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Insights from the Industry

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BIOLOGY

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Introduction

2021 saw an increased focus on R&D innovation, spurred on by the COVID-19 optimise translation from preclinical to clinical models, and improve pharmacokinetics in human models.

At the same time, it is a period of exciting innovation in several areas. In particular, the increased prevalence and takeup of AI and machine learning is critical for the future of pharma R&D, with new generative models promising incredible improvements to drug discovery - if they can be delivered as promised.

Proventa's 2021 event on Medicinal Chemistry and Biology examined these innovations in depth. From the use of AI generative methods and ML in drug discovery to supporting COVID-19 research via in-vitro and in-vivo platforms, to examining the challenges of targeting protein-protein interactions, the changing landscape of research and development was discussed by experts in the field.

This report looks to provide greater information on the near future of both medicinal chemistry and biology fields: using data from our expert facilitators, it will discuss the top strategic challenges facing those who attended Proventa's event, as well as the major investments they will be making over the next 12 months. It will also show the quality of attendees at Proventa's event, and feature an article on an important issue in the field.

We hope this report proves both engaging and useful,

Charlotte Di Salvo, *Writer*
Proventa International

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TOP 10 Challenges 2021:
What Peers are Focusing on

As part of its event, Proventa asked its delegates their thoughts on the greatest challenges facing the medicinal chemistry and biology spaces in the next 12 months.

1 Target validation

This is a crucial part of drug discovery that relies heavily on accurate models representative of human disease pathology. Delegates expressed target validation as a key problem in drug development, often due to drug candidates failing to demonstrate the same therapeutic efficacy in humans as seen in some disease models.

2 Artificial intelligence / Machine learning

AI has shown great potential to innovate many different aspects within clinical research, becoming an area of attention for delegates. One of the challenges, however, is making AI systems accessible to professionals across the field. AI-enabled drug discovery also appears to be a top priority, in addition to the impact of machine learning in preclinical modelling.

3 Data analysis and management

With the accelerated development of virtual trials as a result of the pandemic, data collection and analysis need to evolve in order to keep up. The management of data in particular is a challenge expressed by those attending the meeting. In this context, data visualisation within clinical research was suggested as needing improvement, possibly in relation to data quality which was another concern raised.

4 Resource management

Managing the resources of clinical trials was a shared challenge among delegates. The management of investigative sites, clinical research organisations and supplier relations often raises a number of issues. Estimating resource consumption and being able to rapidly respond to protocol implications are two of the key areas within resource management.

5 Biological models

Choosing a biological model is a common challenge in research - to ensure it is both translatable to human pathology and can also be manipulated for target validation. With a multitude of animal and computational disease models available, it is important that the pathology of the disease model is as close to the human disease as possible to reveal optimum molecular targets for therapeutic treatment.

TOP 10 Challenges 2021:
What Peers are Focusing on

As part of its event, Proventa asked its delegates their thoughts on the greatest challenges facing the medicinal chemistry and biology spaces in the next 12 months.

6 Target identification

Pinpointing a therapeutic target can be a difficult task in complex diseases, hence target identification was a challenge highlighted by delegates. The approach to target identification typically falls under three main categories: biochemical methods, genetic interactions or computational inference. The challenge is deciding which approach will best identify the molecular target and its susceptibility to therapeutic intervention.

7 Funding clinical trials

Fundraising and balancing the costs were some of the financial implications raised as challenges for clinical trials. A multitude of factors can impact the overall cost of clinical trials including extended timelines, increased regulations and rising prices of clinical supplies. Understanding how these factors can be prevented or contained is key to maintaining a steady budget and appropriate allocation of funding.

8 Outsourcing

For smaller functional service providers, outsourcing to outside clinical research organisations was raised as a particular challenge. Outsourcing biochemical assays was highlighted as a specific area of interest, focusing on ADME (absorption, distribution, metabolism, and excretion), in addition to seeking quality partnership for the general sharing of resources and expertise.

