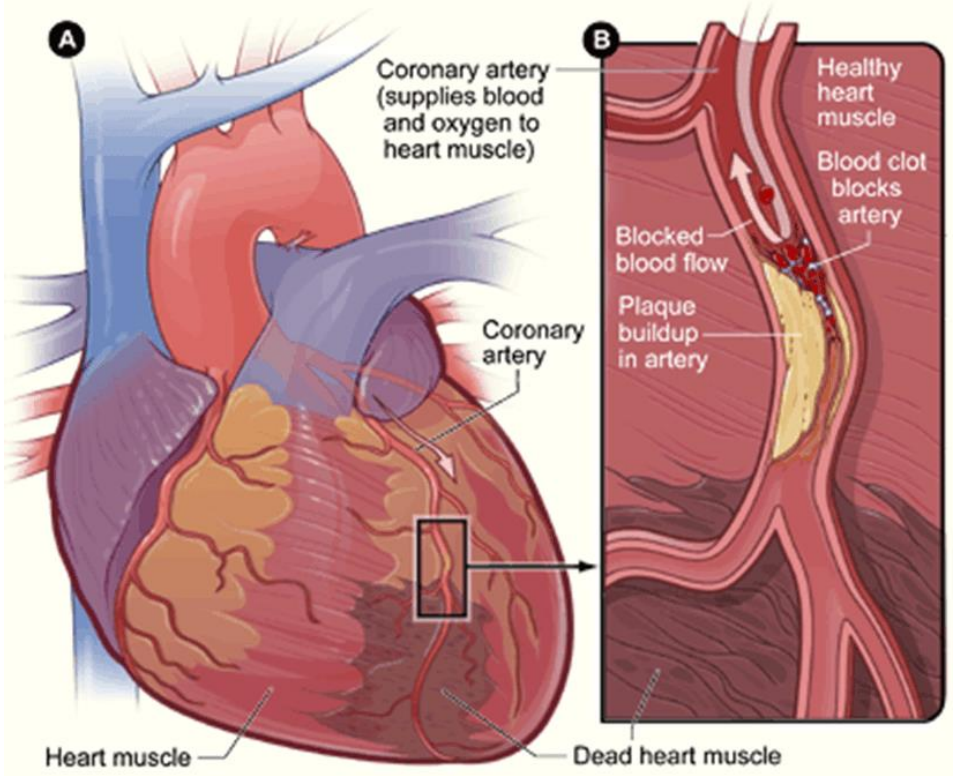
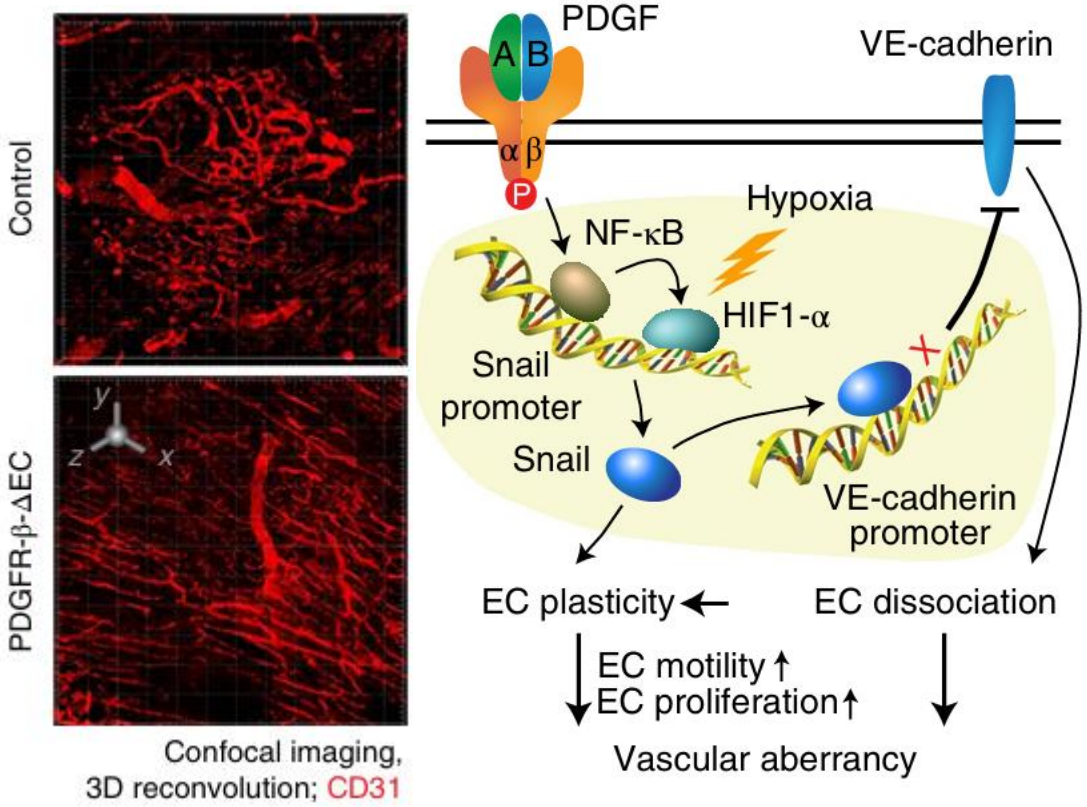
NEXT-GENERATION DELIVERY INNOVATIONS

