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IMMUNO-ONCOLOGY INSIGHTS

SPOTLIGHT ON:

Clinical development strategy

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Broadening I–O clinical trial participation to improve health equity & diversity: current perspectives & future plans

How can the I–O space ensure cancer immunotherapy trials are accessible to the maximum number of patients who could benefit from them? In this interview, **Roisin McGuigan,** *Editor, Immuno-Oncology Insights,* speaks to (pictured left to right) ASCO's **Julie Gralow,** Chief Medical Officer and Executive Vice President and **Elizabeth Garrett-Mayer,** Vice President, Center for Research and Analytics about the current clinical trial landscape for immunotherapy, including current barriers to trial recruitment and strategies to improve the diversity of trial participants.

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Q Can you tell me a bit about your current roles?

JG: I have worked as the Chief Medical Officer and executive Vice President for ASCO for two years now. I am the chief medical spokesperson for ASCO, and I also oversee four of our departments: Care Delivery, Policy and Advocacy, International Affairs, and the Center for Research and Analytics (CENTRA). My daily work is broad, and I provide medical input and oversight as one of the few medical doctors on ASCO's staff.

Prior to joining ASCO I was a Professor of Breast Medical Oncology and Affiliate Professor of Global Health at the University of Washington and the Fred Hutchinson Cancer Research Center and Executive Officer for breast and lung cancer for the SWOG National Clinical Trials Network.

EG-M: I am the Vice President of ASCO's Center for Research and Analytics (CENTRA), and I oversee most of the research-related projects at ASCO. I am a biostatistician by training, and I received my PhD in biostatistics more than 20 years ago from John Hopkins. Prior to coming to ASCO, I worked at National Cancer Institute (NCI)-designated cancer centers; first the Johns Hopkins Cancer Center, then the Hollings Cancer Center at the Medical University of South Carolina.

One aspect of what we do within CENTRA is our own clinical trial, the Targeted Agent and Profiling Utilization Registry (TAPUR) study. This is a precision medicine basket trial with 17 different targeted anti-cancer treatments and over 2500 patients enrolled to date. We also work with key stakeholders in various different areas including patient advocacy, clinical trial enrolment, and improving racial, ethnic, geographic and age diversity in cancer clinical trials.

Q What are the biggest barriers to improving I–O clinical trial recruitment?

JG: One of the issues is overall trial availability, often because of restrictive eligibility criteria that reduce the number of people who qualify. Another reason trials might not be available is the lack of local accessibility – a relevant trial might be available somewhere, but required travel makes participation impractical. A further issue is overall awareness and knowledge about trials. We need accessible and easy to use clinical trial search engines so both patients and clinicians can easily search for possible trials. Part of availability is simply knowing what is out there.

Another reason that accrual is low is that trials can be complicated and burdensome, with all the extra tests, clinic visits, costs, travel, and time away from work. We have heard a lot about financial and time toxicity broadly in cancer care, and this can be further exacerbated by trial participation.

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A key issue we have found is that patients are often not being offered trials due to provider biases and an assumption that the patient would be unwilling or unable to participate. In some underrepresented communities, a lack of trust in clinical research and the general healthcare system leads to concerns about trial participation, based on historical injustices. Data suggest, however, that if a trial is actually offered, enrollment rates are similar across ethnic, racial, gender, and age groups. Our education and communication about trials often lack sensitivity to different cultures, levels of health literacy, and historic concerns. We conducted a joint ASCO-Association of Community Cancer Centers (ACCC) pilot aiming to enhance racial and ethnic accrual to cancer clinical trials, and recently released a set of recommendations to enhance racial and ethnic equity, diversity, and inclusion in clinical trials as well as two freely accessible tools developed to help achieve that.

Q Overly restrictive eligibility criteria are often cited as a major barrier to participation. In your view, why does modernizing criteria continue to remain such a big challenge for the space?

EG-M: It stems from the concern that, especially in the early drug development phase, if you have serious adverse events that could jeopardize the entire development of the drug, it makes sense from a stakeholder perspective to limit the eligibility criteria to those who are less vulnerable to adverse events. But when the drug eventually gets approved, those patients have not been represented in the trials and the risks the drugs pose may be underestimated for the broader population of patients who receive the drug. It is not uncommon to copy the eligibility criteria from Phase 1 to Phase 2 and beyond, which can pose challenges. There is real concern that we are putting vulnerable patients on drugs after the drugs are approved that could be harmful to them.

To help enhance the diversity of clinical trial populations, we have developed eligibility criteria expansion guidelines with input from a broad representation of stakeholders. The first was published in 2017 and the second in 2021 [1, 2]. We recognized it was particularly important to get involvement from our industry partners, so they had a strong voice in both of these efforts.

Q How much of an issue do regulatory considerations pose when it comes to trying to approach trials in a more inclusive way?

JG: Our work on broadening eligibility criteria has been done in collaboration with Friends of Cancer Research, a terrific non-profit, the US Food and Drug Administration (FDA) and the NCI. In 2020, the FDA issued guidance for the industry on enhancing the diversity of clinical trial populations where it focused on eligibility criteria, enrolment practices, and trial design. The problem is not so much with regulatory requirements – these have loosened up, but the guidelines have not resulted in as much uptake as we'd like. A part

"The ASCO-ACCC project to increase racial and ethnic diversity in cancer clinical trials had large stakeholder involvement, and importantly involved a strong patient partner advisory group."

– **Julie Gralow**

of the problem is that industry and the CROs who complete large, randomized Phase III trials use pre-existing templates for trial design.

In 2019, the NCI issued strong statements about the eligibility language to be used in any of the clinical trials in the National Clinical Trials Network or the Experimental Therapeutics Clinical Trial Network.

At the local level, the Institutional Review Boards (IRBs) can be a challenge sometimes. They often do not understand cancer trials well and may want further restrictions. They have less impact on multiregional multisite trials that cannot be modified much, but for investigator-initiated trials, IRBs can become involved. Although they are acting from the perspective of protecting patients, they often do not understand that real-life cancer patients are frequently older and have comorbidities.

One thing we have done that is being promoted by the FDA is taking the upper age limit off our clinical trial eligibility. We want to move forward in our participation with the FDA to overcome the barriers to clinical trials surrounding the enrolment of older populations.

Sponsors, CROs, and people advising sponsors often take the path of least resistance – which can be to just keep doing what they are already doing. We are trying to use our voice in partnership with patient advocacy groups, clinical researchers, and government agencies to help combat this.

Q ASCO and ACCC released a research statement last year looking at improving racial and ethnic equality in cancer clinical trials [3]. Can you tell me more about this work, and any other initiatives that ASCO is doing in this area?

JG: The ASCO-ACCC project to increase racial and ethnic diversity in cancer clinical trials had large stakeholder involvement, and importantly involved a strong patient partner advisory group. Our pilot had two parts: a site self-assessment and implicit bias training. We intended to do this with about 40 sites. We put out a request for applications to see the levels of interest, and we got 75 applications, so people were very enthusiastic about this work. There were a lot of sites asking for help and that wanted to be part of a pilot. We ended up being able to include them all.

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Simply put, the site self-assessment is used to identify who you are screening for trials, who you are offering trials to, and who is enrolling. Fascinatingly, the majority of sites had no idea who they were screening or offering trials to. They could only give definitive data on who actually enrolled in the trial – they weren't tracking this other information. This pilot revealed that there need to be tools and resources in place to collect this data. We can't determine if there are improvements in diversity in trial screening and enrollment if we don't have the data to back it up. Our current focus is identifying and addressing barriers to data collection, and the facilitation of the data collection.

The second piece is the implicit bias training program. Based on prior work done by the SWOG Cancer Research Network and others, we know that if an available trial is offered to a Black/African American patient with cancer, or a Hispanic/LatinX patient with cancer they have the same probability of enrolling in the trial as a white patient with cancer. With this knowledge, we adapted the original Just ASK™ implicit bias training program from Duke Cancer Institute and the Duke Clinical Translational Science Institute into the Just ASK™ Increasing Diversity in Cancer Clinical Research. Both the implicit bias training and the site self-assessment are now available free of charge to all [4].

And as stated previously, as a result of this project ASCO-ACCC recently released a set of recommendations to enhance racial and ethnic equity, diversity and inclusion in clinical trials [5].

We think that the expanded eligibility criteria work that we have done will also help with racial and ethnic accrual because people in racial and ethnic minorities might more typically have lower performance status, functional status, or pre-existing conditions that could exclude them from a trial.

Q Are there any uncertain regulatory pathways that may prove an obstacle to innovation or change in the clinical trial space?

EG-M: Particularly relevant to me as a biostatistician who has designed trials in the I–O space is the mechanism of action of I–O treatments, which is different from traditional cancer treatments like chemotherapy. In oncology drug development, there is a historical paradigm which included phases, endpoints, and designs that represent the traditional approach for anti-cancer agents. We need to expand our thinking to include more than a single paradigm which is narrowly focused on assumptions that made sense for cytotoxic agents.

An example of this is in designing early phase efficacy trials. Historically, in Phase II cancer clinical trials, we have looked at objective response (i.e., tumor shrinkage) as a standard way to measure the early efficacy signal. For cytotoxic agents, it made sense as responses are expected to happen quickly. However, I–O therapies often lead to much slower reactions. Expecting patients tumors to have an immediate reaction to immunotherapy is unrealistic. This creates a challenge in using traditional designs and statistics for measuring success. The FDA is not necessarily interested in seeing an immediate response – they want to see treatments with longer

durations of response and durable responses. Measuring success based on these endpoints requires different trial designs than those simply looking at response.

Another area where we are seeing a much-needed change is in dose selection. Right now, there is a lot of buzz around dose optimization, because it is clear the maximum tolerated dose is not generally optimal for the I–O space. We are still in the mindset of escalating doses to toxic or intolerable levels for up to a third of patients, presuming the highest tolerated dose will lead to the greatest efficacy. We need to change our approach for selecting an optimal dose in the earlier stages of drug development so that chosen doses have a high probability of being tolerated by a large fraction of patients and have a higher chance of succeeding in later phase trials of efficacy.

It is worth noting that the FDA recently released draft guidance for dose optimization which is consistent with ASCO's initiatives in the area. We are supportive of that guidance and hope it will facilitate a shift toward better dose selection in the early drug development phase for both I–O and other targeted therapies.

Q What about your own efforts to promote dose optimizing approaches?

EG-M: In 2022, we had a joint workshop with the FDA on dose optimization [6]. It was a 2-day event focused on promoting better practices in dose finding for cancer therapies. We placed quite a bit of focus on I–O and targeted therapies. There was great enthusiasm, with over 1500 attendees which was a record attendance for our FDA-joint workshops, showing how much interest there is in this area. Due to its success, we are holding a second workshop this fall continuing the topic of dose optimization, with a focus on combination therapies.

Secondly, we recently submitted a proposal for a dosing study with two different dosing approaches. One arm is titrated – starting low and escalating a patient's dose based on how well an individual patient tolerates the treatment. The other arm is starting at the FDA-approved dose of a drug. This will be a randomized trial looking at CDK4/6 inhibitors in patients aged 65 and older with metastatic breast cancer. If this project is funded, we will start enrolment in early 2024. This is just one example of a scenario where lower doses may have similar clinical benefits for patients compared to higher doses. We envision this as a first-of-its-kind in what we hope to be a broader dosing platform where we can investigate other anti-cancer therapies, including immunotherapies, to see if we can achieve improved personalized approaches for dosing in the post-approval setting. There are anti-cancer drugs out there with evidence to show they are given at levels that are likely too high for most patients to tolerate, and they could potentially be equally or more effective at lower doses, allowing patients to stay on the drug longer.

Q What would be your advice on practical steps that can be taken to design and run more patient-centric and inclusive clinical trials?

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How can the I–O space as a whole, and the industry stakeholders within it, better serve diverse patient populations in general?

JG: In the I–O space, we held a workshop in association with the College of American Pathologists (CAP) on biomarkers for immune checkpoint inhibitors. A manuscript for this is now available [7]. The workshop aimed to address the complicated situation we have in the I-O space, with numerous immune checkpoint inhibitors, along with many companion diagnostics, being approved across multiple cancer types and stages and a paucity of data on how best to select patient/tumors that will benefit. PD-L1 antibody staining, tumor mutational burden (TMB), and microsatellite instability (MSI) are among the approved assays to select tumors for I-O use. Within the PD-L1 testing area, we have not only multiple different antibodies being used, but different cut-points for 'positivity', and some approvals that include staining of the tumor, some on the surrounding lymphocytes, and some combining both.

