Uncovering RNA-mediated mechanisms of age-related disease

Lorna Harries earned her PhD from University College London in 1994 and has since worked at several institutions. Following her award of an RCUK fellowship in 2006, she became Professor of Molecular Genetics at the College of Medicine and Health.

Lorna Harries, PhD
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Dr. Harries has developed an interest in gene regulation and alternative messenger RNA processing in endocrine disease and human aging. She now heads the RNA-Mediated Mechanisms of Disease group at the University of Exeter Medical School. She has written over 90 peer-reviewed articles and was awarded the Diabetes UK RD Lawrence Prize Lectureship in 2011.

Thermo Fisher Scientific: Tell us about your research.

Lorna Harries: I'm interested in the nuts and bolts of life. Aging is a big and increasing problem in our society. It underpins most of the common chronic diseases that we're subject to in our society today. Type 2 diabetes is one of those. Diabetes is largely influenced by the environment as well, but age is actually one of the major risk factors. I'm interested in how and why we age, and why it is that the mere number of times you've been around the sun influences your chances of getting diseases like diabetes.

Thermo Fisher: Why RNA biology in particular?

Lorna Harries: I'm fascinated by complexity. I was always the kid who, on the playground, wanted to know how things worked and why they were a certain way. When I started my career in genetics a long time ago, RNA was seen simply as a messenger molecule that was an intermediate between DNA (the interesting stuff) and protein (the other interesting stuff). Of course, we now know that that's not, strictly speaking, true. RNA certainly does act as an intermediate, but it does so much more than that.

People used to describe the bits of the genome that don't make protein as junk, and that makes me very sad because a lot of the dark matter of the genome, which is RNA that is expressed but doesn't make protein, has a fundamental effect on the biological functions of our cells. It goes and it regulates other things. I love the fact that we haven't even begun to scratch the surface of understanding how RNA actually works. We're never going to be finished; there are always going to be interesting questions to answer. So, that's why RNA.

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Thermo Fisher: What are your research goals?

Lorna Harries: I'll concentrate on the aging project because I think that's probably the one where we've got the most traction at the moment. My goals are to understand the mechanisms behind how and why we age, and to use this information to make a new generation of antidegenerative drugs. It used to be thought that each individual age-related disease had its own unique trajectory, causes, and etiologies, and you'd only ever be able to address one at a time. We now know that actually, most of these diseases have common roots, common causes, and common mechanisms. They arise from the failure of a few very basic health maintenance mechanisms, which, as you get older, become less and less efficient at their jobs. By targeting those, we might be able to target multiple diseases of aging at once. And over the last few years, my group has identified that some of the processes around the expression of your genes—and more particularly around how those are regulated and which forms of the gene are expressed—are absolutely critical to healthy aging. We're targeting those to be able to get a handle, first of all, on how it works, but secondly, on where we can intervene to produce a new generation of drugs that will target the diseases of aging. And they won't just be a quick fix to deal with the symptoms—they will be an intervention that will deal directly with the causes.

Thermo Fisher: What are some of your challenges and accomplishments?

Lorna Harries: Well, there are a lot of challenges, but a major one is people are very different. They're heterogeneous as a population. There are people who live into their 90s and their 100s with no problems, and there are other people who don't make it to 70. The fact is that when you're looking at RNA biology, RNA and gene expression are incredibly labile—influenced by everything around them. One of the challenges is being able to distinguish the signal from the noise. It's being able to dissect what it is about the disease in particular that's causing the changes in gene expression, and how you differentiate that from the effects of diet, environment, etc.

As for an accomplishment: On the cellular level, we've managed to identify pathways and interventions that we can tweak, which will allow us to effectively turn back the clock on aging. I think that's a fairly major leap forward; it's going to form the basis for the work that we do going forward. My hope is that we'll end up in the clinic with some new treatments for age-related diseases.

Thermo Fisher: What is the current state of aging research?

Lorna Harries: I think we're at a really, really exciting time for aging research. Historically, people have viewed aging as something that happens that you can do nothing about. It happens to the best of us, and we just have to accept it. But I think that view is changing. Over the past decade, we've begun to realize that aging is not a given, or an immutable thing that you can't influence.

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We can influence it using our knowledge of a phenomenon called cellular senescence—how your cells age. The accumulation of old cells in your tissues is one of the reasons your tissues age. We're starting to realize now that by targeting those senescent cells, we're able to influence how bodies age and protect against diseases and, in animal models, cure those diseases. RNA biology is a really fundamental pivot point for senescence. By influencing the output of your genes, we've been able to reverse senescence in cells. So, it's an incredibly exciting time for aging research. There's an awful lot going on, and I think the future's bright.

Thermo Fisher: How does Thermo Fisher Scientific fit into your workflow?

