No rest for the **wicked**

PROFESSOR SHARON LEWIN

HIV remains dormant in immune system cells even when treatment of the disease is successful. Here, **Professor Sharon Lewin** describes her research to roust it out and improve patient health

Could you begin by outlining the main interest of your team?

Our main interest is understanding how HIV is able to hide from current treatments. HIV does this by entering a resting T-cell, where it enters the patient's DNA and essentially goes to sleep. This is called HIV latency. We are interested in developing novel strategies to eliminate latent infection: one approach we are using is to 'wake up' the virus with drugs called histone deacetylase inhibitors. We are studying how these drugs work in the laboratory as well as in a clinical trial of the histone deacetylase inhibitor, vorinostat, in patients with HIV. This is a very important proof-of-concept study. Once we know what happens in people, we can design more specific studies aimed at eliminating latently infected cells.

What led to the discovery that HIV virus can enter resting T-cells and establish latent infection?

For years it was assumed that latency was established following survival of an infected activated T-cell that reverted back to a memory state. However, we showed that latency could be established via other pathways, including direct infection of resting T-cells. We are now very interested in HIV latency in other T-cell subsets, such as naïve T-cells, as it is likely that the mechanisms in these diverse T-cell subsets are quite different. We have also recently become very interested in the role of dendritic cells in the establishment of latency.

When antiretroviral therapy was introduced in 1996, the general overview was that it would cure HIV. What went wrong?

Nothing went wrong. These drugs were a miracle. They dramatically reduce virus replication, allowing the immune system to recover in nearly all patients. Patients who took these drugs literally got off their death beds and returned to essentially normal lives. However, antiretroviral therapy can only target actively-replicating virus. In a latent infection, virus integrates into the patient's DNA and is able to hide from both the drugs and the

immune system. So there is infectious virus always lurking and the T-cell harbouring it can be woken up at any time. This is why current antiretroviral therapy can't cure HIV.

How have international and multidisciplinary collaborations enhanced your work?

The great joy of my job is the tremendous people I meet and work with. From very bright and motivated students to superb mentors, I gain inspiration from seeing how others approach or overcome problems – both scientific and professional challenges.

In Thailand and South Africa, clinical and scientific resources are limited but there is an unbelievably strong commitment to care of patients and research and training in both countries. We have been able to answer questions about common infections such as hepatitis B and *Cryptococcus* that can be devastating in patients with HIV infection. I have been greatly inspired by the dedication and skills of the people I have worked with in both countries and am strongly committed to providing opportunities to staff from these sites and to grow these collaborations.

I am currently part of a large collaborative research effort funded by the National Institutes of Health, called the Martin Delaney Collaboratory on HIV Cure. Our collaboratory, DARE, includes investigators from the US, Sweden and Australia. It's a tremendously dynamic and exciting group.

What would you highlight as being your most successful moment?

I am most proud of our discoveries around chemokines and HIV latency. These studies identified unique pathways explaining how latent infection is established. I am also particularly proud of our clinical trial on Vorinostat, as it has taken enormous commitment from the laboratory and clinical research teams, as well as tremendous support by the HIV-infected community and participants. I am very confident that this study will inform future studies for eradicating HIV.

The highlight of my career was being asked to deliver the plenary talk on 'Strategies to achieve a cure for HIV' at the opening ceremony of the 18th International AIDS Conference in Vienna in 2010. There were 18,000 participants at this meeting, with over 10,000 at the opening ceremony. Many participants, including HIV-infected patients, had no idea that scientists were seriously working on finding a cure for HIV and this was the first time that they heard of some of the advances being made in the field. I am tremendously grateful for having been given that opportunity to help put the quest to find a cure for HIV on the agenda.

Wake up call for HIV

Research at **Monash University**, the **Burnet Institute** and the **Alfred Hospital** in Melbourne, towards understanding why HIV persists following treatment seeks to discover detailed information about the machinations of the virus and hopes to play a pivotal part in bringing about a definitive cure

SINCE THE ACQUIRED Immunodeficiency Syndrome (AIDS) epidemic started, 30 million people have died of AIDS. Infection by Human Immunodeficiency Virus (HIV) attacks the immune system, depleting the number of white blood cells (CD4+ T-cells), which otherwise would fight infection. People with HIV therefore often succumb to unusual infections and cancers.

