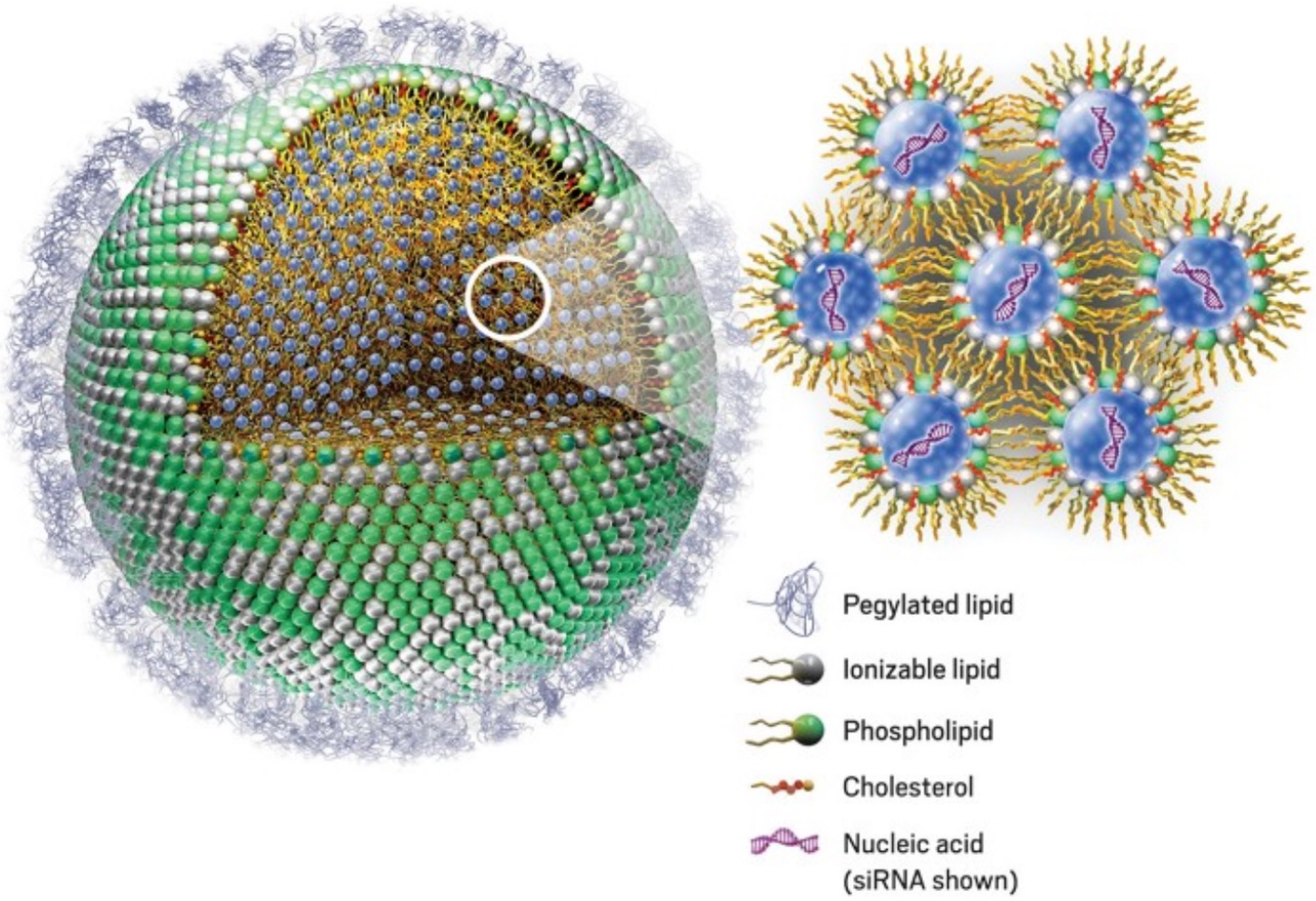
Current Research in Membranes: Lipid Nanoparticles



Credit: Genevant Sciences

A lipid nanoparticle (LNP) contains hundreds of small interfering RNA (siRNA) molecules, each surrounded by ionizable lipids, phospholipids, and cholesterol. The outside of the particle is coated in pegylated lipids. LNPs for messenger RNA (mRNA) are made with similar ingredients but contain only a few mRNA strands.

