Gene Silencing with RNAi

Keeping Up with Biotechnology Innovation

Gene Silencing with RNAi
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Modern biotechnology has been revolutionizing the pharmaceutical industry for three decades, ever since the first synthesis of human insulin in 1978. Groundbreaking innovations such as recombinant DNA, therapeutic proteins, monoclonal antibodies, and novel vaccines have grown the market for biologics to 23% of all pharmaceutical sales in 2008, or nearly $80 billion. Furthermore, future growth of the pharmaceutical industry will be primarily driven by biologics, which have a projected annual growth rate of over 10% through 2012, compared to about 1% for small molecule drugs (see Exhibit 1)\(^1\).

Given the tremendous growth of the biologics market, it comes as no surprise that shrewd investments in new biotechnology innovations have been central to the strategies of some of the most successful pharmaceutical companies in the last two decades. For instance, by investing in monoclonal antibodies early, Roche positioned itself to become one of the fastest growing big pharma companies in the world. By pioneering development of therapeutic proteins, Amgen has built itself into the largest biotech company in the world by revenue.

Today, other pharmaceutical companies are looking ahead and making investments in emerging biotechnology innovations, with hopes of achieving the same type of success Roche and Amgen have enjoyed with monoclonal antibodies and therapeutic proteins. For example, in December 2006,罗切特 positioned itself to become one of the fastest growing big pharma companies in the world. By pioneering development of therapeutic proteins, Amgen has built itself into the largest biotech company in the world by revenue.

In this article, we take an in-depth view of RNAi gene-silencing technology to illustrate how to invest intelligently in biotechnology innovation. Proclaimed as the “breakthrough of the year” in 2002 by Science magazine, RNAi is an emerging therapeutic class with the potential to effectively combat viral infections, cancer, and many genetic diseases. We show how thorough scientific, commercial, and strategic assessments of the technology are prerequisites to any informed investment.

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\(1\) Datamonitor, “The Pharmaceutical Company Outlook to 2012” (December 26, 2007)
GSK entered into a partnership with Genmab valued at up to $2.1 billion to access a proprietary drug discovery platform based on 3D modeling of protein targets and has followed that with a series of additional investments. In November 2007, Sanofi-Aventis initiated a collaboration with Regeneron valued at up to $1.1 billion to develop fully-human therapeutic antibodies. In January 2008, Genzyme entered into an alliance with ISIS pharmaceuticals valued at up to $1.9 billion to access antisense gene-silencing technology, and the list goes on (see Exhibit 2).

RNAi: The Next Big Thing?

To better explore the intricacies of investing in biotechnology innovation, we are going to focus on one of the most exciting technologies that has emerged in recent years – RNA interference (RNAi). RNAi is a natural cellular process designed to suppress virus replication. The basic mechanism is simple: viruses replicate by hijacking cells to create unique viral proteins, which requires intermediate molecules known as messenger RNA (mRNA). When a cell detects the presence of double strand RNA (dsRNA), the genetic material of many viruses, it recognizes that it is likely under attack. To defend itself, cells have developed a natural mechanism, RNAi, that allows them to target and destroy viral mRNA, thus interfering with the protein expression of those viruses.

Unfortunately, viruses are highly adaptable from an evolutionary standpoint, so almost all surviving viruses affecting humans today have proteins that shut off the RNAi response. Consequently, the human body’s primary response to viruses now comes from the immune system, which is distinct from RNAi. However, RNAi is still important because modern biotechnology has provided the tools necessary to “trick” the cell into attacking a virus through RNAi.

Since 1998, when RNAi was initially discovered, the therapeutic potential of this technology has generated significant excitement within the medical community. Scientists have had early success in manipulating the RNAi mechanism to do more than fight viruses—it can also be used to silence disease-causing genes, fight other foreign pathogens, and combat almost any disease that is caused by an excess of harmful proteins. Today, RNAi-based therapies are in development for viral infections (e.g., hepatitis, HIV, influenza), cancer, diabetes, neurological diseases, autoimmune diseases, and a variety of genetic disorders.

