BEST PRACTICE EBOOK

Leveraging Advanced Screening Practices to Improve the Efficiency & Efficacy of Drug Discovery

Catch Up With Industry Experts on Drug Screening Strategies

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Introduction

Screening is the process by which potential drugs are identified and optimised before selecting a candidate drug to progress to clinical trials. It can involve screening large libraries of chemicals for a particular biological activity in high-throughput screening assays.

In drug discovery, there are two distinct approaches, phenotypic screening (classical pharmacology) and target-based drug discovery (reverse pharmacology). Target-based drug discovery is based on the formulation and testing of specific molecular hypotheses, while in phenotypic drug discovery, the molecular mechanism of action is not assumed and does not require knowledge of the molecular target. Phenotypic screens are commonly used at the whole animal level whereas target-based discovery benefits from the advances and evolution of science in biochemistry, structural biology, and genomics. Drug discovery is a lengthy and costly process with the average cost of developing a new drug exceeding $2billion. Furthermore, the average cost has risen unprecedentedly in the last few years. Despite advances in technologies in the last decade, there has been a decline in the discovery of new molecular entities.

The experts in this eBook use specific case studies to demonstrate how best practices in drug screening can lead to the identification and validation of drug targets. Technologies such as AI/ML, automation, and high dimensional experimentation are increasingly being implemented into screening workflows to enhance these key steps in the drug discovery process. The speakers also discuss the advantages and disadvantages associated with different screening methods as well as the potential of combining screening techniques. By adhering to these practices, scientists can drive innovation and continue pushing the boundaries of drug discovery.

Lucia Simmen,
Digital Content Editor, Oxford Global

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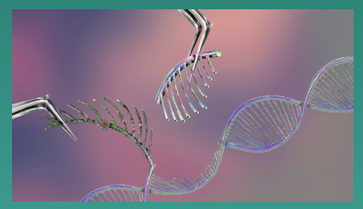
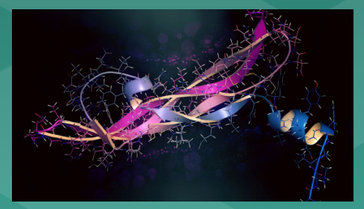




Key Summaries

Nazia Parvez of **GSK** discusses the challenge of identifying novel, effective therapeutic targets for increasing regulatory T cell (Treg) abundance to treat autoimmune diseases. Treg characteristics such as their inherent instability, plasticity, and low abundance in peripheral blood make them difficult to isolate in sufficient quantities for high throughput screening. To tackle this, she suggests using a chemogenomic approach combined with high throughput screening. This allows for the simultaneous identification of biological targets and validation of drug traceability.

Andrew Scott of **Concept Life Sciences** highlights that there is a lack of clinical candidates targeting the BRPF1 protein. Existing tool compounds such as GSK6853 have poor bioavailability and moderate solubility. To address this issue, he suggests a combined approach using fragment-based drug discovery (FBDD) and virtual screening via the Concept Life Sciences BioPALS platform. This method reduces time and cost compared to traditional methods.

Linda Kitching of **AstraZeneca** explains that translating new targets into successful drug discovery campaigns is usually slow and challenging, particularly with complex protein targets. However, AstraZeneca's Protein Degradation NanoSAR platform is a high-throughput system that generates diverse PROTAC libraries which enables faster identification of potent hits with minimal toxicity.

Leire Escudero-Ibarz of **AstraZeneca** analyses the importance of target identification and validation in drug discovery. The main challenge is the lack of efficacy displayed by candidate drugs in clinical trials which prevents them from progressing along the drug discovery pipeline. Escudero-Ibarz suggests integrating in silico evaluation, in vitro screening, and in vivo disease-relevant models with genomic data to advance drug discovery.

