Register Early & SAVE

9th ANNUAL

OPT Congress

Oligonucleotide & mRNA Therapeutics

DISCOVERY | DEVELOPMENT | DELIVERY

MARCH 13-14, 2024 | Seaport Hotel Boston | Boston, MA

CONFERENCE PROGRAMS

OLIGONUCLEOTIDE PROGRAMS

- Oligo Discovery & Delivery
- Oligo CMC & Regulatory Strategies

mRNA PROGRAMS

- mRNA Design & Delivery
- Applications of mRNA Therapeutics *NEW!*

IN-PERSON DINNER SHORT COURSES:

Safety & Toxicity of Nucleic Acids

RNA Editing: Applications & Insights *NEW!*

PLENARY SPEAKERS

Mano Manoharan, PhD
Senior Vice President, Drug Discovery, Alnylam Pharmaceuticals

Laura Sepp-Lorenzino, PhD
CSO, Intellia Therapeutics

Jeffery M. Coller, PhD
Bloomberg Distinguished Professor of RNA Biology and Therapeutics, Johns Hopkins University

Arthur Krieg, MD
Adjunct Professor, University of Massachusetts, Chan School of Medicine

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Welcome to OPT Congress:
Oligonucleotides & mRNA Therapeutics

OPT Congress is the premier conference for scientists and clinicians involved in discovering and developing oligonucleotides as therapeutics. NEW for 2024, we are delighted to expand our content and offer 2 conference programs dedicated to mRNA therapeutics to complement our established Oligo Discovery & Delivery and CMC & Regulatory programs. Now in its 9th year, this unique event brings together leading chemists, biologists, toxicologists, CMC experts, regulatory specialists, and technology providers to discuss advances in next-generation oligonucleotides and mRNA therapeutics. In addition to 2 days of inspiring keynotes, interactive discussions, and more than 95 scientific presentations, we deliver 2 in-depth, pre-conference dinner short courses. We look forward to having you join us for this important scientific and networking event, that also offers robust and customizable programming.

EVENT-AT-A-GLANCE

TUESDAY, MARCH 12TH	WEDNESDAY, MARCH 13—THURSDAY, MARCH 14
Short Course 1: Safety & Toxicity of Nucleic Acids	**Oligonucleotide Discovery & Delivery**
	Oligonucleotide CMC & Regulatory Strategies
Short Course 2: RNA Editing: Applications & Insights	**mRNA Design & Delivery**
	Applications of mRNA Therapeutics *NEW!*

WITH THANKS TO OUR EXECUTIVE ADVISORY BOARD

Ekkehard Leberer, PhD
Senior Life Sciences Consultant, ELBIOCON

Arthur Levin, PhD
CSO, Avidity Biosciences

Muthiah (Mano) Manoharan, PhD
Senior Vice President, Drug Discovery, Alnylam Pharmaceuticals

Lubo Nechev, PhD
Vice President, Process & Analytical Sciences, Alnylam Pharmaceuticals

Dmitry Samarsky, PhD
CTO, Sirnaomics

Chandra Vargeese, PhD
CTO & Head, Platform Discovery Sciences, Wave Life Science

Plenary Keynote Presentations

Biomimetic Chemistry of RNA Therapeutics

Mano Manoharan, PhD, Senior Vice President, Drug Discovery, Alnylam Pharmaceuticals

Achieving success in RNA therapeutics depends on proper understanding of mechanisms of nature. In stages of discovery, delivery, and development of RNA-based therapeutics we follow and mimic many natural processes. We will illustrate this concept by taking several key steps of molecular mechanisms involved and examples of medicines which are either approved or in clinical development.

Applications for mRNA Therapeutics: Immunological Issues and Considerations

Arthur Krieg, MD, Adjunct Professor, University of Massachusetts, Chan School of Medicine

From an immunological perspective, there are 3 distinct categories of mRNA therapeutics, including: 1. Protein expression mRNAs (including e.g., enzyme replacement, antibody expression, gene editing with encoded programmable nuclease), wherein any immune activation is highly undesirable; 2. Infectious disease mRNA vaccines such as COVID (immune activation desirable to induce neutralizing antibodies); and 3. Cancer mRNA vaccines (immune activation desirable to induce CD8+ T cells able to kill tumors). Achieving these distinct immune effects requires intentional design of the mRNA and delivery system, which will be reviewed.

Realizing the Promise of *in vivo* CRISPR Therapeutics

Laura Sepp-Lorenzino, PhD, CSO, Intellia Therapeutics

NTLA-2001 is an investigational CRISPR-based therapy being evaluated in a Phase 1, two-part, open-label study in adults with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) or with cardiomyopathy (ATTR-CM). NTLA-2002 is being developed for hereditary angioedema (HAE), designed to knock out the KLKB1 gene in the liver with the potential to permanently reduce total plasma kallikrein protein and activity, a key mediator of the disease. NTLA-2002 is being evaluated in a Phase 1/2 study in adults with Type I or Type II HAE. Preclinical and clinical data for both programs will be presented.

Harnessing RNA Metabolism for Precision RNA Therapeutics

Jeffery M. Coller, PhD, Bloomberg Distinguished Professor of RNA Biology and Therapeutics, Johns Hopkins University

Short Courses IN-PERSON | DINNER

TUESDAY, MARCH 12: 5:30 – 8:00 PM ET

SC1: Safety & Toxicity of Nucleic Acids

Instructor:

Xiao Shelley Hu, PhD, Vice President, Head of DMPK and Clinical Pharmacology, Wave Life Sciences

Nucleic acid drugs continue to deliver on their promise to become a third therapeutic modality, in addition to small molecules and biologics. Several antisense oligonucleotide drugs have been on the market for some time, while the first RNAi approval was granted in 2018. In addition, numerous mRNA and CRISPR therapeutic programs have entered clinical stages. Despite the common "nucleic acid" component, the mechanisms-of-action and of non-specific effects differ for each of these drug types.

Topics to be discussed include:

- Different types of nucleic acid-based drugs
- Mechanisms-of-action and non-specific effects
- Current approaches to address non-specific and potentially toxic effects**Aimed at both novice and advanced nucleic drug developers, the course will:**
- Introduce and explain the differences among various types of nucleic acid drugs
- Summarize our current understanding of the origins of non-specific and potentially toxic effects
- Provide direction on how to minimize the potential toxic effects of nucleic acid drugs

SC2: RNA Editing: Applications & Insights

Instructor:

Tod Woolf, PhD, Executive Director of Technology Ventures, Beth Israel Deaconess Medical Center; Co-Founder, ETAGEN Pharma

RNA editing is a post-transcriptional RNA processing that is observed in different types of RNA moieties. There are different types of RNA editing observed which involves addition, deletion, or substitution of nucleotide bases. Programmable RNA editing can be used to correct disease-causing mutations and induce transient modulation of protein function, particularly for conditions where permanent genomic alterations are not desired. This course will offer an understanding into the cellular processes involved in RNA editing and offer insights into some of the challenges involved in using it for therapeutic development.

Topics to be discussed include:

- Introduction to different types of RNA editing
- Understanding adenosine deaminase acting on RNA (ADAR) and other editing events
- Tools for designing, delivering and enabling RNA editing
- High throughput screening to study the impact of RNA editing in cells
- Assays exploring the functional consequences of RNA editing for therapeutic development
- Comparing technologies for assessing editing and off-target effects
- Examples of how RNA editing has been used successfully

Oligonucleotide Discovery & Delivery

Optimizing Design and Performance and Reviewing Advances in the Clinic

TUESDAY, MARCH 12

12:00 pm Registration Open

5:30 Recommended Short Course*
SC1: Safety & Toxicity of Nucleic Acids
*Separate registration required. See short course page for details.

WEDNESDAY, MARCH 13

7:00 am Registration and Morning Coffee

8:30 Organizer's Welcome Remarks

INNOVATIVE APPROACHES TO RNAi AND siRNA DEVELOPMENT AND DELIVERY

8:40 Chairperson's Opening Remarks
Ekkehard Leberer, PhD, Senior Life Sciences Consultant, ELBIOCON; Advisor, Neuway Pharma

8:45 Optimizing Oligonucleotides for Extrahepatic Targets through Stereopure Design
Chandra Vargeese, PhD, CTO & Head, Platform Discovery Sciences, Wave Life Sciences
Wave's PRISM platform enables the generation of chimeric backbone-containing stereopure oligonucleotides with improved pharmacological properties through position-controlled chemistry and stereochemical configuration. Here, we will provide an update on our progress in developing oligonucleotides that are optimized for distinct high-priority genetic targets, modalities, and tissues. As illustration, we will describe our development of stereopure phosphoryl guanidine (PN) backbone-containing chimeric oligonucleotides for RNA interference (RNAi) applications in hepatic and extrahepatic tissues.

