POST EVENT PROCEEDINGS

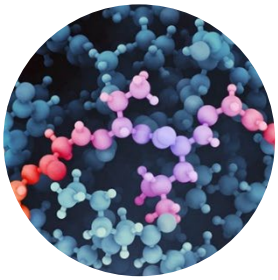
Biologics 2023

30 - 31 March 2023 | London, UK

Oxford Global was proud to host the return of our ever-popular annual Biologics event, consisting of the **16th Annual Proteins & Antibodies Congress**, **10th Annual Peptides & Oligonucleotides Congress** and the inaugural **Sustainability Chemistry Congress**.

Attendees engaged with esteemed pharmaceutical & biotech representatives as well as thought-leaders from academic & research institutions onsite and benefited from attending over 140 presentations. We welcomed over 330 delegates for two days of cutting-edge scientific sessions and case studies bringing the latest biologics developments to the forefront of research.

We are delighted to present you with concise and insightful summaries of presentations delivered by prominent thought leaders in this comprehensive post-event proceedings document.



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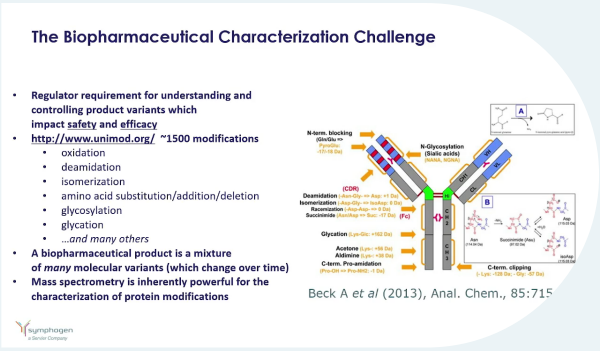
PRE-EVENT DAY, TRACK 1:

Antibody Engineering & Computational Updates

Challenges And Solutions In MS-Based Characterization Workflows For Biologics

DAN BACH KRISTENSEN, Principal Scientist, Symphogen

Dan Bach Kristensen, a Principal Scientist at Symphogen, discusses the challenges and solutions related to their mass spectrometry-based characterization workflows for biologics.



Kristensen provides an overview of their platform and how separation techniques can be combined with mass spectrometry for QC testing, real-release, and stability testing. He highlights their move towards a cloud-based solution for data storage and retrieval.

The speaker delves into their protein ams and peptide mapping workflows, focusing on glycosylation analysis. He explains the process of removing glycoforms and obtaining adeglycosylated forms, which is now done in 96-well formats for lead selection studies. Chromatography techniques are employed to assess sample stability and the loss of basic forms.

Terminal licencing and glycophorin modifications during fermentation are discussed, highlighting challenges in mass spectrometry due to overlapping natural isotope distributions. The importance of sub-unit workflows and intact reverse phase chromatography is emphasized.

Kristensen introduces a study involving eight antibodies, NIST USP maps, internal peptides, and different digestion protocols. Using optimized digestion methods, they achieve improved data interpretation by reducing missed cleavages.

He also discusses the use of lower-retentivity columns for chromatography, particularly C4 columns, to identify impurities in QC testing. The transition from C18 to C4 columns shows no loss of small hydrophilic peptides, and concerns about selectivity on C4 columns are addressed.

The presentation touches upon intact mass analysis, showcasing Symphogen's comprehensive approach to biologics characterization using mass spectrometry-based techniques.

Track Keynote Address: Sustainable Peptide Manufacture?

STEVEN MCINTYRE, Peptide Process Development Manager, Almac Group

Steven McIntyre, Peptide Process Development Manager at Almac Group, discusses sustainability in peptide manufacturing.

He introduces the concept of sustainability in peptide manufacturing and mentions the focus of the morning session on this topic.

McIntyre highlights the use of process mass intensity (PMI) as a metric for measuring greenness. He explains that traditional peptide synthesis processes generate a lot of waste that is not recycled, leading to high PMI scores.

He discusses the use of binary solvents as an alternative to DMF (dimethylformamide) and their positive impact on yield and purity, although there was a slightly lower yield.

Reducing solvent usage and buffer consumption in the production of semi-synthetic cyclic peptides is addressed. Continuous chromatography is mentioned as a significant contributor to reducing buffer consumption.

Nano-filtration is presented as a non-thermal means of concentration that is particularly suitable for peptides.

The group's research on making solid-phase peptide chemistry more sustainable is highlighted, including optimizing resin loading and protection groups for amino acids.

McIntyre emphasizes the importance of reducing steps in chromatography and optimizing resin loading to impact PMI.

In conclusion, he discusses the challenges of finding a module that could work for optimizing multiple peptides in terms of sustainability.

Developing Novel Biologics - Smart Target Selection To Facilitate Focused Early Clinical Development

TOMASZ SITAR, Director, CMC, JJP Biologics

Tomasz Sitar, Director of CMC at JJP Biologics, discussed their approach to developing novel biologics. JJP Biologics is a startup focusing on unique biological entities, with one project targeting IgA-related diseases.

IgA antibodies play a role in autoimmune diseases by activating neutrophils, causing tissue damage. JJP Biologics aimed to target the CD89 receptor to prevent this activation, potentially addressing multiple indications.