Nazia Parvez
Investigator
GSK

Andrew Scott,
Associate Director
Concept Life Sciences

Linda Kitching
Associate Director,
AstraZeneca

Leire Escudero-Ibarz,
Associate Director,
AstraZeneca

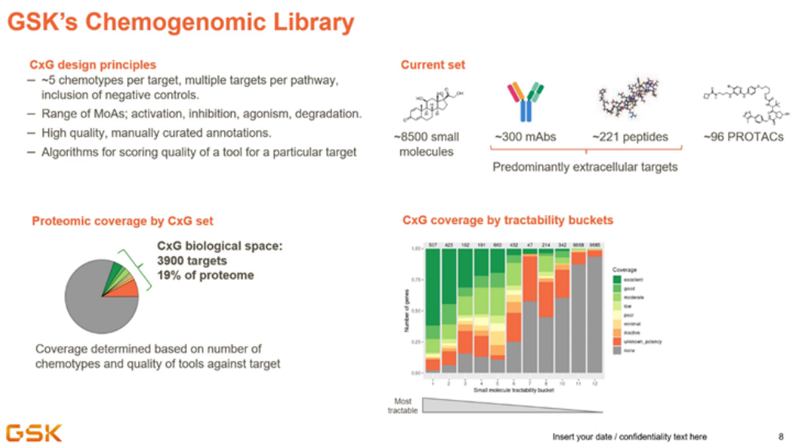
Advanced Screening Stratgies In Drug Discovery

Addressing Autoimmune Disease Through Phenotypic Screening of Tregs: GSK's Chemogenomic Approach to Novel Target Identification

Nazia Parvez, (Investigator, GSK), discusses her work on phenotypic screening of regulatory T cells (Tregs) for autoimmune diseases. Tregs, a subset of CD4+ T cells, play a crucial role in suppressing immune responses, maintaining self-tolerance, and preventing autoimmunity.

Defects in Treg number or function can lead to autoimmune disorders like rheumatoid arthritis or type 1 diabetes. Current autoimmune treatments, such as JAK inhibitors or monoclonal antibodies, have limitations like side effects and loss of efficacy, highlighting the need for novel therapies.

GSK aims to identify new targets to increase Treg abundance using a chemogenomic approach. Chemogenomics combines chemical libraries with cell biology to discover and validate drug targets. The library contains annotated compounds, enabling researchers to explore disease-relevant phenotypes and accelerate drug target identification. The diverse nature of GSK's chemogenomic library is illustrated in the slide below.



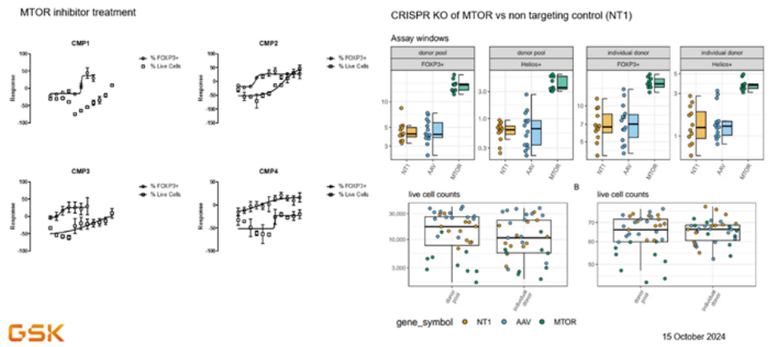
In this project, the focus is on phenotypic screening using high throughput flow cytometry to measure Treg populations based on specific markers like FoxP3, CD25, and CD127.

The workflow involves using human primary CD4+ T cells, isolated from leukapheresis products, and subjected to various screening protocols. The chemogenomic screen, combined with functional genomics (CRISPR knockout), helps identify genetically validated, tractable targets. The screening campaign uses a diverse set of small molecules, antibodies, and peptides, covering various mechanisms of action. Parvez emphasised the importance of donor consistency in the screening process, she aimed to pool donors of the same sex, age group and human leukocyte antigen (HLA) type. The chemogenomic screen consisted of a primary single shot screen. She outlined the hit rate which was 54%.

One example is the MTOR signalling pathway, which is central to autoimmune diseases. Inhibiting MTOR expanded Treg populations in both the chemogenomic and CRISPR screens, linking genetic and pharmacological evidence.

Example

MTOR small molecule inhibition and gene KO expands Treg phenotype within CD4+ T cell Population.



In conclusion, this phenotypic screening strategy offers potential opportunities for early-stage drug discovery by identifying novel therapeutic targets to treat autoimmune diseases.

