Biology & Medicinal Chemistry

Insights from the Industry

BIOLOGY MEDICINALCHEMISTRY

PROVENTA INTERNATIONAL

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Introduction

There are few years in living memory as disruptive and uncertain as 2020 has been. While this is true of almost every sector, the events field has seen unprecedented change in how events are held and how operations will be conducted in the future.

Proventa International was among the companies spearheading this innovation, utilising its trademark versatility to ensure that none of its important meetings were cancelled and its mission was carried out. Moving fully online, Proventa was able to facilitate connections and host expert, sector-critical discussions that would otherwise have been missed.

Despite the unforeseen challenges 2020 brought, Proventa's meetings were as successful as always, bringing together top-tier industry experts to talk through challenges and innovations with one another, make new connections and take back brand new information to their companies. Whatever challenges the rest of the year brings, those who attended the online meetings will be able to face them fully prepared and as informed as possible.

The Future of Biology and Medicinal Chemistry

The related areas of biology and medicinal chemistry are both sectors experiencing rapid, fascinating change, with results that can deliver real solutions for patients across the globe. The roundtables held by Proventa this year took advantage of this, discussing among other things AI's ability to reduce drug discovery attrition rates; the activation of endogenous progenitor cells by small molecules; and accelerating translation through strategic alliances.

From design & custom synthesis to disruptive technologies, Proventa's 2020 event looked at some of the most relevant and important changes in the field today, with leading experts offering their insights and thoughts to those who were there.

This report will look at some of the highlights of the recent Biology and Medicinal Chemistry online events, but will also go further: it will explore what delegates are investing in right now, and look ahead to the next five years in the field and how Biology and MedChem will change as the years roll on.

We hope you enjoy this report, and look forward to seeing you at our events next year,

Joshua Neil, ***Editor***
Proventa International

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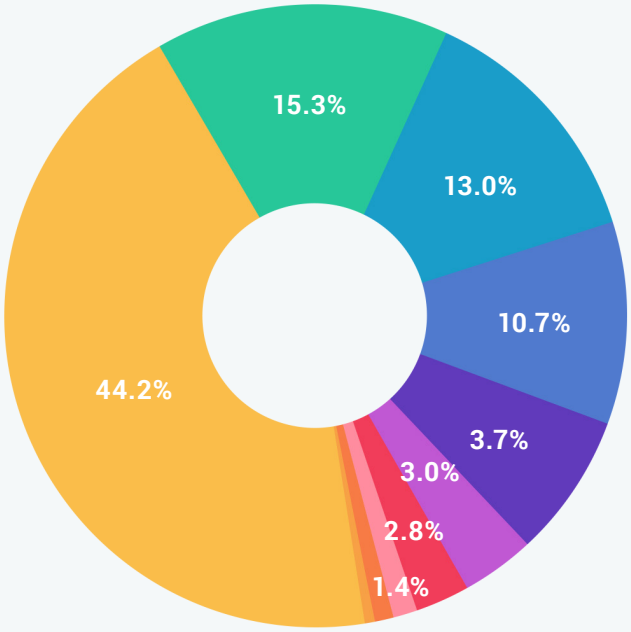


