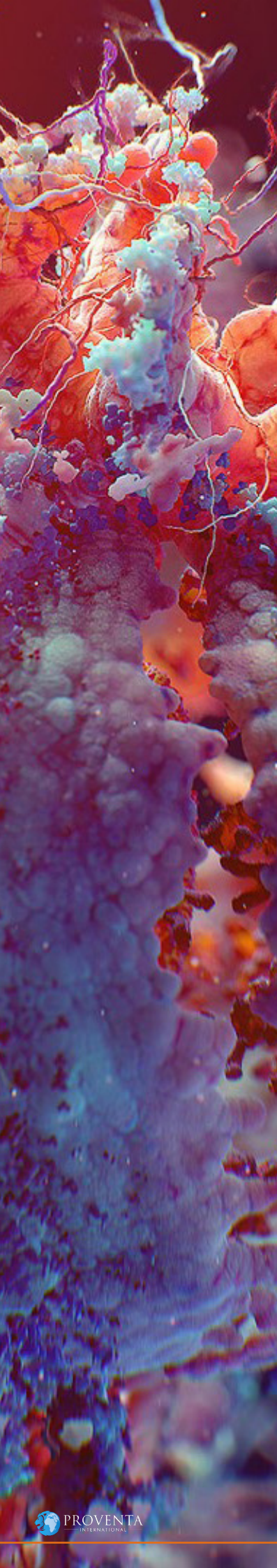


ONCOLOGY

Insights from the Industry





Introduction

Oncology remains the leading field for innovation, as it seeks to tackle the most diverse and multifaceted disease: cancer. Innovations in the field abound - from improved cell and gene therapies (CGT), checkpoint inhibitors, antibody-drug conjugates, and even pioneering modalities such as oncolytic viruses. The breakthroughs achieved by the advent of immunotherapy and CGT are difficult to overstate, and were discussed at length in our Strategy Meetings in San Francisco, Boston and London. In the pursuit of understanding treatment response and resistance, particularly to novel treatment modalities, more complex biomarkers and trial designs are necessary, requiring frequent sampling through improved biopsy methodologies. The industry has had to grapple with these issues during a pandemic, forcing innovation and the adoption of innovative decentralized and virtual technologies; much of the industry remains skeptical regarding the extent to which complex trials can be decentralized. Relatedly, smart technologies and real world evidence are also making their own impact in oncology, particularly in facilitating remote and advanced trial protocols. These and other issues were discussed at length in our unique Strategy Meetings' roundtables, facilitated by leading industry experts. We outline the key challenges facing the industry further in this report, 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 Supply Chains and Manufacturing

One of the main issues arising from the pandemic has been the disruption caused to supply chains - a critical concern for oncology trials utilizing novel treatments. While the global markets and manufacturers recover, delegates cited a need to find ways to provide resilience to their manufacturing pipelines - both for day-to-day operations as well as in the face of possible future emergencies.



2 Hiring and Retention

Talent acquisition has become more challenging - as employers vie for increasingly limited pools of human resources. Another of the marked effects of the COVID-19 pandemic, employees now recognize their value and expect improved standards and recognition from their companies. Delegates cited the need to pursue enhanced recruitment and retention processes to improve the caliber of their staff.



3 Biomarkers for Immuno-oncology

Delegates seek to improve the biomarkers in use to predict treatment response and resistance in patient pools, particularly as novel therapeutics such as CAR-T, CAR-NK, new checkpoint inhibitors and Antibody Drug Conjugates (ADCs) show a close relationship between specific biomarkers and efficacy. Corollary to these, peers cited a need for better sampling techniques to survey biomarkers, such as liquid biopsies and ctDNA.



4 In-vitro and In-vivo Modeling

Shortages in animal models, particularly as the supply chain for live animals was disrupted or diverted by the COVID-19 pandemic, have pushed delegates towards finding ways to improve their own *in vitro* models to future-proof their pipelines. *In vivo* modeling retains its value in preclinical development, but peers seek to find ways to make the most of what may now be a more limited methodology.



