EDITORIAL CALENDAR **2025**

NUCLEIC ACID INSIGHTS

FEBRUARY	MARCH	APRIL	MAY	JUNE
New directions in application	Innovation in engineering and design	Manufacturing: upstream/ synthesis	Platforming	Next-generation approaches to delivery
LNPs: what does the future hold?	Diagnostic/sensor applications	Analytics	Engineering and manufacturing	Upstream/synthesis: sustainability and innovation

JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER
Analytics	New directions, new modalities	Downstream/ purification: issues and ramifications	Delivery	Manufacturing: downstream/ purification
Getting beyond the liver		Preclinical tools and technologies	Stability	At the interface of synthetic biology and DNA

CROSS-PILLAR EDITIONS

Special editions addressing key questions and challenges across the spectrum of nucleic acids

CONTENT PILLARS

- mRNA
- Formulation and delivery
- Oligonucleotides
- DNA

Nucleic Acid Insights provides you with fantastic opportunities to:

- Educate your target market about your company's expertise, capabilities, and experience
- Share your latest data with organizations looking for partners and service providers in your field
- Profile your executives and scientists as thought-leaders and KOLs
- Generate qualified leads from across the global sector
- Increase awareness of your company's role in nucleic acid R&D

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NUCLEIC ACID INSIGHTS

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mRNA — FEB

New directions in application

- Targeting the CNS and other organs/organ systems—opportunities and challenges
  - Achieving delivery to the CNS and related clinical applications (such as replacement therapies for autosomal recessive disorders)
- Exploring potential mRNA applications for enzyme/protein replacement therapy
- What are the next steps in preclinical, clinical, and analytical development terms for mRNA-based cancer vaccines, and what can the mRNA therapeutics field as a whole glean from their recent success in the clinic?

Formulation and delivery

LNPs: what does the future hold?

- Significant hepatic cell transfection and associated toxicity is a cornerstone issue for LNPs: can newer lipids solve it?
- Current innovations in lipid design and optimization
  - What progress in better targeting specific cells and organs?
  - Improving stability
  - Solving endosomal escape
  - Improving immunogenicity (e.g., through immunosilent biomaterials)
  - Reducing complexity
    - Do we need simpler delivery systems? (e.g., one or two component LNPs?)
- Is the capital investment needed to solve the current technical hurdles facing LNPs simply too high? If so, how to address this issue?
- Overcoming freedom to operate barriers
- Functionalized LNPs such as peptide bound targeting
  - Assessing methods for synthesis and analysis to test consistency with binding and localization surrounding the LNP, and successes *in vitro*/*in vivo*
- Currently available technologies to formulate LNPs, and enhance manufacturing scalability
- Are better methods needed to accurately measure encapsulation efficiency?

Oligonucleotides — MAR

Innovation in engineering and design

- Oligonucleotide conjugate approaches to solve targeting and bioavailability issues
  - Extrahepatic targeting: what progress in targeting different tissue and cell types (cardiomyocytes, kidney, retinal disease, tumor cells, etc.)?
  - What are the most promising approaches to crossing the blood–brain barrier
  - How are C16 and other conjugates improving biodistribution/half-life in the CNS?
  - Oligonucleotide-PROTAC (proteolysis-targeting chimera) design
  - Antibody/peptide-based conjugates
  - Lipid-based conjugates
- Optimizing construct/biology for improved targeting and lower toxicity
- Moving towards a better understanding of how structure impacts efficacy, and how structural components interact
- How can novel backbone chemistry and base modifications be translated for practical applications, and to overcome barriers to approval?
- Exploring ways of measuring and understanding the effect of oligonucleotide design on the interaction with lipid components, and the resulting efficacy of the therapeutic
- Addressing difficulties in synthesizing longer oligonucleotides, and the effect design has on synthesis
- RNAi/siRNA production challenges
- siRNA versus single-strand oligonucleotides: differences in chemical building blocks and future designs
- Non-canonical nucleotides/amino acids
- Enhancing ASO targeting of long non-coding RNAs
- How do different modifications impact cost, synthesis efficiency, stability, and silencing efficiency?

