POST EVENT PROCEEDINGS

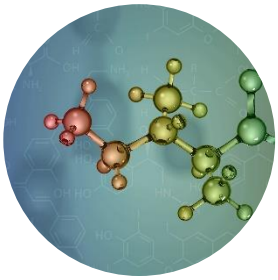
Discovery Europe 2023

06 - 07 June 2023 | Berlin, Germany

Oxford Global was proud to present **Discovery Europe 2023**, the event united senior-level experts to provide a focussed forum for thought-provoking discussion and for gathering insights from key figures in the community.

The event brought together leading experts in the fields of Organoid Discovery, Phenotypic Screening, Targeted Protein Degradation, AI Computational Drug Design and Lead Optimisation.

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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Day 1, Track 1: Target identification And Validation of Novel Targets

Defending a Brave Hypothesis Presentation Summary

Bert Kebl

Bert's presentation was a comprehensive overview of his organization, the Lead Discovery Centre, and their mission in the field of drug discovery and translational research. With over two decades of experience, Bert has been at the forefront of bridging the gap between academic research and practical applications in the pharmaceutical industry.

He started by expressing his gratitude for being invited to give the talk and outlined the structure of his presentation. The Lead Discovery Centre, he explained, has a unique role in Germany, where it translates basic research, often originating from academic institutions, into assets that can be commercialized. Importantly, their mission goes beyond profit-making; they also aim to address societal needs, including antibacterial solutions.

One key aspect of their approach is the validation of novel therapeutic hypotheses. Bert emphasized that they are not afraid to undertake the process of "de-validation" if the research leads in that direction. Their model is based on collaborative drug discovery, meaning they openly share data with academic and sometimes industrial partners. He stressed the importance of making this drug discovery incubator a sustainable organization.

The overarching mission of the Lead Discovery Centre is to provide solutions for unmet medical needs. They have established high-quality drug discovery infrastructure in different locations, collaborating with academic partners and even CROs for access to animal models. Securing financing involves multiple sources, including grants, investments, and support from Max Planck.

Bert then delved into the various departments and capabilities of the Lead Discovery Centre, from assay development and high-throughput screening to medicinal chemistry and therapeutic antibody development. He highlighted the importance of their collaboration with both academia and industry, particularly the role of Max Planck Society in facilitating their work through centralized tech transfer.

When discussing their track record, Bert emphasized the significant number of projects they have initiated, the size of their team, the financial turnover, and the numerous industry deals they've closed. Notably, they have projects in

clinical trials and have supported spinouts, showcasing their ability to advance research to later stages.

He also pointed out the substantial funding dedicated to basic research in Germany and the lack of professional drug discovery within academic setups. Bert raised questions about the incentive structures in place, which sometimes hinder the translation of research into practical applications.

To illustrate their work, Bert presented a case study centered around neutrophil extracellular traps (NETs), an innate immune response mechanism. He detailed their efforts to develop inhibitors for NET formation, focusing on a target called "customer in D." However, he also discussed the challenges they encountered, such as competing research suggesting different mechanisms for similar compounds.

Despite these challenges, Bert's team worked diligently to confirm the mechanism of action for their compounds, providing evidence that customer in D plays a crucial role in NET formation. They conducted experiments to demonstrate the impact of their inhibitors and engaged in further research to understand the intricacies of NETs.

In closing, Bert thanked his team and collaborators for their invaluable contributions to their projects. During the Q&A session, he addressed questions about their business model, managing variability in screening, and even how their work could lead to the early diagnosis of certain medical conditions based on NET formation responses.

Bert's presentation offered a comprehensive look into the Lead Discovery Centre's mission, achievements, challenges, and dedication to advancing drug discovery and translational research in collaboration with academic and industrial partners.

Drugging mRNA with Small Molecules: Recent Progress At Arrakis

Jacques Dumas

In Jacques's presentation, he discussed the fascinating field of drugging RNA, an emerging area that combines genetic medicines with gene-based editing and explores the potential of small molecules in various modalities beyond traditional enzyme inhibitors. He introduced AQIS, a biotech company that has been actively working in this field since 2015 and has grown to around 90-97 employees.

The main focus of their work is to develop RNA-targeted small molecules. They run numerous high-throughput screens to find compounds that bind to messenger RNA (mRNA) and modulate its function. Their research aims to harness the potential of two main modalities: direct inhibitors, RNA degraders, and covalent modifiers.

Direct inhibitors are compounds that bind to specific regions of mRNA, altering its function and ultimately preventing the synthesis of specific proteins. In their research, they have collaborated with Roche to work on direct inhibitors. On the other hand, RNA degraders are compounds that induce the degradation of mRNA by attracting processing enzymes. Covalent modifiers, another modality they explore, involve attaching large molecular components to the RNA, which stalls the ribosome and inhibits translation.

Jacques went on to talk in detail about one of their programs, targeting the oncogene MYC. They have developed selective inhibitors that specifically target the long MYC transcript present in tumor cells while leaving the normal MYC transcript in healthy cells unaffected. This selectivity is crucial to minimize off-target effects and enhance the therapeutic potential of the compounds. They demonstrated promising in vitro and in vivo results against MYC in tumor cells, paving the way for potential clinical trials.

Their platform for screening compounds involves target identification, chemical probing, and high-throughput screening using SEC MS (size exclusion chromatography mass spectrometry). This allows them to efficiently screen a large library of compounds and identify potential hits. They also utilize biophysical methods such as SPR (surface plasmon resonance) and NMR (nuclear magnetic resonance) to further characterize compound binding and interaction with RNA.