9 Molecular assays

Understanding the pharmacokinetic and metabolic profile of a compound is critical in selecting appropriate drug candidates in preclinical studies. According to attendees, one of the main challenges in this area is choosing appropriate assays that can fully assess the pharmacological properties of a biological or chemical compound.

10 Clinical logistics post COVID-19

The COVID-19 pandemic saw clinical operations thrown into disarray. Patient recruitment, supply chains and clinical site management was impacted greatly by the travel restrictions as a result of national lockdowns. Mitigating the impact of this global crisis on clinical research continues to be a challenge.

Moving towards Phenotypic Screening in Drug Discovery:

An Interview with

Prasun Mishra

Despite the technological advances, drug discovery is still a lengthy, expensive, and difficult stage in the drug development process. Screening assays are a critical part of rapidly and thoroughly analysing vast numbers of compounds for desired biochemical activity. In a recent interview with Proventa International, **Dr Prasun Mishra, Founder and CEO for Agility Pharmaceuticals**, discussed the benefits and challenges of phenotypic screening in drug discovery.

P Proventa: You recently spoke about reinstating phenotypic screening (or PDD: phenotypic drug discovery) in drug discovery at our Medicinal Chemistry Strategy Meeting. Could you explain what phenotypic screening is?

PM Prasun Mishra: Phenotypic screening is a type of screening used in biological research and drug discovery to identify substances such as small molecules, peptides, or RNAi screens, that alter the phenotype of a cell or an organism in the desired manner. Briefly, phenotypic screens look at the effects of these substances on genes, pathways, and inhibition/induction, which are causing the desired change in the phenotype.

P PDD is an alternative method of drug discovery that aims to address some of the challenges with target-based drug discovery (TDD). What advantages do you believe PDD offers over target-based methods?

PM Traditional target-based methods are employed once a target is known: By inhibiting this target you get the therapeutic benefit/advantage. While this works for the disease cases where a mutation causes the disease, this is not the case for a majority of diseases. The biology is complex, and usually one or more pathways are involved in driving a complex disease phenotype.

PM So then it becomes important to address that complexity of disease biology, which cannot be done by the classic approach of targeting a single gene. Hence, phenotypic screens can be used to understand both the biology of the disease and the master regulator genes/pathways associated with that disease phenotype. I believe that phenotypic screens are the right approach to address this challenge, which is why the drug discovery field is moving towards PDD right now.

P Could you go into more detail about the relevance of high-content imaging in phenotypic screening?

PM High-content imaging screening is a type of phenotypic screening where the whole cell phenotype can be imaged using various cellular markers. In this manner, high content screening utilises molecular imaging to assess the phenotypic changes at the cellular level - sometimes in real-time - upon treatment with a substance. It's also called cellomics as we are trying to look at the cellular phenotype through the eye of a microscope or a profound assay or imaging system.

> **"I believe that phenotypic screens are the right approach to address this challenge, which is why the drug discovery field is moving towards PDD right now."**

P How well has phenotypic screening been integrated into animal models?

S Phenotypic screening can be utilised to replace animal experiments. For example, in the case of cancer, one can use patient-derived tumour cells and grow them into spheroids. These assays are powerful not only in replacing animal-based screening assays but also can be used as a secondary screen to get an idea of hit confirmation. For example, if you have the top hundred compounds from a large screening, then you can take those molecules and run them through a secondary screen of spheroids to understand how they would be performing in three-dimensional spheroid assays. Essentially, you mimic environments in patient tumours.

Patient-derived spheroids can give you an answer as to how candidate drugs will contribute to the shrinking of 3D tumours. It provides a means to avoid a large-scale secondary screen using animal models. Using complex co-culture screens, one can narrow down the list of hundreds to the top three to five candidate drugs. These few lead compounds can be further optimised utilising animal experiments which are necessary for IND-enabling studies towards FDA approval.

So, in the above example, by utilising PDD, you have not only narrowed down the scope of active molecules but also have budgeted your project with a limited number of animal experiments.

P Are there any limitations of PDD that need to be addressed? The high rate of false positives, for example?

