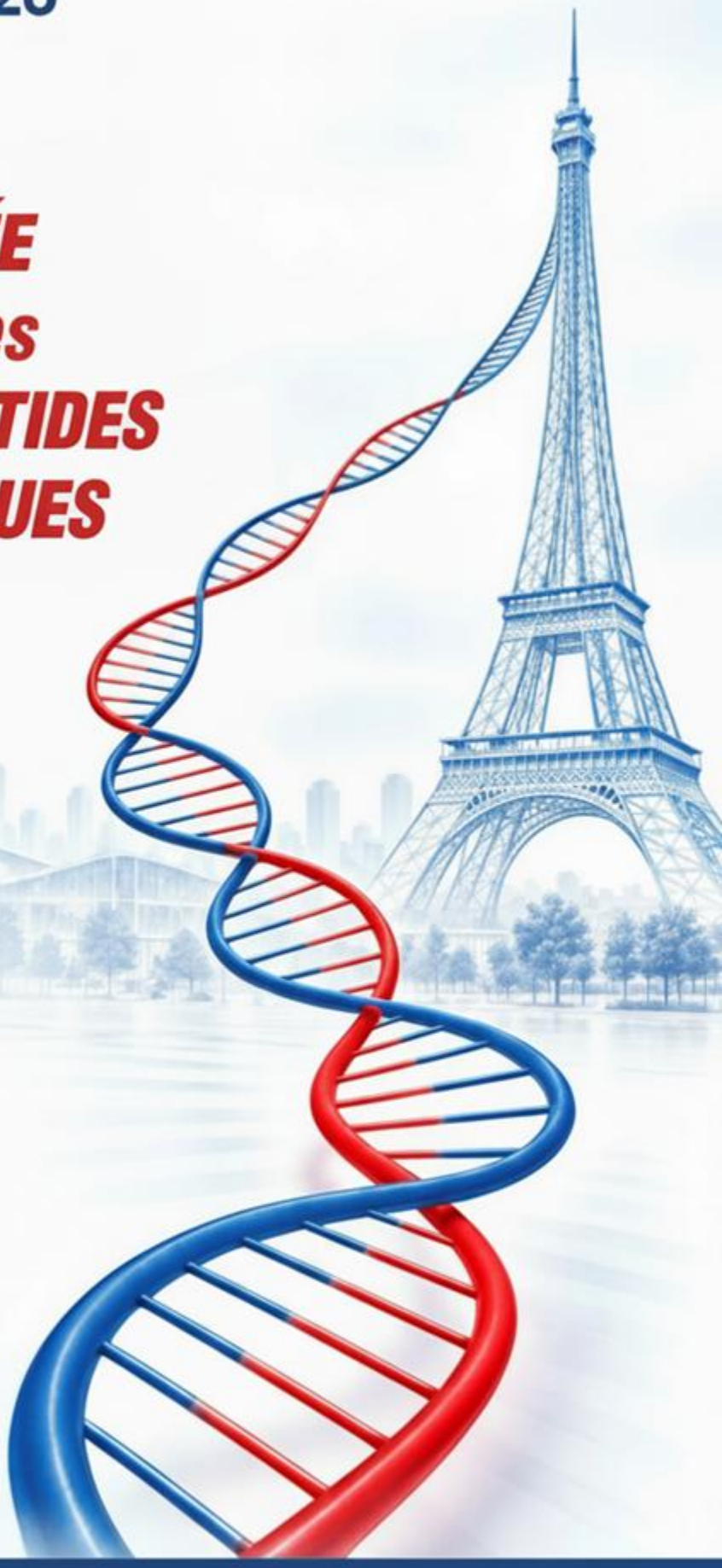
2 novembre 2026

2ème JOURNÉE FRANÇAISE des OLIGONUCLÉOTIDES THÉRAPEUTIQUES



Organisée par

SFOT Société Française des Oligonucleotides Thérapeutiques

PariSanté Campus
2 - 10 Rue d'Oradour-sur-Glane,
75015 Paris

La Société Française des Oligonucléotides Thérapeutiques (SFOT) a pour vocation de rassembler la communauté française des oligonucléotides thérapeutiques afin de renforcer l´expertise, de favoriser le partage des connaissances et de stimuler l'innovation au bénéfice des patients.

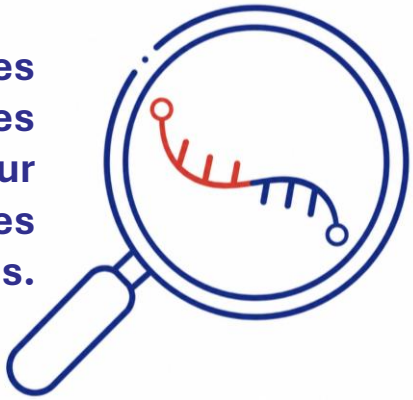
NOTRE VISION

Faire de la **France** un acteur **attractif**, **influent** et **leader** dans le domaine des **oligonucléotides thérapeutiques**, au cœur d'un **écosystème international** dédié au service des **patients**.

NOTRE MISSION

Fédérer l'écosystème français des **oligonucléotides thérapeutiques** au service de la **recherche** et des **patients**, en **renforçant** l'**expertise** et en faisant **progresser** la souveraineté **scientifique** et **industrielle**.

Les oligonucléotides thérapeutiques sont de courtes séquences d'acides nucléiques synthétiques, conçues pour moduler avec précision l'expression des gènes afin de traiter diverses maladies.





ATTRACTIVE ET INFLUENTE

Un pôle **d'excellence** pour les **talents, l'innovation** et la **formation.**

AXÉE SUR LA RECHERCHE

Un **moteur** des **avancées scientifiques** et de l´**innovation** en **santé**.





DÉVELOPPEMENT ET INNOVATION

L'excellence en oligonucléotides thérapeutiques.

AMÉLIORER LES OPTIONS THÉRAPEUTIQUES

Accélérer le **développement** de nouveaux **traitements** pour les **patients**.



À PROPOS DE LA SOCIÉTÉ

Une année de préparation...

La Société Française des Oligonucléotides Thérapeutiques (SFOT) est née d'une conviction commune : la France dispose d'une expertise scientifique de tout premier plan dans le domaine des oligonucléotides thérapeutiques, mais cette excellence nécessitait une structuration nationale renforcée afin d'en révéler pleinement le potentiel translationnel et industriel.

Le 16 octobre 2025, des scientifiques et experts du domaine se sont réunis au **PariSanté Campus** à l'occasion de la **1re Journée Française des Oligonucléotides Thérapeutiques**. Cet événement fondateur a rassemblé près de **150 participants**, illustrant la dynamique exceptionnelle et l'intérêt croissant suscités par cette approche thérapeutique prometteuse.

Les échanges ont mis en évidence une réalité : **la France bénéficie d'un réseau solide et fortement engagé** de chercheurs, cliniciens, partenaires industriels et acteurs du secteur. Toutefois, cet écosystème devait être davantage coordonné et structuré pour **atteindre une pleine compétitivité à l'échelle internationale.**

Cette première rencontre nationale n'était pas une finalité, mais le point de départ de la structuration d'une **filière nationale dédiée aux oligonucléotides thérapeutiques**, avec l'ambition de positionner la France comme un acteur majeur et compétitif dans ce **domaine en pleine évolution.** L'enthousiasme suscité lors de cette journée inaugurale a confirmé la volonté collective d'avancer ensemble.

La **SFOT** a été créée pour capitaliser sur cette dynamique, **fédérer la communauté** et offrir un cadre structuré **favorisant la collaboration, l'innovation et le développement stratégique**. L'aventure est lancée — et elle se poursuit.

ÉVÉNEMENT SOUTENU PAR...

