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INTERVIEW

An interview with Scott Fraser

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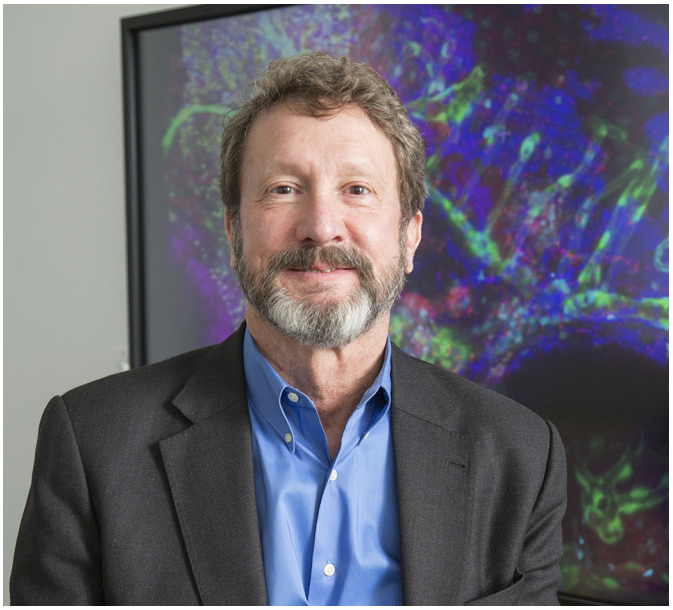
Scott Fraser is a Provost Professor, and the Director of Science Initiatives, at the University of Southern California, USA. Scott has had a long-standing interest in applying the tools of chemistry, engineering and physics to problems in biology and medicine. Amongst other things, Scott is best known for his contributions to developing microscopes and tools to image developing embryos. Earlier this year, Scott was awarded the SDB's 2021 Edwin G. Conklin Medal, which aims to recognize 'a developmental biologist who has made and is continuing to make extraordinary research contributions to the field, and is an excellent mentor who has helped train the next generation of outstanding scientists'. We caught up with Scott to find out more about his interdisciplinary research and his approach to mentoring.



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

So, I guess I always loved trying to figure out how things worked. I was one of those kids who was the object of scorn of my parents at times because any new toy needed to be disassembled as quickly as possible to validate how it worked. I just loved guessing how something worked, taking it apart and finding out how it *really* worked. And I loved being wrong! I realised that you learned as much from being wrong as being right. I think that's probably where I got the science bug from; it was just the desire to make hypotheses and then test them, and then learn from being right or being wrong.

You trained in physics and biophysics – how did you then become interested in embryology and developmental biology in particular?

I think it came from that same desire to figure out how things work. Physics is just so foundational – it underpins so much of science – and it was always super attractive to me as something to study. But there were two things that made it less attractive as I moved forward with my studies. One was that the projects were getting huge and impersonal. In fact, many of the projects are still huge. I had friends that were in physics a few years ahead of me that ended up being one of many dozens of authors on a paper, and that just didn't appeal to me. The other thing was that, as an undergrad, working in a gas station to support myself, I ran into a recent graduate who worked on the Stanford accelerator and, despite having a PhD, he was working in a gas station. On seeing this, I had a moment of clarity, and I started to think again about what I really wanted to do.

I liked the idea of trying to figure out how cells work, how signals get transduced, and how information flows through a cell or between cells. So, I became interested in biophysics and that's what I decided to study. I went off to graduate school to study how photoreceptors transduce light signals and all was going well until I made the mistake of looking at a friend's microscope and seeing an embryo. And that really changed things for me. My friend was doing grafting experiments on *Xenopus* and, within a couple of minutes, the graft had healed and you couldn't even see where the graft had been! It was just fascinating and for almost every question that I asked the answer was 'We don't know'. The number of open questions just sort of pulled me in, and so the biophysics of the embryo was what I went on to study.

You attended the Marine Biological Laboratory (MBL) Embryology course at Woods Hole fairly early on in your career. How did this happen and how much of an influence did this have on you at the time?

My thesis advisor, Richard Kevin Hunt, a developmental neuroscientist, taught at Woods Hole for a few years, so I went along as a student one year. I have to say it was like being dropped into the deep end of the pool! I remember helping somebody put a microscope together and, once we were done, they put a specimen on. It was a sea urchin larva and we were using Nomarski imaging so it looked just spectacular. But when I asked what it was, they said, 'It's a pluteus'. Now that means a lot if you know what a pluteus is…but I had no idea what a pluteus was! So I had to study pretty hard during the course just to figure out what everything was and what the terms referred to. It was great fun, though.

