Ángel Álvarez-Prado

Postdoctoral fellow

Ludwig Lausanne
Johanna Joyce laboratory

Tell us a bit about where you were born and raised.

I was born in Salamanca, a small town in the center west of Spain. It's a very old city, dating to pre-Roman times—I think it's from the seventh or eighth century BC. It has very characteristic architecture. Everything is dominated by a Baroque style and built of a special type of stone, called "Piedra de Villamayor," which gives the buildings a golden tone, so they shine beautifully under the sunlight. It's really a lovely place: small, very easy to live in, and culturally very, very rich. It hosts one of the oldest Universities in Europe. But I was raised in Guadalajara, a green, quiet and small town close to Madrid.

How did you wind up in science?

My interest in science began a very long time ago, probably high school. As a teenager, I was a bit geeky, always attracted by anything related to science and technology. I remember very well, for example, when the first draft of the human genome was published. I was 12 or 13 years old and it coincided with the first time I watched the movie Gattaca. I remember being thrilled by the possibility of manipulating the code of life, but at that point it looked like science fiction. Then, suddenly, the news was "Look, we now have read the human genome!" It was completely mind-blowing, I needed to know more about it.

What did you study for your PhD and what brought you to Lausanne?

I was always very interested in the biology of small things. I was fascinated by how we can operate as large organisms, but based on tiny molecules that work in a very coordinated fashion. An internship I did in my last year in college really shaped my taste for immunology and cancer. I was working on lymphoproliferative disorders, and I decided that I wanted to work in B cells specifically—and at the intersection of cancer biology and immunology. So I applied to the "B lymphocyte biology" lab, led by Almudena Ramiro at the Spanish Center for Cardiovascular Research (CNIC) in Madrid, where I developed my MSc and PhD theses, both successfully defended at Universidad Autónoma de Madrid. My PhD focused on understanding the molecular underpinnings of a fundamental process—antibody diversification—and how it can be derailed and lead to the development of

lymphomas. Back then, when I thought about cancer, I would only think about the malignant cells. But Karin de Visser gave a talk at CNIC that really opened my mind, introducing the concept of the "tumor microenvironment" and how immune cells can not only attack the tumor but also be hijacked by cancer cells to foster tumor progression, therapy resistance and metastatic spread. I was missing the big picture, the idea of tumors as whole ecosystems. I decided almost immediately that for my postdoctoral research, I wanted to work on the tumor microenvironment and specifically on its immune component. And when I looked into the literature for labs doing frontier research in this field, Johanna Joyce's was the obvious choice. I was extremely fortunate to be selected for her lab.

What has the focus of your postdoctoral research been in Johanna's lab?

In very general terms, I study the immune microenvironment of brain tumors, both primary tumors—glioblastomas—and brain metastases, with the idea of manipulating it for therapy. I've been working mostly on two different projects. The first one tried to answer a very simple question: How does the genetic makeup of cancer cells shape the composition and phenotype of immune cells in the microenvironment of brain metastatic tumors? Understanding this would have obvious implications for developing personalized immunotherapies, right? This study was published last year, and there are several spin-off projects derived from this research that I'm now working on.

The second project focused on glioblastomas. These are deadly primary brain cancers with a dismal median survival of around 15 months. They are very, very difficult to treat, firstly, because of their location, and secondly, because they're extremely heterogeneous. Within the same tumor, you can find cells with different genetic and epigenetic alterations belonging to different transcriptional subtypes, which makes it very difficult to find a single therapy able to eradicate all malignant cells. In addition, glioblastoma tumors present a very complex immunosuppressive microenvironment, which supports tumor growth and contributes to therapeutic resistance. This second project aims to reprogram the way in which cancer cells communicate with the immune microenvironment. Cancer cells are tricking the immune system. They're saying, "I'm the good guy. Don't attack me, don't kill me, help me grow." What I'm trying to do, by exploiting an innate immunity checkpoint, is to alert the immune system and foster the recruitment of effector immune cells and to also rewire the cells that are already in place—mostly tumor-associated macrophages—to trigger an antitumoral response.

Where do you see your research heading now, as you complete your postdoc?

I think my research will head towards developing personalized immunotherapeutic approaches for brain tumors informed by their genetic and microenvironmental landscapes. I'm now generating a series of mouse models that we plan to use as preclinical platforms to explore if we see differences in responses to immunotherapy depending on the mutational profile of the tumors plus the associated composition and phenotype of their immune microenvironments. This will be one of the pillars of my future lab, but I have many other ideas that I'm also eager to explore.

Where do you see tumor immunology evolving over the next 20 or 30 years, and what do you think it will have achieved by then?

That's tough to answer. I think that spatial 'omics and artificial intelligence are going to play a major role shaping the way in which we study cancer biology and develop new

therapies. And I think there will be significant advances in data-driven personalized medicine approaches. Artificial intelligence will allow us to exploit the huge amount of clinical, molecular and spatial data we're collecting to develop more effective customized immunotherapies, which will prove more and more effective as we advance our understanding on the mechanisms of immunosuppression that are at play in different cancers. Overall, I'm optimistic that we will have more efficacious treatments for cancer patients and I'm convinced that the immune system will stay at the core of these novel therapeutic approaches.

What are your avocational interests?

I love biking. I bike a lot, road biking mostly. Here in Switzerland, it's truly amazing. The landscapes that we have here are stunning. It's a bit demanding because it's quite hilly, but I think it's good exercise and also a fantastic way to clear your mind and relax. Sometimes new ideas come up during my cycling because it's a time in which I'm free of any other demands or time constraints. The same holds true for hiking, which I greatly enjoy as well.

I also love photography, particularly street photography. I frequently go to exhibitions and I have a ton of photography books at home. I shoot quite a bit, so you will frequently see me in the streets with my camera trying to capture interesting moments. And it has a similar effect to biking and hiking—it's like meditation.

What is the best career advice you've ever received?

I've been very lucky to have excellent mentors at all stages of my training, but I think my favorite bit of advice is something my PhD director told me once, that the quality of a scientist is usually directly proportional to their ability to say "No." We would all love to say yes to every request—to review a paper, to go to a conference, maybe to start a new exciting collaboration—but the reality is that time is finite. We have a limited number of hours per day and so many things on our plate that it's very important to prioritize and, whatever we do, do our best at it.

What would you change about the way we conduct science, if you could?

To begin with, the publication system, which is totally broken. We pay for publishing, we pay for accessing most of the journals, but we review for free. We give impact factors an excessive importance when we evaluate scientists, this is something that we should change. I think peer review must stay and scientists must be evaluated based on their work but it is very detrimental that we concede this dominant position to a few editorial companies and let them have such a large impact on our careers.

Come back to the way in which we used to do science in the past. When I read old papers, I'm always fascinated by how elegant and how simple the experiments were. My feeling is that now we are industrializing science. Now every paper needs to have the latest and fanciest technologies. It needs to have 25 figures. It needs to be extremely complex. I think this is because we are just spinning the wheel faster and faster, so we need to produce more, to produce fancier, to finish faster. So as we have more and more technology, I feel that we are devoting less and less time to just sitting down and thinking. If you see a Nature paper from the '50s, '60s, it's usually three figures and it's the three key experiments. And the experiments are beautiful, and the results are clear, and that was enough. Scientists in the past had the privilege of having a lot more time to just think, to be bolder in the ways in which they would design an experiment. I would like to come back a bit to this more romantic view of being a scientist.