JULY 2023 Volume 4, Issue 6

IMMUNO-ONCOLOGY INSIGHTS

SPOTLIGHT ON

Overcoming mechanisms of tumor resistance part 2: what progress is being made in solid tumors?

Guest Editor
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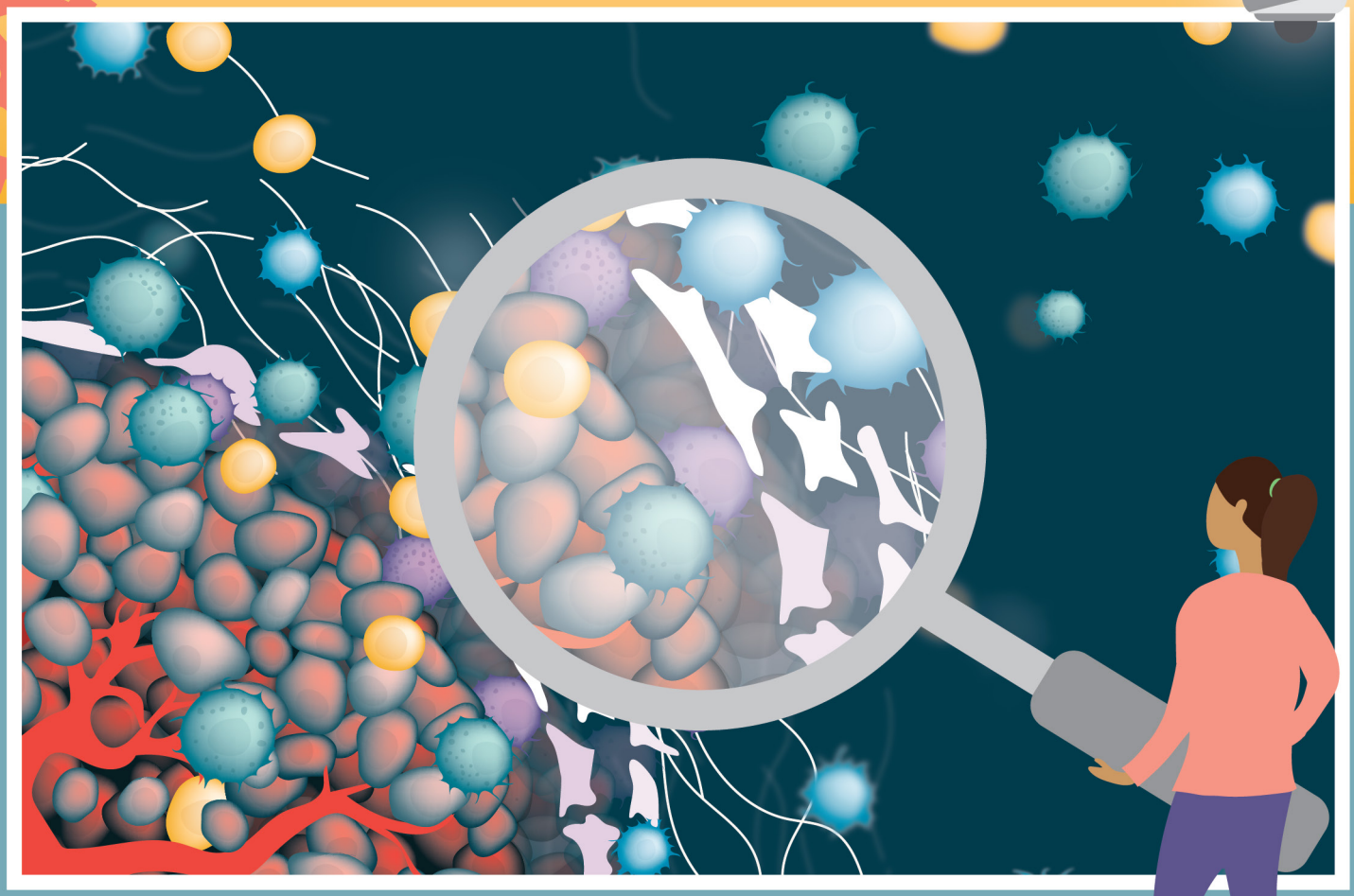

CONTENTS

Spotlight

Overcoming mechanisms of tumor resistance part 2: What progress is being made in solid tumors?

Tools and Technologies

Multiomics

Latest articles

SPOTLIGHT

INTERVIEW

Breaking into the TME with engineered bacteria

Roisin McGuigan, Editor, *Immuno-Oncology Insights*, speaks to **Pedro Correa de Sampaio,** CEO and co-founder, Neobe Therapeutics, about his work utilizing the field of synthetic biology to engineer 'bacterial trojan horses' to overcome biophysical barriers to cancer immunotherapy efficacy.

Immuno-Oncology Insights 2023; 4(6), 227–233

DOI: 10.18609/ioi.2023.030

Q What are you working on right now, and what has been your career journey to get there?

PCDS: At Neobe Therapeutics, we are using synthetic biology to engineer bacteria to remodel the microenvironment of solid tumors as a strategy to enable immunotherapy efficacy in patients that currently do not respond. My journey has been microenvironment-centric, and I was an academic for the majority of my career. I completed my PhD at the University of Cambridge before a postdoc in Houston at the MD Anderson Cancer Center.

My interests have always been in understanding how the different components of the solid tumor microenvironment (TME) interact and affect tumor cell growth, and how they

"There is a lot of promising research on addressing the traditional view of immune 'cold' tumors and immunosuppression, as well as new generation checkpoint inhibitors and chimeric antigen receptor (CAR)-T cells that address immunosuppression through interactions with other cells in the TME."

affect responses to therapies. I started studying vasculature and developing models to study vessel formation in tumors. During my postdoc, I progressed specifically to study the spatial interactions between components of the local tumor stroma and immune infiltrates, which sparked my interest in the problem of immune exclusion. In a significant subset of patients with solid tumors, while there is an immune reaction being generated against cancer cells, you see that immune cells recruited into the macroscopic tumor tissue get trapped on the tumor periphery and stromal regions. The role of the stroma, including the extracellular matrix and cancer-associated fibroblasts in mediating this exclusion was something that I became interested in, and I wanted to address the immune exclusion problem.

As a field, we had been doing a lot of work understanding the microenvironment, and it was finally well accepted that the TME was a significant constraint to the success of immunotherapies in solid tumors. However, I was not seeing many practical solutions reaching the clinic. This set me up on my entrepreneurship journey.

I met with a venture creation studio based in the UK called Deep Science Ventures that were interested in developing new startups in this space. I started working with them to develop ideas around how we could specifically target the obstacles to immune cell infiltration in the tumor without affecting healthy tissues. We came up with the approach of using synthetic biology to engineer bacterial trojan horses to take apart these barriers from within the tumor.

Q If we consider the progress being made by I–O approaches in the solid tumor space so far, what do you see as the most promising avenues—and the biggest remaining barriers?

PCDS: One of the biggest barriers is accessibility. There is a lot of promising research on addressing the traditional view of immune 'cold' tumors and immunosuppression, as well as new generation checkpoint inhibitors and chimeric antigen receptor (CAR)-T cells that address immunosuppression through interactions with other cells in the TME. However, I do not feel that we have been able to make enough progress on the physical aspect of immune infiltration and on the biophysical barriers to getting enough immune cells into the TME.

There are different approaches being developed such as using anti-inflammatories to prevent the deposition of additional components of the extracellular matrix, but these don't

 DOI: 10.18609/ioi.2023.030

address the barriers that are already in place. I am not aware of any approaches out there, at least that are close to the clinic, that directly break down some of these components that trap immune cells in the stroma of solid tumors. This is an area that needs addressing and pharmaceutical companies are aware of this—it's a barrier that we need to jump over if we want to massively increase the efficacy of checkpoint inhibitors and CAR-T cells in solid tumors.

Q Can you expand on the key obstacles posed by the TME—and what approaches are emerging to address them?

PCDS: I think we have two big obstacles. On the issue of immune exclusion and barriers to immune infiltration, there are a few challenges. One of the main ones is that there is still a lot to understand about the heterogeneity of the TME, not just in terms of cancer cells, but of components of the microenvironment itself. We have had a tendency to think about cancer-associated fibroblasts as an overall category of one type of cell in the TME with a fairly monolithic role in aiding tumor progression. We now understand that that is not the case.

There are many different subsets of cancer-associated fibroblasts and some may have a larger effect on the host response against cancer cells, while others may have a larger effect in aiding cancer cell progression. There is still a lot of work to be done to understand the intricacies of the various roles of different subpopulations of fibroblasts in the tumor. In terms of the extracellular matrix, one of the biggest obstacles is the fact that these components, like other components of the microenvironment, are common to healthy tissues and essential for their normal functioning and maintenance.

