A Systems View of T-cell Immunity Provides Multiple Opportunities for Therapeutic Intervention in Autoimmune Disease, Infection and Cancer

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Abstract
Clonal selection theory proposed that individual T-cells are specific for a single peptide–MHC antigen. However, the repertoire of Alpha-Beta T cell receptors (TCRs) is dwarfed by the vast array of potential foreign peptide–MHC complexes and a comprehensive system requires each T-cell to recognize numerous peptides and thus be cross reactive. This compromise on specificity has profound implications because the chance of any ligand being an optimal fit for its cognate TCR is small as there will almost always be more potent agonists. Furthermore, any TCR raised against a specific peptide–MHC in vivo can only be the best available solution from the naïve T-cell pool and is unlikely to be the best possible solution from the substantially greater number of TCRs that could theoretically be produced. This ‘systems view’ of TCR recognition offers a molecular explanation for the root cause of autoimmune disease and allows for manipulation of T-cell immunity so as to improve responses to HLA class I-restricted tumour-associated peptides. In this talk I will explore the therapeutic potential of enhanced T cell receptors and altered peptide [or non-peptide] TCR ligands.

Five Recent Key Papers
Varela-Rohena et al. (2008) Control of HIV-1 immune escape by CD8 T-cells expressing enhanced T-cell receptor Nature Medicine, 14, 1390-95.


Sewell AK (2012). Why must T cells be crossreactive? Nature Reviews Immunology 12, 669-677

Liddy et al. (2012) Monoclonal TCR_redirected tumour cell killing Nature Medicine, 18, 980-7

For further details see: www.tcells.org