

INTERVIEW

An interview with Claude Desplan

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Claude Desplan is Silver Professor in the Department of Biology and Director of the Center for Developmental Genetics at New York University. A biochemist by training, Claude began working on *Drosophila* embryogenesis in the 1980s, and his work now focuses on how neural diversity is established during the development of the *Drosophila* visual system. In 2020, Claude was awarded the Society for Developmental Biology's Edwin G. Conklin Medal, which recognises both his outstanding contribution to developmental biology research and his excellence in mentorship. We recently met with Claude (via Zoom) to find out more about his career and his research.

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

I don't have a very clear answer for this. I wasn't the kind of kid who collected butterflies in the countryside or anything, but science came fairly naturally to me in school. When I was around 14, I had a geology teacher who really inspired me – I wasn't that interested in geology but she got me thinking about science more broadly and that definitely made a difference. And then when I was getting towards the end of college, a family member suggested I try to apply to one of the École normale supérieure (ENS), which are elite schools in France. I didn't know much about it, but I looked into it and realised it was a way to get a career in research, and this was really the beginning for me.

You studied biochemistry and physiology at university, and then went on to do a PhD on calcium-binding proteins – why this topic?

At ENS, most of my cohort were studying natural sciences, but a friend and I chose to study biochemistry, which was a new field at the time. This was quite a brave move for me, but I think it paid off because I was doing really modern science compared with most of my classmates.

When I finished my degree, I then got a teaching diploma, and because of the way the system worked, this meant I had tenure, which seemed amazing to me as a young man! I found a teaching assistant job in a medical school in Paris, which was a paid position for doing my PhD. To be honest, this really wasn't the best lab for me to be working in scientifically, but I liked my boss and I learned a lot of biochemistry techniques. And I had friends at the Institut Pasteur with whom I set up collaborations, so I managed to stay in touch with top-level science even though I maybe wasn't doing it myself.

You then moved to San Francisco for a postdoc position with Pat O'Farrell, working on transcription factors in the early *Drosophila* embryo. How did that come about?

When I was starting to look for postdoc positions, a friend of mine had just come back from UCSF and told me what a great



environment it was and recommended I should try and find a position there. I spent a couple of weeks at Harvard as part of a collaboration, and decided that while I was there I should go over to San Francisco and find out more about UCSF. I turned up on a Saturday morning, and of course the place was empty. But I managed to get in and I found Pat O'Farrell, who at the time was a very young PI. I knew about and was interested in his work, so I went to knock on his door, and we ended up talking for a long time; at the end of the day he told me I could come and join his lab. He did have to call me up in Paris some months later to ask me for a CV and some letters of recommendation – apparently it's pretty unusual to offer someone a position when you don't really know anything about them!

The move to UCSF really changed my life: it was an amazing place to be, and Pat is one of the smartest people you can imagine. I have to say that I got really lucky with this move – I didn't have a grand plan for my career at that point, I came from a small lab where I hadn't read very broadly, and I hadn't been exposed to the kind of exciting science I saw in California. It was really chance that it worked out this way for me and I owe everything to UCSF – it made me the scientist I am now.

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It must have been an exciting time to work on *Drosophila*, given the then-recent Nobel prize-winning work of Lewis, Nusslein-Volhard and Wieschaus identifying patterning mutants in the embryo. Can you tell us a bit about that period?

It was a really great period to be working on the fly embryo – it was a beautiful system, we had great tools and a lot of progress was being made. But at the time, there was no notion that you could try and make it applicable to human – you studied flies because you wanted to study flies. On the other hand, the vertebrate developmental biologists (mainly working with frog) were doing beautiful work, but it was really experimental embryology – many of the major concepts were there, but there were no molecules. Of course, this was the pre-genomics era: it was thought that the human would have maybe 100,000 genes and the fly only a fraction of that number, and that we had become human because we had invented many new genes. But when the homeobox genes were discovered and were shown to be conserved – both in sequence and function (a concept described as ‘The Rosetta Stone of developmental biology’) – this was a huge surprise and completely revolutionised the field.

I was right in the middle of this, as Pat’s lab had recently cloned *engrailed*, a homeobox gene, and I showed that it was a transcription factor and worked on the mechanism by which it recognised its target DNA. But I was still really a biochemist not a geneticist or a developmental biologist; in fact, developmental biology as we know it now was only just beginning to exist. Actually, I remember when the first issue of *Development* came out (after its change in name from *Journal of Embryology and Experimental Biology*). Jean-Paul Vincent, who was a postdoc in the lab at the time, came in and showed us the issue – it felt like an exciting new journal for a new field.