Unmet Need: Targeted Revascularization After MI



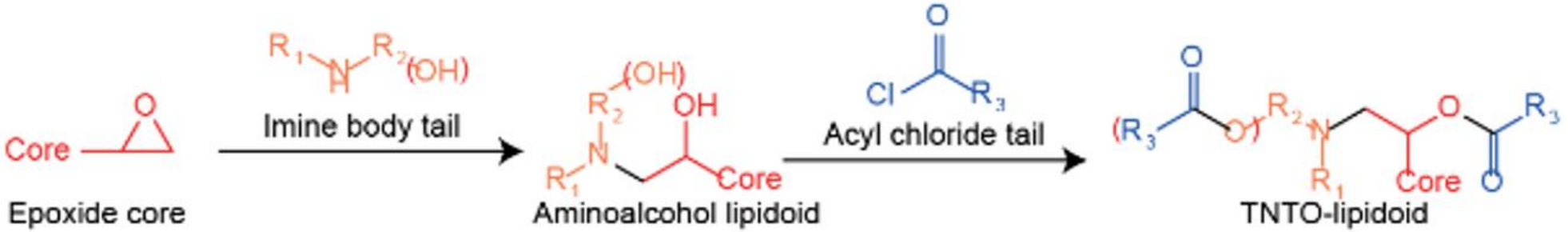
Cardiac-targeted delivery is elusive in current MI therapy.



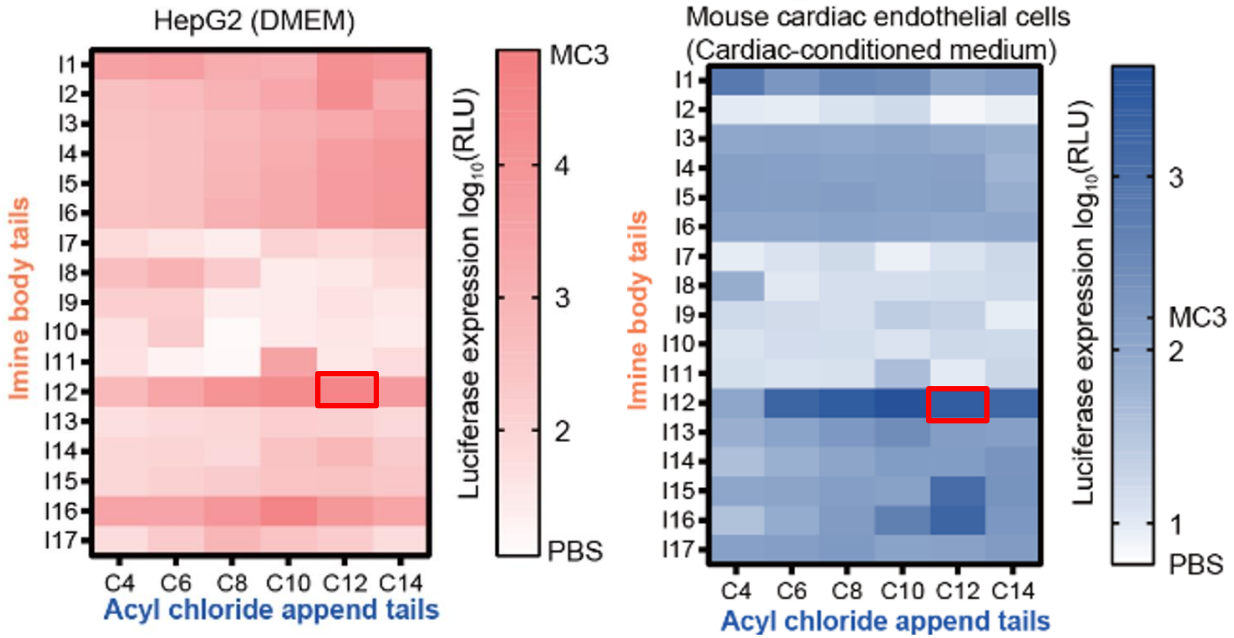
VEGF therapy yields dysfunctional, leaky vessels.

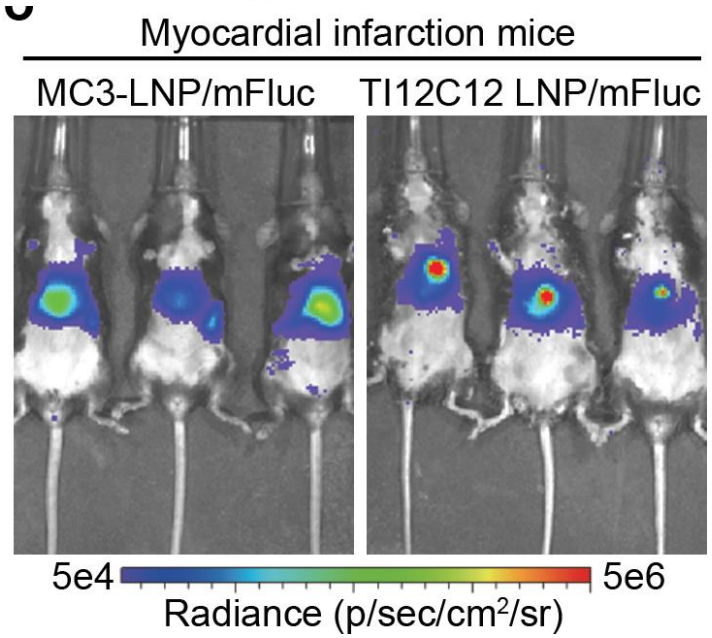
Gu et al. Nature Reviews Cardiology, 2021.
Huang, Yi, Mitchell et al. Nature Cardiovascular Research, 2022.

