

By Dr Toh Han Chong, Editor

Interview with



Professor Peter Doherty, 1996 Winner of Nobel Prize for Physiology or Medicine

Professor Peter C Doherty is the recipient of the Nobel Prize in Physiology or Medicine in 1996. With a research focus on the immune system, he and Professor Rolf M Zinkernagel, the co-recipient of the Nobel Prize in Physiology or Medicine in 1996, discovered how T cells recognise their target antigens in combination with major histocompatibility complex (MHC) proteins.

Professor Doherty currently spends three months of the year conducting research at St Jude Children's Research Hospital in Memphis, Tennessee, where he is a faculty member at the University of Tennessee Health Science Centre. For the other nine months of the year, he resides at the University of Melbourne, Victoria.

THC: What has life been like since you won the Nobel Prize for Physiology or Medicine in 1996?

PROF DOHERTY: The Nobel Prize puts you in the public arena, and that is very unfamiliar for a basic scientist like me. A medical doctor like you would be used to dealing with the public, but we scientists do not deal with them very much. The year after the Nobel Prize was a very heavy year with a lot of people wanting you to give talks and

so forth – but I expected that. On top of that, I was at the St Jude Children's Research Hospital in Memphis, Tennessee, which has an enormous fundraising corporation, and I did a lot of publicity stuff with the actress Marlo Thomas. She was Jennifer Aniston's mother in *Friends*, and her father, the actor-comedian Danny Thomas founded the hospital. Australia also called me up and made me Australian of the Year in 1997 even though I have been living in Memphis for years!

THC: So everybody wants you after the Nobel Prize!

PROF DOHERTY: Yes, everybody loves you. Also, I was the first person with a veterinary training who won the Nobel Prize. I spent a lot of time, particularly in Australia, talking to broad public audiences, giving talks in city halls. I made a few mistakes, but I learnt, very quickly, about the media and public communication. I tried to convey to the public a sense of why science is important and why we need to do it. Back then, there was a retreat from science and a poorer public image of science in the United States, Europe and Australia. So I was trying to talk very positively about science.

I have been doing that for about 10 years now, which is why I eventually wrote *The Beginner's Guide to Winning the Nobel Prize*. Despite the title, it is a book about science and how it works, where it comes from, how we do it, and what the opportunities are, and also about the history of the development of the science of immunity. There is some biography in it but it was never intended as one. The book was written for a lay audience and the people who have said they enjoyed it a lot are people like high school kids, undergraduates and people who have done science because it is familiar to them. It was not written for a highly intellectual audience but some of it may be a bit difficult, like the story of immunity. The book is meant for everyone, and it is easy to read.

THC: Was there the proverbial phone call in the middle of the night formally informing you that you had won the Nobel Prize?

PROF DOHERTY: You get a phone call, which is about 10 o'clock, Stockholm time in the morning. What happens is that they have (the Nobel Committee) a very long process that goes through months. They look at about 300 candidates and get information on all of them, but they gradually whittle it down, and finally choose who they think are their leading candidates. Then they put that to the full group of professors at the Karolinska Institute. If they approve of the final candidates, they go ahead and call the people, and tell them they have about 15 minutes to call friends and relatives because they are going to officially announce the Prize winners to the public. Once that happens, your telephone goes crazy! It becomes a whole media event for October every year.

THC: Was there a Eureka moment in your Nobel discovery?

PROF DOHERTY: We knew we hit something really big when we saw the results at the first experiment. That was totally unexpected. It was very clear and we had a very good experimental system, and we were able to work it out really fast. What we really built on was the whole transplantation genetics that has been done by George Snell, and we were able to map it straightaway using their recombinant mice.

THC: In a nutshell, how would you explain the significance of the Nobel-winning research?

PROF DOHERTY: At the time we were doing our research, people had just come to the conclusion that there were actually separate T cells. That was still controversial in some minds, but most scientists accepted it. So we had the circulating white blood cells and we knew they had some specificity against foreign entities. Other scientists had taken T cells and injected them into mice, and shown there was some protection against infection. But we had no idea how that worked. So what we discovered was that the T cells circulating in the blood were very potent killer cells. They were not directly specific for the virus. But they are specific for something to do with the virus. We did not fully understand the virus-T cell interaction in a molecular sense, but we did propose the idea of "altered self", where parts of the virus (or foreign protein) was combined with a self protein from the host presenting cell called the major histocompatibility complex (MHC).