Neutrophils, constituting 60% of lymphocytes, were chosen due to their abundance and lack of targeted therapies.

Their research focused on linear IgA bullous disease, where IgA antibodies cause tissue damage by activating neutrophils via CD89 binding.

They conducted experiments validating their approach, leading to orphan drug designation approval. Their therapy's final format was IgG to avoid FC-related reactions.

In conclusion, JJP Biologics developed a novel monoclonal antibody for IgA-mediated diseases, advancing it to clinical trials with a concise set of analytical methods.

AI/ML To Accelerate Engineering

VLADIMIR GLIGORIJEVIC, Senior Director of AI/ML, Genentech

Vladimir Gligorijevic, Senior Director of AI/ML at Genentech, discusses the application of AI and machine learning to accelerate protein engineering.

He introduces Protein Design, a collaboration between various researchers, aimed at addressing challenges in protein design. Gligorijevic emphasizes the difficulty of searching through the vast space of possible protein sequences and mentions rational design and directed evolution as approaches.

He introduces the Manifold Sampler, a machine learning method trained on all possible protein sequences to learn the manifold of proteins in the universe. The functional guiding system and its three main problems – binary identification, optimization, and de novo design – are discussed.

Gligorijevic highlights the importance of proper data, including developability data, for these methods to work effectively.

The impact of machine learning on antibody discovery is explored. Gligorijevic describes the goal of replacing animal immunization campaigns with machine learning models in the antibody discovery process. The steps involve selecting the best sequences using active learning and using generative models to design antibodies.

He explains the generative models used by Protein Design, including manifold sampler, gradient-based auto-encoders, and hybrid models incorporating physics-based information. Gligorijevic illustrates the process with an example of generating antibodies with comparable binding affinity to trastuzumab.

The generalizability of the model for various epitopes is discussed, emphasizing the need for more data to enhance the model's ability to work for any design.

In conclusion, Gligorijevic touches on the redesign of the H3 loop in antibodies as an example of their work in de novo design using AI and machine learning

Track Keynote Address: Better Biologics by Design: PKPD Modelling Tools To Support Selection Of Optimal Affinity Of Antibodies In Drug Discovery

YOUSSEF HIJAZI, Distinguished Scientist, DMPK, Sanofi

In the keynote address titled "Better Biologics by Design: PKPD Modelling Tools To Support Selection Of Optimal Affinity Of Antibodies In Drug Discovery," Youssef Hijazi introduces the significance of antibody therapies, highlighting their success and advantages over small molecules in immunotherapy. He discusses the impact of antibody engineering and presents insights from FDA-approved antibodies, emphasizing their role in various therapeutic areas.

Hijazi delves into PKPD binding models for antibodies, exploring the relationships between affinity and the efficacy of immune checkpoint inhibitors and immune checkpoint inhibitor trastuzumab. He outlines the alignment between in vivo and in vitro processes, accounting for administration schedules, target elimination rates, and complex dissolution. The presentation includes examples from Santa Monica to illustrate the utility of PKPD modeling.

Target accumulation and suppression are addressed, focusing on antibodies targeting cytokines and soluble targets. The distinction between target occupancy and target suppression is explained, and dynamic simulations reveal the intricate interplay between parameters, such as target half-life and affinity.

The speaker emphasizes the importance of assumptions for predictive models, covering aspects like target baseline, affinity variability, and complex clearance. He underlines the necessity of PKPD modeling for determining the relationship between antibodies and their therapeutic effects. The need for animal studies to validate in vitro-in vivo relationships is highlighted.

In the context of specific T-cell engagers, the role of PKPD modeling is discussed, particularly in affinity tuning for soluble targets. The talk concludes with the significance of high doses for membrane targets.

Discovery Of Antibodies Against A Complex Target

TREVOR WATTAM, Associate Director, GSK

Trevor Wattam, an Associate Director at GSK, presented a case study on the discovery of antibodies against a complex target. He discussed various challenges and approaches in antibody discovery, focusing on GPCRs and ion channels. The key points from the presentation include:

Trevor Wattam introduced himself as being part of the antibody lead discovery team at GSK, with a focus on in vivo antibody discovery.

The presentation highlighted the challenges of targeting complex proteins like GPCRs and ion channels, which require antigenically relevant, stable, and native conformational immunogens.

The speaker discussed multiple methods employed in antibody discovery, including immunizing transgenic mice, next-generation sequencing (NGS), yeast display platforms, and phage display libraries.

A case study involving a GPCR target was presented. The goal was to deplete target cells in solid tumors, and the project required antibodies with specific pharmacology, half-life, and binding properties.

Various techniques were explored, such as immunizing transgenic mice with modified peptides, generating hybridomas, NGS sequencing of B cell populations, yeast display, and phage display libraries.

Despite applying multiple methods, finding antibodies that met all the desired criteria proved challenging. Different techniques yielded varying degrees of success, and in some cases, the desired specificity and binding affinity were not achieved.

The challenges highlighted the complexity of targeting certain proteins and the need for a diverse range of approaches to increase the chances of success.

The presentation emphasized that the discovery of functional antibodies for challenging targets is complex and requires a combination of different platforms and techniques.

The speaker concluded that while success can't be guaranteed for every target, persistence and a combination of methods can lead to the discovery of viable antibody candidates.

