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Unlocking the money-making potential of RNAi

Ken Howard

Bigger than monoclonal antibodies? More powerful than antisense? Biotech investors say…maybe.

If a biological process could be said to be a media darling, RNA interference (RNAi) would be it. The naturally occurring process of RNA suppression of gene activity within a cell (also referred to as small interfering RNA or siRNA) is now being harnessed for target identification and validation and developed as a possible powerful new therapeutic class. Coming into its own, hard on the heels of the 50th anniversary of the discovery of the DNA double helix, and in the biotechnology trough following the 2000 boom, perhaps it was the next logical biological application to come into the spotlight. But is the media—together with scientists and investors—that has recently showered the technology with praise just looking for some excitement in the morning after the biotech party, or might RNAi truly be the 'next big thing,' and along the way perhaps even make some money?

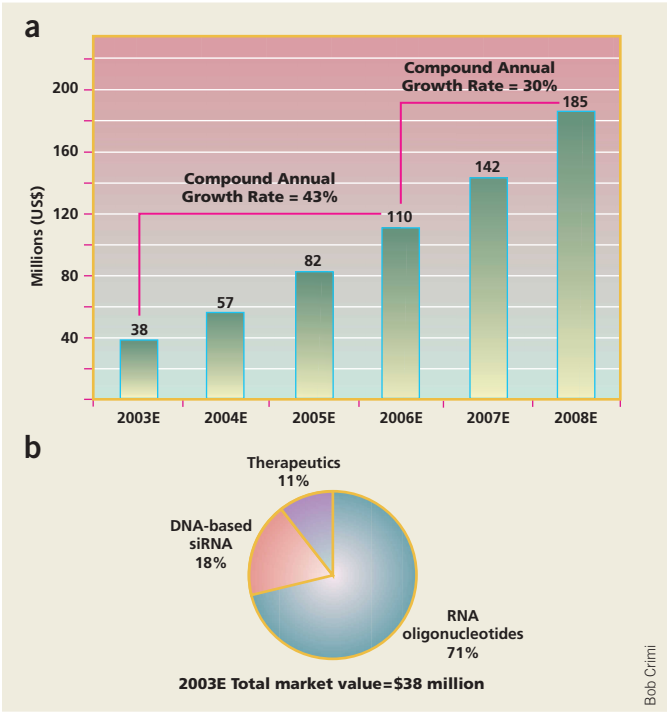

Figure 1 Estimated annual worldwide revenues from RNAi and market segments. (**a**) Although the market for RNAi is new and relatively small, rapid growth has been seen and is projected to continue until 2008 as the potential is realized. (**b**) RNAi market segments. The size of the market reflects the time of adoption—oligonucleotides being the first method employed, followed by vector-based applications. 'Therapeutics,' which includes using RNAi for drug discovery, is relatively new. (Figure from ref. 1; courtesy of Front Line Strategic Consulting, San Mateo, CA, USA).

Emergence of a laboratory tool

Since RNA interference was first described in the late 1990s, the technology has been rapidly adopted in laboratories around the world. "Momentum's built because people perceive that this really does work," explains John Berriman, a director at venture capital firm Abingworth Management Limited (London). "So far, nobody's burst the bubble."

There is also excitement because RNAi could be used as the basis for a new class of therapeutics; Berriman estimates that such therapeutics could eventually capture as much as 10% of the drug market. This, he and others believe, could translate into billions of dollars in a market that sees revenues of hundreds of millions of dollars annually for some drugs. But even if some RNAi-based molecules do show promise, most observers think that they will not make it through clinical trials and Food and Drug Administration (FDA; Rockville, MD, USA) approval until 2008 at the earliest and more likely 2013. And in the process of getting there, the most optimistic estimates do not put RNAi-based molecules into phase 1 clinical studies, a milestone and an indicator of the promise of the technology, until between late 2004 and 2005.

In the meantime, money is already being made. The market for RNAi-based products—including siRNA, RNA oligonucleotides and DNA vectors encoding siRNA—is estimated to be $38 million for 2003, according to Front Line Strategic Consulting (San Mateo, CA, USA). They project that market will reach $185 million by 2008 (ref. 1; **Fig. 1**).

