High-density brush-shaped polymer lipids reduce anti-PEG antibody binding for repeated administration of mRNA therapeutics

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NEXT-GENERATION DELIVERY INNOVATIONS

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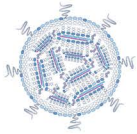
Lipid nanoparticles (LNPs) are the most clinically advanced non-viral delivery system for nucleic acid delivery

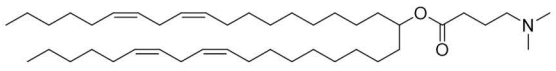


onpattro® (patisiran) lipid complex injection 10 mg/5 mL

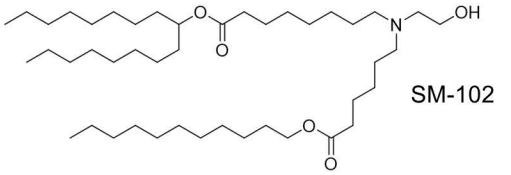
spikevax® by moderna COVID-19 Vaccine, mRNA

COMIRNATY® (COVID-19 Vaccine, mRNA)

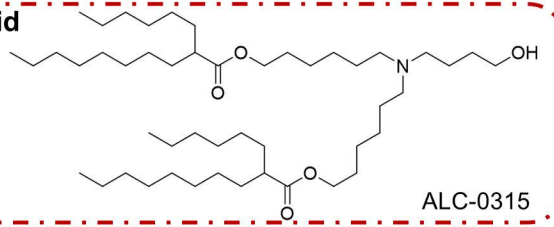
ionizable lipid



DLin-MC3-DMA

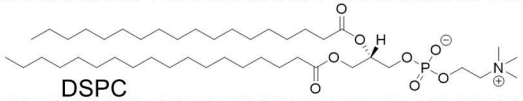


SM-102

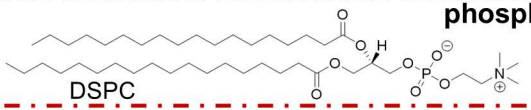


ALC-0315

phospholipid



DSPC



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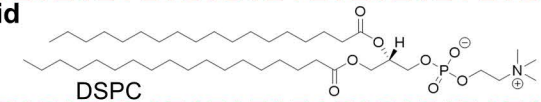
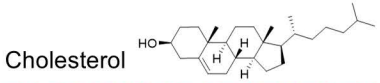
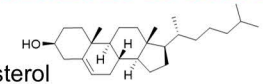


