Background information

To put the Nobel prize-winning research into the context of the immune system, it may help you to read this.

Most of us have suffered from the effects of viruses—the itchy sores of chicken pox, the aches of influenza or the drippy nose from a common cold. But what are viruses and why do they make us sick?

What is a virus?

Viruses are submicroscopic particles composed of nucleic acid and protein. In contrast to other organisms, viruses can only multiply inside living cells.

Viruses cause diseases

The nucleic acid of a virus re-programs its host cell to produce viruses—and lots of them. The cell becomes a virus factory. The newly produced viruses infect other cells and then, if we are the host organism, we feel sick.

Getting better

When we are sick with a viral disease, our immune system works to eliminate viruses from our body. To do this, a virus-infected cell must be identified and killed before it can release a deadly cargo of new viruses. A type of white blood cell called a killer (or cytotoxic) T-cell does this.

Killer T-cells recognise virus-infected cells

A killer T-cell is a lethal weapon so it is important that it only kills infected cells and not normal healthy cells. Fortunately for the immune system, cells constantly break down proteins, including viral proteins. These viral antigens are then transported to the cell surface where they are accessible to the immune system.

The interview

Shortly after the announcement of the 1996 Nobel prize winners, the Australian Academy of Science (AAS) spoke to Peter Doherty about his early life, the process of scientific research and the nature of the prize-wining research. The full text of this interview can be found on the World Wide Web at http://www.science.org.au/educatio/doherty.htm. This extract covers the prize-winning research.

AAS: So what exactly was the discovery that you and Rolf Zinkernagel made back in 1973–4 and how did you go about it?

PD: Well, of course, you don't set out to make a discovery. What you are doing is checking a hypothesis—strictly speaking, you try to falsify a hypothesis. In our case, there was a certain amount of serendipity involved. We started out looking at ways of assaying [measuring the activity of] killer T-cells. We wanted to know how T-cells recognise and respond to viruses in mice. Bob Blanden at the School was then working on the cytotoxic T-cell response to the ectromelia virus in mice. Rolf Zinkernagel worked with him, learning several techniques, including T-cell assays. As Bob's lab got a bit crowded, Rolf moved into my lab. Rolf loved to sing grand opera, and I was the only guy with sufficient musical taste to have him in the lab!

AAS: And then?

PD: Well, sure enough, we found killer T-cells in mice infected with a lymphocytic choriomeningitis virus (LCMV). (See Diagram 1.)

And, in the lab, we could get these T-cells to kill the virus-infected cells. But then we connected this work up with the system of transplantation antigens—something which hadn't really been done before.

AAS: In what way?

PD: Other people had suggested that there was some kind of relationship between the immune response genes, which map in the region of the major histocompatibility [transplantation] antigens and the susceptibility of mice to LCMV. Certain mouse strains, carrying particular histocompatibility antigens, were more susceptible to the virus, others less so. We did experiments to see whether the activity of the killer T-cells correlated in any way with the type of major histocompatibility antigens (MHC) in the mouse from which the T-cells came.

Diagram 1 The different coloured spikes on the virus-infected cell represent different types of MHC antigens. The killer T-cell is covered with a single type of receptor.

AAS: And did it?

PD: Well, yes, but not as we had supposed. It turned out, quite unexpectedly, that killer T-cells from one mouse were not active against virus-infected cells from another mouse—which of course, would have a different class of MHC antigens. In other words, the MHC antigens were certainly having an effect. In fact, the killer T-cells were not doing any killing of virus-infected cells unless the infected cells were showing the 'right' MHC antigens that the killer T-cells expected. (See Diagram 2.)

AAS: So the thing that decides whether or not a virus-infected cell is eliminated by these T-cells is not only the fact of having virus antigens on the outside, but also the possession of the 'correct' variant of the MHC antigens?

