CASE STUDY REPORT

Advancing Drug Discovery Through Innovative Technologies & Strategic Collaboration

A Concise Report Featuring Insights From The Prominent Thought Leaders Of Discovery & Automate 2024

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Introduction

Drug Discovery is a challenging and multifaceted discipline that draws upon expertise from the fields of computer science, pharmacology, chemistry and biology. The global drug discovery market size was valued at USD 59.92 billion in 2021 and is expected to reach USD 120.80 billion by 2030, growing at a CAGR of 9.16%.The market is driven by the rising prevalence of chronic diseases, rising healthcare expenditure and patent expiration of popular drugs across the globe.

At the core of this market reports lies three key themes that point to an important aspect in the drug discovery field.

Integration of Advanced Technology In Drug Discovery

Advancements in Artificial Intelligence (AI) and Machine Learning (ML) and other computational tools are driving innovation in drug discovery. AI recognises hit and lead compounds and provides a quicker validation of drug target and optimisation of the drug structure design. While ML algorithms can be trained to predict drug properties using a database of known compounds.

Challenges and Strategies in CNS Drug Discovery and Development

The complex nature of the central nervous system (CNS) presents unique challenges that require innovative solutions. The main factors responsible for the failures in CNS drug development are a lack of understanding of the basic elements of CNS disease, the possibility of CNS side effects and the inability of drugs to penetrate the blood-brain barrier (BBB).

Recently, nanoparticles, liposomes and other carriers have shown promise in improving drug delivery to the brain. This case study report discusses important challenges such as the translational gap in CNS disorders and ways of overcoming this. A case study on brainshuttle technology as a drug delivery method and its recent success in a Phase 1a clinical trial shows hope for Alzheimer's patients.

Data-Driven Approaches & Predictive Modelling

Collecting, analysing and optimising data helps scientists make informed decisions and optimise processes within drug discovery. This report discusses how high-throughput experimentation (HTE) and mechanistic modelling rely on data to inform drug discovery strategies and improve outcomes. The potential of integrating digital technologies, automation and advanced analytics in pharmaceutical R&D workflows could save time and resources and most importantly improve patient outcomes.

As we dive into this case study report, we draw conclusions from the in-depth insights proposed at the recent Discovery & Automate 2024 event, a gathering of over 650 industry professionals focused on pushing the boundaries of drug discovery. By conducting a rigorous analysis of presentations, data and expert perspectives, this report offers a nuanced understanding of the current landscape, strategic challenges, and emerging opportunities in the discovery field.

Lucia Simmen,
Digital Content Assistant, Oxford Global

Contents

Key Speakers Include

Davide Gianni
Senior Director,
AstraZeneca

Irene Choi,
Senior Director,
Verge Genomics

Henrik Möbitz ,
Director (CADD, Global Chemistry) ,
Novartis

Key Speakers Include

Adriana Savoca,
Associate Director
AstraZeneca

Tom Kissling ,
pRED Lab Automation Partner,
Roche

Ulrike Kuenzel
Associate Principal Scientist
AstraZeneca

Key Speakers Include

Stefan Schiesser,
Director of Medicinal Chemistry
Novartis

Graham Dempsey ,
Founder & CSO
Quiver Bioscience

Julie Fournier ,
Senior Scientist ,
GSK

Integration of Advanced Technology In Drug Discovery

A recent report published by Fortune Business Insights states that the global artificial intelligence in drug discovery market size is projected to grow from $3.54 billion in 2023 to $7.94 billion by 2030, at a CAGR of 12.2%.

The Power of Partnerships in Functional Genomics

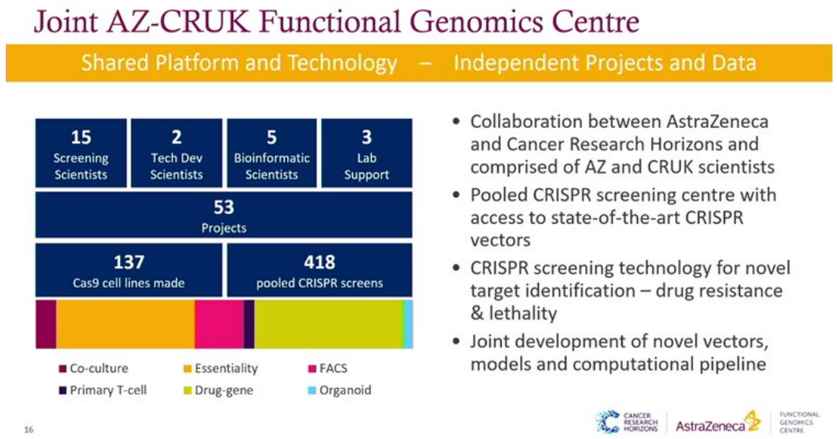
Davide Gianni (Senior Director, AstraZeneca) discusses the importance of partnerships in functional genomics. Functional genomics is the study of how genes and pathways contribute to disease. The presentation addresses how functional genomics tools advance drug discovery and the importance of partnerships in this space.

Gianni also aims to address how CRISPR screening can be applied to various therapeutic areas. Gianni stresses that breaking down the boundaries between industry and academic players is essential to enhancing drug discovery and building on the field of functional genomics.

Why use functional genomics in drug discovery? Not only does functional genomics help discover new targets but Gianni also argues that it helps competitively position portfolio assets. Applying functional genomics and running these screens in the oncology field generates patient selection hypotheses and stratification hypotheses.

Partnerships are critical in functional genomics because drug discovery is a team effort that demands the full use and empowerment of a range of scientific disciplines. Partnerships also require creativity, innovation and problem-solving skills of each scientist involved. From an operational standpoint, it serves as a way of saving costs and avoiding duplication.

Gianni discusses recent collaborations AstraZeneca has taken part in. They have partnered with the Cancer Research UK (CRUK) Functional Genomics Centre. The aim of this collaboration is to create a centre of excellence for CRISPR screening in oncology, generating insights on mechanisms of resistance and sensitisation, which are crucial for effective cancer therapies. The centre also focuses on developing next-generation CRISPR libraries and model systems, moving towards more complex phenotypes.



In conclusion, Gianni highlights the importance of integrating cutting-edge technologies with strategic partnerships to enhance drug discovery processes, ultimately aiming to address complex human diseases more effectively.

Design Principles For Balancing Lipophilicity And Permeability In Beyond Rule Of 5 Space

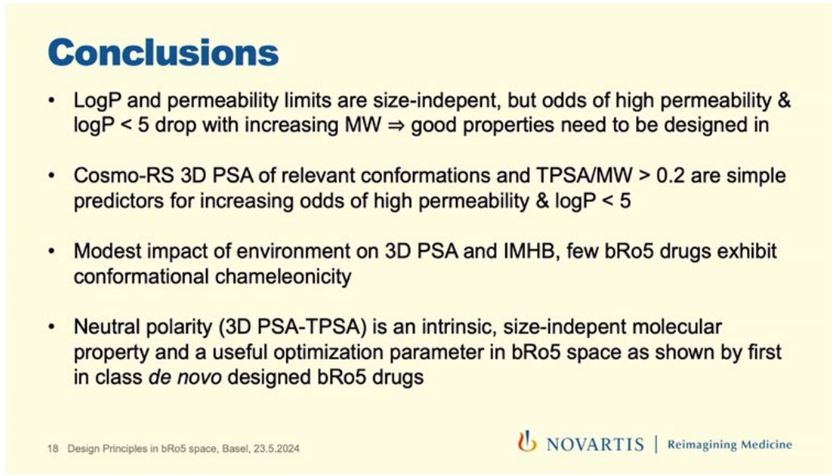
Henrik Möbitz, (Director, Novartis) addresses the challenge of oral bioavailability in drug design, particularly focusing on compounds that do not conform to Lipinski's "Rule of Five." He questions whether new rules are needed or if certain properties make these drugs exceptions. Möbitz refutes the concept of "chameleonicity," which suggests that compounds can change polarity based on the environment to enhance permeability while maintaining low lipophilicity. Instead, he introduces the idea of "neutral polarity," defined as the difference between theoretical polar surface area (TPSA) and 3D polar surface area (3D PSA), as a critical parameter for lead optimization in drug design.

