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SPOTLIGHT

An interview with Claudio Stern

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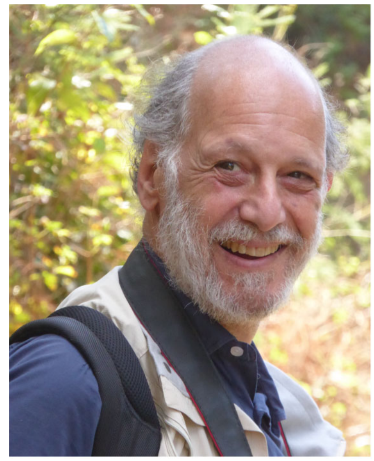
Claudio Stern is the J. Z. Young Professor of Anatomy at University College London (UCL), UK. His lab studies the processes that regulate patterning and cell diversity in the early embryos of vertebrates, mostly in chick. Claudio, an elected fellow of the Royal Society, the UK Academy of Medical Sciences, and the Latin-American Academy of Medical Sciences, was awarded the 2006 Waddington Medal by the British Society of Developmental Biology, and he also served as President of the International Society for Developmental Biology (ISDB) from 2010-2013. At the 18th Congress of the ISDB (Singapore, June 2017), Claudio was awarded the ISDB's Ross Harrison Prize, which recognises an individual's outstanding contributions to developmental biology. We met with Claudio to ask him more about his career, his thoughts on the field, and his advice for early career researchers.



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

As a child, I was always interested in creepy crawlies and everything to do with science. I was forever picking up insects and butterflies – anything that moved really – and enjoyed collecting them. I liked to watch them, to see butterflies hatching from their pupae. I think I must have been only 3 or 4 years old – I guess it all started from there! A few years later I enjoyed a chemistry kit, a microscope, a home planetarium and digging up fossils and archaeological artefacts.

I understand that you grew up in Uruguay. What then brought you to the UK?

I moved mainly due to the unstable political situation there in the early 1970s. I had started to study medicine but things then got rather disruptive so I had to leave. Also, I'd actually wanted to study biology rather than medicine, but it was difficult to study basic science in Uruguay at that time, so I saw the move as an opportunity to switch fields a little and do a degree in biology.

How did you then get interested in embryology in particular?

As an undergraduate, I was fascinated by the realisation that all cells have the same set of genes yet do such different things to generate a functioning organism. I wanted to understand where the 'programme' for development is encoded. At that time, the place where I was studying – the University of Sussex – was a hotbed of evolutionary biologists, geneticists and developmental biologists, so it was the right place to be thinking about these questions. For my PhD I chose to stay at Sussex to work under Brian Goodwin, originally a physicist who did his PhD with the great C. H. Waddington and was one of the pioneers in theoretical biology. I dreamt that it should be possible to master a combination of theory and experiment side by side to understand the 'rules' that govern development. Brian's lab had a mixture of people studying a variety of processes in many different systems: aggregation of the slime mould *Dictyostelium*, regeneration in the unicellular plant *Acetabularia* and of the limbs of axolotl and cockroach, the pattern of spots on butterfly wings. To try to understand how the body pattern arises, I chose to study gastrulation using the chick, where I could film cell movements and transplant cells around, and I used computer models to try to explain the patterns. Contact with the real embryos started to convince me that it may be impossible to arrive at a 'universal theory of everything', so for my postdoc I chose to learn more rigorous experimental science under the guidance of Ruth Bellairs, a wise embryologist at UCL.

> **Why do we study development? I think it's because one can address some of the most fundamental questions about life**

Over the years, you have been studying a number of important developmental processes, such as primitive streak formation. What can we learn from these detailed studies of embryology and development?

Well, why do we study development? I think it's because one can address some of the most fundamental questions about life: how does a functioning organism arise out of a bunch of cells? If all these cells have the same genetic information, where is the programme that controls this? How does complexity arise (both in development and in evolution)? In my mind, these are still key questions that remain unanswered. I'm interested in understanding how things work, but doing good science to discover basic biological principles will often provide information with relevance to medical and other applications. Most of the big

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discoveries that have been made to date have come about in this way, not by directly seeking a drug that cures something. Although I have always been motivated by curiosity, I have also spent most of my career in medical schools, with a particular interest in finding out how human embryos, tissues and cells function, and keeping an eye on pathologies.

You've also been studying stem cells, looking at them in chick embryos and comparing them with their mouse counterparts. Can you tell us more about this work?
We have indeed compared the properties of chick and mouse embryonic stem cells *in vitro*, in collaboration with Bertrand Pain in Lyon. But my interest relates mainly to the stem cells that exist *in vivo*, more than to cells that you culture in tissue culture dishes in artificial conditions. I've been interested in finding out more about the places in the embryo that contain self-renewing cells and the various populations of stem cells in the embryo that have particular functions. For example, we've been looking at a population of stem cells that, by self-renewing whilst staying in a specific position (the tip of the primitive streak), contribute to elongation of the axis of the embryo. The questions there are: what determines their rate of self-renewal, what distinguishes the cells that self-renew from their neighbours that do not, what determines the cell types to which they give rise, and what makes them stop self-renewing at the end? Is there a 'niche' in which they reside such that if another cell is placed there, it will acquire the properties of a stem cell? Much remains to be done to answer these questions.