Despite their progress and success, Jacques acknowledged the complexities of RNA interactions within cells, which can lead to unexpected behaviors and challenges in fully understanding the underlying mechanisms. In particular,

they have observed that compound potency can vary depending on interactions with RNA-binding proteins, leading to different cellular activities. Further research and understanding in this area are critical to maximize the potential of drugging RNA for therapeutic purposes.

Targeting Solute Carriers Developing A Chemoproteomic Drug Discovery Technology Platform

Marko Kljajic

Marko, a highly qualified chemist with a PhD in organic chemistry from the renowned Grass University of Technology, and experience in protein crystallography and biophysics for rational drug design from his postdoc at Philips University Marburg, delivered an engaging presentation at the conference titled "Targeting Solute Carriers: Development of Proteomic Drug Discovery Technology." He is currently working at SolidGate, where their focus lies in fragment-based drug development, chemo proteomics, and the development of targeted degraders of solute carriers (SLCs).

Marko began his presentation by emphasizing the importance of SLCs, a large and diverse group of over 450 proteins responsible for transporting essential metabolites and substrates required for sustaining life. These proteins are not only present in the cell membranes but are also found in various organelles, and some of them exhibit tissue-specific expression patterns. Their significance in cellular functions is immense, and any malfunction in these proteins can lead to the development of diseases. Surprisingly, despite their critical role and wide implications in diseases, there are currently fewer than 20 drugs in the market targeting SLCs. This presents an enormous opportunity for drug development in this area.

One of the primary reasons why SLCs have been challenging to target is the lack of known binders, inhibitors, or activators. This lack of understanding results in a considerable chemistry gap when compared to other membrane proteins like ion channels and GPCRs, which have seen more extensive drug development efforts. SolidGate aims to bridge this chemistry gap by developing innovative and effective drugs that target SLCs.

Marko delved into the process of how SolidGate approaches drug discovery for SLCs. They have an internal database that helps them identify potential SLC targets for drug development. By selecting the right cell line and using proteomics technology, they screen for potential binders among fragments, small molecules that have shown promise as effective starting points for drug development. The use of fragments allows them to efficiently sample chemical space and explore different targets.

Through the proteomic platform, they identify fragments that bind to specific SLCs. To improve the specificity and potency of these fragments, SolidGate performs follow-up assays. They remove the photo-labeling group and the alkine tag from the fragments and replace them with a fluorophore to target proximity. This approach helps them determine the EC50 values of the fragments and understand their effectiveness in blocking the target SLCs.

SolidGate's platform is designed to continuously refine and develop the chemistry of these fragments into more potent and selective compounds. By leveraging various assays and strategies, they aim to identify the most promising drug candidates to move forward with in their drug development pipeline.

During the Q&A session, Marko addressed concerns about tumor plasticity in cancer cells when blocking glucose entrance through SLCs. He acknowledged the complexity of this challenge and mentioned that SolidGate is exploring other non-cancer targets where SLCs play crucial roles. While the field poses various difficulties, Marko remains optimistic about the potential of their platform to discover new drugs targeting SLCs and make a positive impact in various disease areas.

In conclusion, Marko's presentation highlighted the significance of SLCs as important biological targets and the immense potential for drug development in this area. Through their innovative proteomic platform and dedicated research, SolidGate aims to overcome the challenges and bridge the chemistry gap, bringing forth novel drugs that can effectively target SLCs and contribute to better treatments for various diseases.

Identification And Validation Of Novel Targets – Application And Alignment Of Functional Genomic And Chemogenomic Screening In Primary Immune Cells For Drug Discovery

Tim Aslin

Tim's presentation revolved around the integration of chemo-genomic and functional genomic screening techniques within the context of drug discovery. Working at GSK's Screening Profiling and Mechanistic Biology Department in the UK, Tim primarily focused on the identification of potential drug targets using phenotypic screens conducted in primary immune cells.

He initiated his talk with an explanation of functional genomics, a scientific discipline that seeks to connect genetic variations to the malfunctioning of proteins in diseases. He emphasized that this approach necessitates a combination of critical capabilities, such as gene editing, cell biology, omics platforms, and computational biology. These diverse tools and techniques are essential to generate valuable data that can be effectively interpreted to identify potential drug targets.

Tim then introduced chemo-genomic screening, shedding light on the process of systematically assessing the druggable biological space. This involves utilizing a meticulously curated biological compound library to observe the effects of these compounds in phenotypic, cell-based screens. The primary goal of this type of screening is to delve into the biological mechanisms responsible for causing disease-relevant phenotypes. The ultimate aim is to uncover novel drug targets rather than starting points for drug development.

He delved into the composition of GSK's chemo-genomic library, detailing that it comprises approximately 9,000 small molecules, 500 monoclonal antibodies, and around 100 peptides. The library was constructed with a specific set of design principles in mind, aiming to include compounds targeting various types of proteins, offering multiple targets per pathway. Importantly, this library encompasses a range of mechanisms of action, including compounds that activate, inhibit, agonize, or degrade specific targets. The library's annotations are meticulously curated from a multitude of sources, both internal and external, and algorithms are employed to assess the quality of each tool against a particular target. This allows for the quantification and comparison of the effectiveness of different compounds.

One critical point Tim highlighted was that the library provides coverage for approximately 3,900 targets, representing around 19% of the proteome. However, this coverage is not uniform, with more tractable proteins being better represented than those that are less amenable to targeting. This

variability in coverage underscores the importance of integrating chemo-genomic screening with functional genomic screening to enhance the chances of identifying drug-worthy targets.

