Overcoming the RNA Therapeutics Delivery Challenge

The protein barcoding application on the Quantum-Si Platinum® benchtop instrument with Next-Gen Protein Sequencing™ is helping Liberate Bio accelerate development of novel gene therapies with improved targeting capabilities.

"We use the Platinum's protein barcoding application to screen LNP delivery vehicles in vivo. With this approach, we can get a simple readout of delivery and translation efficiency, dramatically increasing the precision, speed, and efficiency of our discovery and development programs."

Melissa Deck
Director of Platform, Liberate Bio

Challenge: Liberate Bio is creating next-gen LNP systems for targeted delivery beyond the liver. Current tools struggle to detect both expression and translation of therapeutic cargo, limiting screening efficiency.

Innovation: Their platform combines high-throughput *in vivo* screening, machine learning, and generative AI to optimize LNPs for various nucleic acid cargos like mRNA.

Protein Barcoding Integration: By using Quantum-Si's Platinum protein barcoding, Liberate Bio can rapidly and cost-effectively track delivery and expression of multiple LNPs across tissues, dramatically speeding up discovery.

Advantages: Protein barcoding offers a low-cost, compact alternative to mass spectrometry, enabling precise, *in vivo* optimization without complex infrastructure.

Nucleic acid-based therapeutics such as mRNA, small interfering ribonucleic acid (siRNA), and antisense oligonucleotides (ASOs), offer great promise for treating a range of diseases. Delivering these therapies to their intended sites in the body, however, can be a formidable challenge.

While lipid nanoparticles (LNPs) have emerged as a powerful tool for delivery due to their ability to encapsulate and protect nucleic acids and facilitate their entry into cells, therapeutic applications have been primarily limited to liver indications. LNPs accumulate in this organ when administered systemically.

Liberate Bio is advancing the development of next-generation LNP delivery systems aimed at tissue-specific targeting of nucleic acid therapeutics beyond the liver. To achieve this, the company has established a high-throughput, *in vivo* LNP screening platform. Liberate's approach allows them to evaluate a wide range of nanoparticle materials, chemistries, and formulations to identify those with distinct tissue targeting capabilities. Insights from these screening studies guide the design of new nanoparticle materials and formulations, thereby enhancing the selective delivery of therapeutics to specific tissues.

We recently spoke with Melissa Deck, Liberate Bio's Platform director, about the need for innovation in nucleic acid delivery and the value of incorporating protein barcoding enabled by Quantum-Si's Platinum® benchtop instrument with Next-Gen Protein Sequencing™ into their platform for developing novel gene therapies with improved targeting capabilities.

Q: Why is there a need for better nucleic acid delivery systems?

A: Significant progress has been made in non-viral nucleic acid delivery systems in the last decade, mainly in lipid nanoparticle (LNP) field, starting from ONPATTRO® for siRNA delivery, then COVID vaccines for mRNA-based immunizations. There are also numerous clinical trials with LNPs with various nucleic acid payloads. However, a significant majority of the available solutions are for liver-focused disease areas simply because that is where delivery systems, including LNPs, are accumulated in the body. This, unfortunately, limits the actual potential of genomic medicines, so the field is eager to expand the nanoparticle delivery toolbox beyond the liver. We think there are major advantages to non-viral nanoparticle delivery over viral vectors, such as scalability and lower toxicity.

With nanoparticles, we can build a suite of delivery capabilities that are tissue-tropic, payload-specific, and can achieve sustained expression of the protein. And all of that translates into the ability to treat more disease and improve the lives of more patients.

Q. What technologies are included in your platform for discovery of extra-hepatic delivery vehicles?

A: Our platform includes high-throughput screening of vast libraries of nanoparticle delivery vehicles in physiologically relevant models. We can generate large, curated data sets and use these data to develop machine learning models to deepen our understanding of biology and generative AI to identify novel lipid chemistries for tailored extrahepatic delivery.

With this approach, we address the need to align the cargo and the delivery system. Every type of nucleic acid cargo is different. For example, circular RNAs are fundamentally different cargos, and self-amplifying RNAs are much larger than the mRNAs in commercial products. The cargo and delivery system must align, which is what we designed our platform to enable us to do. Our high-throughput screening capabilities have the power first to identify fundamentally new components for successful extrahepatic tissue-specific delivery, then further improve those at a significantly higher pace than conventional discovery platforms.

Q: How are you using protein barcoding on the Quantum-Si Platinum Next-Generation Protein Sequencer™?

A: ***Protein barcoding is being integrated into the Liberate platform. We use the Platinum® sequencer's protein barcoding application to screen LNP delivery vehicles in vivo. With this approach, we can get a simple readout of delivery and translation efficiency, dramatically increasing the precision, speed, and efficiency of our discovery and development programs.***

The process is very straightforward. We attach short sequences that encode unique protein barcodes to the mRNAs that are packaged into a range of LNPs with different chemistries and formulations. These LNPs are then administered to non-human primates as they are the most closely related species to humans. The LNPs are taken up by various tissues, and the mRNAs they carry are translated into proteins. Each protein features a distinct barcode that corresponds to the specific LNP that carried it. By extracting proteins from different tissues, sequencing to identify barcodes present, we can identify which LNPs traveled to which tissues. This process allows us to create extensive datasets and gain a comprehensive, unbiased understanding of how different LNP chemistries affect delivery and expression in a biologically relevant model.

Q: What are the advantages of adding the protein barcoding application on the Quantum-Si instrument to your platform?

A: Not only does integration of the barcoding application into the workflow accelerate our discovery and screening efforts, but it also reduces costs and shortens timelines. Without a doubt, this innovation will help us to push the boundaries of what is possible in the development of nanoparticle therapeutics.

The real power in protein barcoding is that we can evaluate multiple factors simultaneously, significantly accelerating the drug discovery process. Instead of the typical three- to five-year timeline, we can identify hits much more quickly. This allows us to redirect our financial and human resources toward developing the drug itself, rather than investing extensive time on early discovery work.

Q: If you were not using the barcoding application on Platinum, what other options would you have?

A: Others in the field have used similar peptide barcoding strategies with mass spectrometry, but we didn't pursue that route due to the high costs associated with acquiring and operating such equipment. As a seed-stage startup, we face challenges with the capital required for mass spectrometry and the need for specialized personnel to run it. ***We chose the Platinum instrument because it allows us to manage our research in a more cost-effective manner with a smaller footprint, making it more accessible for a small company like Liberate.***

Q: What advice would you give other companies considering using protein barcoding on the Quantum-Si instrument?

A: It's a great way to optimize a workflow and I wish that we had it from day one. Determining expression in an *in vivo* setting is the holy grail because, as we all know, *in vitro* studies do not simulate *in vivo* very well. The same is true for comparing studies in mice and non-human primates. Being able to optimize in the right system is really very powerful, in my opinion.

→ **Download the poster**