CONFERENCE PROGRAMS
Oligonucleotide Discovery and Delivery
Oligonucleotide CMC and Regulatory Strategies

SHORT COURSE
Examining the Safety and Toxicity of Nucleic Acid Therapeutics

KEYNOTE SPEAKERS

Isabel Aznarez, PhD
Co-Founder, Vice President & Head, Biology, Stoke Therapeutics

Richard Geary, PhD
Chief Development Officer and Executive Vice President, Antisense Drug Development, Ionis Pharmaceuticals, Inc.

Arthur M. Krieg
Founder & CSO, Checkmate Pharmaceuticals

Arthur Levin, PhD
Executive Vice President, Research and Development, Avidity Biosciences

Michael Segel, PhD
Postdoctoral Fellow, Laboratory of Dr. Feng Zhang, Broad Institute of MIT and Harvard

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Welcome to OPT Congress

Conference Highlights

EXHIBIT HOURS
Tuesday, March 15, 2:50 PM – 6:35 PM
Wednesday, March 16, 10:30 AM – 3:10 PM

NETWORKING RECEPTION & BREAKS
Tuesday, March 15, 5:35 PM – 6:35 PM
Wednesday, March 16, 12:50 PM – 1:25 PM

EVENT-AT-A-GLANCE

TUESDAY, MARCH 15, 2022
- Oligonucleotide CMC and Regulatory Strategies
- Oligonucleotide Discovery and Delivery

WEDNESDAY, MARCH 16, 2022
- Oligonucleotide CMC and Regulatory Strategies
- Oligonucleotide Discovery and Delivery

WITH THANKS TO OUR EXECUTIVE ADVISORY BOARD

Ekkehard Leberer, PhD
Senior Director, R&D Alliance Management, Sanofi

Arthur Levin, PhD
Executive Vice President, Research and Development, 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
Examining the Safety and Toxicity of Nucleic Acid Therapeutics

Instructors: Jeffrey Foy, PhD, Executive Director, Toxicology, Dicerna Pharmaceuticals
Xiao Shelley Hu, PhD, Senior Director, Head of DMPK and Clinical Pharmacology, Wave Life Sciences
Padma Narayanan, PhD, Head, Preclinical Safety, 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 non-specific effects differ for each of these drug types. This course discusses some of the preclinical strategies for ADME/safety/tox evaluations and regulatory expectations.

This conference was both educational and inspirational. My group will pursue at least one new research collaboration based on novel information presented.

Senior Research Advisor, Eli Lilly
Cambridge Healthtech Institute’s 7th Annual

Oligonucleotide Discovery and Delivery
Optimizing Design, Delivery and Performance

MARCH 15-16, 2022

TUESDAY, MARCH 15

7:00 am Short Course Registration

8:00 Recommended Pre-Conference Short Course*

SC1: Examining the Safety and Toxicity of Nucleic Acid Therapeutics

*All Access Premium Pricing or separate registration required. See short course page for details.

9:15 Main Conference Registration and Morning Coffee

10:15 Organizer’s Welcome Remarks

Tanuja Koppal, PhD, Senior Conference Director, Cambridge Healthtech Institute

ADVANCES IN TARGETED DELIVERY

10:25 Chairperson’s Opening Remarks

Dmitry Samarsky, PhD, CTO, Sirnaomics

10:30 mxRNA: Miniaturized RNAi Triggers Composed of Single Oligonucleotides

Dmitry Samarsky, PhD, CTO, Sirnaomics

Sirnaomics has developed proprietary GalNAc-RNAi therapeutic platform GalAhead, with mxRNA comprising one of its key technological components. mxRNAs (or miniaturized RNAi triggers) are composed of single 31-33 nt long oligonucleotides, demonstrating excellent activity in primary hepatocytes and in mice. In addition to these experiments, we will present results of our 13-week study in non-human primates conducted with the candidate molecule for our frontrunner GalAhead therapeutic program.