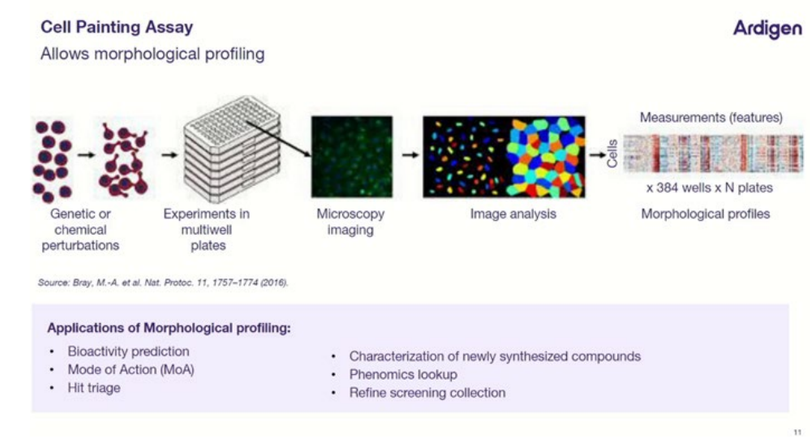
Möbitz's analysis involves comparing marketed oral drugs with high molecular weight, specifically those beyond the Rule of Five, using ab initio conformational analysis. He finds that while reducing lipophilicity typically decreases permeability in larger molecules, a balance can still be achieved. His data shows that most highly permeable drugs fall below a specific 3D PSA threshold, indicating that high permeability is achievable even for complex molecules.

He argues that the strong correlation between permeability and TPSA in various environments suggests that neutral polarity is an intrinsic molecular property, not significantly affected by conformation. Most oral drugs do not exhibit significant chameleonic behaviour; rather, they maintain consistent neutral polarity across different environments. This finding is supported by a near-unity correlation between the conformations of compounds in polar and apolar environments.

Möbitz also introduces a new "Rule of One Fifth," which combines TPSA and molecular weight to predict drug properties better than the traditional Rule of Five. He illustrates this with data from Novartis and other datasets, showing that neutral TPSA is a useful visualisation for lead optimisation. This approach helps design drugs that achieve the necessary balance of permeability and solubility.

In conclusion, Möbitz emphasises that molecular weight alone is not a direct descriptor of drug properties; instead, the design must purposefully balance permeability and solubility. He dismisses chameleonicity in favour of neutral polarity, proposing that it can be used prospectively to design better drug candidates.





Phenotype-Guided Drug Design: From Image To Structure

Ardigen is situated within the top 5% of leaders in the global AI drug discovery market. The company partners with a variety of industry and academic partners to provide cutting-edge AI & data solutions to address challenges in the life sciences industry. The company operates on three pillars: infrastructure for data management and cloud migration, a data universe for handling diverse data modalities, and scientific insights derived from proprietary solutions.

Kryzsztof Rataj (Chemoninformatics Data Scientist, Ardigen) discusses using high-content imaging in screening and the applications of phenotypic screening in drug discovery. Rataj, highlights the challenges associated with high throughput screening, including its time-consuming and costly nature. By using high content analysis or high content screening, instead of producing a single readout the technology produces an image. The image provides more data than the readout and gives insight into phenotypic changes.

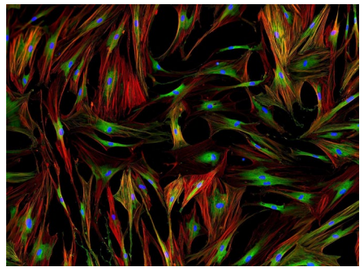
To speed up the screening process he proposes an enhanced approach using high-content imaging and the cell painting protocol developed by the Broad Institute. This protocol uses various staining methods to generate detailed cellular images, offering richer data than traditional single-readout assays. The images provide insights into cellular components and behaviours, such as phenotypic changes. Although, this method is fast and cheap it requires a more complex analytical approach. There are a broad range of applications for morphological profiling, including toxicity assessment and pathway analysis.

A significant advancement presented by Rataj is the integration of multiple data modalities, such as images, small molecules, and omics data, into a unified analytical framework. Ardigen's AI models, use deep learning and contrastive learning techniques to enhance the predictive accuracy and robustness of phenotypic screening. Rataj demonstrates a phenotypic virtual screening approach where compound libraries are scored based on their likelihood to induce specific cellular phenotypes.

The efficiency and effectiveness of cell painting and multimodal data integration accelerates drug discovery. These methodologies offer a faster and more user-friendly alternative to traditional high-throughput screening, providing valuable insights into compound efficacy and toxicity. The presentation emphasises the potential of combining advanced imaging techniques with AI to drive innovation in drug discovery.

Ardigen phenAID

Identify Better Drug Candidates with Morphological Profiling



High-throughput phenotypic data analysis is a major bottleneck for many pharma companies. Without the right tools in place, phenotypic drug screening data requires hundreds of hours to process. This is why at Ardigen, we have created a solution that streamlines phenotypic image analysis and enhances drug activity prediction.

We invite you to explore PhenAID, an AI-powered platform for morphological data analysis.

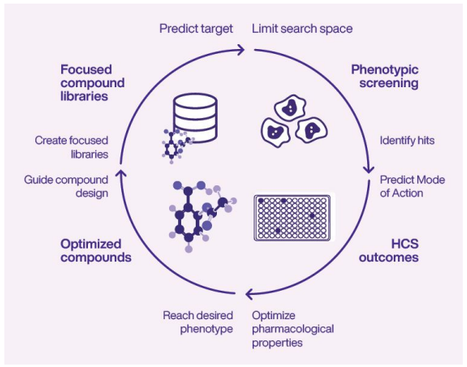
PhenAID uses machine learning to extract insights from high-content screening (HCS) data and combines it with chemical structure analysis. This multimodal approach accelerates discovery efforts through powerful insights into the mode of action and bioactivity property predictions.

