

DRUG DISCOVERY BIOLOGY

Insights from the Industry





Introduction

Drug discovery remains the focal point of efforts across the pharmaceutical industry as it seeks to tackle new challenges. Crucial to this is the need for robust models - with developments in both *in vivo* and *in vitro* methods necessary to further advance new drugs and fully characterize their effects. Improved analysis of pharmacokinetic and pharmacodynamic effects remained at the fore as well. Advancements in phenotypic drug discovery - which seeks to challenge the norm of target-based drug discovery - also drew a lot of attention, as the method promises to provide more holistic characterizations of drug effects. *In silico* approaches are further gaining traction as our computing capacity progresses onwards, while structural biology has experienced a revolution with the growth of protein prediction software such as AlphaFOLD. These and other challenges were discussed in our signature roundtable format, facilitated by leading industry and academic experts at our Strategy Meetings across San Francisco, Boston and London, which sought to cover the full gamut of cutting edge trends in the field. We discuss the challenges for the industry further in this report, which we hope you will find thoroughly interesting to read.

The Editorial Team
Proventa International



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TOP 10 Challenges 2022: What Peers are Focusing on



1 In Vivo & In Vitro Models

Novel models that can accommodate innovative drug modalities remain at the forefront of peers' concerns - particularly as researchers feel the pinch in animal model shortages. Whole-cell assays are gaining traction, while multi-omics techniques continue to advance to support more sophisticated analyses.



2 Collaborations to Accelerate Progress

A major challenge, particularly for preclinical firms in novel therapeutics fields, is the facilitation of collaborations that can quicken progress while saving resources. Firms seek to establish partners for data analysis, improved assays and screening methods - needs that are often not easy to fulfill outside of mainstream drug modalities.



3 Target Identification

Target identification remains one of the most critical processes in the target-based drug discovery pipeline, and delegates seek improvements in their pursuit to develop structure-activity relationships and biomarkers to facilitate the advancement of drugs which work on the target in question.



4 Identifying Patient Populations

Biomarker development goes hand-in-hand with the identification of suitable and appropriate patient populations, which can be one of the main challenges during the transition from preclinical to clinical stages. Firms seek new solutions to overcome this challenge, particularly as they venture to the cutting edge of known drug modalities.



5 Artificial Intelligence & Digitization

Perhaps the omnipresent challenge throughout the pharmaceutical industry, peers cited a need to integrate novel Artificial Intelligence (AI) technologies to their drug discovery and preclinical development pipelines, while keeping costs down. Many hope machine learning can lead to improved integration in multi-omics assays, as well as expand the explorable chemical compound space.

TOP 10 Challenges 2022: What Peers are Focusing on



6 Preclinical Toxicology

Peers highlighted the need for improved preclinical toxicology assays, particularly to reveal the organ, species and dose-specific adverse effects of investigational products. Peers hope to not only improve models, using novel AI technologies, but also go beyond conventional biomarkers of toxicity to minimize Phase I failure rates.



7 Central Nervous System

Peers reiterated the need, but also the challenge, of expanding novel drug therapeutics - such as small-molecule chimeras - to target Central Nervous System (CNS) indications such as Alzheimer's. Corollary to success in this endeavor was the need to diversify and develop further biomarkers specific to CNS conditions, as firms seek to address unmet needs in the neurological and psychiatric fields.



8 Human Dose Prediction

Developing translational best practices to arrive at accurate estimates of human doses remains of unique priority to drug discovery firms, with many hoping for improved pharmacokinetic and pharmacodynamic modeling techniques so that the impact of investigational products throughout the body can be better understood.



9 Talent Acquisition

In a challenge that is common to many parts of industry subsequent to the COVID-19 pandemic, many delegates cited a challenge in attracting and retaining specialized and vital talent. Firms seek solutions to this challenge by re-examining their own internal working environments as well as corporate culture, but a clear one-size-fits-all solution has not yet been determined - if it is at all possible.



