Immunology and innovation

Peter Doherty's life in science

In 1996, over two decades after their discovery of how killer T cells recognise virus-infected cells, Peter Doherty and Rolf M Zinkernagel were awarded a Nobel Prize for their contribution to the field of immunology. Now Doherty, the author of eight books on topics as wide-ranging as tennis and chickens, is still a force to be reckoned with, as well as a voice of reason in the ever-changing world of science.

Peter C Doherty

Professor Peter Doherty has certainly had an impressive and illustrious career as an immunologist. In 1996, he and his colleague Rolf M Zinkernagel were awarded a Nobel Prize for their work on how the immune system recognises virus-infected cells. In 1997, he was named Australian of the Year. Now an indomitable octogenarian, Doherty looks back at his career and reflects on how science has changed in his lifetime.

In this illuminating interview with *Research Features*, we discuss Doherty's remarkable journey, today's global challenges, and ask what advice he'd give young and upcoming scientists.

How did you become interested in science in your early life?

I was the first generation in my family to go to university and I was pretty naïve. I was broadly interested in the medical sciences but didn't want to be a doctor because I thought that all doctors did was sit around in rooms and listen to people talk about their health. I decided I was going to be a vet and save the world by increasing food production. I was 16 years old, and this was back in 1956: a very different world.

At that time, there was great optimism about science, and we thought we could solve a lot of problems (which of course we've done). We'd come out of World War II, there'd been enormous advances in that time. Penicillin came out of that period, as well as a lot of new technologies. There was a general sense after the War that we were all in this boat together and that we needed to work together to improve civil society and ensure opportunity for all. There was more of a collectivist view. That's different today. In the world of Donald Trump for example, there's been a considerable reaction against science. Some of us don't realise that science has transformed our lives. We get on a plane to fly across the planet, or use our iPhone to talk to anybody anywhere, but don't link that to a culture based on curiosity and discovery. That failure to 'connect the dots' has led to an erosion of respect for rational enquiry, reason and truth.

How has science changed in its ability to address global challenges?

If we look at an issue like climate change, given the limitations of what people across the planet can do collectively and can agree to do, we're not really pulling back greenhouse gas emissions yet. We all realise the problem, but at the COP meeting last year it was the first time that global leaders have actually acknowledged that fossil fuels are involved. Part of the solution is convincing people to change and providing people with alternatives. Science, technology, rational inquiry, and acting on that, has never been more important.

> **Technological change has happened with such rapidity that I think people have become very disoriented.**

There's a crucial difference between old and new science, though. The science that served people up until now has always improved economic wellbeing and people's lives, providing more entertainment or better medicine for example. All of that has been positive change. But what we're asking people to do now is to change the way they live and what they value, and what we're forced to value in our capitalist economy is massive consumption. We're being asked to sacrifice. We're being asked not to drive around in a four-litre car. We're being asked to turn down the central heating. Lifestyle changes like this don't always translate very well to large numbers of people.

In addition, technological change has happened with such rapidity that I think people have become very disoriented. They blame, for instance, the political process in the USA for the change in the nature of work and the change in the nature of employment. But it's not politicians who brought in online marketing or who transformed the landscape from family farms to mega farms. It's not the politicians who've destroyed high streets in country towns; it's people's own actions seeking cheaper and more convenient goods.

You were recognised with the Nobel Prize for Physiology or Medicine in 1996 for your work in immunology. How did your journey in science progress to winning prestigious awards?

