Carola Vinuesa: "Science offers many opportunities to reinvent yourself, to travel, to work in different environments, and to meet new people"

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Carola García de Vinuesa is a senior group leader at the Francis Crick Institute in London and the John Curtin School of Medical Research in Canberra.

Carola Vinuesa is a Group Leader and Assistant Director of Research at the Francis Crick Institute in London (UK). Dr Vinuesa has discovered new T cell subsets that control B cell responses (follicular helper T cells [Tfh] and follicular regulatory T cells [Tfr]), as well as the mechanisms by which they regulate antibody responses and limit autoimmunity. Her recent discoveries are connecting genetic variation in humans to autoimmune diseases such as lupus, and shedding light on disease pathogenesis. She has received several awards, including the Gottschalk Medal of the Australian Academy of Science, the Australian Science Minister's Award for Scientist of the Year, the 2023 Lupus Insight Prize (LRA), and the 2023 Johann Anton Merck Award. Her name became famous in Australia, and then throughout the world, following a long judicial process in that country, in which this Spanish immunologist managed to free Kathleen Folbigg from prison, a woman who was imprisoned for twenty years accused of having killed her children, by proving that her four deceased children were not murdered, but carried genetic mutations that would explain their premature death.

- **Your laboratory has been researching the factors that contribute to the development of autoimmunity for many years.**

Over the past 10 years, we have focused on discovering new or very low-frequency genetic variants in patients with severe immunodeficiencies, especially in children. The genetic architecture of these diseases covers a very wide spectrum, from highly polygenic diseases with many contributing variants, to a narrower monogenic spectrum where only one variant can cause the disease. Identifying these variants in monogenic diseases offers us valuable information about the pathogenesis or mechanisms of the disease. Even though these severe and rare mutations are found in few children, understanding how they cause the disease can give us bigger clues to help understand autoimmune diseases, which in many cases are not understood well.

Our team is also working on linking human genetic variation to autoimmune diseases to identify more specific treatments. By sequencing the DNA of patients with various forms of autoimmunity, such as lupus, we have identified new and rare variants that highlight the role of specific genes in immune tolerance. This is helping us create different disease models that we can use to better understand disease development, improve diagnosis, and test new treatments.

For example, in my lab we have found a central pathway in lupus. We have designed a model that replicates the human disease, introducing the mutation from a girl with lupus into a mouse model that develops severe lupus, similar to the patient's. By adding two more sophisticated models, that we have developed ourselves, we can finally answer questions that previously had no answer. Where do the cells that produce antibodies come from? Are they new cells from the bone marrow, or are they autoimmune cells that were generated by some viral trigger and have survived for decades? We can research whether these cells are in a specific tissue or in the bone marrow. This has been very exciting for us, as these models allow us to address fundamental questions that used to prevent us from better understanding these diseases**.**

- **Your research has also had an impact on forensic medicine, at least in Australia.**

Thanks to the genomic work that we carried out in the Kathleen Folbigg case, we have started to understand the differences between clinical genomic analysis and forensic genomic analysis. Unfortunately, there are many cases today where a genomic diagnosis adapted to medical forensics is not being applied. That is, the level of certainty required for a clinical diagnosis is different from that needed to establish reasonable doubt in a trial. However, up until now, the genomic framework we have used, that of the American College of Medical Genetics and Genomics, is rigid because it needs to be so, in order to be useful in the clinic. But we are seeing that it has limitations in medical legal cases and that it needs to be adapted, for example, to look more closely at variants of

uncertain significance (VUS).

- **While working on the Folbigg case, I suppose you faced many obstacles in explaining your discoveries to the judges and the judicial system.**

Part of the obstacle was getting the legal system to understand it, and the other part of it was due to the disagreement between two groups of geneticists. I'm not saying that one was right and the other was wrong, because we were all trying to do our best. However, the framework used in court was very rigid. This approach, although suitable for use in the clinic, did not allow for the exploration of unknown genetic variants, which are often more lethal, precisely because they are severe, and therefore studied less. Because they are so severe, these mutations often prevent individuals from reaching reproductive age and are therefore not transmitted to offspring. That’s why, it is possible that they may only be detected once in a lifetime. Due to their rarity, it is difficult to classify them as likely pathogenic or non-pathogenic variants, but that does not mean that they should be excluded from study, especially in a legal context, such as in cases of sudden infant death.

Unfortunately, this is not the only case. Since we have been working on this case, we have received other similar ones, in which women have been accused – some possibly wrongly – of causing harm or death to their children. In many of these cases, rare diseases are involved. We know that there are already around 10,000 rare genetic diseases affecting 400 million people, and it is not unusual for a child to have two genetic diseases at the same time. However, it is impossible for a pediatrician to have all of these diagnoses in mind or have direct experience with them. Many of these diseases manifest themselves in unusual ways, and sometimes accusations against mothers are made when they insist that something is wrong with the child, or when they make complaints against a doctor, ask for a second opinion, or seek multiple consultations. It is at these times that, unfortunately, they are unfairly accused.

