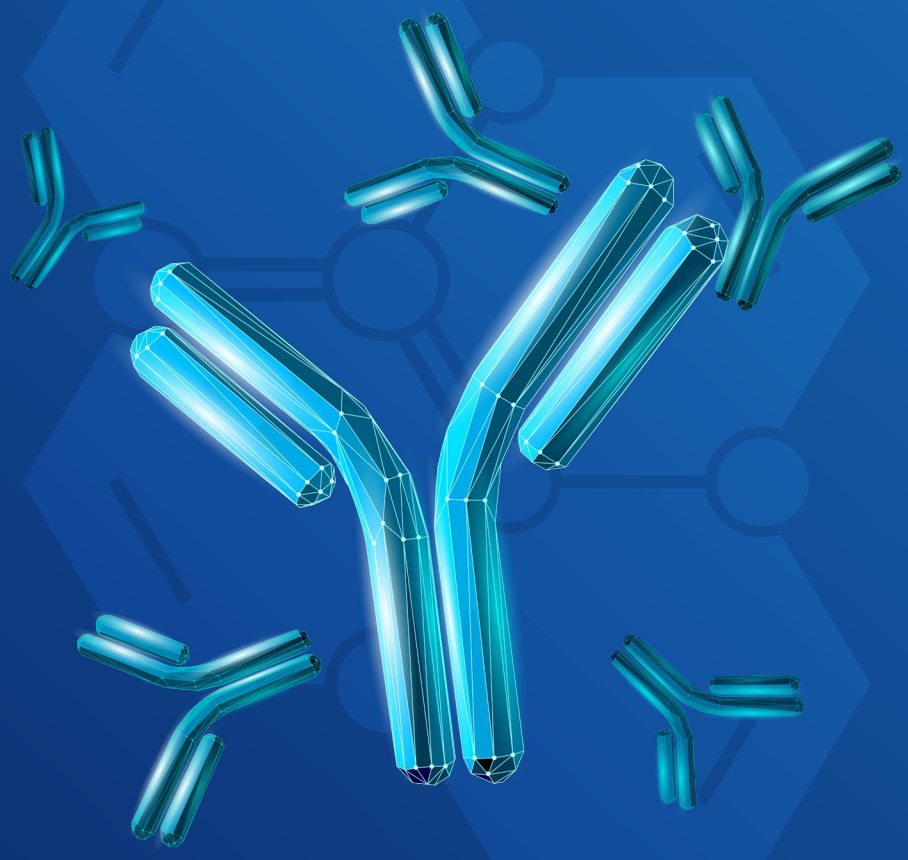
CASE STUDY REPORT

Accelerating Biologics Discovery & Development Through Transformative Technologies & Overcoming Strategic Challenges

A Concise Report Featuring Insights From The Prominent Thought Leaders Of Biologics 2024



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Introduction

In today's rapidly evolving pharmaceutical landscape, characterized by relentless innovation and technological advancements, the quest for novel therapies and improved treatment modalities is more dynamic than ever. This market report serves as a compass, navigating through the intricacies of the industry's cutting-edge technologies, where breakthroughs in antibody discovery, biopharmaceutical analytics, and cancer therapy are shaping the future of medicine.

At the heart of our exploration lie three central themes, each representing a cornerstone in the ongoing revolution of biologics development:

AI-Powered Breakthroughs: Shaping the Future of Antibody Discovery & Engineering

Harnessing the formidable potential of artificial intelligence (AI) and machine learning (ML), pharmaceutical pioneers are redefining the boundaries of antibody discovery and engineering. Through the lens of recent advancements, we illuminate the transformative impact of AI-driven approaches on the speed, precision, and efficacy of therapeutic antibody development.

Exploring Analytical Frontiers: Advancements Shaping Biopharmaceutical Innovation

Venturing into the forefront of analytical development within the biopharmaceutical realm, thought leaders unveil groundbreaking methodologies for characterizing biotherapeutics, optimizing protein stability, and pioneering innovative approaches to glycoprofiling and bioconjugation. Through their collective efforts, we gain insight into the transformative potential of analytical techniques in shaping the future landscape of biopharmaceutical innovation.

Revolutionizing Biologics: Innovations in Immunogenicity Profiling and Cancer Therapy

The pharmaceutical landscape witnesses a paradigm shift towards precision medicine and therapeutic innovation, fueled by groundbreaking advancements in immunogenicity profiling and cancer therapy. From predictive algorithms for immunogenicity assessment to novel antibody-based therapies targeting cancer, these innovations are reshaping the landscape of biologics development and cancer treatment strategies. Our experts delve into these transformative advancements, exploring their implications and potential to redefine the future of medicine.

As we embark on this journey, we draw upon the wealth of insights gleaned from the recent Biologics 2024 event, a convergence of over 650 industry professionals dedicated to driving forward the frontiers of biologics discovery and development. Through a comprehensive analysis of presentations, data, and expert perspectives, this report aims to provide a nuanced understanding of the current landscape, strategic challenges, and emerging opportunities in the realm of biologics.

Lucia Simmen,
Digital Content Creator, Oxford Global

Contents

Key Speakers Include

Rebecca Croasdale-Wood, Director Augmented Biologics Discovery & Engineering, AstraZeneca

Vladimir Gligroijevic, Senior Director of AI/ML, Genentech

Emma Jenkins, Director of Expression and Developability, Alchemab Therapeutics

Key Speakers Include

Sophia Karagiannis, Professor of Translational Cancer Immunology and Immunotherapy, Kings College London

Poonam Vaghela, Scientist, Scancell Ltd

Christian Reichen, Director, Molecular Partners

Key Speakers Include

Thierry Besson, Senior Scientist II, Novartis

Sandra Prior, Principal Scientist, MHRA

Thomas Nittoli, Senior Director, Regeneron

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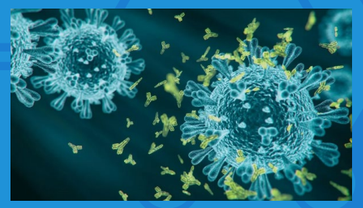
Computational Tools and AI/ML for Antibody Engineering

Overcoming the Hurdles: Navigating the Challenges of Bioconjugate Development

AstraZeneca Buys T Cell Engager for $100 Million



AI-Powered Breakthroughs: Shaping the Future of Antibody Discovery & Engineering

A recent study by MarketDigits highlighted that the antibody discovery market is projected to reach USD 13.7 Billion by 2030, growing at a CAGR of 9.0% during the forecast period of 2023-2030. The future is here: AI-powered breakthroughs in antibody discovery are here to highlight the increasing demand for targeted therapeutics and the adoption of personalised medicine.

Source: Globe Newswire

Integrating-AI-Into-Biologics-Discovery-Workflows

Rebecca Croasdale- Wood's (Director Augmented Biologics Discovery & Engineering, AstraZeneca) presentation at the event delved into the evolving landscape of drug discovery, particularly within AstraZeneca's biologics division, against the backdrop of increasing integration of AI and machine learning. She emphasized a shift from traditional wet lab approaches towards more in silico methodologies, underscoring the pivotal role of AI and machine learning in expediting the identification of therapeutically significant medicines.

AstraZeneca's strategy revolves around four core elements: high-throughput data generation platforms, validation processes, automation, and advanced data science capabilities. Rebecca explained how these elements work synergistically to enhance biologics discovery workflows, ultimately aiming for more efficient generation of high-quality leads.

The implementation of AI and machine learning is central to AstraZeneca's approach. Rebecca highlighted their utility in predicting various parameters critical for drug discovery, such as binding affinity, specificity, and developability. She elaborated on how machine learning models are trained on vast datasets encompassing antibody sequences, experimental data, and structural information, enabling the prediction of key properties essential for lead optimization.

A significant aspect of AstraZeneca's approach is the utilization of deep screening workflows, enabling comprehensive interrogation of antibody libraries. Rebecca emphasized the capacity of deep screening to identify hits that conventional methods might overlook, thereby enriching the pool of potential lead candidates. Additionally, she underscored the role of machine learning in guiding library design and hit selection, showcasing its potential to streamline the drug discovery process.