9:15 Investigating Chemistry and Route of Administration for siRNA Delivery to the Skin
Julia Alterman, PhD, Assistant Professor, RNA Therapeutics Institute, University of Massachusetts Medical School
siRNAs have the potential to target many genetically defined disorders. In this study we investigate the impact of chemical architecture and route of administration on siRNA delivery to human skin *ex vivo* and pig skin *in vivo*. Our data outline an effective strategy for functional delivery of siRNAs enabling efficient silencing of genetic targets for dermal indications.

9:45 Subcutaneous Delivery of siRNA across Blood-Brain Barrier for CNS Therapies
June Park, PhD, CEO, siRNAgen Therapeutics
The talk will focus on the complexities and innovative approaches to RNAi delivery, especially the challenges associated with crossing the Blood-Brain Barrier (BBB). We will explore various mechanisms employed for effective RNAi delivery across the BBB, including our distinctive approach at siRNAgen Therapeutics. Highlighting our GLUT-SAMiRNA platform data, we will demonstrate how our cutting-edge technology is shaping the future of RNAi delivery and overcoming the preeminent challenges in the field.

10:15 Sponsored Talk Given by Scientist at Bio-Techne
Speaker to be Announced

10:45 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

11:35 GalAhead: An Unconventional GalNAc-Based RNAi Therapeutic Technology to Downregulate Single and Multiple Genes
Jim Weterings, PhD, Vice President Research, RNA Therapeutics & Delivery, Sirnaomics
We developed an unconventional GalNAc-based RNAi therapeutic technology, GalAhead, comprising two key components—mxRNA (miniaturized RNAi triggers) and muRNA (multi-unit RNAi triggers). We will present data demonstrating validity of the GalAhead technology *in vitro* and *in vivo*, as well as progress report with quickly expanding and progressing GalAhead-based therapeutic pipeline, with first program entering clinical trials earlier this year.

12:05 pm Improving the Safety and Specificity of RNAi Therapeutics
Maja Janas De Angelis, PhD, DABT, Senior Director, Investigative Toxicology, Alnylam Pharmaceuticals
Nonclinical safety screening of GalNAc-siRNAs is typically carried out in rats at exaggerated exposures in a repeat-dose regimen. We have previously shown that at these supratherapeutic doses, hepatotoxicity observed with a subset of GalNAc-siRNAs is driven by antisense strand seed-mediated off-target activity. To increase specificity, we developed a novel design strategy termed ESC+, which utilizes chemical modifications that thermally destabilize the base pairing between the seed region and off-target mRNAs.

12:35 Transition to Lunch

12:45 Luncheon Presentation Given by Scientist at STA Pharmaceuticals Luncheon Presentation to be Announced
Speaker to be Announced

1:15 Session Break

ENHANCING DELIVERY WITH AOC TECHNOLOGY AND LIPID NANOPARTICLES

2:00 Preclinical Considerations for Successful Antibody-Oligonucleotide Conjugate Development
Aaron Moss, PhD, Senior Director, Pharmacokinetics and Pharmacodynamics, Avidity Biosciences
Antibody-oligonucleotide conjugate (AOC) technology is a promising approach to facilitate the functional delivery of oligonucleotides to a variety of target tissues. We utilized targeting TfR1 to deliver therapeutic oligonucleotides to muscle tissue for the treatment of rare neuromuscular diseases. The preclinical systemic and tissue pharmacokinetics of AOCs *in vivo* will be discussed, including strategies to maximize receptor-mediated tissue uptake.

2:30 Targeted Nanoparticles for Delivery of Nucleic Acids
Mandana Borna, PhD, Senior Scientist, Oligonucleotide Formulation and Drug Product Manufacturing, Biogen
Systemic delivery of oligonucleotides, such as antisense oligonucleotide (ASO) or mRNA, remains one of the most challenging tasks in the field. Lipid nanoparticles (LNPs) have demonstrated great capacity to enhance cellular uptake, protect oligonucleotides from degradation, and prolong circulation. But non-functionalized LNPs are not tissue-specific after systemic administration. We propose to modify the LNP surface with targeting moieties to target receptors and optimize biodistribution.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE SESSION

3:40 Organizer's Welcome Remarks

3:45 Plenary Chairperson's Remarks
Jim Weterings, PhD, Vice President Research, RNA Therapeutics & Delivery, Sirnaomics

3:50 Biomimetic Chemistry of RNA Therapeutics
Mano Manoharan, PhD, Distinguished Scientist & Senior Vice President, Innovation Chemistry, Alnylam Pharmaceuticals
Achieving success in RNA therapeutics depends on proper understanding of mechanisms of nature. In stages of discovery, delivery, and development of RNA-based therapeutics we follow and mimic many natural processes. We will illustrate this concept by taking several key steps of molecular mechanisms involved and examples of medicines which are either approved or in clinical development.

4:20 Applications for mRNA Therapeutics: Immunological Issues and Considerations
Arthur Krieg, MD, Adjunct Professor, University of Massachusetts, Chan School of Medicine
From an immunological perspective, there are 3 categories of mRNA therapeutics. Protein expression mRNAs (enzyme replacement, antibody expression, gene editing with encoded programmable nuclease): any immune activation is undesirable. Infectious disease mRNA vaccines (immune activation desirable to induce neutralizing antibodies). Cancer mRNA vaccines (immune activation desirable to induce CD8+ T cells). Achieving these immune effects requires intentional design of mRNA and delivery system, which will be reviewed.

4:50 Welcome Reception in the Exhibit Hall with Poster Viewing

5:50 Close of Day

THURSDAY, MARCH 14

8:00 am Registration and Morning Coffee

PLENARY KEYNOTE SESSION

8:30 Organizer's Welcome Remarks

8:35 Plenary Chairperson's Remarks
Paloma Giangrande, PhD, Independent Consultant

8:40 Realizing the Promise of *in vivo* CRISPR Therapeutics
Laura Sepp-Lorenzino, PhD, CSO, Intellia Therapeutics
Intellia's investigational *in vivo* genome editing therapies comprise a lipid nanoparticle, formulating a single guide RNA, and an mRNA expressing SpyCas9. NTLA-2001 is being developed for transthyretin amyloidosis with polyneuropathy (ATTRv-PN) and transthyretin amyloidosis with cardiomyopathy (ATTR-CM). NTLA-2002 is being developed for hereditary angioedema (HAE). Preclinical and data from ongoing clinical studies will be presented.

9:10 Harnessing RNA Metabolism for Precision RNA Therapeutics
Jeffery M. Coller, PhD, Bloomberg Distinguished Professor of RNA Biology and Therapeutics, Johns Hopkins University
We have created a therapeutic technique that enhances mRNA translation. This technology has numerous clinical applications and works by binding to mRNA and improving translation. The approach offers key benefits: it is disease-modifying, restoring normal protein levels; it is mutation agnostic; it can be tailored to precisely control expression, reducing the risk of overexpression; and lastly, it is applicable across indications and highly versatile.

9:40 Coffee Break in the Exhibit Hall with Poster Viewing

OPTIMIZING DESIGN, DELIVERY, AND PERFORMANCE

10:30 Chairperson's Remarks
Chandra Vargeese, PhD, CTO & Head, Platform Discovery Sciences, Wave Life Sciences

10:35 KEYNOTE PRESENTATION: Biological Activity of Thiomorpholino Oligonucleotides
Marvin Caruthers, PhD, Distinguished Professor, University of Colorado
Collaborations with over 20 laboratories elsewhere have shown that thiomorpholino oligonucleotides are more active biologically than any of the standard ASOs including 2'-MOE and 2'-OMe oligomers. In several preliminary studies in mice and zebra fish, the thiomorpholino oligonucleotides have been shown to be far less toxic than any other tested analogue. These various studies include research focused on rare genetic diseases, cancer, type II diabetes, and various neurological diseases.

