

# Executive Summary

---

MicroRNAs are a class of small, non-protein-encoding endogenous RNA molecules that exert powerful effects on gene expression by destabilizing transcription and/or repressing translation of target mRNAs. In sharp contrast to the “one gene—one enzyme” paradigm that dominated the beginnings of the field of molecular genetics, the functioning of microRNAs is intricate, with several distinct microRNAs targeting a single type of mRNA and a single type of microRNA targeting more than 100 mRNAs, to varying degrees. The fact that the intricate pathways with which microRNAs and their targets maintain homeostasis—health—have persisted through evolutionary time to be major genomic controls suggests that they have profound functions, which we are just beginning to tease out. The presence of microRNAs in plants and animals, but not fungi or unicellular life, is a testament to their importance in complex body forms. More than 5,000 microRNAs have been identified, mostly in humans and our model organisms.

The human genome sequence encodes hundreds to thousands of microRNAs, and they regulate at least a third of the protein-encoding genes. A typical human cell harbors 1,000 to 200,000 microRNAs, in patterns unique to particular cell types. A mature microRNA, approximately 22 nucleotides long with a distinctive “stem-loop” hairpin secondary structure, is processed from a 70-nucleotide precursor, which, in turn, is cut from a longer primary microRNA. Some microRNAs differ from others, but by only a base or 2, complicating their isolation.

The choreography of target binding has been deduced based on sequence complementarity, even if not all the dancers have been identified. MicroRNAs base-pair with the 3' untranslated regions of mRNA targets, with part of the 5' end forming a “seed” that binds the targets most strongly. The 5' ends tend to be conserved within microRNA families, with the less constrained sequence at the other end the source of microRNA diversity and specificity.

Because microRNAs oversee many aspects of development and physiology, their malfunction may lie behind many illnesses, and their roles beneath our protein-prejudiced radar. Therefore, the potential of tracking microRNA activities or manipulating them to detect, classify, monitor, and even treat disease was apparent from the start—which was not all that long ago.

From an initial unheralded description in 1993 and then a set of stellar foundation papers around the turn of the millennium, microRNAs have been hurtling toward commercialization ever since. However, even though the first diagnostics are set to debut this year—2008—microRNAs are still a fledgling technology that awaits maturation of the science. Companies are beginning to harness the better-studied microRNAs, such as *let-7* and *miR-155*, but not all have been discovered, nor all targets identified.

Despite the remaining questions, microRNAs are riding the wave already set in motion by the field of RNA interference. In a reverse of the chicken-and-the-egg scenario, the small interfering RNAs, which are already a widely used route to control gene expression, may function by mimicking our endogenous microRNAs. Scientists inadvertently discovered a way to imitate what small RNAs were already doing in the cell, and many of those same scientists had been unintentionally discarding said small RNAs.

Recognition of the importance of microRNAs catalyzed development of tools and technologies to ease their investigation. Most have been built on existing capabilities to isolate and analyze RNA, probe expression with microarrays, and stifle expression with oligonucleotides to reveal and isolate function. As more has been learned, bioinformatics prediction tools have evolved, with an oscillation of experiments guiding informatics and then algorithms predicting further discovery. The many kits developed for working with microRNAs have made possible the debut of the first clinical products in less than a decade from the recognition of their discovery. The miRBase database has become a universal clearinghouse for the burgeoning microRNA community.

MicroRNAs will likely enter the clinic as biomarkers and diagnostics, with therapeutic applications awaiting a deeper understanding of microRNA functions and interactions. Most clinical applications are expected to be in oncology, because many microRNAs affect the cell cycle. Half of all human microRNAs discovered so far are expressed

abnormally in at least 1 cancer. Other markets include infectious disease, neurology, metabolic disorders, and cardiovascular disease. In a field that is so aptly described by many clichés, perhaps the best is “tip of the iceberg”; other markets are certain to be recognized.

## Roadmap for This Report

Chapter 1 explores the curious and perhaps unique origin of microRNA science, placing its belated discovery in the context of historical prejudice in favor of protein-encoding genes. Defining criteria and mechanisms are introduced, and the evolutionary significance is considered.

Chapter 2 describes and summarizes the nuts and bolts of working with microRNAs, from isolation to description of function. Chapter 3 deals with clinical applications, which will begin and perhaps remain dominant in oncology, followed by infectious diseases, then neurology, metabolic disorders, and cardiovascular diseases. Chapter 4 pays homage to the youth of the field of microRNAs, with much of the experimental science probing these molecules in various model organisms and cell cultures. Inferring the myriad functions of microRNAs in development and evolution supports the growing appreciation of their importance, while revealing new targets for commercial development.

Chapter 5 evaluates the status of the field, including promises and caveats; categorizes companies; and discusses pertinent patents and intellectual property. Chapter 6 includes interviews with representatives of the types of companies described in Chapter 5: those devoted to microRNAs, those at which microRNAs comprise part of the portfolio, and companies that enable the others. Chapter 7 highlights selected companies that are either developing microRNAs as clinical tools, investigating microRNAs in basic research, or supplying reagents, kits, microarrays, bioinformatics tools, and other essentials.

Finally, the Appendix presents results of an online survey of individuals whose work involves microRNA research and development that was conducted by Insight Pharma Reports in December 2007. The microRNA survey was designed to get at the who, what, where, when, how, and why of this fledgling field that has nonetheless undergone exponential growth since the founding papers were published 7 years ago.

