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Acuitas Therapeutics and Partners Publish Comparative Study of AAV and mRNA-LNP Delivery With In Situ Sequencing for Spatial Genome Editing

Vancouver, B.C. – Acuitas Therapeutics, a global leader in lipid nanoparticle (LNP) delivery systems, recently announced the publication of a new study in *Nature Biomedical Engineering*, titled "Spatial profiling of gene editing by in situ sequencing in mice and macaques."

Co-authored by Acuitas scientists Ying Tam, Sean Semple, Thomas Chamberlain, and Jennifer Moon – together with partners from the University of Zurich and the University of Pennsylvania – the study validates *in situ* sequencing (ISS) as a powerful translational tool to visualize quantitative, spatial maps of editing within organs. It further compares outcomes from adeno-associated virus (AAV) vectors and mRNA-LNP delivery, showing efficient editing with both approaches. Notably, Acuitas LNP achieved uniform delivery and gene editing across all metabolic zones of the liver of mice and nonhuman primates (NHPs), maintaining efficacy and safety, even after repeat dosing.

Advances in genome editing technologies, such as base and prime editing, have significantly expanded the therapeutic possibilities for a wide range of genetic diseases. However, traditional methods for measuring editing outcomes – such as bulk next-generation sequencing – average results across a tissue and fail to capture spatial differences between cell types or tissue regions. By pairing ISS with mRNA-LNP delivery, this study addresses this challenge, offering a powerful method to resolve spatial genome editing in combination with a potent, zone-independent LNP-based delivery platform. Key findings of this study include:

- mRNA-LNP delivery produced widespread hepatocyte uniform editing *in vivo* across all metabolic zones (periportal, intermediate, and pericentral). Dose reduction from 1.5 to 0.5 mg/kg did not affect overall editing rates, editing distribution, or editing ratio.

- In NHPs, targeting two sites in the ACTB locus with mRNA-LNP achieved 12.8% to 14.2% editing at $ACTB^{D25}$ and 32.9% to 34.3% at $ACTB^{T149}$. Initial dose confirmed uniform editing by mRNA-LNP, and second administration of mRNA-LNP was successful, and revealed that the initial dose did not affect the editing efficiency or distribution of the subsequent dose.

- Repeat administration of mRNA-LNP in NHPs was well tolerated and maintained consistent editing efficiency and spatial distribution across doses, supporting the potential of serial dosing to increase editing at a single locus or to target multiple disease-relevant loci.

- In comparison to LNP-based delivery, AAV administration was studied:

    - In the mouse brain, AAV-delivered base editors showed editing in the cortex and cerebellum, with most edited cells exhibiting biallelic conversion, confirming that once base editor expression reaches a threshold, both gene copies are likely to be modified.
    - In the mouse liver, AAV vectors achieved 50% to 75% editing, with higher activity in precentral hepatocytes, compared to other hepatic zones. However, persistent expression raised concerns about off-target edits and potential immune responses.

This study demonstrates how ISS can provide spatially resolved maps of genome editing, and confirms that mRNA-LNP delivery enables broad, repeatable editing across liver tissue. Together, these findings, in combination, provide a strong foundation for developing new therapies for metabolic and polygenic liver diseases, such as urea cycle disorders.

Click here to read the full publication.

About Acuitas Therapeutics

Acuitas Therapeutics, Inc. is a Vancouver-based company focused on developing and optimizing lipid nanoparticle (LNP) delivery systems for nucleic acid based therapeutics. They collaborate with pharmaceutical and biotech companies, academic researchers, and global health organizations to advance a broad range of medicines for a variety of diseases.

Acuitas' clinically validated LNP technology has had a profound global impact – most notably enabling the Pfizer-BioNTech COVID-19 vaccine, **COMIRNATY®**, which has protected billions of people in more than 180 countries. The technology also enables **ONPATTRO®** by Alnylam Pharmaceuticals, the first FDA-approved RNAi therapeutic for treating the rare and fatal disease transthyretin amyloidosis. More recently, Acuitas' LNP technology has delivered other groundbreaking firsts: the **first in-human proof of concept** for genome base editing and the **first personalized CRISPR therapy**.

Today, they are advancing next-generation LNP to support a variety of therapeutic modalities. This includes targeted LNP for extrahepatic and *in vivo* CAR T-cell therapies, epigenetic medicines to modulate gene expression without altering DNA, multivalent vaccines for infectious diseases — such as malaria, HIV/AIDS, and tuberculosis — as well as oncology vaccines, including personalized cancer vaccines.

For more information, visit www.acuitastx.com.

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