Discovering new approaches to understand the HIV reservoir – and learning a lot more beside

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Abbreviations / Glossary

ART	Antiretroviral therapy – treatment for HIV infection
Deuterium	A heavy isotope of hydrogen, with mass 2, which is not radioactive.
HIV	Human Immunodeficiency Virus
ID	Infectious Diseases
MAIT	Mucosal-associated invariant T cells – a specific type of immune cell (T-cell)
MRC	Medical Research Council (UK)
PDI	Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
PLWHA	People living with HIV and AIDS
WEHI	Walter and Eliza Hall Institute of Medical Research

Professional Experience

Having qualified as a doctor in 1983, I trained in General Internal Medicine in Oxford and London. I then followed a clinical-academic career in Infectious Diseases, spending time in both clinical appointments and research. In 1998 I was appointed Consultant Physician in Infectious Diseases & General Medicine at St George's Hospital, London, an appointment I still hold. I was promoted to Professor in 2007 and was Clinical Lead of the Infection Care Group at St George's Hospital from 2011 to September 2018, when I started my WCMT Fellowship.

My previous research attachments include: MRC Travelling Fellow, Department of Nutritional Sciences, University of California, Berkeley (1995–97); MRC-Glaxo Wellcome Clinician Scientist Fellow, Centre for Infection, St George's, University of London (2000–03); Fulbright Distinguished Scholar, National Institutes for Health, Bethesda, MD USA (2008).

Executive Summary

In October / November 2018 I was privileged to spend 8 weeks attached to the Peter Doherty Research Institute (PDI) in Melbourne, Australia, an institute with a worldwide reputation in immunology research. I went to work with the Director, Professor Sharon Lewin, whose laboratory has a strong focus on HIV Immunology.

I went with two main aims:

- My first, broad aim was to learn new approaches to immunological questions in infectious diseases by working in Prof Lewin's laboratory group and by attending seminars and meetings in PDI.
- My more specific goal was to explore how my expertise in measuring the *in vivo* lifespan of immune cells could be combined with their expertise in investigating HIV reservoirs to develop a new research project delineating the lifespan and kinetics of HIV reservoir cells.

The Fellowship gave me the opportunity to work alongside some world-class researchers and to spend time studying not just HIV, but also a broader range of immunology topics. I was able to develop an outline proposal for the study of HIV reservoir cell dynamics, which I am still working on. I have also been able to develop a new (and unanticipated) research proposal around the lifespan of a specific subset of T cells (MAIT) which protect at body surfaces.

I have returned to give two internal seminars to date and organised and delivered a public lecture on HIV infection and immunology in our Spotlight on Science series entitled "HIV – How far have we come?" on 17th October 2019.

Introduction

HIV in context

HIV infection was first recognised in the 1980's. Since that time HIV has resulted in millions of deaths, especially in Sub-Saharan Africa. It is estimated that about 33 million people worldwide are currently living with HIV/AIDS. In the 1990's antiviral drugs (antiretroviral therapy, ART) were developed. These drugs arrest the virus lifecycle and prevent it damaging the immune system. The roll-out of ART, in both developed and developing countries, revolutionised the outlook for people infected with HIV. No longer is HIV a death sentence but is now considered a "chronic manageable condition". On treatment, people living with HIV and AIDS (PLWHA) can anticipate good health and a "normal" life-expectancy. However, this requires a patient to take tablets every day for the rest of their lives. Daily therapy works for many, but is not an ideal solution. Access to treatment may be limited, as in many resource-limited settings, or may be interrupted if supplies run out, whilst some patients find themselves unable to adhere to a regular treatment regime, especially those with mental health issues, and some suffer side-effects or reactions that make therapy a challenge.

Most infections only require a time-limited course of therapy. For example, antibiotic therapy for many bacterial infections need only be given for a week or so and the patient may then be said to have been cured. Even more indolent or chronic infections such as tuberculosis have a finite treatment period (usually 6 months). HIV is unusual in this respect as it relapses very soon after any treatment discontinuation. Apart from a few rare cases who have been "cured" as part of treatment for blood malignancies, there is currently no way to eradicate HIV infection such that a person can come off ART and remain healthy in the long-term.

Scientific Background – HIV reservoirs

The main reason HIV infection is so difficult to cure because it hides in immune cell "reservoirs" from where it reactivates if treatment is stopped. Reservoir persistence requires the virus to remain dormant, by which we mean that it is still viable but in a state that does not reproduce and does not destroy its host cell. It does this by making a DNA copy of itself in the cell's own DNA. This means that for the virus reservoir to persist, the host cell must either live for a long time or have daughter (and grand-daughter) cells which together live for a long time.

My Background – Measuring cell lifespan and turnover

All cells in the body are in a state of dynamic turnover, being constantly renewed and replaced – some, such as brain cells, slowly, and some, such as the cells lining the gut or those making new blood cells, more quickly. My own expertise is in measuring the rates at which cells are renewed and replaced within the human body. I have developed techniques using non-radioactive "heavy" isotopes, such as deuterium, to label or mark cells as they divide and have used this approach to determine which cells are short-lived and which last for a long time. I have mostly applied this technique to immune cells as they are my primary interest (being a specialist in Infectious Diseases) but this approach can be applied to any cell type that can be sampled.

