

## SPOTLIGHT

# An interview with Cliff Tabin

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Cliff Tabin is George Jacob and Jacqueline Hazel Leder Professor and Chairman of the Department of Genetics at Harvard Medical School. His lab aims to understand the genetic control of morphogenesis during embryonic development and its change over evolutionary time. We met Cliff at the Pan-American Society for Evolutionary Developmental Biology's second biennial meeting, held in Calgary in August 2017, and heard about how he got into development, how a long-standing interest in the limb has been complemented by ventures into new models and why he thinks we are in a golden age for evo-devo.

## How are you finding the meeting?

It's been a lot of fun so far. Different scientific fields have different feels to them – for example, individuals in some areas might be more careful about sharing data in advance of publication and more worried about competition, but vertebrate development in general has been a fairly friendly and open field; evo-devo, a younger field, is even more so, and you see that in the meeting. The organizers have also been very conscious to bring together a mix of younger and older people in the sessions; by not having everyone up front being of my generation, I think it encourages people to interact more.

## Let's start at the beginning: is there anything that got you into science, and biology in particular, in the first place?

I always loved math and science, and don't remember a time when I didn't think I'd grow up as a scientist of some sort. My father had been a physicist, and I really was captivated by physics at the start; the fact that you could describe the world mathematically, and from the mathematics you could make predictions that would explain the world, was just marvellous. So I went to college in the mid 1970s fully expecting to become a physicist. However, as I neared graduation, I found that research in the areas of physics I considered to be most exciting involved working in big teams requiring large numbers of people to design, build and run huge and expensive machines (much like the recent, highly publicized hunt for the Higgs boson). In those fields you can't really design experiments or run them yourself until you're on your way to my current age. The style of science that I wanted to pursue just didn't mesh with the sorts of things I was interested in in physics.

So I started looking around for other places where you could apply a physical approach and make a difference. Ultimately, I applied to biology grad school programs thinking of becoming a structural biologist and matriculated at MIT with the intent of doing X-ray crystallography. But not being particularly well-versed in biology before I started, I had no idea that recombinant-DNA



technologies were being pioneered at the time. To be able to purify a specific sequence from all this chemically homogenous nucleic acid, to get your hands on genes, to read the code, was a game changer, and the most interesting and exciting things in biology at the time were clearly going to be in that area. To do recombinant-DNA work you needed to have special facilities and, fortunately for me, the one place with these facilities in the whole of Boston was the fifth floor of the Cancer Center at MIT shared by Robert Weinberg, David Baltimore, Phil Sharp, David Housman and Nancy Hopkins. I joined Bob's lab and also worked to some extent with David, and it was an exciting time: we made some of the first viral vectors, and got our hands on some of the first oncogenes and determined how they were activated.

## How did you transition into developmental biology?

At the Cancer Center it was marvellous to try and understand something so profound as the difference between a gene that causes cancer and its normal counterpart functioning normally in a cell. But I came into science not because I was interested in health, let alone cancer per se, but as someone who was simply excited by fundamental science – initially the idea of using math to understand the universe. So I had no particular drive, at the time, to continue with clinically relevant problems. When I finished my PhD, it was really a question of what do I want to turn this amazing new technology towards? If I'm going to be a biologist, what is biology about? Well, for me the two big questions in biology were 'where do babies come from' and 'how do you get diversity of life'? Within the context of the first question, embryonic development, I was always more intrigued in the higher-order questions of complexity – not so much how you get different cell types, but more how do you get morphology, organization and so on. In a sense, that central developmental question of how morphogenesis is regulated is at the core of understanding the diversity of life too. For example, the difference between a monkey and a tiger and a squirrel is not new

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types of cells, but rather somewhat subtle changes in the organization of animals that are basically the same thing: furry things with noses, teeth, tails and four legs. So, for me, the problems of embryogenesis and evolution boiled down to ‘how is morphogenesis genetically orchestrated through development’ and ‘how is the regulation of morphogenesis modified through evolution’. From the start, those were the two questions that most intrigued me.

