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The accidental biologist: an interview with Jim Smith

Jim Smith has made fundamental contributions to our understanding of early embryonic development. Here, in conversation with *DMM* Consulting Editor Kathy Weston, he discusses his stutter, how he became interested in developmental biology, and his role in helping establish what will be the UK's biggest multidisciplinary research laboratory, the UK Centre for Medical Research and Innovation (UKCMRI).

The determination of cell fate in the early embryo is driven by intercellular signals, which in turn induce the transcriptional activation of regulatory genes that direct morphogenesis and cell differentiation. Work from Jim Smith's lab helped show that transforming growth factor (TGF)-β family members are involved in mesoderm induction, the first inductive interaction in early vertebrate development (the mesoderm eventually gives rise to tissues such as muscle, bone and blood). More recently, he has shown that the transcription factor Brachyury is a target of TGF-β signalling that is only activated at intermediate levels of ligand. Brachyury is both necessary and sufficient for normal mesoderm formation, and its targets include genes that are involved in the regulation of gastrulation and in many aspects of posterior mesoderm formation.

Smith is now using frog, fish and mouse embryos to understand the genetic regulatory network that is initiated by Brachyury, and is finding that the signals that direct cell differentiation have been conserved throughout the animal kingdom. His work may inform attempts to drive stem cells along particular developmental pathways.

Your motivation for choosing a life in science is a bit different from that of many people. Can we talk a little about that?

I was very catholic in what I was interested in at school, and I was reasonably good at exams and liked both arts and science subjects. However, at my secondary school, I realised that anything to do with the spoken word was going to be hard for me to succeed in, as I had a rather bad stutter at that time. So, I suppose I lurched towards science because I felt that having a speech impediment was less restrictive in science than it was in the arts. But I don't want you to think that that's the only reason I went into science. By the age of 11, I had a chemistry set, and I enjoyed making things out of wood and doing things with my hands, so I've always had an interest in how things work, which I suppose is what still drives me.

So you chose to specialise in science at about the age of 15 and got a place at Cambridge to read natural sciences. Why Cambridge? Why the natural sciences option?

All of the universities that I applied to had courses that allowed one to do all three of maths and physics and chemistry because I couldn't decide which of these subjects I was most interested in. I liked the Cambridge course because students could combine maths, physics and chemistry with one other subject. I decided initially to do X-ray crystallography for my fourth subject, but then I met my director of studies, Douglas Barker. Douglas persuaded me to do cell biology and this decision changed my life. I fell in love with cell biology and discovered that I had a passion to understand how cells functioned and how life worked. It was a life-changing event.

Was cell biology a completely new area for you?

Yes. I didn't do biology at school. Biology at my school was for people who didn't do very well at maths, physics and chemistry. And I always struggled with the idea of traditional biology, which seemed to overemphasise the importance of naming things. Richard Feynman wrote about the difference between knowing the name of something and actually knowing what it is. It's not enough just to be able to name things. You have to know what they do, how they work, and how they interact with their environments. But then I also realised that we didn't know the answers to many of the simplest questions in biology, and that's the great thing about it. Again, Feynman sums this up well: you have to know an awful lot of physics and chemistry before you can find a problem that hasn't been solved. In biology, you just have to lift up a leaf.

Photograph courtesy of Samantha Morris.

It was such an exciting time for cell and molecular biology when you were at Cambridge. Knowledge was expanding so quickly in those areas. What was it like to be part of it?

