Final weeks to register

MARCH 26-28, 2019 | HYATT REGENCY CAMBRIDGE | CAMBRIDGE, MA

OPT Congress

4th Annual

Oligonucleotide & Precision Therapeutics: Discovery, Development, and Delivery

CONFERENCE AGENDA

Oligonucleotide Discovery and Delivery

Optimizing Design, Delivery and Performance

Oligonucleotide CMC and Regulatory Strategies

Accelerating Product Development and Commercial Success

SYMPOSIA

New Frontiers in Gene Editing and Repair

Using CRISPR and Other Gene Editing Techniques to Drive Precision Medicine

Drug Discovery for Rare Diseases

Exploring New Technologies, Targets and Drug Modalities

FEATURED SPEAKERS



Richard S. Geary, PhD,
Senior Vice President, Development, Ionis Pharmaceuticals



David Horn Solomon, PhD,
CEO, Silence Therapeutics



Philip John (P.J.) Brooks, PhD,
Program Director, Office of Rare Diseases Research, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)



Troels Koch, PhD,
Vice President & Head of Research, RNA Therapeutics, Roche

OPTCongress.com

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- White Papers
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- Podcasts and More!

For more information regarding exhibit and sponsorship, please contact:

Carolyn Cooke
Business Development Manager
781-972-5412 | ccooke@healthtech.com

HOTEL & TRAVEL INFORMATION

Conference Venue and Hotel:
Hyatt Regency Cambridge
575 Memorial Drive
Cambridge, MA 02142
Phone: 617-494-6600

Discounted Room Rate: $215 s/d
Discounted Room Rate Cut-off Date: February 22, 2019

Reservation: Go to the travel page of **OPTCongress.com**



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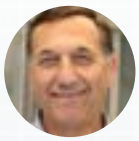
Arthur Levin, PhD, *Executive Vice President, Research and Development, Avidity Biosciences*



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



Dmitry Samarsky, PhD, *CTO, Sirnaomics*



Lubo Nechev, PhD, *Vice President Process and Analytical Sciences, Alnylam Pharmaceuticals*

Event at-a-Glance

TUESDAY, MARCH 26

Opening Plenary Session

Oligonucleotide Discovery & Delivery | Oligonucleotide CMC & Regulatory Strategies

WEDNESDAY, MARCH 27

Oligonucleotide Discovery & Delivery | Oligonucleotide CMC & Regulatory Strategies

Closing Plenary Session

THURSDAY, MARCH 28

New Frontiers in Gene Editing & Repair | Drug Discovery for Rare Diseases

Short Courses (Dinner Included)

MONDAY, MARCH 25
6:30 – 9:30 PM

SC1: Examining the Safety and Toxicity of Nucleic Acid Therapeutics

Nucleic acid drugs continue to deliver on their promise to become a third therapeutic modality, besides small molecules and biologics. Several antisense oligonucleotide drugs have been on the market for some time, while the first RNAi approval was granted last year (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 actions 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 between various types of nucleic acids drugs
- Summarize our current understanding of the origins of non-specific and potentially toxic effects
- Provide certain directions as to how to minimize the potential toxic effects of nucleic acids drugs

Instructors:

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

Dmitry Samarsky, PhD, CTO, Sirnaomics

Richard S. Geary, PhD, Senior Vice President (SVP), Development, Ionis Pharmaceuticals

Thomas Madden, PhD, President & CEO, Acuitas Therapeutics

Jeffrey Foy, Senior Director, Toxicology, Dicerna Pharmaceuticals

TUESDAY, MARCH 26
6:30 – 9:30 PM

SC2: Oligonucleotide-Based Drugs for Cancer Immunotherapy

Oligonucleotide-based therapies are now gaining attention as an alternative to antibody and small molecule-based therapies for cancer immunotherapy. In cancers where current treatment options are limited by efficacy and specificity, oligonucleotide-based drug modalities are offering a better alternative. This course will bring together experts who will share their perspectives on the opportunities and challenges underlying the generation of novel, more targeted and effective oligonucleotide-based therapies for cancer immunotherapy. Some topics that will be discussed include:

- Modulating the tumor microenvironment using novel approaches and drug modalities
- Emerging immuno-oncology targets (TLRs, STING, RIG-1 and more) for intervention using oligos
- Preclinical and clinical evaluation of new immunomodulatory pathways and nucleic acids
- Synthesis and delivery of oligonucleotides (siRNA, antisense, aptamers and others) for cancer immunotherapy

Instructors:

Shanthi Ganesh, PhD, Associate Director, Preclinical Oncology, Dicerna Pharmaceuticals, Inc.

A. Robert MacLeod, PhD, Vice President, Oncology Research and Development, Franchise Head Oncology, Ionis Pharmaceuticals, Inc.

Weston Daniel, PhD, Senior Director Program Management, Exicure, Inc.

WEDNESDAY, MARCH 27
5:30 – 8:30 PM

SC3: CRISPR-Based Gene Editing for Targeted Therapies

While the challenges and risks associated with oligonucleotide therapies still remain, there is a new and better understanding of how genes can be effectively manipulated and delivered. With the rise of gene editing tools and enhanced knowledge of targeted delivery, these therapeutic modalities are once again being embraced with renewed hope and enthusiasm. This course helps you understand how gene editing – particularly the one enabled by the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas9 system – works, and how it can be used to help develop targeted therapies with good efficacy and delivery.

