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SPOTLIGHT

An interview with Robb Krumlauf

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Robb Krumlauf is a developmental biologist who studies the Hox family of transcription factors, aiming to understand how these proteins regulate animal body plans. Robb, who is currently Scientific Director of the Stowers Institute for Medical Research, was recently awarded the 2018 SDB Edwin G. Conklin Award for his extraordinary contributions to the field of developmental biology and for his excellent mentoring skills. We met with Robb at this year's SDB Annual Meeting, where he was presented with the award, to find out more about his research, his career and his thoughts on mentorship.

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

I've always been interested in science at some level. As a child, I loved to read; I had an uncle who was a mining engineer and he gave me books about science, and biology in particular, that really led me to love science and ask questions. What really locked it in for me, however, was that I had a wonderful, inspiring school teacher (in third or fourth grade) who encouraged me to enjoy science but also think about things in a new way. He helped me with many science fairs, lots of experiments, playing with things…I guess I just fell in love with science! I knew from that moment onwards that I'd be involved in science in some way or another.

I gather that you initially trained as a chemical engineer, but how did you then make the switch to biology?

When I was growing up, the public schools really encouraged those of us who enjoyed science and maths to become engineers, chemists or physicists. In fact, we didn't ever have any biology classes in high school! So, I guess I blindly followed that advice and applied to engineering and chemical engineering schools. I ended up going to Vanderbilt University and then worked for 5 years as a chemical engineer. I really enjoyed engineering: computing was coming in at that time and being able to combine engineering processes with computational approaches was exciting. However, I made the switch simply because, as part of my job, I was trying to make carriers that could act as slow releasers of drugs but realised that I needed to know more about physiology and biology. I was very fortunate that the company that I worked for – Stokley Van Camp – allowed me to take university courses to learn more about this. They figured it would help me be better at my job, and they had a deal where if you got an A they'd pay for your tuition, if you got a B you had to split the cost and if you got a C you had to stop! So I started taking all sorts of graduate courses in my spare time, in biology, physiology and developmental biology. This really helped me with my job but it made me realise that I loved doing experiments and the joy of making discoveries, but wasn't so interested in scaling these experiments up, which is what the company wanted me to do. While I was taking these courses, some of my teachers asked me when I was getting my PhD, and when I said I was just taking classes for fun they told me I was crazy and convinced me to get a PhD. They offered me an NIH training grant fellowship, and so I started a PhD at Ohio State University. My parents were a bit surprised that I was going to quit as a well-paid engineer to be a graduate student but they told me that I should do it if that's what I really loved. I think it was the best decision I ever made.

Although I was on a developmental biology PhD training programme, there wasn't actually a developmental biology department at Ohio State. This meant that my teachers were in biochemistry, physiology, zoology and microbiology. However, this really prepared me for doing science in a way that has still lasted; I had friends and contacts in so many departments, which made it easy to learn new things and find out information. It also taught me the value of interacting with people from different disciplines.

So what then got you interested in developmental biology in particular?

What fascinated me were gene regulatory networks and circuits – maybe this stemmed from my engineering background – and I could see that developmental biology was a wonderful fusion of understanding these networks and figuring out how we go from a single cell to an amazing organism. While I was a post-doc in Shirley Tilghman's lab, where I was working with transgenic mice to understand developmental questions, I was fortunate enough to meet people like Anne McLaren, Mary Lyon, Liz Robertson, Rosa Beddington and other incredible embryologists, and this made me realise that I really needed to learn more embryology. That's what led me to the UK: Shirley told me that if I really wanted

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to learn mammalian developmental biology there was an amazing concentration of some of the best mammalian embryologists in Oxford, Cambridge and London, so that's where I went. I guess I was kinda late to the game, but these embryologists welcomed me – both as a colleague and as a friend – and I've never looked back!

So you then moved back to the UK to establish your group at the National Institute for Medical Research site at Mill Hill (now The Francis Crick Institute), focussing on Hox genes. What first drew your attention to the Hox genes?

Well, it's a funny story really. While I was working with Shirley, we were studying α-fetoprotein (AFP) genes using both mice and teratocarcinoma cells: we made transgenic mice to see how these genes were regulated, and also used retinoic acid to trigger the differentiation of teratocarcinoma cells into visceral endoderm cells that express AFP. I wanted to find the earliest genes that respond to this differentiation event and it turned out that the Hox genes were rapidly induced. At the same time, Peter Holland (who was in Brigid Hogan's lab as a graduate student) and I had been taking the homeobox motifs that had just been found in *Drosophila* and trying to find transcription factors that might be mammalian equivalents – Peter doing this in mouse embryos and me in the teratocarcinoma cells – and again the Hox factors came up. I actually thought that someone had mixed up the samples from our different lab projects! We then sequenced these putative Hox genes and found out that they indeed encoded homeodomain proteins. At the time, we knew little about mammalian transcription factors so I decided to use these as models for studying gene regulation in development. I guess the rest is just history!