11:00 Development of a GalNAc-asiRNA Platform for Treatment of Liver Disorders

Behfar Ardeshali, PhD, Senior Scientist, OliX Pharmaceuticals

To address the unmet needs in treatment of liver disorders caused by overabundance of hepatocyte factors, OliX Pharmaceuticals has developed a N-acetyl galactosamine (GalNAc) conjugation platform for high-efficiency, ASGPR-mediated delivery of asiRNA compounds to hepatocytes. We have also established dynamic discovery and preclinical stage programs to target multiple hepatic disorders, among them, nonalcoholic steatohepatitis (NASH) and HBV. Here we present the latest advancements in our liver programs.

11:30 Exploring Chemical Space for Improving Properties of RNA Therapeutics

Thazha Prakash, PhD, Executive Research Fellow, Ionis Pharmaceuticals, Inc.

Advancements in the chemical design of oligonucleotide drugs have improved potency, safety and duration leading to better clinical outcomes. Efforts to expand the boundaries of existing chemical space to further enhance the properties of RNA therapeutics will be presented.

12:00 pm Session Break

Luncheon Presentation to be Announced

Speaker to be Announced

12:40 Session Break

1:15 Chairperson’s Opening Remarks

Leo Ziqing Qian, PhD, Co-Founder & Vice President, Discovery Research, Entrada Therapeutics

1:20 Delivery of RNA Therapeutics: The Great Endosomal Escape

Steven Dowdy, PhD, Professor, Department of Cellular & Molecular Medicine, University of California San Diego School of Medicine

RNA therapeutics have great potential to selectively treat human disease, especially cancer, COVID and neurological disorders. However, due to their size and 20-40 negatively charged phosphates, RNAs have limited (<1%) to no ability to overcome a billion years of evolutionary defenses that prevent RNAs from escaping across the endosomal lipid bilayer membrane into the cytoplasm. Consequently, endosomal escape remains The Technological Problem to solve for wide-spread development of RNA therapeutics.

1:50 Development of Endosomal Escape Vehicles to Enhance the Intracellular Delivery of Oligonucleotides

Leo Ziqing Qian, PhD, Co-Founder & Vice President, Discovery Research, Entrada Therapeutics

We have developed a novel oligonucleotide delivery platform by conjugation with Entrada’s proprietary Endosomal Escape Vehicle (EEV), a class of cyclic peptides designed to facilitate intracellular delivery and endosomal escape. The preclinical results have confirmed the significant therapeutic potential of the strategy for DMD and demonstrated that the EEV platform can serve as a general and highly efficient delivery technology for the extrahepatic delivery of therapeutic oligonucleotides.

2:20 Sponsored Presentation (Opportunity Available)

2:50 Refreshment Break in the Exhibit Hall with Poster Viewing

FEATURED SESSION: EMERGING OLIGO THERAPIES

3:30 Chairperson’s Opening Remarks

Paloma H. Giangrande, PhD, Vice President, Platform and Discovery Sciences Biology, Wave Life Sciences

3:35 FEATURED PRESENTATION: Small Activating RNA from Concept to Phase 2 Clinical Trials

Nagy Habib, ChM, FRCS, Head of R&D and CMO, MiNA Therapeutics Ltd.

Small activating RNAs (saRNA) are double stranded 21-nucleotide RNA that target promoters or enhance genes leading to mRNA upregulation. MTL-CEBPA is an investigational drug that resulted from the conjugation of saRNA CEBPA with NOV 340 liposomes that targets tumour associated macrophages. MTL-CEBPA has been administered safely in over 100 patients with advanced cancer and improved clinical outcome in a sub-set of patients when co-administered with TKI or check point inhibitor.
4:05 FEATURED PRESENTATION: Advancing and Applying Base Editing Technologies
Luke Koblan, PhD, Former Graduate Student, Laboratory of David Liu, Department of Chemistry and Chemical Biology, Harvard University and Broad Institute of MIT and Harvard
Base editors hold significant promise to precisely correct the underlying genetic cause of many diseases. Correcting pathogenic mutations in diseaserelevant contexts has remained challenging due to low editing efficiencies and limited editor delivery modalities. Systematic improvements to base editor performance and delivery enabled efficient adenine base editor-mediated correction of the predominant mutation underlying Hutchinson-Gilford Progeria Syndrome in a mouse model of this disease, ultimately rescuing major hallmarks of disease pathology.