We showed that T cells used a T cell receptor that targeted the virus-infected cells and did not directly attack the virus itself. That was enormously important because while the antibody recognises the virus, T cells do not directly interact with the virus; they ignore the virus and go to the virus-infected cells that present parts of the virus in relation to a self-protein MHC on the presenting host cell.

For the first time, we also understood why we had a transplantation system – why we need an immune system that understood how to recognise foreign proteins but not self-proteins, and how T cells are able to achieve this.

THC: Was this landmark work done in Australia?

PROF DOHERTY: It was all done in Canberra at the Australian National University's John Curtin School of Medical Research during 1973 and 1975. We then both went off in different directions. In 1975, Rolf Zinkernagel went to the Scripps Institute in California, and I went

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to Wistar Institute in Philadelphia. We never worked together after that; we were in other communities. So it was about two and a half years of work together.

THC: Going back to your PhD years in Edinburgh, were you not working on the sheep virus?

PROF DOHERTY: I was studying virus infections of the central nervous system of sheep. I was then really working as a paid diagnostic neuropathologist. I had a job and I did my PhD part-time and just wrote up a thesis. I used to see my supervisor once a year and tell him what I had been doing, and he would only say, "That's very interesting."
[Laughs] I graduated from veterinary school when I was just 22, and I have really been running my own research since then, although I have never been trained properly – I am very badly trained and I would not recommend that! I had scientific training as a vet because the veterinary course was designed towards animal reproduction. So we learnt a lot of population genetics, pathology, infectious diseases and control, breeding, and all that.

THC: There is a picture of you as a young boy on the cover of your book. How old were you at the time?

PROF DOHERTY: I think I was 3, maybe 4 years old at most. I was a kind of dreamy kid. And I was easily sunburnt. I was in Brisbane. I tended to read a lot; I was very imaginative. But I also did the things kids do. My dad had a workshop under the house, so I did a lot with tools. I also did a lot of photography when I was younger, but all those photographs were unfortunately lost. I did not really intend to go into science and sort of just fell into it.

THC: There is a fascinating piece of your biography which mentions that boys in the school that you went to could not do biology.

PROF DOHERTY: Well, it was just a beginning of the stage when they were starting to expand. Brisbane, like a lot of Australian cities, had a system of private schools. So we would all put our kids there. But my parents did not have much money and they just about saved enough to send me to public school – that is, a government school. The school I went to was in its first year, so we were the first graduating class. At that stage, I do not think they taught Biology to boys in any of the state high schools – of course, they do now. But at that stage, it was physics and chemistry, which actually, I think is not a bad thing. I think we often start to learn biology too soon, and we get stuck with a lot of details and stuff that can best be understood with the basics of physics and chemistry, and maths.

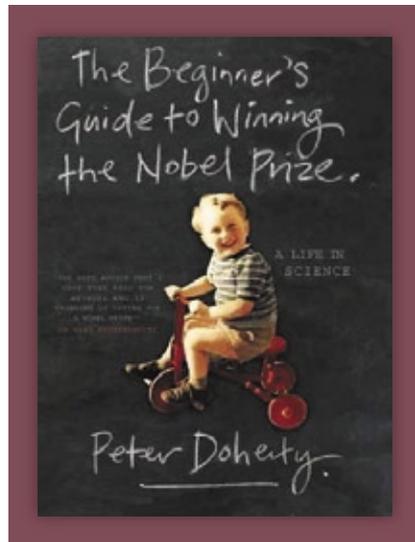
And I think it is important, if you are going to do things like science and medicine, to learn language. And the other thing, which is absolutely essential, is they should learn how to write clearly. If you do not write well, you do not make any sense even in science – unless you employ someone to write for you.

THC: Were you a good student?

PROF DOHERTY: I was not a straight C's student, but I was not a straight A's student either. For many parts of the veterinary course, I just passed the courses and did not do really well at all because I was not really interested in sick cats and dogs.

