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Medicinal Chemistry & Biology Insights from the Industry



MEDICINALCHEMISTRY



BIOLOGY

Introduction

2021 has so far seen an increased focus on innovations within the drug development process across the pharmaceutical industry. Improving preclinical translatability is becoming a priority more than ever, to improve the accuracy of dose prediction and accelerate drug development.

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. The integration of in silico modelling is becoming increasingly prevalent across the field, although the challenge of formulating computational pharmacokinetics remains a challenge.

Proventa's 2021 event on Medicinal Chemistry and Biology examined these innovations in depth. From new tools and technologies like organ-on-a-chip, to the innovative approaches to early drug discovery through novel chemical modalities, to addressing translatability challenges from preclinical studies to bedside, 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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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 Artificial intelligence

Despite the success of AI applications across drug discovery and development, a number of challenges were noted by delegates within the pharmaceutical industry. Firstly, the lack of personnel to operate AI/ML-based platforms was highlighted as an issue for companies hoping to utilise the advantages seen for data analysis. Secondly, smaller organisations are often limited in their budget so cannot afford to invest in AI/ML technology.



2 Data

Integration, annotation, availability were the three most mentioned challenges with regards to clinical data management. With the success of decentralised clinical trials during the pandemic, clinical research is moving towards a more virtual platform. The introduction of cloud-based technology and electronic health records have presented a challenge with regards to integration of data across multiple software. The labelling of data for AI applications, known as data annotation, was also an area for improvement expressed by many.



3 COVID-19 / Pandemic

In the midst of the global crisis, it was noted that big pharma initially struggled to launch telehealth which was essential to allow clinical trials to continue. Furthermore, the various regulations of local lockdowns greatly disrupted supply chains and compromised the rebuilding clinical trial networks post pandemic. One of the greatest challenges with trial continuity was ensuring patients felt safe enough to continue, which required further support and guidance for subjects about changes made to ensure their safety.



4 Preclinical testing

Improving preclinical testing was raised a number of times as an area of concern. One of the main challenges highlighted was the development of models with better translation to human pathology. The optimisation of dose predictions was emphasised as a key part of this challenge. Despite some of the delegates focusing on optimising computational *in silico* modelling, several highlighted *in vitro* and *in vivo* animal models as a particular area in need of focus especially.



5 Target validation

Multiple areas of target validation were raised as particularly challenging during the meeting. Developing assays with greater accuracy with regards to pharmacokinetics was highlighted by several delegates. Preclinical studies which fail to accurately assess drug pharmacokinetics can result in the delay or even early termination of clinical trials if the drug does not behave in the human body as predicted. The challenges of integrating *in silico* models with pharmacokinetics was also emphasised.

TOP 10

Challenges 2021: What Peers are Focusing on

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6 Digitalisation

Adaptation to emerging technologies was highlighted as a particular issue for a number of delegates. Transitioning from older systems to cloud-based software appeared to be a challenging task, in addition to the integration of modern digital tools like wearable devices and apps. Some delegates inferred the difficulty of developing tools and resources for biological data integration was also an issue.



7 Hit-to-lead

Hit finding and hit-to-lead optimisation are both critical parts of early drug discovery, and areas which have posed a problem across drug development. The optimisation of screening assays, of which plays an important part in hit finding, was specifically highlighted by delegates. Following compound screening, *in vivo* and *in vitro* testing occurs, however the supply of animals for preclinical testing was mentioned by one delegate as an issue which needed resolving.



8 Costs

The consensus across the board highlighted a number of potential challenges in the future regarding costs and funding. Delegates currently focusing on research inferred that raising capital for scientific studies and building a high net worth client register was a particular challenge that needed to be addressed. Cost justification, stakeholder management and investments were other areas of focus for improvement in clinical research.



9 Target identification

The development and choice of screening for drug discovery appeared to be an area of priority for many delegates. Fragment and virtual screening in particular were highlighted as challenging areas. Virtual screening in particular was a strategic challenge for many, as a promising *in silico* technique for drug design. Optimizing the speed and attrition rates in early drug discovery was emphasised, in addition to the integration of computational chemistry techniques.



10 Manufacturing

The sourcing raw materials both easily and on budget continues to be a challenge expressed by a number of delegates. As a result, it appears self-sufficiency is the next step in mitigating potential issues with external supply chains. The selection of drug manufactures was also expressed as an issue for pharmaceutical companies with regards to cost-efficiency, time-scale and capacity.

