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Paediatric oncologist Navin Pinto, MD outlines the current use and potential of CAR-T therapies in his field, including the manufacturing challenges that still need to be addressed. Dr Pinto also explains how the work of his CAR-T team at the University of Washington School of Medicine could provide proof of principle for pharma to take forward and make available more widely or expand to different indications.

Can you begin by introducing yourself and your role?

I am an Associate Professor of paediatrics at the University of Washington in Seattle as well as an attending physician at Seattle Children's Hospital. At the hospital, I lead the solid tumour CAR-T cell pipeline, evaluating new CAR-T cell targets, mostly in young patients with relapsed and refractory solid tumours.

How far has the science advanced in paediatric oncology in recent years? Do you believe that sufficient funding is being put into R&D in the field?

I was predominantly drawn to paediatric oncology by our successes. On average, we can treat and cure about 80 percent of children with cancer, largely through large cooperative group trials where children's hospitals have banded together to evaluate changes in therapy over time. Those have predominantly been intensifications or additions of standard cytotoxic chemotherapies.

However, as we have entered the molecular era of medicine, with a greater understanding of the molecular basis of cancers and the promise of targeted therapies or immunotherapies, it feels like paediatric oncology has been somewhat abandoned.

In the United States, for instance, three to four percent of federal funding for cancer is directed towards paediatric oncology. This makes sense in that childhood cancers are much rarer than adult ones, but there are many more potential life years gained for paediatric oncology patients. There is a big push to increase that funding and support young people who hopefully have 80 or 90 years of life ahead of them if successfully treated.

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What was your first impression when you heard about CAR-T?

I first heard about CAR-T around the time that many other physicians that weren't deeply involved in the research did, in 2015. This was not the initial focus of my fellowship, and I was a few years into my independent practice when I began hearing the stories about the first patients treated with CAR-T cells for B cell malignancies, the most common childhood cancer. Some of the very first

patients treated with CAR-T in the world were young patients, such as Emily Whitehead at the Children's Hospital of Philadelphia.

It seemed like science fiction that you could take components of the immune system, genetically engineer them, and reassemble them in a way to activate T cells to fight cancer. Patients receiving CAR-T have already gone through many lines of therapy without success, so this represented a remarkable breakthrough.

What drove you to focus on CAR-T therapies in your work?

Many of the stories that emerged around this technology were truly inspirational. As a paediatric oncologist, it can be challenging to affect change working across large networks of hospitals as a single hospital may only see two or three patients with a given cancer every year due to their rarity.

While the fact that these diseases are quite rare is, of course, positive for children, it is impossible for individual hospitals to drive their own treatment programs when they are only seeing a handful of patients with a particular malignancy every year. One of the things that drew me to Seattle was the CAR-T program it had in place. Despite Seattle being a relatively mid-sized American city, it is situated in the northwest corner of the country and surrounded by several relatively rural states without a lot of access to specialty paediatric care and therefore has a large catchment area of patients.

That positioning allows us to develop novel therapies and test them in sufficient numbers of patients to see whether they have an effect. The lab of our scientific director, Dr Michael Jensen, was evaluating a variety of CAR-T cell targets and working with clinicians to help implement these pre-clinical observations in the clinic. I had already tested out these 12 CAR-T cells and, when they needed clinicians to begin running trials, it seemed like a wonderful opportunity to bring new therapies to children.

What approach, in your view, should corporate sponsors take when collaborating with other stakeholders in CAR-T development?

A few centres have very well-established lab-based programs evaluating therapies like CAR-T. These centres conduct preclinical testing, looking at targets, validating that the CAR-T works in an

animal model or against cell lines, and then work with their staff to implement clinical trials. That is the model we have in Seattle. We have collaborated with pharmaceutical companies in the past, and the work that Dr Jensen did on CAR-T led to the formation of Juno Therapeutics, which is now incorporated into BMS. While that IP was purchased by Juno to form a company and is now an FDA approved treatment, the other 11 targets that Dr Jensen developed in his lab are not owned by corporate sponsors, but by the hospital.

On the other side, there are a handful of FDA-approved CAR-T therapies, both for adults and children. As those get implemented across the country or across the world, the pharmaceutical sponsor does go to centres to carry out training, implementation, and infrastructure building.

Do you foresee CAR-T therapies eventually becoming frontline treatments for solid tumours?

Initially, we were all swept up in a wave of excitement about CAR-T and the amazing effect that it had on patients who had been through fifth-, sixth- or seventh-line therapies with no response. I was brought in at an early phase to evaluate if this technology would work for other malignancies and fight other cancers, solid tumours, nervous system malignancies, and leukaemias.

However, expanding the use of CAR-T beyond CD19 has been a significant challenge, for several reasons. The patients I meet are oftentimes not on their second or third line of treatment, but on their fourth, fifth, or sixth; they are looking for any possible therapies and know that their cancer has no known cure. The same “home runs” that were seen with CD19 have not been seen; there have been hundreds of patients with solid tumours treated with CAR-T therapies without the same miraculous response.

Industry sponsors argue that because CAR-T is being used as such a late line of therapy, by that point the patient’s cells are exhausted, and the results are not as good. Do you agree with that statement?