"Every pharma is using RNAi based on [Tom] Tuschl patents, all are buying reagents based on the patents," says Polaris' Westphal. Westphal was the startup CEO and Polaris' investment lead in the RNAi therapeutics company Alnylam Pharmaceuticals (Cambridge, MA, USA), of which Tom Tuschl is a cofounder and scientific advisor (see **Table 1** for RNAi companies' lineages.) In July, Alnylam merged with another RNAi company, Ribopharma (Kulmbach, Germany), to form Alnylam Holding Company (Cambridge, MA, USA), which now boasts a broad spectrum of technology in the field.

RNAi, validated as a technology in academic laboratories and then by biotech and pharmaceutical companies, has become a mainstream tool. "RNAi wasn't used in mam-

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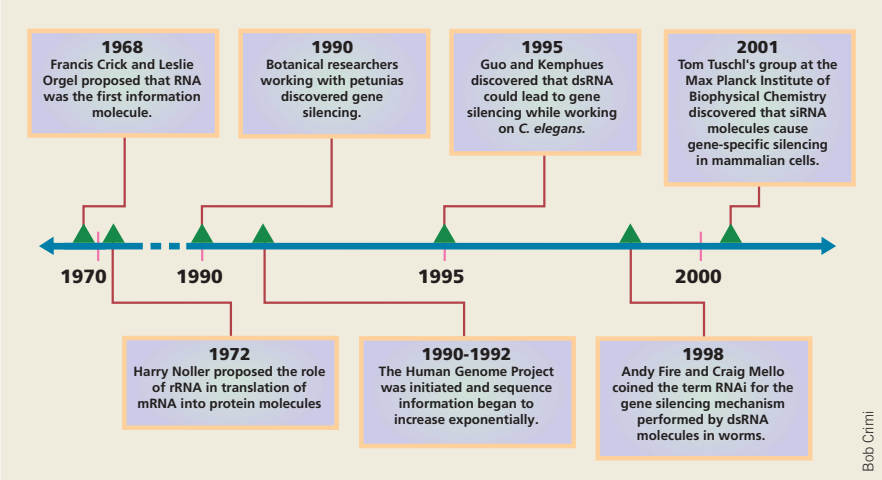

Figure 2 siRNA discovery timeline. (Figure adapted from ref. 1; courtesy of Front Line Strategic Consulting, San Mateo, CA, USA)

malian cells a few years ago; now our clients use it as a main method—there's been a big convergence," says Tod Woolf, president of RNA oligonucleotide product and therapeutics company Sequitur (Natick, MA, USA), which was acquired in November by life science supplier Invitrogen (Carlsbad, CA, USA).

The pace of adoption of RNAi-type technologies can also be measured by the numbers of researchers using siRNA to silence genes. Responding to internal requests, scientists at the Whitehead Institute (Cambridge, MA, USA) designed a tool to quickly search for siRNA molecules most likely to affect a target gene without also affecting other (off-target) genes. The site (http://jura.wi.mit.edu/pubint/http://iona.wi.mit.edu/siRNAext/) was opened to the public in February 2003, and every month approximately 100 new users are registering and between 400 and 500 searches are made, according to Fran Lewitter, head of the biocomputing group at the Whitehead Institute. Most users (~85%) are from academic, government or nonprofit institutions, and the rest from industry, says Lewitter (see **Box 1**).

"Academics have run ahead of the investment community," confirms Michael King, a biotech analyst and managing director at Banc of America Securities (New York). General and biotech investors are still "coming down from the let-down on the genomics bust," explains King. "They are not ready to invest in the next technology. I haven't heard a buzz on RNAi in the analyst community."

"Wall Street has not yet totally woken up to this space," agrees John Maraganore, CEO of Alnylam Holding Company. "It's pretty new. There aren't sufficiently [large] numbers of companies in this space."

But the venture capitalist world focused on life sciences, generally more attuned to research trends and also more willing to take risks, have picked up on RNAi. Gambling on the promise of the technology, some venture capitalists have already loosened their purse strings to fund ~10 companies focused on RNAi therapeutics. Westphal predicts that within a year, the field will increase to 15 companies, with each company following the biotech model of raising an initial round of between $10 million and $30 million from venture capitalists, and down the road looking to bring in additional money through deals with big pharma or, depending on the state of the market, making an initial public offering.

The anti-antisense?