## How morphogenesis is regulated is at the core of understanding the diversity of life

So after graduate school, I went to Doug Melton’s lab for a postdoc and, with another postdoc, Richard Harvey, we cloned some of the first Hox genes in *Xenopus* right around the same time that Eddy de Robertis cloned other frog Hox genes (which led to some initially confusing nomenclature!). The finding that there were genes that had regions of extraordinary homology with flies was clearly going to be important, but figuring out what they actually did was somewhat less obvious. Since Hox genes were involved in segmental identity, I decided to look at the segmented parts of us. At the time there wasn’t a classical literature in somite development, but there was in limb development and in limb regeneration, so I wanted to look and see whether there were any Hox genes involved in the limb. Doug thought it was an interesting idea, but outside the scope of his own lab. So, with his support, I got an independent postdoc position at Massachusetts General Hospital where I could pursue it on my own, as there wasn’t an obvious established lab to move to for such work. At the time, the people studying limb development were using old, classical approaches – a lot of cutting, grafting, rotating, discussions about polar coordinate models and so on – very informative experiments but they were not set up to move to molecular studies; indeed, many didn’t even have a centrifuge in the building! So the independent postdoc gave me the opportunity to initiate such experiments when I would not have been able to do so otherwise. I should point out, however, that a number of these classical limb biologists quickly caught up, and in the years that followed made very fundamental advances at a genetic level.

### And you’ve been researching limb development ever since – what makes the limb such a useful model?

Well, when I started, it was one of the few structures in the vertebrate embryo where classical experiments had given insight into how it was organized. For example, a specialized region of the posterior limb bud, the zone of polarizing activity, had been shown to be critical for organizing the digits; similarly, it had been demonstrated that the proximal-distal growth was driven by a strip of specialized ectoderm called the apical ectodermal ridge. We knew that the dorsal ectoderm determined the dorsal ventral axis within the distal limb, and that the limb was sculpted by programmed cell death. We simply did not know as much about heart, kidney or really anything else, so it seemed like a place where we could start assigning molecules to experimentally defined functions and make sense of them.

Three key aspects of the developing chick limb contributed to its early development as a model, and are still very relevant. First, the chick embryo is extremely accessible to physical manipulations, and the limb bud is particularly so, being external to the rest of the embryo. Second, it is expendable. Compromising its development does not affect the viability of the embryo, allowing late phenotypes to be observed. Finally, the limb is relatively simple in terms of the number of progenitor populations contributing to it and the number of cell types it contains, yet it is a complex anatomical structure,

raising many fundamental questions of patterning and morphogenesis to explore. Even now, three decades into the era of molecular genetics, there are many fundamental questions still unanswered. We still do not really understand why your bicep has two heads, and your tricep has three. The hindlimb and forelimb start off similarly sized, so why is your hamstring so much larger than your bicep? We don’t really know. And we still don’t understand in a fundamental way why different long bones grow to different lengths. These things are pretty fundamental if you want to make a limb, and people in my lab (as well as elsewhere, of course) are working on these questions. We’re also interested in what it means to be a limb progenitor, to have this incredible potential to make these structures that cells outside of the limb bud do not have. And that’s not to mention several projects on how the limb changes through evolution; for example, we are using emus and other ratites to understand the genetic basis for adaptive changes in foot morphology.

### When did questions of evolution enter your lab?

Well, I was always interested in evolution. Quite early on I was joined by a postdoc named Annie Burke, a classically trained evolutionary morphologist who was interested in the roles the recently discovered Hox genes might play in evolutionary transitions. She did a massive expression analysis of every Hox gene we could get our hands on in the chick and in the mouse, and found, in every case, that the location of each gene’s expression in the two organisms correlated with the same morphological boundary. For example, the same Hox genes are expressed at the cervical-thoracic transition, even though chicks and mice have different numbers of neck vertebrae. At the same time, Nipam Patel did similar work correlating Hox gene expression with morphological transitions in crustaceans with different numbers of walking and feeding limbs. It was an exciting developmental and evolutionary result because it provided a potential mechanism to evolutionarily shift morphological boundaries (changing the number of segments of different morphological types) by altering boundaries of Hox gene expression.

These and other early studies of evolution in my lab were essentially extrapolating from developmental studies in our main model organisms: the mouse and chick. We didn’t try to establish a true evo-devo system until a chance discussion with Marc Kirschner, a colleague at Harvard Medical School. Marc had written book with John Gerhart trying to synthesize cell, evolutionary and developmental biology into one framework. He wrote at great length about the neural crest, and gave the beaks of Darwin’s finches as an example of the diversity of structures derived from it. It just so happened that at the time we had been doing a little bit of work on beak development. So as we walked across campus one day, Marc asked ‘when are you going to know enough that you can start asking the question of what makes the beaks of different species of Darwin’s finches different from one another?’. And I just sort of stopped walking: for years I had wanted to get to the stage where we would know enough about development to seriously address evolutionary changes in morphology, and I realised then that we were actually there. Not only did we know enough about craniofacial development to have a context for thinking about beak evolution, but the tools were there to look comparatively at a molecular level between non-model species. Looking at Darwin’s finches was obviously a great thing to try, given their iconic status as an example in *On the Origin of Species*. In addition, two great evolutionary biologists, Peter and Rosemary Grant, had been studying them for years and their work had yielded important insights into the pace of evolution and other questions. The Grants were also instrumental in our initiating these studies on a practical

level, helping us prepare for fieldwork for the first time and assisting my postdoc Arkhat Abzhanov when he was down in the Galapagos to distinguish finches from other birds, let alone distinguish between different types of finches! That was our real first foray into a new model – the cavefish was the second.