Rebecca also addressed the importance of early identification of developability issues and the integration of high-throughput assays for screening liabilities. AstraZeneca's approach involves leveraging machine learning to validate predictions and optimize lead candidates, ensuring that developability challenges are addressed proactively.

In summary, Rebecca's presentation outlined AstraZeneca's commitment to leveraging AI and machine learning technologies to drive innovation in biologics discovery. She underscored ongoing efforts to integrate these technologies across various stages of the drug discovery process, with the overarching goal of accelerating the development of clinically impactful medicines.

Exploring And Exploiting The Mammalian Display Filter

Bryce Nelson's (Antibody Engineering Lead, Orion Pharma) presentation explored Orion Pharma's focus on biologics and the specialized field of mammalian display experiments. He provided insights into the evolving landscape of antibody development, highlighting the crucial role of developability in ensuring the success of therapeutic antibodies. By leveraging a combination of phage and mammalian display techniques, Orion Pharma aims to optimize the selection process for antibodies with desirable properties.

Bryce emphasized the importance of the mammalian display filter, which serves as a critical mechanism for identifying antibodies that exhibit favourable characteristics, such as stability and functionality. This filter acts as a quality control measure, ensuring that only antibodies with the highest potential for success are selected for further development.

To enhance their antibody selection process, Bryce discussed their approach of using various reagents to assess specific attributes, such as aggregation propensity and thermostability. By systematically evaluating these properties, Orion Pharma can better understand the behaviour of candidate antibodies and make informed decisions during the selection process.

Furthermore, Bryce highlighted the integration of machine learning into their workflow, signalling a shift towards more data-driven approaches in antibody discovery and design. By capitalising on the power of machine learning algorithms, Orion Pharma aims to streamline the antibody development process and identify optimal CDRs (complementarity-determining regions) that exhibit superior developability profiles.

Overall, Bryce's presentation underscored the importance of integrating advanced techniques and technologies, such as mammalian display, reagent-based assessments, and machine learning, to drive innovation and accelerate the development of next-generation therapeutic antibodies at Orion Pharma.

Antibodies From Resilient Individuals: A Novel Approach For Antibody Drug Discovery

Emma Jenkins (Director of Expression and Developability, Alchemab Therapeutics), during her keynote presentation, delved into the pioneering endeavours of Alchemy Labs in the realm of drug discovery. The mission of Alchemy Labs is to analyse the antibody repertoires of resilient patients, with the aim of identifying therapeutic avenues for diseases that are traditionally challenging to treat.

One of the hallmarks of Alchemy Labs' approach is their target-agnostic methodology. Unlike conventional drug discovery paradigms, which often revolve around specific molecular targets, Alchemy Labs embarks on their investigations without preconceived notions of what those targets might be. Instead, they focus on deciphering the immune responses of resilient patients, seeking out protective antibodies that may hold the key to combating various diseases.

Emma unpacked the multifaceted nature of resilience, highlighting its diverse manifestations across different disease contexts. For instance, in the realm of oncology, resilience might manifest as prolonged survival rates compared to the median prognosis for aggressive cancers like pancreatic or glioblastoma. Conversely, in neurodegenerative diseases, resilience could entail delayed onset or slower progression of symptoms, even in individuals predisposed to conditions like Alzheimer's.

Central to Alchemy Labs' endeavours is collaboration. Emma emphasized the importance of partnerships with over 30 organizations spanning biobanks, charities, academia, and industry. These collaborations provide access to crucial patient samples and metadata, enabling Alchemy Labs to conduct comprehensive analyses across various patient cohorts.

The methodology employed by Alchemy Labs encompasses bulk sequencing of antibodies from resilient patients, followed by sophisticated computational analyses to identify convergent antibodies with therapeutic potential. Machine learning algorithms play a critical role in this process, aiding in antibody design and selection based on functional relatedness and convergence.

Once promising antibody candidates are identified, Alchemy Labs leverages advanced techniques, including phage display, to generate these antibodies for further evaluation. They utilize a scalable platform for antibody production, ensuring the ability to manufacture antibodies in large quantities for subsequent testing and development.

A significant aspect of their work involves target deconvolution, wherein various methodologies, including display technologies and computational approaches, are employed to elucidate the specific targets of the identified antibodies.

Emma also underscored the importance of robust data management practices, highlighting the creation of a comprehensive "data cube" that consolidates patient metadata, in vitro data, and sequence information. This centralized database facilitates efficient analysis and decision-making throughout the drug discovery process.

In terms of pipeline and development, Emma revealed that Alchemy Labs has made significant strides, with lead candidates emerging in the field of neuroscience and oncology. One such candidate, ATLX - 1282, has progressed to the development stage, targeting neurodegenerative diseases like FTD or ALS.

In conclusion, Emma's presentation showcased the innovative and collaborative approach of Alchemy Labs in drug discovery. By leveraging resilience in patients and employing cutting-edge methodologies, they aim to uncover novel therapeutic targets and usher in a new era of treatment options for challenging diseases.

Antibody Discovery Against Complex Targets

Trevor Wattam's (Associate Director, GSK) presentation delved into the intricacies of antibody discovery at GSK, with a specific focus on targeting G protein-coupled receptors (GPCRs) for potential therapeutic applications, particularly in addressing rheumatoid arthritis. He emphasized the multifaceted nature of the target, highlighting the necessity for precise binding profiles to achieve therapeutic efficacy in treating this debilitating disease affecting millions worldwide.

The presentation provided insights into the various immunization strategies employed by GSK, which included utilizing synthetic peptides, mRNA, and virus-like particles to elicit antibody responses in mice. Trevor detailed the immunisation protocols and the subsequent analysis of serum titres to assess antibody generation. Despite variations in serum responses across different immunization approaches, significant antibody responses were observed, particularly with the synthetic peptide immunization strategy.

Following immunisation, the antibodies were subjected to rigorous screening processes, which involved fluorescence-activated cell sorting (FACS) and other assays to evaluate binding affinity and functional activities such as antibody-dependent cell-mediated cytotoxicity (ADCC). Trevor highlighted the importance of assessing binding specificity to both human and cynomolgus GPCRs, as well as the consideration of epitope diversity to ensure broad coverage.

Through meticulous screening and characterisation, a substantial pool of antibodies was identified, demonstrating varying binding affinities and functional properties. Trevor discussed the subsequent steps involved in selecting the most promising candidates for further evaluation and development, emphasising the collaborative effort and interdisciplinary approach required in the antibody discovery process.

In conclusion, Trevor expressed gratitude to the team involved in the project, underscoring the collective effort and expertise required to advance antibody discovery initiatives. The presentation demonstrated the significance of diverse immunisation strategies and thorough screening protocols in generating a robust panel of potential therapeutic candidates for addressing complex disease targets like GPCRs in rheumatoid arthritis.

Dead Ends & New Approaches: AI+ Mass Spectrometry For Antibody Discovery & Engineering

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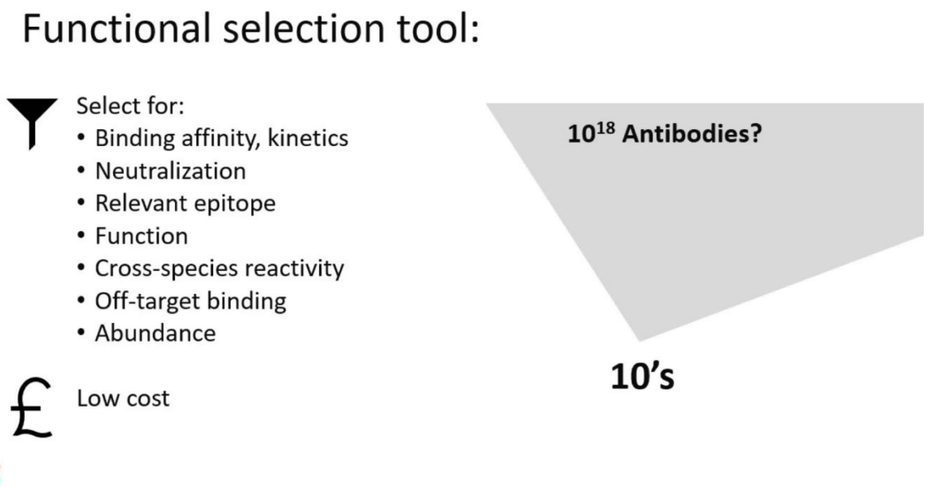
Iain Roger's (Vice President of Sales and Marketing, Rapid Novor) presentation examines the challenges and innovations within antibody discovery. He begins by acknowledging the difficulty in securing funding for early-stage biologics discovery programs and the growing interest in AI technologies. He outlines his agenda, which includes discussing new technology, presenting case studies, and addressing key challenges. Rapid Novor, specialises in mass spectrometry-based services for antibody discovery.

