OPTIMISING THE CAR T CELL MANUFACTURING WORKFLOW FROM END TO END

SPOTLIGHT

INTERVIEW with Dr Nirav Shah, Assistant Professor of Medicine, and **Dr Bryon Johnson**, Professor of Medicine at the Medical College of Wisconsin

"Solid cancers pose a lot more challenges than the hematologic malignancies, but in the next decade we will see a number of major breakthroughs..."

Progress and challenges in the development of bi-specific CAR-T cell therapies

Nirav Shah, MD, MSHP, is Assistant Professor of Medicine at the Medical College of Wisconsin, Division of Hematology and Oncology, specializing in lymphoma, stem cell transplant, and CAR-T therapy at Froedtert Hospital. He graduated with honors and Alpha Omega Alpha Honor Society membership from the University of Illinois at Chicago College of Medicine in 2008. He then completed his Internal Medicine residency at Harvard University and Massachusetts General Hospital in Boston in 2011. Post-residency, he took a position at Northwestern Memorial Hospital in Hospitalist medicine before proceeding to the University of Pennsylvania where he completed

both hematology/oncology fellowship and a Master's degree in health policy research in 2015.

Bryon Johnson, PhD, is a Professor of Medicine, Division of Hematology and Oncology at the Medical College of Wisconsin (MCW). Dr Johnson received his PhD from the University of Health Sciences/The Chicago Medical School (now Rosalind Franklin University), in 1989. Dr Johnson came to MCW in 1989 as a post-doctoral fellow where he studied the basic biology of graft-versus-host disease and the graft-versus-tumor effect after allogeneic hematopoietic progenitor cell transplantation. He joined the MCW faculty in 1994, and eventually transitioned his research more towards the field of cancer immunotherapy. His research subsequently focused on development of cell-based cancer vaccines, immune checkpoint blockade, and adoptive immunotherapies for cancers including myeloma. Dr Johnson was named Director of the MCW Blood & Marrow Transplant Program Cell Therapy Laboratory in January of 2017. Dr Johnson's current research interest is in understanding the biology and immunology of cancer and uncovering new immune-based approaches to treat cancer. His current research focuses on combining the following approaches to improve the use of cancer immunotherapy for treating both blood cancers and solid tumors: immune checkpoint protein blockade; adoptive transfer of cancer-reactive T lymphocytes; and use of novel agents to modify the cancer microenvironment so that the immune system can more effectively eliminate the disease.

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Q What are you currently working on?

NS: I'm an Assistant Professor of Medicine at the Medical College of Wisconsin, within the division of hematology and oncology. My clinical practice specializes in taking care of patients with complex hematological malignancies, with a focus on lymphoma, bone marrow transplant and cellular therapy. My current research focus is in the development of novel CAR-T constructs for patients with hematological malignancies.

BJ: I'm a Professor in the Department of Medicine, Division of Hematology/Oncology, and I've been at the Medical College of Wisconsin in one capacity or another since 1989. I took over as Director of our Blood & Marrow Transplant Cell Therapy Lab at the beginning of 2017, which is my primary responsibility, but I also have a research lab where my interests predominantly lie in adaptive cell therapies for cancers.

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Q Nirav, how and where have you incorporated lessons from both your own, and the wider community experiences in CAR-T to date in your preclinical to clinical translation strategy?

NS: CAR-T therapy is obviously a very exciting modality for patients with relapsed or refractory B-cell malignancies. While there's a lot of excitement and energy surrounding diseases such as lymphoma, the two approved products both target a single antigen on B-cells – CD19 – and the long-term effectiveness of those products is in the 30–40% range. This suggests that the majority of people will fail this treatment approach.

One modality of potential relapse is that the tumor cells can down-regulate or modulate the CD19 receptor, in essence rendering the CAR-T cells ineffective.

That led our team to consider using a dual targeting approach, whereby you're not just targeting CD19, but targeting CD20 in addition. Some of our colleagues with whom we are collaborating, performed preclinical work that suggested duel targeting may mitigate down-regulation of the B-cell target antigens, and it's that concept and hypothesis that led to the development of our Phase 1 clinical trial.

Q Regarding this first-in-man study, what particular trial design did you choose for that and why?

NS: Our Phase 1 study is investigating a bi-specific CAR-T cell that has a single, tandem receptor that can bind both CD19 and CD20. We think that dual targeting could potentially be more effective than single targeting, but obviously we're carrying out the trial to learn more about this CAR-T cell product.

Because this dual-targeted construct has not previously been administered to humans we're studying it first in a Phase 1 study in an attempt to demonstrate safety. We're also testing the feasibility of a novel production platform that will also be assessed in this initial trial, and Dr Johnson can provide more information on that.

In a Phase 1 study what we do is test different dosages of the CAR-T cell products, and we've escalated them in a 3+3 fashion to determine the maximum tolerated dose we can potentially give.

Q Bryon, can you tell us more about this bioprocess platform and what particular challenges have you encountered in the development of this CAR-T platform?

> "...we've shared our results at the recent EBMT conference, and our data indicates that the dual-targeted CAR-T cell is safe and effective in patients."

BJ: One of the things we considered early on was the necessity to manage and optimize our manufacturing costs. Many institutions across the country have invested in expensive clean rooms to do the cell manufacturing, and we were looking for an alternative manufacturing approach that would not require huge investment but would still allow us to generate a quality product that would meet FDA standards.

