MEDICINAL CHEMISTRY

Insights from the Industry

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Introduction

Medicinal Chemistry remains at the forefront of accelerating innovation in the life sciences industry. The last few years of the pandemic have shown great promise in novel vaccines, biologic agents and treatment modalities to counter the pandemic - showing just how rapidly the industry can advance when united by a common purpose. Conjointly, insights gained from the chemistry of existing compounds have led to the "great repurposing", as we have seen compounds expand their indications across - for example, as we saw with older antivirals being recruited in the fight against COVID and contributing to the discovery of novel agents. The pioneers in the field remain focused on novel treatment modalities, including conjugated therapeutics, bifunctional molecules such as small molecule chimeras, innovations in RNA interference, and other treatments hoping to emerge into the pharmaceutical mainstream. This report will examine the key challenges faced by professionals in the industry as they seek to further advance our understanding of the chemistry of pharmaceuticals, as well as detail why our Strategy Meetings provide the best avenue to facilitate discourse in overcoming such challenges and finding solution providers who can help bridge knowledge gaps in these endeavors. This report will detail these and other challenges reported by the industry, which we hope you will enjoy reading.

The Editorial Team
Proventa International

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TOP 10 Challenges 2022: What Peers are Focusing on

1 Clinical Translation

As may be expected, peers are most concerned about the challenge of translating preclinical results to clinical successes. Delegates are looking for ways to improve the assays and models used in development, utilize more accurate biomarkers as well as harness the latest technologies in predicting success.

2 Supply Chains

Diversifying and providing resilience to supply chains remains a key concern in the industry, particularly as it recovers from the extremely disruptive effects of the pandemic. Supply chains remain critical for both preclinical development, including materials and animal model provisioning, as well as clinical development areas.

3 Integration of Machine Learning

Machine learning has made great impacts in providing new ways to optimize drug discovery efforts, as well as diagnostics and data analyses. Delegates seek the best ways to integrate the new technologies to their own companies and workflows, particularly as the Artificial Intelligence (AI) field continues to expand into further niches in the pharmaceutical industry.

4 COVID-19

COVID-19 remains a critical concern among peers, with many seeking to strengthen their resilience to future or similar outbreaks. Those that rely on global partnerships and supply chains which have to deal with varied government stances towards the disease, particularly China, seek to navigate the best path forward.

5 Talent Recruitment

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 talent. Firms seek solutions to this challenge by re-examining their own internal working environments as well as corporate culture. This need is exacerbated as firms look to incorporate experts in areas such as AI, which have not traditionally had a big talent base exclusive to the life sciences.

TOP 10 Challenges 2022: What Peers are Focusing on

6 Effective Collaboration

Key among concerns for delegates was the need to establish effective partnerships, with many seeing collaboration as a crucial response to new technological advancements. Peers also see partnership as a critical way through which to provide resilience to their own responses to emergent situations such as the COVID-19 pandemic, the war in Ukraine and supply chain disruptions.

7 Central Nervous System

The Central Nervous System (CNS) and associated neurological targets and indications are gaining traction in the life sciences industry. Peers seek improved biomarkers as they hope to progress in the field, as well as a better understanding of how to optimize novel drug modalities for chronic diseases of the CNS with significant clinical burdens, including Parkinson's, Alzheimer's, dementia and even rarer conditions.

8 Novel Drug Modalities

Novel drug modalities such as heterobifunctional small molecules, antibody drug conjugates, cytokines, oncolytic viruses, gene therapy, siRNA and others were the subject of much excitement among peers. Many cited a need to find the best candidates and modalities to optimize for their own pipelines, particularly in a pursuit to generate new best-in-class candidates.

9 Data Generation and Management

The industry continues to generate colossal amounts of data, and many delegates seek improved solutions in an endeavor to not only generate the right information, but also translate it to meaningful insights. Relatedly, peers cite the need for improved data storage and management solutions in a bid to reduce costs and comply with increasingly higher data standards.

10 CRO Diversification and Risk Mitigation

With the disruptions resulting from the COVID-19 pandemic and varying government responses to it, delegates are pressed to diversify the CROs and sites upon which they rely. Other global events also increase the urgency of this need - with the war in Ukraine having disrupted many clinical sites and CROs scrambling to adjust to such emerging situations.