As a follow-up to the ASCO-CAP I-O Biomarker summit we created a taskforce on the comparability of immune checkpoint inhibitors and their biomarkers. This means looking from a clinical standpoint at how to pick which drug or biomarker assay to use. We are in the early stages of designing a clinical trial that will let doctors be doctors in selecting I-O agents and biomarkers, but will also collect data and enroll in a pragmatic way with limited study requirements beyond conventional care. We hope to learn more from comparisons between drugs and predictors of benefit.

Beyond I–O trials, we have a Clinical Trials Access and Participation task force. We held a workshop several months ago called 'Bringing trials closer to patients' about the decentralization of trials, and using options like telemedicine, remote screening, remote enrolment, and remote visits. Things like imaging and lab tests can also be done closer to home, rather than at the site of the trial, making trials more patient-centered and also more pragmatic.

Our TAPUR trial is a perfect example – you can use whatever genomic assay you want provided it is validated. We then help supply a drug to match the target, and the doctors decide on the dosing and the dose reductions. We only collect grade three and higher toxicities, and only those that might possibly be related to the study drug. We let doctors decide how to assess the benefits, using investigator assessment of response. We have a TAPUR steering group with many stakeholders, including clinicians, industry, patient advocates, and the FDA to make this easier.

Q What are your own goals and priorities over the next 3–5 years?

JG: I am looking forward to helping with global clinical trials and global research. We have developed three regional councils in Asia Pacific, Latin America, and most recently Sub-Saharan Africa. We have representatives that are ASCO members in each of these regions, and we adapt ASCO programs and services to each region's needs individually. For example, the Latin America regional council requested help with clinical trials, so we are working on partnering in some training. We have, however, found that they have plenty of clinical

researchers who are well-trained, they mainly need more opportunities. They need to be included and offered trials, and to participate in multiregional drug development. We have acquired an industry partner to fund a grant opportunity mechanism for proposals related to metastatic breast cancer which will be led by our Latin America regional council.

Our Sub-Saharan Africa regional council also wants collaboration in clinical trials. We have a memorandum of understanding with the African Organization on Research and Training in Cancer, focused on clinical trials. We want to partner in creating opportunities for them to be able to conduct trials, meaning identifying high-quality sites with the infrastructure to participate on a global scale and also address research questions relevant to Africa.

"We want to encourage better diversity in trials, and then use that network to collaborate with external partners and patient-centric clinical research projects."

– **Elizabeth Garrett-Mayer**

We are working hard to get access to essential oncology medicines globally and ensure it is not only patients in high-income settings who are benefitting from recent cancer research achievements. In this arena we are partnering with the Access to Oncology Medicines (ATOM) coalition, led by the Union for International Cancer Control (UICC).

The WHO's essential medicines list now has immune checkpoint inhibitors listed but only for metastatic melanoma. When they looked at the efficacy, toxicity, and cost, to date that is the only indication that they have felt is justified, in part because there were so few other alternatives. We are struggling to make immune checkpoint inhibitors accessible and affordable. The toxicities can be hard to manage in Low- and Middle-Income Countries where even if the drugs were available, the supportive care and health systems infrastructure necessary to safely mange the toxicities of I-O agents may be limited – so there is still plenty of work to be done going forward.

EG-M: CENTRA turned 6 years old in January, and we feel proud of the work we have accomplished so far. Being researchers, we are always looking to the future to see what we can be doing for patients and providers. We focus on the areas ASCO is uniquely poised to have an impact. We do not want to compete with our members or cooperative groups, and there is so much work to be done that it is easy to find niches where we are the ones who can do the work. For example, we are well-positioned to pursue opportunities in dose optimization, such as our CDK4/6 inhibitor study.

We are also interested in growing the clinical research network created as part of our TAPUR study. We have developed a network of 250 sites around the country, mostly community sites. We would like to strengthen that network and potentially grow it further to encourage diverse patient populations. We want to encourage better diversity in trials, and then use that network to collaborate with external partners and patient-centric clinical

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research projects. We are also open to stakeholders approaching us and initiating collaborations around other important topics for the field where we can contribute.

Another upcoming initiative we have is in partnership with The Society for Immunotherapy in Cancer (SITC). They held a summit last summer on the crisis in clinical research. We were interested in what they were doing because we had similar broad concerns across cancer drug development. They recognized that the clinical trial offices of many practices, including academic medical centers, are getting depleted in terms of turnover and competing for well-qualified clinical research staff.

We have arranged a joint meeting with SITC in June, in Chicago, before ASCO's annual meeting. This will be a stakeholder meeting of 20-30 different organizations interested tackling this problem, including groups like the Oncology Nursing Society, the American Society of Hematology, and others. We are working together to come to a consensus about steps we can take to make a difference in this area.

BIOGRAPHIES

JULIE R GRALOW, MD, FACP, FASCO is the Chief Medical Officer (CMO) and Executive Vice President of ASCO and brings to her role deep expertise in patient care, research, education, and global health. Previously, she was the Jill Bennett Endowed Professor of Breast Cancer at the University of Washington School of Medicine, Professor in the Clinical Research division of the Fred Hutchinson Cancer Research Center, as well as Director of Breast Medical Oncology at the Seattle Cancer Care Alliance. She is a recognized leader in breast cancer clinical research, and has conducted clinical trials in breast cancer prevention, treatment, and survivorship.

ELIZABETH GARRETT-MAYER, PhD, is the Vice President for the Center for Research and Analytics (CENTRA) at ASCO. Prior to joining the staff at ASCO in 2017, she was the Director of Biostatistics at the Hollings Cancer Center and Professor of Biostatistics at the Medical University of South Carolina (MUSC). Before moving to South Carolina, she was a faculty member in the Division of Biostatistics in the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University. She is a fellow of the Society for Clinical Trials and a recognized leader in cancer clinical trials education, conduct, and design.

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CLINICAL DEVELOPMENT STRATEGY

SPOTLIGHT

INTERVIEW

From highs & lows to steady progress: assessing the shifting I–O clinical landscape

Roisin McGuigan, Editor, *Immuno-Oncology Insights*, speaks with (pictured) **Andrew Baum**, Head of Global Healthcare at Citibank for insights on the shifting clinical landscape in I–O, and what's needed to accelerate progress in the space.

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Q What are you working on right now?

AB: I am the Head of Global Healthcare at Citibank, overseeing healthcare research across all the continents within biopharma and beyond. My direct responsibility is covering major pharmaceuticals in the US and in Europe. Prior to that, I spent 14 years at Morgan Stanley, running European pharma. By background, I'm an Oxford-trained medic/surgeon.

Q You have been active in the cancer immunotherapy space for a number of years – when and why did it first attract your attention?

AB: It attracted my attention in 2011 for several reasons. First, I saw a publication of the initial patients who had received chimeric antigen receptor (CAR)-T cell therapy, initially from the University of Pennsylvania by Carl June, in children with acute lymphoblastic leukemia (ALL) and subsequently adults with B cell malignancies. In parallel, the evolving data from Bristol-Myers Squibb on ipilimumab was released, which became Yervoy. An aggregate of those two data points is what sparked my interest.

You often see incremental change in oncology, as well as other therapeutic areas. It is rare to see the durable responses which immuno-oncology (I–O) seems to generate. This demonstrates its transformation as prior to this data being released, I–O had been left as a graveyard due to 30–40 years of high hopes and effectively no results. The stark durability of the responses, coupled with the paucity of transformative data in general across the industry got me intrigued.

Q And what is most exciting you about this space right now?

AB: I–O is rapidly evolving. We have moved past the highs and the optimism, through the disappointment that occurred when many of the next-generation checkpoint inhibitors failed, to a place of steady progress. We are now building on the already-established base with a deeper understanding of how to bridge the gap between translational medicine and clinical experience.

Q How is the global regulatory landscape currently evolving in the I–O field?

AB: In general, the US Food and Drug Administration has been getting more progressive now for many years. The agency is happy to grant accelerated approval on the provision that Phase 3 confirmatory trials are completed and satisfy the requirements of the agency. Clearly, overall survival remains the preferred endpoint but, in some indications, regression-free survival remains a potential endpoint. There is lots of work being done on dose optimization and finding the lowest effective dose, rather than the maximum tolerated dose, which is particularly important for I–O drugs.

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"There is a wide range of developments underway, starting with basic biomarker selection and determination to enrich patient trials; all the way to finding ways to enhance efficacy."

Q How would you define the current state-of-the-art in the checkpoint inhibitor space? Where do you see improvements being made that could open up new opportunities in this area?

AB: There is lots of movement here in many different dimensions. Finding a biomarker is always a good start. At the moment, there are many ongoing Phase 3 trials with checkpoint inhibitors, where there is no biomarker – for example, TIGIT. Instead there is a surrogate biomarker, but it is not directly related to the proposed mechanism.

Moving up the chain, there are attempts to locally activate checkpoint inhibitors, in order to ameliorate some of the toxicities through bispecifics. Some companies, including Xilio Therapetuics and CytomX are experimenting with approaches to mask, in terms of addressing toxicities by local delivery to tumors. These are areas that historically have not yet yielded anything, but have potential. There are also attempts to augment antibody-dependent cellular cytotoxicity (ADCC) through afucosylation. Bristol Myers Squibb, Agenus, and several other companies have performed engineering of Fc and monoclonal antibodies to enhance ADCC. There are also several approaches leveraging dual checkpoint agonism or inhibition in development.

There is a wide range of developments underway, starting with basic biomarker selection and determination to enrich patient trials; all the way to finding ways to enhance efficacy, such as ADCC activation and Fc engineering; and improving safety through masking or bispecifics.

Q Considering novel targets and pathways, how can the I–O space move past the 'low hanging' fruit? Who is likely to pursue/fund high-risk but potentially high-reward strategies in this space?

AB: The sheer number of trials increases with more data validation of a target, and the more participants there are with similar developments in that particular place. If a target has been de-risked, the chance of success goes up. This has happened with TIGIT, and previously with PD-1 and PD-L1. There is certainly no shortage of interest for addressing other targets and other approaches, and once you get a piece of confirmatory data, then the competition builds up.

The biggest risk is separate from this, and it goes back to the mechanism. The totality of data suggesting combination immunotherapy with PD-1, in addition to an agent that does not have single-agent activity, does not show much promise. It is difficult to find any agent without an objective response rate (ORR) of greater than 10–11% that adds anything when given on top of PD-1. There are several Phase 3 trials ongoing with TIGIT, which will be an interesting test of that because these agents do not have an ORR of any magnitude. If these trials, which are all in non-small cell lung cancer, are unsuccessful, it will take a brave company to fund a PD-1/PD-L1 combination trial with a second agent without single-agent activity beyond a certain threshold.

Q How and where are we making real progress in terms of accelerating cancer immunotherapy clinical development and patient access to potentially game-changing therapeutics?

AB: There is clearly a desire to move into the adjuvant setting for PD-1. First, because it is a direct commercial opportunity, often with longer treatment duration, and second, because it lends itself to subcutaneous delivery and therefore allows for IP extension on drugs that would otherwise face similar competitors. Those are the economic forces that are driving interest in the actual setting.

From a biologic perspective, the adjuvant or the neoadjuvant setting is much more appealing, because there is a much lower baseline tumor load, and several of the prognostic factors we know may limit activity are far less problematic. In the case of adjuvant, there is no tumor microenvironment there at all – you are simply mopping up residual circulating tumor cells. That is a key area of focus, as prevention of the recurrence of metastatic disease is far easier to justify as a payer than providing populations with a few more months of life in the metastatic setting. The challenge in the adjuvant setting is that most patients in certain malignancies will not require any additional therapy bar surgery. We are looking for ways to run trials where patients are going to recur, so that we can secure approval and demonstrate this in a clinical trial. To do that, we need to enrich the trial with patients with more advanced disease, which can be done clinically through lymph node involvement. There is also a lot of focus on circulating tumor DNA post-resection as a superior way to enrich.

Adjuvant patient selection biomarkers are going to be critically important for expediting an economically important area for the industry.