5 AI/ML for Drug Discovery

Drug discovery remains one of the key challenges across therapeutic areas - and oncology is no exception. The fight against cancer is one of constant innovation, and ways to accelerate processes to innovate new therapeutics while reducing time and cost investments remain of paramount priority. Artificial Intelligence (AI) models able to screen wide chemical compound spaces promise to do this, and peers seek to find the best way to integrate them into their own pipelines.

TOP 10 Challenges 2022: What Peers are Focusing on



6 Patient Recruitment and Selection

Oncology trials rely on very detailed patient selection procedures - and the pandemic has made the recruitment of patients for novel design protocols yet more challenging, as more vulnerable people are reluctant to leave their homes. Peers seek to navigate this new reality in clinical operations through improved selection methodologies to enhance patient responses, while recruiting from as diverse a pool as possible.



7 Patient Centricity in Clinical Trials

Increasing patient centricity remains a key concern, particularly in the face of more challenging patient recruitment environments. Many peers expressed skepticism about the extent to which oncology trials can truly be decentralized, owing to the frequent sampling and complex treatments required. But patient centricity does not merely refer to decentralization - although finding ways to implement more appropriate decentralization protocols will also be pivotal. Trial organizers have many tools at their disposal to increase trust and appreciation between operators and patients, and doing so is critical.



8 Partnering for Companion Diagnostics

As many trial sponsors seek to increase flexibility in their protocols, while also increasing sampling frequency and detail, novel companion diagnostics will be crucial in enabling such adaptations. Techniques such as liquid biopsy, ctDNA and even more cutting edge technology such as miRNA promise to provide some answers in this department, as does smarter technology and wearable monitoring devices. Delegates cited a need to find the right partners to navigate a path forward for these technologies.



9 Microbiome

The human microbiome has been the subject of increasing research across the field of medicine, and its own relationship and interactions with cancer are no exception. Peers are intrigued by the subject, and wonder whether it can contribute to their own research - whether as a complex biomarker or as an area for intervention.



10 Integrating Genomics with Immuno-Oncology

Genomics can provide powerful insights to guide targeted and immunotherapies, particularly in combination with immuno-oncological biomarkers. Peers sought to leverage pioneering innovations in genomics to find the best way forward to improve their own pipelines.



Oncomirs: miRNA and Cancer - Insights from PharmaFEATURES

The role of circulating tumor DNA (**ctDNA**) is already well established across multiple types of cancer – and its potential for the detection of tumors, as well as its role as a biomarker in studying treatment responses and tumor profiling, is growing. A related, more innovative approach is the use of micro RNA (**miRNA**) as a biomarker for the detection and characterization of tumors. The field of study surrounding miRNA is quite at an early stage, and is faced with multitudes of challenges that need to be addressed as the industry approaches the realization of its use in oncology.



The Nature of miRNA

miRNA molecules play an important role in normal physiological function – they are non-coding RNA molecules which are involved in gene silencing or the regulation of post-transcriptional gene expression. They carry out these functions by binding to messenger RNA (**mRNA**) molecules which normally code for proteins. Recent studies have also elucidated other interactions miRNAs can facilitate – such as binding to Toll-Like Receptors (**TLRs**) to promote inflammatory responses, which may promote cancer development. They can also facilitate the activation of natural killer cells through interactions with TLRs, which can promote tumor suppression.

Unlike short interfering RNA (**siRNA**), which is also involved in RNA interference functionalities, miRNAs are derived from RNA molecules that form the classic hairpin structure instead of longer, double stranded RNA transcripts. Much like ctDNA, miRNA may also be found extracellularly – though this is part of its natural function. This is critical – as it is what makes them available as circulating biomarkers to be used in novel diagnostics for a variety of diseases. The function of miRNAs undoubtedly places them in a position of relevance to tumor regulation – genetic dysregulation is a long recognized hallmark of cancer.