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PROGRAMME

2 NOVEMBRE 2026 — PARISANTÉ CAMPUS, PARIS

08:30 – 09:00 — **ACCUEIL DES PARTICIPANTS & CAFÉ DE BIENVENUE**

09:00 – 09:30 — **OUVERTURE**
Mot de bienvenue et présentation de la Société Française des Oligonucléotides Thérapeutiques (SFOT)
Aurélie Goyenvalle, **Nicolas Babault** et **Frederic Girard** (France Biotech)

09:30 – 10:30 — **TABLE RONDE – LES SUJETS D'ACTUALITÉ & TEMPS FORTS DE L'OTS**
Modérateur: **Nicolas Babault** (NAXIA Discovery)
Panelistes: **Aurélie Goyenvalle** (Université de Versailles saint Quentin en Yvelines), **Héléne Tran** (Servier), **Philippe Barthélémy** (Université Aix-Marseille)

10:30 – 11:00 — **PAUSE-CAFÉ & EXPOSITION DES SPONSORS**

11:00 – 12:00 — **SESSION I – CHIMIE & DÉLIVRANCE**
Modérateur: **Philippe Barthélémy** (Université Aix-Marseille)
Invited speaker: **Michael Smietana**, IBMM - Université de Montpellier, " Chemically Modified Oligonucleotides for Therapeutic Applications"
Short talk: **Regis Cazes**, Midas Pharma,"Synthèse d'oligonucléotides : le diable se cache dans les impuretés"
Short talk: **Sandy Al Bardawil**, Université de Bordeaux, "Beyond a Single Dimension: Orthogonal LC–MS Techniques for Comprehensive Oligonucleotide Characterization"
Short talk: **Nazarii Sabat**, Institut Pasteur, "Next-generation Chemoenzymatic Synthesis of Therepeutic Oligonucleotides"

12:00 – 13:00 — **SESSION II – DÉVELOPPEMENT PRÉCLINIQUE & TRANSLATIONEL**
Modératrice: **Aurélie Goyenvalle** (Université de Versailles saint Quentin en Yvelines)
Invited speaker: **Matthias Titeux**, Institut Imagine, "Splice Modulation Strategies for Epidermolysis Bullosa"
Short talk: **Laurence Faivre**, CHU Dijon Bourgogne, "Ready for the trial, waiting for the drug: Lessons from an ERDERA ASO master protocol"
Short talk: **Imad Kansau**, Université Paris-Saclay, "Novel therapeutic/RNA therapy approach targeting inflammation of the intestinal mucosa"
Short talk: **Sébastien Campagne**, Université de Bordeaux, "Rewiring RBM39 autoregulation overcomes resistance to molecular glue degraders"

13:00 – 14:30 — **DÉJEUNER, SESSION POSTERS & EXPOSITION DES SPONSORS**

14:30 – 16:30 — **SESSION III – BIOTECHS & PHARMA**
Modérateur: **François Macarez** (Diverchim)
Luis Garcia, SQY Therapeutics, "Interim Pharmacokinetics and Pharmacodynamics Results of the Phase 1/2aAVANCE1 Trial on Tricyclo-DNA-Induced DMD Exon 51 Skipping in Duchenne Muscular Dystrophy"
Grégoire Serra, Dolinnov, "Silencing pain at its source: a lipid-conjugated ASO targeting FXYD2 in DRG nociceptors for non-opioid chronic pain"
Cédric Malicet, Vect-Horus, "TfR-Mediated Delivery of Oligonucleotides to the Deep Brain Using the VECTrans® Platform: Initial Learnings and Future Perspectives"
Jessica Nakhle, Servier, "Advancing oligonucleotides into therapies for rare neurological DISORDERS"

SHORT PITCH BIOTECH / INDUSTRIE
Gilles Besin, Valerio Therapeutics, "Valerio Therapeutics: Precision Delivery of RNAs Beyond the Liver"
Pascale Berthet, Harmonix, "Repeatable IV Delivery of RNA Therapeutics to the Brain"
Loïc Roux, CatSci, "Beyond Conventional Gene Silencing: Leveraging the Oligonucleotide Design Toolbox for Therapeutic Innovation"
João Gonçalves, Evotec, "From Patient Mutation to Patient Treatment in a Year or less"
Sébastien Cagnol, Aceso Therapeutics, "ACT-101: a breakthrough RNA therapy (ASO) for Cystic Fibrosis"

16:30 – 17:00 — **PAUSE-CAFÉ: DÉVELOPPEMENT DE CARRIÈRE & EXPOSITION DES SPONSORS**

17:00 – 18:00 — **TABLE RONDE – RENFORCER L'ÉCOSYSTÈME FRANÇAIS DES OLIGONUCLÉOTIDES THÉRAPEUTIQUES : DE L'INNOVATION À LA CLINIQUE**
Modératrice: **Hélène Tran** (Servier)
Panelistes: **Alban Ziegler** (Anddi Rare), **Aurélien Chung** (Association de patient), **Maria-Grazia Biferi** (Genother), **Ermina Rubino** (Institut Imagine), **Luis Garcia** (SQY Therapeutics), **Thierry Dorval** (Servier), **Ana Leticia Maragno** (Jeito capital)

18:00 – 18:15 — **REMISE DES PRIX ET MOT DE CLÔTURE**
Remise des Prix de la meilleure présentation et des meilleurs posters. Mot de conclusion de **Franck Mouthon**

18:15 – 19:30 — **COCKTAIL – NETWORKING**

INTERVENANTS DU JOUR

Ouverture et Table Ronde – Les Sujets d'Actualité & Temps Forts de l'OTS



Aurélie GOYENVALLE · Inserm
Director of Laboratory IMPROVE UMR 1357 UVSQ INSERM



Nicolas BABAULT · NAXIA Discovery
CEO & Co-founder



Frederic GIRARD · France Biotech · DBV Technologies
President- France Biotech
Senior VP, Commercial Operations Europe - DBV Technologies



Hélène TRAN · Servier
Director, Head of Antisense Oligonucleotide Therapeutics Program



Philippe BARTHÉLÉMY · NAXIA Discovery · Aix Marseille Uni
Co -Founder - NAXIA Discovery & Professor- Aix Marseille Université

Session I – Chimie et Délivrance



Michael SMIETANA · Université de Montpellier · IBMM
"Chemically Modified Oligonucleotides for Therapeutic Applications"

Session II – Développement Préclinique & Translationel



Matthias TITEUX · Inserm · Imagine Institute
"Splice Modulation Strategies for Epidermolysis Bullosa"

INTERVENANTS DU JOUR

Session III – Biotechs & Pharma



Luis GARCIA · SQY Therapeutics

"Interim Pharmacokinetics and Pharmacodynamics Results of the Phase 1/2a AVANCE1 Trial on Tricyclo-DNA-Induced DMD Exon 51 Skipping in Duchenne Muscular Dystrophy"



Grégorie SERRA · Dolinnov

"Silencing pain at its source: a lipid-conjugated ASO targeting FXYD2 in DRG nociceptors for non-opioid chronic pain"



Cédric MALICET · VECT-HORUS

"TfR-Mediated Delivery of Oligonucleotides to the Deep Brain Using the VECTrans® Platform: Initial Learnings and Future Perspectives"



Jessica NAKHLE · Servier

"Advancing oligonucleotides into therapies for Rare Neurological Disorders"

Short Pitch Biotech / Industrie



Gilles BESIN · Valerio Therapeutics

"Valerio Therapeutics: Precision Delivery of RNAs Beyond the Liver"



Pascale BERTHET · Harmonix

"Repeatable IV Delivery of RNA Therapeutics to the Brain"



Loïc ROUX · CatSci

"Beyond Conventional Gene Silencing: Leveraging the Oligonucleotide Design Toolbox for Therapeutic Innovation"



João GONÇALVES · Evotec

"From Patient Mutation to Patient Treatment in a Year or less"



Sebastien CAGNOL · Aceso Therapeutics

"ACT-101: a breakthrough RNA therapy (ASO) for Cystic Fibrosis"

INTERVENANTS DU JOUR

Table Ronde: Renforcer L'écosystème Français des Oligonucléotides Thérapeutiques : de l'innovation à la clinique



Alban ZIEGLER · CHU de Toulouse · Anddi Rare
Praticien Hospitalier



Aurélien CHUNG · KCNT1 France - Une étincelle pour Isaure
Pharmacy doctor - Operational Quality Manager - bioMérieu



Ermina RUBINO · Insitut Imagine
Head of Industrial Partnerships



Luis GARCIA · SQY Therapeutics
Co-fondateur & Président



Thierry DORVAL · Servier
Head of Data Sciences & Data Management



Maria Grazia BIFERI · Genother
CSO at GenoTher, Biocluster of excellence dedicated to Gene Therapy and Genetic Medicine



Ana Leticia MARAGNO · Jeito Capital
Director of Translational Science

Remise des prix et Mot de Clôture



Franck MOUTHON · THX Pharma · DIAGAST
Co-founder – THX
President - DIAGAST

Abstracts Selected Short Talks

T 01



Regis CAZES

Chemistry & Delivery

Synthèse d'oligonucléotides: le diable se cache dans les impuretés.