Antiretroviral drugs have significantly increased life expectancyfor people with HIV, especially if treatment is started before the immune system is significantly damaged. The drugs inhibit the ability of HIV to replicate in new cells, so infected cells die over time, virus replication is blocked and the immune system is able to recover. These medications have to be taken daily, usually in combination of three to four different drugs. Once a patient has started treatment, they can never stop: "Antiretroviral therapy has saved the lives of millions of people. But because HIV has developed clever ways to 'hide' in some cells, if a patient stops their treatment, the virus returns within three or four weeks," explains Professor Sharon Lewin, who is researching why and how HIV persists in patients whose treatment has otherwise appeared successful.

Lewin established several years ago that HIV could effectively enter and then 'hide' in resting CD4+ T-cells. She found that incubation of resting T-cells with a family of proteins called chemokines 'unlocked' the door and allowed the virus to bypass defences in the cytoplasm and efficiently integrate into a patient's DNA in the cell nucleus, where it can then remain for years: "This work changed the thinking about how HIV interacts with resting T-cells and how latency is established, but, more importantly, it gave us a model to explore new ways to eliminate latent infection," Lewin declares.

MULTIFACETED RESEARCH

Lewin is currently employed by three institutions in Melbourne: the Alfred Hospital, where she is head of the Infectious Diseases Unit and undertakes translational research; Monash University, where she is Professor of Medicine; and the Burnet Institute, where she co-heads the Centre for Virology and has her laboratory.

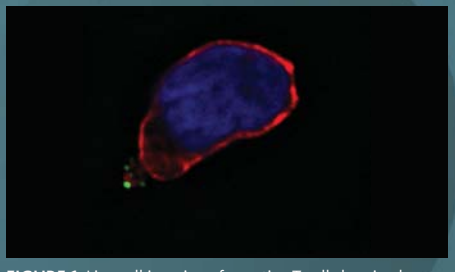

FIGURE 1. Live cell imaging of a resting T cell showing how HIV (green) establishes infection. This technique is used to track the path of the virus across the cytoplasm (red) into the nucleus (blue).

In collaboration with laboratories in Sydney, San Francisco and Florida, Lewin's laboratory is characterising how a resting T-cell is changed when it is latently infected, with a view to finding new ways of identifying latently infected cells in HIV-infected patients. The laboratory is also now focusing on how HIV interacts with dendritic cells. Dendritic cells normally fight infection by coordinating a potent immune response. Dendritic cells are considered to be the 'conductors' of the immune system. Lewin's lab has recently demonstrated that dendritic

INTELLIGENCE

TACKLING HIV LATENCY – A PATH TOWARDS A CURE FOR HIV

OBJECTIVES

The research primarily focuses on where HIV 'hides' in patients on treatment and how HIV interacts with unique infection fighting cells. How the immune system recovers from HIV infection and how HIV interacts with hepatitis B virus are also being investigated.

KEY COLLABORATORS

For HIV latency and eradication: **Rafick Sekaly** and **Nicolas Chomont**, Vaccine Gene Therapy Institute, Florida • **Steve Deeks**, University California San Francisco (UCSF) • **Melissa Churchill**, Burnet Institute • **Damian Purcell**, University of Melbourne • **Anthony Cunningham** and **Sarah Palmer**, Westmead Millenium Institute, Sydney • **Dimitrios Vatakis**, University of California Los Angeles (UCLA)

For optimising treatment outcomes for HIV infection: **Paul Gorry**, Burnet Institute • **Adeeba Kamaralzaman** and **Reena Rajasuriar**, University of Malaya • **Martyn French**, University of Western Australia • **Thumbi Ndungu** and **Yunus Moosa**, University of Kwazulu Natal, Durban, SA

