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Dicerna Offers New Generation of RNAi Therapy: DsiRNA

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The already-crowded RNA interference (RNAi) therapeutic playground is welcoming Cambridge, Mass.-based Dicerna Pharmaceuticals, which enters the space through "a second doorway."

This new kid on the block brings in a second generation of RNAi technology, which the company said is an improvement over the current method and at a more upstream level.

The so-called dicer substrate technology employed by Dicerna works through the same pathway with the current RNAi therapy method that employs synthetic 21-mer small interfering RNA (siRNA). The difference is that the dicer-substrate small siRNA (DsiRNA) "enters the pathway further upstream much like microRNA would," CEO and co-founder James Jenson explained.

DsiRNA bind to an enzyme called dicer, which dice the substrates into shorter fragments, before being incorporated into RISC (RNA-induced silencing complex), triggering the interference of gene translation. The current synthetic 21-mer siRNA pass the dicer enzyme and directly enter RISC.

Advantages of the longer 27-mer DsiRNA over the conventional siRNA therapy, according to Jenson, include increased potency, longer duration of action and the ability to attach targeting moieties for specificity.

"One can attain . . . five- to tenfold greater potency [in knocking] down a specific target than a 21-mer targeting the same sequence," Jenson said, then quickly added that increased property is a tremendous advantage "in a field which delivery is still optimized."

Dicerna, founded in 2007, currently is pursuing three programs internally: solid tumors/oncology, although the specific target molecules are not yet public; diabetes, specifically gluconeogenesis; and hepatitis C virus. For those, Dicerna plans to partner with other companies that already have the FDA-approved delivery methods.

"We consider this to be the most efficient way to begin our drug development program: a well-validated target that is suitable for dicer substrate and combine them with nanoparticle technology that exists today," Jenson said.

Dicerna plans on administrating the DsiRNA-nanoparti-

cles combination intravenously. The longer duration of action, which Jenson said is another advantage of DsiRNA and of a great interest to potential pharma partners, allows DsiRNA to be administrated every few weeks, similar to the "dosing paradigm . . . currently used for monoclonal antibody therapy."

There are several partnering discussions underway, he noted, and Dicerna is going to license existing technologies on a target-by-target basis.

Dicerna also is developing the second-generation approach for its products – targeted moieties, which Jenson said will be "very much a part of the future of RNAi therapeutics: more targeted . . . RNAi drugs, as opposed to the current approach involving nanoparticle encapsulation."

That can be achieved by utilizing the unique advantage of dicer-substrates: the ability to attach targeting moieties to target specific tissue or cells.

"You can attach either a peptide or an aptamer or antibody fragment that will target a specific receptor on the cell surface," Jenson said, explaining that the attached moieties will be clipped by dicer inside the cell and be degraded naturally.

The process recently has been shown in a study by John Rossi, professor of molecular biology and dean of the graduate school of biological science in Beckman Research Institute of the City of Hope in Duarte, Calif., and also Dicerna scientific co-founder. It was published in the August 2008 issue of *Molecular Therapy*.

The study itself was an approach for human immunodeficiency virus-1 (HIV-1) therapy, which Jenson mentioned that Dicerna is not pursuing, but is opened to partnering.

The intellectual property for the DsiRNA, which was invented by Rossi and Mark Behlke, "covers a range of 25- to 35-nucleotide (nt) long" and according to Jenson, that, plus the fact that the dicer-substrates have enhanced biological properties, provides Dicerna with a strong IP position "that is separate from the Tuschl I intellectual property estate that covers the 21-mers."

Jenson noted that City of Hope also provided MDRNA Inc. (formerly Nastech), of Bothell, Wash., with the right to

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dicer-substrate technology, but no other companies have access to that IP now. Jenson added that DsiRNA IP will not interfere with Tuschl II as well. Alnylam Pharmaceuticals, also of Cambridge, Mass., currently holds exclusive rights to the Tuschl II patent on a worldwide basis, and has a license to the Tuschl I IP. Both patents are keys to conventional siRNA methods.

Dicerna aims to have its first investigational new drug application (IND) package by the end of 2009 and to file in early 2010.

Roberto Guercioli, Dicerna senior vice president of pharmaceutical development, was previously chief medical officer and senior vice president of development at Sirna Therapeutics, now part of Merck & Co. Inc., and was part of the team that developed the first IND for chemically modified siRNA then, Jenson said.

The company closed a Series A financing round July 15 for \$214 million, and Jenson said he expected that would get Dicerna to the IND process.

The company plans to employ about 30 people in house, and currently is halfway there, and they will work out the in vivo biology. Integrated DNA Technology Inc., of Coralville, Iowa, is its "chemistry department," Jenson added. Behlke, who is also Dicerna's co-founder, is currently the vice president of molecular genetics and biophysics and chief scientific officer there. Jenson said IDT, a supplier of oligonucleotides, "will make for us anything that fits in our agreed-upon workplan."

Investors of Dicerna include Oxford Bioscience Partners Doug Fambrough, previously the director of investors at Sirna; Skyline Ventures Stephen Hoffman, previously involved with both Alnylam and Sirna; and new partner Abingworth.

"Alnylam is an Abingworth portfolio company," Jenson noted, "we have three investor groups who are very familiar with the RNAi space. . . . We think that's another validation of [dicer-substrate] technology . . . and the validation of the independence of IP doorway." ■