BY DENISE MYSHKO

» RESEARCH

COMING OF AGE: RNAI TECHNOLOGY

As advances in **GENETICS CONTINUE TO IMPROVE OUR UNDERSTANDING OF DISEASE**, RNAi will have the opportunity to create entirely new classes of medicines.

Researchers say RNA-based therapeutic technology will have a tremendous impact on pharmaceutical research in the next five to 10 years. RNAi (RNA interference) represents a breakthrough in understanding how genes are turned on and off in cells.

"RNAi is a transformative discovery in modern biology that has already revolutionized biomedical research," says John Maraganore, Ph.D., CEO of Alnylam Pharmaceuticals. "But the real opportunity with RNAi is to discover entirely new classes of medicines for patients. With RNAi therapeutics, we can harness the RNAi pathway and silence disease-causing genes that were previously 'undruggable' with today's medicines."

Using RNAi, it's possible to silence any given gene, says Louis Renzetti, Ph.D., VP and global head, RNA therapeutics, at Roche.

"Many diseases are the result of the expression of undesired genes or mutated and overexpressed genes — for example, many forms of cancer — so by harnessing RNAi, those target genes can be 'turned off' before their corresponding harmful proteins are produced," he says. "As such, RNAi has the potential to treat disease and help patients in a fundamentally new way."

Jim Jenson, Ph.D., CEO of Dicerna Pharmaceuticals, says because RNAi therapeutics are based on gene sequence and not protein structure, any disease-causing gene is a potential target.

"There is tremendous potential for the broad application of this technology," he says. "Over the last century, advancements in the pharmaceutical industry have been limited to only a few hundred targets. RNAi opens up thousands of new targets to therapeutic intervention. We are confident that therapeutic approaches with RNAi will allow us to intervene much earlier in the progression of a disease than is currently possible in an effort to head off the devastating effects of diseases, rather than just treat those effects."

RNAi therapeutics are forecast to generate sales of about $1 billion by 2015.

BUSINESS INSIGHTS

RNAI AT A GLANCE

The Nobel Prize was awarded in October 2006 to Andrew Z. Fire and Craig C. Mello for their discovery of RNA interference: gene silencing by double-stranded RNA.

By harnessing the natural biological process of RNAi occurring in human cells, the creation of a major new class of medicines, known as RNAi therapeutics, is on the horizon.

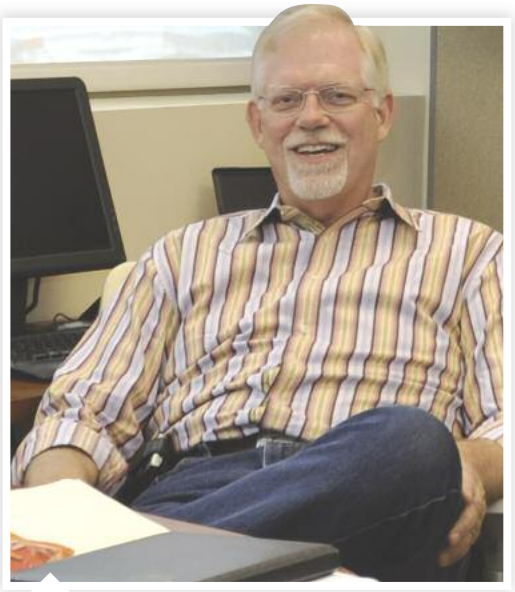
RNAi therapeutics target the cause of diseases by potently silencing specific messenger RNAs (mRNAs) and preventing disease-causing proteins from being made. RNAi therapeutics have the potential to treat disease and help patients in a fundamentally new way.

THE MARKET

The total RNAi therapy market is projected to be valued at $1 billion by 2015, according to a Business Insights report.

Pharma companies are increasingly investing in siRNA (small interfering RNA) optimization or examining siRNA alternatives, in addition to staking out proprietary positions in lipid-based, nanotransporter-based, and alternative delivery technologies. The development and licensing of such platforms will become crucial for developers over the coming years.

Research of RNAi targets is being actively pursued; there are 97 RNAi agents in development and 37 RNAi-based companies, according to Business Insights.



Dr. Jim Jenson
Dicerna Pharmaceuticals

"RNAi opens up thousands of new targets to therapeutic intervention. We are confident that therapeutic approaches with RNAi will allow for a much earlier intervention in the progression of a disease."

THE CHALLENGES

Over the last decade, RNA biology has emerged as a promising and important area of drug discovery and development, but our experts agree that delivery of RNA is the primary challenge.