### So what spurred the cavefish?

When I originally envisioned the Darwin's finch project I thought of a three-pronged approach involving candidate genes from our knowledge of beak development in chicks, a less biased comparative approach probing cDNA arrays on chips, and a third approach: to take a single species where we might be able to obtain DNA from a large breeding population, look at both phenotypic and molecular variation within it, and try to do a quantitative trait genetic analysis. A graduate student in the lab, Meredith Protas, joined the lab to do this. She spent a full year doing wonderful work preparing such a genetic study on Darwin's finches, but for reasons beyond her control the project didn't work out, and she had to switch projects. In searching for a new direction, she did some reading and came across the cavefish. By this point we were already aware of David Kingsley's elegant work doing quantitative trait locus (QTL) analysis on a different aquatic species: the three-spined stickleback. Moreover, several people like Bill Jeffrey and Richard Borowsky were already doing marvellous work studying the evolution of cavefish through developmental and genetic approaches. But no one had made a genetic map or attempted a QTL analysis with this species, so the cavefish seemed to be not only a very rich system to explore, but also one that was ripe for exploiting at a genetic level. It would, however, be a lot of work to set it up (especially with the techniques available then). But Meredith really did pull it off: she made a QTL map, mapped 10-15 traits, focused on one for loss of pigmentation where she found a known human albinism gene right on top of a major QTL, pulled out the gene, was able to show two different loss-of-function mutations in two different caves, and a different non-coding mutation in another cave population. It was a beginning-to-end thesis where she started without any genetics and concluded that the trait arose in different caves through parallel evolution.

### Your talk here was not about cavefish morphology but their metabolism – where did that interest come from?

We are interested, broadly, in how organisms adapt to their environment. Adaptation of cavefish provides a wonderful opportunity to explore this because the cave environment in which they live is completely different from that faced by the ancestral fish in neighbouring rivers. To survive after being trapped in the bleak caves, the fish had to adapt in a variety of ways. Previous students and postdocs in my lab had looked at morphological evolution (both 'regressive' traits, such as loss of pigmentation and vision, and 'constructive traits', such as expansion in the number of taste buds and alteration in tooth number) as well as behavioural adaptations. Most of these changes serve to help the fish deal with living in the dark. However, an additional consequence of the absence of sunlight is that there is no photosynthesis, and hence the cave environment is extremely nutrient-poor. Thus, the fish that have survived there also had to make extreme modifications to their metabolism in order to thrive. A student in my lab, Ariel Aspiras, and a now-former postdoc Nick Rohner became intrigued by this. They quickly confirmed that the cavefish do indeed have extreme and surprising differences in their sugar and fat metabolism. We are continuing to study the genetic underpinning of these metabolic changes in a close collaboration with Nick, who is now at the Stowers Institute.

### I understand you are also interested in the evolution of some of our own unique traits as humans?

I'm as *Homo*-centric as anyone – as human beings we are interested in where we came from. Advances in genomics mean we can now think seriously about human evolution in a way that we couldn't previously. Our own involvement initially stemmed from another discussion with a Harvard colleague, this time Dan Lieberman, who works on evolution of human functional morphology. Dan was discussing the idea that the evolution of human long-distance running required the concomitant development of an efficient system for thermoregulation, which in humans involved an enormous expansion of the number of sweat glands across our body and an absence of terminal hair (to allow efficient evaporation). Dan asked me, as a developmental biologist, what determines the spacing of sweat glands? However, the problem had never been studied, and it is not a trait one would uncover serendipitously – one does not see a change in sweat glands unless one specifically looks for it. Yet changes in their patterning were fundamentally important for human evolution. A new postdoc, Yana Kamberov, happened to arrive in the lab with a keen interest in exploring evo-devo to questions of relevance to humans. We brought together the expertise of several labs and she ended up working with four PIs. We took several approaches to the problem. These included an unbiased mouse genetic study that revealed a role for the engrailed 1 gene in sweat gland specification, and a candidate gene study in which Yana made mouse knock-ins of a variant human allele of the *EDAR* gene (a locus of intense selection in humans) and showed that it too contributed to sweat gland evolution. We now have several other projects currently on-going, relating to other aspects of human morphological evolution.

