OPT Congress Oligonucleotide, mRNA & Peptide Therapeutics

2026 Conference Track Summary

Oligonucleotide Discovery & Delivery

Brought to you by Cambridge Healthtech Institute, a division of Cambridge Innovation Institute

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Executive Overview

The **OPT Congress** 2026 Oligonucleotide Discovery & Delivery track highlighted the continued evolution of RNA therapeutics from platform validation toward increasingly precise, disease-specific applications. Across presentations, speakers emphasized that advances in oligonucleotide chemistry, RNA biology, and targeted delivery are enabling new therapeutic strategies for neurological disorders, cancer, and rare genetic diseases. Discussions focused on improving molecular precision, expanding therapeutic reach, and translating promising preclinical discoveries into clinically meaningful outcomes through thoughtful trial design and collaborative development.

Most Frequently Covered Issues

1. Precision RNA therapeutics
Novel RNA-targeting strategies are enabling more selective treatment of complex genetic and acquired diseases.

2. Next-generation oligonucleotide chemistry
Advances in backbone design and molecular engineering are improving potency, selectivity, and durability.

3. Clinical translation
Presentations emphasized moving promising RNA technologies from preclinical research into well-designed clinical studies.

4. Delivery and therapeutic specificity
Improving delivery, tissue targeting, and cellular uptake remains central to expanding therapeutic success.

5. Expanding RNA biology
Growing understanding of microRNAs, splice regulation, and RNA interference is creating new therapeutic opportunities.

Recurring Takeaways

- RNA therapeutics are expanding into increasingly diverse disease areas.
- Rational chemistry design continues to improve therapeutic performance.
- Precision targeting can enhance efficacy while minimizing unwanted effects.
- Collaboration is essential for advancing rare disease therapies.
- Continued progress depends on pairing biological insight with strong clinical validation.

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The Zorevunersen Story: Insights from the Development of an Investigational ASO for Dravet Syndrome

Full Video Here

Isabel Aznarez, PhD, Vice President, Discovery Research, Stoke Therapeutics

A precision RNA approach can address diseases caused by haploinsufficiency by increasing expression from the healthy copy of a gene rather than altering DNA. By targeting naturally occurring nonproductive splicing events with antisense oligonucleotides, the strategy aims to restore functional protein levels in affected tissues while maintaining dose control and selectivity. (00:00:00-00:06:22)

Dravet syndrome illustrates both the promise and urgency of this approach because the condition affects far more than seizure frequency. Severe developmental, behavioral, and cognitive challenges place a lifelong burden on patients and families, highlighting the need for treatments that target the underlying biology instead of managing symptoms alone. (00:06:22-00:11:16)

Preclinical studies showed that restoring protein expression produced durable improvements in survival and substantially reduced spontaneous seizures in disease models. Early clinical findings also suggested reductions in motor seizure frequency, with larger effects observed at higher initial doses and sustained benefit during long-term follow-up with maintenance dosing. (00:08:11-00:18:12)

Beyond seizure control, investigators reported encouraging trends in overall clinical status, quality of life, and measures of adaptive behavior collected over extended follow-up. Although the early studies were open label and involved relatively small patient populations, the results supported continued evaluation in a randomized Phase 3 trial designed to confirm safety and efficacy. (00:18:12-00:23:34)

Key Takeaways

- RNA-targeted therapies can restore protein expression without modifying DNA.
- Treating the underlying genetic mechanism may improve multiple aspects of complex neurological disease.
- Early clinical data suggested durable reductions in seizure frequency alongside broader functional improvements.
- Randomized Phase 3 evaluation is needed to confirm the encouraging early findings.

