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INTERVIEW

An interview with Matthias Lutolf

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Matthias Lutolf is Head of the Laboratory of Stem Cell Bioengineering at the EFP Lausanne, Switzerland. While Matthias initially trained as a Materials Engineer, his current research sits at the interface between bioengineering and stem cell biology. Matthias recently joined Development as an Associate Editor so we caught up with him at a recent conference to ask him more about his work, why he agreed to take on the role and the types of papers he hopes to see in Development.

Let's start at the beginning – what first got you interested in science?

I think I have to blame my father for that. He was a biology teacher – he actually did a PhD working on *Drosophila* – so when I was a child, he taught me lots about biology in general, from plants to animals. I think at some point during primary school I knew the name of almost every plant that grew in the area where we lived. Then during high school, I was involved in several science projects, for example looking at bumblebees and how they build their colonies. I would build hives for them and study how they collected food and whether they found their way back to the hives when I released them from different distances and directions – I found it fascinating! After high school, I didn't really have a clear idea of what I wanted to do but a teacher mentioned that there was a new program called 'Materials Science' at ETH Zurich and it sounded very interesting and multifaceted, allowing you to study diverse materials – metals, ceramics, polymers – so I enrolled.

You trained as a Materials Engineer at ETH Zurich and stayed on there to carry out your PhD. Can you tell us a bit more about your early research?

During my studies, I realised that what I was missing was an appreciation of how different materials could interact with biological systems and/or be used to study biological questions. Interactions between engineers and biologists were quite rare back then. But around that time, Jeffrey Hubbell joined the ETH from Caltech and he was offering a supercool PhD project that aimed to build new types of materials that could be used to promote tissue regeneration, for example injectable, smart hydrogels that could be used to heal tissues. So I moved into the field of regenerative medicine for my PhD. I worked mainly on bone and skin: we used these as models to show that you could build completely synthetic polymer-based materials that can recruit stem cells and promote the regeneration of large tissue defects that wouldn't otherwise normally heal. We also used these materials to deliver proteins, such as morphogens. It was a very fascinating and gratifying project because the technologies that we developed then moved forward into commercialisation. This involved licensing out our patents to companies and working with start-ups, so it was an exciting time.

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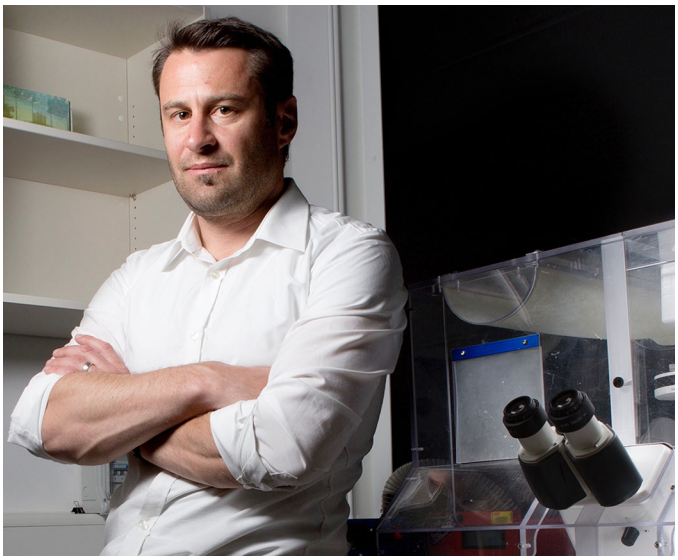

This work was also an important trigger for me as it encouraged me to stay on in research and carry out a post-doc.

For your post-doc, you then switched gears a little to work on stem cells and mechanical control over stem cell fate. What attracted you to this field?

So I realised that, even though I had been working with mammalian cells, I had no clue about their biology. I decided to challenge myself and moved to a lab (the lab of Helen Blau at Stanford) that was working on hardcore stem cell biology. It was a very enriching experience for me. I learnt about the types of questions that biologists ask, the assays that they use and the models that are available to them. I was the only engineer in the lab though, so I really felt like an 'exotic' species, being surrounded by cell biologists, biochemists and even medical doctors. And it wasn't easy: I lacked a lot of the basics, as I had never really studied biology, so I had to read lots and work really hard. It was actually a humbling experience. I think it took at least a year for the people in the lab to understand what I was even doing! But eventually, after playing around with lots of techniques, I came up with a new way of following single live blood stem cells using time-lapse imaging and a simple microtechnology approach. Once people saw those movies then they became much more excited about my project and things started to take off.

