Spotlighting Progress in Cancer Research

Suparna Mundodi, Director of Marketing, Mass Spectrometry for Agilent Technologies interviews four world-renowned cancer researchers to uncover how labs have transformed to meet the increasing demands within this research sector.

Over the past decades, technology has grown at an exponential rate, with the healthcare and life sciences industry seeing, over time, the benefits and opportunities that these changes have brought to the future of cancer research. Advances in analytical technology have been instrumental to the progress made in cancer research and diagnostics over the last few decades, as laboratories have evolved to operate more quickly and efficiently than ever before.

Agilent is committed to supporting current and future laboratories in their growth to be smarter, faster, and more reliable in solving the unsolved in cancer research. We connected with four customers in cancer research from around the globe, to understand how this evolution has benefited their research efforts around cancer research and diagnostics, and their expectations for the future.

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Founder and CSO
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Dr. Ian A. Blair
A.N. Richards Professor
Systems Pharmacology and
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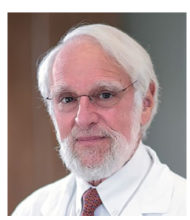
Dr. Michelle Hill
Associate Professor
Precisions and Systems Biomedicine
QIMR Berghofer Medical Research Institute
Royal Brisbane and Women's Hospital
Herston, QLD, Australia



Dr. Cliff Dacso
Professor of Molecular and Cell Biology
Baylor College of Medicine
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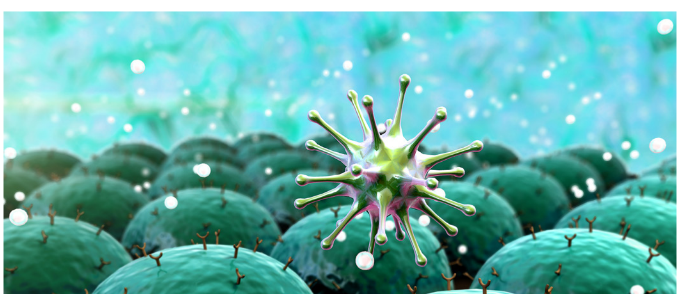


The rise of new technologies and tools in cancer research

Advances in cancer research and diagnostics have accelerated through research in clinical laboratories around the world as a result of enhancements such as automation and improved workflows. To further understand these developments, and how they are facilitating research efforts, we asked experts in the field to explain how these factors have improved their ways of working.

With a focus in cancer research on protein biomarkers and protein targets at Atturos Labs, **Dr. Stephen Pennington,** Founder and CSO, has seen two particular advancements stand out. “One has been the technical capabilities of the instrumentation, and the other is the reliability and the ease of the workflows in getting the samples to the instrument,” he specifies. “For us, the biggest advance has been the ability to do targeted approaches on the mass spectrometer, being able to multiplex and make it more robust and routine.”

“What in the past used to be an experiment with the mass spec is no longer an experiment, it’s now routine. In the past blockage of nanoflow needles and other technical issues made it very difficult to acquire comprehensive and consistent data sets. There’s now no risk of the mass spec failing halfway through large batches of samples.”

For Dr. Pennington, these advances also meant the ability to extend the breadth of the analysis. “To be able to do protein biomarker discovery on large numbers of proteins means that we can now map pathways, and that we can focus on pathways that will give us more mechanistic insight as opposed to focusing a few proteins. It’s that transition from small numbers of proteins to very large numbers that supports reliable pathway analysis.”

“From a diagnostics point of view, it's being able to do the evaluation of biomarkers, not one biomarker at a time the way people used to, but multiple biomarkers using multiplexed targeted measurements. We can now take a long list of potential biomarkers and evaluate them simultaneously using large sample sizes so that the data it becomes more statistically valid. Hopefully that means we’ll have a better chance of success.”

