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# Deciphering anti-HCMV HLA-E-restricted unconventional CD8 T-cell responses in seropositive HCMV+ hosts

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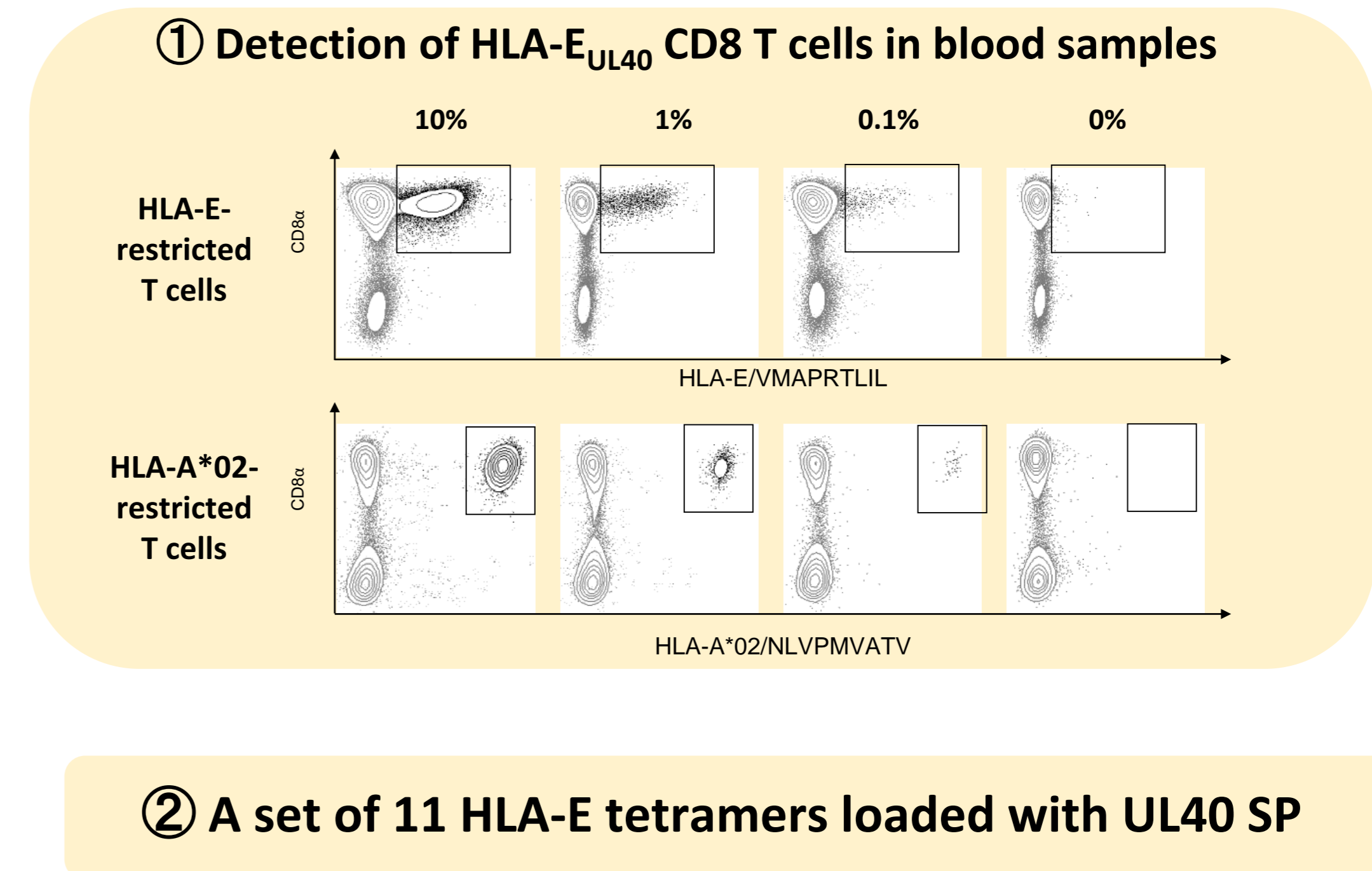
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## Summary