Overall, my time at Stanford was very useful and I learnt a lot about concepts in stem cell biology. I was also embedded in a fantastic environment: we had Irv Weissman next door and lots of amazing people coming to give seminars on a weekly basis, so it was easy to find out about the latest developments and trends in the field. I think I morphed into a sort of a 'hobby biologist' during those years. Of course, this was also at a time when the stem cell field was really exploding (with Shinya Yamanaka's iPSC technology on the horizon and stem cell niches being discovered, etc.) so it was very exciting.

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After your post-doc, you moved back to Switzerland to set up your own research group. What was/is the main question your group is trying to address?

My vision was to build a functional stem cell niche, focusing on blood stem cells (hematopoietic stem cells, HSCs). I wanted to know if it would be possible to provide the key instructive signals needed to maintain and expand HSCs outside of their natural bone marrow environment. To do this, we of course needed to understand the types of factors that are essential for maintaining stemness *ex vivo*. To me, this seemed like a very interesting biological issue that also had medical relevance, as it could help improve the numbers of HSCs available for stem cell transplantations. So I built a group that aimed to address this: I hired biologists who wanted to study the mechanisms controlling stem cell self-renewal, chemists who could build new types of substrates and scaffolds, and microtechnologists who could create microfluidic systems to study stem cells at single cell level in high throughput. We had some successes but I realised that the impact of this type of work was not as I had hoped for and that it was difficult to publish this type of work; although expanding HSCs was an aim for the field, and still is, the clinicians who were actually dealing with HSC transplantations could apparently get by without it. Around that time, ground-breaking organoid papers came out – from the group of Hans Clevers (who was looking at intestinal organoids) and Yoshiki Sasai (who was making optic cup organoids from pluripotent stem cells) – and I found these extremely fascinating. I realised that I needed to switch gears, so we dropped the blood projects and instead turned our focus to organoids. I basically had to re-invent and re-structure the whole lab.

Our main aim now is to understand how stem cells build patterned tissues: what are the principles that underlie self-organisation; can we build better tissues by controlling self-organisation; and can we use advanced bioengineering technologies to leverage this? We focus mainly on the intestine but also on so-called gastruloids – embryo-like structures derived from self-organizing pluripotent stem cell – to study early embryonic patterning and organogenesis.

Your lab sits at the interface between stem cell biology and bioengineering – how does this affect you in terms of keeping up to date with both of these fields and trying to find the right people for the lab?

It has always been a challenge, especially because both fields move so quickly! But I am rather pragmatic with regard to how we approach technology development. This has meant that we've focussed mainly on the biology and the questions that we want to address; we only start developing or refining technologies if there is a clear need. It's very hard to be at the forefront of 'pure' technology development when you work in an interface area. My ambition is to be at the forefront of integrating stem cell biology and bioengineering technologies. This also means that I don't need to be so focussed on keeping up to date with the cutting-edge techniques; we just need to do this when we come across a challenge or hit a barrier with a particular technology.

Finding people to do this type of work has actually become much easier over the years. I get a lot of very skilled biologists who approach me because they want to move away from pure biology and do something that is more applied. Likewise, there are lots of talented bioengineers who want to do more of the biology. In addition, I think that the students that are coming through these days are amazing – they know the biology, they can code, they know about chemistry and bioengineering – just because they've been trained in a different and more multidisciplinary way. They have such a diverse skill-set that they can work on pretty much any project in the lab.

On this note, do you think we should be doing more to bring different fields together? And how might this be achieved and/or improved?

I think this is actually happening spontaneously because students are being trained differently these days and appreciate the importance of this type of cross-disciplinary work. They understand that you have to break the boundaries between fields to be successful. By contrast, I think the generation before them – those that, like me, were trained more classically in one field – has had more of a problem crossing over between fields but this too is definitely changing.