4:35 FEATURED PRESENTATION: Chemically Modified Guides and Donors for Precision Genome Editing
Jonathan Watts, PhD, Associate Professor, RNA Therapeutics Institute, University of Massachusetts Chan Medical School
We describe progress toward complete chemical modification of CRISPR guides and their in vivo genome editing. We have identified patterns of backbone and sugar modifications that allow robust gene editing activity in mRNA and RNP formats, in vitro and in vivo. We describe a broadly accessible modification strategy for DNA donors used as templates for homology-directed repair, which improves the efficiency of HDR up to 8-fold over normal DNA donors.

5:05 FEATURED PRESENTATION: Chemically Optimized Stereopure Oligonucleotides Direct ADAR-Mediated RNA Editing
Paloma H. Giangrande, PhD, Vice President, Platform and Discovery Sciences Biology, Wave Life Sciences
The talk will cover proof-of-concept preclinical in vivo data demonstrating effective and durable editing of human SERPINA1 Z allele mRNA in the liver, resulting in a therapeutically meaningful increase in circulating, functional wild-type AAT protein. These initial in vivo studies utilize Wave's proprietary transgenic mouse model, which has both the human SERPINA1 Z-allele as well as human ADAR that is expressed comparably to human cells.

5:35 Welcome Reception in the Exhibit Hall with Poster Viewing

6:35 Close of Day

WEDNESDAY, MARCH 16

7:30 am Registration Open
10:00 Talk Title to be Announced
Speaker to be Announced

10:15 Sponsored Presentation (Opportunity Available)

10:30 Coffee Break in the Exhibit Hall with Poster Viewing

11:10 MicroRNA Therapeutics: Targeting Fibrotic Diseases
Ekkehard Leberer, PhD, Senior Life Sciences Consultant, ELBIOCON; Scientific Managing Director, COMPACT Consortium
MicroRNAs are short non-coding RNAs that regulate biochemical pathways by RNA interference (RNAi). Dysregulation of microRNAs is associated with many diseases including fibrosis. The presentation shows the development of anti-fibrotic therapeutic strategies using anti-miRs as therapeutic molecules.

11:40 A GalNAc-MCJ siRNA as a Novel Mitochondrial Regulator for Treating NASH
Cynthia M. Arbeeny, PhD, CSO, Mitotherapeutix LLC
Mitotherapeutix has identified MCJ/DNAJC15, a novel negative regulator of mitochondrial metabolism, as a key target to treat NASH and other metabolic diseases. We have performed SAR and selected a lead GalNAc-MCJ siRNA as a clinical candidate for NASH. Treatment targets hepatocytes and effectively knocks down MCJ reducing disease severity in NASH models. Activity has been confirmed in non-human primates. Preclinical toxicology and PK/PD studies are planned to support an IND-filing.