DSPC

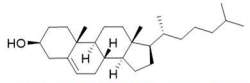
cholesterol



Cholesterol

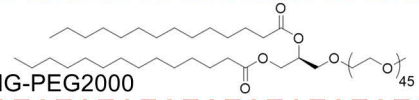


Cholesterol

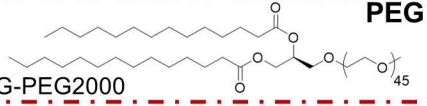


Cholesterol

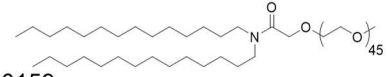
PEG lipid



DMG-PEG2000

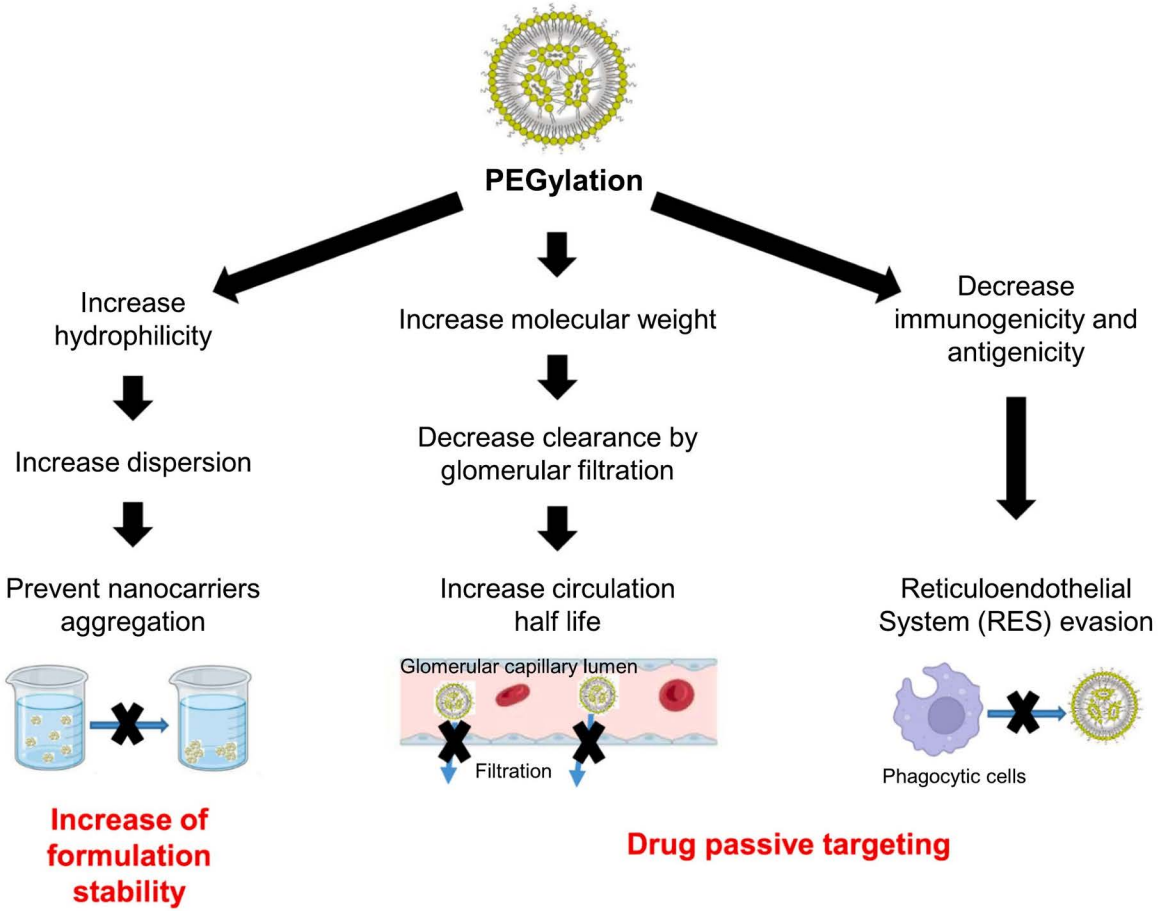


DMG-PEG2000



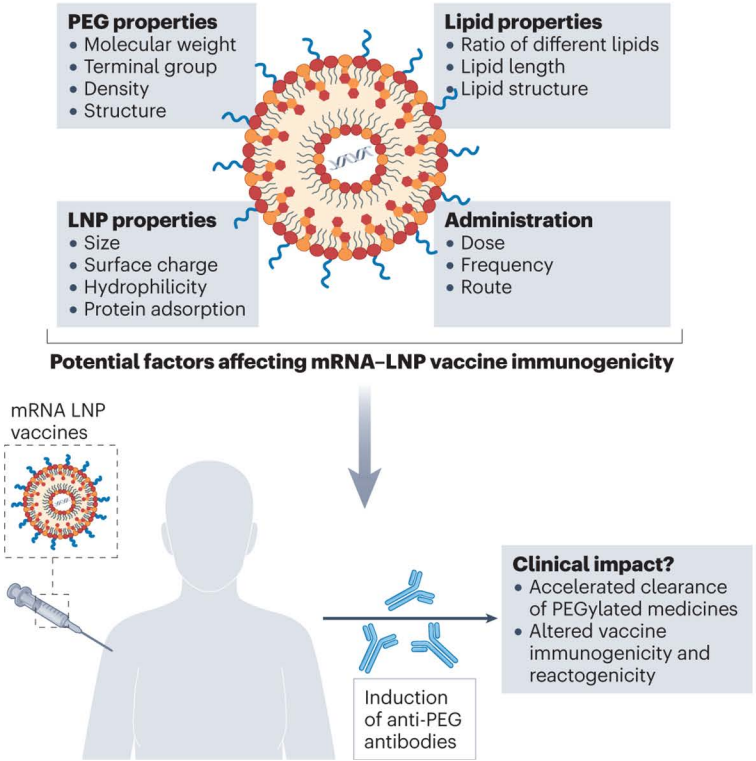
ALC-0159

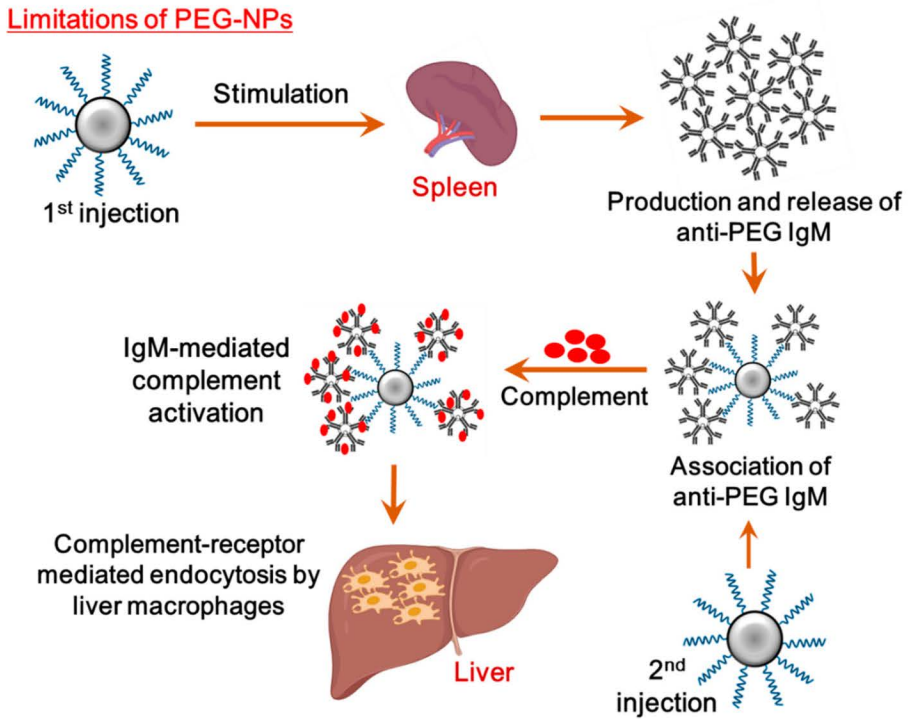
PEGylation is a breakthrough in the field of drug delivery



Ibrahim et al. **J. Controlled Release**, 351, 215-230 (2022)

Anti-PEG antibodies lead to accelerated blood clearance of systemically delivered PEGylated therapeutics and limit their efficacy



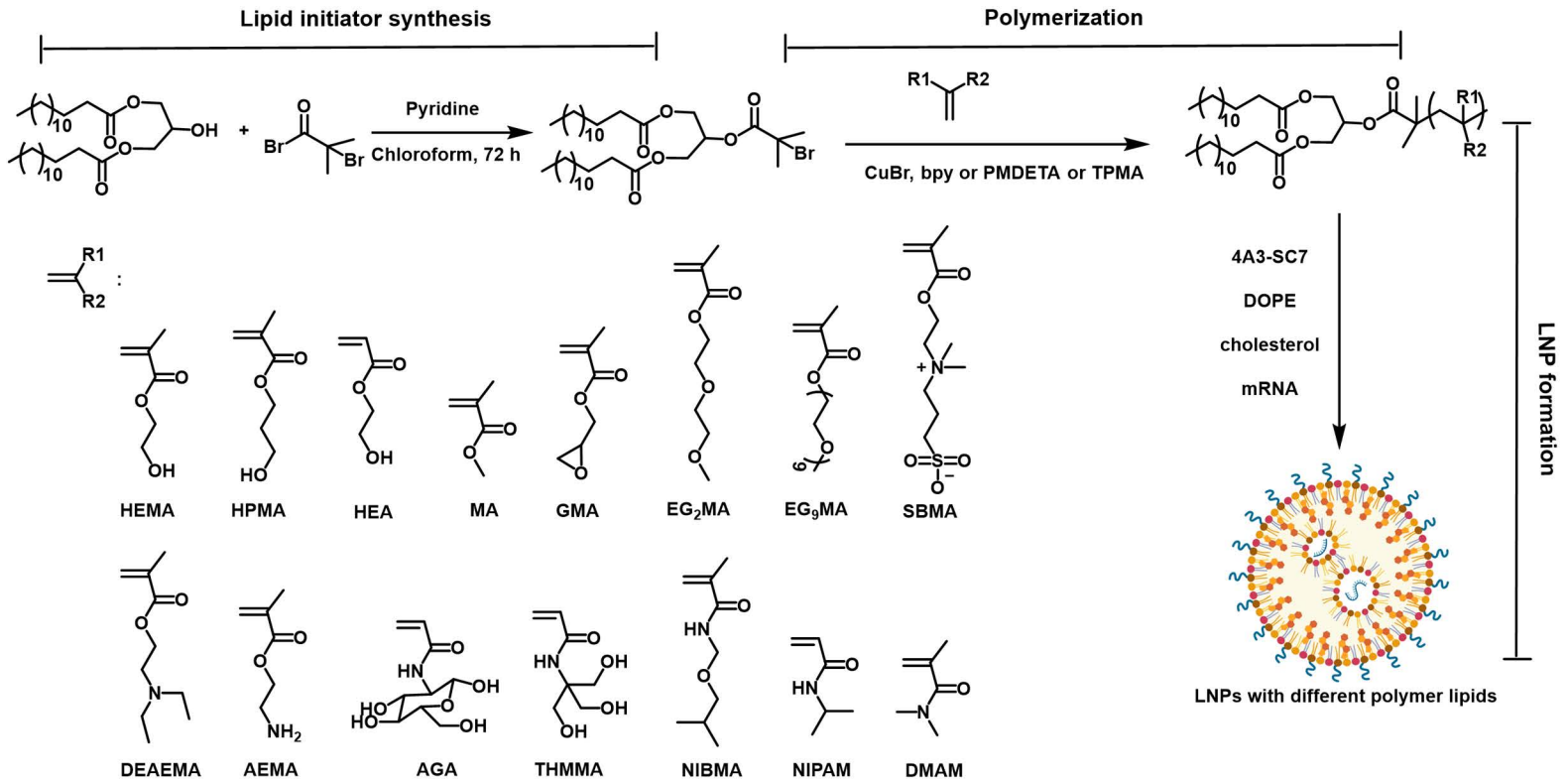


Ju et al. **Nat. Rev. Immunol.**, 23,135–136 (2023)