DNA

Diagnostic/sensor applications

- Exploring the latest applications of DNA technology/nanotechnology in the areas of:
  - diagnostic sensor molecules
  - blood tests
  - lab on a chip
    - comparison of the informative value of organ, organ on a chip, and animal models
  - nuclear medicine and PET imaging
  - off-target effect analysis for gene editing platforms
  - drug delivery systems (e.g., DNA nanostructures)
  - gene delivery using doggybone DNA, minicircles or DNA origami

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mRNA — APR

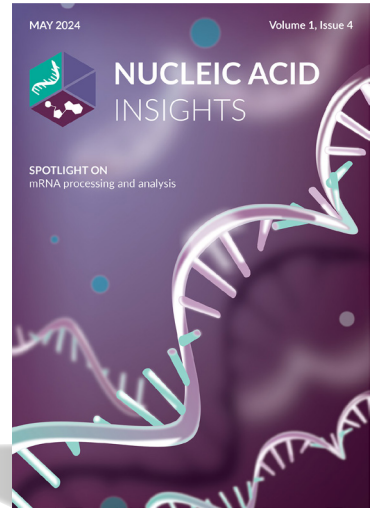
Manufacturing: upstream/synthesis

- How best to address potential downstream purification issues in upstream processing?
- How to reduce CoGs?
  - Prohibitive pricing for raw materials that inhibits the development of new RNA-based drugs
  - Reducing CoGs for key IVT reaction materials and reagents
- Approaches to improve stability while protecting translational efficiency
- Exploring the pros and cons of utilizing plasmid DNA as an IVT template
- Do alternatives to pDNA currently represent a viable alternative in this setting?
- How to effectively leverage AI/ML tools and approaches for sequence optimization?
- Addressing the limitations of solid-phase IVT
  - Is solid-phase appropriate for large indications?
  - How to resolve the issue of limited availability of specific reagents?
- Achieving small-scale mRNA production for the manufacture of personalized therapies
- How and where is flow chemistry being applied to mRNA manufacturing and what benefits does it provide versus traditional batch manufacturing?

Oligonucleotides

Analytics

- Impurity characterization/control strategy—addressing issues of varying quality and molecular mass
  - Impurity grouping via shared characteristics—what is the best approach with existing analytical tools (e.g., by retention time, structural classes, etc.)?
  - Increasing the level of impurity characterization and separation via improved/next-generation analytical tools and methods
  - Detecting and removing truncated sequences
  - Analysis of diastereomeric composition of oligonucleotides
    - Should this method only be used for monitoring of consistency, or can/should it be applied for other purposes?
- How to improve access to quicker and cheaper options for deep analytics (e.g., RNAseq, smallseq)?
  - Progress towards increasing accuracy in RNA sequencing
- Analytical methods and tools for understanding safety, toxicity, and fundamental biology
  - Which analytical approaches can build our understanding of the modes of toxicity driven by nucleotide constructs?
    - Single strand characterization and structural analysis for siRNAs (particularly with respect to the duplex being the API)
      - Stability and forced degradation studies
  - Standardizing protocols and toxicology data generation to enable comparators for assessment between products
  - How to best compare *in vitro* and *in vivo* study data when assessing toxicity?
  - Are cell viability stain results a good indicator of *in vivo* toxicity?
  - Which tests are necessary for different clinical applications? E.g. systemic/location application, different diseases (metabolic disease, oncology), different organs (skin, eye, etc.)
- Analytics for comparability studies when changing manufacturing processes or materials
  - Which quality attributes should be analyzed?
  - How to meet the need for high-resolution methods?
- Harnessing nuclear medicine (e.g., PET imaging) to enable whole-body visualization and dynamic tracking of nucleic acids for ADME and toxicity evaluation *in vivo*



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NUCLEIC ACID INSIGHTS

mRNA — MAY

Platforming

- Exploring potential platform approaches to mRNA to streamline and accelerate development
  - Automation, harmonization, and digitalization of USP and DSP strategies
- Optimizing and standardizing both delivery systems and manufacturing processes
  - How to drive improvements in scalability and consistency?
  - Are LNPs the way forward?
  - Impact of quality by digital design on platform approaches
  - Improving sustainability and reducing carbon footprint
    - What are the keys to successfully adopting green reagents and sustainably-sourced materials?
- Addressing regulatory hurdles to developing a platform approach

