

## SPOTLIGHT

# An interview with Brigid Hogan

Catarina Vicente<sup>\*,‡</sup>

Brigid Hogan is a developmental biologist who has worked extensively on the early stages of mouse development and is now unravelling the mysteries of lung organogenesis. She is the George Barth Geller Professor and Chair of the Department of Cell Biology at Duke University Medical Center. Brigid is also the winner of the 2015 Society for Developmental Biology (SDB) Lifetime Achievement Award.

## How did you develop an interest in biology and was there someone who inspired you?

The first person who inspired me was my grandmother. She liked gardening, and I distinctly remember her showing me how to plant seeds in a little bed that she said was my garden. I was fascinated by how these seeds would turn into flowers. When I grew older I became interested in bird watching and collecting flowers.

When I was in school I didn't do very well in subjects like history and Latin, but I always did really well in biology. I attended an all-girls high school, but the year I reached 16 the women teachers who had taught chemistry and biology retired. The school couldn't find any women replacements, so they hired Mr Jones. He was very interested in DNA, chromosomes and molecular biology in general, so he swept aside all the stuff we had been doing before and said we were going to do experiments, such as dog testis squashes of chromosomes. This was very exciting for me, and a great inspiration. I also joined other activities outside school. On the other side of the hill was the boys high school and Mike Ashburner, the *Drosophila* geneticist, attended that school. We both belonged to the Middle-Thames Natural History Society, and the society's weekend meetings took place in areas such as Burnham Beeches woods, where Mike photographed flowers while I was interested in birds and, indeed, any natural history.

## Both your parents were artists and you have said before that you "view embryos as a thing of beauty". Does your artistic sensitivity influence the way that you view scientific problems?

My father died when I was really young, so it was really my mother who was the biggest influence. She had been an artist, and we had lots of books about art that we used to look at. Developmental biology didn't quite exist while I was at university, but the papers and topics that interested me always had a visual element. I remember hearing about *Drosophila* genes associated with segmentation from David Ish-Horowitz when I was in Mill Hill. I would listen to his talks but didn't really get it. It wasn't until I went to a seminar given by Mike Akam, in which he presented some of the first *in situ* hybridisation patterns for *Ubx*, and saw his pictures of the



stripes of mRNA distributions that I finally understood what it was all about. The visual input was always tremendously important for me and it still gives me enormous pleasure to look down a microscope at embryos and tissues and wonder how they develop.

## It still gives me enormous pleasure to look down a microscope at embryos and tissues and wonder how they develop

## You did your degree at the University of Cambridge, where you experienced negative attitudes from male faculty. How have attitudes towards women in science changed during your career?

Fortunately, attitudes have changed, and there is a lot of external pressure for them to change. In fact, yesterday I was talking to some Cambridge students and recounting some of the bad experiences I had as an undergraduate, and they were quite shocked. If this kind of sexual harassment happened now it would be immediately reported. In those days it was all swept under the rug; you just put up with it. I am amazed that I survived and stayed interested. It would have been terribly easy to give up, and it must have been the sheer passion for what I wanted to do that kept me going. It is a real pity because I think I might've been much happier if the attitudes of teachers to women students would have been different back then.

The harassment has largely gone, but there is still a long way to go. I have just been to the Wellcome Trust meeting on The Biology of Regenerative Medicines and around 85% of the oral poster presenters were young women. I don't know what happens to them, but the number of senior women speakers was by no means the same proportion. The real problem is how to combine a career with having a family. Confidence is also an issue, to overcome all the stresses

<sup>\*</sup>Online Editor, *Development*

<sup>‡</sup>Author for correspondence (catarina.vicente@biologists.com)

and strains during your career progression. These stresses affect both men and women, but I think women often feel more insecure and take criticism much more personally. In addition, although people are much more aware of women's issues, there are other problems to solve. If we think it is difficult for women in science, it is even more difficult if you are an African American or Hispanic, at least in the USA where I work. There is a huge diversity problem.

