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MicroRNA Drugs Startup Miragen Nears Close of Series A, Begins Defining Pipeline

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By Doug Macron

Miragen Therapeutics, a Boulder, Colo.-based startup developing microRNA-targeting drugs for cardiovascular disease and related muscle disorders, is close to closing a Series A round of financing, *RNAi News* has learned.

The round, expected to close in the next week or so, will enable the company to ramp up its operations with the goal of "completing some large animal efficacy studies within a year or so ... [and] moving very quickly toward our first indication for a microRNA-manipulating agent, hopefully within two or two and a half years of financing," according to Miragen President and CEO Bill Marshall.

Marshall said the company is currently operating on seed funding that has allowed it to go through "the process of developing [our] strategy and operating plan." This early financing was provided by two venture capital firms: Atlas Venture, which was an early investor in Alnylam Pharmaceuticals, and Boulder Ventures, which had invested in Dharmacon before it was acquired by Fisher Scientific, now Thermo Fisher Scientific.

Marshall previously held various positions at Dharmacon, most recently serving as vice president of technology and development at Thermo Fisher Scientific.

Miragen is still working out the specifics of its pipeline, Marshall noted, but the company intends to initially pursue heart failure, a condition that he said "has many different etiologies and potential [points of] intervention.

"A big part" of what Miragen will work on over the next six months will be "defining the key microRNAs and ... [specific] clinical indication we want to go after," he added.

Given the fact that delivery continues to be the biggest hurdle for nucleic acid-based drugs, Marshall said that Miragen will initially focus on developing a therapeutic that can be directly delivered to the heart.

"The standard of care for heart failure in a variety of different cardiovascular disorders is catheterization," he explained. "So we're going to leverage some semi-invasive, mechanical delivery technologies that allow us to do pseudo-local delivery."

For instance, most patients presenting with myocardial infarction are stabilized and catheterized, so "post-myocardial infarction would be an interesting opportunity" for Miragen to deliver its miRNA drug, Marshall said.

'Relentless Focus'

According to Marshall, Miragen's establishment last year stemmed from conversations he had at the beginning of that summer with University of Texas Southwestern Medical Center researcher Eric Olson and the University of Colorado at Boulder's Mike Bristow.

The three "got together and started talking about some of [the investigators'] discoveries in terms of microRNA changes in cardiovascular disease," Marshall said. By August, "we ended up formally founding and moving the company forward," along with another co-founder, UC Boulder's Marv Caruthers.

"When they knocked out this particular microRNA, generated the full homozygous knockout animal, and induced heart failure through [a technique called] thoracic aortic banding, that mouse doesn't go through

A number of companies have entered the miRNA drugs space recently, including Asuragen subsidiary Mirna Therapeutics (see *RNAi News*, 4/3/2008), which is developing drugs for cancer, and Alnylam/Isis Pharmaceuticals joint venture Regulus Therapeutics (see *RNAi News*, 9/13/2007), which is focusing on hepatitis C and other viral, metabolic, inflammatory, and oncologic disorders.

According to Marshall, Miragen is unique in its "relentless focus" on cardiovascular disease.

"We're going to go after cardiovascular and [related] muscle disorders and really focus on that," he said. "Our first indications

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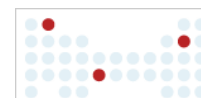
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Ina K. Dahlsveen, Ph.D.
Product Manager



hypertrophy and doesn't develop heart failure, suggesting that this would be an excellent target for [therapeutic] intervention."

will be in heart failure, but the complete focus of the company is cardiovascular disorders — disorders of the heart and vascular system, [as well as] related muscle disorders," which can include cardiomyopathy.

The decision to focus exclusively on cardiovascular disorders is tied to Miragen's "expertise in understanding microRNA differences in muscle cells," he said. For example, research has shown that there is "a very restricted set of microRNAs that are either up-regulated or down-regulated in response to cardiac hypertrophy," a condition that can be triggered by a variety of stresses including hemodynamic overload due to chronic hypertension that often leads to heart failure.

According to a review article published last year by Olson and postdoc Eva van Rooij, the hypertrophic heart experiences abnormal growth that leads to mechanical stiffness and, subsequently, contractile dysfunction.

Another key feature of pathological hypertrophy and heart failure is "the re-activation of a set of fetal cardiac genes, including those encoding ... fetal isoforms of contractile proteins such as beta-myosin heavy chain," Olson and van Rooij wrote.

"The consequences of fetal gene expression on cardiac function and remodeling are not completely understood, but the up-regulation of beta-MHC, a slow ATPase, and down-regulation of alpha-MHC, a fast-contracting ATPase, in response to stress has been implicated in the diminution of cardiac function," they added.

"This kind of gene-program remodeling has been the subject of intense studies by a couple of different pharmaceutical companies in terms of identifying what molecular targets would be the best, and [Olson] identified a variety of microRNAs that are changing," Marshall noted.

Specifically, Olson reported in *Science* last year that miR-208, which is encoded by an intron of the alpha-MHC gene, is required for cardiomyocyte hypertrophy, fibrosis, and expression of beta-MHC in response to stress and hypothyroidism.

"When they knocked out this particular microRNA, generated the full homozygous knockout animal, and induced heart failure through [a technique called] thoracic aortic banding, that mouse doesn't go through hypertrophy and doesn't develop heart failure, suggesting that this would be an excellent target for [therapeutic] intervention," Marshall said.

While Miragen's pipeline is "evolving," miR-208 is "certainly of high interest to us," he added.

Marshall noted that the company is also very interested in a handful of other undisclosed miRNAs that are either up-regulated or down-regulated in the context of heart disease. As a result, Miragen will develop both miRNA inhibitors and miRNA mimics as therapeutic agents.

From an intellectual property standpoint, "our belief is that, in terms of the microRNA manipulation itself, what really counts is attributing function with microRNAs," Marshall said. "What we've been able to do is license intellectual property around the establishment of a particular disease with a microRNA perturbation."

But that is only one piece of the IP puzzle, he stressed. "In terms of developing the [therapeutic] molecules themselves, we're going to look at a broad spectrum of different molecules," Marshall said. This review will include both existing technologies, for which Miragen is going to be "very open to partnering discussions," as well as "novel molecules that would allow us to have a unique intellectual property position."

Miragen's interest in partnering also extends beyond IP, Marshall added.

"We're certainly very interested in talking with any potential partners in terms of moving [our] programs forward," he said. "We've purposely been trying to work on a lot on things very quietly ... [and] haven't been real active in terms of partnering. But that will definitely change as soon as we start ramping up" after the close of the Series A.

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