

Adaptimmune Limited

PRESS RELEASE

Embargoed until 18.00 hrs (London) on 9 November 2008

HIV'S disguises no match for 'Bionic Assassins'

Adaptimmune engineers immune cells able to clear HIV – clinical trials planned

HIV is a master of disguise, able to rapidly change its identity and hide undetected in infected cells. But now, in a long-standing collaborative research effort partially-funded by the Wellcome Trust, scientists from Oxford-based Adaptimmune Limited, in partnership with the Universities of Cardiff and Pennsylvania, have engineered immune cells to act as "bionic assassins" that see through HIV's many disguises.

The findings of the study, published online today in the journal *Nature Medicine*, may have important implications for developing new treatments for HIV and slowing – or even preventing – the onset of AIDS. Over 33 million people were estimated to be living with HIV worldwide in 2007. Although anti-retroviral drugs have been successful in delaying the onset of AIDS for several years, the drugs are expensive, have serious side effects and must be taken for life. No vaccine or cure yet exists and drug resistance is increasingly a problem.

When viruses enter our bodies, they hijack the machinery of host cells in order to replicate and spread infection. When our body's cells are infected with a virus they expose small parts of the virus on their surface, offering a "molecular fingerprint" called an epitope for killer T-cells from the immune system to identify. This triggers an immune response, eliminating the virus and any cells involved in its production.

As with other viruses, HIV enters the body and replicates itself rapidly. However, it also has the ability to mutate quickly, swiftly disguising its fingerprints to allow it to hide from killer T-cells.

Professor Andy Sewell of Cardiff University, co-lead author of the study and long-term collaborator with Adaptimmune, said: "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 immune system we knew there would never be a conventional vaccine for HIV."

Now, Professor Sewell and colleagues from Adaptimmune Ltd and the University of Pennsylvania School of Medicine have engineered and tested a killer T-cell receptor that can recognise all of the different disguises that HIV is known to have used to evade detection. The researchers attached this receptor to the killer T-cells to create genetically engineered "bionic assassins" able to destroy HIV-infected cells in culture.

Dr Bent Jakobsen, co-lead author and Chief Scientific Officer at Adaptimmune Ltd, the company which owns the technology, said: "The T-cell receptor is nature's way of scanning and removing infected cells – it is uniquely designed for the job but probably fails in HIV because of the tremendous capability of the virus to mutate. Now 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."

The researchers believe that HIV's chameleon-like ability may still prevent the virus from being completely flushed out of the body. It could mutate and change its fingerprint further, hiding behind these new disguises and evading detection. However, each time the virus is forced to mutate to avoid detection by killer T-cells, it appears to become less powerful.

Adaptimmune Limited

"In the face of our engineered assassin cells, the virus will either die or be forced to change its disguises again, weakening itself along the way," says Professor Sewell. "We'd prefer the first option but I suspect we'll see the latter. Even if we do only cripple the virus, this will still be a good outcome as it is likely to become a much slower target and be easier to pick off. Forcing the virus to a weaker state would likely reduce its capacity to transmit within the population and may help slow or even prevent the onset of AIDS in individuals."

Pending regulatory approval, Professor Carl June and Dr James Riley from the University of Pennsylvania in Philadelphia will shortly begin clinical trials using the engineered killer T-cells.

Professor June said: "We hope to begin testing the treatment on patients with advanced HIV infection next year. If the therapy in that group proves successful, we will treat patients with early stage well-controlled HIV infection. The goal of these studies is to establish whether the engineered killer T cells are safe, and to identify a range of doses of the cells that can be safely administered."

"The AIDS virus evades human immunity in all it infects," said Professor Rodney Phillips, from the University of Oxford, where the collaborative research effort first began in 2003. "Until now no-one has been able to clear the virus naturally. Immune cells modified in the laboratory in this way provide a test as to whether we can enhance the natural response in a useful and safe way to clear infected cells. If successful the technology could be applied to other infectious agents."

The researchers are now exploring using engineered receptors on killer T-cells as a way of improving immune responses to cancer.

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Contacts

Margaret Henry
PR Consultant
Adaptimmune Ltd, UK
T: +44 (0)1865 811199
E: m.henry@oxin.co.uk

Craig Brierley
Media Officer
The Wellcome Trust, UK
T: +44 (0)20 7611 7329
E: c.brierley@wellcome.ac.uk

Victoria Dando
Public Relations Officer
Cardiff University, UK
T: +44 (0)29 2087 9074
E: DandoV2@cardiff.ac.uk

Karen Kreeger
Senior Science Communications Manager
University of Pennsylvania, PA
T: +1 215-349-5658
E: karen.kreeger@uphs.upenn.edu

Notes for editors

1. Varela-Rohena, A. et al. Control of HIV-1 immune escape by CD8 T-cells expressing enhanced T-cell receptor. Nature Medicine, published online 9 November 2008 at <http://www.nature.com/nm>

