JCB Journal of Cell Biology

PEOPLE & IDEAS

Victoria Sanz-Moreno: Rho together for cancer research

Marie Anne O'Donnell

Sanz-Moreno investigates how the cytoskeleton controls tumor biology.

Traveling with an analytical chemist father and English teacher mother provided an early introduction to the ebb and flow of scientific research for Victoria Sanz-Moreno. After being born in London during her father's postdoctoral studies, her family moved back to Spain and eventually settled in the beautiful Asturias region. Of this time, Sanz-Moreno says, "I have strong memories of walking by the sea, mesmerized by its constant change. Now I live by the Thames River in London, as I love living near water." Learning and questioning were the norm in her family but after dipping a toe in the scientific process with school projects on plant phototropism and how diet affects your body, Sanz-Moreno says, "there was no going back!"

We contacted Sanz-Moreno to find out more.

Where and with whom have you studied?

I studied chemistry and then did a master's in biochemistry at the University of Oviedo. My grandmother died of cancer at quite a young age during my first year and that really had an impact on me. My other grandparents lived longer, but suffered from neurodegenerative disease. My master of science project with Maria Teresa Fernandez and Antonello Novelli was about the toxicity of aluminum on neurons and astrocytes. After that, my passion for understanding cancer took me to Santander (by the sea!) and a PhD at Cantabria University, supervised by Piero Crespo. At the time, Piero was a "rising star" in cancer cell signaling in Spain. I studied oncogenic and stress pathways and was hooked by cancer research and cell signaling. Throughout my PhD years, I read the beautiful work of Chris Marshall on Ras GTPase signaling and how Rho GTPases affect the cytoskeleton of cancer cells. I was so fascinated that I applied to his laboratory and won a fellowship to work with him in London and return to my birthplace. My time in Chris' laboratory at the Institute of Cancer Research was wonderful. I learned microscopy thanks to Hugh Paterson, the importance of 3D matrix studies, and to look at cells in the context of full tumors. And the fun part was applying my molecular biology skills into all the systems available in Chris' laboratory. We made very exciting discoveries about Rho GTPase signaling and plasticity of tumor cell migration (1–3) and I deeply miss my scientific discussions with Chris. He had a tremendous influence on my way of thinking that I pass on to my own mentees: it is important to be excited by your science, at the same time as being highly critical. I was then recruited to be a group leader in the Randall Centre (King's College London) by the Rho GTPase signaling pioneer Anne Ridley. Anne is an inspirational scientist and human being. All my career moves were supported by very encouraging mentors.

"It is important to be excited by your science, at the same time as being highly critical."

What drew you to your current area of study?

3D biology has fascinated me for a long time. From the moment I saw how different cells appear in complex matrices, I could not go back to culturing cells on plastic. At the heart of this, deciphering signaling mechanisms is what I enjoy most. I want to deeply understand how decisions are made after cells sense either physical or chemical stimuli. The cytoskeleton—and actomyosin in particular—integrates these signals into appropriate responses in the nucleus. It can transduce a change in a chemokine/cytokine concentration, or matrix composition, into a specific transcriptional response (3–6). We focus on understanding how cells decide to migrate or invade tissue after

Victoria Sanz Moreno. IMAGE COURTESY OF VICTORIA SANZ-MORENO.

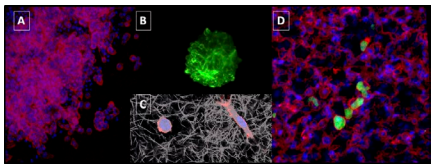
receiving these signals, but we are starting to look at other outcomes such as proliferation, survival, or communication with other cells. In the context of cancer, this is highly relevant as cells in different areas of a tumor may receive different signals resulting in tumor heterogeneity.

What are you currently working on? What is up next for you?

From a series of omics studies to characterize cancer cells, we realized that highly invasive cells are well suited to interacting with the tumor microenvironment (3–6). The laboratory is now trying to understand if different cytoskeletal configurations and invasive abilities in cancer cells favor distinct microenvironments. We are looking in detail at the matrix and the normal cells that surround tumor cells in mouse models and human patient samples using in vitro systems (4). These noncancerous cells are mainly endothelial cells (5), fibroblasts (3), and immune cells. We recapitulate tumor cell–stromal cell interactions in vitro using co-culture systems to understand the complexity we see in vivo.

modonnell@rockefeller.edu.

https://doi.org/10.1083/jcb.201805043



(A) Confocal imaging of A375M2 amoeboid melanoma cells growing as spheroids and invading a collagen I matrix (red, actin; blue, nucleus). **(B)** Lattice light sheet microscopy imaging of LifeAct (green) in A375M2 blebbing cells invading 3D collagen I. **(C)** Confocal imaging of collagen I and cells (red, actin; blue, nucleus; collagen, reflectance), A375M2 amoeboid melanoma cells (left) and HT1080 mesenchymal fibrosarcoma cells (right). **(D)** Confocal imaging of A375M2 melanoma cells (green) lodged in the lung capillaries (red, actin; blue, nucleus) of a mouse during metastatic colonization. IMAGE CREDITS: CECILIA HERRAIZ, PAHINI PANDYA, EVA CROSAS MOLIST, AND FREDRIK WALLBERG.