In ground-breaking work, you and your group discovered Hox gene collinearity in mammals, whereby Hox genes are clustered next to one another in an order that reflects the order of their expression and function in the embryo. This feature had already been observed in *Drosophila* so it must have been hugely exciting to see it also evident in mammals. Can you tell us more about this seminal discovery?

While we were cloning the Hox genes, we realised that they were really quite complex – they were linked to each other and showed some sort of organisation. I could also see that one of these Hox genes looked like the *Drosophila* Hox gene *deformed*. Anthony Graham, my graduate student, started looking at the expression of these and we were shocked that they also showed very precise ordering and boundaries of expression along the axis. I was so excited by this and gave my first public talk on this at a NIMR retreat, and everyone there was also really excited. The following week, I went to an Arolla meeting and Denis Duboule talked before me and presented virtually the same story but on a different Hox cluster! I knew he'd been working on Hox genes but we both had no idea that that we'd discovered the same thing. It was an amazing experience that led us to forming a long-term friendship and collaborative efforts.

The best thing about this discovery was that it indicated that there was an ancient way of patterning embryos. I had always been interested in evolution but never knew quite how to approach it. But if the Hox genes had an ancient role, I could see that, by modifying their levels, expression or function, they could provide us with a way of understanding morphogenesis and evolution. It was an engineer's dream! All the building blocks are there and they can be put together in different ways to build different systems; we just need to understand how this common toolkit can be used to give rise to morphological diversity.

This also must have been an exciting time in general at Mill Hill – you were surrounded by pre-eminent developmental biologists such as Brigid Hogan, Andy McMahon, Robin Lovell-Badge, Jim Smith and Rosa Beddington. What was it like working in this environment?

It really was an interesting and exciting time: Eric (Wieschaus) and Janni (Nüsslein-Volhard) had just done their screens and some of the first genes emerging were those encoding transcription factors. I was very interested in transcription factors, and their role in controlling gene regulatory networks, but I didn't really have a grasp of how they worked, how conserved they were and whether there was a paradigm for how they regulated patterns of expression during development. So to go to Mill Hill and find all of these amazing people who really understood embryology, along with great molecular biologists such as Peter Rigby and Frank Grosveld, was just a joy. It put me in a rich environment where everyone was asking interesting questions about gene regulation in vertebrate development. Beyond Mill Hill, we also had wonderful interactions with members of the local developmental biology community – the likes of Patrick Tam and Claudio Stern – who would point me in the direction of the right papers in the field and could tell me about the history of embryology, in true British style, over a pint in the local pub! And I could see that the molecular and genetic tools that were being developed at the time could really enable us to address important questions in the field. I was fortunate to be immersed in such a diverse and vibrant environment that facilitated the exchange of ideas and technologies: I knew about molecular tools and 'modern genetics' but in return I got wonderful insight in to stimulating questions of embryology…as well as some lifelong friendships. What made it really quite special was the collaborative nature of the NIMR. We had so many fantastic people there: Brigid Hogan, Jim Smith, Tim Mohun, David Wilkinson, Bernhard Hermann, Peter Rigby, Andy McMahon, Robin Lovell-Badge, Frank Grosveld, just to name a few. Everybody was asking questions, developing technologies and offering advice, and it felt like we were all working together as part of one big group. Frank was looking at long-range regulation of globin genes and we were looking at long-range regulation of Hox genes. Andy had just discovered Wnts. Robin had just discovered sex-determining factors. There were just so many exciting things going on!

There's important undiscovered biology yet to be explored…by studying a variety of model and non-model organisms, we can discover new principles and processes that are medically relevant

After a productive 15 or so year term in the UK, you returned to the USA to become Scientific Director of the Stowers Institute, which had only just been founded. What was the initial vision for the Institute, and do you feel that this has been realised?

I wasn't really looking to go back but a unique opportunity came up for me to set up what Jim Stowers referred to as an 'interdisciplinary, Mill Hill-style' research institute in the USA. At

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that time, model systems and technologies were becoming a bit 'compartmentalised' in the UK, with a focus on imaging in one place, biochemistry in another, and not enough intermingling between invertebrate and vertebrate model systems, and so on. Hence, the prospect of bringing all of these cutting-edge approaches and disciplines together was quite an exciting idea. I had also seen the strengths of collegiate and collaborative places like Mill Hill and the Laboratory of Molecular Biology in Cambridge, and knew how they had shaped my career, so I saw it as a way to give back to the community and perhaps make a difference to other people's careers. Initially I thought I would only offer advice but I fell in love with the vision and ended up being recruited to be the Scientific Director of the Stowers. Of course, I was afraid that I wouldn't be able to do the job, or be a good leader, but there was a big part of me that felt so fortunate to have trained in such a stimulating and supportive environment that I just wanted to try to help other people have a similar experience – I guess that was my real motivation. Despite all the hard work and challenges, it's ended up being a real joy. I see the Stowers as a combination of developmental biology, cell biology, biochemistry, genetics and computational biology. I've seen people in the Institute make discoveries in yeast and then jump to studying zebrafish and mice, and there are clearly huge advantages to this type of interdisciplinary science.

