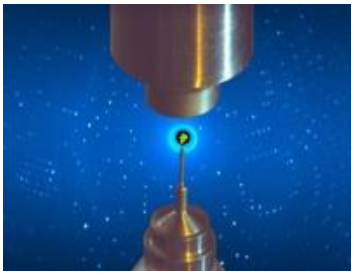

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Structural Investigation of Lipid Nanoparticles is key for Successful mRNA Delivery

Wednesday, 9 June 2021 09:00 (30 minutes)

Lipid nanoparticles (LNPs) constituted by a cationic ionizable lipid and helper lipids as cholesterol, phospholipids and poly(ethylene glycol) lipid as stabilizer have made mRNA therapeutics a reality. 2 mRNA-based vaccines against SARS-CoV-2 have received emergency authorization by many regulatory agencies using LNPs as delivery vehicle. We investigated the structure of mRNA-containing LNPs to understand how this relates to their transfection efficacy. Small angle X-ray and neutron scattering were fundamental to prove that LNPs have a disordered hexagonal internal structure in the presence of mRNA, independently of their size. Additionally, we found that the phospholipid DSPC and cholesterol are localized mainly at the LNP surface. Knowing their lipid distribution allowed us to vary their size and surface composition in order to increase protein production. This improvement is most likely related to the ability of LNPs to fuse with early endosome membranes. Another important consideration is the formation of a protein corona at the LNP surface upon administration and in particular Apolipoprotein E (ApoE), which is responsible for fat transport in the body. We found that binding of ApoE to LNPs induces a redistribution of the lipid across the particle, which can impact endosomal escape. Our findings highlight how neutrons can guide us in the rational design of nanomedicines for gene therapy with improved bioperformance.

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