Instructors:

Clifford Steer, MD, Professor of Medicine and Genetics, Cell Biology and Development; Director, Molecular Gastroenterology Program, University of Minnesota Medical School

Ciro Bonetti, PhD, Scientist, Regeneron Pharmaceuticals

Eric Kmiec, PhD, Director, Gene Editing Program and Senior Research Scientist, Center for Translational Cancer Research, Helen F. Graham Cancer Center & Research Institute, Christiana Care Health System

Oligonucleotide Discovery and Delivery

Optimizing Design, Delivery and Performance

MONDAY, MARCH 25

6:00 pm Dinner Short Course*

6:30-9:30 SC1: Examining the Safety and Toxicity of Nucleic Acid Therapeutics

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TUESDAY, MARCH 26

7:00 am Registration and Morning Coffee

OPENING PLENARY SESSION

8:00 Welcome Remarks
Gemma Smith, Senior Conference Director, Cambridge Healthtech Institute

8:10 Chairperson's Opening Remarks
Arthur Levin, PhD, Executive Vice President, Research and Development, Avidity Biosciences

8:15 RNA Targeting with Antisense Oligonucleotides: Present and Future
Richard S. Geary, PhD, Senior Vice President, Development, Ionis Pharmaceuticals
The number and chemical breadth of antisense oligonucleotide (ASO) medicines has rapidly grown in both clinical development and in market approvals. As the technology matures and innovations in delivery and increased safety margins are discovered, the ASOs currently in development are well balanced between rare and broad diseases. Some of the unique aspects associated with single strand ASO chemistry, distribution, cell uptake, clinical pharmacology and safety will be discussed as applied to clinical development examples and overall research progress.

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

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David Horn Solomon, PhD, CEO, Silence Therapeutics
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Moderator: Arthur Levin, PhD, Executive Vice President, Research and Development, Avidity Biosciences
Panelists:
Richard Geary, PhD, Senior Vice President, Development, Ionis Pharmaceuticals
Dmitry Samarsky, PhD, CTO, Sirnaomics
Lubo Nechev, PhD, Vice President, Process and Analytical Sciences, Alnylam Pharmaceuticals

10:00 Networking Coffee Break

OPTIMISING DESIGN, DELIVERY AND PERFORMANCE

10:45 Chairperson's Opening Remarks
Patrick Lu, PhD, President & CEO, Sirnaomics

10:50 FEATURED PRESENTATION: Advancing RNA Therapeutics: New Molecular Designs and Discovery Concepts
Peter Hagedorn, Senior Principal Scientist and Group Leader, Roche Innovation Center Copenhagen
Over the past two decades, RNA therapeutics has experienced major success. Our understanding of RNA biology and knowledge of RNA as a drug target has expanded tremendously, as has the translation fidelity of pre-clinical *in vitro*/vivo discovery models. The link between disease/target intervention and the principles for safe drug design are also well established. The presentation will focus on new ways to design antisense drugs, strategies and discovery concepts. It will show how structural elements of antisense oligonucleotides can be used for bespoke tailoring LNA oligonucleotide designs.

11:20 Oligonucleotide Therapeutics Now on Target: Activity of Oligonucleotide Antibody Conjugates
Arthur Levin, PhD, Executive Vice President, Research and Development, Avidity Biosciences
Using monoclonal antibodies or Fab fragments, we can deliver both siRNA payloads and single stranded oligonucleotides to specific cell types and tissues. We observed > 90% reduction in the expression of a muscle specific gene after a single 3 mg/kg dose of an siRNA conjugated to an antibody to the transferrin receptor, suggesting that the technology can be used for reducing the expression of disease-related genes in muscle. Similarly, using oligonucleotides designed to induce exon skipping, a single dose of 10 mg oligonucleotide/kg conjugated to the anti-transferrin receptor antibody induced exon skipping in wild type mice and exon skipping and dystrophin expression in the mdx mouse model of muscular dystrophy. For both the siRNA and exon skipping oligo, the activity was related to the concentration of oligonucleotide in muscle. This presentation will explore how we are using antibody oligonucleotide conjugates to develop drug candidates for multiple disease indications.

11:50 Site Specific Incorporation of Chemical Modifications in the DNA-Gap Improves the Therapeutic Index of Gapmer ASOs
Michael T. Migawa, PhD, Director, Medicinal Chemistry, Ionis Pharmaceuticals
The overall activity of antisense oligonucleotides (ASOs) is determined by its sequence, backbone, and particular combination of chemical modification. Recently, we replaced one or more of the phosphorothioate (PS) backbone modifications with a neutral methoxypropyl (MOP) modification or replaced the deoxy sugar with a 2'-OMe substituted monomer in the DNA gap-region and profoundly reduced ASO toxicity, while having only a small effect on potency.

12:20 pm Enjoy Lunch on Your Own

12:50 Session Break

2:00 Novel siRNA Therapeutics for Immune Oncology Therapeutics
Patrick Lu, PhD, President & CEO, Sirnaomics
Using a proprietary and optimized polypeptide nanoparticle-based delivery technology, we have developed the novel anti-fibrosis and anti-cancer therapeutics with siRNAs targeting both TGFβ1 and Cox-2 simultaneously (STP705), resulting apoptosis of human fibroblasts, for initial clinical indication of skin hypertrophic scar (in clinical Phase II study in US). STP705 was further advanced for liver fibrosis (Primary Sclerosing Cholangitis, PSC) treatment and received Orphan drug designation by US FDA. Among Sirnaomics anti-cancer programs, STP705 for treatment of cholangiocarcinoma (CCA) has received not only IND approval but Orphan

drug designation by US FDA. Recent report for immune oncology study using dual targeting PD-L1/PD-1 and TGFβ1 and resulting in promising clinical outcome inspired us for an attempt using STP705 in combination with immune checkpoint inhibitory mAb therapy for treatment of liver cancers. I will discuss the unique advantage of our Polypeptide Nanoparticle (PNP) technology platform for safe and efficient siRNA delivery, and our strategy for advancing multiple clinical studies in both China and USA in near future.

2:30 From Stereopurity to Precision Medicine: Optimizing the Properties of Antisense Nucleic Acid Therapeutics

David Butler, PhD, Vice President, Medicinal Chemistry, Wave Life Sciences

We have developed proprietary synthetic chemistry and manufacturing capabilities that we are using to design and produce stereopure antisense oligonucleotides (ASOs) for patients with serious, genetically defined disease. We will highlight how our chemistry platform allows us to optimize ASOs for mechanism (e.g., gene knockdown or splicing), properties *in vitro* and *in vivo*, and distribution to an array of tissues.