Q Looking at the I–O space as a whole, what would you pick out as your three key predictions or hopes for the field in the next few years?

AB: I think antibody-drug conjugates (ADCs) are likely to replace systemic chemotherapy in several important indications, and depending on payload, there

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may be synergy with other molecules. For example, topoisomerase I synergy with PARP inhibitors is an obvious one. ADCs are going to be incredibly important going forward in many indications. Second, the use of neo-antigen vaccination is going to be important in the adjuvant setting in selected patients, as demonstrated by recent Moderna data as well as some recent BioNTech data. I doubt neo-antigen vaccination will have a role in the metastatic setting, however.

I do not think we are yet done with the existing targets PD-1 and CTLA-4. Both have the potential for augmentation. Yervoy could be dosed higher, but the question is: can it be done so safely? I am intrigued to see some of the masking approaches that are underway.

Similarly, we know IL-2 is an active agent, but it is limited by toxicities and alpha activation. There are now engineered versions of IL-2 which circumnavigate these issues. I am interested to see how that pans out. In addition, it is clear that bispecifics are going to have an important role in hematology settings and I suspect also in some solid tumor settings.

Q What will be your own chief goals and priorities within the same timeframe?

AB: The importance of immunology as a transformative component of multiple diseases is radically shifting, and the intersection of that, with mRNA-based *ex vivo* and *in vivo* approaches, creates entirely new possibilities. For example, one recent paper from Stanford University – seemingly in the realm of science fiction – explored the transduction of macrophages *in vivo* to transform them into antigen-presenting cells to potentiate I–O activity. mRNA is an incredibly powerful tool, and the possibilities that theoretically exist are not just limited to oncology, but clearly exist in immunology as well. My own goals are to deepen my understanding of emergent biology and the possibilities that exist, particularly with mRNA, on both *ex vivo* and *in vivo* levels.

BIOGRAPHY

ANDREW BAUM is the Global Head of Healthcare Research at Citi. Before joining Citi in 2011, Andrew was at Morgan Stanley for 14 years Before this, Andrew was a UK pharmaceutical and biotechnology analyst at Salomon Brothers. From 1994–1996, he was a practising physician at the Royal National Orthopedic Radcliffe Hospital in Oxford (the medical center of Oxford University) where he completed his residency. Andrew is a member of the American Heart Association, American Society of Oncology and the DIA. He is also a Fellow of the Royal Society of Medicine. Andrew holds an MA degree in Physiological Sciences and an MD degree from Oxford University.

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INTERVIEW

Solving challenges in cell therapy clinical trials & effectively delivering complex studies in advanced therapeutics

Cell therapy clinical trials pose a variety of complex challenges. Logistics with cell harvesting, manufacturing, shipments back to sites, patient safety, changing standard-of-care treatments, and patient enrolment due to competing trials can all impact study timelines. In this episode, Vito Romita and Jai Balkissoon outline key obstacles for developing cell therapies in oncology, and provide their insights on overcoming them in order to increase patient access and design safer trials.

Abi Pinchbeck, Assistant Editor, BioInsights, speaks to (pictured above left to right)

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Q What do you see as the three most important challenges with the current development of cell therapies in oncology?

JB: First, it's identifying, training and qualifying non-traditional research-experienced sites to be able to run clinical trials in cell therapy. And in addition, to treat patients with the current standard-of-care cell therapies in the community. This is going to involve collaborations between cell therapy-experienced contract research organizations (CROs), sponsors, academic sites, payers, and also regulators, that are all committed to make this happen.

At PPD we have a site coach training program that is dedicated to supporting the training of new research-experienced community sites. It is crucial that they are motivated, committed, and have the resources to become a cell and gene therapy-experienced site. One question is whether there will be a mechanism for research-experienced community sites to become foundation for the accreditation of cellular therapy (FACT) accredited. We assume it will be similar to large academic institutions, as we need more sites with experience to run these cell therapy studies.

We're going to need more altruistic cell therapy academic sites to not only train and mentor, but also to encourage the next generation of cell therapy-experienced oncologists to consider a career in communities that do not have cell therapy expertise. That's very important. We also need to develop more mentorship and training programs at academic institutions, where not only community oncologists but also site staff including research nurses and study coordinators can attend on-site training sessions to bring back to their community hospitals.

To achieve these goals we need buy-in from research-experienced community hospitals, including the hospital administration, to bring these complex treatments into their hospital systems. Community sites will need to have assurance from insurance carriers that they will be reimbursed for standard-of-care comparator arm treatments for example, as well as for cell therapy treatments given as standard-of-care.

A second challenge to consider is that for autologous cell therapies using viral vectors for gene modification, the vein-to-vein time can be quite long. Patients may require bridging therapies while waiting for their cells, and some patients may develop disease progression during this time and never receive their manufactured cells. Allogenic or off-the-shelf cell therapies can alleviate some of these challenges with no need for patients to undergo apheresis, and cells readily available to infuse into multiple patients without manufacturing delays. Some off-the-shelf cell therapies can also be given at multiple infusions per cycle, which may improve anti-tumor activity and result in more durable responses. Another consideration regarding manufacturing of cell therapies is how to increase their potency with a longer duration of anti-tumor activity without increased toxicity.

The third challenge is in preventing and managing the toxicities associated with cell therapies. For autologous cell therapies the most significant toxicities are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) seen with chimeric antigen receptor (CAR)-T treatment. Although the majority are Grade 1 or 2, the potential for higher grade toxicities that may occur more than 14 days after infusion have fueled our conservative practices. Patients are monitored closely, often in the hospital for seven days, followed by requirements for the patient to remain in the local vicinity of the study site for about a month after infusion of CAR-T cells.

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– **Jai Balkissoon**

We need to design better cell therapies that have fewer toxicities, and identify biomarkers that can predict early onset toxicity and also which patients are more likely to develop severe, life-threatening toxicities. We can then develop risk-mitigation strategies and prophylactic measures that may prevent or decease the severity of these toxicities. It is the potential for severe and sometimes life-threatening toxicities that has prevented these advanced therapies from being used by community oncologists.

There are many more considerations, but I see these as the three biggest challenges right now when we're developing cell therapies, especially in oncology.

VR: One further issue that we have to address is expansion. Jai made reference to some of the logistical complications with respect to running cell and gene therapy trials, and to safety monitoring. You would have to develop a very robust strategy when you start to expand to other countries and other sites, especially as these therapies start to evolve so that they become registrational trials, and as we are entering countries where perhaps there are differences in standard-of-care.

It is crucial to ensure there is a harmonized approach in terms of understanding the different modalities of the therapy in question, and how that impacts training at the site level and execution of the clinical trial.

Q What can industry leaders, stakeholders and sponsors do to improve patient access for cell and gene therapy clinical trials?

VR: This is a perfect segue from Jai's conversation about the three most important challenges impeding clinical trials, specifically in the context of adoptive cell therapies, which are highly complex both logistically and in design.

Among these challenges is the underpinning issue of enrolment, which is common across all clinical trials. The current process and mechanism by which most of us conduct clinical trials can't really evolve without a carefully thought out strategy to enable patients to access available treatment options.

To get back to basics, we need to remember that without understanding the patient's experience, and their specific challenges across the age, gender, race, and socioeconomic spectrum,

we compromise our ability to bring these transformative therapies to market. We are living in an extraordinary era where we now have the capability to introduce precision medicine. This capability is opening up vast possibilities and we – collectively, across all industry stakeholders – have an obligation to make every effort to exploit those possibilities to ensure that no patient remains untreated and left behind.

As an industry stakeholder, we have to make an absolutely concentrated effort to collect data representative of patients across all cultural and societal spectrums. Lack of inclusion and representation of clinical trial data from patient populations and subpopulations limits the scientific and medical validity of treatment-derived outcomes and patient-reported outcomes. Those outcomes are essential for a successful clinical trial from the perspective of the patient, their caregivers, our regulators, and of course our payers.

I'd like to spend a minute or two on some interesting statistics. People of color make up approximately 40% of the population in the US, yet as low as 2% participate in clinical trials. Approximately 52% of the population in North America – and we have similar statistics in other parts of the world as well – possess middle to lower-level performance in relation to literacy and comprehension. This is no doubt a significant obstacle in relation to patient access to clinical trials, their access to sites, and of course the whole patient onboarding process. Finally, a large percentage of racial and ethnic minority groups remain underrepresented in clinical trials – but disproportionately present with higher incidences of chronic disease.

We have to focus on the problem statement, which is maintaining the status quo and complacency around how most clinical trials are conducted. This does not afford society nor our industry the urgency to address many of these unmet medical needs. Without a deliberate and holistic mechanism, and an infrastructure to educate and direct patients to clinical trials, we limit enrolment and we limit our ability to provide for these patients.

Patient awareness of their own conditions and perception of the industry is definitely one consideration and area of focus. Primary care physicians' awareness of ongoing clinical trials, and their own availability to educate and guide patients to their best treatment options is another. And then we have to consider the patient's ability to navigate through publicly available resources, and/or access resources to reach these treatment centers. These areas of focus have now become areas of concern given the massive influx of research and development and information overload with respect to clinical trials in general, but especially with respect to cell and gene therapy trials.

The solution is not by any means a quick fix. Many of the ethnic, racial, and/or other minority groups lack the skills, the resources, and the time, and given their historical context, they view industry with substantial anxiety and mistrust. So how do we engage these communities and patients to develop that trust? How do we remove some of the logistic and financial barriers? And with respect to clinical literacy, how do we educate?

There are a number of approaches we should be considering. One is around cultural competency and training for clinical research professionals across all segments of the industry. This training should be focused on identifying what those barriers are, whether it be bias or discrimination, and the training directed to all site-facing and patient-facing research professionals.

The next area of consideration is identification of sites, and communities, where race and ethnic minority groups are concentrated. We have a number of technologies, using

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epidemiology data, prevalence data, and data mining capabilities, to identify where these disparities are and where these concentrations of minority groups reside with respect to geographic distribution.

The next area is developing a sustained level of trust and engagement throughout the communities. Continuous, sustained outreach to communities must be focused on education and again on developing that level of trust. This is done through a number of venues, whether that be patient advocacy groups, community outreach using social media, involving trusted key opinion leaders, and increasing the visibility of principle investigators and healthcare professionals who are representative of these racial and ethnic minority groups, and that advocate for those communities. Another approach is developing a very strong referral network. Lastly, the development of patient advocacy boards, where we involve academic centers, pharma, CROs, communities, community health networks, patients themselves, and the government, is absolutely key in solidifying this long-term strategy.

Trial design is another aspect of this. We have reliable data to show that if we incorporate the patient's voice in trial design, this will optimize the results on the backend in terms of enrolment and engagement. The US Food and Drug Administration reauthorization act came out in 2017 and encourages the incorporation of patient experience data in all new drug applications. The development of the informed consent form and patient-facing materials as well as other data capture materials should be manifested in such a way that they're culturally competent and relevant. We have mechanisms in place where we can track our success rate in including these diverse patient populations in real-time.

The last point is around patient retention. In the context of cell and gene therapy trials, where we are administrating a genetically modified product or genetically modified cellular entity, the follow-up period is 15 years. So how do we manage patient retention? This leads into my next point, which is about the establishment of patient-centric and supportive services. We can do this by leveraging our technological capabilities such as televisits and telemedicine. We have infrastructure now to ensure we can effectively and efficiently reimburse for travel, time off from work, and childcare. We have mechanisms and infrastructure in place to manage the logistics, meaning we can book air and ground travel, and accommodation. Many of these trials are situated quite a distance from where the patients reside and may require in-campus or in-hospital stays. Another piece is providing educational and support materials for the patient's journey, supporting their schedule compliance by interacting with them pre- and post-visit, and then continuing that dialogue with respect to their involvement and experience.

The last point for this question is about truly overcoming the status quo. We have a plethora of tools, digital technologies, and well-defined strategies available to us. And yet, these aren't widely adopted as part of the long-term strategy to elevate underrepresented communities so that these communities are prepared to make informed choices. The considerations and challenges presented here are not necessarily novel, but certainly the focus on these issues has been intensified.

We have to learn to build the plane while we fly it. Overcoming the inertia around major investment in these tools should be part of a broader strategy to address patient diversity and inclusion, and have a positive impact on enrolment.