Further into his presentation, Tim elaborated on the advantages of aligning these two screening technologies. One key advantage lies in pharmacological modulation using the chemo-genomic library. Hits obtained through this method can validate targets initially identified through genetic screens. This validation offers insights into the tractability of these targets. Additionally, chemo-genomic screening can unveil targets and mechanisms that might be missed in genetic screens due to the use of different modalities, such as target agonists or compounds modulating multiple proteins within a pathway. Moreover, this approach can be used to target proteins with slow turnover rates, which would not be suitable for knockout approaches.

Conversely, Tim discussed the specific advantages of functional genomics. This approach is highly specific in its action and can further validate and clarify target hypotheses generated through pharmacological screens. Importantly, functional genomics can potentially provide genome-wide coverage, overcoming the tractability issues that can limit chemo-genomic screening. This allows researchers to explore previously uncharted biological territory.

Summing up, Tim emphasized that aligning chemo-genomic and functional genomic screening mitigates the risk of false negatives and enhances the identification of genetically validated and tractable targets, greatly benefiting the drug discovery process.

Tim then transitioned to a practical application of these techniques, explaining how they were employed to study the role of B cells in autoimmune diseases. He underlined the significance of B cells in autoimmune diseases, particularly their role in producing autoantibodies, which are a hallmark of these conditions. However, existing B cell depletion therapies have limitations, including partial efficacy and potential long-term side effects. Therefore, understanding the complex mechanisms underlying B cell biology is vital for developing more effective therapeutics.

To investigate B cell biology, Tim described a multifaceted approach involving the isolation of B cells from blood samples, their cultivation, and stimulation in vitro. Importantly, this process included the perturbation of B cells using both the chemo-genomic library and arrayed CRISPR screens. This combination of techniques enabled researchers to assess how specific genes and pathways in B cells respond to various perturbations. Omics technologies, such as single-cell RNA sequencing and CyTOF (cytometry by time-of-flight), were used to track the changes in B cell subtypes and differentiation cascades. Flow

cytometry was employed to investigate surface markers, and cytokine readouts were used to monitor the immune response.

Ultimately, this comprehensive approach aimed to identify tractable, genetically validated targets that are relevant to autoimmune diseases. By combining genetic knockout and pharmacological modulation, researchers could gain a deeper understanding of how B cells function in the context of autoimmunity.

Tim concluded his presentation by sharing an example of how these integrated screening technologies were utilized to study macrophage polarization, illustrating their synergy and complementary nature. In this study, IPSC-derived macrophages were stimulated to adopt pro-inflammatory and anti-inflammatory states, mimicking conditions relevant to both autoimmunity and cancer. Researchers used both genomic and functional screens to identify potential drug targets, focusing on high-content imaging data, multiplex cytokine and chemokine data, and global metabolomics to gain insights into the effects of different perturbations.

In summary, Tim's presentation emphasized the value of combining chemo-genomic and functional genomic screening techniques to enhance the identification of promising drug targets. He provided concrete examples of how these methods are applied in research contexts related to autoimmune diseases and macrophage polarization, showcasing their potential to accelerate drug discovery efforts.

Day 1 Track 2 Animal Models for Disease, Organ Modelling – Organoid Based Discovery & Organ On Chip Development

Application of Patient Derived Microtumours In Drug Development

Christian Schmees

During the presentation on the "Application of Patient-Derived Microtumours in Drug Development," Christian, the group leader at Juma biology NMI in Germany, provided insights into their research involving patient-derived microtumours.

Christian's institution is a non-profit foundation that supports application-oriented research for various organizations, including small and medium-sized enterprises, as well as large pharmaceutical and biotechnology companies. They are actively involved in publicly funded projects covering a wide range of natural medical sciences.

The main focus of the talk was on patient-derived microtumours, which are generated from fragments of tumour tissue isolated from different types of solid tumours. The process involves limited enzymatic digestion to obtain a suspension of microtubules, containing both viable and non-viable cells. Notably, this method is unique because it does not require the use of any matrix or hydrogels, making it cost-effective and ethically sound, free from animal components.

One of the key advantages of using patient-derived microtumours is the speed with which downstream analysis can be conducted. Within just two to three days after isolation, the microtumours are ready for further investigation. Additionally, no specialized equipment is needed for their culture, contributing to its accessibility and ease of use.

Christian highlighted the importance of assessing the viability of the microtumours in the initial stages of their study. The majority of microtumours demonstrated robust viability, making them reliable models for drug testing and other experimental assays.

To better understand the composition of the microtumours and their similarity to the corresponding primary tumour tissue, the researchers performed histological analysis and automated immunohistochemistry. This revealed components of the extracellular matrix, cancer-associated fibroblasts, and

infiltrated immune cells, including T cells and macrophages. Furthermore, the expression of immune oncology relevant molecules, such as PDL-1, was also observed.

Christian presented findings from a perspective study focused on breast cancer, where they successfully isolated patient-derived microtumours from a significant number of samples. The microtumours displayed a high degree of histological similarity to the corresponding primary tumour tissue, confirming their relevance as models for further investigation.

The microtumours were also subjected to protein profiling, which demonstrated similarities in protein signalling pathways between the microtumours and the primary tumour tissue. Additionally, they tested various therapeutic approaches, including tamoxifen treatment, taxane-based chemotherapy, and CDK inhibitors. While some patients responded positively to these treatments, a majority did not, indicating the need for personalized treatment approaches.

The researchers also explored the use of microtumours in drug testing for colorectal cancer and glioblastoma. The microtumours were exposed to standard of care therapies and investigational compounds, revealing their potential for preclinical drug testing.