Human cytomegalovirus (HCMV) causes severe illness and poor outcome in immunocompromised hosts such as transplant recipients and HIV-infected patients. Cytotoxic CD8 T cells against HCMV antigens (pp65, IE1) presented by classical HLA class-I molecules are major cellular components of the protective anti-HCMV immunity. HLA-E-restricted CD8 T cells targeting HCMV UL40 leader peptides (Lp) have been recently reported as unconventional T-cell responses also observed in some hosts but they still need clinical and functional characterization. Our study aimed to provide a qualitative and quantitative *ex vivo* analysis of HLA-E<sub>UL40</sub> CD8 T-cell responses, in a large cohort (n=144) of kidney transplant recipients and healthy volunteers, and to elucidate determining factors. HLA-E<sub>UL40</sub> CD8 T-cells were detected in >30% of seropositive HCMV+ hosts and may represent >30% of total circulating CD8 αβT cells at a time point. We identified host-related genetic factors (HLA-A\*02 and HLA-E genotype) and HCMV strain, determining the sequence of UL40Lp, as critical parameters for this response. HLA-E<sub>UL40</sub> CD8 are effector memory T cells that appear early post-infection as monoclonal/oligoclonal populations and persist for life. Although specifically induced in response to HCMV infection, a key feature of these cells is their potential ability to be also responsive against self and allogeneic HLA resulting from sequence homology between HLA-I<sub>Lp</sub> and UL40Lp. Thus we established that unconventional HLA-E<sub>UL40</sub> CD8 T cells belong to the common immune arsenal against HCMV. Their functions remain to be defined toward infection as well as their potential side effect in contexts such as autoimmunity and transplantation.