"If you believe in antisense or ribozymes, than you have to believe in siRNA" as a good investment, says Tom Tuschl, an associate professor at Rockefeller University (New York), scientific advisor to Alnylam, and one of the researchers whose work lit the fuse igniting the field (**Fig. 2**). "[Small inhibitory] RNA therapeutics is not really different from antisense therapeutic companies, but there is a higher probability of success because it is longer lasting and has a more specific response than antisense and

Box 1 Will RNAi KO knockout mice?

As a research tool, RNAi is rivaling knockout mice for studying gene function *in vivo*, but with possible cost advantages, say researchers. Creating knockout mice—transgenic mice containing disabling mutations in individual genes—can be a costly and lengthy process. In contrast, RNAi, which potentially can have the same effect *in vivo*, is relatively quick and cheap.

"With RNAi, just find a short sequence that can target a particular mRNA to be expressed," explains Fran Lewitter, head of the biocomputing group at the Whitehead Institute (Cambridge, MA, USA). "Get it synthesized for a couple hundred dollars and use for knockout."

Lewitter's team, with rules developed by Tom Tuschl, a former Whitehead postdoc and now an associate professor at Rockefeller University, came up with a biocomputing siRNA search tool to make it easier for researchers to find the specific RNAi for their particular experiments. Similar computational tools are also available at RNA synthesis companies, such as Ambion (Austin, TX, USA) and Dharmacon (Lafayette, CO, USA) and elsewhere (**Table 2**). All these tools are making it easier to use siRNA for gene silencing experimentation. And they can do so at a fraction of the cost of using a knockout mouse: typically several hundred dollars versus several thousand. Does this spell the beginning of the end for knockout mice?

Probably not, conclude several biotech analysts, though they say it has put a significant check on the growth of the use of the mice. Eric Manning, an analyst with Front Line Strategic Consulting (San Mateo, CA, USA), sees siRNA as a screening tool that will the reduce number of knockout mice made. "People can start with siRNA and if they find out they don't need to, they will not invest in knockout mice," says Manning. Gregory Cox, associate staff scientist at The Jackson Laboratory (Bar Harbor, ME, USA) believes "the knockout will still continue," adding "maybe not with quite as much emphasis, but I don't see [siRNA] as a permanent replacement." Cox points out that siRNA does have the advantage of being tissue-specific, but he and others say that until expression silencing using siRNA is complete, as it is with knockout mice, the mice will have the edge.

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Box 2 What's in a name? Sometimes $48 million

In 2002, Ribozyme Pharmaceuticals was in trouble. After 10 years and some $200 million spent on research, the company had failed to produce a ribozyme-based therapy and its market valuation was down to approximately $5 million and sinking, according to analysts. "Unfortunately, ribozymes weren't as potent as we hoped," explains Howard Robin, former CEO of Ribozyme, who holds the same position with a newly focused company. So "we felt it was best to apply the skills to a potentially more robust area of RNA. What to do with skills amassed in RNA chemistry, what else can we work on? We worked on aptamers, RNA decoys, antisense. In the end, partly through wisdom, partly luck, we focused on RNAi." The company's timing proved to be worth $48 million. Just as Ribozyme Pharmaceuticals was taking its last breaths, venture capitalists were on the lookout for an RNAi acquisition or startup. In Ribozyme, they found both.

"Three years ago, none of the Oxford portfolio of companies was using RNAi. Now they all use it in-house as a tool for target development," explains Oxford Bioscience Partners' Fambrough. This led his firm to decide to start an RNAi-focused company or invest in one with the necessary skill sets. "Ribozyme was in dire straights for financing in the middle of a bear market," says Fambrough. "They had already started [RNAi research], but had not focused the company. [We] got it for a song." Oxford Bioscience Partners, along with several other venture capital groups, changed the company's focus in April 2003 with their $48 million investment. With the new focus came a new name.

