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Mouse genetics for studying mechanisms of deafness and more: an interview with Karen Steel

Karen Steel has dedicated her career to unravelling the many mechanisms underlying deafness using mouse genetics. In this interview, she explains how this area has engaged her attention since the first day she began her PhD, and discusses the power of mouse genetics programmes for advancing all areas of biomedical research.

Karen Steel was born in Somerset, UK. After completing a joint degree in Zoology and Genetics at Leeds University, she carried out a PhD at University College London (UCL), where she established her interest in studying deafness in mice. She made significant progress in understanding the mechanisms underlying deafness during postdoctoral work at the Medical Research Council (MRC) Institute of Hearing Research at Nottingham University. There, she also established an animal facility and molecular genetics laboratory from scratch and collaborated with other centres to identify new deaf mutants through ENU mouse mutagenesis screens. In 2003, Karen Steel joined the Wellcome Trust Sanger Institute, where she established the mouse genetics project that aims to generate and characterise knockouts ultimately for every gene in the mouse genome. She is now focussing on characterising the new deaf mutants that have been identified in this screen. Over the course of her career, she has studied more than 100 mouse mutants in detail, and provided great insight into the many mechanisms that lead to hearing impairment and related disorders.

Were you always interested in science as a young person, or was there someone or something that led you to follow a career in research?

Before I began learning about biology at school, English was my first love. Some years after I left school I met a former teacher and she was surprised I had become a geneticist – she thought I was going to become a poet! In any case, I enjoyed biology from the moment I started studying it, during the first year of secondary school. I must give credit to my biology teachers – Mr Savery and Mr Rix. They were very influential, right from the start. One of the things they did was to take us to Bristol University, when I was in the sixth form, to hear a lecture by Dorothy Hodgkin. This was the first lecture I had ever been to, and the first time I had ever heard of a woman being a scientist. There must have been 500 people in a huge lecture theatre. She stood up and gave a talk about how she had solved the structure of insulin. I think that was the most inspiring talk I've ever heard in my life, and I knew then that I really wanted to do research in my future career.

During my PhD I was very lucky to be surrounded by many good female role models. In particular, there was Anne McLaren, who was at that stage setting up a new MRC unit at UCL. I was on the same floor as this new unit, and I used to have lunch with her group every day. I had so much admiration for the way that she worked, for the way that she interacted with people. She was a wonderful role model.

How did you end up focussing your research on deafness?

After my degree at Leeds University, I went to UCL to do a PhD with Professor Malkiat Deol. I knew that I wanted to study early mouse genetics, but when I turned up on my first day, my supervisor said that he wanted me to work on the genetics of deafness using mouse mutants. This was a great surprise to me, because I'd made the big mistake of not reading all of his publications and had no idea that he was interested in the genetics of deafness! So, I was already there and I thought I'd just give it a go – and that's how I got interested in this area.

Credit: Wellcome Library, London

And you've stayed on the same track all these years. What keeps you engaged?

One of the reasons I liked studying deafness initially was that it was a good focus. I had a broad interest in mouse genetics – and in fact in zoology more generally – so to have a focus on deafness meant that I could study the literature much more easily. In those days, you could read all of the papers that had ever been written on deafness. These days it's

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nearly impossible to do that. It's now much more challenging for students to define their focus and to find the right project for their PhD.

When it comes to studying mouse mutants, another attraction for me has always been that mouse mutants are like a puzzle. You start off with a phenotype and you have no idea what's going on inside – you have no idea of what the mechanism might be before you start studying the genetics. So, it's a bit like putting a jigsaw together, or unwrapping a parcel, as you find out what's going on inside. I find that really fascinating.

You've been working with mouse mutants for many years now. How has your work evolved with the advent of new genetic techniques?

When I started working on the genetics of deafness, I began by characterising spontaneous mouse mutants that were available from some of the large laboratories, such as the Jackson Laboratory, MRC Harwell and so on. I started working on them one at a time to try to determine the range of different mechanisms that could lead to deafness using histological and developmental techniques, as well as electrophysiology as a way of assessing hearing impairment. I was surprised to find that every single mutant had a different mechanism underlying deafness.

