animal models. ASOs targeting a site near the 5′ splice site in *SMN2* intron 7 could efficiently promote exon 7 inclusion without the need of an appended peptide moiety. They acted by preventing binding of the splicing repressors HNRNPA1 and HNRNPA2. In addition, chemical modifications in the backbone (phosphorothioate) and nucleotides (2′-*O*-methoxyethyl, or 2′-MOE) of the ASOs improved their pharmacological properties.

With promising results in pre-clinical studies, the ASO nusinersen entered clinical trial phase I and II studies in 2011 and 2013–2014, respectively. A multi-centre, randomized, double-blind phase III study took place in 2014–2016 and included 121 infants up to seven months of age who had been diagnosed with SMA before they were six months old (infantile onset). Participants received the drug injected intrathecally (that is, through a lumbar puncture for delivery into the cerebrospinal fluid, to reach targets in the central nervous system). A control group was treated with a mock procedure (skin prick). An interim analysis conducted with 82 patients showed that 40% of those treated with nusinersen showed improvements in motor function milestones, such as head control, sitting, rolling, crawling, standing and walking, compared to none in the control group. These results led to early termination of the trial in August 2016, so that infants in the control group could start receiving the drug. Beneficial effects observed in another trial, with children aged 2–12 with later-onset SMA, also prompted its early termination in November 2016.

> “…a successful collaboration between researchers in academia and industry, with support and assistance from patient advocacy groups and regulatory agencies”

The FDA approved nusinersen only three months after the new drug application (NDA) was filed by Biogen. This occurred with fast-track designation and priority review, and without an advisory committee, as outside expertise was not deemed necessary given the lack of controversial issues, as noted in the agency's summary report. Nusinersen was approved by the European Medicines Agency in May 2017, and it is currently available for treating SMA in more than 40 countries.

Inês Chen, Chief Editor,
Nature Structural & Molecular Biology

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MILESTONE 15

A new dawn for RNAi drugs

The 10th of August, 2018 marked a new era for the field of RNA therapeutics, with the first approval of an RNA interference (RNAi)-based drug by the United States Food and Drug Administration. The drug — patisiran (Onpattro) — is approved for the treatment of polyneuropathy in people with hereditary transthyretin-mediated amyloidosis (hATTR). This rare and devastating neurodegenerative disease is caused by deposition of amyloid fibrils formed by misfolded transthyretin protein. A double-stranded small interfering RNA composed of two modified 21-mer oligonucleotides and encapsulated in a lipid nanoparticle formulated for hepatocyte uptake, patisiran silences transthyretin mRNAs in the liver to reduce serum levels of the protein. The approval of patisiran brings new hope to patients with hATTR who previously had no effective treatment options.

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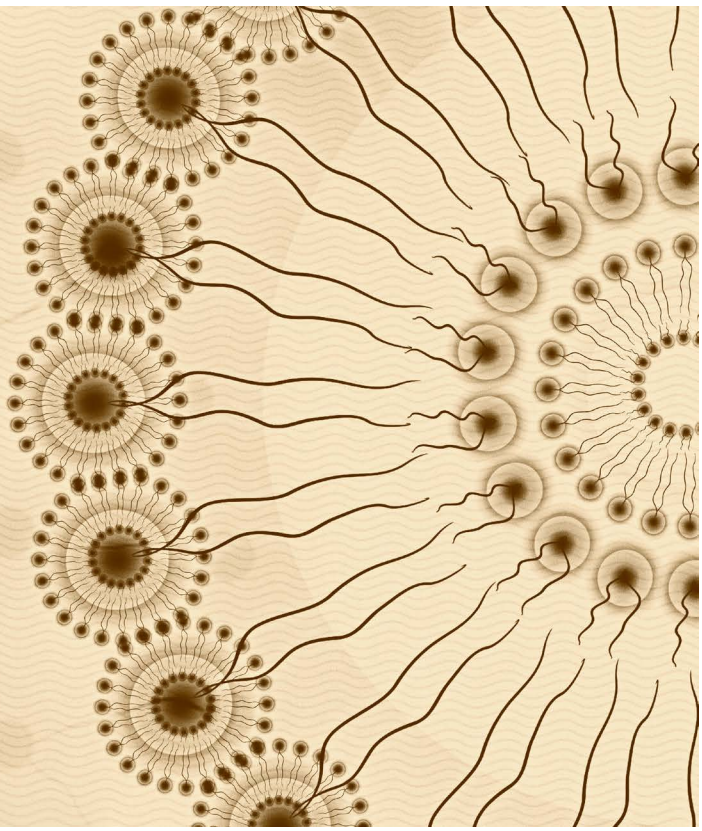

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