Thi et al. **Polymers**, 12, 298 (2020)

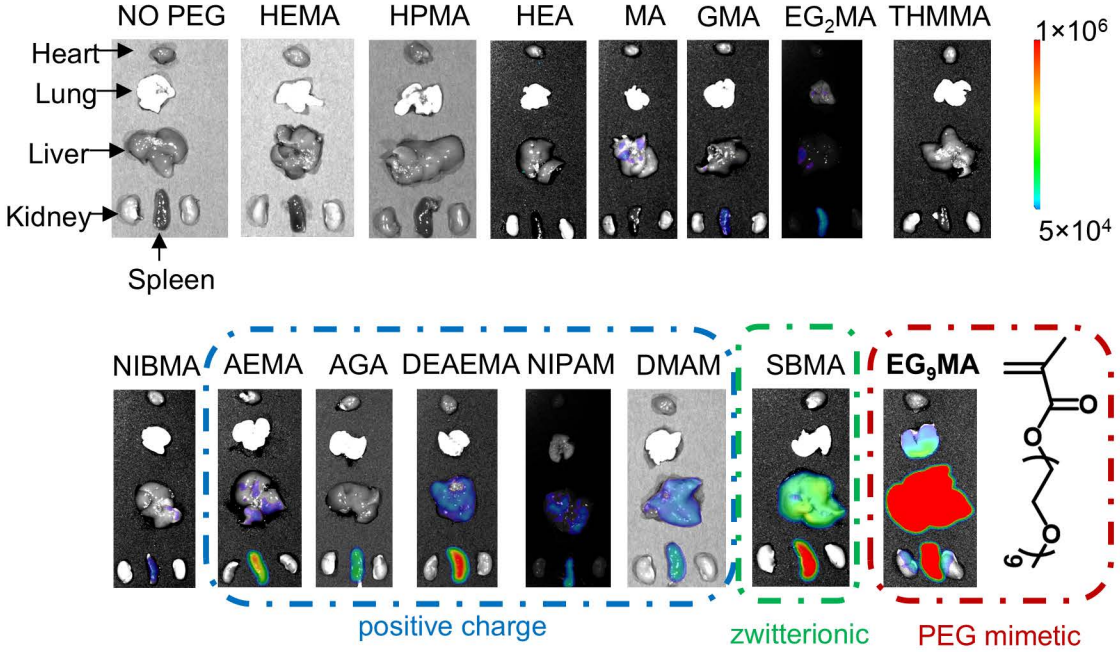
Can alternative surface polymer chemistries and architectures reduce formation of anti-PEG antibodies to improve repeat dose delivery outcomes?

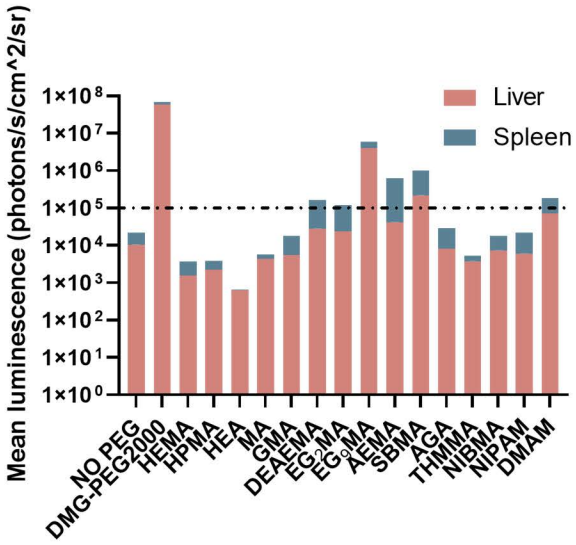
A series of polymer lipids were synthesized by atom transfer radical polymerization (ATRP) with similar molecular weight (MW) to DMG-PEG2000



4A3-SC7:DOPE:cholesterol:polymer lipid = 15:15:30:3

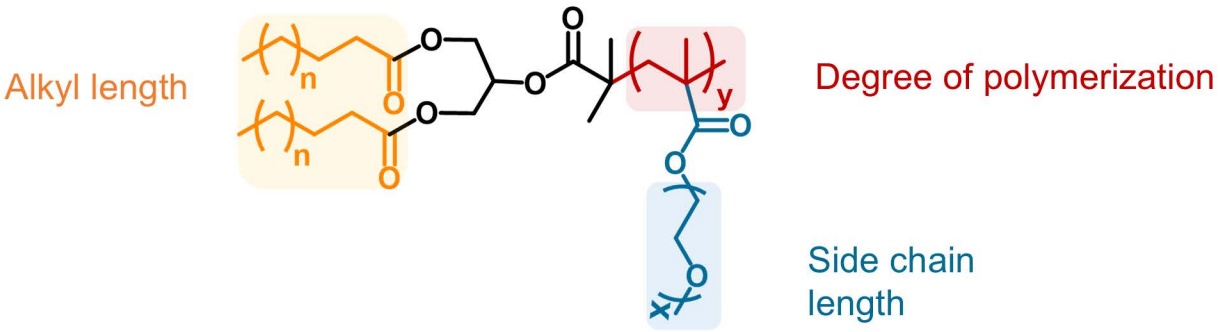
Polymer chemical structure modulates mRNA delivery efficacy





Hit: 1×10^5
Hit rate: 40%
Luc mRNA: 0.1 mpk

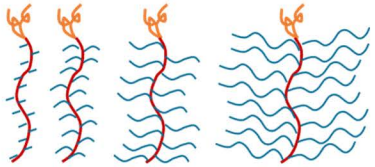
We prepared systematically modulated polymer architectures to correlate structure with mRNA delivery efficacy



