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An interview with Patrick Tam

Patrick Tam's research is focused on the cellular and molecular mechanisms of body patterning during mouse development. He agreed to be interviewed by *Development* to talk about his interest in mouse development, new concepts in gastrulation, X-linked diseases and his dream of an African safari.

Did you always intend to have a career in developmental biology?

I was lured into science at high school as I listened to my biology teacher reminiscing about his romance with plant biochemistry during his university days. It was really no surprise that I chose biology over medicine as my degree and then headed onto postgraduate research without a second thought. It might sound incredible but there was not a proper course on developmental biology (or embryology, as it was known) in the entire Bachelor of Science curriculum of my university in those days. To fill this gap in my education, I made a definite decision to study rodent embryo development – first in Hong Kong, and later in London with Michael Snow. This was a time when research in mouse development was taking off in a big way in the UK and so the rest, as they say, is history.

What has influenced your decisions about institutions and locations?

Before I finished my PhD, I had already accepted a faculty position in the newly founded Medical School at the Chinese University in Hong Kong. Luckily, I did manage to squeeze in one year of postdoctoral training at the University of Texas at Austin. This proved to be critical for broadening my research experience and I learned a great deal more before taking on the job back home.

Joining a young institute happened to be a good decision: there were ample start-up resources and also the flexibility that I needed to be able to run the laboratory the way I wanted it. The academic appointment offered relatively stable support for my research during this formative phase of my career. The downside was coping with the demand of teaching commitments, and being the only laboratory working on mouse development made it quite hard to maintain research momentum. My next move to a research institute in Australia was a very positive one as it allowed me to develop further in a research-intensive and intellectually stimulating environment. Having access to first-rate facilities and interacting and networking with a larger community of developmental biologists enabled me to focus and move forwards much faster.

You have been a great pioneer in applying micromanipulation and embryo culture research for investigating early mouse development: how did you get into this originally?

My PhD project was to characterise the developmental fate of an active multiplying population of cells in the epiblast of the gastrulating mouse embryo. I had little idea how challenging this would turn out to be! Initially, we focused our efforts on developing a reliable whole-embryo culture method by tweaking the protocol established by Dennis New for culturing rat embryos. We then tried to apply the conventional 'slash and burn' and 'cut and paste' techniques to study cell fate and tissue differentiation. I owe Rosa Beddington an enormous debt of gratitude for introducing me to the art of embryo manipulation during my sabbatical at Oxford University in the mid 80s: my collaboration with her has had a lasting impact on my career. Ultimately, my postgraduate project evolved into a consuming exercise of fate-mapping all three germ layers and their immediate derivatives. The work took three decades but realizing that I had completed my original objective to the best of my ability was a very satisfying moment in my scientific career.

What are the greatest technical difficulties that you faced and how did you overcome them?

A major technical hurdle is to be able to track the cell population under study at every stage of differentiation as the embryo develops in culture. Fortunately, the availability of genetically modified mice with transgenic and genetic cell markers has made it possible to follow the cells in real time throughout the experiment. We know where they come from, where they are placed in the host embryo, how they move to their final destination, which tissues they contribute to and the cell type that marks the end of their differentiation process. One of the goals of these fate-mapping studies is to assess the role of specific genetic/molecular determinants in guiding lineage specification and differentiation. For this, we have to introduce mutant alleles with altered gene function into the genome of the cell population we are interested in. The effort required to generate the necessary genetic resources and the complexity of combining a suite of genotypic strategies in these embryological experiments can't be understated.

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How is your current research telling us more about X-linked diseases?

I have a long-term interest in studying the pattern of X-inactivation during lineage differentiation in the early mouse embryo. X-linked transgenic reporters are enabling us to assess how changes in gene function

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impact phenotype, and we are studying female mice heterozygous for X-linked gene mutations to follow the fates of different subsets of cells. The findings suggest that parent-specific imprints may play a role in the manifestation of the X-linked disease phenotype.

If you had to name one finding in your research so far that has really been a surprise, what would it be?

Based on our fate-mapping results, we have been able to construct a geographical map showing exactly where the progenitor cells of the major germ layer derivatives are found. We can also follow the morphogenetic journey taken by these cells during gastrulation and early organogenesis. Since both the destiny and the disposition of the different groups of progenitors are predictable, it seems intuitive that cell fates are determined and morphogenesis follows in a stereotypic manner. It was a surprise that this didn't turn out to be true. By moving cells to different locations in the embryo, we could show that cells can be quite compliant and can adapt to a new environment. In other words, cells well into the gastrulation process still show a high degree of plasticity. We have now established the concept that gastrulation serves to bring specific groups of cells to the right place at the right time but that neither the origin of those cells nor the journey they took has any major impact on their differentiation potency. What matters most is the final destination, the place where the critical inductive interaction takes place. Knowing about the plasticity of the epiblast cells and the newly formed germ layers has also allowed us to harvest renewable and apparently pluripotent stem cells from gastrula-stage mouse embryos.

Do you enjoy teaching as much as your research work and how do you mentor young scientists in your group?

I am working full-time in research and do not have any regular teaching commitments in Sydney, but I have lectured at the Molecular Embryology of the Mouse course at Cold Spring Harbor Laboratory (CSHL) every summer for the past two decades. I particularly enjoy the inquisitive atmosphere of the CSHL class. My approach to mentoring students and postdoctoral fellows is strongly influenced by my experience of being mentored myself. I think the key to bringing out the best of people's ability is to allow them to roam intellectually but to keep track of the general direction of their work. My message to young scientists in my lab is: do whatever interests you but keep in mind the focus of the lab. A very effective and healthy work practice is to take stock of the progress on a regular basis and to publish or present the findings whenever they are ready for the world.

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When did you become an editor at *Development* and what do you hope to achieve?

That was about 3 years ago. I hope that my editorship sends a message to the scientific community that our journal is passionate about the mouse as an amenable experimental model for developmental biology, and that the combinations of genetics and embryological manipulation are the best tools to address pressing issues in human health and development.

What niche does the journal *Development* fill and how would you like to see it increase its influence in the future?

I would like to see *Development* serving as a conduit between basic biology and translational research in organism development. We should redefine the scope of the journal to make it more contemporary and aligned with the research interest of the community, while fostering new subject areas where the interface of research disciplines may be enhanced, such as cellular biological understanding of developmental mechanisms, system-based insights in morphogenesis and organogenesis, and the connection between developmental biology and regenerative medicine.

What do you feel is the main benefit of the journal in this field of science?

Development provides a home for a rich resource of knowledge covering a wide range of cellular and developmental models. It is good that it is a journal run by practising scientists. I think that it is important to set our goal towards developing for the journal a forward-looking scope and editorial policy without becoming a slave to popular trends or the impact factor.

What do you do to take a break from science?

A break from science is a rare luxury. I like to spend my away-time taking a driving trip outside Sydney to small towns up in the Tablelands or to the wine valley. Other pastimes are browsing in bookshops where good coffee is served, playing a few testing games of badminton and tending to my collection of stamps.

If you won an 'all expenses paid' trip to somewhere in the world where you have never been, where would you most like to go and why?

I have so far lived an exclusively urbanized life. My fantasy is to go on a safari in Africa to experience the wild nature and to appreciate the diversity of flora and fauna that I often read about in books.

What would people be most surprised to learn about you?

They are surprised to find out that I am a serious chocoholic, a keen collector of mouse artefacts and that I often send emails at odd hours, irrespective of which time zone I happen to be in.