THC: Were you not an animal lover when you were a young boy?

PROF DOHERTY: No, actually, I killed tons of mice! I mean, I got nothing against animals – I think we have a very complex relationship with animals. That part I found very challenging and very interesting, and I could have gone on working with live animals. It is quite exciting. Well, they can kill you – and horses kill vets all the time; they can kick you to death. They are big, powerful animals, and you are trying to do things to them that they do not want



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done to them, like saw off their arms or cut off their teeth.

THC: So you had no ambition of going on to become a vet?

PROF DOHERTY: Oh, no. When I went into veterinary school, I went in with the idea of doing research on animal disease. I was very altruistic and I had a fairly religious upbringing in the Methodist church. And I very much had the idea that I wanted to do something practical, and I thought I would do what I could to help global food production. I was 16 when I made that decision, and well, you know how naïve you can be when you are 16.

And so I did research in the veterinary field for nine years before I started basic immunology.

THC: So it was at Edinburgh that your interest in immunology began?

PROF DOHERTY: Well, no, not really. I was always aware of immunology because I read a lot of the work of Macfarlane Burnet, the great Australian immunologist. But I was not really doing immunology in Edinburgh. I was working with another guy who was doing the immunology side; and I was doing mainly pathology.

It was only really when I went to Canberra that I started basic immunology. That was at the end of 1971.

THC: What advice would you give to someone who wishes to do a PhD?

PROF DOHERTY: I think if you are doing a PhD, you want to have curiosity. If you are satisfied with the status quo, and you like to be told how things are, do not go into research. Research is for people who ask questions. And to be good at it, you got to be obsessed by that. The other thing you got to be really excited by is finding things out. So it is a good idea that if you are thinking of doing a PhD, to just spend a bit of time in the lab and really find out if you like getting new results. And if you are scared, for instance by the fact that your results do not fit what people say is supposed to happen, well, maybe think about why that is the case. We discover things by finding out things that are not supposed to happen.

THC: In this world of economic bottomlines, there is a shift towards translational research because this is closer to the economic end point. What is your comment on that?

PROF DOHERTY: It is fine as long as you know what you are doing and why you are doing it, and you have a reasonable likelihood that it will work. Unfortunately, with a lot of translational research, people have gone into big translational programmes without having a good scientific base, and you have a disaster – look at the original field of gene therapy. You also need the basic discovery science to get a new aspect on it. So I think you need both. On the one hand, you need to go down the translational research road and try and seek solutions. But one of the problems with translational research is you may do a lot of really bad science just because it is translational. So you really have got to make sure that your scientific base is good because human beings are not mice or monkeys.

THC: A lot of good scientific findings have been through serendipity?

PROF DOHERTY: The discovery stuff has often been serendipitous, and some of it can also go down very logical lines that are likely to lead to positive clinical outcomes, for instance, targeting molecular events in the cancer pathway. A lot of that will be done by drug companies.

I think scientific discovery is enormously important because we still do not understand a lot, especially in immunology.

THC: You are the eighth Nobel Prize winner from Australia. Who are the others?

PROF DOHERTY: You know, I am never sure how many there are. The ones who did their Nobel work in Australia were Macfarlane Burnet, John Eccles, novelist Patrick White, Rolf Zinkernagel, and more recently Barry Marshall with Robin Warren. There is also Howard Florey at Oxford University, and Lawrence Bragg at Cambridge University. Bragg was the youngest at 25 to ever win the Nobel Prize. And then the Australians claimed Aleksandr Mikhaylovich Prokhorov who was born in Australia. His family returned to the Soviet Union when he was 11, in 1923. He won the Nobel for Physics.

THC: Australia is a small and young country. Was it just by accident that there are so many great Australian scientists, or was there a system and culture that encouraged this level of creativity?

PROF DOHERTY: Well, I am not sure if it was more the British culture – the British have done rather well in Nobel Prizes. Australia has two very strong areas in neuroscience and immunology. John Eccles was part of the neuroscience team, and there has not been another neurophysiology-based Nobel Prize but people have certainly been considered. Then there was MacFarlane Burnet and he was a major figure in immunology. You can almost say I am directly in his lineage because he was a virologist and an immunologist. But Burnet was actually much more of a virologist. His contribution was theoretical, but it was a different era – you could think about science and come to conclusions. Now, it is very difficult to do that. It is very complex today.

