

DIA/FDA Oligonucleotide-based Therapeutics Conference

September 25-27 | Washington, DC



PROGRAM CO-CHAIRS

Robert T. Dorsam, PhD

Pharmacologist, OND,
Division Nonprescription Clinical Evaluation
CDER, FDA

Jim Zisek

Director, Global CMC Regulatory Affairs
GlaxoSmithKline

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Development
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Executive Vice President Research and
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OVERVIEW

For the fifth time in seven years, DIA and FDA have convened industry and health authorities to inform, educate, and share advancements in oligonucleotide-based therapeutic product development. The conference will incorporate dialogue between regulators and industry from CMC, Nonclinical, Clinical Pharmacology, and Clinical disciplines to address the developmental advances, safety, and challenges in the field of oligonucleotide-based therapeutics. The 2013 event will address quality risk management, manufacturing advances, specifications, formulation issues, CMC strategies, oligonucleotide pharmacokinetics, nonclinical assessments in support of drug development and clinical advances in therapeutic targets, trial design and safety for antisense, siRNA and microRNA therapies. In addition, the sessions will cover a wide range of current topics in oligonucleotide science and feature expert speakers from industry and regulatory agencies. Each session will consist of presentations and panel discussions in an interactive format designed to promote discussion between industry and the regulators ending with a session on emerging hot topics in oligonucleotide-based therapeutics.

LEARNING OBJECTIVES

At the conclusion of this meeting, participants should be able to:

- Identify accomplishments and challenges in the clinical development of oligonucleotide-based therapeutic drugs
- Describe the critical issues in the nonclinical development of oligonucleotides
- Differentiate the chemistry, manufacturing and controls challenges associated with the development of synthetic oligonucleotides, including formulation and specification issues
- Explain unique aspects and various scientific approaches used during the development of oligonucleotide-based therapeutics
- Recognize the achievements made in the field to date and be able to share the vision with patients about the therapeutic potential that oligonucleotides possess across a wide range of indications
- Discuss industry and regulatory agency efforts to partner and address the unmet medical needs of patients

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FEATURED TRACKS:

Nonclinical

The nonclinical sessions are designed to provide updates and discussion on recent advancements in nonclinical development of oligonucleotide therapeutics. The track will address emerging approaches for development of oligonucleotide therapeutics with focus on the predictivity of animal models and the applicability of ICH guidelines to specific concerns in development. Regulatory challenges in clinical pharmacology, clinical pharmacology assessment, and approaches to animal-to-human dose scaling will be presented. The specific area of oligonucleotide immunogenicity assessment will be examined. The nonclinical track will also join with the clinical track in a combined session discussing the relevance of nonclinical toxicities in kidney to findings in clinical trials. The nonclinical track sessions are intended to address the safety assessment practices, diverse developmental challenges, and emerging potential of oligonucleotide therapeutics.

- Updates and Future Directions for the Oligonucleotide Safety Working Group (OSWG)
- Clinical Pharmacology Assessment and its Regulation
- Approaches to Immunogenicity Assessment for Oligonucleotide Therapeutics
- Regulatory Experience Including Discussion of Dose Scaling, and the Influence of Structure and Sequence on Oligonucleotide Toxicity
- Kidney Toxicities: Translational Relationship of Nonclinical Data to Clinical Findings
- Hot Topics Including Novel miRNA Contributions to Disease and Therapy

Clinical Development

These sessions will provide updates on the recent progress made with oligonucleotides in the clinic. Programs in various stages of development will highlight the challenges faced, lessons learned, and offer potential

solutions and innovative ideas for clinical development of oligonucleotide therapeutics. Local and parenteral routes of administration of simple and complex formulations will be featured, with corresponding focus on the safety and tolerability of this class of compounds in humans. Talks will span programs ranging from early Phase I to late-stage Phase III. Therapeutic areas to be covered will include:

- Metabolic disease
- Oncology
- Liver Targets
- Infectious diseases
- Kidney disease
- Neuromuscular conditions

Chemistry, Manufacturing, and Controls (CMC)

The CMC track will cover a wide range of current oligonucleotide science and feature expert speakers from industry and regulatory agencies. Each session will comprise presentations and a panel discussion in an interactive format designed to promote dialogue between industry and the regulators. The following topics will be discussed:

