# Focus on RNA-based therapies


Ever since Zamecnik and Stephenson first described gene silencing by antisense oligonucleotides (ASOs) in 1979, RNA-based therapy has promised to transform drug development. The exquisite specificity and selectivity of these therapies, together with their ease of design, synthesis and manufacture, have galvanized the development of a new generation of products capable of modulating gene expression or altering transcript splicing and processing. With the emergence of additional RNA-based therapies, such as RNA–DNA aptamers that bind cellular targets and short interfering RNAs (siRNAs) that knock down genes with remarkable potency, drug developers now have at their fingertips a diverse set of modalities to modulate the cellular RNA regulatory machinery, including microRNAs/anti-microRNAs, synthetic mRNAs and now single guide RNA–directed CRISPR–Cas9-based genome editing.

To date, just one aptamer and four ASOs have been approved by federal agencies—two of which, Exondys 51 and Spinraza, were approved in the past six months. Although commercial development is picking up speed with the introduction of efficient chemistries that increase potency and reduce side effects, and delivery strategies that open up new disease sites, it will likely be several years before RNA-based therapies become widely adopted across the industry (**Editorial, p. 181**).

The major challenge for RNA therapeutics has turned out to be their delivery across lipid bilayers. Although highly charged RNA molecules are taken up via endocytosis, their inability to exit the endosome and traffic to their targets in the cytosol and nucleus is a major impediment (**Perspective, p. 222**). Based on an improved understanding of the underlying chemical principles that can be harnessed to overcome issues of stability, specificity, trafficking and uptake, chemical design of RNA molecules has come a long way toward improving efficacy and safety (**Review, p. 238**).

Despite the introduction of *N*-acetylgalactosamine conjugation, which has enabled liver targeting of both ASOs and siRNAs, delivery continues to be a roadblock for many tissues and applications. But progress is being made rapidly, and for now, intrathecal delivery to the cerebrospinal fluid is opening up a range of therapeutic applications in the central nervous system (**Review, p. 249**). A thorough understanding of the cellular machineries that contribute to the uptake of RNA drugs is essential for improving delivery efficiency, yet our understanding of these processes remains rudimentary, as discussed in the context of ASOs by Crooke and colleagues (**Perspective, p. 230**).

There are both marketed ASO and aptamer products, but industry still eagerly awaits the approval of an siRNA drug. Currently, two siRNA oligonucleotides are in late-stage clinical testing, with pivotal results from Cambridge, Massachusetts–based Alnylam's patisiran for transthyretin amyloidosis due by mid-year (**Feature, p. 198**).

Although the therapeutic feasibility of synthetic mRNAs remains unproven, interest is building in the potential of RNA vaccines. Creating an injectable RNA vaccine using the genome sequence of a pathogen or of a tumor is an alluring concept, but the approach still faces formidable challenges, such as antigen discovery, product formulation and delivery (**News Feature, p. 193**).

## Patent roundup

Despite the importance of patent landscape analyses in the commercialization process for life science technologies, the quality of reporting in published articles has been inadequate. Brindley and colleagues suggest ways to improve reporting quality, which will ultimately increase the impact of the research and provide a greater contribution to the scientific community. (**Patent Article, p. 210**).

Recent patents in chimeric antigen receptors. (**New Patents, p. 215**)

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