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SPOTLIGHT

An interview with Susan Strome

Aidan Maartens*,‡

Susan Strome is Distinguished Professor of Molecular, Cell and Developmental Biology at the University of California, Santa Cruz, USA. Recently appointed an editor at Development, her lab studies the regulation of germ cell development in *C. elegans*, with a particular focus on the epigenetic transmission of chromatin states. We caught up with Susan to discuss her early career switch from prokaryotes to worms, her experiences of small and big science, and why teaching is so important to her.

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

When I was young, science and math were my comfort zones. My dad was an engineer, and although I don't like it when people categorise brain types, I think that was the way my brain seemed to work. At university I was a chemistry major, although I don't remember why I chose to go into chemistry. After earning my bachelor's degree in chemistry, I thought about pursuing either medical school or graduate school. I decided against medical school in part because that career path would involve interacting with people all the time, and I saw myself as more of a solo person, not realising of course that going to graduate school and running a lab would be very people-oriented and that I would love that aspect of my eventual career. I also thought that being a doctor and responsible for people's lives requires a really good memory, and I wasn't sure I could rely on my memory. With medical school out, it was natural to gravitate towards graduate school. I decided to move towards more biologically oriented chemistry (i.e. biochemistry), and enrolled in a PhD programme in biochemistry at the University of Washington in Seattle.

From your PhD came three publications in the Journal of Molecular Biology in 1978 and 1980 and focusing on a T7 bacteriophage gene. How did you get into this work?

I selected a research lab and project that would provide me with a good training experience. In my opinion, the aim of PhD research is not to pick the system or question that you want to study for the rest of your life, but to learn how to identify questions, formulate hypotheses, design experiments to test your hypotheses, interpret your results, and design the next experiments. Prokaryotic systems are great for this because everything is so fast – I had a lot of practice going through the scientific method over and over again instead of having to wait weeks or months to see the results. My advisor Ted Young was a great mentor, and I completed my degree in four and a half years, which is relatively rare these days. There was one really transformative event – Ted went away on sabbatical in Switzerland for a year, leaving just me and the technician in the lab. This was pre-email, so we wrote letters back and forth. One day I wrote to tell him I was thinking of trying a certain experiment. I shipped off my letter and started doing the experiment. Three weeks later I got his reply, saying 'I don't think that experiment will work and be informative for these reasons…' But by then I had already done the experiment and had gotten a great result, which turned into one of my three PhD papers. That experience was empowering because I realised that I could think it through on my own – I didn't require that my advisor tell me what to do or how to do it.

My PhD research was great training, but my research area was not what I wanted to pursue for decades. I was more interested in cells, organs, tissues and animals, and what I did in graduate school was very reductionist, test tube stuff. I started taking classes in physiology in the Nursing Department to learn how cells and tissues and organs function, how metabolism works and so on, and that put me on to developmental biology. Then I had to find my niche within the field. I found it, and since 1979 I've been studying the same types of questions in the same organism, while changing with the times and adopting new technologies.

That organism was *C. elegans*, which you first encountered as a postdoc with Bill Wood in Boulder, Colorado – what was the worm field like when you joined it?

It's interesting to note that it was fairly common for the early *C. elegans* investigators to have started as prokaryotic researchers – Sydney Brenner is an obvious example, a lot of the other luminaries

*Online Editor, Development

‡Author for correspondence (aidan.maartens@biologists.com)

A.M., 0000-0001-7112-819X

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of our field also started off there, and so did I. In the late 1970s, studying *C. elegans* development was a budding, young field. I could probably have read every worm development paper in an afternoon! There were no guarantees that it would turn into the premier system that *Drosophila* was, but I wanted to get into worm work at the ground level. There weren't too many worm communities at the time. The mecca was Cambridge in the UK. Notably, Boulder had two labs – David Hirsh's and Bill Wood's – focused on *C. elegans*, and Dick McIntosh's lab also did some worm work. There were a lot of great postdocs and graduate students in Boulder, and we had wonderful worm meetings – I got to know people who I have kept in touch with for decades.

I was also really attracted to Bill Wood's style of doing science. He was a prokaryotic researcher, and had been recognised for his influential work on T4 phage assembly. I imagined and hoped that he would bring to *C. elegans* – and help me bring to *C. elegans* – the kind of thinking that would advance the field, and that turned out to be true. He was a wonderful mentor for me.

