

CELL SCIENTISTS TO WATCH

SPECIAL ISSUE: CELL AND TISSUE POLARITY

Cell scientist to watch – Ginny G. Farías

Ginny G. Farías is an Assistant Professor of Cell Biology at Utrecht University in The Netherlands. She trained in molecular neurobiology with Prof. Nibaldo Inestrosa during PhD at the Pontifical Catholic University of Chile in Santiago, Chile, where she studied mechanisms of neurodegeneration in Alzheimer's disease. She then completed a postdoctoral fellowship with Prof. Juan Bonifacino at the National Institutes of Health in Bethesda, Maryland, USA. As a postdoc, she focused on understanding the fundamental cellular processes that drive polarized trafficking of proteins in neurons. In 2018, she started her lab at Utrecht University, where her group develops sophisticated tools to investigate how the local organisation and dynamics of organelles contribute to neuronal polarity. For our Special Issue on Cell and Tissue Polarity, we spoke with Ginny over Zoom about her perseverance to become an independent researcher, fascination with neuronal organisation and support for open access science.

What inspired you to become a scientist?

When I was very little, I didn't have any family members or family friends around me who were scientists. My mother taught me how to read and do maths before I even started kindergarten. However, this early academic advantage proved to be a double-edged sword, as it led to a diminished interest in the elementary school curriculum. As the academic content progressed on to more challenging subjects, I experienced a period of disorientation, resulting in a temporary decline in my academic performance. Nevertheless, my trajectory took a positive turn during middle school, where the guidance and support of my biology and physics teachers played a pivotal role in igniting my passion for science. When I turned thirteen, it was like a switch flipped and all my curiosities came back to me. I just knew that I wanted to understand the world around me.

What first interested you in studying neurobiology?

The moment that marks the beginning of the career path I'm on now was a middle school biology class where we dissected a cow brain. I became intrigued by this very complex organ. After that, I thought I wanted to study medicine to become a neurosurgeon. Maybe it's destiny, but when I started my bachelor's degree programme in biology at the Pontifical Catholic University of Chile, my first lecture was on cell biology. The instructor was so passionate about what he was teaching: how cells work, how they differentiate and the impacts that can be made on human health just by understanding cells. At that moment, I knew that I wanted to be a scientist, and focus on cell biology of highly complex and beautifully organised brain cells, the neurons.

At that time, I didn't have any courses in neurobiology. At the end of my first year at university, I started looking for labs that worked with neurons, and I found Dr Nibaldo Inestrosa's lab, which focused on Alzheimer's disease. I kept sending emails and going by the lab to talk with the professor, but he didn't have space or the staff to supervise me. However, I was so persistent that he eventually agreed



Ginny Galdames Farías

to let me come to the lab and have a technician train me in some very basic techniques. After six months, I went to Nibaldo's office again and asked to work more independently on an important question. He agreed to let me test a drug called AF267B (an agonist of an acetylcholine receptor) on neurons treated with amyloid- β to induce neurotoxicity, to see if the drug could reduce neuronal cell death. In the end, this project led to me publishing two papers during my bachelor's programme, which I am really proud of. This research experience really inspired me, and it was like opening a Pandora's box. There were so many more questions that I wanted to address that I decided to pursue a master and PhD in Nibaldo's lab studying molecular neurobiology.

You've had the opportunity to do research in Chile, the USA and The Netherlands. How have your international experiences shaped your research and your scientific outlook?

After finishing my PhD in Chile, I decided to join Dr Juan Bonifacino's lab at the National Institutes of Health (NIH) in Maryland, USA, to work more on the fundamental cell biology of neurons. At the NIH, I took on the challenge to set up neuron culture as a model in the lab, and I learned how to do genetic engineering and how to work with fancy microscopes to visualize protein trafficking in living neurons. This was the moment I became fascinated with organelle and protein dynamics. Now in The Netherlands I continue using this strong training background to understand how organelle

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Family adventure – just us and nature.

dynamics contribute to neuronal function. My research experiences at the NIH and Utrecht University have been great. In these places, you have so much diversity and meet people coming from many different countries working together with amazing technology. Especially at the NIH, I had a lot of fun doing whatever experiments I wanted to do. My experience in Chile before this was a little different because we didn't have access to as many resources. Even so, I think it was a very good way to train. I had to think very thoroughly about the experiment that I wanted to perform, why and how I needed to do it, and what I was going to get from it; there was no space for mistakes. It could be stressful, particularly considering that publishing in Latin America at that time was very complicated. When a reviewer asked for new data, it was a challenge even getting an antibody delivered in 3 months, let alone finishing a new experiment in that time.

