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INTERVIEW

An interview with Judith Kimble

Aidan Maartens*,‡

Judith Kimble is Vilas Professor of Biochemistry at the University of Wisconsin-Madison and a Howard Hughes Medical Institute Investigator (since 1994). Her lab is interested broadly in the molecular regulation of animal development, with a focus on stem cell self-renewal, fate specification and reprogramming in *Caenorhabditis elegans*. We caught up with Judith after she delivered her Keynote Lecture at the 2019 Santa Cruz Developmental Biology Meeting, and heard about her circuitous route to basic research, her passion for black boxes in science and why London is her cabin the woods.

Let's go back to the beginning: what convinced you to go into science in the first place?

As a kid, I loved my dog and was pretty good at maths and science. So my early aspiration was to be a vet. That goal morphed in high school to human medicine, so when I started college, at the University of California in Berkeley in 1966, I began as a pre-med. But those courses were so boring! I kept up with pre-med classes over the next few years, but, for sanity, branched out as a sophomore into theatre (acting, directing and constructing stage scenery), and as a junior into archaeology and political science – all much more interesting! Nothing seemed quite right, however, so I dropped out for 3 months to ponder my future. Upon returning, I cobbled together an 'independent' major for graduation and was accepted into medical school.

But in my last semester, I took a class in human embryology with an inspiring professor. One of the amazing things I learned was that early stage cardiac tubes could be taken out of a developing mouse, placed next to each other in a Petri dish and form a heart *in vitro*. I thought: Wow! Is that really possible? How could that work? My place in medical school was soon declined, but it was too late to apply for graduate school. I needed a plan B. As an undergrad, I had worked as a teaching assistant for a professor on sabbatical from Denmark, so I approached him for a job in Copenhagen. Danish union laws did not allow me to work as a technician, but he arranged for me to join the medical school faculty – at the very lowest rung, of course. For the next two years, I taught histology to medical students and learned electron microscopy and histochemistry. We focused on developmental neurobiology in human and rabbit foetuses, and my first papers came from that time. However, I was heavily influenced by the molecular genetics explosion and frustrated with tools available for analysing vertebrate development. My next step was graduate school where I expected to work on *Escherichia coli*, with the idea that I would return to animal development at some later date when it became more tractable to molecular studies.

In graduate school at the University of Colorado in Boulder, a young Assistant Professor, David Hirsh, had launched his lab around understanding development in a tiny nematode worm, *C. elegans*. According to Sydney Brenner's famous joke, these worms were more interesting than *E. coli*, because they ate *E. coli*. I was sold! I started with simple genetics, which never got very interesting from my perspective, but then John Sulston wrote to David describing his new method for lineage tracing. John asked if we might want to do the gonadal lineage? This was fantastic for me – a defined and exciting project in animal development! And it was also my thesis: elucidation of the stereotyped cell lineages of the somatic gonad in each sex. I found that two precursor cells, set aside in the embryo, make very different organs – a male gonad or a female one – with different symmetries and different substructures. Their cell division patterns, however, were intriguingly related. I was watching developmental regulation as it was unfolding – in real time and cell by cell. This was an amazing system and very beautiful. Though I'd started by wanting to understand human embryos, worms provided my much-needed experimental entrée. Their simplicity and genetics suggested I might actually be able to understand them at the molecular level in my lifetime! What I really wanted to do was to use the worm to figure out general principles of animal development.

But back then, was it even clear that conserved molecular mechanisms would exist?

No, it was certainly not clear! Soon after I started as a postdoc, I talked at a BSDB meeting and suggested that worm and human body plans were similar: both have a mouth and anus, a gut connecting them, a brain, nerve cord and muscles. Therefore, the basics are all there in this tractable little worm. If you want to

*Online Editor, Development

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

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

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understand a basic question in animal development – how cell death is regulated, for instance – the worm might hold that secret. What was the reaction to this idea? An apparently well-established, or at least grey-haired, professor stood up during the questions after my talk and declared loud and clear: 'This is total rubbish! Worms have nothing to say about humans.' I have no idea who this was, but history has shown him to be wrong. For my first R01 (written and awarded while I was a post-doc – times were different!), I proposed to identify building blocks that were conserved across animal phylogenies. I thought this was a pipe dream, but an NIH grant clearly required relevance to human health. It has been wonderful to find over the years that those early statements were actually prescient rather than unadulterated hype.

