Negotiating the RNAi patent thicket

Patent disputes haven't materialized in the RNAi field yet, but once products near the market, it might be a different story. Charlie Schmidt investigates.

Last December, Merck of Whitehouse Station, New Jersey paid $1.1 billion for a company whose stock just three years ago was trading at 23¢ per share. Then called Ribozymes, and based in Boulder, Colorado, Sirna Therapeutics climbed to biotech's upper echelons by shifting its focus exclusively to RNA interference (RNAi), a method for turning genes off selectively using short double-stranded RNA molecules.

Currently based in San Francisco, Sirna spent its recent past accumulating one of the broadest RNAi patent estates in existence. Merck now owns that estate, and all the uncertainty that comes with it. As a Nobel-prize winning technology, RNAi could become biotech's third act, after gene cloning and monoclonal antibodies. But no one can say whether it will ever bring useful drugs to market. Though RNAi has become invaluable for basic research, its therapeutic potential is unknown. Delivering RNAi drugs to target cells poses difficult challenges; largely because of this, drug-development with RNAi remains mainly in preclinical stages.

An emerging landscape

In lieu of drug sales (and apart from selling tools for basic research), RNAi generates income by leveraging intellectual property (IP). Patentable 'inventions' in this area include molecular features, modifications that enhance compound efficacy and gene-specific RNAi targets, among others. By licensing their inventions, companies can extract fees for use of their technology. More than 2,000 RNAi patent applications for new inventions have been filed with the US Patent and Trademark Office (USPTO)[1]. Yet only a few have been issued (**Table 1**). Understaffed and wary of errors, the USPTO is moving cautiously on its reviews, according to James P. McNamara, the executive director of the Office of Technology Management at the University of Massachusetts (UMass) Medical School, which along with three other institutions filed an early patent on RNAi. "They're being very deliberate about [RNAi]," he says. "They don't want to make mistakes that could come back to haunt them."

As with any new invention, RNAi patents are awarded only for ideas and products deemed novel, nonobvious and useful. Meeting those criteria isn't easy, and in fact, McNamara suggests many of the RNAi applications submitted so far will fail. "Time will tell," he says. A key challenge for reviewers is to confirm that a given application doesn't overlap with 'prior art', meaning previously patented technology. Reviewers must also wade through overlapping claims, in which case the goal is to determine who proposed a given invention first. Most experts assume patent issues won't be resolved until products near the market. At that point, litigation and patent appeals could force clarification on disputes.

Meanwhile, corporate spin dominates the patent landscape. Companies flaunt their IP as evidence of RNAi invincibility; and use public relations firms to guard those impressions. In most cases, the actual claims are so complex that they can be understood only with the aid of a patent lawyer.

Among the players working this shifting frontier, Sirna is clearly a titan, basking in its new deal with Merck. It's arch rival—the Cambridge, Massachusetts-based firm Alnylam Pharmaceuticals—has also accumulated what it says is an iron-clad estate in IP, worth millions in licensing. Alnylam claims over 150 issued patents of relevance to RNAi, including exclusive access to seven that it believes are fundamental to all therapeutic uses of the technology. "We think anyone developing synthetic RNAs will need to license our intellectual property," says John Maraganore, Alnylam's president and CEO.

That view is, of course, debatable. Others counter that neither Alnylam's position, nor that of its competitors, is as comprehensive as the companies themselves insist. But in Alnylam's case, the strategy seems to be working: its estate has already generated $120 million in licensing fees, according to Maraganore. Some companies have licensed the estate in its entirety. Among them, Quark Biotech, a Fremont, California-based biotech firm developing RNAi drugs for age-related macular degeneration (AMD) and renal failure, views its arrangement with Alnylam as an insurance policy. "It's cheaper to license the technology now during our early development phase," explains Daniel Zurr, Quark's president and CEO. "If you do it later, when you have a drug and you're desperate to move forward, the licensing fee could be much higher."

A history in antisense

Some of the earliest patents pertaining to RNAi date back to a preceding technology, antisense, which silences genes using single-stranded, complementary, synthetic oligonucleotides. Antisense produced a series of patents that describe how the potency and stability of oligonucleotides can be improved. The Crooke patents, of which there are two, offer an example. Developed by Stan Crooke, CEO of Isis Pharmaceuticals in Carlsbad, California (a company with its roots in antisense), the patents cover a range of chemical modifications to stabilize oligonucleotides, so they can reach their targets. Isis also claims patents for chemical 'building blocks', used to make oligonucleotides with drug-like properties. Alnylam has taken exclusive license to the Isis patents, but only for their use in double-stranded RNA.