Q How can we make complex cell and gene therapy trials more understandable to patients and their primary caregivers?

VR: In addressing the previous question I referred to obstacles associated with clinical literacy and potential issues around alienation and trust. Addressing historically embedded biases requires collaboration across academia, community centers, and community healthcare networks, healthcare professionals, pharma, CROs the government, and of course the patient.

> "...within the context of a clinical trial, a mechanism to look at the data – not only on an individual patient basis, but aggregate data to help us make strategic choices and/or provide strategic decisions and direction."
>
> – **Vito Romita**

What we have not discussed is the actual onboarding of the patient. How do you engage with a patient who may have limited reading, writing and/or language skills, and educate them on the complexity of a cell therapy trial? There are short and potentially long-term risks, along with benefits, associated with conditioning and cell infusion in the context of an adoptive cell therapy, or a trial that uses a genetically modified cellular entity. There are genetic and reproductive implications. They need to understand and weigh these considerations against their current conditions, life expectancy, and available treatment options.

I referenced the consent form in my previous response, and simplification of that consent form is absolutely key. Approaches such as videos, illustrations and demonstrations can easily simplify the message and demystify the challenges and, to some extent, the science behind cell and gene therapies. We can use the e-consent process and televisits to engage directly with patients and caregivers in the comfort of their homes, and again provide patient-facing and educational materials that are culturally competent and relevant.

Q Finally, what can be done to help design safer cell therapy trials?

VR: There are considerations that have to be taken into account during the proof of concept. These include establishing and monitoring safety outcomes from first-in-human trials, and continually watching with go/no-go decisions. Development of adaptive trials that will again incorporate go/no-go decisions as we start to enroll patients and as the safety data begins to develop, is another aspect.

Incorporation and inclusion of data safety monitoring boards, as well as clinical oversight, is key to ensuring that there is a manageable approach to safety management and surveillance. Using and relying on digital technologies and trending analysis is another way to incorporate, within the context of a clinical trial, a mechanism to look at the data – not only on an

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individual patient basis, but aggregate data to help us make strategic choices and/or provide strategic decisions and direction.

BIOGRAPHIES

JAI BALKISSOON, MD, FACS, is a surgical oncologist and the medical and scientific lead for immuno-oncology, cell and gene therapy at PPD and is the visionary behind the creation of the PPD Immuno-oncology/Cell Therapy Center of Excellence. With more than 25 years' experience in both clinical practice and clinical research, Dr Balkissoon is committed to capitalizing on advances in the rapidly changing therapeutic landscape to establish PPD as a world-class partner in advancing immunology-oncology/cell therapy studies. His personal immuno-oncology and cell therapy experience includes treating patients with advanced melanoma, kidney cancer and non-Hodgkin lymphoma with adoptive cell therapies and vaccines either with or without gene modification. He developed an immunotherapy program in Northern California for treating advanced melanoma and kidney cancer patients with high-dose interleukin-2. At PPD he has been the therapeutic advisor for cell therapy studies in oncology and provides drug development strategy, medical, scientific and product development guidance to both external clients and internal PPD clinical operations and business development teams. He also consults on investigational new drug submission and clinical input toward protocol development, including adaptive designs when feasible. With extensive clinical oncology experience and as a senior executive in the pharmaceutical and biotech industries, Dr Balkissoon joined PPD in 2013 after previously working at Genentech and Oxigene in South San Francisco where he was Vice President of clinical research. Dr Balkissoon holds a Bachelor of Science in biology from Beloit College in Wisconsin and a medical degree from Howard University College of Medicine in Washington, D.C. He completed a general surgery residency at Howard university and a surgical oncology and immunotherapy fellowship at the National Cancer Institute (NCI) in Bethesda, Maryland.

VITO ROMITA is a clinical research professional with 26+ years of experience in the drug development industry primarily in the CRO environment and has worked with small, mid-sized biotech and large pharma. Vito obtained his PhD from McGill University (Montreal, Quebec, Canada) and graduated with honours. Vito has and continues to dedicate his career to advancing therapies across several indications applying his deep expertise in operationalizing complex clinical trials across all phases; the last 15 + years focused on haematology-oncology with a more recent emphasis in areas of immuno-oncology and adoptive cell and gene therapies, an area rapidly evolving over the last decade.

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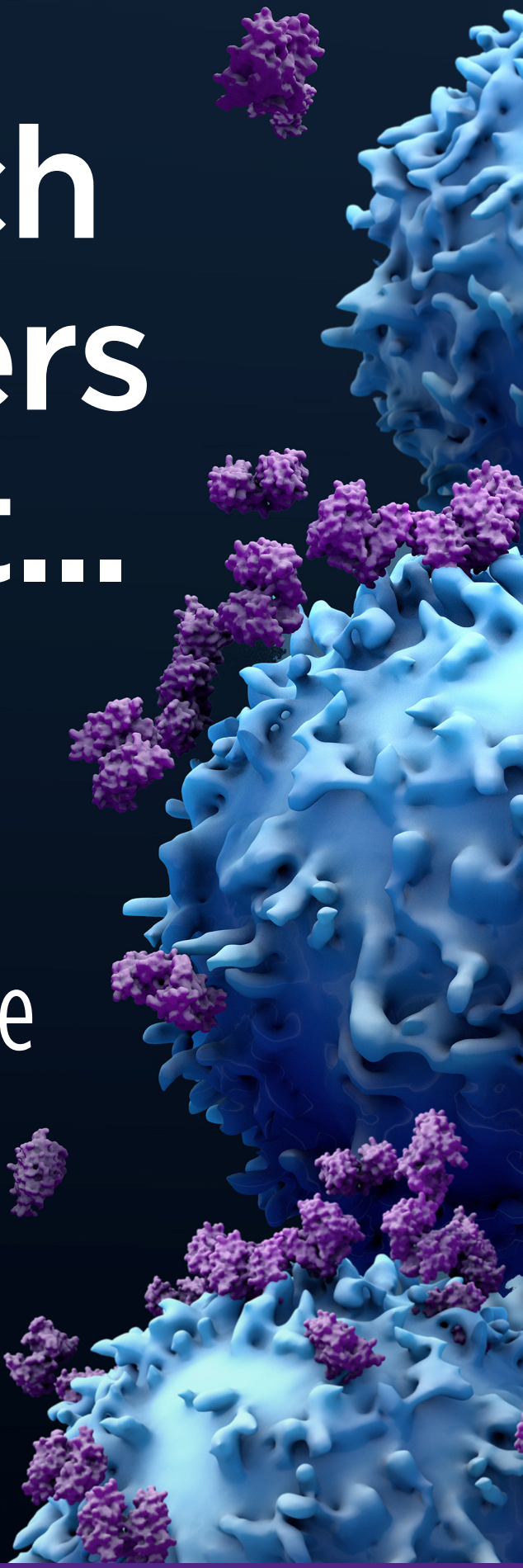

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SPOTLIGHT

Achieving more patient-centered trials in cancer immunotherapy: a patient advocate perspective

Deborah Collyar, President of Patient Advocates in Research

"We are asking them to contribute their lives to these studies, and to furthering cancer research and treatment. It's time we work together to make research more relevant for real people."

VIEWPOINT

Deborah Collyar is the President of Patient Advocates in Research (PAIR), an informal international communication network of ~250 patient advocates who are independent research patient advocates or those who contribute to Patient Advocacy Groups. Here, she explains the existing barriers to clinical trial participation in the immuno-oncology space, and shares her insights on how to modernize eligibility criteria.

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I was an executive in a computer company in the early 1990s when I received my first cancer diagnosis. Prior to the internet, the only resource my husband and I had to learn about cancer was the library. As I was going through treatment, we found out how little had changed for decades. That is when we became involved in a burgeoning cancer patient advocacy movement based in activism, learning from the acquired immunodeficiency syndrome (AIDs) movement [1, 2]. Up to that point, traditional types of patient advocacy existed for fundraising, lobbying, and direct patient support, but there was no patient advocacy within cancer research. Patient Advocates in Research (PAIR) was started to not only change the way the research system worked, but to change the mindset of the researchers doing the work to get more relevant results for patients. PAIR helps everyone who is interested and involved in emerging research issues and advancing patient-relevant research, including companies, sponsors, academics, government-run programs, and patient groups. We connect the dots to solve problems and get better and faster patient results.

I quickly became involved in two different aspects of research [3]. First, the US National Cancer Institute (NCI) did not have active translational research programs. We helped them launch a proposal called the Specialized Program of Research Excellence (SPORE) and got new money through Congress. The first SPORE grants were focused on organ sites, and I was involved on a national level with NCI and at a local level with one of the first grantees (UCSF). This eventually developed into a 4-year grant called the Patient Advocate Research Team (PART) Program to bring patient advocates into 63 SPORE grantees in 24 different US institutions, focused on 14 different types of cancers.

Second, I became the first patient advocate in any of the NCI clinical trial groups, now a part of the NCI Clinical Trial Network (NCTN), and helped bring more patient advocates into these groups to help with concept and protocol development and implementation of clinical trials that are at least partially funded through the US government [4]. This also included helping with recruitment plans, retention strategies, and publishing plain language summaries of publications [5, 6].

I was also asked by Martin 'Mac' Cheever to join a special NCI grant called the Cancer Immunotherapy Network (CITN). My work with the Society of Immunotherapy of Cancer (SITC) started with strategic planning in the early 2000s. Immunotherapy had been a big topic in the 1970s and 80s, and then it fell out of favor. It became more promising again, and SITC grew quickly. I have been a part of their Education and Training Committee for many years and have always pushed to include more plain language initiatives for patient communities. Part of my work with SITC also includes their Diversity Roundtable, which focuses on workforce and clinical trial participation. This has just started with Leisha Emens, MD, PhD as President, and will hopefully accelerate substantive action in the next few years to help every institution and protocol develop successful diversity, equity, and inclusion approaches. I have also been part of the faculty for SITC's Cancer Immunotherapy Winter School each year, and in the SCION workshop where young scholars can work on their own protocol ideas in small groups with amazing faculty.

BARRIERS REGARDING CANCER IMMUNOTHERAPY CLINICAL TRIAL PARTICIPATION

Barriers to all clinical trials share similarities, although there are some specific challenges for immunotherapy. Clinical trial participants bear a lot of costs for the administration of an agent, for tests and procedures, and for getting to treatment sites in addition to time away from work and other obligations. Eligibility criteria are a problem across the board, including in immunotherapy, and they add to diversity disparities. While adverse events are rarer with immunotherapy, they must be carefully considered and dealt with since people who have issues like cytokine release syndrome can die quickly and painfully.

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Another barrier includes 3+3 trial designs in Phase 1 trials. The 3+3 design has been used for decades because it's easy, but it does not work well for statisticians, researchers, or patients. For instance, it is unfair for patients to start at incredibly low doses and not be able to continue at a higher dose if they so choose – would you want to be one of the first three patients in a 3+3 phase 1 trial? We should be looking into optimal therapeutic doses or intra-patient dosing, where a trial participant can receive an increased dose. Crossover design is also important to consider, also known as treatment switching [7]. There are considerations and statistical methods that will allow for crossover design to be possible.

One silver lining to COVID includes changes to clinical trials which should stay in place, including adaptive design, master protocols, and decentralized clinical trials (DCT). Traditional designs for clinical trials often impede recruitment, so having a sensible 'learn as we go' approach is better from a patient standpoint. In addition, Master Protocols offer more options for participants with a common control group. Instead of a 50:50 shot of getting an existing or new treatment, patients will have a better odds at getting a new treatment if there are more than two arms in the trial.