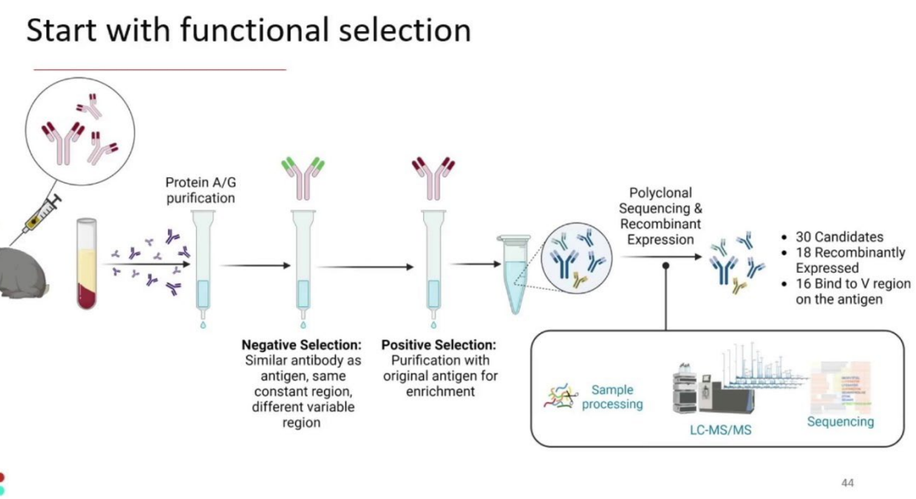
Throughout the presentation, Iain emphasizes the need for increased diversity in antibody screening processes and proposes strategies to achieve this effectively. He also

stresses the importance of developing efficient search strategies to identify relevant antibodies.

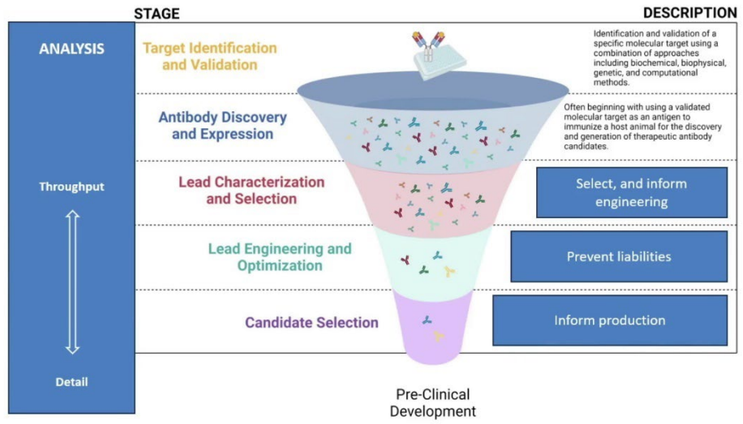
One of the main highlights is Iain's proposal to utilize mass spectrometry and AI to streamline the antibody discovery process. He highlights the critical properties that the functional tool must possess.



He presents a case study illustrating how this approach can lead to more efficient and cost-effective outcomes. The results of his study generated 30 sequences, 18 of which were recombinantly expressed. 16 of the sequences met the company's performance criteria for binding.



Additionally, Iain discusses the significance of antibody characterization. He suggests that using mass spectrometry-based epitope mapping, augmented with AI, enhances throughput and provide valuable insights for downstream processes.



In conclusion, Iain summarises the key points of his presentation and gives a brief overview of the mass spectrometry-based services that Rapid Novor offers.

Solving Big Data Challenges In Therapeutic Discovery

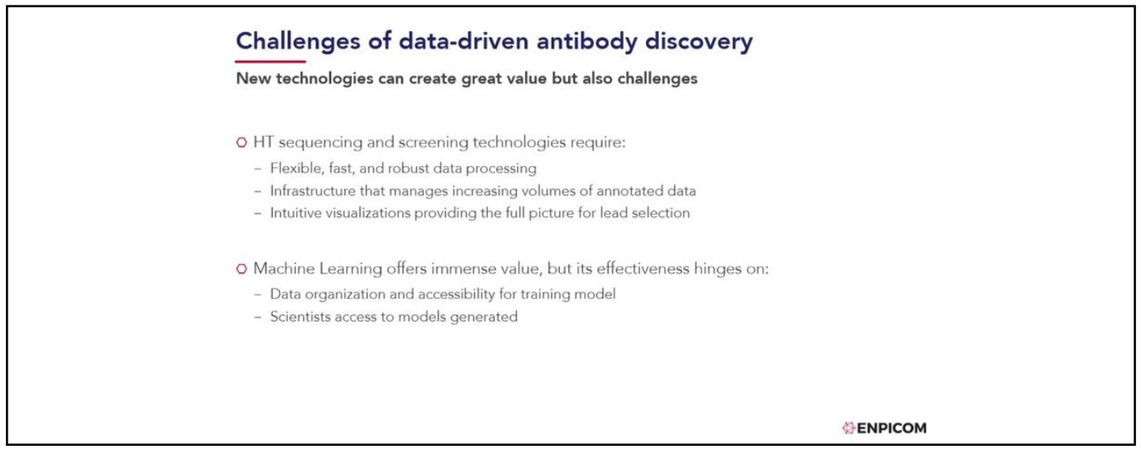
ENPICOM
DECODING THE IMMUNE SYSTEM

Néstor Vázquez Bernat's (Application Science Team Lead, Enpicom) presentation primarily focused on addressing challenges in antibody discovery workflows through data-driven approaches. He began by acknowledging the challenges faced in the field. He emphasized the importance of leveraging data generated from high throughput sequencing and in vitro characterization, both in vitro and in silico, to overcome these challenges.

Nestor highlighted advancements in sequencing technologies, such as Illumina's NextSeq, which allows for increased sequencing data volume and improved quality. He also discussed advancements in in vitro characterization techniques, such as Bruker's Beacon platform, and Carterra's LSA technology, which enable high-throughput screening and accurate affinity measurements and epitope binning for hundreds of antibodies simultaneously. He also mentioned that Enpicom are collaborating with Carterra.

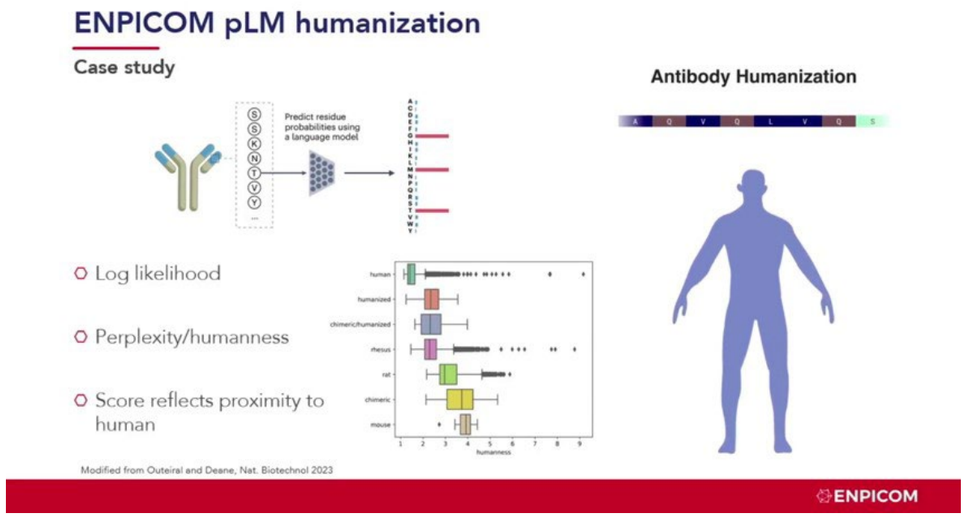
Furthermore, Nestor emphasized the significance of integrating data from diverse sources, including NGS datasets, in vitro characterization data, and in silico predictions, to make informed decisions in antibody discovery workflows. He highlighted the emergence of computational tools, such as AlphaFold and ImmuneBuilder, for predicting protein structures and optimizing antibody properties, including humanization, and binding affinity.

