TIGIT AND THE NEW WAVE OF IMMUNE CHECKPOINT INHIBITORS

Discussing the Challenges and Promise of the Next Clinically Validated Checkpoints

Dhan Chand
Scientific Director Head of Drug Discovery
Agenus Inc.

What are you most excited about in the Immune Checkpoint Inhibitor field now?

We know that TIGIT is an important regulator of the immune response to cancer. Everything from T cell activation to tumor cell killing by both T- and NK cells, but what's really exciting is that TIGIT is starting to emerge as a clinically validated immune check point next to PD-1 and CTLA-4. The early clinical data in non-small cell lung cancer suggest that TIGIT could be a safe add on to PD-1/ PD-L1 therapy. If we could double the response rate as the current clinical data is showing by adding another immune-oncology therapy without significantly increasing the frequency or severity of adverse events, then it's hard not to get excited by the prospects of what TIGIT therapy can be for patients.

What would you say are the biggest hurdles currently to development in the TIGIT field?

In my opinion, the biggest challenge right now is understanding how, when, and where to deploy TIGIT therapy. Part of that will come from a deeper understanding of the biology of TIGIT and how TIGIT therapies work. We know from pre-clinical models and emerging clinical data that the biology of TIGIT and PD-1 are complimentary. The non-small cell lung cancer studies show that patients with high PD-L1 expression respond better to the combination of TIGIT and PD-L1. The question is why, and what are the markers that we can leverage to better develop TIGIT? The role of PD-L1 is starting to emerge, but what about the role of PVR, TIGIT positivity within tumours, and the relative contribution of T-cells and NK-cells. That must be addressed not only with a deeper understanding preclinically but having an aggressive biomarker strategy in the clinic.

Are we just going to be limited to indications or settings where PD-1 is active, or can we extend the therapeutic reach? We know that combinations beyond PD-1 are one way to achieve that. Another way is through the design of TIGIT molecules to really tap into the mechanisms of the immune response to cancer. This is slightly controversial within the field, particularly with regards to Fc binding. The early clinical data is from an Fc-competent TIGIT antibody which shows good activity. We don't know what the Fc-null antibody will look like, but we think it might be a liability based on the data so far. Other considerations include the importance of Myeloid biology in driving anti-tumor activity. We need to investigate broader mechanisms of TIGIT action which we might not be capturing in the design of the molecule. We know that blockade is important, but we don't know how important the presence of the ligand is. For example, PD-1 is an important marker, but what about PVR and other ligands?

With this new wave of emerging immune checkpoint inhibitors, how to you see the immune checkpoint therapeutic landscape evolving?

LAG-3 and TIM-3 entered the clinic before TIGIT therapies, and they were quite well known, but TIGIT is really the only molecule out of those three that started to show some exciting data in the clinic. I would say that TIGIT is a promising target, LAG-3 and TIM-3 could very well be in the same light in the right setting and in the right combinations.

When you think about what's really challenging in the field right now, it's broadening the reach of Immune-Oncology. Molecules like TIM-3, LAG-3 and TIGIT are really designed to act on immunogenic or inflamed tumors. We know TIGIT is bridging both the innate and adaptive immune system with respect to T and NK cell biology, but how do we combine TIGIT therapy with agents that address T cell infiltration? Will molecules that address myeloid biology or even chemotherapy to treat cold tumors in combination with a TIGIT therapy see the doubling of response rates that we see TIGIT and PD-1 combinations?

What milestones are you excited to see in TIGIT development over the next few months?

I'm really looking forward to the data readouts from the Fc-null TIGITs. I think that's really going to address how important is Fc biology with respect to TIGIT therapy. I'll also be looking forward to combinations beyond PD-1/ PD-L1. We know that Merck is looking at CTLA-4 plus TIGIT therapy, I think that's going to be super informative regarding TIGIT applications beyond combination with PD-1. There's definitely a lot of promise for TIGIT given the biology that we know today, and it will be extremely exciting to see how that plays out in the clinic.