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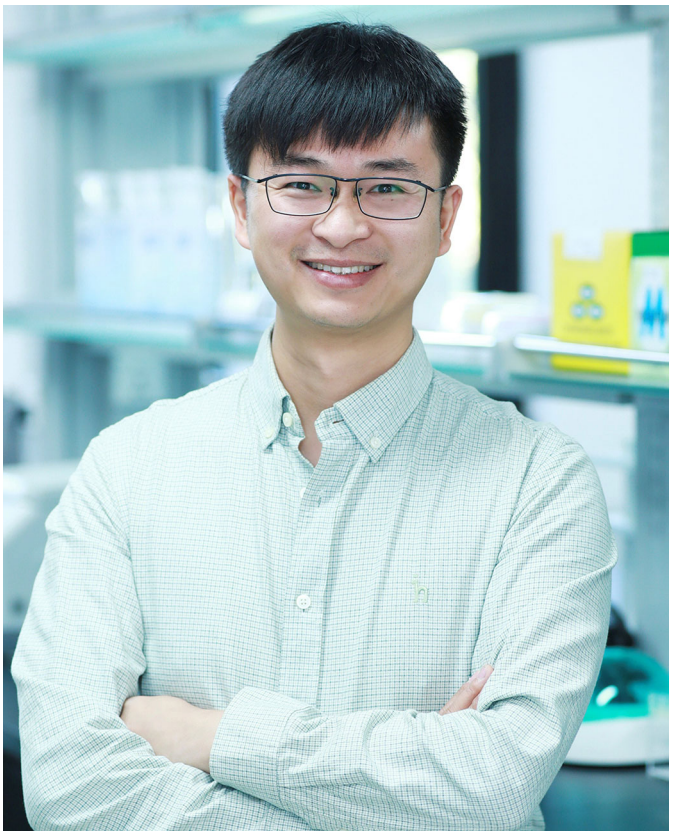
INTERVIEW

Transitions in development – an interview with Fan Zhou

Fan Zhou is a group leader at Tsinghua University, China, where he works on the molecular changes that underpin cell fate transitions during early embryogenesis. We met with Fan over Zoom to discuss his career path so far. He discussed how a chance foray into basic research following his undergraduate degree sparked a lifelong passion for developmental biology, and how his interest in technology development has fed into his independent research.



Let's start at the beginning. When did you first become interested in science?

The journey of life is full of surprises. My father was a part-time keyboardist and trumpeter in a country band; I watched him spend his spare time forming an amateur band and even participating in commercial shows. His love for music deeply affected me, and during my childhood I dreamed of becoming a musician. By coincidence, I began to study clinical medicine at university. I find the patterns and mechanisms of how the human body works to be subtle and fascinating, but our understanding of many diseases is sparse. After that, I was dreaming of becoming a surgeon during the graduate student program, but a failed clinical medical graduate examination led me to accidentally step into the door of basic medical research. So, starting a career in basic research was a romantic accident for me.

You went on to complete a PhD at the Academy of Military Medical Sciences, China, where you were working on hematopoiesis. What drew you to that topic, and what was your PhD project about?

My PhD advisor was Dr Bing Liu, and he's passionate about how hematopoietic stem cells are derived at the embryonic stage. This process is a fascinating model with which to understand how cell fate can change so dramatically, in this case from endothelial cells (the blood vessels) into hematopoietic cells. I built a high-resolution *in vivo* functional assay to identify the molecular events that occur during the cell fate transitions from endothelial fate into hematopoiesis. We established a platform called the 'single cell initiated *in vivo* functional assay' to explore how the hematopoietic stem cells (HSCs) form *in vivo*. Using the newly developed system, we decoded the gene expression patterns and heterogeneity of the newly born HSCs at the embryonic stage.

Are you still interested in technique development?

Absolutely. Over the course of my career, I've realized that applying appropriate technology or developing new technologies to understand the complicated molecular events occurring during biological processes can be a very effective approach; you see a lot of new things compared with previous findings.

After your PhD, you moved to Peking University, China, for your postdoctoral studies. What were you working on at that time?

During my PhD, I was interested in how cell fate changes from endothelial cell function into hematopoietic function. Another model for understanding cell fate *in vivo* is early embryogenesis. We all know that the mammalian embryo begins with the fertilized egg. This single cell divides into two cells, then four cells, then eight cells, and every division step requires a precise decision to be made. If these decisions are not precise, they could go in the wrong direction and result in severe developmental defects. From this point of view, the early embryo is a perfect model for understanding how cell fate can be decided in a precise way. So, I started my new research journey into early embryogenesis by joining Dr Fuchou Tang's lab, with the hope of expanding my skillsets and research visions.