Lorna Harries: We've been using products by Thermo Fisher for decades. We have a molecular epidemiology approach to disease and to research; at the population level, we might be using products like the Applied Biosystems™ QuantStudio™ 12K Flex system to do high-throughput measures of gene expression. In cell systems, we're using a lot of your individual assays [Applied Biosystems™ TaqMan® Assays] and siRNA products. The ability to switch off a particular gene in a particular place is really valuable to us, as is the ability to look at the potential biomarkers.

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We use your high-throughput systems for the assessment of candidate genes, but increasingly we're moving away from a conventional next-generation sequencing approach to whole-transcriptome work. We're using your Applied Biosystems™ Clariom™ D Pico Assay now.

Thermo Fisher: How did you decide on the best platform to use to uncover your insights?

Lorna Harries: Reliability. The money we're using is hard won, so if I'm going to spend the money, I don't want to spend it on something that will take years to optimize. Using products from Thermo Fisher means my group can get results more quickly; we can publish sooner, which leads to more grant funding. I'm looking for simple systems that have been beautifully optimized, are going to work well, and that we can use right out of the box. That's why we use you.

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Thermo Fisher: What do you look for in a solutions provider?

Lorna Harries: I would say the availability of streamlined, efficient, optimized systems. I also look for a bit of creativity. One thing I will say about Thermo Fisher is that you are always pushing your boundaries; you're always looking to the future and what's next. I'm a really eager early adopter of new technologies, so when Clariom D Pico Assays became available, for example, I was really excited to try them. I like new things. I also really like the fact that your company actually pushes the envelope out a little bit, and you're always looking for new and improved ways of doing things.

Thermo Fisher: Tell us about the future directions of your projects.

Lorna Harries: I'm looking to translate my research to the clinic. My group has a real bench-to-bedside ethos. I think we're in a position now where we can accelerate some of these discoveries to market, and take them forward so that we can think about how we might better utilize them in the clinic. We're looking at, from our perspective, stretching that envelope in what we know. But we're also looking at harnessing the things that we've discovered and the great things that the group has done over the last 10 years, and how we might exploit them so people can actually say that these things are available to people in the clinic and to the clinicians and to doctors to help people.

Thermo Fisher: When did you know that you would be interested in a career in science?

Lorna Harries: That's an interesting question; I took a pretty unconventional route to get to where I am now. I've always been interested in science. I did my degree in genetics because I was really excited about the new and expanding area. Then I started a postdoc, and then I had my family, which changed my perspective a little bit. I didn't want to be one of those moms who is never home. So, I actually left the subject completely. I was out of the field for nearly five and a half years to do something that's completely unrelated, but was more amenable to family life.

When my youngest was 2 years old, I started to climb the walls quietly at home and needed something that was going to stimulate my mind a bit. So I looked to get back into science. And I found, actually, that that was a really, really difficult thing to do because things move so quickly in this field. Techniques that were state of the art when I left were now completely routine, and new techniques, which people hadn't even dreamt of, had come about during my time off. I had to go back in at the technician level. Because I'm an ambitious person and very driven, I worked my way back up to where I am now. But it's always been something that I've been really interested in.

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Thermo Fisher: Are there any personality characteristics that our younger generation might possess that would indicate an interest or aptitude for a career in science?

Lorna Harries: I think I can answer that in three words: **Curiosity** is really important. You need curiosity to lead you to ask the questions. **Resilience**, because it's a hard world. Research funding is hard won. You often hear: "No, we won't fund you. No, we won't publish your paper." You've got to be the sort of person that is not going to be fazed by that. You've got to be able to pick yourself up, dust yourself off, and get back on the horse. The third is **enthusiasm**. You should love what you do. Scientists today are salespeople as much as we are researchers—you've got to be able to get other people to buy into your ideas.

Thermo Fisher: Tell us about your role models and/or mentors during your career. Did you have any female role models, specifically? And how did they impact your career choices?

Lorna Harries: Absolutely. As you'll probably gather from my rather unconventional career trajectory, I'm really passionate about getting more women into science; showing them that, actually, they can have a family and a life outside of work and still succeed at science. And I think good mentoring is really, really key to that. I've had some amazing female mentors. Also, there are people here at my university who, frankly, took a chance on me when I appeared on their doorstep and had been out of science for years. I said, "I'm really interested in working with you," and they took a chance and employed me. And I've had just really amazing support. Being a woman in science is still challenging; there is still a glass ceiling. My first postdoctoral advisor who runs our diagnostics laboratory has been amazing. She's been there to say, "Go for it," and also to say, "Let's think about this and make sure you're ready." She's always been there to listen to my crazy ideas, and I have a lot of crazy ideas! A few of them are really, really good, and a few of them are really not so good. I've learned everything that I know about how to manage a research team from how I was managed as a researcher. I try to do the same with my own team.

Thermo Fisher: And finally, what advice would you give to a young woman considering a major in science or medicine?

Lorna Harries: Just do it. I'm very involved in public outreach and public engagement and, particularly, in getting more young women into science. Don't be put off by the fact that it appears to be a very male-dominated area. It kind of still is, but the more of us that actually get in there and make a noise and make ourselves known, the easier it will be for the generations coming behind us.

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