I think that Woods Hole is the most exciting but also the most exhausting place in the world. Everybody came there to show their

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latest results, a year or two ahead of publication, and people would get together to discuss their findings. The seminars were very stimulating with lots of active debates; some might call them aggressive (in fact, people called the neuro seminars 'the Monday night fights'!). But it wasn't because people were just arguing over something to be mean – it was because they really didn't know how things worked. Somebody would present a result and their interpretation of it, and then somebody else would stand up and challenge it. This would go back and forth, and by the end of an hour and a half talk, everyone – including the speaker – knew more than they did to begin with! For me, it was just an amazing way to get immersed in the field.

I went back just a couple of years later to help out on the course again, and key figures like John Saunders, Lewis Wolpert, Peter Bryant and Sue Bryant were there. They had a session arguing about how limbs pattern, and it was the most intense, argumentative session I've seen. But what was interesting was that that set of talks really encapsulated what the next decade or so of papers was going to be on. I really miss those days, where the meetings were an airing of what's known and what's not known.

After your graduate studies, you moved straight on to a faculty position at UCI, i.e. without doing a postdoc. How did that occur and how did you find that transition?

I think accidents play a huge role in science. When I was a second-year graduate student at Johns Hopkins, I was out visiting my parents in Southern California and I had just been at a NATO meeting with some people from UC Irvine so they suggested that I stop by to give a talk. I gave a talk to people from various departments (Physiology and Biophysics, Psychobiology, and Developmental Biology). They all liked what I was doing, and what the results were looking like, so I ended up getting three job offers. I think it was a shock in some ways to imagine getting my own lab but I realised it was a fantastic opportunity, especially for somebody like me who loves to be in the lab thinking about how things work instead of worrying about fellowship applications and interview schedules. While in some ways it was a bit of a mixed blessing, I returned to Johns Hopkins to finish up things and then, a year and a bit later, moved to UC Irvine.

I was also very lucky in some ways because my thesis advisor was not the most organised person, so I spent a good part of my graduate days helping to run the lab and sometimes even covering for him. I felt like I learned a lot during that time that helped me with the transition. By then, I'd also gone to Woods Hole a fair bit, and this allowed me to explore different techniques, build my tool kit and set up some collaborations. I effectively learned almost a postdoc's worth of stuff in an exhausting summer of work at Woods Hole.

So, overall, the transition to becoming a PI wasn't too frightening. The scary experience came after that, when I was maybe only 30 or 31 years old, and the Dean called me into his office and asked if I wanted to become the Department Chair. And he wasn't joking! So then I really did feel like the new kid in school. But I had great fun. My colleagues in the department were all amazing and, in just a couple of years, we were able to dramatically increase the amount of grant funding that was coming in. It was just great to be able to start attacking the many questions that I wanted to go after. We started working on lots of different projects, ranging from how nerves become patterned in the early frog embryo to how cells communicate via gap junctions, and we extended out to use a variety of different systems. We just had a blast.

Lots of your work, from your early days at UCI, your decades at Caltech to your current work at USC, has aimed to trace the fates and lineages of cells. The concept of cell lineage tracing and fate maps certainly isn't new but how have imaging approaches evolved and helped to push the field forward?

It's been fun to watch various approaches evolve. In our early studies, we developed various techniques to study gap junctions in cells. Since we were working on preparations that were hellishly difficult, we became very good at putting small dyes into cells, keeping them alive, so we could observe dye-coupling between the cells as a functional assay of gap junctions. It wasn't hard to imagine using that same set of tricks to inject individual cells in intact specimens with larger dyes (indelible lineage tracers), keeping them alive, so we could later observe their labeled progeny as a direct assay of cell lineage. Through a friend of a friend, we were able to get hold of a low-light-level video camera so we combined the lineage tracers with the low light level imaging and it worked! I guess it was just dumb luck that I had worked on gap junctions *and* knew how to microinject cells *and* had been able to get hold of the right camera when most other people didn't have one.

This, of course, later became the basis of the move towards *in toto* imaging. It's been fun watching as different light-sheet and other technologies are making that easier to achieve. I love some of the techniques that have been developed, and I love the way that imaging is being expanded alongside genomic tools – they're now the belts and suspenders of lineage analysis. But although the family of high-throughput and whole *in toto* imaging techniques are very good at helping you to build models of lineage specification, if you really want to nail it, you've still got to go in and label or follow individual cells to see what the labelled cell and its great, great grandchildren become. Some of the questions that the likes of Sydney Brenner posed so long ago, about intrinsic or extrinsic regulation of lineages, are still there. We still don't know the degree to which cell lineages follow 'the European plan' or 'the American plan' as he put it, so we still have plenty of work to do. What we're working on right now is trying to see if we can reverse engineer some of those molecular decisions to understand how the computer clockwork inside a cell really drives and enables lineages segregation. Being a part of a stem cell department and seeing ways of directing the differentiation of cells or triggering transdifferentiation is making this a fun project.