11:05 Harnessing Nucleic Acid Immunity for Cancer Immunotherapy with Immune-Stimulatory Oligonucleotides
Arthur Krieg, MD, Adjunct Professor, University of Massachusetts, Chan School of Medicine
Synthetic RNA and DNA ligands for nucleic acid immune-sensing receptors induce antibody and T cell responses that underlie the efficacy of mRNA vaccines and may be used for *in situ* immunization to treat cancer. Understanding the different biology of these receptors, including TLR3, TLR7, TLR8, TLR9, cGAS/STING, and the RIG-I-like receptors is essential for optimizing cancer immunotherapy in humans.

11:35 Transition to Lunch

11:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:15 pm Session Break

1:00 Development of Gemcitabine-Modified miRNA Mimics as Novel Anti-Cancer Therapy for Pancreatic Ductal Adenocarcinoma
Jingfang Ju, PhD, Professor, Renaissance School of Medicine, Stony Brook University; Co-Founder, Curamir Therapeutics, Inc.
We developed a new treatment strategy by modifying tumor suppressor miRNAs, hsa-miRNA-15a (miR-15a) with gemcitabine (Gem), to create Gem-modified mimics of miR-15a (Gem-miR-15a). Gem-miR-15a is a potent inhibitor to eliminate patient-derived pancreatic cancer organoids and mouse tumor models without delivery vehicle.

1:20 The Endosomal Escape Vehicle Platform Enhances the Delivery of Oligonucleotides to Skeletal and Cardiac Muscle
Leo Ziqing Qian, PhD, Co-Founder & Vice President, Discovery Research, Entrada Therapeutics
To overcome current limitations of oligonucleotide therapeutic delivery, we have designed a family of proprietary cyclic CPPs that form the core of our Endosomal Escape Vehicle (EEV) technology and covalently conjugated it to oligonucleotides. Using preclinical models of Duchenne muscular dystrophy (DMD), we demonstrated the ability of our EEV platform technology to efficiently deliver oligonucleotides to skeletal and cardiac muscle, the primary sites of pathology in DMD.

1:40 Innovation in Extrahepatic Delivery of Oligonucleotide Therapeutics: A Patient-Centric Approach
Maire Jung, PhD, Associate Vice President, Genetic Medicine, Eli Lilly and Company

2:00 Sponsored Presentation *(Opportunity Available)*

2:15 Presentation to be Announced

INTERACTIVE BREAKOUT DISCUSSIONS

2:30 Interactive Breakout Discussions

Interactive Breakout Discussions are informal, moderated, small-group discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator(s) who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakout Discussion page for a complete listing of topics and descriptions.

IN-PERSON ONLY BREAKOUT DISCUSSION: Successful Oligonucleotides for Extrahepatic Tissues and Strategic Collaboration between Academia and Industry

Ken Yamada, PhD, Assistant Professor, RNA Therapeutics Institute, University of Massachusetts Medical School

IN-PERSON ONLY BREAKOUT DISCUSSION: From Early Discovery and the Clinic to Collaborations Between Big Pharma and Small Biotechs

Marvin Caruthers, PhD, Distinguished Professor, University of Colorado

3:10 Refreshment Break in the Exhibit Hall with Last Chance for Poster Viewing

NOVEL ADVANCES WITH ANTISENSE OLIGONUCLEOTIDES (ASOs)

3:45 Treatment of Cancer with Antisense Oligonucleotides Targeting the Immunosuppressive Tumor Microenvironment

Frank Jaschinski, PhD, CSO, Secarna Pharmaceuticals

The immunosuppressive tumor microenvironment is an efficient barrier that protects the tumor from destruction by the immune system. It comprises several targets that are predestined as targets for therapeutic antisense oligonucleotides (ASOs). As an example, we will present data showing that ASOs suppressing expression of the multifactorial protein NRP1 are a promising option for treatment of cancer.

4:15 Production of Maleimide-Conjugated ASO for Subsequent Functionalization: Lessons Learned during Development

Zifan Li, PhD, Senior Scientist, Analytical Development, Biogen

Functionalization of therapeutic oligonucleotides by conjugating to multiple modalities may be beneficial for their efficacy or delivery. Certain examples like GalNAc have been widely applied in therapeutic ASO and siRNA development. Maleimide-conjugated ASO can be easily functionalized by conjugating to thiol-bearing modalities. During the manufacturing development of such conjugates we have encountered several difficulties, conquered them, and learned lessons. This presentation intends to share what we learned.

4:45 Toehold Nanoarchitecture That Mitigates ASO off-Target Interactions

Tsuyoshi Yamamoto, PhD, Associate Professor, Director, Liid Pharma, Nagasaki University

This presentation introduces a novel nanoarchitecture, BROTHERS or BRO, designed to mitigate off-target interactions of antisense oligonucleotides (ASOs). The BRO, comprising a typical gapmer ASO and a complementary peptide nucleic acid (PNA) strand, deters non-specific protein and RNA binding. Harnessing its inherent free energy, BRO triggers a toehold-mediated strand displacement reaction, which enhances ASO's mismatch recognition, minimizing hybridization to RNA off-targets. Consequently, BRO enhances therapeutic window of ASOs.

5:15 Close of Conference

"I find it really interesting that there's a really nice mix of scientific discovery and discussion, commercial application and translational, and even clinical information being discussed."

- Mark Kay, MD, PhD, Professor of Pediatrics and Genetics, Stanford University

TUESDAY, MARCH 12

12:00 pm Registration Open

5:30 Recommended Short Course*
SC1: Safety & Toxicity of Nucleic Acids
*Separate registration required. See short course page for details.

WEDNESDAY, MARCH 13

7:00 am Registration and Morning Coffee

8:30 Organizer's Welcome Remarks

OPTIMIZING CMC & ANALYTICAL CHARACTERIZATION

8:40 Chairperson's Opening Remarks
Mike Webb, PhD, Founder and CEO, Mike Webb Pharma; Former Vice President, API Chemistry & Analysis, GSK

8:45 Experimental Strategies and Applications of Accelerated Stability Assessment Program (ASAP) Studies of Oligonucleotide Therapeutics
Carolyn Mazzitelli, PhD, Director, Analytical Development & Quality Control, Ionis Pharmaceuticals
An overview of experimental strategies and applications of Accelerated Stability Assessment Program (ASAP) studies of oligonucleotide drug substances and drug products will be presented. Practical considerations related to experimental design and execution specific to oligonucleotides will be presented, along with examples of how ASAP studies may be utilized throughout the development lifecycle of oligonucleotide therapeutics. This includes studies aimed at demonstration of material comparability and to augment platform stability data.

9:15 Analytical Challenges for Antibody Oligonucleotide Conjugates
Matthew McQueen, Associate Director, Analytical Development, Avidity Biosciences
Avidity Biosciences is a clinical-stage company developing a new type of modality, Antibody Oligonucleotide Conjugates (AOCs). These therapeutics consist of a monoclonal antibody as well as an oligonucleotide and are therefore hybrids of a biologic and a small molecule. In this talk, we will discuss workflows to overcome the challenges associated with analytical method development and characterization of these novel hybrid therapeutics.

9:45 CMC Considerations for siRNA Drug Substance Manufacturing
Jeske Smink, PhD, Head of Drug Substance, Manufacturing, Silence Therapeutics
The quality attributes of siRNA drug substances are affected by used raw materials including customized starting materials such as linkers and conjugates, as well as by the manufacturing process, process parameters, and potential degradation products of the compounds. It is important to increase the understanding of processes and products to allow for improvements of processes and product quality as well as to reduce costs.

10:15 Measurement and Control of Oxidation Strength in Iodine/Pyridine Oxidation Reagents used in Oligonucleotide Manufacture
Bruce Flint, Associate Principal Scientist, Analytical Development, Nitto Avecia
Synthesis of oligonucleotides with mixed phosphorothioate (P=S) and phosphodiester (P=O) linkages are prone to formation of impurities in which one or more P=S linkage is replaced by a P=O linkage, aka "PO impurity". One cause for PO impurity formation is insufficient "aging" of oxidizing reagent prior to use in manufacture. A control strategy is introduced via measurement of oxidation strength, setting specifications, and exploring options for reducing the aging time.