Antisense Oligonucleotide Therapies for Neurological Disorders

Full Video Here

Adrian Krainer, PhD, St. Giles Foundation Professor, Cold Spring Harbor Laboratory, CSHL Cancer Center

Antisense oligonucleotides have evolved into a versatile platform for treating neurological disease by targeting RNA rather than altering DNA. Different chemistries enable either gene silencing or splice switching, allowing researchers to restore normal splicing, increase or decrease gene expression, or generate functional proteins from disease-causing genes. (00:00:00-00:06:45)

The development of nusinersen for spinal muscular atrophy demonstrated how splice-switching therapies can transform severe genetic diseases. Careful target selection, highly specific sequence design, and direct delivery into the central nervous system produced durable clinical benefits, particularly when treatment began before symptoms appeared, while also establishing a model for future RNA-based medicines. (00:06:45-00:17:56)

The same principles are now being applied to a broader range of neurological disorders, including approaches that increase expression from healthy gene copies in haploinsufficiency disorders such as Dravet syndrome. Growing clinical experience suggests RNA-targeted therapies can be adapted to different disease mechanisms while maintaining the advantages of selective targeting and long-lasting activity. (00:17:56-00:21:18)

The presentation also highlighted the challenges and promise of developing therapies for ultra-rare diseases. Early clinical experience with an investigational antisense treatment for familial dysautonomia showed encouraging improvements in neurological function and disease measures, illustrating how collaboration among researchers, clinicians, patient foundations, and regulators can help bring personalized therapies to patients with few treatment options. (00:21:18-00:30:16)

Key Takeaways

- Splice-switching antisense oligonucleotides provide multiple strategies for correcting disease-causing RNA defects.
- Early treatment can substantially improve outcomes in progressive neurological disorders.
- RNA-targeted therapies are expanding from established indications into additional rare neurological diseases.
- Progress in ultra-rare diseases depends on sustained collaboration across research, clinical care, patient advocacy, and regulatory communities.

RNAi to Engineer Immune Cells for Therapy

Full Video Here

Reka Haraszti, PhD, Resident & Group Leader, Hematology & Oncology, University Hospital Tuebingen

Cell therapies can produce remarkable responses against cancer, but immune-related toxicities often limit their full potential. The presentation explored how RNA interference could selectively reprogram therapeutic immune cells to preserve anti-tumor activity while reducing harmful off-target immune responses, shifting the focus from broad immunosuppression toward more precise immune control. (00:00:00-00:04:16)

A major challenge is delivering RNA molecules efficiently to rapidly dividing immune cells while maintaining durable activity. The work demonstrated that chemically modified, lipid-conjugated siRNAs achieved effective uptake, extended gene silencing, and remained compatible with existing cell therapy manufacturing processes, including cryopreservation and later clinical use. (00:04:16-00:10:13)

Rather than targeting a single pathway, the research evaluated combinations of siRNAs and microRNA mimics to reshape complex immune cell behavior. Multiplex approaches reduced graft-versus-host disease activity while preserving, and in some cases enhancing, anti-leukemia responses, suggesting that coordinated regulation of multiple pathways may provide greater specificity than single-target interventions. (00:10:13-00:19:03)

The findings also highlighted the importance of understanding patient-to-patient variability. Differences in treatment response pointed to the need for personalized RNA-based strategies that account for individual immune biology, supporting a future in which engineered immune cells can be tailored to maximize efficacy while minimizing toxicity. (00:19:03-00:22:05)

Key Takeaways

- RNA interference can help separate anti-tumor activity from immune-related toxicity.
- Durable RNA delivery is essential for engineering proliferating therapeutic immune cells.
- Multiplex RNA approaches may outperform single-target strategies by reshaping complex immune responses.
- Personalized immune cell engineering could improve both the safety and effectiveness of future cell therapies.

Why Oligotherapy Has Not Reached Its Potential and How New Chemistry Can Change That

Full Video Here

David Tabatadze, PhD, President, ZATA Pharmaceuticals, Inc.

Nearly five decades after the first demonstrations of antisense therapeutics, oligonucleotide medicines have validated the platform but remain limited by the chemistry available to researchers. The presentation argued that future progress depends less on replacing existing approaches and more on expanding the molecular toolbox with new backbone modifications that improve performance while remaining compatible with established synthesis methods. (00:00:00-00:05:50)

One proposed strategy enables site-specific attachment of functional groups at positions throughout an oligonucleotide rather than restricting modifications to the molecule's ends. This approach is designed to support applications such as tracking, delivery, stabilization, or other functional enhancements without disrupting standard manufacturing workflows or altering the nucleic acid bases. (00:03:59-00:08:07)