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So far, US courts haven't been asked to rule on RNAi patents. But that will likely change if any RNAi products near the market.

Table 1 Seminal patents in RNAi

Patent	Patent number	Status	Date	Owner	Licensees	Coverage
Fire and Mellow	US 6,506,559	Issued	January, 2004	Carnegie Institute of Washington	Unrestricted	Inhibition of target genes with double-stranded RNA 25 nucleotides or more in length
Tuschl *et al.* (Tuschl I)	US 108,923	Application pending	NA	UMass Medical School, MIT, Whitehead Institute, Max Planck Institute	Alnylam, Sirna, Cytrx	Inhibition of target genes with double-stranded RNA between 21 and 23 nucleotides in length. Includes overhangs, chemical modifications and data from mammalian cells
Tuschl *et al.* (Tuschl II)	US 7,056,704	Issued	June, 2006	Max Planck Institute	Alnylam	Short RNA fragments 19–23 nucleotides in length are sequence-specific mediators of RNAi in *Drosophila melanogaster*. Describes 3′ overhangs
Tuschl *et al.* (Tuschl II)	US 7,078,196	Issued	July, 2006	Max Planck Institute	Alnylam	Second patent in Tuschl II series. Describes in greater detail the use of siRNA in mammalian cells
Crooke	US 6,107,094	Issued	April, 2000	Isis	Alnylam	Chemical modifications to stabilize RNA
Crooke	US 5,898,221	Issued	April, 1999	Isis	Alnylam	Chemical modifications to stabilize RNA
Benitec	US 6,573,099	Issued then pulled for reexamination	June, 2003 (issuance date)	Benitec	Not available	Genetic constructs for delaying or repressing target gene using expressed system
Kreutzer-Limmer	EP 1,144,623	Issued	2002	Alnylam	Not available	Describes RNAi in molecules from 15 to 21 nucleotides in length. Provides coverage in Europe, Australia and South Africa

According to Crooke, these patents, and others in the Isis portfolio cover most, if not all, the features needed to make useful molecules for RNAi. "It is our contention that our patents dominate the landscape," Crooke claims. "Virtually any chemical modifications that enhance drug properties, stability, delivery or potency infringe on the Crooke patents."

That view irks others in the field, however. Tod Woolf, president of RXi, a wholly-owned subsidiary of CytRx Corporation, a Los Angeles, California–based biotech firm, points out that several stabilizing modifications were developed years before the Crooke patents were filed. For instance, the addition of 2′-*O*- methyl RNA bases, which were identified in the mid-1980s, help oligonucleotides resist nucleases that would otherwise destroy them, he says. "If other companies create a false impression that they have a dominant position with regard to every chemical modification of RNA, it could deter progress in the entire field," Woolf warns.

For the record, Alnylam claims it does own 2′-*O*- methyl chemical modifications, through its access to Isis's IP, in addition to its own patents. However, other sources interviewed for this article dispute that claim, underscoring the degree to which the courts could play key roles in resolving important questions.

RNAi patents emerge

Antisense's early prominence in nucleic acid therapeutics was eroded in 1998 by the finding that gave rise to modern RNAi. With what was to become a Nobel Prize–winning discovery, Andrew Fire, from Stanford University School of Medicine, California, and Craig Mello, from UMass Medical School, showed that double-stranded RNA molecules could interfere with mRNA, to efficiently silence genes in *Caenorhabditis elegans*. Unlike synthetic, single-stranded antisense strands, double-stranded RNA molecules exist naturally in the cells of many species. Thus, they harness the cell's own gene-silencing machinery, making them more attractive for clinical research, many experts say.

Fire and Mello's finding generated a seminal patent—the Carnegie patent—which can be licensed to anyone who wants to use it. Issued in 2003, and named for the Carnegie Institute of Washington, DC (where the research was performed), the patent describes how double-stranded RNA silences target genes in a cell.

But the Carnegie patent has a key limitation: it refers only to RNA molecules of 25 nucleotides or more in length. At that size, the molecules can trigger dangerous immune responses, making them unsuitable for clinical use. Scientists had nearly given up on RNAi for drug development until four researchers—Thomas Tuschl at Max Planck Institute (currently at Rockefeller University in New York), Philip Sharp at MIT, Philip Zamore at UMass Medical School and David Bartel at the Whitehead Institute—found that by making the molecules smaller, they could avoid immune reactions while disabling mRNA.