10:45 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

11:35 Strategies for the Characterization of Stereopure Platform Chemistry
Sridhar Vaddeboina, PhD, Senior Vice President, CMC Operations, Wave Life Sciences
Traditional phosphorothioate (PS) oligonucleotide synthesis methods generate stereorandom mixtures comprising up to several hundred thousand molecules, each with distinct stereochemistry. Wave Life Sciences is pioneering the development and manufacture of oligonucleotides with control over the backbone chirality. We will outline the various analytical tools we have deployed to characterize the platform processes that generate stereopure oligonucleotides, and unambiguously determine the structural composition, identity, and stability of stereopure oligonucleotides.

12:05 pm Demonstrating Comparability with Changes in Oligonucleotide Manufacturing
Nadim Akhtar, PhD, Senior Principal Scientist, New Modalities, AstraZeneca
Effective change management is an essential part of drug product lifecycle. Typical changes include pre- and post-approval changes to drug substance and drug product manufacturing processes and analytical procedures and supply of raw materials to address regulatory, safety, quality, and supply risks. This presentation will share a phase-appropriate, risk-based approach to understand the risk on critical quality attributes and demonstration of comparability.

12:35 Transition to Lunch

12:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:15 Session Break

1:55 Chairperson's Remarks
Robert Dream, PhD, Managing Director, HDR Co. LLC

2:00 Toxicity and Immunogenicity Considerations for Oligonucleotide-Related Impurities: The Impact on Control Strategy Development
Brian Pack, PhD, Executive Director, Eli Lilly and Company
With limited regulatory guidance on the acceptable levels of impurities in oligonucleotides, ambiguity regarding specifications and comparability assessment expectations exists. While impurities are anticipated to exhibit the same safety profile as the parent oligonucleotide, they likely offer no inherent benefit and are expected to be controlled. This work outlines an approach to bridge process capability and oligonucleotide impurity safety from a toxicology and immunogenicity perspective to support specifications and comparability.

2:30 Challenges in Establishing Assay, Purity, and Impurity Levels for Double-Stranded Oligonucleotides
Mike Webb, PhD, Founder and CEO, Mike Webb Pharma; Former Vice President, API Chemistry & Analysis, GSK
Double-stranded oligonucleotides with multiple 2'substituents and several phosphorothioate linkages lead to significant numbers of related impurities. Denaturing UPLC methods to separate single strands and their impurities yields complex and often poorly resolved peaks. Non-denaturing methods are often not specific for duplexed impurities. Despite this, sponsors are required to produce a control strategy that identifies and quantifies impurities. In this presentation we will discuss the challenges and strategies to overcome them.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE SESSION

3:40 Organizer's Welcome Remarks

3:45 Plenary Chairperson's Remarks
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THURSDAY, MARCH 14

8:00 am Registration and Morning Coffee

PLENARY KEYNOTE SESSION

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8:35 Plenary Chairperson's Remarks
Paloma Giangrande, PhD, Independent Consultant

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Intellia's investigational *in vivo* genome editing therapies comprise a lipid nanoparticle, formulating a single guide RNA, and an mRNA expressing SpyCas9. NTLA-2001 is being developed for transthyretin amyloidosis with polyneuropathy (ATTRv-PN) and transthyretin amyloidosis with cardiomyopathy (ATTR-CM). NTLA-2002 is being developed for hereditary angioedema (HAE). Preclinical and data from ongoing clinical studies will be presented.

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9:40 Coffee Break in the Exhibit Hall with Poster Viewing

REGULATORY INTELLIGENCE

10:30 Chairperson's Remarks
Jennifer Franklin, PhD, Executive Director, CMC Regulatory Affairs, Ionis Pharmaceuticals, Inc.

10:35 KEYNOTE PRESENTATION: Regulatory CMC Intelligence for Oligonucleotide Programs
Jennifer Franklin, PhD, Executive Director, CMC Regulatory Affairs, Ionis Pharmaceuticals, Inc.
Current regulatory interactions and intelligence for oligonucleotide programs in all phases of development will be discussed, including common health authority requests and recent regulatory experience and guidance.

11:05 Practical, Quality, and Regulatory Considerations to Manufacture Clinical Trial Materials for First-in-Human Trials—What Do You Really Need to Do?
Kevin Fettes, PhD, Founder & Principal, FTS Pharma Consulting LLC
The complexity of oligonucleotide drug candidates being selected for clinical development has increased in recent years. These oligonucleotides often have significant chemical modifications requiring novel starting materials, as well as technical innovations in process development, analytical chemistry, manufacturing, and controls. This places extraordinary demands on both sponsor companies and contract manufacturing organizations to meet regulatory expectations under aggressive timelines.

11:35 Transition to Lunch

11:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:15 pm Session Break

1:00 Leveraging ICH for Control of Oligonucleotide Impurities
Lori Troup, Director, Analytical Development, Dicerna Pharmaceuticals
For complex drug substances such as oligonucleotides, it is helpful, and sometimes even necessary, to introduce impurity controls throughout the process and not just on the final specification. This presentation will explore opportunities to leverage ICH guidelines to create a comprehensive control strategy, including examples of successes and failures, in a variety of areas, such as starting materials, elemental impurities, and the use of orthogonal HPLC methods.

1:30 Key Pharmacology and Toxicology Elements of the FDA's Assessment Aid
Emily Noonan Place, PhD, Senior Consultant, Biologics Consulting
This talk will focus on the FDA Assessment Aid, a voluntary submission to facilitate FDA assessment of NDA/BLA applications in the Office of Oncologic Drugs. The talk will go over important considerations to include in the pharmacology and toxicology section of the application.

2:00 Sponsored Presentation *(Opportunity Available)*

INTERACTIVE BREAKOUT DISCUSSIONS

2:30 Interactive Breakout Discussions

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IN-PERSON ONLY BREAKOUT DISCUSSION: Analytical Challenges in Controlling Purity in Double-Stranded Oligonucleotide Drug Substances and Drug Products

Mike Webb, PhD, Founder and CEO, Mike Webb Pharma; Former Vice President, API Chemistry & Analysis, GSK

IN-PERSON ONLY BREAKOUT DISCUSSION: In Your Experience, to What Extent is RNA a Multi-Product Platform Technology?

Zoltán Kis, PhD, Assistant Professor, Chemical and Biological Engineering, The University of Sheffield

3:10 Refreshment Break in the Exhibit Hall with Last Chance for Poster Viewing

IMPLEMENTING SUCCESSFUL MANUFACTURING STRATEGIES

3:45 Adoption of Innovative Technologies in Oligonucleotide Manufacturing: Improving the Efficiency of the siRNA Manufacturing Process

Roumen Radinov, PhD, Vice President, Process Sciences, Alnylam Pharmaceuticals

The solid-phase oligonucleotide synthesis based on sequential coupling of phosphoramidite monomers is a well-established industrial manufacturing process, currently performed routinely on kilo-scale mainly due to limitations of synthesis and purification processes. Novel approaches towards more efficient, scalable, and sustainable large-scale manufacture will be discussed supporting future commercialization of the expanding range of high-volume siRNA therapeutics.

4:15 End-to-End Manufacturing: Challenges and Opportunities in Implementation

Robert Dream, PhD, Managing Director, HDR Co. LLC

End-to-end manufacturing represents the next generation of biopharmaceutical manufacturing processes. The US FDA has approved various small molecule products and recently issued draft guidance for industry on continuous manufacturing. The ICH Q13 is adopted by the European Medicines Agency (EMA) to support the technology and give guidance as well. Companies can add flexibility and maximize the value of process analytics ICH Q14 [6] to enhance E-2-E manufacturing.

4:45 PANEL DISCUSSION: Oligonucleotides: From Preclinical to Product Launch

Moderator: Robert Dream, PhD, Managing Director, HDR Co. LLC

From an analytical and regulatory perspective, oligonucleotides are interesting since they present a link between products derived from biotechnology and small molecular chemical compounds. This panel discussion will address the following topics required for oligonucleotides in order to deliver modalities to patients such as manufacturing strategies, operation obstacles, regulatory limitations, and facility requirements.

Panelists:

Brian Pack, PhD, Executive Director, Eli Lilly and Company

Jennifer Franklin, PhD, Executive Director, CMC Regulatory Affairs, Ionis Pharmaceuticals, Inc.

Roumen Radinov, PhD, Vice President, Process Sciences, Alnylam Pharmaceuticals

5:15 Close of Conference

"I came to OPT Congress to learn about the new science, and see what's going on with the CMC sections. It's been going great. I really enjoyed the science, really enjoyed the networking, and meeting new people."

