ADVERTISEMENT FEATURE

Dicerna Pharmaceuticals, Inc.
www.dicerna.com

Taking RNAi under the skin

Dicerna Pharmaceuticals, Inc., is leveraging RNA interference (RNAi) through its versatile and proprietary GalXC platform to advance a pipeline of subcutaneously delivered RNAi-based therapies that silence disease-driving genes in the liver across multiple indications.

The potential of gene silencing via RNAi has long been recognized, and innovations in the delivery of RNAi therapeutics by Dicerna Pharmaceuticals have enabled potent, long-acting gene silencing with a single subcutaneous injection for liver-associated diseases, including various rare diseases, chronic liver diseases (CLDs) such as nonalcoholic steatohepatitis (NASH), cardiovascular disease (CVD), and viral infectious diseases.

Short interfering RNAs (siRNAs) can specifically target messenger RNAs (mRNAs) encoding relevant disease-related proteins through activation of the cell's own RNA-induced silencing complex (RISC); each siRNA is complementary in sequence to its target mRNA. The result is destruction of target mRNAs and reduced levels of the corresponding proteins.

Dicerna's proprietary GalXC (pronounced like "galaxy") technology platform is driving the development of therapeutics consisting of stabilized siRNAs. These product candidates are highly efficacious in targeting disease-driving genes in the liver.

With several programs in advanced preclinical studies and more in the pipeline, Dicerna is poised to advance up to five programs into the clinic by 2019. The company is also looking for partners interested in codeveloping some of these therapeutics, in particular those targeting disorders with large patient populations.

Starring: GalXC

Dicerna's GalXC platform enables the company to generate siRNA molecules that are highly specific to their target mRNAs.

Chemically, the company's siRNAs are conjugates of *N*-acetylgalactosamine (GalNAc) sugars attached to the extended region of a dicer substrate siRNA (DsiRNA-EX) molecule; dicer is the RISC subunit responsible for detecting and binding siRNAs in the initial steps of RISC activation. A unique tetraloop configuration provides enhanced stabilization and properly orients multiple ligands for presentation to hepatocytes (**Fig. 1**).

Functionally, the GalXC molecules bind to the highly expressed asialoglycoprotein receptor on hepatocytes, leading to internalization and engagement of the RNAi machinery in the cells.

A key advantage of GalXC over standard RNAi platforms is the stability of the molecules, which affords the unique ability to administer the conjugates as simple saline solutions, without the need for additional transport technologies such as lipid nanoparticles to facilitate delivery. The improved stability of the GalXC compounds results in long durations of action, simplifying dosing protocols to once monthly or even less frequently.

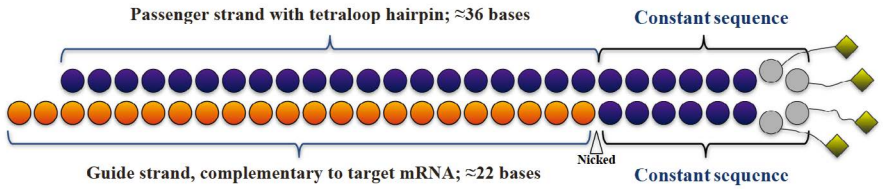

Figure 1: Dicerna's GalXC RNAi therapeutic platform. The guide strand in GalXC is approximately 22 bases long and the passenger strand containing the tetraloop with the GalNAc sugars is approximately 36 bases long. In preclinical models GalXC conjugates have a long duration of action and a very high therapeutic index.

Dicerna streamlined the GalXC platform to support the design, synthesis and *in vivo* validation of a GalXC molecule within 30 days of target selection. This allows Dicerna to rapidly advance the discovery and development of novel research programs as they are identified.

"The longer RNAi duplexes of our GalXC molecules provide greater flexibility to enhance their pharmaceutical properties, including increased potency and reduced toxicity," said Bob D. Brown, CSO and senior VP at Dicerna. "The GalXC platform allows us to screen and optimize therapeutic leads in mice and monkeys with remarkable efficiency."

Therapeutic targets

Dicerna's RNAi strategy focuses on targeting disease-associated genes for a broad spectrum of therapeutic areas, from CLD and viral infectious diseases to CVD and rare diseases. The common thread among all the diseases targeted with GalXC-based RNAi therapeutics is the identification of a disease-associated gene or genes expressed in the liver. The company has identified nearly three dozen such targets for which an RNAi-based inhibitor could provide patient benefit.

A number of diseases are currently being addressed in Dicerna's pipeline, including primary hyperoxaluria (PH), NASH, hepatitis B virus, and PCSK9-driven atherosclerotic CVD.

Most recently, the company has reported the silencing of 12 different disease targets in animal models, half of them in non-human primates (NHPs), providing a solid basis for further development. In NHPs, and after just a single subcutaneously delivered dose, GalXC compounds yielded gene silencing of greater than 90% for multiple genes. Additional preclinical data are available at the company's website.

Preclinical data in CLD models further suggest that the GalXC compounds target hepatocytes with high specificity and can successfully silence injury-responsive mRNAs encoding profibrotic damage signals such as high-mobility group box 1 (*HMGB1*) and β-catenin (*CTNNB1*).

What's next?

Dicerna's first subcutaneously delivered GalXC clinical candidate, DCR-PHXC, is in preclinical development for the treatment of PH, and the company expects to file an investigational new drug (IND) or clinical trial application for the molecule in late 2017.

Dicerna will also launch two other GalXC programs by the end of 2016. One will focus on targeting PCSK9 in CVD, and the other will focus on an undisclosed rare disease program.

Dicerna's long-term strategy is to pursue partnerships that provide enhanced scale, resources and commercial infrastructure to advance therapeutic programs targeting complex diseases with multiple gene dysfunctions and large patient populations. These would include diseases and disease target genes having a strong therapeutic hypothesis, a readily identifiable patient population, availability of predictive biomarkers, and favorable competitive positioning.

"At Dicerna, we believe that strategic partnerships, research collaborations and licensing arrangements should add value to both parties, assisting each in attaining goals beyond those that could be achieved individually," said Douglas M. Fambrough, president and CEO of Dicerna. "Securing strategic partnering agreements is a key part of our pipeline development, and we look forward to communicating our progress on this front."

contact
James Weissman, CBO
Dicerna Pharmaceuticals, Inc.
Cambridge, Massachusetts, USA
Tel: +1-617-621-8097
Email: jweissman@dicerna.com

ADVERTISER RETAINS SOLE RESPONSIBILITY FOR CONTENT