At the beginning of my time at Cambridge, I didn't know enough about cell and molecular biology to realize how much was

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unknown. But in my final year there, in the second epiphany of my life, I did discover how much I loved developmental biology. There was a series of lectures given by John Gurdon, the pioneer of nuclear transfer, and another given by Peter Lawrence, who was studying compartments and cell lineage during development. John's lectures were very good and interesting but Peter's, about pattern formation in Drosophila, really grabbed my imagination. He spoke about Antonio Garcia-Bellido, the compartment hypothesis, and the *engrailed* gene, work that was brilliantly summarised in a paper that Peter wrote with Francis Crick [*Science* (1975) 189, 340-347]. As my friend Phil Ingham knows, I was never very good at understanding insects, but even I could see this was fantastically exciting. There is a lovely logic to development – there are elegant and universal rules – and this really drew me to the subject. Peter introduced me to the work of Lewis Wolpert who explained pattern formation, and what he called the French flag problem, in terms of positional information. The idea is that, by knowing where they are in the embryo, cells will know how to differentiate appropriately and will form, for example, the French flag with blue, white and red stripes. I just got completely turned on by this – I loved it. I decided immediately that I wanted to do a PhD with Lewis because his writing on the subject was so enticing and so exciting.

I like the idea of coordinating groups of people, helping people to do their best science, being around when that good science is being done, and having a say in what happens. Those are quite appealing things

Is that how you first got interested in frogs?

No, for my PhD I worked on chick limb development. When I went for my interview with Lewis, his lab was working on a region in the chick limb bud called the zone of polarizing activity, which when grafted to the anterior region of the limb causes it to develop with mirror image symmetry. They had recently published a paper in *Nature* where Dennis Summerbell and Cheryll Tickle showed that it looked as though this was a dose-dependent response, just like Lewis's French flag. On the day I went there they had just done some experiments, which they had sent to *Nature*, where they had taken the equivalent region from a mouse embryo and grafted that into a chicken and found exactly the same thing. So this demonstrated the universality of the idea and it also demonstrated to me that you could get a paper into *Nature* if you had a good idea and did the right experiment; in other words, you didn't have to sweat and you didn't have to work really hard and for a long time. Luckily, Lewis accepted me. My interview was painful because I really stuttered a lot, but Lewis was kind enough to take me and I haven't looked back.

How did you get rid of your stutter?

Well, I had received speech therapy intermittently from when I was about 7, but it didn't really work terribly well, or maybe I didn't make it work. I even had some therapy when I was a PhD student: Lewis recommended somebody to me, but that didn't work either. Then, when I became a tolerably successful scientist as a postdoc and then as an independent investigator, I realised, you might say belatedly, that having a stutter would be a major handicap in my desire to be a successful scientist. So off my own bat, as opposed to having someone do it for me, I arranged to have speech therapy and I went to see someone called Frances Cook. She took a completely different approach that looked at the whole person rather than just the stutter, and she understood me well enough after a while to know that what would work for me was a dissection of the way you speak. She took my speech to pieces and helped me put it back together again. I did a lot of reading about how you make letters, how you make words, and that was what did the trick – I took a sort of academic approach to the problem. The stutter still comes back occasionally but it's fine now and I don't have any problems. I don't mind having had it, actually.

Do you think there have been any positive things about it?

Well, I think I can claim to have a remarkably large vocabulary! If you have a stutter, you're always thinking ahead to figure out whether there are words coming up that you can't say. So, while you're speaking, you have to try to simultaneously think of a word that will replace the difficult word. That's actually quite tricky as you have to think of an alternative word that has the same meaning but begins with a different letter! It also helped me express myself concisely; even now, I always use the fewest number of words I can when I'm saying something. And it's still true that I try to make sure I know what I'm going to say before I say it. I don't know if that's a good thing or a bad thing – probably good.

So you still feel good when you give talks and they're stutter free?

Well there's a sort of buzz about it and somehow it feels like a success that I've given the talk, no matter what the content!

Where did you go after your PhD?

Well, I had an understanding of the principles of developmental biology from Lewis, but I knew that to make progress I had to learn some cell biology, so I went to work with Chuck Stiles at Harvard Medical School and learned how platelet-derived growth factor (PDGF) makes cells divide. Then I went and did a postdoctoral position with Jonathan Slack, because I wanted to work with embryos again. And that's when the frog connection started.

What has been your best moment as a scientist?

