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INTERVIEW

# Transitions in development – an interview with Antonio Scialdone

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Antonio Scialdone is a Junior Group Leader at the Helmholtz Zentrum München, Institute of Epigenetics and Stem Cells, in Germany. Trained as a theoretical physicist, Antonio now uses multidisciplinary approaches, combining both computational methods and physical models, to study cellular decision making. We met Antonio over Teams to learn more about his experiences moving between different research fields and the transition to becoming a group leader.

**First of all, when did you first become interested in science?**
I've always liked mathematics and physics; I was pretty good at it during my years at school. I've always known that I wanted to do something related to those subjects, although I didn't have any clear ideas in mind. I had the luck of having very good maths and science teachers who helped me nurture this passion and so I went on and did a Bachelor's degree and a Master's degree in physics. It just felt like a natural transition.

**What was it about mathematics that attracted you initially?**
It was the ability of mathematics, and then physics, to describe the world around us in a very precise way. The amazing thing about physics is that it produces mathematical equations that allow you to go beyond your intuition and tell you what will happen in situations that you've never experienced. I think that was what really attracted me to physics during the last year of high school and what led me to go on to do physics at university.

**After your MSc studies at the University of Naples 'Federico II' in Italy, you stayed on there to do your PhD with Mario Nicodemi. When did you become interested in biology and what did you study during your PhD?**
My love for biology started during the last year of my Master's degree. Mario Nicodemi taught a course about the physics of complex systems; the application of statistical mechanics to different fields ranging from quantitative finance to computational biology. Quantitative finance didn't inspire me that much, but the biology part was super fascinating because I got the chance to see a side of biology that I never had a chance to see before. The way I was taught biology during high school was just by a collection of facts: there's a cell, then there are organelles, etc. I didn't find it very attractive at the time but, during that course with Mario, I appreciated how many cool things happen in biology, which we still can't explain. For someone who was studying statistical mechanics and physics, it was even more exciting to learn that I could help answer these questions. I had finally found a field where there was so much to do and to understand, and where I felt I could contribute.

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For my PhD, Mario and I were studying X-chromosome inactivation: how does a cell randomly choose between two X chromosomes and decide to inactivate one? We were applying some models from statistical physics to that question (Scialdone et al., 2011). Another big topic that I was working on at the time was chromatin spatial organisation: how can the cell regulate the spatial organisation of chromatin, which is far from random? I was studying this from a theoretical point of view (Scialdone and Nicodemi, 2010), but I also had the chance to collaborate with the lab of Ana Pombo, who was developing a new experimental technique to look at chromatin spatial organisation called genome architecture mapping (GAM). For that experimental technique, we built the mathematical framework that is used to analyse data and to optimise the experimental protocol (Beagrie et al., 2017).

**Do you find that you can apply the same mathematical principles to a variety of biological questions?**
That's the interesting thing about working in this field – you have a certain toolbox available. Some people like to develop these tools – sharpen them – and then they look for a problem to which that tool can be applied. My approach is quite the opposite: I like to start from the biological problem and then see what kind of tools are available to answer that question. For example, for GAM, geometry, trigonometry and computer simulations were quite important to build the mathematical framework. But, in other

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Development (2022) 149, dev200704. doi:10.1242/dev.200704

problems that I've worked on, the tools that we used were completely different.

**You published in Development during your PhD. How was that experience for you?**

I think it was very useful because what we wanted at the time was to try to get our ideas across to the developmental biology community. Publishing in Development helped our idea – and our model – to become more widespread (Scialdone and Nicodemi, 2010). We were also lucky in our timing; there was an Editorial by Olivier Pourquié, which also cited our paper, explaining that Development aimed to publish more papers from the fields of system biology and mathematical modelling of biological systems (Pourquié, 2011).

**After your PhD, you moved to Norwich, UK, for a postdoc with Martin Howard at the John Innes Centre. What did you work on during this period?**

I was working on a very cool problem: how can a plant survive at night when there is no sunlight? We were studying *Arabidopsis* and the answer is that the *Arabidopsis* accumulates starch during the day using sunlight. Then, during the night, it eats up the starch that is accumulated during the day at a specific rate, in such a way that the whole starch store is consumed exactly by dawn. The funny thing is that you cannot trick the plant; you can turn off the light a bit earlier or a bit later, but the plant knows what time it is, and the rate is adjusted immediately. It seemed to us like the plant is doing an arithmetic division between the starch that it's accumulated and the length of the night. We thought of some mathematical models for how the plant could do this calculation using biochemistry. Then, we made some predictions of what would have happened if the plant had had certain perturbations in, for example, the pattern of light/dark periods. We were collaborating with the group of Alison Smith, who went on to do very cool experiments that validated our predictions (Scialdone et al., 2013).