44.2% Director Level

15.3% Department Head

13.0% President / VP

10.7% C-Level

7.4% Scientist

3.7% Team Lead

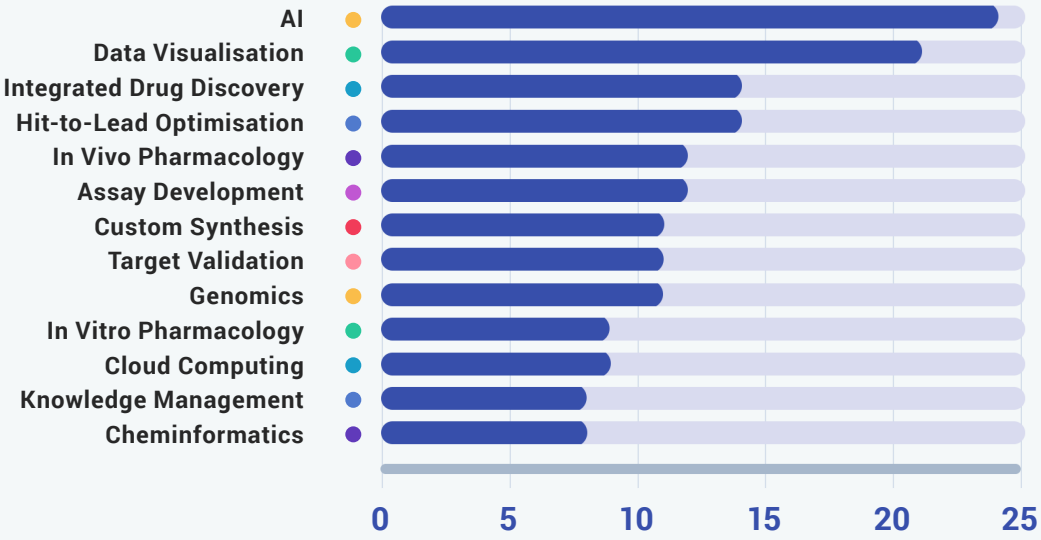
2.8% Other

1.4% Manager

0.9% Academia

0.5% Chairman

Key Investments



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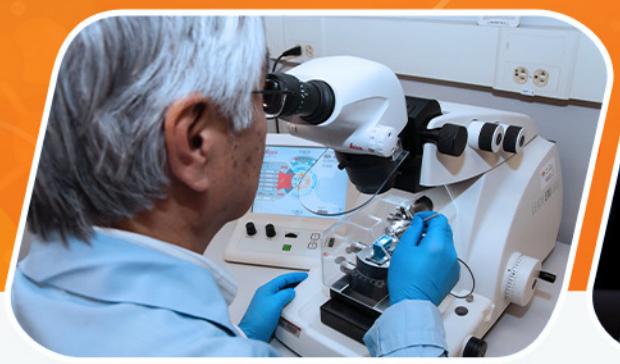

BIOLOGY

Molecular Adventures in 3D and 4D: What New Ground is Being Opened Up by Cloud Computing

Guy Lewy, CSO of computational drug discovery company Sublime, gave a fascinating roundtable on the Biology track focused on innovations in Cloud Computing and its use in pharma. He began by noting the recent developments in the field, including the lowering of costs, and talked about how the bright spark of AI may well have obscured some more - and perhaps more revelatory - developments in the sector.

Guy began by talking about a case that would not have been made possible without Cloud computing. The case related to finding unexpectedly similar molecules through exploration of a complete 3D pharmacophore-space of all molecules in the set, exhaustively. He went on to point out that pharmacophore hypotheses can return unexpected scaffold-hops: two molecules can appear dissimilar in a 2D setting, whereas with the knowledge of a shape they'd make in a pocket, the binding mode can be second-guessed.

The question then arose: when moving into 3D, how can professionals balance against the additional noise present and find innovative binding modes? He said that with the cheap processing power now available to many pharma companies, instead of picking some actives and manually crafting a single pharmacophore hypothesis to see if the generated conformers fit it, instead experts can now take every single molecule they're interested in - even if it's 100,000 HTS hits, and for each feasible conformer that each molecule can make, generate every possible pharmacophore hypothesis that might be a binding mode and see what happens.

This is done by generating as many physically feasible conformers as possible, then make a 3D representation of every possible pharmacophore to be analysed. This representation of the pharmacophores will be very compact, slightly fuzzy and very quick to pairwise compare for identity. Comparing these will identify 'bridge' pharmacophores, with the same four-point pharmacophore represented in different ways across groups.

One delegate then mentioned that their company was attempting to integrate a wide variety of data sources, harmonising them in a Cloud environment. This would allow for asynchronous downloading and retrieval. This all takes time, and to reduce this his company puts an overarching ontology on top of the data sources to define what is an active substance, what is a gene and what is protein - in effect identifying all different concepts within these data sources. The principle was one of a knowledge graph, but extended with a cheminformatics approach.

The group pointed out that the industry is still learning what AI can and can't do, and what problems it is able to solve: one delegate pointed out that often simple solutions, such as a manually coded dictionary of words, are often sold as an 'AI solution'. All agreed that AI simply for AI's sake is not helpful: the application must bring value.

The discussion ended with a talk on data security and providing large corporations with their sensitive data. It was mentioned that this data could all be encrypted, and that any deconstructing or selling of this data would be banned by a number of regulatory measures worldwide. But it was pointed out that potentially more dangerous was companies' ability to mine their ecosystem, look at the services run on them, and develop their own variations of these, undercutting the pharmaceutical sector in a different way.

MEDICINALCHEMISTRY

Practical Advice on the Implementation of AI/ML in Drug Discovery

Another excellent roundtable, this time on the Medicinal Chemistry track, was headed by **Parthenon Therapeutics' CEO and Founder Laurent Audoly**. The discussion began by talking about how AI is spoken about today, and the 'market pull' versus a 'tech push'. It was noted there is a hype occurring in this technology, spurred on by the fact that there have been few concrete demonstrations of the impact of AI/ML.

One delegate pointed out that there is usually some decrease in cycle time using ML: what that decrease actually is would be up for debate. With more recent phenotypic data, the delegate said that his company had had some dramatic productivity gains by taking that data, making models and predicting which of those compounds would be more successful in clinical trials.

Another delegate stated that AI is similar to any other novel technology brought in: it is tried out, learnt through testing and eventually delivers productivity gains. He suggested that while there may not be one concrete demonstration of these gains so far, they would occur soon as more companies tested the software and learnt how to use its strengths.

A third expert mentioned that today's environment has three things going for it that previous iterations did not have, which could change how AI is perceived and used: firstly, phenotypic screening now exists, with data points on countless different types of biology being taken from a single assay. This phenotypic screening has given companies datasets worth using in ML, if they can be used at scale.