At first, this was a very descriptive approach, using mouse mutants that were already available. But it soon became very clear that we needed to identify the genes that were involved. This was in the 1980s, and molecular biology was just beginning to take off, so it quickly became feasible to map and identify the mutations that could complement the phenotyping studies we had already done. So, I learned how to do that and collaborated with several other scientists, including Karen Avraham and Steve Brown, to identify the genes involved.

I was also interested in generating and studying new mouse mutants. The first mutagenesis programmes that I got involved with were large-scale ENU mutagenesis projects, and I collaborated with two programmes – one in Munich and one in Harwell. In both cases I devised a screen for picking out mutant mice that had hearing impairment or balance problems [also indicative of potential hearing defects]. I coordinated a European Commission programme to get funding to run those screens, and together with collaborating groups around Europe we identified the genes involved and characterised the phenotypes of those mutants. That was very productive: we had funding for 3 years [in the late 1990s] to fund the screen, and my group has only just identified the last mutation (by exome sequencing) from that screen! So, that work kept us going for a long time, and we found some very interesting mutations.

Conventionally, deafness was thought to result from degeneration of the sensory hair cells of the inner ear. How has the phenotype-driven approach you've employed in mouse mutants helped to understand more about the mechanisms of hearing and deafness?

The deaf mutants that came out of the ENU mutagenesis programmes allowed us to identify a number of genes that, when mutated, could cause hearing impairment. Characterising these mutants taught us many lessons. First, many of the genes that we found had never been linked to deafness before. That told us that there are many different genes that can cause deafness. Second, there is a wide variety of mechanisms that can cause hearing impairment. Interestingly, I've never found a mutant in which the degeneration of the sensory hair cells is the cause of hearing impairment. Rather, it's always the case that there is something wrong either with the hair cells or some other part of the auditory apparatus to cause the hearing impairment and ultimately this leads to the degeneration of the hair cells as a secondary feature. So, the hair cell degeneration is an epiphenomenon, really.

And how similar is the auditory apparatus in mice and humans? Can your discoveries in mouse genetics be easily translated?

The mouse ear is very similar to the human ear inside. It's smaller, the length of the cochlear duct is a bit shorter and the mouse can detect signals of higher frequency than humans can – but those are small differences. Generally, the features that are key to hearing and deafness (how the sensory hair cells work, how the cochlear duct works etc.) are virtually identical in the human and the mouse. Although other vertebrates such as zebrafish are useful, there are two features in mammals that are key to normal hearing. One is the stria vascularis, on the lateral wall of the cochlear duct, which generates a high resting potential in the fluid bathing the tops of the sensory hair cells (the 'battery' of the cochlea). A second feature is a specialised hair cell called the outer hair cell, which is like a little amplifier of sound. These cells can change their shape and boost the vibration delivered to the inner hair cells – the primary sensory cells in the ear. If you look at the pathology of human deafness, the function of the stria vascularis and the outer hair cells are two of the key things that can go wrong. So, we really must study deafness in a mammalian model.

What is the research question that you are most interested in working on at the moment?

The area I'd really like to focus on in the next few years is understanding more about progressive hearing loss, because it is such an important problem clinically and in society as a whole. With each decade of life, the proportion of people with hearing impairment increases, and most people have some degree of hearing impairment by their 60s or 70s. So, although childhood deafness is important, age-related progressive hearing impairment affects a much larger population. However, it's a difficult problem to address. The tools that we have used with great success to study early developmental defects causing deafness are not necessarily going to give us the answers to questions about progressive hearing loss. For example, there is some evidence of problems with the synaptic connections between the inner hair cells and the nerve endings that they connect with in progressive hearing loss. So, I think that electron microscopy is going to be a very important tool, as it will allow us to visualise the details of those synapses at high resolution. Electron microscopy is very unfashionable these days, but I think it has a lot to tell us. I'm a very visual person – I like to see things with my own eyes.

Can you tell us a bit more about the mouse mutagenesis programme that you established when you joined the Sanger Institute in 2003?