"We went through hundreds of names internally," says Robin, CEO of the company now called Sirna Therapeutics (Boulder, CO, USA). "We like Sirna, it's a nice name. Sirna Therapeutics stresses therapeutics, not a commodities business."

ribozymes," says Tuschl. (see p. 1457)

"Money men got in because of the idea of a major increase in potency," says Sequitur's Woolf. "It sounds great, it is great, it could turn off any gene and cell type." Ribozymes were hyped up but didn't fulfill their promise, says Woolf, adding that researchers are also more satisfied using RNAi than antisense. "You toss it in, there's less tweaking, it lasts longer and there's decreased toxicity. We had [research] collaborations using antisense, then switched to RNAi when it was clear it is less toxic," says Woolf. Similarly, Boulder, Colorado–based Ribozyme Pharmaceuticals shifted its emphasis, and its name, to RNAi—the company now goes by the name Sirna Therapeutics—a move that may have saved the company from perdition (**Box 2**).

The potency issue is particularly alluring to those looking ahead to drug development. If an RNAi-based therapeutic were 100- to 1,000-fold more potent than antisense, which is what people are estimating, then less is needed, theoretically lowering the potential for side effects in humans.

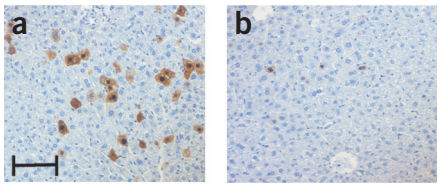

Figure 3 Inhibition of hepatitis B virus in mice by RNAi. Production of nucleocapsid protein in hepatitis B infected liver cells is reduced by greater than 99% in mice transfected with RNAi directed against viral B mRNAs. (**a**) Hepatocytes from infected controls, stained for viral antigens. (**b**) Hepatocytes from mice treated with RNAi. (Adapted from ref. 2; image courtesy of Mark Kay, Stanford University, Stanford, CA, USA.)

Investors and researchers also say that RNAi has less risk of failure than antisense because the process has been screened by evolution. "In every cell in your body, RNAi is active and working," points out Westphal. It is a "natural process, so we know it works in the cell. It's not like antisense, ribozymes [manipulation] or aptamers."

Similar claims have been heard before, however, warns Stelios Papadopoulos, vice chairman of SG Cowen Securities (New York). "There was a time people thought antisense would be the answer to everything," recalls Papadopoulos. "There should always be a healthy dose of skepticism. Monoclonal antibodies, antisense, other approaches were heralded, only to be proven later to be more challenging. [But] all were greeted with excessive enthusiasm."

Box 3 Striving to deliver

A universal obstacle facing companies developing RNAi (or any nucleic acid) therapeutic is how to deliver the molecules into cells, say investors and company executives. After 20 years of development, antisense drug delivery remains problematic. Consider Isis Pharmaceutical's (San Diego, CA, USA) Vitravene, which is used to treat cytomegalovirus-related retinitis and the first (and only) antisense drug to make it into clinical practice. Intravitreal (eye) injection is the delivery system. And Genta's (Berkeley Heights, NJ, USA) Genasense, an antisense drug directed against *bcl-2*, currently in clinical trials for treating certain cancers, is given as a 14-day continuous intravenous infusion.

Different RNAi companies are approaching this challenge in different ways, though some general approaches have emerged. Some companies, such as Benitec (St. Lucia, Australia) and Nucleonics (Malvern, PA, USA), are focusing efforts on using a DNA vector to deliver double-stranded RNA. Another approach is to use RNAi that has been chemically modified for stability, and deliver it via injection, or possibly through liposomes, which is similar to some approaches tried with antisense. Alnylam Pharmaceuticals and Ribopharma, both divisions of Alnylam Holding Company, and Sirna are experimenting with these approaches. Alnylam's director of development, Nagesh Mahanthappa, feels that developing RNAi drugs may offer some advantages over DNA-based systems, which might suffer problems similar to those of gene therapy, including safety concerns and heightened regulatory scrutiny. However, whether current RNAi chemistries will be stable, nontoxic and potent in the circulation and in different tissues *in vivo* remains to be confirmed.

Of course, identifying which approach (if any) will lead to effective delivery in clinical trials is still anyone's guess. "It's so early in the field that you can't call winners," says John Berriman, a director at venture capital firm Abingworth Management Limited (London, UK). It will take "at least one year to see possible winners and losers. And technology will continue to evolve over the next one to five years."

