5th Annual
Genome Editing Therapeutics Summit
Shaping the Future of Therapeutic Gene Editing

December 3-5, 2024 | Boston, MA

An Interview with ReCode Therapeutics

AN EXCLUSIVE INTERVIEW WITH:

Marco Weinberg
Senior Vice President, Head of Research
ReCode Therapeutics

Marco Weinberg, PhD, is Head of Research at ReCode Therapeutics. Previously, he led drug development research teams in gene therapy and gene editing at AskBio/Bayer, CSL Behring and Vertex. Prior to industry, Marco was a PI and faculty at The Scripps Research Institute, La Jolla and The University of the Witwatersrand, South Africa.

Ahead of the 5th Genome Editing Therapeutics Summit (December 3-5, Boston), we sat down with Marco to discuss how the gene editing field is evolving, and the key focus areas of his team at ReCode.

You have over two decades of experience leading in academic and industry teams across gene editing, gene therapy, and nucleic acid therapies. From your experience working across these different therapeutic modalities, how do you assess the state of the gene editing field today?

First of all, in the 25 years that I've been involved in gene therapy (or nucleic acid therapy), it's great to have witnessed how far it has evolved from academic concepts to ones that can be adopted by pharmaceutical and biotechnology companies to become drugs. This modern adoption by industry is the big talking point for the entire field.

Gene editing is no different. It's simply slotting into this fantastic ecosystem of industrialized nucleic acid therapies.

We've seen a number of really important developments in the field of genetic therapies. It goes through these sort of 'high-hype' cycles, if you can call it that, where there's a lot of initial interest and attention paid to these new tools only for them to not necessarily be ready or mature enough to deliver on the promise.

Gene editing, particularly since the discovery of CRISPR, has been one of those fields where there's been a lot of promise being pushed onto its shoulders. Really, what it takes for it to become a reality in the clinic is for the technology to mature; we're seeing the same kind of cycle for gene editing as we have seen with vector-delivered genetic therapies, oligo therapies, and other similar nucleic acid approaches.

How have you seen gene editing technologies and their delivery capabilities evolve since your first involvement in the field, and what have been the key milestones along the way?

I got involved in genetic editing when we were trying to use tools like zinc-finger nucleases and TALENS. Those were incredible

> We're seeing the same kind of cycle for gene editing as we have seen with vector-delivered genetic therapies, oligo therapies, and other similar nucleic acid approaches.

tools that showed the promise of being able to directly target specific sequences of DNA (similar to restriction enzymes) to specifically create double-standard breaks, and then rely on various repair pathways in the cell to enable the type of edits that one wants. So that early promise was there, but the tools were difficult to handle: they were very hard to work with and for the most part they weren't very efficient.

The advent of CRISPR as a technology in 2012/early 2013 was a game changer for everyone. We now had a facile tool to perform double-stranded break editing very quickly and very efficiently. The therapeutic promise of this technology was apparent right from day one.

Since then, it's only gotten more interesting with tools that have enabled not just double- stranded breaks, but also edits such as large-scale deletions, insertions, edits to bases, and epigenetic editing. All these different variations or flavors that have been bolted onto CRISPR have become phenomenally interesting and useful tools for us to apply to all manner of different types of targets in genetic therapies.

Your team at ReCode Therapeutics are developing and applying a selective organ targeting (SORT) lipid nanoparticle (LNP) platform to deliver genetic medicine cargoes. What are the key limitations to current LNP-mediated gene editing delivery platforms your team are trying to overcome?

> Can you target these nanoparticles in some way or do we have to rely on endogenous mechanisms of targeting and uptake?

The biggest area to work on for lipid nanoparticles is how to make these extremely efficient and safe vehicles effective at getting to specific organs and tissues. As we all know, LNPs have been developed over the last two and a half decades, mainly as a tool for generating a vehicle for delivering nucleic acid cargos to the liver, and they've been very successful at that. In fact, we have several different approved therapies that that work that way.

They've also been very successful at localized intramuscular injection and in other very localized scenarios, but so far, there hasn't been a very good way to get them to be 'extra-hepatic'. I think the future for LNPs or intravenous injection is to figure out ways to make them go beyond the liver. That's where a lot of the interest in the field is, and where a lot of the effort of ReCode has been over the last few years to enable this.

The other area to focus on is how to make them more effective at getting past the different biological barriers that they encounter. For example, if you deliver nanoparticles intravenously and want to get them to get past the vasculature, and penetrate deep into tissue parenchyma to enable targeting of specific cell types. One area of interest for ReCode is to enable lung epithelial basal stem cell delivery via delivery from the circulation. This would have tremendous benefit for long-lasting gene editing therapies for many lung diseases.

Lastly, how do you get LNPs to escape from cellular compartments called endosomes – which is where a lot of these nanoparticle vehicles and viruses get trapped – in a safe way? And then can you target these nanoparticles in some way or do we have to rely on endogenous mechanisms of targeting and uptake? These are the questions that the field is spending considerable amount of time trying to address.

You will be delivering a talk at the 5th Genome Editing Therapeutics Summit this year on your work progressing LNP delivery platforms for extra-hepatic indications. Could you provide us a sneak preview for this talk and what will be shared?

What I am looking forward to sharing with our audience is how we're approaching our nanoparticle platform in two different directions. Firstly, how we applied LNPs to target cells of the airway in the lung, specifically the cells responsible for disease like cystic fibrosis and primary ciliary dyskinesia; how we can apply a localized, aerosolized delivery approach to targeting of cells, and how this could then translate to future editing solutions.

Then secondly, to pivot to intravenous delivery, how do we get out of the liver and enable ourselves to get to targeted areas such as the epithelial cells or the stem cells of the lung when delivered intravenously. This approach is the same problem from two different directions: one via the airway, and one via the circulatory route. Can we address the question of a permanent edit that will specifically target the stem cell populations of the lung, so that we can address long term benefits in patients?

And finally, why are you excited to be involved in the summit this year?

It's an important meeting. It brings together a lot of different individuals, researchers and industry players into one forum to address some of the most important and pressing issues that therapeutic gene editing relies on: the questions around delivery, questions around which tools to apply, and issues around ethics and safety.

This is a fantastic meeting, and one that we all learn something from together.