### In an interview with Michael Richardson in 2009 you said you felt we were entering a golden age for evo-devo. How is that age panning out, and what do you see as the key questions for the future?

We certainly are in a golden age. For one thing, the number of people doing really interesting evo-devo studies has grown tremendously (as evidenced by this society and meeting). Moreover, one can do so much more than I was even imagining when I gave that interview, with the dramatic advances in genomic technologies, gene editing and so on. Genomes can be sequenced – not just species, but multiple individuals within each species. The function of genes involved in evolutionary change can be directly tested (how many talks in this meeting mentioned CRISPR, for example?). These new tools, in turn, have opened up the possibility of studying virtually any organism with which you can formulate a good question. My own lab has spawned a series of models, from jerboas to finches to cave fish. It used to be an unusual thing to start working on a new system, but it's not at all unusual any more. You can find the model that is best for the question you want to answer, or you get intrigued by an organism because of what it might tell you about some aspect of evolution, and it is accessible to you. It's an incredibly exciting time for the field.

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**Do you have any advice for young researcher thinking about embarking on a career in biology?**

I think there's never been a better time to do science – the tools are just incredible, and what people will be able to accomplish in the next 30 years will far eclipse anything my generation was able to accomplish.

I know a lot of young people are concerned because the funding situation certainly in the United States is a difficult one at present. However, you asked me about advice for someone just starting out: I try to tell people starting in grad school not to worry about it. It's not like I'm Pollyanna-ish about it, but the funding situation in the United States has shifted multiple times during my career. If you're starting your PhD right now, let's say you take five years to finish your thesis, and then are a postdoc for another five. Then as an assistant professor you'll have a start-up package that can get you through a couple more years, and after that your first grants are hard, but attainable, as people who have never had an NIH RO1 have a significantly higher funding line than established investigators. So, let's add four more years to that. So you're talking about 16 years from now before you're at a mid-career stage in the position where you need to renew a grant or get a second one. People currently in that position are the ones I am really worried about. We, as a community, need to do everything we can to improve the funding situation for these individuals. There has been some movement in that direction at the NIH, but it is not nearly enough. And even with our continued lobbying, I do not see dramatic change in funding occurring in the next few years. But someone entering graduate school shouldn't think too much about it – I don't know what it'll be like in 16 years, but I know it'll be different. And it is such a great time to be doing science in other respects.

**Finally, is there anything that *Development* readers would be surprised to find out about you?**

My best little-known fact is probably that I had a note published in *Science* on how to catch a baseball! It was perhaps the paper I was

most excited about putting in my formal CV as one of my 'top ten publications' when I came up for tenure, along side all the limb stuff, even though my chair at the time was a little dubious about my doing so.

There had been a series of papers, including one in *Science*, by a pair of experimental psychologists saying that humans are not capable of calculating the trajectory of a ball. Rather, they proposed a model where the brain continuously recalculates where the ball is headed and re-adjusts a fielder's path to meet the ball accordingly. However, their algorithm required the fielder to constantly keep his or her eye on the ball, suggesting this was necessary to make a catch. Now, anyone who has played baseball knows this is not correct. For example if a ball is hit over your head, you get a quick read on where it is going, then turn your back and run to the approximate location, and then visually pick it up again. Moreover, the output of their algorithm had a continuously increasing velocity function for the fielder, i.e. the fielder is running at maximal speed when intercepting the ball. But, again, one does not have to do this to make a catch. Ideally fielders want to beat the ball to the location where it will land, so they can be lined up to take the ball and throw it to the infield in one smooth series of motions, with their momentum behind the ball. So I wrote a response to *Science* along with another scientist who had also played some baseball and a third guy, a sports nut who videotaped all these baseball games and was willing to re-watch them and figure out the trajectories of all these pro athletes, which gave us some data.

What I liked most was that when *Science* published the note, it said 'Cliff Tabin, #7' (my baseball uniform number), 'Affiliation – Department of Genetics, Harvard Medical School, and Jansport Baseball Club'. And then an asterisk, and, at the bottom, 'Current Affiliation: Wellsley Monarchs Baseball Club', as I'd just switched teams. These were men's over-30 amateur baseball clubs, nothing at a high level, but it was fun that *Science* listed them as my affiliation and included my uniform number after my name in place of a degree.