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SPOTLIGHT

INTERVIEW

Invariant NKT cells: advances in transitioning to the clinic

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Q Please can you summarize your current research activities for us?

AK: The immunology and immunotherapy programme in my lab focuses on the biology and therapeutic applications of invariant NKT cells (iNKT).

Over the years, we have demonstrated the ability of donor iNKT to modulate graft-versus-host disease. With forthcoming funding, we expect to be able to initiate first-in-human clinical trials in the context of allogeneic stem cell transplantation to see if donor iNKT cells, expanded *in vitro*, are safe to be used for ultimately preventing graft-versus-host disease.

Graft-versus-host disease is the main complication of hematopoietic stem cell transplantation. If you can get around this problem, you will have the possibility of offering this curative procedure to many more patients because at the moment, only younger patients are eligible for it. And a proportion of these patients die because of graft-versus-host disease, despite their leukemia or lymphoma being under control.

The second area of work for us relates to the question of whether introduction of a chimeric antigen receptor (CD19) to iNKT cells would be a worthwhile exercise – and if it were, how would this compare to more established CAR T cell therapy in CD19-expressing B-cell cancers, like B-cell lymphoma?

We demonstrated that CAR NKT cells fit the bill because they can be engineered with a CAR very efficiently. And importantly, despite the fact that they are very rare, they can be expanded to clinical scale and numbers, meaning they can be used for clinical immunotherapy.

Upon comparing their activity against different cancers head-to-head with same-donor CAR T cells, we found them to be more effective, *in vitro* and *in vivo*, against both primary lymphoma cells and chronic lymphocytic leukaemia cells, but also in animal models of lymphoma.

Very importantly, they demonstrated particular activity against brain-based lymphomas, which CAR T cells did not.

So this is the basis for us to now develop the NKT platform further, combined primarily with CARs against other blood cancers – we're working on multiple myeloma, for example. And we're exploring whether this can be used against solid cancers, too, although it is early days in that area.

Q What are the particular advantages of – and challenges in - utilizing iNKT cells in a therapeutic technology platform?

AK: The big challenge has been to make a clinical scale immunotherapeutic product from a very rare cell population. It took us some time to find the best conditions so we could select them to high purity, efficiently transduce them with CAR lentivirus, and then expand them. Although I must say that we expanded them with relative ease – they have an inherent ability to expand tremendously well compared to T cells: starting from something like 50,000-100,000 iNKT cells, you can expand to hundreds of millions of cells within a few weeks.

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In terms of advantages, ourselves and others have repeatedly shown at the preclinical and also clinical observational level that iNKT cells protect from GvHD, which obviously means we can use iNKT cells sourced from healthy individuals as the basis for an off-the-shelf treatment.

This is a big focus for preclinical and clinical research right now in the CAR T field. But in order for CAR T cell immunotherapy to be suitable for off-the-shelf – i.e., utilizing cells sourced from healthy individuals – there's an additional genetic engineering step you need to carry out: as well as introducing the CAR, you have to remove the endogenous T-cell receptor of the CAR T cell by means of gene editing.

So you do two major genetic interventions with CAR T cells. However, with CAR NKT cells, you only have to introduce the CAR – you don't have to interfere with the endogenous T-cell receptor. In fact, the endogenous T-cell receptor is a valuable part of the CAR NKT cell because it adds to the anti-tumour activity when it finds its target (CD1d) and it also protects from GvHD. That's a big advantage, albeit a theoretical one at the moment because we have yet to see it in clinical practice – that would be the next step.

It would certainly solve a lot of logistical issues. For example, it might solve the issue in chronic lymphocytic leukaemia that was the subject of a recent paper from UPenn, which stated that only 20% of patients with chronic lymphocytic leukaemia achieve complete remission following CAR-T immunotherapy, simply because the autologous T cells are not very healthy. We do think there is really a lot of scope to develop CAR NKT immunotherapy in this regard.

There are other potential 'tricks' we can employ to selectively increase these cells' activity – pharmacological glycolipids, which are selectively targeting iNKT cells to make them more active, for instance – but these need to be tested further in preclinical models before they go into clinic.

Q Tell us more about the specific indications in which you have seen promise in the preclinical setting to date.