There is also a delivery issue. How do you address components of the microenvironment in solid tumors specifically, and how do you remodel the solid TME without affecting the structure of healthy tissues? At Neobe, we are working on this by using tumor-colonizing bacteria—but there are other options that have led to promising results, such as nanoparticles, extracellular vesicles, and to some extent viruses. There is a lot of work to be done and many different approaches to target these issues.

As a former academic in this space, the most exciting thing to me is to see the field taking the path toward a more holistic and comprehensive understanding of the heterogeneous TME. This includes understanding that there is not necessarily going to be a one-size-fits-all silver bullet to remodel the TME and make immunotherapies work for everyone. There are different constraints of microenvironments that will be important for therapeutic efficacy in different subsets of patients. We need to understand how these different components work in relationship to each other if we want to drive the field forward.

Cancer vaccines are a particularly exciting area for the future. Part of the reason why these initially did not have the results that people were hoping for is that we needed a better understanding of the inner workings of the immune system, and of which patients were going to respond to these vaccines. Who are the patients for whom this strategy is going to trigger the immune response we want? How do we address immunosuppression in the patients that do not respond? This requires thinking about all of the issues that are associated with a cancer reactive immune response, from immunosuppression with regulatory T cells (Tregs) and

"If you engineer a bacteria to deliver an extracellular matrix remodeling payload into the tumor in a way that is activated by the conditions in the tumor, you can remodel these stromal components without affecting healthy tissues."

myeloid-derived suppressor cells (MDSCs) to accessibility, and considering issues with leaky vasculature in highly fibrotic tumors and those that tend to have the same unique exclusion phenotype. We need to focus on better understanding how all of these issues interact with each other, and which ones need to be prioritized for which patients.

Q What first sparked the idea of your own approach?

PCDS: The idea of using bacteria as a cancer therapeutic is not exactly new. William Coley, who is renowned as the father of immunotherapy, started seeing that patients with bacterial infiltrations could have full tumor remissions at the beginning of the 20th century. It was then left somewhat forgotten, and is now having a rebirth due to an increased understanding of how the microbiome can affect therapeutic responses. The rise of synthetic biology also means that engineering recombinant bacteria to address particular health issues is gaining a lot of traction.

During my postdoc I was involved in a project where we developed a new technology, in the initial stages of the application of spatial biology to cancer. As that field was taking its first steps, we developed multiplex microscopy approaches to understand the spatial interactions between different components of the microenvironment, particularly in pancreatic cancer patients. That was my initial introduction to the correlation between the deposition of the fibrotic components of the extracellular matrix, and how its density and cross-linking affect immune cell distribution into solid tumors.

It was becoming more and more clear that the distribution of immune cells in the microenvironment of a solid tumor was a significant factor that determined whether or not some patients respond to immunotherapies, checkpoint inhibitors, and CAR-T cells. We had known for a while that the extracellular matrix was an important component in solid tumors and an important mediator of therapeutic response, but we still had not been able to take that knowledge and transform it into clinical approaches. When we started investigating why that was, it became clear that the main issue is that the extracellular matrix is essential to maintain the structure of an entire organism. If you develop drugs that break down components of the extracellular matrix and inject them into patients, there is a high likelihood of significant side effects, as the structure of other healthy organs will be damaged. This includes issues like digestive or cardiac side effects.

DOI: 10.18609/ioi.2023.030

I then questioned how we could address this issue. How could we break down the extracellular matrix and take away these fibrotic walls that prevent immune cells from coming into these tumors, but in a way that only affects the tumor? The field of synthetic biology was also exploding at the time and the possibility of engineering cells that respond to particular environmental stimuli and deliver payloads or perform a biological function in a specific space was very attractive to me.

If you engineer a bacteria to deliver an extracellular matrix remodeling payload into the tumor in a way that is activated by the conditions in the tumor, you can remodel these stromal components without affecting healthy tissues. Many people were engineering bacteria for different cancer applications, but most were using bacteria to mediate immune reactions in a more direct way. No one was using bacteria to break down these extracellular matrix barriers to immune cell infiltration.

That led me down the path of creating Neobe. I met my co-founder, Annelise Soulier, who was a talented bacterial engineer working on developing bacterial therapeutics for different disease indications. She had her own ideas of how we could achieve this and about two years ago, we started Neobe and began engineering these products.

Q What have been your most significant milestones to date with this work, and what's next?

PCDS: Whilst we were developing our platform we needed to prove each individual aspect of the strategy. We were able to demonstrate that the bacterial chassis that we are using to develop our products are able to colonize tumors and are safe and well tolerated using *in vivo* models. We then put our platform together and were able to engineer an initial prototype targeted at a specific extracellular matrix component in pancreatic and colorectal tumors.

We used patient-derived tissue explants to show that our initial prototype is effective at breaking down our extracellular matrix target of interest, and that this breakdown can increase infiltration into these tumor tissues and increase the efficacy of T cell-mediated cancer cell killing. We were able to finalize our first patent based on that data, and we are now taking that prototype and a second product targeting triple-negative breast cancer into preclinical development. There is still a lot of preclinical and manufacturing work that we need to do, but our plan is to be in the clinic by 2026 with some initial first-in-human trials. We are excited to get to that point!

Q What are your predictions and hopes for this space over the next 5–10 years?

PCDS: I hope that more attention is paid to exclusion as a mechanism of resistance to immunotherapies, and to the tumor stroma as an important aspect of solid

tumors that needs to be targeted. There has been a lot of work done on reverting immunosuppression and targeting things like Tregs and MDSCs. I hope that the stromal remodeling field takes off because there have been some exciting discoveries in this space. We are only just starting to fully understand the matrisome, which refers to the different components of the extracellular matrix, and how it affects the composition and progression of different tumors. I expect that field to blow up in the coming few years.

The cancer microbiome is also an exciting space, in which we are starting to take our first steps. Over the past year, it has been exciting to see the FDA approvals for Ferring Pharmaceuticals's and Seres Therapeutics's bacterial consortia to treat infectious diseases. I am looking forward to seeing advances and approvals in this space and understanding the interactions between the host microbiome and therapeutic responses to cancer. Specifically, I am excited to see advances in understanding the actual internal microbiome of solid tumors, which is an area that is still in its infancy. Having a much better understanding of how both the microbiome and the mycobiome of solid tumors interact with other components as a microenvironment is key. It has been interesting to see how the microbiome quickly went from a field that many people were skeptical about to a field where each year, promising publications are coming out. One of the most recent ones was Ravid Straussman's paper last year looking at the fungal composition of tumors—i.e., the mycobiome—in addition to the microbiome. How these affect the progression of these tumors and therapeutic responses, and how we can potentially use them to modulate those responses, is an area that I expect to develop in the coming decades.

BIOGRAPHY

PEDRO CORREA DE SAMPAIO is a cancer biologist with a long-standing interest in the study of the tumor microenvironment (TME), as both a mediator of cancer progression and therapy resistance, and an effective therapeutic target. He obtained his PhD from the University of Cambridge, where he initially developed new 3D models to study angiogenesis in solid tumors. Pedro then moved to the MD Anderson Cancer Center in Houston, Texas, for a postdoctoral fellowship studying different cellular components of the TME. Specifically, he co-lead a project developing new technology to assess spatial interactions between different components in the microenvironment. Through the development of this project, Pedro first appreciated the existence of local barriers to immune infiltration in solid tumors that limit the efficacy of existing immunotherapeutic strategies. This led him to return to the UK and work with Deep Science Ventures to co-found Neobe, an early-stage startup engineering bacterial products to remove these barriers to infiltration, with an aim to double the number of cancer patients that respond to immunotherapies.

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DOI: 10.18609/ioi.2023.030

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: de Sampaio PC receives grants/contracts from Innovate UK and CPI. de Sampaio PC also receives consulting fees from Triumvira Immunologics. He has a patent on Neobe's engineered bacteria which is drafted and ready for submission. He is a board member at BIA Engineering Biology Committee. Lastly, he has stocks/stock options Neobe Therapeutics.

Funding declaration: The author received financial support for the research, authorship and/or publication of this article from Deep Science Ventures, Cancer Research UK, Discovery Park Ventures, Nadav Rosenberg, Innovate UK and CPI.

ARTICLE & COPYRIGHT INFORMATION

Article source: This article is based on an interview with Pedro Correa de Sampaio carried out on Jun 2, 2023.

Interview held: Jun 2, 2023; **Revised manuscript received:** Jun 23, 2023; **Publication date:** Jul 12, 2023.

OVERCOMING MECHANISMS OF TUMOR RESISTANCE PART 2. WHAT PROGRESS IS BEING MADE IN SOLID TUMORS?

SPOTLIGHT

INTERVIEW

A wealth of possibilities, but no clear game-changer: tackling the TME with cell therapy approaches

Roisin McGuigan, Commissioning Editor, *Immuno-Oncology Insights*, speaks to **John Haanen,** Director, Center for Cell Therapy at NKI, Amsterdam, about overcoming the barriers posed by the TME using cell therapy.