Table 1 RNAi biotechnology companies

Company	Founded	Founders and advisors	Technology focus	Business focus
Acuity Pharmaceuticals (Philadelphia, PA, USA)	2002	Michael Tolentino and Samuel Reich (University of Pennsylvania)	Use of RNAi against vascular endothelial growth factor in ophthalmic diseases	Therapeutics against macular degeneration and diabetic retinopathy
Alnylam Holding Company (Cambridge, MA, USA) 2003 merger between Alnylam and Ribopharm AG	2002	Phil Sharp (MIT), David Bartel (The Whitehead), Paul Schimmel (Scripps Institute), Tom Tushl (Rockefeller University), and Phillip Zamore (U. Mass Medical School), Roland Kreutzer and Stefan Limmer (founders of Ribopharma)	Therapeutic use of delivered RNA in cells and adult mammals	Therapeutics against viral, cancer, metabolic, central nervous system (CNS), and autoimmune diseases.
Atugen (Berlin, Germany)	1998	Spin-off from Ribozyme Pharmaceuticals (now Sirna Therapeutics)	Exclusive licensee of Sirna's RNAi target discovery and validation technologies	Cancer therapeutics, pathway analysis and target validation
Avocel (Sunnyvale, CA, USA)	2003	Mark Kay (Stanford University)	Exclusive license for expressed RNAi in non-embryonic mammals (Stanford University) and co-exclusive license to deliver RNAi to non-embryonic mammals	Therapeutics against chronic hepatitis B and C
Benitec (Queensland, Australia)	1997	Queensland Department of Primary Industries	DNA-directed RNAi (ddRNAi)	Therapeutics against cancer, autoimmune, HIV/AIDS and chronic viral disease
Cenix BioScience (Dresden, Germany)	1999	Christophe Echeverri, Pierre Gonczy, Anthony Hyman (European Molecular Biology, Heidelberg, Germany; Max Planck Laboratory, Dresden, Germany)	Genome-scale application of RNAi	Custom design of large-scale RNAi libraries (offered by Ambion), target discovery and validation
CytRx (Los Angeles, CA, USA)	2002	Merger with Global Genomics, changed company focus to RNAi	Nonexclusive licensee of U Mass Medical School patents covering gene silencing of specific diseases using RNAi	Therapeutics against obesity, type 2 diabetes and amyotrophic lateral sclerosis
Devgen (Ghent, Belgium)	1997	Thierry Bogaert (MRC, Cambridge, UK), Michael Hengartner (University of Zurich)	Genome-wide *Caenorhabditis. elegans* RNAi feeding library	Therapeutics against metabolic and CNS disorders
Intradigm (Rockville, MD, USA)	2001	Martin Woodle (Novartis, Cambridge, MA, USA)	Gene delivery and gene therapy vectors developed at Genetic Therapy for use with RNAi (subsidiary of Novartis)	Therapeutics against cancer
Nucleonics (Malvern, PA, USA)	2001	C. Satishchandran and Catherine Pachuk (Thomas Jefferson University, Philadelphia, PA, USA)	Expressed long interfering RNA (eiRNA)	Therapeutics from expressed interfering RNA
Polgen (Cambridge, UK), a division of Cyclacel (Dundee, UK)	2000	David Glover (University of Cambridge, Cambridge, UK)	Identifies cell cycle targets from whole genome screens using RNAi in Drosophila cell lines	Cancer targets and pathways. Phenotypic characterization after genetic knock down and small molecule inhibitors
Sequitur (Natick, MA, USA) (The company was acquired in November by life sciences product and services company Invitrogen (Carlsbad, CA, USA).)	1996	Tod Woolf, Craig Mello (U. Mass Medical School), and Richard Wagner (Phylos, Lexington, MA, USA)	Proprietary 'stealth' RNAi technology	Therapeutics against hepatic insufficiency, respiratory syncitial virus, asthma and breast cancer
Sirna Therapeutics (formerly Ribozyme Pharmaceuticals) (Boulder, CO, USA)	1992	Ralph 'Chris' Christoffersen (Morgenthaler Ventures, Boulder, CO, USA)	Therapeutic use of RNAi and expression of siRNA in cells. (Max Planck, MIT, U Mass Medical school, Whitehead). Chemically modified siRNA and RNA. RNA synthesis and manufacturing	Therapeutics against hepatitis C, macular degeneration (VEGF pathway), oncology, inflammation, metabolic diseases and CNS