Innovations in Translational Medicine:

An Interview with



Marcie Glicksman

3D cultures and organ-on-a-chip are a few examples of technologies that hope to bridge the gap from benchside to clinic. Failures that arise during drug development often arise due to poor translatability from models in preclinical studies to the patients in clinical trials. We spoke to **Marcie Glicksman, Head of Biology for Enclear Therapies**, about her thoughts and experience with novel technologies supporting translational medicine.



P Proventa: At our most recent event you discussed some of the new tools/technologies addressing the translational medicine gap - could you explain further what translational medicine is and some of the main challenges that arise in drug development?

MG Marcie Glicksman: People use this term 'translational medicine' very broadly, but it's one of the reasons why I went into the world of drug discovery. Translational medicine is the foundation of science combined with technology for the purpose of better medicine.

There is room for improvement at every stage in drug development. Starting with the clinical stage, finding a patient population can be a huge issue i.e. trying to find biomarkers that define patient populations.

Medicine is not based on mechanisms but on the symptoms. Consequently we have a lot of drugs that alleviate symptoms, which is a step in the right direction, but we're not curing any diseases.



P Do you believe we should be approaching drug development from a bottom-up approach to top-down, or is it dependent on the disease?

MG It can depend on the disease - for example, you have enzyme replacement therapies that can make sense for a bottom-up approach. I like a top-down approach, as it is our purpose to cure or ameliorate diseases so we can understand what is an appropriate approach. As a researcher, having conversations with clinicians at an early stage is good as you are not always aware of the issues that plague patients, and so if you can provide something to address this issue, it can be important for the patient - so that's why I do like the top-down approach..

“I like a top-down approach, as it is our purpose to cure or ameliorate diseases so we can understand what is an appropriate approach.”

P Do you think emerging technologies will support or replace these animal models at the preclinical stage?

MG When I started working with stem cells, eight or nine years ago, I was very hopeful that they would replace animal studies. There have been various studies surrounding cardiotoxicity and liver toxicity in which stem cells may eventually provide better models. Also in terms of predicting patient response, if you can have patient cells which you can test and see they respond, then maybe they can be more predictive than animal models.

Animal models are useful from a target-engagement standpoint, and potentially a dosing standpoint, if you take into account species differences etc... But there are a lot of logistical differences. If you look at rodents for example, their brains are very different and much smaller than humans'. Non-human primates have a complexity to their brain but their brains and body sizes are a lot smaller.

For CNS delivery, we've been using sheep. I don't have the evidence yet, but I think in some ways, sheep could be a better model than non-human primates. They have more cerebrospinal fluid, they have a brain closer to the size of a human's and body weight which is closer to a human.

I also think we have got a lot better in terms of predicting toxicity - a lot of drugs fail because they're not efficacious but they're completely safe.



P 3D cultures are an example of the latest advancements in cell-based assays - how are 3D cultures created? What advantages do 3D cell cultures have over 2D cell cultures in terms of modelling?

MG Cells have a natural affinity for each other - our tissues are formed by our cells creating junctions between each other, as they like to adhere. You can create 3D cultures by creating an environment where culture media are moving, whether this be in multi-well plates or in mini-spinner flasks- you can form them pretty easily.

3D cultures are a lot closer to the physiological state, and so far, a lot of people have been comparing 3D to 2D cultures. One of the roundtables I had at a recent Proventa event involved people who had been using 3D cultures, and sharing how their stem cells had grown and differentiated better in 3D than 2D.

The scientific community is, however, still defining these cultures. If the 3D sphere becomes too large, the cells on the inside can't be supported by the nutrients and tend to die. So working out how to handle and optimise these cultures is being developed, and how to assay them. Some people have said in order to assay them, they have to break them apart and place them on plates - so, first we need to have assays that can support a 3D format.

P Organ-on-a-chip technology is on the list of top ten emerging technologies - do you think it will support preclinical studies? Is there potential to develop a brain-on-a-chip?

MG We'll see, maybe it will be combined with 3D cultures. In terms of modelling the brain, some people have performed 3D cultures of the brain and have seen advantages over 2D. Everybody needs to keep in mind that these are models - and depending on what you want to model, some technologies will be more relevant than others.