The presentation highlighted the intricacies of antibody discovery against complex targets, showcasing the multifaceted nature of the process and the importance of flexibility in approaching such challenges.

DAY ONE, TRACK 2:

Emerging Techniques For Bioanalysis & Characterisation And Quality Control Systems

Emerging Mechanisms Influencing The Disposition & Clearance Of Bispecific Antibodies

AMITA DATTA-MANNAN, Associate Vice President, Eli Lilly & Company

In this presentation by Amita Datta-Mannan, Associate Vice President at Eli Lilly & Company, she discusses the emerging mechanisms influencing the disposition and clearance of bispecific antibodies. She highlights the importance of bispecific antibody design and their clearance and disposition, with a focus on two case studies.

1. **Background and Importance of Bispecific Antibodies:** Amita Datta-Mannan discusses the significance of bispecific antibodies (bispecifics) in targeting multiple disease pathways simultaneously. These antibodies offer advantages over traditional monospecific antibodies due to their ability to bind to two different targets and their potential for extended efficacy in complex diseases.
2. **Bispecific Formats and Mechanisms Influencing PK:** Different formats of bispecific antibodies are explored, focusing on fusion-based formats. Amita explains that the mechanisms governing the clearance of monospecific antibodies are also involved in bispecific antibody disposition. These mechanisms include target-mediated drug disposition, Fc gamma receptor binding, glycosylation, neonatal Fc receptor (FcRn) interactions, and physicochemical properties.
3. **Case Study 1: scFv-Based Bispecific Clearance:** Amita presents a case study involving single-chain variable fragment (scFv)-based bispecific antibodies. She discusses the differences in clearance between two scFv-based bispecifics, one with acceptable clearance and the other with faster clearance. By conducting biodistribution studies, she finds that the faster clearance is due to increased intracellular degradation within tissues, leading to higher urinary elimination. This is attributed to differences in FcRn binding and cellular recycling.
4. **Case Study 2: Protein Fusion-Based Bispecific Clearance:** A second case study is presented, involving protein fusion-based bispecific

antibodies. Here, three bispecifics with protein fusion at different positions show varying clearance rates. Amita demonstrates that the bad PK profile of one bispecific is related to liver sinusoidal endothelial cells (LSECs), likely due to increased hydrophobic interactions. However, the exact molecular mechanism remains unclear.

5. **Key Takeaways:** Amita emphasizes the complexity of bispecific antibody clearance, affected by fusion partner structure, fusion position, and physicochemical parameters. Rational design and thorough characterization of different bispecific formats are essential for optimal in vivo clearance and disposition.

Overall, the presentation highlights the need for a comprehensive understanding of the factors affecting bispecific antibody disposition and clearance, which is crucial for their successful development as therapeutic agents.

Comprehensive Selection Strategies For Novel Inhalable Protein Therapeutics

EVA-MARIA HANSBAUER, Head of Protein Analytics, Pieris Pharmaceuticals GmbH

Eva-Maria Hansbauer, from Pieris Pharmaceuticals, discussed strategies for inhaled protein therapeutics with a focus on Pierce 220 for lung fibrosis treatment. Highlights include:

1. Introduction to Anticalins: Small, stable proteins derived from lipocalins.
2. Pieris' Focus Areas: Immuno-oncology and respiratory diseases.
3. Respiratory Pipeline: Pieris' phase-two candidate, Alaric kebap, and ctgf for lung fibrosis.
4. Developability Approach: Using data-driven predictions to assess candidate suitability.
5. Pierce 220: An inhaled ctgf antagonist for lung fibrosis treatment.
6. Inhaled Therapeutics Advantages: Targeting lungs directly, convenience, and avoiding systemic effects.
7. Stability and Aerosol Behavior: Critical for inhaled protein therapeutics.
8. Pharmacokinetics Studies: Pierce 220 showed lung-specific concentration.
9. Biodistribution: Pierce 220 distributed well in fibrotic lungs.
10. Key Messages: Anticalin proteins hold promise, and Pierce 220 is a potential best-in-class therapy for lung fibrosis.

The talk emphasizes the potential of inhaled protein therapeutics for lung diseases and rigorous candidate selection

Accelerating Drug Discovery: A Refresh Of The Lead Panel Generation Phase Within Biopharm Discovery

GONCALO SILVA, Senior Scientist, GSK

Goncalo Silva, a Senior Scientist at GSK, presents on the topic of accelerating drug discovery, particularly focusing on the lead panel generation phase within biopharmaceutical discovery. He describes the transformation of GSK's process from a traditional manual approach to a more semi-automated and high-throughput platform.

The presentation starts by outlining GSK's motivation for change, which included investing in new capabilities for biotherapeutics discovery, incorporating automation and AI/ML models to accelerate timelines, and expanding the scope of molecule analysis. Silva's team's role in this transformation was to establish a more efficient process for generating antibody lead panels.

Silva breaks down the key components of their new process, which involve transitioning from transient transfection to stable cell lines, incorporating automation at various stages such as expression and purification, and utilizing magnetic beads for improved purification efficiency. He explains how their approach also aligns with GSK's broader digitalization efforts, integrating data management, tracking, and analysis through their digital LIMS systems.

