Cambridge Healthtech Institute's Third Annual

OPT Boston

Oligonucleotide & Peptide THERAPEUTICS

Advancing the Discovery, Development and Delivery of Oligonucleotide and Peptide Therapeutics

March 26-28, 2018
Boston Marriott Cambridge
Cambridge, MA



2018 CONFERENCES

- **Oligonucleotide Discovery and Delivery**
- **Peptide Discovery and Delivery**
- **Symposium: Drug Discovery for Rare Diseases**

SHORT COURSES

- **Overcoming Challenges with Peptide Delivery**
- **CRISPR-Based Gene Editing for Targeted Therapies**

FEATURED SPEAKERS

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

Tomi Sawyer, PhD
Distinguished Scientist, Discovery Chemistry Modalities, Merck Research Laboratories

Melissa J. Moore, PhD
CSO, mRNA Research Platform, Moderna

Lex Van der Ploeg, PhD
CSO, Rhythm Pharmaceuticals

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Event At-A-Glance

SUNDAY, MARCH 25	MONDAY, MARCH 26	TUESDAY, MARCH 27	WEDNESDAY, MARCH 28
Short Course*	Oligonucleotide Discovery and Delivery		
	Peptide Discovery and Delivery		Symposium: Drug Discovery for Rare Diseases
	Short Courses*		

*Separate registration required.

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HOTEL & TRAVEL INFORMATION

Conference Venue and Hotel:

Boston Marriott Cambridge Hotel
50 Broadway, Cambridge, MA 02142
Phone: 617-494-6600

Discounted Room Rate: $199 s/d
Discounted Room Rate Cut-off Date: February 26, 2018

Top Reasons to Stay at the Boston Marriott Cambridge:

- No commute as conference takes place in the hotel
- 5 Miles from Boston Logan International Airport (BOS) via public transportation
- Located within walking distance from the Kendall/ MIT subway station
- Nearby to wonderful restaurants and shopping



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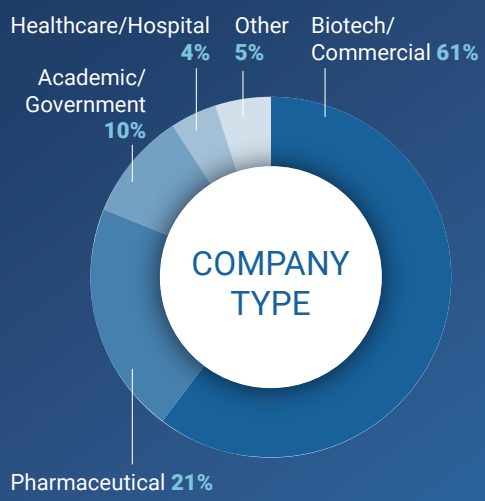
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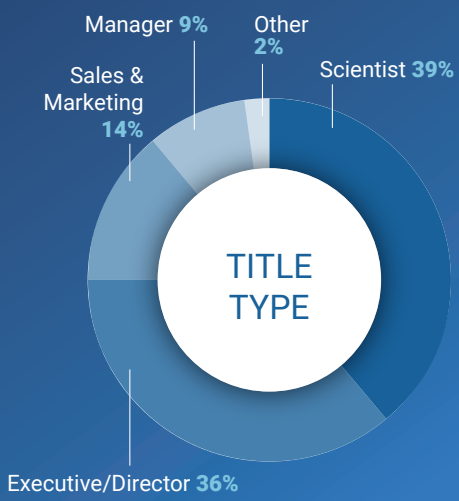
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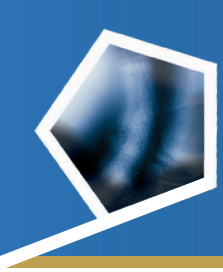
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2017 Attendee Demographics







Oligonucleotide Discovery and Delivery

March 26 - 28, 2018

Advances in the Development and Delivery of Aptamer, Antisense and RNA Therapeutics

Oligonucleotide-based therapeutics have long been considered as forming the third major drug development platform specifically focused on modulating gene expression by targeting RNA transcripts or the genome itself. A key distinguishing attribute of utilizing nucleic acids as therapeutic agents is their ability to access the "undruggable" space left by small molecules and biologics, allowing drug developers to address disease areas currently with limited or no therapeutics options. However, first- and second-generation molecules exhibiting potency and safety issues have hindered the potential of oligonucleotide therapies dramatically impacting the drug development landscape. Recent advances in nucleic acid medicinal chemistry and delivery have led to the creation of a new generation of oligonucleotide therapies harnessing chemical modifications and conjugations to improve their stability, bioavailability, specificity and potency. These advances, along with a robust development landscape, and several late-stage clinical products poised for approval, have led to a sharp resurgence of interest in the discovery of oligonucleotide-based therapeutics.

Due to the remarkable success of the event, Cambridge Healthtech Institute is delighted to host the Third Annual Oligonucleotide Discovery and Delivery conference, March 26-28, in Cambridge, MA. Join leading oligonucleotide developers and discovery scientists to discuss technological and scientific advances in nucleic acid synthesis, medicinal chemistry and delivery, as well as preclinical and clinical findings.

MONDAY, MARCH 26

7:00 am Registration and Morning Coffee

ADVANCES IN OLIGONUCLEOTIDE THERAPEUTICS AND DELIVERY

8:00 Welcome Remarks from Cambridge Healthtech Institute

8:10 Chairperson's Opening Remarks

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

8:15 GalNAc-Conjugated siRNAs as a New Paradigm in Oligonucleotide Therapeutics

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

During this presentation, I will discuss the progress in the advancement of RNAi therapeutics and review delivery of RNAi and where the field is going. I will also discuss conjugated delivery of oligonucleotides to the liver and combining novel chemical modifications with conjugation strategies.

8:45 mRNA as medicine

Melissa Moore Ph.D., Chief Scientific Office, mRNA Research Platform, Moderna Therapeutics

Messenger RNAs (mRNAs) show tremendous promise as a novel therapeutic modality, allowing for creation of prophylactic and therapeutic vaccines as well as medicines for treating inborn metabolic disorders. I will discuss our recent progress in identifying new formulations for the delivery of mRNA vaccines versus mRNA therapeutics.

9:15 Highly Effective Design and Validation of Antisense Oligonucleotides (AON) for Research and Therapeutic Applications

*Ernesto Guccione, PhD, Senior Faculty, Oncological and Pharmacological Sciences, Mount Sinai; Principal Investigator, A*STAR*

Antisense oligonucleotides (AON) are a powerful research and therapeutic tool. In fact, their use has been instrumental to researchers to uncover genes and exons' functions, as well as to treat previously incurable diseases. I will discuss an example of the research use of AONs to dissect the function of alternatively splicing in prostate cancer. We analysed TCGA datasets mining for differences in alternative splicing between normal and cancer tissues. The top hit was represented by the RNA binding protein MBNL1 exon 7, consistently more included in mature mRNA of tumour samples compared to normal prostate. With effective and selective AONs we were able to modulate exon 7 inclusion in cancer cell lines, demonstrating how MBNL1 delta7 alters the mRNA stability of genes linked to migration, cell cycle arrest, DNA-damage repair and mitotic chromosome segregation. The same approach, thanks to our AON's design algorithm, can be applied to a vast number of alternative splicing events. In fact, AON-mediated modulation of the splicing pattern of key genes in androgen sensitive vs androgen resistant prostate cancer lines, is sufficient to significantly affect migration and survival of these cells.

