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RNA INTERFERENCE MARKETS

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Technology and Market Analysis

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1. Overview

1.1 Objectives

The purpose of this report is to review the market for RNA (ribonucleic acid) interference testing equipment and supplies. RNA interference (RNAi) is a mechanism in molecular biology where the presence of certain fragments of double-stranded RNA (dsRNA) interferes with the expression of a particular gene that shares a similar sequence with the dsRNA. This study defines the dollar volume of sales, both worldwide and in the U.S., and analyzes the factors that influence market size and growth for RNAi testing. The main objectives of this study are to:

- Understand the different sectors of the RNAi testing market and to look at a description of the instruments, reagents and supplies marketed by major companies in each segment.
- Obtain a complete understanding of the individual RNAi-testing platforms—from basic principles to clinical applications.
- Discover feasible market opportunities by identifying high-growth applications in different analytical diagnostic areas, with a focus on the biggest and expanding markets.
- Focus on global industry developments and trends through an in-depth analysis of the major world markets for RNAi measurement technology, including growth forecasts.
- Present market figures related to the current value of RNAi testing, market projections, market share, key players and sector growth rates.

Key questions answered in this report include:

- How can RNAi measuring tools and technologies facilitate better research results?
- What are the main types of RNAi-testing technologies that are currently available?
- Who are the key players in this marketplace?
- Which RNAi-testing market areas have the greatest potential for growth?
- What is the current state of the RNAi-testing market?
- Which biotechnology and diagnostic companies are investing in new RNAi-testing technology platform solutions?
- What are the main RNAi-testing business strategies adopted by leading companies?
- What are the benefits of various RNAi-testing technology platforms?

Using this study, readers will be able to:

- Evaluate the effect of strategic factors, such as technology-driven change and industry consolidation.
- Investigate how cost constraints and technological advances are driving change in the RNAi-testing diagnostics market.
- Assess the growth opportunities in all RNAi testing sectors.
- Review the main products in each sector and plan a product entry strategy in line with the strengths and weaknesses of the competition.

1.2 Scope

This report focuses on companies that are actively developing and marketing instrumentation, reagents and supplies for performing RNAi tests. Primary attention has been paid to the technologies and products marketed by major companies for the RNAi market. In addition, the market size, growth rates and market components for the instruments, reagents, controls and consumables used in this area have also been analyzed. Activity and trends in research markets, including the number of institutions that utilize RNAi testing and the factors that influence purchasing, are addressed in this study. Also discussed are trends that have given a fillip to this market and patterns of information processing in different testing instruments.

This examination surveys companies known to market, manufacture or develop instruments and reagents for the RNAi-testing market, both in the U.S. and worldwide for each of the major market segments. Also included are

sections on company history, product lines, business and marketing analyses, and commentaries on the market position of leading companies. This report also contains:

- Detailed analyses of recent trends in the RNAi marketplace.
- In-depth profiles of the leading companies dealing with RNAi tools and technologies.
- A forecast for the RNAi-related market in biotechnology, diagnostic and therapeutic industries.
- Opinions and perspectives on the RNAi-testing industry from leading industry experts.
- Analysis of potential new RNAi-related applications in the clinical sector.
- Market predictions and trend analysis of U.S. expenditures on RNAi-testing solutions.
- The latest industry news and M&A developments in the RNAi-testing marketplace.
- An overview of RNAi-testing business strategies with insights for growth in foreign markets.

Using charts and graphs measuring product growth and trends within the marketplace, this analysis gives company-specific information, including sales figures, product pipeline status and R&D trends. It also attempts to:

- Assess RNAi testing market drivers and bottlenecks from the medical and scientific community perspectives.
- Discuss the potential benefits of RNAi technology for various sectors of the medical and scientific community.
- Establish and analyze the current total size and future growth of the RNAi market and its individual segments.
- Provide current and projected market shares by company.
- Discuss profit and business opportunities by segment.
- Provide strategic recommendations for near-term business opportunities.
- Assess current commercial uses of the RNAi market.