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

3:45 Breakthrough Technology for Intrathecal Delivery of Antisense Oligonucleotides

Sponsored by

Krishna Subramanian, PhD, Senior Scientist, Research & Development, Alcyone Lifesciences Inc

Delivery to the CNS through generic methods results in variable, sub-optimal treatment requiring use of higher doses of ASOs (antisense oligonucleotides) to provide maximum therapeutic benefit. We demonstrate for the first time, a consistent, optimal delivery system designed specifically to enhance the effectiveness of ASO therapies for CNS disorders.

4:15 A New Twist to GalNAc-Conjugated siRNA for Treatment of Liver-Related Disorders

Marie Wikstrom Lindholm, PhD, VP, Head of Technology Innovation, Silence Therapeutics

Silence Therapeutics explores different options for GalNAc conjugated siRNA design such as modification patterns, end stabilisation, linker chemistry, and number and location of GalNAc units. Two single GalNAc units, positioned a distance apart on the sense strand, demonstrated increased activity and duration of action in wild type mice compared to a GalNAc triantennary design. Novel design elements have shown great promise as a tool box for new pipeline projects.

4:35 siRNA Clinical Development Based on the TRiM Platform

James Hamilton, MD, Vice President Clinical Development, Arrowhead Pharmaceuticals

4:55 Case Study from Quark Pharmaceuticals

Elena Feinstein, MD, PhD, CSO, Quark Pharmaceuticals

5:15 Welcome Reception in the Exhibit Hall with Poster Viewing

Sponsored by

6:15 Dinner Short Course Registration*

6:30-9:30 SC2: Oligonucleotide-Based Drugs for Cancer Immunotherapy

*Separate registration required. See page 3 for details.

WEDNESDAY, MARCH 27

8:00 am Breakfast Breakout Roundtable Discussions

Grab breakfast and join a roundtable discussion. These are moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic.

Table 1: New Target Election for RNAi Medicines

Moderator: David Horn Solomon, PhD, Chief Executive Officer (CEO), Silence Therapeutics

Table 2: How to Prepare for a Regulatory Submission and Overcome Common Regulatory Hurdles

Moderator: Jennifer Franklin, Director, CMC Regulatory Affairs, Ionis Pharmaceuticals

Table 3: Recent Developments and Future Outlook of Antisense Therapeutics

Moderator: Troels Koch, Oligonucleotide Expert and Former VP & Head of Research, Roche Innovation Center Copenhagen

Table 4: Can we Push for siRNA Cancer Therapeutics Similar to Experiences with mAbs?

Moderator: Patrick Lu, PhD, President & CSO, Sirnaomics

Table 5: Adoption and Implementation of Innovative Technologies Used in CMC And Manufacturing

Francis Ring, Assistant Director, Manufacturing & Operations, Ionis Pharmaceuticals

Table 6: Can New Generation ONs with Tunable Properties Contribute to the Development of the Optimal Oligotherapeutics?

David Tabatadze, PhD, President, ZATA Pharmaceuticals

9:15 Chairperson's Remarks

Marie Wikstrom Lindholm, PhD, Vice President, Head of Technology Innovation, Silence Therapeutics

OPPORTUNITIES AND CHALLENGES WITH miRNA

9:20 FEATURED PRESENTATION: MicroRNA Therapeutics: Targeting the Genomic Dark Matter in Human Disease

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

The non-coding genome ("genomic dark matter") makes up 98.8% of the human genome. Most of this non-coding genome is transcribed into non-coding RNAs that may play an important role in cellular regulation in health and disease; these non-coding RNAs could be novel targets for future medicines. MicroRNAs are short non-coding RNAs that regulate biochemical pathways and networks of pathways by the mechanism of RNA interference (RNAi). MicroRNA-21 has been implicated in multiple organs as a microRNA associated with fibrotic diseases and cancer. The presentation will summarize the opportunities and challenges of developing microRNA-based drugs and will illustrate the successful generation of an anti-fibrotic microRNA-based therapeutic approach by targeting microRNA-21 with an antisense oligonucleotide (anti-miR-21).

9:50 Novel miRNA-targeting Therapeutic for Non-Alcoholic Fatty Liver Disease

Hyung J. Chun, MD FAHA, Associate Professor of Medicine and Pathology, Yale School of Medicine

MicroRNA based therapeutics offer an attractive treatment modality for liver disease. A novel microRNA based therapeutic target that regulates both inflammation and fatty acid absorption into the liver will be discussed.

Oligonucleotide Discovery and Delivery

Optimizing Design, Delivery and Performance

10:20 siRNA Science Journey as Reflected by the Patent Literature

Sponsored by HGF

Alison Gallafent, Patent Director, Patent Attorney, HGF Limited

Starting with patents that initially reflected manufacturing constraints, moving to patents reflecting greater understanding of chemical modifications, and later product specific patents. Advantages and potential challenges are associated with patent protection at the different stages of this journey. Close interaction between Research and Attorney can help to address potential challenges.

10:50 Coffee Break in the Exhibit Hall with Poster Viewing

ADVANCES IN mRNA

11:35 Advances in mRNA Delivery to Support Therapeutic Applications

Thomas Madden, PhD, President & CEO, Acuitas Therapeutics

Therapeutic applications of messenger RNA (mRNA) are currently being advanced into clinical development. However, mRNA requires a delivery system in order to enter cells and access the cytoplasmic compartment. Acuitas is developing lipid nanoparticle systems (LNP) that allow the efficient delivery and expression of mRNA via different routes of administration. Characteristics of both the LNP carrier and mRNA payload that facilitate efficient delivery and provide a favorable safety profile will be discussed. In addition, we will present preclinical results illustrating the potential application of mRNA-LNP therapeutics in several clinical areas.

11:55 pm The Epitranscriptome: The New Frontier in mRNA Therapeutic Development

Anton McCaffrey, PhD, Senior Director of Emerging Science and Innovation, TriLink BioTechnologies

mRNA therapeutics is one of the hottest new areas in nucleic acid therapeutics. mRNAs are post-transcriptionally modified at the 5' cap and at internal bases. These epitranscriptome modifications license the mRNA as self and prevent activation of innate immune sensors. Recently we developed a novel capping method called CleanCap™ that allows co-transcriptional incorporation of various natural cap forms. These endogenous cap forms have improved activity in mice.