Another point of view comes from **Dr. Ian Blair**, Professor of Pharmacology at the University of Pennsylvania. “We’ve seen a revolution, particularly in the last five years. It’s had a huge impact on how I do things in my lab, particularly with the availability of relatively routine high-resolution high mass spectrometry. For cancer biomarkers the future is in proteoforms. High-resolution mass spectrometry provides the opportunity to dig down into the high sensitivity into proteins, which was unimaginable before.” Dr. Blair notes that the use of immunoaffinity methods, molecular biology, and high-end mass spectrometry is really what has changed his laboratory.

“Recently we’ve turned to immunoaffinity purification methods, not for removing the high abundance proteins but for isolating the proteins that we’re interested in. That, in combination with high-resolution mass spectrometry has really revolutionized the way we do things. The bottom line is, you need multiple techniques, but the ultimate in specificity and sensitivity comes with mass spectrometry, and the ultimate in specificity comes in high-resolution. The next challenge is to implement lower resolution and more robust instrumentation with higher LC flow rates to accomplish similar goals. My laboratory is working with Agilent to validate this important strategy.”

For **Dr. Michelle Hill**, Associate Professor, Precisions and Systems Biomedicine at QIMR Berghofer Medical Research Institute, it’s been about automation in sample preparation during diagnostic biomarker discovery. Her laboratory in Queensland, Australia focuses on early disease detection and non-drug prevention approaches and works with a multi-disciplinary team and interdisciplinary collaborators. “The speed and sensitivity of the mass spectrometers has a big impact on the amount of time and amount of data that can be acquired. For our research we have not altered the approach per se, but I think the reproducibility from the automation has really helped.”

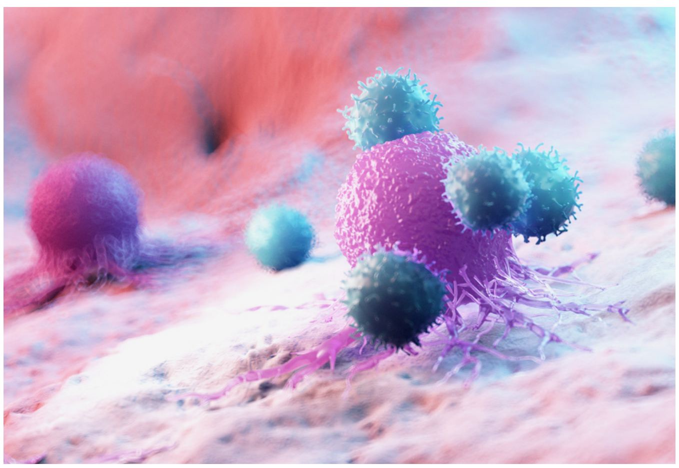
“Using automation in research labs is relatively new. When we started more than ten years ago, proteomics research did not routinely use automation. Most labs were manually preparing all the samples and you’d run into reproducibility issues, and it couldn’t scale up to do clinical cohorts well. In general, the ability and willingness to adopt automation into the research laboratory is very important.”

Dr. Hill does underline that “continuous improvements could be made” when discussing the differences these advances have made in her laboratory. “Many years ago, we developed our own protocols using a standard liquid handler and labware. Now there are pre-made sample preparation protocols available in terms of solutions that you can buy. That may help some labs when they set up new methods, but because we’d already set-up our own we didn’t fully change to a new method. But in terms of translation of research, high-quality, proven commercial products for automated sample preparation will be key.”

To receive a different perspective on the technological advancements made within cancer research, and particularly biomarker identification and clinical applications, **Dr. Clifford Dacso**, Professor of Molecular and Cell Biology at the Baylor College of Medicine, was approached to share his insights. For Dr. Dacso’s research, one of the points of interest is the early detection of prostate cancer in men of African descent, as they statistically have prostate cancer earlier in life, and are affected significantly worse than comparable European-American men. To address this issue, early diagnosis and aggressive treatment is key, and identifying a biomarker that could be followed up periodically would be a remarkable advancement. “It would differentiate the characteristics of that disease, for example, is it an aggressive versus a relatively slow growing tumor? Such a thing would be very useful but has not yet been definitively identified."