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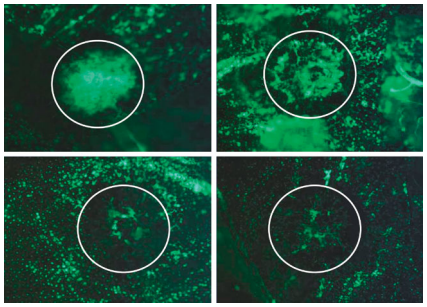

Figure 4 Inhibition by siRNA of neovascularization in a mouse model of age-related macular degeneration (AMD). Intraocular injections of siRNA targeting vascular endothelial growth factor receptor-1 inhibited by 60% neovascularization (green fluorescence) in laser-induced rupture of retinal membranes, which mimics the growth and leakage of blood vessels behind the retina in AMD. (From a study by Shen & Campochiaro, Johns Hopkins, in collaboration with Sirna Therapeutics, Boulder Colorado.)

Table 2 Websites offering RNAi selection tools

Site	URL
Ambion's siRNA Target Finder	http://www.ambion.com/techlib/misc/siRNA_design.html
Cold Spring Harbor's RNAi OligoRetriever	http://katahdin.cshl.org:9331/RNAi/
Dharmacon's siDesign Center	http://www.dharmacon.com/
Qiagen's siRNA Target Sequence Design:	http://www.qiagen.com/jp/siRNA/sirna_design.asp
Sirna's Emboss	http://www.biobase.dk/embossdocs/sirna.html
Tuschl Laboratory siRNA User Guide	http://www.rockefeller.edu/labheads/tuschl/sirna.html.
The Whitehead RNAi Selection Program	http://jura.wi.mit.edu/pubint/http://iona.wi.mit.edu/siRNAext/

Taking aim

Although it remains to be seen whether the approach will ultimately succeed (see **Box 3**), it is clear what diseases are being initially targeted. The focus for many companies, according to company executives, is the hepatitis virus. This combines a disease with a large potential market, a single-stranded viral target and an organ—the liver—with a natural inclination to take up an oligonucleotide (**Fig. 3**).

Other targets being investigated are metabolic diseases like hepatic inefficiency (Sequitur), blood and bone marrow disorders (Alnylam), and retinopathies (Acuity Pharmaceutical, Philadelphia, PA, USA; Sirna; see **Fig. 4**). Also being tackled are certain cancers, such as breast, colon, pancreatic and malignant melanoma, the last two, according to Ribopharma COO Roland Kreutzer, because the high death rate makes the FDA regulatory fast-tracking a possibility. Sequitur's Woolf adds that the lungs might be a suitable target to treat asthma via inhaled RNAi; the targets would be the same genes as acted upon by traditional drugs or targets small molecules can't reach. Cyclacel's Polgen division (Cambridge, UK) is looking into using short-stranded RNA as antimitotic drugs targeting cancer during its nascent stage, says Cyclacel CEO Spiro Rombotis.

Patent battle pending

Another obstacle, but one potentially as vexing as the scientific hurdles for companies trying to attract investors and venture capitalists looking for a place to park their money, is the issue of patents. Who owns what may determine which companies stay in business long enough to get positive results.

"RNAi is kind of an intersection of the two worlds" of academia and private industry, explains Sara Cunningham, vice president of intellectual property (IP) and business development at RNAi therapeutics–focused drug discovery company

Box 4 Life sciences companies eye RNAi

When has a life science technology entered the big time? Some would say when big pharma and other large corporations not only take notice, but also make investments in the technology. At various levels—as a discovery tool, a target validator and even a therapeutic—this is beginning to happen with RNAi.

"RNAi is one of the most exciting technology advances that has occurred in the past decade," says Stephen Fesik, divisional vice president of cancer research at Abbott Laboratories (Abbott Park, IL, USA). Abbott uses RNAi in target validation studies, and has partnered with RNA oligonucleotide provider Dharmacon (Lafayette, CO, USA) to produce an RNAi library aimed at 4,000 gene targets. Fesik, who declines to reveal the financial details of the deal, which was announced in July, says Abbott is also in the process of finalizing deals with other RNAi-oriented companies. While moving ahead in using RNAi as a discovery tool, Fesik points out that Abbott does not have any programs for using RNAi as a therapeutic as there are currently "lots of hurdles" for therapy, including delivery and stability of the molecules. The company, he says, is waiting "to see what happens" with the technology. But "if a biotech came to Abbott and could show they had overcome hurdles, we'd be very interested," he adds.