Well, near the end of my time in Jonathan's lab, he drew my attention to work by Heinz Tiedemann, who had been working on a substance called vegetalising factor that mimicked the effect of vegetal pole cells and could cause animal pole cells to become mesoderm. Tiedemann performed his experiments by grinding up chicken embryos, making insoluble pellets, and using the pellets as the filling of a sandwich in which the pieces of bread were bits of Xenopus ectoderm. I thought this was really interesting because Tiedemann's pellets clearly contained a factor that could change the fate of cells but, from my time with Chuck Stiles, I knew that in order to identify the factor we had to make something soluble. I started working on this. I got hold of two Xenopus cell lines from my colleagues Michael Sargent at NIMR and Liz Jones in Warwick, England, and I asked whether these Xenopus

cells would produce an inducing factor. I initially pelleted the cells and used them for sandwich experiments like Tiedemann's, but then I tried conditioned medium. My most exciting moment in science was undoubtedly the day that I cultured pieces of ectoderm in this conditioned medium and I found that they changed shape after a couple of hours; they began to elongate as if they were gastrulating. Tears welled in my eyes, literally! I knew this was important – I can remember walking along the street hugging this amazing secret to myself. And then I'm proud of dropping everything and following it up. It took a really long time to purify the stuff because I still didn't really know any biochemistry. I had to teach myself, and I'm still so ashamed of the mistakes I made at the time that I won't tell you what they were! Anyhow, I made a lot of mistakes but I succeeded in the end.

Do you think it is possible to get as much pleasure out of the work your lab does as from the work you did yourself?
Good question. I still get a visceral pleasure when people in my lab do something good, but it's not the almighty rush that you get from doing it yourself. For example, shortly after the experiments I just described, I had a terrific postdoc called Jeremy Green and he, with just a little help from me, looked at the concentration-dependent effects of the activin that I had purified. I got great pleasure from him doing those experiments.

Clearly one of the qualities that have made you a successful scientist, apart from being thoughtful and very smart, is that you are extremely tenacious, and you can follow a good hunch. What else has helped?
To make me a good scientist? You have to be good with your hands and I was good with my hands. Actually, I'm completely anal when it comes to doing experiments. I set everything up perfectly in advance; I'm a very organised sort of person. I set it up, and everything works pretty much first time because I'm so careful doing it. Also, I know what's important and I stick at it. And, I don't spend too much time reading the literature. Nowadays there is just so much of it and, as a scientist, it's very easy to get distracted by something else that sounds interesting, drop what you are doing and start working on that. Then the next thing comes along so you cycle through a series of superficial experiments without getting stuck into anything. However, thinking about it, some of the scientists that I admire most have not stuck at one thing. One of my scientific heroes, Sydney Brenner, has made fundamental contributions to many different fields, but he's brilliant – he's a genius. I haven't done that: I've stuck with the one thing. Maybe, to be a better, rounded scientist, I should abandon mesoderm induction and tell myself to do something else.

So what would the something else be?
Well if I knew, I'd be doing it! Actually, now I'm involved in doing all these other things it would be foolish to attempt to do something different.

Let's move on to the other things then. What is it that has led you to become Director of the National Institute of Medical Research (NIMR) and before that Director of the Gurdon Institute? Are you just completely power crazed or is there some other motivation?
Well, I asked Paul Nurse this question in a previous *DMM* interview, and I think I agree with him in that we're essentially doing it to cover our arses. What we both mean by that is you feel that you have to justify your existence in the scientific community to some extent and you worry that you're ability to do good independent science might decline as you get older. So, to continue to show that you're making a contribution, you can start running stuff to use your experience to help people in different ways. To be honest, I also feel truthfully that I do a decent job of it. I like the idea of coordinating groups of people, helping people to do their best science, being around when that good science is being done, and having a say in what happens. Those are quite appealing things.