**You established yourself as a developmental biologist with work on early mouse development and organogenesis. However, this was not how you started your career. You worked on sea urchins during your postdoc and mouse teratocarcinoma cells in the early days of your lab. How did your interest in mouse embryology develop?**

I have always been very interested in embryos, even as an undergraduate, and I would read a lot about developmental biology. However, in those days there weren't any classes in cell biology or developmental biology, so I chose to do my PhD in a topic that was very exciting in Cambridge then – protein synthesis and RNA. However, when I finished my PhD I said to my advisor: "I really want to work on embryos, do you know anybody with whom I can do a postdoc?". My advisor suggested that I worked with Paul Gross, who was studying sea urchin embryos at MIT. In the end, I didn't find sea urchins so exciting, especially because the availability of the material was a little sporadic (during the winter you had to wait for shipments to come from California), but it was a wonderful experience being at MIT. It was so completely different to Cambridge in the UK – I remember being overawed by the size of the biology department!

Mostly for personal reasons I eventually decided to come back to the UK. I got a job as a lecturer at Sussex University but was dissatisfied there, and ended up moving to work with John Cairns at the Imperial Cancer Research Fund (as it was then) Mill Hill laboratory in London. John was hugely influential in my career because he gave me the freedom to look around and find a research topic. Initially, I started working with F9 embryonal carcinoma cells and gene expression changes as they differentiated into extraembryonic endoderm in response to retinoic acid. By this time I had two terrific postdocs, Denise Barlow and Markku Kurkinen, who brought molecular biology skills to the lab. F9 cells start making lots of extracellular matrix proteins when they differentiate, so this led us to beat big groups in Germany and the USA in the first cloning of the genes for laminin and type IV collagen. This work was very exciting, but in the end it wasn't really developmental biology. I still hankered after the embryo, and so I started trying to isolate pre-implantation embryos. I found this really challenging on my own, so I contacted Anne McLaren at the MRC Unit for Mammalian Embryology at University College, London. Besides John Cairns, Anne was the most influential person in my career and the best possible person I could have found to help me. She was such a brilliant scientist, so encouraging and supportive. She and her colleagues, and people like Janet Rossant, Liz Robertson, Ginny Papaioannou and Allan Bradley – all of whom had grown up knowing how to manipulate embryos – were incredibly kind, supportive and generous with me. So was Gail Martin, who was working on embryonal carcinoma cells in London then. So if there is one take-home message from my career it is that it can take a long time to get to where you want to be!

**If there is one take-home message from my career it is that it can take a long time to get to where you want to be!**

**You have been very involved in the development and teaching of techniques in mouse embryology and transgenesis. Did your interest in this develop during those early days?**

In those days I would visit Anne's lab, and people such as Mike Snow and others would answer my questions: "what medium do you use for this?; how do you do this experiment?; show me precisely how you do the dissections". They would pull out a drawer and fumble around for a bit of paper and say "Oh, I think this may be the formula", and I would snatch these pieces of paper and take them back with me. I gradually realised that what beginners like me needed was a handbook like Joe Sambrook's famous cloning manual. I also thought we needed a course where experts could teach us how to collect embryos and manipulate the early post-implantation stages. I kept on mentioning this to people and everybody said it would just be too difficult, that no one would support or pay for the course. Then, when I was at Cold Spring Harbor, I was at lunch and Jim Watson sat down opposite me and just said: "What's new?". I realised that I needed my two-minute elevator speech to say something that would catch his attention. I told him that there were some really exciting developments in mammalian embryology and molecular biology, and that I really wanted to run a course but was being told I couldn't do it. He just stood up and walked off and I thought "Oh, I've annoyed yet another person". I finished my lunch, left the dining hall and started walking away when he ran down from his office with a piece of paper in his hands saying: "It's all arranged, it's all arranged! You'll do a sabbatical here and we'll run a course with Frank Costantini and Liz Lacy". He had been trying to recruit them to Cold Spring Harbor because they had made the first transgenic mice in Oxford and had just started their own labs in New York. So I helped run the course, and wrote the manual, which was eventually published by Cold Spring Harbor. Frank and Liz were co-authors, and of course it included their technologies for making transgenic mice, which is what people were really excited about. Every now and again I would push a little bit of post-implantation embryo at someone and say "Don't you think this is interesting", and they would say "Oh yes, but I want to inject my DNA". It took a while for the course to gradually evolve into what it is now. It moved from transgenic mice to ES cells, making chimeras and now making iPS cells and organoids.

