Transitions in development: an interview with Margherita Turco

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Margherita Turco is a group leader at the Friedrich Miescher Institute for Biomedical Research (FMI) in Basel, Switzerland, where she uses organoid technologies to investigate human placental development. We met with Margherita over Zoom to discuss her career path so far. She told us how her early interest in reproductive technologies led her to a postdoctoral position in Cambridge, UK, where she derived the first human placental and uterine organoids and established her independent research group.

Let’s start at the beginning, when did you first become interested in science?
Since my childhood I had a love of animals, and I became fascinated by biology when I learned that cells were the building blocks of living creatures. So, I became really curious about how cells work. One of my favourite books was ‘Charlie Brown’s Super Book of Questions and Answers’, which explained all sorts of areas of biology. I still have this book, which I gave to my children, but they’re not too interested!

I understand that you started on your research career with a diploma in veterinary biotechnology at the University of Bologna, Italy. What drew you to this subject?
It came from this initial love of animals and then wanting to understand how things worked at a cellular and molecular level, and I realised that veterinary biotechnology brought these two interests together. I was also looking for a degree that would allow me to study development and reproductive technologies, because I was interested in how those could be applied to help conserve endangered animals.

At the end of my diploma, I had to do a project in a lab. I found that there were very few labs in Italy working on reproductive technologies for endangered species. But I came across Pasqualino Loi’s lab in the University of Teramo. Pasqualino had worked with Ian Wilmut as a postdoc at the Roslin Institute. The aim of his lab is to understand the mechanisms behind cloning and how cells reprogramme. They had also cloned the endangered European mouflon using oocytes from its close relative, the domestic sheep (Loi et al., 2001). So, I went to his lab, and I was exposed to embryo development in a dish for the first time. I became fascinated, and that’s how I got into development.

What did you work on during your subsequent PhD studies?
After I finished the project in Pasqualino’s lab, I stayed on as a research assistant. I wanted to look for practical opportunities in the field of conservation, but it was just so difficult as there weren’t many options at that time. So, I started looking for alternative solutions and I came across this international PhD programme at the IFOM-IEO campus in collaboration with the University of Milan. I came across a project that interested me in Luisa Lanfrancone’s group. She works on melanoma, and she was looking at an adapter protein, RaLP, that becomes more highly expressed in the later stages of melanoma. It seemed to be involved in development as it was also expressed in the developing brain. I joined her lab for my PhD and this experience introduced me to the field of stem cell biology, because I used both neural stem cells and embryonic stem cells (ESCs) to study the role of RaLP. What was unexpected was that, when I generated a knockout ESC line for RaLP, the differentiating cells started spontaneously forming cells that looked like trophoblast (Turco et al., 2012). That sparked my interest in the placenta.

Can you tell us about your postdoctoral work, and how this led to the development of the first human placental and uterine organoids?
I was looking for opportunities within the stem cell biology and development field and came across an advert for a postdoctoral position at the University of Cambridge, where the aim was to generate an in vitro model of human trophoblast. This had been
lacking in the field – there were the mouse trophoblast stem cells that had been around for 30 years, but the human equivalent had not been convincingly derived. Researchers were using protocols to derive trophoblast from human ESCs, but it wasn’t clear what their identity was at that time. This area of research is also quite underfunded and under-studied.

The project at Cambridge was jointly led by three PIs: Myriam Hemberger, Ashley Moffett and Graham Burton. I was so lucky to have these three amazing mentors. It opened up a whole new field for me because the placenta is such a fascinating organ, and we know so little about it in humans. It was also a challenging project, and I think what made the difference was the collaboration with two stem cell biologists at the University of Cambridge, Benjamin Simons and Bon-Kyoung Koo. They worked with intestinal organoids that had been developed by Toshiro Sato in Hans Clevers’ lab at the Hubrecht Institute, Netherlands (Sato et al., 2009) not so long ago at that time, so they said, ‘You should take this organoid approach’. That really changed the way I was thinking about trying to establish this model.

