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In 2006, Nobel Prize Is RNAi's Landmark; Small RNAs Expected to Mature in 2007

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The science of RNA interference made strides in 2006 as use of the technology in drug development accelerated and researchers refined their understanding of how it works and how to make it work better.

But topping many industry watchers' lists of the key developments in the RNAi field last year was the issuance of the Nobel Prize to Craig Mello and Andy Fire (see [RNAi News, 10/5/2006](#)).

"The Nobel Prize was an obvious highlight" of the year, William Marshall, vice president of technology and development for Dharmacon parent firm Thermo Fisher Scientific, told *RNAi News* last month. "I think the fact that this was a 1998 publication [for which] the Nobel Prize [was awarded] in 2006 speaks volumes about the fundamental importance of the technology."

The Nobel Prize to Fire and Mello was "an outstanding event," Mark Behlke, vice president of molecular genetics at Integrated DNA Technologies, noted. "To have [it] awarded into a field that is this young is a real testament to the overall importance" of the technology.

And it isn't just the researchers in the field who see the Nobel Prize as a validation of RNAi. Bob Towarnicki, president and CEO of Nucleonics, told *RNAi News* last month that it was "amazing the amount of attention [the prize] created for us" from potential investors.

The award "was a nice plus for the RNAi field," he added.

Rx and IP Strides

Aside from recognition for work already done, the RNAi field experienced a surge in new developments during 2006, especially in the therapeutics arena.

"We saw nice developments by essentially all the companies involved in the development of the modality as a therapeutic entity," Marshall commented. "This was clearly capped off by the recent very high-profile acquisition of Sirna [Therapeutics] by Merck, as well as continued alliances between focused siRNA providers and pharmaceutical development partners."

During 2006, Acuity Pharmaceuticals reported positive phase II data for its siRNA-based age-related macular degeneration drug bevasiranib and made plans to start phase III studies this year (see [RNAi News, 9/14/2006](#)). Meanwhile, Alynlam Pharmaceuticals completed phase I testing of its respiratory syncytial virus drug ALN-RSV01 (see [RNAi News, 10/12/2006](#)).

Additionally, a number of RNAi companies made progress in their drug pipelines and are poised to begin human testing of drug candidates in diseases including influenza, cancer, and hepatitis B in 2007.

As Marshall noted, this work has caught the attention of various pharmaceutical and biotech firms including Merck, which this week closed its \$1.1 billion cash acquisition of Sirna Therapeutics ([see related story, this issue](#)). But while it was undoubtedly the biggest deal of its kind in the RNAi space, the acquisition was not the only tie-up between an RNAi drug maker and a big pharma during 2006.

In September, Quark Biotech licensed to Pfizer its proprietary human gene target RTP-801, as well as an siRNA molecule designed to silence the gene, as part of a deal estimated to be worth more than \$100 million (see [RNAi News, 9/28/2006](#)).

A couple of months earlier, Dharmacon and Abbott forged a multi-year deal to discover siRNA-based therapeutics for multiple indications, with an initial focus on cancer (see [RNAi News, 7/6/2006](#)), while in May GlaxoSmithKline inked a respiratory disease alliance with Sirna (see [RNAi News, 4/6/2006](#)).

According to Beckman Research Institute researcher and Calando Pharmaceuticals co-founder John Rossi, partnerships between RNAi companies and big pharma and biotech are likely to continue in 2007. With small-molecule pipelines drying up, drug makers are going to “have to throw a broader net out there, and RNAi is a natural way to look because it’s going to identify targets [as well as act as] a potential drug in itself if delivered properly,” he said.

At the same time, full-blown acquisitions probably won’t come any time soon, according to IDT’s Behlke, who said that Merck’s purchase of Sirna was largely driven by the RNAi shop’s intellectual property portfolio, not its pipeline. The only other company with an IP estate comparable to Sirna’s is Alnylam, and “the way [that company] is positioned now [with Novartis holding a nearly 20 percent stake], they’re going to be difficult to fully acquire,” he said.