PD: Exactly. The MHC antigens have to be of the same sort as the individual that the T-cells come from. This means that what the killer T-cells are recognising is two things—viral antigens and MHC antigens. Viral antigen by itself is 'invisible' unless it is there with the MHC antigens; and it can't be with any old MHC antigens, it has to be with the MHC type of that individual (or inbred strain of mouse in the case of our work). (See Diagram 3.)

And incidentally all this work was only possible because the inbred mouse strains with different but consistent MHC types already existed.

The significance of the discovery

AAS: After grappling with immunology enough to appreciate your discovery in simple form, people may now cry 'so what—what's the big deal?' So can you tell us the significance of all this?

PD: I'll try....The fact that cytotoxic T-lymphocytes—the killer T-cells—cannot usually recognise foreign antigens unless these antigens are paired with MHC antigens is pretty fundamental.

AAS: That's what you called MHC restriction, isn't it? It's in every textbook now...

PD: It shows us that the immune system can recognise a third state—altered self—as well as self and non-self. When a virus has infected a cell and the cell is displaying viral antigens in addition to its own, it has become altered self. That's what's recognised and dealt with, rather than the viral antigens *per se*. The point is that the body treats altered self in much the same way as non-self. A virally modified cell is destroyed in the same way that a transplanted cell from another individual would be. (See Diagram 4.)

Diagram 2 A viral antigen is transported to the surface of a cell and presented to a killer T-cell by an MHC antigen. The shape of the viral-MHC antigen complex is recognised by a T-cell receptor.

Glossary

altered self. This term describes an MHC antigen whose shape has been changed by complexing with a viral antigen. (Also **self**, those molecules and cells that are produced within an individual; and **non-self**, those molecules and cells that are produced outside an individual.)

antibodies. Proteins produced by specialised white blood cells in response to antigens. An antibody will then react specifically with the antigen that induced its formation and will inactivate or destroy the antigen.

antigen. A compound, usually a protein or peptide, that can be recognised by the immune system thereby triggering an immune response.

ectromelia virus. A natural pathogen of mice. Causes a disease called mouse pox.

HLA (human leucocyte antigens). These are human MHC antigens. They are characteristic of an individual and stimulate rejection of tissue transplants. Also called transplantation antigens.

immune system. The tissues, cells and molecules that are part of the host defence against infection.

killer (cytotoxic) T-cell. Specialised white blood cells that are important in the vertebrate body's defence against viruses. They are called killer or cytotoxic because they can kill cells and T because they mature in the thymus.

lymphocyte. A type of white blood cell that has a role in the immune response.

lymphocytic choriomeningitis virus (LCMV). Causes a viral infection in mice in which the symptoms and disease are largely caused by the immune response.

major histocompatibility complex (MHC). Proteins recognised by T-cells in the immune response. Class I MHC molecules are involved in T-cell interactions and graft or organ transplant rejections.

nucleic acid. The genetic material of organisms is nucleic acid. There are two forms of nucleic acid—DNA and RNA.

protein. A macromolecule built of amino acid subunits held together by peptide bonds.

virus. A particle composed of nucleic acid surrounded by a protein coat. Viruses can only reproduce within a living cell.

white blood cell. A colourless blood cell involved in helping protect the body against toxins, and viral and bacterial infections. White blood cells are also called leucocytes.

AAS: And what does that tell us?

PD: It gives us a biological role for the MHC system. People were wondering why the body should have a system for combating transplanted tissue when this state clearly never arises in nature. We suggested that the recognition of alloantigens—MHC antigens differing from your own—was there not to frustrate transplant surgeons but to help the body 'see' altered self.

AAS: But wouldn't it be easier just to see the viral antigen on an infected cell, rather than recognise the viral antigen in combination with the MHC antigens as an altered self?

