Response of helper (CD4+) T cells is critical to the induction of the adaptive immune response. Peptides derived from exogenous sources are presented on the surface of antigen presenting cells by class II MHC, and CD4+ T cells can recognize these peptides and become activated in a clone-specific manner. Treatment of a number of human diseases, particularly autoimmune disorders, would benefit from the identification of peptide antigens known to activate T cells. A system to identify CD4+ T cell-activating peptides from a combinatorial library is being developed. First, a model system using the hemagglutinin 307-319 peptide antigen and a cognate T cell hybridoma is being tested. Using microbial surface display, the peptide is delivered to antigen presenting cells (APCs) through phagocytosis. Peptide display is validated by flow cytometry. The surface peptide is engineered to be selectively processed and presented by class II MHC, which will in turn activate antigen-specific CD4+ T cells. Optimization of peptide release for specific APC types is underway. Preliminary results indicate that T cell stimulation by peptide delivery to macrophages and dendritic cells is feasible; attempts to screen mock peptide libraries to identify a known T cell antigen are ongoing.