Let's talk about lipid nanoparticles

Lipid nanoparticles have been developed as vehicles for small molecule delivery by the nanomedicine and materials communities and are now a key component of COVID-19 mRNA vaccines.

Vaccines against COVID-19 have been developed with unprecedented speed. In particular, mRNA vaccines — a technology already in clinical trials for other infectious diseases, such as influenza — have shown impressive efficacy in clinical trials. BioNTech/Pfizer's BNT162b2 and Moderna's mRNA-1273 vaccines have already been approved in the UK, raising hopes for a near end of the SARS-CoV-2 pandemic.

mRNA vaccines rely on the delivery of mRNA into the cytoplasm of host cells, where it can be transcribed into antigenic proteins to trigger the production of neutralizing antibodies. However, mRNA is three to four orders of magnitude larger than molecules that readily diffuse into cells; in addition, the dense negative charge of mRNA electrostatically repulses the anionic cell membrane, preventing its uptake. Therefore, mRNA vaccines require a delivery vehicle that not only protects the nucleic acid from degradation but allows the mRNA to get into cells.

BioNTech/Pfizer's and Moderna's mRNA vaccines both use lipid nanoparticles as mRNA carriers. The impressive speed at which these vaccines could be developed is partly owed to the fact that nucleic acid delivery by lipid nanoparticles has long been investigated and optimized by the nanomedicine community, who thoroughly studied lipid nanoparticle chemistry, structure, surface, injection routes, uptake, endosomal escape, cargo release, dosage, clearance and, importantly, safety. This interest in lipid nanoparticle research has been driven by the emergence of promising new mRNA-based therapies and gene editing technologies for a variety of diseases, the success of which depends on the availability of a safe and efficient delivery vehicle.

Lipid nanoparticles are spherical vesicles made of ionizable lipids, which are positively charged at low pH (enabling RNA complexation) and neutral at physiological pH (reducing potential toxic effects, as compared with positively charged lipids, such as liposomes). Owing to their size and properties, lipid nanoparticles are taken up by cells via endocytosis, and the ionizability of the lipids at low pH (likely) enables endosomal escape, which allows release of the cargo into the cytoplasm. In addition, lipid nanoparticles usually contain a helper lipid to promote cell binding, cholesterol to fill the gaps between the lipids, and a polyethylene glycol (PEG) to reduce opsonization by serum proteins and reticuloendothelial clearance. The relative amounts of ionizable lipid, helper lipid, cholesterol and PEG substantially affect the efficacy of lipid nanoparticles, and need to be optimized for a given application and administration route. Moreover, lipid type, size and surface charge impact the behaviour of lipid nanoparticles in vivo.

It was a long road to optimizing lipid nanoparticle formulations for nucleic acid delivery, which is perhaps best exemplified by the development of patisiran. Patisiran is a lipid nanoparticle-based short interfering RNA (siRNA) drug for the treatment of polyneuropathies induced by hereditary transthyretin amyloidosis, and it was the first siRNA-based drug approved by the US Food and Drug Administration (FDA) in 2018. To achieve clinical efficacy, every aspect of the lipid nanoparticle formulation had to be optimized, and more than 300 ionizable lipids had to be screened. Furthermore, all key steps of the lipid nanoparticle journey in the body, from the site of administration to the release of the siRNA payload into the cytoplasm of hepatocytes, had to be understood before clinical trials could begin. Importantly, translational criteria, such as a size range of 100 nm or less, efficient encapsulation, low surface charge, robust, scalable manufacturing processes and adequate product stability were achieved in the development of this therapeutic. This knowledge has certainly contributed to the rapid development of COVID-19 mRNA vaccines.

From a materials science perspective, the success of lipid nanoparticle mRNA vaccines is exciting and important, as it underlines the value of materials science for medical advances and motivates further fundamental and applied nanoparticle research, which will hopefully be reflected in future funding cycles. *Nature Reviews Materials*, together with *Nature Nanotechnology*, will host a webinar and Q&A session on 17 February 2021 with experts in the field of lipid nanoparticles for nucleic acid delivery to discuss the technology and its potential in detail.