Overcoming the Challenge of BRPF1 Inhibition With a Rapid Discovery of Novel Binders Using BioPALS & Virtual Screening

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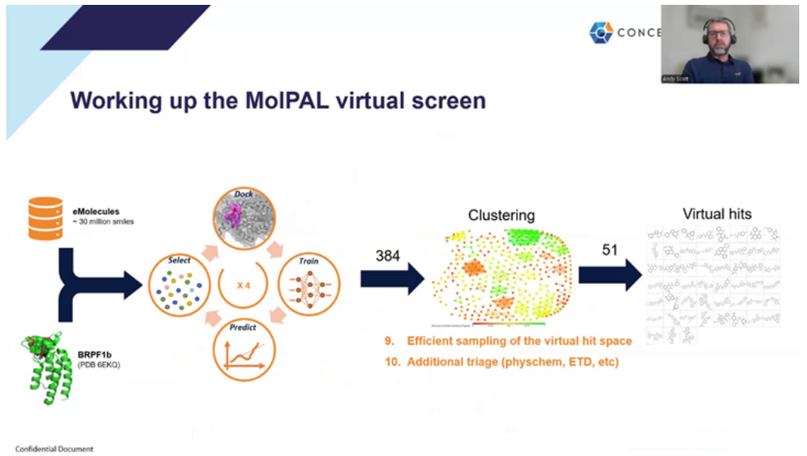
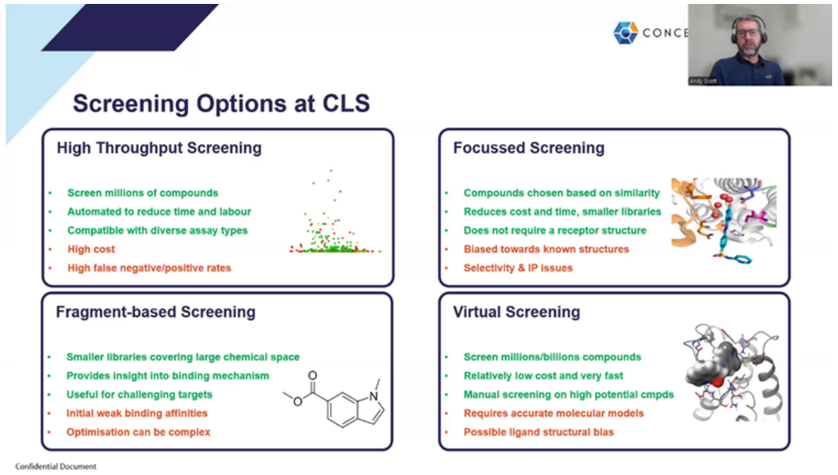


Andrew Scott's (Associate Director, Concept Life Sciences) presentation focused on an internal project at Concept Life Sciences targeting BRPF1, a bromodomain-containing protein linked to liver cancer, hepatocellular carcinoma (HCC) and developmental disorders. The aim was to discover inhibitors for BRPF1, for which no clinical candidates exist despite its strong connection to HCC. The team explored several screening strategies including high-throughput screening (HTS), focused screening, fragment-based drug discovery (FBDD), and virtual screening.

BRPF1 plays a role in gene regulation by recognizing acetylated lysines on histone proteins. Overexpression of BRPF1 is associated with poor survival in HCC patients, making it a key target for cancer therapies. While some tool compounds like NI 57 and GSK6853 have been discovered, they suffer from issues like poor solubility and bioavailability, which limits their potential.

Scott outlined the screening approaches deployed at Concept Life Sciences. He discusses the advantages and disadvantages of each approach.



Given the availability of BRPF1 structures and Concept Life Sciences' expertise in virtual screening and fragment screening, the team opted for a hybrid approach. The virtual screening used a structure-based technique called Molecular Pooled Active Learning (MoPAL), which combines machine learning with chemoinformatics to identify promising candidates. Through iteratively screening and training a model on docking scores of an initial subset, they refined their selection to 51 virtual hits based on properties like solubility, size, and cost.

These hits underwent GCI assays, resulting in 36 compounds with binding affinities within the micromolar range. Subsequently, 20 candidates advanced to orthogonal screening using Differential Scanning Fluorimetry (DSF) to assess binding stability, with nine compounds selected for further analysis. NMR techniques confirmed binding, leading to five prioritized hits, which Concept Life Sciences will develop further.

Overall, Scott highlighted Concept Life Sciences' BIOPALs platform as a versatile and cost-effective screening solution across various target classes. In under six weeks, it enabled the identification of five potential BRPF1 binders, paving the way for further optimisation and potential drug development.