Learn how it works
Watch Demo

Extract More Insights From High-Content Screening Data To Drive Drug Discovery

With PhenAID you can:

- Find the targets and off-targets of your molecules
- Maximize chemical space exploration
- Predict Mode of Action (MoA) and bioactivity properties
- Design focused libraries and improve hit rate up to 40%
- Optimize compounds in just two AI-lab cycles
- Configure and customize pipelines to fit your needs
- Do all this from a user-friendly web browser interface, in the cloud or local network

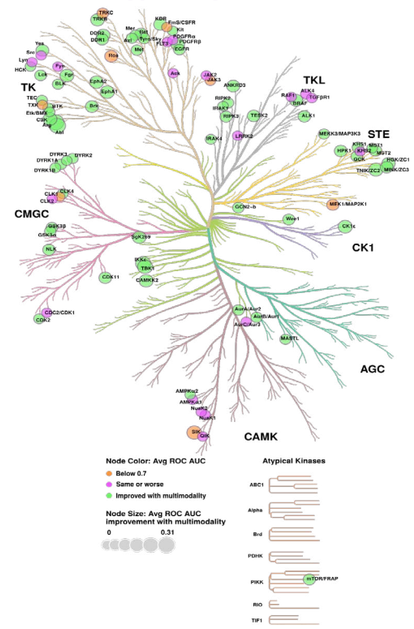


Ardigen PhenAID Platform Boosts Activity Prediction On A Merck Phenotyping Dataset

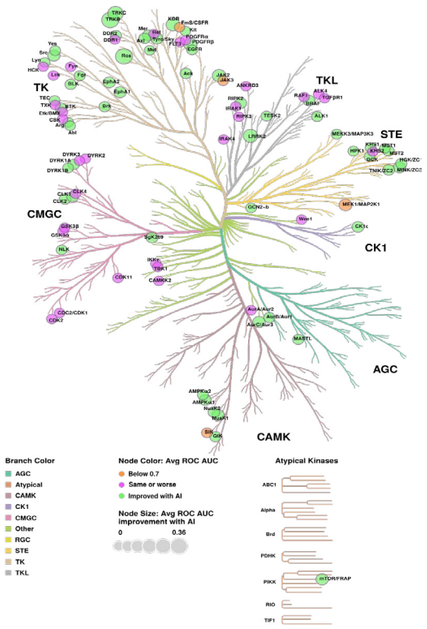
In a pilot project with Merck, we applied the PhenAID platform to analyzed one of their proprietary HSC datasets. The analysis consisted of two different tasks: **mode of action** and **bioactivity properties** prediction. For each task, we compared the performance of using a phenotype-only (image analysis) or multimodal approach (image analysis and chemical structure categorization).

The PhenAID platform consistently improves prediction scores across all tested setups as showcased by our experiments. PhenAID rapidly extracts phenotypic features with deep learning, being 4x faster and 34x cheaper without human input. The multimodal approach improves the quality of predictions on a biologically diverse collection of tasks spanning over the entirety of the kinome.

A. Phenotype-only vs. Multimodal



B. Human-defined vs. AI



This project demonstrated the ability of the PhenAID platform to successfully predict both the mode of action and bioactivity property of diverse functional targets, as confirmed against a validated proprietary dataset.

Download Poster To Learn More

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Visit our **website** for on-demand webinars, case studies and more!

Leveraging AI for Arrayed CRISPR Screening for Target Identification

Ulrike Kunzel, (Associate Principal Scientist, AstraZeneca) explores discovering the right target through functional genomics. CRISPR screening plays a crucial role in functional genomics, it allows scientists to knock out one gene at a time and then target the entire genome.

The hits generated from the CRISPR screens are then validated, this produces novel targets for the discovery pipeline as well as the opportunity to combine CRISPR screening with drug treatment. CRISPR screening has implications beyond the identification of novel targets.

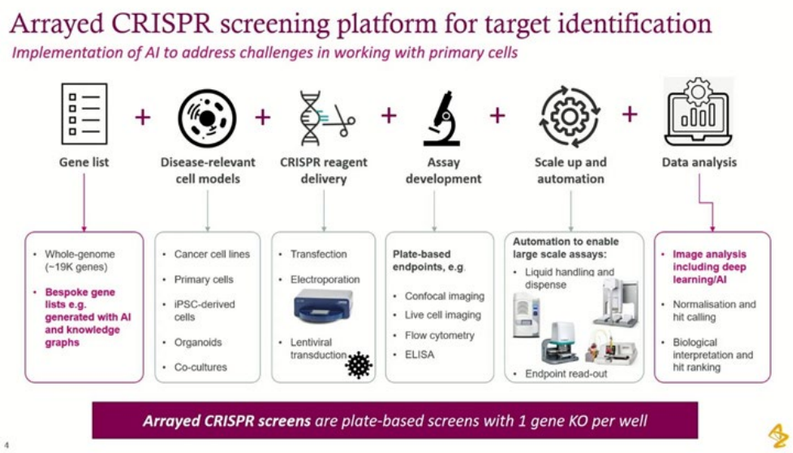


Plate-based assays are amenable to the platform. Kunzel stresses the need to use knowledge graphs to advance target identification. Knowledge graphs are networks of scientific data (genes, proteins and compounds) and the relationship between them. The ML algorithms applied to the knowledge graphs detect patterns not obvious to scientists, with the hope of predicting novel targets. The knowledge graph-derived gene lists advance target identification for chronic kidney disease (CKD). Data is fed into the knowledge graph the more data the knowledge graph is fed, the better trained it will be to make refined predictions.

250 genes were derived from the knowledge graph. Scaling up and automating the screening was a challenge, the assay that they used was dependent on cell numbers so would not be useful without large number of cells. This protocol is adapted to other primary cell models.

Overall functional genomics plays a key role in linking a gene to a disease relevant pathway which is vital for successful identification of right drug target. Kunzel concludes by reaffirming the significance of AstraZeneca's arrayed CRISPR platform in adjusting to different disease models and assay endpoints to enable target discovery. Finally, the role of AI enhances the capabilities of AstraZeneca's arrayed CRISPR platform; it enables scientists to work with a limited number of cells.

Democratization of Lab Automation

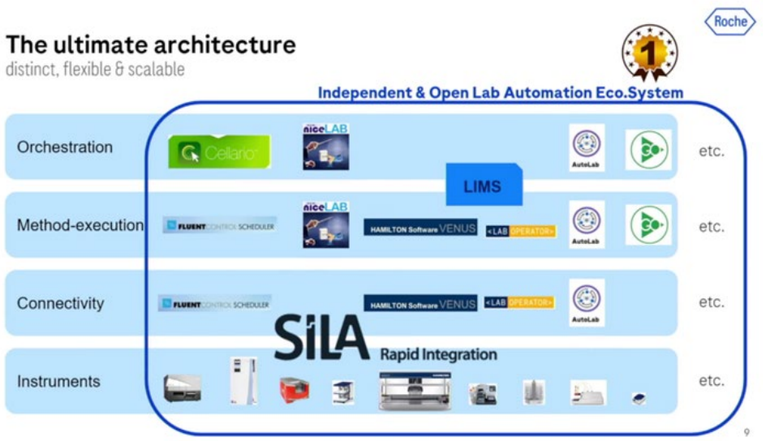
Tom Kissling, (pRED Lab Automation Partner & Head of the Automation Cluster, Roche) presented the ACDC Lab concept. The ACDC (Automation, Connectivity, and Digitalization Concept) Lab, aims to democratise lab automation by making it more accessible, faster, and cost-effective.

Kissling stressed the importance of integrating mobile robots and AI tools into lab automation systems in the future. Inspired by the democratisation of automation, Kissling outlined how ACDC Lab supports this vision by providing modular and flexible systems to streamline lab automation. The goal of the lab is to increase R&D productivity.

Drawing on his extensive experience, Kissling identifies two main challenges: cost and speed. He aims to address these by developing a modular, plug-and-play system. This system relies on digitalisation and automation, allowing for efficient integration of lab processes. The focus is on establishing a foundation of digital data before automation, as digitalisation often constitutes a significant portion of automation projects.

