Gonzalo del Monte-Nieto: "Training at the CNIC is very highly valued and opens up many doors”

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Dr. Gonzalo del Monte-Nieto manages his own laboratory at the Australian Regenerative Medicine Institute at Monash University (Australia).

Dr. Gonzalo del Monte-Nieto received his PhD in 2011 from the Autonoma University in Madrid (Spain). He received training in Developmental and Molecular Biology by Professor José Luis de la Pompa and in 3D Image Analysis by Professor Antoon Moorman (Netherlands). In 2011 he joined Professor Richard Harvey at the Victor Chang Cardiac Research Institute (Sydney, Australia) to do his postdoc. In 2018 he founded his own laboratory at the Australian Regenerative Medicine Institute at Monash University (Melbourne, Australia). Throughout his career, he has made important discoveries about the mechanisms that are behind the formation of cardiac chambers, valves, epicardium, and coronary vessels during embryonic development. His research has led to important breakthroughs to better understand cardiovascular diseases such as noncompaction cardiomyopathy, atrial septal defects, coronary artery disease, gestational hypoxia, as well as pancreatic cancer. His laboratory focuses on the study of molecular mechanisms and developmental processes that orchestrate heart development and the transfer of that knowledge to congenital and adult heart diseases, as well as cardiac regeneration. His laboratory is also developing innovative methods to analyze 2D and 3D images so as to optimize the morphological and molecular characterization of cardiac development and disease.

- **What is a Spanish researcher doing in Australia?**

I studied Biology at the Autonoma University of Madrid and during that time, I was part of José Luis de Pompa's team at the National Center for Biotechnology (CNB-CSIC). After a short stay in Amsterdam, I finished my PhD at the CNIC, also on Jose Luis' (de la Pompa) team. After finishing my PhD, I received an offer from Richard Harvey, a cardiovascular researcher in Sydney, and that's where I finished my postdoc. I'm currently in charge of the laboratory at ARMI (Australian Regenerative Medicine Institute) at Monash University.

- **What does your research consist of in Australia?**

My work focuses on cardiovascular development, especially the integration of not only the communication among tissues, but also the space between them, that is, the extracellular matrix. We have discovered that the extracellular matrix plays a fundamental role in the formation of the heart. We are trying to understand how those processes permit the correct formation of the heart during embryonic development. If we are able to understand how the heart is formed in the embryo, we can identify the critical processes, that, when not working correctly, can generate cardiovascular disease, like congenital malformation that affects babies. Furthermore, we also work on adult cardiovascular diseases that recapitulate certain embryonic processes, but in pathological conditions. Understanding those processes could help us identify new therapeutic targets.

Another important aspect of our research is understanding how the myocardium, the heart muscle, is formed and also what structure it has. Learning about the proliferation of the cardiac muscle cells in the embryo can help us reactivate this proliferation in adults, a process that is lost in adult life. This is relevant, for example, for regeneration after a heart attack.

In mammalian embryos, the heart can regenerate itself, but this regenerative capacity is lost in the first days of life and an adult heart, affected by, for example, a myocardial infraction, cannot be repaired. What is the difference between those cells and those of the adult?

We are investigating the differences. One of the hypotheses that we are tracking in my laboratory is that the extracellular matrix of an adult is very restrictive, whilst that of the embryo is much more permissive, which allows the cells to move more freely. We believe that, if we can create a more permissive environment in the adult, with the help of mitogens, such as neuregulin for example, we can improve cardiac regeneration. We know there is no "pool" of stem cells in the heart of an adult, which is why the cardiomyocytes, the cells of the heart muscle, differ and participate in

regeneration.

- **Do you think this is the most plausible way to regenerate the heart or are there other alternatives?**

It’s just one of the possible ways. I don’t believe there is just one single solution, but rather a combination of various ones. There is research in the immune system that suggests that certain immune cells can prevent the formation of scars, and this is important when the heart suffers a myocardial infarction. When there is a wound, if the heart cells cannot proliferate and regenerate themselves, the body forms fibrous tissue to “close” the wound and maintain cardiac function, but at the cost of losing contractility. If we could reduce the formation of scars and activate proliferation of the cardiac muscle cells in a more permissive environment, we could offer a more effective alternative treatment.

- **Does all your research have a translational focus, intended for clinical application?**

In my laboratory, we work with not only with congenital diseases but also with other fundamental aspects. The first step is always trying to find out what is happening at a basic level. For example, if we identify genes related with a congenital cardiovascular disease, we can understand the process behind the defect and determine what is being altered. Although, the early diagnosis of cardiac defects in fetuses through echocardiography is not viable at this moment, we are advancing in that direction. The more we know about the processes involved in this, the better we can identify therapeutic targets to improve the results and avoid having to do a transplant.

- **Are you working on complete organ models? Can you explain what this consists of?**

Yes, unlike classic developmental biology, we are starting to study complete organs rather than just sections. We use embryonic hearts, and we are developing automated image analysis protocols. The key is to train artificial intelligence systems to learn to identify patterns in the images, something that is quite difficult for the human eye due to the complexity of the parameters involved. This technology allows us to work with complete tissues and conduct specific quantitative analyses.

- **What does your role as student supervisor involve?**

I started supervising during my postdoc, and since I started my research group, I try to apply the best practices that I learned from my previous experiences. I formed my research group almost while the COVID-19 pandemic started, so it was a hard year to establish the laboratory. The Australian borders were closed for two years and we had to work in shifts. It was a challenge, especially because I lost most of the senior researchers whom I worked with. However now, looking back, it was useful because it allowed me to develop automations and methodologies. I currently have a team of 10 people, including PhD students, one post doc student, one laboratory technician and two image analysis specialists.

- **What is the scientific community in Australia like?**

The scientific community in Australia is a little smaller, which allows one to find their own niche and become an expert in their area. This encourages collaboration and allows for a more relaxed work environment, with less competitiveness than in other countries. Nonetheless, what I miss most is the interaction with scientists from other parts of the world. Australia is quite isolated, and although the virtual conferences are useful, they lack that personal contact that you get from the in-person events.

- **What is the perception of the CNIC in Australia?**

The CNIC is a very internationally well-known center. When one says they've done their PhD there, everyone acknowledges it as a leading center, a reference in biomedical research. Training at the CNIC is very highly-valued and opens up many doors.