Powerful packaging, Cross, C&E News Mar 2021

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MC3

"The biggest issue was trying to find the right balance between systems that were effective, but also safe and tolerable." … Nanoparticles based on MC3 required about 1/1000th the dose of LNPs made using older ionizable lipids. … But the drug requires an 80 min infusion every 3 weeks and pre-treatment with multiple anti-inflammatory drugs to minimize reactions to the nanoparticles.

"Delivery into specific cell and tissue populations is still a huge challenge for the field." … Right now, IV injections of nanoparticles can easily reach the liver, and intramuscular injections for vaccines are taken up by immune cells … but the rest of the body remains out of reach.

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Illuminating endosomal escape of polymorphic lipid nanoparticles that boost mRNA delivery†

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Lipid-based nanoparticles (LNPs) for the delivery of mRNA have jumped to the forefront of non-viral gene delivery. Despite this exciting development, poor endosomal escape after LNP cell entry remains an unsolved, rate-limiting bottleneck. Here we report the use of a galectin 8-GFP (Gal8-GFP) cell reporter system to visualize the endosomal escape capabilities of LNP-encapsulated mRNA. LNPs substituted with phytosterols in place of cholesterol exhibited various levels of Gal8 recruitment in the Gal8-GFP reporter system. In live-cell imaging, LNPs containing β-sitosterol (LNP-Sito) showed a 10-fold increase in detectable endosomal perturbation events when compared to the standard cholesterol LNPs (LNP-Chol), suggesting the superior capability of LNP-Sito to escape from endosomal entrapment. Trafficking studies of these LNPs showed strong localization with late endosomes. This highly sensitive and robust Gal8-GFP reporter system can be a valuable tool to elucidate intricacies of LNP trafficking and ephemeral endosomal escape events, enabling advancements in gene delivery.

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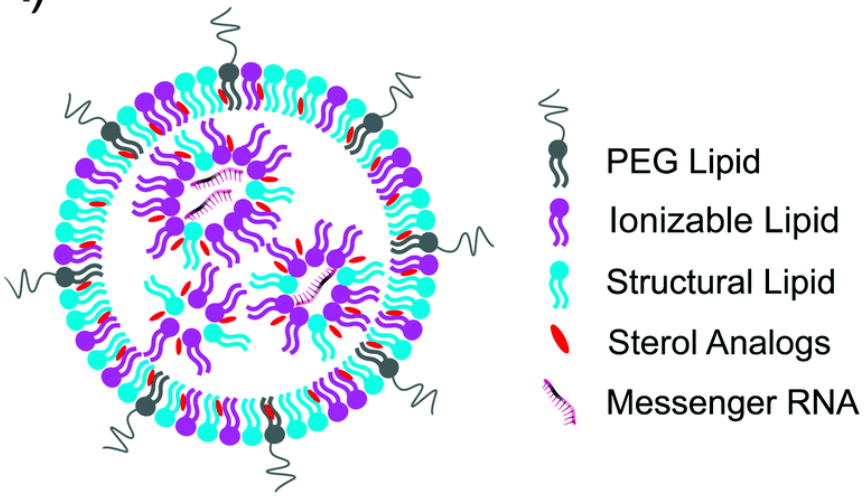
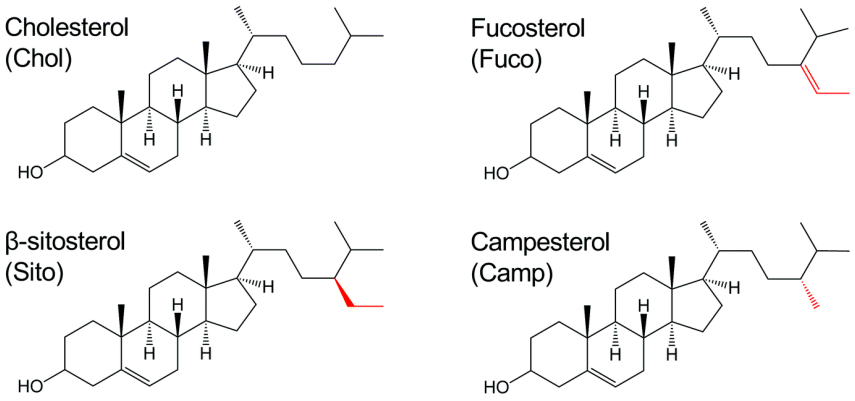


(B)



Herrera *et al* , Biomater Sci 2021