For HIV-HBV co-infection: **Chloe Thio,** Johns Hopkins • **Anchalee Ahavingsanon,** Thai Red Cross, HIV/NAT, Bangkok • **Joe Sasadeusz,** The Alfred Hospital, Melbourne • **Stephen Locarnini,** VIDRL, Melbourne • **Gail Matthews** and **Gregory Dore**, Kirby Institute, Sydney

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CONTACT

Sharon R Lewin, FRACP, PhD
Head, Department of Infectious Diseases, Alfred Hospital and Monash Univeristy
Co-head, Centre for Virology, Burnet Institute

Level 2, Burnet Building
85 Commercial Road
Melbourne, Victoria 3004, Australia

T +61 3 9076 8491
E s.lewin@alfred.org.au

SHARON LEWIN is an infectious diseases physician and basic scientist. She completed her specialist and PhD training in Melbourne and her postdoctoral fellowship at the Aaron Diamond AIDS Research Centre at the Rockefeller University. She is a past president of the Australasian Society for HIV Medicine.

cells play a key role in helping virus enter resting T-cells: "To tackle HIV latency, we need to know everything about it – how it is established, how it is maintained and how it is reversed. If we could understand where HIV hides and how to eliminate it from those places, perhaps we could find a cure for HIV," says Lewin.

Lewin is a project leader in an international network of laboratories funded by the American National Institutes of Health to find a cure for HIV. The initiative is named after Martin Delaney who was a campaigner for fast-tracking HIV/AIDS treatment. The three collaboratories named in his honour draw together the leading researchers in HIV cure research on the premise that pooling their expertise and resources will achieve better results more quickly than if they were to work independently: "Collaboration is a huge part of science: the problems are too big, and the pace of change too quick, to tackle things in isolation," reflects Lewin. "Being part of a large team means that big difficult questions can be asked and, hopefully, answered." The collaboratory in which Lewin and her laboratory are participating is the Delaney AIDS Research Enterprise (DARE), involving the University of California San Francisco, the Vaccine and Gene Therapy Institute, The University of Miami, the Karolinska Institutet and Merck Research Laboratories. Lewin very much welcomes the opportunities for making a difference that the programme provides: "Together, I am confident that we will be able to answer key questions facing the HIV cure field," she enthuses.

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WAKING UP THE VIRUS

HIV persists because it is never completely eliminated by antiretroviral treatment from a range of sites and cells.The virus remains in a dormant state in multiple T-cell subsets, including resting memory, transitional memory and naïve T-cells; it can continue to replicate, mainly in tissues; and as antiretroviral drugs penetrate only to a limited extent in anatomical reservoirs such as the gut, the genito-urinary tract and lymph tissue, a stable repository of HIV lurks in those places and can be triggered into action when antiretroviral treatment stops: "The tissue reservoirs contain not only latently-infected T-cells but also other long-lived infected cells, such as macrophages, dendritic cells and astrocytes. To find a cure for HIV, all of the potential sources of residual virus need to be understood and targeted," asserts Lewin.

A clinical trial of a drug that forces latent HIV to emerge from resting T-cells is currently being led by Lewin at the Alfred Hospital in Melbourne. The drug a member of a new class of drugs being used to treat cancer called histone deacetylase inhibitors (HDACi): "We are looking at the effects of an HDACi called Vorinostat which is used for treating rare skin cancers. We are giving 14 days of Vorinostat to HIV-infected patients on antiretroviral therapy, to see whether Vorinostat is able to 'wake up' latent virus in people," explains Lewin.

Histones are proteins that are responsible for packing DNA; the DNA strands wind around histones. The DNA is controlled by the activity of these histones. By activating histone function, Vorinostat should make the DNA unravel and force the latent virus into an active state – effectively turning HIV genes 'on'. The infected cells containing HIV genes should die or be killed by the immune system; and the antiretroviral drugs that the patients are taking should inhibit new rounds of infection of other cells. While Vorinostat is an approved drug, with known side-effects, its use in HIV is now experimental and extensive testing will be required if the approach is indicated to be successful.