

Executive Summary

“RNA interference”, or RNAi, refers to the inhibition of expression of specific genes by small double-stranded RNAs. Experimental RNAi typically involves the introduction of a foreign or synthetic small RNA into a cell or organism, resulting in silencing or inhibition of expression of specific genes, with the specificity of gene silencing determined by the sequence of the introduced RNA. Since the emergence of RNAi in the late 1990s, it has been seen within the scientific community as breakthrough science. This was recognized most notably via the awarding of the 2006 Nobel Prize in Physiology or Medicine to Craig Mello (University of Massachusetts Medical School, Worcester, MA) and Andrew Fire (Stanford University School of Medicine, Stanford, CA) for the discovery of RNAi. This was only eight years after the 1998 publication of their discovery.

RNAi technology has been extensively utilized in basic research, and in drug discovery. It has become an indispensable research tool in determining gene function, in analyzing pathways, and in target validation, both in academia and in industry. Meanwhile, basic researchers have been studying the biology of microRNAs (miRNAs), which are a class of naturally occurring small RNAs that are involved in gene regulation. Pathways for production of miRNAs, as well as mechanisms of miRNA action, are related to pathways and mechanisms for RNAi. Discoveries in miRNA biology have contributed to the intense interest of the scientific community in the entire field of small regulatory RNAs, which began with the discovery of RNAi.

Since the emergence of RNAi technology, there has been intense interest in applying the technology to the development of oligonucleotide drugs. This nascent field has captured the interests of the investment community, and several venture capital-backed RNAi specialty companies have been launched. In 2004, what is arguably the leading RNAi specialty company, Alnylam Pharmaceuticals (Cambridge MA) went public. In 2006, Merck acquired another leading therapeutic RNAi company, Sirna, for \$1.1 billion. These and other therapeutic RNAi companies are actively developing drug candidates, and other large pharmaceutical companies have also entered into major deals with some of these RNAi therapeutics companies. Specialty companies that focus on development of microRNA-based therapeutics and diagnostics have also emerged, and have also attracted the interest of the investment community and the pharmaceutical industry.

The pharmaceutical industry has special strategic reasons for its interest in RNAi-based therapeutics. Big Pharma is looking to RNAi therapeutics to fill weak pipelines. RNAi therapeutics also have the potential to address targets that are considered to be “undruggable” by small-molecule compounds or biologics. And by getting into RNAi therapeutics early, Big Pharmas may be able to stake out a commanding position once RNAi-based drugs reached the market.

Nevertheless, the therapeutic RNAi field has serious downsides as a field for investment by Big Pharma and the financial community. It is an early-stage or embryonic field, with not one drug on the market to date. The most advanced candidates are in Phase II clinical trials. There are still knowledgeable people in the scientific, biotech/pharma, and financial communities who believe that no RNA therapeutic will ever reach the market. All who are working on RNAi therapeutics realize that there are large challenges to overcome before a successful RNAi drug becomes a reality.

Prior to the discovery of RNAi, several companies have been attempting for around two decades to develop nucleic acid drugs of an older class, known as antisense drugs. Drug delivery has been a critical bottleneck in the development of antisense drugs, and improvement in delivery has been a key motivator in the design of these compounds.

Despite the two decades of development, only one antisense drug has reached the market. This is Vit-ravene (Isis Pharmaceuticals’ fomivirsen, licensed to Novartis Ophthalmics), for the treatment of cytomegalovirus retinitis in AIDS patients. Vitravene is delivered by local injection into the vitreous of the eye. The only other nucleic acid drug to reach the market is OSI/Eyetech/Pfizer’s Macugen (egaptanib). Macugen is a pegylated (that is, modified with chains of polyethylene glycol) aptamer (a single-stranded oligonucleotide that binds to and inactivates a specific target, usually a protein). It is also delivered locally to the eye.

However, more recently Isis Pharmaceuticals (Carlsbad, CA), the leading developer of antisense drugs, has gotten a systemically delivered antisense compound into Phase III clinical trials. This is mipomersen (formerly known as ISIS 301012), a first-in-class apolipoprotein B (apoB) synthesis inhibitor, for treatment of patients with high serum low-density lipoprotein (LDL) who are at high risk for cardiovascular disease (CVD).

Over the course of the development of antisense compounds, researchers have been developing chemical modifications to prevent their destruction by nucleases, improve their pharmacokinetics, and to enhance their target specificity and their binding affinity. For example, second-generation chemically modified antisense compounds such as mipomersen traffic to the liver after intravenous administration, without the need for a carrier such as a liposome.

