

## SPOTLIGHT

# An interview with Paola Arlotta

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Paola Arlotta is a neurodevelopmental biologist based at the Harvard Department of Stem Cell and Regenerative Biology in Boston, MA, USA. Her lab studies the birth, differentiation and assembly of neuronal circuits in the cerebral cortex with the aim of developing novel therapies for degenerative and neuropsychiatric diseases. Paola has recently become an editor for *Development*, and we asked her about her research and career, and her recent efforts to support women in science.

## When did you first become interested in biology?

I can't remember a time when I was not interested in biology. My parents tell me that even as a child I was very curious about nature, and would spend hours in the garden digging up worms and looking at ants. I became seriously interested in biology in high school. I had an incredible science teacher who was very inspirational. He made us think deeply about how nature works, we did experiments, it was always very exciting. I knew that I had to study biology at university, and that is what I did.

## Your lab studies the birth, differentiation and circuitry assembly of neurons in the cerebral cortex. Why does this topic interest you?

The cerebral cortex interests me because it is really the part of the brain that makes us human and controls the most complex functions that human beings are capable of, such as language – we are having this very conversation thanks to our neocortex. The neuronal cell types that underlie those complex behaviours have fascinated neuroscientists for centuries. Now, due to technological advances, we can really examine these cells. We can begin to understand mechanistically how this outstanding numbers of neuron types is made, how they choose their partners in order to make the circuits that underlie cerebral cortical functioning, and so on. Looking at this system is fascinating. I am intrigued by complex systems; they're really hard to study, but it's very rewarding.

## What are the questions that your lab is currently tackling?

The central focus of our work has been to understand cortical development, and the mechanisms of fate specification and maintenance of neuron identity. But lately we have started to address fascinating new questions, some more fundamental while others more applied. For example, we are very interested in understanding how the diversity and function of cerebral cortex neurons, in particular the excitatory pyramidal neurons, affects the behaviour of other cells. We are particularly interested in their interaction with oligodendrocytes, the cells that myelinate the



axons. Starting from this fundamental question – whether there is a special type of communication between neurons and oligodendrocytes – we made a very interesting discovery. It was previously thought that myelin was deposited along the axons of all neurons using the same mechanism. We discovered that this is not in fact true for all neurons. We are realising that the interactions are more complex and involve many different classes of cells. We are following the idea that there might be node-type cells, in this case pyramidal neurons, that can influence the behaviour of other cell types, and this system can evolve and change really quickly, guaranteeing the more complex functions of the cortex.

Another fundamental question that may have translational impact relates to the stability of neuronal identity. All neurons in the mammalian cerebral cortex, including our own, are made during embryonic development. We live and die with the cells that were made when we were embryos, so a human neuron can last 100 years. The dogma in the field is that neurons cannot change. Once they have a certain identity they keep it for the life of the organism. We are beginning to challenge that, although this is a very new field and there is much that we don't understand. It seems that within the first couple of weeks postnatally, the young neurons of the mouse brain can actually change their identity if you challenge them with a powerful enough transcription factor. This suggests that neurons have the ability to change. My lab is building on this initial work. This is a very important question from a fundamental point of view because it can tell us whether neurons stay the same during the life of the organism or not. But it is also interesting from a therapeutic point of view because it might be an alternative way to achieve neuron replacement *in vivo*. Many neurodegenerative diseases affect only certain classes of neurons. Perhaps it might be possible to turn some of the spared neurons into those that the disease affects.

## You recently started using brain organoids to study development and disease. Can you tell us about this technology and why it's useful to you?

I have become very interested in complex neurodevelopmental diseases like autism-spectrum disorder and neuropsychiatric

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diseases. We know so little about these diseases; in some cases we don't even know which neurons or circuits are targeted, although we do know that the cerebral cortex is affected in most cases. We also know that these are diseases of the human brain that fundamentally affect core human capacities, so they are very hard to model in mice. We (like others) are using what we know about the normal development of the cerebral cortex to attempt to induce the formation not just of neurons or glia, but of actual brain tissue, including the cerebral cortex, in a dish. This is what I call 'next-generation' 3D organoids. They are very complex tissue-like structures that start from human pluripotent stem cells, then form embryoid bodies, and later form primitive ventricles and vesicles, a process which, at least morphologically, resembles early brain development. We have built on the protocol that was developed by Juergen Knoblich and others, and we have tried to extend the developmental window of these organoids as much as we can to be able to look at circuits. To achieve this, organoids have to grow and develop for a very long time so that they attain cellular diversity and then form a meaningful set of circuits that we can study. I am very excited about this project because it is the first time that we have been able to build on our knowledge of development to attempt to model a meaningful replica of what we see *in vivo*. And because we are using human cells, these 3D organoids could be incredible screening platforms to understand how disease mutations affect human circuits, and for clinical and drug screening.

#### **Do you think there are ethical issues with 'growing a brain in a dish'?**

I think we need to be confident but careful with this type of work. There is a lot of misconception out there regarding what these models really are. I don't like it when people call them 'mini-brains'. They are only a very oversimplified replica of what you find *in vivo*. We are still trying to understand how to make them develop, even on a micro scale, and attain the cellular diversity and circuits that we know exist in the human brain. So, calling them 'mini-brains' is just making a headline. Yes, we need to be careful not to cross ethical boundaries, but at the same time these models could be extremely powerful to understand devastating human diseases about which we know nothing. We should keep this in mind when we think about what should and should not be done.