Will we ever recreate the human brain or whole body? Unlikely. I definitely think people are using it as a model and applying it. In terms of approval, the FDA will want to see a lot in the form of validation before it is accepted.

“You can create 3D cultures by creating an environment where culture media are moving, whether this be in multi-well plates or in mini-spinner flasks- you can form them pretty easily.”

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.

Artificial Intelligence

1



The trend of AI applications across the industry has seen many companies invest in artificial intelligence to support medicinal chemistry in drug development, improving drug design for example. Most notably, delegates expressed a desire to focus on using AI for automation in target identification and validation i.e. the automation of biomarker and therapeutic target selection in addition to computational ADMET (absorption, distribution, metabolism, excretion, and toxicity) property prediction for small molecules. A number of delegates also hope to utilise the A automation for visual inspection in operations as well as the exploration phase in drug discovery.

Hit To Lead Optimisation

2



Optimising the hit-to-lead process has resulted in many organisations seeking to invest in some of the emerging technologies. Speeding up the process of hit-to-leads and expanding capacities were particular areas of focus in order to optimise the drug discovery pipeline. Some delegates in particular hope to utilise optimised hit-to-lead processes to generate better preclinical development candidates. Others intended to optimise lead compounds across portfolio company assets in general.

Target Validation

3



Target validation is a crucial part of drug discovery that relies heavily on accurate models representative of human disease pathology. The consensus of delegates expressed target validation as a key area of investment to discover novel targets, developing new drug candidates. Others intend to invest in target validation to confirm the mechanism of action for lead compounds and in general, support the drug discovery pipeline.

Integrated Drug Discovery

4



Integrated drug discovery is built upon rapid and efficient feedback of assay data into the design and synthesis of drug molecules which is critical to the timely delivery of drug candidates - this is a priority for all pharmaceutical companies. Investment appears to be designated for improving the efficiency of drug discovery pipelines, accelerating R&D especially. Other companies are seeking investing in support from CROs with regards to integrated drug discovery in their organisations.

Custom Synthesis

5



Custom synthesis is an exciting area emerging in medicinal chemistry, enabling the efficient synthesis of high quality, complex molecules from mg to Kg scale. The ability to customise building blocks and the gram scale scale are key factors influencing investment. In addition to these desirable characteristics, investment in custom synthesis appears to span across targeting single molecule preparations, internal bottlenecks, and complex synthesis competencies.

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Fragment Based Drug Discovery

6



The high sensitivity and hit rates of FBDD make it a promising approach to drug discovery and an area of recent investment to optimise this stage of drug development. Delegates are looking towards fragment based techniques to find novel hit compounds for drug discovery projects by investing in biophysical methods for screening like X-ray crystallography and cryogenic electron microscopy.

Cheminformatics

7



As technology evolves, the use of computational and informational techniques to understand problems of medicinal chemistry, such as in silico modelling, is increasing. Investment within cheminformatics appears to be focusing on improving existing cheminformatic technology. More specifically however, some delegates noted the value of cheminformatics in the access of reagents and producing APIs.

Genomics

8



Genomic technologies are becoming increasingly popular in providing solutions across drug development, especially so in drug discovery. Several delegates expressed investment in the integration of various genomics data and focusing on generating epigenomics and genomic data for upcoming projects. Investment in genomics ranges from drug development applications, specifically target identification and validation, through to personalised healthcare. Those already utilising these technologies hope to standardise genomic pipelines, as well as ensuring a return on their investment.

Structural Biology

9



Structural biology is emerging as an area of interest within R&D and across the pharmaceutical industry. Investment appears to be targeted at developing new research methods in this field, changing providers and scouting for new partnerships. This is a new area for many companies, hence investment in project support was another point raised.