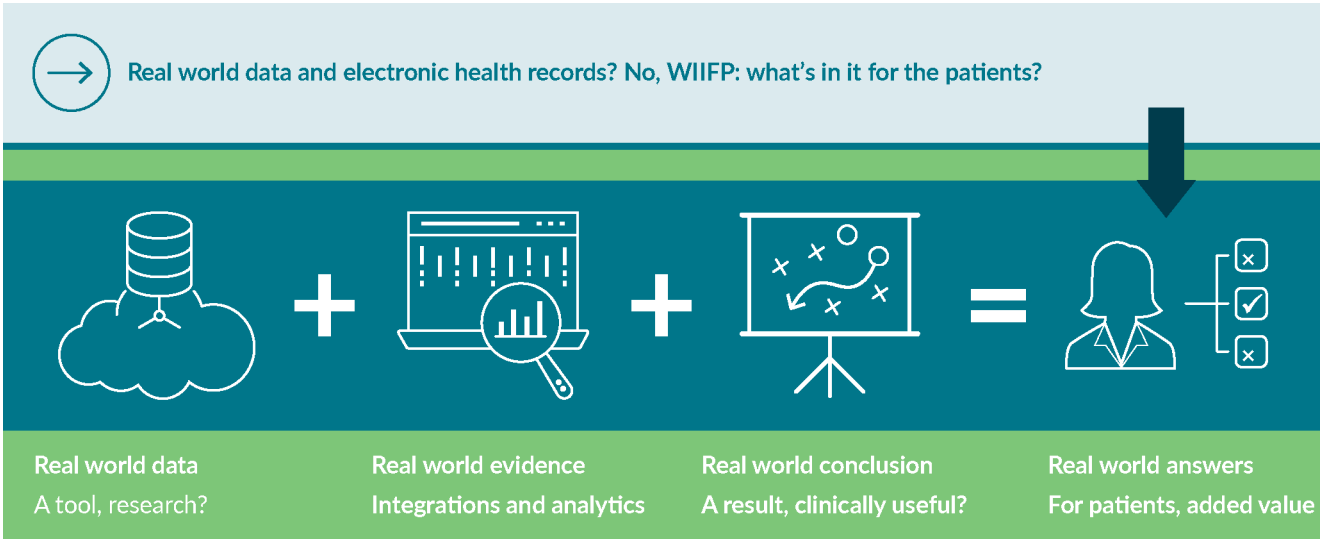
DCTs are also important so trial participants have the ability to do things locally instead of trekking to special centers. We should also have more hybrid clinical trials, with a combination of on- and off-site treatment. Telehealth visits allow more people to participate in clinical trials since location is less of an issue. We also need to give more tools back to the trial participants when digital tools are used – we cannot continue to take from them without being able to give something in return.

Real world data (RWD) is a useful tool to include in clinical trials, though similarly to biospecimens and clinical data, data does nothing on its own. To get anywhere, we need real world evidence (RWE), and we need to take those analytics and interpret them into something clinically useful for providers and for patients. This in turn can give us real world answers (RWA), which is what patient communities and providers need (Figure 1).

It is crucial for trial sponsors to understand that we must incorporate these new tools into every future clinical trial. And as we look at every clinical trial, let's consider certain questions: In this particular trial, how do we get more diverse patients? How do we make it easier for those participants to be involved? How can we collect patient-reported outcomes (PRO) or patient preference

FIGURE 1

The importance of translating data into clinically useful answers.



and experience data, to inform future trials and treatment?

BARRIERS TO MODERNIZING ELIGIBILITY CRITERIA

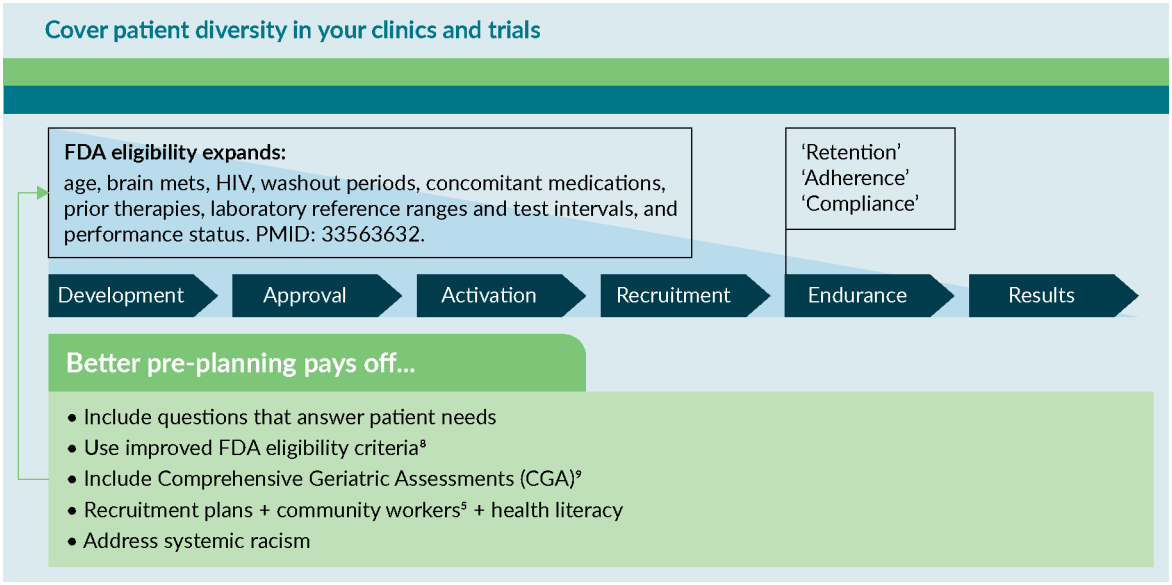
Often, regulators are seen as a barrier to modernizing eligibility criteria. However, in the US, the FDA has supported and published information about broadening eligibility, which is good for all of us. The barriers seem to lie with the reticence of sponsors and companies doing the clinical trials, because change is challenging, and they insist on a narrow interpretation of the regulatory process, thinking about it from a product and regulatory focus. I try to switch that paradigm to considering patient perspectives first by practicing WIIFP: What's In It For Patients? Then, the product and regulatory aspects fall into place. If we think about patient needs first and build that into clinical trials, many of the barriers disintegrate.

The clinical trial process is usually seen through the lens of development, activation, recruitment, and retention, which in the industry means adherence and compliance. These words do not apply to patients. From a trial participant standpoint, this is an endurance test. If we use that word, it changes mindsets. How can we help patients go through their endurance test and make it to the end of the clinical trial, and hopefully, into remission? If we take time to pre-plan these steps, that can help all of us – it helps get trials done quickly and it costs less for the sponsors, which will hopefully transfer to patient communities.

Eligibility is a key factor in clinical trials. The FDA has recently expanded on age, reducing the minimum age from 18 to 12. At the other end of the spectrum, as most people who get cancer are older, we cannot exclude them from clinical trials just because it is convenient, and they must be included with racial, ethnic, and geographic diversity in mind (Figure 2). A comprehensive evidence-based geriatric assessment tool has been built, for example, and should be a part of every adult clinical trial. At the SITC Winter School, they were not aware that the US Food and Drug Administration (FDA) has expanded eligibility criteria, showing the need to spread the word about regulatory improvements. The FDA Patient-Focused Drug Development (PFDD) guidance also offer ways to

FIGURE 2

Strategies for addressing patient diversity in clinical trials [5,8,9].



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include patient perspectives into clinical trial development [10].

Additional FDA eligibility expansions allow for brain metastases, especially when identified and measured. High or low body mass index, human immunodeficiency virus, and other co-morbidities are also traditional barriers to eligibility, and the FDA addresses these along with co-morbidities which are extremely common in cancer patients. According to ethical principles, eligibility criteria should represent the patient community that will be receiving a drug [11]. Addressing comorbidities like heart disease and diabetes also offers potential solutions for diversity issues.

Lab ranges and performance status also require new consideration [12]. Many people have traditionally copy-pasted from old protocols. We need to think about the needs of each specific protocol for safety reasons, and then expand the eligibility as much as possible. That will help sponsors achieve their end goals of both regulatory approval and reimbursement for broader patient populations. Many drugs fail after being approved by regulatory agencies because they simply do not fit the population in which they will be used.

In the early 2000s, I co-chaired a committee in which we put together an accrual/recruitment plan template that included information to consider for the patient population, the study sites, and the referral base [13]. The oncologist's office is the last place the patient ends up, not the first, so it is important to consider how many steps and how many different kinds of medical services (and messages) it has taken patients to travel through. We must put clinical trial messages all along the way for the patient and for the medical community to see. This takes some pre-planning, but it pays dividends.

By including patient perspectives during design, these steps can save money on amendments, for example, once the trial is implemented. When patient representatives are involved in the development of the clinical trial, it runs more smoothly because we look at it from an experiential standpoint. The barriers that are built into trials from a trial participant standpoint can at least be discussed and considered, if not eliminated.

ENSURING PATIENT-CENTERED TRIALS

To ensure patient-centered trials, we must begin with 'tissue issues' [14]. There are an increasing number of publications surrounding the issue of bias and representation of the tissue that we use [15]. A lack of good biospecimens and data from communities of color means that these communities will be left further behind. The solution starts with patient location; we must go where the patients are instead of only to large centers. Patient communities live within their local communities, so we must be able to connect to community leaders in local areas as well as patient groups. We can begin by explaining why this research is important for specific groups of people, and open up a dialogue in plain language that includes privacy protections and a commitment to ongoing security improvements. Biomarker testing awareness and accessibility are major issues for both patient and provider communities. Things are advancing so quickly, especially in immunotherapy, that we need to work together to solve these issues.

In addition, financial issues for patients are not an excuse to filter people out. We have to change the model, provide resources, and connect with communities using better and consistent communication over time. Researchers can learn from it too, so it must be bi-directional, collaborating and co-creating with communities.

ADDRESSING HEALTH LITERACY

When you get diagnosed with cancer, it's like being thrown onto a new planet without any type of roadmap, dictionary, or survival training. We must help patients by providing a roadmap to know whom they can go to in order to learn more and gain the resources they need. It is so important to provide

resources to all patients, rather than filtering for socio-economic status or for race, ethnicity, age, or location. There are outreach departments in almost every cancer center that clinical trial staff should be connecting to. Outside organizations such as the Patient Advocate Foundation and Triage Cancer also have excellent tools to help people navigate the financial side of their treatments, and they have materials for providers to hand out [16, 17]. Most people do not know about these so we must start connecting those dots constantly.

Finally, just because certain language is used in regulatory material does not mean we have to use it in protocols or in conversations, with both colleagues and potential trial participants. For instance, use the term 'trial participant' instead of 'subject'. Most people hear 'subject' as a verb, rather than a noun, which brings up images of guinea pigs and other harmful references to experimentation.

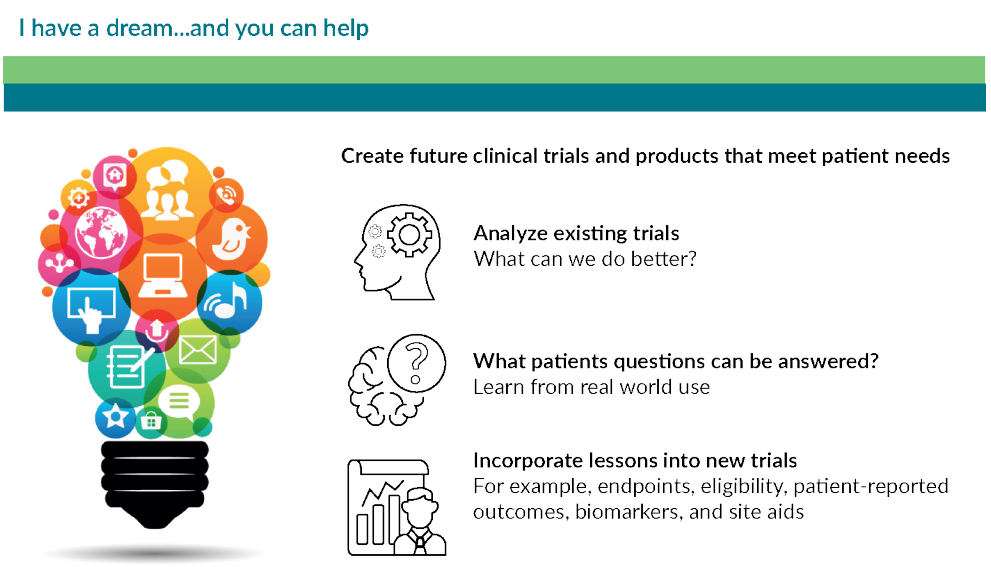
The one thing that is always missing for patients is context. We need to ensure our language is clear so that they do not need a medical degree to understand what we are trying to do. Health literacy principles include numeracy for percentages and fractions, which many people may not understand. We need to bring in people who have the skills to communicate these things in plain language. Results are also important – participants rarely hear about the results of their clinical trial in a way they understand. It is important to be able to share – it pays off for the sponsors by building goodwill, and can even reduce costs.

