ReCode Therapeutics
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Unshackling genetic medicines by enabling delivery beyond the liver

Harnessing its selective organ targeting lipid nanoparticle platform technology, ReCode Therapeutics is facilitating precision delivery of genetic cargos directly to their intended organs and cells.

ReCode Therapeutics is developing genetic therapies for rare diseases by addressing a key barrier for the field: delivery to the right cells, and not just the liver. Lipid nanoparticles (LNPs) are the most clinically mature non-viral delivery vehicle and enabled the mRNA vaccines that helped to bring the coronavirus disease 2019 (COVID-19) pandemic under control. However, because conventional LNPs are primarily taken up by the liver, genetic medicines are hindered in their ability to treat a wealth of diseases that already have validated biological targets.

ReCode, a clinical-stage genetic medicines company, has a solution to this challenge with their selective organ targeting (SORT) LNP platform technology that enables delivery of a wide range of genetic cargos to organs and cells beyond the liver (Fig. 1). Conventional LNPs have four lipid components. To get LNPs beyond the liver and to their intended cellular targets, ReCode adds a chemically distinct fifth lipid that alters the properties of SORT LNPs and mediates predictable and programmable precision delivery.

The fifth lipid can prevent binding of the LNPs to apolipoprotein E, the protein that causes conventional LNPs to be taken up by liver hepatocytes. Effectively de-targeting the liver allows SORT LNPs to reach organs such as the lung or spleen. Different SORT lipids, incorporated in the right amounts, provide distinct properties and facilitate delivery to different parts of the body and even different cell types within a target organ.

While initially developed for intravenous delivery, ReCode's technology has shown the fifth lipid also enables target cell tuning after administration to the lung through nebulization so that the genetic payload reaches the specific cell types of interest that are most important for the disease.

"It really is a dial, not a switch. We're able to titrate and tune using that fifth lipid," said David Lockhart, president and chief scientific officer at ReCode. "We've combined the SORT LNP delivery toolbox with expertise in mRNA design, optimization, purification, and production. The mRNA has been optimized to maximize protein production within target cells, while also minimizing immunoreactivity, which is important when we're giving repeat doses."

Validating the technology

SORT lipids also increase potency and enhance LNP packaging versatility, allowing multiple types of nucleic acids and proteins to be delivered together in one vehicle. The versatility empowers ReCode to combine different types of RNA molecules in a single LNP, for example to facilitate gene editing.

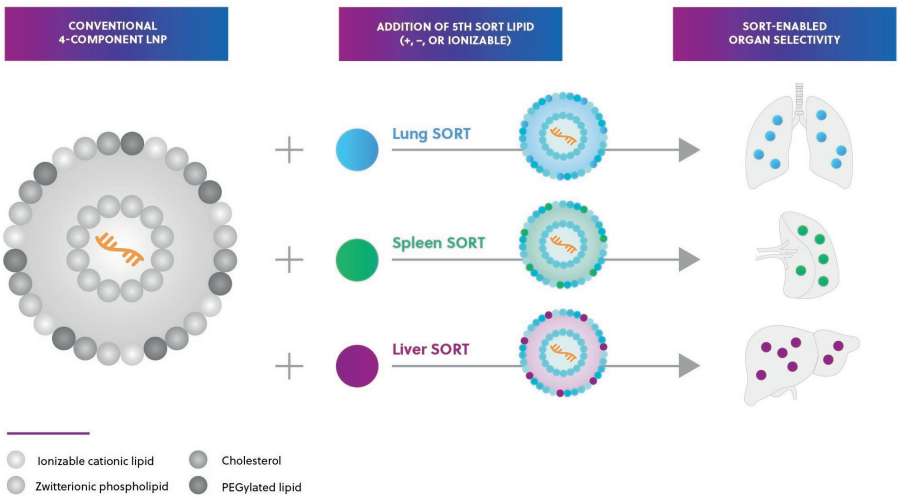

Fig. 1 | ReCode's selective organ targeting (SORT) lipid nanoparticle (LNP) platform. Engineered with a chemically distinct fifth lipid, ReCode's SORT LNP platform powers a library of LNPs that are tuned to reach specific organs and cells.

ReCode's cystic fibrosis (CF) gene correction proof-of-concept experiment illustrates this versatility. The LNPs contained Cas9 mRNA, guide RNA, and the single stranded homology directed repair DNA template—three very different types of molecules—to edit cells from patients with mutations that do not respond to existing treatments. ReCode's CF program is still in research, and the company plans to file to study its inhaled *cystic fibrosis transmembrane conductance regulator* (*CFTR*) mRNA candidate in humans in the US in the second half of 2023.

ReCode's lead candidate, a treatment for primary ciliary dyskinesia (PCD), is already being evaluated in healthy volunteers. In both indications, the mutations causing the diseases are well established. The challenge has been how to address the consequences of the inherited mutations. SORT LNPs are helping ReCode to overcome that challenge.

ReCode's earlier-stage programs are using SORT LNPs for mRNA-mediated gene addition and gene correction in diseases such as alpha-1 antitrypsin deficiency (AATD), surfactant deficiencies, and genetic diseases of the central nervous system (CNS), showcasing the breadth of indications the platform can address.

Partnering the platform

ReCode is looking to partner its platform in areas or indications complementary to its internal pipeline of rare genetic diseases. Having studied the potential for SORT LNPs to improve mRNA vaccines and treat diseases of the CNS, muscle, heart, lung, and liver, the biotech is seeking collaborations that help validate the approach and expand the reach of the technology.

"We are open to multi-target vaccine and/or multi-cargo delivery collaboration deals, where the other party has antigens or cargoes of interest and we work together to create the drug candidates. Whether or not we also bring our mRNA expertise depends on the needs of the partner," said Angèle Maki, senior vice president, business development.

ReCode has also attracted interest from gene editing companies, which see SORT LNPs as a way to deliver editing cargoes and target more diseases, and it may consider partnering one or more of its drug candidates with a large partner down the line. As ReCode and its partners progress the programs, they will break the shackles that currently constrain the genetic medicine field and advance life-changing treatments for patients with a wide range of diseases.

CONTACT
Angèle Maki
Senior VP Business Development
ReCode Therapeutics
Menlo Park, CA, USA
Tel: +1-408-585-1700
Email: partnering@recodetx.com