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A triumph of perseverance over interference

The US approval of Onpattro—the first of a new class of small-interfering RNA (siRNA) drug—is a triumph for Alnylam and vindication for its leadership.

On August 10, the US Food and Drug Administration approved Onpattro (patisiran), Alnylam Pharmaceuticals' trailblazing siRNA treatment for neuropathy in hereditary transthyretin amyloidosis (hATTR). The approval validates siRNA as a new type of disease-modifying treatment that coopts the cell's endogenous microRNA (miRNA) machinery to downregulate aberrant mRNAs. It also represents the culmination of a $2.5 billion drug development program that took just 16 years—a remarkably short time to bring an entirely new therapeutic class to market, especially when one considers the challenges in terms of delivery, immunogenicity, specificity and stability. That Onpattro made it over the finish line is testament to the experience and perseverance of Alnylam's leadership. But for RNA interference (RNAi) to establish its credentials as a bona fide treatment modality, more siRNA therapies must follow in the near future.

Onpattro is a textbook example of how a biotech should develop an experimental moiety into a marketed drug. The 16-year timeline is all the more remarkable when one considers that the basic RNAi mechanism was discovered in worms in 1998 by Nobel prizewinners Andrew Fire and Craig Mello—and that Alnylam cofounder Tom Tuschl and colleagues demonstrated siRNA activity in human cells just one year before the company was founded in 2002. For these insights to be commercialized, Alnylam had to turn naked siRNA into a viable drug.

The drug development team's first challenge was to engineer the siRNA molecule for enhanced nuclease resistance, thermostability and potency without compromising silencing activity. Chemical modifications were identified in the phosphodiester backbone, the ribose 2′ OH group or other parts of the nucleobase ring that could be accommodated either on the siRNA passenger strand or on the guide strand's 3′ overhang (which binds Ago) or five proximal bases. By the time Onpattro entered clinical testing in 2012, the company had settled on 2′-*O*-methyl modifications of ribose and the incorporation of phosphorothioate-linked 2′-deoxy-2′-fluoro–modified thymidines at the 3′ ends.

One lingering safety concern was whether siRNA's mechanism of hijacking the endogenous miRNA pathway might impart deleterious effects—a concern that intensified following work from Mark Kay and colleagues showing that short hairpin RNAs expressed from strong promoters compete with endogenous miRNAs, causing death in mice (*Nature* **441**, 537–541, 2006). Until recently, the low occupancy of cells' RISC enzyme machinery by siRNA drugs was thought to obviate this safety concern. But the advent of new long-lasting siRNA chemistries has now placed RISC saturation and potential toxicities back into consideration. Time will tell whether the concern is real.

None of this would even be mentioned, though, if Alnylam had not addressed RNAi's biggest problem—that of delivery. Eight years ago, the lack of a standout delivery solution prompted several multinationals that had previously showered money on Alnylam—Roche, Novartis, Pfizer, Abbott and Merck—to exit the sector completely, sparking a crisis in investor confidence. It was only after the company licensed stable nucleic acid–lipid nanoparticles (SNALPs; see p. 777) from Tekmira Pharmaceuticals that efficient siRNA delivery to the primate liver became attainable, opening up hepatic indications as Alnylam's central focus; indeed, SNALPs were a key factor in Onpattro's success, albeit one that necessitates steroid pretreatment of patients to minimize infusion site reactions.

Of course, FDA approval of Onpattro does not guarantee commercial success. Investors were disappointed that the drug's label makes no mention of its cardioprotective effects in hATTR—an indication that would have opened up a larger market. The drug's current hATTR-affected population comprises around 3,000 people.

Even if Alnylam is successful in reaching these patients, Onpattro will have precious little time to monopolize the hATTR market as competing drugs are close on its heels. Next month, Akcea Therapeutics and Ionis Pharmaceuticals await a PDUFA decision on their 2′-*O*-methoxyethyl antisense oligonucleotide Tegsedi (inotersen), which is already approved in Europe. Onpattro also faces a challenge from Pfizer's small molecule Vyndaqel (tafamidis; p. 777), which also has cardioprotective qualities.

In the meantime, Alnylam is forging ahead with new backbone chemistries (e.g., glycol nucleic acid in the siRNA's guide strand to reduce off-target activity) and an entirely different delivery platform based on siRNA conjugation to synthetic triantennary *N*-acetylgalactosamine, which ramps up delivery to the liver via hepatocyte asialoglycoprotein receptor binding.

As with any new therapeutic modality, more surprises are to be expected. Just two years ago, for example, a high number of deaths in the treatment arm relative to the placebo arm in a phase 3 trial of another of Alnylam's anti-hATTR siRNA drugs, revusiran, wiped nearly $3.6 billion from the company's stock. It is still not clear whether these deaths were related to background cardiac events in the patients or attributable to a broader class-specific effect. As siRNA drugs are prescribed in the wider population, other unanticipated effects may emerge.

None of this diminishes the Alnylam team's achievement in bringing Onpattro to market. Neither does it diminish the appeal of the company's pipeline; to date, six other siRNA drugs are in late-stage clinical testing. What's more, the increased scalability and short development times for siRNA oligonucleotides compared with traditional drugs promises to disrupt established industry business models and pricing. There's no sign of this happening just yet: the list price of Onpattro is a whopping $450,000 per patient per year. Value-based pricing—a money-back guarantee that will rebate the entire cost of a drug if a patient fails to gain sufficient benefit—is, however, being offered to US insurers.

Certainly, more siRNA drug approvals are needed to validate RNAi as an important new therapeutic modality. As the saying goes: "One swallow does not a summer make." But it is still thrilling to see a new class of experimental therapeutic take flight for the first time.