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I was in Cambridge for many years, and it was quite an adventure because it was hard to find the initial conditions to grow these cells. I followed the approach used for other tissue-derived organoids and used a similar medium composition, and I found that cystic structures were coming up consistently. Trying to identify trophoblast in vitro was not easy, because they’re epithelial cells and they share a lot of markers with other epithelial cell types. So, at the same time as trying to derive the organoids, we were also trying to develop robust criteria to help the field define a good trophoblast model (Lee et al., 2016). One of the defining features of human trophoblast is their unique human leukocyte antigen (HLA) profiles. So, when we looked at the HLA profiles in our cultures, we were surprised that they didn’t look right; they weren’t like the in vivo trophoblast profiles. How could this be? We were only using placental tissue, so we wondered if this could be an in vitro artefact. It took quite a while to figure that out. In the end, we did some genotyping because we realised that it could be maternal cells, since that was the only other epithelial cell type that could be in our source material. This is because the placenta is so embedded in maternal tissue that, even though we were taking the material and we were washing it, there could have been maternal contamination. Indeed, it turned out that these were organoids from the endometrial glands, established from the placenta. This was disappointing at first, but it was a great discovery because we needed organoids of the maternal side, too. So, I had established first the maternal organoids, the endometrial organoids (Turco et al., 2017), but then it was a question of rethinking the entire approach to identify the conditions that we needed to get trophoblast (Turco et al., 2018). It took several years of work after that, but we finally got it. It was a very special place and time to do this postdoc in Cambridge. I learned so much and had the chance to collaborate with great scientists.

You went on to establish your own lab in Cambridge. What were your most important considerations when you were looking for group leader positions?

When I was in Cambridge, after I got the project going, I’d already managed to secure some funding, including the Marie Curie Intra-European Research Fellowship and the Royal Society Dorothy Hodgkin Research Fellowship. So, I was establishing my place in the department where I had done my postdoc and I was fortunate that Ashley Moffett created space for me in her lab and allowed me to do independent research there. It became this natural progression where I continued to apply for larger grants, and eventually I got a European Research Council (ERC) Starting Grant. That was the first one that allowed me to hire people and really start my lab. So, I wasn’t looking to move in that moment – I had my niche there, and I stayed there.

So, you continued to collaborate closely with Ashley Moffett during that time in Cambridge?

Yes, we went through a lot together. And it was really wonderful working with her and Graham Burton. They have been major influences on my scientific development. I do continue to work quite closely together with both of them and we’re still finishing some collaborative projects.

Can you summarise the research themes of your group at the moment?

So, now we have these organoid systems from both the foetal side and the maternal side. The main, overarching questions of our research are how the human placenta develops, how it interacts with the uterus and how this is important for pregnancy success. Within this theme, we have questions that are more focused on how the different placental cell types are generated, how the endometrium prepares for pregnancy in response to hormones and what the underlying signalling mechanisms are. We are also interested in the importance of cell-cell interactions in this process. So, as well as studying the two organs separately, we also have projects now where we’re trying to combine the systems and study their interactions. We are also trying to develop new model systems in the lab, because organoids are great but they’re not perfect and there’s still quite a lot to do to understand the model itself. We are excited that we can begin to unravel these critical, early developmental processes occurring during human pregnancy, which have been so difficult to investigate.

What is the best thing about being a group leader?

For me, it’s being able to follow the questions that you’re most passionate about. The FMI has great core funding support, which also allows you to explore new ideas and curiosities that may be difficult to get funding for; I find it exciting that you can follow where the science leads you. And I love doing this together with a team. Of course, as a postdoc you do collaborate within your group, but it’s not the same thing as leading a group of really enthusiastic, motivated people. From my experience as a postdoc, I also enjoy when you have unexpected findings, which can be disappointing sometimes, but you just never know where it might lead you.

And what has been the most challenging thing about setting up your own group?

I think it’s having this big responsibility for the projects and the careers of the people who trust in you and come to work with you. You want to make sure that they do well, and that they’re happy. Learning how to organise my time is still a challenge, because quite often a lot of it gets spent in meetings and the admin side of things, and you realise that you can’t spend as much time on the science. That’s sometimes hard. So, I think trying to achieve a good balance, finding a good way of working and ensuring that everyone is thriving are the major challenges for me.
What advice would you give to other people who are looking to start their own lab?