Stage 1 – Lipid Library Yields a Heart-Tropic LNP (Liver-Evasion Achieved)



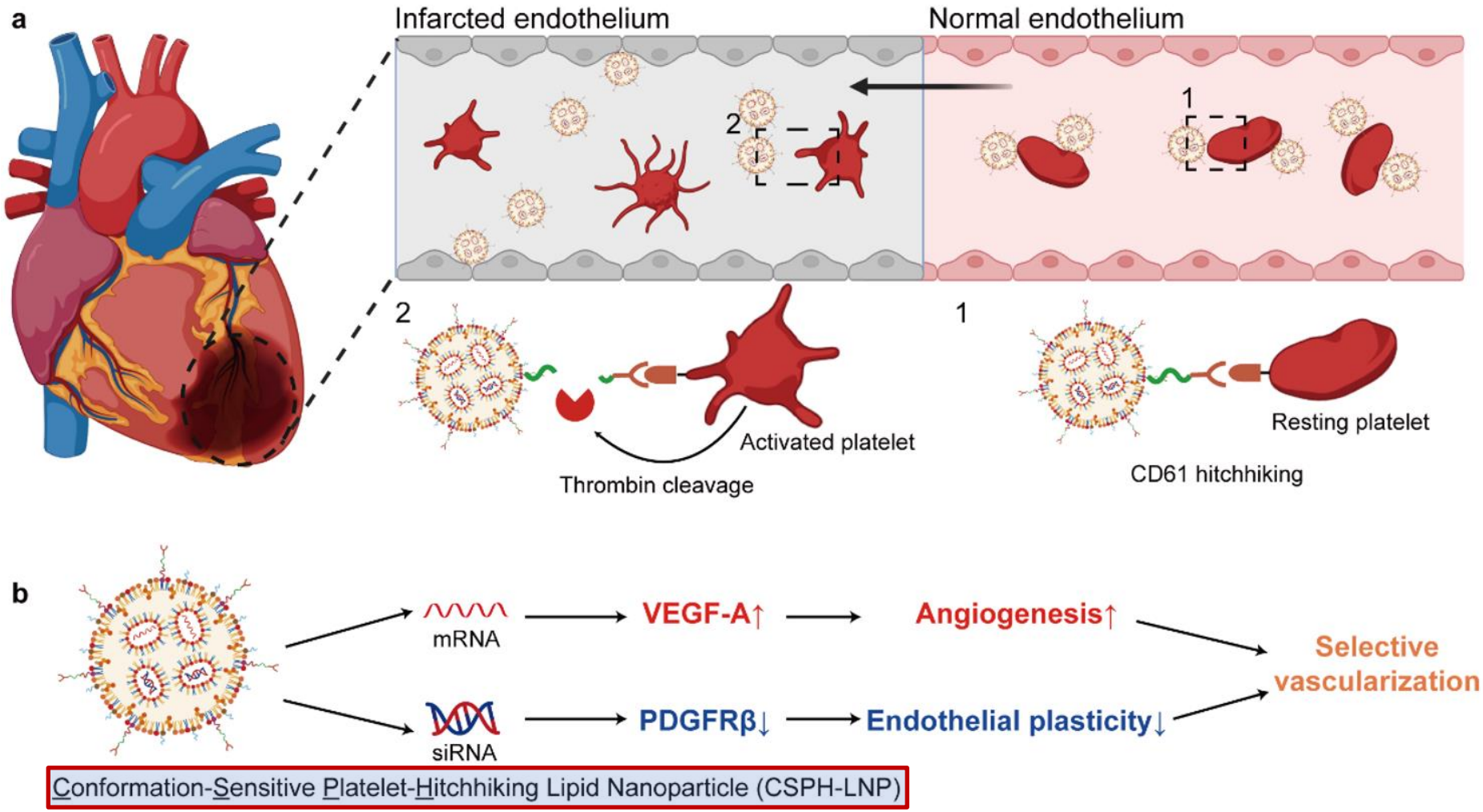
Han, Xu, Mitchell *et al.*
Nat Comm, 2024.





We screened a library of ionizable lipids and identified TI12C12-LNP with >10× heart-to-liver delivery ratio relative to a benchmark (MC3-LNP).

Stage 2 – Platelet Hitchhiking for Infarct-Specific Targeting

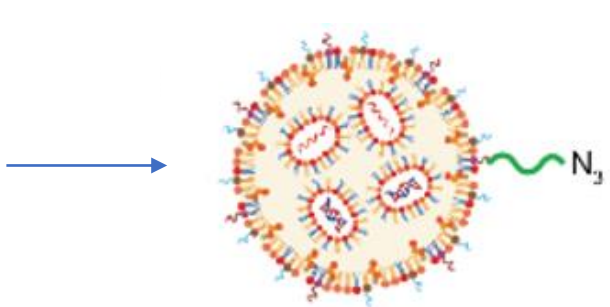


Attach LNPs to platelets that naturally home to and are activated at cardiac infarct sites.

