New innovations in immunology

By elucidating the processes involved in the human immunological response to HIV-1, the Immunotherapy Group, based at the Department of Medicine, Imperial College London, UK, is helping to hasten the widespread use of novel immune-based therapies in the fight against HIV-1 infection.

HIV HAS CLAIMED more than 36 million lives worldwide, with around 35.3 million people living with the virus at the end of 2012. HIV-1 – the most common strain of the virus – weakens the body against infections and some cancers by targeting the immune system, reducing the numbers and effectiveness of CD4 T (‘helper’) cells and responsiveness of CD8 T (‘killer’) cells, which normally fight viral attack. Left untreated, 99 per cent of infected individuals succumb to AIDS, which typically results in death within 10 years.

CURRENT TREATMENT

The introduction of combination antiretroviral therapy (cART) in 1996 was a significant breakthrough in modern medicine and has revolutionised the treatment of HIV-1, but it is not a cure; the drugs are expensive, not always readily obtainable and often associated with many unpleasant side-effects. Although cART controls HIV-1 replication, it does not fully restore HIV-1 immunity, which is essential for the total eradication of the virus from the system. This means lifelong treatment is required in order to delay progression to AIDS. The immune system therefore suffers hyperactivation and exhaustion, and this increases the risk of death from non-AIDS complications commonly associated with accelerated immunological ageing.

Interestingly, a small proportion of HIV-1-infected individuals show a significantly slower progression to disease than others. These long-term non-progressors (LTNP) or elite controllers (EC) are able to maintain stable CD4 T-cell counts and fully functional CD4 and CD8 T-cell responses. Research carried out on their genetic background and immunology has proved enlightening.

KICK-STARTING THE IMMUNE SYSTEM

The Immunotherapy Group, set up by the Department of Medicine at Imperial College London in the UK, comprises a team of cellular immunologists studying the processes that determine the course of HIV-1 disease, including the T-cell component of the immune system, which plays a central but incompletely understood role. Head of Group Dr Nesrina Imami and Research Associate Dr Anna Herasimtschuk are clear where their research can help improve current therapies: “As we do not fully understand the clinical side-effects of long-term toxicity, immune-based therapies (IBT) are being considered for HIV-1-positive subjects (within the context of cART) with the aim of inducing LTNP or EC status. If successful, this has the potential to rid the host of virus, cure infection and lower transmission rates”.

Over the last 15 years, the Immunotherapy Group has developed strong links with the clinical research team at the Department of HIV/GU Medicine at the Chelsea & Westminster Hospital, which has the largest cohort of HIV-1-positive patients in Europe. This collaboration has been crucial to the Group’s research, as have the sophisticated technologies used to measure the anti-HIV-1 immune responses in blood.

Currently working at the forefront of international HIV-1 research, viral immunology experts Drs Nesrina Imami and Anna Herasimtschuk describe their wide-reaching collaborations to improve knowledge and treatment of HIV-1 infection.
What are your respective backgrounds, and how did you become interested in immunology?

**NI:** I qualified in medicine, microbiology and immunology, and specialised in viral immunology – in particular HIV-1 – with a focus on cell-mediated immunity and immunotherapeutic development. I received a PhD from the University of London, UK, in 1992 and, after a period of postdoctoral work, was awarded a Wellcome Trust Fellowship. This enabled me to establish my HIV-1 research group and work in an area that integrates basic biological science with clinical science, with direct application to human health.

**AH:** I am a research associate and joined Imami’s group in 2008. After studying the immunomodulation of HIV-1-specific T-cell responses for my PhD thesis at Imperial College London, UK, I continued working with the group on a clinical trial in collaboration with the St Stephen’s AIDS Trust investigating the impact of immune-based therapies in treating HIV-1 infection.

How has your partnership proved advantageous to meeting the study’s broader objectives?

**NI:** Our joint efforts focus on the assessment of T-cell phenotype and function in HIV-1 infection, investigating specific patient groups of interest, host and viral genetics, co-infections and co-morbidities, and development of novel methodology and interventions. The benefits of our collaboration have been reflected in our completion of growth hormone studies and, most recently, a phase I clinical trial. We are also very proud to have been awarded the prestigious Medical Research Council Experimental Medicine Award.

**AH:** Our group has been extremely successful in technology transfer to complementary research work in Europe (through EC funding) and Africa, particularly Uganda. We have been collaborating with Professor Pontiano Kaleebu (Uganda Virus Research Institute) for over 10 years, working on two cohorts: the LTNP and the exposed seronegative (individuals who have been repeatedly exposed to HIV-1 but not infected). The co-supervision of PhD students and our involvement with a European & Developing Countries Clinical Trials Partnership-funded vaccine study of healthy, uninfected adults in Tanzania and Mozambique (TaMoVac) has been particularly important work. HIV-1 research relies on sharing and transferring technology, and we remain committed to such collaborations and partnerships.

---

Experimental work the group has conducted on HIV-1-specific T-cell defects suggests that immunotherapeutic interventions can beneficially influence T-cell populations, from initial production by the thymus through to maturation. Understanding the precise mechanisms involved is crucial before IBT can be developed and optimised.

A number of successful pilot studies and clinical trials have indicated ways in which the immune system can be ‘kick-started’ and HIV-1-specific T-cell responses improved.

**testing a novel approach**

The Group has recently completed a phase I clinical trial in which cART-treated HIV-1 patients with RNA viral loads of less than 50 copies/ml of plasma and CD4 T-cell counts of over 400 cells/μl blood undertook a course of immunotherapy. Participants were given a carefully timed therapeutic vaccine in order to induce specific cell-mediated responses, in addition to cytokines and growth hormone.

The aim of the trial was to produce long-lived mature memory cells similar to those seen in LTNP/EC with the ability to successfully control the virus in the bloodstream. Imami and Herasimtschuk have been encouraged by the findings: “We found that patients who received all of the treatments had increased CD4 T cells, improved HIV-1-specific T-cell responses and reduced immune activation, suggesting improvements beyond the effects of cART alone”.

---

**remaining challenges**

Immunotherapy has the greatest chance of success in patients whose cART is started early. Only transient benefits have been induced by IBT in chronic HIV-1-infected patients and the Group is now investigating long-term immune reconstitution in chronic disease using a stepwise combination approach of IBT and cART. They are also undertaking detailed analysis of T-cell polyfunctionality and viral epitope mutation, which is thought to enable the virus to escape normal cellular immunity: both must be understood before effective vaccines can be developed.

In the absence of an effective prophylactic vaccine, thousands of people are newly infected with HIV-1 every day. Imami and Herasimtschuk are aware of the challenges ahead but remain positive: “We are optimistic that the HIV/AIDS vaccine field is moving forward and are aware that development of a preventative vaccine is the way to halt the pandemic. The ultimate aim of HIV-1 research is to find a cure and the Imperial scientists believe that identifying a way to protect CD4 T cells is central to this, but that a multifaceted approach is needed: ‘We anticipate the development and use of novel antiretrovirals, immune-modulating therapies, viral eradication strategies and gene therapy as we strive for a world completely free of HIV-1 and AIDS’.”