The first discovery of miRNA's direct involvement in tumor progression was in chronic lymphocytic leukemia. Researchers discovered, as early as 2002, that deletion and downregulation of genes coding for specific miRNA molecules on chromosome 13q14 were associated with progression of the disease. Later research provided mechanistic reasons for this cause – identifying the 13q14 miRNAs as a tumor suppression locus. It is now known that miRNAs can act as either oncogenes – which promote tumor growth, or tumor suppressors. This understanding gave rise to the term **oncomirs**.

Oncomirs – Links to Cancer

Subsequent to the findings linking them to chronic lymphocytic leukemia, further investigation elucidated multiple links to a variety of other cancers. These included other blood malignancies, such as lymphoma but also various solid tumors, such as melanoma, ovarian, breast cancer. There are three key stages through which miRNAs may be involved in tumor progression: the disruption of transcriptional control mechanisms, dysregulation of epigenetic modifications, or defects in the cellular machinery which is involved in generating miRNA – such as the Drosha, DICER, Argonaute and other proteins.

Dysregulation of the proper physiological function at any of these three stages has been linked to all milestones of tumor development: the evasion of growth suppression, resistance to cell death, replicative immortality, as well as the development of metastases and angiogenesis. miRNA involvement in cellular metabolism has also been described as a key factor in tumorigenesis – such as in lung cancer.

Examples of miRNA as a Biomarker

Given their deep correlations with tumor development, and their fundamental role in cellular regulatory processes, miRNAs have vast potential to serve as biomarkers for the detection and description of tumors. miRNA has been found to circulate in bodily fluids – either in a free form, bound to other proteins or lipids, or contained within exosomes. This places miRNA as a possible candidate for non-invasive biopsies, much like ctDNA.

The key challenge remains the detection of tumor-related miRNA: the amount in circulation is expected to be small, and noise can be generated by the presence of unrelated miRNA.

Studies have [shown](#) that miRNA can circulate in stable form in human plasma, where it can remain undegraded by RNAase enzymes. The study in question was able to use miRNA as an early detector for prostate cancer in mice. Prostate cancer remains an area where early detection can serve to save and extend lives dramatically. Yet the only forms of diagnosis entail Prostate-Specific Antigen and Digital Rectal Examination. The former entails high false positives – while the latter is not as efficacious for the earliest stages. Detecting cell-free miRNA with tumor-specific signatures could provide earlier diagnoses – however, the concentration of miRNA in circulation remains extremely low. [Research](#) has shown that ultrasound sonoporation can amplify the release of miRNA and facilitate the detection of prostate cancer.

Other research has established the second largest miRNA cluster, MIR-379/656 as a potential [breast cancer](#) biomarker. Decreased expression of the cluster was associated with larger tumors and poorer prognoses and overall survival. The findings were similar to earlier investigations of the cluster in [glioblastoma](#) – indicating the systemic importance of miRNA. Such research has only been made possible through next-generation sequencing advancements and innovations such as [miRTarBase](#) which aim to categorize the full extent of interactions of known miRNAs. Technological advancements and collaboration in this regard will be pivotal in advancing the progress of the oncomir field.

Future Outlooks

The role of miRNAs in regulating drug and treatment resistance will also be of extreme importance in the future of oncology – particularly as we move to an era of increased precision oncology, where treatments are tailored to specific biomarkers. For example, miRNAs have been shown to contribute to drug resistance in [colorectal cancer](#). [Advancements](#) in machine learning (ML), as well as deep learning, have also improved our understanding of miRNAs by enabling better predictions of the targets of any sequenced miRNA molecules – and the possible interactions that may entail.

It is also important to note that miRNAs do not merely originate from within the body – but are also found in food or other substances that are ingested. Controversy has been generated around the subject of these [xenomiRs](#) – as it is possible they are transferred to the consumer’s organism and remain biologically active. Though they have not been causatively implicated in disease progression as of yet, they posit another avenue for future investigation. The role of miRNA in oncology merits much further exploration – and holds potential to revolutionize the way we approach cancer and its treatment.