The challenges faced and lessons learned include maintaining sample quality, repeatability, and flexibility as they work with a wider range of molecules. Silva also highlights the importance of using off-the-shelf solutions and adopting a modular approach for better adaptability and troubleshooting. He concludes by acknowledging the collaborative efforts of various departments and teams that contributed to the successful implementation of the new lead panel generation process.

Glycosylation Challenges In Biopharmaceutical Manufacturing

HORST BIERAU, Associate Director - Head CMC Science & Intelligence, Merck Group

Horst Bierau discusses the challenges of glycosylation in biopharmaceutical manufacturing. He emphasizes the importance of glycosylation in the production of biologics, particularly monoclonal antibodies, which are a rapidly growing sector in the industry. Glycosylation impacts the stability, clearance rate, and functional properties of these molecules.

Bierau highlights the complexity of glycosylation, as antibodies exhibit a distribution of various glycan forms, each with different biological effects. He discusses the implications for manufacturing, including the selection of production hosts and the need to closely monitor glycan profiles to ensure they are close to the physiological state.

Two case studies are presented. The first focuses on high mannose glycans, which can enhance antibody-dependent cell-mediated cytotoxicity (ADCC) but decrease thermal stability and increase the risk of aggregation. The second case study discusses non-human sugar N-glycolylneuraminic acid (NGNA), which can lead to immunogenicity and clearance issues due to pre-existing antibodies in humans.

Bierau mentions various approaches to analyze glycosylation, including mass spectrometry, peptide mapping, and fluorescent labeling of glycans. He also discusses strategies to engineer glycosylation profiles through metabolic, genetic, or chemoenzymatic modifications.

In summary, glycosylation is a critical quality attribute for biopharmaceuticals, impacting efficacy, safety, stability, and pharmacokinetics. It is influenced by various factors in the manufacturing process, making consistency, comparability, and biosimilarity challenging. Advanced analytical methods and engineering strategies are essential to address these challenges and ensure product quality.

Structural Characterisation And Developability Assessment Of Novel Biologics

MARTIN EBNER, Director, Analytical Development, Immunocore

The talk by Martin Ebner, Director of Analytical Development at Immunocore, focuses on structural characterization and developability assessment of novel biologics, particularly T cell receptor (TCR) based therapeutics. Ebner discusses the challenges in biologics development, emphasizing the importance of early development strategies and improved approaches to characterization for reducing failure rates and improving clinical success. Immunocore's INTACTS platform, which converts TCRs into soluble molecules, is introduced as a novel biologic. The advantages of TCR-based therapeutics, including their ability to target a wider range of proteins, are highlighted.

Ebner emphasizes the significance of early product characterization in the biopharmaceutical development cycle. He discusses three structural characterization approaches for derisking: improved sequence liability assessments using mass spectrometry and predictive algorithms, native mass spectrometry for variant characterization, and higher-order structure characterization using crosslinking mass spectrometry. These approaches aid in identifying and mitigating potential issues early in the development process.

The talk concludes with the key takeaway that understanding critical quality attributes and using improved characterization methods can lead to better decision-making during candidate selection, resulting in fewer failures and improved drug molecules for patients.

Better Biologics By Design: Developability Risk Assessment And Strategies To Mitigate Chemical Degradation Hot Spots

MELANIE FISCHER, Head of Assays and Analytics, Sanofi

In her presentation, Melanie Fischer, the Head of Assays and Analytics at Sanofi, discusses their integrated developability strategy for multi-specific molecules, focusing on identifying and mitigating chemical degradation hotspots. Sanofi's large molecule research platform operates globally, covering a range of biologic candidates. Fischer describes their diverse modality space, from antibodies to multi-specific formats, fusion proteins, and more. Their

workflow involves target selection, lead nomination, optimization, and final candidate selection, all with a keen emphasis on developability.

Fischer delves into chemical degradation, particularly focusing on side chain degradation of amino acids. She explores the impact of degradation on physical-chemical attributes, structure, binding affinity, pharmacokinetics, yields, and immunogenicity. Sanofi employs in silico tools, in vitro assays, and tailored studies to assess chemical stability. Fischer shares an example where they grafted CDR sequences into different IgG-related formats to predict the impact of chemical stability on multi-specific molecules. She emphasizes the importance of addressing chemical degradation early and categorizes mitigation into engineering and CMC strategies, considering factors like impact on function, timeline, and regulatory compliance.

Fischer presents a case study where Sanofi's colleagues in Boston engineered variants of an antibody targeting CD52 to counteract aspartic acid isomerization and glycine-mediated degradation while retaining binding affinity. The presentation underscores the significance of understanding chemical degradation pathways and employing effective strategies to enhance the developability and stability of biologic candidates.

Better Biologics by Design: Integrated Bioanalytical Approaches For Complex Modalities

SAMUEL PINE, Global Head of Bioanalysis and Immunogenicity, DMPK, Sanofi

Samuel Pine, the Global Head of Bioanalysis and Immunogenicity at DMPK Sanofi, delivered a presentation on integrated bioanalytical approaches for complex biologics. He emphasized the challenges of measuring and characterizing the increasingly complex biologics and how advanced tools and strategies are needed for this purpose. Key points from his talk include:

1. Modality Complexity: Biologics have evolved into various modalities, including antibodies, bispecifics, fusions, small molecules, ADCs, conjugates, oligos, LMPs, gene therapies, and cell-based therapies, presenting new challenges for measurement and characterization.
2. Bioanalysis Significance: Bioanalysis involves measuring drugs in biological matrices to understand exposure, pharmacokinetics, and pharmacodynamics. Integrated strategies are essential for addressing these aspects effectively.
3. Strategic Considerations: Bioanalytical strategies need to account for differences in biologic characteristics, such as Ada, total assay

measurements, multi-specific compounds, target levels, and assay limitations.

