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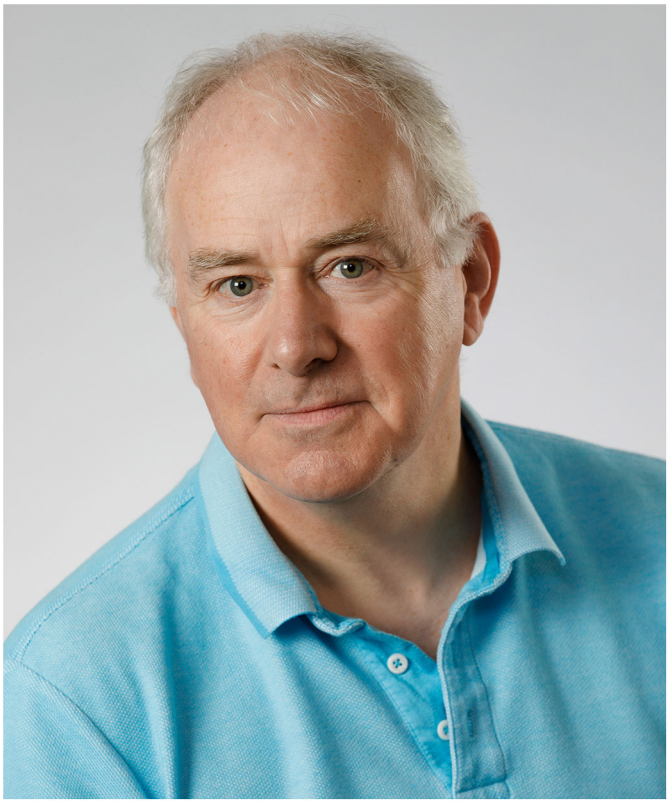
CELL SCIENTISTS TO WATCH

Interview with 2020 Hooke medal winner Ian Chambers

Ian Chambers studied biochemistry at the University of Strathclyde in Glasgow, UK. He then did his PhD in the laboratory of Paul Harrison at the Beatson Institute for Cancer Research, also in Glasgow. Ian studied the control of gene expression during the differentiation of erythroid precursor cells, discovering that the amino acid selenocysteine is encoded by UGA, which until then was thought to work only as a termination codon. Ian did his post-doctoral work on the regulation of the human immunodeficiency virus (HIV) with Paul Berg at Stanford University in California, USA. In 1991, he returned to Scotland to work on stem cell regulation with Austin Smith at the Centre for Genome Research (later the Institute for Stem Cell Research) at the University of Edinburgh, UK. During that time, Ian identified the transcription factor Nanog, which directs efficient embryonic stem cell self-renewal. Ian started his research group in 2006 at the University of Edinburgh, where he is also a Professor of Pluripotent Stem Cell Biology. His laboratory tries to understand the regulatory networks and transcription factors that control the identity of pluripotent embryonic stem cells, and how these modulate cell fate decisions during the differentiation process. Ian is now the Head of the Institute for Stem Cell Research at University of Edinburgh, an EMBO member and a Fellow of the Royal Society of Edinburgh. Ian is the recipient of the 2020 Hooke Medal from the British Society for Cell Biology (BSCB).



Ian Chambers

What inspired you to become a scientist?

Most of my schooling was in Ayrshire, and because Alexander Fleming was born in Ayrshire, we heard about penicillin from an early age. However, there was one instance in secondary school, when the chemistry teacher had everyone in the class around the front bench and he asked what would happen if he mixed two measuring cylinders, one with dried peas and the other with dry rice grains. He said, "I've got 100 ml of each, so if I pour one into the other I'll get 200 ml, won't I?" and I said "No, I disagree because there's space between the peas for the rice to fit in." He was talking to us about differently sized atoms and how space exists between atoms. I thought, "Anybody can do this, this is easy." Another thing that made me curious about science was a BBC television dramatization of Louis Pasteur's life, which I found very interesting, and it was through listening to it that I started thinking about what an amazing person Pasteur was. We'd all learnt about pasteurisation, but the fact that Louis Pasteur was able to use reason to discover the basis of a disease like rabies without being able to really see any of the causative agents involved was quite a profound thing for me. I still find it quite amazing that by pure reason he was able to advance knowledge.

What questions are your lab trying to answer just now?

We want to know, and this is something that many other people are trying, too, how a cell with more than one fate can choose to do one thing rather than another. Specifically, what we're interested in is how transcription factors work – how these molecules interact with other partner proteins and also with DNA to deliver function. And how these protein–DNA complexes connect to RNA polymerase is an important part of the puzzle that I don't believe has been fully worked out yet.

What has been the most influential publication or work in your field recently?