To further investigate the immune response in the tumour microenvironment, the researchers co-cultured the microtumours with tumour-infiltrating lymphocytes (TILs). This allowed them to study the release of cytotoxic mediators, such as interferon gamma and TNF alpha, and assess the efficacy of checkpoint inhibitor treatments.

In conclusion, Christian's presentation shed light on the valuable application of patient-derived microtumours in drug development and preclinical testing. Their ability to closely mimic the tumour microenvironment and their ethical and cost advantages make them promising tools for personalized medicine and future drug discovery efforts.

In Vitro Dog Stomach Organoid Model To Evaluate Compound Bioavailability

Matthaus Brandt

In this presentation, Matthaus Brandt from Novo Nordisk introduces an innovative approach in the pharmaceutical industry—implementing an in-vitro dog stomach organoid model to evaluate compound bioavailability. The presentation falls under the track of animal models for disease organ modeling, organoid-based discovery, and organ-on-a-chip development.

Matthaus starts by explaining the different routes of administering biologics, such as peptides and smaller proteins, namely the parenteral (injection) and oral routes. While the parenteral route is effective in delivering drugs directly to the bloodstream, it comes with some downsides, including complex processes, storage challenges, and patient discomfort associated with injections. On the other hand, the oral route is non-invasive, pain-free, and convenient, leading to higher patient compliance.

The conventional method for assessing drug absorption involves in-vivo studies in dogs. However, this approach has its limitations, such as restricted combinations of tests, low repeatability, significant variations in results, and ethical considerations due to the use of animals. To address these challenges, Matthaus's team aimed to develop an in-vitro model that could simulate the in-vivo environment of the stomach, where drug absorption is known to occur.

They established the in-vitro dog stomach organoid model, a 3D structure that mimics the cellular composition of the stomach. Starting with the isolation of primary cells from the dog's stomach tissue, the team cultured and grew the cells into spherical organoids using Matrigel and a cocktail of different ligands and growth factors. These organoids were characterized by identifying different cell types, such as mucus-producing cells, chief cells, enteroendocrine cells, and stem cells, confirming the presence of a complex, well-organized model.

However, to conduct absorption studies, the researchers needed a 2.5D model. They achieved this by placing the organoids onto Transwells pre-coated with Matrigel and subjecting them to specific culture conditions. The resulting 2.5D model retained essential features of the 3D organoids and closely resembled the in-vivo stomach environment.

With the 2.5D model ready, they performed permeability studies using a small set of compounds. The results showed promising correlations between the in-vitro and in-vivo data, indicating the model's effectiveness in assessing compound bioavailability. The team's next steps include expanding the sample

size and diversifying the compounds tested to validate and enhance the model's capabilities.

The presentation highlights the growing interest in using organoid-based techniques in drug development and reducing reliance on animal testing. It emphasizes the potential of the in-vitro dog stomach organoid model to support compound screening, drug candidate selection, and formulation screening. Future research aims to explore the use of human cells and absorption enhancers to further advance pharmaceutical research and development. The establishment of a microphysiological system center in the US signifies the company's commitment to investing in this technology across various therapeutic areas.

Day 1 Track 3: On Target, Phenotypic, Affinity And Virtual Based Screening

Use of DNA-Encoded Libraries in Drug Discovery At Anagenex

Meghan Lawler

During her presentation, Meghan discussed the potential of using DNA-encoded libraries (DELs) in drug discovery and how her team at Anagenex is rethinking the DEL process to make it more efficient and effective.

DELs are a powerful tool in drug discovery as they allow researchers to generate and screen a vast number of chemical compounds. The process involves linking unique DNA barcodes to building blocks, which results in a large library of compounds. However, the traditional DEL screening process has limitations, as it can only test one compound at a time, leading to a bottleneck in the drug discovery pipeline.

To address this issue, Meghan and her team have integrated machine learning (ML) into the DEL process. They use the data from the initial DEL screening to train an ML model, which can predict potential binders. The ML model provides two valuable outputs: firstly, it suggests external compounds from extensive catalogs that are likely to be binders, and secondly, it creates an "evolve library," a focused set of compounds tailored to the protein of interest.

The evolved libraries allow for rapid exploration of a new chemical space. By combining ML predictions with iterative screening processes, they significantly improve hit rates and reproducibility. The ML model's ability to learn from the data and refine its predictions in each iteration allows for a more efficient drug discovery process.

Meghan shared two case studies during her talk to illustrate the effectiveness of the ML-integrated DEL approach. In one case, they targeted a protein with multiple protein-protein interaction regions and DNA binding domains. Using the evolved library, they identified compounds that could disrupt these interactions, and subsequent biochemical and cell-based assays showed promising activity.

In another case, they aimed to optimize selectivity between two structurally and sequence-wise similar proteins. Through an evolved library and a titration gradient strategy, they identified compounds that showed good selectivity for the desired target.

The incorporation of ML in DEL screening not only accelerates the drug discovery process but also allows researchers to explore a more diverse chemical space efficiently. This approach enhances the identification of potential drug candidates and increases the chances of success in finding selective and effective compounds. Overall, Meghan's presentation highlighted the potential of ML-integrated DELs in revolutionizing drug discovery research.

DELs in Cells

Nils Jacob Vest Hansen

Nils's presentation focused on the innovative DELs-In-Cells assay, which allows the screening of approximately 500 million compounds within a single living cell. The uniqueness of this approach lies in the use of DNA-encoded libraries, where each compound is attached to a specific DNA code, enabling accurate synthesis and subsequent screening.