PROTACs Enter the Clinic: A Brief History - Insights from PharmaFEATURES

Protein degradation has been an evolving technology for decades. The principle is simple: to co-opt the cell's own in-built machinery for destroying target proteins by marking them as unwanted, prompting their degradation. It offers significant advantages in a number of therapeutic areas over other modalities. Chief among these advantages is the potential to open up a vast space of currently undruggable proteins, such as those which have no active sites and cannot be targeted by more conventional means – such as small molecule inhibitors.

PROTACs: How they work

When referring to targeted protein degradation, the primary modality to achieve this is proteolysis targeting chimeras – PROTACs, although similar technologies that achieve degradation also exist. **PROTACs** are heterobispecific – binding to two different proteins inside the cell. One end of the PROTAC binds to the target protein, while the other end recruits a ubiquitin ligase and brings it in proximity to the target protein which is then ubiquitinated, marking the target for subsequent degradation by proteasomes. The PROTAC is not used up in the process, which means that it can perform this function repeatedly – enabling lower dosage of possible drug candidates and more durable responses.

The first compound of this kind to be published in a study, Protac-1 which targeted methionine aminopeptidase-2 (MetAP-2) – a cancer-related protein. The effects of Protac-1 were clear, showing the compound was capable of driving MetAP-2 degradation. The study also identified what would be the major challenge of delivering these results in humans: PROTACs were simply too big and unlikely to penetrate cellular membranes without further modification or assistance. This limitation kept the technology on the fringes of pharma for a long time, even though PROTACs showed great functionality and promise.

Structural and Chemical Considerations

PROTACs were thus understood to be "pharmacokinetically risky" molecules that violated the most commonly accepted rules for what makes a drug safe: low molecular weight, low lipophilicity, low surface polarity – and others. Various modifications can be made to improve either their passive permeability, or facilitate active transport across cell membranes. Among them is the development of PROTACs with lower molecular weight, or compounds which can assume different conformations depending on the environment they find themselves in. Newer research also shows the potential to replace amide bonds with ester bonds to improve permeability. Future innovations in the field are only expected to improve the pharmacokinetic and pharmacodynamic profile of the modality – particularly their distribution in the body and their internalization by targeted cells.

Like many conjugated drugs, PROTACs rely on linkers to connect the two main parts of the compound together. Studies have determined that the nature of the linker can play a crucial role in its function: too short, and function may be impaired. Different lengths have also demonstrated changes in target selectivity, possibly related to the conformation the PROTAC and its targets assume, and their subsequent steric interactions, when binding occurs. One of the most promising advancements in improving our understanding of the protein-protein interactions of PROTACs and the complexes they form is PRosettaC. This is a tool, based on the Rosetta protein structure prediction suite of algorithms and computational models, which has the potential to truly jumpstart the development of future PROTAC drug candidates.

PROTACs enter the Clinic

Over the last decade, PROTACs made their transition to the industry – with multiple large pharmaceutical companies and startups showing interest and pouring resources into improving the viability of the technology. This has resulted in multiple product candidates moving from preclinical development into the clinic, making PROTACs the first drug modality of multispecific chimeras to do so. There are currently 15 different candidates in clinical trials – the majority of which target solid or liquid tumors, with one also investigating the treatment of autoimmune diseases. Three of those products are still at the IND stage, while only two have made it to Phase II trials so far.

Both Phase II products were developed by Arvinas, a company dedicated to the advancement of PROTACs. Their first, and earlier, product, ARV-110, targets prostate cancer. Phase I investigations of ARV-110 in castration-resistant metastatic prostate cancer showed an acceptable safety profile, as well as potential tumor reductions. Combined with interim Phase 2 results, ARV-110 has so far demonstrated a >50% reduction in

ARV-110 has so far demonstrated a >50% reduction in Prostate-Specific Antigen (PSA, one of the chief markers of prostate cancer) in over 46% patients. This shows the potential for PROTACs to provide solutions in areas where all other current treatment modalities have failed.

ARV-471 is the only other PROTAC in Phase II trials, developed to combat breast cancer by Arvinas in partnership with Pfizer. ARV-471 targets estrogen receptors, and is currently being investigated in patients with locally advanced and metastatic breast cancer. ARV-471 has so far shown great reductions in estrogen receptors in treatment groups – up to 89%, with partial responses also observed in at least two patients. Additionally, ARV-471 is also being investigated in combination therapy palbociclib – which is currently in Phase 1b trials.