12:10 pm Session Break

12:20 Luncheon Presentation (Sponsorship Opportunity Available) or Enjoy Lunch on Your Own

12:50 Dessert Break in the Exhibit Hall with Poster Viewing

KEYNOTE SESSION: OLIGO THERAPIES – OPPORTUNITIES & CHALLENGES

1:25 Chairperson's Opening Remarks
Isabel Aznarez, PhD, VP, Discovery Research, Stoke Therapeutics

1:30 KEYNOTE PRESENTATION: A Novel RNA-Based Approach to Treat Genetic Diseases
Isabel Aznarez, PhD, VP, Discovery Research, Stoke Therapeutics
Targeted augmentation of nuclear gene output (TANGO) is a novel technology that exploits antisense oligonucleotide (ASO)-mediated modulation of pre-mRNA splicing to increase full length, fully functional protein expression. In haplo insufficiencies; e.g., Dravet syndrome and autosomal dominant optic atrophy, TANGO ASOs increase protein expression by leveraging the wild type allele. TANGO can target a wide range of gene types, functions and sizes to address genetic diseases amenable to protein upregulation.

2:00 KEYNOTE PRESENTATION: RNA Targeting Progress in Severe and Rare Disease
Richard Geary, PhD, Chief Development Officer and Executive Vice President, Antisense Drug Development, Ionis Pharmaceuticals, Inc.
More than ten RNA targeted products have been approved and launched in the rare and severe disease space. Both increase and decrease in protein target production have been utilized with RNA engaging oligonucleotides. Pipeline progress will be summarized along with the challenges and opportunities that have become apparent as the research continues.

2:30 Refreshment Break in the Exhibit Hall & Last Chance for Poster Viewing

3:10 KEYNOTE PRESENTATION: Intratumoral Delivery of a CpG-A TLR9 Agonist Using a Virus-Like Particle Can Overcome Resistance to PD-1 Blockade in Patients with Advanced Melanoma
Arthur M. Krieg, Founder & CSO, Checkmate Pharmaceuticals
Innate immune activation is an appealing approach to overcoming resistance to PD-1 blockade in patients with advanced cancer, and yet positive results in murine tumor models have usually not translated into human clinical data. CpG-A TLR9 agonists have unique immune effects that are enhanced by delivery using an immunogenic virus-like particle, leading to enhanced systemic anti-tumor effects in preclinical models and in humans.

3:40 KEYNOTE PRESENTATION: Engineering Antibody Oligonucleotide Conjugates (AOCs): Taking Receptor-Mediated Uptake One Step Further
Arthur Levin, PhD, CSO, Avidity Biosciences
The promise of oligonucleotide therapeutics is to use Watson-Crick-Franklin base-pairing rules to design drugs directly and rationally based on genomic information. Until recently, that has remained elusive because of cell barriers to oligonucleotide uptake. Receptor-mediated uptake through bioconjugation oligonucleotides has changed that. Avidity's AOC technology uses monoclonal antibodies to cell surface proteins that are internalized to facilitate the functional delivery of oligo into a broad range of cell/tissue types.

4:10 KEYNOTE PRESENTATION: Harnessing Endogenous Retroviral-Like Proteins for RNA Delivery
Michael Segel, PhD, Postdoctoral Fellow, Laboratory of Dr. Feng Zhang, Broad Institute of MIT and Harvard
Retroelement derived proteins are scattered throughout the human genome. One such protein, the retroviral-like Gag protein PEG10, can be harnessed to facilitate efficient intercellular delivery of cargo RNAs in mammalian cells.

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10:15 Organizer's Welcome Remarks

OLIGONUCLEOTIDE DESIGN & SYNTHESIS

10:25 Chairperson's Opening Remarks
Mike Webb, PhD, Independent Consultant, MikeWebbPharma Ltd.; Former Vice President, API Chemistry & Analysis, GSK

10:30 FEATURED PRESENTATION: Living in the World of RNA Therapeutics
Mano Manoharan, PhD, Distinguished Scientist & Senior Vice President, Innovation Chemistry, Aylam Pharmaceuticals
This talk will cover chemical modifications and structure-activity relationships; delivery mechanisms and clinical advances and going beyond liver using oligonucleotide therapeutics.