Nestor outlined several challenges associated with data integration and analysis.



To address these challenges, Nestor introduced the IGX platform, a software solution designed to facilitate data-driven antibody discovery. The IHGX platform offers various functionalities, including gene annotation, quality control, and custom algorithm integration, to streamline data analysis and decision-making processes.

Finally, Nestor provided a practical example of how the IGX platform can be used to analyse complex antibody datasets and make informed decisions in antibody discovery. He demonstrated how the platform can process sequencing data, cluster antibodies into lineages, and predict binding affinities to guide candidate selection. Additionally, Nestor showcased the platform's humanization tool, which enables iterative optimization of antibodies for therapeutic applications while considering binding predictions.

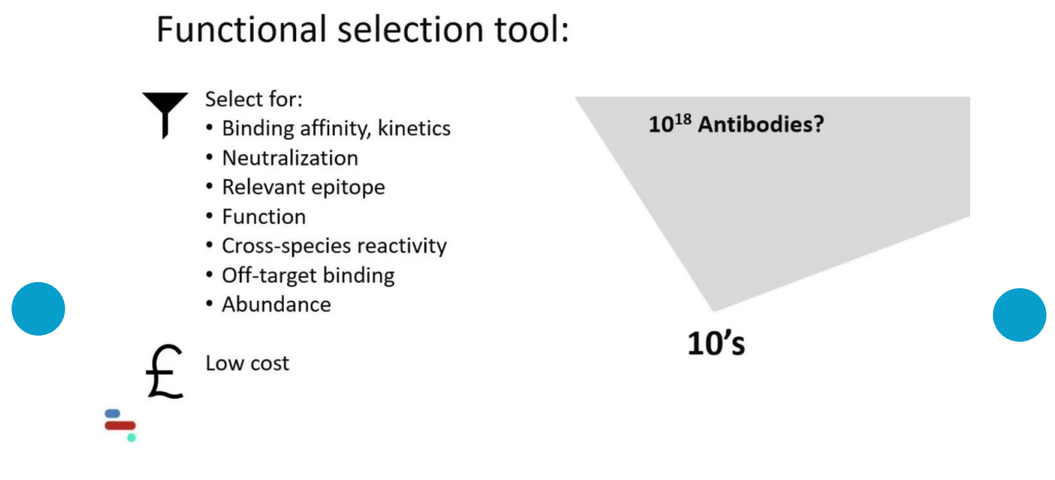


In summary, Nestor's presentation highlighted the importance of data-driven approaches in antibody discovery workflows and demonstrated how the IGX platform can facilitate data integration, analysis, and decision-making to accelerate the discovery of novel antibody therapeutics.

Computational Approaches For The Design & Development Of Multispecific Therapeutics

Soraya Höpler's (Project Lead, Sanofi) presentation focused on computational approaches for the design and development of multispecific biotherapeutics. She began by highlighting the growth of the large molecule research organization at Sanofi and its mission to translate innovative science into novel biologic candidates to improve patient health.

Soraya outlined Sanofi's modality toolbox, which includes antibodies and nanobodies in various formats to address unmet medical needs across therapeutic borders. She emphasized



the need for next-generation multispecific antibodies to be flexible, simple in design, highly active across different disease biologies, and developable within fast timelines.

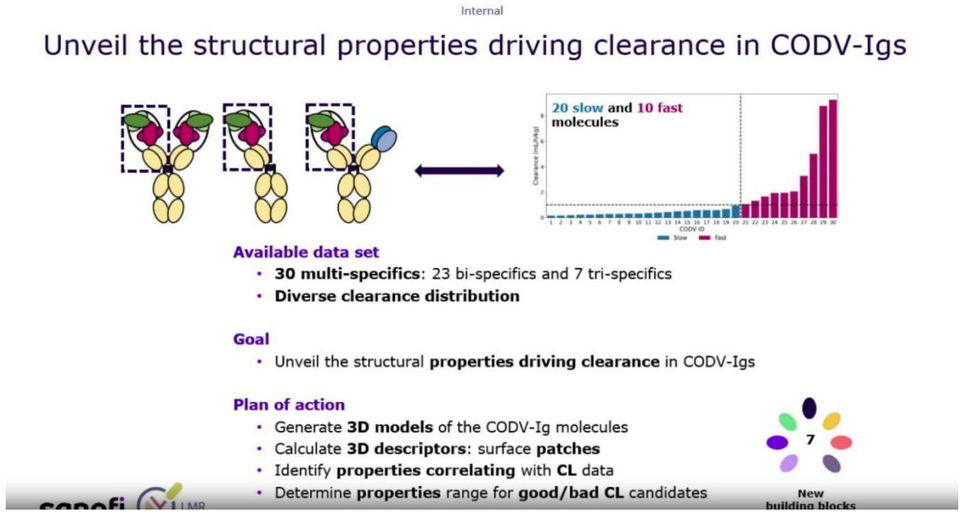
She introduced an end-to-end automated engineering platform in ultra-high throughput fashion, allowing for the modification of protein formats to optimize attributes like productivity, aggregation, and stability. This platform enables genotype-phenotype mapping and feeds data directly into AI models.

Soraya discussed the importance of high-throughput technologies for data generation and analysis, including physical stability measures, solubility prediction, intact mass analysis, and peptide mapping. These data feed into a screening tree for molecule selection based on expression, binding, polyreactivity, potency, and extended characterization.

She acknowledged the limitations of current molecule selection processes and highlighted the need for computational and AI-based methods to enhance selection confidence. Soraya presented three computational approaches: In silico developability analysis, diversity analysis using a software called SCALOP, and a predictive model for pharmacokinetics based on surface properties of multispecific molecules.

The In silico developability analysis involves using a therapeutic antibody profiler to assess surface properties and sequence features correlated with developability

characteristics. Diversity analysis identifies conformational clusters in CDR regions to boost diversity in the dataset.



Soraya then detailed the development of a predictive model for pharmacokinetics, focusing on a proprietary multispecific format called CODV – Ig (Cross-Over Dual Variable Ig-like proteins). The model correlates surface properties with clearance rates, allowing for the prediction of PK behaviour for new molecules. Validation studies showed 100% accuracy in predicting PK behaviour. Details of the data set used to build their predictive model can be seen above.

In conclusion, Soraya emphasized that sequence and structure-based virtual screenings can enhance the selection process in drug discovery, improving the probability of success. She highlighted the importance of computational methods in addressing complex characteristics and expressed confidence in the potential of AI to revolutionise drug discovery processes.

Generative AI For Antibody Optimization & De Novo Design

Vladimir Gligroijevic's (Senior Director of AI/ML, Genentech) provided an overview of Prescient Design's journey since its acquisition by Genentech, highlighting the growth and integration of teams within the Genentech R&D department over the past two and a half years.

The central focus of the presentation was on leveraging artificial intelligence (AI) and machine learning (ML) to advance antibody discovery and development processes. Vladimir emphasised the importance of this work in reducing both cost and timeline associated with drug discovery at Genentech. The overarching goal of Prescient Design's efforts is not merely to design antibodies with high affinity for specific targets, but also to ensure that these antibodies are therapeutically effective and safe.

To achieve this goal, Prescient Design collaborates closely with Genentech's antibody engineering department, addressing a diverse array of challenges in antibody design. Vladimir explained that their approach involves the development of AI/ML models tailored to specific tasks, including binder optimization, repertoire mining, and de novo design.