Exhibit 2: Major Investments in Biotechnology Platforms

2006 to 2008

<table>
<thead>
<tr>
<th>Partners</th>
<th>Date</th>
<th>Technology</th>
<th>Potential Deal Value ($B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK - Genmab</td>
<td>Dec. 2006</td>
<td>Fully Human Monoclonal Antibodies</td>
<td>$2.1</td>
</tr>
<tr>
<td>Genzyme - ISIS</td>
<td>Jan. 2008</td>
<td>Antisense Gene-Silencing</td>
<td>$1.9</td>
</tr>
<tr>
<td>Celgene - Acceleron</td>
<td>Feb. 2008</td>
<td>Bone Morphogenetic Proteins (BMPs)</td>
<td>$1.9</td>
</tr>
<tr>
<td>Boehringer Ingelheim - Ablynx</td>
<td>Sep. 2007</td>
<td>Nanobody Therapeutic Proteins</td>
<td>$1.8</td>
</tr>
<tr>
<td>GSK - Targacept</td>
<td>Jul. 2007</td>
<td>Neuronal Nicotinic Receptor (NNR) Therapeutics</td>
<td>$1.6</td>
</tr>
<tr>
<td>GSK - ChemoCentryx</td>
<td>Aug. 2006</td>
<td>Chemokine-Based Therapeutics</td>
<td>$1.5</td>
</tr>
<tr>
<td>GSK - OncoMed</td>
<td>Dec. 2007</td>
<td>Cancer Stem Cell Antibody Therapeutics</td>
<td>$1.4</td>
</tr>
<tr>
<td>BMS - Adnexus</td>
<td>Feb. 2007</td>
<td>Oncology Protein Therapeutics</td>
<td>$1.3</td>
</tr>
<tr>
<td>GSK - EPIX</td>
<td>Dec. 2006</td>
<td>3-D Modeling of Protein Targets</td>
<td>$1.2</td>
</tr>
<tr>
<td>Merck - ARIAD</td>
<td>Jul. 2007</td>
<td>Cell-Signaling Regulation</td>
<td>$1.1</td>
</tr>
<tr>
<td>Janssen - Galapagos</td>
<td>Oct. 2007</td>
<td>Adenoviral-Based Drug Discovery Platform</td>
<td>$1.1</td>
</tr>
<tr>
<td>Sanofi - Aventis - Regeneron</td>
<td>Nov. 2007</td>
<td>Fully-Human Therapeutic Antibodies</td>
<td>$1.1</td>
</tr>
<tr>
<td>GSK - Synta</td>
<td>Oct. 2007</td>
<td>Oxidative Stress Anti-Tumor Therapeutics</td>
<td>$1.1</td>
</tr>
<tr>
<td>Merck - Sirna</td>
<td>Oct. 2006</td>
<td>RNAi</td>
<td>$1.1</td>
</tr>
</tbody>
</table>
When considering making an investment in a novel biotechnology platform, the first step is to build a detailed understanding of the science to better assess the potential applications, limitations, and challenges of the technology. As previously discussed, RNAi-based therapies could potentially treat any disease that is caused by an excess of harmful proteins. However, this also highlights the key limitation of the technology—that it will not be able to fight diseases caused by the absence or mutation of an important gene that causes the lack of a beneficial protein. Such diseases include cystic fibrosis, Tay-Sachs disease, and sickle-cell anemia.

Today, there are still a number of prominent technical challenges to RNAi therapy design, most notably overcoming potential adverse effects caused by the interferon and sequence effects. The interferon effect occurs when the immune system misinterprets an RNAi therapy as an infection, triggering an immune response resulting in cell death. The sequence effect occurs when the sequence of the targeted mRNA occurs elsewhere in the genome, in which case the RNAi might accidentally destroy mRNA coding for beneficial proteins needed for healthy cell function. Due to the seriousness of these side effects, some RNAi players have turned to bioinformatics to custom design RNAi therapies that avoid the interferon and sequence effects. Beyond preventing adverse effects, there are three other scientific challenges that any company looking to develop an RNAi-based therapy must address. First, the stability of RNAi needs to be improved, as natural RNAi molecules are rapidly broken down by the cell, limiting their therapeutic efficacy. Second, better RNAi delivery platforms are needed, as natural RNAi is not readily taken up by cells and targeted delivery is challenging. Third, the mRNA sites that serve as the target for RNAi need to be carefully chosen, as improper target selection reduces or eliminates efficacy (see Exhibit 3).