The use of AONs to modulate splicing goes beyond the use in research. Immunotherapy with TCR-redirected T cells to treat HBV-positive hepatocellular carcinoma (HCC) is now in clinical trials. T cells from patients are expanded ex-vivo and transduced with an HBV-specific TCR mRNA. We demonstrate that AONs targeting immuno-suppressive genes (e.g. PD1, CTLA4, TIM3) offer a potential avenue to improve killing efficiency of the target tumor cells, opening important therapeutic options in the growing field of immunotherapy.

9:45 Networking Coffee Break

ADVANCES IN OLIGONUCLEOTIDE THERAPEUTICS AND DELIVERY (CONT.)

10:30 Temporary Inhibition of p53 for Tissue Protection: from Therapeutic Concept to Prevention of Acute Kidney Injury Following Kidney Transplantation and Cardiac Surgery

Elena Feinstein, MD, PhD, CSO, Quark Pharmaceuticals

Although therapeutic inhibition of the master tumor suppressor p53 is counterintuitive, its temporary inhibition for tissue protection under conditions of genotoxic and/or oxidative stress was proven not only safe but also efficient. Using an siRNA compound targeting p53, we have achieved efficacy proof-of-concept (POC) in the animal models of ischemia-reperfusion and toxic kidney injury as well as in the model of chemotherapy-induced hair loss. Clinical POC was achieved in two large multicenter double-blinded placebo-controlled Phase 2 trials studying efficacy of QPI-1002, a p53-targeting siRNA compound, in prevention of delayed graft function following kidney transplantation and of acute kidney injury following cardiac surgery.

11:00 Sarepta's Exon Skipping PMO-ASOs

Marco Passini, PhD, Senior Director, Biology, Sarepta Therapeutics

Phosphorodiamidate morpholino oligomers (PMOs) are uncharged single-stranded oligonucleotides that bind to target RNAs to modulate activity. Cell penetration has been cited as a challenge for PMOs to reach their full potential. Delivery into cells and overall activity of these oligomers can be improved by chemically modifying the PMO by modifying internucleoside linkage(s) or by adding a cell-penetrating peptide (PPMO). A series of proprietary classes of compounds that includes PPMO, PMO-X® and PMOplus® are being developed by Sarepta Therapeutics that have the potential to treat a wide variety of indications including Duchenne muscular dystrophy, neuromuscular and neurodegenerative diseases.

11:30 Development of Stereopure Nucleic Acid Therapeutics

Chandra Vargeese, PhD, Senior Vice President and Head, Drug Discovery, WAVE Life Sciences

WAVE Life Sciences is utilizing its innovative and proprietary synthetic chemistry drug development platform to design, develop and commercialize stereopure nucleic acid therapeutics that precisely target the underlying cause



of rare genetic diseases, delivering exceptional treatment options for patients. Given the unique versatility of its chemistry platform, WAVE's pipeline will span multiple oligonucleotide modalities including antisense, exon-skipping and single-stranded RNAi.

12:00 pm Enjoy Lunch on Your Own

SYNTHESIS AND MEDICINAL CHEMISTRY

1:25 Chairperson's Remarks

Gunnar J. Hanson, PhD, Senior Director, Research Chemistry, Sarepta Therapeutics, Inc.

1:30 Breakthrough Innovation in Phosphorodiamidate Morpholino Oligomer (PMO) Delivery Chemistry

Gunnar J. Hanson, PhD, Senior Director, Research Chemistry, Sarepta Therapeutics, Inc.

Phosphorodiamidate morpholino oligomers (PMOs) enable Watson-Crick binding to pre-mRNA in the nucleus and thereby enable the control of new definitions of intron-exon junctions within the spliceosome. Such splice alteration is limited by the efficiency of PMO delivery into the cytosol and nucleus. To solve this 40-year old delivery problem, new cell-penetrating peptides (CPPs) were designed, which by covalent attachment to PMOs, dramatically enhance the delivery of these macromolecules into the cytosol and nucleus.

2:00 Stereodefined Phosphorthioate LNA Oligonucleotides

Nanna Albaek, PhD, Principal Scientist and Group Leader of New Chemistry, Roche Pharma Research and Early Development, Roche Innovation Center Copenhagen

The continuous refinement and development of the LNA oligonucleotide drug discovery platform has lead to utilizing the improvements induced by introducing fully stereopure LNA oligonucleotides. Phosphorthioate (PS) backbone oligonucleotides have for a long time been used as diasteremeric mixtures in drug discovery for improved properties such as stability and biodistribution. By defining the PS stereochemistry improvements of eg. potency and tolerability are found compared to the diastereomeric mixture.

2:30 The GLP1 Receptor for Targeted Delivery of Antisense Oligonucletoides to Pancreatic ß-Cells

Thazha P. Prakash, Executive Research Fellow, Ionis Pharmaceuticals

Antisense oligonucleotide (ASO)-based drug development is evolving as an effective therapeutic approach. To fully realize the potential of this technology, it is necessary to improve the potency of ASOs in extrahepatic tissues. Inability to selectively deliver antisense therapies to ß-cells is a substantial barrier to the development of innovative and safe treatments for ß-cell specific diseases. Here, we used a GLP1 receptor (GLP1R) peptide agonist conjugated to ASO to explore the concept of delivering ASO using GLP1R mediated internalization. We show that the GLP1 receptor can be used as a targeting approach for efficient and selective delivery of ASO to pancreatic ß-cells in cells and in animals.

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

DELIVERY TO THE CNS

3:45 Natural Selection: The Evolution of siRNA Delivery at Arrowhead Pharmaceuticals

James C. Hamilton, MD, MBA Vice President, Clinical Development, Arrowhead Pharmaceutical Inc.

Results from animal and human studies using multiple different delivery technologies have driven the evolution and optimization of ligand targeted siRNA delivery at Arrowhead. These experiences have facilitated development of Arrowhead's TRiM (Targeted RNAi Molecule) platform which now serves as the foundation for Arrowhead's drug development efforts and has been used to develop two new investigational agents, ARO-HBV and ARO-AAT which will enter clinical studies this year.

4:15 Expanding the Chemical Diversity of Therapeutic Oligonucleotides

Maire Osborn, PhD, Research Scientist, Khvorova Lab, RNA Therapeutics Institute, University of Massachusetts Medical School

Lipid conjugation markedly enhances the biodistribution, efficacy, duration of effect, and safety of chemically modified siRNAs, both in the central nervous system and systemically. Direct conjugation of a fully chemically modified siRNA to docosahexaenoic acid (DHA), the most abundant polyunsaturated fatty acid in the brain, results in sustained neuronal mRNA silencing in the striatum and cortex after a single injection. When administered systemically, lipid-conjugated siRNAs elicit potent mRNA silencing in liver, kidney, ovary, and adrenal gland, with no increase in systemic toxicological markers. Mechanistically, we show that lipid conjugation drives spontaneous siRNA partitioning into defined classes of circulating plasma lipoproteins *in vivo*, which increases half-life and promotes oligonucleotide uptake in lipoprotein receptor-expressing cells. Our results establish that hydrophobic modifications can be leveraged to target siRNAs to endogenous lipid transport pathways without the need for synthetic formulation.

