M & I
Microbiology
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DISSERTATION SEMINAR

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“CD8+ T Cell Immunity in HIV-1 Infection.”

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ABSTRACT

Joanna Warren: CD8+ T Cell Immunity in HIV-1 Infection
(Under the direction of Nilu Goonetilleke)

There is no cure for HIV-1, largely because HIV-1 establishes a small but sustained pool of latently infected cells that are not cleared by antiretroviral therapy. We and others are investigating strategies to firstly reactivate the latent HIV-1 reservoir and then use T cell immunotherapy to clear reactivated cells. However, the presence of pre-existing T cell escape variants in the reservoir may limit CD8+ T cell recognition of HIV-1, and therefore the clearance of the reactivated cells. Currently, the level of pre-existing virus escape in the reservoir is unclear. In order to design effective T cell immunotherapies to boost and, or induce *de novo* T-cell responses, we investigated the landscape of T cell responses in durably suppressed HIV-1 infected participants.

HIV-1 specific T cell responses in HIV-1 infected durably suppressed participants were examined both cross-sectionally and longitudinally (weekly, monthly and yearly). T cell responses were measured against either overlapping peptides spanning the HIV-1 clade B consensus proteome, or previously defined optimal CD8+ T cell epitopes using *ex vivo* IFN-g ELISpot. Despite long-term viral suppression, HIV-1 specific T cell responses were maintained, robust, and were remarkably stable. Power calculations derived from these data suggest that group sizes as low as six are sufficient to examine the immunogenicity of T cell vaccines.

We next mapped HIV-1 specific T cell responses in HIV-1 durably suppressed participants against the HIV-1 clade B consensus proteome using *ex vivo* IFN-g ELISpot. In parallel, replication competent viruses derived from supernatants of autologous resting CD4+ T cells following mitogenic reactivation were sequenced, and variant peptides corresponding to reactive T cell epitopes were synthesized and tested for their impact on T cell response. HIV-1 escape was defined as a > 50% decrease in the average magnitude of the HIV-1 specific T cell response. We observed a cohort-level T cell escape frequency in the HIV-1 reservoir of 32% (49/151 epitopes) and an average within-participant escape frequency of 34%. HIV-1 escape was most commonly observed in Pol, Env and Nef HIV-1 proteins and occurred in less conserved regions of HIV-1. These data show that the majority of replication competent latent HIV-1 viruses do not harbor CD8+ T cell escape mutants, suggesting that immunotherapy approaches that boost CD8+ T cell responses can successfully target the latent reservoir in HIV curative and or remission strategies.