Immuno-Oncology Insights 2023; 4(6), 221–226

DOI: 10.18609/ioi.2023.029

Q What are you working on right now?

JH: I am a medical oncologist working at the Netherlands Cancer Institute (NKI) in Amsterdam. I also have a 25% appointment as a medical oncologist and Head of Melanoma Clinic at the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland, and I am a Professor at Leiden University Medical Center, the Netherlands, in translational immunotherapy for cancer.

I've been involved in immunotherapy for many years—from before the field became as active as it is now—working on vaccines and cell therapies for immunotherapy applications. I'm a group leader at NKI in cellular therapies and immunotherapy of cancer, and I'm also director of the Center for Cell Therapy at NKI. So I've acquired a number of positions here and elsewhere, all directed towards creating better immunotherapies for cancer patients.

Q How can the success of cell therapies in blood cancers be translated to solid tumor indications?

JH: It's still early days, but we have started seeing responses in solid cancers. So far all the studies are still small, Phase 1 dose-escalating studies. For instance, a study of Claudin18.2-targeted chimeric antigen receptor (CAR)-T cells in gastric cancers was published last year in *Nature Medicine* [1]. I'm also involved in a study with a Claudin6-directed CAR-T cell in patients with metastatic solid cancers like ovarian and testicular cancer patients for whom all prior lines of therapy have failed.

We do see very interesting responses occurring, even including durable partial response or complete response. So successes are possible, but again, it's still early. There are many trials ongoing directed at different targets that are expressed on solid cancers. In general, we can say that the cells do expand the same way as we see in heme malignancies, and the cells can persist for quite a while in some of these patients.

At the moment we are treating truly end-stage patients, but I hope that once we see some initial approvals, we can move to earlier lines where I expect to see more efficacy occurring. One common theme of discussion is that the tumor microenvironment (TME) of solid cancers is quite different from heme malignancies, and the cells we infuse have to be able to infiltrate into these tumors. We know that for some tumors this occurs well. In others it may not occur, or the cells don't persist in circulation, or the TME is already very hostile and there may be initial response but it only lasts a very short time.

When considering ways to improve CAR-T cell therapy for solid cancers, an obvious approach is to combine it with immune checkpoint inhibitors like anti-PD-1/PD-L1, in order to overcome potential resistance that occurs once the cells arrive at the tumor site. There may also be other ways of trying to modulate the TME. One possibility is to increase the number of targets, although this is still an issue in both solid and blood cancers. For instance, we know that CD19, CD22 and BCMA can be safely targeted, although they are expressed on normal tissue. This means the side effects are things we can anticipate and deal with—for example, we can deal with a period of time without B cells, because we can give immunoglobulins.

This may be a very different story in solid cancers if the antigen is also expressed on vital tissue. In this case you cannot use a CAR-T cell because it's too dangerous—but there are ways to overcome this by making expression or activation of the CAR-T cell dependent on the tumor.

To summarize, there are barriers, but we have a variety of potential solutions to overcome them. How exactly these will work in patients is yet to be determined, because most of these

DOI: 10.18609/ioi.2023.029

"There are so many possibilities. One could target multiple antigens. Tumor-infiltrating lymphocytes (TILs) are a way to do this—we can derive them from the TME where they are found naturally, then reactivate them *in vitro* and expand to billions of cells."

trials either haven't begun or are just starting. There is a lot of information to be gathered, and this is something the field can look forward to.

Q What promising avenues do you see in terms of creating cell therapies that can address the known barriers posed by the TME?

JH: There are so many possibilities. One could target multiple antigens. Tumor-infiltrating lymphocytes (TILs) are a way to do this—we can derive them from the TME where they are found naturally, then reactivate them *in vitro* and expand to billions of cells. We know there are T cells targeting different antigens in these TILs. One of the problems with targeting a single antigen, like we do with CARs, is the possibility of escape—for instance, by loss of the antigen or in the case of T cell receptor gene-modified cells, loss of major histocompatibility complex expression or both. With TILs, we can achieve deep responses lasting for many years in some cancers. Melanoma is a good example, and we have seen early promising results in non-small cell lung cancer. TILs can give long-term remissions and perhaps even cures.

This is just one possibility, and there are many more being explored—such as CAR-T cells or T cell gene-modified cells that upon activation start producing cytokines such as IL-12, in order to help overcome the hostile TME by activating dendritic cells and improving the immune response. You can use the T cell as a manufacturing site for all kinds of proteins that are released into the TME. These are currently being explored mainly in preclinical settings.

Q How are approaches in this space currently evolving?

JH: I think that people—especially pharma companies—have focused mainly on anti-PD-1/PD-L1 and CTLA-4 inhibitors. We are now seeing a bit of a broadening into other checkpoint molecules, mostly on T cells and other immune cells like TIGIT and LAG-3. We know that there is some merit in combinations of anti-PD-1 with other T cell-based checkpoints, but I doubt that this is the complete story.

One particular area that needs further investigation is the myeloid compartment of the TME. At the American Association for Cancer Research annual meeting this year, there were

quite a number of presentations focusing on so-called myeloid checkpoints. The idea is to change tumor-associated macrophages that are pro-tumorigenic into more immunogenic macrophages. This may in turn change the results from checkpoint inhibitor treatment. Combining myeloid checkpoint inhibitors with T cell checkpoint inhibitors may seem to be a straightforward method, but it's quite difficult to target myeloid checkpoints because of the high plasticity of these tumor-associated macrophages. Yet another tactic could be to attract other cell types to the TME, such as NK cells, either with CAR NK or even CAR macrophages, and this can also change the TME so that checkpoint inhibitors may function better.

There are so many different areas of research ongoing that involve looking at the TME and trying to overcome the inhibitory factors that are currently present. However, there are many more avenues for cancer to escape immunotherapy than to respond to it. Do we have to find a way to address them all, or are there some dominant forms as we've seen with T cell checkpoints? The jury is still out. We are seeing incremental increases in knowledge in this area, but I have yet to see a true game changer.

Q What about tools and technology—what is the cutting edge, and where are improvements still needed?

JH: The current technologies that we have access to such as single-cell technologies where we can interrogate different cells in the TME on a single-cell level are already a huge achievement. They are giving us a lot of information we didn't have before. The problem is that it's only a static picture. You look at them at a certain time point, but ideally you would like to see things developing over time. How does a new treatment lead to a change? We don't have a good way of doing that yet.

One option is multiple biopsies for neoadjuvant immunotherapies, where we can take biopsies prior to and during treatment, and then we get the full tumor material at surgery. This can help us understand changes inside the TME following certain treatments, and be extremely helpful in giving a better understanding of what we are truly doing with our interventions.

My hope is that once the pharma industry has safety data for new assets in stage four disease patients, they will be able to move earlier into these neoadjuvant settings, and leverage these window of opportunity trials to see how these drugs are changing what is happening inside tumors. This could then teach us the best way to use these therapies in the future.

For some other approaches—such as myeloid checkpoints, toll-like receptor agonists and costimulatory molecules—we don't know exactly how and when to sequence them with the current standard of care immunotherapies. These kinds of trials may also help us in that direction. Going early to these kinds of trials will provide us with new insights into what's happening over time. Approaches using spatial resolution of immune-histology are likely also going to help, but as long as this is static, I'm not convinced it will give us the whole story.

DOI: 10.18609/ioi.2023.029

Q What will you be focusing on in the next few years, and what are your predictions for the field?

JH: I've been mainly focusing on cell therapy development at NKI, and we will go forward in trying to improve on current strategies. Firstly, this will focus on development of TILs. With all the knowledge we have, there are many possibilities to improve this area. Secondly, I will be focused on developing strategies more on the personalized cell therapies side, using T cell receptor gene therapy programs.

Looking at the wider field, I don't think cell therapies can single-handedly solve the challenges of cancer. We are still dependent on a lot of research coming from industry, and I really hope that the pharma side not only focuses on the already existing checkpoints, but comes up with new developments targeting completely different molecules in the TME. I see a movement going in that direction, but it's still early. Perhaps we'll see some breakthroughs, but it is difficult to predict.

Finally, I'd add that single-agent treatment may be important for a very small group of patients. For the majority, we will need combinations. The question, of course, is what will be the best combination for each patient? This is going to be difficult to sort it out, and we will need to continue to gather a lot of data. Newer tools such as single-cell 'omics and AI may aid in answering some of these outstanding questions.