These models are designed to handle different aspects of the drug discovery pipeline, with a focus on improving multiple properties simultaneously while navigating the trade-offs inherent in multi-objective optimization.

A key innovation highlighted by Vladimir was the "Lab-in-the-Loop" system, which integrates AI/ML models with wet lab experiments. This system enables rapid iteration of design proposals, experimental validation, and model refinement, ultimately leading to the generation of improved antibody candidates. Vladimir emphasized the importance of active learning techniques in selecting designs for experimentation, ensuring that the process remains efficient and effective.

Throughout the presentation, Vladimir underscored the challenges faced by Prescient Design, including data limitations and model performance. However, he also highlighted the diverse range of AI models developed by the team to address these challenges. These models include structure-based models and generative models like diffusion models for de novo design.

In presenting results from the lab in the loop system, Vladimir demonstrated significant improvements in expression levels and affinity of antibody candidates over multiple rounds of iteration. He showcased the team's AI/ML-driven approach, which yielded comparable or superior performance to traditional methods such as NGS-based expert selection.

Overall, the presentation provided valuable insights into the innovative use of AI and ML in accelerating antibody discovery and design processes, demonstrating the potential for transformative advancements in the field of drug discovery.

Multiple Antigen Formats For Improved Antibody Discovery Against Membrane Proteins

Rajesh Sundaresan's (Scientific Leader, GSK) presentation focused on the challenges of discovering antibodies against membrane proteins and how they've addressed them using multiple antigen formats, particularly mRNA-LNP (lipid nanoparticle) platform. He highlighted the need to improve the discovery pipeline for membrane proteins, which make up a significant portion of potential drug targets but are difficult to work with due to supply issues and functional relevance.

They employed various methods, including genetic and cellular immunogens, as well as protein immunogens, to address these challenges. Rajesh emphasised their use of the mRNA-LNP platform, leveraging GSK's expertise in mRNA-based vaccine technologies. He described the process of generating mRNA from target DNA sequences, formulating them into lipid nanoparticles, and evaluating expression and protein production.

Through confocal microscopy and other assays, he demonstrated successful protein expression and surface localization, indicating functional relevance. Rajesh shared examples of his findings, including increased hit rates with mRNA-LNP compared to cell-based immunization, and highlighted the potential of AI in analysing antibody hits.

Rajesh addressed questions about comparing different immunisation methods, clustering antibody hits, and the timeline for reagent preparation and QC. He discussed the advantages of mRNA-based immunisation in terms of speed and flexibility, while also acknowledging the challenges in protein production timelines. Overall, the presentation showcased GSK's efforts to overcome obstacles in antibody discovery against membrane proteins using innovative approaches.

Exploring Analytical Frontiers: Advancements Shaping Biopharmaceutical Innovation

GMI's latest market report, released February 2024 showcases that rising advancements in bioanalytical technology play a pivotal role in large molecule bioanalytical development as they drive innovation and improve analytical capabilities, as well as expand the scope of applications.

Source: GMInsights

Native – Mass Spectrometry: A Powerful Tool To Characterize A Wide Range Of Biotherapeutics.

Thierry Besson's (Senior Scientist II, Novartis) presentation delved into the intricacies of employing Native Mass Spectrometry (MS) as a robust tool for scrutinizing a broad spectrum of biotherapeutic molecules. Throughout his talk, he highlighted the pivotal role of Native MS, contrasting it with denatured MS and elucidating how it preserves the inherent structure of molecules, thus furnishing invaluable insights into their composition and interactions.

A key aspect Thierry pointed out was the procedural intricacies of conducting Native MS, which necessitates altering the buffer conditions to uphold the native conformation of the protein prior to analysis. By providing a step-by-step overview of this process, he demystified the technical nuances involved in harnessing Native MS effectively.

Furthermore, Thierry presented a series of compelling case studies to underscore the versatility and utility of Native MS across various biotherapeutic modalities. These case studies spanned diverse areas, including the analysis of specific Fab-Fab interactions, the characterization of noncovalent trispecific complexes, and the examination of oligonucleotide conjugates to antibodies. Through these real-world examples, Thierry showcased how Native MS serves as a linchpin for elucidating complex molecular architectures and unravelling intricate binding mechanisms.

Moreover, Thierry delved into the challenges associated with analysing complex molecules like Adeno-associated viruses (AAVs) using traditional MS techniques. He introduced Charge Detection Mass Spectrometry (CDMS) as a promising alternative for overcoming these challenges and obtaining precise mass measurements of such intricate molecules.

In his concluding remarks, Thierry emphasized the adaptive nature of analytical techniques in the biotherapeutics realm, emphasizing the need for continual innovation to keep pace with evolving scientific inquiries and technological advancements. Overall, Thierry's presentation provided a comprehensive overview of the significance and applications of Native MS in contemporary biopharmaceutical research.

Improving Stability & Activity Of Therapeutic Proteins With ML & Computational Tools

Throughout the presentation, Paul Dalby (Professor in Biochemical Engineering and Biotechnology, UCL) outlined his approach to research, which revolves around facilitating capabilities in manufacturing and formulation. He emphasized the importance of understanding aggregation mechanisms, protein engineering, formulation strategies, and the development of new analytics. This approach aims to enhance the stability of therapeutic proteins, a crucial aspect in ensuring their effectiveness and safety in medical applications.

Paul presented data from aggregation profiling experiments conducted on antibody fragments under different environmental conditions, such as varying pH, ionic strength, and temperature. These experiments aimed to elucidate the factors influencing protein stability and aggregation kinetics. By examining the behaviour of the proteins across a range of conditions, Paul's team gained insights into the role of native state dynamics in driving aggregation.

In addition to experimental approaches, Paul discussed the use of computational tools such as molecular dynamics (MD) simulations and hydrogen-deuterium exchange mass spectrometry (HDX-MS). These computational techniques allowed his team to study protein dynamics at a molecular level and identify aggregation-prone regions (APRs). By leveraging MD simulations, they could predict protein stability and design engineering strategies to mitigate APR exposure, thereby enhancing protein stability.

Moreover, Paul delved into the role of formulation excipients in protein stability, challenging conventional notions of preferential exclusion. Through a combination of experimental and computational approaches, his team investigated the selective interactions between excipients and proteins, shedding light on the mechanisms underlying protein stabilization in different formulation environments.

Towards the end of the presentation, Paul touched upon the application of machine learning techniques in predicting protein stability based on sequence variants and MD simulation data. By integrating computational modelling with experimental data, his team could develop predictive models for protein stability, offering valuable insights into protein engineering and formulation strategies.

In summary, Paul's presentation provided a detailed exploration of his research efforts in understanding and enhancing the security and activity of therapeutic proteins. By combining experimental techniques with computational modelling and machine learning approaches, his work contributes to advancing the field of biomedical engineering and targeted healthcare manufacturing.

From A Synthetic Methodology Towards A Bioconjugation Tool: 5HP20s As NextGeneration Maleimide Alternatives

Jan Meffert's (Early Stage Researcher, Ghent University) presentation focused on the challenges and solutions in chemically linking therapeutic entities, such as antibodies and small molecule drugs, to oligonucleotides for therapeutic applications. Oligonucleotides pose challenges due to their polyanionic backbone, leading to difficulties in cell uptake despite their specificity in targeting intracellular molecules.

To overcome these hurdles, Jan's research aims to combine oligonucleotides with antibodies using the system modification approach, particularly by modifying antibodies with maleimide chemistry. However, traditional maleimide chemistry has drawbacks, including instability and retro-Michael reactions. To address these issues, Jan's team developed 5HP20s which serves as a stable bioconjugation tool.

Jan explained the synthesis process of 5HP20s, which involves a three-step procedure resulting in a complex but elegant molecule. The molecule provides a stable linkage between the therapeutic entities and exhibits better stability compared to traditional maleimide chemistry, as demonstrated by experiments.

Furthermore, Jan discussed the application of 5HP20s to in conjugating oligonucleotides to proteins, highlighting the advantages in terms of stability and yield compared to traditional maleimide chemistry. The stability of the conjugates was evaluated through glutathione exchange reactions, demonstrating superior stability for 5HP20 conjugates.