PM We as a community have addressed some [major] challenges associated with PDD. The key is to run a very good positive, negative, and no treatment control (blank). This then allows us to run our data analytics against these controls to give us true hits. Analysing the spectrum of data through these provides very good insights into the candidate drugs. We have also developed a list of common false positives and false negatives associated with a screening assay. So, utilising the proper controls and getting rid of false hits, we have overcome some of the key limitations associated with phenotypic screens.

There is a saying in our field: "Garbage in, garbage out." If your screen is designed poorly, you will have a high rate of false positives. Designing a high-throughput screen is a robust process. One has to spend some time diligently designing and validating a phenotypic screen to gain confidence in a screen. Furthermore, gaining confidence in a readout helps precisely measure what you want to measure. Once the screen and readout are optimised, you can screen millions, if not billions, of compounds in a very short time using this powerful tool.

If a phenotypic screen is designed well, it can lead to amazing findings. This can transform basic biology into what I call "high-throughput biology." Many research projects and brilliant minds have been stuck on one protein, one pathway, one drug hypothesis. Since then, a lot of progress has been made in the field of PDD. Also, the whole genome is not druggable, PDD allows us to identify upstream and/or downstream effectors to an undruggable gene to be able to still inhibit a pathway.

PM Some of the new papers in the PDD field are very promising, reiterating the importance of phenotypic screens as well as the importance of high-throughput approaches to find ways to inhibit certain disease phenotypes. I am confident that if we utilise PDD and high-throughput approaches to understand disease biology, it will propel us faster in finding curative therapies for some of the incurable diseases.

P Can phenotypic screens replace animal models?

PM Yes, I think that if we use at least some of these smart assays that we have developed, such as co-culture assays, as well as various complex phenotypes/ tissues, we can replace the need for animal screens with phenotypic screening. That said, I would acknowledge that this is an optimistic statement, as you still have to do IND-enabling studies utilising animal experiments to gain FDA approval. However, as I said before, you can narrow your leads, and then utilise very few animal experiments for confirmation studies. So, I hope I have convinced you that one can minimise costs as well as spare animal lives by smartly utilising phenotypic screening.

P In general, how important is AI and ML in further improving PDD?

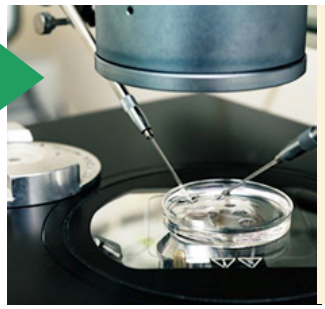
PM AI and ML will help mainly with data analytics of high-throughput biology. Because of the complexity within the body, the cells, the pathways, and complex interactions, phenotypic screening is the way to go. However, one of the downsides is that you are bombarded with massive datasets, so you have to be prepared to analyse and have a way to make useful conclusions in the right way. So, this is where AI, ML, and smart algorithms are very helpful.

You can automate not only the cell culture process and screening but also the data analysis process. So, once you've streamlined everything, you get the best possible insights into high-throughput biology using a phenotypic screen accompanied by the AI/ML tools.

TOP 10 Delegate Investments for the Next 12 Months

Proventa asked delegates at its events to speak about their investments for the coming year. Those surveyed attested to increasing moves towards technology and innovate developments such as AI, as well as the need to further develop target validation, data analysis and resource management.

1 Target validation



Target validation is a crucial part of drug discovery. The complexity of human physiology however, presents a challenge when choosing a model that is translatable and can also be manipulated for target validation. Hence, significant investments are being made into optimising current animal models and artificial simulations.

2 AI/ML

Significant investment in computational technology has seen a number of new innovations arise in drug discovery – perhaps most notably machine learning (ML). The Generative Adversarial Network is an example of a recent innovation in deep learning for drug discovery. Deep learning is a specialised area of ML that filters out irrelevant data from large data sets using deep neural networks. In addition to reducing human error, the automation of ML software can analyse data from many sources more accurately and in a shorter period of time.