4:45 Targeted Augmentation of Nuclear Gene Output

Charles R. Allerson, Ph.D., Vice President, Chemistry, Stoke Therapeutics

Most human genetic diseases are due to loss or reduction of function of a single gene, and currently approved therapeutic strategies are unable to directly increase protein expression to treat most of these inherited deficiencies. Stoke Therapeutics is developing first-in-class medicines to treat such monogenic diseases by leveraging antisense oligonucleotides to exploit naturally-occurring reservoirs of non-productive, untranslated pre-mRNA species to increase target protein expression without relying on viral or nanoparticle delivered technologies.

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

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6:15 Dinner Short Course Registration

6:30-9:30 SC2: Overcoming Challenges with Peptide Delivery*

* Separate registration required. See page 14 for details.

TUESDAY, MARCH 27

7:30 am Breakfast Breakout Roundtable Discussions

Grab a cup of coffee 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.

For more details, please visit OPTCongress.com

ADVANCES IN RNA THERAPEUTICS AND DELIVERY

8:25 Chairperson's Remarks

Michel Janicot, PhD, CDO, InteRNA Technologies BV

8:30 Development of Novel miRNA Therapeutics to Eliminate Resistant Cancer Stem Cells

Jingfang Ju, PhD, Professor, Pathology, Department of Pathology, Stony Brook University

Resistance to 5-FU based chemotherapy is the major reason for failure of treating patients with advanced colorectal cancer. Novel therapeutics are needed to overcome the challenge of resistance as well as recurrence. We have developed a novel modified miR-129 mimic with enhanced therapeutic potential. The miRNA mimic is more potent at inhibiting cell proliferation and inducing cell cycle arrest at G1 phase than native miRNA while retaining target

specificity. It completely prevents colon cancer metastasis *in vivo* without toxicity. The miRNA mimic can also be delivered to cancer cells without any transfection reagents (e.g. lipids, viral vector, nanoparticles). This represents a significant advancement in the development of a nontoxic and highly potent miRNA based cancer therapeutics.

9:00 miR-195 Potentiates the Efficacy of Microtubule Targeting Agents in Non-Small Cell Lung Cancer

Xiaojie Yu, PhD, Postdoctoral fellow, Greehey Children's Cancer Research Institute, University of Texas Health San Antonio

We report the identification of miR-195 as a sensitizer to microtubule-targeting agents in NSCLC, mediated by its repression of CHEK1. Mouse xenografts with induced or constitutive over-expression of miR-195 show that tumors with high miR-195 expression are more sensitive to drug treatment and that induction of miR-195 potentiates the efficacy of eribulin in repressing tumor growth. These results highlight the possible application of miR-195 expression as a biomarker to predict patient response to MTAs and the potential for delivery of miR-195 mimic as an adjuvant to chemotherapy.

9:30 INT-1B3 – a Chemically-Modified microRNA Mimic Targeting Multiple Hallmarks of Cancer and Representing Potential New Approach to Immunotherapy

Michel Janicot, PhD, CDO, InteRNA Technologies BV

To explore miRNAs as therapeutic agents for the treatment of cancer, InteRNA Technologies has performed functional screens in cell lines covering different types of cancer. Lead candidates are now advancing in preclinical development programs with a focus on hepatocellular cancer. This presentation will provide insights into the latest progress in the preclinical development of InteRNA's lead miRNA compounds.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

EMERGING NUCLEIC ACID DEVELOPMENT PLATFORMS

10:30 Chairperson's Remarks

Michel Janicot, PhD, CDO, InteRNA Technologies BV

10:35 RNA Aptamer Delivery Through Intact Skin

Caitlin Vestal Tibbetts, Team Leader, Aptamer Discovery, GlaxoSmithKline

This study demonstrates that in contrast to expectations, a very-large-molecular-weight RNA based aptamer capable of binding to endogenous IL-23 can permeate across the intact human skin barrier to therapeutically relevant levels into both the epidermis and dermis. The aptamer, highly specific to the human IL-23 cytokine has demonstrated penetration in to intact human skin via fluorescence detection, is at quantifiable levels above the cellular IC50, and remained biologically intact as confirmed by a dual hybridization assay (DHA) and oligo precipitation assay respectively. Target engagement was confirmed by measuring the decrease in IL-17f and IL-22 with topical application of the aptamer but did not show significant changes to IL-23 mRNA levels. This study demonstrates the potential for topically delivering aptamers as therapeutics.

11:05 ZATA's Novel Oligonucleotides (ZONs) with Self-Neutralizing Backbones

David Tabatadze, PhD, President and CEO, R&D, ZATA

We developed a nucleic acid platform enabling the new generation oligonucleotides (ZONs) comprising target number of branched charge-neutralizing groups (CNGs) on the internucleoside phosphates of ON by phosphotriester bonds. The CNGs are terminated with positively charged amino groups, and are optimized to form ion pairs with the neighboring phosphate groups. ZONs can be synthesized by standard automated phosphoramidite chemistry in good yield and purity.

11:35 Enjoy Lunch on Your Own

12:30 Dessert Break in the Exhibit Hall with Poster Viewing

ADVANCES IN OLIGONUCLEOTIDE DELIVERY

1:15 Chairperson's Remarks

Torsten Hoffmann, PhD, COO, Silence Therapeutics

1:20 Development of Novel Therapies Using Advanced GalNAc-siRNA Technology

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

Silence Therapeutics utilizes RNA interference (RNAi) technology to develop a new generation of drugs to treat serious human diseases with unmet needs. Attachment of the N-acetylgalactosamine (GalNAc) moieties to the RNAi triggers (siRNA) allows the resulting conjugates to travel to the liver and to downregulate genes specifically in hepatocytes. We will present our advances with the GalNAc-siRNA technology, as well progress with company's therapeutic programs.

1:50 Oligonucleotide Therapeutics – Now on Target. Using mAb-directed Delivery and Uptake to Modulate Gene Expression

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

Delivery remains a key limitation to the use of oligonucleotide-based therapeutics. Uptake of oligonucleotides is limited by their high molecular weights and hydrophilicity, independent of whether the oligonucleotide works through siRNA, antisense or splice switching mechanisms. It is now known that siRNA and antisense molecules conjugated to GalNAc bind to and are internalized by the asialoglycoprotein receptor on hepatocytes, and recent data demonstrate receptor-mediated uptake increases the efficacy of the GalNAc-conjugated oligonucleotides up to 30-fold. Although there are multiple diseases of hepatocellular origin, effective delivery of oligonucleotides to a larger repertoire of cell types would enable oligonucleotide technologies to be applied more broadly and effectively across a range of diseases. We have generated antibody-oligonucleotide conjugates with double stranded and single stranded payloads that deliver oligonucleotide payloads in multiple tissues and cell types. Applications of the technology in various disease indications will be discussed.

2:20 LUNAR™: A Novel, Potent, Safe and Versatile Nucleic Acid Delivery Platform

Priya P. Karmali, PhD, Senior Director, Pharmaceutical Development, Arcturus Therapeutics

Arcturus has developed a novel, potent and safe delivery platform called LUNAR™, a proprietary lipid-enabled delivery system for nucleic acid medicines. Versatility of LUNAR™ platform enables effective delivery of a wide range of nucleic acids including mRNA, siRNA, miRNA, antisense and DNA to the liver, lung and other target tissues. This presentation will provide an update on advancements made for LUNAR™ platform in terms of its potency improvements, manufacturability, scalability and *in vivo* proof of concept achieved for multiple RNA medicine programs.