While promoting technology use, he also emphasises a people-first approach, advocating for defining processes and then selecting appropriate technology, rather than being swayed by vendors. The agile approach encourages early and frequent failure (smart failure) to learn and improve quickly, avoiding large, late-stage project failures. This approach will reduce chances of overspending and improve the likelihood of meeting project goals

Kissling details their ultimate architecture, ensuring strict separation between connectivity, method execution, and orchestration layers. This separation allows flexibility in changing or adding components without extensive costs or delays. He illustrates this with examples of how different systems and instruments can be integrated seamlessly, creating a plug-and-play environment.



He provides an example of a successfully implemented project, "Barcode Hero," which demonstrates the plug-and-play concept's effectiveness. This project allowed quick integration and deployment of lab automation systems, significantly reducing setup time and costs.

Kissling summarises by reiterating the importance of standardisation for democratisation.

Standardised components and systems ensure that new instruments can be easily integrated, encouraging innovation and flexibility in lab automation. The ACDC Lab's success lies in its modular, standardised approach, enabling rapid, cost-effective deployment of automation solutions.

Accelerating Drug Discovery Through Innovative Functional Groups And Novel Synthetic Methods

Stefan Schiesser, (Director Of Medicinal Chemistry, AstraZeneca)began by stating that synthetic methods are overlooked in drug discovery yet they are vital in molecular design. Synthetic chemistry can drive medicinal chemistry. He explores the symbiotic relationship between medicinal chemistry, synthetic chemistry and innovative functional groups.

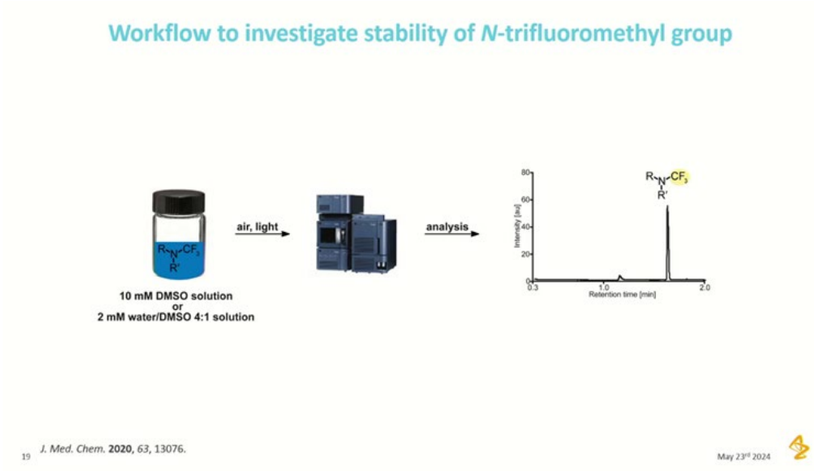
Innovative synthetic chemistry is required to address emerging opportunities in medicinal chemistry. He highlights two areas in which synthetic chemistry can play a role in addressing emerging opportunities in medicinal chemistry: functionalisation of biomolecules and increasing use of automated chemistry.

Aryl triflates are key intermediates in synthetic chemistry but require novel synthetic approaches to be fit for future medicinal chemistry. Schiesser discusses the need for new methods to functionalise peptides and proteins, especially given the booming interest in antibody-drug conjugates and peptide therapeutics. These biomolecules present unique challenges, such as the need for mild, selective reactions that do not disturb sensitive functional groups.

He showcases a new synthetic method for incorporating aryl triflates into phenols. This method, which uses tetramethylammonium fluoride, is simple, fast, and effective, even for complex, functionalized peptides. This has a critical advantage over existing methods, which are often incompatible with delicate biomolecules and automated chemistry setups.

Stefan introduces the synthesis of NC3 compounds, which were previously underexplored in medicinal chemistry due to synthetic challenges. A breakthrough two-step synthesis method developed in 2017 enabled the creation of these compounds under mild conditions.

He investigates the stability and properties of NC3 compounds, finding that while some are hydrolysed rapidly, others, particularly those with electron-deficient or aromatic nitrogen atoms, are stable and potentially useful in drug design. He presents the workflow used to investigate stability of N-trifluoromethyl group.



He provides examples where NC3 groups improved properties such as metabolic stability and permeability, suggesting that NC3 compounds could be valuable additions to the medicinal chemistry toolkit.

Stefan concludes by emphasising the need for continued collaboration between synthetic

and medicinal chemists to develop new methods and explore novel functional groups.

A Direct To Biology Approach To Drug Discovery

Julie Fournier, (Senior Scientist, GSK)introduces Direct-to-Biology (D2B). The D2B platform merges nanoscale synthesis with biological assays, allowing crude reaction mixtures to progress directly into biological testing without purification. By working on a smaller scale and using automation, the platform enables the rapid exploration of chemical diversity with minimal material and reagents. D2B reduces timelines from the chemistry to the acquisition of biologically relevant data.

How an Automated End-to-End D2B Chemistry Process Works

Fournier explains the multi-layered optimisation process within D2B experiments, where hundreds of reactions are set up in a single experiment to maximize efficiency and data collection. She pointed the platform's ability to rapidly expand structure-activity relationships (SAR) and drive key decisions in lead discovery.

The presentation discusses the automation setup of the D2B platform, including liquid handling robots and analytical tools for reaction analysis. Fournier also discusses the concept of pre-validation, which evaluates the suitability of D2B for specific targets and assay readouts early in the project lifecycle.

To ensure the platform's applicability across different projects, Fournier introduces the concept of pre-validation, which assesses potential assay interference from reagents, byproducts, and solvents. She notes that D2B had shown broad tolerance across various assay types and targets.

Fournier highlights the specific case studies that implemented D2B which demonstrated the broad applicability of the D2B platform, including the discovery of novel PROTACs, as detailed in a publication by PhD student Rebecca Stevens. She emphasises the role of modern tools like automation, data science, and in silico modelling in reshaping medicinal chemistry. Finally, Fournier stresses the importance of collaboration and upskilling within her team to implement automation effectively.

Challenges and Strategies in CNS Drug Discovery and Development

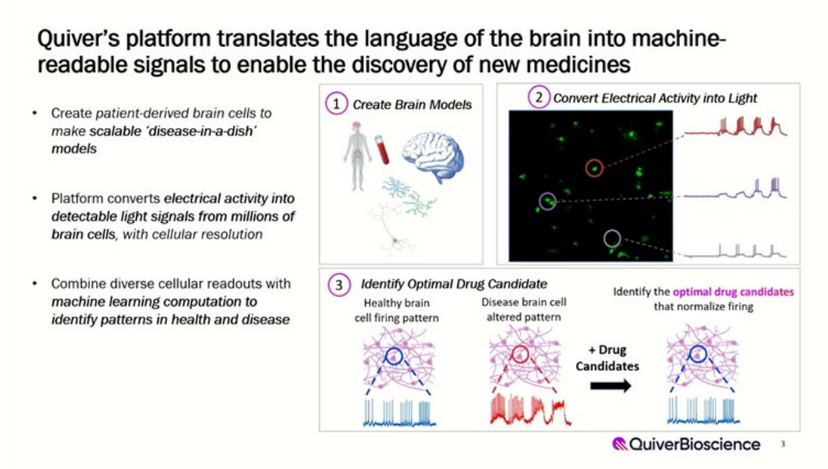
According to Precedence Research's market report, the global neuroscience market size was valued at $3.32 billion in 2023 and is projected to hit$6.42 billion by 2032. Continuous breakthroughs and research drive ongoing innovation in neurological treatments. Increasing awareness around neuroscience prompts early diagnosis and intervention, contributing to patient outcomes.