You've been Director of the NIMR since the beginning of this year. What have you been up to?
NIMR has been through a torrid time since before the previous Director John Skehel retired, because it hasn't been clear for a very long time what was going to happen to it, whether it was going to close, or move, or stay the same. One of my first tasks, which I hope I'm achieving, is consolidating the institute, calming things down, making NIMR people feel valued, and having the excellence of the science recognised both within and without. The second thing I'm trying to do is to remedy a lack of investment in some aspects of science at NIMR, for example, bioinformatics, genome biology, that sort of stuff. I'm trying to address this, and I hope that the new people coming in will complement all sides of the Institute and benefit us enormously. I also think it's important for me to be as visible as possible, and as accessible as possible to everybody. The senior scientists need to be supported, but so do the postdocs, the students, and the technical and administrative staff. And, importantly, I am very keen on celebrating the successes of the institute – Dimitris Kioussis was elected a Fellow of the Royal Society this year and we had a very nice party for him.

You've mentioned this entity UKCMRI. Could you explain briefly what exactly UKCMRI is?
UKCMRI stands for United Kingdom Centre for Medical Research and Innovation and the idea is that there will be a big lab built in central London where NIMR will move to, together with the Cancer Research UK London Research Institute and some people from University College London. It is jointly funded by the Medical Research Council, Cancer Research UK, the Wellcome Trust, and University College London. We want to create a big multidisciplinary research institute that brings together the strengths of all of the constituent institutes and labs. It's a fantastic opportunity to make something really new. I think that critical mass is really important in creating a multidisciplinary institute. When I was in Cambridge, we were so close to everything else that the city itself was effectively a big multidisciplinary institute. If you wanted to do something, then the place was small enough to get on your bike and go and find anybody you really wanted to interact with. That's harder to do in London, so you do need a big institute.

Does this mean that NIMR will lose its identity at some point?
Well, we will all be merged physically into the same building, and the challenge undoubtedly is to maintain a sense of identity in a building of that size. NIMR is a fantastically friendly and interactive place. It was like that when I was there from 1984 to 2000, and it is still like that. I think that one of the worries is that, by creating an institute that is twice the size, we have to

work very hard to maintain that ethos and atmosphere. But I'm optimistic at the moment. The science planning committee, chaired by Paul Nurse, is trying to make a building and infrastructure that will encourage those interactions, and help to build new ones.

I'd like to ask you now about that hackneyed phrase 'work-life balance'. You've got three children, you still live in Cambridge so you're commuting to London, and your wife Fiona Watt is also a prominent scientist, so you have solo child care to do when she's away at meetings. How on earth do you fit all this into your life?
I work almost all the time!

Do you resent that?
Mostly I don't, because I like it, but there are times when I think a bit less to do would be nice. Actually, I should tell you that my hobby is running and when I was at the Gurdon Institute I ran five days a week. The truth is that, nowadays, I'm finding it difficult to find the time to go running and this is irritating the hell out of me!

So, is the only way that one can succeed in science, and have a life outside of science, to work as you do? Or, do you see that ever changing? For example, there wouldn't be any question in your mind of people being given a bit of a break because they have small children and cannot function at one hundred percent while their children are little. Is that just too bad?
I know what you're saying of course, but the truth is that in any career if you want to succeed in it, you have to work hard. The difficulty in science is that success is measured by publications, and although committees take account of maternity and paternity leave, it is difficult to quantitate this properly. However, I'll come back to what I was saying at the beginning, which is that it's not always the case that success comes from the numbers of hours worked. I think that if you are passionate about science, have good ideas and plan your time efficiently, then you will succeed. One advantage of science as a career is that we do have a much more flexible working day than many other people, so it is possible to fit work in and still see your kids. You just don't have time for anything else!

Finally, what would you still like to do? Is there anything left that you haven't done?
I want to succeed in what I'm doing now. Is there anything left that I haven't done? We'll see what I do next.

DMM greatly appreciates Jim Smith's time and willingness to share his personal story. We are grateful for the opportunity to present his story here as A Model for Life.

Jim Smith was interviewed by Kathy Weston, Consulting Editor for DMM. This piece has been edited and condensed with approval from the interviewee.