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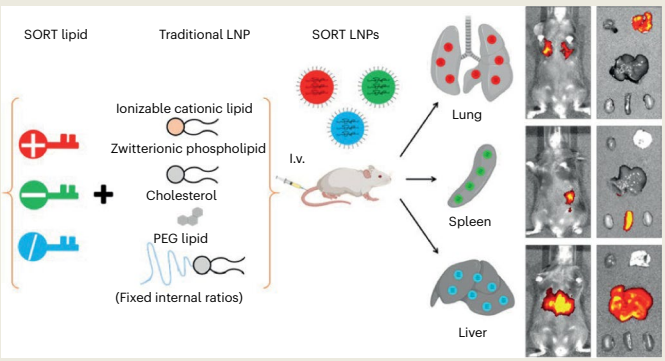
After publication story

Gene delivery beyond the liver

Lipid nanoparticles (LPNs) are used to carry therapeutic nucleic acids, such as mRNA (as in the case of the mRNA-based COVID-19 vaccines), short interfering RNA, and gene editing complexes. Researchers have investigated them for a long time, in pursuit of therapies for untreatable genetic diseases (K. Hajj et al. *Nat. Rev. Mater.* **2**, 17056; 2017 and R. Kanasty et al. *Nat. Mater.* **12**, 967–977; 2013), but their almost exclusive liver localisation upon intravenous injection has limited widespread application of LPNs in gene therapy.

In a paper published in *Nature Nanotechnology* in April 2020 (Q. Cheng et al. *Nat. Nanotechnol.* **15**, 313–320; 2020) the authors addressed this limitation and proposed an approach dubbed SORT, a short for Selective ORgan Targeting, to extend LPNs targeting to organs other than liver. Daniel Siegwart, corresponding author of the paper from the University of Texas Southwestern Medical Center in Dallas, USA, recounts: "We started this project because we wanted to understand the mechanisms that drove liver tropism and then made specific changes designed to avoid liver delivery". Key observations came when investigating



the physico–chemical characteristics of liver-targeting LPNs: they noticed that their apparent global pKa was always between 6.2 and 6.5, and were highly enriched in Apolipoprotein E, just like very-low-density lipoprotein found in nature.

LPNs are traditionally made of four components: ionizable cationic lipids, zwitterionic phospholipids, cholesterol and PEG lipids (Fig. 1). To control and tune their physico-chemical properties, Cheng et al. included a fifth component in their formulation, such as a quaternary lipid DOTAP (red SORT lipid in the figure). LPNs containing increasing percentages of DOTAP displayed altered biodistribution profiles, with 50% DOTAP delivering mRNA preferably to the lungs. Notably, Cheng et al. proceeded directly to carry out animal experiments bypassing cell culture experiments, in this way deviating from the conventional dogma of nanoparticle design for biomedical applications. This bold move was rendered necessary because cell cultures do not recapitulate the complexity of living models, as the plasma components that contribute to the protein corona are absent.

Another key property of SORT is that it can in principle allow delivery of therapeutically relevant genetic material to specific cells within the targeted organs. A single dose of LNPs directed to the lungs for example, target around 40% of all epithelial cells and 65% of endothelial cells in this organ. "A major accomplishment is to be able to achieve gene editing in the specific cell types relevant to treating a specific disease" says Siegwart, who expects that cell selectivity will be determined in follow-up clinical trials.

Siegwart and his group are now exploring how to deliver LPNs to several other organs, such as the bone marrow, lymph nodes, kidneys and pancreas. At the same time, the start-up ReCode Therapeutics (https://recodetx.com/about/), which has acquired the licence to the technology, is performing preclinical assessments to determine the safety, tolerability and optimal therapeutic window of SORT for two genetic diseases affecting the lungs: cystic fibrosis and primary ciliary dyskinesia. Early phase clinical trials for the application of SORT to treat primary ciliary dyskinesia will start in 2023.

The implications for gene therapy and personalised medicine here are significant, because cystic fibrosis is a debilitating genetic disease caused by mutations in an ion channel protein, expressed on the surface of lung epithelial cells. Having the possibility of targeting these cells to correct the channel protein mutations provides hope for the development of cystic fibrosis treatments.

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