A second platform focuses on engineering the oligonucleotide backbone itself through charge-neutralizing and cationic modifications. By selectively tuning backbone properties, the goal is to improve stability, cellular delivery, endosomal escape, and other pharmacological characteristics while preserving solubility, hybridization, and compatibility with existing antisense, siRNA, and gene-editing formats. (00:08:07-00:17:32)

The presentation emphasized flexibility as a guiding design principle, allowing researchers to combine functional attachments with backbone engineering to tailor molecules for specific therapeutic needs. Rather than introducing an entirely new chemistry, the approach seeks to extend current platforms with additional design options that could improve therapeutic performance while fitting within familiar development processes. (00:17:32-00:22:49)

Key Takeaways

- Expanding oligonucleotide chemistry may unlock broader therapeutic potential.
- Site-specific functionalization offers greater flexibility than end-only modifications.
- Backbone engineering can be used to optimize delivery and pharmacological properties.
- New chemistries are intended to complement, rather than replace, existing oligonucleotide platforms.

Patient-Scientist Led Development of a Divalent siRNA Therapy for Prion Disease

Full Video Here

Sonia Vallabh, PhD, Prion Scientist, Broad Institute

A personal experience with inherited prion disease became the foundation for a research program focused on preventing a fatal neurodegenerative disorder. The presentation described how decades of biological research identified prion protein as the central driver of disease, creating a clear therapeutic strategy centered on lowering its expression before irreversible neurological damage occurs. (00:00:00-00:06:37)

Multiple preclinical studies using different technologies consistently showed that reducing prion protein extends survival across animal models. This convergence of genetic, antisense, siRNA, and other approaches strengthened confidence that target reduction, rather than any single therapeutic platform, is the key mechanism underlying potential clinical benefit. (00:06:37-00:12:02)

The session highlighted the development of an investigator-led divalent siRNA program that progressed from laboratory discovery through manufacturing, toxicology, and regulatory review without commercial sponsorship. Alongside advances in chemistry and delivery, the work underscored the importance of designing clinical studies that can measure target engagement early while building the evidence needed to support both treatment and future prevention strategies. (00:12:02-00:24:29)

Broader lessons focused on the unique realities of rare disease development, where scientific progress must be matched by regulatory flexibility, rapid execution, and greater collaboration. Sharing clinical tools, biomarker data, and placebo information across programs was presented as a practical way to accelerate learning while reducing duplication for future therapies. (00:24:29-00:28:22)

Key Takeaways

- Strong genetic and preclinical evidence can substantially reduce uncertainty around a therapeutic target.
- Durable target reduction remains a central objective for treating and ultimately preventing prion disease.
- Academic investigators can advance complex therapeutic programs through close collaboration with regulatory and manufacturing partners.
- Open sharing of clinical data and research resources can accelerate progress in rare disease drug development.

Clinical Translation of the Pharmacological Properties of Phosphoryl Guanidine-Containing Stereopure Oligonucleotides

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Elizabeth Wagner, PhD, Director of Translational Medicine, Biology, Wave Life Sciences

Chemical design plays a central role in determining how oligonucleotide therapeutics behave in the body. The presentation showed how precise control of backbone stereochemistry and phosphoryl guanidine modifications can be combined with sequence selection and machine learning to optimize potency, selectivity, durability, and mechanism across multiple RNA-targeting modalities. (00:00:00-00:03:28)

One application focused on allele-selective silencing for Huntington's disease, where preserving the healthy copy of the gene is as important as reducing the mutant form. Stereopure antisense oligonucleotides demonstrated selective lowering of mutant huntingtin RNA and protein in preclinical models, with clinical findings showing encouraging evidence that this selectivity can translate to patients. (00:03:28-00:06:56)

The presentation also highlighted advances in siRNA design using stereopure phosphoryl guanidine chemistry. Systematic optimization improved Ago2 loading, increased potency, extended duration of gene silencing, and reduced off-target effects, illustrating how subtle chemical changes can substantially influence biological performance without altering the underlying RNA sequence. (00:06:56-00:16:18)

These platform improvements are now being applied across multiple therapeutic programs, from metabolic disease to central nervous system targets. Early clinical translation and durable target engagement support the broader concept that rational chemistry design can improve both efficacy and flexibility while providing a common foundation for future oligonucleotide therapeutics. (00:16:18-00:19:24)