***Drosophila* has been your major model system ever since – why the fly?**

Because we can do everything with *Drosophila*, and so much more quickly than in mouse! I really think the fly is such a great system in terms of our power to manipulate things genetically, and I think we (the fly community) have shown over and over that work in the fly can be directly applicable to mammals and human. It’s been difficult sometimes, though. For example, when I was at Rockefeller I was told that the big hope they’d put into fly research over the previous 10 years hadn’t really panned out and I wasn’t really supported there. But I still believe that we can learn a huge amount from fruit flies.

You set up your own lab (first at Rockefeller, before moving to NYU), initially continuing to work on the embryo. Why did you then shift your focus to the nervous system?

When I started my lab, I was more a biochemist and a structural person – I was interested in how the homeodomain can bind DNA, how it finds its specific binding site and so on. And we went quite deep into the mechanism and the structure of homeodomains. We were working a lot on Bicoid, but we also got interested in other homeobox proteins such as Pax6, which has a paired domain as well as a homeodomain. Pax6 controls the development of the eye, and this is what got us started working in the eye. I was reading about the fly eye, and I discovered this paper from Gerry Rubin’s lab in which they described that the colour photoreceptors express rhodopsin genes tuned to detect different wavelengths of light in a stochastic manner. I found this fascinating, but nothing had really been published on the topic since then. By chance, Gerry came to visit NYU and I asked him about this work – he thought it was interesting

but had no plan to follow up on the initial observation. So we decided to start working on it – and it’s something we’re still interested in. So this is how we got into the eye, which was our first step into neural development.

I have a policy in my lab that when a postdoc leaves, they get to take their project with them and I stop working on it. Of course, this means I have to keep shifting the focus of my lab, and it felt like a natural step to move from the eye into the optic lobe. And as people leave the lab, we move deeper and deeper into the brain and I’ve had to become a neurobiologist!

Your lab also takes evolutionary approaches to understanding neural development. What do you learn from these approaches and why is it important to consider the evolutionary angle?

Our first foray into this was working with *bicoid*, which is a hugely important gene for fly development, but isn’t even conserved throughout the Diptera. I met Mary Anne Pultz, who was working with the wasp *Nasonia*, which develops in a way very similar to the fruit fly – using a long germ-band mode of segmentation – but of course doesn’t have *bicoid*. We started collaborating to figure out what replaces the function of *bicoid* in the wasp embryo, and showed that it was the homologue of *orthodenticle* (*otd*). And what was particularly interesting for us about this was that the homeodomain of Otd, like Bicoid, has a particular amino acid substitution that allows it to bind a very different target sequence than other homeodomain proteins, such as the Hox proteins. So this was a case in which two molecules acquired the same specificity and a similar function but from very different origins – a very good example of convergent evolution.

Unlike the fly, I’m not very faithful to my other model species – we pick something up to answer a specific question and then drop it again once we’ve finished that project. I don’t really work with *Nasonia* anymore. The next system we started playing around with was the butterfly, because they have an amazing eye in which there are three (rather than two as in the fly) types of ommatidia (the unit eyes) and we were interested in looking at how the stochastic fate choice works with this extra complexity. Michael Perry, one of my ex-postdocs, still works with the butterfly, but I don’t.

So for us the idea of using different systems is to address a particular question that relates to either diversification or convergence in a developmental process we’re studying and to learn something about the underlying mechanism.

Recently, you’ve started a collaborative project looking at ageing and rejuvenation in ants. Why are ants an interesting system to look at from this perspective?

This has been a really fun project with my NYU colleague Danny Reinberg (who works on chromatin and epigenetics). It came about because HHMI put out a call to its investigators to propose new and innovative projects – something different from their mainstream research. Danny suggested working on ants because they have multiple castes (workers, soldiers, queens) that look very different from each other but that all share the same genome – so these differences must be under epigenetic control. He set up a consortium with Shelley Berger (University of Pennsylvania) to start developing ants as a model system. There weren’t any genetic tools available, but Danny knew that we’d done some work developing tools in *Nasonia* (a Hymenoptera, like ants) and other systems and so got in touch and asked if we wanted to get involved.

Doing genetics in ant species where you have one queen per colony – only one female that’s reproductive – is almost

impossible. So the consortium decided to work on an early-branching species of ant in which the female workers can gain reproductive capacity in response to the loss of pheromone signalling from the queen – becoming what's known as a gamergate. It's known that workers live for only around 6 months, but queens can live for 4-5 years, and what's really interesting is that when you transform a worker into a gamergate, you also transform its lifespan – so an individual born to live for only 6 months can now survive for almost ten times as long. And this is reversible – if you put the gamergate into a colony with a real queen, she reverts back to worker status and her lifespan shortens. Another thing that happens when a worker becomes a gamergate is that her brain shrinks and changes quite dramatically. So we're using single cell sequencing approaches to try and understand the changes in the brain during this transformation.