Modelling Simulation

10

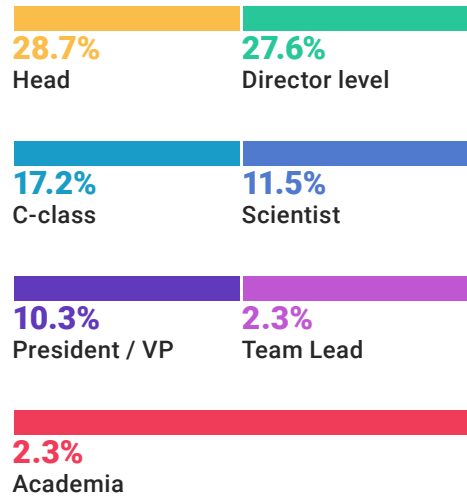
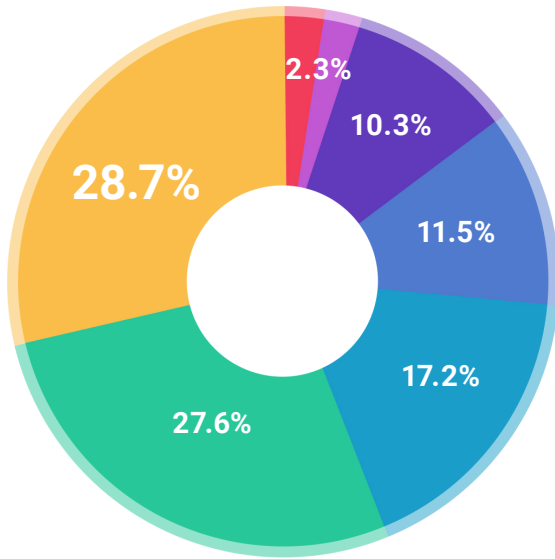


Modelling simulation is a process whereby key program decisions, supported by mathematical models and simulations, predict the likelihood of success for the drug. This is a key area of focus for drug development, to which investment is focused on utilising it for human dose prediction, drug profiling and drug selection. A key point raised was how important modelling simulation could be to saving time and money if the modelling matches with real animal studies.

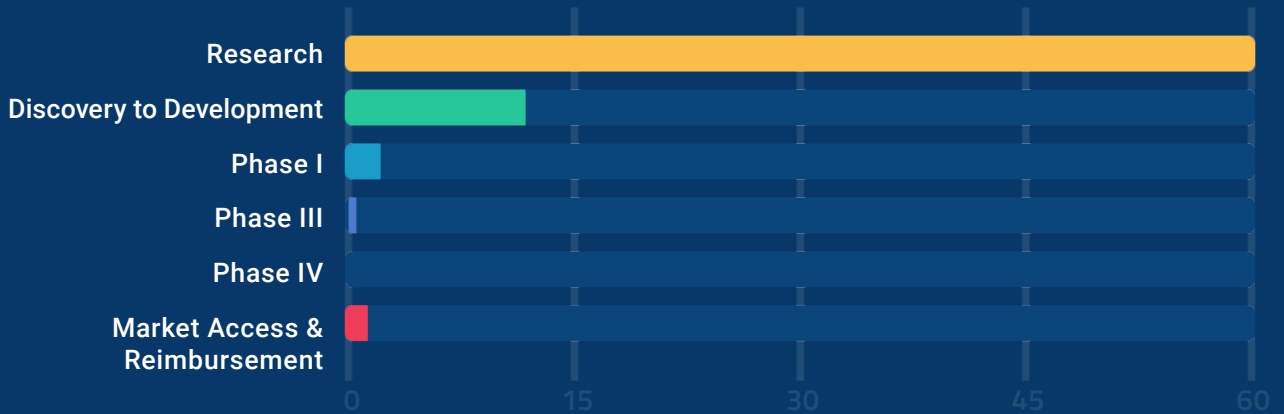
Delegate Breakdown:

Attendees at Proventa's 2021 Strategy Meetings

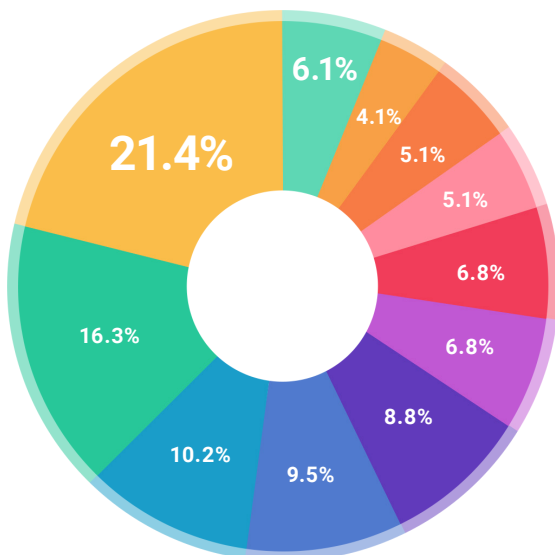
2021 Attendee Breakdown



Delegate's drug Development Phase



Therapeutic Areas



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