

SPOTLIGHT

An interview with Doug Melton

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Doug Melton is Xander University Professor at Harvard University, co-director of the Harvard Stem Cell Institute and a Howard Hughes Medical Institute Investigator. His lab investigates the development of the pancreas, and uses insights from this process to direct the production of insulin-producing beta cells from stem cells. We met Doug at the 2016 Society for Developmental Biology-International Society of Differentiation (SDB-ISD) joint meeting in Boston, USA, where he gave the Jean Brachet Lecture.

You're at the SDB-ISD meeting to deliver the ISD Jean Brachet Lecture. What does the award mean to you?

Of course it's nice to get recognised, particularly so with an award named for Jean Brachet, who in a sense was a molecular biologist, though at the time he would have been called a chemical embryologist. In my own career, I was in a wave of people applying molecular biology and cloning to embryological problems, so it's nice for me to imagine that I fit into his tradition.

Brachet was responsible for showing the importance of RNA and was right on a path to demonstrate that protein synthesis occurred at ribosomes when World War II intervened. After the war, in the early 1950s, researchers in Brussels couldn't get hold of radioactive amino acids, but the Americans could, and they won the Nobel Prize. When Brachet read the papers demonstrating protein synthesis from RNA, for which he had all the circumstantial evidence, he said he couldn't have been happier even if he'd been the author. I just thought: what a gracious thing to say! So it's especially nice to have been asked to speak in his honour.

What inspired you to become a biologist?

There wasn't really one event, one moment of epiphany. When I was a little boy I liked frogs and salamanders, and remember being puzzled by how the eggs, which looked so similar, knew how to make a tail or not make a tail, and that sort of piqued my interest.

But more seriously, when I got into college, I read an article in *Scientific American* by John Gurdon on cloning, and I thought that was the coolest thing, just so, so cool! John is one of the clearest writers of science, and that sort of simple reporting on an important question – what the scientist is interested in and why is it important – is extremely powerful.

So you did your BSc in Illinois, went to Cambridge as a Marshall Scholar and got a BA in the History and Philosophy of Science, and then did a PhD with John Gurdon at the LMB. How did these academic experiences influence your career?

In the late stages of my undergraduate degree, I got interested in philosophy of science and philosophy in general. I was very lucky



to get this Marshall Scholarship – I'd never really been outside of Illinois – and Cambridge University in the UK was really good for me. It taught me right away that the philosophy of science was really interesting, but also – and this is maybe the embarrassing part – that I would never do anything original in philosophy but would instead spend my life commenting on really original thinking by others. My ego didn't want me to spend my life commenting on what others did.

So then I remembered the article in *Scientific American*, and I showed up at John's door and asked if I could wash dishes or just help out. He didn't really know what to make of it! But he let me play around in the lab while I was finishing up this degree, which was unusual: there weren't other undergraduates at the MRC LMB at that time. And I'm forever grateful to John for taking a chance on me: I cannot overestimate the influence he had on me, in showing me how to do science and have fun, and how to think about what questions are worth asking. The simplicity with which he's approached science is breathtaking. He's a great example for how to do science.

You then returned to the USA and established your own lab at Harvard. What were the main questions you were interested in, and what were the main contributions of the lab?

When I left John's lab, what really interested me was an older embryology question concerning things in the egg called cytoplasmic determinants. This was around the time that factors such as Bicoid in *Drosophila* were being discovered, and I worked on a localised mRNA in the frog egg to see if we could find things that help explain Nieuwkoop's induction work. It was a very exciting time: great people all working in the same area. You'd come to a meeting like this and someone would have pointed their finger to a gene to say 'that gene's important'; that was where we were, just trying to find genes responsible for induction.

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In terms of contribution, I like to think my lab was one player in that general movement. One technology that we developed and turned out to be useful was to make RNA *in vitro* with SP6. And I think we were one of the first to make the argument that when development occurs, paradoxically the nervous system is the default pathway, and to make endoderm is harder. This really seemed to annoy some neurobiologists, who thought that being a neuron was the highest thing to which you could aspire!

The most important thing to me was the students I got, and being part of this exciting community of excellent scientists. Jim Smith, Eddie de Robertis, Jonathan Slack, Masamoto Asashima, Mark Kirschner; a really large group of people trying to figure out the genes responsible for induction. It really was a lot of fun and just a very exciting time, as I'm sure being in development now is.

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I guess now it's still as exciting, just bigger?

Maybe that's it. I think developmental biology has expanded, to take on morphology formation in other animals (evo-devo), and into something that I try to practise, applied developmental biology. Rather than asking how nature works, in an almost anti-intellectual way we ask how we can apply this to something, for instance human health.

I love developmental biology because of how lucky one is to be able to work in a field that answers questions about nature, but also can offer something to help people.

In the late 1990s, your lab shifted focus to work on pancreas development and diabetes. What were the big open questions at the time?