BIOGRAPHY

JOHN HAANEN is Consultant Medical Oncologist, scientific group leader at the Division of Molecular Oncology and Immunology, CSO Immunotherapy and Director of the Center for Cellular Therapy at the Netherlands Cancer Institute (NKI) in Amsterdam, Netherlands. Since 2008 he is endowed professor of Translational Immunotherapy of Cancer at Leiden University Medical Center, Leiden, Netherlands. As of April 1, 2023, he is Head of Melanoma Clinic at Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland (one day a week). From 2009 till 2018 he headed the Division of Medical Oncology at NKI. His current research spreads over development of cellular therapies for solid tumors, neoadjuvant immunotherapies (renal cell cancer, involvement in GI cancers and head and neck cancers), and biomarker research. His clinical specialty is in melanoma and other skin cancers, kidney cancer and management of immune-related adverse events. He co-authored over 500 peer-reviewed articles, is currently Editor-in-Chief of ESMO IOTECH. John Haanen was scientific co-chair of ESMO IO Symposium/ Congress from 2016–2019, and Scientific Chair of the ESMO 2020 Congress. Since 2018 he is member of the Central Committee for Research involving Human Subjects (CCMO).

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1. Qi C, Gong J, Li J, *et al.* Claudin18.2-specific CAR-T cells in gastrointestinal cancers: phase 1 trial interim results. *Nat. Med.* 2022; 28(6), 1189–1198.

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: Haanen J is on the scientific advisory board for Achilles Therapeutics, BioNTech US, Bristol-Myers Squibb, Gadeta, Immunocore, Instill Bio, Neogene Therapeutics, PokeAcel, Scenic, T-Knife and Vaximm. He receives grant support from Amgen, Asher Bio, BioNTech US, Bristol-Myers Squibb, Merck Sharp & Dohme Corporation and Novartis. Haanen J has a consultant role/or on advisory board/role for Bayer, Eisal, Instill Bio, Merck Serono, Merck Sharp & Dohme Corporation, Molecular Partners, Novartis, Pfizer, Roche /Genentech, Sanofi and Seattle Genetics. Lastly he is part of the Manuscript Development Group at SITC.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

ARTICLE & COPYRIGHT INFORMATION

Article source: This article is based on an interview with John Haanen carried out on Jun 19, 2023.

Interview held: Jun 19, 2023; **Revised manuscript received:** Jun 23, 2023; **Publication date:** Jul 26, 2023.

DOI: 10.18609/ioi.2023.029

OVERCOMING MECHANISMS OF TUMOR RESISTANCE PART 2. WHAT PROGRESS IS BEING MADE IN SOLID TUMORS?

SPOTLIGHT

INTERVIEW

Mapping immunotherapy sensitivity with multiomic approaches

Roisin McGuigan, Editor, *Immuno-Oncology Insights*, speaks to **Arutha Kulasinghe**, Group Leader, Frazer Institute, The University of Queensland, about applying muti-omic approaches to understanding the tumor microenvironment.

Immuno-Oncology Insights 2023; 4(6), 235–237

DOI: 10.18609/ioi.2023.031

Q Can you tell us a bit about yourself

AK: I'm a Group Leader and Senior Research Fellow at the Frazer Institute, University of Queensland. My lab focuses on understanding the tumor microenvironment in lung, head and neck, and skin cancers using a lens of spatial biology. Spatial profiling enables us to understand how cells communicate within a tumor, and with the surrounding immune context. This is important as locations, activation, and signaling between these cells can provide us with cues for which therapies may work in which patients. Our focus at the moment is on understanding immunotherapy sensitive and resistant disease.

"Metabolic mapping of the tumor microenvironment is one of the most exciting spaces currently. It's giving us insights into how different areas of the tumor microenvironment metabolize glucose. These areas of high metabolic activity tend to highlight areas of therapy resistance."

We traditionally used unbiased whole transcriptome profiling of the tumor microenvironment to discover new markers associated with therapy response and resistance. We've recently pivoted to ultra high-plex spatial proteomics as a discovery tool, as this is very much aligned with pathology-interpretable signals. We are excited about developing spatial 'signatures' and 'scores' that may be predictive of benefit of therapy.

Q What impact are these tools having on our understanding of the underlying biology of solid tumors and the tumor microenvironment?

AK: They're providing a new lens of discovery for understanding therapy responses across a number of solid cancers. We are able to gain an understanding of how tumor cells communicate with their environment, the types of cells In close proximity, the different cellular neighborhoods, and how these change during different stages of cancer development.

However, these technologies are often quite cost-intensive and as such we need to plan the most cost-efficient experiment—this can often mean that we use tissue microarrays (many core biopsies per slide, e.g., 45 patient samples) as opposed to 45 whole slides which would cost a lot more. With time, the costs of these assays will come down, but as we're on the bleeding edge, these come at a premium.

Metabolic mapping of the tumor microenvironment is one of the most exciting spaces currently. It's giving us insights into how different areas of the tumor microenvironment metabolize glucose. These areas of high metabolic activity tend to highlight areas of therapy resistance. In our own recent study looking at creating a spatial metabolic map of immunotherapy sensitivity in lung cancer, we showed that areas of high glucose uptake had lower levels of T cell infiltration and B cell/lymphoid structures.

Q What about the search for better biomarkers of response?

AK: Using the spatial profiling of the tumor microenvironment, we can start to identify new biomarkers associated with response and resistance to therapy, as a

DOI: 10.18609/ioi.2023.031

discovery tool. We can then screen these markers using a lower-plex panel (e.g., 10–15 biomarkers) in a high-throughput manner to determine their utility for the clinic.

Q What's next?

AK: The development and uptake of spatial signatures in translational cancer research studies and a move towards adopting spatial-scores. Using spatial biology, we'll be able to discover new cell types, neighborhoods and receptor-ligand interactions which may be new targets for immunotherapy.

BIOGRAPHY

ARUTHA KULASINGHE leads the 'Clinical-oMx Lab' at the University of Queensland. Dr Kulasinghe has pioneered spatial transcriptomics using digital spatial profiling approaches in the Asia-Pacific region, contributing to world-first studies for lung cancer, head and neck cancer, and COVID-19. His research aims to understand the underlying pathobiology by using an integrative multiomics approach.

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AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: Kulasinghe A discloses he receives consulting fees from European Spatial Biology Center.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

Article source: Invited.

Revised manuscript received: Jun 26, 2023; **Publication date:** Jul 12, 2023.

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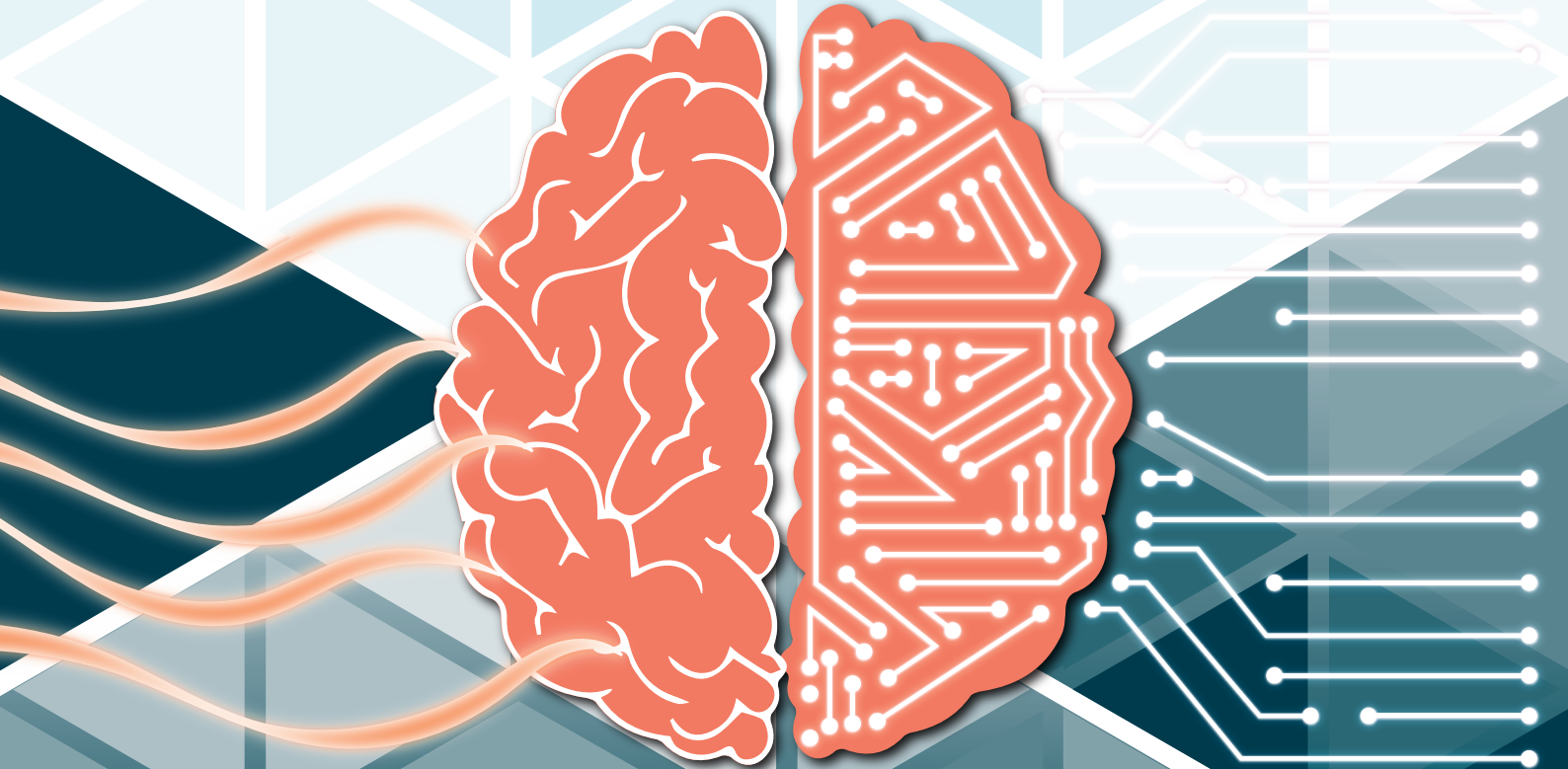
Multiomics