The history of the development of antisense and aptamer drugs illustrates the difficulty that researchers and companies have had in successful development of oligonucleotide drugs. The hurdles encountered in the development of these two classes of drugs are also expected to apply to RNAi therapeutics as well, and researchers and companies have in fact come up against these same hurdles.

The two main issues that must be addressed are:

The design of the therapeutic oligonucleotide molecules themselves (e.g., structure, nucleotide sequence, length, and chemical modification)

Drug delivery (e.g., local delivery, the use of delivery vehicles such as liposomes, or the design of self-delivered oligonucleotides).

Therapeutic RNAi researchers universally cite drug delivery as the biggest hurdle to the development of RNAi drugs.

Laboratories and companies that have been engaged in the development of antisense drugs, and research products companies that develop antisense, RNAi, and/or other oligonucleotide reagents for researchers have been a major source of ideas and people for new RNAi therapeutic specialty companies. A major reason for the movement of researcher, entrepreneurial, and investor interest away from antisense toward RNAi is that RNAi is more potent than antisense in inhibiting gene expression.

This report is a discussion of the therapeutic RNAi and miRNA field, including the science behind therapeutic RNAi and miRNA, technologies for design of therapeutic oligonucleotides that work via an RNAi or miRNA-modulating mechanism, technologies for design of delivery vehicles, and leading companies in the therapeutic RNAi/miRNA industry sector. Company discussions include RNAi and miRNA specialty companies, as well as the role of large pharmaceutical companies in the sector.

Chapter 1 and Chapter 2 provide a general introduction to the therapeutic RNAi/miRNA field and describe the science of small silencing RNAs, and mechanisms of RNA interference, respectively.

Chapter 3 begins with a brief discussion of RNAi therapeutics now in clinical development, and includes a table listing these agents. It then discusses the design of therapeutic oligonucleotides that work via an RNAi mechanism, including means to overcome such hurdles as nuclease degradation and activation of the innate immune system. The chapter goes on to discuss alternative designs of interfering oligonucleotides being developed by Dicerna and RXi.

Chapter 4 discusses delivery of interfering oligonucleotides, including local delivery and development of delivery vehicles for RNAi drugs by such leading companies as Alnylam, Tekmira, RXi, Calando, Silence, and Pfizer, as well as leading university research groups such as the MIT laboratory of Robert Langer and Daniel Anderson, and the University of Massachusetts Medical School laboratories of Tariq Rana, Gary Ostroff, and Michael Czech.

Chapter 5 is a discussion of leading companies in the therapeutic RNAi field, including their strategies, technologies, alliances and products. Companies discussed include Alnylam, Tekmira, Sirna/Merck, RXi, Calando, Silence, Quark, and Dicerna. The chapter also includes a discussion of activity in therapeutic RNAi of Big Pharma companies, including alliances with therapeutic RNAi specialty companies, therapeutic RNAi-focused subsidiaries, and in-house laboratories.

Chapter 6 is a discussion of leading companies in miRNA therapeutics with a similar format to Chapter 5. Companies discussed include Regulus, Santaris, and miRagen. The chapter also discusses the role of Big Pharma in the development of miRNA therapeutics. It concludes with a brief discussion of miRNA-based diagnostics, and its commercialization by Rosetta Genomics and Asuragen.

Chapter 7 discusses the outlook for the therapeutic RNAi/miRNA industry sector, including strategic issues such as technological prematurity and the development of enabling technologies, the role of Big Pharma investment, the impact of patent litigation and cross-licensing in shaping the RNAi/miRNA sector, and a scenario for the development of drugs in the therapeutic RNAi/miRNA sector.

This report concludes with Chapter 8 containing five interviews with thought leaders in the RNAi field in order to provide the reader with additional context and commentary to better understand the future of RNAi.

According to this scenario (which includes antisense oligonucleotide drugs as well as RNAi and miRNA oligonucleotide drugs), an approved oligonucleotide drug, which is likely to be a locally delivered or a liver-targeting drug, may be about 1-3 years away from approval. The approval of Quark's systemically delivered kidney-targeting RNAi drug QPI-1002 might occur soon thereafter. The first miRNA drugs might be approved a year or two after that. Other systemically delivered oligonucleotide drugs that target organs and tissues other than liver or kidney may be a long way off, and the timing of their appearance would be difficult to predict. However, companies such as Tekmira, Calando, and RXi are developing delivery systems and products that may be able to target tumors in sites other than liver and kidney, and macrophages throughout the reticuloendothelial system. As in all drug development, early formulations of oligonucleotide drugs could fail in Phase III, which would thwart the scenario's predictions.