However, one thing that we can still do more of is to make sure that there are platforms (e.g. journals, meetings, workshops) that really value and promote the interfaces between fields. For example, it's sometimes difficult to publish this type of work because it may be that the technological aspect of the work is not particularly novel or fancy, even though the study provides a new approach to tackling a biological question. What tends to happen in this situation is that the bioengineers reviewing the paper say that the technology is not novel, and the biologists say that the technology is cool but that there's not enough mechanistic insight. So nobody really appreciates the work! For this reason, we really need to make sure that the importance of this type of work is recognized and that there's a place for it in the community. I think it is getting better and, for example, there are now an increasing number of meetings that focus on the interface between biology and engineering.

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You recently joined Development as an Associate Editor. Can you tell us why you decided to get involved and what your role entails?

I like Development a lot: it's a journal that I read early on in my career and one that I really valued. If you want to do what we're doing – if you want to engineer functional tissues – you really need to understand development and morphogenesis, and how tissues form and are patterned *in vivo*, and this is exactly what the field of developmental biology aims to do. So it's really important that bioengineers and tissue engineers can go to a place where they can find information about these topics and, for me, Development has always been this place. Also, one of my favourite reviews of all time, the one written by Yoshiki Sasai (Sasai et al., 2012), was published in Development.

What areas of research do you feel are particularly exciting right now?

I think the field of 'synthetic embryology', which aims to build embryo-like *in vitro* structures as models for early embryos, is really exciting right now, especially as it provides a means to understand early human development or the stages of mouse development that are very tricky to study *in vivo* (e.g. at peri- and post-implantation stages). The interplay between mechanics and developmental signalling, and understanding how the two come together to control self-organisation and patterning, is also super-interesting and is now something that can be tackled using engineering 'tricks'. Synthetic biology, when applied to developmental problems such as

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patterning, is also cool. For example, it's now possible to engineer cells with completely artificial cell-cell signalling networks to 'program' multicellular tissues, and we can use these to learn the principles of cell communication during development. We're also getting closer to being able to grow truly functional tissues *ex vivo* and possibly image them long-term at single cell resolution, which is something that has always been difficult to do.

What sort of papers would you like to receive at the journal?

I still feel that we've not seen a lot of examples of how engineering tools can really be applied to answer a biological question; we see a lot of bioengineers developing fantastic new technologies and systems but these aren't always then put to use to answer a relevant biological question. So I'd like to see papers that use a bioengineering tool or technique in a truly unique way to answer a biological question or solve a problem that wouldn't otherwise be able to be addressed. I also see the journal as a place where we can highlight some of the emerging techniques in bioengineering and basically 'translate' these (and the language of bioengineering) to a developmental biology audience, whether that's in the format of a review article or a technique-based article. There are now just so many tools available that it's not easy to figure out which is best for your application, so I think the journal could also play an important role in pointing people in the right direction.

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You seem to be in support of preprints. Have you found the preprinting experience to be useful? And do you think it will change the way scientists communicate and disseminate their research?

I was quite sceptical about preprinting for a while – I couldn't really see the benefit – but I thought I'd give it a try. So we put our first paper out on bioRxiv and we actually got a lot of good feedback. I was really surprised! I was even contacted by a group who worked on a similar system and we started to collaborate with them; we had a Skype call with them and they sent a student over, and we have obtained exciting new results that would have been difficult to achieve alone. It just opened up new doors. It's also been great for the people who actually did the work in the lab as they don't have to wait years for the work to be published. I think we'll use bioRxiv more and more, although I don't think this (preprinting) can replace the traditional journal and peer-review system. Based on my experience, I think papers are generally improved when they go through peer-review.

And what would be your advice to young researchers starting out in your field today?

I think, ideally, you need to be exposed to different fields. If you want to be a good bioengineer, you really need to have some experience of working in biology (and vice versa) if you truly want to have a deep understanding of the field. Of course, this will probably mean that you have to make some sacrifices, for example you're not likely to become a world-class hardcore engineer. I also think that you need to choose the right environment that fits your needs and your expectations. Everyone is different, so you just have to choose whatever feels right for you.

Finally, is there anything that people would be surprised to find out about you?

I knew how to fly an airplane before I was able to drive a car. And I love almost every outdoor sport: hiking, climbing, windsurfing, mountain biking, etc. I think people in my lab are joking about that and saying that in order to be able to join my lab you will either have to be a great skier/snowboarder or willing to learn it very quickly. But maybe that's not all that surprising for a Swiss guy who grew up in a small village in the Alps…

Reference

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