Among other things, this study includes:

- A comprehensive overview of the several categories of RNAi technology platforms that are, or will be, revolutionizing the use of diagnostic tests and therapeutic applications in hospitals.
- A section on each of the important RNAi-testing categories and applications, including reagents, vectors, kits, design tools and custom services.
- Detailed descriptions of the technologies involved and comparisons with the existing and emerging technologies.
- Analyses of the technological approaches undertaken by various competitors, as well as industry and end-user response to these products.
- Market forecasts for each category of product, including profiles of selected competitors.

In addition, readers can get the following insights from this analysis:

- An understanding of the most exciting RNAi market segments, current and future.
- The latest information on leading products and R&D initiatives.
- An overview of the recent developments and their effects on selected markets.
- Knowledge of the RNAi-testing market as an area of growth, research and investment.
- An extensive review of the current market for target validation and development of RNAi-based therapeutics, including strategies, equipment and supplies used by the pharma/biotech industry.

The emphasis in this report is on companies and products that are actively developing and marketing bioscience laboratory instrumentation, reagents and supplies for performing RNAi analysis. The reader should consult other TriMark Publications reports available at www.trimarkpublications.com for detailed information on the important individual market segments that are related to the biotech market, such as molecular diagnostics, DNA sequencing and polymerase chain reaction (PCR), genomics world markets, pharmacogenomic testing, clinical chemistry analyzers and diabetes, metabolic syndrome and cardiovascular disease.

1.3 Methodology

The information in this report is also based upon interviews with sales and marketing professionals of companies in the RNAi marketplace. People from virtually every company mentioned in this study were queried, some several times, about their companies' products and marketing strategies as well as their overall thoughts about their industry segment. Information was also obtained from interviews with chief executive officers, vice presidents, marketing and sales people of many of the companies discussed in the report. The structure of the laboratory facilities was derived from interviews with scientists and technologists working in these areas.

Other sources of information for the study were trade association publications and meetings, product brochures and catalogs and company literature. Where the companies under discussion were publicly held, an examination of the annual reports, 10k filings and financial reports was used as the basis of the data reported. Some of the information obtained for the report was taken from Biotechnology Associates' proprietary databases and from the private data stores of TriMark Publications.

The principal author of this report has served as vice president of business development at DiscoverRx Corporation. Before DiscoverRx, at LJL BioSystems, he served as senior director of business development and played a major role in developing LJL BioSystems' single nucleotide polymorphism (SNP) genotyping business. Subsequent to the acquisition of LJL BioSystems by Molecular Devices Corporation, he ran Molecular Devices' Genomics business. He holds a doctorate in biomedical sciences from the University of Massachusetts Medical School, and completed post-doctoral work at The Rockefeller University in New York and at Harvard Medical School.

Primary Sources: TriMark collects information from hundreds of Database Tables and many comprehensive multi-client research projects and Sector Snapshots that we publish annually. We extract relevant data and analytics from TriMark's research of the past three years as part of this data collection. We also extract qualified data feeds from e-questionnaire responses and primary research responses for this compilation.

Secondary Sources: TriMark uses research publications, journals, magazines, newspapers, news letters, industry reports, investment research reports, trade and industry association reports, government affiliated trade releases, and other published information as part of our secondary research materials.

The information is then analyzed and translated by the Industry Research Group into a TriMark study. The Editorial Group reviews the complete package with product and market forecasts, critical industry trends, threats and opportunities, competitive strategies and market share determinations. The report conclusions are verified through intensive interviewing of top ranking companies in the industry.

TriMark Publications Report Research and Data Acquisition Structure

The general sequence of research and analysis activity prior to the publication of every report includes the following items:

- Completing an extensive secondary research effort on an important market sector, including gathering all relevant information from corporate reporting, publicly available databases, proprietary databases, direct meetings and personal interviews with key personnel.
- Formulating a study outline with the assigned writer, including important items:
 - Market and product segment grouping and evaluating their relative significance.
 - Key competitors evaluations including their relative positions in the business and other relevant facts to prioritize diligence levels and assist in designing a primary research strategy.
 - End-user research to evaluate analytical significance in market estimation.
 - Supply chain research and analysis to identify any factors affecting the market.
 - New technology platforms and cutting edge applications.