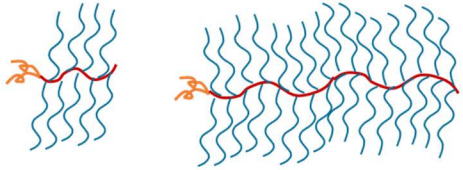
Brush shaped polymer lipid (BPL)

mRNA delivery efficacy correlated with polymer architecture

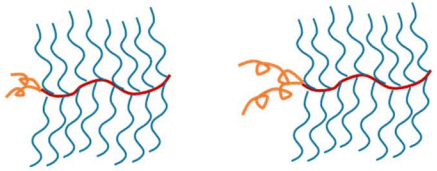
Longer EG side chain

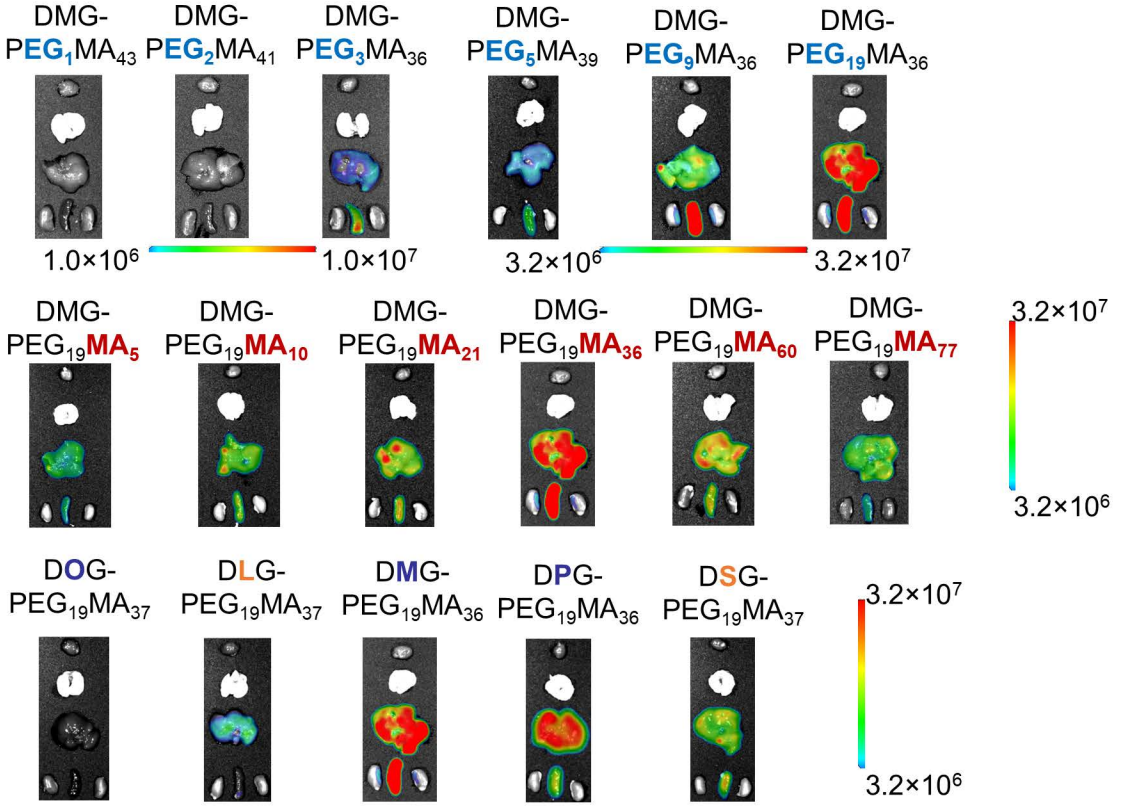


Intermediate degree of polymerization

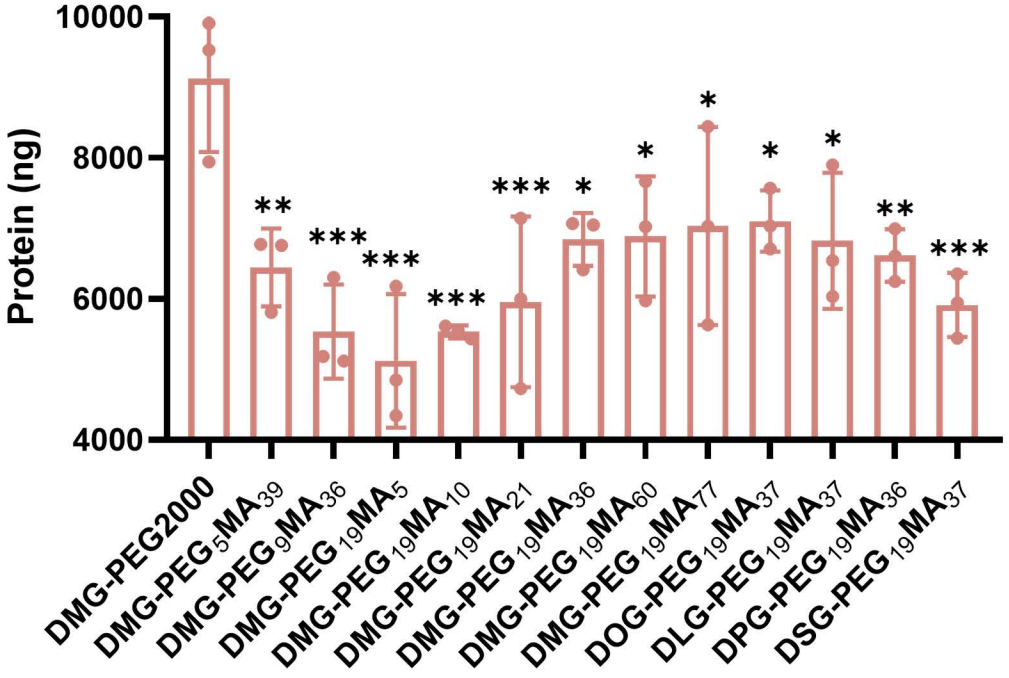


Intermediate alkyl length

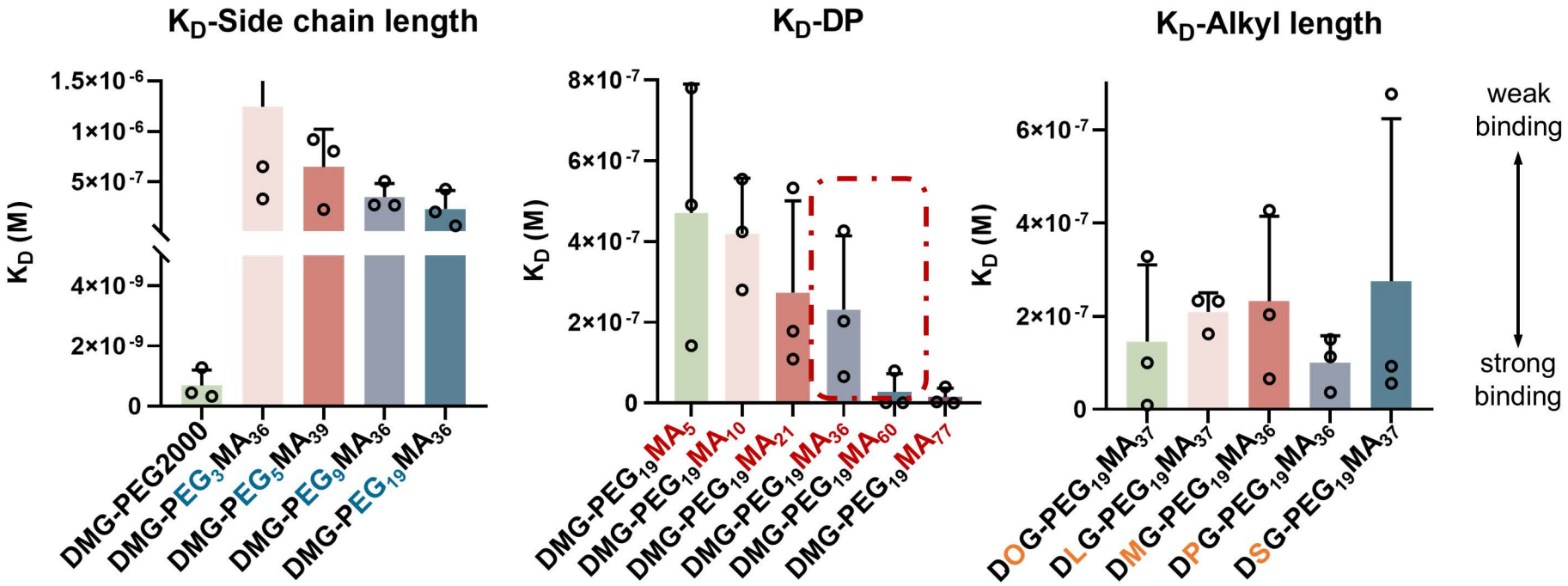




BPL LNPs reduce protein adsorption due to the comb structure



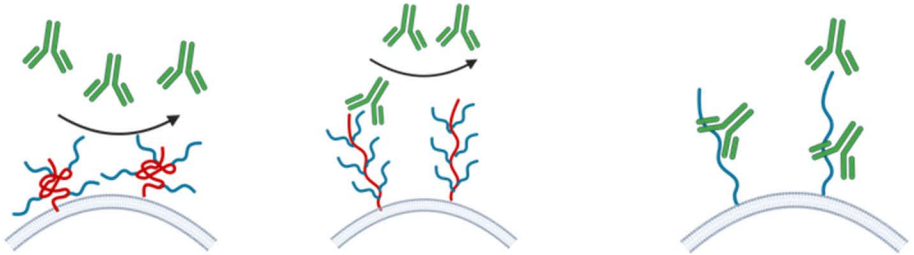
BPL LNPs reduce anti-PEG antibody binding more than DMG-PEG2000 LNPs