DNA

Engineering and manufacturing

- Manufacturing of DNA payloads
  - Enzymatic reactions/non-viral dsDNA production
  - Bacterial fermentation-based production
- How to address the ongoing plasmid DNA supply bottleneck?
  - Animal-free enzyme sourcing
  - Nucleotide manufacturing
  - Cell banking and characterization challenges
  - How are new production methods and DNA vectors solving and simplifying supply issues?
- Novel engineering approaches and structures to solve current challenges
  - How does DNA payload affect delivery?
  - Applications of ssDNA (less toxic and more flexible than dsDNA)
  - Nuclear delivery of DNA beyond viral systems
  - Addressing the limited time window for lesion targeting, payload release, and disease theranostics
  - Novel DNA backbones
- Scalability—current challenges and opportunities
  - How to successfully scale research processes to manufacturing scale?
  - Does the field need better scalability, or is better GMP-grade manufacturability (thus reducing the amount of DNA needed for a given application) the optimal solution?
  - Scaling out versus scaling up
    - How are manufacturers addressing the challenge of 'scaling small', but at an ultra-high throughput?
    - Can increased automation play a greater role in enabling ultra-small scale pDNA manufacturing?
    - Do compendial analytical methods need to be reconsidered when dealing with large numbers of batches manufactured at small-scale?
  - As demand for pDNA increases, how are processes being streamlined to manage the waste streams?
    - What are the opportunities to minimize the carbon footprint of the process—including the large amounts of disposables consumed in each manufacturing run?
- Exploring the potential of DNA/RNA interaction systems
- Applications for structural DNA nanotechnology
  - Leveraging DNA's robustness versus RNA to build structures and combine with other biomolecules

mRNA — JUN

Next-generation approaches to delivery

- Are novel LNPs the solution—or do we need new delivery vehicles entirely?
  - Assessing the limits and constraints still facing LNP approaches
  - Branched polymer systems/polymers for mRNA delivery—which classes are showing most promise?
    - Polymeric nanoparticles, polymer-lipid hybrid nanoparticles, and polyester-based nanoparticles
  - Extracellular vesicles
  - Virus-like particles (VLPs)
- Optimizing RNA stability through the advancement of non-temperature-dependent formulations
- What can we learn from the polymer field, and how can this information be translated into the lipid space?
  - ...and vice versa—what can we learn from lipids to design better polymers for RNA delivery?
- Assessing the potential of various routes of administration to improve safety, efficacy, and patient experience
  - IV and oral delivery
  - Inhaled delivery for targeting the respiratory tract
  - Intramuscular injection

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NUCLEIC ACID INSIGHTS

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Oligonucleotides

Upstream/synthesis: sustainability and innovation

- Novel versus traditional synthesis methods and tools—what are the key emerging alternatives? What data and insights do we have to date on the benefits and advantages they offer, and the challenges and considerations they present?
  - Transient transfection, cell lines or chemical synthesis?
  - Blockmers—does combining blockmers and enzymatic technology result in enhanced benefit?
  - Enzymatic biocatalytic technologies
  - Addressing the limitations of solid-phase synthesis—is liquid-phase technology the solution?
  - Reducing CoGs (including cost of key raw ingredients)
  - Addressing issues of yield, capacity, and scalability
  - What can we expect to see in terms of emerging regulatory guidance pertaining to novel synthesis techniques moving forward?
    - Can the different chemical building blocks currently being used in solid-phase synthesis be used (and are they appropriate) for new manufacturing technologies? Should other chemical building blocks be considered?
- How can the sustainability of oligonucleotide manufacturing be improved?
  - Expanding the range of alternatives to traditional synthesis techniques to contribute to environmentally sustainable manufacturing
  - Solutions for reducing waste and environmental damage
    - Pros and cons of recycling of acetonitrile
- Addressing manufacturing and regulatory challenges for longer oligonucleotide constructs (>20 bps)
- What are the key opportunities to establish platform technologies for the benefit of the oligonucleotide synthesis field?
  - Platforming ASOs: will utilizing the same chemistry with different genes prove promising for platform submissions?
- Scaling up oligonucleotide synthesis and tackling long lead times for production in order to support the growing field
  - Making manufacture of ASOs for small/ultrarare indications cost and manufacturability friendly
  - Achieving large-scale production for bigger indications—particularly in the siRNA field
- Tackling key challenges for RNAi/siRNA upstream processing, including:
  - oligonucleotide synthesis and purification
  - duplex synthesis and purification
  - the impact of racemic mixtures of phosphoramidites
- Reducing the cost of raw materials that impact RNA-based drug development
- How and where is flow chemistry being applied to oligonucleotide manufacturing and is it proving to be a promising alternative to traditional batch manufacturing?
- Which models are best suited to in silico design?
- What influence is increasing competition from GMP manufacturers having on price development?
- Solving workforce issues—how can the field address lack of people trained to synthesize oligonucleotides/conjugates and develop/research new targets and ligands?