12:15 Nucleoside-modified mRNA Immunization Elicits Durable Protective Immune Responses Against Infectious Diseases

Norbert Pardi, PhD, Assistant Professor of Medicine, University of Pennsylvania

Nucleoside-modified, lipid nanoparticle (LNP)-encapsulated mRNA vaccines demonstrated safety and protective efficacy against various infectious pathogens (influenza, Ebola and Zika viruses) in small and large animals. This vaccine platform has the unique ability to develop potent T follicular helper cell and durable, broadly protective neutralizing antibody responses. This presentation will highlight some of the most recent findings on nucleoside-modified mRNA-LNP vaccines.

12:35 Enjoy Lunch on Your Own

1:05 Dessert Break in the Exhibit Hall with Poster Viewing

2:00 mRNA Therapies: Momentum and Progress of a Disruptive Technology

Ingmar Hoerr, PhD, Founder and Chairman of the Supervisory Board, CureVac

This talk will cover 1) approaches for the application (delivery) of mRNA. Encapsulation through packaging in LNP (lipid nanoparticles) and other delivery options 2) mRNA optimization: Protein therapies, like enzyme replacement, require a high and steady expression for longer term therapeutic benefit 3) production of mRNA – upscaling of an industrial pharmaceutical process with high throughput and lowest possible production costs as significant challenge.

2:30 PANEL DISCUSSION: Examining Developments in the Discovery and Delivery of mRNA Therapies

Moderator: Marie Wikstrom Lindholm, PhD, Vice President, Head of Technology Innovation, Silence Therapeutics

Panellists:

Anton McCaffrey, PhD, Senior Director of Emerging Science and Innovation, TriLink BioTechnologies

Ingmar Hoerr, PhD, Founder and Chairman of the Supervisory Board, CureVac

Norbert Pardi, PhD, Assistant Professor of Medicine, University of Pennsylvania

3:15 Refreshment Break in the Exhibit Hall with Poster Viewing

CLOSING PLENARY SESSION

3:55 Chairperson Remarks:

R.P. (Kris) Iyer, PhD, Co-Founder & CSO, Spring Bank Pharmaceuticals

4:00 Synthesis and Biological Activity of Thiomorpholino Oligonucleotides

Marvin Caruthers, PhD, Distinguished Professor, University of Colorado

The synthesis and biological activity of thiomorpholino DNA will be presented. Recently thiomorpholino oligonucleotides have been found to be far more active than any other tested analogue in exon skipping assays involving a mouse model for Duschenne Muscular Dystrophy. This analogue is also extremely active in a dual luciferase cell culture assay.

4:20 The Development of Nucleic Acid Delivery Platforms; a pan-RNA approach

Bo Rode Hansen, PhD, President & CSO, GeneVant Sciences

At Genevant, we are pursuing a modality agnostic "pan-RNA" approach to develop a diverse pipeline of RNA therapeutics; including delivery of RNAi payloads targeting both viral and endogenous gene targets, and mRNA in vaccine applications.

4:40 Implementing the Use of Antisense in the Brain

Jonathan Watts, PhD, Associate Professor, UMass Medical School

5:00 Close of Oligonucleotide Discovery and Delivery

5:00 Dinner Short Course Registration*

5:30-8:30 SC3: CRISPR-Based Gene Editing for Targeted Therapies

*Separate registration required. See page 3 for details.

Oligonucleotide CMC and Regulatory Strategies

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

10:00 Networking Coffee Break

INNOVATIVE CMC AND MANUFACTURING STRATEGIES

10:45 Chairperson's Opening Remarks
Marc Lemaitre, PhD, COO, Sirnaomics and ML Consult

10:50 FEATURED PRESENTATION: Developing the CMC Strategy for ONPATTRO™ (patisiran)
Lubo Nechev, PhD, Vice President Process and Analytical Sciences, Alnylam Pharmaceuticals
ONPATTRO (patisiran), the first RNA interference (RNAi) therapeutic approved in the United States and the European Union is targeting transthyretin (TTR) for the treatment of hereditary ATTR amyloidosis. Patisiran comprises a double stranded RNA API in a lipid nanoparticle formulation for intravenous administration. The presentation will discuss the development of the CMC strategy for patisiran from early stage to approval.

11:20 Stage 3 Continued Process Verification of Commercial Oligonucleotide Synthesis: Monitoring Strategy and Process Observations
Francis Ring, Assistant Director, Manufacturing & Operations, Ionis Pharmaceuticals
As more Oligonucleotide Therapies are approved, it is important to develop appropriate Continued Process Verification procedures, both to satisfy regulatory requirements and to inform future process development. Since 2010, across three compounds, Ionis has been performing validated solid-phase syntheses. The process data collection, analysis, and reporting strategy will be described, along with their evolution over time. Additionally, notable process trends and observations will be presented.

11:50 Enabling Rapid Start-Up with End-to-End Antisense Oligonucleotide Capability and Streamlined Business Processes
Sheron Branham, Associate Director, ASO Process Engineering and Manufacturing, Biogen
Biogen is the first innovator to internalize end-to-end ASO manufacturing capability while others have chosen to outsource. By vertically integrating their ASO supply chain, Biogen has been able to significantly reduce turnaround time and supply risk. The presentation will highlight how the facility and the business processes were designed to maximize flexibility and prepare for potential rapid growth in the future.

12:20 pm Enjoy Lunch on Your Own

12:50 Session Break

2:00 siRNA Case Study: Development and Implementation of Late Stage CMC Strategies
Vidhya Gopalakrishnan, PhD, Senior Vice President, Pharmaceutical Development, Quark Pharmaceuticals
Assay testing or weight-based determination of API content is an important aspect of release testing. Determining the assay of double-stranded oligonucleotide therapeutics is complicated. Because the duplex is formed by annealing two single strands, there will likely be closely related duplex variants arising from annealing of the impurities of the single strands thus making it difficult to discriminate variants from the parent duplex. This presentation will discuss findings from a comparative assessment of specific denaturing and non-denaturing chromatographic methods for assay measurement of a siRNA duplex and implications for release testing.