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

NOVEL AND EMERGING APPROACHES FOR *IN VIVO* DELIVERY

3:35 GalXCTM RNAi Technology: Towards Functional Cure of Chronic Hepatitis B Infection

Marc Abrams, PhD, Senior Director, Preclinical Development, Dicerna Pharmaceuticals, Inc.

GalXCTM technology represents a novel structural class of subcutaneously-



administered, hepatocyte-targeting RNAi therapeutics which can silence any expressed RNA with high specificity and long duration. Chronic Hepatitis B Virus (HBV) infection is a significant cause of worldwide morbidity and mortality. We will report data from multiple preclinical models and discuss a novel mechanism which differentiates GalXC-HBVS from other oligonucleotide-based approaches.

4:05 Therapeutic Protein Expression *in vivo* Using Messenger RNA-Lipid Nanoparticles

Thomas D. Madden, PhD, President and CEO, Acuitas Therapeutics

Therapeutic applications of messenger RNA (mRNA) are currently being advanced into clinical development. However, mRNA is relatively labile and requires a delivery system to efficiently access the cytoplasmic compartment where the mRNA is translated. Acuitas is developing lipid nanoparticle systems (LNP) that allow the efficient delivery and expression of mRNA via different routes of administration. Biophysical characteristics that facilitate efficient mRNA delivery and provide a favorable safety profile will be discussed.

4:35 Development of Anti-Fibrosis siRNA Therapeutics Using HKP Polypeptide Nanoparticle Technology

Patrick Y. Lu, PhD, President & CSO, Sirnaomics, Inc.

Using a proprietary and optimized polypeptide-based delivery technology, we have developed the novel anti-fibrotic therapeutics with siRNAs targeting both TGFß1 and Cox-2 simultaneously, for initial indication of skin hypertrophic scar followed with liver fibrosis and other fibrotic conditions. I will discuss the unique advantage of HKP polypeptide nanoparticle technology for efficient siRNA delivery, its pharmaceutical properties for manufacturing and its preclinical safety profile.

5:05 Delivery of RNAi and Oligonucleotide Therapeutics and Diagnostics via Self-Assembled Nanopieces

Qian Chen, PhD, Professor, Medical Science, Brown University; Chair, SAB, NanoDe Therapeutics Inc.

There is a great need for RNA delivery technology for non-liver and hard-to-deliver tissues. We developed NanopiecesTM (NPs), a novel platform delivery technology to penetrate dense tissues and deliver RNAi intracellularly in a non-toxic manner. NPs disassemble within target cells spontaneously, releasing RNAi therapeutics to modify diseases including bone tumors, post-traumatic joint injuries, and rheumatoid arthritis in animal models. NPs can also achieve *in vivo* mRNA diagnostics by delivering molecular beacons to live animals for monitoring pro-inflammatory gene expression in real time.

5:05 Dinner Short Course Registration

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

* Separate registration required. See page 14 for details.

WEDNESDAY, MARCH 28

8:00 am Morning Coffee

TOLL-LIKE RECEPTOR (TLR) AGONISTS AND CHECKPOINT COMBINATIONS

8:25 Chairperson's Remarks

Art Krieg, MD, Founder and CEO, Checkmate Pharmaceuticals

8:30 Making "Cold" Tumors "Hot" with Intratumoral Injection of CpG-A Oligonucleotide

Art Krieg, MD, Founder and CEO, Checkmate Pharmaceuticals

CMP-001 is a formulation of a CpG-A oligonucleotide, G10, within a virus-like particle, Qb. We are performing a Phase Ib dose escalation study of intratumoral CMP-001 given in combination with systemic pembrolizumab in advanced melanoma patients whose cancer has previously progressed on an anti-PD-1 Ab, or who have failed to respond to at least 12 weeks of such therapy.

9:00 TLR9-Targeted Spherical Nucleic Acids for Cancer Immunotherapy

Ekambar Kandimalla, PhD, CSO, R&D, Exicure

Spherical nucleic acids (SNAs) are dense and radially arranged synthetic oligonucleotides on a central nanoparticle core. The 3D structure of SNA provides enhanced cellular uptake, and nuclease stability, compared with linear oligonucleotides with advantages for local delivery. A novel TLR9-targeted SNA has shown greater antitumor activity as a monotherapy and in combination with an anti-PD-1 antibody compared with a linear oligo in syngeneic tumor models with the induction of innate immune responses and long-term tumor-specific memory responses to subsequent challenge with the same tumor cell line.

9:30 Bi-Functional CpG-STAT3 Antisense Oligonucleotides for Immunotherapy of Metastatic Prostate Cancer

Marcin Kortylewski, PhD, Associate Professor, Department of Immuno-Oncology, City of Hope

Here, we describe a bi-functional oligonucleotide with immunogenic and tolerance-breaking activities, which overcome STAT3-dependent resistance of prostate cancers to immunotherapy. STAT3 antisense oligonucleotide (ASO) tethered to immunogenic CpG-A oligonucleotide showed improved, compared to STAT3ASO alone, biodistribution into the bone marrow and potency of STAT3 knockdown after systemic administration. Treatment with CpG-STAT3ASO conjugate, but not CpG or STAT3ASO alone, led to regression of bone-localized prostate cancers in mice through potnent immune-mediated effects, with the increased tumor infiltration by CD8+ T cells and reduced percentage of regulatory T cells and PD-L1+ MDSCs.

10:00 Networking Coffee Break

NOVEL IMMUNOMODULATORY NUCLEIC ACIDS

10:30 RNAi-Based β-Catenin Inhibition Results in Regression of Highly Immunosuppressive Wnt-Activated Tumors in Combination with IDOi/PD-1 Immunotherapy

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

DCR-BCAT is an RNAi-based experimental drug targeting β-catenin, formulated in a tumor-selective nanoparticle. Wnt/β-catenin signaling has been implicated as a mechanism of resistance to cancer immunotherapy. In preclinical models, systemic administration of DCR-BCAT induced rapid increases in tumor T-cells and dramatically improved responses to immunotherapy agents. Additionally, Wnt signaling promotes constitutive IDO1 expression in some tumor contexts, which in turn promotes recruitment and expansion of immunosuppressive cell types to the tumor microenvironment. DCR-BCAT counteracts immunosuppression by T-cell recruitment and causes regression, when co-administered with anti-PD(L)-1 and IDO1 inhibitors.

11:00 SB 11285, a Novel STING Agonist for Immunotherapy of Cancer

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

Immunotherapy has emerged as a transformative approach for the treatment of cancer. Evidence suggests that the activation of Stimulator of Interferon Genes (STING) pathway in tumor cells and/or immune cells induce type I Interferon production leading to apoptosis of tumor cells, as well as induction of adaptive immune response, thereby providing a powerful anti-cancer strategy. Herein, we describe the discovery and preclinical studies of SB 11285, a novel STING agonist for application in immuno-oncology.

11:30 Opportunities for Antisense Oligonucleotides in Cancer Immunotherapy

Frank Jaschinski, PhD, CSO, Secarna Pharmaceuticals

Immunotherapy has emerged as a promising approach for treatment of cancer. Secarna is targeting immunosuppressive factors within the tumor microenvironment using 3rd generation antisense oligonucleotides. Preclinical data will be presented that show the progress of Secarna's program targeting immunosuppressive factors such as the ectonucleotidases CD39 and CD73.