Stage 2 – Platelet-Hitchhiking Implementation

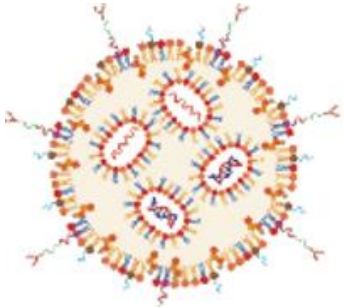
TI12C12 lipid
DSPC-PEG-(Thrombin cleavable peptide)
DMG-PEG, Cholesterol, DOPE

VEGF-A mRNA
PDGFR siRNA

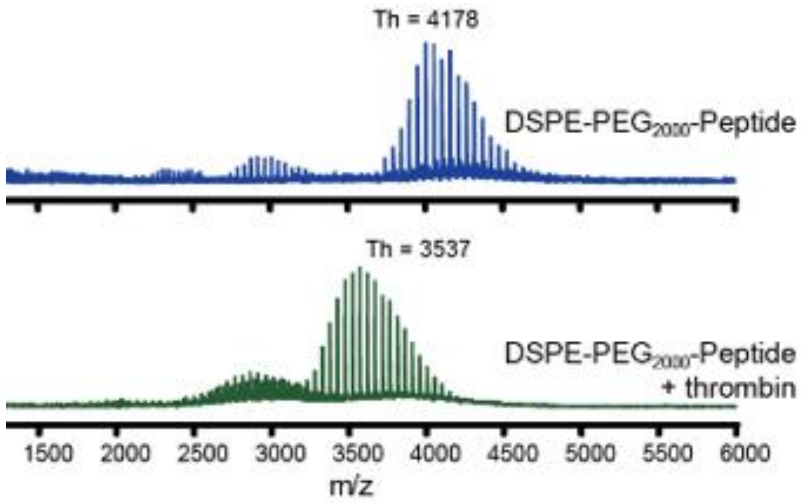


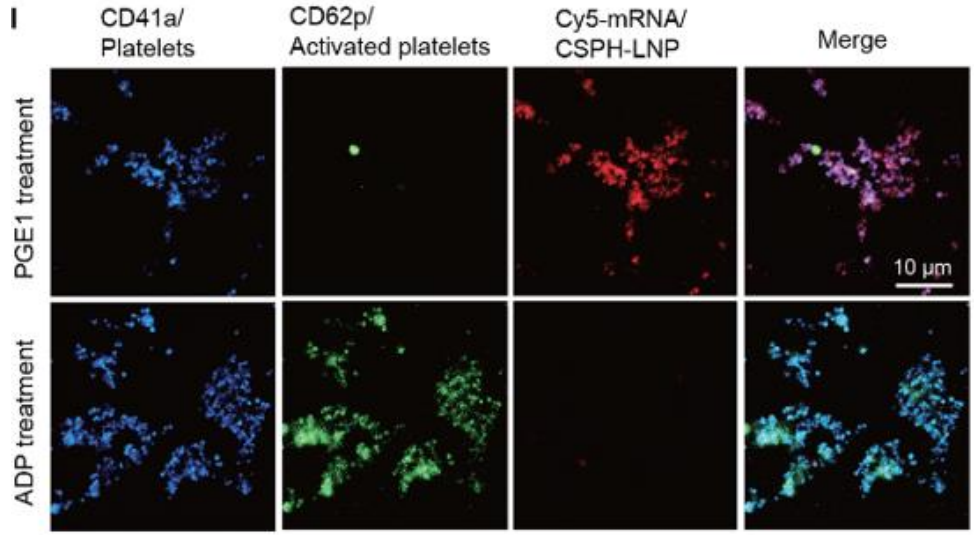
Peptide-modified TI12C12 LNP

DBCO-aCD61



CSPH-LNP

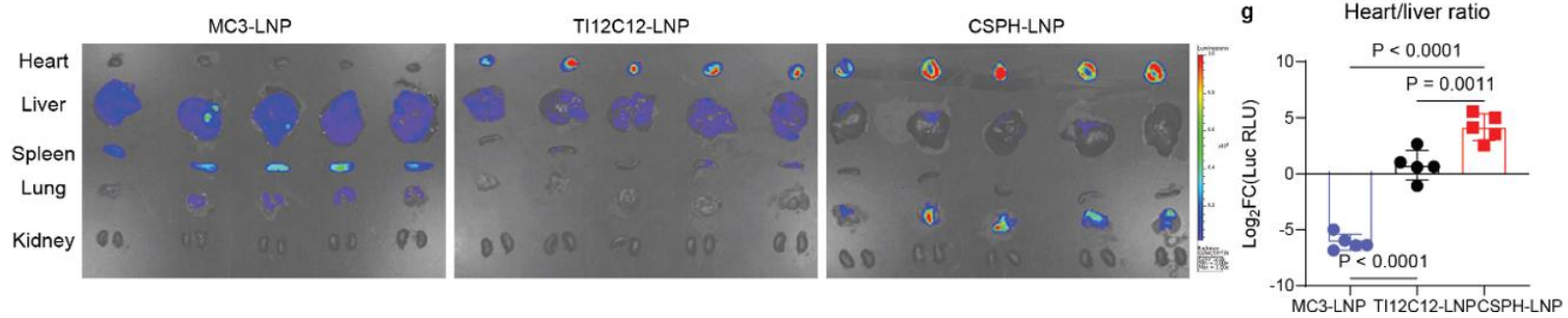




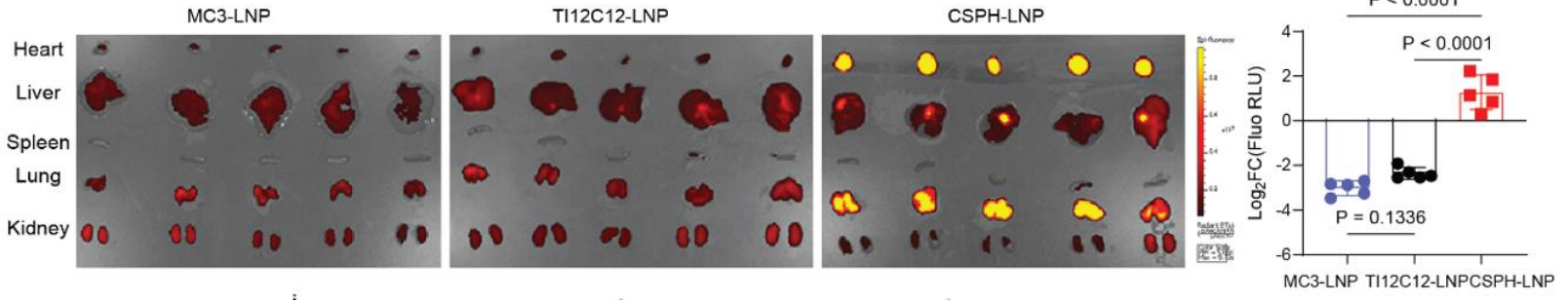