- Identifying the key technology and market trends that drive or affect these markets. Assessing the regional significance for each product and market segment for proper emphasis of further regional/national primary and secondary research.
- Launching a combination of primary research activities including two levels of questionnaires, executive-direct focused, company-specific and region-specific communications to qualified and experienced senior executives worldwide.
- Completing a confirmatory primary research assessment of the report's findings with the assistance of Expert Panel Partners from the industry being analyzed.

1.4 Executive Summary

Since its discovery in [REDACTED], the naturally occurring RNAi effect has been acclaimed as the most exciting technical breakthrough in biological research in the last decade. Some industry analysts predict that RNAi may even surpass PCR as a top technology. RNAi allows scientists to silence the expression or effect of a gene under study. This is known as gene knockdown. This field has emerged as a fast-growing new market. The study assesses this emerging commercial marketplace and maps the players on the market landscape.

Initially, pioneering companies produced reagents and kits for the biological research reagents market to support basic and applied research in academia, government and industry. A number of companies then decided to take the long road to developing therapeutics. Others have developed drug delivery approaches for emerging RNAi therapeutics. Some companies have decided to focus on offering RNAi-based target validation products or services for drug discovery to companies, such as large pharmaceuticals or biotech drug discovery firms. Certain other companies are trying alternative approaches, such as making libraries or databases of the results from their experiments. Such content or related services may help researchers see the big picture sooner, at a lower cost.

RNA interference offers tremendous therapeutic promise to silence genes that exhibit aberrant behavior and, therefore, disease. Theoretically, any gene can be targeted for silencing by RNAi; hence, the possibilities are limitless. The principle has already been proven, not only in cell culture but also with major *in vivo* disease-related animal models.

RNAi research is accelerating. Three clinical trials are in progress to determine RNAi's effectiveness for treating age-related macular degeneration. Other clinical indications for which RNAi-based drugs have entered clinical trials include acute renal failure, respiratory syncytial virus (RSV) infection and chronic hepatitis B virus (HBV) infection. Before RNAi came on the scene, finding gene function by knockdown or knockout technology was a laborious and time-consuming process. Many products have already reached the market to test the promise RNAi holds. As RNAi technology progresses, many companies are now trying to increase their shares in the research market by shifting some of their resources to *in vitro* and *in vivo* work. The real prize, however, is in therapeutics, and a few companies have been started solely with this objective. In this context, key points discussed in this report include the following:

- A background is provided on various attempts to silence genes before the advent of RNAi, namely aptamers, antisense and ribozyme. Also discussed are the lessons learned from the failures of antisense clinical trials.
- The promise of tackling diseases using RNAi is evaluated in detail. Included are examples that support this technology, from human cell cultures to pre-clinical models, to the first batch of clinical trials using small interfering RNA (siRNA) in a wide range of diseases—cancer, influenza, malaria, HIV, rotavirus, Huntington's disease and Lou Gehrig's disease.
- Advanced *in vitro* work with cultured cells is examined. Progress made with *in vivo* gene silencing is catalogued, including the latest results in the detection of *in vivo* knockdown in whole mice.

- The problems of RNAi delivery and possible solutions to overcome them are presented from the point of view of leading scientists in academia and pharmaceutical companies.
- The therapeutic potential, specific applications, and advantages and challenges of RNAi are considered, including, in particular, the prospects of improving on the existing treatment modalities for some cancers, such as chronic myelogenous leukemia.

The following market sectors are examined:

- RNAi reagents.
- RNAi delivery tools.
- RNAi screening and analysis tools.

The technologies covered in this analysis include the following:

- Custom, pre-designed or validated siRNA; siRNA sets; genome-wide libraries; short hairpin RNA (shRNA); expression cassettes; micro RNA (miRNA).
- Lipid-based transfection reagents; RNAi-specific transfection reagents; electroporation devices and buffers; viral vectors; nanoparticle technologies.
- Quantitative real-time PCR assays; Northern blot kits; gene expression arrays.
- Western blot kits; 2-D gel electrophoresis consumables; proteomics arrays; phenotypic assays.