Metastatic disease and drug resistance are the major challenges for treating cancer patients. Moreover, inflammation fuels both primary tumor growth and metastatic dissemination (3, 4). The next step for the laboratory is to define the exact mechanisms by which the cytoskeleton and Rho GTPase signaling regulates communication between cancer and stromal cells, matrix remodeling, and cell fate. You could say we are interested in mechanoinflammatory signaling. We aim to define the specific molecular pathways and transcriptional responses regulated by the cytoskeleton that favor metastasis, inflammation, and drug resistance via cross talk with the microenvironment. The long-term goal would be to target those pathways as a therapeutic approach for cancer patients.

What kind of approach do you bring to your work?

You have to carry out science very rigorously, but it should be enjoyable. You need to be very thorough and demonstrate the same concept in multiple ways, preferably using multidisciplinary approaches to engage a larger scientific community. For me, discussing a piece of exciting and solid data with other scientists is unbeatable. Now, once you start understanding and controlling your system, it should be used to its full potential, even to test the boundaries in your field.

What did you learn during your training that prepared you for being a group leader?

I learned the hard way to never give up. During my PhD, there were times when things did not work at all. I learned the value of troubleshooting, changing each variable until I understood exactly why my experiments were not working. I fear the new generations of scientists could lose the ability to troubleshoot as technology is getting so complex. As a group leader, I often question laboratory members about how they have done experiments, to see if they payed enough attention to detail, took good notes, or used the right controls. I think that distinguishes the good scientists: they can solve a problem in the laboratory. For me, developing critical thinking and problem-solving skills are equally important.

I was not prepared for the more pastoral roles of the job. People in the laboratory are very important to me. I want them to get excited about their project and drive it successfully, but I also care about their well-being. And science can be tough at times. For that reason, I value my mentors much more now that I run my own laboratory. I am very grateful for their support and the confidence they infused in me.

"Don't let a rejected paper or grant bring you down, you need to develop resilience to criticism."

What has been the biggest challenge in your career so far?

I started my laboratory and became a mother at the same time, so that was challenging, but super exciting. The second time I felt really challenged was last year, when I was applying for a senior fellowship. I committed a lot of my time to preparing the application and interview and felt like I was not fully dedicated to the laboratory. In the end I got the fellowship and the laboratory managed very well. When faced with challenges, you need to set priorities and focus on them.

What is the best advice you have been given?

I have a few pearls of wisdom. A good piece of advice from Piero was not to get overexcited about preliminary data. Until you are sure about a result, you should not jump to conclusions. Chris Marshall used to tell me, "To do good science you need a very simple thing: money. If you have money you can hire clever people and they will use the money to do good science." I strive to provide the laboratory with enough funding so that ideas are the limit to what we can achieve. Having said that, an incredible set of very clever and generous collaborators are crucial to our laboratory and allow us to take those ideas much further.

What hobbies do you have?

All my free time is for my family. We really enjoy music, dance, theater, movies, and good food. We do take advantage of living in London. My son is old enough to enjoy a nice restaurant and then a good show. There is something a bit magical about theaters. . . maybe the passion I feel from the artists in their art is similar to my passion for science!

Any tips for a successful research career?

I am a strong believer in team work and encourage laboratory members to help each other using their different strengths to drive projects faster. Communication is also crucial; people in the laboratory know they can talk to me about science, but also if they have a problem outside the laboratory. Don't let a rejected paper or grant bring you down, you need to develop resilience to criticism, it is supposed to improve your science. Keep an open mind to ideas from different fields and disciplines, so you can drive new concepts forward. It can be a challenge, but it is very rewarding. Be passionate about what you do, if you don't believe your research is important, no one else will.

1. Sanz-Moreno, V., et al. 2008. *Cell.* 135:510–523.
2. Calvo, F., et al. 2011. *Nat. Cell Biol.* 13:819–826.
3. Sanz-Moreno, V., et al. 2011. *Cancer Cell.* 20:229–245.
4. Orgaz, J.L., et al. 2014. *Nat. Commun.* 5:4255.
5. Cantelli, G., et al. 2015. *Curr. Biol.* 25:2899–2914.
6. Herraiz, C., et al. 2016. *J. Natl. Cancer Inst.* 13:108.

Victoria Sanz-Moreno with her husband Fredrik and their son Oliver in Asturias. IMAGE COURTESY OF VICTORIA SANZ-MORENO.