One of the key challenges in screening DNA-encoded libraries inside cells is efficiently delivering the library into the cell due to its relatively large size. Nils's team overcame this obstacle by micro-injecting the library into large frog cells known as oocytes. These oocytes, which have a diameter of one millimeter, are ideal for such injection and have been widely used in protein production since the 1970s.

The screening process involves discriminating between library members that bind to the target protein of interest and those that bind to endogenous cell proteins. To achieve this, the researchers specifically label the protein of interest with DNA and introduce it into the cell. By doing so, they create a system similar to their screening setup for purified proteins. The DNA-labeled complex formed by the binding of the library member to the target protein can then be identified and analyzed.

The screening process itself is carried out by lysing the cells, adding certain reagents, and shaking the mixture to create emulsions with numerous water droplets suspended in an oil phase. The number of droplets significantly exceeds the number of target molecules, ensuring that any library member bound to the target will consistently end up in a droplet with the target. In contrast, library members that do not bind will only rarely end up in the same droplet by chance. This mathematical principle allows for the identification of potential hits during the screening process.

Nils highlighted several advantages of this approach over traditional screening methods. By conducting the screening in living cells, the assay provides more physiologically relevant conditions, leading to a lower attrition rate in drug development. Furthermore, there is no need to purify active target proteins or

manipulate proteins in plastic, resulting in reduced workload and shorter turnaround times.

The presentation showcased the success of the DELs-In-Cells assay in various partner projects involving different types of targets, including transcription factors, large proteins, and complexes. The researchers have achieved a success rate of over 95% in expressing the target proteins within the cells, making the assay highly efficient and reliable.

While screening in human cells would be ideal, it presents significant challenges and costs. The frog cell model used in the assay offers a suitable alternative, providing a good representation of physiologically relevant conditions without the complexities associated with human cell screening.

In conclusion, Nils's presentation on DELs-In-Cells showcased a cutting-edge screening technology with high fidelity, applicable to a wide range of targets, and offering several advantages over traditional methods. The ability to conduct large-scale screenings within living cells has the potential to revolutionize drug discovery and development processes.

Day 1, Track 4: Automation And Computational Drug Design

Annotating Chemical Space For Automated Drug Design

Baptiste Canault

Baptiste's presentation revolved around the concept of "Annotating Chemical Space for Automated Drug Design" and how his team at GSK (GlaxoSmithKline) is leveraging advanced technology to optimize their drug discovery pipeline. The presentation started with a note of gratitude for the opportunity to discuss the topic at the conference.

The primary goal of GSK's drug discovery cycle is to identify and optimize potential candidate compounds efficiently. To achieve this, they employ a platform called Bradshaw, which plays a pivotal role in the drug discovery process. Bradshaw is an automated platform that guides their drug discovery pipeline, enabling them to reduce the time needed to identify and select candidate compounds.

The process begins by designing molecules and conducting experiments on them. The results of these experiments are then analyzed to extract valuable knowledge, which is used in designing the subsequent cycles. This iterative approach is designed to multiply the number of cycles, refining the project's expectations and rapidly identifying candidate compounds.

The main objective of GSK's Molecular Design Group is to create and implement the Bradshaw system, which streamlines the drug discovery pipeline. By utilizing the data available in their database, they generate a product profile that outlines the goals and optimization criteria for the project.

Bradshaw employs various molecule generators, such as reaction-based, knowledge-based, and deep learning-based generators. This allows them to generate thousands or even millions of chemical solutions or radiations. However, the challenge arises in filtering this vast amount of data to create a manageable list of compounds that can be further processed by chemists.

To address this, GSK uses the GSK Model Collection, which houses both high-throughput and low-throughput models. These models estimate different endpoints based on the project steps. The estimation data is then utilized in the selection protocol, which aims to reduce the number of compounds to a few hundred or thousand, making it feasible for chemists to work on them. Various techniques, such as multi-parametric optimization and active learning experiment design, are employed in this process.

The presentation emphasized the significance of similarity in drug discovery. Baptiste introduced the Chemical Annotation (CA) Score, a novel scoring system developed internally at GSK. The CA Score is designed to effectively distinguish between minor modifications and significant scaffold extensions in chemical structures.

The CA Score considers different molecule representations and combines 13 dissimilarity components using machine learning techniques. This results in a weighted score, with each dissimilarity component assigned a specific weight. The weightings are derived from machine learning models trained on extensive datasets.

Baptiste showcased the validation of the CA Score on real-life examples. It demonstrated that the CA Score outperformed traditional similarity approaches, accurately dissociating chemical patterns and prioritizing compounds of interest. By using the CA Score, GSK was able to explore chemical space more effectively and efficiently, reducing the need for extensive compound screening.

In conclusion, the presentation highlighted the significant role of CSGO (Chemical Annotation Score) in GSK's drug discovery process. The CA Score has become an integral part of their selection and visualization protocols, enabling them to identify compounds that fill the gaps in drug discovery and explore new areas of chemical space. Its superior performance in distinguishing between various modifications and scaffold extensions makes it a valuable tool for accelerating the drug discovery pipeline at GSK.

BAY 069 A Novel Trifluoromethyl pyrimidinedione Based BCAT1 2 Inhibitor And Chemical Probe

Judith Guenther

Judith's presentation was centered around the discovery of BAY-069, a novel trifluoromethyl-substituted BCAT1/2 inhibitor and chemical probe. The talk was structured into two distinct parts, each addressing critical aspects of the research and development process.