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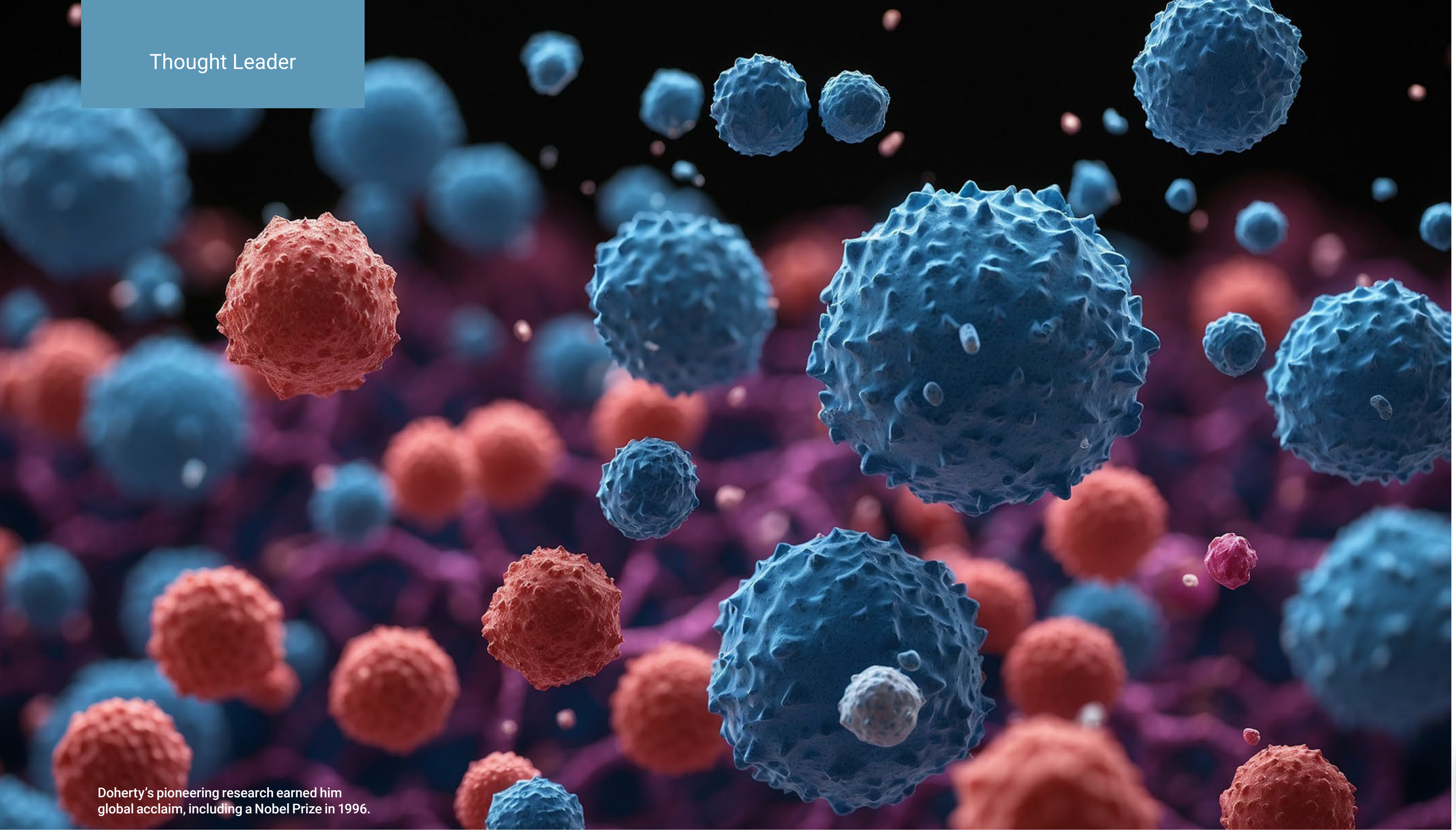
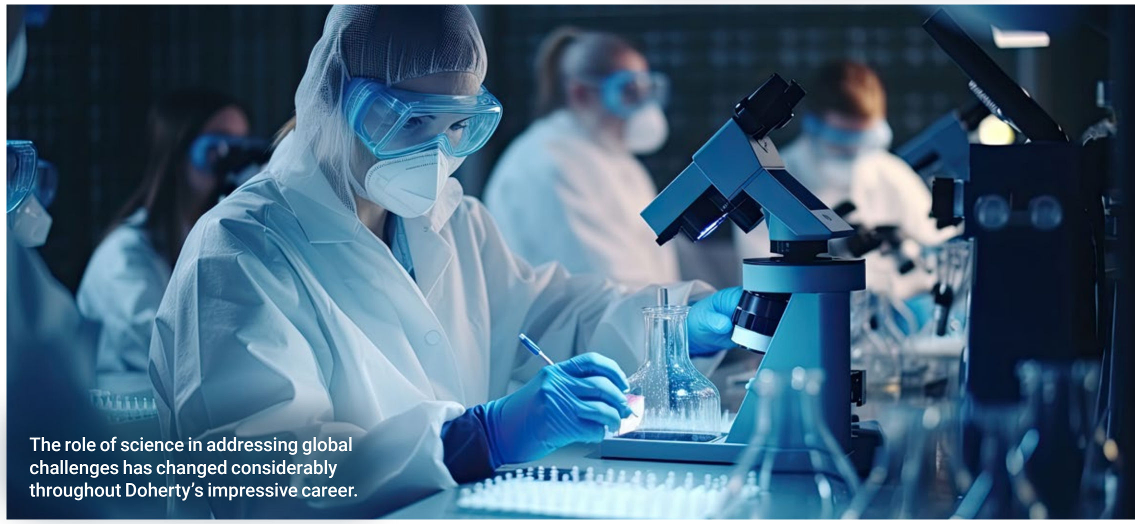


Doherty's pioneering research earned him global acclaim, including a Nobel Prize in 1996.

Learning to embrace uncertainty in the pursuit of original discovery, Doherty encourages young scientists to be patient and curious.



The role of science in addressing global challenges has changed considerably throughout Doherty's impressive career.