3 Data analysis and management

Significant investments are being used to optimise data analysis in clinical trials. Data mining is emerging as a useful tool within clinical research. This digital method can be used to either describe a target dataset or predict outcomes via machine learning. Outlier detection model is an example of data mining that can signify noise or variation within data sets. This particular model has the potential to identify human error or negligence in clinical data entry. This is an important part of reducing inaccurate data that could otherwise lead to a misconception of results.

4 Resource management

With the pressure to reduce costs and expansion of global clinical operations, investment in modernised clinical trial management systems has been a particular area of growing interest. Furthermore, the increasing number of virtual trials has seen some organisations struggle to manage resources with legacy CTMS' and the vast amounts of data from multiple sources. Cloud-based software is emerging as a popular choice to better manage resources, providing a single platform to collate documents and data and the direct sharing of information with external partners.

5 Biological/ AI models

Advancements in computational biology have enabled the representation of organic models through artificial intelligence. In silico is an example of a computer modelling which can test hypotheses within a simulation human disease pathology. AI models, while initially costly, are becoming popular as they are cost-effective in the long run, in comparison to animal models which are expensive to maintain and often limited by translatability to human physiology.

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Target identification

6

Biochemical assays, genetic screening or computational models are the primary methods for target identification in drug discovery. Recently, investments in identifying novel small-molecule drugs have expanded to screening large libraries of compounds. DNA-encoded libraries represent a modern, versatile tool used to better identify a greater range of novel biological compounds. These libraries are capable of screening drug targets with an extensive number of compounds with great efficiency.

Funding clinical trials

7

With a growing number of diagnoses of chronic conditions globally, the pharmaceutical industry has seen a rise in demand for biopharmaceutical products. Unfortunately, this has led to spiralling costs to manage clinical trials of increasing complexity and immense pressure to accelerate the drug approval process. As a result, significant investments are being made to make drug development more cost-effective. One example is increased outsourcing to CROs to reduce the financial burden of sponsors coordinating clinical operations.

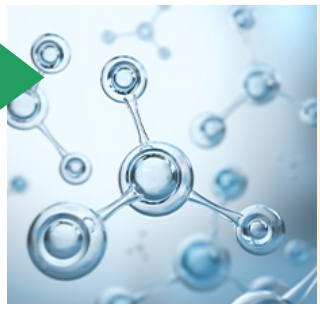
Outsourcing

8

In comparison to in-house management, an increasing number of pharmaceutical companies are outsourcing to CROs for clinical operations. Globalisation, digitalisation and personalised medicine are three primary reasons for recent investments in outsourcing. In the case of personalised medicine, the complexity of trial designs requires increased monitoring and workloads for researchers which can otherwise be outsourced. Using local CROs for multi-national clinical trials is becoming a popular choice for pharmas, to ensure consistent communication between sites and smooth running of clinical operations.

Molecular assays

9



Understanding the pharmacokinetic profile of a compound is critical in selecting appropriate drug candidates in preclinical studies which are tested via in vitro early-stage predictive assays. Despite the popularity of animal models, it appears the computational biological assays are increasing in interest and investment. Pharmacokinetic mathematical modelling for example, can depict the major organs and tissues of the mammalian body without confounding factors like species differences or human error in the lab.

Clinical logistics post COVID

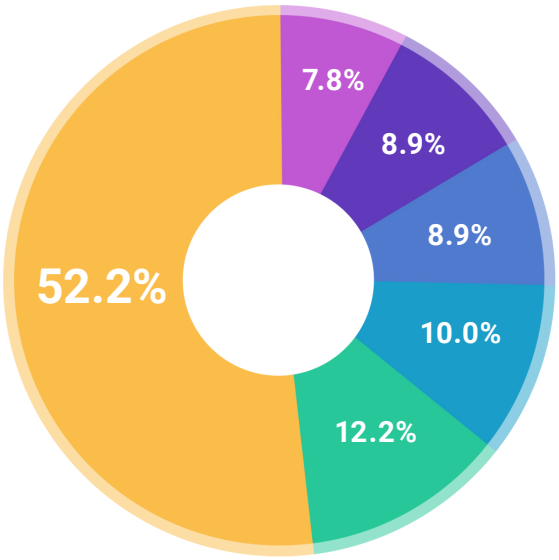
10

In unprecedented circumstances, digital innovations in clinical research enabled clinical trials to continue running in extenuating circumstances. However, the success of virtual clinical trials also demonstrated the benefits of a patient-centric approach to clinical research. Disruptive technologies and blockchain systems are a few examples of the digital innovations which have seen significant investment in the transition from traditional to modernised clinical operations post COVID-19.

