Carla Rothlin: “Research is an intellectual challenge that you can take up throughout your life”

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Dr. Carla Rothlin is Dorys McConnell Duberg Professor of Immunobiology and Professor of Pharmacology at the Yale School of Medicine, and co-leader of the Cancer Immunology Programme at Yale Cancer Centre. She studied biochemistry and pharmacology at the University of Buenos Aires, where she also undertook her postgraduate research under the direction of Dr. Ana Belén Elgoyhen, focussing on nicotinic receptors expressed in the inner ear. Later, she completed her doctorate and moved to San Diego to join Dr. Greg Lemke's laboratory at the Salk Institute for Biological Studies. In 2009, Dr. Rothlin was named Assistant Professor in Immunobiology at Yale Medical School

Dra. Carla Rothlin's research focusses on the mechanisms underlying inflammation regulation and homoeostatic control of immunological function. Her laboratory has been able to identify the function of TAM receptor tyrosine kinases in negative regulation of immune response and resolution of inflammation. Her contributions to this field have received the recognition of various institutions such as the Pew Foundation and the Howard Hughes Medical Institute. In addition to her research work, Dr. Rothlin is also committed to Yale's educational mission, and has been Director of Graduate Studies in Immunobiology since 2018.

- ***Your training is in biochemistry and pharmacology. How did you come to immunology?***

I studied biochemistry and pharmacology at the University of Buenos Aires and, in 2002, after completing my doctorate with **Dr. Belén Elgoyhen**, I went to the Salk Institute in La Jolla to work on my post-doc.

During my doctorate I studied nicotinic acetylcholine receptors, which are very special receptors that mediate information from the brain to the inner ear. What these receptors do is modulate the ear's sensitivity. And, very interestingly, without really looking for it, in my post-doc I ended up finding another family of receptors, tyrosine kinase receptors, which mediate regulation of inflammatory response.

That is to say, we change response and model, but I understood that in many physiological processes, or maybe also in physiopathological ones, there are regulation mechanisms. Our organism does not always want to always respond, or with the same intensity. But many mechanisms exist that regulate how response should be and how long it should last. In the same way that regulation exists at auditory level, there is also inflammation regulation. And that's what my laboratory does: try to understand the nature of the internal mechanisms our immune system has to be able to regulate how large your inflammatory response is and how long it should last.

We believe this is important because if you respond a lot or for a long time, this could be the origin of chronic inflammatory responses and of many of the diseases that **affect humankind**.

I made this first finding at the Salk Institute, despite not having trained as an immunologist. I knew that to be able to really understand the implications of what we had discovered in terms of inflammation, it was very important to set up my laboratory in a place where there were a large number of scientists devoted to studying the immune system.

And I was very **lucky** to start at Yale University's immunology department, an exceptional place for the analysis of immune response and, in particular, what is known as innate immune response, which is the response we are all born with and is largely responsible for forming inflammation.

It was a real honour for me, and a great opportunity, because I was able to surround myself with scientists who were very knowledgeable about inflammatory response.

To progress in science, it's essential to understand the importance of the environment where you ask your questions. The possibility of answering them in the best way doesn't just depend on the ideas you have, but also on how these ideas grow, on what is shared with colleagues in and outside

the laboratory.

We must be very careful, as human beings but particularly as scientists, not to say that by X day we will be able to cure a given disease

- ***When a researcher formulates their questions, do they think about the possible medical benefits for society?***

Yes, of course. Recent decades have seen giant leaps in recognition of immune response and its great impact on many biological functions; it isn't just a mechanism that lets us attack bacteria, viruses, parasites, fungi, and so on… Acting as a defence system against infectious diseases is one great role of the immune system. But it can also regulate functions inside our organism that are not part of what defence response is.

Our laboratory is devoted to understanding how immune response is regulated, not only when it's acting as a defence against external threats, but also, for instance, when it suddenly activates to try and eliminate a cell that has become cancerous. We are also very interested in understanding how the immune system activates when the cells of our organism die. For instance, if we have suffered a trauma and many cells have died, the immune system is also able to recognise this and activate a repair response for the damaged tissue.

We study how these responses are regulated in our **laboratory**. We have discovered mechanisms that allow us to develop a much more effective response against a cancerous or other cell, which offers us the opportunity to create a response against tissue damage that can regenerate the damage in an organ in a more efficient way.

New technologies have been added to this acquired knowledge in the field of **immunology**. How important have they been in producing this qualitative leap?

We are at the ideal moment to combine this foundational knowledge, gathered over many generations, thanks to which we know more about the immune system. But now we have more molecular knowledge and, what's more, we have mechanisms that allow us to modify how the immune system reacts. That's how we can ask what changes we have to make in an immune response to obtain a better response against cancer, to stop the progression of Alzheimer's or to regenerate a damaged heart.

- ***Immunotherapy has revolutionised the treatment of certain cancers and it looks like it will be the answer to many diseases, if not all of them. What about the possible collateral effects of manipulating the immune system?***

Basic research is essential to be able to distinguish what physiological or pharmacological effects we want to induce to prevent Alzheimer's or to treat a cardiovascular event, etc. and not induce effects on the immune system that could be prejudicial.

We must be very careful, as human beings but particularly as scientists, not to say that by X day we will be able to cure a given disease. But I think that science has shown many times that understanding how a system works and how it does so aberrantly in a disease is basic for designing a way to intervene that could be successful.

You have to be committed because things don't always work out in experiments. The aim is always to be able to answer the questions we have set ourselves

We contribute to knowledge, but I believe that technology has brought unquestionable benefits. Both areas are very important and obviously, as a person who is devoted to basic science, I perceive how the system works in one way, which is not the only way, but is one of the ways that enables a potential therapy for all of these diseases.