12:00 Enjoy Lunch on Your Own

EXPLORING INNOVATIVE STRATEGIES

1:15 Chairperson's Remarks

James J. Hickman, PhD, Founding Director, NanoScience Technology Center; Professor, Nanoscience Technology, Chemistry, Biomolecular Science, Material Science and Electrical Engineering, University of Central Florida

1:20 From Rare to Common: Targeting Gaucher Defects for the Treatment of Parkinson's Disease

S. Pablo Sardi, PharmD, PhD, R&D Director, Sanofi Genzyme

Clinical, genetic and experimental evidence underlies the relevance of lysosomal dysfunction in Parkinson's disease. Stimulation of the lysosomal GBA pathway in the CNS can improve the pathological and behavioral abnormalities in animal models of disease. Modulation of this lysosomal pathway may represent a new disease-modifying treatment for GBA-related Parkinson's disease. This research underscores the study of rare diseases as a new paradigm for drug discovery.

1:50 Orphan Indications as a Step to Developing Therapeutics for Major Unmet Medical Needs

Elena Feinstein, MD, PhD, CSO, Quark Pharmaceuticals

This talk will present Quark's strategy of drug development from proof-of-concept in orphan indications to major ones with similar underlying pathogenesis. A case study of development of QPI-1002, an siRNA targeting p53, from an orphan indication such as delayed graft function following kidney transplantation towards acute kidney injury following cardiac surgery will be discussed.

2:20 Preclinical Development of a CRISPR Medicine for the Treatment of Leber Congenital Amaurosis Type 10

Gerry Cox, MD, CMO, Editas Medicine

A common mutation in intron 26 of the CEP290 gene, c.2991+1655A>G, leads to retinal degeneration and infantile-onset blindness known as Leber congenital amaurosis type 10 (LCA10). A therapeutic approach involving subretinal delivery of AAV5 encoding CRISPR components is being developed to remove the mutation and potentially restore vision. Opportunities and preclinical challenges of developing human genome-based medicines for LCA10 will be discussed.

2:50 Efficient Delivery and Nuclear Uptake for Gene Editing in CD34+ Cells Directed by a CRISPR/Cas9 Ribonucleoprotein Complex

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

Successful editing of the beta globin gene in CD34+ cells is a milestone for *ex vivo* cell therapy. While dramatic advances have been reported in the literature, by and large, the experimental protocols and conditions have been less than robust. We began a systematic evaluation of the relationship among cellular delivery, nuclear uptake and gene editing activity and defined the critical parameters for CRISPR/Cas9 RNP and ssODNs delivery into CD34+ cells.

3:20 Networking Refreshment Break

3:35 Developing a First-in-Class Drug for Familial Amyloid Polyneuropathy: A Case Study

Christine Bulawa, PhD, Senior Director, Rare Disease Research Unit, Pfizer

This talk will present a case study of drug development for familial amyloid polyneuropathy (FAP), a disease caused by mutations in the circulating protein transthyretin. Insights gleaned from biophysical studies of transthyretin and clinical observations of FAP patients led to the therapeutic strategy of native state stabilization and ultimately to development of tafamidis, the first disease modifying therapy for an amyloid disease.

4:05 Human-on-a-Chip Systems Applied to Rare Disease Investigations for Efficacy and Toxicity

James J. Hickman, PhD, Founding Director, NanoScience Technology Center; Professor, Nanoscience Technology, Chemistry, Biomolecular Science, Material Science and Electrical Engineering, University of Central Florida

Our focus is on establishing functional *in vitro* systems where we seek to create organs and subsystems to model motor control, muscle function, myelination and cognitive function, as well as cardiac and hepatocyte subsystems for neurodegenerative diseases such as ALS as well as other rare diseases. Functional 2 and 4-organ systems where multi-organ toxicity as well as efficacy are evaluated will be discussed.

4:35 Case Study: Identification and Development of SLN124, a Conjugated GalNAc-siRNA Therapeutic for the Treatment of Iron Overload Disorders

Torsten Hoffmann, PhD, COO, Silence Therapeutics

Conjugation of the N-acetylgalactosamine (GalNAc) moieties to siRNAs allows precise and highly effective knockdown of various genes in the liver, specifically in hepatocytes, of the vertebrate organisms. We will describe how Silence Therapeutics develops novel therapeutic programs addressing hepatocyte-associated diseases using its proprietary GalNAc-siRNA technology. In this case study, the discovery of SLN124 will be described in greater detail.

5:05 Close of Conference

CHI's Peptide Discovery and Delivery conference reveals the latest strategies at the forefront of peptide discovery, chemistry and delivery with in-depth sessions on new chemistries, novel delivery mechanisms and the most important preclinical and clinical updates, helping you develop the next generation of peptides therapeutics, including latest developments in antimicrobial peptides, peptide vaccines and macrocyclic and constrained peptides.

MONDAY, MARCH 26

7:00 am Registration and Morning Coffee

NEW PEPTIDE DISCOVERIES AND CHEMISTRIES

8:00 Welcome Remarks from Conference Director
Daniel Barry, Senior Conference Director, Cambridge Healthtech Institute

8:10 Chairperson's Opening Remarks
Waleed Danho, PhD, Distinguished Research Leader and Consultant for Peptides, Danho Associates, Inc.

8:15 KEYNOTE PRESENTATION: Peptide Drug Hunter: An Extraordinary Trek into Intracellular Target Space
Tomi Sawyer, PhD, Distinguished Scientist, Discovery Chemistry Modalities, Merck Research Laboratories
A deeper understanding of peptide science and technology is driving a renaissance in peptide drug discovery. This presentation will highlight past achievements and future opportunities to advance novel peptide therapeutics in tackling intracellular target space and complex diseases thereof.

8:45 High-Throughput Selection of Peptides with Biological Function
Alex Batchelor, PhD, CEO, Orbit Discovery
Peptide therapeutics has been greatly enhanced by the evolution of display technologies. These technologies enable the move from peptide discovery which uses endogenous peptides as a starting point to discovery which uses large, random libraries to identify novel structures. This means we can address targets for which there are no known peptide binder. Phage display is used to present natural peptides to both purified and cell-surface targets.

9:15 Genetic Encoded Peptide Libraries, 48 Hours Hits Identification
Ratmir Derda, PhD, Assistant Professor, University of Alberta
Genetically-encoded (GE) libraries of peptides are one of the major sources of discovery of biological drugs and development of ligands. We use GE libraries as starting materials for multi-step organic synthesis. Examples are N-terminal conjugation and cyclization of linear peptides with simultaneous introduction of glycan entities. We developed the Genetically-Encoded Fragment-Based Discovery (GE-FBD) platform, which combines >109 peptides with GE-modifications. The talk will describe the progress and challenges in application of GE-FBD platform.

9:45 Sponsored Presentation *(Opportunity Available)*

10:15 Networking Coffee Break

NEW DEVELOPMENTS

10:30 Is Glucagon a Suitable Drug Target?
Thomas Kruse, PhD, Senior Principle Scientist, Novo Nordisk
The pharmaceutical industry has pursued glucagon as a drug target for years with no clear consensus on the way forward. Agonists or antagonists? Long-acting or short-acting? This talk summarizes the literature and the Novo Nordisk efforts to understand glucagon pharmacology in greater depth.