2. Since the discovery of the human immunodeficiency virus (HIV) in 1984 and its role in the cause acquired immunodeficiency syndrome (AIDS) the HIV pandemic has become one of the most serious challenges to human health in the 21st Century. UNAIDS estimates indicate that over 33 million people are now living with HIV rising by approximately 1 million per year. Whilst combinations of highly active anti-retroviral therapy have been relatively successful in crippling the virus and delaying by years the onset of AIDS, crucially such therapy does not represent a cure and the combined problems of drug resistance mutations, toxicity and patient adherence raise questions about the long-term efficacy of treatment as well as the cost and availability of such drugs in poorer parts of the world where the pandemic is most acute. More recently, hopes that vaccines could be used to control the disease by provoking an immune response to the virus have also begun to fade as it has become apparent that HIV's phenomenal capacity for variation enables it to out-run, and eventually over-run, the human immune system. New approaches are needed that reach beyond these existing efforts, barrier methods and behavioural changes which can truly prevent or cure HIV infection.

3. **Adaptimmune Limited** is focused on the use of T cell therapy to treat HIV and cancer. It aims to utilise the body's own machinery – the T lymphocyte cell – to target and destroy cancerous or infected cells. Adaptimmune's mission is to take so-called "adoptive T cell therapy" to the next level by leveraging its expertise in engineering high affinity T cell receptor proteins (TCRs) which recognise the cancerous or infected cells as a means of "supercharging" the strength of patient's own T cell responses. Established in July 2008 as a separate spin-out company, Adaptimmune was set up to develop Immunocore Ltd's (formerly Avidex/MediGene Ltd's) unique T cell receptor engineering technology for adoptive T cell therapy, technology originally developed by Avidex when it was spun out from Oxford University. Adaptimmune holds an exclusive licence to the adoptive therapy use of the technology and is aiming to exploit this unique capability in the development of targeted T cell therapy in HIV and cancer through partnership and collaboration with leading institutions in both fields. <http://www.adaptimmune.com>

4. **The Wellcome Trust** is the largest charity in the UK. It funds innovative biomedical research, in the UK and internationally, spending over £600 million each year to support the brightest scientists with the best ideas. The Wellcome Trust supports public debate about biomedical research and its impact on health and wellbeing. <http://www.wellcome.ac.uk>

5. **Cardiff University** The School of Medicine at Cardiff is one of the largest in the UK, employing nearly 500 academic and 300 support staff with over 1,000 undergraduate and 1,100 postgraduate students currently enrolled on medical and science courses. The School has an annual financial turnover of over £50 million, of which nearly 50% comes from competitive external research funding. This will increase in the next one to three years as the recent increase in research funding awards feeds through into annual income. The relationship of the School of Medicine with the National Health Service (NHS) is a positive and dynamic one, driven by the close links of the University with the Welsh Assembly Government. Over 750 staff from the Medical School are on clinical contracts with the NHS, and staff from across all seven NHS Trusts within Wales are similarly involved in teaching activity with the University. <http://www.cardiff.ac.uk/medic>

6. University of Pennsylvania

PENN Medicine is a \$3.6 billion enterprise dedicated to the related missions of medical education, biomedical research, and excellence in patient care. PENN Medicine consists of the University of Pennsylvania School of Medicine (founded in 1765 as the nation's first medical school) and the University of Pennsylvania Health System.

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Penn's School of Medicine is currently ranked #4 in the nation in U.S. News & World Report's survey of top research-oriented medical schools; and, according to most recent data from the National Institutes of Health, received over \$379 million in NIH research funds in the 2006 fiscal year. Supporting 1,700 fulltime faculty and 700 students, the School of Medicine is recognized worldwide for its superior education and training of the next generation of physician-scientists and leaders of academic medicine.

The University of Pennsylvania Health System (UPHS) includes its flagship hospital, the Hospital of the University of Pennsylvania, rated one of the nation's top ten "Honor Roll" hospitals by U.S. News & World Report; Pennsylvania Hospital, the nation's first hospital; and Penn Presbyterian Medical Center. In addition UPHS includes a primary-care provider network; a faculty practice plan; home care, hospice, and nursing home; three multispecialty satellite facilities; as well as the Penn Medicine at Rittenhouse campus, which offers comprehensive inpatient rehabilitation facilities and outpatient services in multiple specialties.

7. **Oxford University's** Medical Sciences Division is one of the largest biomedical research centres in Europe. It represents almost one-third of Oxford University's income and expenditure, and two-thirds of its external research income. Oxford's world-renowned global health programme is a leader in the fight against infectious diseases (such as malaria, HIV/AIDS, tuberculosis and avian flu) and other prevalent diseases (such as cancer, stroke, heart disease and diabetes). Key to its success is a long-standing network of dedicated Wellcome Trust-funded research units in Asia (Thailand, Laos and Vietnam) and Kenya, and work at the MRC Unit in The Gambia. Long-term studies of patients around the world are supported by basic science at Oxford and have led to many exciting developments, including potential vaccines for TB, malaria and HIV, which are in clinical trials. <http://www.ox.ac.uk>