THC: We always thought that Barry Marshall was the first Nobelist to experiment on himself by swallowing the *Helicobacter pylori* bacterium, but I have heard that you once injected flavivirus into yourself.

PROF DOHERTY: Oh, not on purpose! [Laughs] That was purely an accident. I was injecting these viruses into sheep and the guy who was helping me was in a rush. So we were rushing and one of the sheep bumped my arm and the needle grazed my finger. I thought I was probably okay but I took my temperature every eight hours and had someone bleed me every day to test my blood out. Then my temperature shot up, so I knew I had it. The blood tests demonstrated the viraemia and then the specific antibody response. I did not get very sick but I was a

bit dull for a couple of weeks. My friend Hugh Reid, who was working with me and doing the immunology side, did the plaque assays and blood tests, and this was actually written up in the *Lancet*. The virus has actually caused some very severe infections in humans at about that time. They had a vaccine for a number of years but it was not working, and that was one of the reasons why I was working on it. So there was a lot of concern about it. But for a while, I was very reluctant to work with lymphochoriomeningitis virus (LCMV) because it could be fatal.

THC: And studying the immune response to LCMV was really the crucial experiment for the Nobel Prize.

PROF DOHERTY: Yes, because if we had used any other virus, it would not have worked quite as well. It was just the perfect experimental system. You know, when I started out and came to Canberra, I did not want to work with it but Cedric Mims who was a senior professor there advised me that I should.

THC: What areas of research are you doing in Memphis right now?

PROF DOHERTY: We are doing research on the H5N1 avian influenza virus. And the reason I went to Memphis in the first place is because of Rob Webster, who has been working there on avian influenza for probably 50 years. He is now 75.

THC: Can you tell us more about St Jude Children's Research Hospital? It is a unique hospital and one of the world's stellar children's hospitals, with seemingly endless funding.

PROF DOHERTY: Early on, actor Danny Thomas went into St Jude's and decided that this was a charitable thing that he would do,



Professor Peter Doherty and Professor Rolf Zinkernagel win the Nobel Prize for Physiology or Medicine in 1996.

after he had made a lot of money – he was the person who produced *Gilligan's Island*. And he used his Hollywood contacts. Liz Taylor raised money for the hospital, and Frank Sinatra too, and this has continued over the years. Robin Williams and John Goodman have also helped quite a bit.

The other thing Danny Thomas did – he was a Lebanese Catholic immigrant to the US – was that he organised the Arab-American Christian community towards this altruistic focus. They raised funds for the treatment of children's leukaemia at St Jude, and the progress using aggressive therapy brought the death rate from over 90% down to 50% very fast. Now, it is below 20%. They use this success story of childhood leukaemia treatment as a tremendous publicity machine. They raised US\$350 million a year in the US, from general subscriptions, big stores like Target and philanthropists. St Jude also brings in about US\$80 to US\$100 million in federal grants, and gets cost recovery where people do have medical insurance – but otherwise, it treats the kids without cost. They also bring the kids and the parents there, and they accommodate and feed them. It is probably one of the biggest philanthropic corporations outside one of the major societies like the American Cancer Society.

THC: So research funding is also quite a luxury then for a top scientist who wants to go work at St Jude's.

PROF DOHERTY: Because they have so much money, they are already happy if you raise 50% of your research funds. Whereas if you are at Harvard or Johns Hopkins, you raise 100%.

THC: If you are on a desert island, what are the CDs and books you would bring along?

PROF DOHERTY: I would take classical music: Bach, Mozart, opera. I love opera, Italian, French, any opera.

I would not want to read the books I already know quite well. But I would still bring the great books such as *War and Peace* and the *Bible*. I would like to read more about Buddhism. I have never read the *Koran* – I would like to read that. I think these books of wisdom and history are interesting. I tend to read the fashionable writers. I try to keep up

with the books that people are talking about. I also read a lot of junk books on aeroplanes, murder mysteries and stuff. It depends on the mood I am in. I like books, particularly novels because they give you ideas and a different perspective. I recently finished the autobiography of novelist Patrick White. And I have an autobiography of Aldous Huxley who interests me because he was a writer who used some of the science from his time in his book; and his brother Julian was a famous scientist.