Regis Cazes[1], Jasmin Schwarz

[1] *Midas Pharma*

Un certificat d'analyse peut indiquer une pureté de 99 %, mais qu'en est-il du 1 % restant ?

Dans l'univers des oligonucléotides thérapeutiques, cette fraction apparemment minime peut faire toute la différence entre un procédé de fabrication robuste et des difficultés de production inattendues. Le coût réel d'un Building Block va bien au-delà de son prix d'achat. Dissimulées dans cette fraction résiduelle d'un phosphoramidites qualifié de « haute pureté » peuvent se trouver des impuretés susceptibles d'influencer de manière significative la robustesse du procédé.

Si de nombreuses impuretés non critiques peuvent être efficacement maîtrisées lors des étapes de synthèse et de purification, les impuretés critiques peuvent entraîner une baisse des rendements, une augmentation des opérations de traitement en aval, des non-conformités, ou encore des obstacles réglementaires.

À travers des exemples et retours d'expérience concrets, cette présentation examinera l'impact des profils d'impuretés sur la fabrication d'oligonucléotides et expliquera pourquoi la sélection de l'intermédiaire de synthèse et de son fournisseur joue un rôle déterminant dans la réduction des risques et la sécurité d'approvisionnement à long terme.

Keywords: Phosphoramidites, Impuretés, Oligonucleotides

T 02



Sandy AL BARDAWIL

Chemistry & Delivery

Beyond a Single Dimension: Orthogonal LC–MS Techniques for Comprehensive Oligonucleotide Characterization

Sandy Al Bardawil[1], Philippe Barthélémy, Ludivine Ferey

[1] *Univ. Bordeaux, CNRS, INSERM, ARNA, UMR 5320, U1212, F-33000 Bordeaux, France*

The landscape of oligonucleotide therapeutics is rapidly expanding, with 24 products approved or under regulatory review since the first FDA approval in 1998[1]. Structural complexity arises from phosphorothioate (PS) backbone modification, 2'-O-methoxyethyl (2'MOE) sugar derivatization, and diverse bioconjugation strategies. These features generate heterogeneous impurity and degradation profiles that cannot be resolved using a single chromatographic dimension. As regulatory expectations for identity, purity, and stability increase, orthogonal analytical strategies have become essential[2].

Complementary liquid chromatography–mass spectrometry (LC–MS) approaches were evaluated for modified antisense oligonucleotide characterization.

Ion-pair reversed-phase LC–MS (IP-RPLC–MS) [3], using hexafluoroisopropanol (HFIP) and triethylamine, was optimized to achieve high-resolution separation of a 20-mer PS antisense oligonucleotide[4]. The method enabled discrimination of synthesis-related impurities, including truncated species (n–1, n–2) and depurinated products (G, A), demonstrating strong resolving power for subtle heterogeneities.

To enhance selectivity, hydrophilic interaction LC–MS (HILIC–MS) [5] was developed as an orthogonal, fluorinated-alcohol-free alternative. Systematic evaluation of stationary phase chemistry, solvent composition, salt concentration, pH, and temperature revealed retention mechanisms distinct from IP-RPLC. HILIC effectively separated truncated and oxidized species and improved discrimination of lipid-conjugated oligonucleotides from closely related impurities.

Forced degradation studies under controlled stress conditions assessed stability-indicating performance and selectivity toward degradation products.

Together, IP-RPLC–MS and HILIC–MS establish a multidimensional analytical framework that strengthens impurity profiling, stability evaluation, and structural characterization of therapeutic oligonucleotides, advancing robust and sustainable quality control platforms.

[1] Demelenne A. et al., J. Chromatogr. A, 2021, 1651, 462283.
[2] Al Bardawil S. et al., Anal. Chem., 2026.
[3] Goyon A. et al., Anal. Chem., 2020, 92, 5944–5951.
[4] Udu-Ituma S. et al., Pharmaceutics, 2023, 15, 1930.
[5] Lardeux H. et al., TrAC, 2024, 176, 117758..

Keywords: Therapeutic Oligonucleotides, LC-MS, IPRPLC, HILIC, Quality Control

T 03



Nazarii SABAT

Chemistry & Delivery

Next-generation Chemoenzymatic Synthesis of Therepeutic Oligonucleotides

Nazarii Sabat[1], Marcel Hollenstein

[1] *Institut Pasteur, CNRS UMR3523*

Therapeutic oligonucleotides have emerged as an important class of medicines for the selective modulation of RNA and gene expression. Their pharmacological performance often depends on chemical modifications that improve nuclease resistance, binding affinity, pharmacokinetics, and tissue-specific delivery. Efficient access to structurally diverse and precisely modified oligonucleotides therefore remains a major challenge for the development of next-generation therapeutics.

Current production relies mainly on solid-phase phosphoramidite chemistry or enzymatic synthesis using modified nucleoside triphosphates. While both approaches are powerful, they present limitations in terms of modification scope, stereochemical control, sustainability, and scalability. Recent advances in biocatalytic and chemoenzymatic oligonucleotide synthesis highlight the potential of combining chemical and enzymatic methods to overcome these limitations.[1]

In our lab - Bioorganic Chemistry of Nucleic Acids (Institut Pasteur-CNRS), we have developed a next-generation chemoenzymatic strategy that combines the versatility of chemical synthesis with the selectivity of enzymatic assembly, enabling efficient access to chemically modified oligonucleotides beyond the scope of conventional approaches.[2]

This platform has been further extended to the stereoselective synthesis of phosphorothioate-containing oligonucleotides, providing access to stereodefined backbone modifications of direct relevance to therapeutic development. [3] In parallel, we have explored enzymatic strategies for oligonucleotide functionalization with triantennary N-acetylgalactosamine (GalNAc), a key ligand for targeted delivery to hepatocytes.[4]

Together, these developments establish chemoenzymatic synthesis as a versatile and modular platform for the preparation of increasingly complex therapeutic oligonucleotide architectures.

References

[1] Bizat, P. N.; Sabat, N*.; Hollenstein, M*. ChemBioChem 2025, 26, e202400987.
[2] Sabat, N*.; Hollenstein, M*. et al. Nat. Commun. 2024, 15, 8009.
[3] Lecombe, E.; Sabat, N*.; Hollenstein, M*. et al. ChemRxiv 2026.
[4] Bizat, P. N.; Sabat, N*.; Hollenstein, M.* et al. ChemBioChem 2026, 27, e70454.

Keywords: Therapeutic Oligonucleotides, Chemoenzymatic Synthesis, Chemical Modifications, Galnac Conjugation

T 04



Laurence FAIVRE

PreClinical Dev & Translation

Ready for the trial, waiting for the drug: Lessons from an ERDERA ASO master protocol

Laurence Faivre[1], Alban Ziegler, Caroline Stevenel, Julia Berthod, Margot Wenzel, Amélie Cransac, Marc Bardou, Maxime Luu

[1] *CHU Dijon Bourgogne*

Antisense oligonucleotides (ASOs) are opening therapeutic possibilities for patients with ultra-rare genetic diseases, particularly those with neurodevelopmental disorders (NDDs) for which individualized molecular approaches may be feasible. However, translating these therapies into clinical trials remains challenging, especially when each genetic condition involves very small numbers of patients.