Platelet hitchhiking strategy was achieved by sequential conjugation of thrombin-cleavable peptide and CD61 antibody on TI12C12-LNP.

Infarcted heart targeted RNA delivery

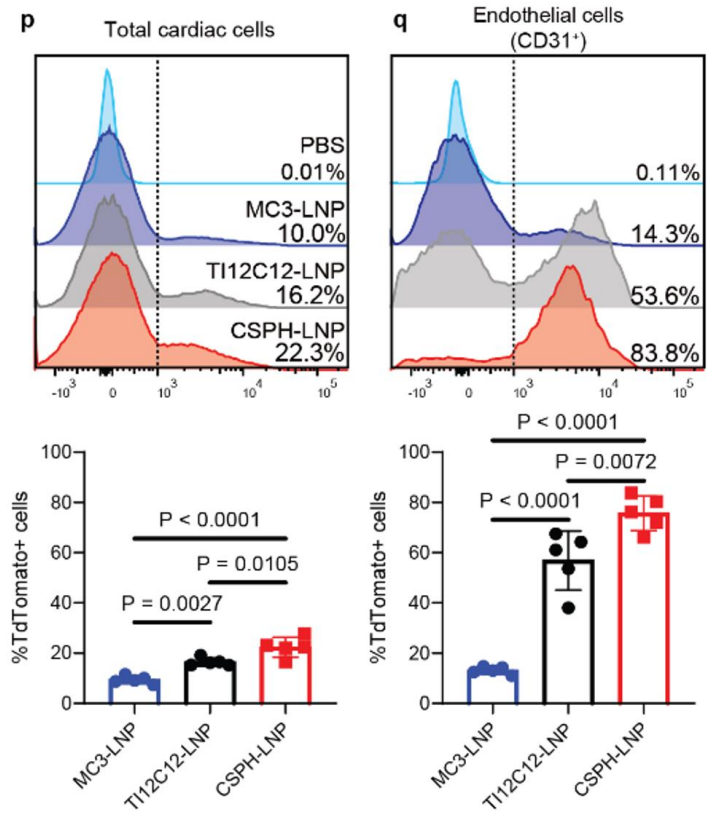
A. Firefly luciferase mRNA expression



B. Cy5-siRNA organ distribution



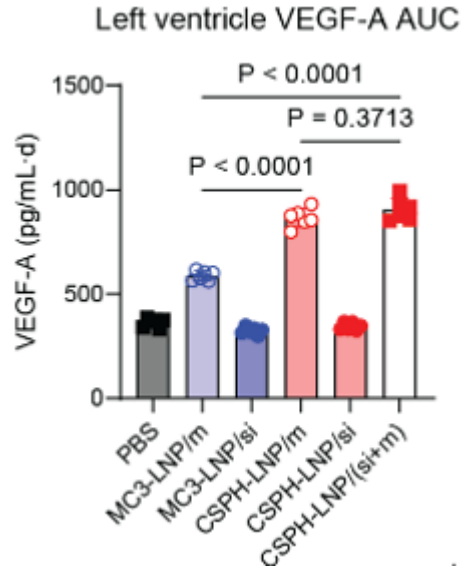
C. Ai14 mouse lineage tracing



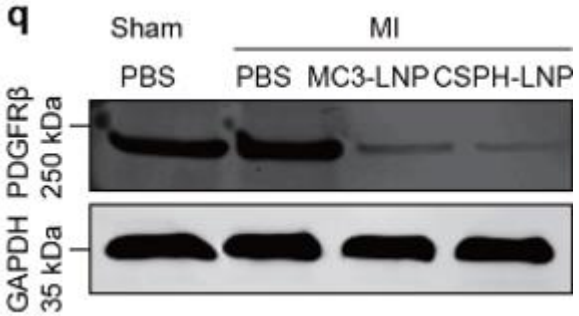
Combined strategy delivers both mRNA and siRNA predominantly to the infarcted heart.