- The Role of Quality Risk Management in Oligonucleotide Drug Development
- Advances in Oligonucleotide Manufacturing and Control Strategies
- Analytical Advancements and Oligonucleotide Specifications
- Novel Excipients and Other Recent Advances in Formulation Development
- CMC Strategy and Summary of Regulatory Interactions for Mipomersen

CO-SPONSORS



Oligonucleotide Therapeutics Society (OTS) is an open, nonprofit forum to foster academia and industry-based research and development of oligonucleotide therapeutics. Formed in 2004, OTS is a registered 501(c)6 nonprofit with the US government.



American Association of Pharmaceutical Scientists (AAPS)

The American Association of Pharmaceutical Scientists provides a dynamic international forum for the exchange of knowledge among scientists to enhance their contributions to health. They offer timely scientific programs, ongoing education, opportunities for networking, and professional development.

DIA'S CERTIFICATE PROGRAM

This program is part of DIA's Certificate Program and is awarded the following:

- Clinical Research Certificate Program: 10 Elective Units

For more information go to diahome.org/certificateprograms



WEDNESDAY, SEPTEMBER 25

7:30-8:30 AM REGISTRATION AND CONTINENTAL BREAKFAST

8:30-8:45 AM WELCOME AND OPENING REMARKS

SPEAKERS:

Robert T. Dorsam, PhD

Pharmacologist, OND,
Division Nonprescription Clinical Evaluation, CDER
FDA

Jim Zisek

Director, Global CMC Regulatory Affairs
GlaxoSmithKline

8:45-10:00 AM KEYNOTE

Oligonucleotide Therapeutics: Progress, Promises and Complexities

SPEAKER:

Arthur A. Levin, PhD

Executive Vice President Research and Development
miRagen Therapeutics

Over the past 3 decades since the first in vitro antisense experiments were performed there has been remarkable progress in the field of oligonucleotide therapeutics. Significant advancements have been made in everything from sourcing raw materials through design of drug delivery systems. The initial concepts of antisense working through steric interference that was conceived in the early days has been supplanted by multiple approaches to employ oligonucleotides with mechanisms that range from aptameric interactions with protein targets, enzymatic degradation of RNA targets, to oligonucleotide mediated alterations in RNA processing. A greater understanding of the multiple roles of RNA that extend beyond the transfer of information from the genome to RNA's role in regulating gene expression has broadened the horizon for oligonucleotide therapeutics and at the same time added new levels of complexity. The field is poised to now exploit many of these mechanisms and to sort through the levels of complexity.

10:00-10:30 AM REFRESHMENT BREAK



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10:30-12:00 PM SESSION 1

SESSION 1A (NONCLINICAL TRACK)

OSWG Summaries and the Path Forward

SESSION CHAIR(S):

Doug Kornbrust, PhDPresident
Preclinsight**Shwu-Luan Lee, PhD**Pharmacologist, Office of New Drug
CDER, FDA

The Oligonucleotide Safety Working Group (OSWG) is an organization of industry and health authority professionals dedicated to advance the development of oligonucleotides. Included in this session will be OSWG summaries of recent activities and discussion from the OSWG Reproductive and Carcinogenic Risk Subcommittee and the Genetic Toxicology Subcommittee. The session will end with a panel discussion about future organizational and investigative directions for OSWG.

SPEAKERS:

Considerations in Assessment of Reproductive and Developmental Risk for Oligonucleotide-based Therapies

Tacey E. White, PhDManaging Scientist, Toxicology and
Mechanistic Biology
Exponent®, Inc.