In 2018, you started your own lab at Utrecht University in The Netherlands. What challenges did you face as a new PI that you didn't expect?

The main challenge when you start your own lab is learning how to be a team leader. You have to motivate people and teach them how to be team players. I love this part of running my own lab, but nobody really teaches you this beforehand. I was fortunate that Utrecht University has many courses supporting new PIs; their leadership and PhD supervision courses helped me a lot during my first year as a PI.

Something I didn't expect at all as a PI is the huge number of emails I receive now! My first six months were practically spent just figuring out how to deal with my email inbox. Now I've learned to send short and efficient responses that get to the point. An

additional challenge I don't think many PIs talk about is the increased number of social activities expected of you. I am an introverted person, and I used to spend a lot of time alone at my bench when doing my PhD and postdoc. When I am around people, I am very sociable, but after a social event my energy is drained. Now, I have so many meetings and conferences to go to, and I am still learning how to manage this.

What are the main questions your lab is currently trying to answer?

We study neuronal polarity. Neurons are highly polarised cells with two distinct domains that emerge from the cell soma: multiple dendrites and a single axon. This structural polarisation is required for neuronal function in receiving and transmitting information. Neuronal polarity is established and regulated by tightly organised protein trafficking and organelle distribution. We want to understand how the organelles in a neuron are organised and how this contributes to neuronal function. Organelles don't exist in isolation; they are very dynamic and are constantly interacting with each other. This includes contacts between membrane-bound organelles, but also their interactions with membrane-less organelles. We are trying to understand how these interactions contribute to neuronal polarisation, development and function. For example, how are organelles locally distributed in distinct regions of a neuron? How are local organelle interactions established and regulated? How do a neuron's organelles behave when the cell receives a stimulus, and how do they deal with stress? All the components within a cell need to act in harmony to communicate a signal or message, and that is beautiful, but how that happens is an enormous unanswered question.

My current work is very much on the fundamental side, but I always keep in mind how the cellular processes we study go wrong in disease. For example, in amyotrophic lateral sclerosis (ALS) and spastic paraplegia, two diseases that affect neurons, many different proteins are mutated and cause dysfunction in multiple organelles, but we don't know why and how. We first need a better understanding of organelle dynamics and inter-organelle communication in neurons. What are the mechanisms behind these organelle interactions, and what are the local roles of these proteins in neurons? This knowledge will help to develop new targets for disease.

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What do you find most fascinating about the phenomenon of neuronal polarity?

Neurons are extremely well-organised cells, and this organisation is what allows them to receive and transmit information. Neuronal polarity is a crucial part of this, but we just know so little about it. For example, we know that the cytoskeleton plays an important role in the polarisation of neurons, but it's not the only factor. What other proteins, processes or organelles help establish and maintain neuronal polarity? What trafficking rules ensure that the right proteins and organelles get to the correct neuronal compartments? How is this regulated? You can see some similarities in these mechanisms in neurons and other polarised cells, such as epithelial cells, but there are also some differences. I'm fascinated by understanding the unique mechanisms neurons use to establish and maintain neuronal polarity and how these factors fit together to support neuronal development and function.

What new techniques have you adapted to better understand organelle dynamics in neurons?

The challenge of working with neurons is that they are very delicate, non-dividing cells that are highly sensitive to manipulation. When developing tools to work with this model, you need to consider all these technical problems. When I came to The Netherlands, I had the idea to control the distribution of the endoplasmic reticulum (ER), which is one of the largest organelles in the cell. In contrast to vesicles, lysosomes or mitochondria, the ER is one contiguous organelle that fills the entire neuron. When I decided that I wanted to try to remove the ER only from the axon, people were sceptical that this could be feasible. I am very proud that by using protein dimerization systems we were actually able to achieve this in the lab by coupling a specific microtubule-driven motor protein to an ER-resident protein in order to control the position of this organelle in different neuronal domains. This is a very specific tool, as we demonstrated that removal of axonal ER does not alter transport of non-associated organelles along the axon. Controlling the distribution of the ER is a great starting point to try to understand the local roles of organelles in neuronal function. Then, you can aim to identify the role of specific proteins in the local function of an organelle. We have also adapted tools such as split proximity labelling and reversible split fluorescent proteins to study protein–protein interactions at the nanoscale (<20 nm distance) in fixed and living neurons. With these tools, we are currently studying local organelle interactions, their dynamics and regulation in neurons.

Are you still doing experiments yourself?

