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INTERVIEW

Transitions in development – an interview with Ariel Waisman

Ariel Waisman is a CONICET Junior Researcher in the Laboratory of Applied Research in Neurosciences at FLENI in Buenos Aires, Argentina. Ariel's group studies gene regulatory networks in human pluripotent stem cells to address mechanisms of development and cardiac differentiation, among other topics. We spoke to Ariel over Teams to learn more about his career path, the research interests in his group, and the challenges faced by researchers in Argentina and the Global South.

When did you first become interested in science?

When I was a child, like many kids, I was fascinated with magic and sorcery. I think there is a kind of connection between being a scientist and being a magician, right? Experiments, potions, etc. So the 'cartoonish' stereotype of a scientist has always intrigued me. If you ask me about a particular time in life, what comes to mind is a trip to Patagonia with my family to watch the stars. That was the first time I saw the Milky Way and my father, who is a fan of science, told us that the light of those stars had been travelling for thousands of years and that we were looking at the past. I was completely fascinated with that – I still remember it. Later, when I was in high school in the early 2000s, the Human Genome Project was frequently on the news. DNA was everywhere, so I loved watching documentaries about that on Discovery Channel. I think by the time I was 15 years old, I already knew I wanted to be a biologist.

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When did you decide to do a PhD?

I studied Biology at the University of Buenos Aires, which is a rather long programme – 6 years. Unlike the USA or Europe, there aren't many industry positions, so when you start a scientific career, you expect to stay in academia. This has somewhat changed in recent years, but it's still hard to do research in the private sector. When I started college at 18, I emailed scientists to see if I could work at their labs, for free, to get experience. A senior scientist close to retirement took me into his lab and began teaching me about molecular biology – it was amazing. Throughout my career, I've volunteered in many different labs: plant molecular biology, human virology and then a cancer stem cell lab. Finally, I went into Alejandra Guberman's lab for my Bachelor's thesis. Not many people can afford to work for free for so many years; I was lucky because my parents could support me. In the end, I had a good idea of what it was to work in a laboratory – and I loved it – so it seemed natural to do a PhD.

You stayed in Alejandra Guberman's lab for your PhD. What did you work on?

Initially, chromatin remodelling in stem cells. Right before my PhD, I became fascinated with the concept of nuclear architecture: that the nucleus has territories and domains. I wondered how nuclear architecture changes during differentiation and how it's dismantled and re-established following DNA replication and cell division. I convinced Alejandra to study that – she was very supportive. It is a hard question to answer, and I still think it's an interesting topic. I began with a simple observation that, indeed, inhibiting DNA replication during differentiation, blocks transcriptional changes associated with differentiation; I had two papers published out of my PhD, one of which was on the cover of the Journal of Molecular Biology (Waisman et al., 2017) and another in Scientific Reports (Waisman et al., 2019a). It is a challenging topic to study and, had I more time, I would have pursued it further.

You also spent some time at Rockefeller University in New York, USA. What was that experience like for you, culturally and scientifically?

Alejandra's laboratory was young so, during the first years of my PhD, I was setting up techniques, cell lines, etc. But the project needed equipment and expertise that were not available in Argentina. At that time, the Argentinian government, together with the Fulbright Foundation, had short-stay fellowships available. Coincidently, my boyfriend at the time had been the room-mate of a PhD student in Ali Brivanlou's lab and he connected us. Ali was wonderful and completely supportive. I got the fellowship, and I went to Rockefeller for 6 months. As I had been setting up techniques for the last 3 years, I didn't have many results. I obtained a big part of my PhD results in those 6 months…I worked a lot!

