Government of **Western Australia**
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Fiona Stanley Fremantle Hospitals Group

HIV-specific T cell clonotypes may contribute to the abacavir hypersensitivity reaction via heterologous immunity

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Introduction

Drug hypersensitivity (DHR) is a common immune mediated reaction which can be associated with severe illness including rash, hepatitis, DRESS/SJS and occasionally death. How sensitization occurs and the underlying immunological mechanism by which a drug can induce an immune response is unclear. One proposed theory is that of heterologous immunity whereby virus-specific T cells may cross-react against drug altered peptide repertoire presented on autologous HLA molecules. We hypothesized that HIV-specific T cells themselves may be capable of recognising the abacavir altered peptide repertoire presented on autologous HLA-B*57:01.

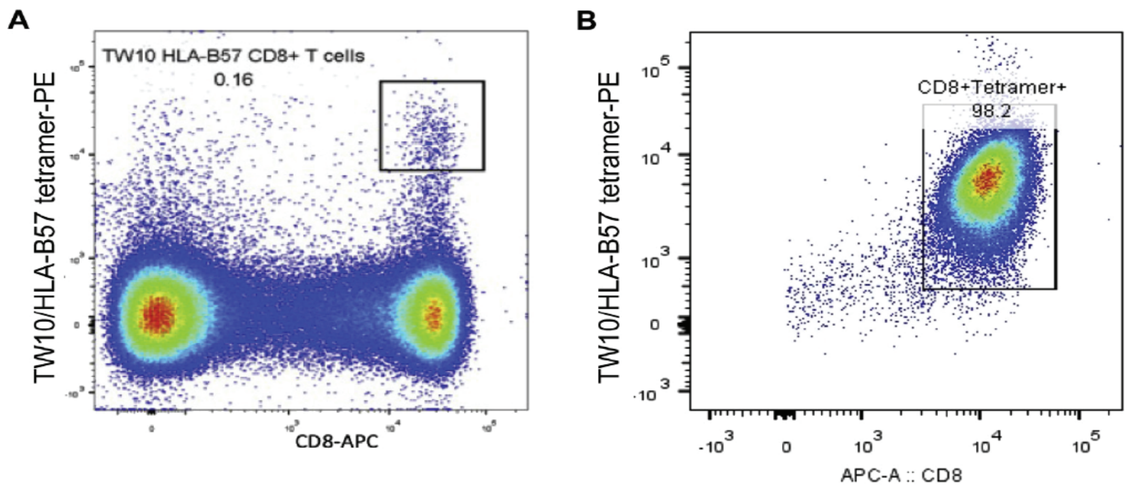
Methods

Multiple HIV-specific HLA-B57 restricted CD8 T cell clones were generated from HIV seropositive individuals, using single cell sorting based on HIV peptide/HLA tetrameric complex staining. The generated T cell clones were assayed for autologous HLA-B57 specific reactivity, in the presence (or absence) of abacavir. Cytokine assay, CD137 upregulation and cytotoxicity were used as readout.

Results

Abacavir exposure did induce *de-novo* recognition of autologous HLA-B57 by HIV-specific T cells. A HIV Gag TW10/HLA-B57 specific CD8 memory T cell clone with TRBV10-3 usage recognised autologous HLA-B57 only in the presence of abacavir. Other HIV-specific T cell clones sorted from the same individuals with the same specificities, but with different TCR Vβ usage, did not recognize HLA-B57 in the presence of abacavir suggesting TCR Vβ specificity of drug induced HLA-class I immunorecognition.

Figure 1: Generation of HIV-specific T cell clones. **A.** TW10/HLA-B57 tetramer staining of PBMCs from patient 2. The identified HIV Gag TW10-specific T cell population then underwent single-cell sorting into 96-well plates. **B.** An HIV-specific T-cell clone was generated by using single-cell sorting based on Gag TW10/HLA-B*57:01 tetramer staining. Clone 457 is shown here. Clone 484 is identical to clone 457 and produced identical results. *APC, Allophycocyanin; PE, phycoerythrin*. **C.** TCR sequence of abacavir/HLA-857-reactive clones. Clonality of HIV Gag TW10/B57-restricted CD8 memory T-cell clones 457 and 464 confirmed by means of single-cell sorting and TCR sequencing. Both clones expressed identical TCR CDR3s and cross-reacted against autologous HLA-B57 only in the presence of abacavir.