So we took a different approach and partnered with Miltenyi Biotec who manufactures a device called the CliniMACS Prodigy. This device is a completely closed, GMP compliant system that allowed us manufacture CAR-T cells in our current cell processing facility, avoiding the need to build out a costly clean room. The Prodigy device is about two and a half feet long by about foot and a half wide, and it sits on a bench top in our clinical cell processing laboratory, providing a minimal footprint. The device also significantly reduces the amount of technical time that's required to generate a cell product. Finally, it allows us flexibility in providing cells to patients, since we can immediately deliver cells fresh to the patient, or cryopreserve the cells for future administration, depending on the health status of the patient.

It does provide some challenges in terms of timing, because our goal is to generate and deliver a fresh product for our patients, although as noted, if necessary, we can freeze these cells down for later administration. That does pose a bit of a challenge in terms of scheduling, because right now we are conducting a 14-day manufacturing process. We have to coordinate delivery of the CAR-T cell product with other treatments the patient is receiving in preparation for getting the CAR-T cells. This can present some challenges in terms of scheduling the patients.

However, now that we have treated several patients, we have streamlined the process, and we feel that there are significant advantages to patients due to the fact they are able to get their cells when they need them, without delays that can occur when CAR-T cells are manufactured off-site.

NS: On the clinical side, we've shared our results at the recent EBMT conference, and our data indicates that the dual-targeted CAR-T cell is safe and effective in patients. Now that we've identified a safe dose, we're looking forward to a larger Phase 2 study where we can truly learn more about the efficacy of this product in treating patients with relapsed refractory, non-Hodgkin's lymphoma.

On the bioprocessing side, I work very closely with Dr Johnson and his staff to try and find a way to balance the clinical needs of the patient and the lab requirements to make the CAR-T cells in a safe and timely manner.

We're working together to develop a novel platform where we can have a flexible manufacturing process, one that can be personalized for the patient and their clinical needs, whilst also being able to adjust the process to ensure that we are able to achieve the correct dose of CAR-T cells.

> "...we're looking forward to a larger Phase 2 study where we can truly learn more about the efficacy of this product in treating patients with relapsed refractory, non-Hodgkin's lymphoma.."

Q Beyond this trial as you move into Phase 2 and hopefully further, what do you anticipate being the major challenges you expect to encounter?

BJ: I think the biggest challenge is going to be capacity – we utilize the CliniMACS Prodigy device and we are limited to manufacturing one product per device in a 10–14-day timeframe. Therefore, the biggest challenge for us moving forward is going to be ensuring that we have sufficient number of instruments to be able to accommodate the demand for what we need to do on the clinical side.

And, of course we want to be able to treat as many patients as possible who need this type of therapy.

Q What sort of patient numbers would you anticipate your clinical center potentially treating with this product?

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NS: At the moment, the current CAR-T manufacturing model is typically a third-party centralized process. If you order FDA-approved CAR-T cells, you perform the apheresis at your local institution, but the cells get shipped out and are manufactured by a third-party company.

There could be some challenges for a center such as ours being able to meet the potential clinical demands using only localized manufacturing, should this CAR-T construct gain FDA approval. Mainly, because nobody has tried this before on a large scale. But obviously it is our goal, and the vision of the people we're collaborating with, to actually show through our experience and experiences of other centers, that this localized manufacturing is safe, reproducible, and a reasonable way to deliver CAR-T cells.

I think this is a challenge for the entire field because it's changing the way people are used to doing things. Whenever there's a drastic change like that, it takes a lot of time and patience in order for something like this to become standard of care.

> "The CAR-T field is exploding and it's fairly safe to say the product we're delivering now will likely be outdated in 5 to 10 years."

Q What is your vision for how CAR T and other cellular immunotherapy modalities will fit into the oncology healthcare playbook, ultimately?

JS: The CAR-T field is exploding and it's fairly safe to say the product we're delivering now will likely be outdated in 5 to 10 years. Mainly because there are a variety of companies and academic centers developing the next generation of CAR-T cells, ones we hope will be more effective, easier, and safer to deliver.

I think CAR-T cell therapy is here to stay and will move up from a last-line option to a second or even first line treatment for some patients. With time studies will be performed that may show CAR-T is more effective and potentially safer than some of our current standard options such as chemotherapy.

The future for CAR-T therapy is incredibly bright and there's so many different ways to harness this technology, not only in blood cancers but I think in time we will find ways to harness this technology in solid malignancies as well.

Q What is your expectation for the on-going evolution of these genetically engineered cell therapies, and specifically what methods and enabling tools do you expect or hope to see coming to the fore?

BJ: I think what's remarkable about CAR-T cell therapy is a lot of people don't realize that this took years – in the range of 15–20 years – to develop and get where we are today. The first patient was successfully treated about 7 years ago now, so CAR-T as an implemented therapy is still very new.

There are lots of facets that can continue to evolve and improve, geared at making these therapies more effective and targeted. Right now, CAR-T cell therapy is almost exclusively used for treating so-called B-cell hematologic malignancies – leukemia's and lymphomas. I think what's really going to be a huge breakthrough, as Dr Shah eluded to, is when we learn how to use this treatment more effectively for solid cancers. Solid cancers pose a lot more challenges than the hematologic malignancies, but I am confident that in the next decade we will see a number of major breakthroughs that will further utilize these innovative cellular immunotherapies.

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