Viral Genetic Circuits: How Noisy Transcriptional Feedback Controls Latency in HIV & Herpes

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Latent viruses exist in a dormant state and are thus problematic to treat, difficult to detect, and typically ensure life-long persistence of the virus in the host. For most viruses, the molecular regulation governing entry into, and exit from, latency is not understood. We focus on elucidating how transcriptional auto-regulatory circuits in HIV and the human herpesvirus cytomegalovirus (CMV) control latency in these two viruses. We previously showed how stochastic fluctuations in the HIV-1 Tat feedback circuit can control viral entry into latency by utilizing a simple *feedback-resistor* motif (Weinberger et al., **Cell** 2005, Weinberger et al., **PLoS Biology** 2006). Now, we present joint experimental and computational evidence that CMV, an important human pathogen that causes serious disease in newborns, transplant recipients, and AIDS patients, may control its lifecycle decisions via its regulatory "master circuit", the Major Immediate-Early (MIE) circuit.

CMV exhibits diverse replication behaviors in different human cell types: CMV rapidly lyses fibroblasts, persistently infects endothelial cells, slowly replicates in epithelial cells, and enters latency in CD34+ progenitor cells (Goodrum et al., 2004). The mechanisms driving this replication diversity remain unknown and understanding its basis is paramount for effective viral therapy. I will present joint experimental and computational analysis of CMV's MIE circuit and demonstrate how

dynamic switching inherent in the MIE circuit allows CMV to toggle between alternate replication behaviors in different cells.

Thus, we demonstrate how viral circuits (in particular HIV-1 and HCMV circuits) present novel and tractable systems for the quantitative study of mammalian regulatory feedback circuits.

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3. Goodrum, F., Jordan, C. T., Terhune, S. S., High, K., and Shenk, T. (2004). Differential outcomes of human cytomegalovirus infection in primitive hematopoietic cell subpopulations. Blood *104*, 687-695.