Final Recommendations of the OSWG Genetox Subcommittee: Standard Battery and Beyond

Cindy L. Berman, PhD

Independent Consultant

Measurement and Prediction of Hybridization-induced Off-target Effects of Oligonucleotide Drug Candidates

Morten Lindow, PhDGroup Leader, Integrative Systems Biology
Santaris Pharma A/S, Denmark

PANELISTS:

Jennifer Marlowe, PhDHead, Biomedical, Molecular and
Cellular Toxicology
Novartis Institutes for Biomedical Research**David H. Schubert**Vice President of Regulatory Affairs
& Quality Assurance
MediVector, Inc**Arthur A Levin, PhD****Scott Henry, PhD****Rosanne Seguin, PhD****Cindy Berman, PhD**

SESSION 1B (CMC TRACK)

Role of Quality Risk Management in Oligonucleotide Drug Development

SESSION CHAIR:

James V. McArdle, PhDPresident
McArdle and Associates, LLC

Risk Management is the identification, assessment, prioritization, mitigation and communication of risk, which is defined as the probability of occurrence and severity of harm. Risk Management has recently become more widely adopted in the pharmaceutical industry, where it is now recognized as an integral component of an effective Quality System. Scientific advice regarding the application of Risk Management to the manufacture and use of pharmaceuticals is provided in ICH guideline: Quality Risk Management, Q9. This session will feature two presentations. The first presenter will summarize the general principles of Quality Risk Management delineated in Q9; the second presenter will discuss the specific application of some of the principles to oligonucleotide drug development. The presentations will be followed by a 30 minute panel discussion.

SPEAKERS:

ICH Q9 Quality Risk Management — Perspective and Examples

H. Gregg Claycamp, PhD, MSSenior Scientist for Risk Analysis
and Decision Analysis
ONADE, CVM
FDA

Applications of Risk Assessment in the Manufacturing Development Cycle

Paul Van NormanDirector, Manufacturing Operations
NITTO DENKO Avecia, Inc

PANELIST(S):

Paul Van NormanDirector, Manufacturing Operations
NITTO DENKO Avecia, Inc**H. Gregg Claycamp, PhD, MS**Senior Scientist for Risk Analysis
and Decision Analysis
ONADE, CVM
FDA**Mohan Sapru, PhD**Regulatory Chemist
OMPT/OPS/ONDQA/DNDQ/CDER
FDA**Susann Rosmus**Head Quality Management
BioSpring GmbH, GermanySESSION 1C
(CLINICAL DEVELOPMENT TRACK)

Neuromuscular

SESSION CHAIR(S):

Lois M. Freed, PhDSupervisory Pharmacologist, CDER
FDA**Steve B. Shrewsbury, MD, FFPM**Senior Vice President, Clinical
Development & Chief Medical Officer
Aquinex Pharmaceuticals, Inc., Canada

This session will review the encouraging emerging clinical data generated over the last 18 months with therapeutic oligonucleotides in neuromuscular disease, where splice switching using the alternative splicing pathway is emerging as a natural process to be harnessed by modern medicines.

SPEAKER(S):

Update on Sarepta's AVI-4658 in Exon 51 Skipping Amenable Duchenne Muscular Dystrophy Boys

Jerry R. Mendell, MDProfessor of Pediatrics, Neurology
Pathology & Physiology; Director
of the Center for Gene Therapy
Nationwide Children's Hospital

Update on GSK's Drisapersen in Exon 51 Skipping Amenable DMD

Craig McDonald, MD

UC Davis Children's Hospital

Antisense Therapies for Neurodegenerative Diseases

Richard Stephen Geary, PhDSenior Vice President
Development
Isis Pharmaceuticals, Inc.

Update on Prosensa's other Splice Switching Oligomers (PRO044) in DMD

Giles V. Campion MD, PhDChief Medical Officer
Senior Vice President Research
and Development
Prosensa Therapeutics B.V.
Netherlands

12:00-1:30 PM LUNCH

1:30-3:00 PM

SESSION 2

SESSION 2A (NONCLINICAL TRACK)

Oligonucleotide Clinical Pharmacology

SESSION CHAIRS:

Richard Stephen Geary, PhDSenior Vice President of Development
Isis Pharmaceuticals, Inc.**Jian Wang, PhD**Senior Clinical Pharmacologist
OCP, DCPV, CDER
FDA

The development of oligonucleotide therapeutics requires pharmacokinetic and clinical pharmacology assessments that provide a framework for regulatory decisions. This session will focus on the clinical pharmacology of oligonucleotide products, recommended assessments, and current regulation. Presentations include one from the FDA addressing current regulatory practices governing the clinical pharmacology of oligonucleotides and a presentation reviewing clinical pharmacology decisions in the early development of Mipomersen. The session will continue with two complementary presentations, one from Pharma and one from the FDA discussing real-world measurements and pertinent factors to consider in the important calculation of animal-to-human dose scaling.