11:00 Identification of Long Acting GIP/GLP-1 Dual-Acting Peptide Hormones
Pernille Tofteng Shelton, PhD, Senior Scientist, Medicinal Chemistry, Zealand Pharma
Research showing beneficial metabolic effects of GIPR and GLP-1R co-activation in T2D patients has led to a renewed interest in GIP biology. Here we present the design and characterization of long acting novel balanced GLP-1-GIP receptor dual agonists. We will describe optimization of enzymatic stability, chemical and physical stability, and half-life extension through albumin binding with a Lys17 acylation. These novel potent dual-agonists have a significantly increased half-life and demonstrate pharmacodynamic effects in mice.

11:30 FEATURED PRESENTATION: Setmelanotide for the Treatment of Severe Obesity Resulting from MC4-Pathway Deficiency
Lex Van der Ploeg, PhD, CSO, Rhythm Pharmaceuticals
Setmelanotide is a once daily injectable cyclic octapeptide MC4R agonist that acts as a precision medicine 'replacement' therapy to compensate for the lack/reduction of endogenous MC4R-pathway activation, leading to re-establishing weight and appetite control. Setmelanotide is currently in Phase III trials for the treatment of POMC, PCSK1 and LEPR deficiency related obesity. Our epidemiological studies have unveiled the predicted prevalence of MC4R-pathway genetic deficiencies. We are currently addressing the position of other MC4R-pathway genes to identify additional at-need patient populations that could benefit from setmelanotide therapy.

12:00 pm Session Break

12:10 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:40 Session Break

MACROCYCLIC AND CONSTRAINED PEPTIDES

1:25 Chairperson's Remarks
Waleed Danho, PhD, Distinguished Research Leader and Consultant for Peptides, Danho Associates, Inc.

1:30 Properties of Orally Bioavailable Peptide Macrocycles beyond the Rule-of-5
Alan Mathiowetz, PhD, Director, Discovery Network, Pfizer, Inc.
Peptidic macrocycles with properties beyond the Rule-of-5 (BRo5) have the potential to be effective modulators of difficult targets. Oral delivery of BRo5 molecules is challenging and requires a balance of competing properties such as permeability, clearance, and potency; macrocyclization has the potential to impact all of these properties. This talk provides an overview of structure/property trends we have found spanning multiple series of BRo5 peptidic macrocycles.



2:00 Macrocyclic Peptide Inhibitors of the Hedgehog Signaling Pathway

Rudi Fasan, PhD, Associate Professor, Department of Chemistry, University of Rochester

The Hedgehog signaling pathway plays a central role during embryonic development and its aberrant activation has been implicated in the development and progression of several human cancers. This talk will describe the design and optimization of macrocyclic peptides capable of inhibiting the Hedgehog pathway by targeting and disrupting the Hedgehog protein/Patched interaction, the most upstream event in the ligand-induced activation of this cell signaling pathway.

2:30 Turning Full Circle from Linear to Cyclic Azapeptide Modulators of the Cluster of Differentiation 36 Receptor

William D. Lubell, PhD, Département de Chimie, Université de Montréal

Azacyclopeptides were identified that exhibited unprecedented CD36 binding affinity and ability to reduce the overproduction of nitric oxide, an important marker of inflammation produced by macrophages when stimulated by the Toll-like receptor-2 agonist fibroblast-stimulating lipopeptide. Our presentation will describe synthetic methods, structure-activity relationships and conformational analyses to provide understanding of the requirements for azacyclopeptide CD36 modulator activity.

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

3:45 Discovery and Development of Novel Macrocycle Drugs: Outer Membrane Protein Targeting Antibiotics (OMPTA), a New Class with a Novel Mode of Action

Daniel Obrecht, PhD, CSO & Co-Founder, Pharma, Polyphor Ltd

We have recently shown exceptional *in vitro* activity on the most recently emerging antibiotic-resistant strains, and in animal model studies we have shown excellent *in vivo* efficacy against relevant bacterial strains, including resistant strains. We will also give an update on our lead antibiotic Murepavadin (POL7080), which is a narrow-spectrum, targeted therapy for Pseudomonas infections in critically ill patients in the ICU. POL7080 has successfully completed Phase II and we are preparing the path forward for a Phase III registration trial.

4:15 Targeting Intracellular Protein-Protein Interactions with Structure-Based Designed Macrocyclic Peptides

David Spellmeyer, CSO, Circle Pharma

Circle Pharma deploys a structure-based design/synthetic chemistry platform for macrocycle therapeutic discovery that incorporates prediction of intrinsic cell permeability as a key step in the design workflow. While this platform is target-agnostic, Circle's internal pipeline is directed to intracellular protein-protein interactions that are key drivers in oncology pathways, including p53:MDM2/4, MCL1:BH3, cyclinA:cdk2 and beta-catenin:TCF4. Examples of Circle's development work will be presented.

4:45 Sponsored Presentation *(Opportunity Available)*

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: Overcoming Challenges with Peptide Delivery*

* Separate registration required. See page 14 for details.

TUESDAY, MARCH 27

7:30 am Breakfast Breakout Roundtable Discussions

Grab a cup of coffee 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.

For more details, please visit OPTCongress.com

PEPTIDES FOR CANCER

8:25 Chairperson's Remarks

Jesse Dong, PhD, Vice President, Peptide Chemistry, Neon Therapeutics

8:30 Engineering Potent NaV1.7 Inhibitory Peptide-Antibody Conjugates

Justin Murray, PhD, Principal Scientist, Hybrid Modality Engineering, Amgen

We describe NaV1.7 inhibitory peptide-antibody conjugates for potential prolonged channel blockade. A GpTx-1 peptide was conjugated to a carrier monoclonal antibody, and variations in attachment site, linker, and peptide loading established design parameters for potency optimization. Antibody conjugation led to *in vivo* half-life extension by 130-fold relative to a nonconjugated GpTx-1 peptide. Further improvements in potency have been achieved through the conjugation of selective analogs of JzTx-V.

9:00 Development Strategies of Neo-Antigen-Based Personalized Cancer Vaccines

Jesse Dong, PhD, Vice President, Peptide Chemistry, Neon Therapeutics

Neon Therapeutics is pursuing an exciting clinical development program of a personalized cancer vaccine, NEO-PV-01, which targets patient-specific tumor neoantigens to engage the immune system to precisely and selectively attack tumors. Our objective is to create and deepen anti-tumor immune responses and broaden the range of cancers treatable via immuno-oncology approaches.

9:30 Nanofitin-Drug Conjugates for Solid Tumors: From Imaging to Treatment

Olivier Kitten, PhD, Founder & CEO, Affilogic

The putative advantage of small targeting scaffolds in comparison with antibodies lies in their small size, at the expense of a short plasma half-life. The 7 kDa, highly specific Nanofitins are protein scaffolds that exhibit high tumor invasion capability. This feature is conserved after addition of cytotoxic payloads and radiotracers. Combined with Nanofitin-based half-life extension moieties, these assemblies constitute a novel set of therapeutically relevant modalities that will be illustrated.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

PEPTIDE DEVELOPMENTS

10:30 Chairperson's Remarks

Jesse Dong, PhD, Vice President, Peptide Chemistry, Neon Therapeutics

10:35 The Development of Stapled Peptide Therapeutics

Loren D. Walensky, MD, PhD, Professor of Pediatrics, Investigator, Linde Program in Cancer Chemical Biology, Dana-Farber Cancer Institute – Boston Children's Hospital, Harvard Medical School

11:05 Preclinical Studies on P8, a Novel Disease-Modifying Peptide Drug Candidate for the Treatment of Alzheimer's Disease
Nazneen Dewji, PhD, Associate Adjunct Professor of Medicine, UCSD and President and CEO, Cenna Biosciences, Inc., USA
We previously demonstrated that two small, non-overlapping peptides, P4 and P8, from the PS-1 NH2-terminal domain, can substantially and specifically inhibit the production of total Aβ as well as Aβ40 and 42 in model systems of AD without affecting the catalytic activities of β- or γ-secretase, or the level of APP. These peptides and their derivatives offer new disease-modifying drug candidates for the treatment of AD. We now provide data on the preclinical development of the lead peptide drug candidate P8.