The “mushroom regime” architecture is critical to most effectively repel protein binding due to high surface coverage

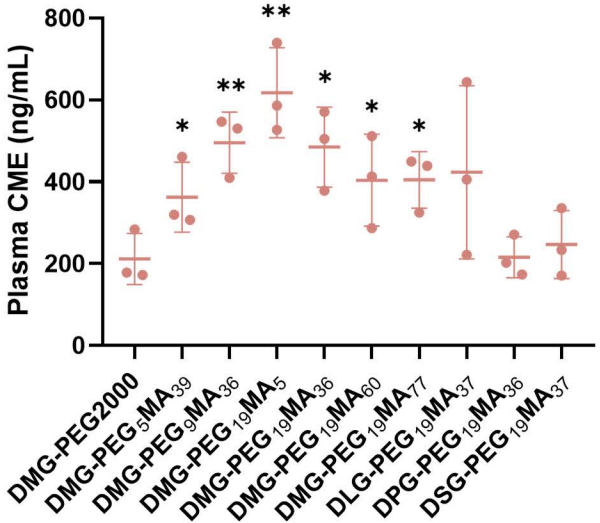
side chain length	R_F (Å)	Regime
EG_3	6.8	brush
EG_5	9.2	brush
EG_9	13.1	brush
EG_{19}	20.5	brush

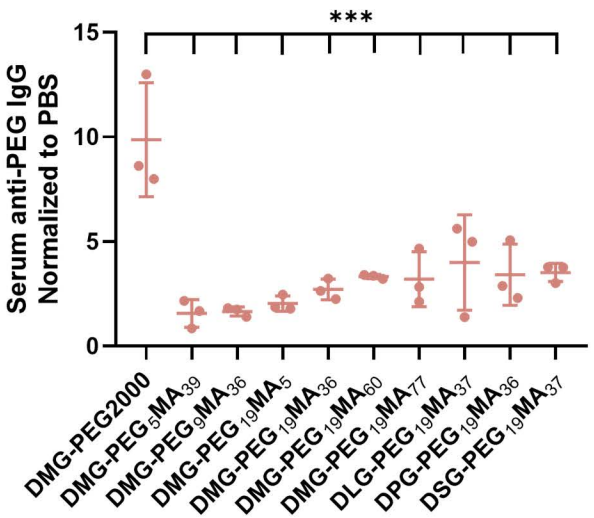
DP	R_F (Å)	Regime
$PEG_{19}MA_5$	8.0	mushroom
$PEG_{19}MA_{10}$	12.1	mushroom
$PEG_{19}MA_{21}$	18.9	mushroom
$PEG_{19}MA_{36}$	26.1	mushroom
$PEG_{19}MA_{60}$	35.5	brush
$PEG_{19}MA_{77}$	41.2	brush

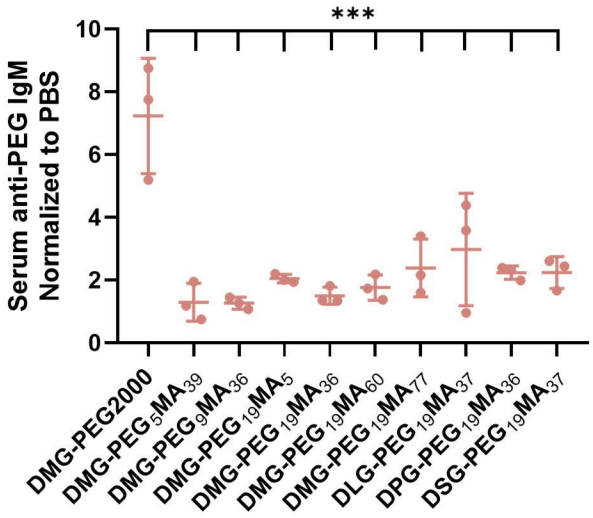


Mushroom Brush Linear

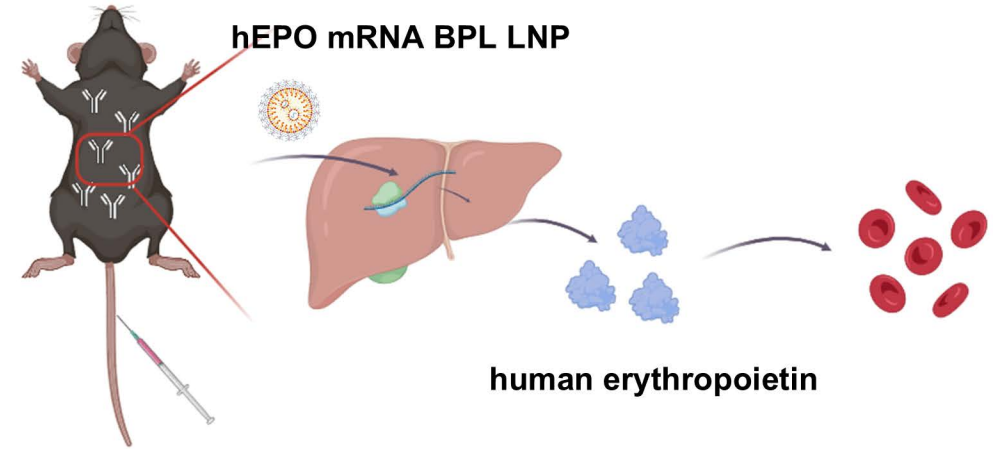
BPL LNPs prolong blood circulation with weaker immune response in repeat doses

