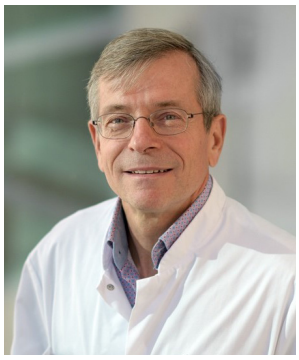
OVERCOMING MECHANISMS OF TUMOR RESISTANCE PART 2. WHAT PROGRESS IS BEING MADE IN SOLID TUMORS?

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

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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.

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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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REFERENCE

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