The Tuschl patents

That stunning revelation produced a fundamental patent—Tuschl I—which covers both modified and unmodified short interfering RNA (siRNA) molecules, 19 to 25 nucleotides long. Tuschl I has yet to be issued, though the application was filed in 2000. The USPTO can't comment publicly on why the review is taking so long. Sources who track progress on the assessment expect Tuschl I will be issued this year, but the timing can't be confirmed.

In 2002, three of the four schools involved in the discovery agreed to license Tushl I exclusively to Alnylam. UMass Medical School chose not to, and granted a nonexclusive license to CytRyx. Then, in 2003, Sirna took a coexclusive license to Tuschl 1 from UMass Medical School, the end result being that Sirna, Alnylam and Cyrix (to a more limited degree) can operate under Tuschl I in the US.

After that move, Tuschl, who sits on Alnylam's scientific advisory board, performed some new experiments resulting in a different patent called Tuschl II. Issued in June 2006, that patent was licensed exclusively to Alnylam, which has since proclaimed its superiority.

The fact that Tuschl I hasn't been issued is, of course, a complicating factor. Maraganore stresses that because Tuschl I hasn't moved beyond the application phase, no one knows what it might cover when it issues, assuming that it does. Sirna, meanwhile, argues the patent will issue, and moreover, that it contains most of the major features found in Tuschl II. Bharatt Chowrira, Sirna's vice president for legal affairs and chief patent council, says the Merck buyout speaks to the strengths of Tuschl I's claims. "Why else would Merck have bought the company?" he asks.

Maraganore counters that Tuschl II's supremacy derives from three key features. First, whereas Tuschl I's findings are limited to fruitflies, Tuschl II describes how siRNAs "work in mammalian cells, to silence mammalian genes." To this, Chowrira counters that the "Tuschl I describes the use of siRNAs in mammalian systems throughout the application." Second, Maraganore claims that Tuschl II

Box 1 First salvo comes in Europe

The Kreutzer-Limmer patent is among the best known RNAi patents outside of the US. Kreutzer-Limmer was issued by the European Patent Office (EPO) to Ribopharma, a German biotech, in 2002. Alnylam purchased Ribopharma in 2003, and soon after was embroiled in a battle with its competitors over the patent's coverage, which extends to Germany, Australia and South Africa. As issued, Kreutzer-Limmer had broad claims covering double-stranded RNA molecules less than 21 nucleotides in length. Under pressure from Sirna, AstraZeneca, Autgen, Janssen Pharmaceutica and Sanofi-Aventis, which objected to the patents 'ambiguous' coverage, the EPO in 2006 eviscerated Kreutzer-Limmer's claims to cover blunt-ended, double-stranded RNA molecules 15 to 21 nucleotides long, joined by a chemical linker. The consequence of EPO's action is debatable. Alnylam's spokesperson, Cynthia Clayton, describes Kreutzer-Limmer—which is featured on the company's website—as a "fundamental patent." Sirna's Bharat Chowrira, meanwhile, claims the EPO's 2006 changes rendered Kreutzer-Limmer irrelevant. "This is a structure that no one uses anymore, so it's not commercially important," he says.

describes the need for certain siRNA architectures, particularly three prime overhangs, which he argues are crucial to drug efficacy. (Overhangs refer to unpaired nucleotides that dangle off the end of an siRNA, like a tail.) "They're required to generate optimal biological activity," Maraganore stresses. "And the other feature is that the overhang structure helps to allow the double-stranded RNA to escape the immune system." In response, Chowrira claims Tuschl I covers three prime overhangs. Finally, Maraganore claims that "Tuschl II covers chemical modifications of siRNAs, without any limitations whatsoever." But Chowrira claims that Tuschl II covers a restricted set of chemical modifications, some of which infringe on Sirna's own patents.

What would be the consequence to Sirna if Tuschl I never issued? To this, Chowrira reiterated his belief that the Tuschl II claims still can't block Sirna from pursuing RNAi-based therapeutics.