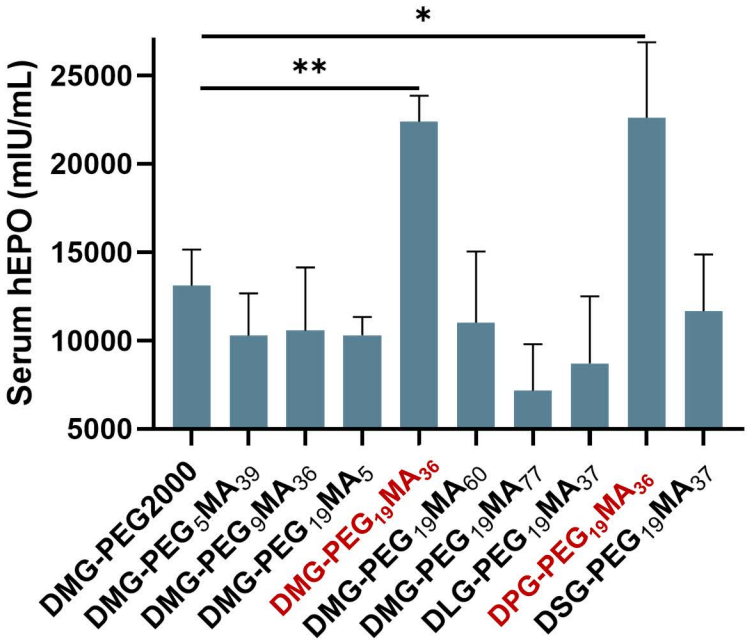




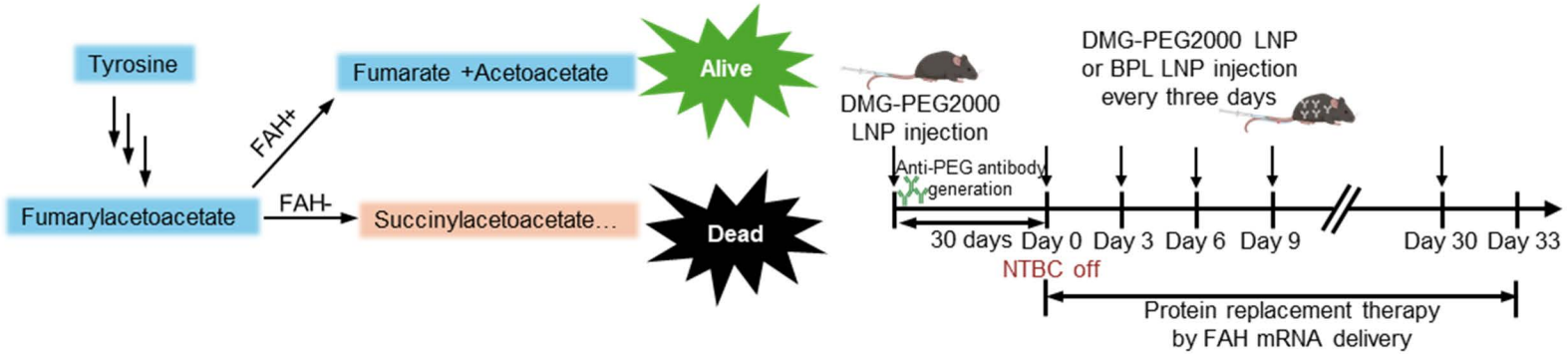


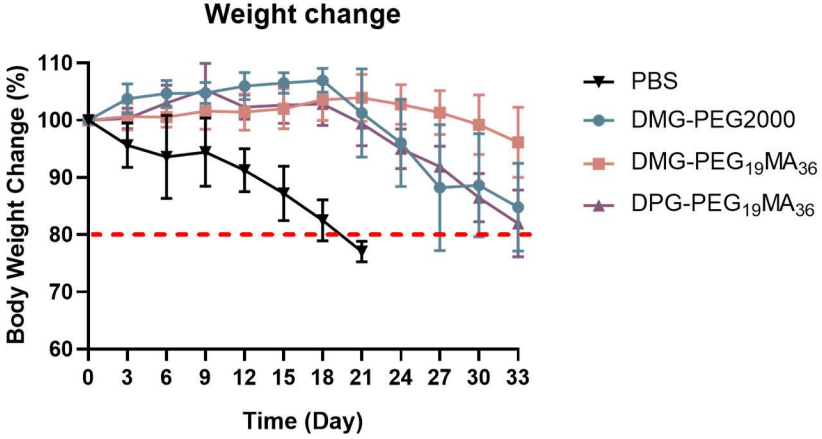
BPL LNPs overcome anti-PEG antibody inhibitory effects and maintain high protein production

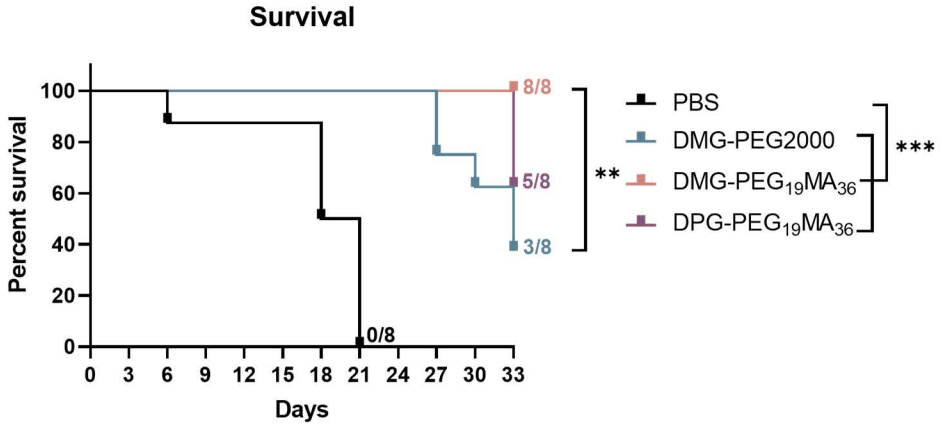




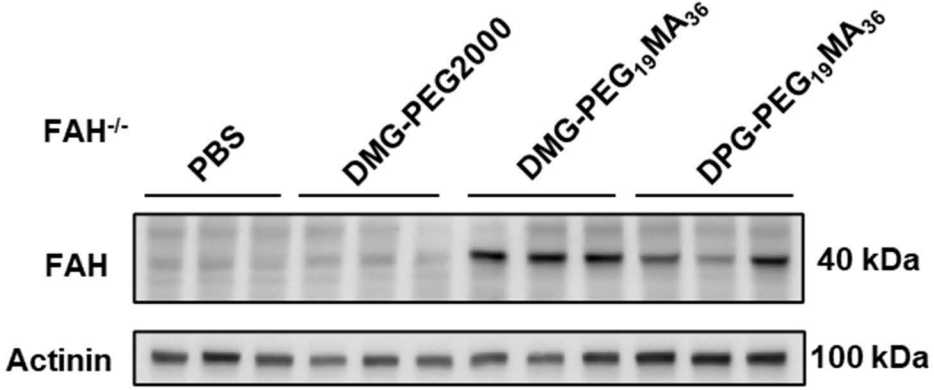
FAH mRNA BPL LNPs extended survival (100%) in FAH$^{-/-}$ mice over DMG-PEG2000 LNPs (37.5%)