With PROTACs making their journey across the clinic, their other uses are also becoming apparent. These include uses beyond the pharmaceutical field altogether – with possible applications in agriculture and the wider food industry. The protein degradation offered by PROTACs can enable fine-tuned manipulation of the proteome of crops, and other industrial microorganisms such as yeast, at a level similar to gene editing or transcription interference, showing the extremely wide horizons for the modality in the future.

After years of investigation, PROTACs have shown that their inherent advantages over other modalities – their oral bioavailability, low dosage, persistent effects and potential to provide solutions to unmet needs – make them worth investigating despite their inherent challenges. These challenges are slowly being overcome through chemical and structural innovations in our drug discovery process – and PROTACs have already entered the clinic. The future remains bright for chimeric modalities – with other modes of treatment such as RIBOTACs expected to follow soon in the future.

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. Enhancing how new technologies are utilized while improving efficiency across the board in preclinical development remain key areas of investment.

Artificial Intelligence

Artificial Intelligence (AI) remains the key investment area for peers in the Medicinal Chemistry space, with delegates hoping to find the best models to accelerate their own drug discovery pipelines. Relatedly, peers hope to apply AI approaches to other stages of the pipeline - including text mining for literature screening, companion diagnostics, biomarker discovery, and others.

Hit-to-Lead Optimization

Optimizing hit screening processes for potency, off-site activity, specificity and sustainability remain key areas of investment, 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.

Integrated Drug Discovery

Peers recognize the importance of integrating target validation, translational investigations, therapeutic discovery, and preclinical development while operating on iterative feedback loops at each part of the process which optimizes the overall workflow pipeline. Many hope to improve their own approaches to integrated drug discovery, or find partners who can enable this.

Custom Synthesis

Delegates at our Medicinal Chemistry Strategy Meetings are investing in ways to improve their own synthesis workflows, particularly as their companies seek to expand towards novel drug modalities and personalized medicine. This need places unprecedented demands on the chemical manufacturing pipeline, which peers are eager to meet.

Data Integration

As new therapies demand an improved, more comprehensive understanding of how they affect the entire body, delegates are investing in techniques to improve the integration of 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.

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ADME, DMPK and Modeling

In a bid to improve screening for preclinical toxicity, as well as characterize the full spectrum of effects a candidate may have on the body, delegates are investing in new methods to model Absorption, Distribution, Metabolism and Excretion (ADME). Protein structure and ligand/ affinity prediction models remain crucial in enabling such approaches, as does the development of new technologies.

Fragment Based Drug Discovery

Delegates are starting to invent 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.

Laboratory Information Management Systems (LIMS)

Laboratories are becoming increasingly more complex spaces. As new technologies are adopted and novel drug modalities are tackled, multi-disciplinary approaches are often required. This, along with increased regulatory demands, require improved Laboratory Information Management Systems (LIMS), with many peers investing in the area.

High Throughput Screening

High Throughput Screening is still one of the dominant strategies towards drug discovery, and improvements in computational power, AI models and protein prediction strategies are expected to further expand its scope. The chemical libraries which can be processed are becoming even larger, particularly as new drug modalities open up undruggable spaces - and delegates are keen to invest in efficient solutions in the field.

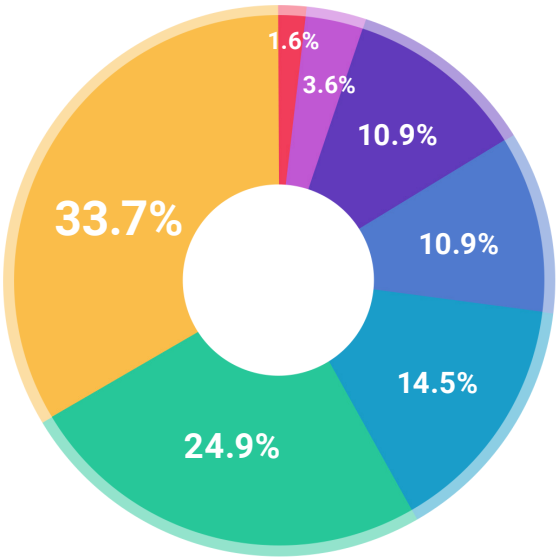
Cloud Computing

In a world and global landscape that places increasing focus on agility, firms are finding it increasingly necessary to move their own systems to the cloud. Additionally, cloud computing can provide unique solutions to increased computational power demands - with scalable cloud computing solutions aiming to bring novel technologies to every research team.