Localized VEGF Expression & Receptor Modulation in Infarcted Heart

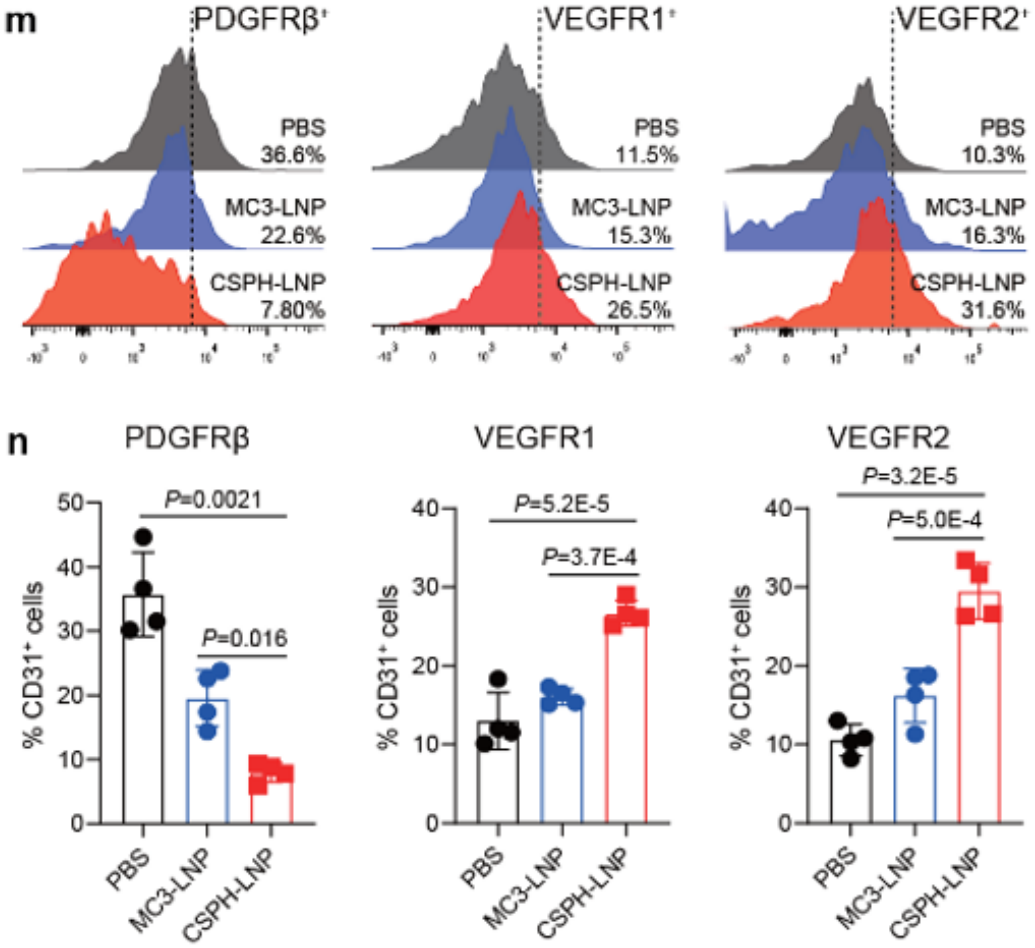
Cardiac VEGF-A expression



Cardiac PDGFR knockdown

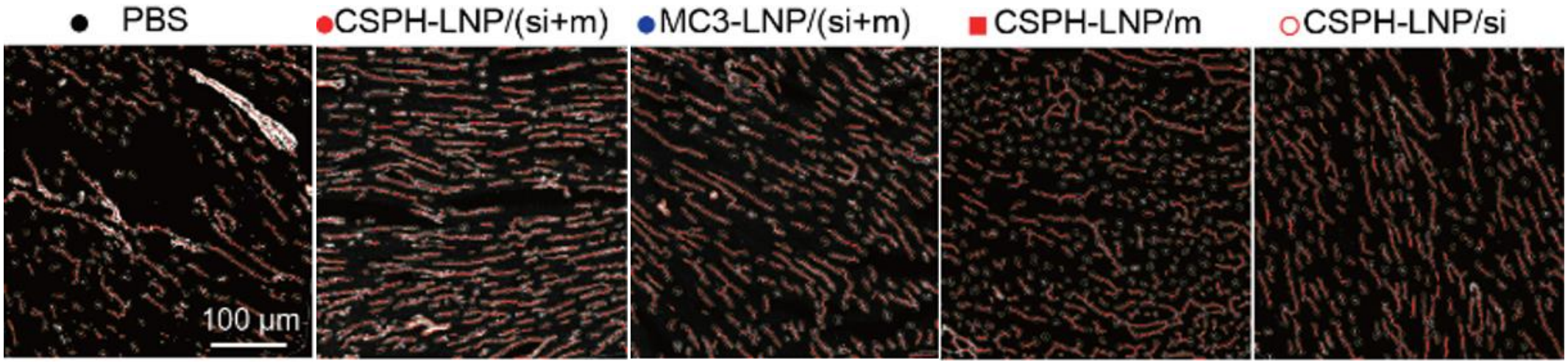


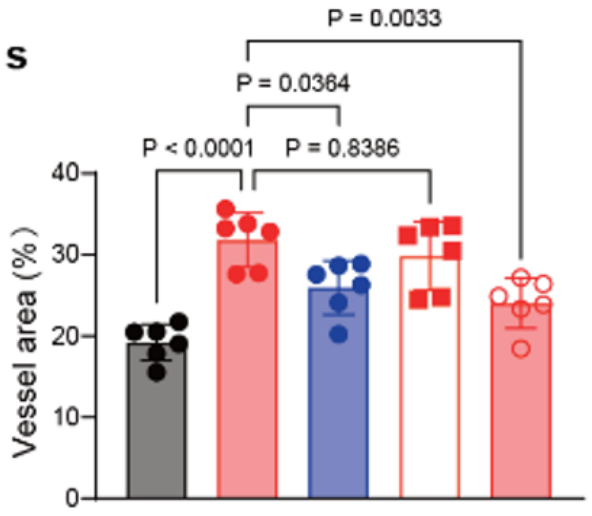
Endothelial receptor levels

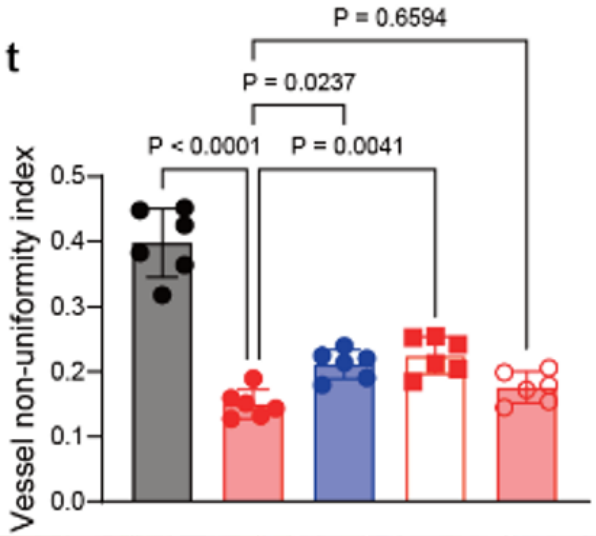


