

TOPIC 08: IMMUNE ESCAPE**P08.01****Quantifying factors determining the rate of CTL escape and reversion during acute and chronic phases of HIV infection**

V.V. Ganusov¹, N. Goonetilleke², B. Korber³, G.M. Shaw⁴, A. McMichael² and A.S. Perelson³

¹University of Tennessee, Knoxville, Tennessee, USA; ²Oxford University, Oxford, United Kingdom; ³Los Alamos National Laboratory, Los Alamos, New Mexico, USA; ⁴University of Alabama, Birmingham, Alabama, USA

Background: Human immunodeficiency virus (HIV) often evades cytotoxic T cell (CTL) responses by generating variants that are not recognized by CTLs. However, the importance and quantitative details of CTL escape in humans are poorly understood.

Methods: We use a novel technique of single genome amplification (SGA) to identify longitudinal changes in the transmitted/founder virus from the establishment of infection to the viral set point at 1 year after the infection.

Results: We find that HIV escapes from virus-specific CTL responses as early as 30-50 days since the infection, and the rates of viral escapes during acute phase of the infection are much higher than were estimated in previous studies. However, even though with time virus acquires additional escape mutations, these late mutations accumulate at a slower rate. Depending on the mechanism of control of viral replication by the CTL response, we show that a number of factors could potentially contribute to a slower escape from CTL responses in the chronic phase of infection such decreased killing efficacy of epitope-specific CTLs, increased fitness cost, or increased diversity/magnitude of the CTL response. A poor correlation between the rate of CTL escape in a particular epitope and the magnitude of the epitope-specific CTL response suggests that the lower rate of late escapes is unlikely due to a low efficacy of the HIV-specific CTL responses in the chronic phase of the infection. Instead, our results suggest that late and slow escapes are more likely to arise because of high fitness cost to the viral replication associated with such CTL escapes.

Conclusion: Targeting epitopes in which virus escapes slowly or does not escape at all by CTL responses may, therefore, be a promising direction for the development of T cell based HIV vaccines.