SPEAKERS:

Clinical Pharmacology Considerations in Development of Antisense Oligonucleotide Based Therapeutics

Jian Wang, PhDSenior Clinical Pharmacologist
OCP, DCPV, CDER
FDA

Clinical Pharmacology Decisions in Early Development

Richard Stephen Geary, PhDSenior Vice President
Development
Isis Pharmaceuticals, Inc.

Animal to Human Dose Scaling for Oligonucleotides: Pertinent Factors

John S. Grundy, PhDVice President
Pharmacokinetics and Clinical
Pharmacology
Isis Pharmaceuticals, Inc.

A Question of Scale: Equating Oligonucleotide Doses Between Species

Ronald L. Wange, PhDPharmacology & Toxicology Reviewer
Division of Metabolism and Endocrinology
Products
FDA

SESSION 2B (CMC TRACK)

Advances in Oligonucleotide Manufacturing and Control Strategies

SESSION CHAIR:

Steven BroadbentVice President, Quality
NITTO DENKO Avecia, Inc.

It is widely recognized that process and product knowledge comprise important components of any strategy designed to assure the quality of pharmaceutical products. The first presenter will discuss recent advances in understanding the chemistry of solid phase oligonucleotide synthesis through the application of process analytical technology (PAT). The second presenter will describe efforts aimed at establishing a design space and how the knowledge obtained can be leveraged to develop a robust control strategy. The presentations will be followed by a 30 minute panel discussion.

SPEAKERS:

Application of Process Analytical Techniques (PAT) in Oligonucleotide Synthesis

Hüseyin Aygün, PhDChief Scientific Officer
BioSpring, GmbH, Germany

Design Space Understanding Using LCMS Impurities Analysis

David MacdonaldDirector, Commercial Launch
Agilent Technologies

PANELISTS:

David MacdonaldDirector, Commercial Launch
Agilent Technologies**Anthony Scozzari**Vice President, Development
Chemistry & Manufacturing
Isis Pharmaceuticals, Inc.**Hüseyin Aygün, PhD**Chief Scientific Officer
BioSpring, GmbH, Germany

SESSION 2C

(CLINICAL DEVELOPMENT TRACK)

Non-Liver Targets

SESSION CHAIRS:

Peter S. Miele, MDMedical Officer
Division of Antiviral Products, OND
OMPT, OAP, CDER
FDA**James D. Thompson, PhD**Vice President Pharmaceutical
Development
Quark Pharmaceuticals, Inc

Clinical update for nonhepatic targets. While many oligonucleotide therapeutics target the liver to exploit the propensity of hepatic delivery, a substantial number of clinical programs aim at non-hepatic targets for activity. Viral replication has always been a prime candidate for therapeutic intervention with oligonucleotide therapeutics. In fact the first antisense oligonucleotides in clinical trials and the first to be approved targeted viral replication. In this session two of the talks describe more recent efforts to use siRNA to inhibit viral replication: one with a locally delivered siRNA and the other with a systemically delivered siRNA targeting the Ebola virus.

SPEAKERS:

Phase 2 Data on ALN-RSV01 for the Treatment of Bronchiolitis Obliterans Syndrome in RSV-infected Lung Transplant Patients

Jared Gollob, MDVice President Clinical Research
Alnylam Pharmaceuticals, Inc.

Ebola

Ian MacLachlan, PhDExecutive Vice President and
Chief Scientific Officer
Tekmira Pharmaceuticals Corporation

iCo-007 in Treatment of Diabetic Macular Edema

Peter Hnik, MD, MHScChief Medical Officer
iCo Therapeutics Inc.

SESSION 3A (NONCLINICAL TRACK)

Immunogenicity Assessment for Oligonucleotides

SESSION CHAIRS:

Rosanne Seguin, PhD

Academic Associate
Montreal Neurological Institute
McGill University, Canada

L. Peyton Myers, PhD

Pharmacologist
OMPT/OND/OAP/DAVP/CDER
FDA

Instances of immunogenicity have been shown to affect the safety and pharmacokinetics of individual drug products. Is immunogenicity an important consideration for oligonucleotide therapeutics? This session will begin with a general overview of oligonucleotide immunogenicity then continue with presentations exploring assessments of immunogenicity associated with short and long duration oligonucleotide therapy.