- Chad Ratterman, Process Development, Nitto Avecia

mRNA Design & Delivery

Increased Efficacy, Better Stability, Targeted Delivery, Improved Safety

TUESDAY, MARCH 12

12:00 pm Registration Open

5:30 Recommended Short Course*
SC2 : RNA Editing: Applications and Insights
*Separate registration required. See short course page for details.

WEDNESDAY, MARCH 13

7:00 am Registration and Morning Coffee

8:30 Organizer's Welcome Remarks

IMPROVING RNA EDITING & SPECIFICITY

8:40 Chairperson's Remarks
Venkat Krishnamurthy, PhD, Senior Vice President & Head of Platform, Korro Bio, Inc.

8:45 Edit the Message; Edit the Future
Venkat Krishnamurthy, PhD, Senior Vice President & Head of Platform, Korro Bio, Inc.
ADARs are a new class of oligo-directed precision medicines to address a myriad of previously undruggable targets. At Korro, we use ASOs to recruit endogenous ADARs, to carry out (A-to-I) edits that can repair G-to-A mutations and modulate protein function by changing the amino acid code. This presentation will focus on Korro's approach to ADAR-mediated RNA editing and provide an update on progress towards clinic.

9:15 Protein Restoration and Repair in Extrahepatic Tissues through RNA Editing
Chikdu Shivalila, PhD, Director, Biology Wave Life Sciences, Inc.
Wave's AIMers are oligonucleotides that engage endogenous ADAR enzymes to induce highly efficient and specific A-to-I RNA base editing. CTA submissions are expected in 2H 2023 for our first RNA editing program, WVE-006, which aims to correct a disease-causing protein-coding mutation in a liver mRNA. We provide an update on our preclinical efforts to broaden the potential applications for RNA editing by expanding the target space and tissue targeting capabilities.

9:45 miRNA-Based Logic Circuits Encoded on Self-Amplifying RNA for Highly Specific Cancer Cell Classification
Ron Weiss, PhD, Professor, Biological Engineering, Massachusetts Institute of Technology
We developed self-amplifying RNA and modified RNA platforms into vectors capable of carrying synthetic circuitry payloads that can provide a variety of desirable dynamics. We also encoded miRNA target sites on our RNA vectors to provide for highly specific cell type classification. We are using this technology to create next-generation cancer immunotherapy RNA vectors capable of activating therapeutic payloads discriminately in cancer cells.

10:15 Novel Cap Analogs and Modified NTPs to Enable Therapeutic mRNA Development
May Guo, Chief Commercial Officer, Areterna
We will discuss our process for developing and testing novel cap analogs and share our findings. The manufacturing of mRNA drug substance requires high-quality starting materials; we will share our practice to ensure quality and compliance. Once mRNA is made, robust analytical methods are needed to support the product release. We offer much needed impurity testing kits and standards for analytical development.

10:30 Sponsored Presentation *(Opportunity Available)*

10:45 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

11:35 Decoding the Untranslated to Engineer Next-Generation mRNA Therapeutics
Wendy Gilbert, PhD, Professor, Molecular Biophysics & Biochemistry, Yale University
mRNA therapeutics offer a universal strategy for efficient development and delivery of therapeutic proteins. Current mRNA vaccines include chemically modified nucleotides, N1-methylpseudouridine, to reduce cellular immunogenicity and increase protein production. We have developed a method—direct analysis of ribosome targeting, DART—to screen modified mRNAs for increased translation by human ribosomes. Our results identify small changes in 5' UTR sequence and chemical modification that increase protein production in human cells.

12:05 pm Mapping and Designing mRNA Lifecycle
Xiao Wang, PhD, Assistant Professor, Department of Chemistry, Broad Institute of MIT and Harvard
mRNA translation is tightly regulated in mammalian cells. In this talk, I will present high-resolution 3D *in situ* sequencing approaches (STARmap, RIBOmap, TEMPOmap) that enable simultaneous mapping of RNA lifecycle of thousands of genes within intact cells and tissues. Following that, I will explore strategies to improve mRNA translation and stability using mRNA-oligonucleotide conjugates.

12:35 Transition to Lunch

12:45 LUNCHEON PRESENTATION: Strategic Approaches to Scaling Up mRNA Production: A Comprehensive Guide
Jovanka Bogojeski, Senior Director Scale-up & Tech Transfer, Process Sciences, ReciBioPharm
- Methods to optimize mRNA product yield, dsRNA content, and kinetics for high-efficiency IVT will be discussed.
- Scaled up IVT processes in multiple reactors shows replicated kinetics and proportional yield from small scale work.
- mRNA stability has been characterized and addressed during process scale up, allowing for mRNA handling and processing to occur within defined limits.

1:15 Session Break

TARGETED CANCER THERAPIES

1:55 Chairperson's Remarks
Wendy Gilbert, PhD, Professor, Molecular Biophysics & Biochemistry, Yale University

2:00 Developing mRNA Cancer Immunotherapies
Sushma Gurumurthy, PhD, Director, Oncology Research, Moderna, Inc.
Modified mRNA technology has been successfully applied in the development of vaccines. In oncology, while several novel immunotherapies have demonstrated striking responses in several hard-to-treat cancers, there is still a need for innovative therapeutic approaches to overcome mechanisms of relapse, resistance, and immune suppression. I will present some of our efforts to develop novel mRNA-based therapies that activate the ability of the immune system to develop durable anti-tumor immunity.

2:30 A Multifaceted Approach to Optimize and Develop Therapeutic Synthetic Circular RNA (oRNA)
Nelson Chau, PhD, Senior Vice President, Platform, Orna Therapeutics
Linear messenger RNA (mRNA) is being investigated for other therapeutic applications. We are developing a new class of synthetic, protein-coding, circular RNA (oRNA). It is a scalable, cap-independent, and immunoquiescent protein-coding RNA platform. Strategies and results of optimizing oRNA to drive high protein expression and durability will be presented. When combined with an efficient immune cell delivering LNP, effective *in situ* CAR T tumor killing is observed in preclinical models.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE SESSION

3:40 Organizer's Welcome Remarks

3:45 Plenary Chairperson's Remarks
Jim Weterings, PhD, Vice President Research, RNA Therapeutics & Delivery, Sirnaomics

3:50 Biomimetic Chemistry of RNA Therapeutics
Mano Manoharan, PhD, Distinguished Scientist & Senior Vice President, Innovation Chemistry, Alnylam Pharmaceuticals
Achieving success in RNA therapeutics depends on proper understanding of mechanisms of nature. In stages of discovery, delivery, and development of RNA-based therapeutics we follow and mimic many natural processes. We will illustrate this concept by taking several key steps of molecular mechanisms involved and examples of medicines which are either approved or in clinical development.

4:20 Applications for mRNA Therapeutics: Immunological Issues and Considerations
Arthur Krieg, MD, Adjunct Professor, University of Massachusetts, Chan School of Medicine
From an immunological perspective, there are 3 categories of mRNA therapeutics. Protein expression mRNAs (enzyme replacement, antibody expression, gene editing with encoded programmable nuclease): any immune activation is undesirable. Infectious disease mRNA vaccines (immune activation desirable to induce neutralizing antibodies). Cancer mRNA vaccines (immune activation desirable to induce CD8+ T cells). Achieving these immune effects requires intentional design of mRNA and delivery system, which will be reviewed.

4:50 Welcome Reception in the Exhibit Hall with Poster Viewing

5:50 Close of Day

THURSDAY, MARCH 14

8:00 am Registration and Morning Coffee

PLENARY KEYNOTE SESSION

8:30 Organizer's Welcome Remarks

8:35 Plenary Chairperson's Remarks
Paloma Giangrande, PhD, Independent Consultant

8:40 Realizing the Promise of *in vivo* CRISPR Therapeutics
Laura Sepp-Lorenzino, PhD, CSO, Intellia Therapeutics
Intellia's investigational *in vivo* genome editing therapies comprise a lipid nanoparticle, formulating a single guide RNA, and an mRNA expressing SpyCas9. NTLA-2001 is being developed for transthyretin amyloidosis with polyneuropathy (ATTRv-PN) and transthyretin amyloidosis with cardiomyopathy (ATTR-CM). NTLA-2002 is being developed for hereditary angioedema (HAE). Preclinical and data from ongoing clinical studies will be presented.