FUTURE HOPES

I hope that sponsors will consider master protocols, which means platform trials, umbrellas, and baskets, to help us learn more quickly and utilize the resources that we have. Trial participants should always be prioritized (Figure 3). We need to answer as many questions as possible with our trial participants, even if that leads to more complex trials, since correlative science and biomarker signatures are critical for better targeted therapies. We need to learn about biomarkers at the same time as the drugs or agents themselves. Immunotherapy is a promising area, but it can be overhyped, and there is no single answer to cancer. In my view, the real answer is a combination of treatments and approaches that will

FIGURE 3

Considerations for designing future clinical trials that center patient needs.



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hopefully help us identify and treat smaller groups of patients who can be helped by individual therapies, including immunotherapies. Ultimately, we need to offer as many choices and possibilities to trial participants as we can. We are asking them to contribute their lives to these studies, and to furthering cancer research and treatment. It's time we work together to make research more relevant for real people.

BIOGRAPHY

DEBORAH COLLYAR founded the Patient Advocates in Research (PAIR) international communication network, 'where research meets reality'. Her leadership in patient engagement and advocacy started in the 1990s after her first cancer diagnosis. Deborah applies her business leadership, IT, and communication skills to bridge gaps between scientists, medical providers, governments, and patients. Deborah infuses patient representatives into projects and gathers relevant patient input, encompassing many diseases, programs and policies at grassroots, national and international levels with companies, academia, and governments. Key insights are delivered throughout development, clinical trials, results reporting, data-sharing, standards, genomics, and into practice.

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CLINICAL DEVELOPMENT STRATEGY

SPOTLIGHT

INTERVIEW

Investigating the I-O clinical trial landscape: a focus on diverse patient enrolment

Abi Pinchbeck, Assistant Editor, *Immuno-Oncology Insights*, speaks to Cancer Research Institute's (CRI) **Samik Upadhaya,** Assistant Director of Scientific Affairs and **Jay Campbell,** Managing Director of the Clinical Accelerator and Venture Fund

SAMIK UPADHAYA, PhD is the assistant director of scientific affairs at CRI. He is passionate about harnessing the full potential of scientific advances in cancer immunotherapy to help patients live better, longer lives. Together with the Clinical Accelerator team, he leads the program's scientific diligence efforts, including analyses of emerging trends and challenges in the global cancer immunotherapy landscape. He assists in the team's collaborative ventures, clinical trial design, drug development plan, and maintenance of immuno-oncology landscape databases. He is also involved in all of CRI's research programs, and closely follows the research done by CRI grantees, evaluating their potential contributions to the field as a whole. Prior to joining CRI, Samik completed his doctoral studies in Pathology and Molecular Medicine at Columbia University where he focused on investigating the spatiotemporal dynamics of blood and immune cell production. Following his PhD, he pursued a postdoctoral research fellowship at New York University School of Medicine where he developed new techniques to visualize and analyze *in-vivo* behaviors of stem cells of the immune system. He also received his MSc in Chemistry and a dual BSc, *summa cum laude*, in Biochemistry and Biomedical Sciences from Central Michigan University.

JAY CAMPBELL is a proactive, results-oriented, life sciences, corporate development, and finance executive with a proven track record of cultivating relationships with strategic partners and the investment community. Demonstrated ability to leverage corporate finance knowledge and life sciences experience to formulate and execute value creating strategies and transactions. Over 15 years of experience in the financial services industry, including 13 years focused on the life sciences as an investment banker working with private/public companies on strategic/M&A and financing transactions. Eight years of biotechnology industry experience working at private/public companies with core responsibilities of alliance management, business/corporate development, capital raising, and investor relations. Established venture investing practice, including leading sourcing, due diligence, and investment process. Successfully worked on 36 strategic and financing transactions and investments representing over $13.4 billion.

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This interview is about their work interrogating the I–O clinical trial landscape and their findings relating to the barriers to diverse patient enrolment in trials.

Q How did you get involved in the I–O field, and go on to join Cancer Research Institute (CRI)?

SU: I am an academic bench scientist by training where the focus of my doctorate and post-doctorate research was in immunology. I serendipitously learned of an opening at CRI and applied for the position, which was where my real journey into the immuno-oncology (I–O) field began. Since joining CRI 3 years ago, my role has evolved from curating databases in the I–O drug and trials landscape to also supporting our grant programs. As a not-for-profit organization focused on I–O research, we support translational and clinical research as well as fund various academic research grants, and I have had the opportunity to assess how we can be more effective in advancing immunotherapy.

JC: I first became broadly involved in life sciences back in 2003 as an investment banker, and I was then able to migrate over to the corporate side after a decade. In 2017 I joined a company called Immutep which was focused on the I–O target LAG-3, and worked on business development and investor relationships. I then joined CRI in October 2020. Since then, I have worked in the clinical accelerator, engaging with our science network to leverage their understanding of the field to help guide CRI in which clinical trials to pursue. This includes getting to know various investigators and counterparts. As CRI is a not-for-profit, we look to work with third parties and bring in collaborators and I–O combinations to clinical studies.

Q What are you working on right now?

JC: We focus our clinical efforts and ensure that our collaborators' missions align with CRI's mission to save more lives by fueling the discovery and development of powerful immunotherapies for all types of cancer. We have been clinically active for over 12 years, and recently, our focus has turned to platform studies. We also react to interesting initiatives that are brought to us by our investigators. An example of this is some of our work during the pandemic. As COVID patients commonly become severely lymphopoietic, we have worked with a company called RevImmune evaluating their interleukin (IL)-7 therapy in a clinical trial aimed to help cancer patients that contract COVID.

Our focus on platform studies has given us an opportunity to interrogate multiple combinations in a particular tumor type, to allow us to run multiple smaller studies in an indication where each cohort receives a unique combination. These studies are always designed to be hypothesis-driven, with an adaptive design so we can expand a cohort should a predetermined signal be seen. We currently have three active platform studies in prostate cancer, pancreatic cancer, and ovarian cancer.

Q How is the clinical trial landscape for cancer cell therapies currently evolving?

SU: At the clinical accelerator, we have been monitoring the landscape of I–O therapies and clinical trials, including cell therapies. We frequently publish our analyses based on our proprietary database of curated data of the I–O landscape. Over the past three years, we have observed an increase in the overall drug development pipeline for cell therapies. As of spring 2022, there are over 2700 active cell therapy agents in the drug development pipeline, with chimeric antigen receptor (CAR)-T cell therapy leading the modality space.

One area of interest is cell therapies that do not fit cleanly into a category of therapy like CAR-T cells or natural killer (NK) cells. These therapies include dendritic cell therapies, B cell-based therapies, and myeloid-based therapies. In our analyses, we categorized these into 'other' cell therapies for the time being. Recently, this 'other' cell therapy category has seen a dramatic increase, indicating a rising interest in the industry to leverage other types of immune cells.

We also looked at the proteins that are being targeted by cell therapy agents. It is no surprise that the usual suspects, such as CD19, BCMA, and CD22, continue to be the most frequently targeted proteins. However, the exploration of new targets, such as class D G protein-coupled receptors (GPCR5D) and CLEC12A, has also shown a marked increase. In terms of targeting solid tumors, we observed a sharp rise in therapies exploring targets like CLDN18, CD276, and KRAS. We also observe a trend towards a higher year-over-year increase in allogeneic modalities compared to autologous ones.

> "Among community oncologists, the top three reasons cited for not referring a patient to cell therapy centers included the patient's health status..., the cost to patients, and geographic barriers..."
>
> – **Samik Upadhaya**

With respect to the clinical trials landscape, we found 1800 active clinical trials in cell therapy, with a split between hematologic and solid cancer of 60:40. Historically, hematological malignancies comprised the largest bucket of indications that cell therapies were targeting, but in our most recent update, we see that trials in solid tumors have seen the highest year-over-year increase since this analysis began. Cracking the solid tumor code for cell therapies is the 'holy grail' for the field right now and we see a lot of effort there.

Q Where do the issues lie in terms of real-world access to cell therapies?

SU: Compared to our previous analyses, our most recent cell therapy analysis was unique because we specifically focused on real-world access to CAR-T cell therapies. We collaborated with IQVIA, a health information technology and clinical research company to leverage their proprietary datasets.

We see that CAR-T cell therapies are being used in the clinic – however, based on our dataset, we observe that the uptake has been lagging behind US Food and Drug Administration (FDA) approvals. By leveraging surveys conducted by IQVIA, which included 100 community oncologists and 50 oncologists at CAR-T specialized centers, we identified potential sources of barriers impacting CAR-T usage in the clinic. The survey comprised questions about treatments, deferral decisions, and perceptions of cell therapy which included accessibility to treatment, the efficacy of treatment, and the logistics of treatment administration.

Among community oncologists, the top three reasons cited for not referring a patient to cell therapy centers included the patient's health status (which would preclude them from undergoing the treatment), the cost to patients, and geographic barriers (the distance the patient would need to travel to CAR-T therapy treatment sites). Separately, we conducted a survey to assess the diversity landscape for all I–O trials (not just cell therapy) and observed similar findings.

Q Your survey of population diversity in I–O trials outlined the racial and ethnic disparities in trial recruitment. Can you summarize

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the main findings? What are the key barriers to diverse patient enrolment in I–O clinical trials?

SU: We looked at the I–O trials that led to FDA approvals between January 2010 and August 2022. Over this period, FDA approved 92 I–O drugs and combinations across 20+ different cancer indications. In total, this data included over 100 different clinical trials and nearly 60000 patients.

When we looked at the racial and ethnic information that was reported in these trials, one of the first findings we observed was that racial and ethnic demographic information is underreported in pivotal I–O trials. For example, among trials that led to approvals between 2020 and 2022, ~20% did not report any race or ethnicity information, which is something that needs to be improved. We do see a trend of increased reporting over the years, which is encouraging for the field because the more data we have, the more we can understand the barriers. Our data also indicates substantial disparities in the enrolment of Black and African American patients in pivotal I–O trials. Overall, we see a 2% representation of Black and African American patients in trials, while they constitute 13% of the US population.

As a part of this analysis, we conducted a survey to identify barriers to diverse patient recruitment in I-O trials. We learned that geographic barriers (i.e., travel to trial sites) and financial hurdles to patients pose the greatest challenges to recruitment. Our data suggest the need for initiatives to build trust among patients, address racial and ethnic disparities among medical professionals, and build solid relationships with affected communities.

We also found that there is a need to broaden and modernize eligibility criteria in trials. Our findings revealed that some eligibility criteria may disproportionately affect certain racial minority groups. The FDA has proposed guidance and recommendations to broaden and modernize these eligibility criteria to help with diverse patient recruitment.

JC: When looking at the geography of clinical trial sites across the USA, there are clusters at the east and west coasts as well as certain hubs in the middle. As a not-for-profit, we have been advocating for increased access to clinical studies in I–O settings, including breaking down these geographical barriers. In our last publication on the clinical trial landscape, it was found that the enrolment rates (the time it takes to find patients for a clinical trial) for I–O studies have increased for the first time. The lack of access to clinical studies between the coasts is something the industry should focus on for multiple reasons. For patients who have exhausted their current treatment options, the option to get experimental treatment is of key importance. From the industry and research perspective, we require patients who can access these trials to advance the therapeutic development of these candidates. This is an issue that is truly actionable.

We are fortunate that we get to work with some of the leading academic centers around the country and we know that different members of our network of sites are looking to increase their presence and their ability to do this. I look forward to helping support our researchers with the network to increase access for patients.

Q What will be your key goals for your work over the next few years?

> "One of the cornerstones of our clinical strategy is platform studies. Over the next 6–12 months, we are working towards announcing our next cohort or mini-study in our pancreatic and ovarian platform studies."
>
> –**Jay Campbell**

JC: One of the cornerstones of our clinical strategy is platform studies. Over the next 6–12 months, we are working towards announcing our next cohort or mini-study in our pancreatic and ovarian platform studies. This will build upon some of the lessons learned from the prior cohorts. In both of those studies, we have currently enrolled between two and three cohorts, and we are eager to add additional cohorts which will each be treated with a novel combination immunotherapy in that tumor type. We are looking forward to working with our investigators, clinicians, and partners on advancing those studies.