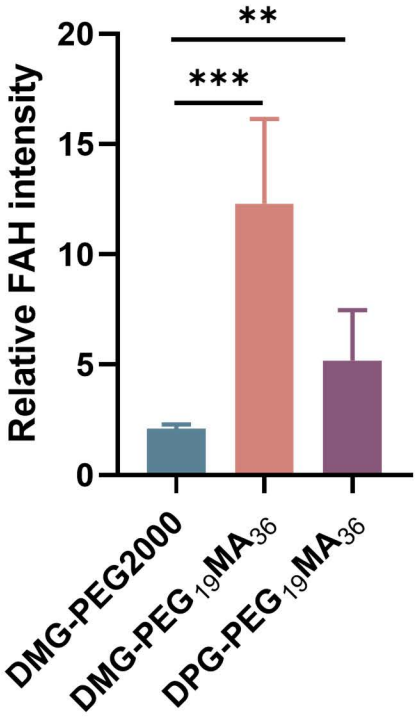




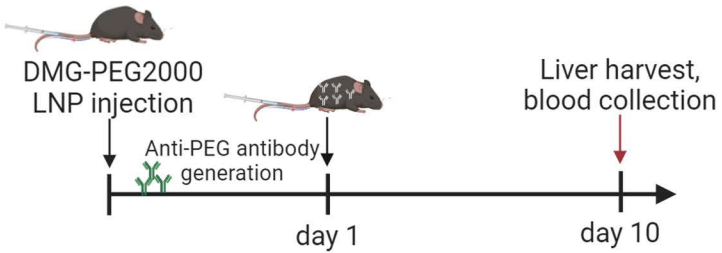


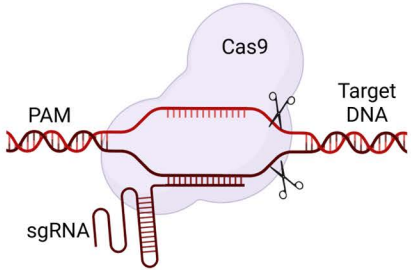
FAH mRNA BPL LNPs maintain high FAH protein expression following multiple doses

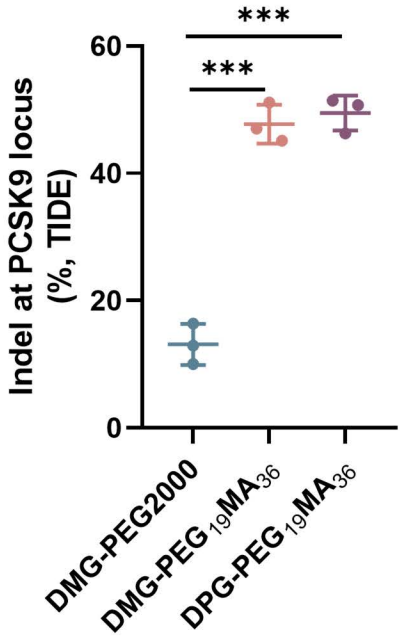


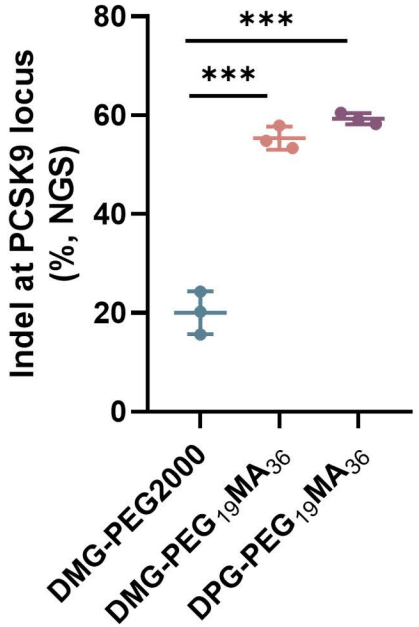


BPL LNPs achieve higher levels of CRISPR/Cas genome editing than the DMG-PEG2000 LNP benchmark