4. Complexity of Biologic Samples: Biologic samples in vivo undergo metabolism, target binding, clearance, and can develop antibodies against the biologic, leading to the presence of various drug species and ADA.
5. Multiple Assays: The complexity of modern biologics often requires multiple assays, even for a single compound, to measure different aspects accurately, resulting in a broader toolbox of analytical methods.
6. Toolbox of Analytical Methods: The current state of bioanalysis involves using various platforms, including LCMS, ligand binding assays (LBAs), and PCR for nucleic acid modalities, to address the diverse needs of characterizing complex biologics.

Samuel Pine's presentation highlighted the need for integrated approaches and a diverse toolbox of analytical methods to effectively measure and characterize complex biologics, ensuring their safety and efficacy in clinical settings.

DAY ONE, TRACK 3:

Peptide Chemistry, Computational Approaches & Novel Application Areas

Expanding The Non-DNA Encoded Amino Acid Palette For Peptide Optimization

LEONARDO DE MARIA, Principal Scientist, AstraZeneca

The speaker, Leonardo de Maria, a Principal Scientist at AstraZeneca, presents a collaborative research effort that aims to expand the range of non-DNA encoded amino acids for peptide optimization. De Maria underscores the unique position of peptides bridging chemistry and biology. The project involves structural insight, amino acid enumeration, virtual screening, and affinity enhancement to discover non-natural amino acids that improve peptide-protein interactions and binding affinities. The talk emphasizes the significant chemical space available and showcases computational results suggesting enhanced binding. Considerations of solubility, immunogenicity, and synthesis feasibility are discussed. De Maria expresses the intention to further explore and validate these findings through experimental testing.

Discovery Of AMG133, A Novel GIPR Antagonist Antibody/GLP-1 Peptide Multispecific Conjugate For The Treatment Of Obesity

LES MIRANDA, Executive Director, R&D & CMC Operations, Amgen

Les Miranda, an Executive Director at Amgen, gave a presentation on AMG133, a novel therapy for the treatment of obesity. He highlighted the approach of following biology first and then selecting the modality, and discussed the discovery and engineering of AMG133. The molecule is a hybrid multispecific conjugate that combines an antibody antagonist for the GIP receptor with a GLP-1 peptide agonist. The talk covered genetic insights supporting GIP receptor antagonism, the role of receptor dimerization, peptide and antibody engineering, conjugation techniques, pharmacokinetics, and the results of a Phase 1 clinical trial. The presentation showed promising results, including dose-proportional weight loss of around 14.5%, lasting up to 150 days beyond

the final dose. The adverse effects were mild and well-tolerated. The molecule has progressed to Phase 2 trials.

Glucose-Sensitive-Insulin-Stimuli-Triggered-Bioactivity

THOMAS HOEG-JENSEN, Scientific Director, Novo Nordisk

Thomas Hoeg-Jensen, Scientific Director at Novo Nordisk, presents "Glucose-Sensitive-Insulin-Stimuli-Triggered-Bioactivity." Insulin's historical use in diabetes treatment is introduced, with its isolation from animal pancreas a century ago. The two types of diabetes are mentioned. An insulin variant responsive to broad glucose levels was first published in '79, with subsequent developments benefiting numerous individuals. The concept of creating an inactive single-chain version through cross-linking is discussed.

Regarding glucose binding, large glucose binding proteins are less suitable for drugs. Instead, small weak acid molecules forming covalent bonds with glucose are explored. Response to low glucose levels is detailed, and alternatives to boronic acids for binding glucose are sought. A '12 publication presents a glucose-binding structure functional in organic solvents.

Scaling the macronutrient involves around 10 steps, with challenges related to carboxylates addressed using orthogonal chemistry. Nobel laureates Milldale, Sharples, and Petrosian are noted for their contributions. Glucose affinity of the insulin construct is measured using native MMS, with a binding constant of two millimolar due to competition between glucose and the clinical side.

Receptor affinity data for the compound is presented, showing variation with rising glucose levels. The interaction between insulin and the insulin pump receptor is discussed. Lower glucose levels lead to the macrocycle adopting a closed structure, influencing glucose drop significantly.

The application of this concept in meal and patient settings is outlined. The strong glucose factor's potential for addressing hyperglycemia is highlighted, even demonstrated in a pig model. Compounds similar to 20-15 can be developed into practical drugs. A partnership with organic chemistry provider Park FPGA-NIX is mentioned, aiding in building blocks and services.

However, the expensive nature of EFmc's macrocyclization, primarily due to high dilution, is acknowledged. In summary, Hoeg-Jensen's presentation introduces Glucose-Sensitive-Insulin-Stimuli-Triggered-Bioactivity, detailing its historical context, molecular approaches, practical implications, and potential for addressing diabetes.