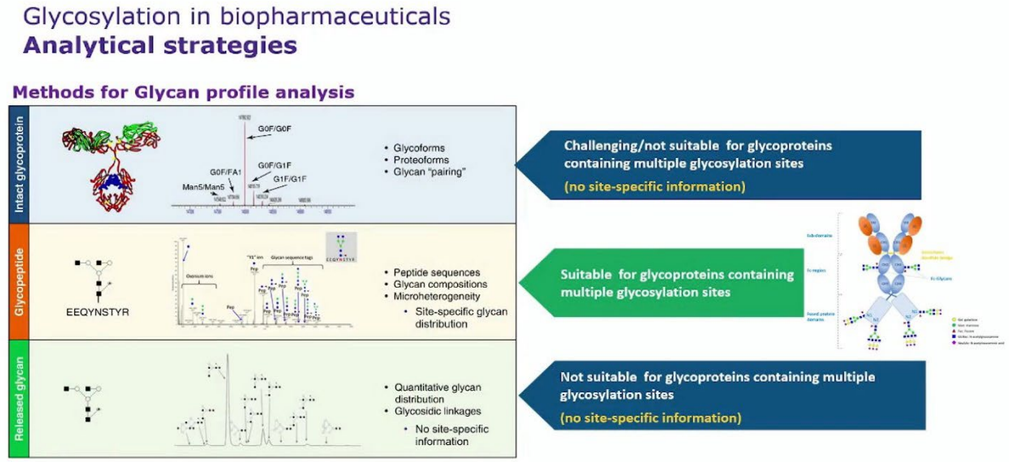
In addition to protein conjugation, Jan's team explored the conjugation of peptide nucleic acids (PNAs), which face solubility issues when using traditional maleimide chemistry. By modifying the 5HP20 linker, they achieved soluble PNA conjugates, enabling further conjugation chemistry.

Finally, Jan presented ongoing research on direct dual DNA modification using modified purines and oligonucleotides as a mine in the 5HP20s to reaction, offering a faster and more efficient method. Overall, Jan's presentation showcased the development and application of 5HP20 as a versatile bioconjugation tool, addressing key challenges in linking therapeutic entities for therapeutic applications.

Innovative Metrics For Standardized Glycoprofiling Of Biopharmaceuticals

Horst Bierau's (Associate Director, MSD) presentation explores glycosylation analysis within the realm of biopharmaceuticals. He introduces the audience to the pivotal role that glycosylation plays as a critical quality attribute, emphasizing its multifaceted impact on various aspects of biologics, including biological functions, pharmacokinetics, and immunogenicity.

Throughout his talk, Horst highlights the complexity inherent in glycosylation due to the diverse structures and modifications present in biopharmaceutical compounds. He underscores the necessity of robust analytical methods to effectively monitor and analyse glycosylation as part of quality control processes. Horst outlines different approaches to glycosylation analysis, ranging from whole molecule analysis to peptide mapping, each method offering unique advantages and challenges. He reiterates the importance of considering site-specific information in glycosylation analysis, particularly in complex molecules with multiple glycosylation sites.



Amidst the discussion, Horst elucidates the challenges encountered in glycosylation analysis, including ensuring consistency in manufacturing processes, coping with the increasing complexity of molecules, and the absence of standardized metrics for evaluation and comparison.

To address these challenges, Horst introduces the concept of standardized matrices of glycosylation indices. These matrices aim to provide a harmonized and meaningful way of presenting glycosylation data, facilitating comparison and risk assessment across different biopharmaceutical compounds.

Horst elaborates on the workflow for glycosylation analysis, which involves selecting relevant indices based on compound characteristics, conducting peptide mapping analysis, and computing numerical values for comparison. He emphasizes the importance of tailoring the approach to specific compounds and their glycosylation profiles.

Through compelling case studies, Horst illustrates the practical application of glycosylation indices in process optimization and comparability studies for biopharmaceutical compounds. He showcases how this approach offers detailed insights into subtle variations in glycosylation profiles, aiding in decision-making regarding process improvements and product comparability assessments.

In conclusion, Horst underscores the comprehensive and intuitive nature of glycosylation indices in visualizing glycosylation-related data. He highlights their potential to increase product knowledge, facilitate risk assessment, and streamline quality control and release testing procedures within the biopharmaceutical industry.

Computational Tools For Process Design

Cleo's Kontoravdi's (Professor of Biological Systems Engineering, Imperial College London) presentation examined the use of computational tools in biologics manufacturing, particularly in process engineering. She highlighted the need to blend experimentation with computational methods to expedite process development and enhance process

control. Cleo outlined three primary challenges in the field:

Firstly, she discussed the disparity between upstream and downstream processing and how computational tools can aid in designing flexible processes to accommodate variability from upstream operations. Cleo presented a framework for designing such flexible processes, focusing on protein A chromatography.

Secondly, Cleo addressed the issue of limited measurements in upstream bioprocessing, proposing a generic model based on cell metabolism to predict reactor dynamics and product concentrations. This model allows operators to anticipate process behaviour in advance and take proactive corrective actions.

Lastly, she emphasized the integration of mechanistic knowledge with machine learning components to facilitate online applications, control, and optimization in biologics manufacturing. Cleo underscored the potential of computational tools to accelerate process development and improve efficiency, paving the way for Industry 5.0 in biologics manufacturing.

In essence, Cleo's presentation highlighted the transformative role of computational tools in complementing experimental approaches and revolutionizing biologics manufacturing by addressing critical challenges and enabling advanced process control and optimization.

Site-Specific Antibody Conjugations Using Bacterial Transglutaminase & The Diels-Alder Cycloaddition Reaction

Thomas Nittoli's (Senior Director, Regeneron) presentation offers a nuanced perspective on the use of two-step conjugations in bioconjugation chemistry. Rather than positioning himself strictly as an opponent or proponent, he emphasises that they are just another tool available to researchers. He supports his viewpoint by providing a practical example where a linker payload exhibited solubility issues, making direct conjugation to an antibody challenging.

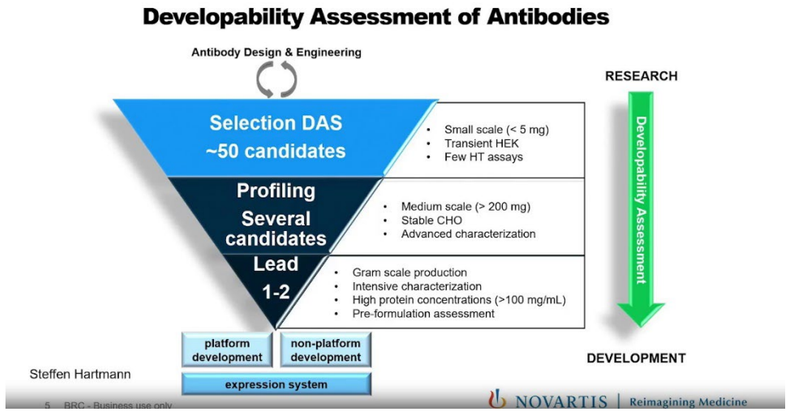
In the example, Thomas describes the payload's insolubility in solvents, highlighting the difficulty of incorporating it into a mixed buffer system with the antibody. However, he proposes a solution: dissolving the payload first in a suitable solvent to render it slightly soluble. This preliminary step facilitates subsequent conjugation to the antibody, overcoming the initial solubility obstacle.

Thomas emphasizes that two-step conjugations can be particularly beneficial in scenarios where conjugation processes are problematic and prone to aggregation. By breaking down the conjugation process into multiple steps, researchers gain greater control and flexibility, ultimately improving the efficiency and success rate of the bioconjugation procedure.

Overall, Thomas suggests that while two-step conjugations may not be suitable for every situation, they offer valuable advantages in specific cases characterized by challenging conjugation conditions. He invites further discussion and questions, indicating his willingness to provide additional insights and guidance on the topic.