Much of your research has focused on imaging, which is a rapidly moving field. Has it been difficult to keep up with all of the various technologies that have been developed and put to use?

Back when there were meetings, I went to a lot of meetings and that really helped to keep me up to date. But it's not the way any one technique moves forward that matters; it's how we can answer questions. Anytime anybody invents a new lattice light-sheet microscope or any other sort of seemingly crazy new instrument, we love taking that technology and applying it to our questions. And it might be that we use these technologies to create hybrid instruments that perhaps do not offer as high resolution as the originals but, say, deal with lower light levels or faster frame rates. I guess we try to 'steal' what we need and see how it could be applied to what we're doing at that given time. Having been at the 'Monday night fights', and watching people compete in neuroscience for who can develop the fastest voltage clamp as its own goal, I learned that it was actually better to use the equipment that you have in hand to get answers to interesting questions.

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So, we've really enjoyed watching the developments that others have made and applying some of them to our work. But, we have to be realistic and recognise that there will be trade-offs. There will be times when we don't need the best light microscope in the field to answer a particular question – we just need a microscope that can capture something the size of an embryo – even if it might not have the highest resolution, we can still use it to answer questions. It's almost impossible to remain cutting edge on all of the techniques we use, but we have such a great set of colleagues, and access to so many techniques, that we can always find new solutions that match our problems.

Your current research spans a number of disciplines; you've been described as 'a biophysicist, microscopist, engineer, developmental biologist and translational biologist'. What triggered this multi-disciplinary approach? And has it been difficult recruiting the right people for this approach and bringing them together?

I think if you're focused on finding the right tool that can solve a particular problem, then you need to wear a lot of hats. I guess I always felt that drawing on a suite of tools or techniques was important – they all blend together and help you tackle questions. For me, taking this sort of multi-disciplinary approach just happened naturally. It's also very easy for me to keep my interests broad because the young folks that come into the lab end up defining their projects, and those projects often extend to things that are beyond what we're doing at the time. We attack new projects with the idea that they will leave again when the investigator leaves the lab. So we end up needing to develop new tools to attack their problem...and then we need to find new problems when they leave. That adoption and graduation of problems sort of forces us to go into new areas and disciplines.

You've worked on a number of model systems throughout your career, from chick and quail embryos to zebrafish, mice, and cells in culture, just to name a few. This might be a difficult (and controversial) question to answer...but what's your favourite model organism?

All of them! I really feel that there's strength in a 'hybrid' approach. What I love doing is working on a technique in a particular system – usually the model system that's easiest to work with for that technique – then applying the technique to other systems that can help you ask the question you really want to ask. So, it's worth having a variety of models to hand, whether they're invertebrates or vertebrates, organoids or cell lines. All of them are a part of the proving ground for the suite of tools that we can use, and it really is this cross hybridisation of models that allows for exciting things to happen.

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More recently, you've been involved in translating some of your imaging approaches into clinically relevant technologies. How has this aspect of your research been compared with the more 'basic' research?

I think translational work is interesting – it's sort of the ultimate test of the utility of your tools. But it's an amazing challenge. You can only really translate something if you've done some sort of customer discovery first to find out if somebody really needs that tool. It's one thing to have made what you consider the best diagnostic in the world, but if it's a diagnostic no-one needs then it doesn't matter. So the customer discovery side of things is good for seeing the flaws in your new 'baby', focusing your efforts and figuring out the unmet needs. For me, the translational work has also been a very fun way to have parts of the lab that are involved in developing technologies that have ways to live on beyond their use in the lab. It's probably the world's worst way to get rich, though. Our first start-up company was just sold to Roche for 1.8 billion dollars. But that's after 25 years, and long after I was involved in the company! It's definitely not a 'get rich quick' scheme. But, it is a way of trying to make technologies that are robust and can answer real-life questions. In this case, it was a technology we developed to have very low false-positive rates for molecular diagnostics. We've also translated some of our work on developing microscopes. For example, some of the confocal microscopes that are on the market now are 'grandchildren' of ours and they've got some of our patents inside them. I love seeing them out there in the field and I love seeing the science that they generate.