SU: In collaboration with our partners the Canadian Cancer Trials Group, The Mark Foundation for Cancer Research, and Personal Genome Diagnostics (PGDx), we have been participating in a circulating tumor DNA (ctDNA) study, which is essentially a biomarker study to understand whether ctDNA status can be used as a proxy of response for immunotherapy treatments compared to conventional radiographic measurements. The potential for this study is great, and from what we have seen, the I–O field is accelerating towards using non-invasive, cost-efficient, and quick real-time diagnostic approaches to measure response and resistance to immunotherapy. We have been involved in these studies for a few years now and are building upon the learnings and the trajectory that we have seen so far in the studies.

In addition, we have ongoing data curations and publications that we will be working on this year. We are continuing to monitor the I–O landscape in terms of the drugs and clinical trial development pipeline, exploring biomarker usage, and understanding how resistance to immunotherapy is being addressed in the clinical trials space, especially in the anti-PD–1/anti-PD–L1 therapy space. We want to see how the patient inclusion or exclusion criteria look based on prior exposure to those therapies.

We also have a new program launching at CRI called the Clinical Innovator, which is designed to support novel clinical studies that address areas of high unmet medical need in cancer. The main goal is to seek mechanistic insights into clinical response or resistance with the goal of predictive biomarker discovery. This program is open to academic investigators or clinical scientists who are aiming to launch innovative Phase 1/2 or Phase 2 clinical studies using immunotherapies. We are excited to see what the pipeline will bring and what studies we can support.

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JC: One type of study that we have not had the chance of supporting thus far is a cell therapy study for solid tumors. As mentioned, cell therapy in solid tumors is viewed as a 'holy grail'. We want to see if we can translate the potentially curative effects we have seen in the hematological space to the solid tumor setting. CRI is continuing to evaluate opportunities to get involved in the solid tumor space and we are looking forward to the opportunity to support cell therapy studies here, hopefully in the not-too-distant future.

When conducting studies, all parties involved are interested in the clinical response, i.e. whether the therapy is working. CRI prioritizes the translational side of that. When a patient goes to a clinical study and different samples are drawn, the translational aspect is running those samples through different assays and deep diving into the data to understand the mechanistic implications of a therapy. This is one aspect of clinical research that CRI investigates which is often overlooked by other players in the space. We place a lot of value on this because it is how we learn from one study to the next. We can then take those learnings and apply those to our future studies, and communicate those findings to the field so that others can learn from our efforts.

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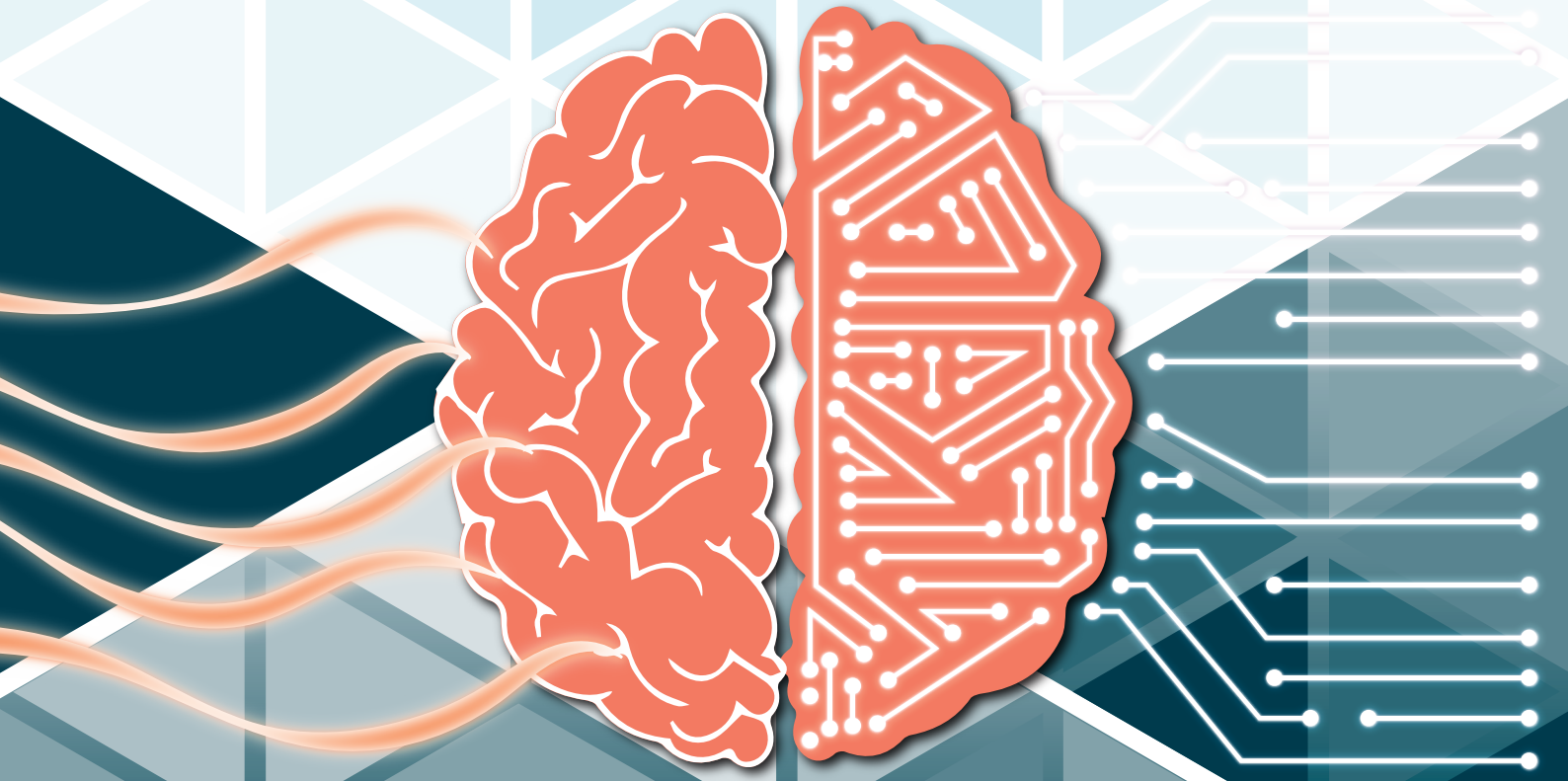
IMMUNO-ONCOLOGY INSIGHTS

AI and machine learning



IMMUNO-ONCOLOGY INSIGHTS

TOOLS & TECHNOLOGIES CHANNEL: AI & MACHINE LEARNING

March 2023

Volume 4, Issue 2

AI AND MACHINE LEARNING

CHANNEL CONTENT

INTERVIEW

Innovation at the intersection of computational biology & immuno-oncology

Abi Pinchbeck, Associate Editor, *Immuno-Oncology Insights*, speaks to **Mi Yang,** Senior Scientist, Sanofi

MI YANG has a dual background in pharmaceutical sciences and cancer bioinformatics, and uses machine learning to elucidate disease mechanisms, with the ultimate goal of new drug discovery and combination. Mi began his training by completing a pharmacist program at the University of Paris-Sud. Later, he obtained his PhD from Heidelberg University in cancer bioinformatics, where he developed methods for drug synergy prediction and mechanistic exploration from cancer drug screening datasets. During his time at Stanford, he designed a computational framework for drug discovery in immuno-oncology. Subsequently, Mi held a position at PrognomIQ, where he conducted research on multi-omics cancer early detection from liquid biopsy. Mi currently works as a senior scientist in oncology bioinformatics for Sanofi.

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This interview will explore his work about employing machine learning tools to investigate the tumor microenvironment and aid immuno-oncology drug discovery efforts.

Q How did you become involved in both immuno-oncology (I–O) and computational biology?

MY: At the end of my PhD at Heidelberg University, I was working on machine learning and artificial intelligence (AI) applied to drug synergy prediction on cancer cell lines. We have extensive molecular insights about the cancer cell, but there is a lack of translatability to the clinics. Cancer cell lines do not faithfully represent primary tumors.

Around 2018, I started to think about switching from studying the cancer cell lines to a focus on I-O, such as answering the key question of why some people respond to checkpoint inhibitors, and why others do not.

Q What exciting developments are you seeing at the junction between machine learning and I–O?

MY: When I became interested in this area in 2018, the space was primarily focused on immune checkpoint inhibitors and patient response, particularly PD–1 and PD–L1. At that time, a lab from Stanford, which I later joined, developed CIBERSORTx, a digital cytometry framework to estimate the fractions of different immune cell types from bulk RNAseq. This now well-recognized tool marked the beginning of the space. CIBERSORTx can also infer cell type-specific gene expression. Prior to the advent of this tool, correlating the gene's expression to an outcome or drug response had limited actionability as the cell type from which the gene was expressed was frequently unknown. With CIBERSORTx, we can know from which cell type a certain gene of interest is expressed, which is hugely important.

The advent of single cell technology has enabled the development of tools for the inference of cell to cell communication, which has been instrumental in studying the tumor microenvironment. Following the success of single-cell technology, spatial transcriptomics has also been developed and answers the question of which cell type is closely located to another cell type. We note there is a strong link between intratumor infiltration of lymphoid cells and treatment response. This is where spatial transcriptomics has huge potential.

Many tools have been developed in the last few years such as Monocle 3 for cellular trajectory, which can be used to measure how far cells have moved in terms of developmental process. It can be used to represent the different decisions a cell has to make to switch from one state to another. Another group of tools I have been working with are deep learning-related tools to predict antigen peptide presentation by human HLA-I/II. This could potentially be used for vaccine development.

Q How can computational tools help to address the current challenges in I–O drug discovery?

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"Computational tools to integrate different omics should also be helpful, such as tools developed in genomics, epigenetics, transcriptomics, and proteomics. Integrating these different omics layers might help to better capture the state of the TME."

MY: First, we need better ways to define the different immune cell types in single-cell data. All the knowledge about cancer cells we acquired using cancer cell lines must be somehow connected to the TME, which does not only involve cancer cells, but also other immune and stromal cells. We need not only to connect our knowledge of the cancer cell to new I-O discoveries but also to bridge the previous tools to the new tools we are developing.

Another goal of I-O computational tools is to help find which immune cells have been recruited by cancer cells and find new subtypes of interest with an application in mind. It is important not to simply find subtypes for the sake of it, but to do so based on how the TME could react to drug response and treatment.

There is also work in the space surrounding machine learning explainability. Even if a model is good at predicting patient survival or response, it must tell us why. Machine learning explainability is extremely important, not just for legal reasons, but also for scientific reasons to gain plausible explanations about the mechanism of action. This can help build an understanding of why a response is happening to enable certain decisions to be made.

Computational tools to integrate different omics should also be helpful, such as tools developed in genomics, epigenetics, transcriptomics, and proteomics. Integrating these different omics layers might help to better capture the state of the TME.

Q You worked on multi-omics machine learning methods applied to cancer detection. Can you tell us more about this technology?

MY: In my previous job, we were building a framework to detect cancer in the early stages while it is still treatable. This involved both a machine learning part and a multi-omics part. The main reason we chose to use multi-omics was that we think it can better capture the true signals of different stages of cancer. There are many different omics involved used to measure blood samples, meaning the detection is non-invasive.

Q How do you see AI and machine learning impacting the I–O space over the next five to ten years?

MY: There are many things in common between the way AI is affecting I–O and the way it affects oncology space in general. Overall, AI and machine learning have led to more rational decision-making, and more and more industry leaders understand the technology's importance. Organizations have evolved to become more database friendly, including in the ways in which data can be stored in a place that can be queried, used, and standardized. That is important for any machine learning exercise.

Recent trends in AI have seen a shift toward the transformer model, with Generative Pre-trained Transformer 3 (GPT-3) emerging as the novel technology of choice. As such, there is optimism that this technology could be leveraged for biomedical research applications in the future.

Overall, data should be established and kept in a format that is 'machine learning trainable'. This means that data scientists should be involved in every step of the data generation process from experimental design to data storage.

Q What are the biggest barriers right now to the progress or more widespread adoption of AI and machine learning tools in oncology?