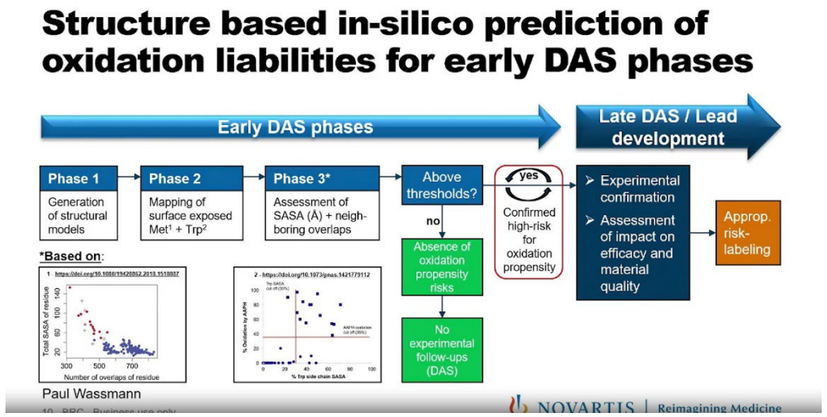
Developability Assessment Concept In The Light Of Emerging Biologics Modalities

Patrick Schindler's (Senior Principal Scientist, Novartis) presentation focused on the work of his unit at the Biologic Research Centre (BRC), which aims to bring future biologics to patients by starting from early research and identifying promising molecules for development. The graph below highlights the workflow that the BRC uses to identify lead candidates.



However, with the emergence of new biologic formats like ADCs, bispecific antibodies, multispecific formats, and others, the assessment process becomes more complex due to the presence of unknown liabilities.

To address these challenges, Patrick emphasized the need for flexible assessment strategies and the incorporation of in silico prediction methods. He shared the following example of using an algorithm for early prediction of oxidation liabilities, which helped in making informed decisions about candidate molecules.



Patrick also highlighted the importance of adapting analytical workflows to accommodate the diverse properties of new biologic formats. He discussed the use of native mass spectrometry, charge detection mass spectrometry, and mass photometry to assess various aspects of biologic molecules such as glycosylation, particle composition, and modifications.

Additionally, he stressed the significance of early-stage analysis in identifying and addressing potential issues, such as immunogenicity risks associated with glycosylation patterns. By implementing detailed analysis techniques early in the development process, Patrick demonstrated how teams can optimise cell line development and avoid time-consuming setbacks later on.

Overall, Patrick's presentation outlined the significance of leveraging advanced analytical techniques and predictive methods to navigate the complexities of developing novel biologics effectively. He emphasised the need for a comprehensive toolbox of analytical approaches to support the development of diverse biologic formats and ensure successful translation to clinical applications.

Monoclonal Antibody Reference Reagents For Bioassays: Supporting Global Harmonisation & Traceability At Different Stages Of The Product's Lifecycle

Sandra Prior's (Principal Scientist, MHRA) presentation focused on the importance of WHO (World Health Organization) international standards and reference reagents for monoclonal antibody products. She introduced the role of international standards in assigning biological potency to medicines, emphasising their contribution to global harmonisation and traceability. She highlighted the unique role of WHO standards in providing public reference preparations that allow for the calibration of in-house reference standards, thus supporting performance and global harmonisation.

Sandra discussed the WHO standardisation programs for monoclonal antibodies (mAbs) and shared data from international collaborative studies for rituximab, trastuzumab, and cetuximab, illustrating the variability in potency estimates among different laboratories. She emphasised the role of WHO international standards in reducing variability and harmonising the reporting of activity.

Sandra also introduced a new program for the development of WHO reference reagents for Fc domain interactions, which are critical for understanding mAb functions and their impact on efficacy and safety. These reference reagents aim to support the evaluation of assays, comparison of different platforms, and improvement of understanding regarding Fc effector functions and structure.

Sandra addressed questions regarding the use of different assays for studying Fc effector functions, cautioning about interpreting results based on assay suitability for specific cell types. She also discussed the participation of laboratories in collaborative studies, emphasising that while WHO doesn't formally monitor GLP standards in participating labs, they encourage robust assay development and rely on a diverse group of stakeholders, including manufacturers, national control laboratories, and service providers.

Revolutionizing Biologics: Innovations in Immunogenicity Profiling and Cancer Therapy

New In Silico Immunogenicity Profiling Approach Based On Drug-Pathogen Analogy

Michael Gutknecht's (Principal Scientist, Novartis) presentation introduced the field of immunogenicity within the context of biologics development. He began by defining the fundamental concept of immunogenicity, which revolves around the ability of substances like antigens or therapeutic antibodies to trigger immune responses. Even antibodies engineered to be fully human may still provoke immune reactions due to the presence of unique regions called complementarity-determining regions (CDRs), which the immune system recognises as foreign.

A crucial aspect discussed was the process by which biologics interact with antigen-presenting cells, get broken down into peptides, and then displayed on HLA Class II molecules. This interaction activates T cells, which in turn stimulate B cells to produce antibodies. Michael stressed the importance of identifying both T cell epitopes, which are linear and can arise from any part of the protein, and B cell epitopes, which can be linear or discontinuous but are always exposed on the protein's surface.

The presentation also explored the potential ramifications of immunogenicity, spanning from adverse reactions to the drug failing to gain approval or being withdrawn from development altogether. Michael emphasised that managing immunogenicity is not only crucial for ensuring patient safety but also for maintaining a competitive edge in the pharmaceutical market.

To address these challenges, Michael introduced the concept of in silico immunogenicity profiling, which involves screening large sets of candidates early in the drug development process to identify potential immunogenic hotspots. He outlined the advantages of this approach, such as its cost-effectiveness and ability to detect problematic candidates early on. However, he also acknowledged the limitations of current prediction accuracy, particularly concerning the identification of B cell epitopes.

To enhance prediction accuracy, Michael detailed Novartis' proprietary algorithm, "iSHAPe," (In Silico HLA Aggregetope Prediction) which is trained on meticulously curated in vitro data. He underscored the significance of considering factors like CDR overlap and sequence similarity to pathogens in candidate ranking to provide a more comprehensive assessment of immunogenicity risk. Additionally, he discussed the complexities involved in normalizing scores for bi-specific antibodies and emphasised the necessity of employing multifactorial analysis in candidate ranking. This case study raises the question of whether there are additional parameters that should be included in Novartis's assessment to improve candidate ranking.

In conclusion, Michael highlighted the importance of multifactorial analysis in candidate ranking to develop biologics with minimal inherent immunogenicity potential. By integrating considerations such as peptide counts, hotspot identification, and sequence similarity to pathogens, pharmaceutical companies can better mitigate the risks associated with immunogenicity in biologics development.

First-In-Class IgE immunotherapy In Solid Tumours

Sophia Karagiannis' (Professor of Translational Cancer Immunology and Immunotherapy, Kings College London) presentation delved into the intricacies of antibody engineering for cancer therapy, focusing on the potential of IgE antibodies as an alternative to the traditional IgG class. She began by contextualizing the urgent need for improved therapies, particularly in cancers like ovarian cancer, which still lack effective treatment options. Drawing parallels with the success of checkpoint inhibitors in certain cancers like melanoma, she outlined the persistent challenges, such as limited response rates and recurrence post-treatment.

Highlighting the diverse functions of antibodies in the immune system, Sophia advocated for a more nuanced approach to antibody design tailored to different cancer types and patient populations. She introduced the concept of engineering antibodies with an Fc region distinct from IgG, citing IgE as a promising candidate due to its unique characteristics, including high affinity for Fc receptors and prolonged tissue persistence.

Sophia detailed their research journey, selecting folate receptor alpha as a target for IgE antibody therapy based on its expression in various cancers and association with poor outcomes. Through preclinical studies in mouse and rat models, they demonstrated the efficacy of IgE immunotherapy in inhibiting tumour growth and stimulating a pro-inflammatory immune response, potentially mediated by macrophages.

Transitioning to clinical translation, Sophia shared insights from their phase one clinical trial, highlighting the successful demonstration of safety and efficacy. She addressed concerns regarding production challenges, reassuring the audience that manufacturing IgE antibodies was feasible and had been accomplished without significant obstacles.

Overall, Sophia's presentation provided a comprehensive overview of their pioneering work in exploring alternative antibody classes for cancer therapy, showcasing the potential of IgE immunotherapy to revolutionize treatment approaches and improve patient outcomes.