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What question were you aiming to answer in your postdoc?

I wanted to test whether the site of sperm entry dictates the polarity of the embryo, and I wanted to understand how cells acquire their fates. Work from the lab had shown that different cells develop into different tissues, and at the time it was thought that the embryo was a lot more 'mosaic' than subsequent analyses showed (we weren't aware that there was as much cell signalling as we know now). So I was interested in how the embryo initially learns anterior from posterior, and then divides such that the smaller daughter cell will generate germline and the bigger daughter cell will generate somatic cell types.

I started by raising antibodies to sperm components, to see whether they mark the sperm entry point and might dictate which end of the embryo becomes posterior. I took an inelegant, brute-force approach of collecting sperm or grinding up *C. elegans* embryos, injecting them into mice, making monoclonal antibodies, and screening them for interesting staining patterns – could I find anything that was anterior, posterior, or cell fate specific?

I was screening antibody-by-antibody for an interesting staining pattern, and I had gone through a few rounds of screening without seeing anything notable. And then I launched into a new experiment. It was late at night, and I was screening through many eight-well slides, each well with a different antibody in it. I went into the dark microscope room and in my first sample on my first slide I saw bright little granules, but only in certain cells of the embryo – they were in one cell of the two-cell embryo, one cell of the four-cell embryo, one cell of the eight-cell embryo, etc. I thought, wow, the little granules are uniquely in the germ cell of each embryo! The granules were clearly a lineage-specific marker. I was so excited, I ran out into the lab to tell a lab mate, but no one was there (it was 11:30 at night), so I ran out into the hallway and grabbed the janitor and made him look through the microscope at my beautiful granules. I wanted him to say 'Oh, that's amazing!', but he just said 'Oh, that's nice', of course not really understanding why I was so excited. After my super-exciting sample 1, I went to sample 2 – and saw the same little germline-specific granules. Then sample number 3 – again little granules in the germ cells. Then I went to my 'no primary antibody' control, and saw the same thing! It was the secondary antibody that was staining those granules – it wasn't the antibody source I wanted, but it did tell me that the granules exist, and the antibodies enabled me to see them.

Bill Wood and I bought up the entire batch of that secondary antibody to use as a reagent, and I launched into screening for primary monoclonal antibodies that would similarly stain the granules, and found some. That set me on a path of pursuing germ granules – which we called P granules in worms because they are segregated to the P lineage. The granules had been observed by electron microscopy in *Drosophila* and frogs and even worms, but you can't study the composition and role of a granule using microscopy alone. The antibodies paved the way for the questions I would tackle when I started my own lab at Indiana University. What are germ granules made of? How are they sent to the germ lineage? What do they do? Are they required for fertility?

You've worked on germ cells for 30 years – what has kept you interested for so long, and what are the key unanswered questions in the field?

I would say P granules pointed me towards germ cells. What further focused my attention on germ cells was doing massive forward genetic screens for sterile mutants that have maternal-effect genetics, the goal being to identify mutants defective in P granules. We didn't find any P-granule mutants, for reasons we understand now but at the time were mysterious. Instead, we identified a small set of genes that we called maternal effect sterile (MES) genes; when the mother is homozygous mutant for a MES gene, she generates offspring that are all sterile. The MES genes turned out to be histone modifiers: three make up polycomb repressive complex 2 (PRC2), which methylates an amino acid in the tail of histone H3, and another (MES-4) methylates a different histone H3 tail amino acid near where PRC2 does. All of a sudden we were in chromatin, we were in epigenetics – the MES proteins are epigenetic regulators needed for germ cell development, and not needed for development of the somatic body.

Interestingly, from the get-go, pursuing the MES chromatin regulators was an easier path than pursuing P granules. P granules were challenging to dissect biochemically and functionally. A turning point came when Dustin Updike, who now runs his own lab, joined my lab as a postdoc. He brought great imagination, determination, and excellent technical skills to his project, and published several seminal papers on P granules. When he left my lab to start his own lab, I pretty much said 'you take P granules, and I'll focus on chromatin'. So P granules launched me and have been an important part of the lab for 30 years, and now Dustin is following up on them. Currently, my lab is mainly studying chromatin regulation – it's been a very exciting story. We got to jump on the tidal wave that is epigenetics, which David Allis and others launched a few decades ago, and which continues to be a really hot field.