After your PhD you moved to Cambridge for a postdoc at the MRC Laboratory of Molecular Biology (LMB): what was the LMB like at the time?

It was an amazing place to do science. Funding was provided to the institution, not the lab, so lab structures were minimal and all researchers were expected to be independent. John Sulston was my official advisor, but he made it clear from the start that I should work on what I wanted and not rely on him for much guidance. John White had developed a laser microbeam that could be focused though a microscope lens, and I spent my first year doing laser ablation experiments. At the time, most developmental biologists thought that the development of invertebrates with stereotyped cell lineages was controlled very differently from 'regulative' development in vertebrates. Ancestry was a key mechanism for defined lineages, whereas cell interactions governed vertebrates – the 'European versus American' modes of developmental control, according to Sydney. I was confident that view was wrong and that cell interactions were crucial even in *C. elegans*. The lineage provided a rich descriptive substrate to map cell interactions and that was my goal – to find them. From that first year of experiments, I published two research articles – one on 'distal tip cell' maintenance of germline stem cells and the other on now classic examples of interactions that control cell fate, lateral signalling (the AC-VU decision) and vulval induction.

As much as I loved development at the level of individual cells, I needed to learn molecular biology and genetics if I wanted to run my own lab. The LMB was a fabulous place for that and my next couple of papers were done with that in mind. I have one amusing anecdote: when I started one of my first experiments using biochemistry, I scoured the floor for an ice machine. After some searching, I found it in the men's cloakroom. Okay, I said to myself – if that is where it is . . . I went in to fill my ice bucket and was stopped by a gentleman telling me I had the wrong cloakroom. But I was in the cloakroom with the only ice machine. Truly different times.

The best thing about the LMB from my perspective were the people and the intensity of their passion for science. LMB postdocs and students worked all the time, but in some sense never worked. We'd arrive in the morning around nine or ten o'clock, start an experiment and then go for coffee and scones; lunch was at one o'clock, post-lunch deliberations over coffee went for another hour and then tea at four o'clock. Dinner was much later and often at the Addenbrooke's hospital cafeteria across the street, where 19 pence was enough for a giant plate of fries and sausages, finished off with pud. We typically did experiments until the wee hours, but also talked a lot with science always at the centre of our conversations – articles we were reading, questions we were thinking about, ideas we had about cracking the problems we were struggling with. It was extremely stimulating – such a strong community of smart people who cared deeply about science. And staff scientists, like John Gurdon, Fred Sanger, Max Perutz – they were freed from grant writing, teaching and committees, so had time to be engaged, to work at the bench themselves and to be curious about what we were discovering. They often joined us in the cafeteria, which made conversations wide-ranging and lively.

Once a year at the MRC LMB, a week was set aside for 'Lab Talks' – the entire place shut down so that everyone could hear the latest developments. I had discovered the distal tip cell and other cell interactions early on in my time there, and was asked to give a talk. The whole institute attended and in the front row, a string of Nobel Prize winners. I thought, if I can make it through this, I can get through anything! It was a watershed moment and went well. I even got insightful questions from the front row, who all stayed awake and seemed genuinely interested in my results. Another similarly important early experience was a talk at the Biological Regulatory Mechanisms Gordon Conference. The meeting focused on molecular regulation in phages, bacteria and yeast but had a 'zoo' session at the end, on Friday morning just before everyone got on the bus for the airport. Janni Nüsslein-Volhard of *Drosophila* patterning fame and I both spoke in that final zoo session. But neither of us knew others at the meeting and in the days before our session we spent time together worrying about our talks and getting to know each other; she's been a close friend ever since. Barbara McClintock sat in the front row during our talks, and I can still picture her smiling face and glittering eyes as I spoke about how the distal tip cell maintains stem cells and induces generation of the germline tissue. It was very reinforcing.

What was your main scientific aim when you started your own lab?

My aim was broad – to understand animal development at a molecular level. Most *C. elegans* development labs in those early days were focusing on the early embryo and somatic cell lineages. I decided to focus instead on germ cells, cell divisions of which are stochastic and regulated by cell interaction. Perhaps germ cells were better poised to yield principles relevant to vertebrate development. I started the lab with genetic screens to get a toehold into germline regulation, and was very lucky to be joined by a great postdoc, Tim Schedl, and fantastic students (Kathy Barton and Julie Ahringer were among the early cohort). We worked together day in and day out, and isolated mutants as entrées into distal tip cell regulation of stem cells and germline sex determination. These mutants led us to the discovery of the Notch receptor GLP-1 and the first germline-specific regulators of the sex determination pathway. I had not done much genetics before that, and I loved it!