In the first part of the presentation, Judith began by expressing gratitude to the organizers for providing her with the opportunity to share their work on the development of BAY-069. She mentioned that her talk would be divided into two main sections. In the first section, she aimed to provide an overview of the discovery process, focusing on the years 2016 and 2017. While she intended to briefly touch upon the structure-activity relationship (SAR) data, her primary goal was to help the audience understand the complications encountered during their journey.

The target of interest was the branched-chain amino acid transferases (BCAT1/2), which are crucial enzymes responsible for the first step in the catabolism of essential amino acids valine, leucine, and isoleucine. These enzymes transfer the alpha amino group to Alpha-ketoglutarate, leading to the formation of an alpha-keto acid. Judith emphasized that alpha-ketoglutarate is known to have a significant impact on tumor growth, making BCAT1/2 potential targets for tumor treatment.

The team embarked on an HTS campaign and discovered around 800,000 compounds, of which 800 were confirmed as primary hits through dose-response studies. Applying a cutoff of about 20 micro molar to the IC50 values, they narrowed down the list to about 400 compounds. Judith pointed out that BCAT1 had a preference for negatively charged compounds, which guided their focus on balancing the acidity in the series. Achieving the right balance of acidity was essential to drive potency while maintaining suitable pharmacokinetic (PK) properties.

During the optimization process, the team prioritized structural diversity while ensuring modulability of acidity through chemical handles. They found promise in a series of trifluoromethyl-substituted pyrrolidines that they had in their collection. Crystallography was employed to gain insights into the binding modes of the compounds. Interestingly, the structures revealed that some compounds exhibited a flipped binding mode, a phenomenon that recurred throughout the project.

After a thorough optimization process, the team successfully identified BAY-069, a potent and selective inhibitor of BCAT1/2 with excellent cellular activity, stability, and permeation properties. The compound was donated as a chemical probe to the Structural Genomics Consortium, and its publication received significant attention from the scientific community, making it the most successful probe of its kind.

In the second part of her talk, Judith shifted the focus to the potential of machine-driven Drug Metabolism and Pharmacokinetics (DMPK) cycles to expedite the drug discovery process. She introduced the concept of employing automation and in silico tools to generate large sets of possible analogs and selecting the best candidates based on prediction tools for relevant optimization parameters.

The critical optimization parameters she highlighted were pKa (acid dissociation constant) and target affinity. The team had access to an advanced pKa predictor by simulations plus, which recognized the potential for acidity in the core and various substituents to modulate pKa. Although this tool was useful, Judith explained that the output of pKa predictions depended on the input terms, such as the specific tautomer used, which could lead to variations in numerical results.

Judith then presented recent data from simulations plus, showing improvements in the accuracy of pKa prediction, indicating progress towards enabling machines to optimize pKa values for a series like BCAT1/2 inhibitors. She also highlighted ongoing work on a term-independent pKa prediction tool, which would further enhance the predictability and robustness of the process.

The second critical optimization parameter, target affinity, presented more challenges. Free Energy Perturbation (FEP) methods, such as FEP Plus, were considered gold standards for target affinity prediction. However, these methods required all analogs in a series to adopt the same binding mode, which was not the case for the BCAT1/2 inhibitors, where flipped binding modes were observed.

In her search for alternative methods, Judith mentioned that Absolute Binding Free Energy (ABF) calculations were explored, but they did not yield the desired discriminative power between regular and flipped binding modes. Additionally, she discussed the recent IFD (Induced Fit Docking) protocol by Schrodinger, but it also faced challenges in handling diverse binding modes.

In conclusion, Judith expressed satisfaction with the successful discovery of BAY-069 as a novel BCAT1/2 inhibitor and chemical probe. She emphasized that the project's success was a result of close interdisciplinary collaboration, careful analysis of structure-activity and structure-property data, and access to

advanced in silico tools. She reiterated the potential of machine-driven DMPK cycles to accelerate drug discovery but stressed the need for continuous scientific improvements and precise technical implementation to achieve robust and reliable results.

Day 2 Track 1: Emerging Modalities Targeted Protein Degradation

QUANTROseq Drug Discovery Based On Transcriptional Fingerprinting

Arriana Sabo

Arianna, the Head of Molecular Biology at Quantro Therapeutics in Vienna, Austria, delivered a compelling presentation on their groundbreaking NGS-based HTS platform. As the head of her team, she leads a group of scientists and informaticians who have made significant strides in developing a platform that seeks to discover drug candidates capable of inhibiting previously undruggable oncogenic transcription factors. The company, Quantro Therapeutics, is a relatively young startup, having been operational for about two and a half years. They are located at the Vienna Biocenter, which houses various research institutes, including the labs of Contra's two founders.

Quantro Therapeutics was founded with the support of Behringer, England venture fund, and Everted. They have also engaged in research collaboration with Boehringer Ingelheim, a major pharmaceutical company in Germany.

The main focus of Quantro Therapeutics is to target transcription factors, specifically oncogenic ones, that have emerged as crucial players in cancer cell growth based on CRISPR screening data. Transcription factors have proven challenging to target with traditional small molecules, and thus, Contra is exploring alternative approaches to inhibit their function.

During her presentation, Arianna highlighted the significance of their technology in identifying drug candidates for transcription factors. The platform exploits the idea of target protein degradation, particularly through glue-mediated degradation. This approach is crucial in screening their library for potential drug candidates.

The key challenge they face is screening in a cellular context, where the complexity and noise of the system make it difficult to find selective inhibitors. Quantro’s team believes that the best way to observe direct effects is by focusing on transcription as a direct readout, given their interest in transcription factors. They emphasize the importance of looking at ongoing transcription rather than steady-state RNA levels to capture real-time effects.

