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# T-Cell Receptor Sequencing in Liquid Biopsies from NSCLC Donors

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## ABSTRACT

**Introduction:** T-cell clonal expansions can be measured by sequencing the antigen-specific loci in the T-Cell Receptor beta gene (TCRβ). TCRβ sequencing is being explored in oncology research as a predictor for response to immunotherapy as well as immune related adverse events. In this study peripheral blood lymphocyte (PBL) specimens from donors previously diagnosed with NSCLC were evaluated using TCRβ sequencing. Additionally, to model T-cell repertoire changes due to antigen stimulation, primary peripheral blood mononuclear cells (PBMC) were challenged *in vitro* with cytomegalovirus (CMV) antigen.

**Methods:** PBMC from 4 healthy donors were challenged with whole-cell lysate from CMV-infected cells or CMVpp65$_{495\text{-}503}$ peptide (NLVPMVATV). T-cell repertoire perturbations were assessed using the Oncomine TCR Beta-SR Assay and Ion GeneStudio S5 Sequencer. A pp65 tetramer flow cytometry assay was used as an orthogonal method to assess clonal expansion of pp65-specific T-cells. For evaluation of the assay in PBL from NSCLC donors, five whole blood specimens were evaluated using the same sequencing workflow.

**Results:** The TCR Beta assay identified 6,683-61,936 unique clones from 1-2 million reads per sample and an average of 80% of the total reads were usable for TCR profiling. In the NSCLC donors, TCR convergence and clonality values were consistent with published results and ranged from 0.016-0.033 for convergence and 0.09-0.48 for clonality. In the model antigen study, TCR sequencing detected the expansion of a family of clones common to all donors in response to pp65 peptide stimulation and the rate of expansion correlated to % increases in pp65 tetramer staining.

**Conclusions:** This study demonstrates the utility of profiling of the TCRβ repertoire in a model system and in donors with NSCLC. It additionally demonstrates correlation of RNA-seq methods and protein-tetramer analysis using flow cytometry. These techniques represent an emerging solution that could complement other liquid and tissue diagnostic assays in the clinic and may be of value in predicting host responses/resistance and adverse events to immunotherapies. Prospective clinical studies are on-going in which the developed TCR Beta assay will undergo further validation.

**Keywords:** TCR Sequencing, Liquid biopsy, Ion torrent, Immunotherapy

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