10 Protein Characterization

Protein characterization remains vital to any structure-based drug discovery effort. Models such as AlphaFOLD and Rosetta have increased the cost efficiency with which new proteins can be described, freeing up valuable working hours to better understand the impact of these structures and their role. Improvements in characterization, as well as better ligand and affinity modeling are also expected.



Chemoproteomics for Phenotypic Drug Discovery - Insights from PharmaFEATURES

Phenotypic drug discovery (PDD) stands in contrast to target-based drug discovery (TDD) – the former seeks novel compounds through observing the alterations they impose on disease pathophysiology. The latter identifies new drugs based on known mechanisms of action and interactions with drug targets. PDD is often more useful in discovering first-in-class medications: penicillin, the famous antibacterial, and zidovudine, the first treatment for HIV, were both discovered phenotypically. But perfecting and refining such compounds will inevitably require a better understanding of how they actually work at the molecular level – and this is where chemoproteomics becomes invaluable.

The Value of Phenotypic Screening

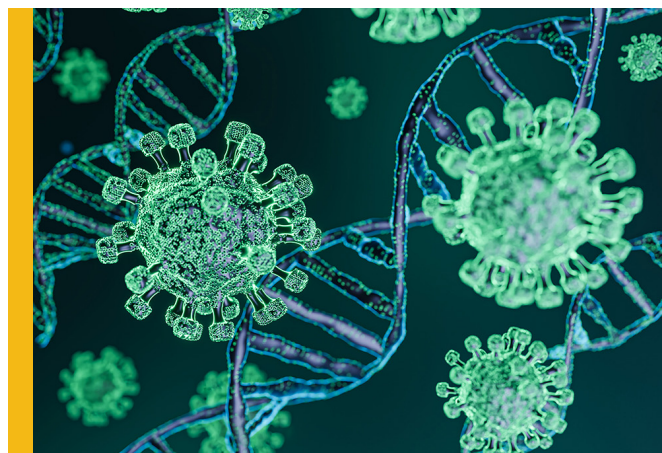
TDD has dominated drug discovery pipelines for decades, providing streamlined development cycles and more predictable milestones. Despite this, an influential review comparing both PDD and TDD found that phenotypic approaches yielded 28 first-in-class drugs, compared to 17 for TDD – at a time when interest in PDD was not particularly strong. This work by Swinney & Anthony revitalized interest in phenotypic drug discovery, which is now considered part of mainstream pharmacology. Phenotypic screening is typically done in vitro on cell-based assays, or in vivo on animal models. Advancements in the field of cell-based screening, such as induced Pluripotent Stem Cells (iPSC) as well as gene editing using CRISPR, have also provided traction to PDD – improving the toolkit it can use to evaluate disease modulation.

Chemoproteomic Screens

Chemoproteomics refers to a vast array of methods used to characterize the interactions between proteins – which are typically the drug targets, and small molecules: the drug candidates. Chemoproteomics techniques are natural companions for PDD, as they can illuminate the molecular mechanism of action of what is otherwise a relatively target-agnostic approach for drug discovery. Applications of chemoproteomics have recently highlighted the potential of the field to expand the druggable proportion of the proteome. This is particularly significant for non-traditional treatment modalities which are not restricted by known binding, active or allosteric sites on proteins – such as Proteolysis Targeting Chimeras (PROTAC).

The Intersection of PDD with Chemoproteomics

Chemoproteomics has led to intriguing discoveries from phenotypic screens throughout recent times. In a 2006 study, affinity chromatography revealed that results observed during phenotypic assays of stem cells can be explained through interactions with multiple target proteins rather than just one – which is typically what TDD aims for. There are a number of novel methods in chemoproteomics which can be used to deconvolute targets in native environments, and are therefore less likely to produce artifacts. These include Drug Affinity Responsive Target Target Stability (DARTS), Thermal Shift Profiling, Stability of Proteins from Rates of Oxidation (SPROX), and others.



Additionally, while phenotypic screens may often be employed to expand druggable space, chemoproteomics has often revealed the interactions between novel compounds used in PDD and druggable targets. Such insights expand our knowledge of the druggable proteome, and illustrate how we need to widen our efforts even in the better understood, druggable, space.. This is indicative of just how much we have yet to learn even about the parts of the proteome we consider to be tractable.