JUL

mRNA

Analytics

- How and where are cutting-edge RNA analytics driving improvements in terms of scalability, speed, cost, and accuracy?
- Building capabilities in deep RNA biology analytics to enable less complex and cheaper RNA production
- Meeting challenges in validating next-generation/deep sequencing across applications and platforms
- Standardization of analysis techniques—progress and challenges
  - Assessing and addressing variation in methods of analysis of intact mRNA post-IVT
- How can existing analytical tools and methods be adapted for mRNA applications (e.g., through specific softwares) and where are new methods needed to address current needs and gaps?
  - Tools/software for sequencing based on mass to charge ratio
  - Size exclusion
  - Zetasizer for particle size charge
  - Membrane technologies
  - Leveraging HTPS and AI

Formulation and delivery

Getting beyond the liver

- What approaches hold the greatest promise for achieving extrahepatic delivery?
  - Exploring different routes of administration (e.g., with regard to crossing the blood–brain barrier)
  - Assessing the pros and cons of different *in vivo* delivery technologies beyond LNPs, including:
    - DNA vectors
    - polymer delivery
    - exosomes and EVs
    - covalent lipid-based delivery-molecules
  - What progress in achieving effective nucleic acid delivery into solid tumors?
  - Assessing the current state-of-the-art and future directions in specific cell and tissue targeting
    - Focus on delivery to the CNS
    - Exploring new receptors
    - Strategies for avoiding non-specific uptake

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NUCLEIC ACID INSIGHTS

mRNA — AUG

New directions, new modalities

- Analyzing recent preclinical and clinical data for mRNA, circRNA, saRNA, and microRNA therapeutics—what do they tell us about their relative future prospects and likely areas of application?
- Advances in structure and design
  - How can we further develop RNA structure to improve stability?
- Modified versus unmodified mRNA: in which specific settings is each option most appropriate?
- How to leverage the relative advantages of circular RNA/synthetic circular RNA in therapeutic application? (e.g., improved stability and storage characteristics versus mRNA)
- The potential of delivering base editors as mRNA rather than plasmid DNA to reduce off-target editing
- Addressing commercial challenges in a changing landscape
  - As investment in rare disease areas wanes, how can developers pivot their commercial strategy?
- mRNA-LNP delivery for *ex vivo* CAR T cell modification

Oligonucleotides — SEP

Downstream/purification: issues and ramifications

- How to address the issue of complex impurity profiles in the oligonucleotides space?
- Considerations for and challenges in purifying single-stranded oligonucleotides/ASOs versus double-stranded siRNAs
- How can downstream process innovation help address outstanding questions around long-term toxicity and tolerance?
  - What assays can best answer the questions that regulatory agencies are asking?
- How to successfully adapt platform technology and knowledge for the oligonucleotides space to accelerate regulatory approval?
- Tackling uncertainty in terms of regulatory CMC requirements in the oligonucleotide field
  - What progress is being made through collaborative efforts to harmonize regulators' requirements?
  - Are one-size-fits all platforms feasible for oligonucleotide-based therapeutics?
    - How can AI and HTPS be leveraged in order to integrate our understanding of material properties, intracellular function and modifications, and disease characteristics?
- Addressing downstream processing challenges for RNA products and the requirement for reverse phase chromatography
  - Inherent challenges with reverse phase materials (e.g., use of solvents, requirement for more specialized facilities)
  - Advantages of single-step purification (e.g., RP versus AIEX or double-step purification)
- Reducing the cost of key materials and reagents for IVT reactions, such as dNTPs, polymerases and other capping reagents
- Analyzing RNAs for product- and process-related impurities and activity requires double the methods of other modalities such as monoclonal antibodies—can analysis be improved upon and streamlined?
  - What progress is being made in developing analytical tools and methods specifically for nucleic acid applications, instead of borrowing from other fields?
    - Tools/software for sequencing based on mass to charge ratio
    - Size exclusion
    - Zetasizer for particle size charge
    - Membrane technologies
  - How can the high costs of analytical methods and equipment be reduced?
- How are purification strategies affected by changes in the way oligonucleotides are manufactured?
  - Such as solid phase versus liquid phase versus blockers and enzymatic
- Flow chemistry approaches versus traditional batch manufacturing—what are the associated pros and cons of each?