The other interesting aspect to this is that new queens will only mate once in their life, and yet can go on producing eggs for many years (up to 30 in some species of ant). In general, we know that there's a trade-off between reproductive capacity and lifespan, mediated by insulin signalling. So we're also interested in understanding how queen ants can maintain high metabolism to produce many eggs over multiple years, without dying from the adverse effects of high insulin levels.

It's very difficult to manipulate these animals genetically, but we are making some progress and it's very exciting.

And where do you think your lab's work will be taking you in the next 5-10 years?

So the evo-devo type projects I've talked about are really fun, but they're hard to get funded and they're never going to be the main focus of my lab, which at the moment is really trying to understand neural diversity. Flies are very visual animals, and have a very sophisticated optic lobe, and we want to understand the principles that allow the fly to see and function so well. In recent years, following on from the work of Chris Doe, I think we've made some important contributions to understanding how neural stem cells produce different cell types using temporal patterning – the idea being that, in contrast to, for example, the traditional view of the mammalian neural tube, it's not where but when a cell is born that matters.

Now, the new single cell sequencing technologies really allow us to address neural diversity in a way that was never possible before. We're now able to describe the transcriptome of all the neurons of the optic lobe across multiple time points during development. And thanks to the work at *Janelia*, we can also understand how each neuron is connected to its neighbour. My dream is to be able to connect the transcriptome to the connectome and to understand how the specificity of connectivity is determined. You can't just look at the adult transcriptome to understand the connectome; you have to go back in time to find the transcriptional differences that determine the patterns of connectivity when they're being established.

I have to say it took me a long time to be converted to the advantages of genomic technologies, but the single cell approaches are proving really important for us. It requires a lot of bioinformatic work, and I'm not an expert, but my lab has become very good at this, and we initially received great support from our colleague Rahul Satija who is the one who 'invented' Seurat, the program everyone uses to analyse these data.

So yes, my aim is to try and connect the transcriptome and the connectome – not so much at a cell-by-cell level, but to understand the underlying principles.

This year, you were awarded the SDB's Edwin G. Conklin Medal, which recognises not only your scientific achievements but also your mentorship of the next generation of scientists. What does this award mean to you?

Well, my fear was that I might get awarded the lifetime achievement award, but I don't think my life has yet been achieved and we have a lot more to do in the lab! As scientists, we all crave recognition and of course it's really great to receive that recognition for what the lab has done. But it's the mentorship aspect that's really important to me.

So what is your approach to mentoring students and postdocs?

I don't think I really have a strategy; I take a much more romantic approach. My way of mentoring is just to talk to my people, to encourage them, to respect them and to like them. I think I've trained some very good people, but it also comes down to the fact that good labs attract good people, and that even if someone who's maybe a bit difficult comes to a good lab, they will change their behaviour. So I work hard to make sure that there's a nice atmosphere in the lab and that people are happy. So, for example, I never tell people they need to work harder – they're here for their career, and it's not really my business to tell them how hard they should work. Though in general, because the lab is happy, they work hard anyway!

For postdocs, I also think that the fact that they know they'll be able to take their project with them when they leave makes a big difference – they don't need to compete with their neighbour and they won't have to worry about competing with me. I've had amazing postdocs, many of whom have gone on to set up their own lab, and I have a good relationship with all of them. With the students, I generally attract people who are quite independent-minded. I'm not very hands-on, but they have good postdocs to work with, we have really interactive lab meetings, and I make the time to talk to them all about their work.

Do you have any advice to young researchers starting out in the field today?

I think it's important not to get discouraged by drawbacks. I've definitely had difficulties through my career – starting with my choice of PhD – but I managed to recover. And one of the things that really helped me was having good connections and working at good places: as I said earlier, my time at UCSF was completely transformative, and that's mainly down to being around bright people and being exposed to great science. Then, after over a decade at Rockefeller, where I did very well, I didn't get tenure – I still don't know why to this day. That was very difficult, but I've recovered and I think that now the lab is doing some of the best work we've ever done. It's not easy, and you have to be in good mental health to be able to get through it, but it is possible to overcome some fairly major drawbacks.

Finally, how have things been during the pandemic for you and your lab?

The labs started to reopen in June, and I was lucky that my close colleague and friend Steve Small down the hall was retiring so I was able to expand into his space, which meant that more of my lab could be in at the same time while still respecting social distancing. So we've been basically back up and running since then. And because my lab does so much bioinformatics, we've been able to keep going with that the whole time. To be honest, I don't think we've lost any time at all, although I know it's been frustrating for

people not to be able to do all the experiments they were planning. The period of slowing down gave us all a good opportunity to think more about what we wanted to do, so I don't think we've suffered

badly – in work terms at least. Of course, it's been really tough on a personal level for some people, particularly those with kids, but overall I think we've coped OK.