Next-Generation DARPin Therapeutics: From Small Size Single-Domain Radio-DARPin Therapeutics To Multispecific T-Cell Engagers

Christian Reichen's (Director, Molecular Partners) presentation examined Molecular Partners' groundbreaking DARPin technology and its transformative potential in therapeutic development, particularly in the context of cancer treatment and T-cell engagement. He pointed out the distinct attributes of DARPin molecules, highlighting their compact size, robust stability, and facile production process, all of which render them highly promising contenders for targeted therapeutic interventions.

Christian's presentation discussed the design principles and optimisation strategies underlying DARPin-based therapeutics. He pointed out the intrinsic advantages of DARPin molecules, citing their diminutive size relative to antibodies, exceptional stability, and straightforward expression in bacterial hosts. These attributes not only facilitate deep tissue penetration but also enable high-concentration dosing, if necessary, thereby augmenting their therapeutic efficacy.

Moreover, Christian illustrated Molecular Partners' endeavours in crafting DARPin-based radiotherapeutics, which harness the power of targeted radiation to precisely eradicate cancer cells while mitigating collateral damage to healthy tissues. By leveraging DARPin's unique properties, such as its stability and customisable binding sites, Molecular Partners aims to revolutionise cancer treatment paradigms, offering patients more effective and less toxic therapeutic options.

Christian also provided insights into the development of multi-specific T-cell engagers, exemplified by Molecular Partners' MP0533. This innovative therapeutic agent, designed to target multiple antigens implicated in acute myeloid leukemia (AML), holds promise for addressing the heterogeneous nature of AML and enhancing therapeutic efficacy. Through preclinical studies and early-phase clinical trials, Christian demonstrated MP0533's remarkable efficacy and safety profile, highlighting its potential to usher in a new era of precision medicine in oncology.

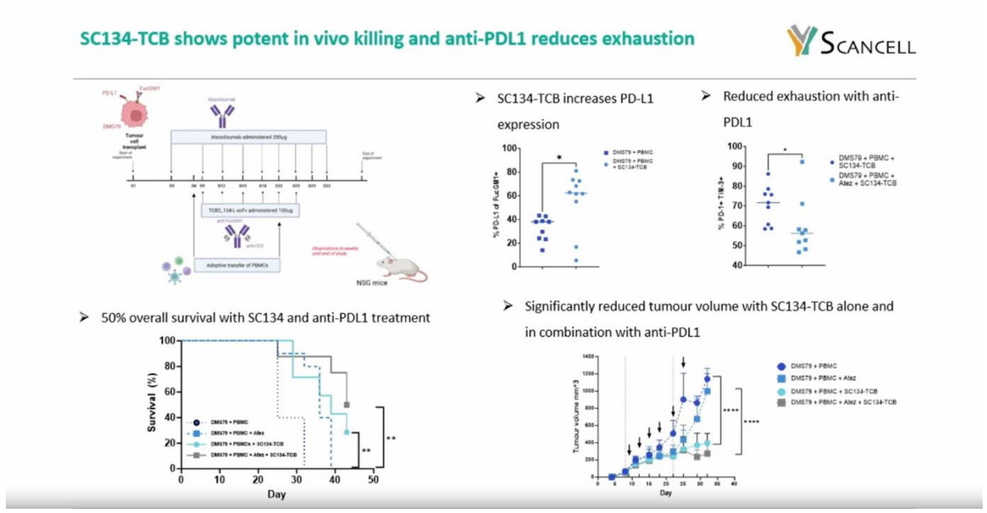
Christian fielded queries from the audience, addressing concerns regarding immunogenicity, toxicity studies, payload conjugation, and expression of complex constructs. His responses provided valuable insights into the practical considerations and challenges encountered in DARPin-based drug development, reaffirming Molecular Partners' commitment to advancing the frontiers of biotechnology and therapeutic innovation.

Glycan Targeting Antibodies For T Cell Redirection

Poonam Vaghela's (Scientist, Scancell Ltd) presentation examined the development and preclinical evaluation of SC134-TCB, a novel antibody product designed as a T cell redirecting bispecific antibody. She provided background information on tumour antigens, particularly focusing on GlyMab, a platform developed by Scancell, which consists of anti-glycan antibodies. Poonam highlighted the significance of Fucosyl GM1 (fGM1) in certain cancers like small cell lung cancer, emphasising its role in various oncogenic processes.

The SC134 antibody specifically targets fGM1 and exhibits high affinity binding to small cell lung cancer cell lines.

Preclinical data presented by Poonam demonstrated the efficacy of SC134-TCB in inducing potent killing and activation of T cells in coculture experiments. Moreover, in vivo studies in mouse models showed significant increases in overall survival and tumour reduction, particularly when combined with anti-PD-L1 therapy. Findings of the study are summarised in the slide below.



Safety assessments indicated minimal off-target cytokine production, further supporting the therapeutic potential of SC134-TCB.

Poonam concluded by acknowledging the team and addressed inquiries about antibody generation, FC gamma receptor silencing, and future assay plans. Overall, her presentation provided comprehensive insights into the development and promising preclinical evaluation of SC134-TCB as a potential therapeutic for small cell lung cancer.

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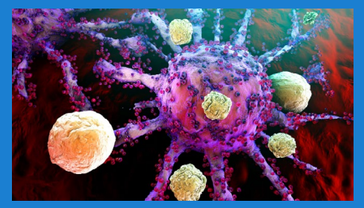

Report Summary

The landscape of biologics discovery is rapidly evolving, driven by innovative technologies that enhance efficiency and precision. In this report, we provide a summary of key technologies revolutionizing the biologics discovery process.

Advancements in Biologics Discovery Technology:

AI/ML: The application of AI/ML is becoming increasingly utilised biologics discovery. This versatile technology can be used to predict protein structure, analyse data, and screen antibodies. By applying these tools at various stages scientists can streamline and refine their biologics discovery and development workflows.

In silico prediction: Used to assess new biologic formats such as ADCs and bispecific antibodies to predict potential liabilities early in the development process. Not only are several in silico prediction models, capable of predicting antibody and protein characteristics but also creating candidate rankings of biologics. This makes the biologics development process more cost-effective and streamlined.

Mass Spectrometry: Mass spectrometry is offers crucial insights into antibody structure and antibody-antigen interactions. This technique is often used in protein sequencing and epitope mapping.

Bioconjugate Tools: Bioconjugates improve design and development for complex ADCs and are useful when direct conjugations processes face challenges like solubility issues.

Phage and Mammalian Display: This technology is used to accelerate the development of antibodies by selecting therapeutic antibodies with desirable characteristic such as stability and functionality. This enables scientists and researchers to identify promising therapeutic candidates.

Addressing Challenges in Biologics Discovery:

Furthermore, the landscape of biologics discovery is marked by various challenges that demand innovative solutions to ensure the development of safe, effective, and efficient therapies. The five prominent challenges and strategies to overcome them are the following:

Manufacturing: Biologics are larger and more complex than small molecules and are therefore more difficult to manufacture. Even small variations manufacturing processes can impact the quality control which could influence the biologic's safety, efficacy, and function.

Regulatory challenges: Defining the parameters for best regulatory practice requires extensive documentation and a deep understanding of regulatory guidelines. Regulatory bodies must ensure that there is regulatory compliance throughout clinical trails and the

commercialisation process. This may slow production timelines.

Complexity of New Biologic Formats: With the emergence of new biologic formats such as ADC, bispecific antibodies and multispecific formats can cause the assessment of antibodies to be highly complex. Due to the presence of unknown liabilities scientists must continuously adapt their processes to include flexible assessment strategies and predictive methods.

Funding for Early-Stage Biologics Discovery: Securing funding for early-stage biologics discovery programs remains challenging, despite growing interest in AI technologies and innovative approaches.

Data Limitation and Model Performance: A lack of data or a lack of heterogenous data can negatively influence model performance in AI and ML driven antibody discovery processes. Furthermore a shortage of diverse data sets could pose challenges when screening and identifying antibodies with relevant therapeutic qualities.