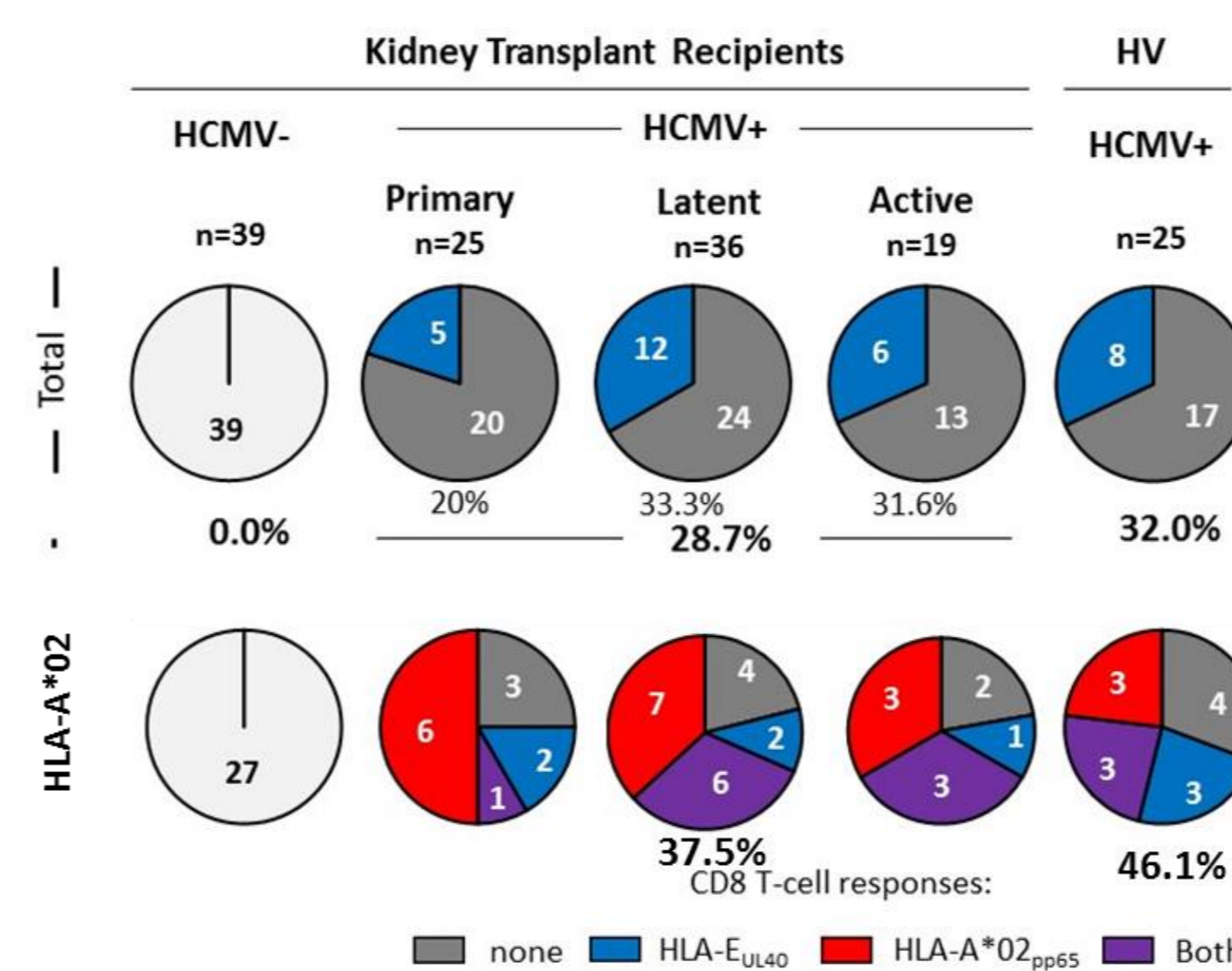
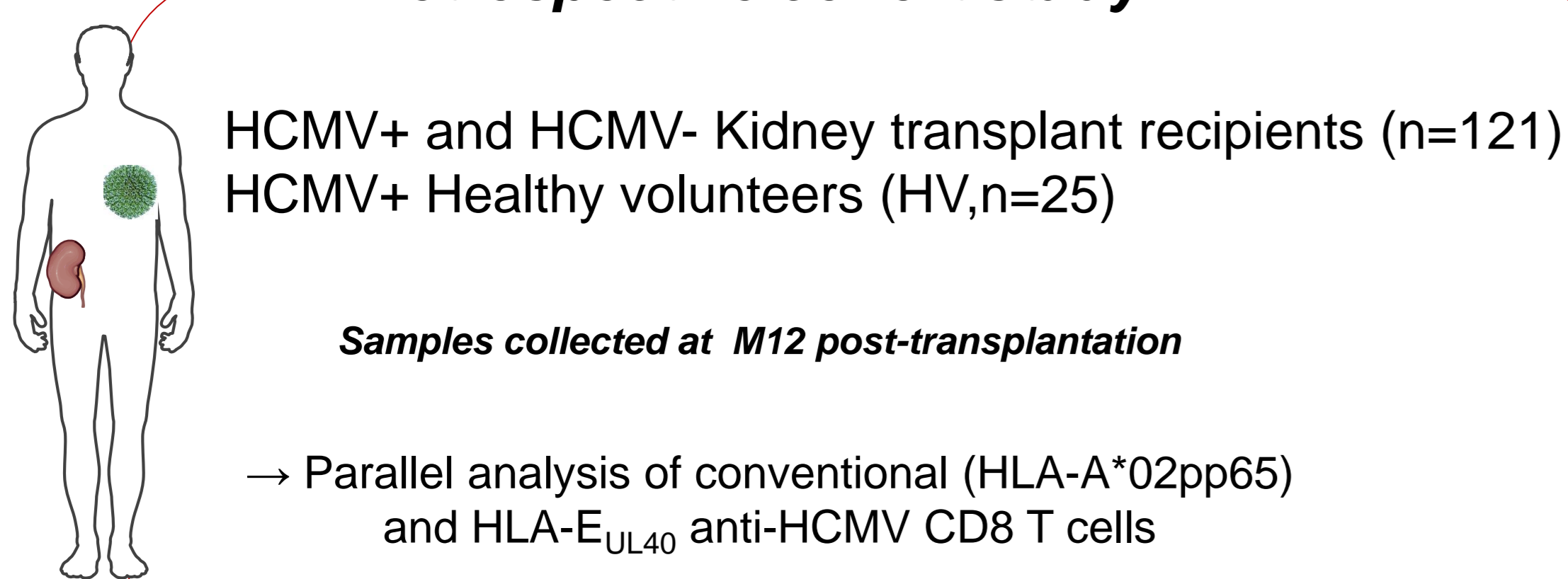
## 1. Starting point: A specific & sensitive assay