9:10 Harnessing RNA Metabolism for Precision RNA Therapeutics
Jeffery M. Coller, PhD, Bloomberg Distinguished Professor of RNA Biology and Therapeutics, Johns Hopkins University
We have created a therapeutic technique that enhances mRNA translation. This technology has numerous clinical applications and works by binding to mRNA and improving translation. The approach offers key benefits: it is disease-modifying, restoring normal protein levels; it is mutation agnostic; it can be tailored to precisely control expression, reducing the risk of overexpression; and lastly, it is applicable across indications and highly versatile.

9:40 Coffee Break in the Exhibit Hall with Poster Viewing

GUIDED mRNA DESIGN

10:30 Chairperson's Remarks
Yujian Frank Zhang, PhD, CEO, Belem Therapeutics

10:35 Boosting mRNA Medicine Performance through Sequence Design
Yujian Frank Zhang, PhD, CEO, Belem Therapeutics
Irrespective of the specific drug delivery system employed, the inherent druggability of mRNA molecules can be significantly enhanced through the optimization of either translatability or thermal stability. In a recent endeavor, we developed a novel algorithm—LinearDesign, derived from natural language processing—to identify optimal vaccine molecules characterized by greatly augmented immunogenicity. This innovative approach extends its applicability beyond conventional linear mRNA molecules to encompass circular variants as well.

11:05 Machine Learning-Guided mRNA Design for Vaccine Development
Vikram Agarwal, PhD, Head of mRNA Platform Design Data Science, mRNA Center of Excellence, Sanofi
Here we develop and deploy CodonBERT, an mRNA codon optimization tool to optimize protein expression from delivered RNA. We also demonstrate Saluki, our state-of-the-art, hybrid convolutional and recurrent deep neural network which relies only upon an mRNA sequence annotated with coding frame and splice sites to predict half-life. Collectively, this group of tools represents the power of machine learning–guided approaches in the design of mRNA vaccines.

11:35 Transition to Lunch

11:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:15 pm Session Break

INNOVATIVE mRNA DELIVERY

12:55 Chairperson's Remarks
Iris Grossman, PhD, Chief Therapeutics Officer, R&D, Eleven Therapeutics US, Inc.

1:00 Therapeutic Genome Editing in Cancer via Targeted Lipid Nanoparticles
Dan Peer, PhD, Professor & Chair, Cancer Biology Research Center, Laboratory of Precision Nanomedicine, Tel Aviv University
We describe a safe and efficient lipid nanoparticle (LNP) for the delivery of mRNA and sgRNAs that use novel amino-ionizable lipids and a strategy to target RNA payloads to specific cell types *in vivo*. We show selective and highly efficient *in vivo* therapeutic genome editing in glioma, ovarian, and blood cancers, with more than 80% editing and increased survival of 90%. This approach opens new avenues in cancer therapeutics.

1:30 Lipid Nanoparticles for Overcoming Biological Barriers to mRNA Delivery
Michael Mitchell, PhD, Skirkanich Assistant Professor of Innovation, Department of Bioengineering, University of Pennsylvania
I will discuss our efforts towards development of lipid nanoparticle (LNP) platforms that enable the delivery of RNA therapeutics and vaccines to a range of target cells and tissues in the body. Furthermore, I will describe new therapeutic strategies utilizing these LNPs *in vivo* reprogramming of immune cells for cancer immunotherapy and vaccination, *in utero* gene editing for treating disease before birth, and mRNA prenatal therapeutics for treating pregnancy disorders.

2:00 TLR7/8 Sensing of Exogenous circRNAs Activates Innate Immune Response in Human Cells
Li Li, PhD, Assistant Professor, RNA Therapeutics Institute, University of Massachusetts Chan Medical School
Circular RNAs (circRNAs) are a promising platform for mRNA-based therapeutics. However, the immunogenicity of circRNAs has not been studied using human immune cells. We found that while purified circRNAs are nonimmunogenic in A549 cells, they elicited strong immune responses in PBMC and macrophages. Using CRISPR knockout cell lines, we found that TLR7/8 mediates the innate immune sensing of unmodified circRNAs.

INTERACTIVE BREAKOUT DISCUSSIONS

2:30 IN-PERSON ONLY BREAKOUT DISCUSSION
Interactive Breakout Discussions are informal, moderated, small-group discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator(s) who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakout Discussion page for a complete listing of topics and descriptions.

IN-PERSON ONLY BREAKOUT DISCUSSION: Designing and Optimizing mRNA Therapeutics
Vikram Agarwal, PhD, Head of mRNA Platform Design Data Science, mRNA Center of Excellence, Sanofi
Wendy Gilbert, PhD, Professor, Molecular Biophysics & Biochemistry, Yale University
Yujian Frank Zhang, PhD, CEO, Belem Therapeutics

IN-PERSON ONLY BREAKOUT DISCUSSION: Tackling Challenges with mRNA Delivery
Charles Chen, PhD, Senior Scientist, Advanced Drug Delivery, Pharmaceutical Sciences, AstraZeneca Pharmaceuticals, R&D
Iris Grossman, PhD, Chief Therapeutics Officer, R&D, Eleven Therapeutics US, Inc.
Dan Peer, PhD, Professor & Chair, Cancer Biology Research Center, Laboratory of Precision Nanomedicine, Tel Aviv University

3:10 Refreshment Break in the Exhibit Hall with Last Chance for Poster Viewing

3:45 High Durability, Fully Synthetic xRNA and the Introduction of Ex-hepatic Delivery by Targeted Small Molecule-conjugates
Iris Grossman, PhD, Chief Therapeutics Officer, R&D, Eleven Therapeutics US, Inc.
Eleven Therapeutics ushers in the next generation of RNA therapeutics by mastering combinatorial chemistry, synthetic biology, and AI. Our extended-release mRNA, dubbed xRNA, utilizes non-canonical building blocks to boost the durability of mRNA technologies. Our *in vitro* and *in vivo* experiments show superiority of this technology over standard mRNA, and our massively parallel assay is designed to deep-learn the SAR of xRNAs. This addresses unmet medical needs across multiple diseases.

4:15 Protein-Based Nano-Capsules for Delivery of mRNA across the Blood-Brain Barrier
Ekkehard Leberer, PhD, Senior Life Sciences Consultant, ELBIOCON; Advisor, Neuway Pharma
The presentation will describe the generation and the use of protein-based nano-capsules to deliver mRNA across the blood-brain barrier to treat CNS diseases. The therapeutic potential of this delivery technology will be illustrated for the mRNA treatment of monogenetic CNS disorders such as metachromatic leukodystrophy (MLD), a lysosomal storage disease.

4:45 Close of Conference

"What is interesting to me about this conference is meeting all the experts in the field. This conference brings all of us together, gives us the opportunity to present our great work, socialize with people, and have very productive and open conversations to build new medicines."

- Chandra Vargeese, PhD, CTO & Head, Platform Discovery, Wave Life Sciences

Applications of mRNA Therapeutics

Unlocking the Potential of Innovative Therapies

TUESDAY, MARCH 12

12:00 pm Registration Open

5:30 Recommended Short Course*
SC2: RNA Editing: Applications and Insights
*Separate registration required. See short course page for details.

WEDNESDAY, MARCH 13

7:00 am Registration and Morning Coffee

8:30 Organizer's Welcome Remarks

INNOVATIONS IN MANUFACTURING DRIVING NEW APPLICATIONS

8:40 Chairperson's Remarks
Craig Martin, PhD, Professor, Chemistry, University of Massachusetts, Amherst

8:41 FEATURED PRESENTATION: Flow Manufacturing of mRNA Free of dsRNA, DNA, and Protein—Before Purification
Craig Martin, PhD, Professor, Chemistry, University of Massachusetts, Amherst
Functional immobilization of RNA polymerase to promoter DNA, with coupling of the pair to a solid support, allows the direct manufacturing of RNA free of both protein and DNA. It also largely eliminates formation of dsRNA and allows for much higher yields of RNA per DNA and enzyme. Synthesized reporter mRNAs show significantly reduced innate immune response and higher expression of mRNA transfected into cells—before any downstream purification.

9:05 Innovating and Digitalising mRNA Vaccine and Therapeutics Production Platform Processes
Zoltán Kis, PhD, Assistant Professor, Chemical and Biological Engineering, The University of Sheffield
To reach the full potential of the disease-agnostic RNA platform, we are developing a set of synergistic technologies consisting of continuous manufacturing processes (continuous enzymatic RNA synthesis, continuous downstream purification, and continuous lipid nanoparticle formulation), analytical technologies, computer models, and bespoke software. These technologies are co-developed under a patient-centric Quality by Digital Design (QbDD) framework to obtain a multi-product design space with CQAs as a function of CPPs.

