Manel Juan â?? Head of Immunology, Hospital Clinic Barcelona

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Dr Manel Juan is part of the team behind the development of the first European CAR-T-cell therapy to treat multiple myeloma, the second most common type of blood cancer. As head of immunology at the Hospital Clinic Barcelona, he walks us through his personal journey with the project, the challenges the team encountered, including misunderstanding with â??regulatorsâ?• about cell and gene therapies, and a simple step that could significantly reduce side effects. In addition, Dr Juan comments on the autologous-vs-allogeneic debate and explains why every major Spanish centre could have its own production.

Dr Juan, can you begin by introducing our audience to your background and explain how you became involved with the successful CAR-T-cell therapy program at the Hospital Clinic Barcelona?

I earned my PhD in immunology almost 30 years ago and have been working in the Hospital ClÃnic Barcelona since 2007. Together with colleagues, we created the Immunotherapy Section in 2017 which I have led for almost three years.

My involvement with CAR-T cells began a decade ago after they proved their efficacy in treating patients. At that time, after contacting groups from Philadelphia and Bethesda, I was able to visit the

group from the University of Pennsylvania, led by Dr Carl June. The collaboration was advancing but, after Novartis signed an agreement with UPenn, the Swiss company decided to conduct development by themselves, leaving aside our offer for treating patients in our centre.

Since we thought that we had the expertise and the patients could benefit from this new treatment, we opted to develop our own chimeric antigen receptors (CAR). We were in contact with the Novartis team at the beginning, trying to include our centre in their program, but they decided that it was not a priority at that moment.

During a conversation with Dr June, where we explained what our team knew after two decades of immunotherapy experience using dendritic cells (DCs) and T cells, he suggested that we should be able to develop our own CAR; therefore, we decided to do it and successfully developed CAR-T cells. In hindsight, it was the right decision because it took Novartis a long time to get a product approved.

In 2017, the Spanish regulatory agency AEMPS approved our first CAR T-cell clinical trial, ARI-0001, and finally, in 2021, they approved the local use in patients over 25 years of age with lymphoblastic leukaemia that is resistant to conventional treatments. Not long before, in May of 2020, we received approval for the clinical trial of our second CAR-T, ARI-0002h, that is being used in multiple myeloma patients. These developments were possible with the help of crowdfunding and support from several institutions.

The name of our project, ARI, officially stands for Advanced Research Initiative but is also in honour of Ari, the girl that inspired the crowdfunding movement which made the development of our pipeline possible. Since we lacked the resources to move beyond the pre-clinical phase the crowdfunding helped us move to clinical trials and prove that the therapy worked. The ARI Project has raised near EUR two million from companies, foundations, associations, and individuals.

Our original idea was simply to treat patients because we knew that CAR-T worked and that many of our patients would die in the 6-7 years that it would take for the industry to bring therapies to the market. It might sound naive to some, but we wanted to make our findings openly available, sharing protocols just as it is done in other medical areas.

Why were you so determined to make the findings of your research openly available?

The reasoning is that if we accept that the system in place is good enough and that pharmaceutical companies alone should manage gene and cell therapies, then many patients with rare conditions, like paediatric or infrequent cancers, will be left out.

Among other things, our project helped us detect the most relevant issues associated with these treatments, one of them being the fact that, generally, immunotherapies are considered to be drugs and managed as advanced therapy drugs. However, that approach is not completely accurate since CAR-T-cell therapies are developed using patient cells, at least for now; patients provide his/her cells and companies change them through gene therapy. This is conceptually quite strange for me, because companies are economically benefiting from the cells that patients give.

Some regulators, including Swissmedic, categorise CAR-T as a â??gene technology procedureâ?• instead of simply a therapy. It appears that you agree with them more than you do with the EMA or FDA, correct?

Switzerlandâ??s decision to move in that direction makes more sense today. The EMA and FDA have failed to adapt their thinking around cell and gene therapies, opting to manage them under a similar regulation as traditional drugs. I believe that CAR-T and similar therapies are similar to medical procedures or even transplantations; autologous transplantations are essentially the same. The downside of the EMA and FDAâ??s approach for non-industry developers is that, once you clear the obstacles associated with clinical trials, taking the next step and moving to the market is a big problem, at least in Spain. We are trying to do it but, unless the rules change, development will have to move to pharmaceutical companies; there are too many rules.

There are few options currently available for organisations and institutions like ours. The one we chose is the EMAâ??s Hospital Exemption (HE) rule which allows for unlicensed, developmental advanced therapy medicinal products (ATMPs) to be used to treat patients under certain conditions through a specific authorisation.

We agree with the head of the Spanish Committee of Advanced Therapies â?? part of the Spanish Agency of Medicine and Health Products (AEMPS) â?? that the HE path could be a first step to arrive at national authorisations because, as soon as you have a local authorisation, you have the possibility to receive reimbursement of expenses. However, if the product is good, it should be available across the country and not only in certain areas.