**Exhibit 3: Potential Scientific Challenges to RNAi Based Therapy**

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Side Effects**   | • Therapy may be misinterpreted by the immune system as an infection (interferon effect)  
• RNAi attacks all RNA with target sequence, regardless of source, interfering with the replication of “good” genes/proteins (sequence effect) |
| **Instability**    | • Breaks down in the cell in minutes  
• Half-life < 1 minute  
• Limits medical efficacy |
| **Delivery**       | • RNAi not readily taken up by cells  
• Specific delivery is challenging |
| **Target Identifications** | • Because mRNA sites are limited (e.g., short segments with limited number of base pairs), identifying “unique” targets is a challenge  
• Improper target selection reduces/eliminates efficacy and can result in serious side effects |
How Much Is It Worth?

When assessing the potential value of a novel biotechnology platform, understanding the market context is just as important as understanding the science, since both have a significant impact on shaping the commercial opportunity. As with other new therapeutic technologies, RNAi will face competition from existing technologies, including other gene-silencing technologies, and established therapies for its target diseases.

There are a handful of gene-silencing technologies, with mechanisms ranging from mRNA blockage (e.g., antisense, pepetide nucleic acid, and locked nucleic acid) to protein blockage (e.g., aptamers) and mRNA cleavage (e.g., ribozymes, and RNAi). Of these, however, only RNAi-based therapies take advantage of a process already present in human cells. This distinction offers two advantages: first, effective doses of RNAi-based therapies are less toxic than those of other gene-silencing technologies, thus significantly improving safety. Second, the RNAi mechanism offers superior gene-specificity, making it more effective than other gene-silencing technologies.

Given the large investments required to develop novel therapies, most RNAi-based candidates in the pipeline are targeting significant medical needs that are not met by existing therapies. These include a number of diseases currently lacking effective treatments like cancer, age-related macular degeneration, Huntington’s disease, and chronic hepatitis. As a result, the commercial potential for RNAi-based therapies is significant.

Specifically, the market for RNAi-based therapies across all targeted disease areas is projected to surpass $10 billion by 2015 (see Exhibit 4)\(^2\). The market opportunity, along with the competitive landscape, cost of development, and probability of success, will determine the expected return on any potential investment in RNAi or other novel technology platforms. It is important to note, however, that decisions to invest in novel biotechnology platforms cannot be made in a vacuum—the strategic implications of the investment for the company must also be considered.

\(^2\) Jain Pharmabiotech, “RNAi: Technologies, Companies, and Markets” (April 2007)

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**Exhibit 4: RNAi Therapy Market Projections**

2006 to 2015

<table>
<thead>
<tr>
<th>Market Size ($MM)</th>
<th>2006 Market</th>
<th>2010 Market (Projected)</th>
<th>2015 Market (Projected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0</td>
<td>$100</td>
<td>$3,500</td>
<td>$10,500</td>
</tr>
<tr>
<td>$2,000</td>
<td></td>
<td>$750</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>$8,000</td>
<td></td>
<td>$1,500</td>
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</tr>
<tr>
<td>$10,000</td>
<td></td>
<td>$1,300</td>
<td></td>
</tr>
<tr>
<td>$12,000</td>
<td></td>
<td>$2,400</td>
<td></td>
</tr>
</tbody>
</table>

- All Other Disorders
- AMD and Other Eye-Related Neurological Disorders
- Cancer
- Infections including Viruses
Is Investment Strategically Sound?