We proposed a multinational Phase I/II clinical trial program, with a master protocol using individualized ASO therapies in patients with genetic NDDs, aiming to answer the 2026 ERDERA (European Rare Diseases Research Alliance) call for funding (https://erdera.org/call/ctc2026/). Two disorders, KAND and PACS1-NDD, were selected as pilots, with the objective of establishing a common framework that could subsequently provide a scalable pathway for other genetic NDDs.

Within months, a European consortium was assembled across eight countries, bringing together disease experts, clinical centres, potential treatment hubs, patient networks and clinical-trial infrastructure. The master protocol combined a shared clinical, methodological and operational backbone with disease-specific components, allowing prospective recruitment and evaluation of individualized ASOs within a common trial structure.

During protocol development, despite a global consensus within the European consortium on the overall project, adaptations were required to accommodate the proposed development model of an ASO provider, particularly regarding efficacy measures, within-patient comparisons and evidence-generation objectives. Although these methodological issues appeared manageable, differences in development strategy could not be resolved before submission, leading to the provider's withdrawal and discontinuation of the project.

This experience suggests that a master protocol built around initial genetic NDD cohorts could provide a framework for extending individualized ASO trials to additional disorders, while maintaining shared methodological, regulatory and operational standards. European clinical expertise, infrastructure and patient networks are ready to support such an approach. The remaining challenge is to align this trial-ready framework with sustainable drug-development partnerships, ready for the trial, waiting for the drug.

Keywords: Rare Diseases, Clinical Trial, Antisense Oligonucleotides, Neurodevelopmental Disorders

T 05

Imad KANSAU

PreClinical Dev & Translation



Novel therapeutic/RNA therapy approach targeting inflammation of the intestinal mucosa

Imad Kansau[1], Philippe Hussein Kobeissy, Cécile Denève-Larrazet, Jean-Christophe Marvaud

[1] *Université Paris-Saclay*

Inflammatory Bowel Diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract that affect millions of people worldwide. IBD impact children as well as older adults (15-30 average set) with a higher risk of emerging colon cancer. Current therapies have improved patient outcomes but remain insufficient. MicroRNAs (miRNAs) have emerged as powerful regulators of gene expression in health and disease especially because of their ability to modulate multiple pathways at once and to act precisely. They function as fine tuners of cellular pathways by dampening, rather than completely silencing, gene expression. This property makes them attractive therapeutic candidates capable of modulating inflammation. Our mechanistic analysis in vitro and in vivo mice models revealed that miR-27a-5p mediates modulation of the NF-κB signaling pathway and acts as a potent regulator of both pathogen- and chemically induced intestinal inflammation, thus providing a robust proof-of-concept for a crucial role of miR-27a-5p in regulating intestinal inflammation. We will try to elucidate the precise anti-inflammatory mechanism of this miRNA within a translational R&D framework, to clarify how miR-27a-5p regulates the intestinal inflammatory response and to provide the way for its use as a therapeutic tool against inflammatory disorders.

Keywords: Inflammatory Bowel Diseases, IBD, Inflammation, microRNA, miRNA, NF-kB

T 06

Sebastien CAMPAGNE

PreClinical Dev & Translation



Rewiring RBM39 autoregulation overcomes resistance to molecular glue degraders

Sebastien CAMPAGNE [1]

[1] *INSERM U1212*

RNA Binding Motif Protein 39 (RBM39) is a cancer-associated splicing factor required for tumour cell survival. Current therapeutic strategies rely on aryl sulphonamides that induce RBM39 degradation via recruitment to the DCAF15 E3 ubiquitin ligase complex. However, resistance to RBM39-degraders occur when the cancer cell has low DCAF15 expression or when mutation fall at the molecular glue binding interface, explaining the low clinical efficacy of aryl sulphonamides. Here, we report a DCAF15-independent strategy to deplete RBM39 by targeting its autoregulatory splicing mechanism. We identify a splicing-switch antisense oligonucleotide (AS3a) that promotes poison exon inclusion in RBM39 transcripts, leading to nonsense-mediated decay and inhibition of RBM39 synthesis. When modified by 2'-metoxyethyl and phosphonothioate linkages, AS3a induces RBM39 depletion, impairs proliferation, and promotes apoptosis in colorectal cancer cells independently of DCAF15 expression. Systemic delivery using lipid nanoparticles enables tumour targeting and results in significant antitumour activity in xenograft models. Furthermore, AS3a is effective across multiple cancer cell types, including breast, liver and pancreas cancers. AS3a shows systematically stronger potency than RBM39-degraders. Our findings establish poison exon targeting as a precise and broadly applicable therapeutic strategy to disrupt RBM39 homeostasis in cancer and overcome resistance to specific small molecule degraders.

Keywords: RBM39 Autoregulation, Resistance To Molecular Glues, Poison Exon, Pan-cancer, Spliceosome

Abstracts
Posters

P 01

Koffi ASSA

Chemistry & Delivery

Access to inter-nucleoside c-c links by metal catalyzed cross-coupling reaction on insatured nucleoside.

Koffi Assa[1], Latifa Illia Magagi, Victor Monnot, Morgane De Robichon, Jacques Uziel, Marc Lecouvey, Evelyne Migianu-griffoni, Angelique Ferry

1 BioCIS, CY Cergy Paris Université

Nucleosides and nucleotides represent a ubiquitous family of biomolecules involved in many key processes in biology. Given their importance, it is not surprising that this class of molecules is emerging as prototypes for the discovery of bioactive compounds. In particular, the development of unnatural mimicry is an important area of research.[1] The modification on the 3' position of the furanoside ring is particularly interesting because it is the location of the phosphate bond in DNA/RNA polymers. The AZT drug bearing an azido group at this position attests to the importance of such derivatives. However, modulation at the 3' position is synthetically difficult according to current methods. We therefore propose to develop a new method to insert at the 3' position of the nucleoside a phosphorylated function bonded to the nucleoside by an unnatural carbon-carbon bond (C-C). This synthesis is carried out by metal-catalyzed coupling reaction between an unsaturated 3'-iodonucleoside and a metallic phosphonates reagents. The synthesis of small oligomers is planned in order to obtain mimics of oligonucleotides. This method provides a new pathway to access non-natural oligonucleotide analogues.

Keywords: Nucleoside, Metal-catalyzed Cross Coupling, Carbon-carbon Bond, Non-natural Oligonucleotides, Phosphonates

P 02

Karim BENSALAH

PreClinical Dev & Translation

Targeting fibrosis to enhance Antisense therapy in Duchenne Muscular Dystrophy

Karim Bensalah[1], Olivier Le Coz, Mathilde Doisy, Aurélie Goyenvalle

1 Université Paris-Saclay, UVSQ, Inserm, IMPROVE, U1357, 78000 Versailles, France

Duchenne muscular dystrophy (DMD) is a severe X-linked disorder caused by mutations in the DMD gene, leading to the absence of dystrophin protein. This results in progressive muscle degeneration and premature death due to cardiac and respiratory dysfunction.

Antisense oligonucleotide (ASO)-based therapies have emerged as a promising treatment strategy for DMD, and several ASOs have already received FDA approval. However, their therapeutic efficacy remains limited by poor tissue biodistribution and consequently low levels of dystrophin restoration.

While many efforts aim to improve ASO chemistry directly, we focused on fibrosis, a hallmark of DMD characterized by collagen accumulation that may further limit ASO diffusion within muscle tissue. Our strategy consisted of downregulating the Connective Tissue Growth Factor (CTGF), a key profibrotic factor, using conjugated siRNAs developed in collaboration with Alnylam Pharmaceuticals.

In vitro screening identified two lead candidates, AD75 and AD38, who achieved up to 93.5% CTGF knockdown and were selected for in vivo evaluation in mdx mouse model. We first characterized fibrosis in 9-month-old mdx mice and confirmed increased CTGF mRNA expression associated with significant collagen deposition compared to wild-type mice.