Those months at Rockefeller were the greatest opportunity and they made a profound change in my scientific thinking. Back in Alejandra's lab, we were studying gene regulation, focusing on molecular biology alone. But at Ali's lab, they analysed everything through the lens of developmental biology and evolution, which

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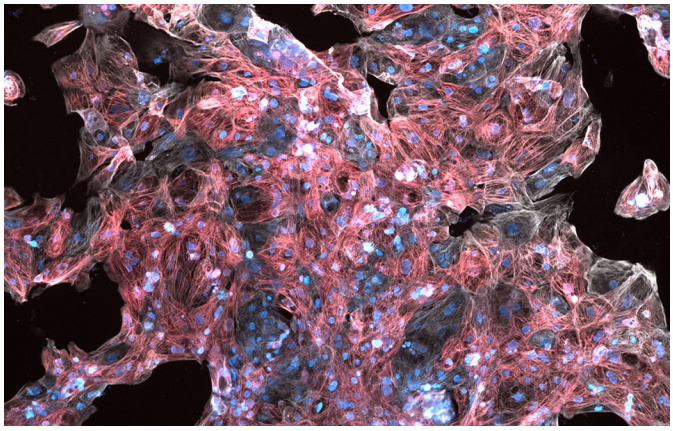

An immunofluorescence image of human IPSC-derived cardiomyocytes at day 26 of differentiation. There is a mixture of different cardiomyocyte subtypes, enriched in the left ventricular phenotype (triple positive cells). Gray, cardiac troponin (TNNT2); red, myosin light chain 2 (MYL2); cyan, HAND1.

was a game-changer for me. Something else that struck me was that many of the PhD students were physicists working in biology. I thought that was incredible because they were applying super-interesting ways of thinking and used computer programming all the time. They introduced me to Python, and I ended up spending many of the nights in New York learning to code. Overall, those months at Rockefeller were amazing, and I also made good friends in the lab, with whom I am still connected 9 years later.

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Why did you decide to join Santiago Miriuka's lab at FLENI, Argentina, for your postdoc?

It was a tough decision because my partner and I were deciding whether to stay in Argentina or do a postdoc abroad. We decided to stay, and I wanted to keep working on pluripotent stem cells, but also switch labs. There are only two laboratories in the whole of Argentina that work regularly on pluripotent stem cells: Alejandra's lab was one, which works with mouse cells, and the other one was Santiago's laboratory at FLENI, which works on human cells. Both Alejandra and Santiago had collaborated, so it was natural for me to go there. Santiago completely opened the doors of his group and was super-generous and supportive.

What projects were you involved in?

My initial postdoc was for only 2 years. I needed to switch projects fast to publish and have a chance to apply for a permanent position as a researcher. I had learned to program in Python, including a lot of automated image analysis. It was 2017, and Santiago was interested in delving into the field of artificial intelligence (AI) and applying it to biological research. We started this proof-of-concept project, to see if the artificial neural networks that were available back then could be trained to recognise the early stages of cell differentiation from light microscopy images. It worked well and was published on the cover of Stem Cell Reports (Waisman et al., 2019b). After that, I started another project from a collaboration, during an extension of my postdoc. Already in the confinement of the COVID-19 pandemic, I met Daniel Kopinke from the University of Florida in an online seminar. His lab worked on skeletal muscle, and I realised that I could help them analyse complex images to avoid the laborious work of manual segmentation. We teamed up and did a small project to generate a software tool that end users without any programming skills could use to automate their research. It was published in Scientific Reports (Waisman et al., 2021), and I believe it's helped a lot of people so far. At the same time, I missed the bench, so I started this new project to study a transcription factor and its role during different phases of pluripotency, which was published a few weeks ago (Waisman et al., 2024). Apart from that, I was always actively collaborating with different studies from the lab, mainly in cardiac differentiation of human pluripotent stem cells.

When did you start looking for independent positions?

At the end of 2019, I applied for a permanent position as a researcher at the National Council of Scientific Research (CONICET). The Argentinian system doesn't have a tenure track. It is a system similar to the French one, where you apply for a permanent position as a researcher for the state. The directors at FLENI asked me to stay and start my own group, so I had to choose whether to do another postdoc abroad (my initial idea) or to stay here and apply for a researcher position. I was happy in Argentina and, of course, this was a great opportunity. Besides, FLENI is a great place to do science: it is a non-profit, private neurological hospital – one of the few examples in Argentina of the private sector actively doing science and supporting basic research. This was important since most of the research done in Argentina is financed by the state, either in universities or public institutions. Although our lab is sustained by public grants and has recently joined CONICET as an associated institution, working in human pluripotent stem cells is expensive, so we couldn't do it without support from FLENI and from the Perez Companc Foundation, which also supports our research.