11:35 Sponsored Presentation *(Opportunity Available)*

11:50 Session Break

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

12:30 Dessert Break in the Exhibit Hall with Poster Viewing

PEPTIDE DELIVERY

1:15 Chairperson's Remarks
Steve Prezstelski, PhD, CSO, Xeris Pharmaceuticals

1:20 How Can Nanosystems Help Address Present and Future Challenges in Peptide Delivery?
Joël Richard, PhD, Senior Vice President, Peptides Development, Ipsen
Peptides, which have become very attractive drugs in the last decades, remain difficult-to-administer molecules, because they have a short plasma half-life and are very sensitive to enzymatic and pH-driven degradation. Moreover, they show a poor cellular membrane permeability. Then, nanodelivery systems (e.g., nanotubes, nanoparticles) can provide appropriate solutions to address present and future challenges of peptide delivery, especially for sustained release, or to cross cellular membranes and target intracellular receptors.

1:50 Cell Penetration Profiling for Biotherapeutics
Joshua Kritzer, PhD, Associate Professor, Department of Chemistry, Tufts University
Several classes of biomolecules have emerged as exciting potential therapies, but their development has been impeded by imprecise measurements of intracellular delivery. The Kritzer lab has devised a new method for quantitating cell penetration, the ChloroAlkane Penetration Assay (CAPA). CAPA is inexpensive and high-throughput, and it can quantitate penetration to individual cellular compartments. We are using CAPA to comprehensively profile cell penetration for diverse biomolecules and drug delivery systems.

2:20 Update on Xeris Peptide Development and Delivery
Steve Prezstelski, PhD, CSO, Xeris Pharmaceuticals

2:50 Sponsored Presentation *(Opportunity Available)*

3:05 Refreshment Break in the Exhibit Hall with Poster Viewing

PEPTIDE STABILITY AND LATE-STAGE DEVELOPMENT

3:35 Stable and Effective Formulations of Peptide Drugs in Phospholipid Micelles
Hayat Onyuksel, PhD, Professor, Department of Biopharmaceutical Sciences, University of Illinois, Chicago
Poor stability of peptide drugs causes a major problem during manufacturing, storage and *in vivo* use. Stability of peptide drugs can significantly be improved when delivered in sterically stabilized phospholipid micelles (SSM). In this talk, using vasoactive intestinal peptide (VIP) as a model drug, data obtained with free peptide or in SSM on two disease models, RA and IBD, will be compared. Reasons for significant improvements in peptide drug stability, efficacy and safety when used as a nanomedicine (VIP-SSM) will be explained.

4:05 Transitioning Manufacturing Processes from Clinical Trial Supply to Registration and Pre-Commercial Readiness
Dave Garman, PhD, CTO, NoNO, Inc.
There are vast differences in the manufacturing and testing requirements between supplying a drug for clinical trials and registering a drug for market access. For small to midsize companies, these development expenses are often pushed to late stages when the risk of failure in clinical studies is lower. We examine the transition to commercial development of drug substance and drug product manufacturing processes to mitigate risks of a FDA refusal to file in the context of our Phase III peptide therapeutic NA-1.

4:35 High Throughput Purification of Synthetic Peptides by Reversed Phase Chromatography
Mathias Schaffrath, PhD., Group Head, Sanofi-Aventis Deutschland GmbH
The purification of synthetic peptides (25-55 amino acids) is still a challenge. The unwanted by-products of these peptides are often peptides with only one wrong amino acid in the sequence. Therefore, the peptide and the by-products elute at the same time during the chromatographic separation. The reversed phase chromatography is in many cases the method of choice. Sometimes orthogonal reversed phase methods with two chromatographic steps and two different column selectivities are needed to increase the purity to more than 95%. Chromatographic experience, a thorough method development and up scaling is needed for successful separations. Partial automation of the process leads to a remarkable throughput, which is particularly important in the field of research.

5:05 Close of Conference



SUBMIT A POSTER WHEN REGISTERING AND BECOME A STUDENT FELLOW

**Full-time graduate students and PhD candidates qualify for the student rate. Students are encouraged to present a research poster and receive an additional $50 off their registration fee and will be recognized as a Student Fellow of the event.

Student rates cannot be combined with any other discount offers. Students must present a valid/current student ID to qualify for the student rate. Limited to the first 25 students that apply.

Student Fellows must register and submit a poster abstract by February 9, 2018

"This three-day meeting combines frontier works from both academic and industry which truly illustrated the current status of oligonucleotides therapeutics."

- Patrick L., PhD, President & CEO, Sirnaomics, Inc.

Drug Discovery for Rare Diseases | March 28, 2018

Focus on Genomic and Proteomic Targets and Drug Modalities

Rare diseases, or diseases that affect only a small percentage of the population, have been growing in significance and prominence in recent years. According to the National Institutes of Health, there are nearly 7,000 rare diseases and more than 25 million Americans who are affected. Approximately 80% of these rare diseases are genetic in origin. Cambridge Healthtech Institute's symposium on Drug Discovery for Rare Diseases will bring together leading scientists, clinicians, executives and experts who are deeply involved in bringing to market the treatments for such rare disorders. This symposium will bring to light some of the new drug targets, and peptide and oligonucleotide-based drug modalities that are being pursued. This unique one-day event will bring together people from diverse backgrounds to tackle translational challenges and to discuss potential opportunities in this field. The goal is to help attendees and sponsors meet scientific and technical experts who are involved in rare disease research to exchange ideas and set up collaborations.

WEDNESDAY, MARCH 28

7:30 am Registration and Morning Coffee

EXPLOITING DIVERSE DRUG MODALITIES & TARGETS

8:15 Welcome Remarks from Conference Director

Tanuja Koppal, PhD, Conference Director, Cambridge Healthtech Institute

8:25 Chairperson's Opening Remarks

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

8:30 Targeting microRNA-155 as a Therapeutic Strategy for Rare Hematological Malignancies

William Marshall, PhD, President and CEO, miRagen Therapeutics

microRNA-155 is an important control point for regulation of pathways implicated in oncology and inflammatory disease. Its overexpression has been shown to be an indicator of poor prognosis in a variety of rare hematological malignancies. MRG-106, an inhibitor of miR-155, is currently being evaluated in Phase I in patients with Cutaneous T-cell Lymphoma (CTCL). An overview of our latest clinical observations will be presented.

9:00 Chemistry and Biology of Rare Diseases Treatable with Hepatocyte Targeted RNAi Therapeutics

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

9:30 The Natural History of Alpha-1 Antitrypsin Storage Disease and RNAi Intervention in PiZ Transgenic Mice and Implications for Treatment in Humans

Bruce D. Given, MD, COO, Arrowhead Pharmaceuticals

A large majority of patients with alpha-1 antitrypsin deficiency produce a mutant protein that mis-folds in the hepatocyte leading to deficiency in the plasma, but a storage disease in the liver. The PiZ transgenic mouse expresses the human mutant Z protein and recapitulates most of the human natural history in the liver. We have intervened throughout this natural history with RNAi trigger compounds and showing beneficial effects and are now entering the clinic with a second-generation RNAi compound.