That probably plays some role, although it is not the sole reason. Patients that responded well to CD19, for example, received it as fifth, sixth, or even seventh line of therapy, although it is now a second- or third-line treatment. These patients have been through extremely intensive therapies, including bone marrow transplants, which have a highly detrimental effect on their own immune systems and replaces it with their donor’s immune system, which are also not robust.

Do you think greater numbers of clinical trials will increase the potential successes of CAR-T?

There are hints in many clinical trials of extraordinary responders, but the responses are not as robust as we have seen in CD19. However, we have seen some CAR-T patients having partial responses, a prolongation of disease stability, or hints of immuno-activation. We know these immune cells can shrink or eradicate tumours in some cases, but not all.

Many experts in the CAR-T field believe that this is an engineering problem that can be fixed by better equipping these T cells to more robustly handle tumours through unique target selection which limits their exhaustion of repetitively fighting a cancer cell.

When you say there is an engineering problem, do you mean there is something about the manufacturing process that needs to change?

There are multiple manufacturing issues that probably need to be addressed. The first is the actual construction of the CAR. This is a completely artificial construction and usually introduced into T cells with viruses. The genetic signal for this CAR-T is not a structure that necessarily exists in nature. They are taking components of the immune system, and assembling them together like building blocks, to make a new protein that can recognize a tumour and engage the immune system to target it.

The building blocks that are selected to make a CAR are very important and very minor adjustments in the building blocks have led to major differences in the T cells' ability to withstand exhaustion. For a given malignancy or given target, unfortunately, it is not the same pattern of building blocks that worked for CD19, and it might not be the same pattern that would work for EGFR, another target of interest in solid tumors.

Within solid tumours, we find that the building block pattern is probably different for each target, so it is a very challenging problem. But that is just one issue. The second manufacturing or engineering issue is how to do this to scale if a target is found. This is a very expensive and time-consuming proposition, meaning that the manufacturing time needs to be shortened. There is also the issue of creating off-the-shelf products that are not necessarily derived from a given patient but are sitting in a laboratory or in a pharmacy waiting for a patient in need of CAR-T.

What is the extent of your ambitions in terms of what your work in CAR-T at the Seattle Children's Hospital can achieve for patients?

Our hope with our relatively small university-led CAR-T program is that we can provide proof of principle which pharma could then potentially take forward and make available more widely or expand to different indications. In many of the paediatric trials that I am running our target is also a target in breast, prostate, or ovarian cancer, which have 1o, 20 or 50 times more patients. We hope to see some signal of efficacy in our Phase I and II trials, but our hospital is not at all interested in bringing a product to market and we do not have the capital to run a national or international Phase III trial.

Can you give us some insights into the patient experience and journey in CAR-T?

It is a very frightening prospect for patients. This is not like other therapies where a patient meets the eligibility criteria for a treatment, has a few tests and a meeting with a doctor to describe the therapy, and the next day begins. CAR-T often involves traveling to another centre far away from the patient's home to collect their T cells. For very young children, that often involves surgical placement of a catheter into a large vein, to have enough blood flow to allow for a large collection of T cells, and then the process of manufacturing takes anywhere from two to four weeks. Many of these cancer patients have multiple relapsed aggressive cancers, and for them, that is a very long period of time.

Many patients that come in are eligible for CAR-T, and one month later, when their cells are ready, they are too sick to receive treatment. That is often the scariest prospect and probably where pharma will have some role in shortening the manufacturing time. We need to think about how to provide off the shelf therapies so that we do not have to collect the cells from everybody and can make a more feasible and widely applicable therapy for patients.

Do you present CAR-T to patients as the preferred solution when the eligibility criteria is met?

It varies. For my own patients, this may be one of several options that are discussed. We do not have a track record of this CAR-T therapy being the solution for the solid tumours that I treat. I

usually present this to families as one of many options that could be tried; these are just a novel therapy that has a chance of having an effect, but the issues around time to manufacture and the procedures that need to be undergone to collect the T cells often lead families to choose another route.

Then there is a second group of families and parents who have sought us out from another centre or even country and who have decided that CAR-T is the way to go.

Is the data robust enough to put CAR-T as an up-front therapy? How many years of data would you feel comfortable with?

For the tumours I treat we are very far away from that and lack the long-term successes to even move into Phase II trials; these are all Phase I safety studies for the time being. However, for CD19 we are very close to this being an upfront therapy. There are Phase III trials underway for very high-risk patients with CD19 malignancies where CAR-T is being compared to the standard of care. I suspect that CAR-T will be less toxic, will have lower long term side effects, and although it is quite expensive in the upfront setting, there may be a long-term health savings benefit for doing a very expensive one-time therapy, as opposed to multiple rounds of chemotherapy or bone marrow transplants. These alternatives are also quite expensive and come with a lifetime of long-term side effects that need to be medically managed.

Is there any message that you would like to share with other CAR-T stakeholders around what can be done better?

Academic partners working in this space must look for wider applications. As an example, I am working on a CAR-T for a paediatric cancer called high-risk neuroblastoma. That affects about 300 children a year in the United States, so it is a very rare cancer but with a very high rate of relapse. However, the same target is expressed in adult prostate cancer, which affects 100 times more patients. These kinds of connections could be better picked up on by industry to assess the wider applications for CAR-T.

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