

Ángela Nieto: "Talented people leaving Spain is not a problem as long as they can come back"

17/06/2019

La Dra. Ángela Nieto es una de las investigadoras más relevantes en el campo de la Biología del Desarrollo y su carrera ha sido merecedora de numerosos galardones

Professor Ángela Nieto received her PhD in 1987 (Autónoma University, UAM, Madrid) after working on the interactions of nucleic acids in nucleosomes and ribosomes. In 1988, she moved to the Biomedical Research Institute (CSIC-UAM), also in Madrid, to study programmed cell death in lymphocytes. In 1989 she moved to the National Institute of Medical Research in London to work with David Wilkinson, where she isolated a number of genes involved in the morphogenesis of the nervous system. In 1993, she got a position as a Scientist at the Cajal Institute in Madrid. Since then, she has led a research group interested in studying cell movement and plasticity. In particular, her group has studied the transition from epithelium to mesenchyme in development and disease, and her main contribution has been the impact of the reactivation of this embryonic program in adult disease, including tumor progression, fibrosis, bone growth and mineralization. She was elected member of EMBO in 2000 and member of the Academy of Europe in 2009. Among others, she received the "Carmen and Severo Ochoa Award" (2004), "Francisco Cobos Foundation Prize" in Biomedical Research (2005); "Alberto Sols" for the best research career (2008), "Rey Jaime I" in

Basic Research (2009), QUO Magazine of the Spanish Science Team (2015), Recognition of Scientific Merit of the Generalitat Valenciana (2015), Prize of Basic Research in Nephrology "Iñigo Alvarez de Toledo" (2016), Mexico Award in Science and Technology (2017) and Lilly Foundation Prize in Preclinical Research (2018).

- **What is your current line of research?**

For more than 25 years we have been working in the field of cell movements. Starting from Developmental Biology, we want to understand how cell movements occur to form tissues formed by cells that have been born far from their final location. It is what is called, in cellular biology terms, 'mesenchymal epithelium transition'. Initially we have studied it in embryonic development, although the concept that we have developed in the last 15 years is the reactivation of these embryonic programs in adult pathologies. Thus, we have seen that this reactivation brings with it the spread of cancer cells from the primary tumor to subsequently lead to metastasis or secondary tumors. In the same way, we have also observed that this reactivation occurs in other pathologies, such as organ degeneration, specifically in fibrosis.

The CNIC is one of the great research institutes in Spain that also has a very important international recognition

- **And in the heart?**

Although externally we have bilateral symmetry in the left-right axis, internally there are many asymmetries in this axis, for example, the apex of the heart points to the left, the liver is to the right... The primordium of the heart, that initially is in the center, receives input from cells from both sides of the embryo that are directed to the middle line, and what we have seen is that there are many more cells that come from the right side, exerting a different force, and, therefore, they push the heart to the left side.

When this process does not occur, and the heart stays in the center, a pathology called mesocardia occurs, a condition that is not viable. There are other alterations, such as dextrocardia, in which the heart is located on the right, which in certain cases is viable. The displacement of the heart is essential not only for all organs to be optimally packaged, but also for concordance with the vasculature.

- **The heart is the first to be placed. Does that determine if the rest are placed correctly?**

It does not determine where the other organs are positioned, but it is the first to do so. Now we are studying what is the mechanism that positions the other organs and we are observing that it is something similar, but it is not determined by the heart. In 1 of every 10,000 humans there are alterations of the left-right axis of the embryo, which in many cases produce congenital cardiac malformations. Understanding the mechanism that positions the heart is also important to understand how different malformations occur.

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- **Can these malformations be corrected in humans?**

If we know the mechanisms, we will always have more chances to detect it beforehand and, in some way, to stop it.

- **Your work provides information on metastasis.**

The formation of metastasis implies, among other mechanisms, a reactivation of the embryonic program that directs cellular movements. As I mentioned earlier, there are many cells in the embryo that are born far away from their final destination. By activating this program of cellular movements, the cells are able to move until they reach their destination. There, they nest and begin to differentiate themselves in a particular organ; that is the normal process. It is easy to understand that, if this does not work well, the embryo cannot progress. In cancer there is a reactivation of this embryonic program and the cells of the primary tumor detach and nest in different organs where they will form new tumors, which are metastases, the cause of more than 90% of deaths associated with cancer.

- **You are part of the highly-valued school of Development Biology? How relevant is this in Spain?**

Development Biology is a very important subject in Spain. The school in Madrid was essential for this, and it is true that, for a long time, the main model of study was the *Drosophila* fly. But at the end of the 80s and 90s, some scientists began to work in the biology of the development of vertebrates, especially of mice, but also in chicken, and years later in zebrafish. There is a long tradition of development biology in Spain, thanks to Antonio García Bellido, Ginés Morata or Juan Modollet, etc. We have one of the most important schools of Development Biology in the world. It is a pleasure to have such important people in this field in our country.