The Great Repurposing

Phenotypic Drug Discovery does not merely focus on novel drugs – instead, the repurposing of drugs for new indications is also one of its strengths. This has been acutely demonstrated throughout the SARS-CoV-2 pandemic, where the pharma industry scrambled to discover new therapies and test old treatments against a new foe. Many antivirals approved for use in patients with COVID-19, such as remdesivir, ritonavir, and others, were previously known and had shown activity against the novel coronavirus. While the molecular modes of action of these compounds were understood – at least in the context of how they act upon the virus, their full effects on the body were less characterized.

A study aiming to uncover these was done using Cellular Thermal Shift Assay Mass Spectrometry (CETSA MS), the first of its kind to use this chemoproteomics method to compare multiple antivirals. The study uncovered multiple protein interactions, the most notable of which was remdesivir's potential to destabilize the TRIP13 protein. TRIP13 overexpression is implicated in multiple cancer indications, such as squamous head and neck carcinomas. The combination of PDD assays with cutting-edge chemoproteomics methods holds great promise for expanding our horizons – both in novel drugs, and what we know of current pharmaceuticals.

The Technological Revolutions

Chemoproteomics assays are often time-consuming and cost-prohibitive – particularly in high-throughput scenarios. This has given rise to multiple computational approaches, particularly molecular docking – which aims to simulate how small molecules will interact with proteins. Molecular docking can produce powerful pharmacophore models, which can reduce the resource commitment for drug development.

A promotional banner for Pharma FEATURES. It features a laptop and a smartphone displaying the website, a pen holder with pens, and a blue background with a white grid. The text 'Pharma FEATURES' is prominently displayed in the top left. Below the image, the text 'Fresh Life Science Insights' is written in white on a dark blue background. Underneath, three icons represent 'Articles Daily', 'Interviews', and 'White Papers'.

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A recent study showed potential for repurposing existing drugs for mental health indications through the use of computational chemoproteomic models.

Similarly, PDD also faces resource issues – particularly over the front-loaded expense and complexity of PDD investigations. Considering that early drug discovery is accompanied by high failure rates, it is unsurprising that TDD has remained the dominant form of studying new drugs. Novel developments in the space of Artificial Intelligence hold immense promise for solving these issues across both fields. Exploratory studies showed the potential of machine learning chemoproteomics models to predict binding site concentrations and targets in whole-cell lysates.

New methods promise to increase the sensitivity of discovering new drug targets within phenotypic screens, a limitation of current chemoproteomics methods. As we see AI penetrate further in pharma, particularly the drug discovery space, it is inevitable that it will galvanize further chemoproteomics efforts in accelerating PDD. PDD has shown unique advantages in innovating drugs for unmet needs, and further improvements in the method promise to revolutionize both the druggable and undruggable proteome.

Read more on the latest trends in the life sciences industry on [PharmaFEATURES](#)

TOP

Investment Areas 2022

Proventa asked delegates at its events to speak about their investments for the coming year. Delegates cited heavy investment in novel modeling techniques, as well as a desire to integrate the latest technologies in their own pipelines, with many seeking partners to enable these.



Integrated Drug Discovery

Delegates saw urgent priority in developing their own integrated drug discovery capabilities, or finding partners who can provide them. Peers see the value in integrating target validation, translational interrogation, therapeutic discovery, and preclinical development while operating on iterative feedback loops at each part of the process which optimizes the overall workflow pipeline.



Artificial Intelligence/ Machine Learning

Firms are actively investing in cutting-edge technologies - with Artificial Intelligence (AI) and Machine Learning (ML) providing certain value in drug discovery. Peers also highlighted investments in employing AI in diagnostics, image recognition or other data interpretation and analyses approaches for assays - with the use cases of AI expected to grow in the field as it finds cost-effective niches to fill.



In Vivo Pharmacology

Peers saw value in committing investments to improved in vivo modeling techniques, particularly as firms seek to make the most of limited animal model supplies as well as secure new partners who can provide animals or in vivo testing services. While in vitro and in silico approaches continue to improve, the value of at least some animal testing will remain indispensable for the foreseeable future.