UL40-specific HLA-E-restricted CD8 T cells were analysed *ex vivo* in blood samples after PBMC isolation using a multi-parameter (CD3+CD8α+TCRβδ-) flow cytometry assay subsequent to the blockade of the CD94 receptor. Our protocol allows a sensitive (threshold of detection: 0.1% of total CD8 TCRαβ T cells) and peptide-specific analysis of HLA-E<sub>UL40</sub> CD8 T-cell populations. Banked blood samples, harvested at M12 post-transplantation, were investigated using a set of HLA-E tetramers loaded with 8 different UL4015-23 peptides to encompass the usual UL4015-23 variability among common HCMV strains. The 8 HLA-E tetramer/peptide complexes were tested individually.

## 2. Detection of anti-HCMV HLA-E-restricted CD8 T cells in HCMV seropositive kidney transplant recipients

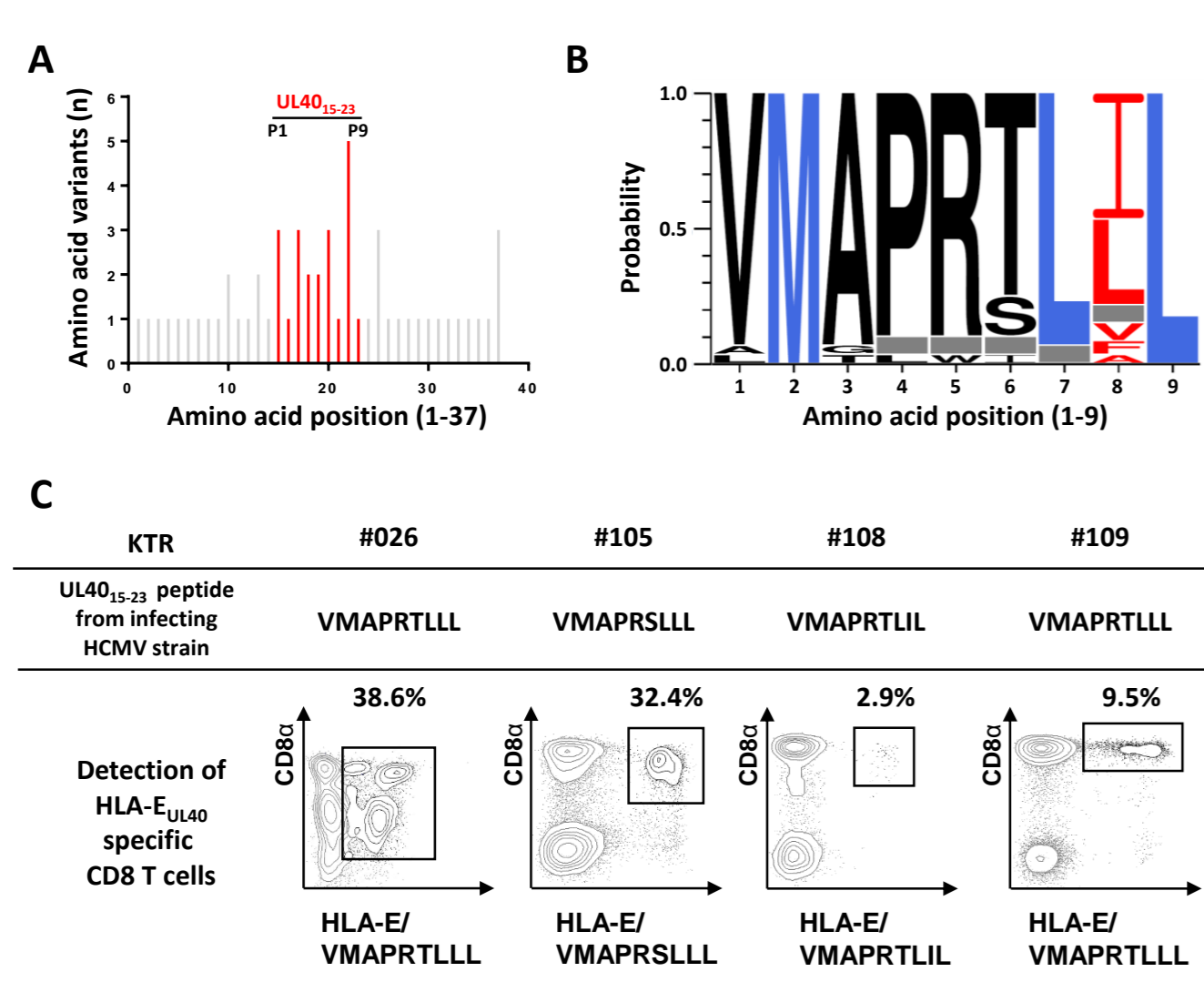