PD: But altered self recognition allows the body to conduct surveillance on its own cells. A cell's antigens can be changed not just in virus infections but in certain cancers, for instance.
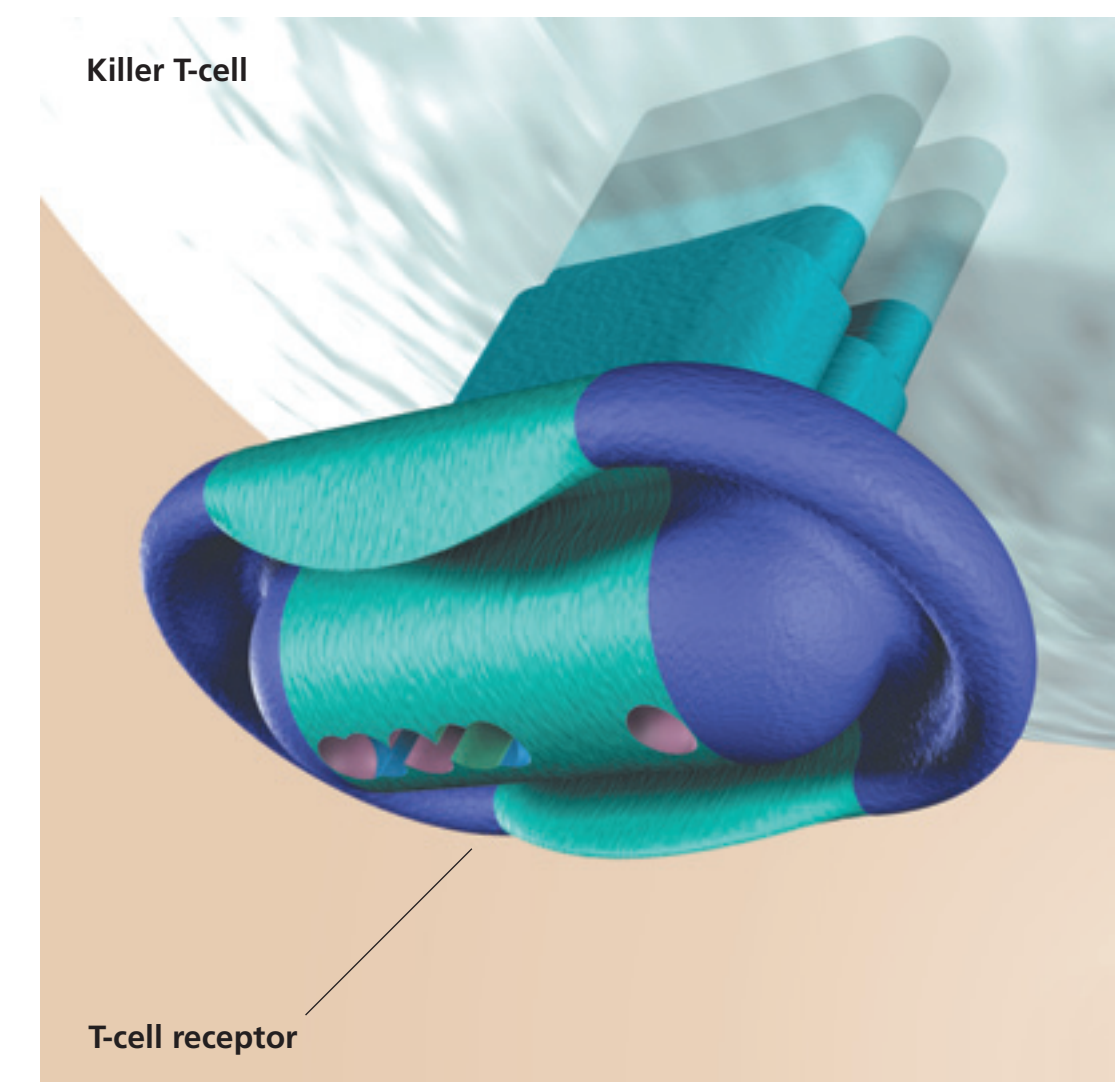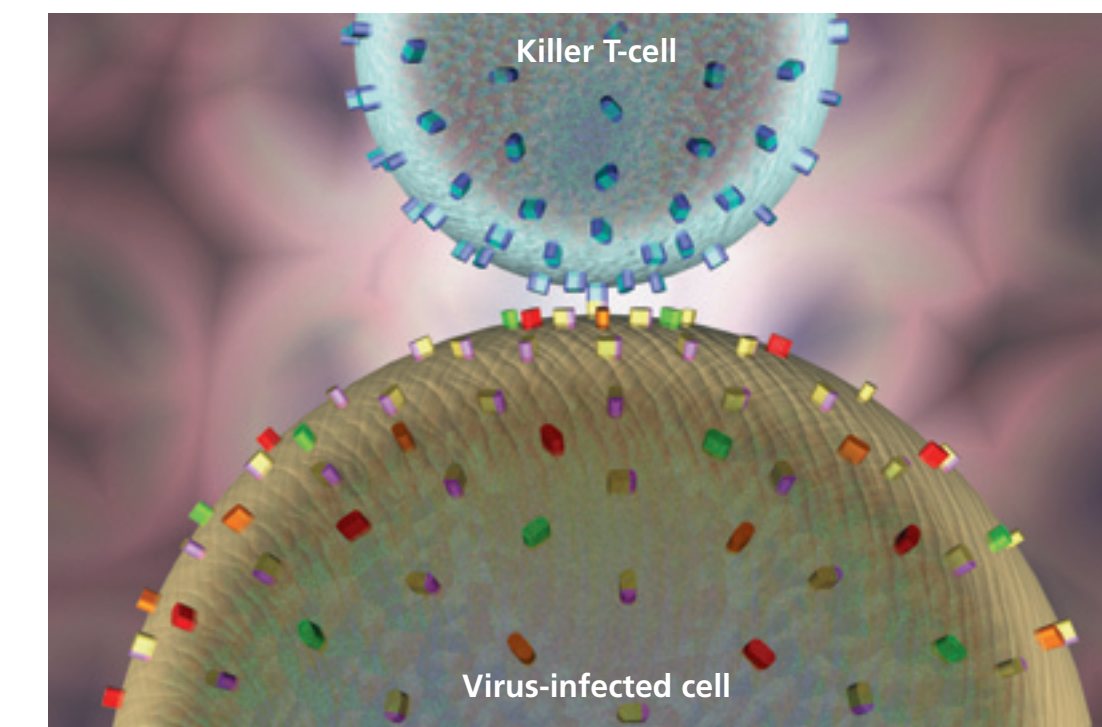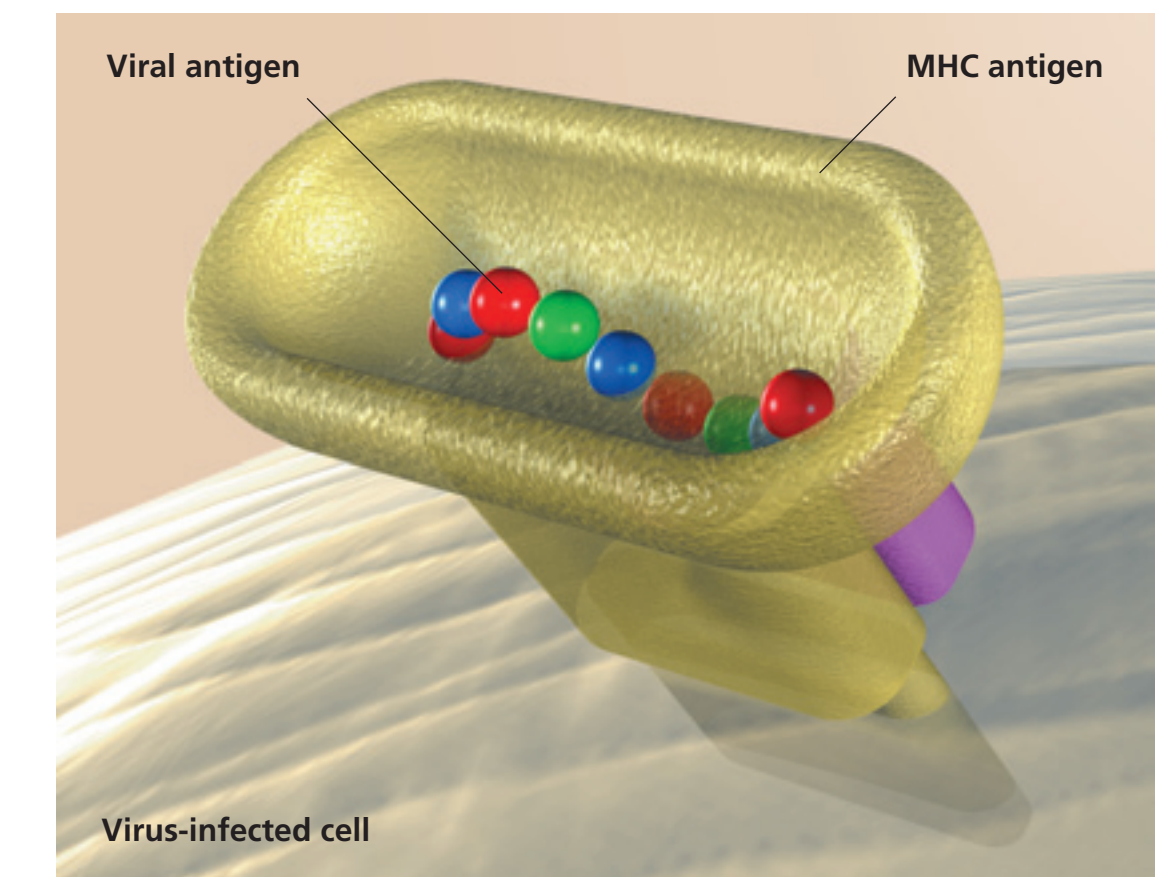

