Discovery of Candidate T-Cell Antigens for HSV-1 Vaccines

February 20, 2012

J Graham

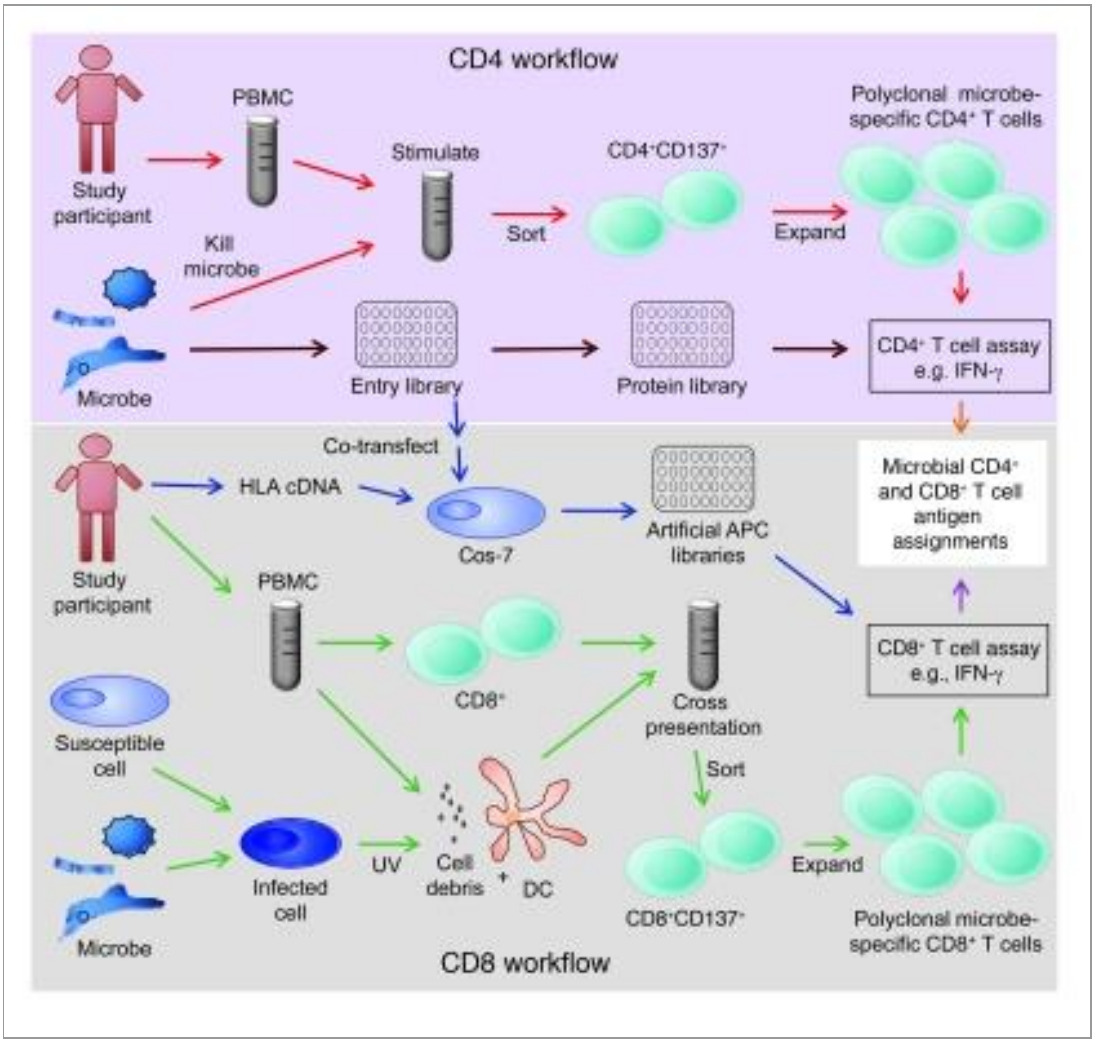
Herpes simplex virus type 1 (HSV-1) infects 60% of the US population, causing painful oral-labial infections and in some cases, permanent brain damage and blindness. Currently, all candidate HSV vaccines have failed in clinical trials, as they have been unable to stimulate coordinated CD4+ and CD8+ T-cell responses. Due to the large size of the genome and the low frequency of HSV-1-specific T cells, it has been difficult to select the best T cell antigens to be included in a candidate vaccine. To overcome this problem, lead author Lichen Jing and Vaccine and Infectious Disease Division affiliate investigator David Koelle have developed a novel method to efficiently generate a genome-wide map of responsiveness of HSV-1-specific T cells.

HSV-1-specific CD8+ T cells were detected and enriched using cross-presentation, in which HSV-1 antigen loaded dendritic cells presented the antigen to the T cells. Next, CD4+ T cells were reactivated by exposure to the whole killed HSV-1 antigen. Then, both types of HSV-1-specific T cells were enriched by selecting for CD137, a protein that identifies recently activated CD4+ and CD8+ T-cells. By sorting these specific cells from study participants, the cells could then be expanded for downstream testing to determine which antigens were most reactive. Because each person has a unique set of antigen presentation HLA genes, a personalized set of designer cells was created for the CD8+ T-cell discovery work.

The Koelle Lab found that the proteins for HSV-1 genes UL39 and UL46, previously not known to be CD8+ T-cell antigens, appeared to be the most useful vaccine candidates for coordinating both CD4 and CD8 T-cell responses. The gD antigen, which had previously been unsuccessful in a phase III clinical trial, was identified as a poor CD8+ T-cell antigen using this novel approach. Importantly, these methods were also successful for radically enriching CD8 and CD4 T-cells reactive with vaccinia virus. The methods outlined in this report may help streamline the antigen selection process for other pathogens with large genomes.

Jing L, Haas J, Chong TM, Bruckner JJ, Dann GC, Lichun D, Marshak JO, McClurkan CL, Yamamoto TN, Bailer SM, Laing KJ, Wald A, Verjans GMGM, Koelle DM. 2012. Cross-presentation

and genome-wide screening reveal candidate T cells antigens for a herpes simplex virus type 1 vaccine. *Journal of Clinical Investigation*; 122(2): 654–673



Thanks to Mindy Miner, PhD, for technical art