Source: Precedence Research

Functional Genomics for Next Generation CNS Therapeutic Discovery

Graham Dempsey, (Founder and CSO, Quiver Bioscience)begins by giving an overview of the CNS landscape. Few CNS drugs are effective because the human brain cannot easily be accessed to study the different effects of diseases, many scientists still rely on non-neuronal in vitro models and rodent models. Moreover, electrical signals are difficult to measure at the scale required for drug discovery.

Quiver's platform translates the language of the brain into machine readable signals to enable the discovery of new medicines. The platform leverages two proteins: a blue-light activated ion channel and a red-light voltage indicator, enabling stimulation and recording of neuronal activity using photons. This approach generates high-dimensional datasets that machine learning algorithms analyse to identify patterns in health and disease, optimising therapeutic candidates. Functional genomics is used to link gene expression changes to disease outcomes, bridging molecular targets to clinical phenotypes.



Quiver's functional genomics approach links changes in gene expression to the dynamic network properties of cells and circuits that result in disease outcomes. Using optogenetics they express two proteins in neurons. Optogenetics allows one to read synaptic transmission using light-based methods.

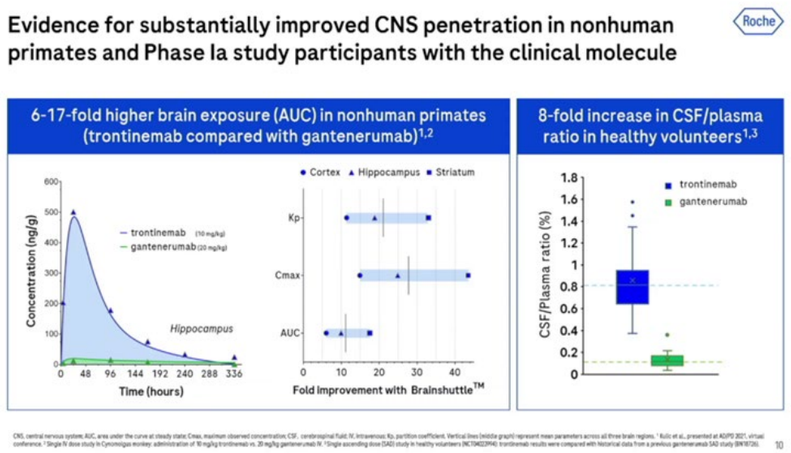
Multidimensional data sets allow for assessment of disease rescue and off-target effects across a range of modalities allowing researchers to identify the candidates with the optimal balance of efficacy and the fewest side effects.

The company is now running a program to treat Tuberous sclerosis complex (TSC). TSC is an autosomal dominant, multisystem disorder that is characterised by cellular and tissue dysplasia in several organs. The platform has applications in various diseases, including seizure and neurodevelopmental disorders, and chronic pain. For instance, in Tuberous Sclerosis Complex (TSC), the platform identified phenotypic features and screened compounds to discover new therapeutic candidates. Moving forward, Quiver Bioscience plans to expand the platform to address hundreds of diseases using CRISPR genomic screening and annotated pharmacology, building a comprehensive knowledge graph of neurobiological data for better target and drug validation.

Brainshuttle Technology In the Clinic: Trontinemab for Alzheimer's Disease

Geoffrey Kerchner, (Vice President, Global Head of Early Development – Neuroscience & Rare Diseases, Roche) discusses Roche's novel drug delivery method, brainshuttle technology. The blood brain barrier (BBB) presents a major challenge for the delivery of large therapeutic molecules to the brain. Trontinemab is a molecule that uses a brain shuttle technology. Alzheimer's disease occurs when there is a build up of amyloid plaque around the brain. Gantenerumab failed to display clinical efficacy. Brainshuttle technology not only enables higher CNS exposure but also a broader brain biodistribution of therapeutic antibodies, furthermore the point of entry is right where the target is.

Trontinemab demonstrated efficient target engagement and plaque clearance in an ex vivo human amyloid plaque model. Trontinemab is more efficient than gantenerumab; in a nonhuman primate study and a phase Ia study there was uptake, trontinemab showed a 20-40-fold increase in the C max, and the delivery of the drug to its target is highly efficient with brain shuttle compared to a conventional antibody.



Kerchner conducted a 6-month study with 15 Alzheimer's patients aged between 50 and 85. From the data, he generated a PK profile. Patients in the group receiving the highest dose of trontinemab achieved 91% amyloid removal in 12 weeks which was significantly faster than other drugs in the study. The results showed that trontinemab could cross the BBB and display pharmacodynamic responses in people with Alzheimer's disease. Furthermore, Trontinemab achieved higher amyloid reduction in a shorter timescale compared to other anti-amyloid drugs. Additionally, results from this clinical trial showed no significant imbalance in adverse events and low incidence of amyloid-related imaging abnormalities (ARIA).

Overall, Trontinemab effectively crosses the blood-brain barrier and reduces amyloid plaques in Alzheimer's patients. Moreover, low incidence of adverse events and ARIA, indicate a favourable safety profile. However, Kerchner acknowledges that the sample size of this study is small, and this ongoing study aims to expand cohort size and gather more robust data.

In conclusion, Kerchner's presentation highlights the promising potential of brain shuttle technology in overcoming the challenges of drug delivery to the brain, offering hope for more effective Alzheimer's treatments.

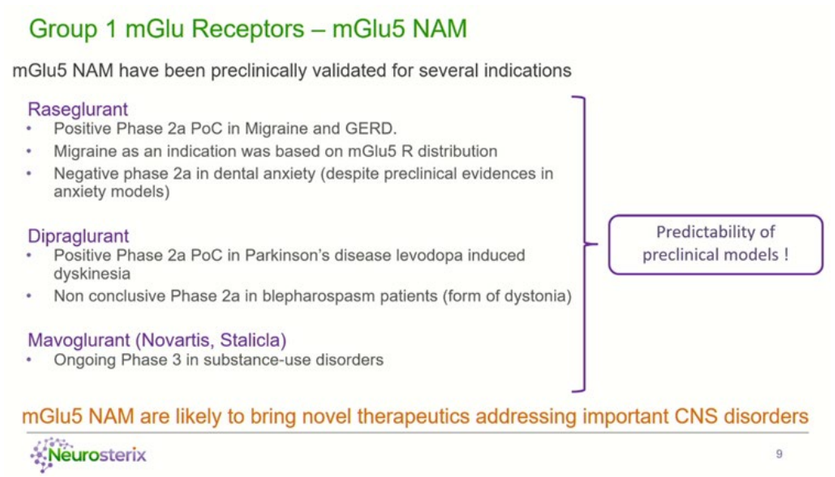
Discovery Approaches In The mGlu Allosteric Modulators Field Both On Early Discovery Up To Clinical Development

Jean-Philippe Rocher, (Head of Discovery, Chemistry, Neurosterix)opened by stating Neurosterix's mission: to discover novel allosteric modulators to address unmet medical needs in CNS diseases.Allosteric modulators are relatively new modalities that activate or inhibit signal transduction. Allosteric modulators, bind to receptor sites distinct from active sites, allowing them to modulate receptor activity without competing with endogenous ligands. This mechanism can fine-tune signalling to restore balance, potentially addressing disorders involving neurotransmission dysregulation.

The key advantage of these modulators is that they show high selectivity due to less conserved binding sites, leading to fewer side effects and better targeted therapies.