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July 2023
Volume 4, Issue 6

INTERVIEW

Applying multiomics to novel target discovery in immuno-oncology
Eran Ophir & Yaron Turpaz

MULTIOMICS

CHANNEL CONTENT

INTERVIEW

Applying multiomics to novel target discovery in immuno-oncology

In this episode, **Róisin McGuigan,** Editor, *Immuno-Oncology Insights*, speaks with **Eran Ophir,** Chief Scientific Officer, Compugen, and **Yaron Turpaz,** Senior Vice President and Senior Advisor, Data and Informatics Solutions, Compugen, about the advantages of using multiomic and computational approaches for the discovery of novel targets and mechanisms of action (MoA) of novel drug candidates in immuno-oncology.

Immuno-Oncology Insights 2023; 4(6), 249–255

DOI: 10.18609/ioi.2023.034

Q What are you working on?

EO: I'm responsible for the scientific strategy from computational target identification, to experimentally validating the novel targets that we identify and studying their biology, then once in the clinic identifying biomarkers, indication selection, and studying the MoA of first-in-class drug candidates against the novel drug targets.

YT: I lead the Data and Informatics Solutions team, and work on the analytics, machine learning, and application of target and biomarker discovery with a focus on immuno-oncology (I–O) as the main theme of Compugen. In terms of background, I've been in the pharmaceutical industry, genomics, and biotech companies, leading data science and software development teams.

Q Can you outline how you are applying multiomics to novel target discovery in the I–O space?

YT: At Compugen, we integrate data from multiple sources of omics information, both those available in the public domain and those generated in-house as proprietary data. We focus on genomics and transcriptomics. In our newly adopted technologies, we are focusing on single-cell transcriptomics as well as spatial transcriptomics. When clinical metadata is available from the source of the tumors or the patient's data, we integrate that as well. We are building predictive models to help us identify novel targets. As we identify different targets with potential novel mechanisms of action, we work to better understand the specific indications in which those targets would be found and would make an impact.

We also try to understand resistance mechanisms based on this omics analysis and study aspects of patient stratification that relate to biomarkers. This is a more challenging aspect within I–O, but it gives us a new resolution and insight into the biology of the tumor and the patient.

Q What advantages do multiomics approaches offer? What is the cutting edge currently in this space?

YT: We now have an opportunity to gather insights into the biology in an unprecedented resolution. With single-cell and spatial transcriptomic approaches, it is like having a microscope that looks into a depth that has never been seen before. We have the ability to look at each cell type within the tumor and its microenvironment and understand its three-dimensional orientation and level of gene expression.

That level of insight is fascinating from a biology perspective, but it is also impactful and useful in the discovery of novel targets and new mechanisms of action within I–O.

We are also using proteomics and immunohistochemistry imaging to identify different patient responses. We combine image analysis, omics analysis, clinical metadata, and a proprietary knowledge base that has been built over the years at Compugen to help us derive powerful insights.

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"By using multi-omics analysis, looking at the data from different angles, and using our proprietary algorithms, we are able to identify novel I–O targets. Once the target is identified, it is important to identify the right indication, or the rightpatients, that will benefit the most from this treatment."
— Eran Ophir

Q Can you tell us more about Compugen's computational approach to developing its I–O pipeline?

EO: I–O and immunotherapy revolutionized cancer treatment. Certain tumor types went through dramatic changes in the paradigm of treatment, although many patients still do not respond to immunotherapy treatments. We use multiomics data and unique algorithms that Yaron described to identify novel targets in the field of I–O, and to discover mechanisms of resistance for current therapies.

By using multiomics analysis, looking at the data from different angles, and using our proprietary algorithms, we are able to identify novel I–O targets. Once the target is identified, it is important to identify the right indication, or the right patients, that will benefit the most from this treatment. This can be predicted even before starting clinical trials by using our data sets and different computational approaches.

Once we start treating our patients, we invest a lot of effort into multiomics analysis of the samples taken from the patients treated with our drugs. For example, we analyze serum samples for 1,500 proteins from patients' blood, sequence biopsies from patients pre and on-treatment, and analyze specific markers in biopsies from patients and more. We combine all of that data to fine-tune the exact patient indication that will respond best, and ideally find a biomarker to select the patient who will benefit the most from our treatment.

YT: We aim to achieve a multidimensional view of the problem. There is a higher chance of identifying the true biology and the mechanism of action when you take different views, using different sources of data and different algorithms and predictive models.

Q What have been your biggest milestones to date in terms of this work? And what's next?

EO: More than a decade ago, we computationally identified a checkpoint T cell immunoglobulin and ITIM domain (TIGIT). It was around the same time that Genentech identified this checkpoint. A few years later, we discovered another player in the same pathway.

This pathway is called the DNAM1 axis, which also contains the poliovirus receptor-related immunoglobulin domain containing (PVRIG) gene. We were the first to identify this novel target.

Following this identification and after studying the DNAM1 pathway for some time, we are now leading clinical trials evaluating the triple blockade of TIGIT and PVRIG with PD-1. This is based on our understanding of this path in patients with hard-to-treat cancers in places where checkpoints do not normally work. This is a great example of how we took drug targets from novel target identification computationally all the way to the clinic, where we are actually seeing clinical signals.

We have encouraging Phase 1 data mainly in two indications which are typically not responsive, not only to I–O: platinum-resistant ovarian cancer and microsatellite stable colorectal cancer. We are now in ongoing clinical studies again with a triple blockade using our COM701 and COM902 antibody compounds, which target PVRIG, TIGIT, and pembrolizumab to confirm the clinical signal in larger patient numbers. AstraZeneca is using our TIGIT antibody as part of their PD-1/TIGIT bispecific antibody, for which they expect to start Phase 3 studies later this year. Overall, the DNAM1 axis that we identified computationally is a major milestone for Compugen and hopefully, we will take it all the way to clinical approval.

More recently, we computationally identified another resistant mechanism in cancer. We identified a known protein, interleukin-18 (IL-18) binding protein (BP), and found a novel way to target it. IL-18 is a potent cytokine found in increased levels in the tumor microenvironment, but is blocked by an IL-18 BP. Using multiomics approaches and big data we identified this specific resistant mechanism, and subsequently we have obtained preclinical results that show blocking this interaction with an antibody leads to modulation of the tumor microenvironment, and unleashing the natural activity of IL-18 to stimulate immune activation.

This approach modulates only the tumor microenvironment without affecting the periphery, which suggests a beneficial therapeutic window and therefore hopefully, efficacy without toxicity. This is the holy grail in cytokine treatment.

YT: The beauty of generating internal data that progresses targets in the pipeline is that every piece of data, both positive and negative, can feed back into the knowledge base. This allows us to continually optimize and train the algorithm. Our knowledge base continuously gets fed with validation results from experiments and strengthens our confidence in the initial hypothesis generated by the computational approach.

Q The development of diagnostic and prognostic biomarkers remains a key challenge for the I–O space. How can computational approaches help in these efforts?

EO: When targeting specific surface markers on the tumor cell with a toxin or a small molecule, if the surface marker or mutation is not there, there is no reason to treat this patient. For example, if there is no HER2-positivity on the tumor, you would not treat it with HER2 targeting agents. The biomarker for these kinds of treatments is relatively straightforward.

DOI: 10.18609/ioi.2023.034

"We are both contributing to and utilizing the global community effort of development. Over the coming decades, as those technologies are matured and are utilized in I–O target and biomarker discovery, it is exciting to think about what further developments will come."
— Yaron Turpaz

When it comes to I–O, it is much more challenging. Eventually, you want to modulate a complex immune system to treat cancer. The biomarkers are not straightforward. PD-L1 is the only one which is currently relevant, but we do need more and better biomarkers for I–O.