My Host's Background – Expertise in HIV Immunology

The Peter Doherty Institute for Infection and Immunity (PDI) in Melbourne, Australia has a worldwide reputation as a centre for Immunology and Infectious Diseases Research. It was set up as a joint venture between the University of Melbourne and The Royal Melbourne Hospital, combining research, teaching, public health and reference laboratory services, diagnostic services and clinical care in infectious diseases and immunity. Its Director, Professor Sharon Lewin has a worldwide reputation as an expert in HIV immunology and her laboratory currently has a major focus on HIV cure research. This is what attracted me specifically to her group.

A Meeting of Minds

The idea behind setting up this Fellowship was to see if I could bring together my background in measuring cell dynamics in human studies with Sharon Lewin's expertise and interest in HIV Cure with a particular goal of setting up a project to measure the lifespan of HIV reservoirs using deuterium-labelling approaches.

Aims of this Project

The broad aim of my project was to gain new insights into Infection and Immunology from working in and attending seminars and meetings in PDRI.

My specific goal was to explore how my expertise in measuring the in vivo lifespan of immune cells could be combined with Prof Lewin's group's expertise in investigating HIV reservoirs to develop a new research application measuring the lifespan and kinetics of HIV reservoir cells.

My WCMT Fellowship

I spent most of my 8 weeks embedded in Sharon's Lewin's group. She kindly gave me desk space, access to the University of Melbourne's resources, opportunities to attend seminars and meetings at PDRI, and, most importantly, an open door to her research group meetings. I was able through these means to learn what researchers there were thinking and doing and to discuss with them one-on-one how their research was informing the wider debate about HIV reservoirs.

Attending seminars on research in progress in a number of areas outside of my usual remit led me to think about potential future research opportunities that I would not have otherwise been aware of (more of this below). In addition, I found myself with time to read, reflect and focus on my research – something that I have found difficult at home in the context of a busy clinical-academic-managerial role.

Furthermore, as a clinician, I was keen to learn how clinical care in Infectious Diseases (ID) was delivered in Melbourne. I was granted Clinical Observer status at the Royal Melbourne Hospital and at the Alfred Hospital, both of which have active ID units. I regularly attended ward rounds and clinical meetings.

Two key invaluable learning opportunities also occurred while I was in Melbourne. The first was a research retreat by a group of laboratories, including Prof Lewin's, all working on HIV infection. This was an intense but enormously enjoyable time away from Melbourne with inspirational researchers. The other was an annual Clinical ID training week ("Forbes Week") with an international guest speaker as well as local contributors which occurred while I was in Melbourne – it proved an excellent opportunity to update my clinical ID knowledge-base, alongside my research experiences.

I also gave seminars at PDI, to Sharon Lewin's research group, at the Walter and Eliza Hall Institute of Medical Research (WEHI), a prestigious independent research laboratory in Melbourne, and at the Alfred Hospital.

Perhaps one of the most useful and powerful things I was able to do during my Fellowship was to set up on-on-one meetings with leading researchers in Melbourne. These sessions, each rather like a "masterclass", proved to be highly instructive and formed the basis for much of my later thinking. Having the WCMT Fellow "badge" definitely opened doors for these opportunities.

Outcomes of the Fellowship

At a global level, I returned from my Fellowship better informed, better motivated and with a greater depth of insight into several key areas within the field of immunology and infection.

In terms of the specific project I went to set up, measuring the turnover of HIV reservoir cells, I was able to make a great deal of progress formulating the research plan and establishing optimal techniques. However, it also became apparent that this project would be technically very demanding and would depend upon some laboratory developments that are still in progress. I plan to submit a research grant proposal to do this work later this year once we have done some more method development both here and in Melbourne and once I have generated some preliminary data. We have an outline proposal but the feasibility studies are still to be completed. This is a particularly challenging study as the number of cells that make up the reservoir is very small.

An unexpected research opportunity also became apparent during discussions about a group of immune cells called mucosal-associated invariant T cells (MAIT). Several groups in Melbourne are looking at these cells and it became apparent that these cells would be a good target for an in vivo cell turnover study of the kind I have been doing in other cell types. Inspired by research on this fascinating and important family of cells, since my return, I have teamed up with MAIT cell experts in the UK and we have now submitted a major research proposal to the Medical Research Council (MRC) to undertake a detailed analysis of their lifespan, regulation and dynamics with a specific focus on MAIT cells in HIV infection.

I also extended my clinical knowledge-base, seeing how different clinical approaches can be applied by attending rounds at different hospitals, and learnt how more community-based care is necessary when patients are spread over an enormous geographical area.

Finally, I learnt the value of the “masterclass”, a meeting without predetermined outcomes (unlike most of the meetings I usually attend which are more often purpose-directed or agenda-driven). These sessions were a great tool for learning and generating new ideas.

Melbourne was also a great place to live and learn. We enjoyed cycling the Melbourne Capital City Trail (a 29km long trail encircling the city), getting to know the “locals”, exploring the Great Ocean Road and the Mornington peninsula locally, as well as visiting more-distant Sydney and Perth. We also met up with some other WCMT fellows in their transit through Melbourne.

In terms of dissemination, since my return I have presented three seminars at my home Institution and have given a public lecture in our “Spotlight on Science” series in the autumn. I was also able to talk about the Churchill Fellowships in a video blog with our Principal in a series that she produces for internal distribution.

I am very grateful to WCMT for this opportunity which I am sure will continue to yield positive outcomes over many years to come.