Lipid nanoparticles - a soft matter perspective on programmable nucleic acid carriers

Lipid Nanoparticles (LNPs) represent the most advanced technology for delivery of nucleic acid. The particles exhibit a well-designed core-shell structure containing ordered lipid mesophases that encapsulate nucleic acid. We discuss distinct pH dependent structural transitions in bulk phases of cationic ionizable lipids (CILs) and their role in nucleic acid transfer. Using high resolution small angle X-ray scattering we elucidate the distinct role of a pH-driven transitions from inverse cubic Fd3m to inverse hexagonal HII phases. These structural transitions are related to gene delivery activity. Gene expression time courses, taken by live cell imaging on single cell arrays (LISCA), yield delivery delay times, mRNA translation efficiency and mRNA stability. We show that understanding the content and release kinetics of lipid nanoparticles that contain multiple nucleic acid species, allows for the design of regulatory motives, e.g. feed forward loops, resulting in tailored expression kinetics.