A single subcutaneous injection of CTGF siRNA (10 mg/kg) reduced CTGF mRNA levels by at least 30% in all muscles except in the diaphragm, with greater downregulation observed at 20 mg/kg. Although treatment with AD75 at 10 and 20 mg/kg did not reduce collagen deposition, AD38 at 20 mg/kg managed to significantly decrease it by a mean of 28%. Interestingly, a single subcutaneous injection of CTGF siRNA (10 mg/kg) in 4-month-old mdx mice not only reduced CTGF mRNA expression but also decreased collagen deposition by a mean of 25% in TA, GAS, QUAD and TRI.

Overall, these findings suggest that CTGF inhibition may help reduce fibrosis in dystrophic muscles and that early intervention may be required to achieve stronger therapeutic benefits.

Keywords: DMD-Fibrosis-ASO-siRNA-CTGF-mdx mice

P 03

Laura CHARNAY

PreClinical Dev & Translation

Targeting the splicing machinery with Splice-Switching Oligonucleotides to modulate exonisation of transposable elements and tumour immunogenicity

Laura Charnay[1], Blandine Baudon[1], Christophe Hong[1], Sandrine Heurtebise-Chrétien[1], Yago Arribas[1], Federico Marziali[1], Sebastian Amigorena[1], Marianne Burbage[1]

1 Institut Curie, Université Paris Sciences et Lettres, INSERM U932, 75005 Paris, France.

In immuno-oncology, a key goal is to bypass tumor immune escape. Cytotoxic T-cells are key immune effectors that recognize antigens presented on class-I major histocompatibility complex (MHC-I) by tumor cells via their receptor (TCR). Identifying antigens that could be targeted by anti-tumor vaccines or adoptive T-cell therapy is a promising strategy. The best characterized tumor antigens arise from mutations that are patient-specific, hindering therapy development. It is thus necessary to find other antigen sources. In tumors, abnormal splicing can result in the exonisation of transposable elements combined with an exon (JET). JET-derived peptides (pJETs) represent a recurrent and immunogenic antigen source presented on MHC-I. My PhD project explores the possibility to target pJET expression to overcome tumor immune escape mechanisms and improve immune detection of cancer cells.

To boost pJET expression and recognition by the immune system, we have developed a strategy that directly targets the splicing to modulate JET expression. To do this, we transfected tumor cells with splice-switching oligonucleotides (SSO). SSOs bind to a specific region of pre-messenger RNA and skew the splicing outcome.

To assess whether SSOs modulate tumor immunogenicity, we developed an in vitro tumor-T-cell co-culture system. The initial results showed that modulating pJET expression significantly altered T-cell activation. To validate this effect in vivo, we are developing SSO encapsulated in lipid nanoparticles (LNP-SSOs). The in vitro implementation of this technique shows promising results. The future objective will be to inject LNP-SSOs directly into a murine model tumor to increase pJET expression, and then to inject T-cells transduced with the specific TCR of the pJET of interest. This set-up mimics adoptive cell therapy (ACT) protocols that can be used in human patients.

Research developed in this project will result in an innovative, targeted, therapeutic solution to skew splicing reactions in vivo and improve immune tumor detection.

Keywords: Transposable Elements, Splicing, Tumor Antigen, Splice-switching Oligonucleotides, Lipid Nanoparticles

P 04

Nicolas CHOPIN

Chemistry & Delivery

Versatile N-Quencher and GalNAc Reagents for the Design of Modified and Targeted Oligonucleotides

Nicolas Chopin[1], Jean-Christophe Truffert, Sébastien Picard, Florent Bodinier, Tirtsa Kleinmann

1 Nucleosyn.

Designing modified and targeted oligonucleotides requires access to reliable reagents that can be easily incorporated into standard solid-phase synthesis. Here, we present a range of N-Quencher and GalNAc building blocks, which are available in CEP and CPG formats. These have been developed to support both probe construction and ligand-mediated delivery strategies.

The N-Quencher reagents were designed to provide a stable and synthesis-compatible quenching function that tolerates the full range of conditions used in solid-phase oligonucleotide assembly. Their protecting groups and electronic environment support clean couplings, reliable incorporation, and resistance to oxidation, sulfurization, and basic deprotection. Importantly, the quencher retains its photophysical properties after synthesis, enabling both internal and terminal placement with consistent and efficient fluorescence suppression across multiple fluorophores.

The GalNAc reagents were developed to provide a dependable ligand for hepatocyte targeting while remaining fully compatible with solid-phase oligonucleotide synthesis. Their protecting-group strategy and linker design were selected to preserve the integrity of the triantennary motif throughout coupling, oxidation, and deprotection steps. In both CEP and CPG formats, they incorporate cleanly and withstand standard synthesis conditions without loss of functionality. After assembly, the GalNAc units retain their binding properties and are suitable for terminal attachment or spacer-based positioning, enabling efficient and reproducible hepatocyte targeting in oligonucleotide constructs.

The synthetic routes were optimized to ensure consistent purity and compatibility with automated synthesizers. CEP derivatives incorporate cleanly during chain elongation, and the corresponding CPG supports allow straightforward terminal functionalization.

Together, these reagents provide a practical and scalable toolkit for researchers aiming to expand the chemical diversity and functional properties of oligonucleotide constructs, from diagnostic probes to targeted therapeutic candidates..

Keywords: N-quencher, Galnac, CEP/CPG Reagents, Targeted Oligonucleotides, Fluorescence Quenching

P 05

Julien DANG

PreClinical Dev & Translation

SKIPPing exons in genetic KIDney diseases with truncating mutations: a proof-of-concept in autosomal dominant polycystic kidney disease (ADPKD)

Julien Dang[1], Olivier Le Coz, Anouar Nabti, Marie Essig, Aurélie Goyenvalle

1 Université Paris-Saclay, UVSQ, Inserm, IMPROVE, U1357, 78000 Versailles, France

Autosomal dominant polycystic kidney disease (ADPKD), most often caused by a loss-of-function mutation in the PKD1 gene (78%), which encodes polycystin-1 (PC1), is the most common inherited kidney disorder and accounts for about 8% of end-stage renal disease cases. PC1 is a large 462-kDa transmembrane
glycoprotein expressed in the primary cilium of tubular cells, whose precise function remains only partially understood. Remarkably, restoring the expression of a short 200-amino acid C-terminal fragment in mice with inducible biallelic Pkd1 deletion prevented cyst formation and preserved renal function, highlighting the crucial role of the C-terminal domain. Among known PKD1 variants, ~60% are truncating mutations leading to loss of the C-terminal region and a more severe phenotype. We hypothesize that ADPKD patients carrying truncating PKD1 mutations could benefit from an antisense oligonucleotide (ASO)-mediated exon skipping strategy. These ASOs are designed to bind splicing regulatory sequences of mutant exons to promote their exclusion, thereby restoring the open reading frame and enabling the production of a shorter yet functional PC1, retaining its critical C-terminal region. Based on in silico analysis, we propose to target part of the extracellular domains encoded by 3 consecutive exons whose deletion maintains the reading frame, potentially correcting up to 25% of known PKD1 mutations. This strategy could subsequently be extended to other exon groups. Our project aims to provide a proof of concept using a human kidney tubule-on-chip model that reproduces cystogenesis from patient-derived cystic epithelial cells. This work could open a novel therapeutic avenue for ADPKD based on exonskipping–mediated functional restoration of PKD1.