It is true that **immunotherapy** has made great progress in certain types of cancer. We have seen that certain types of cell in the immune system, T cells, attempt to eliminate the cancer but tire in the effort and become exhausted. We have seen that they can recuperate and attack the cancer.

But this is not the only reason we may have a cancer. As researchers, we have to know what the other causes are for a poor immunological response. And when we know these, we might find new strategies for the patients who do not yet respond to immunotherapy, which is a very high percentage. And the reason is probably because the target is different.

- ***And how is it possible to modulate the immune system to treat a cardiovascular disease or Alzheimer's?***

The **first step is to understand whether there are certain immune system responses**. For instance, in Alzheimer's, now we have started to discover that there is a response from cells with immunological functions —microglia— that prevent the progression of this disease in animal models.

If the microglia response also exists in humans and prevents the progression of Alzheimer's, then we could try to find certain targets, for instance receptors, in the microglia. And depending on the type of receptor we could design different molecules.

In fact, we have discovered a **microglia** receptor that causes the microglia to have the function of preventing the progression of Alzheimer's in animals.

Then, we have to ask ourselves if we can do the same in humans, if we have the same function and, if that is the case, a new therapy could be found, maybe not to cure, but at least to prevent at very early stages.

That's why early diagnosis mechanisms are important. In general, to treat diseases, first you need to have a good diagnosis and then a good treatment.

- ***Could the immune system be used as a warning sign to identify other diseases?***

If a person has an infection, the immune system warns us very soon if the infection is being responded to. Or something even simpler can be done, like measuring inflammation in blood to know that it has activated.

We can think of it as a sensor of both internal damage and the damage caused by external factors. I think it could be very interesting to use the immune system to diagnose and treat diseases in the future. In reality, it is a warning system that something is happening.

- ***The pandemic revolutionised science and many researchers found themselves having to work on Covid. Did you have to interrupt any lines of study to devote yourself to this worldwide problem?***

No. You have to remember that scientists train over many decades and that implies we have a high degree of specialisation. We are specialists. That's why we have to devote ourselves to our specialism, in which society has invested so much, in areas where we can help achieve progress. I did not have to pay to study at Buenos Aires University, I was trained for free, and afterwards I had the opportunity to continue this training thanks to many institutions. That's why I have the responsibility to apply my knowledge to make progress in inflammation regulation and give back to society, which is now global, what it has invested in me.

- ***Do you remember how old you were when you became interested in science?***

The truth is that I have a very personal reason, but one that is obviously influenced by what I have

lived and read. My parents are physicians, my father is also a scientist, and I am the eldest daughter. But I remember that when I was a very little girl, I wanted to be a palaeontologist because I was blown away when they discovered Lucy. My parents had bought me a beautiful book with some spectacular pages on palaeontology. Later, I became fascinated by biomedical aspects and that's why I chose to train in biochemistry. In Argentina, biomedical training allows you to go into research. So yes, I have wanted to be a researcher since I was little. And I love it because research is an intellectual challenge that you can take up throughout your life; you are always thinking about trying to answer new questions. For me, that's fascinating. The intellectual challenge of having to find answers to something we don't understand well.

- ***As director of a laboratory how much time do you have for research?***

All the time: I am co-director of my laboratory and all the activities I do are related to science. As I am a professor, there are certain aspects of what I do that are more related with service to my community, but everything is related to science.

- ***Apart from the intellectual commitment, there is also the commitment to the scientific training of the people who are in the laboratory.***

In science, as in many walks of life, there is commitment, and it is precisely because of that commitment that some days are hard, whereas others are incredible. But you have to be committed because things don't always work out in experiments. The aim is always to be able to answer the questions we have set ourselves.

I am Director of Graduate Studies in Immunobiology at the university and we have a programme with many people training to do their doctorate. In my opinion, it's important to generate the ideal critical-scientific atmosphere and provide the next generations of scientists with the tools they need.

I also have a general commitment to making sure that immunology, in reality science, reaches many people who have not had the privilege that I had of going to university.

Along with a good friend of mine, **Elina Zúñiga**, professor at California University San Diego, I began a programme called Global Immunotalks during the pandemic. The seminars take place on Zoom every Wednesday, except during vacations.

- ***You talk about giving back to society what it has invested in you. Have you ever considered returning to your country to practice science?***

I've thought about it a lot. For a scientist, like anyone else, it is very painful not to return to your country of origin. But I think that as we live in a more globalised world, one can be useful from another perspective.

In personal terms, and more so at my age, I realise that it has been one of the great costs of practising science as I do. Not living in Argentina means not being near many friends and family members. I've had to make a choice about my professional life. I understand a great investment is made in many of us who do not return. However, I think we can be a great positive influence on a worldwide scale, where one can make a contribution not only to one's country, but to more nations.

Obviously, each country has to think about the equation: **how much is invested and how many people leave, because the people who leave don't return**.

It's clear that science needs funding, but not just that. It also needs a critical mass, which is something I see at CNIC. It's an institution that has a critical mass that enables progress to be made in research.

- ***Women and science. Are you tired of being asked the question?***

I noticed a marked difference in the representation of women and other minorities when I began teaching. Before, I hadn't noticed it.

I think, as a professor, I have the responsibility to achieve a more balanced representation, not just of women but of other minorities.

- **Dr. Carla Rothlin participated in the seminar "Principles of resolving and non-resolving inflammation" in CNIC at the invitation of Dr. Guadalupe Sabio.**

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