Delegate Breakdown:

Attendees at Proventa's 2021 Strategy Meetings

2021 Atendee Breakdown



52.6% Director level

14.5% Scientist

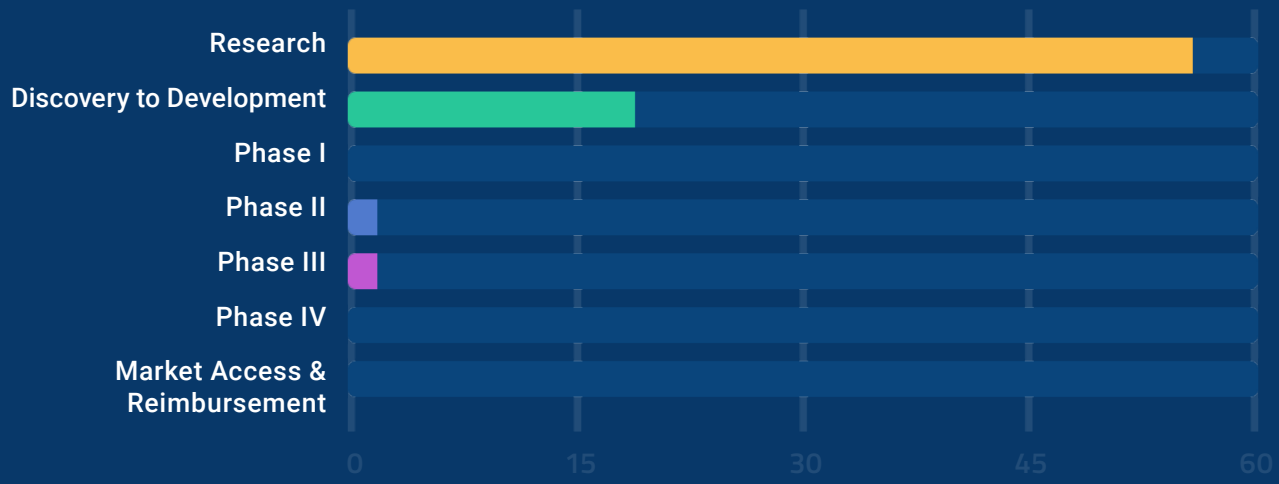
13.2% President / VP

7.9% C-class

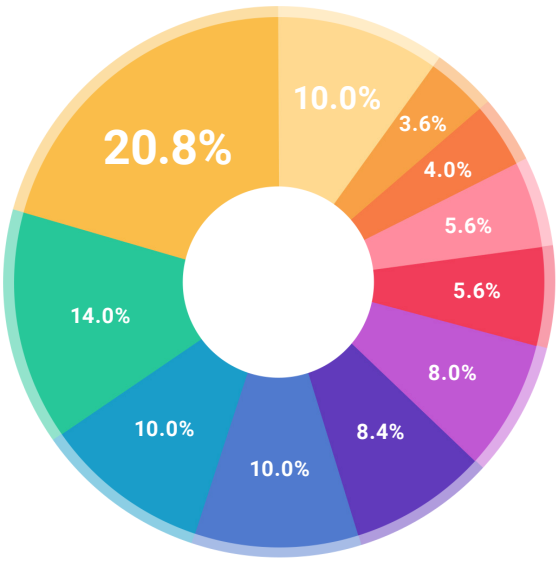
5.3% Head

5.3% Team Lead

Delegate's drug Development Phase



Therapeutic Areas



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

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