There are two strategic considerations that will inform any potential investment in novel biotechnology platforms. First, how does the investment align with the company’s current goals, assets, and core capabilities? Companies need to evaluate what impact the investment would have on their near- and long-term growth goals, therapeutic area focus, and level of vertical integration. In 1990, when Roche took a majority stake in Genentech, it did so as a long-term investment to solidify a successful biologics development collaboration dating back to 1980. Genentech’s sales at the time were insufficient to support the large R&D spending needed to develop its pipeline of monoclonal antibodies, so Roche provided a critical $492 million cash infusion. Furthermore, Roche structured the deal to keep Genentech as an independent entity to avoid integration disruptions at that critical point in Genentech’s development, but acquired the ex-U.S. rights to Genentech products to leverage its global commercialization infrastructure. Whereas Roche lacked internal biologics R&D capability, it had strong global sales and marketing skills making this a mutually beneficial deal.

The second strategic question is: what additional investments/acquisitions will be needed to achieve success? To maximize the value of the initial investment, companies will often need to strengthen their intellectual property portfolio, scale-up manufacturing capabilities, and/or create a specialized sales force. While Amgen’s growth has been driven primarily by a series of blockbuster therapeutic proteins, including Epogen, Neupogen, and Aranesp, even it chose to consolidate its position in the therapeutic protein market by acquiring Immunex in 2002. The deal not only gave Amgen control of Enbrel, an anti-inflammatory therapeutic protein that achieved $4.4 billion in 2006 worldwide sales, but also an experienced specialty arthritis sales force, promising pipeline products, and a proprietary bioinformatics-based drug discovery system.

How Do We Invest?

Once a company decides that a novel biotechnology platform is worth investing in, the key question becomes “how to play?” Investments in novel technologies can take many forms—development collaborations, joint ventures, product licenses, technology licenses, or outright acquisitions, each offering different risk/reward trade-offs. To determine which type of investment is most appropriate, it is important to understand the three basic ways to play:

“Integrated Players” are typically larger biotech or pharmaceutical companies that build internal capabilities to discover, develop, and ultimately commercialize drugs using the new technology platform.

In the RNAi market, integrated players include Alnylam, Merck, and Opko.

“Piece Players” are typically small biotech firms that focus on solving one piece of the puzzle, with the plan of licensing that solution to larger players, or being acquired. An example of a piece player in the RNAi market is Cequent, which is developing a solution to the delivery challenge. Through genetic engineering of E. coli, Cequent hopes to achieve highly specific delivery of RNAi to the gastrointestinal tract. Other piece players developing solutions to the four key scientific challenges include Benitec and CytRx.

“Rich Uncles” are typically large pharmaceutical companies that make limited investments through collaboration or licensing deals with smaller integrated and/or piece players to gain access to the technology platform. If these initial investments deliver promising results, the company may then ramp up its investments and become an integrated player. Merck followed this strategy by making an early purchase of Rosetta, followed by licensing RNAi products and technology from Alnylam and Benitec in 2003-2004 as a rich uncle, and later becoming a fully integrated player through its $1.1 billion acquisition of Sirna in 2006.
With regard to RNAi, large pharmaceutical companies including Pfizer, GSK, Sanofi-Aventis, AstraZeneca, Novartis, Roche, Abbott, and Takeda have initially chosen the rich uncle approach for investing in this technology platform. This approach allows players to gain a foothold in the RNAi market while limiting the potential for large losses if the technology fails to meet expectations. However, the drawback is that if the technology is successful, the rich uncle approach limits the upside and will ultimately deliver lower profits than acquiring the technology at an early stage. Furthermore, this approach provides limited development of internal expertise with the technology, and project success becomes largely dependent on the partner’s performance.

Industry trends indicate that biotechnology innovation will continue to drive growth within the pharmaceutical industry, and from the example of RNAi, it is clear that many companies are investing in novel technologies to profit from “the next big thing.” To succeed in this competitive environment, companies will need to expand their business development capabilities to be able to critically evaluate opportunities driven by new technologies. This means building an internal team and advisory network capable of understanding the scientific, commercial, and strategic implication of investing in these novel biotechnology platforms.

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DEAN & COMPANY
8065 Leesburg Pike, 5th Floor
Vienna, VA 22182
703.506.3900
www.dean.com
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