But, for each story, we ran into experimental roadblocks where traditional methods were no longer moving us forward. Genetics is great for getting your toe in the door, but it does not allow you to open that door and understand molecular functions; for that, we needed molecular biology and biochemistry. In my talk here at Santa Cruz, I used the metaphor of wandering through the desert from oasis to oasis – basically, wandering through times where we really had no idea what was going on or how to approach it and then reaching a breakthrough, either in our understanding or in the ability to ask the question in a different way. For instance, we spent years working on Wnt signalling without really knowing it. Our very early screens yielded a mutant with a tantalizing somatic gonadal phenotype, but the somatic gonad was too complicated to tackle in a meaningful way and I guided the lab in more tractable

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directions – regulation of the mitosis/meiosis and sperm/oocyte decisions. Fifteen years later, a student asked to do something different from the rest of the lab so I gave her this mutant. She isolated more alleles, cloned the gene (by then named *sys-1*) and found it to encode a novel protein. This may have been a good time to stop wandering in this particular desert, but the phenotype was interesting and we kept at it. Eventually, we discovered that SYS-1 is a key player in the Wnt pathway underpinning nearly all asymmetric divisions in the *C. elegans* somatic cell lineage. A major mystery in that pathway had been the lack of a β-catenin, and we uncovered a number of clues that made SYS-1 'smell' like a β-catenin. But the SYS-1 amino acid sequence bore little similarity to β-catenin. Finally, we worked with an X-ray crystallographer to show that SYS-1 has the structure of a β-catenin, despite its sequence. SYS-1 appears to have lost its connections with the cytoskeleton but retained its activity as a transcription factor with TCF/LEF. My bet is that other SYS-1-like β-catenins exist but they would be hard to find by sequence gazing.

SYS-1 was a real learning experience for me. It taught me that novel proteins with clear biological significance can have conserved functions and be of broad interest. The bottom line: if a protein screams out to you of its biological importance, it's worth the effort to figure it out. There are many novel and mysterious proteins in every genome, and working on them in an experimentally powerful system such as *C. elegans* may be the only way to crack their functions. But the functional hook, afforded by genetics, is crucial. Remarkably, nothing I've worked on so far has been totally worm specific, but I continue to test that claim. My lab is currently tackling two novel but key stem cell regulators that, like SYS-1, offer no clues to molecular function from their amino acid sequences.

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One of the aspects of your work that has had broad applicability is the stem cell niche – how did that concept evolve?

Hans Schofield introduced the concept of the 'stem cell niche' in 1977. In 1981, we reported that a mesenchymal cell, the distal tip cell, maintains germline stem cells and suggested that similar regulatory cells might maintain stem cells in other systems. At the time, I had not seen Schofield's paper, which was published in the journal *Blood Cells*. It was only later that I realised that the distal tip cell was the first concrete example of a stem cell niche.

The story behind the discovery of the distal tip cell might be of interest. After Copenhagen, but before starting grad school, I spent the summer in Woods Hole and read experimental embryology papers from the early twentieth century in their amazing library. A number of those classical lineages generated tiny cells that stopped dividing and seemed to be set aside: people referred to them as 'vestigial'. In grad school, I found two tiny cells in the worm that I thought might be similarly vestigial, born because of lineage logic but not used and therefore set aside. So my first laser ablation experiment at the LMB was to test this idea. But, remarkably, those two tiny cells had a profound function – they maintained germline stem cells and were the male distal tip cells. I only later did similar experiments in hermaphrodites, which have a larger distal tip cell with a morphogenetic 'leader' function, which hence was not a candidate for being vestigial. But the distal tips cells in both sexes have the common niche function of stem cell maintenance. I have always wondered if other non-dividing and apparently useless tiny cells, such as those reported in the early literature, might also be key regulatory cells the functions of which have still not been investigated.

If we move on to what your lab is doing now, what are the problems that keep you up at night?