Heart endothelial cells: VEGFR1/2 upregulated, PDGFRβ silenced – indicating a shift toward mature vessel formation.

CSPH-LNP Produces Dense, Organized Vasculature in Infarct



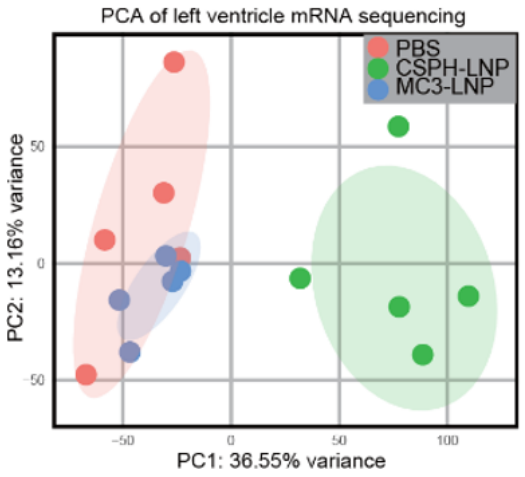




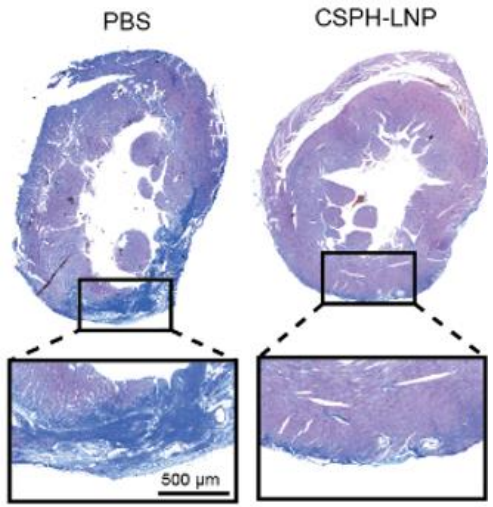
CSPH-LNP (dual cargo) induced more vessels than control, yet with fewer branches and longer average length, indicating mature, perfusable vasculature.