10:00 Networking Coffee Break

10:30 Targeting the Pulmonary Vasculature with Oligonucleotide Therapy: Fact or Fiction?

Hyung Chun, MD, FAHA, Associate Professor of Medicine, Section of Cardiovascular Medicine, Yale School of Medicine

Pulmonary arterial hypertension is a rare disease that leads to right heart failure and ultimately death. While many studies have implicated the potential therapeutic role of oligonucleotides (including microRNAs, microRNA inhibitors, and short interfering RNAs), challenges have surrounded the efficient delivery of such oligonucleotides to the pulmonary vasculature. Current state of technology and future directions will be discussed.

11:00 PANEL DISCUSSION: Tackling Rare Diseases: From Conviction to Cure

Moderator: Michael Liebman, PhD, Managing Director, Strategic Medicine, Inc.

Panelists:

Iris Melendez, President and Founder, The Nathaniel Adamczyk Foundation

Torsten Hoffmann, PhD, COO, Silence Therapeutics

Robert N. McBurney, PhD, CEO, Accelerated Cure Project for MS

Heather Siefers, MS, Senior Manager, Clinical Biorepository Operations, Aeras Chair, iConquerMS™ PPRN Governing Board

11:30 Sponsored Presentation *(Opportunity Available)*

11:45 Session Break

11:55 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:25 pm Session Break

EXPLORING INNOVATIVE STRATEGIES

1:15 Chairperson's Remarks

James J. Hickman, PhD, Founding Director, NanoScience Technology Center; Professor, Nanoscience Technology, Chemistry, Biomolecular Science, Material Science and Electrical Engineering, University of Central Florida

1:20 From Rare to Common: Targeting Gaucher Defects for the Treatment of Parkinson's Disease

S. Pablo Sardi, PharmD, PhD, R&D Director, Sanofi Genzyme

Clinical, genetic and experimental evidence underlies the relevance of lysosomal dysfunction in Parkinson's disease. Stimulation of the lysosomal GBA pathway in the CNS can improve the pathological and behavioral abnormalities in animal models of disease. Modulation of this lysosomal pathway may represent a new disease-modifying treatment for GBA-related Parkinson's disease. This research underscores the study of rare diseases as a new paradigm for drug discovery.

1:50 Orphan Indications as a Step to Developing Therapeutics for Major Unmet Medical Needs

Elena Feinstein, MD, PhD, CSO, Quark Pharmaceuticals

This talk will present Quark's strategy of drug development from proof-of-concept in orphan indications to major ones with similar underlying pathogenesis. A case study of development of QPI-1002, an siRNA targeting p53, from an orphan indication such as delayed graft function following kidney transplantation towards acute kidney injury following cardiac surgery will be discussed.



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Conjugation of the N-acetylgalactosamine (GalNAc) moieties to siRNAs allows precise and highly effective knockdown of various genes in the liver, specifically in hepatocytes, of the vertebrate organisms. We will describe how Silence Therapeutics develops novel therapeutic programs addressing hepatocyte-associated diseases using its proprietary GalNAc-siRNA technology. In this case study, the discovery of SLN124 will be described in greater detail.

5:05 Close of Symposium

PRESENT A POSTER AND SAVE $50!

Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by **February 9, 2018**.

Register online, or by phone, fax or mail. Please indicate that you would like to present a poster. Once your registration has been fully processed, we will send an email with a unique link and instructions for submitting your abstract using our online abstract submission tool. Please see below for more information.

Reasons you should present your research poster at this conference:

- Your poster will be seen by our international delegation, representing leaders from top pharmaceutical, biotech, academic and government institutions
- Receive $50 off your registration
- Your poster abstract will be published in our conference materials

Note: Posters should be portrait orientation, with maximum dimensions of 36 inches wide (3 feet) x 48 inches high (4 feet).

Please note, there are no posters Wednesday, March 28.

** We reserve the right to publish your poster title and abstract in various marketing materials and products.*

Poster inquiries: jring@healthtech.com



Short Courses*

** Separate registration required*

TUESDAY, MARCH 27 | 5:30 - 8:30 PM

DINNER SHORT COURSE

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 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





"No events go without a hitch, but your crack team met all the obstacle[s] head on, to our complete satisfaction. We've already signed up for the next event."

- Rick N., President, Oligo Factory

"It was my first time attending the show, and I was very impressed with the variety of speakers and content."

- Chris M., PhD, Director, Business Development, Bachem Americas, Inc.



Pricing and Registration Information

CONFERENCE PRICING

	Commercial	Academic, Government, Hospital-affiliated
BEST VALUE REGISTRATION Includes access to entire 3-day Oligonucleotide and Peptide Discovery and Delivery programs, as well as 1-day Rare Diseases Symposium. (Does not include access to any short courses)		
Early Deadline until December 15, 2017	$2,249	$1,149
Advance Deadline until February 9, 2018	$2,449	$1,199
Registration after February 9, 2018, and on-site	$2,599	$1,299
BASIC PACKAGE Includes a 2-day access to any combination of Oligonucleotide Discovery and Delivery, Peptide Discovery and Delivery, or the Symposium on Rare Diseases. (Does not include access to any short courses)		
Early Deadline until December 15, 2017	$1,699	$879
Advance Deadline until February 9, 2018	$1,849	$899
Registration after February 9, 2018, and on-site	$2,049	$1,049

SYMPOSIUM REGISTRATION

Includes access to symposium. (Does not include access to other conference programs or short courses)

Symposium: Rare Diseases	$999	$579

SHORT COURSE PRICING

Single Short Course	$699	$399
Double Short Courses	$999	$699
Triple Short Courses	$1,199	$799

~~SUNDAY, MARCH 25 | 5:00 - 8:00 PM~~ ~~Pre-Conference Dinner Short Course~~	~~MONDAY, MARCH 26 | 6:30 - 9:30 PM~~ ~~Dinner Short Course~~	**TUESDAY, MARCH 27 | 5:30 - 8:30 PM Dinner Short Course**
~~SC1: Oligonucleotide Therapeutics: From Discovery to Manufacturing~~	~~SC2: Overcoming Challenges with Peptide Delivery~~	SC3: CRISPR-Based Gene Editing for Targeted Therapies

CONFERENCE DISCOUNTS

Attention Students: Become a Student Fellow to this event. Register online at a discount, submit a poster and be recognized as a Student Fellow.

Poster Submission - **Discount ($50 Off)**: Poster abstracts are due by February 9, 2018. Once your registration has been fully processed, we will send an email containing a unique link allowing you to submit your poster abstract. If you do not receive your link within 5 business days, please contact jring@healthtech.com. *CHI reserves the right to publish your poster title and abstract in various marketing materials and products.

REGISTER 3 - 4th IS FREE: Individuals must register for the same conference or conference combination and submit completed registration form together for discount to apply.

Alumni Discount: Cambridge Healthtech Institute (CHI) appreciates your past participation at Oligonucleotide and Peptide Therapeutics Boston (OPT Boston). As a result of the great loyalty you have shown us, we are pleased to extend to you the exclusive opportunity to save an additional 20% off the registration rate.

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