And what are your thoughts on the fields of developmental biology and stem cell biology – are these related in your mind?
To be honest, I don't understand why some people want to say that stem cell biology is not developmental biology. Developmental biology includes stem cell biology but also includes lots more than that. Understanding the principles of developmental biology is essential for understanding stem cells and how they behave, *in vivo* and *in vitro*. Without that background, we can't understand much about stem cells; one can't begin from scratch, ignoring all that we know about development when we're trying to understand something that is effectively a developmental situation. I see developmental biology as a discipline that encompasses not only development in an embryo (embryology), but also reproduction, ageing, regeneration and repair, the stem cells that maintain tissues in the adult, as well as cancer (development gone wrong). These are processes that rely on developmental biology principles (cell determination/commitment, intercellular signalling and induction, morphogenesis, regulation of cell division and cell death, and so on), which continue throughout life.

In your Ross Harrison Prize lecture, you mentioned that, as an undergraduate, you were really interested in three subjects: genetics, experimental embryology and computational modelling. We've seen technological advances with regards to all three of these, so is this now making it easier to address the open questions in developmental biology, and are you still interested in all three approaches?
I really like what these three disciplines have in common. They offer the possibility of designing logical, orderly and rigorous experiments; you can pose a question and try to isolate the variables cleanly, and then design an approach to study the variable you're interested in. Experimental embryology in particular allows you to look at the general rules that control how a system behaves, even before you know what the components of the system are. Classical genetics is also about uncovering principles even before you know what the genes encode, and also allows the design of beautifully clean experiments. Modelling has the same attribute – it allows you to distil the key elements of a system to test the rules that govern its behaviour. It can also be great fun. However, there are only a few examples where modelling has gone beyond description and has led to the design of experiments that you wouldn't have done otherwise. I think modelling is most useful if you can make counter-intuitive predictions that you can then test using experiments. So experimental embryology, classical genetics and modelling all have in common that they stimulate elegance of experimental design.

You mentioned some exciting studies looking at twinning studies in chick embryos but also in humans – how has it been working with humans rather than chick embryos?
Making monozygotic twins is a feature that only amniotes, including humans, can do. However, you can't really do experimental embryology in humans, and rodents do not make viable identical twins, so chicks are the perfect system. On the other hand, human genetics is an incredibly powerful way to identify the components of a mechanism. So, if it turns out that the mechanisms that control twinning are the same, which is very likely, then the two systems can complement each other. Humans offer a situation where the experiment has been done already, by nature, so it's just a case of extracting the data. The existence of several populations around the world that have high rates of spontaneous twinning provides a unique opportunity to understand the mechanisms responsible. The project is moving forward pretty quickly and is starting to give us some surprising results!

It is useful to bring together people who think differently; the result can be more than the sum of the parts

Over the years, you've been involved in bringing developmental biology societies together, in your capacity as President of the ISDB and also in terms of strengthening links between the Latin American Society for Developmental Biology (LASDB) and other societies. Why do you feel this is important?
By getting involved in international activities (like those you mentioned and also the Royal Society and various international committees that I sit on), I can learn more about the different ways of thinking of different communities. Some of this, of course, is influenced by language, cultures, background, education, local politics and funding systems, and different approaches to life. I believe that it is useful to bring together people who think differently; the result can be more than the sum of the parts. Also, local funding doesn't always provide adequate support for cross-disciplinary activities; international collaborations can help overcome this to some extent.

I gather that you've also been interested in the history of science, for example the work of Waddington and how this has influenced modern-day biology. What got you interested in this?
I've been mostly interested in ideas and principles, so it is interesting to look at how ideas evolved over time and how we can build on what other people have done before: we are 'standing on the shoulders of giants'. Many of the big questions that we are asking now have been asked for hundreds of years. Knowing what others

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have done before helps us to address the questions more intelligently. Waddington was particularly wise in this respect. He noted that we learn by returning over and over to the starting point, each time equipped with new knowledge. His book *Principles of Embryology* (1956) ends with this quote from T. S. Eliot's poem *Little Gidding*:

And to make an end is to make a beginning.
The end is where we start from.
* * * *
We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.

What would be your advice to young researchers starting out in developmental biology?

Choose a question to which you really want to know the answer, then let that curiosity be your driver. If you don't really care about the question – or the answer to it – you'll struggle to do good science. Then, when designing experiments to address this question, ask yourself: 'if I do some particular experiment, will the likely results really help me to answer the question?'. If you pick a question that really, really interests you, this should provide you with the motivation to do good science and help you to avoid doing stupid experiments.

What are your thoughts on mentoring and the role of the PI; how best can you 'nurture' your lab members and help them to be successful?

I think it's important to encourage everyone to be original and come up with their own questions, and not be afraid to ask really big questions. I try to guide them to learn to think, to speak and to write clearly, because these qualities will greatly influence their capacity to succeed later. I also encourage them to question everything: whenever confronted with what appears to be a fact, one should always question: how do we know that, what is the evidence? This protects us against dogma, and can help to build up confidence.

And how about people who are thinking about a non-academic career path – what's your advice to them?

I think that the principles of the scientific method (epistemology) are useful for everything. So, if you learn a way of thinking that mimics the sections of a classical paper – what's the question, what's the method, what do you observe (objectively), and then use this to reach a conclusion or make a decision – it is applicable to absolutely everything in life. Armed with this, follow your heart and do what you really like.

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

Perhaps that I love cooking and eating, or maybe that I am interested in renaissance and baroque music and play several woodwind instruments.