

## Packaging mRNA for the Pancreas



2023-04-09

Lipid nanoparticles engineered to specifically target pancreas in mouse model.

Therapeutics that use mRNA—like some of the COVID-19 vaccines—have enormous potential for the prevention and treatment of many diseases. These therapeutics work by shuttling mRNA ‘instructions’ into target cells, providing them with a blueprint to make specific proteins. These proteins could help tissues to regenerate, replace malfunctioning proteins, or prompt an immune response, providing a variety of different treatment strategies.

However, a therapeutic is only useful if it can reach its target. The mRNA is typically packaged inside a lipid nanoparticle, which keeps the delicate cargo intact until it reaches its final destination. As the field stands now, mRNA-filled lipid nanoparticles generally reach just a handful of cell types, such as immune cells and cells in the liver or spleen. Designing such lipid nanoparticles that can target hard-to-reach organs, such as the heart or pancreas, could revolutionize treatment options for a wide range of conditions.

In response to this need, researchers at [Carnegie Mellon University](#) are developing lipid nanoparticles that are designed to carry mRNA specifically to the pancreas. Their study in mice, recently published in [Science Advances](#), could pave the way for novel therapies for intractable pancreatic diseases, such as diabetes and cancer.

“Lipid nanoparticles are essentially tiny spheres of fat, and fats have all kinds of chemical properties that can affect their ability to travel through the body and target specific organs,” explained Luisa Russell, Ph.D., a program director in the Division of Discovery Science & Technology at the National Institute of Biomedical Imaging and Bioengineering (NIBIB). “By

optimizing these fat molecules and investigating alternative drug delivery routes, the study authors were able to design a lipid nanoparticle that can safely deliver mRNA to pancreatic tissue in mice.”

Current mRNA drug delivery routes include intramuscular injection (used in COVID-19 vaccines) and intravenous administration (used in some investigational cancer therapeutics). As a first step towards targeted delivery, the study authors wanted to know if a different administration route might help deliver the mRNA cargo directly to the pancreas. They investigated mRNA delivery via intraperitoneal injection, which involves injecting a drug directly into the fluid that surrounds the organs of the peritoneal cavity (including the kidneys, intestines, and pancreas). “While intraperitoneal injection is not commonly used in humans, this type of administration is used clinically for some difficult-to-treat diseases, such as ovarian cancer,” said senior study author Kathryn Whitehead, Ph.D., a professor at Carnegie Mellon University. “With very serious pancreatic diseases, the benefits of intraperitoneal injection outweigh the risks.”

The researchers packaged mRNA instructions for firefly luciferase—a bioluminescent protein often used in research—into lipid nanoparticles, and then injected them into mice either intravenously or intraperitoneally. Using the glowing firefly luciferase to see where the mRNA had traveled, they found that intraperitoneal injection resulted in more abundant and more specific delivery to the pancreas compared with intravenous injection.

Next, the researchers began to optimize the composition of fat molecules that make up the nanoparticle. Different fats have unique chemical properties—such as size, electrical charge, and hydrophobicity—that can affect what happens to the nanoparticle once it enters the body. One type of fat molecule used is called a ‘helper lipid,’ so named because it helps to stabilize the nanoparticle and improves its potency. The researchers wanted to know if changing the charge of the helper lipid might affect the targeting of the nanoparticle and direct it towards the pancreas. After trying a variety of different nanoparticle compositions, the researchers found a combination of lipids that improved pancreatic targeting in mice.



Simplified schematic of the treatment approach under investigation. Note: this treatment was not evaluated in humans.

“Within the past couple of years, there’s been much more appreciation for how the lipids in nanoparticles can redirect mRNA delivery to different cells and organs,” said first study author Jilian Melamed, Ph.D., a postdoctoral researcher at the [University of Pennsylvania](#). “The precise ways that lipid chemistry affects the potency and specificity of nanoparticles are still being uncovered, and we are still working to understand how individual lipid components influence overall mRNA delivery.”

When the authors investigated where exactly their optimized nanoparticles were going in the pancreas, they were surprised to discover that mRNA was most abundant in pancreatic islet cells, which comprise only 1-2% of total pancreatic tissue. Pancreatic islet cells are responsible for producing hormones that control glucose in the blood (such as insulin). Such specific targeting could have potential downstream clinical applications.

“With further development, our research may lead to the creation of therapies for diabetes or certain types of pancreatic cancer,” said Whitehead. “These potential treatments, however, would require more preclinical research before advancing to clinical trials.”

Read the [original article](#) on National Institute of Biomedical Imaging and Bioengineering (NIBIB).