Hit-to-Lead Optimization

Optimizing the process by which hits are screened for potency, off-site activity, specificity and sustainability remains a pillar of drug discovery, with strong demand for methods to optimize the process of converting hits to leads. Solutions and partners who can improve standards for structure-activity relationships, as well as the effects of candidates throughout the body, remain in demand, as does the need to find more effective alternatives for lead compounds which fail to meet these criteria.



Drug Metabolism and Pharmacokinetics (DMPK)

Improved solutions for characterizing drug metabolism and pharmacokinetics can provide improved efficiencies throughout the development life cycle, by determining more accurate doses as well as limiting toxic side effects. Peers highlighted the need to improve models to characterize drug metabolism, investing heavily in the field.

TOP

Investment Areas 2022

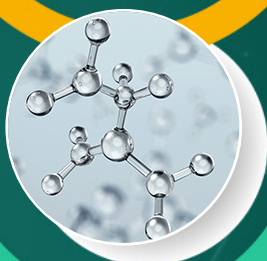
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Toxicology



Related to DMPK, delegates are expending considerable resources in preclinical toxicology analyses to minimize costs and time wasted in progressing unsuitable candidates further. Animal models remain of critical importance in preclinical toxicology studies, but the potential to further employ whole-cell assays as well as in vitro techniques remains an attractive alternative.

Custom Synthesis



Custom chemical or biological synthesis solutions are seeing increased investment, particularly as peers highlighted the need for more sustainable and cost-effective processes for synthesizing novel investigational products, especially for underexplored treatment modalities.

Biomarker Discovery



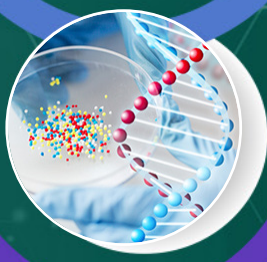
Expanding the portfolio of biomarkers available to early drug discovery efforts remains a key concern, particularly as peers seek to establish common standards and comparisons for drug indications in diseases without comparable existing treatment options.

Data Integration



Data integration remains of paramount importance, with many investing in techniques to better utilize heterogeneous datasets - such as those generated through multi-omics approaches. Delegates cited the potential for AI investments to improve data integration in such approaches, providing more holistic pictures of drug effects and disease physiologies.

Fragment Based Drug Discovery

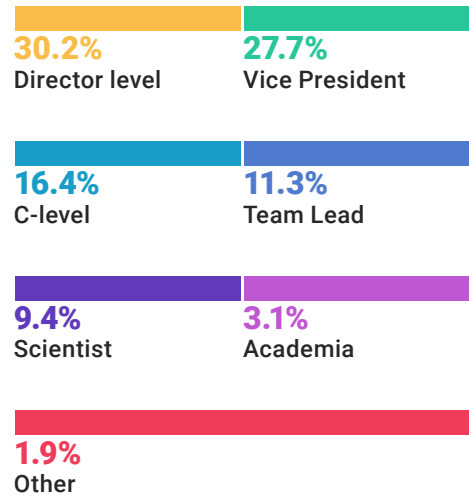
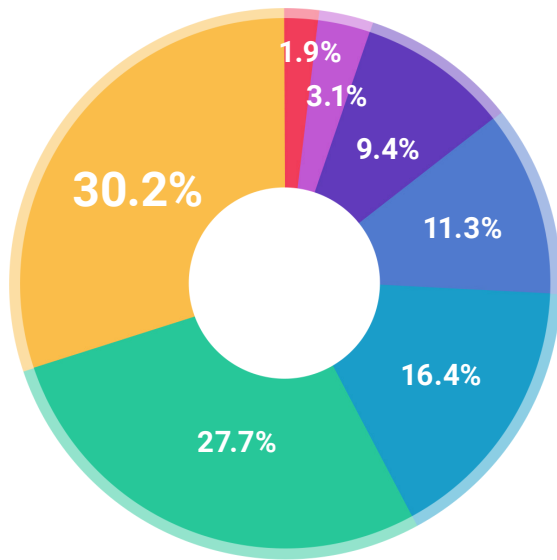


Delegates are starting to invest in fragment-based drug discovery (FBDD) approaches, hoping to develop potent small molecule therapeutics, as well as more novel modalities such as heterobifunctional small molecules. Owing to its inherent advantages when it comes to and its ability to be carried out through different biophysical and computer-based methods, FBDD is expected to further rise in prominence.