**What was it like for you to move between countries?**

I remember I arrived in Norwich in November 2010, which was one of the coldest winters in the UK. It was full of snow and I just arrived from Naples where temperatures were completely different. It was kind of a climatic shock and I had to get used to that environment!

**After that, you moved to Cambridge, UK, to join John Marioni's group at the EMBL-EBI. What drew you there and what projects did you work on during that time?**

At the end of my postdoc with Martin in the John Innes Centre, I had been reading a lot about the single-cell 'omic' revolution that was happening at the time. I was intrigued and I wanted to try to get my hands dirty with more data than I had worked with previously. That desire motivated me to look for positions in bioinformatics and single-cell omics. I got a postdoc position with John and we were developing tools for single-cell RNA-sequencing data analysis and applying those tools to study mouse embryonic development. We collaborated with different groups in Cambridge, such as Magdalena Zernicka-Goetz and Bertie Göttgens, etc. It was a beautiful experience; I enjoyed my time with John in Cambridge because the lab was growing so fast and there were loads of data coming in, on many different topics. I got to learn lots of new biology, in addition to bioinformatics, which was a completely new world for me as well.

**How was it moving between fields, from physics to plant biology and then to single-cell bioinformatics and embryology?**

When I was in Naples, I was working in the Department of Physics, so I didn't have any first-hand contact with biology or biologists. I transitioned from there to a place that was focused on plant biology, and the computational/systems biology department was really small compared with all the other departments around. It was a big transition and I was attending lots of seminars on plant biochemistry where, initially, I understood very little, but it was very stimulating. When I moved to Cambridge, there was also lots of new things and a lot of learning to do, which is possible and very exciting, but you need to be careful about the environment – you need to make sure that you're working with a supportive supervisor and lab. I got these things in John's lab.

**Do you think that interdisciplinary research is valuable?**

I totally recommend it. It's a useful exercise to try to learn something in a certain field and to then step out of your comfort zone to apply these ideas in new areas. That's a very effective way to start innovating and to give an original contribution to answering a question. There are some barriers. For example, the *Arabidopsis* project taught me a lot about how to interact with an experimental lab; again, you use a certain set of tools as well as a certain language within the lab where you work. However, you then need to try to translate these results in a way that they can be understood by people who have a different background. From there, you can build something new, together with the collaborators. And it's not only a matter of giving new ideas, but also receiving new ideas; you need an open mind. When I went to Mario to talk about doing a thesis on that topic, he took a copy of *Molecular Biology of the Cell* (Alberts et al., 2014), put it in front of me and said, 'let's talk again when you've studied this or that chapter'. After that, I started reading lots of papers about X-chromosome inactivation. If you want to move to a new field and try to give a contribution, you need to learn what's been done so far. Otherwise, perhaps, you'll just end up reinventing the wheel.

**At what point did you begin to look for group leader positions?**

During the first one or two years of my postdoc with John, I wanted to capitalise on the things that I had been learning until that moment and to get to a point where I felt comfortable about working in this new field. Perhaps starting from the third year, I had new ideas and John also allowed me to co-supervise a few students in the lab. It helped me to gauge whether becoming a group leader was something that I could do or not, which was very important. I realised that I was ready to take the next step and I started to look for independent positions. Before applying, I started talking to people trying to understand what kind of place might work better for me and I was thinking about what kind of research proposal and projects I might work on.

**What were the most important considerations when you were looking for positions and how did you decide which offer to accept?**

One of the things that I had been doing during my PhD and postdoc was collaborating a lot with experimental labs; at the same time, my work is fully computational, so I needed to find an institute where both the computational and the non-computational communities were very strong. One of the places where I think this thing happens very strongly is where I am now, at Helmholtz. I chose this offer because I felt I had enough freedom to pursue what interested me, but they also had enough labs around – computational and non-computational – to interact with.

Development (2022) 149, dev200704. doi:10.1242/dev.200704

**What was it like when you became a group leader at Helmholtz?**
Very exciting and scary, perhaps in that order. Suddenly, you're on your own and you need to set up something from scratch: hiring new people, getting started with the projects. The clock starts ticking from the moment that you've been hired. It's quite hard because you've been working on the research proposal for quite a while and you have in your mind how many things you want to do, but it's just you. So, you're in a rush to hire new people but one of the key suggestions that pretty much everyone gets when they start a group is to not rush hiring; take time to find the people that you feel you would be comfortable working with.