### **We need to be careful not to cross ethical boundaries, but [organoid] models could be extremely powerful to understand devastating human diseases**

#### **Your work is at the crossroads between the neural development and stem cell fields. How do you think the relationship between these two fields is evolving?**

When I was interviewing for a lab head position, I had to make a choice about the kind of department that would be ideal for my work – either a neurobiology department or a stem cell department. At the Harvard Department of Stem Cell and Regenerative Biology I can have both, because I am also surrounded by an incredible community of neuroscientists. What I have learned from being at the interface between neuroscience and stem cell biology is that if you are trying to model complex tissue and organ physiology, you

really need both expertises. You need a stem cell biologist to understand the starting point and the potential, and to really push the technological boundaries. But you also need to have a deep understanding of the type of tissue and cells that you are trying to model. If you are working on a disease of the brain, chances are you need a neuroscience background, or to collaborate closely with a neurobiologist. I think this interface is growing. When I first started there was not as much participation by neuroscientists as I see today. It was necessary for people to appreciate the limitations of the neuron differentiation protocols to allow the field to develop. Now the cream of neuroscience is really embracing the idea that you can make meaningful neurons, and now even meaningful tissue, in the dish that resembles what they are used to seeing *in vivo*. I think that's wonderful because we do need neuroscientists working with stem cell biologists to push this field to the next level. The more this interface is fostered via funding and meetings that bring people together the better it will be.

#### **You have recently become an editor for Development. How do you hope to contribute to the journal?**

I was very excited to join. I grew up as a scientist reading the journal and I really respect the other editors. I think my contribution is related to this interface between stem cell biology and neurobiology. My roots, and the majority of the work done in my lab, is on neurodevelopment, but I am a faculty member in a department submerged in stem cell biology. I can see from the colleagues around me where the field is going and where the excitement is. I think I can bring this unique perspective. I would really like to see more high-level papers in Development that bring together neurobiology and stem cell biology, regenerative biology and disease modelling.

#### **Recently you and other prominent scientists proposed a list of seven actionable strategies for advancing gender equality in science, technology, engineering and mathematics (STEM). Why did you think it was important to write this document and what do you hope to get out of it?**

It was very important for me to write this document. As a woman in science I always felt respected and valued. I never felt that because I was a woman I couldn't get the faculty position I wanted, for example. However, even in an ideal situation like mine, I still feel that there were times in my life when I really had to make very difficult choices between being the mother and the scientist that I really wanted to be. I probably had my children at the worst possible times. I had my daughter in the last two years of my postdoc, when you do most of your work and interviews, and my son during the first year of my lab. But it turned out ok and I am of the firm belief, which I try to tell to all the young women that train in my lab, that you should do things for your personal life when you think is the right time for your personal life, and not when people think it is a good time for your career. You will then find a way to make it work. That said, I feel that certain practical things that can be addressed with money could have made the process much easier, especially in the first year after my children were born. I would have liked to have been able to spend a little more time with them, or stay at home a little longer on maternity leave, without fearing that my lab would not progress as fast as it should. It is important to raise awareness of this issue. There are not many women that choose to go onto a faculty position after their postdoc that will lead them to leadership in their field, and this is true both for academia and industry. This is

because it requires you to invest so much of your personal time when you also have to invest so much effort and love in your own family – if you have one.

I am a practical person and I think there are practical solutions that can be implemented at an institutional level. I and others at the New York Stem Cell Foundation started with this first but, I hope, meaningful step. With these first seven points we tried to highlight the issues in the field, and we suggested ways to address them. Since the publication of this article we have met twice more as a group and have expanded our score card to include many other detailed points, but we wanted to start with a simple strategy so that the idea could take ground. We would like to make the leaders of major institutions accountable for the number of women they recruit and retain, in order to receive certain funding. Many funding agencies are becoming sensitive to this issue, and are considering ways to raise awareness and implement changes. This is by no means our own original idea, and we were inspired by what the Athena SWAN project is doing in the UK. Our project aims to find real solutions that are practical, doable and implementable, and that can change the situation for women in science. And these changes will benefit male scientists as well. I want my postdocs to know that this is the most beautiful job that they could have. It doesn't have to be done with difficult decisions that neglect some of their fundamental needs.

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### **What is your advice for young scientists?**

I think that they should follow their dreams, and I really mean it. If they have a great idea, if they have a certain vision, they need to be brave from day one to implement it. Be brave, be bold, don't be conservative! Then science becomes fun, and all the other things we have to deal with, like politics, don't matter.

### **What would people be surprised to find out about you?**

I was a figure skater for many years, with all of the costumes and jumps that come with it! I am also a pretty hard-core skier. I've skied since I was 2 and skated since I was 5 (although I stopped in college). I grew up in Northern Italy and my mum is from the Alps, so it runs in the family. My mum was a climber and a very good skier. She could probably still beat us on the slopes at 72!