PR. DANIEL OLIVE EPISODE – ICT01 ANTIBODY

"In 2008, I contacted a friend of mine, Marc Bonneville, who is a researcher and world expert in the field of innate immunity, in particular the immune system. I said to him at the time, "Marc, we've made some surprising observations in our in-vitro tests and we've realised that one of our antibodies has the ability to activate the population you're working on". Like any researcher he didn't believe me, which is normal, I would have done the same thing, and a week later he called me to tell me that it was true, which is already pleasant, and that it was exactly what he had been waiting for for 20 years."

Credits

Introduction

How do you make a scientific discovery? What paths must be taken, and what role do time and chance play?

"Dans les pas d'Archimède" is a series of podcasts from Aix-Marseille Université in which some of its most eminent researchers tell the story of a discovery they have made.

In this episode, immunologist Daniel Olive takes us into his laboratory in search of treatments to combat cancers and other infectious or auto-immune diseases.

Episode

My name is Daniel Olive and I am a Professor of Immunology at Aix-Marseille Université. I also work in the hospital at the Institut Paoli-Calmettes and, within the University, I'm responsible for the Oncology Research pathway for the Masters and PhD programmes.

I discovered the ICT01 antibody, whose main capacity is to amplify immune responses and whose purpose is to activate immune responses in cancerology, but also in viral infections, and to inhibit these responses in autoimmune inflammatory diseases.

Musical interlude

The story of ICT01, the way it was discovered at the time, is a matter of chance. A friend of mine, Pierre Pontarotti, who works at Saint-Charles, is a specialist in the study of genes and he specialised in genes from the Butyrophilin family.

He came to see me for a chat because he knew what I was doing in immunomodulation and he asked me if I'd be interested in working on a gene family he'd identified. I replied "of course! He had three genes and we took one of them. Not that the other two weren't interesting, but because we were starting with a family of potentially immunomodulating genes.

Once the choice had been made, a student called Elsa agreed to make the antibodies corresponding to the target. She carried out all the classic tests of those years - since the article had been published in 2002 - and by the time she passed her thesis, we knew where the antibody was located, but we hadn't found any function for it.

At that time, there were no possible leads and by chance I obtained a grant from the Institut National du Cancer for a student, Yves, who started his work in 2008. You'll notice the break

between 2002 and 2008, when nothing was produced because we couldn't find anything. He then redid the tests using more sophisticated techniques.

He was annoyed because he still couldn't find anything. Once again, by chance, he had forgotten a plate in the incubator. It still makes me laugh to see his face. He asked me what was wrong and I told him that they were living cells, so the antibody had done something!

They wasn't classic cells, and he started all his experiments which showed that it was a unique activator of a very small population of cells, which make up 1 to 2% of blood cells, but which have very powerful anti-viral, anti-bacterial and anti-cancer functions in tissues. Would it be an effective drug? We don't know yet, but we have found something that really is what we call an immunomodulator.

Musical interlude

The hypothesis is that if we stimulate an innate immunity cell in a very specific way, we know what it will do in vitro, in animals: it will kill an infected cell, a bacterium, a virus or a cancerous cell, but at the same time, the power of these cells is to be in the front line. Normally, it acts on a viral infection, for example, within a few hours or days, and its other function is to act as a "spark", because at that point it is able to recruit all the other immune cells.

If we want to go further, academia can no longer do much, because we're moving into another world, which combines two things: on the one hand, a therapeutic agent and how to create a drug, but above all how to manufacture it for use in humans, because the product has to be produced in very large quantities; on the other hand, there have to be very important safety criteria, i.e. the product has to be less than 0.1% purity, whatever the contaminant. When I started the project, the cost was around €5 million. We can't do that with our budgets.

So I approached several investors, and at the time it was impossible to get any French money, so everything came from Germany, Holland and Belgium. A French fund did join us a little later, but it was a private fund.

The company, called ImCheck THERAPEUTICS, was set up on campus in 2015. Now we could move on to the drug production stage.

We tested for months that the monkey's ICT01 worked exactly the same as the human ICT01. Then it was time to take the next step and inject it into the monkey: fortunately, there were no side effects in the monkey. The cell was activated and was able to act on other immune populations.

We were quite pleased. There was a great deal of enthusiasm among our colleagues at the Institut Gustave Roussy, the equivalent of Paoli-Calmettes in Paris, who treated the first patients. And things went well. That's why the story goes on.

So if you're keeping track: end of the 1990s, 2015, creation of the company, 2020 start of clinical trials, and here we are in 2023 with a product with which several hundred patients have been treated. We know that there is no toxicity, and that there are effects in some of them.

Our current work is to understand why a particular patient responds or does not respond, and how it can be combined with broad-spectrum or more targeted immunotherapies. We hope to have more conclusive evidence by 2024, so that we can provide a clearer answer. I think it's important for students and researchers to know things that go beyond what was expected.

Musical interlude

The idea, based on what we had done between late 1990 and 2000, was that the main action of the ICT01 product would be to kill an infected cell, and we realised that this did work, but the most important effect is this 'spark' effect, i.e. the action of recruiting all the other immunity players that we know. And my current hypothesis is that the major effect comes from the cells recruited. This means that additional drugs will have to be added, and the other immune cells will have to be helped at the same time. This is going to be a gradual process, because some of these drugs are already available, while others are not.

Musical interlude

Clinical trials require a lot of money, and ImCheck THERAPEUTICS has obtained more than €150 million since 2015. Unfortunately, this will not be enough to test all the hypotheses, given the cost of clinical trials.

What we hope, at least with the budgets acquired so far, is to be able to clarify the absence of toxicity, since this is an inherent problem with any immunotherapy. I've seen so many promising immunotherapies flop or have had deleterious effects on the patient, so we really have to be very careful. Despite the joy for a patient of being cured for a while or seeing their health improve, we mustn't forget that, in medicine, there always has to be a cost-benefit ratio.

At the moment, we're in Phase 1, and we're not asking ourselves that question, because we have patients for whom all treatments have failed. But it's a question that always lingers in the back of our minds, especially when we want to treat patients at less advanced stages.

Musical interlude

You have to be positive. You have to remain highly critical. You have to be really clear with yourself and imagine, sometimes excessively, what the risks might be.

All my colleagues told me I was crazy, but as I'm a rather stubborn person, when I believe in something I tend to go for it all the way.

Conclusion

You have just listened to (or read) "Dans les Pas d'Archimède", the podcast series revealing the scientific discoveries of Aix-Marseille University researchers.

This episode was recorded on the premises of the Aix-Marseille School of Journalism and Communication (EJCAM). It was written, directed and edited by Charlotte Henry de Villeneuve and Merry Royer. The music was composed by Hdv, who also handled the mix. Special thanks to Élodie Choquet for her contribution.