mRNA lipid nanoparticle phase transition

Marius F.W. Trollmann[1,2], Rainer A. Böckmann[1,2*]

[1] *Computational Biology, Department of Biology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen*
[2] *Erlangen National High Performance Computing (NHR@FAU)*
**Correspondence: rainer.boeckmann@fau.de*

Crucial for mRNA-based vaccines are the composition, structure, and properties of lipid nanoparticles (LNPs) as their delivery vehicle. Using all-atom molecular dynamics simulations as a computational microscope, we provide an atomistic view of the structure of the Comirnaty vaccine LNP, its molecular organization, physicochemical properties, and insight in its pH-driven phase transition enabling mRNA release at atomistic resolution. At physiological pH, our simulations suggest an oil-like LNP core that is composed of the aminolipid ALC-0315 and cholesterol (ratio 72:28). It is surrounded by a lipid monolayer formed by distearoylphosphatidylcholine (DSPC), ALC-0315, PEGylated lipids, and cholesterol at a ratio of 22:9:6:63. Protonated aminolipids enveloping mRNA formed inverted micellar structures that provide a shielding and likely protection from environmental factors. In contrast, at low pH, the Comirnaty lipid composition instead spontaneously formed lipid bilayers that display a high degree of elasticity. These pH-dependent lipid phases suggest that a change in pH of the environment upon LNP transfer to the endosome likely acts as trigger for cargo release from the LNP core by turning aminolipids inside out, thereby destabilizing both the LNP shell and the endosomal membrane.