DAY ONE, TRACK 4:

Oligonucleotide Discovery: Chemistry, Analytical Development, Delivery

GalAhead™: A Novel Therapeutic GalNAc-RNAi Platform To Downregulate Single And Multiple Genes

JIM WETERINGS, Senior Director, Head of Technology Development, Sirnaomics

The presentation discussed Sirnaomics' GalAhead™ platform, which is a novel therapeutic technology for gene regulation using GalNAc-RNAi. The presenter, Jim Weterings, introduced the company's global presence and funding, highlighting its success stories in RNAi oncology. The GalAhead™ platform is designed for targeted delivery of therapeutic molecules, specifically siRNAs, using the GalNAc moiety. This approach utilizes a natural pathway to deliver siRNAs to hepatic cells for effective gene downregulation. The presentation focused on two aspects of the GalAhead™ platform:

1. **MX RNA (Miniaturized Single Targeting RNA Triggers):** This involves a hairpin-like structure, where a single strand with a GalNAc moiety attached folds back on itself to form a duplex. It interacts with the RISC complex, leading to cleavage of the target mRNA. The advantage of this design is its efficiency, requiring fewer synthesis steps and having a lower risk of off-target effects.
2. **m mu RNA (Multi Unit Multi Targeting RNA Triggers):** This approach involves designing RNA constructs that target multiple positions on a gene or multiple genes simultaneously. The concept of "Sollbruchstelle," meaning "weak spot," was introduced. These constructs break apart to release individual RNAi triggers that independently target different positions or genes. This approach can address complex diseases with multiple pathways involved.

The presentation provided experimental data showing the efficacy and potency of these RNAi triggers in in vitro and in vivo studies. The company's pipeline includes various targets, including Factor 11, APC free, and others, with plans to progress them into clinical trials.

The presentation highlighted the advantages of Sirnaomics' GalAhead™ platform, including potent activity, ease of manufacturing, potential for combination therapy, and a solid intellectual property position. The company also utilizes a humanized liver mouse model for efficient evaluation of candidate compounds. Overall, the GalAhead™ platform represents a promising approach for targeted gene regulation with potential applications in various therapeutic areas.

Digital Tools For Oligonucleotide Process Development

MARTIN OLBRICH, Principal Scientist, Process Research, F. Hoffmann-La Roche

Martin Olbrich, discusses the importance of digital tools in the development of oligonucleotides, with a focus on improving productivity, cost-efficiency, and sustainability in the pharmaceutical industry. He emphasizes the need to deliver medicines at cheaper prices while maintaining quality. Olbrich explains that the automation of key processes in oligonucleotide development, such as synthesis, purification, desalting, and isolation, provides an ideal opportunity for digital transformation.

He describes specific digital tools and instruments used in the process, highlighting their capabilities for data collection and analysis. These tools enable real-time monitoring of reactions, immediate response to alarms or deviations, and the ability to compare data across multiple experiments. Olbrich also mentions the integration of analytical data into a centralized database, which allows for efficient data retrieval and analysis.

Overall, Olbrich emphasizes the significant benefits of digital tools in improving the efficiency, quality, and cost-effectiveness of oligonucleotide process development, ultimately contributing to the pharmaceutical industry's broader goals of providing affordable and sustainable healthcare solutions.

Introduction To RNA Activation And Its Use To Restore Normal Function To Cells

NAGY HABIB, Founder & Chair of Scientific Advisory Board, MiNA Therapeutics

In this presentation, Dr. Nagy Habib, Founder & Chair of Scientific Advisory Board at MiNA Therapeutics, discusses RNA activation and its applications in

various medical fields. He introduces different types of RNA, such as mRNA, siRNA, and saRNA. He explains that saRNA (small activating RNA) is used to increase gene expression, while siRNA is used to decrease it. SaRNA is particularly relevant for diseases with low gene expression, while siRNA is suitable for diseases with high expression.

Dr. Habib discusses the mechanism of saRNA, which involves opening up chromatin to allow transcription to occur. He presents studies demonstrating how saRNA can be used to upregulate genes related to autoimmune diseases and cancer treatment, particularly focusing on its effects on myeloid cells and tumor-associated macrophages. He also explains saRNA's potential for addressing fatty liver and genetic diseases, such as hereditary diseases that involve gene activation.

Dr. Habib highlights the success of their saRNA treatment in animal studies and clinical trials, particularly in liver cancer, solid cancers, and fatty liver disease. He emphasizes the importance of selecting the right patients for treatment based on predictive signatures and discusses collaboration efforts to advance this field of research.

Overall, the presentation showcases the potential of saRNA as a powerful tool for gene activation and its promising applications in treating a range of diseases.