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

A promotional banner for PharmaFEATURES. The background is a blue desk with a laptop, a smartphone, and a pen holder. The laptop screen displays the PharmaFEATURES website. The text 'Pharma FEATURES' is prominently displayed in the top left. Below it, a dark blue box contains the text 'Fresh Life Science Insights'. At the bottom, three icons represent 'Articles Daily', 'Interviews', and 'White Papers'.

**Pharma
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Fresh Life Science Insights

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TOP

Investment Areas 2022

Proventa asked delegates at its events to speak about their investments for the coming year. Key oncology topics included genomics, improving biomarkers, precision medicine and targeted therapeutics - all guided by a need to better link disparate datasets to better understand cancer.

Data Integration



Multi-modal and multi-omics data integration is at the forefront of areas where delegates are spending to improve their workflows and pipelines. While we possess vast data from disparate sources regarding the biology of cancer, researchers hope to piece them together to paint a holistic, comprehensive picture of how specific cancers work - and use this information to advance their own therapeutics.

Genomics



Genomics remains a key investment area for oncology, with peers citing a need for newer tools, newer models and cutting-edge technology to keep pace with innovation. The relevance of genomics for the field is expected to be an evergreen concern - particularly as targeted therapies continue to rise in prominence.

Biomarker Discovery



The discovery of novel biomarkers remains crucial - with many hoping to identify definitive predictors of treatment response, progression or resistance to improve investigational efficiency. Many cite the need for more complex biomarkers, and a move away from binary biomarkers. Properly utilizing such composite biomarkers will require strong collaboration and industrial coordination, with many investing in the area.

Immune Checkpoint Inhibitors



Approved checkpoint inhibitors, particularly PD-1 and PD-L1, have firmly established the treatment modality in the pharmacological mainstream. Delegates cite investment in the area, whether that be investigating new inhibitors or combinations with existing compounds, as a pressing concern - particularly with regards to expanding the range of indications which can benefit.

Integrated Drug Discovery



Delegates seek to provide increased resilience to their own pipeline through enabling multiple feedback loops throughout the drug development pipeline. Achieving this integrated approach to drug design can deliver iterative processes to highly optimize drug development, with peers being keen on leveraging the data generated by their downstream development practice to improve all aspects of their workflow.

TOP

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In Vivo Pharmacology

Animal models retain their immense value in informing oncology development pipelines. Despite supply chain disruptions, delegates seek to improve how they utilize this increasingly precious resource and maximize the insights generated from animal studies. Peers seek to improve the translational potential of animal models through novel study designs as well as improved methodologies and investment in the area is likely to continue.



Precision Medicine

Innovation in oncology has shown a steadfast movement towards precision-guided practices, informed by the acceptance that cancer is not a singular disease. Rather, it is a broad spectrum of conditions, many of which exhibit dissimilar qualities and vastly heterogeneous biology. Delegates seek to invest further in targeted approaches to tackle these different physiologies.



In Vitro Pharmacology

In vitro models remain crucial, and can save immense resources and precious development time when used appropriately. Peers continue to invest in ways to improve their own in vitro approaches, including multi-omics whole-cell assays which can provide comprehensive pictures for cancer biology.



Artificial Intelligence

Artificial Intelligence (AI) is a field seeing strong investments across the pharmaceutical and healthcare industries - and oncology is no exception. Whether it is used in drug discovery models, or patient selection and treatment prediction algorithms, the technology is here to stay. Peers hope to leverage the novel tech to streamline their own work, but also find novel niches to apply it to.