Killer T-cell

T-cell receptor

Diagram 3 The surface of a killer T-cell has numerous receptors which are unique to a particular individual. The shape of a correct T-cell receptor can lock into a matching viral-MHC antigen complex.

AAS: And such cells could be destroyed before they spread and threaten the whole organism?

PD: If all is working well, yes.

AAS: So you found a biological role for the MHC antigens....

In fact, Doherty and Zinkernagel had opened up a whole new highway that led to major advances of great significance to clinical medicine. Many common and severe diseases depend on the function of the cellular immune system and thus on the mechanisms for specific recognition.

Viral disease is only one part of the story; various long-term inflammatory illnesses such as rheumatism, rheumatoid arthritis, multiple sclerosis and even diabetes involve damage caused by the cellular immune system, probably as a result of altered self.

Certain forms of cancer, where the body's cells escape the controls on their multiplication, are also a form of altered self.

And we are now in a position to explain better the associations between tissue types (ie, HLA) and susceptibility to various diseases. Knowing a person's HLA-type it is possible to give a statistical likelihood of their developing certain diseases, based on the observed correlations between HLA-type and disease. Why particular tissue types are associated with a greater propensity towards certain conditions is under investigation.

Diagram 4 A killer T-cell does not lock into an MHC antigen (self) without a viral antigen. But when a viral antigen binds to an MHC antigen, the shape of the MHC antigen is altered and a matching receptor on a killer T-cell can recognise the viral-MHC antigen complex (altered self). When a T-cell receptor locks into a viral-MHC antigen complex, the killer T-cell releases molecules that penetrate the infected cell and kill it. This shuts down the virus factory. Receptors on killer T-cells are unique because they are specific for both the viral antigen and the MHC antigen.

Killer T-cell

T-cell receptor

Viral-MHC antigen complex

Virus-infected cell