The development of these modulators relies on three key platforms: biology, chemistry, and translational. The biology platform involves conventional and proprietary biological assays for high-throughput screening and characterising allosteric modulators. The chemistry platform focuses on creating libraries, using biophysical methods for hit validation, and applying computational methods for drug design. The translational platform uses in vivo models to study disease and mechanisms of action and evaluates pharmacokinetics, pharmacodynamics, and biomarkers.

Neurosterix has developed a series of compounds targeteing metabotropic glutamates receptors (mGlus). Some have progressed to clinical trials. While there have been clinical failures, notable successes include promising data in migraine and Parkinson's disease models. For instance, mGlu Group I molecules like Dipraglurant showed potential in migraine and Parkinson's disease but failed in some anxiety trials.



Collaborations with Johnson & Johnson on mGlu Group II led to compounds showing partial efficacy in schizophrenia and epilepsy models. The focus on mGluR Group III includes negative allosteric modulators, such as a new tool molecule (ADX94827) showing efficacy in PTSD models.

Rocher points out the challenges of translating preclinical success to clinical efficacy;obstacles included tailoring molecules to specific indications and considering factors like receptor occupancy and partial agonistic activity. Lack of efficacy in phase II is a challenge that the company aims to address. He concludes by highlighting the progress made over the past decade, including the clinical development of allosteric modulators and the ongoing research to refine these compounds.

Application of AI/ML in Discovery from Target ID to Clinical Proof of Concept

Irene Choi, (Director, Head of Drug Discovery, Verge Genomics)begins by introducing CONVERGE, the company's platform used to identify novel targets. CONVERGE is a fully integrated discovery and development platform, at the centre of it lies human data. Human data is the foundation of their platform, leveraging this data can be used to create pre-clinical models of validation.

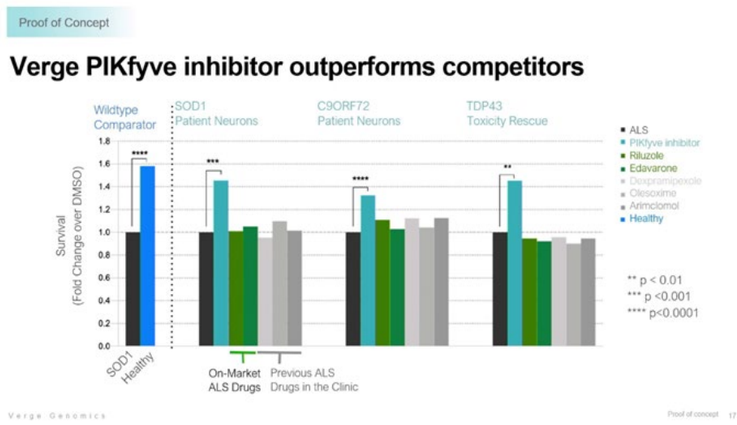
The platform is used in target discovery, target validation and drug development. The platform has allowed the company to advance their lead program and expand the portfolio into several neurodegenerative diseases including Parkinson's, dementia and schizophrenia. Choi gives an overview of their PIKfyve program. This program is a small molecule program being tested in Amyotrophic Lateral Sclerosis (ALS) patients. The PIKfyve kinase inhibitor rapidly advanced from target identification to Phase I clinical trial in less than five years which is highly impressive and much faster in comparison to the average timeline.

The platform uses a unique disease signature derived from over 1000 RNA-seq samples from ALS patients, identifying key gene networks involved in the disease. Regarding the mechanism of action, PIKfyve kinase is targeted to correct lysosomal defects associated with ALS, by increasing PI3P levels to enhance lysosomal and autophagy functions. The PIKfyve kinase inhibitor, currently in clinical trials, aims to address lysosomal defects seen in ALS.

The Converge platform uses human-centric models, such as IPSC models, to test and validate drug targets, ensuring better translatability to human disease. Choi emphasises the importance of selecting preclinical models that accurately mimic human disease signatures. They have identified biomarkers to measure drug efficacy in patients.

In terms of mechanistic insights, Choi discusses the C90RF72 mutation, a significant genetic mutation in familial ALS, which causes protein aggregates and lysosomal dysfunction. The PIKfyve inhibitor targets lysosome biology to correct these defects. Experimental results showed improved survival and reduced toxic aggregates in patient-derived models treated with the inhibitor.

The PIKfyve inhibitor also showed broad application across other ALS mutations, including TDP-43 and SOD1, demonstrating significant rescue effects. Compared to existing ALS treatments and other failed clinical drugs, the PIKfyve inhibitor was more effective.

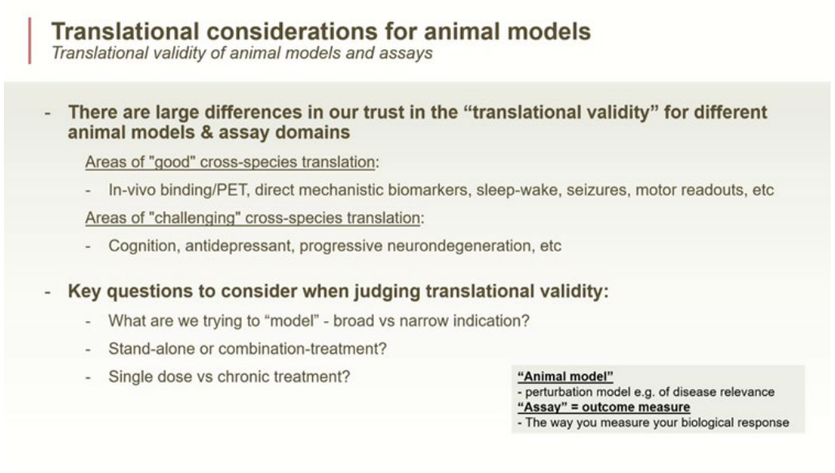


Choi concludes by discussing current clinical trials, emphasising patient stratification and biomarker use to enhance drug efficacy. Looking ahead, Verge Genomics plans to expand the Converge platform to address a wider range of neurodegenerative diseases. She also mentions the importance of refining and leveraging AI to facilitate drug discovery.

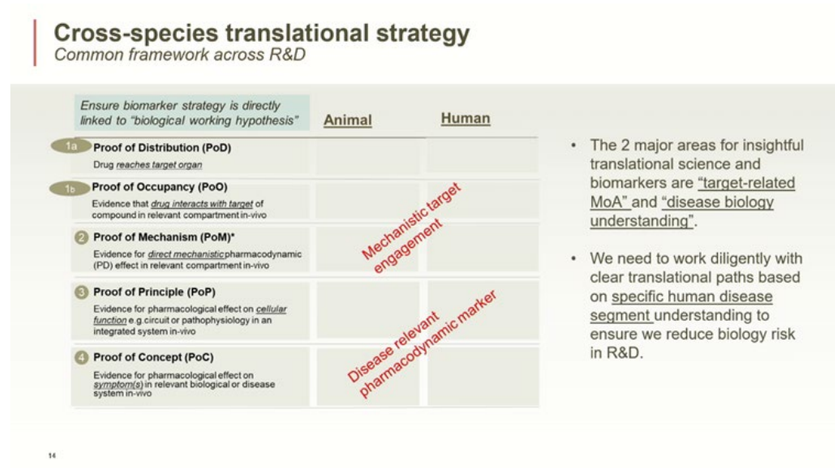
Translation Tools for Predictability in Neuroscience Diseases

Morten Grunnet, (Vice President & Head of Neuroscience, Lundbeck), discussed Lundbeck's novel translation tools and their application within the CNS space. Lunbeck occupies 4 key areas in the CNS field: circuitry/neuronal biology, protein aggregation, folding and clearance, hormonal/neuropeptide signalling and neuroinflammation/ neuroimmunology. The key modalities used by Lunbeck include small molecules, ASO (antisense oligonucleotide) and antibodies.

