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Chasing the Therapeutic Potential of miRNAs

SREPORT

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The action around miRNA-related patent filings, cross-licensing, company spinouts, and research product proliferation has achieved feeding-frenzy status. The biotech industry is reaping multiple benefits from this latest lemming leap into new drug discovery in terms of investment and large pharma deals.

Research tools already in place engendered by the relatively mature siRNA industry will facilitate and abbreviate up-front discovery and development timelines for miRNA therapeutics, according to scientists. Frost and Sullivan reported that miRNA tool providers have seen extraordinary growth in their research product portfolios. The market achieved revenues of over \$20.3 million in 2008 and is estimated to reach \$98.6 million by 2015.

The investments chasing miRNA are fueled by over 10 years of research establishing a diverse and widespread regulatory role for these nucleotides. miRNAs are small, single-stranded RNA molecules of 21–23 nucleotides in length and play key roles in controlling gene expression. miRNAs bind to untranslated regions of mRNAs to interrupt ribosomal synthesis of the proteins they encode, make adjustments in translation, and target mRNAs for degradation.

Each miRNA is thought to regulate as many as 50 to 100 genes, influencing fundamental biological processes from cell development to cell death. miRNA expression, the lack thereof, or miRNA mutations have been associated with multiple diseases including cancer, as well as cardiovascular, metabolic, autoimmune, and viral diseases.

The Surge in miRNA Research

This year miRNAs have been the focus of at least three major scientific meetings to date, with more to come before we head into 2010. In the first eight years or so following miRNA's discovery in 1993, scientists published just four articles on the topic; by August 2008 at least 1,500 miRNA-related publications were included in the PubMed database.

In oncology alone miRNA-expression pattern profiling comparing expression in normal and cancer tissues shows an unexpected greater reliability in classifying cancer types than the signatures of protein-coding genes. Researchers have also successfully classified poorly differentiated tumors using miRNA expression profiles. In contrast, mRNA profiles proved highly inaccurate when applied to the same samples.

Along with their diagnostic potential, miRNAs have also reportedly proven to be of prognostic value. In one colorectal cancer study, miR-21 was expressed in 87% of patients with colon cancer and was shown to be an independent prognostic marker of poor survival. High miR-21 expression predicted worse survival among treated colon cancer patients and poor responsiveness to adjuvant chemotherapy.

The Therapeutic Side of miRNAs

On the therapeutic side, preclinical data has established antitumor effects of specific miRNAs in animal models of human cancers. The therapeutic potential of miRNAs has spawned several new companies including [Regulus](#)

[Therapeutics](#), jointly owned by [Isis Pharmaceuticals](#) and [Alnylam Pharmaceuticals](#), [Mirna Therapeutics](#), formed by [Asuragen](#) in April of 2008 with an oncology focus, Denmark's privately held [Santaris Pharma](#), and [Mirina](#), formed in 2008 by Accelerator.

For companies like Isis with its early stranglehold on critical nucleic acid synthesis chemistry patents, the discovery of any novel, potential oligonucleotide therapeutic widens the royalty field as well as the opportunity for partnerships and leveraging its technology. For example, Alnylam reported that the increase in R&D expenses during this year's second quarter in comparison to the same period last year was due primarily to \$11 million in license fees paid in connection with the company's agreement with Isis.

In September 2007 Alnylam and Isis established Regulus to combine their RNA therapeutic drug discovery expertise, unique oligonucleotide-based technologies, and a broad intellectual property estate specific to miRNA-based therapeutics. Regulus' current patent estate includes over 600 patents and more than 300 pending patent applications pertaining primarily to chemical modifications of oligonucleotides targeting miRNAs for therapeutic applications.

In April 2008 [GlaxoSmithKline](#) and Regulus announced a discovery, development, and marketing deal for novel miRNA therapeutics to treat inflammatory diseases including rheumatoid arthritis and inflammatory bowel disease. It is worth up to \$600 million in up-front, option, and milestone fees.

Mirna plans to develop therapeutic miRNAs based on research that began in 2002 at Ambion. "Ambion was the perfect incubator for identifying miRNAs that contribute to human disease and that might be used to treat patients," notes Matt Winkler, CEO of Asuragen and Mirna executive chairman. "Ambion had freezers full of RNA isolated from diseased tissues, a full-time tissue-acquisition staff, cutting-edge technologies for miRNA expression and function analysis, and a group of scientists interested in characterizing this recently discovered class of genes."

Mirna was spun out in 2008 with seed funding of \$3 million and a directive to develop a cancer therapy modeled after a naturally occurring tumor suppressor miRNA. One of the miRNAs that the company selected for therapeutic development is miR-34. It has been shown to be a part of the p53 pathway and to have potent anticancer activity. A mimic of the miR-34 complex with a lipid-based delivery agent inhibited the growth and metastasis of established human tumors in mouse models of lung and prostate cancer, according to Mirna's director of discovery, David Brown, Ph.D.

"Our research is based on the concept that a small number of key miRNAs are consistently down-regulated in human tumors and that re-introduction of these missing miRNAs into cancer cells reactivates cellular pathways that drive a therapeutic response," Winkler explains.

"The early research at Ambion and continuing studies at Asuragen and Mirna have resulted in a very significant patent portfolio that includes claims for both therapeutic and diagnostic applications of miRNAs." Dr. Winkler indicated that Mirna's primary focus has been on finalizing the chemistries of its lead miRNA mimics and the formulation of a systemic delivery technology that it licensed this year. Mirna expects to file an IND application for the treatment of solid tumors in 2011.

On August 24 Santaris Pharma, which is also developing drugs targeted to disease-related mRNAs, announced a multiyear worldwide strategic alliance with Shire to discover and develop new RNA-based medicines to treat rare genetic disorders. The deal provides for Santaris to receive initial payments of \$6.5 million covering technology access, exclusivity for three predefined targets, and initial discovery funding. It also stands to earn an early-stage payment of \$13.5 million upon successful completion of certain initial studies.

Santaris completed a Phase I trial of its miRNA-targeting HCV therapeutic, SPC3649, earlier this year. It was the first to test an miRNA antagonist in humans. An additional Phase I study, examining multiple doses of SPC3649, is expected to begin before the end of 2009. SPC3649 is a locked nucleic acid targeting miR-122, a liver-expressed miRNA shown to play a role in HCV replication.

Lastly, Seattle-based Mirina is focusing on developing drugs using minor groove binder (MGB) technology licensed from Nanogen. MGB agents are chemical groups with high affinity for helical DNA or RNA. Nanogen has applied this technology for molecular diagnostics, licensing it to Applied Biosystems and Thermo Fisher Scientific

for research applications. Mirina will target selected miRNAs with its MGB-oligonucleotide compounds, which it hopes will exhibit enhanced target selectivity and potency.

miRNAs may provide an entirely new approach to potential treatments for a variety of diseases as is evidenced by the recent onslaught of related drug development. Being an entirely new technique, though, it will take a significant amount of time for a miRNA-based therapy to reach the market. Perhaps more immediately, new markers for disease classification, progression, and therapeutic responses will surface through the immense investment in miRNA research.

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