Accelerating Success with Advanced Assays, Automation, and Innovative Screening to Enhance Efficiency in Drug Discovery

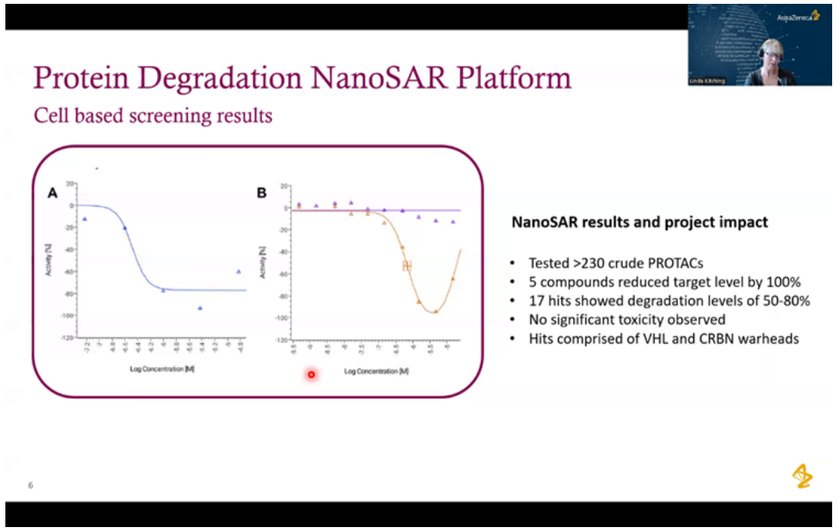
Linda Kitching (Associate Director at AstraZeneca) focused on accelerating drug discovery through three key strategies employed by her team at AstraZeneca. They work in the assays, profiling, and cell sciences department to support oncology and neuroscience projects. She highlighted three key approaches.

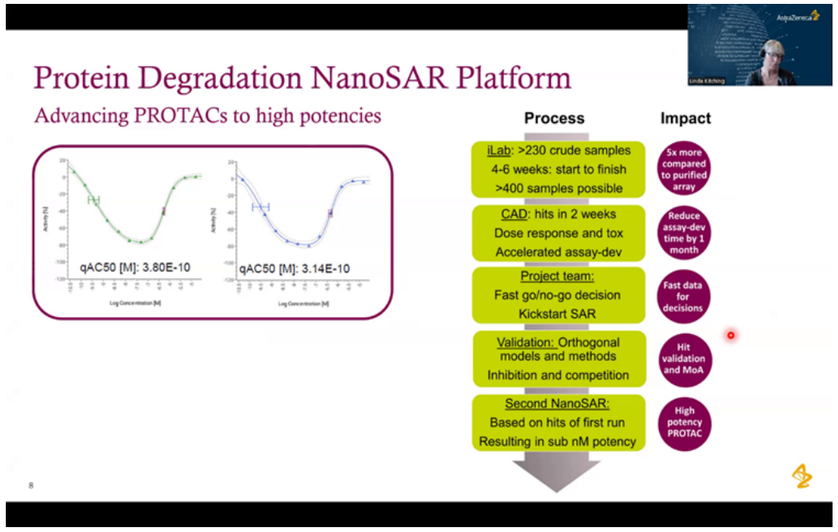
Protein Degradation NanoSAR Platform

The team developed a high-throughput system to produce diverse Proteolysis Targeting Chimeras (PROTACs), which target specific proteins for degradation. AstraZeneca's NanoSAR platform enables the rapid and cost-effective generation of diverse PROTAC compounds. This approach allows rapid identification of potent compounds with low toxicity, providing accelerated timelines for hit identification and validation. Their optimised workflow generated decision-enabling data quickly, improving the efficiency of the drug discovery process.

Kitching highlighted the challenge of the PROTAC hook effect which refers to a phenomenon when excessively high concentration of PROTACs can lead to reduced efficacy in targeted protein degradation. This takes place when the concentration of PROTACS overwhelms the machinery.

Kitching conducted an experiment to test 230 crude PROTACs which yielded 17 hits showing degradation levels greater than 50%. Furthermore, there were no signs of significant toxicity. The hits were then validated, and confirmation of activity was shown via Western Blot.