He discusses the translational gap in CNS research, particularly the limitations of animal models in reflecting human brain complexity and the challenges of psychiatric disorder modelling. Lundbeck emphasises understanding underlying biological mechanisms to bridge this gap effectively. Lundbeck assesses animal models for predictive validity and balance efforts based on achievable translatability, especially within psychiatric-based models where challenges are more pronounced. They use a guiding tool to prioritize programs based on mechanistic insight, proof of principle, and proof of concept.



Lundbeck aims to bridge this gap by understanding the underlying biology rather than direct behaviour-to-behaviour translation, enhancing the predictive validity of their models.



Grunnet highlights the variability in translational validity across different models, noting reliable translation in areas like epilepsy, but challenges in psychiatric models. Lundbeck addresses these challenges by focusing on mechanistic insights, disease relevance, and balancing the achievable aspects of their models.

In PK-PD assessment, Lundbeck integrates in vitro and in vivo profiles early to optimize and prioritize compounds. They focus on predicting human dose, therapeutic index, and functional consequences in the brain and plasma, feeding data into PK-PD modeling for improved predictions and dose selection. Lunbeck prioritizes understanding the balance between efficacy and toxicity, using a holistic approach to therapeutic index determination.

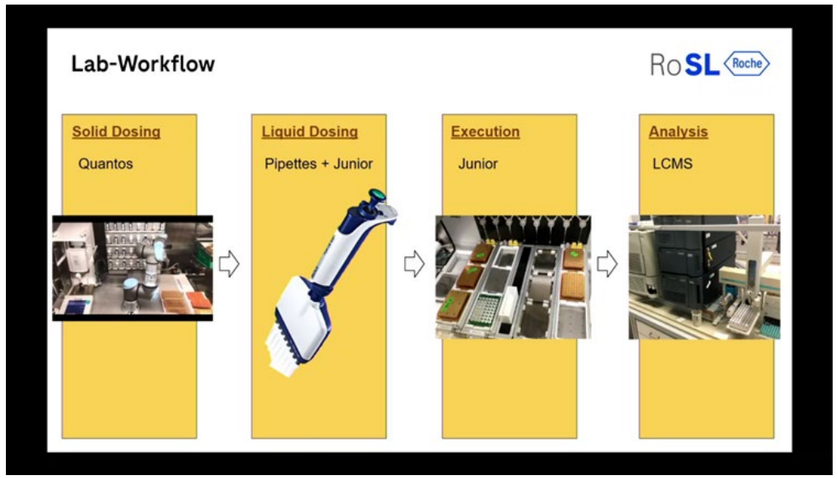
Overall, Grunnet stresses the importance of early de-risking, strong biomarker strategies, and the need for thorough biological understanding to prevent costly clinical failures. He concludes by reiterating Lunbeck's focus on quality and strategic approaches in CNS drug discovery and development.

Data-Driven Approaches and Predictive Modelling

HTE OS: An HTE-Workflow At Roche Built From The Ground Up

Vera Jost (Principal Associate Scientist, Roche) and Georg Wuitschik (Senior Principal Scientist, Roche) present on their latest high-throughput experimentation application.

HTE aims to efficiently tackle complex chemical reactions with numerous variables. The HTE goal is to find good quality data and train ML to recognise patterns and predicting optimal experimental conditions. Jost notes that aim is to build proprietary data set for machine models to be trained on so it is specific to the projects needs, meaning the ML is biased. Jost states that to generate vast quantities of data must conduct experiments. Jost outlines the typical lab workflow.



Solid dosing is automated with a robot, whereas liquid dosing is manually handled due to speed constraints. Electronic laboratory notebooks (ELNs) and google sheets were the key tools in data handling. These tools ensure that there is no manual data handling thus minimising human error. Spotfire is a self-service data visualisation platform that Jost and Wuitschik use to interpret and visualise their data.

Jost and Georg's talk focuses on their development and use of a high-throughput experimentation (HTE) platform for chemical reactions, specifically showcasing its application in optimising the Buchwald-Hartwig reaction. They highlight several key aspects of their workflow, emphasizing the integration of automation and data analytics to streamline and improve experimental processes. Furthermore, automated label printing and data synchronisation was carried out across various lab instruments. A robust system notifies users about the status of experiments and equipment.

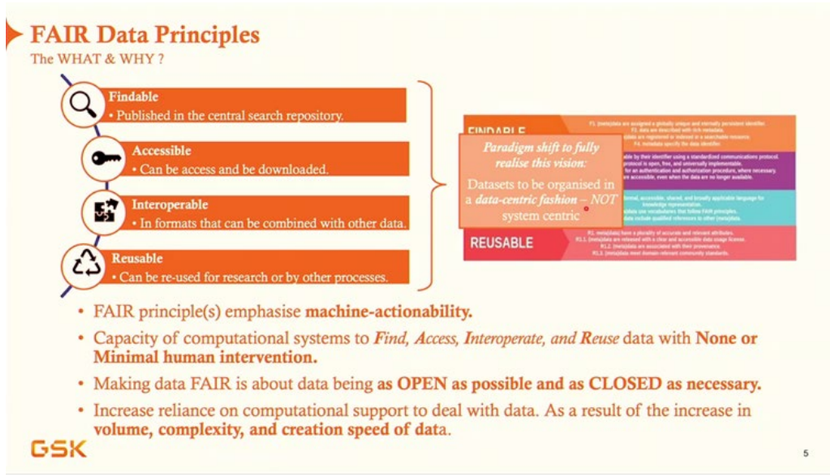
The future goal is to expand into more advanced data analysis and AI-driven predictions. Improvements in solubility screening and principal component analysis should further optimize experimental processes.

Jost and Georg showcase a highly integrated and automated HTE platform that leverages extensive data and advanced analytics to optimize chemical reactions efficiently. Their approach minimises manual errors, maximizes the use of existing data, and continuously evolves to incorporate advanced AI and machine learning capabilities for better predictions and optimisations.

FAIR Data Principles in Pharmaceutical R&D

CK Ong, (Director Data Product, GSK) gives an overview of the drug discovery landscape. Drugs tend to fail due to efficacy levels; Ong suggests that target identification is responsible for this failure. Therefore, risk mitigation is critical in the target identification stage. Implementing systematic novel target discovery, pulls disparate data across the value chain.

AI-driven discovery is becoming more common, for example, Exscientia and Sanofi have recently collaborated to develop an AI-driven pipeline of precision-engineered medicines. Constant changes in the data landscape, proliferation of distributed data sources, experimentation needs, and long response times are the key challenges associated with data collection and analysis. Ong claims that data ownership, data quality, and lack of common standards for cross modalities and discipline integration all influence whether FAIR data can be achieved. Ong briefly explains FAIR data principles:



Ong states the importance in changing our attitude towards technology. He likens data to oil refining; the true value of the data can only be extracted if the data undergoes important quality checks and is integrated correctly. Better data beats more data and there has been a paradigm shift in the opinions around data.

Data fabric refers to the importance of turning data into products, data fabric provides a unified, consistent user experience and access to data for any member of an organisation

worldwide and in real-time. It delivers data-centric integrations between business systems in a uniform way.