9:30 Continuous Purification Methods for the Rapid Manufacture of mRNA-Based Products
Harris Makatsoris, PhD, Professor, Sustainable Manufacturing Systems, Kings College London

9:55 Prospects and Challenges in Sterile Filtration of mRNA-Lipid Nanoparticles
Kevork Oliver Messerian, Graduate Research Assistant, Penn State University
mRNA-based vaccines use lipid nanoparticles (LNPs) to ensure mRNA delivery for effective protein translation. However, the large size and unique behavior of the LNPs create significant challenges in the design and implementation of the sterile filtration step. Filter capacities can be significantly smaller than those for traditional biotherapeutics, and the fouling behavior does not follow traditional mechanisms. The results provide important insights into the mechanisms controlling sterile filtration of LNPs.

10:20 Creating an mRNA Vaccine Manufacturing Platform for Hands-on Training
Baley Reeves, PhD, Interim Director, National Center for Therapeutics Manufacturing (NCTM)
The National Center for Therapeutics Manufacturing (NC™) partnered with the Biomedical Advanced Research and Development Authority (BARDA), Pfizer, the US Pharmacopeia (USP), and other solution providers to develop the first commercial-scale, hands-on training course for mRNA vaccine production in the US. This presentation will give an overview of the company-agnostic, in-house platform process that was developed for the production of mRNA-LNPs, beginning with pDNA production and continuing through bulk filling/freezing.

10:45 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

NOVEL PLATFORMS FOR mRNA CANDIDATES

11:35 Developing Synthetic DNA Template (SDT)-Based Platforms for the Fast *in vitro* Transcription, Screening, and Validation of mRNA-Therapeutic Candidates
Lorenzo Franceschini, PhD, Postdoctoral Researcher, Laboratory of Molecular & Cellular Therapy, Vrije Universiteit Brussel
A rapid, flexible, and affordable mRNA manufacturing workflow is necessary to unlock the full potential of mRNA therapeutics. mRNA transcription relies on the rigid sequence design and laborious bacterial cloning for each plasmid preparation. Here, we introduce a synthetic DNA template (SDT)-based platform, allowing cost- and time-efficient production of mRNA encoding different protein candidates for therapeutic evaluation, enabling applications such as T cell receptor (TCR) screening, and neoantigen immunogenicity validation.

12:05 pm Programming mRNA for Cancer Immunotherapy
Prashant Nambiar, DVM, PhD, MBA, Senior Vice President, R&D, Strand Therapeutics
mRNA therapeutics face challenges like limited patient response due to inadequate T cell activation in the tumor microenvironment. Addressing this, we present STX-001, a novel synthetic self-replicating mRNA technology for intratumoral delivery. It provides sustained IL-12 cytokine expression, specifically within the tumor microenvironment, improving T cell recruitment and activity. STX-001 exemplifies the next step in personalized immunotherapy, combining the precision and adaptability of mRNA therapeutics to overcome existing immunotherapy limitations.

12:35 Transition to Lunch

12:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:15 Session Break

2:00 Long-Acting Nucleic Acid Formulations With Silica Matrix
Marcus Reay, MS, Business Development Manager, DelSiTech Ltd
Thomas McCauley, PhD, CSO, Omega Therapeutics, Inc.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE SESSION

3:40 Organizer's Welcome Remarks

3:45 Plenary Chairperson's Remarks
Jim Weterings, PhD, Vice President Research, RNA Therapeutics & Delivery, Sirnaomics

3:50 Biomimetic Chemistry of RNA Therapeutics
Mano Manoharan, PhD, Distinguished Scientist & Senior Vice President, Innovation Chemistry, Alnylam Pharmaceuticals
Achieving success in RNA therapeutics depends on proper understanding of mechanisms of nature. In stages of discovery, delivery, and development of RNA-based therapeutics we follow and mimic many natural processes. We will illustrate this concept by taking several key steps of molecular mechanisms involved and examples of medicines which are either approved or in clinical development.

4:20 Applications for mRNA Therapeutics: Immunological Issues and Considerations
Arthur Krieg, MD, Adjunct Professor, University of Massachusetts, Chan School of Medicine
From an immunological perspective, there are 3 categories of mRNA therapeutics. Protein expression mRNAs (enzyme replacement, antibody expression, gene editing with encoded programmable nuclease): any immune activation is undesirable. Infectious disease mRNA vaccines (immune activation desirable to induce neutralizing antibodies). Cancer mRNA vaccines (immune activation desirable to induce CD8+ T cells). Achieving these immune effects requires intentional design of mRNA and delivery system, which will be reviewed.

4:50 Welcome Reception in the Exhibit Hall with Poster Viewing

5:50 Close of Day

THURSDAY, MARCH 14

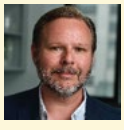
8:00 am Registration and Morning Coffee

PLENARY KEYNOTE SESSION

8:30 Organizer's Welcome Remarks

8:35 Plenary Chairperson's Remarks
Paloma Giangrande, PhD, Independent Consultant

8:40 Realizing the Promise of *in vivo* CRISPR Therapeutics
Laura Sepp-Lorenzino, PhD, CSO, Intellia Therapeutics
Intellia's investigational *in vivo* genome editing therapies comprise a lipid nanoparticle, formulating a single guide RNA, and an mRNA expressing SpyCas9. NTLA-2001 is being developed for transthyretin amyloidosis with polyneuropathy (ATTRv-PN) and transthyretin amyloidosis with cardiomyopathy (ATTR-CM). NTLA-2002 is being developed for hereditary angioedema (HAE). Preclinical and data from ongoing clinical studies will be presented.



9:10 Harnessing RNA Metabolism for Precision RNA Therapeutics
Jeffery M. Coller, PhD, Bloomberg Distinguished Professor of RNA Biology and Therapeutics, Johns Hopkins University
We have created a therapeutic technique that enhances mRNA translation. This technology has numerous clinical applications and works by binding to mRNA and improving translation. The approach offers key benefits: it is disease-modifying, restoring normal protein levels; it is mutation agnostic; it can be tailored to precisely control expression, reducing the risk of overexpression; and lastly, it is applicable across indications and highly versatile.

9:40 Coffee Break in the Exhibit Hall with Poster Viewing

mRNA VACCINES

10:30 Chairperson's Remarks
Gilles Besin, PhD, CSO, Orbital Therapeutics

10:35 sa-mRNA Vaccine Development
Yingxia Wen, PhD, Executive Director, Head, Discovery Research and Research Strategy, Seqirus
A/H2N3 influenza has posed a particular pandemic threat. Self-amplifying mRNA (sa-mRNA) vaccine emerges as the counter measurement. We evaluated sa-mRNA A/H2N3 vaccine designs, including codon optimization and co-expression of neuraminidase (NA), in addition to hemagglutinin (HA). Mouse studies showed robust neutralizing antibody and CMI responses to both HA and NA, and strong cross-reactivity to another A/H2N3 virus, demonstrating the sa-mRNA pandemic vaccine as the effective approach for pandemic preparation.

11:05 Design and Optimization of a VLP-Forming mRNA Vaccine for HIV-1
Paolo Lusso, MD, PhD, Chief, Senior Investigator, Viral Pathogenesis Section, NIAID, NIH
We developed an original mRNA vaccine platform that simultaneously expresses HIV-1 Gag, Env, and Pro to produce virus-like particle (VLP) *in vivo*. In pre-clinical studies in macaques, sequential immunization with VLP-forming mRNA-expressing rationally selected Envs from different clades induced broad-spectrum neutralization and protection from heterologous tier-2 SHIV infection. A clinical trial to test the safety and immunogenicity of this mRNA vaccine will be launched in 2024.

11:35 Transition to Lunch

11:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:15 pm Session Break

1:00 Next-Generation Lipids & LNPs for Enhanced Oncology & Infectious Disease Vaccine Responses
Robert W. Georgantas, PhD, President, CTO, Providence Therapeutics
The COVID-19 pandemic and the recent outcomes in personalized oncology studies have demonstrated that first-generation mRNA LNPs can alter disease course and outcomes. Yet, space remains for significant improvements. Within our mRNA medicines ecosystem, Providence Therapeutics has developed next-generation lipids and LNPs rationally designed to induce enhanced immunologic responses to break immune tolerance and maximize cytotoxic T cells for cancer treatments or neutralizing antibodies for infectious diseases.

