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Alnylam prepares to land first RNAi drug approval

With Alnylam's rare disease drug candidate patisiran nearing the regulatory finish line, the RNA interference community is now turning its attention to next-generation delivery technology to solidify the future of the emerging modality.

Chris Morrison

Drug developers have been fishing in the bumpy RNA interference (RNAi) waters for years without a catch in sight. They probably won't have to wait much longer. In December 2017, RNAi pioneer Alnylam Pharmaceuticals finalized its regulatory submissions to the FDA and the European Medicines Agency of patisiran, for the treatment of hereditary transthyretin-mediated (ATTR) amyloidosis, a rare and potentially fatal disease characterized by the build-up of amyloid in peripheral nerves, the heart and other organs. The breakthrough-designated drug could hit the US and European markets this summer.

An approval will be a "landmark moment in a 15-year journey to harness the RNAi pathway as a source of medicines," says John Maraganore, CEO of Alnylam. It will also "facilitate new approvals in the future," he adds, providing regulators with an opportunity to come to grips with the modality.

Drug developers have of course already had success with oligonucleotide-based drugs. Regulators approved Ionis Pharmaceuticals' and Sanofi's high cholesterol treatment mipomersen in 2013, for example, highlighting the ability of single-stranded DNA-based oligonucleotides to silence mRNA via antisense mechanisms. And Ionis has also filed its mRNA-silencing antisense inotersen for hereditary TTR amyloidosis, as a potential competitor to patisiran. But patisiran — which uses a double-stranded RNA-based oligonucleotide to dampen protein expression via the RNA-induced silencing complex — now stands to broaden the biological range of oligonucleotide agents and add another option to the therapeutic tool box.

Enthusiasm ebbs ...

RNAi, a natural process for gene silencing, was discovered in 1998 (see *Nature*'s RNAi animation). It quickly became a powerful research tool to control protein expression, and by 2002 a field of start-ups emerged to turn RNAi oligonucleotides into drugs. Those start-ups captured the imaginations and enthusiasm of venture capitalists and public investors, and industry's largest companies eventually bought into the hope and hype as well. Novartis committed hundreds of millions of US dollars for access to Alnylam's platform in 2005, and Roche followed suit in 2007. In 2006, Merck & Co. paid $1.1 billion to acquire Alnylam's main rival Sirna Therapeutics, which prior to that deal had signed pacts with GlaxoSmithKline and others. The scientists who discovered RNAi won the Nobel Prize in 2006.

But owing to difficulties delivering RNAi therapeutics to systemic targets, RNAi's status as the next big thing in drug development subsequently waned. "When Sirna was sold to Merck, we were expecting the first generation of programmes to pan out in the clinic," says Douglas Fambrough, CEO of the RNAi therapeutics company Dicerna Pharmaceuticals and an early Sirna investor and board member. But those programmes were unsuccessful. Naked delivery of RNAi candidates to the eye to treat conditions such as age-related macular degeneration failed. Early iterations of lipid nanoparticle (LNP) delivery platforms — designed to encase and protect RNA from degradation before it reaches its target — required extremely high dosing to show even modest efficacy, and then only worked in liver-mediated diseases. "None of the respiratory stuff worked, none of the cardiovascular stuff worked, and as that became clear the big pharma partners began to peel away," says Fambrough.

In late 2010, Novartis and Roche both cut ties with Alnylam, delivering a combination punch that forced the biotech to restructure.

> Targeting liver RNAs with single-stranded or double-stranded RNA? Boy, I pretty well think we have it nailed

"We've had our near-death experiences," concedes Maraganore.

Merck continued to outwardly express enthusiasm for RNAi for a few years longer, but never moved any RNAi therapies into its publicly disclosed pipeline, and eventually sold its Sirna intellectual property (IP) to once-arch-rival Alnylam in early 2014 for less than a sixth of the Sirna purchase price.

"I think that large companies, and large pharma in particular, really stink at innovation around platforms, and we saw that with RNAi," Maraganore says. The near-death experiences that strengthened Alnylam's resolve are culturally incompatible with large organizations, he argues. And so when early generation RNAi candidates failed to deliver on their promise, it was unsurprising to see big companies cut back or abandon the space.

Alnylam was able to persevere, however, with support from hold-out partner Sanofi. Sanofi first signed on in 2012, and expanded this alliance in 2014 by buying $700 million worth of Alnylam stock in exchange for options to license rights to Alnylam's leading pipeline assets outside of North America and Western Europe. In January 2018, the partners renegotiated the deal such that Alnylam gained worldwide rights to patisiran as well as to ALN-TTRsc02, a subcutaneously administered ATTR amyloidosis follow-on programme that will enter phase III in 2018. Sanofi now has worldwide rights to phase III candidate fitusiran, a once-monthly, subcutaneously administered antithrombin RNAi for haemophilia A and haemophilia B.

... and flows

With RNAi now on the verge of its first approval, the biopharma industry is re-engaging with this technology. Amgen partnered with Arrowhead Pharmaceuticals (which in 2011 acquired Roche's RNAi programmes and IP) in 2016 in a deal that could be worth up to $675 million, for example, to work on cardiovascular projects. And Boehringer partnered with Dicerna in 2017, pledging up to $200 million, to work on non-alcoholic fatty liver disease and other chronic liver diseases. In part, says Maraganore, the interest is driven by the ability to evaluate the potential of experimental candidates like they would a small molecule or an antibody. "When these medicines start coming forward and start showing high-impact results like patisiran has, [large companies] will be interested in specific products," Maraganore says.

But renewed enthusiasm is also a product of how quickly the RNAi field is moving.