We've also been helped by the fact that we've had some amazing and well-respected developmental biologists – Eric Olson, Eric Davidson, Mike Levine, Doug Melton, Janet Rossant, Ruth Lehmann – on the scientific advisory board of the institute who've been a great influence during our formative years. We've managed to attract good young people, and we've always had a commitment to studying basic research. We believe strongly that there's important undiscovered biology yet to be explored and that by studying a variety of model and non-model organisms, we can discover new principles and processes that are medically relevant. This is especially important at a time when there seems to be an increasing pressure from funders to only support work that is medically relevant.

In fact, one of the best things about developmental biology is that it provides a hub of interesting problems and questions that capture the amazing diversity of nature. It attracts biologists but also physicists, mathematicians and engineers to work on these questions. Many people in other fields work on developmental biology problems but do not necessarily consider themselves as developmental biologists…but I'm okay with that! This is part of the modern face of developmental biology. Some people are worried about what's happening in the field but I'm an optimist and see a bright future: we're answering important questions and generating deep mechanistic insight into the fundamental decision-making events that govern development, organogenesis, homeostasis and regeneration. This is providing a rich framework for interdisciplinary science to exploit and build upon. I believe that the best is yet to come for the field.

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For many years now, you've played a lead role in the Society for Developmental Biology (SDB), serving as President of the SDB (in 2016) but also as Editor-in-Chief of Developmental Biology, the society's journal. What role do you think societies such as the SDB, and society-run publications, play in the community?

I really believe that societies – the SDB in the USA, the BSDB in the UK, as well as the other developmental biology societies around the world – play a great role in helping people understand what it's like to part of a scientific community. They also play key roles in training, education, outreach and career development. We clearly need to reach out to the public to explain why what we're doing is important, and societies play an important role in this process. Societies also have a very important role in making sure that the government and funding bodies are supporting initiatives that inspire and train future scientists. By exposing more people to biology and developmental biology at an early age (which is something that I, for example, missed out on), we can really inspire people and promote the field. The professional societies should and do play an essential role in this regard.

That's why I felt that it was important to devote my time to the SDB, as President but also as an editor for Developmental Biology. I also try to help the BSDB whenever I can: I think the relationship between the BSDB, Development and The Company of Biologists is just wonderful, and provides not only a great way of publishing good work but also a brilliant way of supporting scientists. It's a fantastic model! We are very fortunate to have so many exceptional and dedicated people associated with these societies who drive these activities and really keep our community vibrant. It's an effective way to honour all those who played roles in our success by giving forward to help the next generation.

You're about to receive the SDB's Edwin G. Conklin Award, which recognizes a developmental biologist who has made extraordinary contributions to the field, and who is also an excellent mentor. What is your approach to mentoring?

Well, I just want to help and care about people, so I try my best and hope that it works! I was shocked but deeply honoured to be given this award as I know there are so many deserving people out there. I'm especially honoured to be given this award not only because Conklin was such a great mentor but also because he really was one of the forerunners of applying the field of developmental biology to evolution; he was one of the founding fathers of evo-devo. He was a hero of mine in that regard, so to be given this award is pretty special to me.

In my mind, what makes a good mentor is to really understand what motivates someone. I know that I've benefited from having such great mentors over the years, and I appreciate how valuable it is to talk to someone who's had experience or who's been through the same things and had similar struggles. There's no one formula for success. The hard part, though, is that you can't live someone's life for them; it's a bit like being a parent, and you have to let people make mistakes and learn from them. It's hard to strike the right balance, but by caring about people and their careers you can help them make good decisions.

I've been fortunate to have had some wonderful people mentor me throughout my career. Shirley Tilghman really helped me see what it's like to run a lab and enjoy science. One of my PhD mentors, Phil Perlman, was also an unbelievable teacher and mentor who would challenge you, take you through tough problems and help you solve them. I also have people that serve as role models and still mentor me today, and actually I think that's another really great

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thing about the developmental biology community. We have so many talented people who care and are motivated to offer advice about science and career options. Taking advantage of this resource has been instrumental in helping me throughout my career. In return, I've always tried to make sure that I'm accessible and available to people who want to talk or need advice.

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

I would advise people to find out what they really love – find something that they're genuinely interested in. Of course, you need to get funding so you need to think about the relevance of your work but I don't think it necessarily needs to be medically relevant, as long as you can explain to people why what you're doing is important. Also, don't be afraid to change – I think that science can take you in unusual directions and you mustn't be afraid to follow new paths. Keeping some sense of perspective is hard, but this is where good mentorship and talking to colleagues can really help.

Finally, what would people be surprised to find out about you?

People are often surprised to find out that I love hiking and mountaineering, and also canal boating. We still share a canal boat in the UK, and we've had some great times taking friends and colleagues on the boat. Driving through the British countryside on a boat, working the locks, stopping at pubs, seeing some of the more rural parts of Britain and the stars at night – these are some of the most fun things I've ever done.