Improved Cardiac Repair and Function

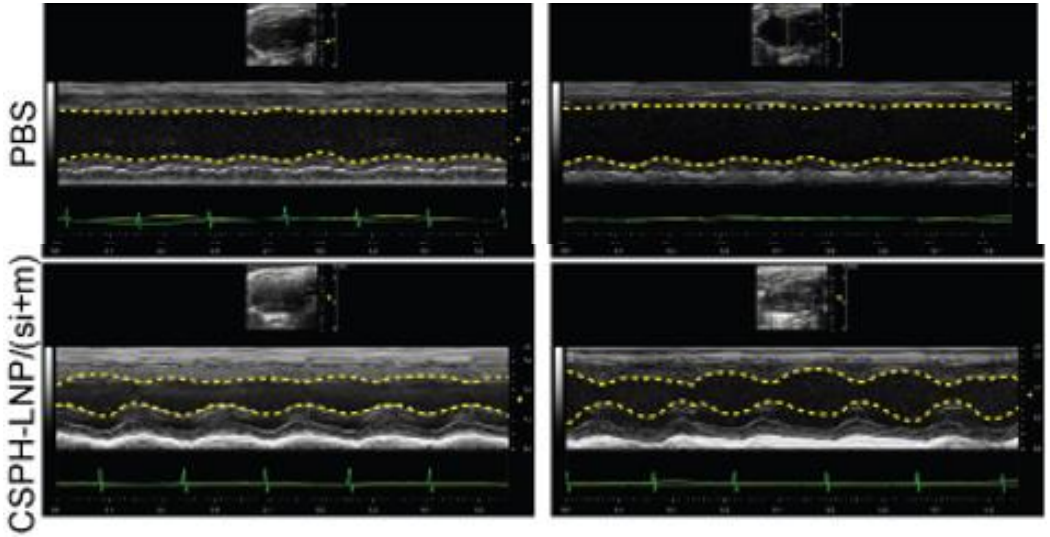
PCA of transcriptome

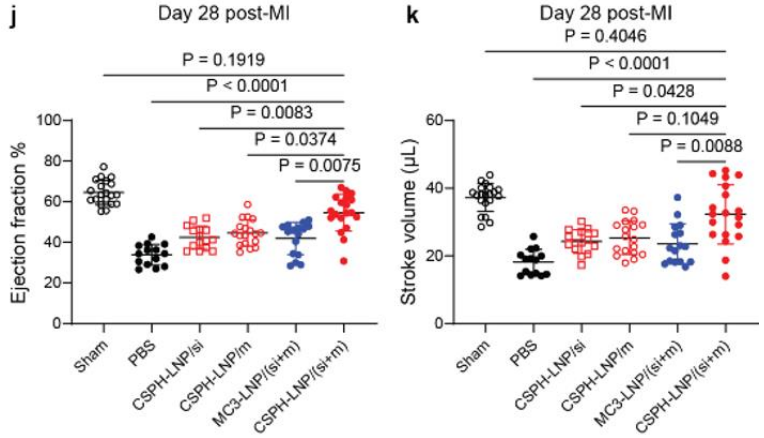


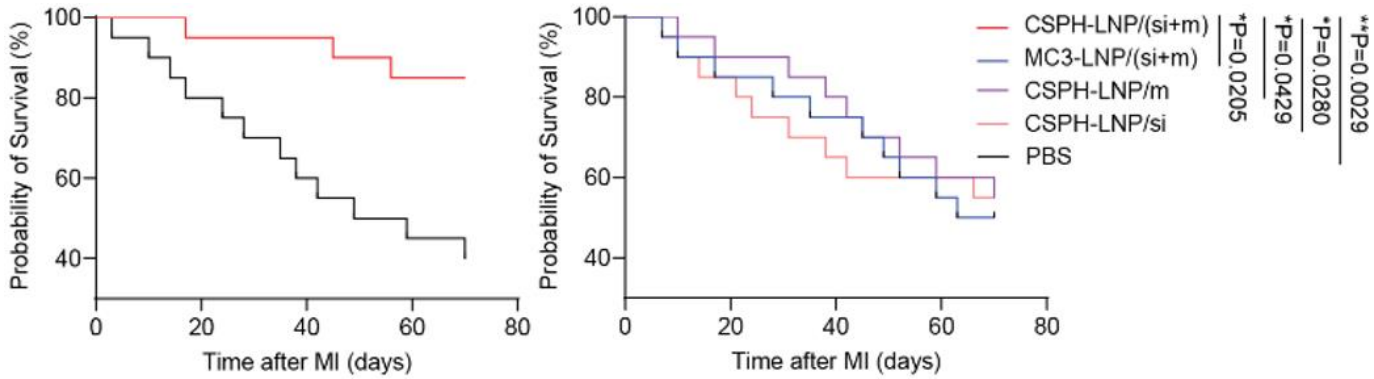
Masson's staining



Echocardiogram



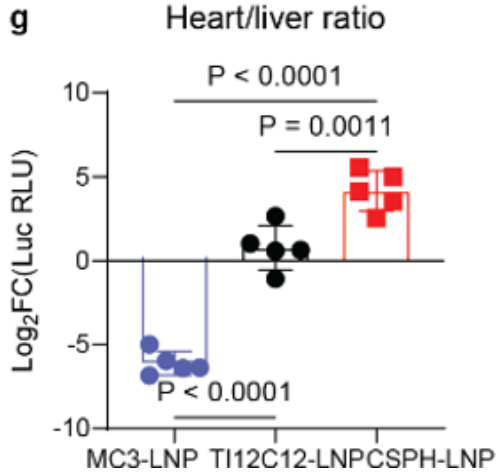




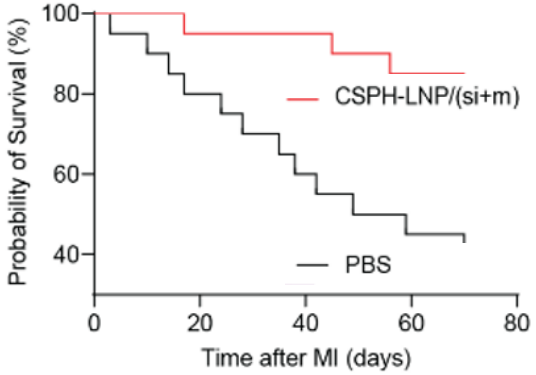
Dual-treated hearts exhibit smaller scars and a myocardial ejection profile closer to healthy tissue, indicating genuine functional recovery.

Conclusions

1. **Platelet hitchhiking enables injury-specific LNP targeting.**
2. **Ionizable lipid screening for infarct tissue boosts mRNA transfection.**
3. **Achieved efficient co-delivery of VEGF mRNA + siPDGFRβ to the heart.**
4. **Improved therapeutic angiogenesis and cardiac repair in post-MI mice.**



>1000-fold cardiac specific expression



Prolonged survival in MI mice

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Thank you for your listening!

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