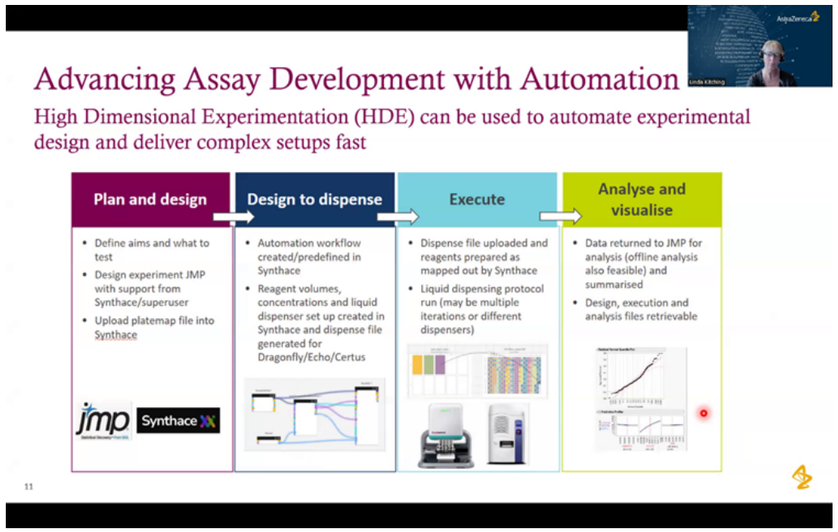




Advancing Assay Development with Automation

Automation through high-density experimentation (HDE) has reduced manual work, increased throughput, and improved the quality of assay development. By partnering with Synthace, her team designed an automated workflow that allows multifactorial experimental setups with reduced resource equipment. The experimental design is developed in a statistical package, such as JMP, which optimises the setup for the most efficient use of resource.

By uploading the plate map and required reagent concentrations, Synthace generates a dispense file compatible with automated liquid dispensers like the Dragonfly and Echo systems. This dispense file directs the machine to precisely handle and distribute reagents, minimising manual intervention.

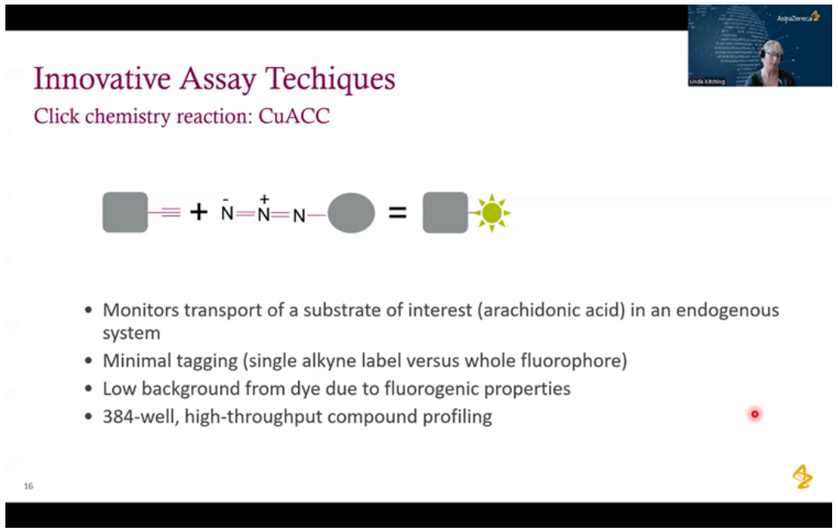


By using multifactorial experimental designs, they could test complex conditions quickly, saving time and resources, while making the experimental process more sustainable. Furthermore, this method allowed researchers to identify optimal conditions to build a

robust assay.

Innovative Assay Techniques – Fluorogenic Click – IT Probes

The team developed a novel assay technique to address the challenges of targeting complex proteins. The team applied copper-catalysed click chemistry and fluorogenic dyes to develop novel assays for studying complex proteins and their interactions. The key advantage of this method is that minimal tagging is required and the fluorogenic dye generates minimal background fluorescence, ensuring that the signal is specific to the transport activity being monitored. This innovative method allows for the detection of substrate transport in cells, producing robust data and enabling high-throughput screening.



HDE was used to identify optimal assay conditions, minimising signal variability and ensuring the assay's robustness for high-throughput applications. Moreover, Kitching's team was able to rank compound activity. She also stressed the need for a collaborative working environment to run experiments like these.

Kitching concluded by emphasising the positive impact these approaches have had on accelerating drug discovery, improving efficiency, and enabling faster delivery of potential new therapeutics.