The platform employs a cutting-edge technique called "slam seek," which is a modified version of RNA-seq. This technique allows the team to label newly produced RNA using modified nucleotides, giving them the ability to observe

changes in transcription within a couple of hours rather than waiting for a day or more. This real-time resolution is a significant advantage over traditional methods.

The slam seek technique involves incorporating modified nucleotides into the newly produced RNA in cells. Subsequently, the RNA is treated with a chemical that results in the introduction of mutations during reverse transcription and sequencing. This approach allows them to differentiate between newly produced RNA and older RNA in the cell. Consequently, they can analyze the direct targets of transcription factors with great precision.

Arianna explained how Quantro Therapeutics created a repository of fingerprints using slam seek on various tool compounds and engineered target proteins. This repository serves as a reference for comparing the transcriptional fingerprints of molecules from their screening library. Their goal is to identify drug candidates that match these fingerprints, indicating potential inhibitors of their target transcription factors.

The presentation touched on a successful proof of concept experiment, where they tested compounds targeting the K RAS pathway provided by Boehringer Ingelheim. The team was able to differentiate compounds that targeted the pathway from those unrelated to it based on their transcriptional fingerprints.

Arianna highlighted that the platform is sensitive enough to detect early chemical leads with limited potency. Additionally, the technique allows them to multiplex and screen multiple targets simultaneously, making it cost-effective and powerful.

However, it's essential to clarify that the technology is still in its early stages, and specific data from their screening efforts were not provided in the presentation. Further validation and optimization are ongoing before moving forward with large-scale screening.

In the Q&A session, Arianna addressed additional inquiries about comparing their platform's performance to classical RNA-seq analysis and the possibility of exploring alternative splicing or different promoter sites, providing valuable insights into their approach's advantages and scope.

Overall, Arianna's presentation demonstrated an innovative and promising approach to discovering drug candidates for previously undruggable transcription factors, potentially revolutionizing cancer research and drug discovery efforts.

Function First Strategy That Enables Efficient And Productive Generation Of Degraders With Identification Of Novel E3 Ligase Binders

Yusuke Tominari

Yusuke, the co-founder and CEO of YMax, delivered an insightful speech that shed light on their company's ambitious mission: to target undruggable proteins through targeted protein degradation. With an impressive background, including positions of increasing responsibility at Takeda pharmaceutical company and a PhD in organic chemistry from the University of Tokyo, Yusuke presented himself as a highly knowledgeable and experienced speaker.

He began his speech with gratitude for the opportunity to introduce YMax's groundbreaking work in the field of science. He explained that YMax's mission is to tackle undruggable targets by employing targeted protein degradation. The company was co-founded in 2018 with Dr. Khanna, emerging as a spin-out company from Takeda. Their proprietary platform, named "Rapid," played a crucial role in facilitating the discovery of degraders.

Yusuke elaborated on the challenges in targeted protein degradation, emphasizing the importance of selecting the most suitable "E3 ligases" to ensure the effectiveness of degrader development. He discussed their innovative approach to identifying such ligases, focusing on proprietary Israelites binders like X, IP, and USA.

To demonstrate the practical application of their approach, Yusuke presented two examples using "Rageous B" and "AR" proteins. He explained how YMax successfully identified suitable binders for these degrader programs and went on to design effective degrader molecules based on the obtained information.

One of the most remarkable aspects of their work was the high hit rate they achieved in identifying potential binders for their degrader programs. This efficiency allowed them to develop new compounds at an impressive rate, making significant progress in a relatively short time.

Yusuke highlighted the significance of drug permeability in targeted protein degradation. He shared valuable data showcasing the impact of different parameters, such as molecular weight and the number of rotator bonds and hydrogen bond donors, on the compounds' permeability. This information guided their optimization efforts to enhance drug permeability and improve compound properties.

Throughout the presentation, Yusuke's expertise and enthusiasm were evident as he confidently discussed the progress made by YMax. He emphasized the

importance of robust screening systems and the use of high-throughput approaches to accelerate their work. The results they achieved showcased the potential of targeted protein degradation as a promising solution for previously undruggable targets.

In conclusion, Yusuke's speech provided an in-depth understanding of YMax's mission, their proprietary platform "Rapid," and their approach to identifying suitable E3 ligases for targeted protein degradation. He showcased examples of successful degrader development using their methodology and highlighted the high productivity they achieved in identifying potential binders for degrader programs. The audience was left inspired by YMax's cutting-edge research and potential impact on drug discovery and development.

Day 2 Track 2: Hit Finding Advancements And Molecular Drug Design

Evolving Hit Discovery For Challenging & Novel Targets

Ian Storer

During the presentation, the speaker highlighted the company's strategic focus on exploring novel targets and leveraging emerging technologies to advance drug discovery efforts. They emphasized the importance of investing in lead identification and expressed optimism about the opportunities that lie ahead in the coming years.

A key aspect of their approach involves utilizing artificial intelligence and machine learning to analyze vast amounts of data, including genomic research and multi-omics data. This enables them to identify potential targets and patient cohorts for their therapies more effectively. Additionally, they are collaborating with research organizations to benefit from their expertise and gain access to diverse resources.

Automation and AI are central to their drug discovery process. The company envisions achieving autonomous operations where robotics and AI work cohesively to make informed decisions and optimize experiments. The goal is to operate 24/7, enhancing productivity and data quality.

As part of their expansion plans, the company is building a new state-of-the-art facility with advanced robotics and high-throughput screening capabilities. This infrastructure will allow them to process and analyze large compound libraries quickly, enabling faster and more efficient drug discovery.