My laboratory has received some of these cases and by conducting more in-depth genetic studies, we have discovered variants that were at first considered uncertain. However, by analyzing the family tree, we can see that some mutations are new. These are things that are not researched in routine laboratory diagnostics. Even though diagnostic laboratories do a good job, they may not have the appropriate resources or methods to approach these complex legal cases

- **Aren’t you worried that you have become a reference for these types of legal cases?**

We can’t do very much about this. Of all the things that have been mentioned to me, I have only been able to help in a few cases because I do everything in my free time and without remuneration. We are talking about a group of people concerned about this problem, trying to create a foundation. The problem is that at the moment there is no money to pay geneticists, pediatricians or lawyers who want and can analyze these cases in depth. It is a very big setback, because there are hundreds of mothers - mostly women, although also some fathers - accused of having caused harm, when in many cases it seems that they are dealing with rare genetic diseases.

We can’t do everything, so it is necessary to educate and explain the need to conduct a broader and more in-depth diagnosis, including variants of uncertain significance (VUS). I’m not saying that we shouldn’t aim for certainty that the variant is pathogenic, that is what we actually aim for. What we have observed is that, as soon as you contact experts, analyze the family tree, and obtain more samples from the family, in some cases functional tests are performed and those variants are reclassified. However, it is important to incorporate them into the genetic study from the start, and also not to limit yourself to gene panels only, as many times the mutation occurs in a gene that was not previously anticipated, but which makes more sense later.

- **Your approach to genomics seems to be more dynamic, not as fragmented as in other fields.**

Current genomics is fragmented, routine, and focused on the clinic and on actionable variants, for which, it is true, a very high level of certainty is required. However, in many of these cases of sudden death, the cause can be very different pathologies, which is sometimes difficult to anticipate. From sudden death related to epilepsy, to cardiac death, or even to mitochondrial or metabolic diseases. Therefore, it is necessary to address these cases in a much broader way, without restricting ourselves to gene panels only, and with more inclusive entry criteria.

Many of these variants, precisely because they are so pathogenic, lethal, and rare, have not been seen before, which makes their initial classification as pathogenic variants difficult.

- **Do you think your medical vocation influences your approach to research?**

I think that those of us who practice medicine, in general, do so because we are attracted by the idea of being able to solve problems. It is a vocation of service. At first, I thought that I wanted to be a Doctor Without Borders and go to work in some country in Africa, for example. But then I changed direction a little because I was very interested in research and I saw that through it, large-scale problems that affect many people could be resolved, and that was very gratifying for me.

Why do I dedicate myself to this? I am very affected by injustice. When I see cases in which there have been accusations and, from the start, it seems obvious that it is a medical problem, it worries me. I have a medical background and, for example, in the case of Kathleen Folbigg, the mother accused of murdering her four children, when they tell you that the children died, and that one of them had epilepsy with blindness and another myocarditis, it is natural to think that something does not add up. Furthermore, all the evidence was circumstantial, because no one had seen this woman harm her children, which is very different from other cases.

You immediately think it makes sense to do a more in-depth investigation, and currently genetics has provided us with tools that we did not have 10 years ago. We were already doing this type of work, so why not apply it, if it can help other people. I was contacted after they tried to speak to several people who for various reasons, could not or did not want to do it. So, I thought: “well, if we can help, and they can’t find anyone else to do it, why wouldn’t we?”.

- **There are researchers who are more motivated by pure knowledge, discovering a gene or a specific pathway. In your case, it seems that you are not only interested in the knowledge itself, but also on its applicability, like in this case where it served to defend a person, or for example, in the lupus case.**

I have always been motivated by knowledge. I love asking important and difficult questions, and facing the challenge of solving important dilemmas in science. However, it is true that when you come across cases like these and you get involved, even though it is very satisfying, it can also be very painful and difficult. In fact, in this case that we discussed earlier, I felt quite attacked; anyone who has undergone a judicial process knows that. You are criticized, and during these years, I felt very stressed out. But looking back, I think it has been one of the things that has given me the most satisfaction in my life. Being able to help a person, prove their innocence... and it is not just one person. This has also led to a review of the legal system in Australia.

This case was recognized as the biggest miscarriage of justice in Australian history: 20 years in jail, plus 5 previous years, arrested and charged. It was a huge mistake, with multiple trials, many judges involved and numerous legal reviews. This has caused Australia's legal system to consider the need for an independent criminal case review commission, which did not exist up until now. Before, it was a politically elected figure who decided whether a case was reviewed or not.

It is gratifying to think that a legal system can be improved. Cases like this exist all over the world, and there is now a greater awareness of how easy it is to give a wrong verdict or diagnosis. There are 4 or 5 diseases within this spectrum where, without proper genetic testing, it is very difficult to conclude that the child has been harmed, and not recognizing that it could be a rare disease. We already know that there are 10,000 rare diseases, and sadly, many of the children we see have more

than one. For example, a mutation that causes chronic pain syndrome and, at the same time, a mutation that causes aphasia, intellectual disability or epilepsy.

