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# Arcturus Releases Data Showing Potential of Delivery Technology for CRISPR Drugs

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By Doug Macron

**Arcturus Therapeutics this week** announced new data showing that its proprietary lipid nanoparticles are capable of functionally delivering messenger RNA into the livers of mice, which a company official said opens the door for the use of the technology with CRISPR-based drugs.

The firm also released rodent and non-human primate data, generated as part of its TTR-mediated amyloidosis (ATTR) program, demonstrating the safety and efficacy of the technology for siRNA delivery.

Arcturus was founded in 2013 around a biodegradable lipid nanoparticle technology, dubbed Lunar, and RNAi payloads known as unlocked nucleobase analogs, the rights to which Arcturus acquired from Marina Biotech.

Given the background of its founders in RNAi, the company is primarily focused on developing drugs based on the gene-silencing technology. However, Arcturus has also been testing the ability of Lunar nanoparticles to deliver RNA molecules other than siRNAs.

At the Biocom Global Life Science Partnering conference this week, Arcturus presented some of the results of this work, including data showing high levels of luciferase expression in the livers of mice following intravenous delivery of Lunar-encapsulated luciferase mRNA at a dose of 0.05 mg/kg.

While companies like Moderna Therapeutics are aiming to develop mRNA drugs that direcly produce therapeutic proteins, Arcturus sees Lunar-delivered mRNA as the key to enabling a new class of therapies based on a gene-editing approach known as CRISPR.

CRISPR, or clustered regularly interspaced short palindromic repeats, works when a single-stranded RNA complementary to a specific DNA sequence is introduced into a cell and acts as a guide for a complex containing the nuclease Cas9, which creates double-strand breaks in target DNA.

A key hurdle to using CRISPR therapeutically, Arcturus Co-founder and CSO/COO Pad Chivukula said, is that Cas9 can be difficult to deliver. However, this problem could potentially be circumvented by delivering mRNA encoding the Cas9 protein, along with a guide RNA, in Lunar nanoparticles, he said.

"We are collecting data [on this approach] as we speak," he said, adding that Arcturus aims to publish its findings soon.

But the work with mRNA is only a side project for the company, which remains "laser focused" on its lead research and development program in ATTR, which is on track to enter investigational new drug application-enabling studies this summer.

In naming ATTR as its first pipeline indication, Arcturus is going head-to-head with RNAi heavyweight Alnylam Pharmaceuticals, which already has an intravenously delivered ATTR drug in phase III and a subcutaneously administered one in phase II.

But to Chivukula, the advantages of Lunar will give Arcturus an edge despite Alnylam's headstart.

The company has generated data showing that Lunar-delivered siRNAs targeting factor VII can achieve greater target knockdown than ones delivered with a variety of other lipids, including the MC3 lipid used in patisarin, at 0.3 mg/kg.

Additionally, Lunar nanoparticles have proven to be safe even when used at high doses. In rat toxicology studies, Arcturus delivered three 10 mg/kg doses of its nanoparticles over two weeks and observed no adverse effects.

And when it comes to ATTR specifically, the company has found that a single 0.3 mg/kg dose of its drug candidate could cut target protein levels by more than 75 percent in non-human primates — an effect that lasted over three weeks with no injection site reactions. Based on this, Arcturus believes its drug can be dosed in man once a month, compared to the weekly doses being used with Alnylam's candidates.

"We've shown a superior toxicity profile and … superior potency in non-human primates," Chivukula said. When a potentially once-a-month dosing regimen is factored in, "we think we will bring a better product to the patient."

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Doug Macron is the editor of GenomeWeb's *Gene Silencing News*. He covers research and therapeutic applications of RNAi, miRNA, and other gene-silencing technologies. E-mail Doug Macron or follow his GenomeWeb Twitter account at @Genesilencing.

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