I don't think it's an exaggeration to say that most people in the diabetes field at the time were working on how to provide insulin, the molecular biology of the insulin gene, how to manipulate the protein's solubility, and what happens when a patient presents with the disease. For a developmental biologist, that's not how you would think about it: the obvious question is where do pancreatic cells come from? What genes are involved, and can we remake pancreatic tissue?

This is not some flash of insight: it's the sort of question an undergraduate might ask. If there were people asking these questions at the time then they were few and far between, and it wasn't discussed at a meeting like this. So when I went into the lab and told them we were going to change our focus, some people were a little disappointed as it didn't quite align with what they were doing, but I like to think that the transition was handled well and they could all finish up their projects. Within a year we were working on really basic problems, such as which cells make the pancreas. At that time if you looked in the textbooks, the pancreas was unquestionably a derivative of the neural crest, not the endoderm. The idea came from the fact that three particular genes were expressed in the neural crest, and also in the pancreas! I actually use this as an example when I'm teaching: I'm a big fan of the Boston Celtics, and I'll wear my Celtics jersey and say: 'this is a marker, like a gene, but does it make me a Boston Celtic?' They remember this, especially as the jersey's hanging down to my knees!

But back to your question, the lab was really going back to basics: where do the cells come from and what genes are important? The long-term idea being that you might be able to use that information for diabetes.

And then, after that, there was the excitement surrounding stem cells. Before human stem cells became well known – and this is probably a Whiggish form of history – I would say most of the people who worked on stem cells were using them as tools to knock genes out and study gene function. At that time, there wasn't a huge enterprise in trying to control their differentiation, and that's the side that we ended up working on.

What does developmental biology bring to the table for understanding and treating diabetes?

In simple form, diabetics either don't have beta cells or have dysfunctional beta cells, and stem cells can make any cell in the body. Let's try and connect the dots.

You've been working with stem cells to understand diabetes for many years. How has the stem cell field grown and changed since the early days?

This field has grown slowly, but is now burgeoning. Fortunately, we're past the political concerns and restrictions that characterised the 1990s and early 2000s. People just don't talk about that sort of thing any more. The restrictions did not stop the research but made it hard, and I feel those days were a real missed opportunity for the field.

Your group has recently shown that you can produce beta cells *en masse*. Are you now done with the developmental biology and left with the practicalities of getting the cells into the body?

We're close to it. The developmental aspects for me now come in with the longevity of the cells we can make, moving more towards developmental physiology and function and away from developmental anatomy (in the sense that making the cells, and making the embryo, is an anatomical problem).

The other part of the problem is the immune attack: we don't really know much about why beta cells are picked out for autoimmunity. As a card-carrying developmental biologist, I would like to reconstruct the system, and watch which cells and genes are involved. This will be quite a challenge. My grant applications regarding this question have been uniformly rejected for two reasons. One is that I'm not an immunologist – that's true! And two, that my plans are simple-minded and overly ambitious, and I'd say both of those are also true! But I'm a persistent person, and I'm going to work on the question of how beta cells are mistakenly targeted by the immune system.

I don't mean to imply that we're done with the first part, but we're at the goal line. I'd like to get more clinicians involved to understand how the disease develops. There's this fascinating period called the honeymoon period where you present with the symptoms, then your body suddenly makes enough insulin that you're not 'diabetic'. So in that period your body must be ramping up the amount of insulin made by residual beta cells; it's an interesting problem.

You were an editor for *Development* from 1987 to 2001 and are on our Advisory Board today. How has the field and the journal changed since the eighties, and where do you think it's going?

When Chris Wylie took over the *Journal of Experimental Embryology and Morphology* (JEEEM), changed it to *Development*

in 1987 and recruited me as an editor, we thought a little bit about what we're today calling applied developmental biology. That is a shift that has started and is worth thinking a bit more about. Not that Development should become a medical journal, but let's think about how to use the basic ideas of development – induction, lineage, things like that – to think about disease. Developmental biology will also be deeply informative as to the question of whether we call ageing a disease or not.

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I'd also like to see Development expand its activities in 'non-model organisms'. It's interesting to reflect on what model organisms

have and haven't been. If you look back in history there were a lot of papers at one point on *Dictyostelium*, but we don't seem to have many 'Dicty' talks here at the SDB. Also, the sea urchin: still important, but not so central. And if you go to a *Xenopus* meeting today, they angst over whether or not it's still relevant. The age-old question is: what does it mean to be a model? Philosophically, it's an interesting one – it depends so much on what we think is important at the time to be able to do or to look at.

Do you have any advice for young researchers today?

Read and think about the history of the field. And go read John Gurdon's early papers!

What might people be surprised to find out about you?

This might not be surprising, but I've tried to give up cars and I ride my bike all the time. I just treated myself to a new road bike and just came back from a cycling trip and hiking in the Dolomites.