2:30 Combining siRNA and Peptides for Improved Delivery – CMC Aspects
Marc Lemaitre, PhD, COO, Sirnaomics and ML_Consult
Branched peptides containing histidines and lysines (HK) have been shown to be effective carriers for DNA and siRNA. We will discuss the specific aspects of CMC for the development of such a product.

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

3:45 Biophysical Characterization of RNA Structures Using Solution State Approaches
Christina Bergonzo, PhD, Research Chemist, National Institute of Standards and Technology

4:15 CMO Outsourcing: An Integrated Approach
Joe DeCourcey, Head Manufacturing Science and Technology, Sarepta Therapeutics

4:45 CMC Challenges Associated with Oligonucleotide Products for Intravitreal Administration
Bianca Matthee, Vice President, Manufacturing & Pharmaceutics, ProQR Therapeutics
Oligonucleotide product design for intravitreal administration can be challenging from a formulation, analytical and manufacturing perspective. There are stringent specifications these products need to adhere to for the purpose of safely delivery the oligo into the eye. This presentation will elaborate on CMC challenges to overcome in manufacturing and will include some examples.

5:15 Welcome Reception in the Exhibit Hall with Poster Viewing
Sponsored by OLIGO FACTORY

6:15 Dinner Short Course Registration*

6:30-9:30 SC2: Oligonucleotide-Based Drugs for Cancer Immunotherapy
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Moderator: Patrick Lu, PhD, President & CSO, Sirnaomics

Table 5: Adoption and Implementation of Innovative Technologies Used in CMC And Manufacturing
Francis Ring, Assistant Director, Manufacturing & Operations, Ionis Pharmaceuticals

Table 6: Can New Generation ONs with Tunable Properties Contribute to the Development of the Optimal Oligotherapeutics?
David Tabatadze, PhD, President, ZATA Pharmaceuticals

CRITICAL FEEDBACK ON REGULATORY SUBMISSIONS

9:40 Chairperson's Opening Remarks
Paul Manley, President & Principal Consultant, Orvieto Consulting

9:50 Regulatory CMC Experience for OnpattroTM (patisiran), a First-in-Class siRNA Therapeutic
Saraswathy (Sara) Nochur, PhD, Chief Regulatory Officer, Alnylam Pharmaceuticals
OnpattroTM (patisiran) became the first FDA/EMA-approved treatment of polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR), and the first regulatory approval of a new class of drugs called small interfering ribonucleic acid (siRNA). CMC development of OnpattroTM involved extensive innovation, challenges due to complexity of the product (consisting of double-stranded siRNA and lipid components including novel excipients), and well-planned interactions with regulatory agencies. Regulatory CMC experience on Onpattro development and registration will be provided.

10:20 Late Breaking Presentation

10:50 Coffee Break in the Exhibit Hall with Poster Viewing

11:35 Strategies for Identity Testing of Oligonucleotide Therapeutics
Hong Jiang, Scientist II, Analytical Development, Biogen
Due to their polymeric nature and high molecular weight, establishing identity of oligonucleotide therapeutics is significantly more challenging compared to synthetic small molecules. The commonly accepted identity tests for small molecules, such as IR spectrum and retention time matching with a reference standard, are generally insufficient for identity confirmation of an oligonucleotide. In this presentation I will discuss various risk factors during the manufacturing process that can potentially lead to an oligonucleotide of an incorrect structure, along with currently available analytical methods that can detect certain structural changes and confirm the identity. A risk-based framework for the selection of identity tests and how it can be integrated into a robust control strategy will be proposed.

12:05 pm Regulatory Agency Questions and Learnings from Recent Commercial Submissions
Jennifer Franklin, Director, CMC Regulatory Affairs, Ionis Pharmaceuticals
Recent CMC questions received from global regulatory agencies for an antisense oligonucleotide drug will be detailed, along with a discussion of the response strategies that led to their successful resolution, and ultimately, to drug approval. Regulatory challenges and learnings from the review and approval process in the US, EU, and Canada will also be examined.

12:35 Enjoy Lunch on Your Own

1:05 Dessert Break in the Exhibit Hall with Poster Viewing

2:00 Accelerating Pathway to Approval: Points to Consider in Conducting Productive Regulatory Interactions and Making Successful IND/CTA Submissions
Paul Manley, President & Principal Consultant, Orvieto Consulting
FDA and EU National Authorities have similar approaches to how they review and approve clinical trial applications, however key areas of difference need to be appreciated in order to achieve successful applications. This presentation provides advice for oligonucleotide companies covering: pre-submission dialogue, differences in application content and Regulatory Agency review approaches and commitments during and after trial completion.

2:30 **PANEL DISCUSSION: How to Successfully Prepare for a Regulatory Submission and Overcome Common Hurdles**
Moderator: R.P. (Kris) Iyer, PhD, Co-Founder & CSO, Spring Bank Pharmaceuticals
Panelists: Jennifer Franklin, Director, CMC Regulatory Affairs, Ionis Pharmaceuticals
Saraswathy (Sara) Nochur, PhD, Chief Regulatory Officer, Alnylam Pharmaceuticals
Paul Manley, President & Principal Consultant, Orvieto Consulting

3:15 **Refreshment Break in the Exhibit Hall with Poster Viewing**

CLOSING PLENARY SESSION

3:55 **Chairperson Remarks:**
R.P. (Kris) Iyer, PhD, Co-Founder & CSO, Spring Bank Pharmaceuticals

4:00 **Synthesis and Biological Activity of Thiomorpholino Oligonucleotides**
Marvin Caruthers, PhD, Distinguished Professor, University of Colorado
The synthesis and biological activity of thiomorpholino DNA will be presented. Recently thiomorpholino oligonucleotides have been found to be far more active than any other tested analogue in exon skipping assays involving a mouse model for Duschenne Muscular Dystrophy. This analogue is also extremely active in a dual luciferase cell culture assay.

4:20 **The Development of Nucleic Acid Delivery Platforms; a pan-RNA Approach**
Bo Rode Hansen, President & CSO, GeneVant Sciences
At Genevant, we are pursuing a modality agnostic "pan-RNA" approach to develop a diverse pipeline of RNA therapeutics; including delivery of RNAi payloads targeting both viral and endogenous gene targets, and mRNA in vaccine applications.

