Approximately 33 million people live with the human immunodeficiency virus (HIV) and 2.6 million new infections are acquired each year. The development of an effective HIV vaccine that induces robust mucosal immunity represents a major global public health challenge. Large human efficacy trials of simple antibody-based and cytotoxic T cell-based vaccines have failed to provide any protection. The recent RV144 HIV vaccine efficacy trial in Thailand using a prime-boost combination of vaccines, however, showed modest efficacy (31%, p=0.04 on the primary analysis). Although the efficacy was marginal, the study has provided considerable hope that a vaccine to prevent infection by HIV may be feasible.

HIV infection is usually acquired sexually across genital or rectal mucosal surfaces. However, most candidate HIV vaccines to date have used vectors or delivery routes (for example, intramuscular injections) that are unlike to induce robust immunity at the common mucosal portals of entry. HIV vaccines that are delivered to (and preferably replicate at) mucosal surfaces are the most likely to induce effective mucosal immunity, but these vectors are not at advanced stages of testing.

Considerable evidence from studies of HIV-infected people and monkey models of SIV infection have demonstrated the importance of CD8 T cell immunity in controlling HIV infection in humans and simian immunodeficiency (SIV) infection in non-human primates. We predict that HIV vaccines inducing CD8 T cells that rapidly home to mucosal sites of viral entry will likely result in a more effective vaccine.

Our group is currently studying monkey models of HIV to measure the homing of vaccine-induced antiviral T cells to mucosal sites. The ability of vaccine strategies to induce mucosal, HIV-specific CD8 T cells can be studied by measuring the expression of a homing marker, alpha4beta7 (α4β7) integrin on HIV-specific CD8 T cells. This homing marker plays an essential role in the migration of CD4 and CD8 T cells to mucosal tissues, including the gut. The gut lymphoid tissues are a primary site of CD4 T cell loss during acute HIV infection. Unfortunately, α4β7 integrin also serves as a co-receptor or target for HIV. The destruction of α4β7 expressing CD4 T cells in blood has been shown to correlate with the depletion of gut CD4 T cells in monkey models. Inducing the right levels of α4β7 expression on CD4 T cells and CD8 T cells creates further challenges for HIV vaccine design. We predict that the optimal HIV vaccine will induce high-level mucosal, HIV-specific CD8 T cells on one hand without generating more targets or (“fuel”) for HIV (that is, an increase in α4β7 on activated HIV-specific CD4 T cells), that will lead to greater viral replication.

One way to reliably induce mucosal T cell immunity is to immunise with live vectors via mucosal routes. We have been studying recombinant attenuated influenza viruses modified to express HIV antigens. These viruses replicate efficiently in the respiratory tract that leads to induction of mucosal immunity at genital sites. Upon virus exposure of the genital mucosa of monkey models, mucosal-homing CD8 T cells dip during acute infection, suggesting they are homing to mucosal tissues (Figure 1). Recent reports on recombinant cytomegalovirus (CMV) vectors also show great promise in monkey models. These CMV vectors continually replicate and maintain high levels of activated T cells at multiple sites. A challenge for all live vector HIV vaccines is ensuring that they are safe and work effectively in people with pre-existing immunity to the vector. Recent studies of recombinant adenovirus vector HIV vaccines showed they were less effective and even could be promote infection in people with pre-existing immunity to adenovirus.

An additional major challenge for all HIV vaccines is the ability of the incoming HIV virus to mutate to escape immune responses. Immune escape occurs for both antibody and T cell-based vaccine strategies and likely occurs at both peripheral blood and mucosal tissues. Reducing replication to very low levels...
During early infection reduces the likelihood of escape and will be critical in future vaccine studies (Figure 1).

In summary, a major challenge for improved HIV vaccines is to understand how HIV vaccine regimens can induce effective peripheral and mucosal HIV-specific T cell immunity. The ability to quash the initial local mucosal replication of HIV following exposure should lead to protective immunity.

References

Biographies
Stephen Kent obtained his MBBS and MD degrees from Monash University and trained as an infectious diseases physician and vaccine immunologist in Melbourne and Seattle. He heads a vibrant HIV vaccine laboratory at the University of Melbourne.

Jeanette Reece completed her BSc (Hons) degree at the University of Melbourne in 1990 and has worked in the field of HIV vaccine research, both at Burnet Centre and the University of Melbourne. Since completing a Master of Public Health (MPH) in 2003, she worked in Professor Stephen Kent’s HIV vaccine laboratory at the University of Melbourne before taking up an NHMRC PhD scholarship in 2010. Jeanette is currently studying the ability of innovative vaccines to induce antiviral CD8 T cells in the mucosa using the SIV/macaque model.