Other advancements **Dr. Dacso** mentions are: "Biomarker detection would be most useful if available at point-of-care. That is something that could be done in a clinic setting. The second would be the molecular sensitivity to be able to detect early disease. The third would be to differentiate aggressive from less aggressive disease."

"The use of new technologies, particularly desktop instruments, and specifically focused columns that don't do a broad range of tests, but do narrowly focused tests very well, could bring the price of mass spectrometry down to a level where it could be widely affordable and available. The dream would be to have the specificity and sensitivity of laboratory-based mass spectroscopy available at point-of-care."



The hiccups of technological advances

Advancements do not come without hiccups; and there will always be improvements to be made to new technologies to optimize them further. While the first steps would be to overcome these initial challenges, from a logistical point of view, other more urgent challenges for labs showed up during the COVID-19 pandemic.

"The instruments weren't as reliable in the past as they are now, so things didn't happen as smoothly as they do now," **Dr. Pennington** explains. "The challenge when you get a new technology is that you think it's going to solve everything, and to some extent it does solve some things but certainly not everything. There's still a long way to go to incorporate that technology into a workflow where you can move from sample to data, and know you're going to be able to do that without any major hiccups along the way." Once initial hiccups are reduced, labs such as Atturos Labs still had to adapt to working through the pandemic, which they did do successfully.

"We analyzed over three and a half thousand clinical samples, in batches of around a thousand samples, with the instrument running 24/7 for up to three months." According to **Dr. Pennington**, the instruments were all reliable. "And that was during lockdown, so key criteria that enabled us to keep going was having a well-defined workflow, and also having remote access to the instruments. We took advantage much more last year than we ever have of remote access to the instruments. It's also about teamwork, it's about someone in the lab who understands the importance of placing the samples, someone else driving the instrument remotely, and then another person doing the data analysis. Not just one person, a team of people generate the data."

It's a similar story for **Dr. Hill**. "New things can often cause some issues. When trying new methods you may discover quite quickly that you can't yet analyze the data, as the software may not yet be available. Sometimes new technologies also have incompatibility between the workflows. The workflows need to be validated before use, so if any new technique or technology hasn't been validated at the start, we wouldn't move ahead with it."

However, looking back to automation, this advancement has shown increased efficiency within **Dr. Hill's** lab. "By incorporating automation, we find that the results are much more reproducible. The accuracy of the results makes a big difference, and that has a knock-on effect when you are confident in your measurements."

Sometimes the hiccups are not only technology focused, but a result of combining two different specialties, which require increased expertise and knowledge. While **Dr. Blair** highlights that "the biggest ongoing pain is nano LC. I don't think anyone has come up with a good solution to that. The lower the flow rate the higher the sensitivity," the more prominent issue seems to be a human focused challenge. "The problem is, having discovered that the key is combining molecular biology and mass spectrometry, there aren't that many people trained to do these things. So, you either have to find a molecular biologist who wants to learn how to do mass spectrometry or have someone who is an expert in mass spectrometry wanting to learn how to do molecular biology. Those people are not easy to find. It makes you realize you're only as good as the people around you, and I've been lucky."

With a more distanced world in mind, the human challenge also expanded into addressing COVID-19 and the consequences thereof. For **Dr. Blair**, having remote access to the instruments in his lab was important. "I think remote access to instruments had a huge impact. We have to keep a certain number of people in our lab, as at the end of the day someone has to be there to work-up the samples and put them on the instrument. I'm hoping to learn in the future on how to implement this better."

In the clinical application space, the number one innovation would be sample collection that addressed the new distanced world of today. "It's not impossible to think about collecting specimens remotely. If we are able to develop remote sample collection and put it in the mail or deliver it to a central place where the mass spectroscopy could be done. Having remote sensing with central processing would be really useful," **Dr. Dacso** shares.