Multiomics analysis and computational approaches can be combined to find complex gene signatures and the modalities of biomarkers to identify patients who will respond the best. This is exactly what we try to do at Compugen. We take samples from patients treated in our trials and we analyze them with multiple omics analysis. We then integrate that computationally to differentiate between responder and non-responder, and try to identify the more complex biomarkers, which could be relevant for selecting patients for trials. This is an approach that could also be employed for other I–O agents.

Q What would be at the top of your wishlist for new tools or innovations in this space?

YT: One of the challenges from a data scientist's point of view is that you are always thirsty for more data. Within I–O and the discovery of biomarkers, we are always in need of larger-scale I–O datasets that include both high-quality, longitudinal patient response information, as well as multidimensional omics characterization of the tumor. This is expensive to generate on a large scale, so we look forward to having a more global community effort in generating such data, which can then feed into our algorithm and predictive models.

Both single-cell and spatial transcriptomics are relatively new technologies still in the growth process. This is true for both the actual instrumentation and the assays that are becoming more robust and accurate over time, as well as the algorithm for downstream data analysis. We are both contributing to and utilizing the global community effort of development. Over the coming decades, as those technologies are matured and are utilized in I–O target and biomarker discovery, it is exciting to think about what further developments will come.

EO: People often talk about employing AI in I–O prediction of biomarkers, but to have an efficient AI, you need to have a decent training set. For this, you need big data. We need a community-based effort, as many people are not currently sharing data, especially commercial organizations. Incorporating these cutting-edge technologies into the

day-to-day clinical facilities to generate a large amount of data that should be publicly shared is the key. We would then be able to employ more sophisticated AI and other data mining tools for data identification and potentially even better biomarker selection. At Compugen, we put a lot of effort into generating this data, as well as developing sophisticated tools to take limited amounts of data and utilize it as if it were big data. This is a challenge, but we are making the best out of the limited data we have available.

BIOGRAPHIES

ERAN OPHIR serves as Chief Scientific Officer, responsible for the company's scientific, translational medicine and biomarker strategy, underlying the Company's innovative portfolio of product candidates, overseeing computational discovery and the research and drug discovery activities. Eran brings significant expertise in immunology and immuno-oncology from his research work at the Weizmann Institute of Science and the Ludwig Institute for Cancer Research in Lausanne, Switzerland. Eran joined Compugen in 2015 as a senior scientist and has since held various positions in the R&D department, with increasing responsibilities including appointment to the management team in March 2020 and Senior Vice President of Research and Drug Discovery in April 2022. Eran received a BSc in Bioinformatics from Tel Aviv University and a PhD in Biology from the Weizmann Institute of Science.

YARON TURPAZ was appointed as Senior Vice President and Senior Advisor, Data and Informatics Solutions in May 2023. In his role Yaron is responsible for the overall data flow inside and outside the organization. Yaron supports the Computational Discovery unit in the ongoing development of the computational platforms, and also oversees the establishment of systems for data analytics across the organization. Yaron joined Compugen in 2019 as Senior Vice President and Senior Advisor, Computational Discovery. Yaron has more than 15 years of experience in the fields of research and development informatics, data sciences, and technology in the biotech and pharma space with hands-on experience using cloud-based high throughput computational, machine learning and genomics platforms for drug discovery and development applications in precision medicine. In his extensive pharma and biotech career, he has held senior R&D Informatics roles at Human Longevity, AstraZeneca, Eli Lilly, Global Gene Corp. and Affymetrix. Yaron continues to serve as Chief Information Officer and Senior Advisor at Engine Biosciences. Yaron received a BSc in Biology from Tel Aviv University, a PhD in Bioengineering from the University of Illinois and an MBA from the University of Chicago, Booth School of Business. He also held an Adjunct Assistant Professor position at the Centre for Quantitative Medicine of Duke-National University of Singapore, Graduate Medical School.

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DOI: 10.18609/ioi.2023.034

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.
Acknowledgements: None.
Disclosure and potential conflicts of interest: Ophir E and Turpaz Y work for Compugen. Turpaz Y discloses that he serves as Chief Information Officer and Senior Advisor at Engine Biosciences. The authors have no other conflict of interests.
Funding declaration: The authors received no financial support for the research, authorship and/or publication of this article.

ARTICLE & COPYRIGHT INFORMATION

Article source: This article is based on a podcast with Eran Ophir and Yaron Turpaz which can be found here.
Interview held: Jul 11, 2023**; Revised manuscript received:** Jul 27, 2023; **Publication date:** Aug 8, 2023.

We hope you enjoyed reading this interview.
You can also listen to the recorded podcast here:

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JULY 2023 Volume 4, Issue 6

IMMUNO-ONCOLOGY INSIGHTS

LATEST ARTICLES:

INTERVIEW

Modulating the tumor microenvironment through chemokine disruption

Roisin McGuigan, Commissioning Editor, *Immuno-Oncology Insights,* speaks to **Avital Barak,** VP of Clinical Development and Medical Affairs, TME Pharma, about chemokine inhibition as an approach to modulating the TME, current tools and approaches to tackling the tumor microenvironment, and the explosion of innovation in this space.

Immuno-Oncology Insights 2023; 4(6), 243–248

DOI: 10.18609/ioi.2023.033

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

AB: As VP of clinical development and medical affairs at TME Pharma I am responsible for designing and implementing clinical trials to assess the safety and efficacy of our drug candidates. I'm also involved in analyzing and interpreting clinical trial data and ensuring compliance with regulatory requirements.

In addition, I interact with key opinion leaders and present our data at conferences, and am involved in pharmacovigilance activities to ensure that our treatments are safe and well-tolerated.

Q Can you give me an overview of TME Pharma's current I–O pipeline?

AB: Currently there are two assets in our pipeline—NOX-A12 and NOX-E36. They are both L-stereoisomer RNA aptamers—dubbed Spiegelmers—and were originally discovered

using TME Pharma's proprietary Spiegelmer platform technology. Spiegel in German means mirror, referring to a mirror image of the RNA aptamers.

NOX-A12 is an inhibitor of the chemokine CXCL12 and NOX-E36 is an inhibitor of the chemokine CCL2 and some other related chemokines. Both molecules bind and neutralize their targets, and due to their non-natural stereochemistry, they are resistant to nuclease degradation and do not elicit a response from the innate immune system. Chemokines are molecules that orchestrate the trafficking of immune cells as well as bone-marrow-derived cells involved in tissue repair, and by neutralizing them, we can modulate the TME from immunosuppressive to immunoactivated and prevent repair of damaged tumors.

For NOX-A12, we have a running Phase 1/2 trial in first line O6-methylguanine-DNA methyltransferase (MGMT) unmethylated (chemotherapy resistant) glioblastoma showing promising results. In addition, we have an ongoing scientific collaboration with Merck in pancreatic cancer and we recently opened an investigational new drug (IND) for a Phase 2 study in the US. We are also exploring the potential to treat solid tumors with NOX-E36.

Q What have been the most significant milestones to date, and what's next?

AB: Our most significant milestones are the amazing discoveries we had in the GLORIA glioblastoma trial; we found a potential predictive biomarker in patients receiving NOX-A12 and radiotherapy which could tell us which patients will respond best to our treatment. In the treatment arm receiving NOX-A12, radiotherapy, and the anti-VEGF antibody bevacizumab, all patients had a radiographic tumor response and 83% of patients are still alive at a 15-month time point. The median survival for this population is expected to be around 10 months. In addition, earlier this year we opened an IND in the US, which is the first time that NOX-A12 has been authorized for clinical trials in the US.

Q Outside of your own work, what promising approaches or innovations do you see in terms of creating therapies that can address the barriers posed by the TME?

AB: The field is currently bursting with interesting innovations. Some of the approaches currently being investigated include targeted therapies, which aim to specifically inhibit molecular targets that are essential for tumor growth and survival. By identifying genetic mutations or specific proteins present in cancer cells or the tumor microenvironment (TME), these therapies can disrupt key signaling pathways involved in tumor progression while sparing healthy cells.

Another growing field is nanomedicine and targeted delivery. Nanoparticles and nanotechnology-based approaches are being explored to deliver therapies directly to the TME. These

DOI: 10.18609/ioi.2023.033

"By targeting different aspects of tumor biology simultaneously, combination therapies can improve treatment efficacy and overcome resistance mechanisms."

approaches can improve drug accumulation in tumors, enhance drug stability, and overcome barriers such as poor penetration into the tumor tissue or drug resistance mechanisms.

And of course, immunotherapies, such as immune checkpoint inhibitors, bispecific antibodies, and CAR-T cell therapy, have also shown promising results in leveraging the body's immune system to target and destroy cancer cells. These therapies can help overcome immune suppression within the TME by blocking inhibitory signals or enhancing the immune cell activity of the adaptive immune system. Unfortunately, not all solid tumors react to the increased stimuli and treatment can lose its efficacy over time. Recently, the importance of myeloid cells in the overall balance of the fighting immune system has become more evident.

