Improving intracellular delivery of antibiotics against pulmonary infections using liquid crystalline lipid nanoparticles

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Bacteria have developed several strategies to avoid the action of antibiotics, including their ability to invade and survive within host cells. Currently available antibiotics suffer from limited penetration across host cell membranes, resulting in suboptimal treatment against the bacteria[1,2]. Liquid crystalline lipid nanoparticles (LCNP) are gaining significant research interest as a promising drug delivery carrier; however, they have not been reported for targeting intracellular bacteria. Furter, their activity in presence of biological molecules, i.e proteins are also poorly understood[3]. In this study, the cellular interaction of LCNPs in two types of pulmonary cells, RAW 264.7 macrophages and A549 epithelial cells was investigated in presence of biological proteins and via the incorporation of a cationic lipid, dimethyldioctadecylammonium bromide (DDAB). LCNPs displayed a honeycomb-like structure, while the inclusion of DDAB resulted into an onion-like organisation. Cationic LCNPs enhanced the cellular uptake in both cells, reaching up to ~90% uptake in cells. Interestingly, in presence of a protein corona formed using fetal bovine serum (FBS) or bronchoalveolar lavage fluid (BALF), LCNPs also demonstrated improved cellular uptake. The LCNPs were encapsulated with tobramycin or vancomycin to improve their activity against intracellular *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The enhanced cellular uptake of LCNPs in presence of a protein corona corresponded with improved antibacterial killing. Similarly, cationic LCNPs resulted in significant reduction of intracellular bacterial viability (above 50%), compared to antibiotic dosed in its free form. The outcome of this research highlights the ability of LCNPs to be engineered for improved performance and the importance in understanding the role of biological fluids in mediating cellular interaction and performance of nanoparticles.

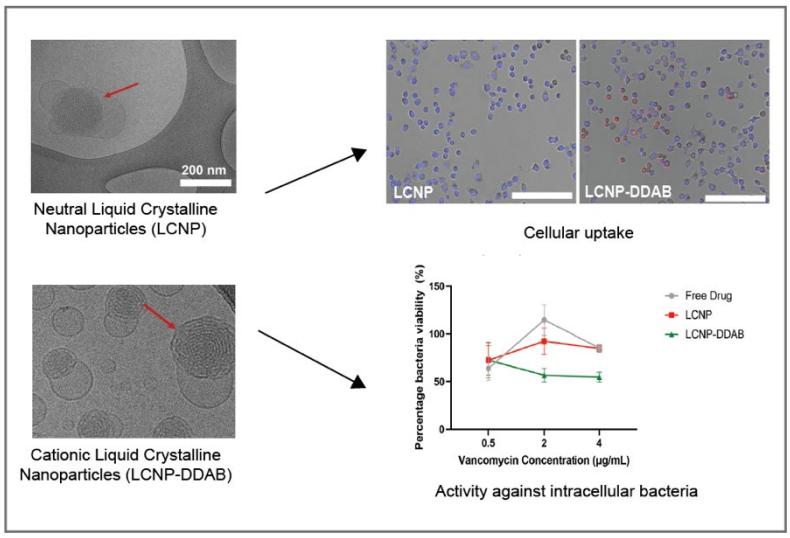

Figure 1: *Schematic illustrating synthesis of LCNPs and their cellular uptake and activity against intracellular bacteria.*

References:
[1] Subramaniam, S.; et al. *Antibiotics* **2019**, 8(2): 39.
[2] Subramaniam, S.; et al. *Advanced Drug Delivery Reviews* **2021**, 177 (12): 113948.
[3] Subramaniam, S.; et al. *Journal of Colloid and Interface Science* **2023**, 641: 36-47.