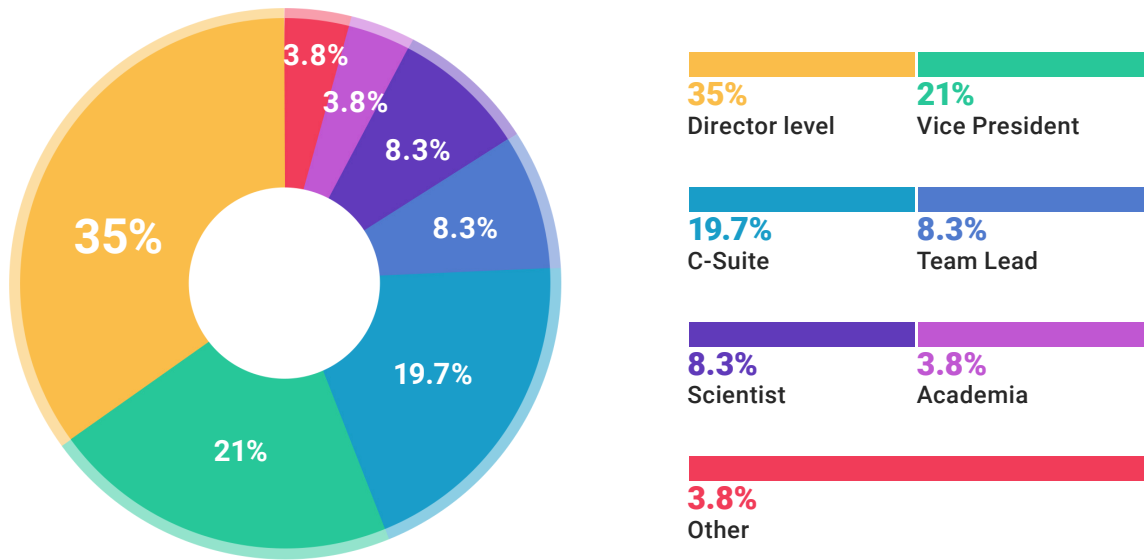
Target Validation

Delegates seek improved ways to facilitate drug target validation, both using *in vitro* as well as *in vivo* models. Novel modalities, such as using RNAi technology to validate drug targets, also show promise, as does the use of AI models to accelerate workflow processes.

Delegate Breakdown:

Attendees at Proventa's 2022 Strategy Meetings

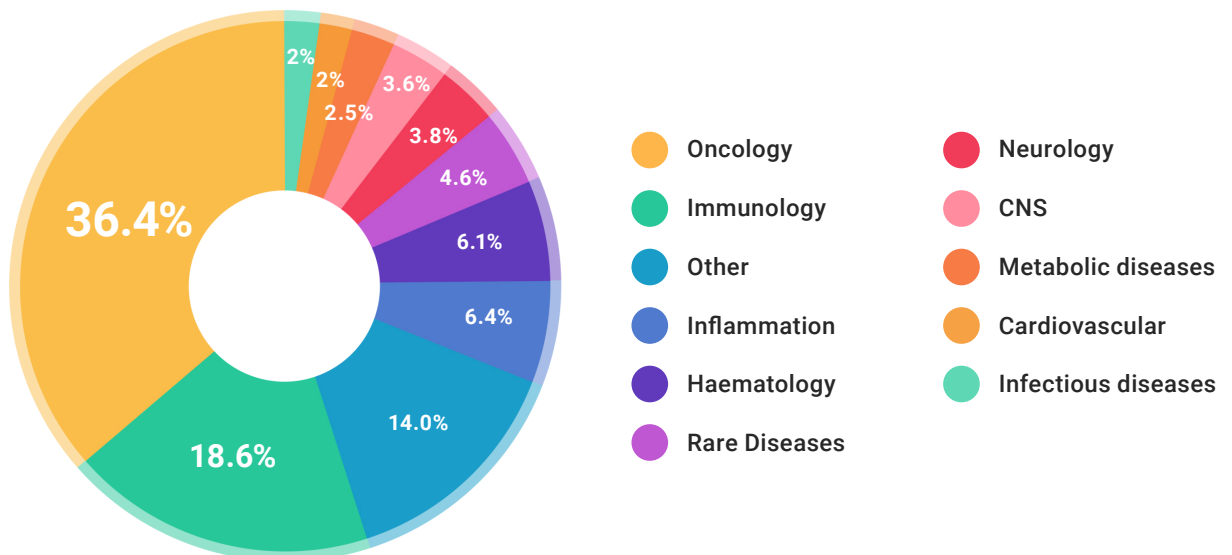
2022 Attendee Breakdown



Drug Development Stages



Therapeutic Areas



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