"Effective targeted delivery and overcoming stigmas associated with the real potential of the technology are the challenges involved with RNA-based therapies," says Daniel Zurr, Ph.D., CEO and president of Quark Pharmaceuticals.

The challenges and risks presented with RNA technology are similar in many regards to all drug discovery and research and development efforts, says Kleanthis Xanthopou-

Dr. Stuart Peltz
PTC Therapeutics

"A significant challenge of RNAi is the translation of the research into the development of viable treatments because of the high cost of manufacturing."

Dr. Kleanthis Xanthopoulos
Regulus Therapeutics

"In many diseases, the disease-causing protein is refractive to traditional approaches, making it 'undruggable.'"

Dr. Louis Renzetti
Roche

"Effective and safe siRNA delivery still represents the primary bottleneck to achieving therapeutic success using RNAi. However, each year, delivery continues to improve."

Dr. John Maraganore
Alnylam Pharmaceuticals

"The molecular delineation and redefinition of human disease will change the overall treatment paradigm for all therapeutic modalities. RNAi has the potential to translate into more impactful therapeutics for patients."

los, Ph.D., president and CEO of Regulus Therapeutics.

"Since RNA therapeutics are based on RNA targeting, either mRNA or microRNA, the main challenges include broad delivery to all tissues or targeted delivery to certain tissue types," he says.

"To date, much of the R&D activity has focused on RNAi and antisense, but the method of delivery still needs to be addressed," says Stuart Peltz, Ph.D., president and CEO of PTC Therapeutics. "RNA-based therapies, such as RNAi, will continue to be important, but approaches other than RNAi may result in new products for patients sooner.

"The most significant challenge of RNAi is the translation of the research into the development of viable treatments because of the high cost of manufacturing and the inherent challenges of drug delivery with such large molecules," Dr. Peltz continues. "Other approaches, such as post-transcriptional control, which rely on small molecule pharmaceuticals may benefit patients sooner." ✦

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EXPERTS ON THIS TOPIC

JIM JENSON, PH.D. CEO, Dicerna Pharmaceuticals, a private, venture-backed biopharmaceutical company developing novel therapeutic agents using proprietary technology that triggers RNA interference. For more information, visit dicerna.com.

JOHN MARAGANORE, PH.D. CEO, Alnylam Pharmaceuticals Inc., a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. For more information, visit alnylam.com.

STUART W. PELTZ, PH.D. President and CEO, PTC Therapeutics Inc., a biopharmaceutical company focused on the discovery, development, and commercialization of orally administered, proprietary, small-molecule drugs that target post-transcriptional control processes. For more information, visit ptcbio.com.

LOUIS M. RENZETTI, PH.D. VP and Global Head, RNA Therapeutics, Roche, a research-oriented healthcare group with core businesses in pharmaceuticals and diagnostics. For more information, visit rocheusa.com.

KLEANTHIS G. XANTHOPOULOS, PH.D. President and CEO, Regulus Therapeutics Inc., a biopharmaceutical company aiming to discover, develop, and commercialize microRNA-based therapeutics. For more information, visit regulusrx.com.

DANIEL ZURR, PH.D. CEO and President of Quark Pharmaceuticals Inc., a development-stage pharmaceutical company discovering and developing novel RNAi-based therapeutics. For more information, visit quarkpharma.com.

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» RESEARCH

CURRENT RNA RESEARCH EFFORTS

RNA INTERFERENCE CONTINUES TO OFFER SIGNIFICANT PROMISE

for a host of therapeutic treatments.

Pharma companies are increasingly investing in siRNA optimization or examining siRNA alternatives, in addition to staking out proprietary positions in lipid-based, nanotransporter-based, and alternative delivery technologies. The development and licensing of such platforms will become crucial for developers in the coming years.

RNAi research is active; there are about 155 companies involved in developing RNAi technologies, in addition to more than 200 collaborations, according to a recent report by Jain Pharmabiotech. Out of these, 30 are developing RNAi-based therapeutics, and 25 are involved in microRNAs. Below are selected ongoing RNAi development programs.

ALNYLAM PHARMACEUTICALS

John Maraganore, Ph.D.
Alnylam Pharmaceuticals

"Alnylam and collaborators have made significant progress over the years, demonstrating the ability with both direct and systemic administration to mediate RNAi in clinically relevant settings."

Alnylam's lead program, ALN-RSV01, is being developed for the treatment of respiratory syncytial virus (RSV) infection. This therapeutic was designed to target the gene that is required for the replication of the RSV. ALN-RSV01 silences this gene, thereby reducing the virus' ability to reproduce.