4:40 **Implementing the Use of Antisense in the Brain**
Jonathan Watts, PhD, Associate Professor, UMass Medical School

5:00 **Close of Oligonucleotide CMC and Regulatory Strategies"**

5:00 **Dinner Short Course Registration***

5:30-8:30 **SC3: CRISPR-Based Gene Editing for Targeted Therapies**
*Separate registration required. See page 3 for details.

New Frontiers in Gene Editing and Repair

Using CRISPR and Other Gene Editing Techniques to Drive Precision Medicine

THURSDAY, MARCH 28

7:30 am Registration and Morning Coffee

DRIVING PRECISION IN GENE EDITING

8:15 Welcome Remarks from Conference Director
Tanuja Koppal, PhD, Conference Director, Cambridge Healthtech Institute

8:25 Chairperson's Opening Remarks
Søren Warming, PhD, Senior Scientist, Genentech, Inc., a Member of the Roche Group

8:30 Gene Editing Approaches to the Treatment of Liver Diseases
Clifford Steer, MD, Professor of Medicine and Genetics, Cell Biology and Development; Director, Molecular Gastroenterology Program, University of Minnesota Medical School

Among the novel approaches in gene editing, CRISPR/Cas9 technology has become the most popular, in part due to its ability to carry out gene editing at the target site with great precision. With considerable successes in animal and preclinical studies, CRISPR/Cas9-mediated gene editing has paved the way for its use in human trials, including patients with a variety of liver diseases. Gene editing is a logical therapeutic approach for liver diseases because many of the metabolic and acquired disorders are caused by mutations within a single gene.

9:00 Switchable Genome Editing via Genetic Code Expansion
Yu-Hsuan Tsai, PhD, Lecturer in Chemical Biology, School of Chemistry, Cardiff University

Multiple applications of genome editing by CRISPR-Cas9 necessitate stringent regulation. We have developed heritable Cas9-mediated mammalian genome editing that is acutely controlled by a non-natural amino acid. Using this approach, we demonstrated stringently amino acid dependent, heritable editing of transgenic and native genomic at the onset of mouse embryonic development. This approach promises broad applications, including therapeutic genome editing and gene drives.

9:30 CRISPR Off-Target Analysis in Genetically Engineered Rodents
Søren Warming, PhD, Senior Scientist, Genentech, Inc., a Member of the Roche Group

We generated deep-sequencing data from 81 genome-editing rodent model projects at 1,423 predicted off-target sites and confirmed editing at 32 off-target sites. Using whole-genome sequencing data from ten CRISPR-treated mouse embryos and their genetic parents, we found a total of 43 off-targets. This data was recently published (Nat Methods 2018: 15(7):512-514) and I will discuss how we have implemented our findings into our workflow and provide recommendations for the use of CRISPR in rodent models.

10:00 Networking Coffee Break

10:30 CRISPR: An Evolving Tool for Studying and Eliminating HIV Disease
Will Dampier, PhD, Assistant Professor, Department of Microbiology & Immunology, Center for Molecular Virology & Translational Neuroscience, Drexel University College of Medicine

HIV-1 infects millions of people across the world. While current anti-retroviral therapy manages viral proliferation, the early formation of a persistently integrated latent reservoir is a major cure barrier. CRISPR gene editing provides a potential avenue for addressing this therapeutic limitation. This talk will focus on computational design strategies for overcoming genetic variation inherent in HIV-1 infection in an effort to create broad-spectrum CRISPR targeting strategies.

11:00 Elucidating the Mechanism of Action and Regulatory Circuitry of CRISPR-Directed Gene Editing in Human Cells
Eric B. Kmiec, PhD, Director, Gene Editing Institute; Senior Research Scientist, Center for Translational Cancer Research, Helen F. Graham Cancer Center & Research Institute, Christiana Care Health System

CRISPR-directed gene editing is being tested for clinical feasibility. We have taken a decidedly reductionist approach to understanding the regulatory circuitry that surrounds it. Using a human cell-free system, a ribonucleoprotein (RNP) particle and a defined template, we have uncovered regulatory factors that provide guidance for achieving productive outcomes with a level of precision. This system lays the foundation to study the relationships among MMEJ, NHEJ and HDR pathways simultaneously in a controlled reaction environment.

11:30 Sponsored Presentation *(Opportunity Available)*

12:00 pm Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:30 Session Break

GENE EDITING FOR CANCER CELL THERAPY

1:15 Chairperson's Remarks
Alexandra Hicks, PhD, Executive Director, Hemoglobinopathies, Bioverativ, a Sanofi Company

1:20 Genetic Modification of NK Cells Opens a New Era of Cancer Immunotherapy
Meisam Naeimi Kararoudi, DVM, PhD, Postdoctoral Fellow, Cell Therapy and Cancer Immunotherapy Program, Center for Childhood Cancer and Blood Disorders, Nationwide Children's Hospital

NK cells have the potential to treat a wide range of cancers, and genetic modification may enhance their potency as cancer immunotherapeutics. Recently, we developed a new strategy for genetic modification of NK cells in which CRISPR/Cas9 elements are introduced as ribonucleoproteins (RNPs) via electroporation, followed by expansion on feeder cells. This method enabled us to genetically modify NK cells with enhanced cytotoxicity against several cancer targets.

1:50 Gene Editing Cancer Cells: A New Frontier in Cell Therapy for Cancer
Khalid Shah, MS, PhD, Director, Center for Stem Cell Therapies and Imaging, Harvard Medical School; Vice Chair of Research, Brigham and Women's Hospital

We have developed tumor cell surface receptor targeted adult stem cells expressing novel bi-functional immunomodulatory proteins and oncolytic viruses and shown the efficacy of engineered cells in different cancer models. Recently, we have reverse engineered cancer cells using CRISPR/Cas9 technology and demonstrated self-tumor tropism and therapeutic potential of receptor self-targeted engineered cancer cells. This talk considers the current status of cell-based treatments for cancer and provides a rationale for using CRISPR/Cas9 edited cancer cells for treating different cancer types in primary, recurrent, and metastatic settings.