Key Takeaways

- Precise oligonucleotide chemistry can significantly improve potency, selectivity, and durability.
- Allele-selective RNA silencing offers a strategy to preserve healthy protein while reducing disease-causing variants.
- Optimized siRNA chemistry enhances Ago2 loading and reduces off-target activity.
- Platform-based chemical innovations can be applied across diverse therapeutic modalities and disease areas.

miRNAs: The Case for Renewed Focus on Basic Science and Clinical Development

Full Video Here

David Corey, PhD, Professor, Department of Pharmacology, UT Southwestern

MicroRNAs remain an underused therapeutic opportunity despite the success of RNA-targeting medicines directed at messenger RNA. The presentation argued that advances in analytical tools and a better understanding of RNA biology now make it possible to revisit microRNA drug development with greater confidence and more rigorous target selection than was feasible in earlier years. (00:00:00-00:10:23)

A central message was that many long-standing assumptions about microRNA biology have proven to be oversimplified. Rather than relying on sequence matches alone, effective target identification requires considering expression levels, cooperative binding, structural context, and the biological significance of individual interactions before investing in therapeutic development. (00:04:31-00:13:33)

New experimental methods, particularly chimeric eCLIP, provide a more direct way to identify authentic microRNA-target interactions inside cells. By linking individual microRNAs to their specific RNA binding sites, these approaches help distinguish meaningful regulatory events from the large number of interactions that may have little biological consequence, allowing researchers to prioritize the most promising therapeutic targets. (00:10:23-00:20:38)

The presentation also highlighted evidence that microRNA regulation begins in the nucleus and continues into the cytoplasm, expanding the range of potential RNA targets beyond traditional messenger RNA regulation. This broader view of RNA biology suggests future therapies may focus on disrupting specific microRNA binding sites within disease-relevant genes rather than altering the activity of an entire microRNA family. (00:13:33-00:24:57)

Key Takeaways

- Improved analytical methods are renewing interest in microRNAs as therapeutic targets.
- Biologically meaningful microRNA regulation depends on more than simple sequence complementarity.
- Chimeric eCLIP helps identify high-confidence microRNA-target interactions for drug discovery.
- Targeting specific microRNA binding sites may provide greater precision than broadly modulating microRNA activity.

TTX-MC138: Targeting microRNA-10b with Antisense Therapy for Metastatic Cancer

Full Video Here

Zdravka Medarova, PhD, Co-Founder, President & Chief Scientific Officer, TransCode Therapeutics

Antisense oligonucleotides offer an opportunity to expand precision cancer therapy by reaching molecular targets that remain inaccessible to conventional drugs. Their programmable design enables highly specific targeting while supporting rapid optimization, although successful clinical development still depends on overcoming challenges such as delivery, safety, biomarker selection, and rational combination strategies. (00:00:00-00:07:52)

The presentation focused on TTX-MC138, an antisense inhibitor of microRNA-10b, a non-coding RNA associated with metastatic progression across multiple tumor types. A proprietary nanoparticle delivery platform was developed to improve tumor uptake, and preclinical studies demonstrated durable suppression of metastatic disease together with prolonged retention of the therapeutic within tumor tissue. (00:07:52-00:15:07)

Early clinical studies confirmed that the investigational therapy reached metastatic lesions and produced evidence of target engagement while maintaining a favorable safety profile. Although objective tumor shrinkage was not the primary outcome, durable disease stabilization in several heavily pretreated patients reinforced the importance of evaluating molecular therapies with endpoints that reflect their biological mechanism rather than relying solely on traditional response measures. (00:15:07-00:21:12)

Future development is centered on biomarker-guided patient selection and treatment earlier in the course of metastatic disease. Planned studies will evaluate whether targeting molecular relapse before radiographic recurrence can delay progression, while additional work will explore rational combinations with immunotherapies based on emerging evidence that microRNA-10b also influences immune regulation. (00:21:12-00:29:04)

Key Takeaways

- Antisense therapeutics can address cancer targets that are difficult to reach with conventional drugs.
- Effective delivery and biomarker-driven trial design are critical for successful clinical translation.
- Disease stabilization and molecular activity may be more informative than tumor shrinkage for targeted RNA therapies.
- Earlier intervention and rational combination strategies may expand the clinical impact of microRNA-targeted treatments.