Mirna Releases Preclinical Data on miRNA-Replacement Rx, Aims for Clinic in 2011

June 18, 2009

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Newsletter: RNAi News
RNAi News - ,

Asuragen subsidiary Mirna Therapeutics this week unveiled preclinical data showing that one of its microRNA mimics inhibited tumor growth and metastases in a variety of animal models without toxicity.

These data, along with the publication last week of a report showing that therapeutic miRNA delivery could suppress tumorigenesis in a mouse model of liver cancer, suggest that miRNA replacement could be a safe and effective therapeutic strategy for cancer, Mirna CEO Matt Winkler told *RNAi News* this week.

As such, Mirna expects to begin clinical testing of its first drug candidate by 2011, he said.

Mirna's drug, dubbed miR-Rx34, is designed to mimic miR-34, which has been shown to be down-regulated in multiple human cancers and associated with the p53 tumor-suppressor network.

According to Mirna, systemic administration of the agent to mouse models using a recently in-licensed neutral lipid-based delivery vehicle inhibited the proliferation and viability of a "variety of cultured cancer cells, including those derived from patients with melanoma, lung, prostate, liver, and colon cancers."

Additionally, miR-Rx34 inhibited the growth and metastasis of established human tumors in mouse models of lung and prostate cancer, the company's two primary indications of interest. Mirna researchers also compared the effects of the lipid delivery vehicle, either alone or with the miRNA payload, and found no signs of toxicity or immunogenicity.

Winkler attributed miR-Rx34's apparent safety to a combination of the drug's potency and the fact that miRNAs are a natural part of human biology. Importantly, Mirna is also focusing on miRNAs that are already present at high levels in normal cells, but

suppressed in tumors.

While the drug is not targeted to cancer cells, the doses required to achieve a therapeutic effect are so low that normal cells appear to be unaffected, he said. "But when you add a small amount to tumor cells, it triggers cell death [and] tumor regression, [and] inhibits metastases."

At the same time, "microRNAs have a billion years of evolution fine-tuning their sequence," Winkler noted. As a "natural part of normal cells," agents that mimic the small RNAs are unlikely to have any adverse effects.

In addition to miR-Rx34, Mirna has another mature miRNA mimic at roughly the same stage of development. Winkler said that, like miR-Rx34, the other drug is "minimally modified" to enhance uptake and stability, but he declined to provide additional details.

Although Mirna announced its plan to reach the clinic by 2011 in conjunction with the release of data on miR-Rx34, Winkler noted that a decision has not been made on which of the company's drugs will enter human testing first. Selection of a lead candidate, he added, will be driven by data from work leading up to an investigational new drug application.

Mirna has publicly disclosed three oncology indications — non-small cell lung cancer, metastatic prostate cancer, and acute myeloid leukemia — as its areas of interest. In addition, the company has investigated the possibility of using miRNA-replacement therapy to sensitize cancer cells to conventional chemotherapeutics (see *RNAi News*, 6/19/2008).

But it has now limited itself to developing miRNA mimics as stand-alone drugs for lung and prostate cancer, Winkler said.