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Emerging Company Profile

Dicerna: Going long in RNAi

By Stephen Hansen
Staff Writer

Most work in RNAi has been focused on short, double-stranded RNA no more than 23 nucleotides in length because it was thought that longer molecules would have reduced activity. **Dicerna Pharmaceuticals Inc.** believes its longer oligonucleotides, called Dicer substrates, can provide greater potency and a longer duration of action than short interfering RNA. Perhaps more importantly, the extra nucleotides may help the company solve the systemic delivery problems that have so far dogged RNAi.

Co-founder and CEO Jim Jenson attributes the potency of the Dicer substrates to the manner in which they enter the RNAi pathway. The molecules are 25 or more nucleotides long and target the Dicer enzyme. The enzyme cleaves them into siRNA that becomes integrated into the RNA-induced silencing complex (RISC). RISC uses the bound siRNA molecule to identify complementary mRNA, which the complex then cleaves.

In contrast, siRNA bypasses Dicer, entering the pathway downstream at the RISC.

“By entering upstream in a more natural way, the longer molecules pick up some extraordinary properties, including

Dicerna Pharmaceuticals Inc.

Watertown, Mass.

Technology: Dicer substrate double-stranded RNA

Disease focus: Cancer, metabolic

Clinical status: Preclinical

Founded: 2007 by Jim Jenson, Doug Fambrough, Roberto Guercioli, John Rossi and Mark Behlke

University collaborators: City of Hope National Medical Center

Corporate partners: Archemix Corp. and Integrated DNA Technologies Inc.

Number of employees: 23

Funds raised: \$21.4 million

Investors: Oxford Bioscience Partners, Skyline Ventures and Abingworth Management

CEO: Jim Jenson

Patents: None issued

a very high level of potency,” Jenson told BioCentury.

Dicerna has generated Dicer substrates with single-digit picomolar potencies, which is “often times a log more potent than a short interfering RNA, and 3-5 logs more potent than a conventional antisense

molecule. By entering the pathway upstream and taking advantage of the entire pathway, we get a potency that far exceeds even our own expectations,” he said.

The reason for the increased potency is still not entirely understood, but the working theory is that by using the Dicer machinery, the Dicer substrate picks up unknown co-factors as it progresses through the pathway, which results in a more complete RISC. This more complete RISC is thought to be more stable than the complex formed by siRNAs, which leads to a longer duration of action for Dicer substrates.

Jenson said unpublished *in vitro* data show that 21-nucleotide siRNAs “may show activity for a couple of days, but then the activity will diminish over the course of a week. These Dicer substrates have sustained potency in many cases out to a week and sometimes beyond.”

The focus on longer molecules also allows Dicerna to work around RNAi patents held by other companies, such as **Alnylam Pharmaceuticals Inc.**'s Tuschl patents, which cover double-stranded RNA up to 23 nucleotides in length.

More recently, Dicerna has discovered
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that the additional nucleotides can function as a handle for attaching targeting molecules such as aptamers, mAbs or peptides. The company believes this may provide a solution to one of RNAi's biggest challenges: how to systemically deliver the siRNA to the correct cells and have them taken into the cell.

In an *in vitro* study published in *Molecular Therapy* in August 2008, Dicerna scientific co-founder John Rossi showed that an aptamer conjugated to a Dicer substrate was able to target a specific blood cell receptor. The cell internalized the conjugate, fed the Dicer substrate into the RNAi machinery, and knocked down the target gene.

This discovery was the basis for a July deal between Dicerna and **Archemix Corp.** to develop conjugated aptamer-Dicer substrate therapeutics. Dicerna has an option to license exclusive rights to develop and commercialize resulting therapeutics. Further terms were not disclosed.

While Dicerna has yet to disclose its preclinical pipeline, Jenson said the company's core disease areas are cancer and metabolic diseases. The company plans to find partners for its internal pipeline after Phase I or Phase II testing, while the technology platform could be out-licensed for non-core targets or disease areas.

Dicerna has rights to IP from **City of Hope National Medical Center** and **Integrated DNA Technologies Inc.** covering composition, method of use and method of synthesis of dsRNA molecules 25-35 nucleotides in length.

Roche and Dicerna have co-exclusive rights to two of three core patents held by City of Hope. Dicerna has exclusive rights to the third, which the company said covers the "preferred configuration" of Dicer substrates, which exhibit the best pharmacologic profile.

COMPANIES AND INSTITUTIONS MENTIONED

Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY), Cambridge, Mass.

Archemix Corp., Cambridge, Mass.

City of Hope National Medical Center, Duarte, Calif.

Dicerna Pharmaceuticals Inc., Watertown, Mass.

Integrated DNA Technologies Inc., Coralville, Iowa

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland