



Mirna Therapeutics Researcher Says miRNA Replacement May Be Promising Rx Approach

June 19, 2008

Byline: Doug Macron

Newsletter: [RNAi News](#)

[RNAi News - June 19, 2008](#)

Although the number of companies working in the microRNA drugs space continues to grow, most of these firms are developing drugs designed to inhibit the small, non-coding RNAs. But one company, Mirna Therapeutics, is taking a different tack by focusing on an miRNA-replacement approach to treating cancer.

"There are [three] compelling scientific reasons that favor microRNA-replacement therapy," Andreas Bader, senior scientist of drug discovery at Mirna, said at Cambridge Healthtech Institute's Beyond Genome conference in San Francisco last week.

"Number one, numerous studies show us that the majority of differentially expressed microRNAs are down-regulated in tumor tissue," he said. Second, inhibition of endogenous miRNA-processing machinery such as RISC has been shown to trigger oncogenic cell transformation.

Lastly, "a microRNA mimetic is the closest equivalent to a naturally occurring molecule and, therefore, less likely to induce non-specific side effects," Bader said.

Mirna became a stand-alone company in April when it was spun out from miRNA diagnostics shop Asuragen (see [RNAi News, 4/3/2008](#)), which was born two years earlier when Applied Biosystems acquired reagent shop Ambion but left untouched the company's diagnostics and services division (see [RNAi News, 1/5/2006](#)). These operations were re-branded as Asuragen.

Mirna currently focuses on three indications: non-small cell lung cancer, metastatic prostate cancer, and acute myeloid leukemia. The company is also collaborating closely with Yale University researcher Frank Slack, who has studied the role of the miRNA let-7 in cancer (see [RNAi News, 1/11/2007](#)).

During his Beyond Genome presentation, Bader said that Mirna has identified let-7 as a key target for its lung cancer program, citing work from a collaboration between Slack's lab and Ambion. In 2005, the investigators [published](#) data in *Cell* showing that the let-7 family regulates the oncogene RAS.

"The 3' UTRs of the human RAS genes contain multiple [let-7 complementary sites], allowing let-7 to regulate RAS expression," according to the paper. Further, "let-7 expression is lower in lung tumors than in normal lung tissue, while RAS protein is significantly higher in lung tumors, providing a possible mechanism for let-7 in cancer."

"This was pretty much one of the first demonstrations that functionally implicated a microRNA in human cancer," according to Bader, who added that research suggests that let-7 essentially

“A microRNA mimetic is the closest equivalent to a naturally occurring molecule and therefore less likely to induce non-specific side effects.”

“puts out the stop sign and blocks [certain specific] oncogenic pathways.”

Under normal conditions, let-7 is expressed at levels required to maintain normal gene expression and prevent dysfunction in those pathways, he explained. “Due to genetic aberrations, let-7 might get lost or [become] expressed in reduced levels, which now uncouples these genes from let-7 and leads to an increase of gene expression and/or associated pathways,” which could result in cancer.

In additional experiments comparing let-7 expression in samples of tumors and adjacent normal tissue from patients with non-small cell lung cancer, “about 85 percent of all tumor samples displayed reduced expression of let-7, and reduced expression was not limited to any particular tumor type,” he said. Additionally, let-7 was found to “robustly inhibit the proliferation of ... lung cancer cells in comparison to cells treated with a so-called negative control microRNA” *in vitro*.

Further supporting let-7’s potential as a therapeutic target is *in vivo* data coming from Slack’s lab and published in *Cell Cycle* earlier this year showing that the miRNA could reduce tumor growth.

The researchers “took advantage of a transgenic mouse model for lung cancer that closely resembles lung tumor formation in a human being ... [and] asked the question whether ... administration of an adenovirus that encodes the let-7 microRNA would interfere with this tumorigenesis process,” Bader said. “The answer is yes.”

Specifically, the researchers found that the lungs of mice treated with the miRNA-encoding adenovirus were either free of lesions or had lesions significantly smaller than the ones observed in the lungs of those animals who received treatment with an adenovirus encoding the negative-control miRNA, he said.

In addition, the histologies of mice receiving let-7 were “indistinguishable” from those that received no treatment, suggesting that miRNA replacement is safe, Bader said.

“Of course, this is not a very thorough assessment of microRNA safety, but it was at least the first indication that microRNA expression was well tolerated,” he noted.

While the researchers were encouraged by the finding that let-7 can inhibit lung cancer, “the ultimate question really is, especially from a therapeutic standpoint, whether let-7 is able to tackle established tumors,” Bader said during his presentation. “This is, in fact, the case.”

In an H460 lung-cancer xenograft mouse model, let-7 that had been complexed in a cationic lipid and administered through intratumoral injection triggered a “robust inhibition of tumor growth,” Bader said.

The tumors did not regress as the research team had hoped, but since neither the chemistry nor the delivery aspects of the experiment had been optimized, “we were pretty excited,” he noted.

Although Mirna’s overall goal is to develop miRNA-based drugs as stand-alone treatments for cancer, “we have already begun to combine microRNAs with other treatment regimes to see if the microRNAs can sensitize cancer cells to conventional therapies,” Bader said.

Mirna researchers previously screened “a library of microRNAs and transfected [them] into breast cancer cells, and then followed up with ... a pro-apoptotic treatment,” he said. Through this work, “we identified a list of microRNAs [including let-7] that can sensitize these cancer cells about two-fold to ... treatment.

“So clearly let-7 seems to have great therapeutic potential, although we have ... identified other tumor-suppressor microRNAs [that have shown] ... universal therapeutic activity” both *in vitro* and *in vivo*, Bader said. For competitive reasons, he declined to name these miRNAs.

Genomeweb system

These settings are generally managed by the web site so you rarely need to consider them.

Issue Order: 2

Browser Title:

RNAi News: Mirna Therapeutics Researcher Says miRNA Replacement May Be Promising Rx Approach

Full Title:

Mirna Therapeutics Researcher Says miRNA
Replacement May Be Promising Rx Approach

IPS ID: 147658

-->