1:30 Introducing circRNA Vaccine Platform as Novel Alternative to RNA Vaccine
Gilles Besin, PhD, CSO, Orbital Therapeutics
Since the discovery of circular RNA, a new class of single-stranded RNA, their biogenesis, regulation, and function have been characterized, allowing for better understanding and their adoption as new tools for therapeutics. With the development of molecular biology, circRNAs have been engineered as a novel class of therapeutics. Compared to linear mRNA vaccines, mRNA vaccines offer an improved approach to RNA-based vaccination with increased stability, simplicity of manufacture, and scalability.
Heinrich Haas, PhD, NeoVac

INTERACTIVE BREAKOUT DISCUSSIONS

2:30 Interactive Breakout Discussions

Interactive Breakout Discussions are informal, moderated, small-group discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator(s) who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakout Discussion page for a complete listing of topics and descriptions.

IN-PERSON ONLY BREAKOUT DISCUSSION: Lipids and LNPs as Signalling Molecules in the Immune System

Robert W. Georgantas, PhD, President, CTO, Providence Therapeutics

3:10 Refreshment Break in the Exhibit Hall with Last Chance for Poster Viewing

mRNA THERAPEUTICS FOR NON-ONCOLOGY INDICATIONS

3:40 Chairperson's Remarks

3:45 Modified mRNA Therapeutics for Cardiovascular Diseases

Ajit Magadum, PhD, Associate Scientist, Lewis Katz School of Medicine, Temple University

Modified mRNA (modRNA) technology, lauded for its triumphs in COVID-19 vaccine development, is emerging as a promising strategy against cardiovascular diseases (CVD). With 19.1 million global deaths in 2020 and prevalence of 620 million, CVD demands innovative solutions. My presentation spotlights our work on modRNA therapies fostering cardiac regeneration and combating cardiac fibrosis, hypertrophy, and cell death in CVD animal models, and development of cell-specific modRNA expression platforms for CVD.

4:15 Targeted LNP-mRNA for Developing the Next Generation of mRNA-based Therapeutics

Hamideh Parhiz, PharmD, PhD, Research Assistant Professor, Infectious Diseases, University of Pennsylvania

In vivo cellular reprogramming via targeted delivery of RNA-based therapeutics to selective cells could be highly valuable. In this talk, I will discuss some of our recent efforts in developing targeted mRNA therapeutics for non-oncology indications.

Patrick Finn, PhD, Vice President, Rare Disease Research & Preclinical Development, Moderna Inc

5:15 Close of Conference

Poster Information

Present a Poster and Save $50!

Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster session. To secure an onsite poster board and/or ensure your poster is included in the conference materials, your submission must be received, and your registration paid in full by **February 2, 2024.**

Reasons you should present your research poster at this conference:

- Your research will be seen by our international delegation, representing leaders from top pharmaceutical, biotech, academic and government institutions
- Discuss your research and collaborate with other attendees
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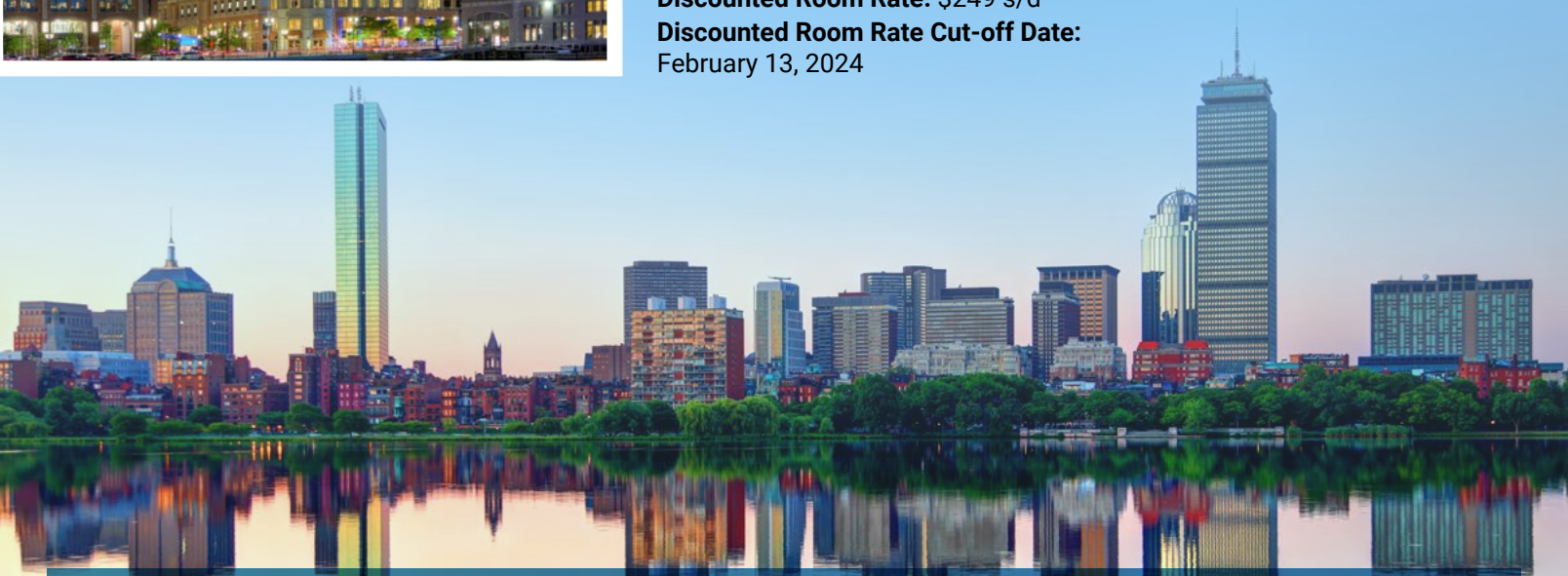
Conference Venue and Hotel:
Seaport Hotel Boston
One Seaport Lane
Boston, MA 02110 USA

Discounted Room Rate: $249 s/d
Discounted Room Rate Cut-off Date:
February 13, 2024



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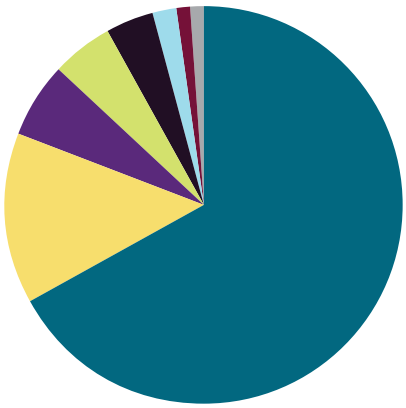
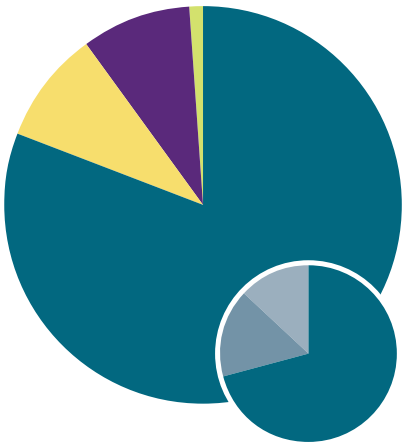
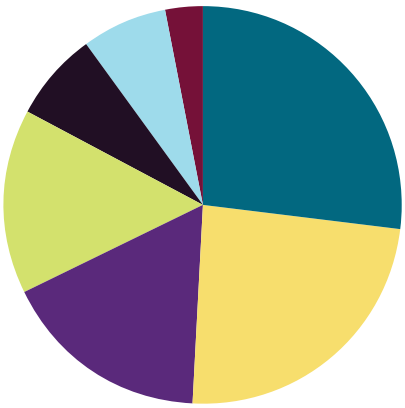
2023 Attendee Demographics







COMPANY TYPE

Biotech	67%
Pharma	14%
Academic	6%
Healthcare	5%
Services	4%
Financial	2%
Government	1%
Societies	1%

GEOGRAPHIC LOCATION

USA	81%
Europe	9%
Asia	9%
Rest of World	1%

US BREAKDOWN

East Coast	71%
West Coast	16%
Midwest	13%

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Executive	17%
Sales & Marketing	15%
Manager	7%
Professor	7%
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