Keywords: Polycystic Kidney Disease, Exon Skipping Therapy

P 06

Julie FAGIOLI

PreClinical Dev & Translation

Tricyclo-DNA antisense oligonucleotide compounds to tackle toxic CUGexp-RNA in a mouse model of Myotonic Dystrophy type 1

Julie Fagioli[1], Cyriaque Beley, Marine Geoffroy, Geneviève Gourdon, Luis Garcia, Denis Furling, Arnaud F.Klein

1 Centre de Recherche en Myologie, Sorbonne Université, INSERM

Recently, strategies and trials using antisense oligonucleotides (ASO) have shown therapeutic potential for neuromuscular disorders, including Myotonic Dystrophy type 1 (DM1), a rare disease characterized by myotonia, muscle weakness and wasting, as well as cardiac defects and caused by expanded CTG repeats in the 3'UTR of the DMPK gene. In DM1, ASO have been developed to target mutant transcripts containing expanded-CUG repeats (CUGexp), which form nuclear ribonucleoprotein aggregates or foci. These ASO aim to degrade pathogenic RNAs or prevent abnormal sequestration of MBNL RNA-binding protein associated with RNA toxicity. However, their efficacy after systemic administration remains limited. Here, we describe the use of a highly potent ASO chemistry, the tricyclo-oligodeoxynucleotide (tc-DNA) as a therapeutic antisense approach for DM1. These conformationnaly constrained DNA analogs show enhanced RNA binding, high biostability, exonuclease resistance and promising therapeutic effects in other neuromuscular diseases such as Duchenne muscular dystrophy. As a proof of concept, we evaluated a tc-DNA gapmer targeting mutant HSA-CUGexp transcripts in skeletal muscle of the HSA-LR DM1 transgenic mouse model expressing the Human Skeletal Actin (HSA) gene containing 220 CTG repeats. A single intravenous injection of tc-DNA-HSA gapmer induced near-complete degradation of CUGexp-RNA, with a decrease in the number and the intensity of CUGexp-RNA foci. Consistently, we observed a significant correction of alternative splicing defects characteristic of the disease in skeletal muscles, the normalization of the muscle transcriptome, and the suppression of myotonia. Beneficial molecular and functional effects lasted up for 6 months without adverse events. Moreover, repeated low-doses (1, 2.5 or 5mg/kg) also showed robust improvements, confirming the enhanced properties of these tc-DNA gapmer and their potential as therapeutic approach for DM1.

Keywords: DM1, Antisense Oligonucleotide, Tricyclo-DNA

P 07

Olivier LE COZ

PreClinical Dev & Translation

Cibler la vascularisation musculaire pour améliorer l'efficacité des approches ASO dans la dystrophie musculaire de Duchenne

Olivier Le Coz[1], Daniela Vieira Rodrigues, Hassan H. Fakih, Anastasia Khvorova, Aurélie Goyenvalle

1 Université Paris-Saclay, UVSQ, Inserm, IMPROVE, U1357, 78000 Versailles, France

La dystrophie musculaire de Duchenne (DMD) est une maladie neuromusculaire sévère causée par l'absence de dystrophine fonctionnelle, entraînant une dégénérescence musculaire progressive. Bien que les approches de saut d'exon par oligonucléotides antisens (ASO) et les thérapies géniques basées sur les vecteurs AAV (adeno-associated virus) aient démontré des résultats prometteurs, leur efficacité reste limitée par une distribution insuffisante aux muscles dystrophiques. Au-delà de la dégénérescence des fibres musculaires, la DMD se caractérise également par d'importantes altérations du réseau microvasculaire, notamment une diminution de la densité capillaire et une altération de la perfusion tissulaire, susceptibles de compromettre la biodistribution des thérapeutiques existantes.

Nous avons récemment démontré que l'amélioration de l'angiogenèse dans le muscle dystrophique augmente significativement l'accumulation des ASO, l'efficacité du saut d'exon et la restauration de la dystrophine dans le modèle murin mdx. Ces résultats suggèrent que la vascularisation musculaire constitue un déterminant critique de la réponse aux thérapies à base d'acides nucléiques.

Fort de cette preuve de concept, nous développons une stratégie innovante pro-angiogénique reposant sur l'inhibition, par ARN interférents (siRNA), de Flt-1 (VEGFR1), un régulateur négatif majeur de la signalisation du VEGF-A. Nos résultats préliminaires obtenus in vitro grâce à un siRNA ciblant la forme soluble de Flt-1 (sFlt-1) ont confirmé qu'une forte diminution de l'expression de Flt1 était associée à une augmentation de la prolifération, de la migration et de la survie des cellules endothéliales, confirmant le potentiel pro-angiogénique de cette stratégie. Suite à un large screening de siRNA ciblant à la fois les formes transmembranaire et soluble de Flt-1, nous avons identifié plusieurs candidats capables de down-réguler très efficacement l'expression de Flt-1 in vitro dans des cellules endothéliales C166. Les deux candidats les plus prometteurs ont été injectés dans des souris mdx et nous avons pu confirmer une down-régulation efficace de Flt-1 in vivo dans plusieurs muscles. Par la suite, le traitement combiné « siRNA Flt-1 et ASO » sera évalué in vivo dans le modèle murin mdx pour déterminer l'impact de cette association sur la distribution des ASO dans les muscles et sur la restauration de dystrophine.

Contrairement aux stratégies conventionnelles centrées sur l'optimisation des molécules thérapeutiques elles-mêmes, cette approche cible des mécanismes propres au tissu musculaire. Elle pourrait ainsi être applicable à un large éventail d'oligonucléotides thérapeutiques et, plus généralement, à différentes modalités de thérapies administrées par voie systémique.

Keywords: DMD, Dystrophine, siRNA, Saut D'exon, Vascularisation Musculaire, Angiogenèse, FLT-1 (VEGFR1)

P 08

Lisa LE DORTZ

Chemistry & Delivery

Improvement of Adeno-Associated Viruses (AAV) purification : an aptamer-based chromatography approach

Lisa Le Dortz[1], Mailys Pennors, Cécile Robin, Fabio Mirabella, Noelle Dufour, Alexis Bemelmans, Oumeya Adjali et Frédéric Ducongé

1 CEA FAR

Adeno-associated virus (AAVs) are the most widely used vectors for in vivo gene therapy. However, clinical translation requires high vector doses, making large-scale manufacturing a major bottleneck. In particular, downstream purification of AAV from cell lysates is critical, as residual impurities can compromise both product safety and efficacy. Affinity chromatography is the gold standard for large-scale AAV purification and mainly relies on Camelidae-derived nanobody ligands.
However, these antibodies present limitations, including high production costs and the need for acidic elution, which can affect capsid integrity and potency. Moreover, the emergence of engineered AAV capsids requires the fast development of new and specific affinity ligands, a process that remains time-consuming using conventional antibody-based approaches.
To overcome these challenges, we developed innovative synthetic affinity ligands based on nucleic-acid aptamers. Aptamers are short oligonucleotides selected in vitro through a molecular evolution process from libraries containing up to 1015 sequences. Their synthetic production, chemical stability and possible oriented immobilization make them highly attractive for chromatography applications. Using an in vitro selection strategy against AAV8 combined with high-throughput sequencing (HTS), several aptamers were identified. Their high affinity for AAV8 was demonstrated using biolayer interferometry. Efficient AAV capture was demonstrated directly from cell lysates, and optimized elution at physiological pH enabled particle recovery. Altogether, these results highlight aptamer-based chromatography as a promising alternative for scalable AAV purification, with strong potential to reduce the cost of gene therapy products.

Keywords: Aptamer, Purification, Bioproduction

P 09

Pilar MAESTRE FERNÁNDEZ-FLORES

PreClinical Dev & Translation

Targeting intracellular trafficking proteins to improve ASO therapeutic activity

Pilar Maestre Fernández-Flores[1], Aris Gaci, Grégory Menchon, Rémy Pedeux, Aurélie Goyenvalle

1 Université Paris-Saclay, UVSQ, Inserm, IMPROVE, U1357, 78000 Versailles, France

Antisense oligonucleotide (ASO) therapy has emerged as a promising therapeutic approach for genetic diseases, including neuromuscular disorders such as Duchenne muscular dystrophy (DMD). Despite the clinical approval of several ASOs, their therapeutic efficacy remains limited by inefficient intracellular trafficking and, in particular, endosomal entrapment. Only a small fraction of internalized ASOs escapes the endolysosomal compartment to reach its intracellular target, while the majority remains trapped and is ultimately degraded, contributing to the need for high and repeated dosing.