In July 2009, along with partner Cubist, the company reported the complete data from a Phase II study in adult lung transplant patients naturally infected with RSV. Overall, the study achieved its primary objective of demonstrating safety and tolerability of ALN-RSV01. In particular, there were no drug-related serious adverse events or discontinuations, and there were no clinically significant differences in the overall adverse event profile between ALN-RSV01 and placebo.

The partnership with Cubist is structured as a 50/50 co-development and profit-share arrangement in North America and a milestone- and royalty-bearing license arrangement in the rest of the world. The ALN-RSV program is in partnership with Kyowa Hakko Kirin Co. Ltd. in Asia.

DICERNA PHARMACEUTICALS

Jim Jenson, Ph.D.
Dicerna Pharmaceuticals

"At Dicerna, we are focusing on using DsiRNAs that can be conjugated to targeting moieties such as peptides, antibody fragments, aptamers, small molecules, or in other ways to provide targeted molecular therapies."

Dicerna is developing novel therapeutic agents in multiple therapeutic areas based on its proprietary Dicer Substrate Technology, which triggers RNA interference (RNAi) in a potent and specific manner. The company's proprietary Dicer Substrate Technology and dicer substrate RNA (DsiRNA) molecules use an earlier step in the gene slicing process.

"This results in the knockdown of the expression of a targeted gene in a way that is highly selective, leading to greater potency and longer duration of action than other RNAi approaches," says Jim Jenson, Ph.D., CEO of Dicerna Pharmaceuticals. "Dicerna's DsiRNA can link to a variety of tissue or cell targeting agents — aptamers, peptides, MAbs, lipid-based nanoparticles, etc. — providing multiple options for delivering drug candidates to the intended target. Our focus is initially in the areas of oncology and metabolic diseases."

He says a recent collaboration with Archemix exemplifies this approach.

"We are collaborating on DsiRNA-aptamer therapeutics, which leverage the potent gene silencing of our DsiRNA molecules and the intracellular delivery capabilities of Archemix's aptamers," Dr. Jenson adds. "This collaboration points to the unique adaptability of our DsiRNA molecules to a number of targeting and delivery approaches, which we believe to be an important benefit of RNAi therapeutics."

Aptamers are synthetically derived oligonucleotides, or short nucleic acid sequences, that bind to protein targets with high affinity and specificity and can be designed to have a specified duration of action. DsiRNA-aptamer conjugates represent an emerging class of potential therapeutic agents that could have broad application to treat a variety of human diseases.

PTC THERAPEUTICS

Stuart Peltz, Ph.D.
PTC Therapeutics

"We are positioned to be one of the first companies to successfully bring to market a product explicitly developed to target the emerging field of RNA biology."

PTC Therapeutics approaches RNA biology by developing small molecules that target a series of processes collectively referred to as post-transcriptional control.

"Our approach has generated multiple clinical-stage programs, including ataluren, which is in pivotal stage trials for nonsense mutation Duchenne muscular dystrophy and cystic fibrosis," says Stuart Peltz, Ph.D., president and CEO of PTC Therapeutics. "PTC299 is in Phase I and II trials for several tumor types."

Post-transcriptional control mechanisms are all of the regulatory events that take place after a messenger RNA (mRNA) molecule is

copied from DNA (i.e., after the transcription process). These mechanisms include the decoding of the mRNA molecule so that a protein is synthesized, the determination of how efficiently an mRNA is used to make protein, and how long an mRNA lasts in a cell. PTC's approach is to discover and develop small-molecule drugs that affect — inhibiting or enhancing — protein production by targeting post-transcriptional control mechanisms.

Small molecules that target post-transcriptional control to either up- or down-regulate protein production may have the potential to treat a variety of diseases, including genetic disorders, cancer, anemia, and inflammation that can result from the production of too much or too little of a particular protein.

PTC has an exclusive collaboration with Genzyme Corp. for the development and commercialization of ataluren. PTC has collaborations with other companies, including a research collaboration and licensing arrangement with Gilead for the development of orally bioavailable small molecules through the application of PTC's proprietary GEMS (Gene Expression Modulation by Small-molecules) technology; an exclusive research collaboration and licensing agreement with Pfizer for the development of pharmaceuticals through the application of GEMS; and a $200 million collaboration with Schering-Plough for the development and commercialization of the compounds in the hepatitis C program.