We published a paper in 2014 that has been very influential – it showed that chromosomes bearing repressive marks put down by PRC2 are transferred to the one-cell embryo from both gametes (sperm and egg) and that the repressive marks are then passed in *cis* to daughter chromatids during DNA replication. We invoked that the MES factors are sending a memory of gene expression patterns that are appropriate for germ cells from parent germ cells to progeny germ cells. We're continuing to study this now. We hope it will help us address one of the key questions in epigenetics: how is epigenetic information passed across generations? The conduit for passing information between generations is germ cells. A burning question

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is if and how a memory of parental experience – environment, diet, stress – can be sent via the germ cells to progeny. My lab is well positioned to tackle that question in worms.

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What do model organisms like worms contribute to epigenetics as a whole?

Those of us who have studied invertebrate model organisms throughout our careers have been nervous that NIH study sections will shut the door on our funding in favour of funding studies in mammals. But my last grant application to the NIH proposing experiments in *C. elegans* got a perfect score! There is recognition that in model organisms we can ask really detailed mechanistic questions, while also trying to control for all the variables that could influence epigenetic inheritance. Edith Heard and Ruth Lehmann ran a wonderful meeting funded by The Company of Biologists in Sussex in 2015. At that meeting, I was in a break-out group with Marcus Pembrey and others discussing how hard it is to control for everything that might influence the transmission of information from mouse parents to their offspring, such as the lights in the animal room, who takes care of the mice, and whether the plastic water bottles are leaching out toxic compounds. Even in worms we wonder if we are controlling for all possible variables. As I said, model organisms offer the opportunity to drill down into detailed mechanistic questions. Most epigenetic inheritance – not all of it – boils down to DNA methylation, histone modifications, and RNAs. We can identify the epigenetic carriers and dissect how they work in different systems, and then feed that information to the mammalian folks. Worms, flies, frogs, fish and yeast are making huge contributions to the epigenetics field, revealing how epigenetics might influence development and health in more complicated organisms.

You were part of the worm unit of modENCODE – what was your experience with the project?

modENCODE was focused on flies and worms, and followed from the ENCODE project, which was mainly human. I was in an eight-lab consortium – Jason Lieb was the primary investigator, and the co-PIs were myself, Abby Dernburg, Julie Ahringer, Arshad Desai, Eran Segal and Shirley Liu (the last two are bioinformaticians). We put forward a proposal to characterise histone modifications and the distribution of chromatin regulators across the worm genome. Interestingly, we were charged with characterising and cataloguing – not doing experiments. This was very different from most NIH funding, which would not fund catalogues, but our mission was to catalogue and to put the data out there for the community to pursue. It was an interesting lesson in big science, and working in big groups – we had to be highly organised and very cooperative. When we started, we didn't even know how to do ChIP in worms, so we first had to figure that out. The NIH wanted high-quality data, so every antibody we used for ChIP had to be validated by various means, which of course by itself was a lot of work but useful for the community (when people do analyses using bad antibodies, it can muddy the field and be a disservice).

I think that there was some resentment in the worm community over the amount of money that was going into this – but if I think about taking the same amount of money and distributing it among many labs to try to accomplish the same thing, I don't think as much would have been achieved. So overall I think the modENCODE consortium model was successful – it was a different kind of science, my group learned a lot, and I think the community inherited a nice body of data to work with.

In 2013 you were awarded the UCSC Excellence in Teaching Award – how important is teaching to you?