In the past, when a child had seizures and pain, it was considered a possible sign of abuse. But nowadays, we have to consider the possibility of rare diseases. I think this is positive, because it means there is a lot of potential for change, both in medicine and in justice, and in how mothers are treated, who are 90% of the defendants in these cases. This is because they are usually the caregivers.

- **If you could change something in the judicial system, what would it be?**

I would like to change two things. Firstly, to establish clear guidelines on who should be consulted when statistics or probabilities are used in court, because the misuse of statistics has contributed to many wrongful convictions. If the court needs to use statistics to back up a conviction, it should consult impartial expert entities such as the Royal Society of Statistics in London.

Secondly, before accusing a father or mother of harming or killing a child, when there is no strong evidence or history of abuse, a thorough genomic investigation should be conducted, including variants of uncertain significance, and that are not part of routine clinical genomic diagnosis.

- **In some ways, you got rid of the pressure of living in Australia.**

It wasn't because of this case, although yes, I went through a hard time because of it. However, it made sense for me to go back to Europe; I had been at the same university for 20 years and my family is in Spain. I liked life in Australia and I have very good memories.

It was the time of the transition. I started with the case in 2018. The first interview was between 2018 and 2019, and in 2021 we requested the petition of forgiveness, because we published the article in 2020. In August 2021 I came to England, and in2022 they called me for the second consultation. We had the second interview between 2022 and 2023. In fact, I went to Australia twice, in November 2022 and in February 2023.

- **How does someone go from wanting to be a Doctor Without Borders to studying immunology? It’s quite a big change.**

My residency years in the United Kingdom were very hard. I think the health system had very few resources: there were few doctors and we suffered a high level of pressure and lack of supervision, which was very stressful for me. In addition, I was always interested in understanding diseases better and how they work. I like asking questions. So, I asked myself what I would be interested in studying if I could choose a field to research. Despite my experience in India and Ghana, where the biggest problems are infections, I must say that I have very fond memories of my immunology teachers during my degree. For me, it was one of the subjects I liked the most. Both Eduardo Ortiz de Landázuri and Francisco Sánchez Madrid were my teachers at La Princesa Hospital, where I studied the last three years at the Autonomous University. I have wonderful memories of how they taught us immunology, which nowadays, we know is at the root of many diseases, such as inflammation, autoimmunity or immunodeficiencies. I found it to be a very attractive field, and that's why I decided to pursue it.

- **Do you transmit this passion for research to the young generations in your laboratory?**

We are lucky to continue having very motivated students. Science is still a vocation, and those who come to do doctorates or postdocs are people who are really interested. I think it's easy to spread passion and interest when you have them yourself. I love seeing how they fall in love with research, how they begin to formulate their own hypotheses. It's a wonderful process, and one of the things I

enjoy most is working with young people and watching them grow and get excited about important questions, although to some they may seem a little dark.

- **Mentoring is not something that is formally taught, it’s more a question of trial and error. What advice do you give your students?**

I think the best advice I can give them, and I see it with my daughters too, is that they believe in themselves. If I can get them to finish their PhD or post-doctorate believing in their capacity to generate good hypothesis, I will have done my job. Giving them space to ask questions, to design their own experiments and believing that they are good and capable, is an art. If they reach that level, they don’t need any more advice. If they believe in themselves, they will have a good career ahead of them and they will be good researchers. And it is hard, because it is a competitive career and sometimes you receive negative criticism. The scientific articles are always harshly reviewed, and everything is very competitive. But, if despite that negative atmosphere, they believe in themselves, they can succeed.

- **If you could say something to your 20-year-old self, what would you say?**

Maybe I would tell her not to worry so much about the future. Deciding whether to leave medicine or go into research was very stressful for me. Over time, you realize that life takes you down paths you never imagined before, and you end up finding things that you are passionate about. Don't worry, life takes many turns, and change is good. I would tell myself to allow me to be guided by my own instinct. Many of my decisions, in reality, were coincidental. I never went to do job interviews; opportunities just came up randomly. That’s life, and change is positive. You learn from everything, and there is no experience that I look back on and think was negative. I'm sure I learned something important from all of my experiences. Science gives you many opportunities to reinvent yourself, to travel, to work in different environments and meet new people. I would tell myself: take advantage of the positive side in every situation and learn from your mistakes. Don't stress out about not knowing which way to go. Life is full of changes and opportunities, and you never know what lies ahead.

- **Much is said about researchers returning to their countries of origin. Have you felt the need to return to Spain, or do you believe that science can be conducted from anywhere**

I have never felt that need, because life has taken me to different places. For practical reasons, I had young daughters, and sometimes you just can’t make certain changes. Returning was never something I considered. But I feel sentimental about it: I love Spain, I love Madrid and Cádiz, where I was born. I love my family and I have a very strong emotional bond with Spain. So, at some point, yes, I would love to return. Although for now I am very happy in England.