### A retrospective cohort study



Detection of UL40-specific HLA-E-restricted CD8 T cells. Our results reveal a very high incidence (>30%) of HLA-E<sub>UL40</sub> CD8 T-cell responses in HCMV+ hosts with no significant difference between transplanted patients and healthy individuals suggesting that antiviral and immunosuppressive regimens have no impact of these cell subsets at M12. These cells are detected more frequently in hosts carrying an HLA-A\*02 allele. Unconventional CD8 T cells can be detected independently of detectable conventional HLA-A\*02pp65 T-cell response. Presence of HLA-E<sub>UL40</sub> CD8 T cells early post-infection (primary or reactivation) as well as at latency suggests long lived cell subsets consistent with memory anti-HCMV response.

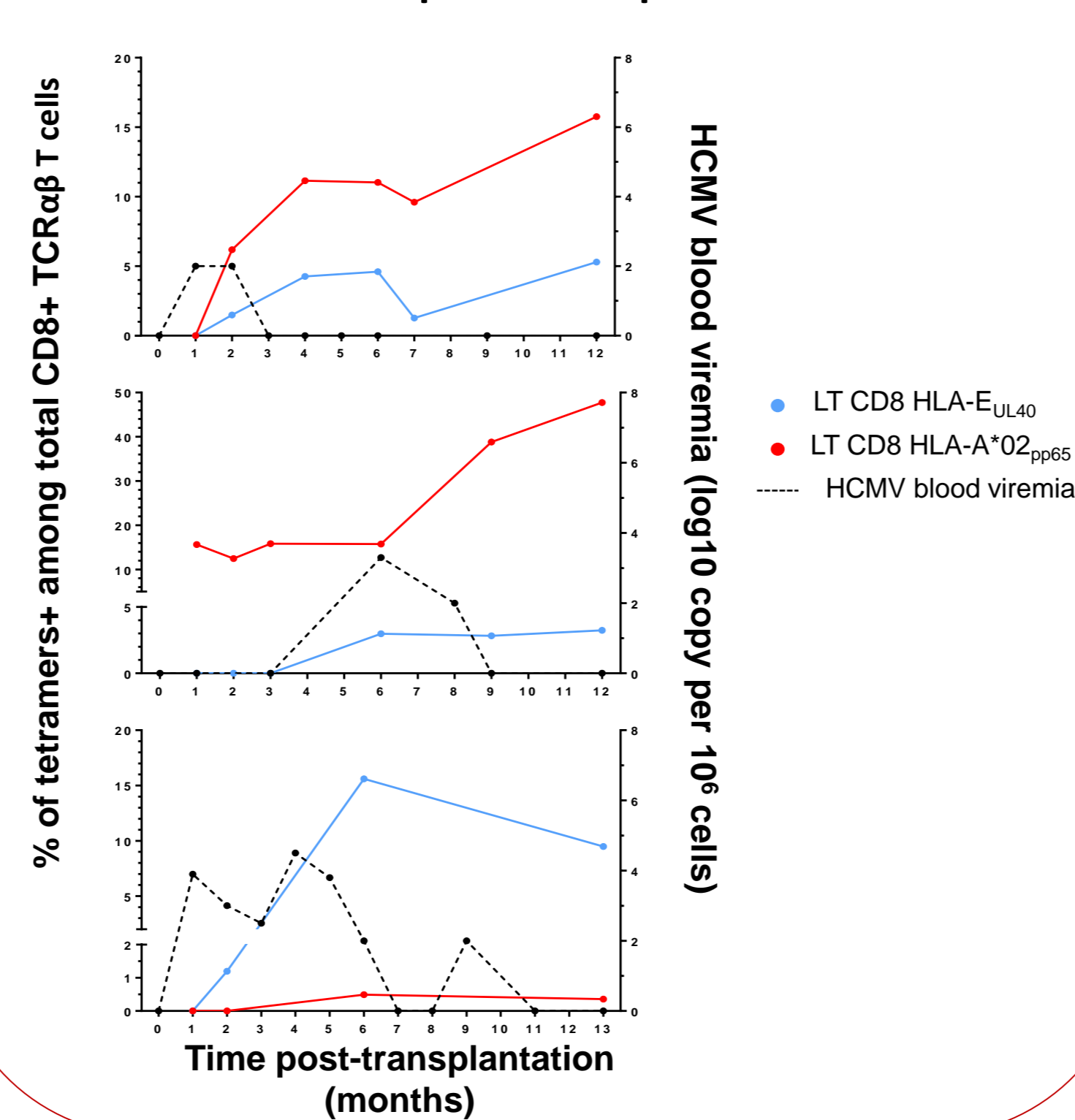
## 3. Characteristics of anti-HCMV HLA-E-restricted CD8 T cells in hosts