Your postdoctoral work was awarded the 2019 Top Ten Advances in Life Sciences by China Association for Science and Technology. What did this award mean to you?

It was great honour for me and the whole team, especially for my supervisor, Dr Fuchou Tang. After postdoctoral work at Cambridge University, UK, he had come back to Peking University as a PI, where he established a lab to develop new single cell-omics technology and apply this technology to different fields, including early embryogenesis. I joined Dr Fuchou Tang's lab and started a project that was decoding multi-dimensional molecular dynamics occurring during human peri-implantation development. This was a black box for human embryogenesis because of ethical concerns and limited sample availability. When the work was published, its

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potential influence for embryogenesis and biomedical research meant that both our peers in the research community and international media outlets took notice. The award was definitely a recognition and encouragement for the whole team. So, it was an amazing experience for me and, most importantly, for my mentor, Dr Fuchou Tang, who has inspired me a lot.

You subsequently went on to establish your own lab at Tsinghua University, China. How did you form your own research niche for your group?

I was trained in traditional stem cell research and developmental biology. So, in my lab, I wanted to create an environment to gain a deeper understanding of the molecular events regulating embryogenesis, especially peri-implantation development. When I started my own lab, I applied the technology that I was already trained in, as well as developing new technologies and combining gene editing and epigenetic editing to perturb molecular regulation during early embryogenesis. These approaches reveal how epigenetic factors functionally regulate cell fate and lineage specification during early embryogenesis.

With the multi-omics profiles, we now have the ability to narrow down the set of candidate genes and identify those that are functionally important during the dynamics of the cell fate transition. For example, when a cell in Cell State A transitions into Cell State B, we can do a lot of profiling to understand what kind of gene programs change during the transition. This gives us a list of the top correlation genes, and we can then test these to confirm that they play a role in the functional regulation of the cell fate transition. By perturbing the candidate genes in Cell State A, we can see if these cells can still transition to Cell State B, or if they are just maintained at Cell State A, or if they go a totally different way to a Cell State C. So, we're still applying and developing new technologies a lot, and our ultimate goal is to understand cell fate in a functional way.

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What sort of technologies are you using in the lab to answer your questions?

As a first step, we apply a lot of single-cell, low-input, multi-omics technologies, where we combine sequencing and analysis with bioinformatics. When we've narrowed down the candidate molecules, we use epigenetic and genome editing technology to perturb these candidates. We use *in vitro* models to mimic embryo development in the plate, and *in vivo* models, like the mouse, to test how perturbing these candidate molecules affects embryogenesis.

What were your most important considerations when looking for group leader positions?

I looked for an institute with active academics, who would encourage me and my team to think differently and to actively collaborate across the institute. I was also looking for a place where the researchers are answering important scientific questions with solid support. I feel fortunate that Tsinghua supports us very well.

What has been the most challenging aspect of transitioning to a group leader role?

A wonderful postdoc stage doesn't guarantee that you are going to be an excellent PI. Running a lab requires different skillsets, such as writing funding applications and team building. It's tough at the beginning, but I really enjoy it, especially having discussions with the lab members and seeing the improvements in their experimental design, drawing conclusions from data, writing and, most importantly, scientific thinking.

What do you most enjoy the most about being a group leader?

I enjoy talking about science with the lab members, discussing their new results or the difficulties they encounter during project progression. Being a group leader is a fascinating job with a free spirit to explore new knowledge, and, in my opinion, this makes it the perfect career.

What is your approach to mentorship within your lab?

I think that as a PI, one of our most important jobs is to help students and postdocs to find their own motivation and passion; to light up the fire in their hearts. I encourage the trainees to initiate discussions with me or with the senior lab members regularly, to keep reviewing the difficulties they meet and to establish a clear next step and research vision.

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How do you approach the process of hiring new team members?

Their long-term motivation and the compatibility of their scientific experience with our laboratory's research direction is important. After evaluating their application email and CV, I invite them for a face-to-face interview, which gives us a chance to get a sense of each other to evaluate whether we will work well together for the next few years.

What advice would you give to people starting their own labs?

Keep striving to do the important and difficult research in your field. Recruiting team members that match your lab's research direction matters. And, finally, it is important to actively interact with senior PIs in your institute because they can offer advice about both the science and running the lab.

Finally, what do you enjoy doing outside the lab?

I enjoy basketball, photography and playing the guitar. I also enjoy running or hiking with the lab members; I originally decided not to talk about any academic things during these excursions, but it turned out that the students really wanted to talk about science, and sparks of ideas started coming out!

Fan Zhou was interviewed by Laura Hankins, Reviews Editor at Development. This piece has been edited and condensed with approval from the interviewee.