Under the current rules, only a handful of big pharma companies have the opportunity to succeed, a situation that is made worse by some revolving doors between the regulator and industry; it is quite a strange situation, at least for us looking to treat patients.

Representatives from Novartis and Gilead, two companies involved in CAR-T cell-therapies, have argued that hospital exemptions should only be used when there is no approved alternative. What is your view on this?

That is not entirely accurate because we began our clinical trials before any company had received EMA authorisation. We obtained a hospital exemption for a very specific condition not covered because the regulator wanted to avoid overlaps. I do not understand why since at least three companies are working on the same indications and they are doing it through exemption rules, too. Nevertheless, the rules are the rules, and we must do what we can.

Is there a specific element to your CAR-T-cell therapies that separates them from others?

These therapies are usually developed with the idea of providing them through a single infusion, but we modified ours to fractionate the doses which significantly reduces side effects. It is not uncommon for patients to develop cytokine storm syndrome â?? similar to the hyper-inflammation caused by COVID-19 â?? or central nervous effects, such as immune effector cell-associated neurotoxicity syndrome (ICANS), with the approved products.

There are too many side effects that we have reduced just by fractionating infusions. Unfortunately, we are not allowed to do it because of the pharma rules. I believe that all patients, not only ours, would benefit but companies are not so interested, because under ordinary rules, it will require additional clinical trials.

How did your team come up with the fractioning of infusions?

Our project started with the idea of conventional one-shot infusion first developed at UPenn. After detecting problems in three patients, we decided to modify the protocols with the blessing of the authorities and found that side effects were extremely reduced in patients with fractionated doses.

Just as we learned during the COVID-19 pandemic, we can modify current protocols in certain cases to accelerate the development of innovative solutions. If we wait for companies to approve our treatments, many patients will perish.

It is interesting that Spanish authorities have dared to provide you with flexibility to modify protocols and approve your therapy when not many governments have done so across the world.

Clearly it takes courage, yes, but we are talking about a treatment that costs only a third of what others do. Although AEMPS is not deciding anything under cost concept, as a Spanish citizen, I expect that our public health system to make wise use of the budget. This kind of innovative effort should continue to be supported by our representative government; the problem is that Spain has the knowledge and expertise but a low-cost economy. Anecdotally, the first time I disclosed my salary to colleagues in the US, they were astounded considering my role as head of section at a major hospital, confusing a month salary as a salary per week!.

Can you comment on the projects in your pipeline? Are there any more CAR-T-cell therapies coming soon?

We expect to develop a dual targeted CAR-T cell therapy soon, combining both ARI 1 and 2, and are in the pre-clinical stage in seven different CAR-T therapies. Our current resources â?? which are coming from grants, crowdfunding and La Caixa Bank â?? should be sufficient to complete the early stages; problems will arise when moving to clinical trials.

How would you react to pharmaceutical companies having an interest in you pipeline?

I am confident that we are developing different products to those of private industry. Our goal is to treat our patients as long as our treatment is as good or better than anything available in the market. In fact, we are working with colleagues in the Netherlands, helping them develop the first comparative study of our CAR-T and others. If the results indicate that our treatment has a lower efficacy, we will forget about it. We will not treat patients with a worse alternative, but if we find that it works, has lower side effects or is cheaper, why should we stop?

I do not believe that our work is opposed to that of pharma companies, â?¦ they complement each other. We want to develop treatments because the industry should not be the owner of our health, â?¦ they are one part of the health system. Public health systems must work for the people, not the other way around. There is a lot to be gained by finding alternative paths to innovative treatments.

One interesting element that we have not yet discussed is the importance of having cell and gene therapy production close to patients in order to avoid environmental contamination and to find globally sustainable ways for any kind of products; and there is no question that and transportation

has an impact on global sustainability.

How would you solve that issue, do you believe that each major urban centre should have its own production of cell and gene therapies?

It would be possible only if rules allow it. At the end of the day, these therapies are based on biological elements provided by each patient and the number of general elements that can be standardised in the final product is quite low. All major hospitals, at least in Spain, have the basic capabilities to do it as long as they use the right protocols. We are currently producing in Barcelona and Pamplona, at the *ClÃnica Universidad de Navarra* (CUN), for five centres: our hospital, the CUN, and three in Salamanca, Seville, and Murcia. The next step is to help all involved centres conduct their own production. At the end of the day, it is all about having the knowledge and protocols.

Do you expect that the move to allogeneic CAR-T cells will solve the issue of accessibility?

Currently, there are two main sources of T cells that can be engineered into CAR-T cells: from a patient (autologous) and from a healthy donor (allogeneic). From the information we have today, allogenic products have lower efficacy.

The situation might or might not change in five or ten years, but we must have in mind that biological elements are completely different from chemical or molecular elements. Cells have thousands of different molecules, different polymorphisms and too many variables that complicate the process.

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