We're understanding more and more about many of the molecules that are involved in embryonic stem cell (ESC) self-renewal and the decisions to differentiate. Obviously, the most important experiment was the one that Kazutoshi Takahashi and Shinya Yamanaka did 14 years ago (https://doi.org/10.1016/j.cell.2006.07.024) [where they induced pluripotent stem cells from fibroblast cultures]. I think more recently, in terms of gene transcription, there has been a lot of excitement around the concept of phase separation in biochemical systems; this has received a lot of attention but it's not uncontroversial. The idea that high concentrations of molecules can somehow gather into a different phase, with separate physical properties from the liquid around them, and be important in controlling cellular events is interesting from the point of view of transcription. One of the experiments that has been used to support phase separation is shown in the paper from Takashi Fukaya and Mike Levine (https://doi.org/10.1016/j.cell.2016.05.025). They showed that a developmental enhancer placed between two

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Ian with his wife and fellow biologist Helen Wallace during a walk on Irvine beach, Ayrshire, with the hills of Arran behind.

separate promoters would activate transcriptional bursts from both promoters simultaneously. That certainly suggests that promoters are activated in response to whatever that enhancer-emanating event is, and people have used that argument to say that phase separation may occur, but I think there are other possibilities; for instance, local concentrations of regulators may be sufficient to explain that.

In terms of development, if I had to pick out one paper from the last ten years I would choose the paper from Emma Farley, again from Mike Levine's lab, which was published in Science in 2015 (https://doi.org/10.1126/science.aac6948). It talks about the sub-optimisation of developmental enhancers. It's a really great piece of work. They study a particular enhancer in the sea squirt *Ciona*, and show that if they increase the affinity of transcription factor-binding sites or optimise the spacing between transcription factor binding sites within the enhancer, the enhancer works better. That's no surprise, right? But then they show that development doesn't work properly and cells don't perform the way that the developing *Ciona* would like them to. I think that is quite profound and has echoes in other systems. For example, in ESC cultures, some cells self-renew while others differentiate. We can make self-renewal uniformly efficient by increasing the concentration of some pluripotency transcription factors, such as Nanog, or by halving the concentration of another pluripotency transcription factor, Oct4. What this means is that the normal transcription factor circuitry in ESCs is suboptimal and that the demise of the pluripotent state is encoded within the network of transcription factors that are required to maintain pluripotency. In the embryo, the cell type that is equivalent to ESCs is transient and differentiates quite quickly, which of course, is what is required developmentally.

"There's nothing like failure to sharpen your mind."

Have you had any 'eureka' moments, for example, when you discovered the selenocysteine codon or the transcription factor Nanog?

Well obviously, luck is a big part of this. Before we cloned Nanog, we spent quite a bit of time trying to clone a cDNA encoding an activity from a conditioned medium that modified ESC growth. What we ended up cloning was LIF, which everybody had known for over ten years drives ESC self-renewal. We still don't know how that plasmid got into the libraries. That was a wee bit of a setback. When we were designing the experiment that finally led to the cloning of Nanog, we decided that we would increase our chances of catching something by casting as wide a net as possible. We knew that self-renewal was more efficient when ESCs were grown on top of a heterologous feeder layer of fibroblasts. We didn't really know why that was at the time, but we thought it might be because fibroblasts need to be in direct contact with the ESCs in order to provide them with a signal that optimised self-renewal. Anyway, that worked. We cloned Nanog from the resulting library. There's nothing like failure to sharpen your mind. Thinking things through from a previous experiment helped us do things better. The 'eureka' moment was when we sequenced individual plasmids from the self-renewing colonies. There were multiple copies of a single transcription factor in there so at that point I knew that we had it. But I didn't talk about it and I didn't tell my boss about that for several months until it was totally nailed down.

The 'eureka' moment from my PhD was quite interesting. I was studying the basis of differentiation of red cell precursors by focussing on the control of gene expression of non-globin genes (many groups were already working on globin). We didn't know much about the gene I was working on. So, one of the things I had to do was sequence the gene. This was in the mid-1980s, so we were running our own sequencing gels. There was something that was puzzling me because I could see a stop codon right in the middle of the open reading frame. I thought it must be a mistake. We ran homology searches and found nothing. Finally, we got a match to a protein that had just been published, but we couldn't access the paper at the University of Glasgow, so I had to go across the city to the University of Strathclyde library, which was a 40-min bus ride. Once I had the photocopied paper, I looked at the sequence and thought 'there's this funny amino acid and it's sort of in the same position as this funky stop codon is'. I was a wee bit excited, so I zipped across the city back to the lab, which took me another 40 min, and by this time it was about eight or nine o'clock at night. I put it all together but at that point I think there was only one other PhD student in the lab. But that was definitely an 'eureka' moment.

You mentioned failure is an opportunity to learn. How do you mentor your students or postdocs to deal with mistakes or failures?