Overcoming Target Discovery Challenges in Drug Development by Using Functional Genomics and CRISPR to Unlock Novel Therapeutic Solutions

Leire Escudero- Ibarz (Associate Director in Discovery Sciences at AstraZeneca), discussed a platform for identifying and validating novel therapeutic targets as part of AstraZeneca's drug discovery pipeline. The presentation emphasised the critical importance of target identification in drug development, noting that failure in drug efficacy, rather than safety, is the leading cause of clinical trial failure. AstraZeneca's platform integrates human genetics, omics data, and advanced disease models to improve target discovery and validation, with a focus on leveraging CRISPR screening technologies.

Escudero-Ibarz highlighted the company's use of the "5R framework" (right target, patient, tissue, safety, and commercial potential) to guide decision-making and improve R&D productivity. She detailed how the functional genomics platform, particularly CRISPR-based screening, is used to explore the genetic links between diseases and potential therapeutic targets across various disease areas.

Case Studies

Idiopathic Pulmonary Fibrosis

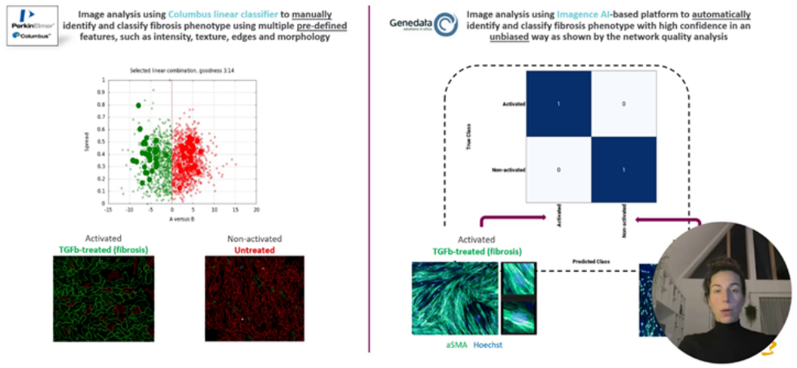
The first case study focused on idiopathic pulmonary fibrosis (IPF). Escudero-Ibarz elaborated on the harsh nature of this disease; IPF is a chronic disease that results in progressive lung scarring (fibrosis) and causes life threatening complications including respiratory failure. There is no effective cure for this condition, therefore it is vital to identify and understand key pathways in IPF.

CRISPR screening and AI-driven knowledge graphs were used to identify key targets related to fibrosis and senescence. The team were able to distinguish between hits that exacerbated or inhibited fibrosis.

Machine learning was used to refine target lists and high-content imaging helped monitor phenotypic changes and target effects, allowing the researchers to single out promising hits. Hits from the CRISPR screen were validated based on their ability to reduce fibrosis markers and align more closely with non-fibrotic (baseline) cell profiles. Promising targets from this process moved forward for additional validation steps, including safety and pharmacology assessments.

Case study 1

Target discovery in IPF by deploying KG for target prediction, arrayed CRISPR screening and AI/ML image analysis



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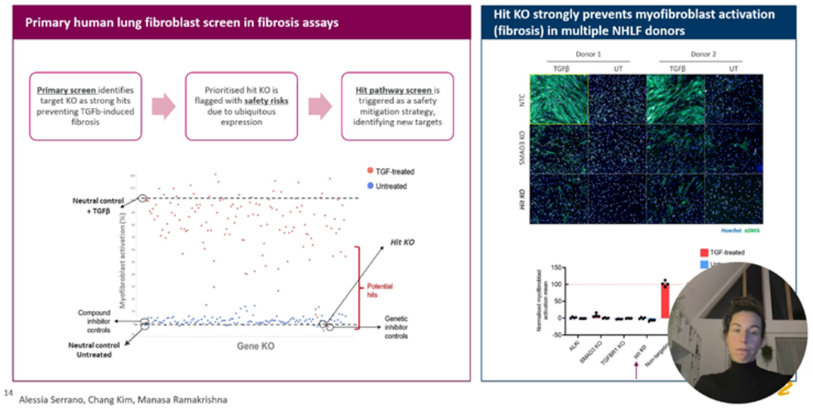
Case study 1

