advances

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New weapons in the fight against HIV

Engineered immune cells that can see through HIV's disguises

Llywodraeth Cynulliad Cymru
Welsh Assembly Government

Seeing through the diverse disguises of HIV

Scientists at Cardiff University in South Wales have engineered immune cells that can beat HIV at its own game

First recognised in 1981, human immunodeficiency virus (HIV) infection, the cause of acquired immunodeficiency syndrome (AIDS), is now a pandemic, and is a particular scourge in Africa. No vaccine or cure exists and HIV has become one of the biggest health challenges to face the modern-day world.

HIV destroys the human immune system, leaving the body vulnerable to infection and illness. Anti-retroviral drugs can be successful in delaying the onset of AIDS, but these are expensive and have serious side-effects, and drug resistance is an increasing problem.

Scientists at Cardiff University have discovered a new way of tackling HIV, which may offer new hope in the fight against the disease.

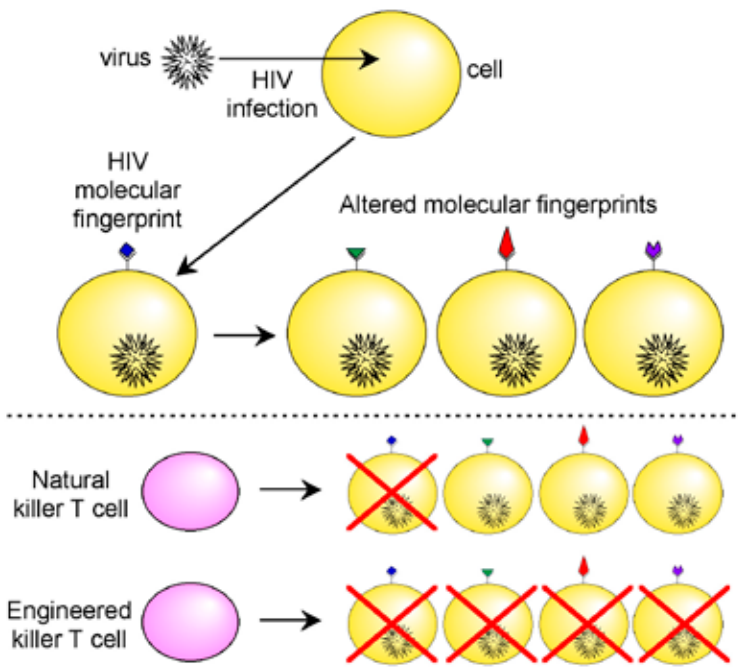
> "We have managed to engineer a receptor that is able to detect HIV's key fingerprints and is able to clear HIV infection in the laboratory. If we can translate those results in the clinic, we could at last have a very powerful therapy on our hands."
>
> Dr Bent Jakobsen
> Chief Scientific Officer
> Adaptimmune Ltd