- **In this sense, how important is the mentor figure?**

It is very important. Especially, because in the first years of the scientific career you have to make decisions, you have to make them yourself, but with a global knowledge of what happens. And that is transmitted through the mentor.

- **Do you remember any of your mentors?**

I remember my family's support, which I believe is truly fundamental. In my family, there are no scientists. Since I was little I liked chemistry and 'putting things together'. Every week my father brought me the "*Investigación y Ciencia*" (Science and Research) magazine. I also remember my high school teacher, when I was hesitant to study chemistry or biology. She was the one who piqued my interest in biology, from the cell and biochemistry point of view. And so I decided to study Biology and then Molecular Biology at the Autónoma University of Madrid. And the truth is that I think it was a very good decision.

- **Are you a mentor too?**

I am part of a mentoring program in the Community of Valencia and I also participate in programs especially with young scientists. The important thing is having the possibility to decide what each one really wants to do. In Spain, the scientific career has always been seen as a linear career, at the Academy. But there are many other possibilities, however, in our country unfortunately, many of these options are still missing. It is about finding the niche where one can develop more.

- **Why is the scientific career in Spain almost always associated with the Academy?**

In addition to lack of information about other options, there is a lack of possibilities in the area. The truth is that we have had some very bad years, which fortunately came after some very good years, which allowed for the system not to be irreversibly lost during the crisis, but we have to keep pushing a lot. Otherwise, we are doomed to lose a generation of scientists.

There is also a lack of information at the universities because the students do not know that, if they

do not have a good profile, in the future they will not be able to compete to get predoctoral contracts or do the thesis at a good center. It is essential that from the first moment you enter the university, you know that the performance will determine your chances. And if education in science can be promoted earlier on, it would be even better. For example, our postdocs will give talks to schools to promote science.

- **You mentioned that there could be a lost generation.**

I hope we can recover it. Talented people leaving Spain is not a problem as long as they can come back. Unfortunately, this is not the case on many occasions. In addition to investment, which is important, the management of different institutions within the science and technology system must be flexible, especially universities and public research institutes, where administrative constraint makes us lose competition in comparison with other centers and institutions, both from Spain as well as from other countries.

- **You have become more of a manager of your team now than a researcher, haven't you?**

I don't think it can be separated. What do we call research? To mix things in a test tube or to think and develop projects? You have to do both. It would be great if I had to invest less time in solving administrative problems. But what would not make any sense, at this time when there are 20 people in my laboratory, is that I was in a corner doing an experiment and was not available for what they need or was not thinking about the next project.

The interesting thing about this job is that no day is the same as another. This is a message I give to young people, to children. There are very few jobs in which there is such an important decision capacity only limited by your imagination. It is very enriching from the personal point of view. Although it requires a lot of effort and dedication, it is very rewarding.

- **What about failures? How do they influence things?**

If one is able to overcome difficulties, the rewards can appear. You have to have resilience, patience and perseverance. These three things together are not easy or hard, but the rewards are obtained after the effort. Effortless rewards are not as satisfying. With this I do not mean that you have to suffer but, work, discipline and rigor are important. Together with the freedom and passion that we put into this job, I think they create a mix that, if balanced, is rewarding for the person.

This job is something that has to be done not only as a way of life, but as a way to fulfill oneself. Seeing things for the first time that nobody has ever seen is real, although it is difficult to explain. Great discoveries are not made every day nor every 10 years, but those small advances are fundamental for the progress of science and for that of humanity. That's what we are here for.

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- **Do you think society values scientists?**

Society really appreciates scientists: we are highly valued and we have credibility. But it is important to transmit to society that our work has or will have an impact on society. And what is certainly not yet transmitted is that this requires an effort on behalf of the state, and public and private funding, to keep it working. And, even if it were a high amount of funding, it is not an expense, it is an investment. People know that research is the most profitable activity. Now it is up to society to demand more investment from the politicians, and this is not something that usually comes up in the election campaigns, because there are other more visible needs.

- **It is not your first visit to the CNIC. What is your opinion of the center?**

The CNIC is one of the great research institutes in Spain that also has a very important international recognition. Being here is always a pleasure. The CNIC scientists, together with the type of management, make it a very competitive center and I wish other Spanish centers, universities and public research organizations also had a more flexible management that would allow us to be, in global terms, more agile and more competitive.

Do you currently have any collaboration with the CNIC?

Currently, I don't have any collaboration with groups from the CNIC, but in the past I have worked a lot with researchers from this center. For example, Miguel Manzanares was in my laboratory when he returned from England, and we are still in contact, and with Miguel Torres I also have a lot of relation for many years. He is the current president of the Society of Developmental Biology and I was the former president. Also with José Luis de la Pompa and Juan Miguel Redondo, who were my classmates at the Autonomous University.

- *Dr. Ángela Nieto gave the Seminar "The epithelial to mesenchymal transition in heart laterality" invited by Drs. Miguel Torres y Miguel Manzanares.*

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