A further area of growth is in TME modulation and targeted drug delivery. In addition to malignant cells, the TME includes a multitude of non-cancerous cells and extracellular matrix components which contribute to tumor establishment, growth, and therapy resistance. Modulating the TME using agents that target specific stromal components or disrupt signaling interactions can improve drug delivery and enhance treatment response. Developing drug delivery systems that can selectively deliver therapies to the TME is an area of active research. These systems can be designed to release drugs in response to specific TME characteristics, such as low pH, high enzymatic activity, or altered oxygen levels, thereby increasing treatment effectiveness. Anti-VEGF drugs are a well-known example for the blockage of angiogenesis. NOX-A12 is another good example that modulates the TME, reducing immune-suppressive monocytes, whilst also preventing vasculogenesis.

As evident from classical chemotherapeutic approaches, most of which are cocktails of different compounds, finding the right combination is key to developing successful new treatment options. Combining multiple treatment modalities, such as chemotherapy, radiation therapy, immunotherapy, and targeted therapies, has shown promise in addressing the complex nature of the TME. By targeting different aspects of tumor biology simultaneously, combination therapies can improve treatment efficacy and overcome resistance mechanisms. Good biomarkers, particularly predictive biomarkers, will be an extremely important aspect to enable the optimal use of available drugs.

Q What should be the next specific targets for the field?

AB: Improving our knowledge of the underlying biology of the TME is an ongoing area of research with several specific targets and unanswered questions. The TME consists of diverse cell types, including immune, stromal, and cancer cells. Understanding the

heterogeneity and spatial organization of these cell populations is crucial for identifying key players and interactions. Further investigations are needed to unravel the roles of specific cell subsets and their contributions to tumor growth, invasion, and therapy response.

Another challenge surrounds mapping signaling pathways and crosstalk between cells. Signaling pathways within the TME regulate critical processes, such as immune cell activation, neovascularization (both angiogenesis and vasculogenesis), and tissue remodeling. Elucidating the complex signaling networks and crosstalk between different cell types will enhance our understanding of TME dynamics and potential therapeutic targets.

A further challenge lies in unraveling immune suppression mechanisms. The TME can create an immunosuppressive environment that hinders immune cell activity and facilitates tumor immune evasion. Identifying the mechanisms responsible for immune suppression, including immune checkpoints, regulatory T cells, and myeloid-derived suppressor cells, is essential for developing strategies to overcome immune resistance.

TME plasticity and adaptation also require further exploration. The TME is highly dynamic and can undergo changes in response to therapeutic interventions, leading to treatment resistance. Investigating the mechanisms underlying TME plasticity, such as epithelial-to-mesenchymal transition or metabolic adaptations, will provide insights into how tumors adapt and evolve, guiding the development of effective therapeutic interventions.

Finally, TME-driven metastasis needs investigation. The TME influences cancer cell dissemination and metastatic spread. Understanding the processes that promote metastasis, such as such as dissemination of tumor cells via the bloodstream, extravasation vascular formation, tumor cell intravasation, extravasation, and colonization of distant sites, is crucial for developing strategies to prevent or target metastatic disease.

Q What tools or approaches will be key for these efforts?

AB: I see several new and upcoming tools and approaches: *in vitro* analyses is like single-cell analysis, omics approches such as genomics, transcriptomics, proteomics, and metabolomics, and computational modeling and bioinformatics might be able to help decipher TME interactions, predict responses to therapies, and identify potential biomarkers for patient stratification. In order to explore TME biology *in vivo*, animal models can will continue to play an important part, including genetically engineered mice and patient-derived xenograft models.

Clinical assessments during and after clinical trials are crucial for the understanding of ever-changing tumors and their TME. Advanced imaging techniques, in addition to standard MRIs, can provide more information regarding tumor development. For example, in our GLORIA trial, diffusion/perfusion, cerebral blood volume, and tumor burden are being measured to differentiate better between progression and pseudo-progression, to assess if a patient is responding to treatment. Pathological evaluation of patient biopsies provides valuable information, and multiplexed immunofluorescence staining allows for simultaneous

DOI: 10.18609/ioi.2023.033

"The future is progressing towards a greater level of personalized medicine where treatments are tailored to individual patients based on their specific tumor characteristics, including the TME."

visualization and quantification of multiple markers within intact tissues, providing a comprehensive view of the cellular composition and spatial organization of the TME.

A great challenge still to be addressed will be finding predictive biomarkers to assist in targeting the population that will benefit most from the treatments.

Q What are your predictions for the next 5–10 years in this space?

AB: The future is progressing towards a greater level of personalized medicine where treatments are tailored to individual patients based on their specific tumor characteristics, including the TME. Advances in genomic profiling, biomarker identification, and technologies for assessing the TME's molecular features may lead to more precise and targeted therapies. Having a predictive biomarker could help find patients that will benefit from treatment.

Integration of AI, big data, and machine learning algorithms could assist in better understanding complex networks. The development of novel therapeutic approaches, like nanoparticles, might lead to the discovery and development of new therapeutic approaches specifically targeting the TME. Combination therapies that leverage the strengths of multiple treatment modalities are likely to continue to be explored. Understanding the complex interactions within the TME and designing treatment regimens that target multiple pathways simultaneously will hopefully lead to improved treatment outcomes.

BIOGRAPHY

AVITAL BARAK is the Vice President of Clinical Development and Medical Affairs at TME Pharma, an innovative clinical-stage biotechnology company based in Berlin. TME Pharma's primary focus lies in pioneering novel therapies to combat the most aggressive forms of cancer, specifically targeting the tumor microenvironment (TME) where cancer cells thrive. Prior to joining TME Pharma, Dr Barak had several roles at Miltenyi Biomedicine, initially contributing to early development and later leading as the Head of Medical Affairs in Europe, where she promoted various cellular therapy programs. She earned her MD from the Hebrew University in Jerusalem, underwent intensive internal medicine residency training and also practice hematology at Tel Aviv Medical Center Hospital. Moreover, Dr Barak holds a PhD in Immunology from the Weizmann Institute of Science.

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Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given her approval for this version to be published.
Acknowledgements: None.
Disclosure and potential conflicts of interest: Barak A is an employee of TME Pharma AG. She also has stocks/stock options from TME Pharma AG.
Funding declaration: The author received no financial support for the research, authorship and/or publication.

ARTICLE & COPYRIGHT INFORMATION

Article source: This article is based on an interview with Avital Barak carried out on Jul 4, 2023.
Interview held: Jul 4, 2023; **Revised manuscript received:** Jul 20, 2023; **Publication date:** Aug 23, 2023.

DOI: 10.18609/ioi.2023.033

FASTFACTS

Using a data-driven approach to deliver complex studies in advanced therapeutics

Vito Romita PhD, Senior Director, Global Project Management, PPD & **Jai Balkissoon MD FACS,** Medical Science and Strategy Lead, Immuno-Oncology, Cell and Gene Therapy, PPD

Cell therapy clinical trials can pose complex challenges due to a number of factors, including cell harvesting logistics, manufacturing, shipments back to sites, patient safety, changing standard-of-care treatments, and patient enrollment due to competing trials—all of which can impact study timelines. In this poster, specific data-driven approaches for cell therapy clinical trials that can help avoid enrollment challenges and delays in study timelines will be explored using case study examples.

CHALLENGES IN ONCOLOGY CELL THERAPY DEVELOPMENT

The first identified challenge for the development of cell therapies in oncology is identifying, training, and qualifying non-traditional research-experienced sites to participate in cell and gene therapy clinical trials and treating patients with approved standard of care cell and gene therapies in their communities. This requires cell therapy-experienced CROs, sponsors, academic sites, research-experienced community sites, payers, and regulators to collaborate.

Secondly, autologous cell therapies that are genetically modified pose the challenge of long vein-to-vein times that includes apheresis, manufacturing, and shipment of cryopreserved cells back to sites for a single infusion of cells into one patient. Allogeneic or off-the-shelf cell therapies can help alleviate some of these challenges by avoiding the need for patient apheresis, a supply of cells from healthy volunteers or cord blood with cells readily available to infuse into many patients without significant manufacturing delays. Patients receiving allogeneic cell therapy could receive multiple infusion with potential for improved antitumor activity.

The third challenge is preventing and managing the toxicities associated with cell therapies, such as cytokine release syndrome and neurotoxicity. The potential for severe and sometimes life-threatening toxicities requiring hospitalization has prevented these advanced cell therapies from being used by community oncologists. Future cell therapies need to have fewer toxicities and we need to identify biomarkers that can predict early onset of toxicities and determine which patients are more likely to develop severe life-threatening toxicities. Developing a one-size-fits-all lymphodepletion regimen prior to cell therapy infusion would also be advantageous.