Engineered assassin cells

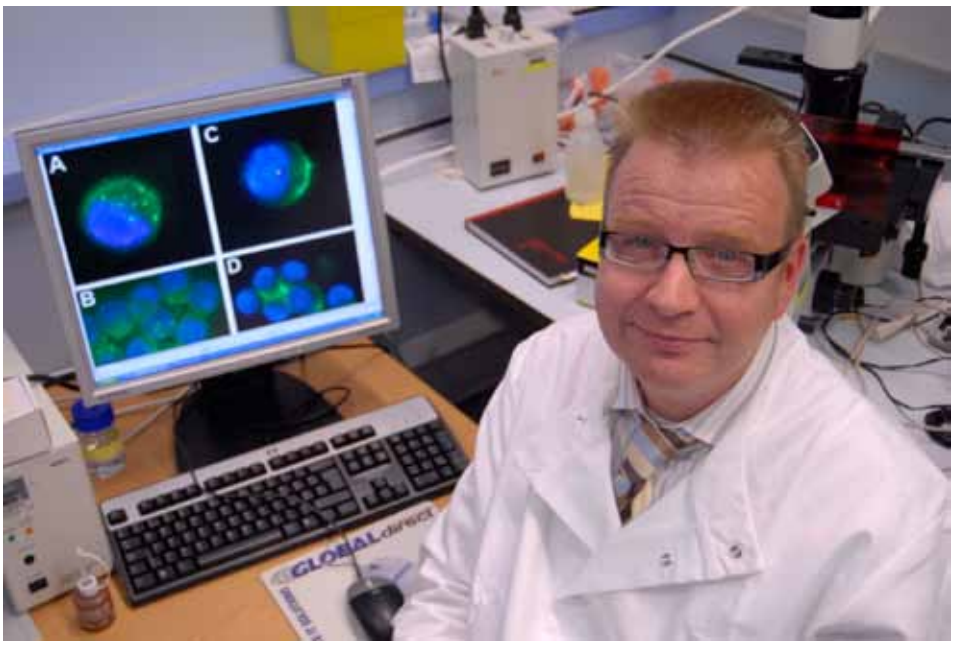
When viruses enter our bodies, they hijack host cells in order to replicate and spread infection. Small parts of the virus become exposed on the surface of the cell, offering a 'molecular fingerprint' for killer T-cells from the immune system to identify and destroy.

However, HIV has the ability to mutate and disguise its fingerprints, allowing it to hide undetected from killer T-cells. This capacity for 'immune escape' enables HIV to stay one step ahead of the killer T-cell response mounted against it and ensures that the human immune system is unable to rid the body of the virus.

But, in collaboration with colleagues at University of Pennsylvania's School of Medicine and Adaptimmune Ltd UK, a



TOP: Virally infected cells present surface 'molecular fingerprints' to the immune system's killer T-cells. HIV rapidly alters these fingerprints once they are targeted. BOTTOM: Our natural immune response is unable to recognise HIV's altered molecular fingerprints. Bioengineered killer T-cells can see through these disguises and neutralise all forms of the virus that have been seen to date



Professor Andy Sewell, with fluorescent images of killer T-cells

> "When the body mounts a new killer T-cell response to HIV, the virus can alter the molecular fingerprint that these cells are searching for in just a few days. It's impossible to track and destroy something that can disguise itself so readily. As soon as we saw, over a decade ago, how quickly the virus can evade the human immune system, we knew there would never be a conventional vaccine for HIV."
>
> Professor Andy Sewell

team of scientists at Cardiff's School of Medicine, led by Professor Andy Sewell, has engineered cells that can see through HIV's disguises – a research step that could have important implications for the future treatment of HIV.

Redesigned receptor

The Cardiff scientists targeted part of a protein that is essential to the functioning of HIV – a small part of the p17 Gag protein called SL9, which has a vital role in holding the virus together. When HIV infects cells, the SL9 molecule can act as a molecular fingerprint for immune cells to recognise. However, HIV can rapidly change this fingerprint once an immune response is mounted against it, allowing the virus to stay one step ahead of our killer T-cell response.

Professor Sewell's team redesigned the receptor molecule that recognises SL9 so that it incorporates the ability to see all mutant forms of the virus. Killer T-cells bearing this engineered receptor were then able to 'see through' HIV's disguises and control the virus in the laboratory when natural receptors failed.

When faced with the genetically engineered cells, the virus will either die or be forced to change its disguise again, weakening itself along the way. Although the former is preferable, the latter still represents important progress as it would be likely to delay the onset of AIDS and would reduce the capacity of the virus to transmit within the population.

The HIV SL9 molecular fingerprint targeted by the Cardiff group. The green and blue at the top is part of the virus, and the rest is the immune molecule that 'presents' the virus to the immune system

This work was partially funded by the Wellcome Trust, and was published in the journal *Nature Medicine*. The researchers are now waiting for final approvals to test the discovery in a series of clinical trials in the USA. ■

Profile

Product	Genetically engineered T-cells
Applications	Destruction of HIV-infected cells
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