"CNIC is like an oasis for science in Spain"

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Dr. Amelia Escolano runs her own group in Philadelphia (USA) where she is an Assistant Professor at the Wistar Institute's Center for Vaccines and Immunotherapy

Dr Amelia Escolano was destined to be a scientist. Both of her parents were chemists, and research seemed to form part of her DNA. After completing her degree in biochemistry at the Universities of Oviedo and Turku (Finland), followed by a masters at the Centro de Biología Molecular Severo Ochoa in Madrid, she arrived at the Centro Nacional de Investigaciones Cardiovasculares (CNIC), where she obtained her PhD in biochemistry and molecular biology. After a placement at the Rockefeller University of New York to complete her post-doctoral training, she now leads her own research group in Philadelphia (USA), where she is assistant professor at the Vaccine and Immunotherapy Center of the Wistar Institute. With the goal of producing a universal vaccine against HIV, Escolano's group is working on a novel vaccination strategy called sequential vaccination, which consists of injecting a series of different versions of a viral component, in this case the HIV envelope protein, to induce an immune response giving broad protection against the AIDS virus. She also believes that SARS-CoV-2 and other viruses with the capacity to mutate can also be targeted with sequential immunisation

Where does your interest in researching vaccines stem from?

During my pre-doctoral placement at CNIC, I studied the anti-inflammatory role of macrophages. But, on starting my postdoctorate in Dr Michel Nussenzweig's laboratory at the Rockefeller University in New York, I took a radically different route. Dr Nussenzweig's laboratory is internationally renowned for its research into HIV and B-cell biology, the cells that produce antibodies. That is where I began to work on the design of a universal vaccine to prevent infection by HIV, the virus that causes AIDS.

Now, I lead my independent laboratory at Philadelphia's Wistar Institute, where my research into vaccination continues. My group is working on the design of new vaccination strategies against HIV and on analysing the immune response induced by our vaccination regimes, in particular the response to B and T cells.

- ***So, how important has the knowledge acquired from COVID vaccines been for application to other diseases?***

In fact, the opposite is true: all of the efforts that the research community has made to understand HIV or the flu virus over the years are what has facilitated the development of a vaccine for SARS-CoV-2 so quickly. The same techniques, the same methods, the same studies have been used and applied to analyse infection from SARS-CoV-2 and to design treatments and vaccines.

Many researchers who were working on HIV, influenza, and so on, threw themselves into studying SARS-CoV-2, and have used all of their methodologies to study cellular and antibody response after infection or vaccination. It's been interesting to see how all of these efforts and prior research devoted to other viruses has facilitated and accelerated the design and production of a vaccine against SARS-CoV-2.

What's more, the success of mRNA vaccines and their validation in millions of people have promoted them being considered for other viruses, including HIV. It will be interesting to see the results of these trials in the near future.

- ***Why is there still no vaccine for HIV?***

HIV is very special. On the one hand, it is a virus that mutates very quickly, creating a wide diversity of different strains. This is the same problem we find with the flu virus, which is why we have to update the vaccine every year because the strain in circulation differs. We don’t have a universal vaccine for the flu. An effective vaccine against HIV would have to induce production of a specific type of antibody that can neutralise a large number or the majority of HIV strains. These antibodies,

called neutralising antibodies, cover a wide spectrum and attach to specific parts of the HIV virus that are conserved in all of the circulating HIV strains. To design a vaccine that can generate this type of antibody, we use the envelope protein of HIV, which is the equivalent of SARS-CoV-2's spike protein. When this protein is used as an immunogen, the antibodies that are produced generally attach to areas of the envelope protein that are variable and are not conserved between the different strains, so those proteins would not protect against wide viral diversity. This immunity could protect you against strain 1, but would not protect against strains 2, 3, 4, 5 ... This is one of the great challenges when designing a vaccine for HIV: it's very difficult to focus the antibody response to given areas of the envelope protein so that these antibodies can protect you against all of the existing strains.

There are currently many researchers working on how to modify this protein so that, for instance, certain areas (epitopes) are not immunogenic, or to make the epitopes of interest more immunogenic, which is very complicated.

- ***How are you trying to solve this problem in your research?***

What we are using is a type of vaccination called sequential vaccination. Unlike traditional vaccination systems, where the immunogen itself is administered several times, for instance, in the case of SARS-CoV-2, what we do is inject different versions of the immunogen, one after another, in order to target antibody response to the epitopes of interest and induce maturation of these antibodies so they acquire the capacity to neutralise HIV. We start by injecting a version of the HIV envelope that is highly modified and subsequently, instead of re-injecting the same one, we inoculate another that is a little less modified, more similar to the natural protein of the envelope. The envelope proteins are administered sequentially, with increasingly less modification until the final injection, which is the unmodified, natural type.

We are currently designing different sequential vaccination protocols that we are testing on different animal models including murine and simian ones.

- ***Is it used for other diseases apart from HIV?***

Sequential vaccination is being tested in the context of other viral infections like the flu or COVID. It is a type of vaccination that can be very useful to induce immunity against viruses that are highly variable. In that way, we could get antibodies with the capacity to neutralise a wide spectrum of flu, SARS-CoV-2 or HIV viruses. What's more, sequential vaccination could be useful to induce immunity to bacteria and cancer, an area that we would like to explore in the near future.

- ***Did your research at CNIC already focus on viruses?***

At CNIC, I worked on macrophages and their anti-inflammatory role in different pathological contexts. What we saw was that in macrophages, when the phosphatase calcineurin is inhibited or deleted, they acquire an anti-inflammatory phenotype that contributes to reducing different models of inflammation in mice. My thesis research project was in the field of immunology, but not related with virus, vaccines or B-cells, which is what I am currently studying in my Philadelphia laboratory. The step to post-doctoral work was a radical change as regards the focus of my research.