We – myself and Professor Rolf M Zinkernagel – made a big discovery back in 1973–74, and the Nobel Prize came 22 years later, which is not an unusual interval. Being an Australian, I didn't expect to win the Nobel Prize though; we're very modest! Where I grew up in Queensland, we used to say 'it's a beautiful day and we've had a great time' but then the sentence would end with, 'but you can't win mate'.

We discovered that very specific, killer T lymphocytes (the CD8+ T cells, a subset of white blood cells) bump-off virus-infected cells after recognising virus-induced changes in our own transplantation molecules. These cell-surface proteins, that form patterns unique to any individual, had long been studied by researchers interested in skin and organ graft (transplant) rejection, but nobody had answered the question: what is the transplant system for? Why do vertebrates like us have a mechanism that, for example, could potentially react against a growing foetus?

We answered that question by showing that transplant rejection is, in reality, a manifestation of immune surveillance of self, an essential mechanism for eliminating dangerous cells to maintain our own bodily integrity. This was a revolution, a 'paradigm shift', which turned the field of cell-mediated immunity on its head. We (and thousands of others) then continued – in our case, for another 40 years with lots of bright young people in laboratories in the USA, Switzerland, and Australia – to define the nature of CD8+ T cell recogniton, immune responses, effector function and protective memory.

What was your approach to collaborative work back then?

Collaboration works at different levels. For instance, early-career scientists join the laboratory because they want to train with you and learn something from you. You've got the benefit of knowing a particular field, but as the principal investigator (PI) someone like me brings in money by writing grant applications, often with help from younger people. It's a two-way street. For people who are leading a substantial programme, there may be ten, 20 or 30 people in the laboratory at any one time, with most of the faces changing regularly. I never worked with more than 12 or so people. The junior scientists are doing the lab work, getting the data together. Part of the job of the PI is to train people to write the work up and get it published, the primary product of any research laboratory.

Something that has become relevant with the complexity of modern biomedical science and the power of molecular technology is the fact that you can't do everything yourself within one group. You need to collaborate with other groups and people. A paper, which may have had two or three authors back in the 1970, now ends up with 20 or 30 contributors. And in actual fact, on that research paper, there's probably no single individual who, though they may understand the principles behind the various types of manipulations that are done, is really informed across the whole thing. It works on trust and there's always a great fear of fake data. This, of course, destroys the person who cheats, but also damages reputation of the person who was running the lab.

What advice would you give to young scientists?

My advice to a young scientist is not to move on with further experiments too quickly; look at the data you've generated, try and understand it, live with it, sleep with it. Love your data, really look at it closely and try to see what it's telling you, because biology, biomedicine particularly, is so complicated. If you put together the complexities of the human immune system, which are massive, then insert the 'added variable' of a novel virus infection, for instance, you end up with extraordinary complexity. Biological systems evolve. Unlike the 'invariant' laws of physics, biology is not 'designed' from first principles, and it builds on what is already there. That leads to unexpected solutions and massive complexity. So the researcher has to be alert to possibilities. Look for the odd result. Look for something that doesn't quite fit. Maybe your thinking will change and maybe, just maybe, you'll discover something new.

My advice to a young scientist? Live with your data, love your data, ask: what is it trying to tell me?

I think a lot of people coming into science don't fully understand that you must expect to get things wrong. In fact, you should hope that your ideas will be a bit 'off' sometimes. Otherwise, you're not going to discover anything! Biologists need to be very careful about getting locked-in to a conceptual framework that's rigid. You need to be prepared to shift. That, of course, is one of the problems that politicians and the general public have with scientists. When the public and politicians listen to us, they want to be told something that they can really grab hold of. But what we tell them is, in effect, 'our best understanding is that...' We can't say, as Donald Trump does when he invariably lies: 'this is the truth'.

You were involved with science communication surrounding COVID-19. Could you tell us about that?

I was going to retire in 2020 at the age of 80, but then COVID-19 came along, right in my field. As a result, I spent another three years intensively involved in science communication around COVID-19 and actually found it quite exhausting. I wrote weekly essays called 'Setting it Straight' which went onto a website, a sort of blog. I was trying to get the message across about the science but eventually I had to stop because there was nothing more I could say. The science wasn't coming out quickly enough. It was too complicated.

I was also on Twitter a lot, which was good as a means of discussion. People were putting up feeds where, you know, a researcher would look into a particular issue with COVID-19, and put up a whole series of posts with links to research data and papers. It was very useful. Despite the unfortunate changes in Twitter which often make it a hostile environment, I still put up posts and if you see them being retweeted 50 or 60 times, then you think, well, someone's getting something out of this.

Is there anything that you're planning on working on in the future?

I intend to keep writing books, even though a blog post is a better way of communicating with young people. I like to write books because my instincts are to look in depth and link ideas and observations that others may not have connected. In that, I'm a total academic. I'm always asking, 'Why are we doing this? What are the underling drivers? What can we do better?'

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A joint venture between The University of Melbourne and The Royal Melbourne Hospital

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