

By Kim Ribbink



RNAi on the Verge of Therapy Breakthroughs

PharmaVOICE's November/December 2017 Pipeline Disrupters article explored the progress being made in RNA as potential therapies. Now experts take a deeper look at RNAi's ability to take advantage of the body's own natural processes to silence genes.

One of the most exciting innovations in the field of drug discovery is ribonucleic acid interference (RNAi), where researchers are making huge progress toward a new class of therapeutics.

RNAi occurs naturally in living organisms to protect against viruses. Papers published in 2013 demonstrate that it does so through a biologic process that replicates a virus' genetic material, causing the viral genome to become temporarily double-stranded. This, then, triggers initiation of RNAi to target and destroy a virus' single-stranded genome.

What makes RNAi so exciting is the potential to overcome the limitations of traditional drug therapies.

"RNAi is a highly potent and specific mechanism for silencing the activity of a targeted gene and reflects a new approach in the development of powerful therapies to treat a range of diseases by silencing some of the most well-validated, yet previously inaccessible or 'undruggable' drug targets," says Douglas Fambrough, Ph.D., co-founder and CEO of Dicerna Pharmaceuticals.

Historically, the pharmaceutical industry has been very successful in deploying two fundamental classes of drugs — small molecules and antibodies — against well-defined disease

targets. However, both of those classes are limited by the nature of the targets they can inhibit, Dr. Fambrough says.

"For instance, small molecules need to make their way to specific binding pockets of protein targets, and many disease-associated proteins lack small-molecule binding pockets," he says. "Similarly, antibody therapeutics are limited to easily accessible targets found in the circulation or expressed outside of cells."

By attaching to the mRNA instruction set, RNAi can attack any target, Dr. Fambrough says. This includes disease-causing genes that are expressed exclusively inside cells and that lack good small-molecule binding pockets, putting them beyond the reach of conventional antibody and small-molecule modalities.

RNAi therapeutics hold great promise to address a wide range of human diseases because they can be designed to specifically target essentially any messenger RNA and thereby inhibit the expression of the corresponding protein, says Pushkal Garg, M.D., chief medical officer at Alnylam Pharmaceuticals.

According to Mark Murray, Ph.D., president and CEO of Arbutus Biopharma, RNAi technology's greatest promise is for genetic diseases for which simple small molecules are not active, as well as for infectious diseases.

Dr. Fambrough adds that RNAi-based therapeutic approaches hold promise in offering more convenience for patients via infrequent subcutaneous dosing and a very long duration of effect, while reducing the side effects that can occur with small-molecule and antibody therapy.

Addressing RNAi Challenges

Since RNAi therapeutics emerged 15 years ago, there have been opportunities and challenges. Because RNAi drugs are more complicated than traditional drugs, the development path is more complex, Dr. Murray says.

Another major challenge in the RNAi space is the ability to specifically and effectively deliver the investigational therapy into the cytoplasm of targeted cells.

"Fortunately, we and others in the RNAi space have overcome this challenge, at least for gene targets expressed in the liver," Dr. Fambrough says. "Dicerna's unique GalXC RNAi structures and chemical modifications have enabled us to deliver potent and long-lasting RNAi therapies to the liver."

The approach at Alnylam has been to develop a lipid nanoparticle and an Enhanced Stabilization Chemistry (ESC)-GalNAC-siRNA

conjugate delivery platform, both of which will enable the company to deliver RNAi therapeutics to the liver.

“The ESC-GalNAc conjugates, which can be delivered subcutaneously at a frequency of once a month or less, constitute the bulk of our clinical pipeline today,” Dr. Garg says. “We’re now advancing the technology by developing ESC+ GalNAc conjugates, which incorporate advanced design features to further improve the specificity of our RNAi therapeutics.”

RNAi Technologies Explored

In the past year alone, extensive progress has been made in RNAi. Several companies are leading the way, including Dicerna Pharmaceuticals, Alnylam, and Arbutus Biopharma.