2:20 Networking Refreshment Break

2:40 PANEL DISCUSSION: Rare Diseases - From Simple to Complicated, Complex and Cure

Moderator: Michael N. Liebman, PhD, Managing Director, IPQ Analytics, LLC

Panelists:

Debbie Lin, PhD, Executive Director, Venture Fund Digital Health, Boehringer-Ingelheim

Jon Morris, MD, VP Provider Solutions & CMIO, IQVIA

Durhane Wong-Rieger, President & CEO, Canadian Organization for Rare Disorders

This panel will focus on the complexities of diagnosing and stratifying rare diseases using both traditional clinical observations and the application of digital health methodologies. Rare diseases share many real-world issues with common diseases, but patient numbers limit the application of conventional statistical analyses. Discussion of approaches and examples of how novel methodologies and technologies can improve patient care and drug development will be presented, as well as the stratification of some common diseases into rare disease subtypes.

3:10 FEATURED PRESENTATION: Gene Therapy Projects at NCATS and the NIH Common Fund Somatic Cell Genome Editing Program

Philip John (P.J.) Brooks, PhD, Program Director, Office of Rare Diseases Research, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)

This talk will cover: Perspectives on gene therapy from the National Center for Advancing Translational Sciences, with an emphasis on platform approaches; the Rare Diseases Clinical Research Network as a clinical trial platform for gene therapy and genome editing; and the NIH Common Fund Program on Somatic Cell Genome Editing.

3:40 Disrupting a BCL11A Enhancer with Zinc Finger Nucleases (ZFNs) for the Potential Treatment of Sickle Cell Disease and Beta Thalassemia

Alexandra Hicks, PhD, Executive Director, Hemoglobinopathies, Bioverativ, a Sanofi Company

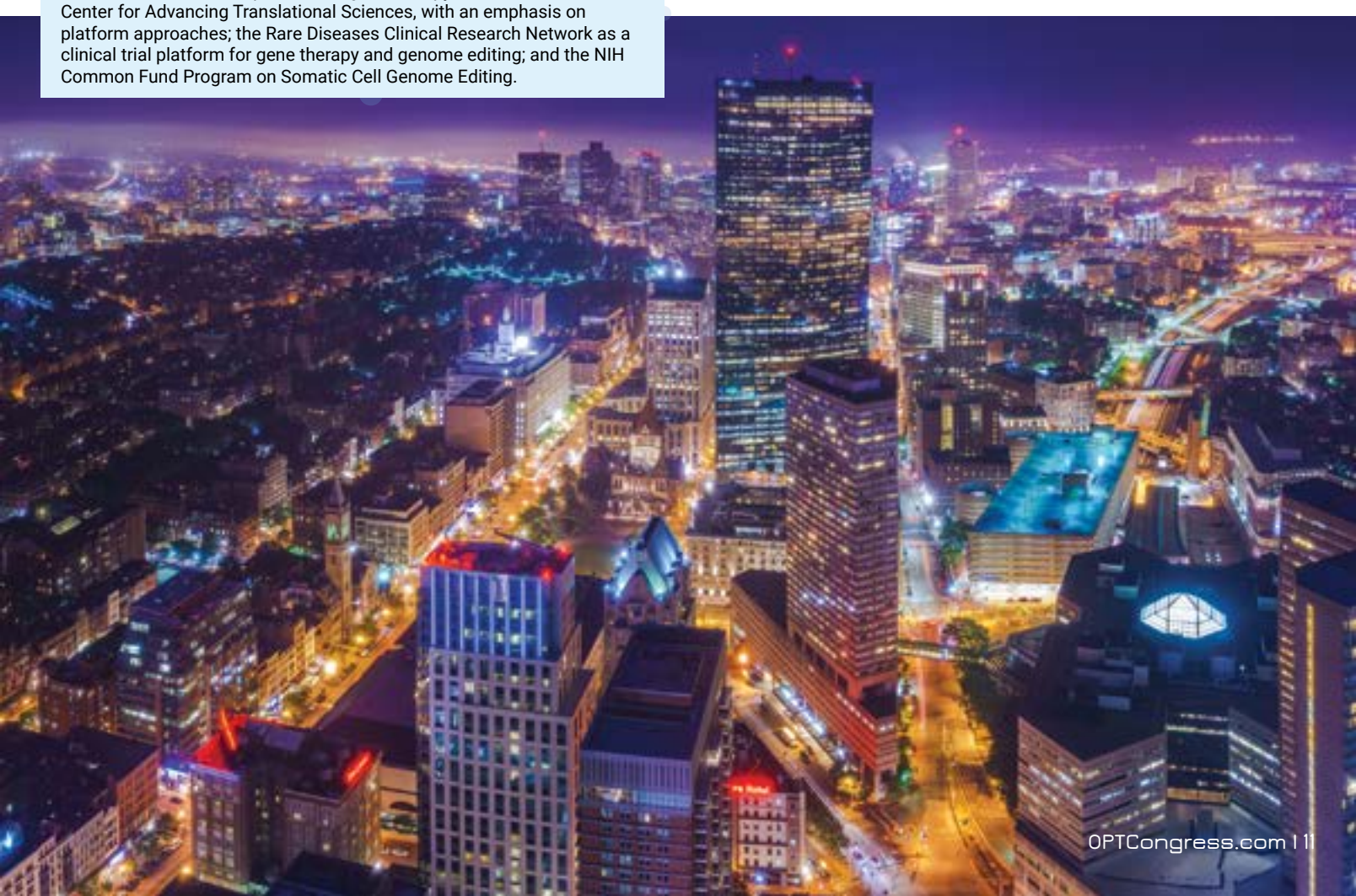
High fetal hemoglobin (HbF) levels are associated with asymptomatic sickle cell disease and less severe beta-thalassemia. BIVV-003 is a novel gene editing treatment comprising autologous HSPCs modified with ZFNs targeted to the erythroid-specific enhancer sequence of BCL11A, a key transcriptional regulator of fetal to adult hemoglobin switching. We will present preclinical data showing that the human HSPCs of BIVV-003 are efficiently and reproducibly edited at the BCL11A enhancer with high specificity resulting in reactivation of HbF expression. These edited HSPCs exhibit normal functionality and are capable of long-term engraftment *in vivo*.