Absolutely! I am still preparing primary cultures of neurons for the lab. Before the COVID-19 pandemic, I was also continuously working at the bench, primarily doing live-cell microscopy. During and after the pandemic, I have been doing live-cell imaging on the weekends to get some alone time – just me, the cells and the microscope! Working at the bench has never felt like a job to me, more like a hobby. This is something that I really enjoy, and want to do more of again. One of my New Year's resolutions for 2024 is to come back to the bench at least one day per week.

You're part of the Open Science Team at Utrecht University. What does your role involve, and why is promoting open science important to you?

Open access science is important to me because I come from Chile. During my PhD, it was very difficult to keep up to date with the science that was published in my field because I didn't have access to the full papers and data; I was often only able to read abstracts. To me, this lack of access is a limitation to the advancement of science. I also feel that open science is important for the public to be aware of the important role of fundamental and applied science in society. If we as scientists want to prevent miscommunication or misinformation on social media about our science, we should be more open with the public about what we are doing.

I am currently the Open Access (OA) Fellow for our Faculty of Science at Utrecht University. My role in the Open Science Team is to promote and facilitate OA publication in our faculty. We have a very good track record; we have about 94% OA publications at this point, and we want to reach 100%, but we are still trying to solve some problems. For example, there are researchers without any grant funding for publishing OA. As a short-term solution we've recently opened a fund to help them. However, we need to find long-term solutions, and this requires more communication between universities and publishers. I think that we can work together to create incentives to promote high-quality OA science. For example,

journals could incentivise researchers to both publish and be reviewers by offering OA publication discounts for reviewing a certain number of papers. I really think that there are win–win systems that can allow both parties to benefit.

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Who are your scientific role models?

I've been guided during my career by the people that have marked my life as a scientist. During my PhD, I learned from my supervisor Nibaldo Inestrosa how to be very independent, learn new techniques on my own and ask for help when I needed it. I am very thankful for that. During my postdoc at the NIH with Juan Bonifacio, I really appreciated having an open environment to discuss data, exchange new ideas and get excited about the research questions we were trying to solve; it was super fun! Casper Hoogenraad also had a great impact on my career. He gave me the opportunity to start my own line of research when I joined Utrecht University; I got a lot of support from him to become an independent researcher. Currently, I am surrounded by scientists like Anna Akhmanova, Lukas Kapitein, other PIs and my own team, who help me to push scientific boundaries through innovation to reveal new insights.

My parents are also my role models, even though they are not scientists. As managers of a company sales team, they had amazing leadership skills. I learned so much from them about leadership, hard work, and having the passion to pursue my goals and dreams. I still like to contact them for advice when I have teamwork issues in my lab!

What is the best science-related advice you ever received?

My best piece of advice came from my husband, who is also a scientist. After my first 5 years as a postdoc at the NIH, I decided to extend my J1 visa for one more year, but because of this extension, I had to leave the USA for two years. I didn't know what my next step should be, I was afraid it was too late for me to start looking for PI positions and I just felt that I wasn't ready. My husband asked me "What do you want to do? What are you passionate about?" My answer, in short, was that I wanted to do research on neurons, I wanted to have fun with cool microscopes, I wanted to write grants and start my own lab! I mentioned that there was a group of PIs doing cool research with nice microscopes at the Utrecht University in The Netherlands, and he just said, "go for it". The same day, I contacted Casper Hoogenraad, and after few weeks we were planning our next adventure. So, my best advice is to ask yourself the essential questions about what you want to do and what you are passionate about. If you can make that clear for yourself, you can move on to figuring out how to achieve it. I still have the feeling that I am not ready, and I'm learning as I go. You are never going to feel ready to be a PI, so don't wait too long to follow your passion!

Finally, could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?

I really enjoy gardening, because I get to have some silent time and be with my thoughts. I have two daughters, 14 and 18, who were both born while I was doing my PhD. I had a lot of support from my husband and family raising young kids during

that time, and the bigger challenge started when we moved to the USA with a six-month-old baby and a four-year-old girl. Day-care was very expensive, and we had to make a lot of sacrifices, but it has been good for my daughters to experience different cultures and learn new languages. When we decided to move to The Netherlands, they just wanted to support my dream to start my own lab. Fortunately, the environment here is very peaceful and good for them. We like outdoor activities to be connected with nature and have some time without access to internet! We also like to

play our huge collection of board games, play ping pong and watch Japanese anime together. I try to spend as much time as possible with my daughters and my husband, because they give me the energy to go back to 'work' in the lab (by 'work' I mean replying to emails!).

Ginny Farías was interviewed by Amelia Glazier, Features & Reviews Editor for Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.