Indeed, IP has long been a key issue for the RNAi field. As Behlke noted, RNAi “has been an area where there have been more patents filed in a short amount of time than anything I can remember in biology,” which has led to a lot of confusion and litigation.

But the fog covering the RNAi IP landscape began to lift during 2006, primarily with the issuance of two key US patents: the Tuschl-2 patent, No. 7,056,704, which covers the use of siRNAs between 19 and 25 nucleotides long to mediate RNAi, as well as the use of overhangs on the 3' ends of dsRNAs to mediate target RNA cleavage, and is licensed exclusively to Alnylam (see [RNAi News, 6/8/2006](#)).

The other patent is Sirna’s, No. 7,022,828, which covers the use of siRNA to treat diseases associated with IKK-Gamma. It is the first of the more than 250 target-specific RNAi patent applications Sirna has filed to be granted by the patent office (see [RNAi News, 4/6/2006](#)).

These two patents will help rid the RNAi industry of some of its IP murkiness, “which is going to be important to facilitate people in fully developing [RNAi molecules] to their full potential,” Behlke added.

A Look Ahead

Although making predictions is never easy, it seems that just about everyone expects to see a bigger role for small, non-coding RNAs — especially microRNAs — in the coming year.

“MicroRNAs really have been abuzz in the field for some time,” Dharmacon’s Marshall said. “I think what we’re going to see now is ... better profiling techniques to look at these things, new designs for the inhibitors, [and] more applications and understanding of the microRNA pathway. We may also see certain applications [of miRNAs having] importance in therapeutics development.”

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During 2006, a slew of peer-reviewed publications came out detailing new aspects of miRNAs and linking the small RNAs to a host of diseases and cellular processes. At the same time, companies have begun jumping into the miRNA ring to establish a presence in this growing field.

As reported by *RNAi News*, startup Rational Affinity has begun developing a microarray platform to profile human, mouse, and rat miRNA levels using molecular beacons (see [RNAi News, 10/19/2006](#)), while bigger life sciences player Luminex introduced in December its first microRNA product ever (see [RNAi News, 12/21/2006](#)).

Also in 2006, companies including Alnylam, Santaris Pharma, and Isis Pharmaceuticals expressed their interest in harnessing miRNAs for therapeutic purposes. Meanwhile, Asuragen, which was

formed at the beginning of last year with money from Applied Biosystems' purchase of Ambion (see [RNAi News, 1/5/2006](#)), began ramping up to develop cancer diagnostics in part based on miRNAs (see [RNAi News, 1/12/2006](#)).

Although miRNAs have received a lot of press recently, they won't likely be the only newsmakers in the small RNA field during 2007.

"I think in general we're going to see more and more appreciation of the importance of and more classes of non-translated RNAs that have high importance in biology," Marshall said.

BRI's Rossi agrees. Recent findings "suggest that small RNAs are regulating the genome at the level of DNA and also are very important in spermatogenesis and oogenesis in terms of shooting down genes that should be silenced during those critically important processes," he said. "There have been a number of papers on using small RNAs to direct transcriptional gene silencing at the level of DNA ... [and] this field is really going to break wide open next year. I think we're going to see whole new classes of regulatory RNAs that are going to be very important in terms of global gene regulation."

Just last month, David Bartel and colleagues at the Massachusetts Institute of Technology published a paper in [Cell](#) describing the discovery of a new class of small, non-coding RNAs in *C. elegans*. According to the paper, the researchers discovered a class of small RNAs called 21U-RNAs, which are "21 nucleotides long, begin with a uridine 5'-monophosphate ... are diverse in their remaining 20 nucleotides, and appear modified at their 3'-terminal ribose."

"We're [seeing] the tip of the iceberg," Mark Kay, a researcher at Stanford School of Medicine, told *RNAi News* last month. "These RNAs and the mechanisms are going to be much more complex than originally thought, and I think there is going to be a lot more fine-tuning of gene expression at levels that really haven't been uncovered yet."

"Once this information is known, it will be interesting to see how it can be applied for understanding biological function of genes, as well as using it in therapeutic avenues," he added. "For the next several years, I think it's going to be a very interesting time in the areas of RNAi and small RNAs and how they regulate genes."

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