MS02-1-1 Disulfide bond formation between T-cell receptor and peptide epitope lowers the threshold of activation
#MS02-1-1

C. Szeto [1], P. Zareie [2], A. Riboldi-Tunnicliffe [3], N. La Gruta [2], S. Daley [4], S. Gras [1]
[1]Department of Biochemistry and Chemistry, La Trobe Institute for Molecular Science, La Trobe University - Bundoora (Australia), [2]Infection and Immunity Program, Monash Biomedicine Discovery Institute and Department of Biochemistry and Molecular Biology, Monash University - Clayton (Australia), [3]Australian Synchrotron, Australian Nuclear Science and Technology Organisation - Clayton (Australia), [4]Centre for Immunology and Infection Control, School of Biomedical Sciences, Faculty of Health, Queensland University of Technology - Brisbane City (Australia)

Abstract
The immune system is vigilant in detecting foreign pathogens. Our cells present peptide epitopes (p) atop Major Histocompatibility Complex (MHC) glycoproteins on the cell's surface. They are monitored by T cells that use their unique T cell receptors (TCRs) to recognize and bind to pMHCs, where the quality of binding influences T cell activation. Activated T cells can eliminate and control infection, clearing the body of infectious diseases. The binding parameters that dictate T cell activation for this inter-cellular TCR-pMHC interaction remains unclear. The long reigning hypothesis is that a binding affinity threshold controls T cell activation. However, T cell therapeutics that engineer T cell receptors to increase binding affinity have had limited success in generating safe and efficacious therapeutics. Here, we have engineered a disulfide bond (S-S) between a TCR and peptide epitope within a well-studied TCR-pMHC model. The formation of this S-S bond was validated using X-ray crystallography and biophysical assays. We show that the covalent S-S bond does not allow dissociation of the TCR-pMHC complex and indefinitely prolongs the bond lifetime. This leads to a 50-fold increase in sensitivity for T cell activation, without loss of epitope specificity or change in binding affinity. Thus, we reveal a novel design for the engineering of T cell receptors that could be useful in future T cell therapeutics.