4:10 Paving a Legal Path for Translational Genome Editing

Paul Enríquez, JD, LLM, PhD Candidate, Structural and Molecular Biochemistry, North Carolina State University

CRISPR systems are pushing the frontiers of genome editing applications with remarkable speed. Exciting prospects for revolutionizing personalized medicine and gene therapies are on the horizon. However, uncertainty looms concerning how law and policy will promote or hinder development of this nascent biotechnology. This talk identifies regulatory gaps, examines current challenges and opportunities in the field, and outlines a practical legal path for translating genome editing into the clinic.

4:40 Close of Symposium



Drug Discovery for Rare Diseases

Exploring New Technologies, Targets and Drug Modalities

THURSDAY, MARCH 28

7:30 am Registration and Morning Coffee

NEW TOOLS AND TARGETS FOR RARE DISEASES

8:15 Welcome Remarks from Conference Director
Tanuja Koppal, PhD, Conference Director, Cambridge Healthtech Institute

8:25 Chairperson's Opening Remarks
Timothy J. Miller, PhD, President & CSO, Abeona Therapeutics, Inc.

8:30 Human-on-a-Chip Systems for Utilization in Rare Disease Therapeutic Evaluations
James J. Hickman, PhD, Professor, Nanoscience Technology, Chemistry, Biomolecular Science, and Electrical Engineering, University of Central Florida
Phenotypic screening systems for rare disease investigations are one of the few methods of providing useful information for therapeutic development without a known target. Human-on-a-chip systems can potentially establish a therapeutic index before evaluation in clinical trials and also gives the possibility of target identification.

9:00 Precision Medicine for Targeting a Rare Neurological Disorder Using Human Cell-Based Models
Wei Chou Tseng, PhD, Senior Scientist, Cell Biology, Q-State Biosciences
We have created a powerful platform for probing diseases of the human nervous system. This platform brings together advances in stem cell biology, optical electrophysiology, genomics, and computation to create cell-based models of human neurologic diseases as a path to developing novel therapeutics to address unmet needs. This talk will describe strategies to devise treatments for a patient with a mutation in the autophagy pathway.

9:30 Considerations for Late-Stage Gene and Cell Therapies
Timothy J. Miller, PhD, President & CSO, Abeona Therapeutics, Inc.
The recent success of multiple Phase I/II gene therapy clinical trials has highlighted challenges in manufacturing and clinical efficacy assessments. These promising trials have helped increase potential treatment options for rare disease patients, and the field is now focusing on considerations for approval endpoints, how a single-administration of a life-saving drug can be reimbursed, and what the next era of gene therapy will bring.

10:00 Networking Coffee Break

10:30 Apelinergic Therapy in Pulmonary Arterial Hypertension
Hyung Chun, MD, FAHA, Associate Professor of Medicine and Pathology, Yale School of Medicine
Pulmonary arterial hypertension remains a rare disease of the lungs and the heart without a curative therapy. Apelin, a secreted ligand for the G protein coupled receptor APLNR (APJ), has been found to have multiple beneficial effects in this disease context, including promoting pulmonary vasorelaxation, reverse vascular remodeling, and improvement in the right heart function. The promise and challenges of targeting this pathway as a novel therapy in PAH will be discussed.

11:00 Value of a Patient-Centered Approach to Discovery of Drugs for Rare Diseases
Durhane Wong-Rieger, President & CEO, Canadian Organization for Rare Disorders
Researchers engaged in the very early stages of understanding a rare disease and the potential diagnostic and therapeutic interventions would benefit from understanding the perspectives of patients and families, how the disease affects them beyond the biomedical and clinical symptoms including quality of life as well as the realities of the healthcare system and policy environment. Similarly, patients and their groups would benefit tremendously from better understanding the drug discovery process and how they can potentially contribute.

11:30 Sponsored Presentation *(Opportunity Available)*

12:00 pm Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:30 Session Break

RNA THERAPIES FOR RARE DISEASES

1:15 Chairperson's Remarks
Paloma H Giangrande, Director, Research, Rare Diseases, Moderna Therapeutics

1:20 mRNA Therapy for Rare Metabolic Diseases
Paloma H Giangrande, Director, Research, Rare Diseases, Moderna Therapeutics
Many rare inherited metabolic disorders are caused by deficiency of essential intracellular enzymes responsible for maintaining proper homeostasis. Enzyme replacement and gene therapy-based approaches are not an option for treating these disorders due to drug-delivery and efficacy/safety



considerations. To develop new treatments for these enzymopathies, we encapsulated nucleoside-modified, codon-optimized mRNAs encoding these genes in lipid nanoparticles. Preclinical data demonstrating the efficacy and safety of our mRNA-LNP therapy will be presented.

1:30 Patient-customized Oligonucleotide Therapy for Batten disease

Timothy Yu, MD, Attending Physician, Division of Genetics & Genomics & Manton Center for Orphan Disease, Boston Children's Hospital, Assistant Professor, Harvard Medical School and Associate Member, Broad Institute of MIT and Harvard

We will discuss our experience with the accelerated development of the patient-specific drug milasen, as rescue therapy for a young girl with rapidly progressive neurodegenerative disease, which raises questions about opportunities and challenges in the deployment of antisense oligonucleotides for personalized medicine.

1:50 Delivering on the Promise of RNAi Therapeutics

David Erbe, PhD, Distinguished Investigator, Alnylam Pharmaceuticals

2:20 Networking Refreshment Break

2:40 PANEL DISCUSSION: Rare Diseases - From Simple to Complicated, Complex and Cure

Moderator: Michael N. Liebman, PhD, Managing Director, IPQ Analytics, LLC

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4:40 Close of Symposium



Pricing and Registration Information

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March 26-27, 2019	March 28, 2019
C1: Oligonucleotide Discovery and Delivery	S1: New Frontiers in Gene Editing and Repair
C2: Oligonucleotide CMC and Regulatory Strategies	S2: Drug Discovery for Rare Diseases

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