Merck & Co. (Whitehouse Station, NJ) is also investing in RNAi; Rosetta Inpharmatics, a subsidiary of Merck, announced a collaboration with Dharmacon in October to study factors affecting the potency and specificity of siRNA reagents. And therapeutic applications are "under evaluation" at Merck, according to Stephen Friend, senior vice president at Merck Research Labs (Westpoint, PA, USA). It is "unquestionably early days, [but] it is a tantalizing field," says Friend. "Our attitude is to partner with the most expert and professional groups out there." One such partnership is with Alnylam Holding Company (Cambridge, MA, USA) in a multi-year collaboration, announced in September, to develop RNAi-based therapeutics. The deal includes up front and annual payments by Merck in addition to an equity investment in Alnylam. Merck has other collaborations, adds Friend, though declining to name them.

One of the world's largest medical device manufacturers is also looking to get in on RNAi. "My job is to keep an eye on the long ball for new technologies, also to look at what threatens this company and look at it as an opportunity," says Stephen Oesterle, senior vice president for medicine and technology at Medtronic (Minneapolis, MN, USA). "Combination products will categorize medical devices in the next 10 years. Medical devices are necessary to deliver RNAi. Ultimately to realize many RNAi potential treatments, you need to get them to where they can work." To that end, says Oesterle, Medtronic has internal research programs aimed at delivering RNAi to target organs, though he declined to offer specifics. Oesterle says the company is at least five years away from a product.

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Avocel (Sunnyvale, CA, USA). "In this case, the academics were savvy enough, as were their tech transfer offices, to patent broadly and aggressively. So you've got this multimillion dollar industry, almost all from private equity funds, springing up with only two patents issued and no real clarity as to who has or even who will likely get *in vivo* rights," says Cunningham.

"IP is a key area that needs to get sorted out before investors embrace [the field]," says Michael King. "The problem is that the IP position can't be boiled down to a sound bite and only the most dedicated investors will sort [it] out. IP is clouded right now and nobody wants to make an investment and find out it is wiped out the next morning based on an adverse ruling."

Front Line Strategic Consulting analyst Eric Manning agrees: "A lot of people are standing off until these patents resolve. Who will get a US patent and market is the big question. It's all about the IP."

But, Christophe Echeverri, CEO of the RNAi company Cenix BioScience (Dresden, Germany), points out that questions about RNAi IP are no different than with any other new field: "Patent holders will have to sort out who owns what, there's lots of overlapping, [but] parties are negotiating in good faith so the field can move on. There always will be chest thumping; that's necessary for negotiations."

In using RNAi as a research tool, "most patent holders have set out reasonable nonexclusive patent terms," adds Echeverri. However, "for therapeutics, the stakes are much higher, and it's where heated discussions are centered."

"The big battle will come when you have a big target, [such as] cancer or liver disease with large numbers of patients," predicts Tom Tuschl. "It will take time to sort it out, and probably not without court action."

Big pharma, along with the investment community, will probably wait out those battles before making significant collaborations or deals, say observers, although partnerships between pharma and biotech companies are starting to appear (**Box 4**). As for the scientific obstacles and IP issues, "As an early stage investor, you have to have some faith that they are solvable problems," explains Doug Fambrough, a principal with venture capital firm Oxford Bioscience Partners (Boston, MA, USA).

Future prospects

In the few years since biotechnologists have adopted RNAi, it has already earned a place among the major technology platforms. Although still in the proving stages as a therapeutic, RNAi nonetheless is providing a number of business opportunities, from supplying research tools and services to licensing deals and collaborations. But many challenges lie ahead before the technology can reach its full potential. Patent issues need to be sorted out, and more research is needed to discover the rules for making and delivering RNAi.

"There is no debate that [RNAi] is incredibly important from a basic science standpoint," says Westphal. "The question is how much time and money will it take to turn it into a drug?"

1. Front Line Strategic Consulting. *siRNA: A Strategic Market Outlook and Business Analysis* (Front Line Strategic Consulting, San Mateo, CA, USA, February 2003).
2. McCaffrey, A.P. *et al.* Inhibition of hepatitis B virus in mice by RNA interference. *Nat. Biotechnol.* **21**, 639–644 (2003).

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