**What approach did you take to hiring new group members?**
When I hire, one of the crucial things that I always try to understand is whether the person is genuinely curious and interested in biology. I often try to recruit people with solid computational physics/mathematics backgrounds, so I need to understand whether this person would be comfortable working outside of the things that they have been studying until that point. The question that I ask myself is, 'would this person be ready to face *Molecular Biology of the Cell*?' Having enough interest and curiosity about biology is really what have driven – and still drives – me. I think if it can work for me, it can also work for other people.

**If you had to pick the most challenging and the best moment since becoming a group leader, what would you choose?**
The best moment is a three-way tie. It's when you see the first results coming from people in your lab – things are happening, which is exciting. Then, the first paper gets accepted. But I think these moments will be superseded this year by the graduation of the first students from the lab; this will be really cool to see. The most challenging moment was trying to overcome the anxiety of having these ideas and not still having the manpower to start working on them.

**How did you overcome such challenges?**
I think it's important to find an environment where you feel you get enough support from your peers. Some advice I received, which might also be useful for a lot of people, is don't keep things to yourself. Go out and talk to people because, chances are, the very same problem that you're having has already been faced by someone else. Another important thing is, whenever I get stressed, I go back and think about what excites me about what I'm doing to find the motivation to keep going. That's been my approach and, so far, it has worked.

**Don't keep things to yourself. Go out and talk to people because, chances are, the very same problem that you're having has already been faced by someone else**

**Could you summarise what your lab is researching now?**
We are fascinated by how cells can adopt different identities starting from the same genetic instructions. Our ambition is to understand the principles and mechanisms of cell identity changes in space and time, and we use different model systems to address this question. For example, we are studying how spatial patterns of cellular identities start being established in mouse and human embryos around gastrulation (Tyser et al., 2021; Thowfeequ et al., 2021 preprint). We have recently shown that, during mouse embryonic development, cellular competition acts as a safeguard against cells with mitochondrial defects before cell identity specification in the epiblast (Lima et al., 2021). Another model system we work on is olfaction: it is a longstanding and mind-blowing question of how olfactory sensory neurons can diversify into hundreds of different subtypes, and why these subtypes are located in different areas of the olfactory epithelium. We have tackled the latter question in a recent preprint using spatial transcriptomics (Ruiz Tejada Segura et al., 2021 preprint). In our work, we combine techniques from physics and machine learning; integrating these two different fields is not always straightforward, but it can be very powerful.

**How did you navigate the research environment to find your niche?**
What makes all of us unique is the set of experiences that we've had: the kind of research that we've done, the places where we've been and the things that we've learned. I think a good strategy is to try and pick elements from all these experiences and then combine them to have a different approach or a different answer to a question. This is also another good reason to do interdisciplinary research and to move between fields!

**Do you think mentorship has been important for your career?**
Yes, it's been fundamental and I think having good mentors is particularly important in science for many reasons. In addition to advising on practical issues, mentors help navigate your career. They provide encouragement during challenging moments and can help you become aware of your strengths and weaknesses, which is very useful, especially during the transition to scientific independence. I've been very lucky in having good mentors throughout my career and I'm trying my best to pay it forward.

**Coming from a physics background where preprints are the norm, what do you think about the rise of preprint popularity within biology?**
As you said, coming from that field I've always seen preprints as something normal that people should do to get their ideas out there. You get very good advice and feedback, and it helps you to fine-tune your results. Preprints are especially helpful for junior group leaders, postdocs and PhD students, because getting a paper published in a journal can sometimes be a long and painful process. Having a few preprints when you apply for a postdoc or group leader position helps a lot. All the papers from my lab have first been published as preprints.

**Is there anything that Development readers will be surprised to learn about you?**
One of my research papers (the one on *Arabidopsis*) was featured on Jimmy Kimmel Live, a famous show in the US. They mentioned it, not for the science, but to make jokes about it because this work was also featured on some media outlets, often with the headline 'scientists discover that plants can do math'. I guess that is an obvious thing for comedians to pick up on and you can still find it on YouTube (https://www.youtube.com/watch?v=KC2LywnhGuc).

**On that note, do you think science communication and press coverage is important?**
I believe it's important on at least two levels: first, because we need more science-informed public decisions. Second, it's not just about informing on scientific facts, but also on how the scientific process works; to help people understand that, although science is not

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perfect, it's still our best bet when it comes to making decisions. I believe conveying this point is key to building more trust in science. As scientists, we should get more involved in science communication; I personally like it a lot and we are organising a few new public outreach activities at Helmholtz.

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