In parallel, the company is exploring various modalities, including small molecules and RNA-based therapies, to target challenging diseases effectively. They are particularly interested in RNA-targeted approaches and are actively developing methods for screening and binding affinity assessment.

Despite their progress, the speaker acknowledged that challenges remain, especially in translating RNA-binding affinity from in vitro to in vivo conditions. The company is actively working to bridge this gap and develop strategies for screening RNA-targeted therapies effectively.

Overall, the company's multifaceted approach to drug discovery involves the integration of cutting-edge technologies, collaborations, and infrastructure investments. Their commitment to innovation and continuous improvement

reflects their dedication to advancing drug development and bringing novel therapies to patients in need.

Address Biophysical Tools For Small Molecules & Difficult Targets

Matthias Frech

In the speech, the speaker began by expressing their excitement to present on biophysics and drug discovery, reflecting on their experiences over the past 20-25 years at Merck healthcare kGA. They emphasized the role of biophysics in understanding the interactions between small molecules and target proteins and the significance of affinity measurements.

The talk covered the implementation of kinetics in drug discovery and the growing importance of on and off rates in understanding molecular interactions. The speaker highlighted the use of various biophysical methods, including Surface Plasmon Resonance (SPR), X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy (cryo-EM). These methods are used to obtain high-quality data on the interactions and kinetics of compounds with their targets.

Although biophysics is a supportive part of drug discovery, the speaker emphasized its essential role in selecting the right compounds and guiding optimization efforts. They mentioned that biophysical methods help in identifying the right compounds by considering kinetics, affinity, and binding signatures, in addition to traditional assays like IC50 determinations.

Examples were provided to illustrate the application of biophysics in drug discovery. One such example involved the Spleen Tyrosine Kinase (STK) program, where biophysical platforms were used to screen different activation statuses and select compounds based on their interaction kinetics and affinity.

The speaker also discussed the challenges in drug discovery and the need for proper integration of biophysical methods into the research process. They mentioned the preparatory phase involved in setting up the assays, including screening across different assay buffer conditions and immobilization techniques.

Regarding biophysical techniques like MicroScale Thermophoresis (MST) or Native Mass Spectrometry (Nathalia), the speaker stated that they can offer value and complement other biophysical methods. However, they emphasized that their preference lies with technologies that provide more parameters, such as SPR and ITC, which offer richer information content.

Furthermore, the talk touched upon the importance of understanding protein dynamics and flexibility in compound optimization. The speaker mentioned that NMR studies and relaxation dispersion analysis can provide insights into these aspects and can aid in the selection of the most appropriate compounds for further optimization.

In conclusion, the keynote address underscored the significant role of biophysics in drug discovery, enabling researchers to select the right compounds and understand the mechanisms of interaction between small molecules and their target proteins. The integration of various biophysical methods, along with other assays, allows for a comprehensive and effective approach to drug discovery.

Integration Of Technologies For HIT Triage & Early Exploration

Uli Schmitz

In Uli's presentation, he provided some background information before delving into the main topic of antiviral therapies. The backbone of their research and drug development efforts consisted of antivirals targeting HIV, HPV, and hepatitis C and B viruses. A key focus was on nucleoside-based drugs, which act as prodrugs for active ingredients.

Uli emphasized the significance of single tablet regimens, which combine multiple drugs, making treatment more convenient for patients. Additionally, he highlighted the importance of nucleus sites, a special category of drugs known for their high barrier of resistance and broad genotype coverage. These nucleus sites are crucial for effective antiviral therapies.

However, Uli recognized that developing antiviral drugs required effective cell-based systems to ensure proper metabolism and action of the compounds. For instance, in the case of hepatitis C, replicants were used to study viral replication partially.

The focus then shifted to the challenge of targeting cccDNA transcription in hepatitis B. This virus establishes a permanent presence in liver cells through its unique life cycle, involving specific entry points and nuclear DNA introduction. The viral replication process produces not only full variants but also envelope proteins that become HPV antigens, specifically the small antigen and the E antigen.

Uli's team sought to explore mechanisms for targeting cccDNA transcription directly, which required delving into host factors, a complex and challenging task. To achieve this, they employed a screening approach called Point library,

which involved an SI RNA screen for host targets and several phenotypic screens under different conditions and in various cell types.

The presentation then delved into two compounds that sparked excitement in their HPV efforts. The first was an epigenetic KDM5 inhibitor, which showed potent antiviral activity against multiple HPV genotypes. Of particular interest was its continuous increase in antiviral activity even after a single pulse dose, suggesting the possibility of less frequent dosing.

The second compound was retinoic acid, specifically Accutane, a well-known drug for juvenile acne treatment. Accutane displayed impressive antiviral activity against HPV in vitro, but the results were less promising in an immunocompromised mouse model with humanized liver.

To understand the complex phenotypic screening data, Uli's team performed extensive transcriptome analysis. However, they discovered that this analysis often produced hypotheses without clear explanations.

In the case of Accutane, the team made an intriguing observation about culturing hepatocytes. The culturing process, involving dexamethasone, seemed to downregulate the SHP gene, leading to reduced viral replication in hepatocytes. Accutane, on the other hand, reversed this process, making hepatocytes less hospitable to viral replication.

In conclusion, Uli's presentation highlighted the challenges and complexities of antiviral drug development, particularly in deciphering phenotypic screening hits. The data analysis and validation of assumptions are crucial in understanding the mechanisms of action in complex cellular systems, and it often requires a multidisciplinary approach.