According to Richard Smith, a biotech analyst with JP Morgan in New York, many companies license with Alnylam simply to gain access to both patents. That affords them a degree of protection should Tuschl I never see the light of day, he says. But that view is far from universal. Other companies don't believe Alnylam's patents pertain to their own strategies. Atugen, for instance, based in Berlin, develops blunt-ended siRNAs (that is, siRNAs that lack overhangs) indicated for AMD, acute renal failure and cancer. The company has patented the technology in Europe (**Box 1**). Thomas Christély, Atugen's CEO, insists blunt-ended molecules—which he says are promising therapeutically—aren't covered by Tuschl II, nor any of Alnylam's other patent claims. Similarly, Acuity Pharmaceuticals, in Philadelphia, develops unmodified siRNAs for ocular conditions, particularly AMD. Sam Reich, the company's executive vice president for R&D, notes the company's lead product—an AMD treatment called bevasiranib (previously Cand5), currently in clinical trials—has an unmodified siRNA structure covered by Acuity's own IP. Tuschl II, meanwhile—consistent with Maraganore's view that siRNAs must be chemically modified to be effective—limits its coverage to chemically modified structures.

Target-specific patents

Adding to the fundamental patents already described, Sirna was recently granted the first target-specific RNAi patent in the US. Issued in April 2006, the patent (designated no. 7,022,828, or simply '828'), covers any chemically modified siRNA targeting a gene called I Kappa B kinase-gamma (IKK-gamma). According to Chowrira, the gene participates in numerous diseases, including asthma, arthritis and cancer, among others. The 828 patent covers all chemically modified siRNA sequences used against the gene, including both blunt-ended and overhang varieties, he says.

Chowrira says the new US patent is comparable to similar protection obtained by Sirna for other gene targets in Europe, Japan and Australia. Sirna has filed applications at the USPTO for over 250 mammalian and viral genes targeted by siRNA. "So 828 sets an important precedent for us in the United States," he says.

But that precedent is controversial. Some believe it was inappropriate for the USPTO to issue the patent without narrowing the claim to a specific siRNA sequence. "We're sure the siRNA community will address these kinds of patents and unite to stop them," said one source, who wished to remain anonymous. "I think there will be fierce fighting among companies when it comes to these [target-specific] patents; this will be a future battlefield."

To these concerns, Chowrira stresses that Sirna invested millions to characterize IKK-gamma and the other targets for which it now seeks protection in the US and elsewhere. "We put a lot of work and effort into each of them," he says. "We had [a] dedicated group at Sirna that did nothing but design siRNAs and test them in the lab for patent purposes. The days of patent protection based on paper evidence are over."

Delivery, delivery, delivery

As RNAi research moves forward, a key question remains: how will siRNA compounds be delivered to their targets? It can be notoriously difficult for oligonucleotides to penetrate cell membranes, and evade immune system attacks. Without solving the delivery problem, drug makers will be unable to deliver on RNAi's therapeutic promise. Some companies avoid delivery issues by focusing on local, rather than systemic targets. Acuity's product bevasiranib, for instance, gets injected directly into the eye. But for other indications like heart disease, or cancer, siRNAs must reach internal organs, through systemic delivery routes.

Delivery appears to offer new patenting opportunities for RNAi. Among the emerging approaches, the use of lipid-based nanoparticles is perhaps the best known. However, there are no clear winners when it comes to delivery, and hence no fundamental patents to speak of.

Scientists can also silence genes with expression systems that incorporate siRNA-making instructions into the cell's genome. Viral or nonviral vectors transfect cells, allowing researchers to bypass systemic delivery challenges. Integrated expression systems run the risk of producing cancer, however, and so are highly experimental. Most of the IP in this area is owned by Benitec, in Melbourne, Australia. Benitec lays claim to a seminal US patent—no. 6,573,099—that describes "genetic constructs for delaying or repressing the expression of a target gene." Issued in 1998, the patent is currently being reexamined by the USPTO.

Meanwhile, RNAi researchers don't have to worry much about patent infringement yet. Thanks to the Supreme Court's 2005 decision in *Merck v. Integra*, biomedical scientists can use patented inventions for research as long as they're working towards an approved drug. But although *Merck v. Integra* offers some breathing space, it also poses a challenge: how long should researchers wait before licensing someone else's technology? That's not an easy question to answer—companies set licensing fees on a sliding scale. The closer a drug gets to market, the higher the fees climb. But then again, RNAi may never succeed therapeutically. So for now, the patent landscape, like the drugs it may spawn, has time to evolve.

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1. Angrist, M. & Cook-Deegan, R.M. *The New Atlantis* **11**, 87–96 (2006).