Market Overview

The RNAi markets in the U.S. are rapidly evolving. A growing number of scientists are transitioning their research focus from low-throughput to medium- and high-throughput in one dimension, and from *in vitro* to *in vivo* in a second dimension. Numerous opportunities exist for vendors of RNAi content and tools, especially as technologies advance to provide greater selectivity and specificity of knockdown. RNAi technologies are proving to be indispensable tools for functional genomics research and for identifying and validating potential drug targets.

RNAi has become a vital tool for examining both gene and protein expression analyses, especially with regard to understanding the pre- and post-transcriptional function of genes in relation to disease. Using RNAi, researchers are able to simply turn genes on and off and observe what happens, thereby gaining insights into how genes participate in cellular processes. RNAi is, by far, the most widely used gene-silencing technique employed in research.

The U.S. RNAi markets are experiencing a transition to *in vivo* research and a shift toward high-throughput research. This study segments the market in an innovative way with market drivers, market restraints, technology trends, market trends, revenue forecasts, competitive landscape analyses, and market share analyses for the RNAi content market, RNAi delivery tools market, and RNAi screening and analysis tools market. The analysis also offers forecasts about RNAi-related technologies, such as siRNA, shRNA, miRNA, transfection reagents, electroporation devices, viral vectors, nanoparticle agents, gene expression assays, protein assays and phenotypic assays.

Transfecting RNAi into target cells proves to be a significant challenge. Delivering or transfecting RNAi into mammalian cells is one of the biggest challenges facing researchers. In addition, a tedious optimization process is a prerequisite for the transfection of standard cell lines with commonly used lipofection reagents. Successful delivery of RNAi depends on a few key factors, such as the target cell line, RNAi concentration, the ratio of RNAi to the transfection reagent, cell confluence during transfection and incubation time.

Another challenge lies in improving the target specificity of RNAi. In this regard, a well-designed RNAi has greater chances of success in targeting the messenger RNA (mRNA) of interest and minimizing off-target effects. In order to test and compare RNAi sequences, researchers need to monitor and optimize RNAi purity and integrity, its uptake and cell viability. The failure or underperformance of many related technologies has stimulated interest in RNAi projects. After disappointing results from genomic projects involving antisense technologies and ribozyme projects for gene therapy, researchers are looking at RNAi for better results.

Since [REDACTED], the number of published research papers on RNAi has skyrocketed from [REDACTED] to nearly [REDACTED] in [REDACTED]. The potential this technology holds is phenomenal, since it provides a new approach to drug discovery, validation and delivery. Given its recent successes in managing viruses, such as HIV and hepatitis B and C, RNAi holds tremendous potential for rapid drug delivery. RNAi's reach is expected to expand in the future, as it attains the capabilities for treating renal and metabolic disorders, as well as diseases, such as cancers and those pertaining to the central nervous system.

RNAi has moved from the realms of high-throughput screening (HTS) to drug therapeutics. While RNAi expertise currently lies primarily in HTS, the technology is set to begin clinical trials, and RNAi-based drugs might be a reality by [REDACTED]. RNAi therapies that are likely to reach humans first are those targeting macular degeneration, a leading cause of blindness. This disease is caused by over-expression of vascular endothelial growth factor (VEGF) in cells in the back of the eye. The disease has several attributes that make it an ideal RNAi showcase.

The RNAi therapeutic market is estimated to grow to more than \$[REDACTED] by [REDACTED] if the first few RNAi therapies in development, started in [REDACTED], are successful in human clinical trials. RNAi therapeutics will achieve initial traction in the therapeutic areas of anti-infectives and ophthalmology as early as [REDACTED] or [REDACTED], but will expand into cardiovascular, CNS, respiratory and inflammatory disorders, as well as into oncology and diabetes, by [REDACTED].

Key applications for RNAi research in functional genomics are target validation, basic research and therapeutics. The markets for each of these applications are growing rapidly and are expected to continue growing for the next several years. Moreover, since RNAi drug development is still in its infancy, these figures may skyrocket with successful clinical trials.