FOREWORD

SPOTLIGHT ON • Ongoing efforts to enhance stability

Ongoing efforts to enhance stability

Adrian Keller

FOREWORD

"The contributions in this issue underscore the great importance not only of addressing specific challenges in nucleic acid stability with existing technologies, but of exploring completely new avenues..."

Over the last few decades, a large variety of nucleic acid-based therapeutic approaches and drug formulations have been developed in the lab, tested in the clinic, and brought to market, ranging from antisense oligonucleotides (ASOs) and siRNAs to aptamer inhibitors and mRNA vaccines, with DNA and RNA nanostructure therapeutics already looming on the horizon. However, being susceptible toward hydrolysis, oxidation, non-specific binding, and nuclease digestion, unmodified nucleic acids are rapidly degraded *in vivo*, resulting in poor therapeutic performance. Therefore, several stabilization strategies have been developed in order to protect those fragile molecules against adverse conditions during storage and in the body, while simultaneously accommodating their various mechanisms of action such as cellular uptake, target binding, or translation. These strategies include chemical modifications at the nucleoside level, complexation with proteins and polymers, and encapsulation in lipid nanoparticles (LNPs). Despite this variety of available methods, the field still faces many challenges, and this issue aims to provide an overview of the ongoing efforts to enhance the stability of therapeutic nucleic acids.

Nucleic Acid Insights 2026; 3(6), 461–463 · DOI: 10.18609/nai.2026.055

In his **Expert Insight**, Ken Yamada summarizes the current state of the art and discusses unmet challenges of the metabolic stabilization of siRNA. He addresses the role of chemical modifications that are used to protect siRNA against hydrolysis and nuclease degradation and to reduce immune activation, with a special emphasis on emerging terminal modifications. However, as the article highlights, such chemical modifications may also have negative effects on therapeutic performance by affecting Argonaute 2 engagement, which constrains the accessible design space. Furthermore, the article also discusses recent evidence that enzymatic siRNA degradation is tissue- and compartment-specific, which may necessitate the incorporation of tissue-adaptive chemical architectures. At the same time, however, this might also enable the development of novel siRNA systems with tissue- and mechanism-dependent stability and improved therapeutic performance.

The **Viewpoint** article by Pintu Kanjilal focuses on the aspect of LNP stability and its impact on RNA-LNP formulations. Despite being in clinical use for considerable time, LNP formulations often suffer from limited stability with lipid degradation presenting a particular challenge. Most critical in this regard is the possible N-oxidation of ionizable lipids within the LNP, which may lead to lipid-RNA adduct formation and production of aldehyde. Since small amounts of such impurities can already have severe effects on therapeutic performance, highly sensitive methods for impurity detection and lipid characterization must be applied. However, as the article further explains, lipid degradation may also be mitigated by lipid engineering and buffer optimization.

In their **Expert Insight**, Olavi Reinsalu *et al.* review the young and emerging field of hybrid RNA/DNA origami nanostructures (RDONs). Utilizing the same principle and general mechanisms as well-established DNA origami technology, RDONs are based on RNA scaffolds that are folded into nanoscale shapes by hybridization with DNA oligonucleotides. As detailed in the article, this folding into hybrid nanoparticles not only results in improved stability of the RNA scaffold against RNase H compared to linear RNA/DNA duplexes but also enables the introduction of additional modifications and the application of coatings, which can be used for instance to further protect the RDONs against nuclease digestion or to enhance cellular uptake and cell targeting. Most importantly, successful translation of mRNA scaffolds from RDONs into protein was achieved in both extracellular environments and mammalian cells. For this, however, the overall RDON design and especially the routing of the mRNA scaffold must be optimized. Although the molecular mechanisms of RDON translation are yet to be elucidated, these early results hint at the exciting possibility to engineer and program customized translation profiles by the rational design of RDON structural properties.

Finally, to address stability-related issues of therapeutic nucleic acids adequately, one must realize that the term 'stability' may refer to very different settings and mechanisms. This is discussed in the **Viewpoint** article by Stanislav Kan. Focusing on mRNA-LNP formulations, the article highlights four stability aspects and how they can be addressed. Sequence design and the introduction of chemical modifications can protect against hydrolysis and degradation. LNP composition and behavior in relevant environments must be engineered to ensure therapeutic integrity during storage. Drying is a critical aspect that not only affects storage conditions but may also severely impact therapeutic performance and dosing. All these steps together determine *in vivo* durability after administration, which in turn dictates treatment outcomes. Thinking about stability in such a holistic way will advance the development and manufacturing not

Nucleic Acid Insights 2026; 3(6), 461–463 · DOI: 10.18609/nai.2026.055

only of mRNA-LNP formulations but of therapeutic nucleic acids in general.

The contributions in this issue underscore the great importance not only of addressing specific challenges in nucleic acid stability with existing technologies, but of exploring completely new avenues beyond the established methods and approaches. While such new approaches may present new challenges of their own, they may also present exciting opportunities to perfect existing therapeutic strategies and develop completely new ones.

BIOGRAPHY

Adrian Keller, leads the Nanobiomaterials Group at Paderborn University, Germany. His research is focused on DNA nanotechnology with an emphasis on biomedical applications. He has done extensive work on the impact of design factors and molecular interactions on DNA origami stability in physiological and non-physiological environments. His other research interests include DNA nanostructure-based antimicrobial drug delivery and the interactions of DNA nanostructures with solid surfaces.

Adrian Keller, Technical and Macromolecular Chemistry, Paderborn University, Paderborn, Germany

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given their approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author has no conflicts of interest.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

AI process statement: No AI tools were used in the preparation of this article.

Article source: This article was written by the named author and reviewed by BioInsights' Editorial team to ensure clarity and alignment with BioInsights' editorial standards.

Revised manuscript received: Jul 1, 2026.

Publication date: Aug 5, 2026.