Secondly, he said, there is the potential of generative machine learning - that is, not only making a predictor, as has been done in QSPR/QSAR for the last few years. The delegate pointed out that the AI/ML can predict the next experiment or molecule for you, providing more starting points than a chemist could determine on their own.

Finally, he pointed to laboratory automation of assays running at scale. With this companies can have an ML environment which directly chooses the molecule to put into screening. While the sector hasn't yet realised broad-based high-throughput synthesis for this, it is certain to appear in the next few years.

Looking at the convergence of these three technologies is something that's changed the industry from the days of QSPR. The phenotypic screening and the datasets machine learning can be applied to at scale is a real game-changer, he said.

Another delegate agreed about the data aspect of this point. He said that deep learning gives a company no real advantage over older methods in drug discovery, beyond the analysis of images or text. The push to get more phenotypic data is more vital, and could lead to acceleration of drug discovery.

A case study of a recent compound was then provided. This involved a generative model, building an intelligent sampling from the chemistry space and embedding over the chemistry space, before experts sampled from the embedding space to find different areas of chemistry. The difficulty in this case involved exactly what the chemical structures were being embedded into. If the embedding was happening into a space of fingerprints, no guidance would be given on the biology whatsoever. Something was needed to anchor the generative model in terms of the biology. The delegate explained that a company must add scores into the generative model to penalise badly synthesized compounds - training the model to understand reactions, not just chemical and structural property relationships.

This meant, in effect, that the model must have a reaction component, an availability/synthesize ability component, as well as a biology component. With this combination, interesting results can be found. But again, he stressed that data is the most important thing: generating and using the right type of data.

The discussion then ended with a note on the difference between machine learning and solid computational chemistry. One expert noted that standard computational chemistry is the use of molecular or quantum mechanical simulation toolboxes to understand the surface of the molecule or crystal structure for potential bindings. This can generate a large virtual library, with a company then able to dock to a compound crystal structure and optimise within that through more specific techniques, finding virtual hits.

The equivalent ML approach, he elaborated, would take a smaller dataset of actual chemistry/biology and build a model, which could suggest compounds based on how it understands the variants. The model would predict new compounds based on what it has learnt around biology reactions. So it would not be computing and ranking those hits: it would instead build a model in the chemistry space. It would be sampling, not performing an exhaustive search.

Key Delegate Challenges - 2020 and Beyond

Research

When surveyed, delegates at the recent Biology/MedChem event pointed to research as their most challenging area for the next few years: among other things, those surveyed pointed to aligning external opportunities to internal research needs, translational research for oncology programs and progressing research during the COVID-19 pandemic.

Money and Resources

The second most cited challenge for biology and medchem professionals related to money and other resources: delegates noted reimbursement, speed and cost of development, and access to funding in the infectious diseases space as particular troubles that would challenge them in the near future.

Data (harmonisation, integration)

A major challenge for a large number of delegates related to issues around data: particular challenges cited included harmonisation and integration, finding opportunities to showcase the quality, reproducibility and depth of data, connecting heterogeneous data sources with varying models of ownership together and the availability of large enough datasets with consistent and valid metadata.

Outsourcing and Collaboration

Delegates pointed to both outsourcing and seeking collaborators as another challenge for the next few years. Particular difficulties experts found included effectively managing internal work versus outsourced work, finding strategically-fit assets for collaboration, particularly in the vaccine area; and successfully managing CROs and university partners to run the company almost virtually.

Finding and Validating Therapeutic Targets

Finding and validating therapeutic targets was another area challenging delegates for the foreseeable future. Delegates discussed looking for novel therapeutics, growing their pipeline over the coming years, validating the targets they have, and integrating multi-omic datasets for target discovery and validation.

Key Delegate Challenges - 2020 and Beyond

Covid-19

Unsurprisingly, one of the biggest challenges for delegates for the foreseeable future is the COVID-19 pandemic. Among the specific worries of surveyed experts, major fears included recruitment during the pandemic, dealing with working from home and progressing research.

Streamlining and Increasing Efficiency

A number of delegates professed their roles in streamlining the company and increasing efficiencies, with projects set to continue into the near future. Specific challenges in this area included improving the effectiveness and efficiency of drug discovery and deconvoluting target.

AI and New Technology

Surprisingly low on delegates' list of challenges for the coming years, AI and new technologies were still featured as one of the bigger overall problems of the near future. Specific mentions by delegates included phenotypically testing AI-generated molecules, research and development for the AI part of bioinformatics projects, and working with new hit-finding technologies.

Regulatory Challenges

The regulatory side of the sector was another concern for delegates, albeit with fewer mentions than the above difficulties. Nevertheless, delegates noted regulatory comprehensiveness, overall regulatory strategy and navigating specific risk assessment frameworks with regard to investing in preclinical technology as issues for the coming years.

Models

The final major problem delegates noted revolved around new and existing modalities, with experts noting that current issues include screening and in vivo models for rare disease, and leveraging new drug discovery modalities.

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