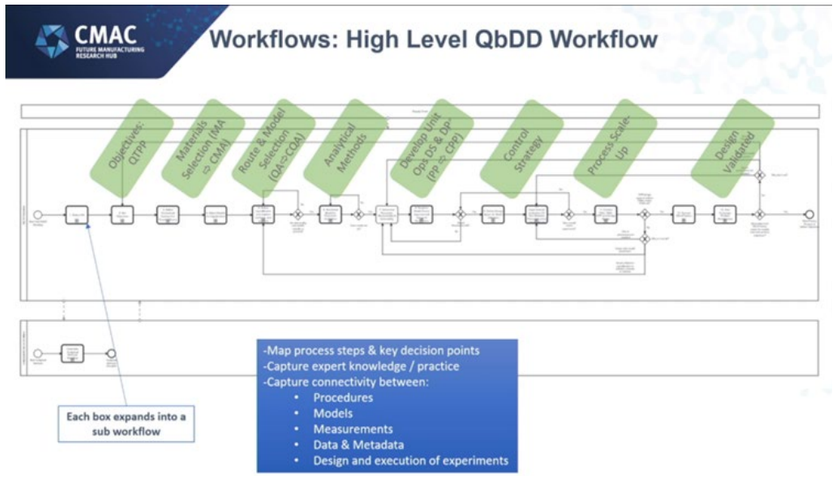
Data governance is another important element of data fabric. Federated governance is driven by domain owners who abide by a set of global rules that ensure interoperability, compliance and quality among data domains. Ong concludes by reaffirming that data is a valuable product that requires thorough management and governance to maximise its potential.

Digital Transformation of CMC: DataFactories And Digital Twins

Alastair Florence, (Director CMAC, University of Strathclyde) provides an overview of the collaborative efforts in CMAC a program focused on accelerating pharmaceutical development post-discovery.

CMAC collaborated with various pharmaceutical partners to address common challenges in accelerating development, particularly in product and process development (CMC processes). He emphasises the importance of using data and predictive technologies for better decision-making, developing platform technologies to streamline the portfolio, and improving end-to-end processes from drug substance to drug product.

Building on Quality by Design (QbD) principles, the program develops predictive toolboxes and workflows, integrating automation, and FAIR data principles to enhance consistency and usefulness of data.



Data Factories use cyber-physical systems to create systems that couple models and physical processes to automate and improve reproducibility, leading to better predictive capabilities and decision-making.

He gives an example of a data factory, the crystallisation screening data factory where reactors run independently and parallel to produce real-time image analysis output. In the drug product space, CMAC has another factory that conducts micro-scale dosage form manufacture. Optimisation algorithms help propose operable process conditions for larger scales.

Florence states that addressing data integration issues with a focus on building real-time data pipelines and databases to visualise interactions and improve model training are the main priorities to improve this technology. The future goals are to expand the program, integrate cobots, and tap into Industry 5.0 principles to create sustainable, resilient, and human-centric manufacturing processes.

Overall, the talk highlights the integration of advanced digital and automation technologies to streamline pharmaceutical development, emphasising collaboration, data usage, and human creativity in driving progress.

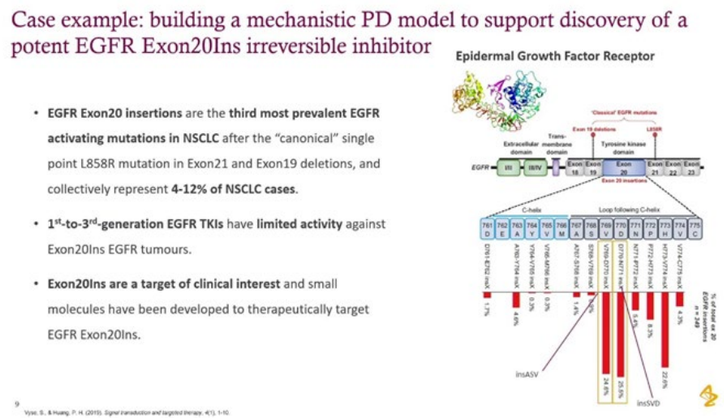
Integrating In Vitro Data Into Mechanistic Modelling For Prediction And Interpretation Of PKPD And Anti-Tumour Activity Of Irreversible TKIs

Adriana Savoca, (Associate Director, Translational PKPD, AstraZeneca)claims that due to the unprecedented number of new modalities that are emerging, understanding their mechanism of action and how this relates to clinical efficacy and outcomes is still ongoing. Designing these modalities in a way that improves likelihood of success is essential.

Mathematical modelling can help inform decision making across drug discovery and development. Combining holistic and quantitative approaches can help understand the link between population characteristics, compound properties and the compound targeted interaction and effect.

When there is a temporal disconnect between concentration and effect this is the indirect effect. Savoca presents a case study that aims to characterise the PK/PD

relationships. Her team have built a mechanistic PD model to support discovery of a potent EGFR Exon20Ins irreversible inhibitor.



The model is not a fully mechanistic model, however it is still able to take into account processes such as phosphorylation as well as the compound-target interaction. The model has been informed by extensive data. Once an understanding of pre-clinical data has been established, the goal is build confidence in pre-clinical to clinical translation.

Model calibration and validation is based on in vitro data. Model simulations help understand the impact of kinetic parameters differences on the time course of in vitro potency to inform compound optimisation and screening.

Establishing a PK/PD efficacy link informs FiH dose selection. Savoca presents data on other inhibitors and investigates the link between target engagement and efficacy of irreversible inhibitors in EGFR Exon20Ins patients.

Savoca concludes by stating that mechanistic models offer opportunities to investigate interplay of systems characteristics, compound properties and interactions with targets. Furthermore, these models inform decision-making throughout all preclinical phases to improve probability of clinical success.

Report Summary

Overall, this market report gave detailed insights into the emerging themes within the drug discovery space, mainly focusing on the integration of advanced technologies across the various stages of drug discovery.

Harnessing and integrating advanced technology is crucial to speeding up and improving drug discovery processes. The market report spans a wide range of technologies including phenotypic screening, CRISPR screening, and synthetic methods, exploring how can these methods can be applied to target identification, target validation and drug optimisation. Many of the experts featured in this report also debated the need for partnerships and a movement toward bridging the gap between industry and academia through collaborations. Gianni presented AstraZeneca's recent successful collaborations in advancing CRISPR screening and functional genomics for better target identification.

Moreover, this report unpacked the latest innovations in neuroscience drug discovery aiming to address significant challenges such as the inaccessibility of the human brain for direct study, the limitations of current animal models, and the difficulty of delivering therapeutic molecules across the blood-brain barrier (BBB). Approaches and technologies like functional genomics, AI/ML-driven platforms, and brain shuttle technology are being leveraged to address these obstacles. These strategies aim to improve target identification, optimise drug candidates, enhance translational predictability, and ensure efficient delivery of treatments to the brain. The ultimate aim is to develop more effective therapies for complex CNS disorders such as Alzheimer's disease, ALS, and other neurodegenerative conditions.

The market report analyses the critical role of data utilisation and predictive modelling in advancing pharmaceutical R&D and drug discovery. From Roche's high-throughput experimentation (HTE) platform that integrates automation and data analytics to optimise chemical reactions, to GSK's emphasis on FAIR data principles to minimise risks and late-stage failures in drug discovery, the presentations outline the significance of high-quality, well-managed data. The CMAC at the University of Strathclyde demonstrates how data factories and digital twins enhance reproducibility and predictive capabilities in pharmaceutical manufacturing.