**Your lab is currently interested in understanding lung development. Why did you decide to focus on this organ in the last few years?**

There was a short period of time when you could become interested in almost any organ system, because you would make a knockout homozygous mutant mouse and you didn't really know what sort of phenotype you were going to get. My lab went through a stage when we were interested in many different organs and their development, because of the role of the BMPs and Fox genes that we had cloned and for which we had reporters.

But the lung has fascinated me since my early days in London. At Mill Hill we had access to about twenty different strains of mice and you could just ask for mated, timed embryos of these different strains. I looked at all of them and was fascinated by the fact that the lung branching pattern was the same. When we were working with BMP4 and FGF10 we noticed that these proteins are expressed in the developing lung, in the epithelium and mesenchyme of the growing buds. I had a brilliant student, Molly Weaver, who loved doing manipulations, cutting up buds and showing that they grew towards beads soaked in signalling factors. This work was incredibly exciting

to me, and it seemed that it was opening up an important area of developmental biology: epithelial/mesenchymal interactions and organogenesis. I also ultimately focused on the lung owing to funding. I had grants from the National Institute of Child Health and Development, but they always cut their grants by 25% after you've got one, so it was very difficult to keep going. So I applied to the National Heart, Lung, and Blood Institute and got a grant to look at lung development. They didn't cut the grant by 25%, so I wrote another... There were lots of interesting questions, but you can't really focus and ask important questions about many tissues simultaneously. It is difficult to be competitive in many fields.

**You have been involved in the past in high-level discussions of the ethics and regulations of embryology. You were the co-chair of the 1994 NIH Human Embryo Research Panel, and a member of the 2001/2 National Academies Panel on Scientific and Medical Aspects of Human Cloning. What do you think are the next big ethical challenges in the field, and what role should scientists play in these discussions?**

In the ethics discussions I was involved in at the NIH my role was very much just to tell the committee the basic facts of early embryonic development. I remember explaining that if you separated an embryo into four blastomeres and put them back, you weren't necessarily going to get four babies. I suppose I was quite good at explaining, perhaps from having taught in courses. It was a hugely interesting experience and I was deeply inspired by Anne McLaren, who had been the pioneer in being involved as a scientist in such ethical discussions.

At the moment the hot topic is undoubtedly the genetic manipulation of the human embryo by CRISPR/Cas9 technology. It is a very powerful technique, but it is far too soon to apply it to humans. A lot more basic research has to be done on possible side effects. If one of the parents carries a mutation, you don't know which embryos are carrying the mutation. So which ones do you

choose to repair? Is this necessarily better than just pre-implantation genetic diagnosis, where you keep the embryos that don't have the mutation? You could also apply this technique to stem cell populations that could be replaced without having to change the genome of the whole human. However, this strategy has the problem of how you get these cells back into the damaged tissue. The real danger is that the promise is all blown out of proportion based upon preliminary results. The big challenge is going to be to make sure that people don't move too fast, getting everybody's consensus and agreeing on a course of action together.

**Later this year you will receive the SDB Lifetime Achievement Award. Does this prize have a special significance for you?**

I'm very grateful. The SDB is a great organisation and I've got many friends there. It gives me enormous pleasure and is a boost to keep going. It is very gratifying to feel that, in spite of all the early struggles one had, I have been very lucky in the colleagues, friends and people who helped me. This is another example of people recognising me and being nice to me.

**What is your advice for young scientists?**

You have to be passionate. That is what kept me going during the dark days of my undergraduate, PhD and early postdoc. It took quite a long time before I found the mouse embryo, Anne McLaren and the community of mammalian developmental biologists. I kept going because I just felt I wanted to work on embryos and probably because I picked up a tenacious attitude along the line. Maybe that has not necessarily always been good, since I have the reputation of being a little abrasive at times, unlike someone like Anne who was enormously diplomatic. You mustn't be too aggressive in what you want, but you still have to be very tenacious. It is also important to find a community, a life partner and/or a group of friends who will support you and encourage you.