Identification of CRISPR hits inhibiting TGFβ-induced fibrosis



14 Alessia Serrano, Chang Kim, Manasa Ramakrishna

Regulatory T Cell Engineering

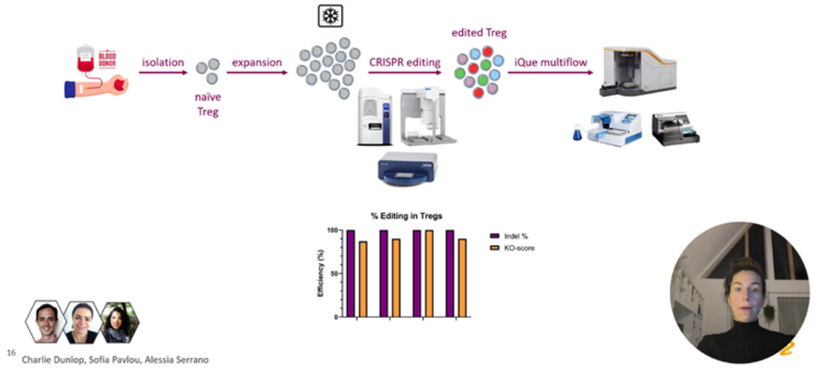
The second case study discussed using CRISPR technology to enhance regulatory T cell (Treg) stability and functionality for autoimmune diseases by identifying genes that help boost Treg effectiveness under inflammatory conditions.

The team was able to identify gene knockouts (KO) that were able to modulate Treg stability. Furthermore, the group built on their research by optimising assay conditions that gave insights into the stability and functionality of Treg cells in the disease context. The team conducted high-dimensional experimentation (HDE), adjusting variables such as cytokine combinations, treatment durations, and concentrations to replicate the complexity of inflammatory environments. This setup allowed them to systematically determine the best conditions to destabilize Tregs. This allowed for a more realistic assessment of which gene knockouts could counteract inflammation-induced loss of Treg stability.

Hits that showed a significant positive impact on Treg stability across multiple donors were identified as potential therapeutic targets. These hits not only demonstrated efficacy in maintaining Treg function in inflammatory conditions but also showed reproducibility, a key factor for progressing to therapeutic development.

Case study 2

Novel Treg cell therapy strategies in immune-mediated diseases by deploying our immune arrayed CRISPR editing platform



16 Charlie Dunlop, Sofia Pavlou, Alessia Serrano

In conclusion, Escudero-Ibarz stressed that collaboration across teams and disciplines is essential —both internally within AstraZeneca and with external partners—is critical for driving innovation in drug discovery. She encouraged participation in future collaborations through AstraZeneca's open innovation portal.

Report Conclusion

Overall, this eBook explored significant developments in phenotypic screening and target-based screening. The featured industry experts demonstrated how best practices such as multi-disciplinary collaboration, automation, AI/ML, chemogenomic approaches, and data analysis are crucial to pushing more candidates through the drug discovery pipeline to clinical trials.

The implementation of AI/ML saves time and resources and increases the likelihood of a drug candidate's success. AI/ML tools can quickly identify novel compounds and targets to speed up drug discovery. Given the financial costs associated with drug discovery and its time-consuming nature, it is key to save resources wherever possible. Furthermore, due to the size and inter-disciplinary characteristics of drug discovery projects, the speakers stressed the importance of multi-disciplinary efforts: drawing from expertise from quantitative biologists, medicinal chemists, computer scientists, and screening experts is essential to advancing drug discovery efforts.

If data is biased this can lead to false positives. However, active efforts are being made to mitigate this issue; it is essential to integrate various data sources, such as omics data, human genetics, and advanced disease models as this approach will give scientists a more well-rounded understanding and allow them to draw meaningful conclusions from highly complex information. As a result, this could improve the selection of higher-quality drug candidates. Off-target effects remain a challenge in drug discovery, they can produce false positives or false negatives in screening assays which can lead researchers to misinterpret screening results. Therefore, researchers may accidentally invest in compounds that lack efficacy.

To keep up to date with the latest trends in drug discovery don't miss out on our Discovery & Development Europe 2025 event taking place 23rd - 24th of June in Basel, Switzerland. With 3 tracks dedicated to identifying and validating novel targets, innovative hit identification for target protein degradation, and implementing robotics and automation into screening workflows, this event provides an unparalleled opportunity to connect with key opinion leaders and industry experts in the drug discovery space.