### HLA-E<sub>UL40</sub> CD8 T cells target viral UL40<sub>15-23</sub> sequence in a strain-specific manner

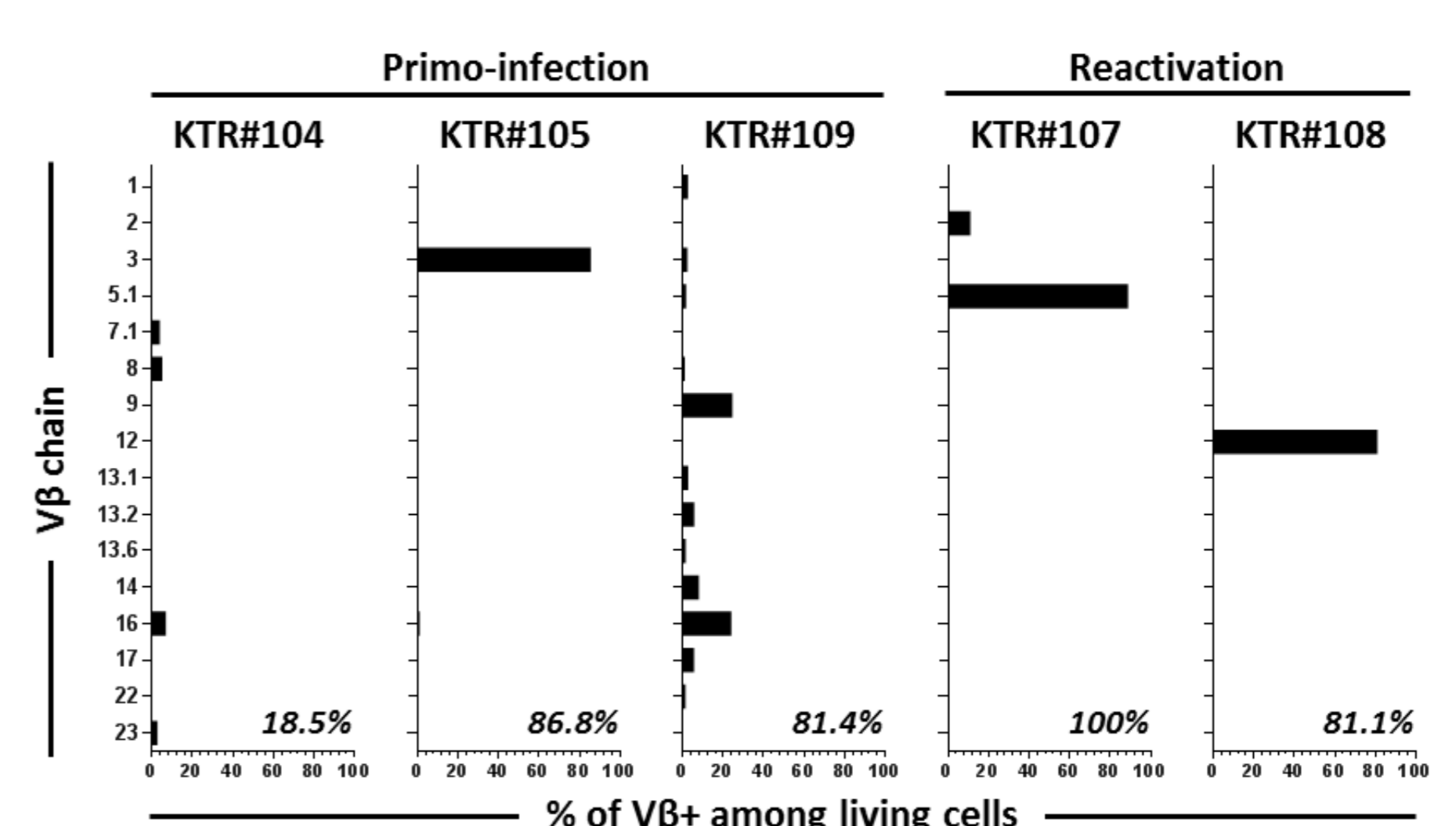


HLA-E<sub>UL40</sub> CD8 T-cell responses were investigated using HLA-E tetramers loaded with the UL40 peptide that we identified in their own infecting strain, HCMV strain-specific HLA-E-restricted T cells were detected in patients. Importantly, percentages of total HLA-E<sub>UL40</sub> CD8 T cells vary from 2.9% up to 38.6% of total CD8 αβT cells in the blood sample at the time of detection.

### Time course and magnitude of HLA-E<sub>UL40</sub> and HLA-A\*02pp65 CD8 T-cell responses are parallel

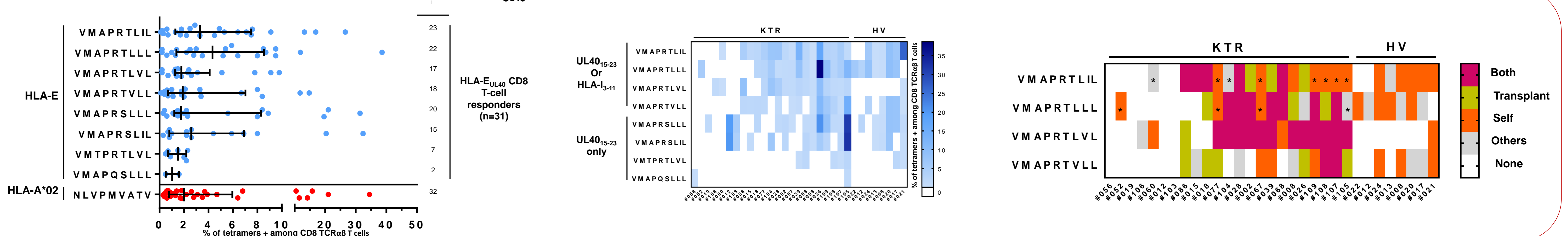


### UL40<sub>15-23</sub>-specific HLA-E-restricted CD8 T cells are effector memory T cells with broad TCR Vβ repertoire and peptide recognition



HLA-E<sub>UL40</sub> CD8 T-cell population expressing a dominant Vβ chain sub-family was obtained for 3 patients while another one gives rise to oligoclonal populations (from 2 to 6 subsets detected) with variable distribution. This suggests the sorting of multiple, coexisting, HLA-E<sub>UL40</sub> CD8 T-cell populations in this patient. Interestingly, a broad TCR-Vβ repertoire was found with 16 Vβ identified (Vβ1, 2, 3, 5.1, 7.1, 8, 9, 12, 13.1, 13.2, 13.6, 14, 16, 17, 22 and 23) thus enlarging the Vβ repertoire previously described for these cells.

### HLA-E<sub>UL40</sub> CD8 T-cell responses display potential recognition of self and allogeneic HLA peptides



## Conclusion

HCMV infection frequently leads to the long-term persistence of a large subset of unconventional, HLA-E-restricted, CD8 T lymphocytes directed against a strain-specific viral peptide but that display potential autologous and allogeneic recognition.