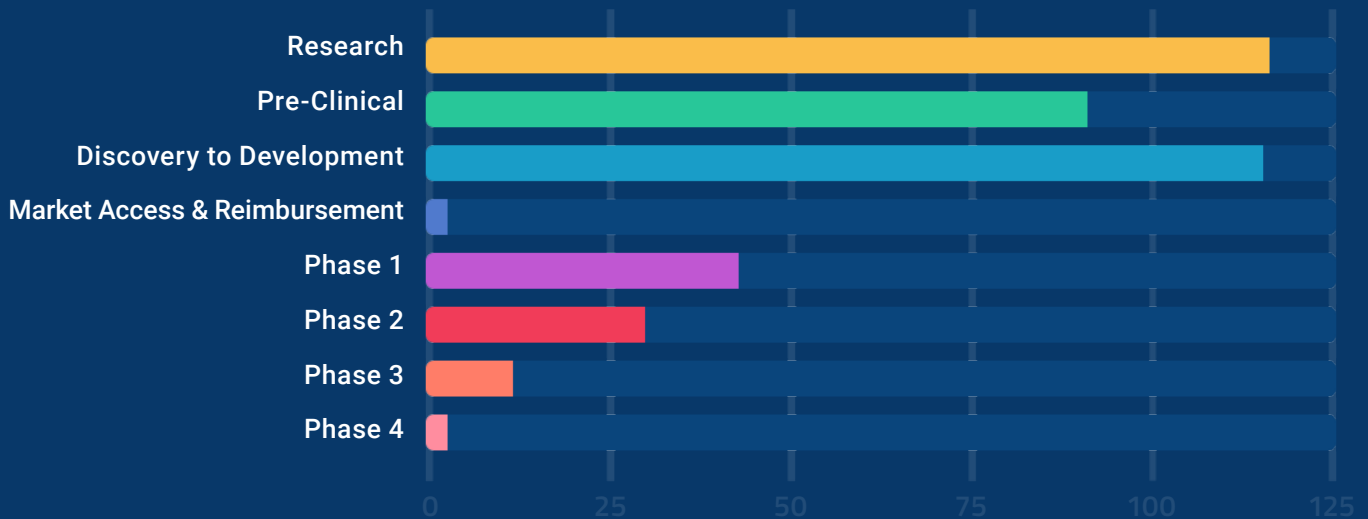
Delegate Breakdown:

Attendees at Proventa's 2022 Strategy Meetings

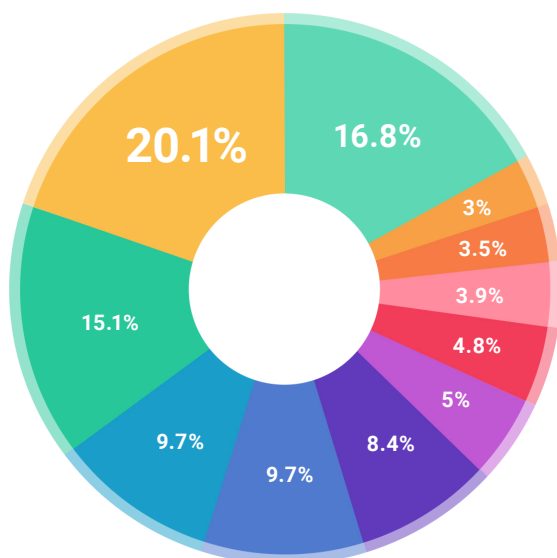
2022 Attendee Breakdown



Drug Development Stages



Therapeutic Areas



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