To overcome this limitation, we aim to identify intracellular trafficking proteins that restrict productive ASO release and whose inhibition could enhance target engagement. Starting from 18,883 candidate proteins identified through a genome-wide CRISPR knockout screen, candidates were prioritized based on their inhibitory potential, overlap with publicly available screening datasets, and involvement in endosomal trafficking. This identified several candidates, including ATP6V1G1, a subunit of the V-ATPase complex involved in endolysosomal acidification.

ATP6V1G1+/- DMD myoblast clones were generated by CRISPR-mediated gene editing and validated at the genomic, mRNA, and protein levels. ATP6V1G1+/- myoblasts were then treated with 2'MOE- and LNA-modified splice-switching oligonucleotides targeting DMD exon 51, and exon-skipping efficiency was quantified by RT-qPCR.

ATP6V1G1 downregulation increased exon 51 skipping by up to 70% compared with ATP6V1G1+/+ control myoblasts, with enhanced activity observed for both ASO chemistries. To investigate the cellular mechanisms underlying this effect, LysoTracker-based analyses were performed to assess changes in lysosomal acidification, abundance, and morphology following ATP6V1G1 downregulation.

Although ATP6V1G1 primarily serves as a proof-of-concept target due to its limited translational potential, these findings validate endolysosomal trafficking modulation as a strategy to enhance ASO activity. Ongoing characterization of additional candidates with greater therapeutic potential may identify actionable targets to improve ASO intracellular bioavailability and ultimately increase their therapeutic index.

Keywords: DMD, ASO Efficacy, Endosomal Entrapment

P 10

Ana PENA VELLAZ

PreClinical Dev & Translation

Developing Oligonucleotide Based Therapies for H ABC Leukodystrophy

Yalda Sedaghat, David Rigby, Andreea Dreau, Sebastien Benizri, Rosaria Remelli, Jacopo Oieni, Matthias Billaud, **Ana Pena Vellaz**[1], Valentina Sassano, Annalisa Mercuri, Giovanni Pellegrini, Silvia Corbioli, Pedro Royero Rodriguez, Shadaan Zulfiqar, Laure Humbert, Dan Williams, Hilary Brooks

1 Evotec (France) SAS

Evotec, in collaboration with SynaptixBio, is leveraging its fully integrated, end-to-end oligonucleotide drug discovery platform to develop a mutation-agnostic antisense oligonucleotide (ASO) therapy targeting TUBB4A mRNA. The goal of this program is to treat Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum (H-ABC), a severe, rare monogenic leukodystrophy caused by sporadic heterozygous TUBB4A mutations. H-ABC leads to progressive motor impairment and cognitive decline in children, and there are currently no disease-modifying treatment options available.

End-to-End Discovery and Preclinical Development Platform
Developing CNS-targeting oligonucleotides presents severe technical challenges, including progressive neurodegeneration, early disease onset, and the necessity for direct delivery into the cerebrospinal fluid. Evotec addresses these obstacles by deploying an expansive internal drug discovery pipeline that seamlessly spans the entire developmental spectrum, from initial candidate sequence design and chemical optimization all the way through to IND-enabling preclinical development. Here, we present the initial part of the discovery workflow:

Bioinformatics & Design: Utilizing advanced computational workflows to generate, evaluate, and optimize ASO candidates at the sequence level.
Comprehensive In Vitro Safety Assays: To mitigate key toxicity risks before animal testing, Evotec deploys a suite of predictive assays, including Caspase-based hepatotoxicity profiling, Bjab assay for immunogenicity, and microelectrode array (MEA) electrophysiology to flag toxic sequences.
In Vivo safety Translation: Seamlessly connecting functional electrophysiological screening with early tolerability profiling to streamline candidate selection.

Key Outcomes
Combining in vitro safety, bioinformatic design, and targeted in vivo tolerability drastically reduced the number of acutely toxic ASOs synthesized and advanced into animal models. This integrated strategy highlights Evotec's end-to-end capabilities in de-risking complex oligonucleotide candidates, significantly decreasing reliance on extensive animal testing while efficiently driving a novel CNS-directed therapy for H-ABC toward clinical development

Keywords: Antisense Oligonucleotides, Oligonucleotide Therapeutics, Hypomyelination With Atrophy Of The Basal Ganglia And Cerebellum (H-AB, Central Nervous System, End-to-end Drug Discovery Platform

P11

Maria QUEROL CANUT

PreClinical Dev & Translation

Understanding what is driving antisense oligonucleotide biodistribution in the central nervous system

Maria Querol Canut[1], Arnaud François, Aurélie Goyenvalle, Hélène Tran, Hélène Aerts

1 Neurology Therapeutic Area, R&D Servier Paris-Saclay Institut, Gif sur Yvette, France

Antisense oligonucleotide (ASO) therapeutics are emerging as a potentially transformative approach for the treatment of certain brain disorders that currently lack effective therapeutic options. However, the pharmacokinetics, biodistribution, and brain uptake of ASOs are not yet well characterized. Gaining a deeper understanding of their distribution and uptake in the central nervous system (CNS) could significantly advance the development of new ASOs targeting specific pathologies.

My project aims to investigate the factors that drive the differential biodistribution of ASOs observed in the CNS following an intrathecal injection. The hypothesis is that this variation in distribution and uptake is driven by protein binding and chemical modifications. To address his question, I plan to undertake a cross-functional project, using various resources and collaborating with several departments.

For this project, I will conduct a pull-down assay using non-human primate cerebrospinal fluid to identify which proteins bind (or not) to specific, well-characterized ASOs that have shown superior distribution. The goal is to uncover patterns or families of candidate proteins associated with enhanced ASO uptake (or non-uptake). I will also perform an in vivo study to assess the impact of chemistry in ASO biodistribution using a wildtype mouse model. I want to see the effect of ASO chemical modifications in the biodistribution of each oligo. I will then perform RNA Scope assays to target the ASO sequence and see the location of each ASO on the brain, as well as quantifying it in different areas using a fluorescent beacons technique.

This comprehensive and transversal approach aims to enhance our understanding of ASO behavior in the CNS and pave the way for the development of targeted therapies for brain disorders.

Keywords: Antisense Oligonucleotide, Biodistribution, Central Nervous System

P 12

Gael QUESSEVEUR

PreClinical Dev & Translation

Beyond Target Knockdown: Integrating Clinical, Functional and Pathological Endpoints in the Preclinical Development of CNS-Targeting Antisense Oligonucleotides

Gael Quesseveur[1], Pierluigi Fant

1 Charles River Laboratories SA, France

Antisense oligonucleotides (ASOs) have emerged as a transformative therapeutic modality for neurological disorders, enabling selective modulation of disease-associated targets within the central nervous system (CNS). While advances in oligonucleotide chemistry and CNS delivery have accelerated clinical development, successful translation requires more than demonstrating tissue exposure and target knockdown. A comprehensive understanding of the functional and pathological consequences of target modulation is essential to support clinical relevance, safety assessment, and regulatory decision-making.

This presentation will discuss key considerations for the nonclinical development of CNS-targeting ASOs, with a particular focus on the integration of molecular, clinical, functional, and pathological endpoints within translational development programs. The role of preclinical species commonly used in neuroscience research, including rodents and non-human primates, will be reviewed in the context of evaluating pharmacological activity, biodistribution, and safety.

Particular emphasis will be placed on the clinical evaluation of animals following CNS-directed administration. Routine clinical observations, neurological examinations, and Functional Observational Battery (FOB) assessments provide critical information for detecting, characterizing, and monitoring neurological effects throughout drug development. These endpoints contribute not only to the identification of potential adverse findings but also to the interpretation of pharmacological activity and translational relevance.

The presentation will also address the importance of local tolerance assessment and neuropathological evaluation in characterizing the safety profile of CNS-administered ASOs. Histopathological examination of the CNS and administration sites, together with molecular and anatomical investigations, provides complementary information to support risk assessment and interpretation of nonclinical findings.