Dr. Garg says Alnylam is specifically focused on diseases with a genetically validated, liver-expressed protein, as the company has optimized its ability to deliver its RNAi therapeutics to the liver.

“We also look for diseases where we can assess clinical activity using measurable biomarkers, including genetic, cardio-metabolic, and hepatic infectious diseases,” he says.

In 2017, Alnylam presented positive results from the APOLLO Phase III study of patisiran, a treatment for patients with hereditary ATTR (hATTR) amyloidosis, which has the potential to be the first RNAi-based therapy to reach the market. The FDA is expected to rule on patisiran in mid-2018; European authorities are expected to respond by late 2018.

With the potential global launch of patisiran, Alnylam will mark the birth of a whole new class of medicines, which will have the potential to transform the treatment of diseases with high unmet need, he adds.

“In addition, based upon encouraging clinical activity and safety data, Phase III trials were initiated for givosiran for the treatment of acute hepatic porphyrias and fitusiran for the treatment of haemophilia,” Dr. Garg adds. “In addition, we have accumulated human safety experience with approximately 20,000 doses administered across our programs.”

Dicerna’s GalXC technology platform was developed to advance the development of next-generation RNAi-based therapies designed to turn off individual disease-associated genes expressed in the liver.

“Compounds produced via GalXC have the potential to reach important, well-validated targets in liver-targeted diseases, targets that the pharmaceutical industry has not been



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DR. MARK MURRAY
Arbutus

able to access with the conventional therapies,” Dr. Fambrough says. “Additionally, these targets are intended to be broadly applicable across multiple therapeutic areas, including rare diseases such as primary hyperoxaluria, chronic liver diseases, cardiovascular diseases, and viral infectious diseases.”

GalXC molecules are delivered by a convenient subcutaneous injection, every other month or perhaps even less frequently.

“Our technology uses a natural sugar that signals normal biological molecules, for example partially degraded proteins, that are taken out of the bloodstream in the liver, broken down, and then recycled,” Dr. Fambrough says. “When a few of these natural sugars are added to our GalXC RNAi molecules, they are taken up by the liver and delivered into liver cells, and instead of being degraded they are released inside the cells where they reduce the expression of specific genes.”

“For treating certain diseases, this is an excellent quality because the liver is the nexus of metabolism,” he says. “This is key to treating metabolic disorders such as primary hyperoxaluria, as well as cardiovascular diseases, chronic liver diseases, and infectious diseases of the liver such as hepatitis B virus.”

Dicerna has developed a growing pipeline of RNAi product candidates. In December 2017, the company announced the first human dosing in a Phase I clinical trial of its lead program, DCR-PHXC, to treat all forms of primary hyperoxaluria. Dicerna expects to have human proof-of-concept data in the second half of 2018. The company intends to file an investigational new drug application in the United States in the first quarter of 2018.

With its RNAi technology, Arbutus has reported deep reductions in Hepatitis B surface antigen levels in chronic HBV patients.

“We will shortly initiate a combination study with our RNAi agent ARB-1467 and an immune stimulator in HBV patients,” Dr. Murray says. He says there is potential for both ARB-1467 and the HBV therapy to reach the market in the next three to five years. ^{PV}



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DR. DOUG FAMBROUGH
Dicerna Pharmaceuticals

The Evolution of RNAi

- 1990** – Post transcriptional gene silencing (PTGS)
- 1992** – Quelling in *Neurospora*
- 1998** – RNAi in *C. elegans*
- 1998** – 2001 – RNAi in yeast, *Drosophila*, plants, trypanosomes
- 2001** – Successful siRNA experiments in mammalian cells
- 2002** – Science named RNAi Technology of the Year
- 2002** – Recombinant Dicer generated siRNA
- 2003** – Improved synthetic design; modified reagents; RNAi mechanism; toxicity responses; controls
- 2004** – Design improvements; validated reagents; in vivo applications; micro RNA; large screens
- 2005** – Specificity concerns; super-active reagents; more on in vivo; unique apps
- 2006** – Nobel Prize Fire & Mello

Source: Thermo Fisher Scientific, thermofisher.com