PARTICIPATION IN CELL THERAPY TRIALS: LEVERAGING OPTIONS & EXTERNAL NETWORKS

Given the competitive cell therapy landscape, there is a growing need to involve sites beyond the large academic centers that are currently participating cell therapy trials to address the issue of saturation.

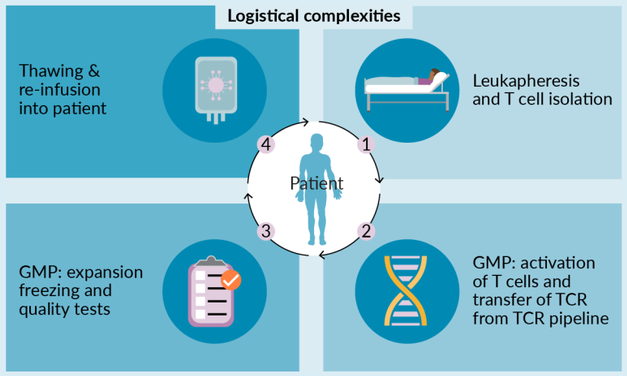
Figure 1. Master case study (Phase 1, 2 & 3 trials of varying cell therapy modalities).

Situation

- Implementation of Phase 1, 2 and Phase 3 cell therapy trials of varying modalities (gene- and non-gene-modified) in a highly competitive & volatile landscape (COVID)
- Overcome challenging regional and country start up requirements to ensure site activation and subject enrollment
- Establish & maintain the CoC (chain of custody), CoI (chain of identity) (Sponsor, study, site and processes, and tools)
- Short falls in availability in relation to clinical and non-clinical supplies vital to procurement of cellular starting material
- Gap in experience, processes and infrastructure across all stakeholders potentially limiting operational efficiency and/or clinical trial participation
- Ensuring high data currency and data quality during rapid enrollment and data acquisition

Solution

- Established executive governance to monitor, mitigate, and solution challenges
- Applied PPD CGT regulatory and start-up expertise (10+ years/137+ CGT studies) to secure start-up
- Applied data mining and operational process to assess and reconfirm C&GT accreditations and TE licenses during site selection
- Partnered with sponsors and premier oncology centers to develop capabilities to conduct cell therapy trial through gap analyses, training and process enhancement inclusive of ATIMP shipment and process mock runs, development of CoC/CoI tracking process and communication platforms
- Developed communication platforms and tools for management and tracking of the patient and cell journey
- Created predictive tools for resources needs to manage data volume, currency and data quality
- Applied state-of-the-art data visualization tool monitoring patient data, safety and efficacy endpoint



Impact

- Alignment on goals and solutions led to smooth operational performance
- Successful management of the patient and cell journey of hundreds of subjects (autologous and allogenic combined)
- Data driven process and start up expertise culminating in site activations and successful enrollment across the globe
- Reduction of site and patient burden, through effective supply chain management
- Data currency, data quality at steady state 'data lock readiness' through adaptive resourcing strategies and monitoring processes

There is a spectrum of sites that could participate in cell therapy trials based on their various capabilities and infrastructure, from more limited sites which rely on Foundation for the Accreditation of Cellular Therapy (FACT) accredited centers and vendors, to those with established infrastructure. Leveraging external networks may be a 'stop gap' solution while developing a more robust investment strategy and infrastructure over time.

CHALLENGES & STRATEGIES FOR OPTIMIZATION

PPD's successful management approach to cell therapy clinical studies spanning all phases has stemmed from responses to several identified risks, potential gaps, or challenges encountered during the conduct of these studies.

This has involved a focus on key challenges and opportunities for optimization including:

- Clinical trial design
- Patient and cell journey; supporting logistics
- Infrastructure considerations for participating sites
- Accessibility to clinical trials in relation to patient enrollment

CASE STUDY: MITIGATION STRATEGIES FOR CELL THERAPY TRIALS

Figure 1 demonstrates the successes of PPD's management approach to cell therapy clinical studies spanning all phases. These successes have stemmed from responses to several identified risks, potential gaps, or challenges encountered during the conduct of these studies.

IMMUNO-ONCOLOGY INSIGHTS

Immuno-Oncology Insights 2023; 4(4), 171; DOI: 10.18609/ioi.2023.022

In partnership with: PPD Part of Thermo Fisher Scientific

INTERVIEW

ASGCT turns the spotlight on immuno-oncology: where have we been & where are we going?

This August, the American Society of Gene & Cell Therapy (ASGCT) will run its inaugural Spotlight on Immuno-Oncology Conference. This two-day meeting, running in-person in Seattle and virtually, will feature a roster of I-O experts and highlight key topics for the field, including:

- Novel CAR designs;
- TCR-based approaches;
- Moving beyond B Cell malignancies;
- Genome/epigenome editing;
- Direct *in vivo* delivery;
- Looking beyond T cells.

To find out more, **Roisin McGuigan,** Editor, *Immuno–Oncology Insights,* spoke to **Hans-Peter Kiem** MD PhD, ASGCT's Immediate Past President and Stephanus Family Endowed Chair for Cell and Gene Therapy, Fred Hutchinson Cancer Center, about the inspiration behind creating this new event.

Immuno-Oncology Insights 2023; 4(6), 239–242

DOI: 10.18609/ioi.2023.032

Q What was the motivation for launching a specific I-O focused meeting—and why now?

HPK: Many of our ASGCT members have spent their careers in this field performing the underlying research and developing the gene therapy and gene editing tools

that have led to the development of these transformative immunotherapies for cancer. There are now several approved therapies, with many more to come. The field of immunotherapy has evolved from the use of unmodified T cells, with genetically modified T cells now being developed for most indications and cancers—and this new field of synthetic biology and immunology will only continue to grow and evolve. For these reasons, now felt like the perfect time to take stock and examine all of these fascinating tools, and explore how they can further improve these very promising cancer therapies.

Q Who should attend the event?

HPK: This event will offer something for everyone, from junior investigators who want to learn more about the field, to more experienced scientists who want to catch up on the latest cutting-edge developments, to clinicians who want to see what the next generation immunotherapies might look like in the clinic.

Q What do you hope will be the key takeaways?

HPK: Our attendees will learn all about the latest amazing advancements in genetic engineering tools, and the potential of applying these tools to genetically engineer immune cells. Ultimately, everyone in the field is working towards the goal of making these approaches safer and more potent for the treatment of both cancer and also other diseases.

ASGCT's Spotlight on Immuno-Oncology will run on August 1–2, 2023 at the Hilton Motif Seattle Hotel, US, and virtually—to secure your spot and hear expert speakers including Carl June, Michel Sadelain and Chiara Bonini share their perspectives on the future of the field, visit the conference registration page.

BIOGRAPHY

HANS-PETER KIEM is a physician-scientist studying hematopoietic stem cell (HSC) biology, transplantation, immunotherapy and gene therapy/genome editing. He's also a trained and clinically active oncologist seeing patients on the marrow transplant and immunotherapy services. Dr Kiem is currently the Stephanus Family Endowed Chair for Cell and Gene Therapy at Fred Hutchinson Cancer Research Center. As a fellow and junior faculty, Dr Kiem was part of the Fred Hutch team developing nonmyeloablative transplantation. As an independent investigator, he developed a research laboratory and program focusing on the biology and transplantation of HSCs and the development of novel technologies to expand and/or genetically modify HSCs or T cells for the treatment of cancer, HIV, and genetic diseases such as Fanconi anemia, severe combined immunodeficiency, and hemoglobinopathies. Recent studies in the lab include CRISPR/Cas-based genome editing of HSCs for hemoglobinopathies and *in vivo* gene therapy approaches with viral vectors and nanoparticles with the goal to make gene therapy also more accessible in resource-limited settings in the world. Dr Kiem has extensive experience training students and postdoctoral

DOI: 10.18609/ioi.2023.032

fellows and has mentored more than 70 trainees in his lab over the past 25 years. He has been the sponsor and PI of several clinical stem cell gene therapy studies.

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AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.
Acknowledgements: None.
Disclosure and potential conflicts of interest: The author has no conflicts of interest
Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

Article source: Invited.
Revised manuscript received: Jul 14, 2023; **Publication date:** Jul 17, 2023.

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Spotlight on Immuno-Oncology

Transcend the basics of cell therapy and CAR T, and dig into gene engineering at the intersection of cell and gene therapy in this hybrid event.

Speakers Include

Carl June, MD
University of Pennsylvania
CAR T Cell Clinical Trials

Rayne Rouce, MD
Baylor College of Medicine
CAR T for T-Cell Malignancies

Chiara Bonini, MD
Vita-Salute San Raffaele University
TCR and Inhibitory Receptor Genome Editing

Saar Gill, MBBS, PhD, FRACP
University of Pennsylvania
CAR T Cell Targeting In Vivo

Catherine Bollard, MD
The George Washington University
Native T-Cells for Adoptive Cell Therapy

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