Practical examples will illustrate how biodistribution, target engagement, clinical observations, neurobehavioral outcomes, local tolerance, and pathology endpoints can be integrated to strengthen translational confidence and support clinical development.

Keywords: Antisense Oligonucleotides, Central Nervous System, Functional Observational Battery, Neurological Examination, Local Tolerance, Neuropathology, Biodistribution, Target Engagement, Translational Science

P 13

Mathieu REPELLIN

PreClinical Dev & Translation

Lipid Nanoparticles for Therapeutic Antisense Oligonucleotide Delivery to Skeletal Muscle in Myotonic Dystrophy Type 1

Mathieu Repellin[1], Laurine Merriadec, Laurent Coudert, Lise Morizur, Fabrice Brunel, Pierre-Yves Dugas, Michael Smietana, Isabella Scionti, Cécile Martinat, Laurent Schaeffer, Arnaud Jacquier, Giovanna Lollo

1 LAGEPP - Université Claude Bernard Lyon 1

Myotonic dystrophy type 1 (DM1) is an inherited neuromuscular disorder caused by a CTG repeat expansion in the DMPK gene. The resulting toxic CUG-expanded transcripts sequester MBNL proteins, leading to widespread splicing defects. Although antisense oligonucleotides (ASOs) can target pathogenic RNA, their therapeutic potential is limited by inefficient delivery to skeletal muscle. Here, we investigated a patented lipid nanoparticle (LNP) platform for nucleic acid delivery and ASO-mediated therapeutic activity in muscle models relevant to DM1.

LNPs were produced by microfluidic mixing and loaded with either eGFP mRNA as a delivery reporter or a therapeutic CAG gapmer ASO. Delivery was assessed in C2C12 myoblasts, human DM1 muscle cells, and 3D-engineered human skeletal muscle tissues. mRNA transfection was quantified by flow cytometry, while ASO activity was evaluated by RT-qPCR and RNA fluorescence in situ hybridization.

Both formulations exhibited an average diameter of approximately 150 nm and a polydispersity index below 0.2. mRNA-LNPs achieved transfection efficiencies of up to 80% in immortalized DM1 muscle cells. Robust, homogeneous reporter expression was also observed throughout 3D-engineered muscle tissues, supporting effective delivery within these constructs. Therapeutic ASO-LNPs significantly reduced DMPK transcript levels and nuclear CUG RNA foci in DM1 muscle cells. Ex vivo, ASOs distributed throughout isolated muscle fibers, with prominent intracellular and nuclear localization.

These findings support the potential of this LNP platform for delivering therapeutic ASOs to skeletal muscle and reducing pathological RNA accumulation in DM1. Further studies are underway to evaluate in vivo therapeutic efficacy.

Keywords: Antisense Oligonucleotides, Nanoparticles, Gene Delivery, Muscular Dystrophy

P 14

Brune VIALET

Chemistry & Delivery

New glycosyl conjugates to address biological targets: an approach leading to the downregulation of KRAS proteins

Julien Verget, Julien Verget, Faith Kivunga, Virginie Baylot, Jean Dessolin, Haythem Abda, Biju Majumbar, Léa Mulot, Henri Barry, Patricia Korczak, **Brune Vialet [1],** and Philippe Barthélémy*

1 ARNA INSERM U1212

Glycosylation of oligonucleotides [1] facilitates the recognition of nucleic acids by extracellular receptors. GalNac ligands have been introduced in siRNA designs to target the asialoglycoproteins receptors on the surface of hepatocytes [2]. From this approach, we have developed new glycosyl conjugates. We have successfully prepared several glycosylated monomers that can be inserted anywhere inside an oligonucleotide sequence.

This glycosylation strategy has presented promising results in AsPC1 pancreatic cell lines. The GLUT1 receptor is overexpressed at the surface of KRAS-driven tumors [3]. In silico studies have demonstrated that our glycosyl conjugate binds to the GLUT1 receptor. Antisense sequences (ASO) were designed to target the KRAS oncogene. The most active ASO sequence was selected by western blot. Lipid and glycosyl conjugates were incorporated on the ASO during automated synthesis. These modifications lead to a significant downregulation of KRAS expression [4]. This study exhibits multi-conjugations with both sugar and lipid. This approach can tackle challenges in the field of therapeutic oligonucleotides.

Keywords: Oligonucleotide, Synthesis, Characterization

P 15

Brune VIALET

Chemistry & Delivery

ARNA OligoTech Solutions: Oligonucleotides synthesis and characterization platform

Kyllian Larrue, **Brune Vialet** [1]

1 ARNA INSERM U1212

The ARNA OligoTech Solutions platform, managed by the ARNA unit (INSERM U1212 – University of Bordeaux), supports academic teams and industrial partners in their research and development projects by providing expertise in custom oligonucleotide synthesis. Drawing on historical expertise in the field of nucleic acids, it designs and functionalizes bespoke sequences with properties tailored to specific applications, particularly therapeutic ones, through advanced molecular modification strategies.

The quality of the synthesized molecules relies on rigorous purification processes and analytical control, notably through liquid chromatography coupled with mass spectrometry (LC-MS). Complementary biophysical characterization methods, such as circular dichroism and UV-melting, DLS, and native gels (PAGE and agarose), enable the assessment of their structure, conformation, and stability.

Building on 30 years of fundamental research at INSERM's ARNA laboratory, ARNA OligoTech Solutions combines scientific expertise and advanced technologies to support your oligonucleotide projects. We aim to encourage scientific exchange, foster synergies, and develop new collaborations within the SFOT community.

Keywords: Oligonucleotide, Synthesis, Characterization

P 16

Alban ZIEGLER

PreClinical Dev & Translation

Establishment of the AnDDI-ASO consortium to structure antisense oligonucleotide clinical trials for rare neurodevelopmental disorders in France

Alban Ziegler[1], Laurence Faivre, Maxime Luu, Amélie Cransac, Julia Berthod, Patrick Edery, Zakia Nejjari, Marie-Dominique Galibert, Sandra Mercier, Michaela Semeraro, Grégory Pugnet, Vincent Laugel, Marc Bardou

1 CHU Toulouse

Antisense oligonucleotide (ASO)–based therapies represent a rapidly expanding and promising therapeutic avenue for rare genetic diseases, particularly in the field of neurodevelopmental disorders. These approaches usually require repeated intrathecal administrations, entailing substantial logistical constraints and the involvement of highly trained and committed multidisciplinary teams. Within the French rare disease network AnDDI-Rares, which focuses on developmental/neurodevelopmental disorders, we have established the AnDDI-ASO Consortium. This multidisciplinary consortium brings together clinical geneticists, neurologists, pharmacologists, clinical trialists and pharmacists with the shared objective of structuring ASO evaluation and improve access in France. The consortium aims to (i) identify and coordinate centers capable of conducting ASO trials, including those involving highly resource-intensive sham procedures; (ii) to identify translational researchers in France who could join and contribute to the consortium; (iii) engage industrial partners to support ASO development and manufacturing; (iv) develop training initiatives for healthcare professionals in this emerging field; (v) collaborate with the recently organized network of French Clinical Investigation Centers (CICs) specialized in advanced therapy medicinal products (CLEIO). Beyond the national level, AnDDI-ASO seeks to (vi) interface with other groups developing ASOs such as N-Lorem to facilitate access to patient-specific ASOs and explore opportunities for targeted clinical trials or basket trial designs, (vii) connect with other ASO European consortia to promote data sharing and to build collaborative European projects, particularly for ultra-rare conditions for which single-country trials are challenging. This initiative aims to create a coordinated framework to accelerate equitable access to ASO therapies for patients with rare neurodevelopmental disorders.

Keywords: Antisense Oligonucleotide, Rare Genetic Neurodevelopmental Disorders, AnDDI-ASO Consortium

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MERCI POUR VOTRE PARTICIPATION !

NOUS ESPÉRONS QUE VOUS AVEZ PASSÉ UNE EXCELLENTE JOURNÉE