- ***How did that change come about?***

Towards the end of my thesis at the CNIC, I decided to do a pre-doctoral placement abroad with the idea of exploring laboratories for my post-doctoral research. Thanks to the recommendation of Dr Almudena Ramiro, I decided to go to Dr Michel Nussenzweig's laboratory at the Rockefeller University in New York, where I did a three-month placement. After those three months, I returned to

CNIC, defended my thesis, published my article and afterwards returned to the Rockefeller to do my post-doctoral work. During the first months I worked with macrophages and dendritic cells, helping a colleague to complete their studies, but I soon gravitated towards HIV and the design of vaccination protocols. At the time I arrived in New York, this was a hot topic and a completely new area for me, with all of the attendant difficulties, but I could never have imagined a better place to make that transition. My post-doctoral period was extremely productive and enriching. Dr. Nussenzweig was a fabulous mentor, and I received the first-class training that meant I could become an independent researcher in the USA.

- ***What change did you notice between working at CNIC and in the United States?***

The first difference I noticed when I arrived in the USA was that society in general values and gives recognition to scientists. Spain still does not understand that science and innovation are pillar stones of the economy and progress.

Rockefeller University is one of the top scientific institutions in the world. Its policy is to try to provide scientists with everything we need to do our job without having to worry too much about other things. And, judging on the amount of recognition it receives, it seems to work.

My experience at CNIC was fantastic. My mentor, Dr Dr. Juan Miguel Redondo, and my colleagues offered me everything I needed in my training as a scientist, and even today they continue to support and help me all they can, for which I am profoundly grateful. I don't think that my experience is representative of what doing a doctorate in Spain is like. I never felt that my work was limited by laboratory resources, but the CNIC is like an oasis for science in Spain. Colleagues of mine doing their theses in other Spanish institutions, and students that I have spoken to recently, have had to work on their thesis without receiving a salary. Their situation is precarious, and it is deplorable.

- ***When you were studying at university or in CNIC, did you see going abroad as a necessary step?***

From the very start of my degree, I knew that I would go abroad. In my case, it was not a forced decision. Going abroad is a way of developing, coming into contact with new stimuli and environments, meeting people and learning. Leaving Spain, or your comfort zone, is highly recommendable whenever possible. The last semester of my degree was spent in a laboratory at Turku University in Finland. That was my first experience abroad and it was one of the best of my life. It helped me gain a better understanding of myself, to know other cultures, other ways of seeing things, improve my English, and I had a great time. It was a very enriching experience. These experiences serve to put yourself to the test, discover your limits, and gain maturity and vision.

- ***What were your professional decisions based on?***

I now realise that when I finished my degree I did not have enough information to evaluate all of the options open to me, so my decisions were somewhat limited by a lack of information. My first decision was to stay in Oviedo and do the thesis. However, before starting the thesis, and almost unexpectedly, I received a grant from the Spanish National Research Council, the CSIC, for an introduction to research in Madrid. This period of time in Madrid made me rethink and reconsider my options. I changed my mind and decided to start my thesis in that laboratory in Madrid and a few months later I was recruited to Cincinnati. After a time in Cincinnati, I realised that it was not what I wanted and I returned to Spain to start a new thesis at CNIC, in Dr Redondo's laboratory, where I received an extraordinary training. When I made that decision, I did not even consider the option of saying in the USA, which could have been better or worse. Nowadays there is more information. It is important that students devote time to studying their own options and learning from the mistakes and successes of others so they can make informed decisions. The end of a degree and a thesis are stressful moments when we are expected to make decisions that can mark our future careers. In my case, it was not until the post-doctorate that I felt mature and informed enough to make my next

decision, which was to establish myself as an independent researcher at the Wistar Institute in Philadelphia.

- ***Did your predoctoral and post-doctoral experiences help when it came to forming your own group?***

Both my thesis and my post doctorate were very long, six to seven years each, so I had time to mature and the training necessary to tackle the new stage. During my thesis I learned to design experiments, to analyse them and, to conclude, I learned a multitude of techniques, to work in a team, to present my work in public...My post-doc was also very complete and highly productive. It allowed me to specialise and gain a foothold in my area of research. When I finished my post-doc, and even before that, I felt that I was ready for independence. It has been a long journey, but each and every complication I have had to face in my career has helped me to become resilient, which is an indispensable quality in science.

- ***What is your experience of being a woman in science?***

The world of science, like many others, is still dominated by men, and the lack of female presence in some contexts is surprising. Little by little, women are carving out a niche in positions of greater responsibility, and conditions are becoming more equal. From my position, I would encourage all women not to let themselves be intimidated and to pursue their goals without fear. During my career I have worked with some extraordinary women, who have incredible strength, women who forged the path for those of us who have come later. I hope that my career also serves to forge a path for new generations of women in science.

- ***You are now the mentor of the researchers in your group. How important is mentoring?***

The role of mentor is indispensable, and one that we have to prepare for mainly during the post-doc. It is not a trivial thing; each student is different and needs to be treated differently. You have to know whether to give the help or independence that each person needs to develop in the most efficient way. You need to know how to give recognition and thanks, but also how to call things to order when necessary. My hope and aim are that all of the people who work with me enjoy their jobs. I have enjoyed myself enormously doing what I do, and I hope to be able to transmit my enthusiasm for science to my students. I also trust that my experience serves them when it comes to making their decisions.

- *Dr. Amelia Escolano participated in the Sequential vaccination to induce somatic hypermutation Seminar: From naïve PhD student to group leader*