We just have to be rigorous and systematic. There's nothing wrong with failure; we learn more from our failures than we do from our successes, so it's an opportunity for 'growth and self-realisation'. We always have to try to look at the evidence as critically as we can and try to figure out what's gone wrong. Sometimes there are too many parameters to troubleshoot but we still have to try to approach things in a systematic manner. You need to look at your data critically and always be rational; one reason people can fail is because they don't always look at the evidence carefully enough. When you are doing something and you get a setback, it's easy to quit, but it's important not to.

What is the best science-related advice you ever received?

There are a number of them. Louis Pasteur said: "Chance favours the prepared mind", which just means read, read, read! And then when you find something odd, you're prepared to make sense of it. I also like a quote from Mohammed Ali. I have a poster in my office with a picture of him training, and it says "The fight is won or lost away from witnesses – behind the lines, in the gym, and out there on the

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road, long before I dance under those lights." I think it's important that people get this. Everybody wants to succeed. There was a mock version of the Lady Gaga hit, a few years ago, out of Baylor University (https://www.youtube.com/watch?v=Fl4L4M8m4d0) about being stuck in a bad project. People want to have something interesting to say that means that they have succeeded on a project – something they can talk about, describe their fantastic findings at a conference and get feedback on from the top people in the field. But to get there you need to work hard and you need to put in the hours when many other people won't be there. People get lucky, but it's not all about luck, it's about work.

"People get lucky but it's not all about luck, it's about work."

What is the most important advice you would give to someone about to start their own lab?

I think probably the best thing you can do is find a positive but critical and sympathetic mentor to talk things through with. That's not something that everybody does. There are also networks of new PIs. Not long ago, I went to an EMBO course on how to be a PI; maybe I should have done that a long time ago, but you can always learn something. Most of the people there were just starting their labs. This is a great opportunity to get together with people who are in the exact same position, leading to a network of support that might help take people through their earliest years.

How are circumstances different now for early-career researchers compared with when you started your lab?

I think many things remain the same; the biggest difference in the research landscape now is our [UK's] changing relationship with Europe. We don't know what is going to happen with the European Research Council funding going forward. We don't know about the Marie Curie postdoctoral fellowship scheme, which is a very prestigious fellowship programme run by Brussels; also the Erasmus mobility programme for much younger students. These things are unknowns and may limit who we can bring to the lab. I've had many more non-British than British people in my lab, including a lot of Europeans. I think there are going to be fewer Europeans in newly established labs [in the UK] in the future, which is a shame.

How did you and your lab cope with the lockdown due to the SARS-CoV-2 pandemic?

There's definitely been an element of fatigue that I couldn't have predicted at the beginning. At the very start, it felt like a great opportunity to get up early in the morning and follow Mark Twain's advice – he said something about getting up at 5 am and starting by eating frogs – I think he meant do the ugliest thing that you have to do first, and you'll feel better and be more productive. That worked for some time, but not for four months. One of the first things that we did was try to normalise our timetables so that we were meeting regularly. We couldn't really do lab meetings, but we did journal clubs every week. And at 4 pm every Friday, we had a virtual happy hour to try and talk over what we'd achieved during the week and just interact socially. Then we began to come out of lockdown and people are now back in the lab part-time doing experiments. Things are beginning to change.

You were due to receive your Hooke Medal at the British Society for Cell Biology annual meeting in Paris. Unfortunately, the meeting, like many others, was postponed, whereas others have gone virtual. How do you see the future of scientific conferences changing?

I was really looking forward to receiving the medal at the Institut Pasteur, as you probably could tell! But I'm looking forward to the meeting in spring in Bristol. I'm actually organising a meeting that was due to run in Kyoto in November, but we've had to postpone that until spring 2022. We now have the opportunity to rethink how we do things, and one thing we will be doing is offering the speakers the chance to deliver their talks remotely, rather than travelling to the meeting. That's as far as I've thought about it. But at [The University of] Edinburgh, we're changing our teaching to an online format, and thinking about other ways that we can engage students. Hopefully, there might be some new ideas for us to take forward to meeting organisation in the future, as we have to find new ways to deliver an experience that is good for all the participants.

Could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?

When I left school, I didn't go to university straight away. I worked for three years in a local factory that made amoxicillin, which is a semi-synthetic penicillin. I worked in a chemical plant in the first year as a lab technician. The goal of the plant was to separate a racemic mixture of the D- and L-stereoisomers of p-hydroxyphenyl glycine, a synthetic amino acid. If you look at the β-lactam group in penicillin, there is an organic R group at the side. In order to get a broad-spectrum antibiotic, that R group is taken off and, in the case of amoxicillin, is replaced by the D-form of p-hydroxyphenylglycine. The plant was the first industrial-scale processing plant on the planet, as far as I'm aware, that used this approach to separate out stereoisomers into pure D- or L-forms. Pasteur had separated D- and L-tartaric acid crystals using a microscope. So here I was doing something that connected Pasteur and Fleming. And that was quite something. I thought I was just going to work in a factory!

Ian Chambers was interviewed by Inês Cristo, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.