Taking inspiration from extracellular vesicle lipid compositions to design nucleic acid delivery vectors

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Lipid nanoparticle (LNP) delivery vectors comprise a broad class of lipid-based particles with diameters of 10s to 100s of nanometres. They include biologically[1] and synthetically derived vesicles, as well as LNPs with ionisable lipids[2] such as those employed in the COVID-19 vaccines, and have shown huge promise as nucleic acid delivery vectors[3]. Due to the variety of possible nucleic acid cargoes, target cells, and therapeutic applications, a "one size fits all" approach to designing LNPs is insufficient. There has therefore been intense focus on developing LNPs tailored to specific applications. Within this field, naturally occurring extracellular vesicles (EVs) are one promising avenue. These nanosized vesicles are produced by most cells, via a variety of different routes of biogenesis, and are adept at transferring nucleic acids between cells. Although the roles of EV proteins and nucleic acid cargoes in EV biological function are well studied, the role of their lipids is less understood[4].

In our lab, to address this challenge, we take inspiration from EV lipidomics data to formulate vesicles with complex lipid architecture, that mimic EVs. We are also investigating the effect on vesicle biological activity of arranging the lipids asymmetrically across the vesicle membrane leaflets. We are developing methods to formulate such vesicles using in-house and literature[5] techniques, and have observed that they can functionally deliver oligonucleotides to Hela cells. Using small angle neutron scattering, we have probed the overall morphology and detailed lipid arrangement of the membrane bilayers of such vesicles. Taken together, our findings contribute to understanding the role of lipid composition, particle morphology and membrane asymmetry of EV-mimicking vesicles, with complex lipid architecture, on their potential as therapeutic nanocarriers. More generally, a long-term aim is to contribute to uncovering roles of lipid composition on EV activity in cells.

References:

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