I still love germ cells and their regulation. Our work, as well as that of many other labs, has found time and again that RNA regulation is central to germ cell regulation. Transcriptional control kicks things off upon signalling from the niche, but then RNA regulation takes over. RNA regulators control self-renewal, entry into the meiotic cell cycle and fate specification as sperm or oocytes. An elaborate network of RNA regulators balances the decision between self-renewal and differentiation, but we have little understanding of how the transition is made from one hub of the network to the other. And until recently, we had no idea how niche signalling was linked to that RNA regulatory network. In 2017, we found that missing link – two novel proteins that are essential for stem cells, albeit redundantly, and drive tumour formation when overexpressed. How did we find them? Not genetics because of their redundancy and not homology because of their novel sequences. Instead, they were discovered through a combination of genomics and creativity, led by a talented student, Aaron Kershner. So, in answer to your question, understanding these recently found stem cell regulators is what keeps me up at night, and we are making progress. But what is most exciting is that these proteins turn out to be the key to understanding the molecular basis of a network transition. We have ideas about how that transition is regulated but only bits and pieces of concrete evidence. I'm also really interested in the kinetics and reversibility of the transition, which underpin developmental plasticity. This a huge and mysterious black box, and I love black boxes. Learning details is clearly very important and can be satisfying, but tackling a black box from the beginning and figuring out what it's made of and how it works – that is exhilarating!

You have been President of both the Genetics Society and the Society of Developmental Biology, as well as being on the Council of the National Academy of Sciences. How important are such professional organisations in today's science?

My talk here in Santa Cruz is titled 'Niches, naivety and networks'. The title has obvious scientific relevance for stem cell regulation, but its concepts also have relevance for professional societies, which bring mentoring and networking together with fantastic science. Many students are seeking their professional identity and can be considered 'naive, in the best sense of the word, and that quest can be helped immeasurably with nurturing from a niche and networking with others in the community. Professional societies can be an important part of that niche and help forge connections within the scientific community. One of my mantras for all researchers is that in addition to doing science, they need to protect their niche. These days, societies are especially important niches with the many difficulties being faced by the next generation of researchers.

You were a signatory of a 2017 letter to Science calling for action in all institutions to deal with gender discrimination. A year on from that letter do you think the issue is getting the required attention and action?

That's a hard question – we were calling for cultural change in that letter, and cultural changes take time. In thinking back through my

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career, it took me a while to even realise that I was a 'woman scientist'. This tag seems odd as I've always thought of myself as a scientist, full stop. Does a man think of himself as a 'man scientist'? But I live in the real world. Gender bias has to change as do so many biases in science and society. We all need to keep pushing for change, and I do think that we are making progress.

Do you have any advice for young researchers considering a career in developmental biology?

My primary advice is to think about science first and foremost. Think about what the new and important questions are, and think about strategies to tackle those questions. This advice comes from what worked for me. When I started into research, my goal was to solve a scientific problem, not to have a scientific career. It was only when I had success solving problems and realised that I loved the process, that I understood that a research career might be an option for me. With that said, I must admit that I gave this advice to my son a few years ago and he was quick to respond: 'Mom that's crazy – you've got to focus on your career these days!' That is certainly the common wisdom now, but is it right? I worry that brilliant young researchers waste their energy on career strategies at the expense of their science. To really understand what's important and interesting in science and do it creatively, it helps to use your whole brain and not worry all the time about your career. That's me – I'm old fashioned!

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

Perhaps how incredibly important my husband has been to me and my science. It's hard to express in how many ways he has touched my life. We met as postdocs at the MRC – he was a molecular biologist interested in RNA and I was a developmental biologist interested in cell regulation. Remarkably, our science converged years later – about 15 years after we started our faculty positions. In a remarkable confluence of my genetic mutants and his molecular innovation, we discovered FBF and PUF RNA-binding proteins as central to germ cell fate specification! We continue to collaborate to this day. On another note, Marv has always been an Anglophile (his father was British) but when I first arrived in Cambridge, I was there for the science, not the experience abroad. Copenhagen was more my style. My distaste for England was a challenge and Marv set out to change my views. And of course, he prevailed! We now even have a tiny flat in London, which I love as my cabin in the woods. My typical day there is to work, still in my bathrobe, until two or three o'clock in the afternoon – six or seven hours without interruption! And then London is at my doorstep with its amazing theatre, music and art: it's a great combination! When possible, I couple those trips with other commitments in Europe. Recently, I joined the Wellcome Trust interview panel, which brings me to London every few months and lets me take advantage of my cabin in the woods.