11:00 FEATURED PRESENTATION: Rethinking Oligonucleotides in a P(V) World
Phil Baran, PhD, Chair & Professor, Department of Chemistry, Scripps Research Institute
This talk will discuss the development of new tools to synthesize and potentially manufacture small (cyclic dinucleotides, CDNs) and large oligonucleotides using the naturally occurring oxidation state of phosphorus: P(V). A suite of commercially available reagents, developed in collaboration with BMS, will be described and showcase how they can be used to generate exotic CDNs, chimeric oligonucleotides, and other P-based nucleoside analogs such as di- and tri-phosphates.

11:30 BOOST- Biocatalytic Oligonucleotide Synthesis Technology
Dr. Jill Caswell, Biology Technical Leader, Almac Sciences, Almac Group
Biocatalysis has transformed chemical synthesis of small molecule APIs. Enzymes are now seeing applications beyond small molecule and are being exploited in the application of oligonucleotide synthesis. This presentation will showcase how enzymes can be used in both single and double stranded oligonucleotide synthesis. It will highlight Almac's '3-2-3-2' hybrid biocatalytic approach for oligonucleotide synthesis that alleviates the pressures on existing solid phase capacities and utilizes more convergent synthesis.

11:45 Sponsored Presentation (Opportunity Available)

12:00 pm Session Break
12:10 Luncheon Presentation to be Announced
Speaker to be Announced
12:40 Session Break

OLIGO IDENTITY & STABILITY TESTING

1:15 Chairperson's Opening Remarks

Mike Webb, PhD, Independent Consultant, MikeWebbPharma Ltd.; Former Vice President, API Chemistry & Analysis, GSK

1:20 Computational Prediction of RNA Higher Order Structures
Christina Bergonzo, PhD, Research Chemist, National Institutes of Standards and Technology
Computational modeling can be used to screen covalent modifications to RNA structure quickly and at low cost, relating to the intended function of the drug product through thermodynamic measurements. Previous work has shown that dsRNA modeled in silico quantitatively agrees with solution state experimental data. Combining high quality all-atom models with the predicted behavior of oligonucleotide modifications, we propose a set of primary sequence-based rules which direct oligonucleotide product stability.

1:50 Strategies for Identity Testing of Therapeutic Oligonucleotide Drug Substances and Drug Products
Daniel Capaldi, PhD, Vice President, Analytical and Process Development, Ionis Pharmaceuticals
A risk-based approach for routine identity testing of therapeutic oligonucleotide drug substances and drug products will be presented. Risk analysis of solid phase oligonucleotide synthesis indicates that intact mass measurement is a powerful technique for confirming synthesis of the intended oligonucleotide. Further risk assessment suggests the addition of a second, sequence-sensitive identity test, which relies on comparison of some property of the sample to a reference standard of proven identity.

2:20 Considerations for Terminal Sterilization of Oligonucleotide Drug Products
Nadim Akhtar, PhD, Senior Principal Scientist, New Modalities, AstraZeneca R&D
The terminal sterilization process has always been the preferred choice of the regulators. The recent EMA guidance demands a substantial effort to enable terminal sterilization and a robust data package to justify an aseptic sterile filtration process. This guidance also applies to oligonucleotides which due to their structural complexity and lack of regulations pose many challenges. This presentation will discuss specific considerations and challenges associated with terminal sterilization of oligonucleotides.

2:50 Refreshment Break in the Exhibit Hall with Poster Viewing

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Interactive Discussions are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. For in-person events, the facilitator will lead from the front of the room while attendees remain seated to promote social distancing. For virtual attendees, the format will be in a Zoom room. 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 Interactive Discussion page on the conference website for a complete listing of topics and descriptions.