THC: What do you think are some of the progress in science that will change the world in the next five to ten years?

PROF DOHERTY: Well, clearly genomics is having a substantial effect. A lot of things are just getting on the way, for instance, rational drug design and targeted therapies. The problem really has got to be cost; it is an enormous problem. I just spoke recently at the Health Technology Assessment meeting that was held in Australia. They are very good people – they are government people – who are looking at the cost of drugs and how governments are going to handle it.

THC: With the wider usage of such expensive drugs from pharmaceutical companies, will it bring down costs?

PROF DOHERTY: I think we would have to work out something with Big Pharma. A lot of the basic science for drug development is done in the public sector anyway. Also, I really wonder about the enormous cost of licensing of these drugs. We get a mistake with something like Vioxx, and I mean, it was overplayed and it is not a bad drug. We have to convince people that you cannot take these things without some risk. Certainly, we have to educate people a lot better about drugs, to be much more realistic. Of course, this does not really include newspapers who want to sell their papers and want sensational news.

THC: A product that has really made a huge impact in medicine is vaccines.

PROF DOHERTY: There have been some hostility towards vaccines though – people who would not vaccinate their children. There have been problems in Japan, Australia and California. There are people out there who think that if they feed their children the right

food, they do not need vaccines, and nobody was going to tell them what to do with their child! China has a real problem and there are a lot of people not vaccinated. We even had the United States Congress opposing it because the period after you vaccinate hundreds of thousands of children, some of them will coincidentally develop various other conditions, and people would blame the vaccine.

THC: The bird flu pandemic concern is a big issue in Asia. Do you think there is going to be an effective vaccine against bird flu?

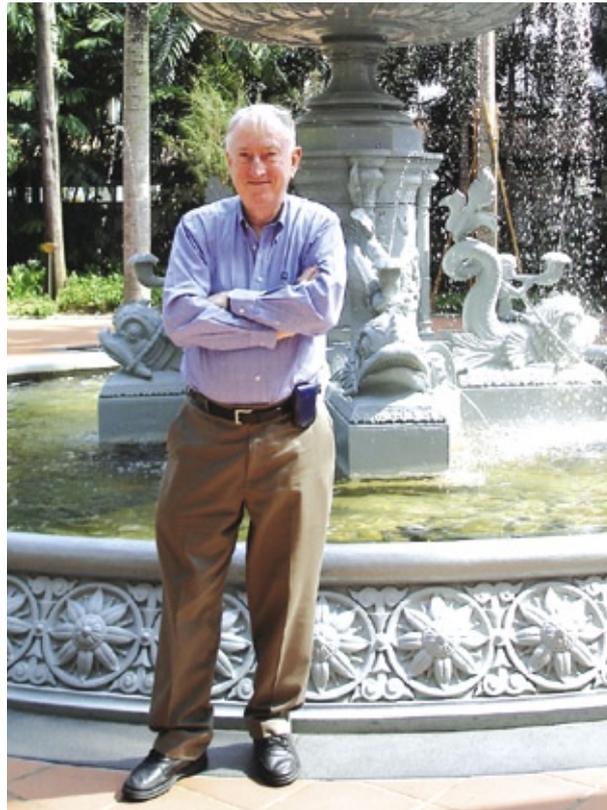
PROF DOHERTY:

There is a vaccine now. It is not a great vaccine but it probably would protect people if it is exactly the right one. The problem is that it is not very immunogenic. Vaccines are being produced and being stockpiled in the US, Australia, and elsewhere.

President Bush just gave US\$1 billion to the vaccine companies to produce vaccines and another US\$1 billion to develop research into vaccines. President Bush has been very proactive on this.

THC: We were hit by SARS a couple of years ago and it was quite a mysterious virus. Any comments on such pandemics coming through Asia?