SPEAKER(S):

Immunogenicity of Oligonucleotides**David Pisetsky, PhD**

Department of Medicine
Duke University Medical Center

Assessments of Immunogenicity Associated with Long-Term Oligonucleotide Administration**John S. Grundy, PhD**

Vice President
Pharmacokinetics and
Clinical Pharmacology
Isis Pharmaceuticals, Inc.

Immunogenicity of Oligonucleotide Therapeutics – Points to Consider**Philip Oldfield, BSc, MSc, PhD**

President & CEO
Bioanalytical Consulting

SESSION 3B (CMC TRACK)

Novel Excipients and Other Recent Advances in Formulation Development

SESSION CHAIR:

René Thürmer, PhD

Deputy Head Unit Pharmaceutical
Biotechnology
BfArM, Federal Institute for Drugs
and Medical Devices, Germany

In large part, the successful development of oligonucleotide therapeutics is predicated on the development of safe and effective drug product formulations. This session will examine recent advances in formulation development, including those in the field of liposomal, polymer and nanoparticle-based delivery vehicles. Strategies aimed at mitigating or eliminating the toxicity associated with oligonucleotide formulations will be presented. Recommendations for designing studies to determine potential toxicities of novel and functional excipients will be discussed. Two presentations will be followed by a 30 minute panel discussion.

SPEAKERS:

Complex Polymeric Formulations of Oligonucleotides**Jeremy Heidel, PhD**

President
Informulate, LLC.

Solid Lipid Nanoparticle Formulations of Oligonucleotides**Bob D. Brown, PhD**

CSO and Senior Vice President
Research
Dicerna Pharmaceuticals

PANELISTS:

Robert T. Dorsam, PhD

Pharmacologist
OND, Division Nonprescription
Clinical Evaluation, CDER
FDA

Jeremy Heidel, PhD

President
Informulate, LLC

Bob D. Brown, PhD

CSO and Senior Vice President
Research
Dicerna Pharmaceuticals

SESSION 3C
(CLINICAL DEVELOPMENT TRACK)**Liver Targets**

SESSION CHAIR:

Richard Stephen Geary, PhD

Senior Vice President, Development
Isis Pharmaceuticals, Inc.

This session will provide updates on antisense and siRNA development programs focused on liver targets. Included in this session are two second generation antisense drugs targeting apoC-III and C-reactive protein (CRP), respectively, as well as two approaches to delivering siRNA for targeting transthyretin in TTR amyloidosis. All of these disease associated targets are primarily synthesized in the liver. This session will also provide insights into clinical study designs and development plans as well as proof of concept and safety assessments for two platform approaches to targeting mRNA transcripts in the liver.

SPEAKERS:

Targeting APOC-III in Severe Hypertriglyceridemia**Walter Singleton, MD**

Chief Medical Officer
ISIS Pharmaceuticals, Inc.

Clinical Trials of ALN-TTR02, an siRNA Therapeutic for Transthyretin Amyloidosis**Jared A. Gollob, MD**

Vice President, Clinical Research
Alnylam Pharmaceuticals, Inc.

Isis CRPRx: Pharmacokinetics, Pharmacodynamics, Safety and Tolerability**Marshelle Smith Warren, MD**

Executive Director
Isis Pharmaceuticals, Inc.

5:00-6:00 PM NETWORKING RECEPTION

THURSDAY, SEPTEMBER 26

9:00-10:00 AM SESSION 4 (NONCLINICAL, CMC AND CLINICAL TRACKS)

**Registration, Continental Breakfast,
Recap from Day 1 and Poster Session**

SESSION CHAIR

Jim ZisekDirector, Global CMC Regulatory Affairs
GlaxoSmithKline

This meeting offers a unique opportunity for industry and regulators to discuss the successes, challenges, and "pearls of wisdom" in oligonucleotide therapy development. In this session the track chairs will present a recap of important developments from day 1 of the meeting. As part of another forum to share and discuss recent advances in the field, attendees will have a chance to view posters which will encompass clinical and nonclinical issues.