Cross-pillar edition

Pre-clinical tools and technologies

- Developing appropriate models for safety and toxicity
  - For oligonucleotides, toxicology models are proving particularly challenging—what progress is being made here?
- How is the field addressing the lack of appropriate preclinical models to assess mRNA efficacy?
- Applying AI/ML to nucleic acid drug discovery and development
  - Screening databases and predicting potency based on sequences and expression profiles
  - Applying computational modeling to find new targets using patient data
  - What specific modeling tools can reveal relationships between biological activities and the structural properties of chemical compounds (e.g., QSAR modeling)?
  - Assessing AI models for optimal LNP formulation
  - Predicting RNA:oligonucleotide therapeutic interactions
  - Predicting RNA folding for small molecule targeting
  - Applying AI/ML for oligonucleotide therapeutic design
- Moving away from animal systems and towards patient-derived cell lines and organoids for preclinical applications—opportunities and limitations
- Establishing best practice guidelines and appropriate controls and protocols for reliable *in vitro* validation

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NUCLEIC ACID INSIGHTS

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Oligonucleotides — OCT

Delivery

- Are antibody-drug conjugates being replaced by oligonucleotides for targeted delivery applications?
- Where is the field heading in terms of finding new receptors and uptake pathways into other tissues and organs besides the liver?
- What are the latest innovations in chemical modification achieving in the way of enhanced specificity of delivery?
- What avenues are being explored to enable efficient delivery to cells, in order to enhancing the potency and safety profile of oligonucleotide therapeutics?
  - Addressing endosomal escape
- Assessing the advantages and drawbacks/CMC requirements of both established and newer delivery vehicles
  - Cell penetrating peptides
  - Bacteria and viruses
  - LNPs and ligands
- Targeting productive versus unproductive uptake pathways—how best to direct oligonucleotides?
  - How to avoid recycling/removal from the cell?
  - Understanding/explaining long terms effects of siRNAs, which seems to last much longer than they can be detected in the body (e.g., the depot effect)
- Exploring conjugation-based solutions to delivery challenges
  - Achieving CNS delivery with lipid-oligonucleotide conjugates—current progress and future directions
  - Conjugates with antibody/drug
  - Oligo-PROTAC designs
  - Decoy oligodeoxynucleotides that targeting undruggable transcription factors
- Progress on improving targeting via dual/double targeting with two siRNAs—e.g., taking two liver targets and combining into one conjugate using a GalNAc
  - Combining complementary targets and achieving a synergistic effect
- Addressing outstanding challenges in delivery nucleic acids to the corresponding active site inside the cell:
  - low *in vivo* stability
  - rapid host clearance outside cells
  - poor permeability through the cellular membrane due to negatively charged backbone
- Leveraging chemically modified aptamers for customized design and screening

Formulation and delivery

Stability

- Profiling current innovation in non-temperature-dependent formulation development across the nucleic acids arena
- Leveraging accelerated stability studies to set shelf life
- Addressing ongoing mRNA stability issues
  - What progress in alleviating dependency on cold and ultra-cold chains for transport and storage? How do the various contenders compare?
    - Lyophilization
    - Liquid-to-solid formats
    - Lipid design/optimization

mRNA — NOV

Manufacturing: downstream/purification

- Exploring current opportunities and challenges in downstream process development and validation
  - Avoiding the creation of product-related impurities from upstream processing
  - Assessment of alternative purification strategies involving advanced chromatography resins (e.g., multimodel binding principles) for impurity clearance
  - Minimization of process step-related impurities
- Assessing current and emerging tools and approaches for removal of product-related impurities (e.g., dsRNA)
  - What have been the key recent improvements in methods for dsRNA content analysis?
- How and where is flow synthesis being applied in the mRNA space, and with what impact/benefit?
- Process individualization for specific indication-driven dose regimens (i.e., high doses which require a low impurity level)
- Addressing LNP formulation and analytical challenges for mRNA manufacturing
  - LNP formulation IP issues
  - Ensuring proper combination of LNPs with target molecule to ensure stability
  - Assessing LNP stability, identity, dispersity index, size, and more
- Reducing complexity and cost of methods for assessing mRNA purity
  - Nucleic acid-specific LC-MS tools and software
- Addressing precipitation issues when upscaling