PROF DOHERTY: We did not know what SARS was initially because it was a completely new virus. The people who worked it out thought initially that it was the H5N1 avian flu virus because we already had a bird flu outbreak in 1997. Eventually, they worked out



Professor Peter Doherty enjoying the Raffles Hotel in Singapore.

within three months – it was really very good science – that this new virus had come from Himalayan civet cats who were being sold as food in live animal markets in southern China. It is now known that the virus came to the civet cats from bats, and then from these civet cats to humans. That has probably been happening over the years because many of the people in the market were found to be antibody-positive to the SARS coronavirus. So what happened back then was that it was

the Chinese New Year period, and people went home and so it spread more quickly. One person took it to Hong Kong and another to Toronto.

Once we understood what the virus was, we also understood it was not like flu. We also understood that it survives well on a surface. And it was because the medical professionals did not understand that initially, that some of them got sick – they did not expect it to be all that infectious.

But once we understood that, we stopped the spread pretty much in its tracks.

THC: There were a few observations from the Singapore experience which were pretty unusual, like the whole concept of “Super-spreader”. There were people who never died but they were “Super-spreaders”, like the Singaporean air stewardess who contracted SARS.

PROF DOHERTY: I do not think we understand the whole “Super-spreader” thing. We really do not know.

THC: Any views about the evolving dynamics between viruses and human beings?

PROF DOHERTY: Since 1979, 30 new infections have come into humans, and one of them is AIDS which comes from chimpanzees. They developed the serology, so they carry the virus but do not get sick.

THC: The question is why, before the 1980s, we did not hear about HIV and AIDS?

PROF DOHERTY: I think it was because it did not get across in humans in a big way. It could be possible that it was coming across in humans occasionally over the years, but then you know, if the whole African village died, who would notice – especially under colonial rule. Then of course, the health authorities and the US government did not get onto it as quickly as they should have. The then US President Ronald Reagan did not even want to know about it. It was politically explosive but a lot of activists acknowledge now that they have made a serious mistake of not being more proactive then and they are now being much more aggressive about it. You need the government to be open about it.

But the HIV infection rates are going up again.

THC: What do you think are some of the features that will make Singapore progressive in R&D?

PROF DOHERTY: The fact that you are really focusing on science education is very impressive. If you read my book for instance, you will find that one high school produced seven Nobel Prize winners: The Bronx High School of Science in New York City. What goes into making that is basically the Jewish immigration culture – they are very focused culturally on education; and a very good school which is teaching science and offering opportunities to the kids to go on to pursue science seriously.

Singapore, from what I understand, is putting those sets of conditions together. They are streaming kids into science. They are picking the very bright ones and giving them very good opportunities. I do not think you can do better than that because if you really want to do well in science, you have to provide the resources, but you really want the bright people –

really bright people. Some of them are going to be very good at passing examinations but they are not going to be all that innovative in science. So you also got to have a mechanism that says: “We love you, you are very bright, but you are not the world’s greatest scientist.”

THC: How do the big American institutes sustain such a high level of successful research and development activity? Is it just getting good people?

PROF DOHERTY: Very good people and from all over the world. And very generous funding. The National Institutes of Health (NIH) offers competitive grants. The standard NIH grant does not ask for the tangible outcome. All it asks are: Is it good science? Can the person do it? Is it worth asking those questions?

THC: Perhaps you could share something interesting about yourself not very many people know about?

PROF DOHERTY: There is nothing interesting about me. [*Laughs*] Well, I guess I have had a lot of fun doing science and that is a pretty demanding activity. None of my children have gone into science as such – my neurology son writes clinical papers; he does clinical research and sees patients and is based in Seattle. The other is a lawyer.

Like a lot of scientists, I am still a bit of an outsider. Because of the way we are trained, we always look at everything from the point of view of “What is the evidence?” Of course that is not the way politicians think. The ‘evidence’ they look at is the evidence of the latest opinion polls. But I think most people do not look at world in a very evidence-based way.

THC: Any hobbies outside work?

PROF DOHERTY: In Australia, I used to play a lot of squash. But coming to US, it has been racquet ball. I enjoy playing sports but I am not really interested in watching it. I get very bored very quickly. So I rather read a book or even watch a mystery movie. A good movie which I have seen recently is *The Constant Gardener*.

THC: Thank you for giving us a good interview. ■