Before I came to the Sanger Institute, I had been working on mutants from ENU mutagenesis programmes, which were a very rich resource for finding mutations causing all sorts of different phenotypes. But one of the problems with that type of screen is that when you find an interesting phenotype you need to go on to identify the gene involved by positional cloning, which was a lot more

complicated in those days than it is today. When I moved to the Sanger Institute, Bill Skarnes and Allan Bradley were setting up a new project to generate a resource of targeted ES [embryonic stem] cells covering all the genes in the mouse genome, which is a fantastic resource – they're now half way to getting all genes targeted. One of the reasons I came here was to set up the mouse genetics project, which aims to use those ES cells to generate around 200 new mouse mutant lines every year and to screen them for lots of different phenotypes, including signs of disease. One of the most important things about the project is that these mouse mutants are available to other people so that they can study them in more detail and add value to those mutants. The basic philosophy was that we'd have a high-throughput system to get through a reasonably large number of genes each year, and that we would do phenotypic screening. The screening is more of a triaging process, rather than a complete characterisation, as complete characterisation involves a huge investment in generating a large number of animals, a large number of tests and so on. What we really wanted to do was to get as many genes assessed as possible, so we had to aim for a balance. Our aim was to identify robust phenotypes of large effect size, rather than to analyse large numbers of animals to find phenotypes of small effect size. We felt that this approach would give us the biggest impact on the progress of medical research.

The mouse genetics project is just one way of interrogating what genes are doing. It's interrogating them in a simplistic way: the project aims to knock out each mouse gene, creating a null line, which differs from many humans affected by diseases, who often will carry a hypomorphic mutant allele rather than a null allele. But knockout mice can tell us a lot about what each gene is essential for, as well as which genes are nonessential. For example, the fact that a gene is highly expressed in a given tissue is often thought to indicate a vital role for that gene. But in some cases, knocking out that highly expressed gene has no effect. One of the things that the mouse genetics project will do is to rule those hypotheses out – we won't have the same bias as the literature, where knockouts lacking a phenotype are under-represented. The literature also focuses on relatively small sets of genes, in many cases those that are relevant to human disease. There are many other genes that haven't been studied well at all. The mouse genetics project looks at genes that nobody has studied and assesses their functions. We are finding a lot of new information that wouldn't find its way into the literature by other means, and this will really open people's eyes to genes that haven't yet been studied.

Another advantage of the project is that a large number of mutants are studied in exactly the same way – in the same environment, by the same people. So, comparing two different mutants is much easier than comparing two papers produced by different labs where people have asked different questions. In the case of deafness, we know that there will probably be hundreds of genes involved, and having a mutation in every one of those genes is a very powerful way of understanding how the whole system works together as a network.

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I know that you are a supporter of Open Access and exchange of resources. What encouraged you to adopt these views?
I'm a passionate believer in making resources available to others. When I started working on deaf mutants, people that had had mouse lines in their laboratories for many years were very happy to send them to me with no strings attached. I've always been impressed by people that do that, because if you don't have the materials you need – the deaf mouse mutants in my case – you really can't do your work. Access to resources is critical for making progress. So, based on those early experiences I have always thought that anyone else should be able to have access to what I have access to. Open Access as a principle to published studies is a part of that. I've always been very happy to provide mouse mutants to other people – including my competitors. And I'm always very flattered when someone else wants to follow up a finding that I've published and contacts me to ask for mice or reagents. As I mentioned earlier, that was one of the very important factors in considering how we were going to run the mouse genetics programme when I came to the Sanger Institute. I would not have set that programme up without there being a clear understanding that we would make the mutants available to anyone that wanted access to them.

Have you ever felt at a disadvantage as a woman in your field? Do you have advice for other women that feel this way?
I think it's difficult to generalise. More important than being male or female, I think, is the variety of different personalities of people working in science. I do recognise that it can be difficult to get your voice heard, especially if it's a female voice, even though you might be saying exactly the same thing as the man standing next to you. But my approach has always been to ignore it, because I think people can get really hung up on this issue, and it isn't productive to focus unduly on the things that you believe are stopping you from making progress. Usually, what prevents you from making progress is something inside yourself – it's not discrimination from outside. I think that if a person can recognise that then they are much more likely to move forward.

Excerpts from this interview can be heard in the podcast associated with DMM Vol. 4, Issue 6 at http://www.biologists.com/DMM/podcasts/index.html. DMM greatly appreciates Karen Steel's willingness to share her unique thoughts and experiences. She was interviewed by Sarah Allan, Scientific Editor for DMM. This piece has been edited and condensed with approval from the interviewee.