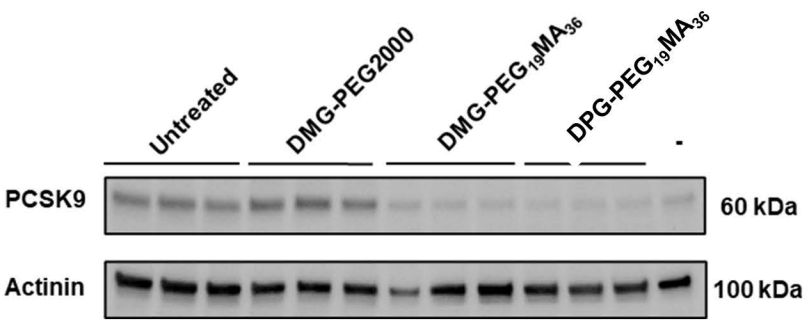


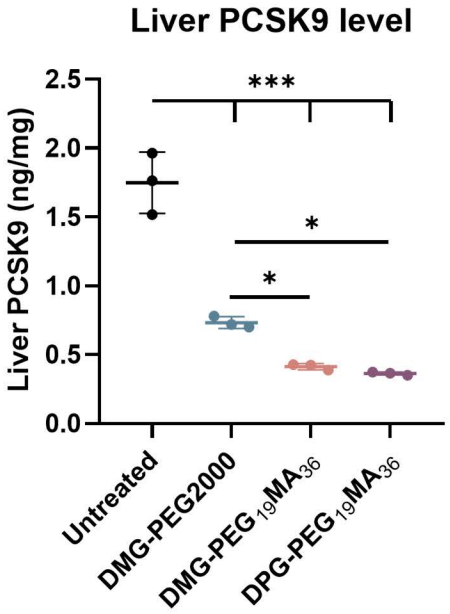


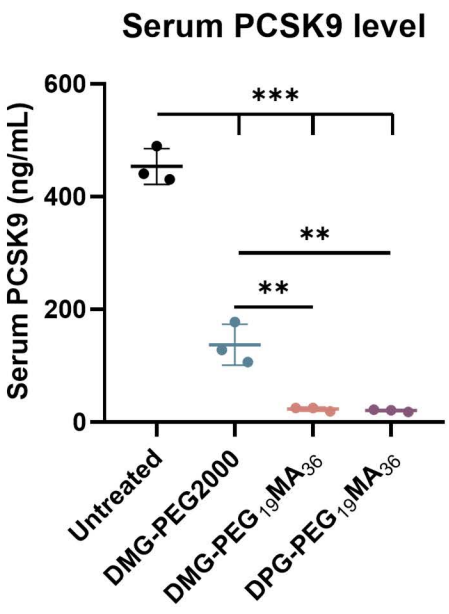




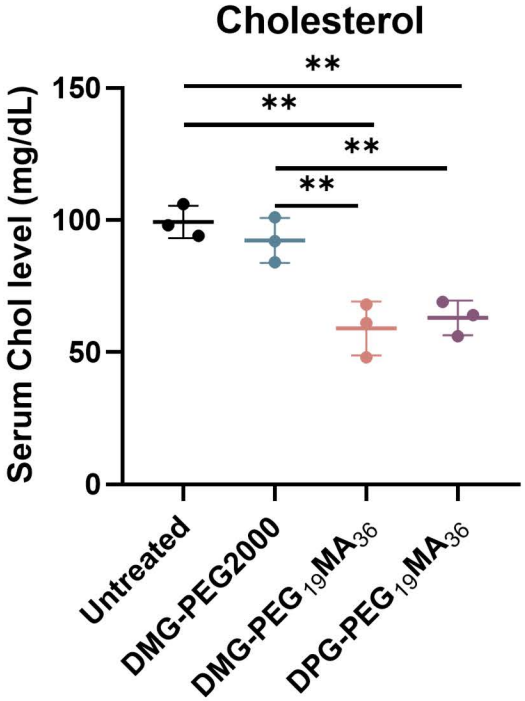
Co-delivery of Cas9 mRNA and sgPCSK9 using BPL LNPs reduced liver and serum PCSK9 protein levels more effectively than benchmark PEG-DMG2000 LNPs

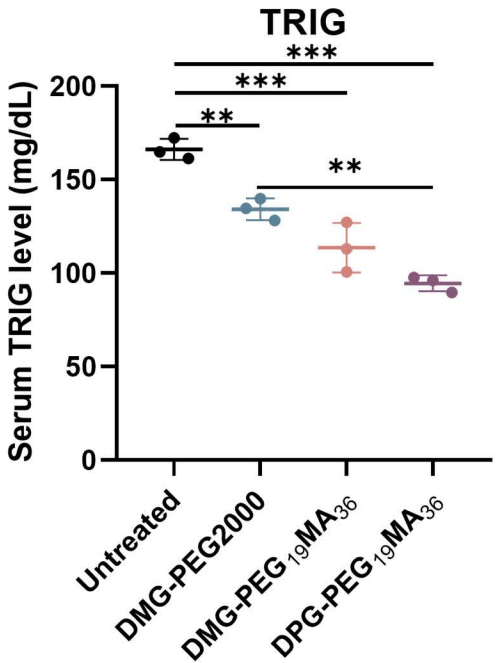




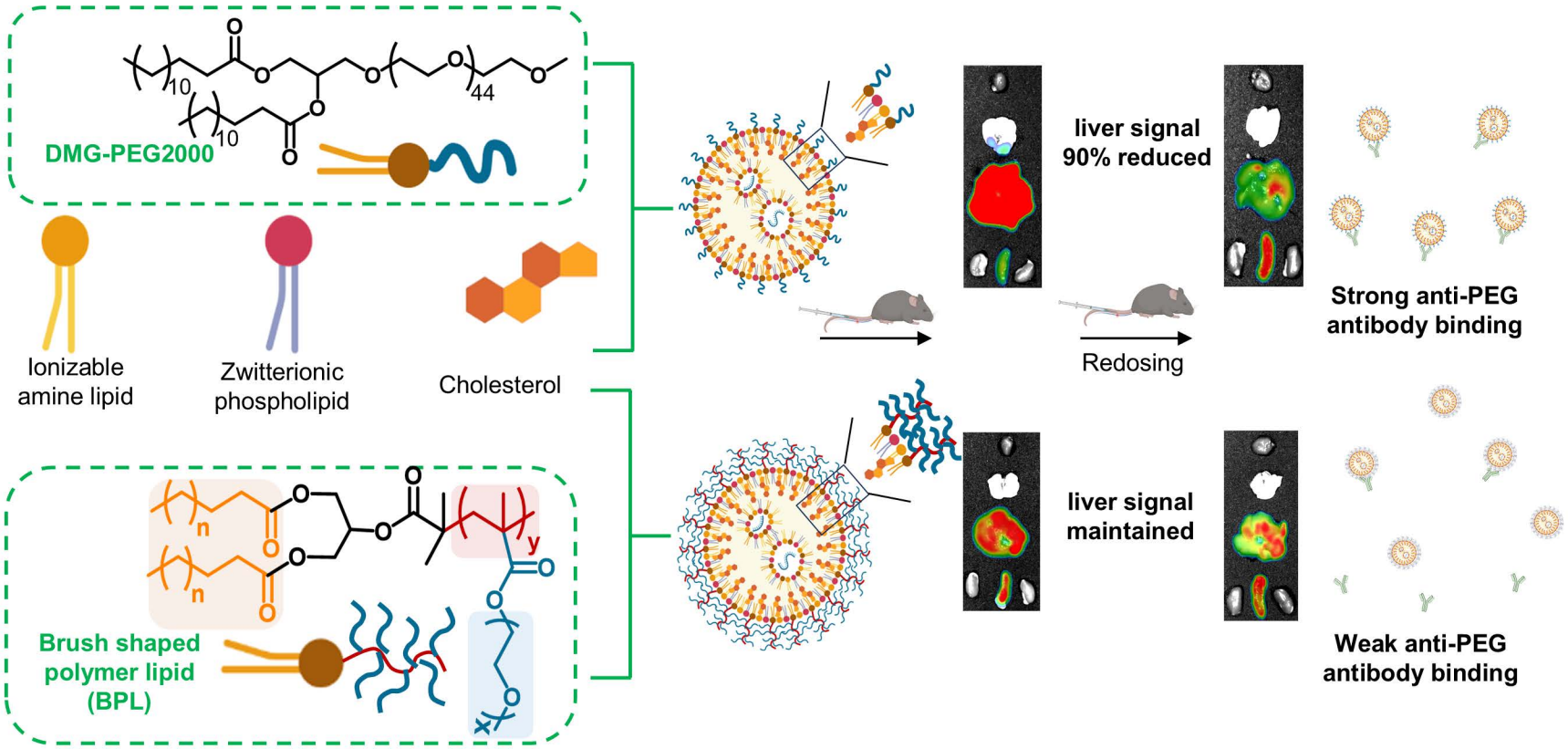


Co-delivery of Cas9 mRNA and sgPCSK9 using BPL LNPs reduced serum cholesterol and triglyceride levels more effectively than benchmark PEG-DMG2000 LNPs





Xiao et al. ***Nat. Mater.*** (2025). https://doi.org/10.1038/s41563-024-02116-3



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