Objectives: To test the hypothesis that low or absent ERAP1 activity alters CD8 T cell immunity through changes in the HLA-B51 peptidome and shapes the CD8 T cell immune response in affected subjects.

Methods: We generated HLA-B51* ERAP1 KO LCL clones using CRISPR-Cas9, performed mass spectrometry of the immunoprecipitated MHC-class I peptidome with subsequent computational deconvolution for HLA-B51-binding peptides. We then assessed single cell (ICS), bulk (ELISA) and proliferative (CFSE) CD8 effector (IFNγ, granzyme B, perforin) T cell responses through stimulation of allogeneic donor cells with WT vs KO LCL and determined ERAP1 haplotypes in 49 untreated Turkish BD patients with ocular and/or major vascular involvement and other cardiovascular abnormalities as heart donors (HD) whose PBMC were profiled using 6 multiplex flow cytometry panels. Results: WT and KO peptides differed significantly (p<0.0005 Fisher's exact test) with a distinctive shift of peptide length frequencies exceeding 9-mer (binding optimal) in the KO vs WT. This held true for computationally deconvoluted HLA-B51 binders, which were enriched in peptides with a specific shift in length distribution exceeding 9-mer. We show that absence of functional ERAP1 alters human CD8 T cell function. This is mediated by an HLA-class I peptidome with propensity for longer peptides above 9mer and suggests loss of de novo presentation of peptide-HLA-B51 complexes to cognate CD8 T cells. The reciprocal changes in antigen-experienced vs naive CD8 T cell subsets point to biological significance of HLA-B51/Hap10 in BD. Collectively, our findings suggest that a modified HLA-B51 peptidome modulates immunogenicity of CD8 effector T cells in ERAP1/KO carriers with BD and identity targets for future drug development.

References:

Conclusion: Once remission is reached in GCA patients under TCZ treatment, optimization of dose with IV TCZ or by prolonging dosing interval with SC TCZ may be performed. Based on our experience it could be performed by reducing the dose of IV TCZ or by prolonging dosing interval with SC TCZ.