Nucleic Acids Research, 2018, Vol. 46, No. 4 ***1563–1564***
doi: 10.1093/nar/gky059

Editorial: *Nucleic Acids Research* and Nucleic Acid Therapeutics

Barry L. Stoddard[1], Anastasia Khvorova[2], David R. Corey[3], William S. Dynan[4] and Keith R. Fox[5]

[1]Division of Basic Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Seattle, WA 98109, USA, [2]RNA Therapeutics Institute, University of Massachusetts Medical School, 368 Plantation Street, Worcester, MA 01605, USA, [3]Departments of Pharmacology & Biochemistry, University of Texas Southwestern Medical Center, 6001 Forest Park Road, Dallas, TX 75390-9041, USA, [4]Departments of Biochemistry and Radiation Oncology, Emory University School of Medicine, 4127 Rollins Research Center,1510 Clifton Rd. NE, Atlanta, GA 30322, USA and [5]Centre for Biological Sciences, University of Southampton, Life Sciences Building 85, Southampton SO17 1BJ, UK

Over the past several decades, the concept of using molecules composed partially or wholly of nucleic acids as therapeutic moieties, and the modification of such molecules via synthetic strategies, has been discussed and actively pursued by many academic and industrial laboratories. As compared to small molecules (and more recently antibodies and other protein-based drugs) the use of oligonucleotides and related compounds as therapeutics has advanced more slowly—a fact that is not surprising, given the challenges that such molecules (and their investigators) face. Nucleic acids are large, highly charged, rapidly degraded and cleared from the body, and offer generally poor pharmacological properties. The development of nucleic acids as potential therapeutic agents has nonetheless moved forward at a steady pace, owing in large part to important discoveries regarding their role in regulating gene expression, and in part to the development of increasingly sophisticated synthetic and biochemical methods to alter many of the physical properties that might limit their potential as drugs.

Nucleic Acids Research has recently commissioned the publication of a series of Survey and Summary articles that encapsulate the current 'state of the art' surrounding the creation, function, behavior and optimization of nucleic acid molecules that may be adopted for clinical applications. These reviews are focused on:

- Antisense oligonucleotides and duplex RNAs that directly regulate translation and gene expression (1)
- Transcriptional gene silencing RNAs that result in long-term epigenetic modifications (2)
- Antisense oligonucleotides that interact with and alter gene splicing patterns (3)
- The *in vivo* delivery of therapeutic oligonucleotides (4)

These reviews, along with research articles recently published in *Nucleic Acids Research* on the characterization and development of nucleic acid molecules for potential therapeutic use, are now provided as a special collection at the journal's website. The research articles include descriptions of the chemical modification of oligonucleotides for the purpose of altered and improved *in vivo* properties (delivery, stability, life-time, folding, target specificity), as well as basic studies of their biological function and mechanism that directly inform investigators with an interest in therapeutic application.

The major advances being made in the development of nucleic acid therapeutics are evident in recent clinical achievements, such as the recent approval of Spinraza, the first central nervous system (CNS)-active antisense oligonucleotide (ASO) for the treatment of spinal muscular atrophy and the filing for regulatory approval in both the United States and Europe of Patisiran, a lipid-siRNA particle for the treatment of hereditary ATTR Amyloidosis.

In addition, the field is witnessing the realization of the original promise of nucleic acid therapeutics: compounds for which the development of second generation drug candidates (targeting the same tissue) occurs with a significantly reduced timeline and price tag. For example, while the development of the first CNS-active ASO took several decades, the pipeline has now produced several other compounds addressing the needs of patients with a wide range of neurodegenerative diseases. On 11 December 2017, Ionis Pharmaceuticals announced preliminary results from a Phase 1/2a study designed to test the ASO HTT_{RX} in patients with Huntington's disease. The study demonstrated a dose-dependent reduction of mutant huntingtin protein, the factor known to cause the disease. The safety/tolerability profile supports continued development of this

compound and others of similar chemical configuration targeting other genes. This compound has been licensed to Roche, which will now be responsible for subsequent studies. Though much remains to be learned about whether HTT_{RX} can reduce huntingtin levels sufficiently to affect the course of the disease, these findings are an important landmark for using ASOs to treat a currently incurable adult-onset neurological disease.

Similarly, the development of advanced stabilization chemistries in combination with multivalent GalNAc conjugates has resulted in an expanded pipeline of liver-targeting drug candidates, in which a single administration has been shown to modulate gene expression in patients for 6–9 months. These GalNAc conjugates represent a major design breakthrough at the interface of nucleic acid chemistry, biology, and medicine and are likely to have an increasingly broad clinical impact.

Moving forward, basic science will continue to drive the long-term development of oligonucleotide therapeutics. Many important questions remain unanswered and topics of special interest include improved delivery methods, identification and exploitation of new therapeutic targets, new cellular targets and mechanisms, and new chemical approaches to improving oligonucleotide function.

NAR looks forward to continuing to publish groundbreaking research in this area. As described in our posted Scope and Criteria for Consideration webpage, we welcome submissions in all areas related to the development of nucleic acid therapeutics. Reports must include rigorous controls and statistical analysis. Advances in mechanistic understanding should be stressed. Studies describing clinical results will be considered, but only if studies address key questions related to drug mechanism of action, distribution or pharmacokinetics. Studies relating to cellular uptake, delivery and oligonucleotide chemistry are particularly encouraged.

REFERENCES

1. Shen,X. and Corey,D.R. (2017) Chemistry, mechanism and clinical status of antisense oligonucleotides and duplex RNAs. *Nucleic Acids Res.*, doi:10.1093/nar/gkx1239.
2. Weinberg,M.S. and Morris,K.V. (2016) Transcriptional gene silencing in humans. *Nucleic Acids Res*, **44**, 6505–6517.
3. Havens,M.A. and Hastings,M.L. (2016) Splice-switching antisense oligonucleotides as therapeutic drugs. *Nucleic Acids Res*, **44**, 6549–6563.
4. Juliano,R.L. (2016) The delivery of therapeutic oligonucleotides. *Nucleic Acids Res*, **44**, 6518–6548.