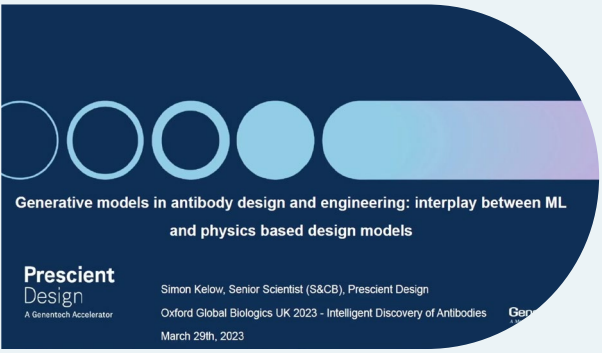
DAY TWO, TRACK 1:

Computational Tools, AI/ML & Structural Approaches In Engineering

Generative Models In Antibody Design And Engineering: Interplay Between ML And Physics Based Design Models

SIMON KELOW, Senior Scientist, Structural and Computational Biology, Prescient Design, Genentech

Simon Kelow, a Senior Scientist at Prescient Design | Genentech, presented on generative models in antibody design and engineering. He discussed the interplay between machine learning (ML) and physics-based design models, emphasizing the following key points:



1. **Prescient Design**: Prescient Design, acquired by Genentech in 2021, focuses on antibody molecule research, specifically in epitope diversification, optimization, and de novo design, utilizing available antibody sequence data.
2. **Motivation for Generative Models**: Kelow highlighted the traditional protein design paradigm, discussing advancements in structure prediction and the role of large language models like transformers in sequence proposal.
3. **Generative Models in Antibody Design**: Kelow explained various generative models used in protein design, including statistics-based, latent space models, and diffusion models, all aimed at learning complex data patterns.
4. **Energy-Based Models**: The Modular Manifold Sampler, an energy-based model, was introduced as a sample-efficient alternative for generative protein design, which can be guided by external classifiers.
5. **Hybrid Design Approach**: Kelow proposed a hybrid approach that combines generative models with traditional structure-based design. This method involves generating sequences using generative models and refining them with physics-based models like Rosetta.
6. **Experimental Results**: Results were presented, demonstrating the performance of generative models with and without structural

information. The hybrid approach showed promise, achieving higher binding affinity in a benchmark dataset.

7. **Future Directions**: Kelow discussed ongoing research, particularly diffusion models that simultaneously design sequence and structure, offering exciting prospects for antibody design projects.

Simon Kelow's presentation highlighted the potential of combining generative and physics-based models in antibody design, with promising results and future directions in the field.

Multi Specific Antibodies, Cell Engagers & Other New Modalities

BEPO(r) For The Long-Acting Delivery Of Proteins

ANDREA GONELLA, Senior Research and Innovation Associate, MedinCell France

Andrea Gonella, a Senior Research and Innovation Associate at MedinCell France, discusses "BEPO(r) for the Long-Acting Delivery of Proteins." MedinCell is a drug delivery company that specializes in the BEPO technology, which stands for "Biodegradable Injectable Polymer." BEPO is used to formulate various molecules, including small molecules and proteins, for controlled and sustained release. Andrea's presentation provides an overview of the BEPO technology, its applications in protein delivery, and a case study involving a bispecific antibody.

The BEPO technology involves creating a formulation that consists of solvents, copolymers, and the active pharmaceutical ingredient (API). The copolymers are a combination of hydrophilic and hydrophobic polymers that allow for controlled release of the API. When the formulation is injected, it undergoes a phase separation mechanism that leads to the encapsulation of the API, ensuring sustained release.

Andrea discusses the challenges in long-acting injectables for proteins and compares the limitations of existing technologies like microspheres and solid implants. BEPO offers advantages such as the ability to retain proteins in specific locations (e.g., synovial fluid for localized treatment) and control release kinetics.

The presentation provides an example of formulating a bispecific antibody using BEPO technology. The bispecific antibody is designed to target both a tumor antigen and a T-cell co-receptor. The BEPO-formulated bispecific antibody showed a sustained release profile in vivo, achieving a longer half-life and controlled release compared to standard administration methods. Moreover, in a tumor growth control experiment, the BEPO-formulated bispecific antibody demonstrated better tumor growth inhibition and enhanced T-cell infiltration at the tumor site.

Andrea emphasizes the importance of studying not only the drug delivery system but also the protein's structure and potential immune reactions. He

also highlights that BEPO can be administered subcutaneously or locally, providing flexibility in delivery routes. The presentation concludes by inviting further discussion and exploration of BEPO technology's applications in protein delivery.

T Cell Engager Design And Combinations

DAN SNELL, Vice President, Translational Sciences, Numab Therapeutics

In this presentation by Dan Snell, Vice President of Translational Sciences at Numab Therapeutics, he discusses T cell engager design and combinations. Numab Therapeutics is a clinical-stage multispecific antibody development company based in Zurich, Switzerland.

Dan talks about two T cell engagers in their pipeline:

1. Nm 28: It's a mesothelin-targeted T cell engager designed for the treatment of various cancers, including mesothelioma, pancreatic cancer, ovarian cancer, triple-negative breast cancer, and non-small cell lung cancer. The molecule is designed to preferentially target tumor cells with high mesothelin expression while sparing normal cells with low mesothelin expression. This specificity leads to a more significant therapeutic window.
2. Nm 32: This is a rule one-targeted T cell engager intended for treating both solid tumors (such as ovarian, lung, pancreatic, and breast cancers) and hematological malignancies (including B cell lymphomas and chronic lymphocytic leukemia). Unlike Nm 28, Nm 32 is monovalent for rule one but includes a serum albumin binder and a CD3 engager. This design allows it to effectively target cells with both high and low rule one expression.