Delegate Breakdown:

Attendees at Proventa's 2022 Strategy Meetings

2022 Atendee Breakdown



33.7% Director level

24.9% Vice President

14.5% Scientist

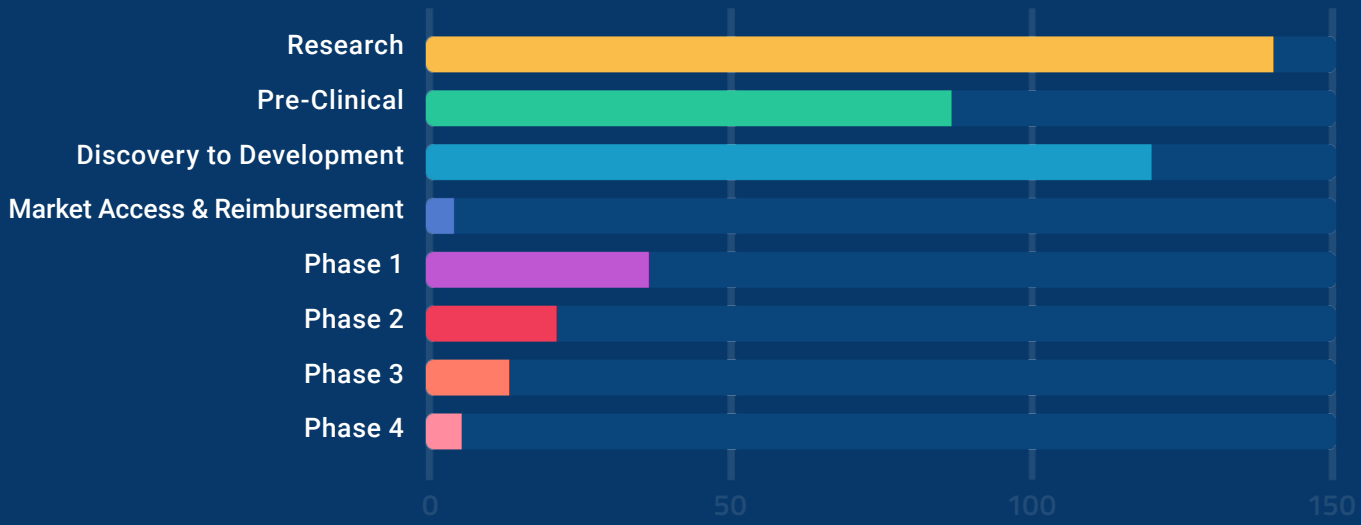
10.9% Team Lead

10.9% C-level

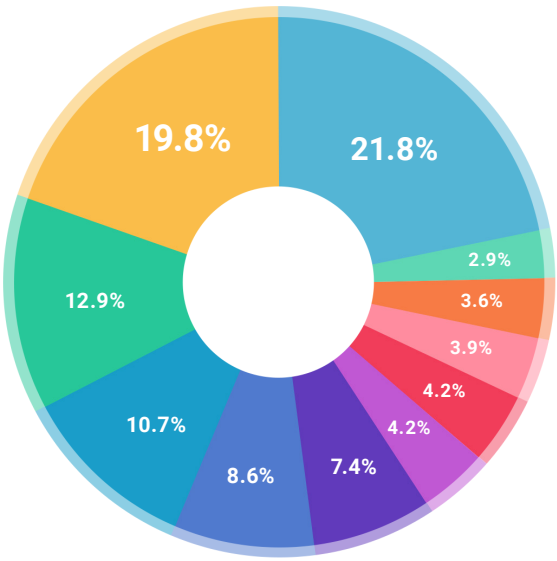
3.6% Academia

1.6% Other

Drug Development Stages



Therapeutic Areas



- Oncology
- Immunology
- CNS
- Inflammation
- Rare Diseases
- Cardiovascular
- Infectious diseases
- Metabolic diseases
- Neurology
- Respiratory
- Other

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