How was the transition to becoming a group leader?

It was gradual. I got my position as a researcher in 2020, during the COVID-19 pandemic. I was happy that I could start my own group but, at the same time, it was tough because we stayed at home for over a year. I used those months to study a lot about gene regulatory networks and developmental biology, and to learn about computer programming. I also volunteered to process COVID-19 tests and we even developed a cheaper approach to analyse swabs, which was published as a methods paper (Genoud et al., 2021). I also focused on a collaboration with Daniel Kopinke about image analysis in skeletal muscle. I was lucky that I could do a lot of things during that year, but the development of my group had to be postponed. In 2021, once we could go back to the lab, I took my two first Bachelor's degree students. It was a great experience that paved the way for mentoring my first PhD student in 2022. These past few years I had to learn a lot of things: apply for funding, think about new projects and recruit new PhD students. All of that while becoming a father, and with the complication that my son had to go through surgery a couple of times in his first year, which was tough but fortunately it all went well. So, although these last 2 years were quite challenging, I am quite happy now, both on a personal and professional level, and I am eager to continue growing my group.

Are there any skills you've needed to develop since becoming a PI?

One of the most important things I am trying to learn is multitasking. As a young PI forming a group, many things cannot

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wait. Applying for funding or dealing with bureaucracy while, at the same time, meeting with students regularly or solving important issues that appear out of the blue can be quite overwhelming.

Regarding students, I also want to be a present mentor for them. I have a lot of expertise on the bench and, since this is my first batch of students, I like to be available for them to discuss experimental design and approaches to obtaining and analysing results. My goal is to eventually count on the more senior students to teach the younger ones, but in the meantime, I like to be part of the big decisions, as well as small ones (e.g. how many microliters of enzyme are you using?). Basically, a bit of micromanaging! I realise too much of the latter is also a problem, and I am trying to learn to delegate and create smaller organisational structures in the lab so that everyone can be more productive – and so that my students don't want to kill me(!). Another important thing has to do with the fact that every student is different. I still talk to Alejandra (my PhD advisor) regularly, and she always stresses the importance of understanding that the role of a good mentor is to find the strategy that best suits each student's personality. In that sense, one of the most common things I have seen so far is that dealing with frustration is one of the toughest parts of the PhD. And from my end, that also requires a bit of patience and understanding. I would say that, at this stage, the mentoring part is the one I am trying to dedicate myself to the most. I want to be a good group leader and generate a good working environment – I take that responsibility very seriously.

What is your recruiting style?

Nobody is born knowing how to recruit. I'm still learning, because this job is about learning all the time. For me, it's important to recruit people that are compatible with me and the group, people who are passionate about research. My opinion is that you only become a scientist when you become independent in pursuing your own questions and how to answer them. You start the PhD without knowing that, but the idea is that you finish your PhD being a scientist. Sometimes, PhD students embark on a PhD without knowing what it will be like. I try to be honest from the start about what a PhD involves and what I expect from them, so they can decide if they truly want to do it and manage the frustration that comes with research work.

This job is about learning all the time

Who have been your own mentors?

I would name two mentors: Alejandra is a wonderful person; the years of my PhD were fantastic; she's super-supportive and enthusiastic about science; she also thinks of the lab like a family, and I share that philosophy. Santiago has also been an important mentor for me; I learned how to develop a strategy from him, both in the near, mid and long terms.

What are the research themes of your group?