SPEAKERS:

Clinical**John E. Kraus, MD, PhD**Head of Medical Governance, Neurosciences Therapy Area Unit
GlaxoSmithKline Research & Development**Nonclinical****James Wild, PhD**Pharmacologist
CDER, FDA**CMC****Emma Wright, PhD**Senior Director, Process Development
Avecia Biotechnology Inc

10:00-10:15 AM REFRESHMENT BREAK

US Conference on Rare Diseases & Orphan Products: The New Era in Health Care

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SESSION 5A (NONCLINICAL TRACK)**Oligonucleotide Regulatory Experience**

SESSION CHAIRS:

Arthur A. Levin, PhD

Executive Vice President,
Research and Development
miRagen Therapeutics

Barbara Wilcox, PhD

Pharmacologist
OMPT/OND/ODEI/DNP/CDER
FDA

Do oligonucleotide therapeutics represent a special class of drugs warranting specific regulatory policies? Is sufficient evidence available to guide new regulatory policy? This session will be devoted to examining what evidence is available to support class-specific regulation for oligonucleotides. Specifically, the contributions of structure and sequence to oligonucleotide toxicity will be discussed in complementary presentations from Pharma and FDA representatives.

SPEAKERS:

Development of siRNA Lipid Nanoparticle Formulations**Garvin L. Warner, Ph.D.**

Vice President, Preclinical Development
Alnylam Pharmaceuticals

Oligonucleotide Toxicity and its Relationship to Compound Structure: FDA Experience from Nonclinical Testing**Paul C. Brown, Ph.D.**

ODE Associate Director for
Pharmacology and Toxicology, OND,
CDER, FDA

Potential Attributes of a Platform Technology: How Best to Capitalize on Cumulative MOE Oligonucleotide Safety Data**Scott Henry, Ph.D**

Vice President, Nonclinical Development
Isis Pharmaceuticals, Inc.

SESSION 5B (CMC TRACK)**Analytical Advancements and Oligonucleotide Specifications**

SESSION CHAIR:

Nigel R. Richardson

Analytical Manager
GlaxoSmithKline, United Kingdom

Drug substance and drug product specifications focus on critical quality attributes useful for ensuring safety and efficacy. In this regard, the general requirements to confirm identity, determine strength and assess impurities apply to oligonucleotides. However, the size and complexity of oligonucleotides relative to small molecule drugs can make fulfilling these basic requirements challenging. A review of the state of the art of oligonucleotide analysis will be presented. The presentation will enable a discussion of the challenges associated with developing and justifying meaningful specifications for oligonucleotide therapeutics.

SPEAKERS:

Advances in Analytical Approaches to Impurity Control for Commercial Oligonucleotides**Mike L. Webb**

Vice President, API Chemistry
& Analysis
GlaxoSmithKline, United Kingdom

PANELISTS:

Mike L. Webb

Vice President, API Chemistry
& Analysis
GlaxoSmithKline, United Kingdom

Rao V. Kambhampati, PhD

Senior Regulatory Review Scientist
(Chemistry)
ONDQA, CDER
FDA

René Thürmer, PhD

Deputy Head Unit Pharmaceutical
Biotechnology
BfArM
Federal Institute for Drugs and
Medical Devices, Germany

Christoph Rosenbohm, PhD

Director, Chemistry and CMC
Santaris Pharma A/S, Denmark

SESSION 5C**(CLINICAL DEVELOPMENT TRACK)****Oncology**

SESSION CHAIRS:

Steve Hughes, MD

Vice President, Clinical Development
Isis Pharmaceuticals, Inc.

Yang-min (Max) Ning, MD, PhD

Medical Officer
Division of Oncology Products I
OND, OHOP, CDER
FDA

Clinical programs utilizing oligonucleotide therapeutics have been around since the days of polyIC induction of interferon as a mechanism of oncolytic activity. These programs were followed by attempts using first generation phosphorothioate oligodeoxynucleotides to target single genes known to be critical for tumor survival or replication. This session will focus on more recent efforts to use newer generation antisense (Gen2.5) and siRNA to target key genes and a novel approach of administering a microRNA mimetic that represses key evolutionarily conserved pathways to alter tumor growth.