MY: There are several barriers to the use of AI in organizations: first, data needs to be made more accessible to everyone, both in a way that is easier to query and in a format that can be used for machine learning. Second, data scientists must be real scientists, who are truly interested in the scientific questions. People have their own definitions of what a data scientist should be; some think it is a scientist of the data. I think it is simply a scientist who is using more data and in a clever way. Lastly, any technology that allows the use of human data without revealing it could be an important factor in data confidentiality.

Q What are your hopes for the future of the field – and your fears?

MY: There are lots of things to be optimistic about. For instance, there is much better curated data for clinical trials. It would be advantageous to have more tumor gene expression data, with multi-omics. There are cost issues, in addition to condition issues, such as requirements for all omics before and after treatment.

The promise of liquid biopsy is exciting, as it is non-invasive. There are technologies being developed around this technique, such as new bioinformatics tools for mRNA expression inference. It is a promising technology and I am curious to see how it is going to develop over the next few years.

I hope for the establishment of more AI friendly organizations, and the success of new AI technologies such as deep learning, natural language processing, and transformers. The

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success of these technologies in any field is also a success for us as it contributes to creating an AI friendly environment.

My fears are also connected to hope. It is a huge advantage to have more data, but spending too much money on multi-omics can be an issue. When considering sample size, you need to think about the trade-off between how many patients you want to profile versus how deeply you want to profile, i.e. how many omics you want to perform. Sometimes it is better to connect multiple data sets together from different sources, but you cannot always do that if you spend a lot of money for one data set to have five or six omics. Publishing incentives are not necessarily purpose-driven. You can spend a lot of money to add more omics to a data set, but you must ensure that the new omics are really providing new information. Lastly, we should strive to confront difficult questions, rather than avoiding them. Gathering data for the sake of it without thinking about the AI-driven scientific questions can be problematic, as we can spend a lot of time gathering data and realize it is still not enough.

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AI AND MACHINE LEARNING

CHANNEL CONTENT

INTERVIEW

New tools for spatial biology transcriptomics & proteomics in immuno-oncology

Roisin McGuigan, Editor, *Immuno–Oncology Insights*, speaks to **Mario Flores,** Assistant Professor, University of Texas, San Antonio

MARIO A FLORES is an Assistant Professor of Electrical and Computer Engineering, joint appointment Biomedical Engineering, at the University of Texas at San Antonio. His research includes the development of novel deep learning and AI models that can perform cancer phenotype predictions, identify biomarkers, and generate explainable mechanisms. His lab has developed several genomics-based deep learning (DL)/AI tools for disease gene dependence prediction and identification of regulatory elements dysregulated during cancer progression. At present, his work is focused on integrating spatially resolved transcriptomics, single-cell RNAseq, and RNA fluorescence *in situ* hybridization (FISH) images to characterize the tumor microenvironment in liver models.

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Q What are you working on right now?

MF: I have been at the University of Texas at San Antonio (UTSA) for three years. Prior to that, I was at the National Institute of Health working at the National Center for Biotechnology Information (NCBI), where I began working in artificial intelligence.

"The most important new tools are single and spatial transcriptomics, which are offering a new perspective for the space at the cellular and intracellular level."

When I arrived at UTSA I started working on single-cell analysis of Zika virus in the mouse brain. I then moved to studying liver cancer. A few months later, I became interested in high-resolution spatial transcriptomics technologies.

Now, my two main focuses are on liver cancer and diabetic foot ulcers, which are big problems here in South Texas where we have a large Hispanic population who have a much higher risk of amputation associated with diabetic ulcers. Texas also has a significantly higher proportion of people who develop liver cancer than in any other southern state. I am researching the reasons behind this, including whether there are genetic or molecular components to this. People used to believe that the explanation is simply demographic or lifestyle reasons, but I do not believe that is true.

Q In recent years, what have been the most important advances in terms of the application of computational tools to precision oncology and immuno-oncology?

MF: The most important new tools are single and spatial transcriptomics, which are offering a new perspective for the space at the cellular and intracellular level. With these tools, we are already able to ask questions that we previously would not have even thought to ask, because of the single-cell resolution that we can now work at.

However it's important to emphasize that, with a disease like cancer, you cannot just look at one aspect. Although this is an advanced technology, we should not be so naïve as to think that this is the whole solution. The solution is more likely to be reached by looking at multiple different layers of information.

In addition, we should always continue to utilize the tools and knowledge that have previously been gathered. In the case of pathologists, many of them do not accept the use of this technology and I can understand some of their reasons. However, there is still a lot of interest.

I believe these tools could be used just as a microscope would be, to gain knowledge about molecular components, and in combination with artificial intelligence algorithms, machine learning, and deep learning – which also have their own limitations. We need combinations

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of tools for human experts to use. They will not replace the human experts, but they can be extremely useful to help ask questions that we could not ask before.

Q Where are we seeing these tools begin to impact I–O?

MF: We are already seeing companies using single and spatial transcriptomics to identify molecules that are of interest for further research. I think we will start seeing these tools being used in the personalized medicine space in the next 5–10 years.

These tools provide more information to analyze. For example, if a certain tumor does not respond to established treatments, using this technology could allow further analysis of the tumor tissue, including its heterogeneity, to suggest alternative treatments. This kind of technology can be applied to personalize the solution to these problems.

Q What are the key obstacles to implementing these tools further?

MF: There are two major categories of challenge: technical, and acceptance. Technical challenges include the case of cell segmentation, where it can be difficult to identify the shape of cells, especially in certain sites such as in the brain. In addition, cell typing is a challenge as there is no standardization or standard with which to compare. However while often thought of as complex, technical problems can often be easier to solve with advances in technology.

Acceptance of these technologies within the community will likely come along with standardization. Without standardization across the different companies that produce these technologies, it is going to be very difficult for the field to embrace them.

Q What should be the next target for the field in terms of further improving our knowledge of the underlying biology of cancer, and role do you see machine learning playing in that?

MF: I once heard someone say that whenever we think we have found a solution in the cancer space, the next day we'll find a person it doesn't work for. These technologies will help us gain a better understanding of the bounds of what we call heterogeneity. Heterogeneity is a big problem in cancer, as even within a tumor there are various regions that behave differently at the molecular level.

Once we have more data, I believe that we will be able compare the intratumor heterogeneity across a good number of patients. Then, we can better establish the limits of the complex problem of heterogeneity both across individuals and within the same individual, in a personalized way.

Q What do you see as the current and potential future utility of spatial biology in the I–O field? And how are deep learning approaches helping to better leverage pathology data?

MF: One of the main areas of utility would be to standardize pipelines to be able to categorize individual responses.

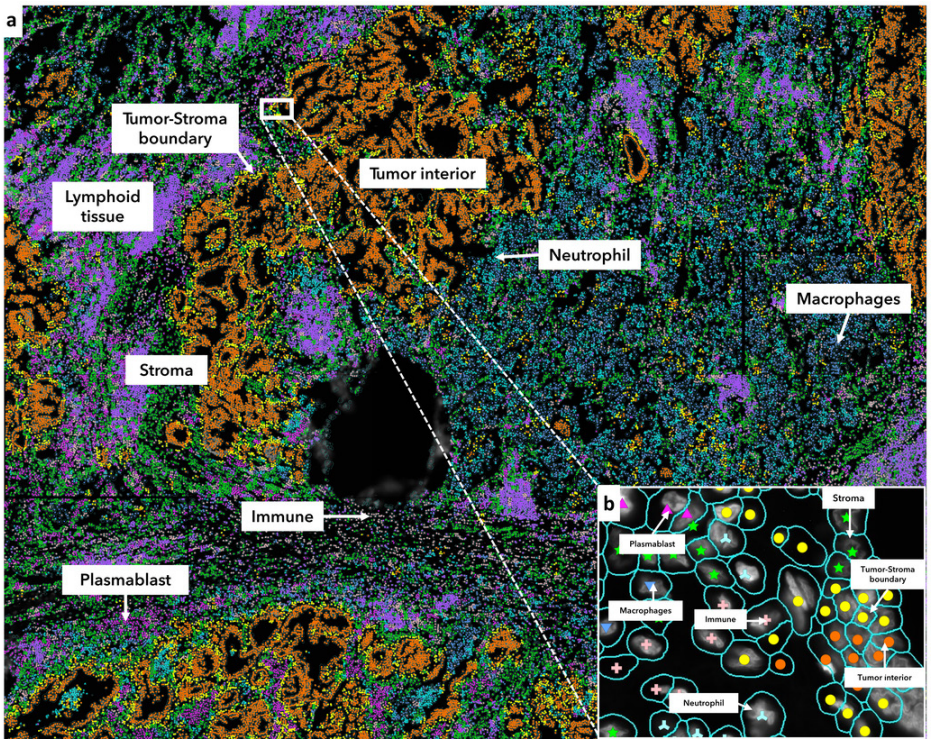
Machine learning can help in two big areas. It can help to categorize immune responses as general responses (ones that we see in most individuals or tumors) or as individual responses that are rarer and more difficult to explain. In the case of spatial biology, we will first be able to categorize responses and then look more closely at the individual ones in high resolution to observe the interactions for those special cases that don't occur often.

With deep learning, we are able to identify patterns that a human would take a long time to find. Using these tools we will reduce the search time. We call this artificial intelligence, but it is not human intelligence – they are great algorithmic machines, so I prefer the term machine learning.

These machines can identify patterns within samples of tumor data. There are millions of individuals with many different characteristics, and machine learning can help us to look at all this data incredibly quickly and in great detail. For example, it could help to find upregulated or downregulated molecules at the tumor-stroma boundary or in the tumor interior, and identify the associations between them that can be used for further study (Figure 1).

FIGURE 1

Spatial visualization of a sample of non-small cell lung cancer.



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A pathologist can use a microscope to identify the regions and the marks that tell you something significant. With a machine learning algorithm, we can train the algorithm with classifications given by a pathologist in order to make predictions. We can put that human expertise into a machine to reduce the search space and reduce time.

Q What are your predictions for this field in the next 5 to 10 years? How do you expect to see big data and computational approaches evolve in that timeframe?

MF: The pipelines today are promising, and I expect technical problems like cell segmentation to be solved. However, standardization will remain the key. I think this might have to come from academia. Recently when I spoke at the 2023 Spatial Biology for Immuno-Oncology Summit, it was clear that many experts from various companies in the field of spatial biology know that standardization is necessary. However, I do not think it will be easy, as each company has to protect its own interests. Government incentives could be used to enable standardization. This would lead to companies more freely sharing their ideas whilst also receiving the benefit of their product being standardized so anyone can use it.

Q What will your own goals be in the next few years?

MF: This year, I want to complete my study on diabetic ulcers severity using electronic health records. My target is to acquire funds to perform spatial transcriptomics studies of diabetic ulcers. I have a collaboration with the San Antonio Vascular and Endovascular (SAVE) Clinic. They have a number of clinics in south San Antonio that help patients on low incomes with diabetic ulcers, and I want to perform sample analysis on some of these patients in collaboration with the clinic.

In the case of liver cancer, I am working on a collaboration with a colleague in Egypt and we have applied for funding. I am planning to obtain samples from ten Hispanic patients and 10 non-Hispanic white patients. We don't want to study just Hispanic populations – the idea is to study them in comparison to other groups in order to identify any molecular element to their risk of disease. We also have a collaboration with a group in Mexico that may provide us with tumor tissue samples. This means we can obtain formalin-fixed paraffin-embedded (FFPE) tissue to do a study on the spatial transcriptomics of liver cancer.

We are also collaborating on separate projects on the use of spatial transcriptomics, including for Zika and COVID-19.

Currently, my interests surround single-cell analysis and spatial transcriptomics. But it is also important to remember that there are other omics and multi-omics, with which we can look not only at transcription but at the single-cell level, like in the case of enhancers, such as using ATAC-seq for open chromatin. I wish I had more time and more students to work with!

Right now, my lab is composed of two PhD students, three master's students, and four bachelor's students working on projects with me. I started working at UTSA in January 2020, right before the COVID pandemic, and it was difficult to recruit any students at that time. When everyone started going back into the lab, I began recruiting. Now, I see many bachelor students who are interested in this type of work and want to learn more. Young people have incredible brains and they are motivated. It is important to give them training and then let them tackle challenges in the field for themselves.

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AUTHORSHIP & CONFLICT OF INTEREST

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