Dan also presents data supporting the efficacy of these T cell engagers in preclinical models and highlights the promising results of combining them with a PD-L1/PD-1 checkpoint inhibitor, 4-1BB (CD137) stimulator. The combination approach demonstrates increased potency in stimulating T cells.

In summary, Numab Therapeutics is developing innovative T cell engagers targeting mesothelin and rule one with the potential for improved safety profiles and enhanced therapeutic outcomes, especially when used in combination therapies.

DAY TWO, TRACK 4:

Therapeutic Development Of Oligonucleotides & Antisense Oligonucleotides

Developing An Effective Analytical Control Strategy For Oligonucleotide Drug Substances

AHMED ELMEKAWY, Associate Principal Scientist - Oligonucleotides Project Lead, AstraZeneca

The speaker, Ahmed Elmekawy from AstraZeneca, discussed the development of an effective analytical control strategy for oligonucleotide drug substances. He emphasized the importance of building a comprehensive strategy to ensure product quality and safety. The speaker introduced three control points: process control, analytical control, and release control. He highlighted the significance of defining critical quality attributes for the product and developing corresponding control points. The speaker also discussed tools such as a ragged analysis that links quality attributes with control points and a visualization tool to understand impurity behavior during manufacturing stages. Additionally, he touched on the importance of understanding starting materials and applying in-process testing. The speaker emphasized the complexity of setting appropriate drug substance specifications, considering various factors such as regulatory guidelines, safety, efficacy, and historical data. He concluded by stressing the need for a thorough understanding of the product and process to establish an effective analytical control strategy.

Preclinical Development Of A Lipophilic- Conjugated antimiR To Treat Myotonic Dystrophy Type 1 (DM1)

BEATRIZ LLAMUSI TROÍSI, Chief Executive Officer & Chief Scientific Officer, ARTHEx Biotech

Artex Biotech, under the leadership of CEO Beatriz Llamusi Troísi, is making significant strides in the development of a groundbreaking treatment for Myotonic Dystrophy Type 1 (DM1), a rare and currently untreatable neuromuscular disease. Their innovative drug, known as ATX One, targets a crucial player in DM1's pathological mechanism, namely MiR-23b.

The journey towards ATX One's development has entailed thorough preclinical work, involving extensive testing in animal models. This has allowed Artex Biotech to demonstrate the drug's remarkable efficacy. Importantly, the company has garnered orphan drug designation from both the FDA and EMA, signaling the recognition of ATX One's potential in addressing this pressing unmet medical need.

Artex Biotech is now gearing up for pivotal milestones with planned IND (Investigational New Drug) and CTA (Clinical Trial Application) submissions slated for 2023. The forthcoming clinical trial will primarily focus on assessing the safety and tolerability of ATX One in patients, a critical step in advancing its development. Additionally, the trial will include secondary objectives such as evaluating pharmacokinetics, monitoring MBL (Muscleblind-Like Protein) levels, and measuring the splicing index. These parameters will provide essential insights into the drug's mechanisms of action and therapeutic effects.

Notably, Artex Biotech's commitment extends beyond safety and efficacy assessments. The trial will also explore functional outcomes, including measures of muscle function, and investigate potential extra-muscular effects. Given that DM1 can manifest in various ways, including cognitive dysfunction, the study's comprehensive approach seeks to uncover the full spectrum of ATX One's impact on patients' lives.

In summary, Artex Biotech's mission revolves around addressing high unmet medical needs, and their remarkable progress in the DM1 field holds the promise of a potentially groundbreaking treatment for this severe and currently untreatable disease.

Modulation-Of-RNA-Processes-Using-Antisense-Oligonucleotides

ISABEL AZNAREZ, Co-Founder and Senior Vice President, Discovery Research, Stoke Therapeutics

Isabel Aznarez, Co-Founder and Senior Vice President of Discovery Research at Stoke Therapeutics, presents "Modulation-Of-RNA-Processes-Using-Antisense-Oligonucleotides." Stoke Therapeutics employs tango technology for targeted gene output augmentation in severe genetic diseases and autosomal dominant disorders. The presentation outlines how tango works in the context of these conditions.

The speaker discusses a disease caused by a 50% reduction in functional protein due to non-productive splicing events. Around 50% of human protein coding genes have such events. The focus is on selecting alternative splicing

events that lead to premature termination codons and degradation. Approximately 2900 gene disease-causing genes exhibit non-productive splice events. One example highlighted is Dravet syndrome, an epileptic encephalopathy with severe comorbidities.

Clinical trial design and results are explored. A single dose of SDK 001 upregulates protein levels in Dravet syndrome mice. Toxicology studies in non-human primates are detailed. The trial of stosomar-2 demonstrates a reduction in convulsive seizures and improved comorbidities.

Stoke Therapeutics addresses Leber's hereditary optic neuropathy (LHON), the most common inherited optic nerve disorder globally, caused by mitochondrial dysfunction. Upregulating Nopa-1 in retinas is discussed, presenting improved mitochondrial respiration in vitro. Clinical candidate STK 002 is mentioned for non-human primates.

The presentation concludes by noting clinical trials of the compound in the UK. Stoke Therapeutics' work in utilizing antisense oligonucleotides for RNA process modulation, demonstrated through tango technology, holds promise in addressing severe genetic diseases and disorders.