I guess this is a given, but make sure you have a clear question that you want to address and that really motivates you, because it can be tough. Surround yourself with really good, motivated people, especially at the beginning when you’re setting up your lab; things are slow, and things might not work, so you really need people who can persevere. And have those mentors that you can ask for advice who will give you very honest feedback. I maintain very good relations with my mentors, and they’ve been really supportive and helpful. And start very quickly with experiments! The most daunting thing is when you see an empty lab, so just start with something small and start growing your confidence. I did also attend some leadership courses, which were helpful because postdoctoral experience, even if you get to mentor people, doesn’t quite prepare you for managing a team of people and all the other challenges that come with it.

What has been your approach to hiring new team members?

I like hiring people with diverse experiences because they bring fresh ideas. I have a person in my team who worked with Caenorhabditis elegans, for example, and has never worked with organoids or placenta. If they’re motivated, they learn very quickly and get into the topic. So, I like bringing in people from different fields, and with different characters, because it gives the group diversity and balance and makes it fun.

“I like hiring people with diverse experiences because they bring fresh ideas”

What is your mentoring style for the people in your lab? Has it developed over time?

I’m still developing it and exploring different approaches. But, generally, I try to provide some sort of structure, like having fixed one-to-one meetings with my PhD students. The aim is to have a framework where they feel like there’s an anchor and a time to come and speak to me, but at the same time I try to give them the space to explore ideas and think of new experiments. It’s a balance, and I think this needs to be adjusted a little bit to different personalities, because I think some people still thrive when they have a bit more space. I also have an open-door policy, and I really encourage my lab members to just pop by and chat to me. Other important aspects are to encourage teamwork and open communication.

You recently took up a position at the FMI in Switzerland. What was the process of moving your lab to a new country like?

I did my interview during the pandemic, so the entire thing took place online. My family and I were going to visit Basel, but we couldn’t because of COVID restrictions. So, I went alone, and they had to trust my judgement of whether it would be a nice environment for us. I was also pregnant, so I set up my lab and then I had my baby, so there was this huge change on the personal side of things as well. But I have to say it all went well because I had such great support from all levels at the FMI, from the Director to facility heads to administrative staff, in setting up the lab and on the practicalities of moving there. I also had help from Ashley, my mentor in Cambridge. So, we had support from everywhere and I think it went as smoothly as it possibly could have done. Two people I was already working with in Cambridge came with me, a PhD student and a technician. So that was wonderful; I wasn’t completely alone in setting up the lab as I had people that I trust and work well with to help get started. Overall, it was a great start, I think.

Together with Ashley Moffett, you authored one of our most read articles (Turco and Moffett, 2019). What was your experience of writing this Review?

I have to say it was challenging to write it, because the scope of the Review was quite wide; we wanted to have enough information so that it would be interesting for people in the field, but at the same time we really wanted to provide an introduction for people who don’t know about the placenta or are thinking of entering the field. We wanted to promote this understudied organ and I’m so happy to hear that people are reading it.

Did you ever consider an alternative career path?

When I had finished my diploma, I was thinking more about field work, looking into endangered species, instead of work at the bench. As I said, opportunities were lacking and so that brought me back to the bench. But even though I haven’t really entered the field of reproduction in endangered species, what was really nice was that, a few years ago, Graham Burton and I got contacted by Budhan Pukazhenthi at the Smithsonian Conservation Biology Institute. They were interested in deriving endometrial organoids from Przewalski’s horse, which is an endangered wild horse. So, we did a little project together, which we published (Thompson et al., 2020). I was excited because it brought together my initial passion and my current research. I hope to have more opportunities like this in the future.

Finally, is there anything that Development readers would be surprised to learn about you?

During my diploma and my PhD, I had some musician friends that had a recording studio. I dabbled in singing and some of the songs got onto their CDs. I haven’t sung in ages, but I was thinking it would be nice to pick it up in a different context; maybe I could join a choir in Basel. That would be fun.

References


INTERVIEW

DEVELOPMENT

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