You've been part of the SDB from early on in your career, serving as an Associate Editor and as an Editor for the society's journal *Developmental Biology* for over 25 years. What role do you think societies and society-run journals play in the community?

I love society-run and society-focused journals – they just seem to be associated with the community in the right way. I worry that, with time, the publishing process has become almost too professional and although we're publishing more papers, it's not often that a paper says what we *don't* know; every paper claims to have solved the entire field! There are no open questions left. What I loved when I was a student getting into developmental biology was that the end of papers would say what wasn't known. I think societies can play a big role in acting as clearing houses where a lot of the open questions can be discussed. This could be at their annual meetings or at smaller workshops, like those run by The Company of Biologists.

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I'd also love to see some of this sort of discussion reinfused into the journals, so that an article can really talk about what is or isn't known and what the open questions are. I think societies and society-run journals can help to push that forward because they're much closer to the community. Right now, we seem to be in a situation where, by saying there's an open question, we're asked by reviewers and editors to solve it, which means that the supplement ends up being longer than the paper itself! I just worry that much of that information gets lost. The fun part of every project is thinking about the open questions or the unknowns. It should be the same for papers.

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Lots of trainees have passed through your lab and have gone on to be leaders in the field. Indeed, you were awarded the SDB's 2021 Edwin G. Conklin Medal, which aims to recognise 'a developmental biologist who has made and is continuing to make extraordinary research contributions to the field, and is an excellent mentor who has helped train the next generation of outstanding scientists'. What's your approach to mentoring?

What works for me is to provide some sort of 'match-making'. I guess I try to offer mentorship and guidance instead of instead of being a boss. I think it's important that a trainee's success is their success, not mine – it's because of what they're doing, not because they did everything I said to do. In fact, what used to be great about going away to Woods Hole was that I'd come back and everybody would have worked five times harder, just to show that I really wasn't necessary!

For me, the goal is to bring in people and to let them define the project and then refine it, with some guidance (and heckling!) from me. Then, as the project becomes more theirs, I'm fine with them taking it with them. There have been many projects in the lab, ranging from gap junctions to developmental neuroscience, that left when postdocs and grad students left. But that's been great because it allows the fellows to shape the project, to apply our tools and to add new tools to the lab, and to force the lab to master new things. It's good way of keeping the lab fresh. Although I know it's super powerful to be a focused lab that specialises in a certain question in a given system, knowing every trick and detail inside out, for me the real thing that keeps me going is bringing in new minds that are constantly reshaping what the lab does.

I actually think that, as a field and as a community of academics, we really need to reacquaint ourselves with the idea of 'trainees and mentors' instead of thinking of people as, say, 'bosses' and 'workers'

I actually think that, as a field and as a community of academics, we really need to reacquaint ourselves with the idea of 'trainees and mentors' instead of thinking of people as, say, 'bosses' and 'workers'. In fact, I worry that some of the funding agencies and organisations have led people towards that type of thinking. I've had issues with funding agencies complaining that I'm not the last author on enough papers. Of course, I'm often not the last author because the postdoc who was the driving force behind the study should be the last author. I think that's more honest and is fantastic for building their careers. I don't think it should count against me if people in the lab do great things. As researchers, we've got to be willing to take chances, go after new problems and look at them with fresh eyes, and that's where trainees can really help out, with some good mentoring.

And what would be your advice to young researchers starting out in developmental biology today?

First, I'd say that developmental biology is just the best field because it's got so many open questions and because it touches so many other fields. Some of the best cell biology questions and some of the best neuroscience questions and some of the enhancer-related questions, you name it, can all be looked at in a developmental biology context. It's the world's best playground. But, in that playground, I think you need to find your question. There are a lot of open questions but you just need to find the question that excites you and isn't the same question that the other ten labs in the field are looking at. The more separated it is from the rest the better, because you won't be racing to see who can get their results submitted first. Make sure you give yourself some breathing room so you can allow the whole project to grow. I know many scientists have gotten ahead by trying to find the obvious next experiment and doing it quickly. But, I think it's much more fun to find the unique question that nobody else thinks is interesting and go after it. That's often when doors open up and new fields are created.

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

Some people might not be surprised to find this out but I guess I'm a compulsive 'do-it-yourselfer'. Whether it's building microscopes for lab or building loudspeakers and amplifiers for my home office, I like to do it myself. Even when it comes to coffee: it's not like you can't buy really nice coffee, but I just love roasting my own. The same is true for cooking. Being a compulsive 'do-it-yourselfer' might not be a surprising trait…but the degree to which I carry it out might be a surprise – perhaps even carrying it to the point that it is a mental pathology of some sort.