AK: We can cover the whole spectrum of mature B-cell malignancies, including multiple myeloma.

BCMA is a myeloma-specific target that investigators are looking at – there are several clinical trials with anti-BCMA CAR T cells. We're developing a preclinical programme around this idea, but we also have other targets that we will be developing CAR against including specific ones for both myeloma and lymphoma cells.

Q What is your approach to transitioning this platform to the clinic in terms of developing robust manufacturing protocols?

AK: That's our next challenge: moving outside the research lab, taking the research protocol and making it a clinically suitable one.

The current manufacturing platforms and protocols in this field are all focused around T cells, where you manipulate tens of millions of cells with lentivirus or other CAR transfer means. In our case, though, we start with a very small number of cells, and we take a 'scale-down scale-up' approach. That transition from scale-down to scale-up is where we will now be investing a lot of effort with our partners to see how we can make this into a seamless, streamlined manufacturing process. It is going to be quite different to what is currently out there and being applied in CAR T cell therapy manufacturing.

Q How and why did you come to work with Miltenyi and the Prodigy system?

AK: What we are doing with Miltenyi in the first instance is introducing their CAR T cell immunotherapy programme into our institution. So we will be hopefully using the Prodigy to make CAR T cell therapies in-house in our clinical cell therapy lab, using Miltenyi's own lentiviral CAR vector-what I would call CAR T cell manufacturing by the bedside, effectively.

Over the slightly longer term, the aim will be to try to adjust our own CAR NKT manufacturing to the Prodigy platform, because it's ideal as a closed manufacturing system.

But of course, the Prodigy system itself has been adjusted to the needs of CAR T cell therapy manufacturing, which as I mentioned involves tens of millions of cells. So alongside Miltenyi, we will be exploring how we can adjust our 'scale-down scale-up' approach accordingly to hopefully work on the Prodigy.

Q And what are, and will be, the particular advantages to this approach – in terms of impact on Cost of Goods, for example?

AK: First of all, the nature of CAR NKT immunotherapy will be such that the manufacturing process will use healthy individuals' cells, and can be done under controlled conditions without the

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time pressures one associates with autologous CAR T cell immunotherapy. That will immediately reduce the costs of manufacturing and logistics. Additionally, if the manufacturing is done on the Prodigy system, Milteny's initial assessments are that this will reduce the cost even of autologous CAR T cells by a significant margin.

Imagine having two aspects of manufacturing that will between them reduce both the costs of logistics and of the manufacturing process itself?

Hopefully, if the therapy is effective in the end (and we're all convinced it can and will be used early in the journey of the patient – much earlier than we're using them now in clinical trials) then there's the prospect of well-equipped academic cell therapy labs manufacturing CAR NKT products against different targets in their own time – only producing as many as they think they will need. They will then be able to immediately make these therapies available to patients as and when they are required.

Q Finally, where would you ideally see your work going over the next 3–5 years? What's on your list of aspirations?

AK: Well, it's hard to predict because of the very fluid field. And again, I think the Milteny approach is going to throw some spanners in the works of the established way of manufacturing and distributing CAR T cell immunotherapy.

My expectation is that we will be able to deliver effective immunotherapy at the lowest cost possible, which will be really affordable to all types of health systems in different geographies.

Certainly, given the way that manufacturing processes are developing, costs will become more sustainable. Combine this with what I believe is going to be a very effective and compelling treatment option – a curative one, in many cases – and I think this gives you a lot of advantages. But of course, if it is to be made available earlier in the patient journey, then it simply has to become affordable so that the larger patient population can access it – that's what I want to see.

"My expectation is that we will be able to deliver effective immunotherapy at the lowest cost possible..."

One possibility, as I've said, is that if we can get these new therapies to be manufactured on the Prodigy system, then facilities like ours can make their own products and have them ready to be delivered to patients.

Alternatively, I can see central, perhaps national, facilities like the blood transfusion service making this type of product and distributing it to hospitals in much the same way as blood is delivered today. I think the Prodigy can be adjusted for that purpose, too. This would mean all the commissioning, validation and quality control could be done centrally, which would only add to the potential to deliver these products to patients at a very affordable cost.

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