Like many of my favourite scientists, I am a firm believer that a large part of our job is training students. We reach relatively few students in the lab, even if we regularly have undergraduate students do research projects. When I go into a class of 300 to teach genetics, I can have an impact on a lot of students. If I can give them a really solid grounding in the chromosomal basis of meiosis, mitosis, inheritance, and genetic diseases, that is a real gift. I don't want them to memorise, spit out memorised 'facts' in the exam, and then forget the important concepts once the class is over. I want them to leave the university with a deep understanding of the concepts that we cover, as informed citizens who can talk through something like a cancer diagnosis or treatment with their family and friends. My strategy has been to try to figure out what the students really struggle with, and then try to design a lesson activity, something that gives them more practice, to get more comfortable with it. My big thing is chromosomes, in part because I used to get to the end of a genetics course and the students still didn't really understand the difference between homologues and sister chromatids. We really tackle that, coming at it from many different directions. For example, we use pipe cleaners and beads, pool noodles, and fingers to model chromosomes, aiming to form a lasting memory instead of a temporary one. I also have students work in groups – they bring different perspectives and may explain concepts differently from how I would, in a way that might resonate with other students.

Almost a year into the new administration, how do you see the prospects for science, and basic research in particular, in the US?

I think scientists are scared – how much damage will occur in the course of Trump's four-year term? Trump and the Republicans are dumping on science. For example, they proposed a tax bill that would tax graduate students on the tuition and fees that their universities pay on their behalf, which would have been devastating. Graduate students are barely scraping by financially, and that bill would have been a huge financial blow to them. Fortunately, the proposed tax on graduate student tuition and fees was not adopted. One bright note is that the current political scene in the US is prompting lots of people to be more proactive and to do as much as they can to oppose bad legislation. But we all wonder what four years of a Trump administration will do to science. I and my colleagues are deeply concerned!

You've recently joined Development as an editor, having first published with us in 1986 – what do you hope to achieve in your new role, and where do you see the future of the journal?

I'm very excited to have started this position. Geraldine Seydoux, my much-esteemed colleague, was stepping down and asked if I would step in, since we have expertise in many of the same areas. I was willing and enthusiastic about doing it because I want to play my part in seeing that high-quality papers continue to be published in Development – as journals scramble to recruit papers, I don't want the bar to be lowered at all. Already, just a few months in, I'm learning a lot from looking at the early versions of papers, selecting reviewers, and reading reviews. As I get a better feel for the journal,

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I'll be able to contribute to trying to figure out what's in the future for Development – where should we be headed? As I've said, I think epigenetics is a fascinating and fast-moving topic in the development field, and there is a lot of amazing technology that is advancing our understanding. For example, single-cell RNA sequencing is allowing us to analyse gene expression in single cells instead of populations of cells. Single-cell sequencing is opening up a whole frontier that I think we will be mining for the next few years if not decades. Additionally, there's amazing imaging, such as super-resolution microscopy, being applied to answering questions in new and informative ways. I'm excited to work with Development to figure out where to go next.

Do you have any advice for young scientists thinking of a career in research?

I have two children who both said that they weren't going to do what mom and dad do (my husband is also a researcher), and who proceeded to get degrees in pretty much what mom and dad do, and then decided they wanted to go to graduate school. Mom and dad advised them to be technicians for two years to make sure that full-time research is what they like to do and that they have the temperament to weather the ups and downs. Both of them followed our advice, and applied to graduate school after experiencing full-time research. That would be my first piece of advice – sample intensive research before making the jump into a PhD programme.

I'd also advise new students to follow your passion – graduate training can be exciting, thrilling and stimulating, but it can also be tiring, and when students don't experience success it can be discouraging and disappointing. You have to be able to weather the ups and downs – the ups and your fascination with your project have to keep you going. I think it's crucial to pick a good mentor, a good lab, and a system in which you'll learn lessons, and I don't think the system has to be the one you want to work on long term. We have students who come in and say 'I want to work on XYZ' – they don't necessarily have to do their graduate work on XYZ. Students should pick labs in which they'll get good training, where they and their mentor have identified great questions to tackle, where they can learn at least some state-of-the-art technologies, and where they will leave poised to move on to what they want to study for decades, their XYZ area.

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

I don't feel like I have a part of my life that is particularly wild or surprising – I haven't cultivated too many extracurriculars, being mainly kept busy and gratified by family and science. I am in a family of scientists – married to one and with two kids on the science path. That's not so surprising, since scientists tend to find each other, and kids often follow in their parents' footsteps. What people might not know is that I was an aspiring ballet dancer, even through graduate school, but it was never serious, just my outlet to do something physical and aesthetically pleasing. Maybe that will be something to pick back up in retirement, although I don't think I want to go back on toe!