I consider myself a pluripotent stem cell biologist, but I'm interested in thinking of our research through the lens of developmental biology too. Some of the main projects that we have in my group right now are related to cardiomyocyte differentiation. For example, the main problem with cardiac disease is that we mammals do not regenerate our hearts – why? It's complex, but one aspect is that mature mammalian cardiomyocytes do not proliferate after injury. I have two PhD students embarking on that topic to see if we can induce proliferation of human pluripotent stem cell-derived mature cardiomyocytes. For this, we set up a maturation protocol to produce cardiomyocytes with a postnatal phenotype because embryonic cardiomyocytes are more prone to proliferate; however this, in the end, does not reflect the behaviour of adult cells. Importantly, most of the techniques available to analyse proliferation in cell culture are indirect measures, such as nucleotide incorporation or metabolic analysis; cardiomyocytes, because they are multinucleated and change their metabolism, aren't suitable for these techniques. So, we are setting up a system to robustly assess cardiomyocyte proliferation. I'm also interested in more basic questions, such as developmental tempo and the speed of cell differentiation. I have a project with one postdoc and a student that studies how the speed of differentiation varies between mouse and human cells during early cardiac differentiation. I also have another wet lab project – that a brilliant PhD student from Santiago's lab started and I have recently taken the lead in – studying microRNAs during the early stages of mesodermal differentiation. This is a cool project that is being followed up by another of my students. Overall, my group focuses on basic and applied research, mainly in cardiac differentiation, early mesodermal commitment and mechanisms that regulate the different stages of pluripotency.

Do you have any advice for new principal investigators?

This might be considered a bit obvious, but I would suggest choosing a topic of study that you love, and that you believe has a future and an available niche to dive into. It's important to have a strategy: short-, mid- and long-term goals, because you can easily become distracted on a day-to-day basis. It's good to consider your lab culture because once it's established, it's difficult to change. Finally, know that every scientific-career stage has different kinds of commitment. Starting a group is a lot of work and can be quite overwhelming. In that sense, having mentors in a similar situation with whom you can discuss and strategise, and from whom you can get advice can be very useful. I have friends at similar stages in their career and we frequently discuss our approaches to running a lab, while understanding our own style and adapting to fit our personalities.

What would you be doing if you were not a permanent researcher?

I love science communication. We are learning so many incredible things about development and evolution. And it's a pity that this knowledge is reserved for scientists, right? I always tell my friends and family about cool discoveries, how animal development is super-conserved, about synthetic embryos or things like that, and people are usually super-interested. If I had all the time in the world, I would love to develop a career in science communication, maybe creating a YouTube channel for sharing science with a Spanish-speaking audience. Something in the style of Veritasium or PBS-Eons. Who knows what the future will bring, right?

What is the current situation for research in Argentina?

If you had asked me about this last year I would have told you about the difficulties of running a lab with grants that are less than $10,000 USD a year, how reagents take months to get to the lab, how that affects the possibility of carrying out innovative research, and even the differences between the Global North and the Global South regarding access to publishing. But today the situation is so much worse. We are currently going through the greatest scientific crisis in decades. Argentina's economy is in a delicate situation, and, of course, that will have consequences on the local funding for science. But the current administration, which took office only a

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few months ago, has declared a war against the public scientific system. They even stated during the presidential campaign that if they won the elections, they were going to dismantle public research. Argentina has a long-lasting tradition in science and is the Latin American country with the highest number of Nobel laureates. The current situation is quite dramatic: applications for public grants have been postponed; the grants that have already been assigned are not receiving the funds. The number of PhD fellowships has been more than halved and, in the context of a ∼200% annual inflation, the real salaries of researchers and students have been severely reduced. At the same time, the government is trying to pass a law that, if approved, could allow them to effectively dismantle a good part of the public scientific institutions. Most Argentinean scientists are quite frightened, and rightly so. If this continues, it will undoubtedly lead to a brain drain, with young scientists leaving the country. It is quite sad because science and technology are not a 'cost' but an investment for the development of the country.

What do you get up to outside of the lab?

Right now, my life is divided between work and raising my son. It is not easy to do both, but I love it. I also play the violin as a hobby, and I love spending time with my husband, friends and family. I am a bit of a science geek; I spend most of my free time trying to learn new things, especially those not connected directly to my work, such as astronomy and human evolution. The latter has fascinated me since my son was born, I guess because I wonder how the heck our ancestors managed to raise children in the wild.

Ariel Waisman was interviewed by Alex Eve, Senior Editor at Development. This piece has been edited and condensed with approval from the interviewee.

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