SPEAKERS:

Development of MRX34, the First microRNA Mimic in the Clinic**Sinil Kim, MD**

Vice President Oncology and
Chief Medical Officer
Mirna Therapeutics

Development of Next Generation Anti-sense Molecules for Therapeutic Utility in Oncology**David Blakey, PhD**

Chief Scientist, Oncology
AstraZeneca, United Kingdom

Tekmira**Ian MacLachlan, PhD**

Executive Vice President and
Chief Scientific Officer
Tekmira Pharmaceuticals Corporation,
Canada

1:30-3:00 PM SESSION 6

Pharma/FDA Case Study

SESSION CHAIR:

David H. SchubertVice President of Regulatory Affairs & Quality Assurance
MediVector, Inc.

Oligonucleotide therapeutic development presents various challenges to CMC, Pharm/Tox, Clin. Pharm., and Clinical disciplines at early-, middle-, and late-stage development. This session will include three real and hypothetical case studies that identify challenges faced by these disciplines across the development cycle. Case study presenters will engage the audience in discussions about development issues, decision-making, and lessons learned based on prior experience.

SPEAKER(S):

A Case Study of Challenges Faced during Early Stage Oligo Development**Doug Kornbrust, PhD**President
Preclinsight**Decisions During Mid-Stage Development****Akshay Vaishnav, MD PhD**Chief Medical Officer
Alnylam Pharmaceuticals, Inc**Late Phase Development Issues****Mike L. Webb**Vice President, API Chemistry & Analysis
GlaxoSmithKline, United Kingdom

3:00-3:30 PM REFRESHMENT BREAK

A Model of Patient, Payer, and Product Developer Collaboration to Support Innovating for Value

October 30-31 | Washington, DC



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Health Care Reform
at BROOKINGS

3:30-5:00 PM SESSION 7

**SESSION 7A AND C
(NONCLINICAL AND CLINICAL DEVELOPMENT TRACKS)**
**Translational Assessment of
Oligonucleotide Effects in the Kidney**

SESSION CHAIRS:

Jan Kevin Losos, PhD

 Director, Safety Assessment Projects
GlaxoSmithKline

Imran Khan, PhD

 Pharmacologist
OMPT/OND/ODEI/DPP/CDER
FDA

In this joint session for the nonclinical and clinical tracks, the importance of renal toxicology for oligonucleotide therapeutics will be considered. Renal toxicity occurs in a dose-related fashion for some oligonucleotide products in nonclinical studies. Are nonclinical results predictive of what can be expected with therapeutic doses in clinical administration? This session will discuss two instances of renal toxicology in nonclinical studies as well as potential underlying mechanisms including exaggerated pharmacology. A final presentation will examine an instance of renal toxicity associated with the clinical administration of an oligonucleotide and its importance.

SPEAKER(S):

**Glomerular Effects of Antisense Oligonucleotide
Therapies and their Potential Mechanism**
Kendall S. Frazier, DVM, PhD

 SM Director of Cellular Pathology
Glaxosmithkline

**A Novel Antisense Oligo Targeting SGLT2 in the
Kidney: Twists and Turns In Preclinical Development**
Tom Zanardi, PhD

 Director of Toxicology
Isis Pharmaceuticals, Inc.

Renal Effects and Clinical Monitoring of Drisapersen
Kevin E. Meyers, MBBCh

 Assistant Chief, Division of Nephrology
Associate Professor of Pediatrics,
Perelman School of Medicine at the University of Pennsylvania

SESSION 7B (CMC TRACK)
**CMC Strategies: Process Development, Validation
and Control Strategies**

SESSION CHAIR:

Anthony Scozzari

 Vice President, Development Chemistry & Manufacturing
Isis Pharmaceuticals, Inc.

An approach to process development based on platform and compound specific data will be presented. Critical process parameters of solid phase oligonucleotide synthesis will be discussed. The benefits of traditional and enhanced approaches to development will be presented. A proposed drug substance manufacturing process validation strategy will be discussed. Drug substance controls, including suggested specification limits based on platform data will be presented. Two presentations will be followed by a 30 minute panel discussion.