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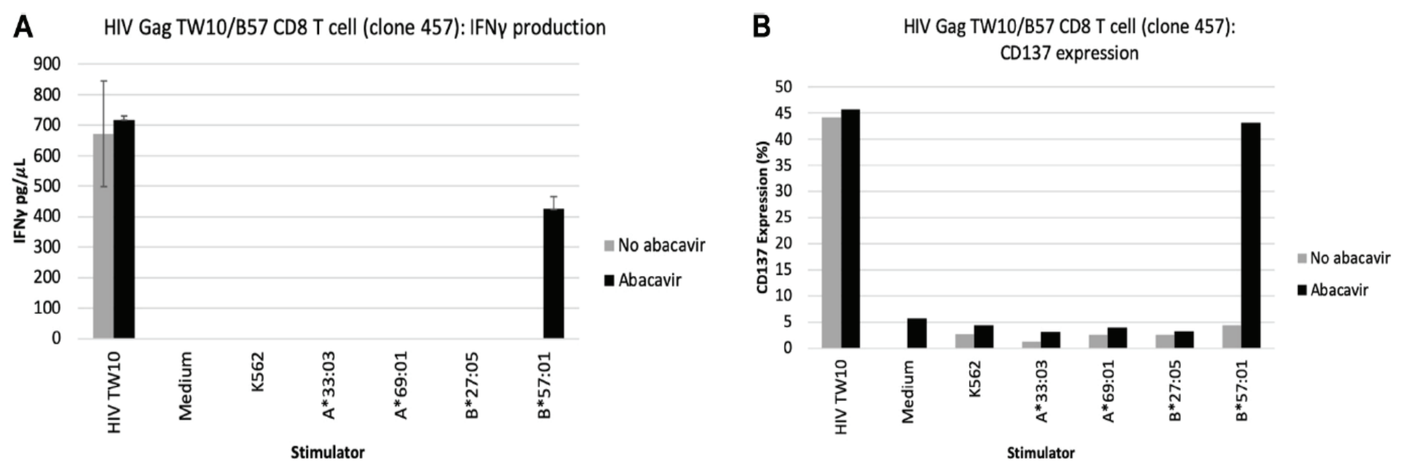
Clone	Specificity	V	D	J	CDR3 AA	CDR3 DNA
457	HIV Gag TW10/HLA-B57	TRAV39*01 TRBV10-3	 TRBD1*01	TRAJ40*01 TRBJ2-5*01	CAVDINTSGTYKYIF CAISRQGARQETQYF	 TGTGCCATCAGTAGACAGGGGGCGAGGCAAGAGACCCAGTACTTC
464	HIV Gag TW10/HLA-B57	TRAV39*01 TRBV10-3	 TRBD1*01	TRAJ40*01 TRBJ2-5*01	CAVDINTSGTYKYIF CAISRQGARQETQYF	 TGTGCCATCAGTAGACAGGGGGCGAGGCAAGAGACCCAGTACTTC

Figure 2: A HIV Gag TW10/HLA-B57 restricted T cell clone recognizes autologous HLA-B57 only in the presence of abacavir. (A and B) A Gag TW10/HLA-B57 specific T cell clone 457, from an HLA-B*57:01 expressing HIV seropositive individual, did recognize autologous HLA-B*57:01 only in the presence of abacavir, using IFNγ production and CD137 upregulation as readout. Abacavir did not induce recognition of any other autologous HLA molecules. Therefore exposure to a drug can induce de novo recognition of autologous (self) HLA molecules by virus-specific CD8 T cells. IFNγ experiments performed in duplicate.
*** p<0.001.



Conclusion

Pre-existing HIV-specific CD8 memory T cells themselves may participate directly in abacavir-induced HSR. It is likely that immune activation following modification of the HLA peptide repertoire by drugs is a generalized phenomenon that leads to autologous HLA-recognition from all cell populations, including pre-existing virus-specific T cells. Results presented here may have major clinical implications for investigation and management of drug HSR reactions.

Reference

1. Almeida et al. Virus-specific T cell clonotypes might contribute to drug hypersensitivity reactions through heterologous immunity. J Allergy & Clinical Immunology 2019 *(In press)*

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