Looking into the future for clinical laboratories and cancer diagnostics

Asking our experts how we must evolve to meet the demands of future challenges associated with cancer and cancer biomarker approvals brought a variety of responses. Labs yearn for collaboration between clinicians and scientists to progress this in rapid succession, while from a clinical and translational aspect further innovation and studies in population biology is required.

"Technology improvement will be there, but apart from the technology, researchers should be more open-minded in thinking about clinical questions and outstanding needs," Dr. Hill states. "It requires close interdisciplinary collaboration; the scientists need to go and find out what the outstanding clinical needs are, what the patients would like, and then work together with address the question." Collaboration does already exist and has become even more integrated in recent years with interdisciplinary team approaches.

However, for many of the questions there currently aren't straightforward research solutions. "Early detection is probably one of the big questions asked in regard to improving cancer outcomes. I'm talking to clinicians and researchers in various cancer areas and hear that a cancer is not diagnosed at the right time, or very late, because there's no appropriate test. But early detection is a tough question to answer because the early stage cancer samples are not easy to collect, so research teams need to start from feasible clinical cohort design to collect the right samples for biomarker discovery."

Dr. Dacso supports the need for studies to answer pre-defined questions. "We have to do more highly directed studies, answering specific questions such as, how could you do early diagnosis, how could you do staging, how could you detect metastasis, and then, how do you assess efficacy of therapy, and how do you sweep for recurrences. Each one of those pieces is a separate question and has to be studied. And since we don't have a common cancer gene or cancer test, this has to be done in each specific malignancy being looked at. It's an enormous amount of study that needs to be done and much of it is in large populations."

Moving further into the direction of how research must evolve to meet current and future challenges within cancer research, **Dr. Dacso** describes four particular aspects: "One is moving the instrumentation out of the lab and into the clinic. Second is getting the cost down so that widespread use is feasible and not quite so specialized. Third is limiting the detection of compounds by mass spec to those marker compounds that are known to be discriminative variables. The last innovation that is going to be really critical is informatics and population biology. What we're looking for is an integration of human disease all the way from population biology and epidemiology, to molecular biology, and metabolomics and proteomics. From the presence and prevalence of disease in populations, all the way to its manifestations from the point of cell biology. That's translational biology."

Dr. Pennington shares similar thoughts. "It's challenging because there are a number of discrete steps, and a number of discrete phases, and even within each step there are silos of expertise. Then, across the steps there are multiple silos of expertise. For me, the way for this to happen is a greater understanding of the end needs of the patient. When you do that, you realize that a cancer patient doesn't necessarily just have cancer." Collaboration seems to be key to progression, in order to conduct studies and answer those tough questions.

Another way to look at innovation and progress in biomarker identification is turning to the regulatory bodies. In the United States, the Food and Drug Administration (FDA) oversees drug approvals, but are also involved with clinical processes. **Dr. Blair** mentions that "the FDA are encouraging us to be ground-breakers, and to get some of our biomarkers approved." However, this isn't as easy said as done. Academics are usually not geared towards the many facets of regulatory processes. With that in mind, other conversations are taking place around **Dr. Blair**. "Another way we're thinking about it is that to some extend it could be platform specific, so a platform for multiplexing protein analysis. If that got approval from the FDA then everyone would be forced to use those. That would then be a driver during these rigorous assays, rather than endless numbers of biomarkers that don't stand the test of time."

The future looks promising

Progress in cancer research is greatly due to technological advancements in the laboratory, particularly in the field of mass spectrometry, which has significantly accelerated industry understanding of cancer detection and testing. Scientists worldwide are witnessing how the implementation of new, and innovative technologies into their labs can potentially change the way patients with cancer are treated and diagnosed. The future of cancer research therefore looks promising if scientific labs continue to evolve to become smarter, faster, and more effective in their day-to-day operations.

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