SPEAKERS:

Process Development and Validation
Daniel Capaldi, PhD

 Vice President, Analytical and Process Development
Isis Pharmaceuticals, Inc.

**Establishing Specification Limits for
Phosphorothioate Oligonucleotides**
Claus Rentel, PhD

 Executive Director, Analytical Development and Quality Control
Isis Pharmaceuticals, Inc.

PANELISTS:

Daniel Capaldi, PhD

 Vice President
Analytical and Process Development
Isis Pharmaceuticals, Inc.

Ramesh Raghavachari, PhD

 Acting Branch Chief in Division III, CDER
FDA

Claus Rentel, PhD

 Executive Director, Analytical Development and Quality Control
Isis Pharmaceuticals, Inc.

Fran Wincott, PhD

 President
Wincott & Associates LLC

FRIDAY, SEPTEMBER 27

7:30 -8:30 AM REGISTRATION AND CONTINENTAL BREAKFAST

8:30-10:00 AM SESSION 8 (NONCLINICAL, CMC AND CLINICAL DEVELOPMENT TRACKS)

Hot Topics

SESSION CHAIRS:

Arthur A. Levin, PhDExecutive Vice President, Research and Development
miRagen Therapeutics**Haw-Jyh Chiu, PhD**Toxicologist
OMPT, Office of New Drugs, DHOT, CDER
FDA

This hot topics session will present cutting-edge information of interest to all three tracks. This year the hot topics will focus on miRNA roles in disease and therapy, and a novel form of crop protection against insects based on ingestion of siRNA. As a whole the presentations will explore rivaling forces governing RNA expression in maintaining, enhancing, and disrupting function.

SPEAKERS:

Viruses and Micro RNAs

Bryan R. Cullen, PhDJames B. Duke Professor
Department of Molecular Genetics and Microbiology
Director, Duke University Center for Virology
Duke University Medical Center

The Placental-specific Chromosome 19 miRNA Cluster (C19MC) Exerts Antiviral Effects Against Diverse Viruses

Carolyn B. Coyne, PhDAssistant Professor
Department of Microbiology and Molecular Genetics
University of Pittsburgh

Using RNAi in Food Crops as Pesticides

Gregory R. Heck, PhDWeed Control Platform Lead
Monsanto Company

The Chance of a Lifetime: Developing Antisense Oligonucleotide-mediated RNA Modulation as a Cure for Cystic Fibrosis

Tita RitsemaProgram Manager
ProQR Therapeutics B.V., Netherlands

10:00-10:30 AM REFRESHMENT BREAK

10:30-12:00 PM SESSION 9

Conference Highlights

This panel discussion is meant to highlight the challenges and issues with the development of oligonucleotide-based products in general and as brought forth at this conference. The intention is to transform this discussion into action-oriented objectives to address the regulatory and industry issues and challenges affecting us all.

DISCUSSANTS AND PANELISTS:

Non-Clinical Track

Scott Henry, PhDVice President, Nonclinical Development
Isis Pharmaceuticals, Inc.**Arthur A. Levin, PhD**Executive Vice President, Research and Development
miRagen Therapeutics

CMC Track

Daniel Capaldi, PhDVice President, Analytical and Process Development
Isis Pharmaceuticals, Inc.**René Thürmer, PhD**Deputy Head Unit Pharmaceutical Biotechnology
BfArM, Federal Institute for Drugs and Medical Devices, Germany

Clinical Track

James D. Thompson, PhDVice President Pharmaceutical Development
Quark Pharmaceuticals, Inc**Saraswathy (Sara) V. Nochur, PhD**Senior Vice President, Regulatory Affairs & QA
Alnylam Pharmaceuticals, Inc

12:00-12:15 PM CLOSING REMARKS

SPEAKERS:

Robert T. Dorsam, PhDPharmacologist,
OND, Division Nonprescription Clinical Evaluation, CDER
FDA**Jim Zisek**Director, Global CMC Regulatory Affairs
GlaxoSmithKline

12:15 PM

CONFERENCE ADJOURNED