Table 1 | **Select late-stage RNA interference programmes**

Drug candidate	Developer	Clinical stage	Target	Therapeutic indication	Delivery method
Patisiran	Alnylam Pharmaceuticals	Registration	TTR	Hereditary ATTR amyloidosis	Lipid nanoparticle
QPI-1002	Quark Pharmaceuticals[a]	Phase III	p53	Delayed graft function	Naked
QPI-1007	Quark Pharmaceuticals	Phase III	Caspase 2	Non-arteritic anterior ischaemic optic neuropathy	Naked
Tivanisiran	Sylentis/PharmaMar	Phase III	TRPV1	Moderate to severe dry eye	Naked
Fitusiran	Sanofi/Alnylam Pharmaceuticals	Phase III	Antithrombin	Haemophilia A, haemophilia B	GalNAc conjugate
Givosiran	Alnylam Pharmaceuticals	Phase III	ALAS1	Acute hepatic porphyrias	GalNAc conjugate
Inclisiran	The Medicines Company/ Alnylam Pharmaceuticals	Phase III	PCSK9	Hypercholesterolaemia	GalNAc conjugate

Source: Biomedtracker. ALAS1, 5-aminolevulinic acid synthase 1; GalNAc, *N*-acetylgalactosamine; PCSK9, proprotein convertase subtilisin/kexin type 9; TRPV1, transient receptor potential vanilloid 1; TTR, transthyretin. [a]Novartis holds an option to license QPI-1002 following a phase III study.

Patisiran uses an intravenous LNP delivery technology that Alnylam and other RNAi hopefuls have almost entirely abandoned in favour of next-generation alternatives. The leaders in this field are instead now conjugating RNAi to *N*-acetylgalactosamine (GalNAc) or similar ligands to generate products with better therapeutic indices, which can be injected subcutaneously, at higher doses and with better side-effect profiles.

The most advanced GalNAc-conjugated RNAis are now in phase III (see TABLE 1). The biotech Arrowhead shut down multiple intravenously delivered RNAi programmes in 2016 when the FDA placed a clinical hold on its lead experimental hepatitis B treatment due to toxicity in a non-human primate study, and has shifted instead to a new pipeline of ligand-conjugated products. Dicerna, too, has transitioned to subcutaneous delivery using a GalNAc-based platform, and dosed its first patient with its new line of product candidates near the end of 2017.

These products, which make a bee-line for hepatocyte receptors, play to the biological tendency of oligonucleotides to traffic to the liver. And, notes Maraganore, "the entirety of the modern pharmacopeia" for liver-mediated diseases represents more than $50 billion worth of marketed products, not including long-genericized drugs such as statins. In other words, even if RNAi remains confined to liver targets, the opportunity here is significant. RNAi drugs are on the horizon for rare liver-mediated diseases such as haemophilia as well as more common liver-associated diseases including hypercholesterolaemia (PCSK9 is predominantly expressed in the liver) and hepatitis B infection.

Getting RNAi to work in other therapeutic areas is still challenging, says Art Krieg, CEO of Checkmate Pharmaceuticals and former head of oligonucleotide therapeutics at Pfizer. "But targeting liver RNAs with single-stranded or double-stranded RNA? Boy, I pretty well think we have it nailed. And there are a lot of liver targets," he says.

And for these targets, RNAi exhibits extraordinary drug-like properties that rival or exceed those of antibodies, argues Fambrough. The technology is "incredibly safe", with a high therapeutic index and a long duration of effect. At least in the liver, Fambrough says, "there's now a comfort level that this probably works and it's got a bunch of uses in some interesting areas in cardiovascular disease, chronic liver disease and rare disease."

Indeed patisiran met all primary and secondary end points in its phase III pivotal trial, and common side effects including injection-site reactions and peripheral oedema after 18 months of dosing were mild or moderate. The follow-on GalNAc-conjugated candidate ALN-TTRsc02 should theoretically achieve even better results.

Executives still hope however that the liver is just the beginning for RNAi. "We have data in extrahepatic delivery that we think are very promising and that might open up the door further, for RNAi therapy in cancers, in central nervous system disease and other areas," Maraganore says. Some companies have also persevered in the development of late-stage products that use naked RNAi to target the eye and the kidney.

Emerging technologies may yet extend the reach of RNAi and other oligonucleotide therapies further still. The biotech Codiak BioSciences, for example, has raised nearly $170 million since 2015 to harness membrane sacs called exosomes to deliver oligonucleotides. Whereas LNPs are synthetic lipid-based vehicles, exosomes are naturally secreted from cells and are part of what Codiak CEO Doug Williams calls a "fascinating and ancient communication system". Codiak's lead drug candidate, which should enter the clinic in late 2018, is an anti-KRAS RNAi designed to treat pancreatic cancer. "We're letting the exosomes lead the way," says Williams, "and the pancreas seems to be a tissue to which exosomes go in abundance." The reasons for this trafficking pattern remain unknown, he says.

Other companies are working to exploit exosomes for drug delivery as well. Several pharma and biotech companies "have been exploring exosomes in many cases to solve delivery problems for payloads they have access to," says Williams. "This is an idea that has come of age," he says.

Arrowhead is meanwhile developing an inhaled formulation of RNAi, to act in the lung, which is set to enter clinical trials this year.

RNAi therapies are also just one piece of the broader ecosystem of oligonucleotide technologies, which include antisense and exon-skipping drugs, viral-mediated gene therapies, mRNA-based drugs and genome-editing CRISPR therapeutics. And development and delivery success with these oligonucleotides could lift the RNAi tide.

"I really am feeling more confident than ever that oligonucleotide therapeutics are going to represent the third major platform of drug development," says Krieg, placing the emerging modality alongside small molecules and biologics. "At the beginning, I was skeptical about RNAi. But the progress in that field has been extraordinary."