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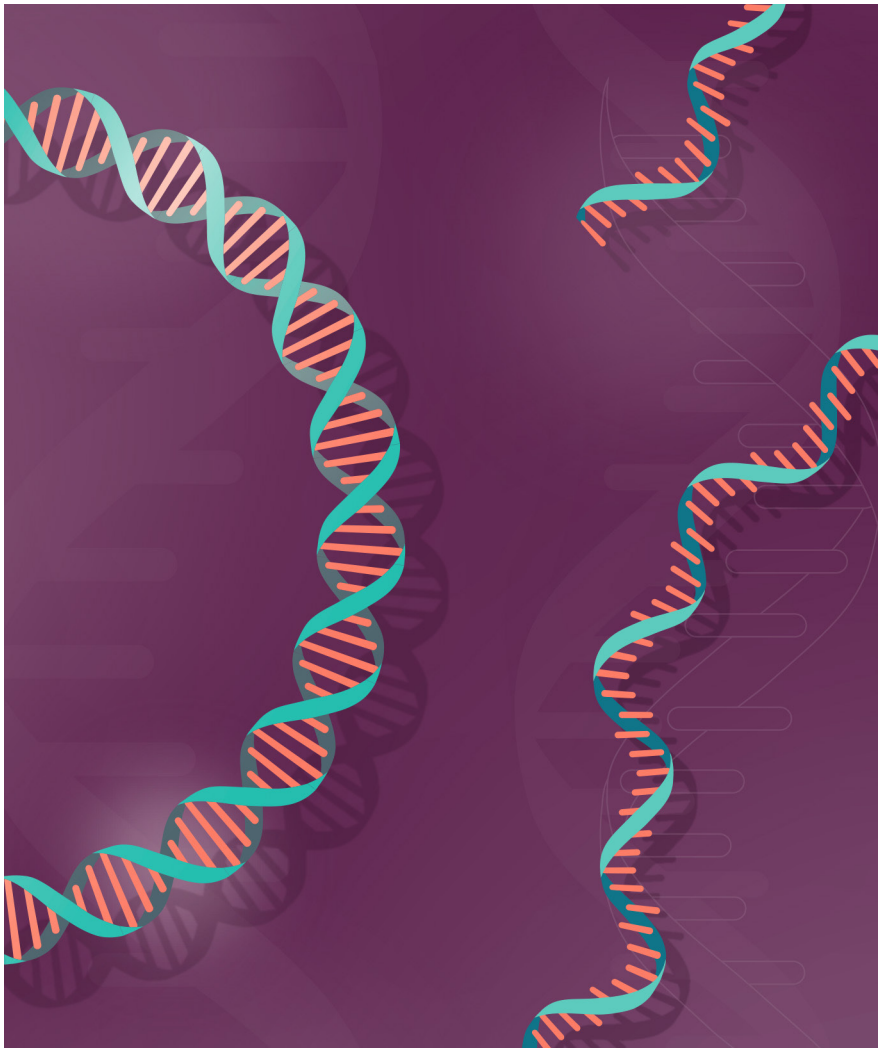
- Current challenges in the manufacture and analysis of circular RNA
  - Achieving purification of circular RNA with scalable methods
    - Purification of circRNA versus nicked circRNA
    - More scalable methods for purification (eliminating reliance on enzymatic purification, e.g., RNaseR, CIP),
    - CircRNA analytics lagging behind mRNA
- Fill-finish challenges for mRNAs

DNA

At the interface of synthetic biology and DNA

- Solving design, production, and supply challenges for DNA starting material
- Cell-free/synthetic DNA versus plasmid DNA—how do they compare both in strategic terms and in practical application?
- Addressing outstanding questions and challenges around DNA synthesis
- If synthetic DNA is used as a drug substance, what are the regulatory implications?
- Optimizing the sourcing and assessment of high-quality enzymes and reagents for DNA synthesis
- Should one fully synthesize DNA regardless of length?
- Tackling manufacturing scale-up challenges
- Potential applications of “mirror image” technologies in synthetic biology



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