**CO-PRESENTATION: INTERACTIVE DISCUSSION: CMC & Regulatory Considerations for Oligo Drug Development**

Marc Lemaitre, PhD, Oligonucleotide Therapeutics CMC/Strategy Consultant, ML_Consult LLC

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

Mike Webb, PhD, Independent Consultant, MikeWebbPharma Ltd.; Former Vice President, API Chemistry & Analysis, GSK

- Oligonucleotide drug substance specifications
- Starting material for oligonucleotides
- Identity testing of oligonucleotides and impurity limits

**CMC & REGULATORY INSIGHTS**

8:55 Chairperson's Opening Remarks

Marc Lemaitre, PhD, Oligonucleotide Therapeutics CMC/Strategy Consultant, ML_Consult LLC

9:00 CMC/Regulatory for Oligonucleotide Therapeutic Submission

Marc Lemaitre, PhD, Oligonucleotide Therapeutics CMC/Strategy Consultant, ML_Consult LLC

CMC (chemistry, manufacturing and control) for oligonucleotides synthesized by solid phase synthesis and purified by chromatography is an unusual regulatory situation compared to small molecules and synthetic peptides due to the relative short experience and the various types of oligonucleotides. Some of the usual ICH guidelines for drug substances and drug products do not fully apply. This talk will provide some suggestions on what can be done based on experience.

9:30 Challenges in Establishing Commercial Analytical Control Strategy for the Lifecycle of a Therapeutic Oligonucleotide

Mike Webb, PhD, Independent Consultant, MikeWebbPharma Ltd.; Former Vice President, API Chemistry & Analysis, GSK

The talk will discuss how the analytical control strategy for an oligonucleotide drug substance and product needs to address the challenges of oligonucleotides, satisfying regulatory requirements and supporting QC for a fast-moving supply chain. We will discuss the regulatory strategies required to deal with issues of control of starting materials and drug substance identity, diastereomeric control (of phosphorothioates), assays, impurity profiling, and reducing testing with no value to the patient.

10:00 Turning Tides Together: Oligonucleotide Manufacturing at Bachem

Joseph Fraone, Business Development Manager, Oligonucleotides, Business Development, Bachem Americas, Inc.

Bachem known as the leading CMO for pharmaceutical grade peptides is expanding its technology platform...
to offer chemical manufacturing services for nucleic acid based APIs. We would like to take the opportunity to present Bachem’s capabilities as the first CMO servicing the global TIDES market.

10:15 Sponsored Presentation (Opportunity Available)

10:30 Coffee Break in the Exhibit Hall with Poster Viewing

11:10 Regulatory Interactions and Intelligence for Development and Late Phase Programs
Jennifer Franklin, PhD, Executive Director, CMC Regulatory Affairs, Ionis Pharmaceuticals, Inc.
Current regulatory intelligence for early development and late-phase filings will be discussed, including common health authority requests and recent regulatory guidance, and approaches for their phase appropriate implementation. Use of agency interactions for guiding development activities will also be discussed and examples provided.

11:40 CMC Challenges and Regulatory Strategies for the Development and Approval of RNAi Therapeutics
Sergei Poletaev, Associate Director, Regulatory Affairs CMC, Alnylam Pharmaceuticals
The development and approval of several RNAi therapeutics denote a significant milestone in the field of oligonucleotide-based drug development. This talk explores the CMC challenges and regulatory strategies for the development and approval of RNAi therapeutics including the delivery challenges of siRNAs and the applicability of available guidance on regulatory control strategies for oligonucleotides.

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4:40 Close of Conference
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Discounted Room Rate: $205.00
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For additional information please go to the TRAVEL PAGE of OPTCongress.com.

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Your Safety is Our Top Priority

To ensure maximum safety, CHI has instituted a mandatory COVID-19 vaccination policy for all in-person participants of our events. Attendees will be asked to furnish proof of vaccination. Additional details on the vaccine policy will be provided upon registration.

Attendees that cannot participate because of this policy, or due to travel restrictions, are encouraged to participate using our virtual event platform. CHI virtual events provide you with an in-person experience at your convenience, anywhere, anytime. See our website for details.

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All in-person attendees must agree to CHI’s Code of Conduct
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