QUARK PHARMACEUTICALS

Daniel Zurr, Ph.D.
Quark Pharmaceuticals

"Our areas of expertise and success have been in systemic delivery in humans, limiting off-target effects, and the recent clinical-stage advancement of products."

Quark is engaged in siRNA drug discovery and development.

"We have an advanced clinical-stage program, which includes multiple Phase II trials and the highest number of products in the business being tested in humans," says Daniel Zurr, Ph.D., CEO and president of Quark Pharmaceuticals.

The company has partnered with Pfizer and initiated patient dosing in a Phase II trial evaluating PF-4523655 (RTP801i-14) in patients with diabetic macular edema. PF-4523655 was designed to inhibit Quark's proprietary target RTP801, a gene involved in abnormal blood vessel development and leakage in the eye.

The company is progressing with a Phase I/IIa clinical trial of AKIi-5 for prevention of acute kidney injury in patients undergoing major cardiac surgery. In June 2008, the FDA approved an IND for the drug candidate DGFi, having the same active ingredient, for treatment and prevention of delayed graft function in kidney transplantation patients.

REGULUS THERAPEUTICS

Kleanthis Xanthopoulos, Ph.D.
Regulus Therapeutics

"Regulus is targeting microRNAs in several therapeutic areas, including immune-inflammation, fibrosis, oncology, hepatitis C infection, and metabolic diseases."

Regulus was established by Alnylam Pharmaceuticals and Isis Pharmaceuticals in September 2007 to discover, develop, and commercialize microRNA-based therapeutics.

"The company is working with a broad network of academic collaborators and pharmaceutical partners," says Kleanthis Xanthopoulos, Ph.D., president and CEO of Regulus Therapeutics.

In April 2008, GlaxoSmithKline and Regulus Therapeutics announced a microRNA-focused strategic alliance to discover, develop, and commercialize novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory disease. The deal is valued at about $600 million.

MicroRNAs represent a new approach for the treatment of human disease. Many RNAs, such as messenger RNAs (mRNAs), are transcribed from genes and are used to make proteins through the process of translation. Like mRNAs, microRNAs are also transcribed from genes. But these small RNA molecules do not encode proteins; instead they regulate the expression of other genes. MicroRNAs function by preventing the translation of mRNAs into proteins and/or by triggering their degradation.

Regulus is developing a portfolio that is built on microRNA biology, chemistry, and informatics to support several therapeutic programs in oncology, immunology-inflammation, and metabolic diseases.

ROCHE

Roche scientists are focused on advancing RNA molecules as novel therapeutics for the treatment of disease at three sites: Nutley, N.J.; Kulmbach, Germany; and Madison, Wis. The goal is to discover and develop siRNA for respiratory, oncology, and metabolic indications, and bring an RNAi therapeutic into the clinic by 2010.

Louis Renzetti, Ph.D.
Roche

"Our three global RNA centers are focusing on the potential therapeutic benefits of applying RNAi to silence individual genes in the body, thereby stopping disease progression."

According to Louis Renzetti, Ph.D., VP and global head, RNA therapeutics at Roche, the robust way in which RNAi prevents a gene from generating the protein that its codes has already made it a critical tool in drug discovery.

Dr. Renzetti says Roche is also using key technologies for siRNA delivery to advance drug discovery. These include Dynamic Poly-Conjugates (DPC) technology, which is being refined as an enabling nanotechnology platform for siRNA therapeutics.

"DPC makes it possible to target previously undruggable targets, represents a first-in-class polymer-based nanoparticle that allows for targeted delivery of siRNAs to various cell types in the body, and has great potential for many diseases," he says. "In addition, SNALP technology, developed by Tekmira, has been shown to be a safe and effective way to deliver RNAi drugs to disease sites."

Roche also has an active collaboration on Spiegelmers, a novel and proprietary form of RNA aptamers (peptide molecules that bind to a specific molecule), to block protein-protein interactions of inflammatory cytokines (proteins released by the immune system).

In 2008, Roche acquired Mirus Bio Corp. (now Roche Madison), a company that focuses on the discovery and development of innovative nucleic acid-based technologies, including a proprietary RNAi delivery platform (DPC). Mirus' delivery platform provides an innovative way of effectively getting RNAi therapeutics to specific disease targets.

Additionally, Roche recently gained access to new classes of therapeutics based on ribonucleic acids through an alliance with Alnylam. With global efforts around the Center of Excellence for RNA Therapeutics in Germany, Roche focuses on the discovery and development of therapeutics using RNAi for the treatment of oncological, respiratory, and metabolic diseases. ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.