

Emerging Company Profile**Miragen: The heart of miRNA**

By Aaron Bouchie
Senior Writer

While currently approved drugs and devices to treat heart failure are palliative, **Miragen Therapeutics Inc.** is developing drugs against microRNA targets that it believes will be disease modifying. The company raised \$8 million in a series A round in May, which should get it to an efficacy study in large animals.

MicroRNAs are noncoding RNAs consisting of 22 nucleic acids that base pair with mRNAs and inhibit translation or promote mRNA degradation. miRNAs that pair perfectly with target mRNA sequences result in mRNA degradation, whereas miRNAs that are not perfectly complementary generally result in translational inhibition.

CEO William Marshall said miRNAs coordinate the expression of sets of genes by targeting multiple mRNAs. Thus, targeting an miRNA should make it possible to affect an entire pathway.

"This is different from targeting a single gene product," Marshall said, which has been tried to treat heart failure without much success. He cited beta blockers as an example of a highly lucrative class of drugs that target a single protein but are not curative.

Miragen's lead program is based on miR-208, an miRNA encoded by an intron of the alpha myosin heavy chain (MYH6) gene. Expression of MYH6 and beta myosin heavy chain (MYH7) controls cardiac contractility.

In normal adult hearts, MYH6 constitutes about 30% of total myosin heavy chain. The heart responds to stress by up-regulating MYH7 and down-regulating MYH6, which results in hypertrophic growth accompanied by fibrosis and eventual diminution of contractility.

A group led by company co-founder Eric Olson, professor of molecular biology at the **University of Texas Southwestern Medical Center**, discovered that miR-208 is required for cardiomyocyte hypertrophy, fibrosis and expression of MYH7 in response to stress.

Miragen Therapeutics Inc.

Boulder, Colo.

Technology: miRNA modulators

Disease focus: Cardiovascular and musculoskeletal

Clinical status: Preclinical

Founded: 2007 by William Marshall, Eric Olson, Michael Bristow, Marvin Caruthers and Bruce Booth

University collaborators: University of Texas Southwestern Medical Center and University of Colorado

Corporate partners: None

Number of employees: 1

Funds raised: \$8 million

Investors: Atlas Venture, Boulder Ventures and private individuals

CEO: William Marshall

Patents: None issued

Olson also showed that knockout mice lacking miR-208 exhibit virtually no hypertrophy of cardiomyocytes or fibrosis in multiple models of heart failure, including thoracic aortic banding (TAB).

"The results validate the notion that one targeting miRNA can reduce hypertrophy and maybe eliminate heart failure altogether," said Marshall.

miR-208's expression is specific to the heart, Marshall added, so its inhibition is less likely to result in off-target events that are associated with siRNA and antisense therapeutics.

The company has an oligonucleotide that complements the entire 22-nucleotide miR-208; it is being tested in small animal models. Marshall hopes to move into porcine models — which he called the gold standard for cardiovascular drug development — by YE09. He expects the company's \$8 million to get it that far.

Olson also is developing different models of CV disease to discover additional miRNA targets, for example in chronic hypertension and myocardial infarction,

according to Marshall. "Different types of miRNAs can be targeted to treat different types of vascular disease, not just in the heart," he said.

Miragen has an exclusive option to license Olson's miRNA-related inventions.

The company also will look to create miRNA mimics, such as short double-stranded RNA (dsRNA), which would exert their therapeutic benefit by stimulating mRNA degradation or translational inhibition.

Marshall noted that because the cardiovascular system is made of cardiac and smooth muscle, the company will be exploring opportunities in other muscle diseases. "There have been some discoveries that some of the miRNAs we're looking at are altered in other muscle diseases," he said.

Though the company's patent applications also cover diagnostic uses of miRNA, Marshall said he will likely look to partner out those rights.

Other companies working on miRNA therapeutics include **Santaris Pharma A/S** and **Regulus Therapeutics LLC**, a JV of **Alnylam Pharmaceuticals Inc.** and **Isis Pharmaceuticals Inc.** **Rosetta Genomics Ltd.** also is developing miRNA-based therapeutics and diagnostics. **Asuragen Inc.**, which is developing miRNA diagnostics, spun out **Mirna Therapeutics Inc.** to develop miRNA cancer therapeutics. All the miRNA-targeted therapeutics are in preclinical development.

COMPANIES AND INSTITUTIONS MENTIONED

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

Asuragen Inc., Austin, Texas

Isis Pharmaceuticals Inc. (NASDAQ:ISIS), Carlsbad, Calif.

Miragen Therapeutics Inc., Boulder, Colo.

Mirna Therapeutics Inc., Austin, Texas

Regulus Therapeutics LLC, Carlsbad, Calif.

Rosetta Genomics Ltd., Rehovot, Israel

Santaris Pharma A/S, Horsholm, Denmark

University of Texas Southwestern Medical Center, Dallas, Texas

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