

NGS-BASED IMMUNOLOGY PANEL: APPLICATIONS IN PRECLINICAL IMMUNO-ONCOLOGY RESEARCH

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Background Cancer immunogenomics encompassing tumor cells and tumor microenvironment (TME) is critical for unravelling the complexity of tumor immunity, understanding the mechanism of action (MOA) for immunotherapies, and revealing potential predictive/pharmacodynamic biomarkers. We previously described a new and comprehensive 1080 mouse immuno-oncology (I/O) gene RNA-Seq panel (mouse I/O RNA-Seq panel) that has an improved dynamic range for rare IO transcripts and is more cost effective over conventional microarray assays (e.g., NanoString nCounter Mouse Pan-Cancer IO 360™ Panel) when analyzing bulk tumor samples. In this study, we set out to explore its applications in preclinical IO studies evaluating immune checkpoint inhibitor (ICI) response.

Methods A panel of 14 mouse syngeneic tumors was profiled using the mouse I/O RNA-Seq panel to benchmark the baseline expression of IO transcripts and compared to the tumor-infiltrate leukocyte (TIL) analysis of the same tumors by flow cytometry. The pharmacodynamic profiles of selected syngeneic models upon ICI and CD4+ cell depletion treatment was also examined to reveal potential MOAs.

Results The panel of syngeneic models had a differential profile of response to ICI, TIL infiltration and IO gene expression. The mouse I/O RNA-Seq panel gene expression highly correlated with that from whole transcriptome sequencing (RNA-Seq) across the panel of syngeneic models, but mouse I/O RNA-Seq panel showed generally > 12x higher sensitivity for comparable sequencing data sizes. Using a collection of comprehensive gene signatures for TIL lineage identification, the mouse I/O RNA-Seq panel revealed rich TIL components in syngeneic mouse tumors that were confirmed by flow cytometry demonstrating the value and depth of coverage in studying TME at the gene expression level without the need for a wide array of antibodies and complex gating operations in flow cytometry and also the potential scalability of mouse I/O RNA-Seq assay. The mouse I/O RNA-Seq panel was then used for pharmacodynamic profiling upon anti-PD-1 antibody and CD4+ cell depletion treatment, and revealed different IO related pathway activity changes, with higher accuracy than the NanoString 360™ Panel.

Conclusions With NGS-based technology becoming ubiquitous, our mouse I/O RNA-Seq panel can be a powerful, fast and cost-effective solution in the preclinical IO research, improving our understanding of the tumor and immune cell interactions in unprecedented detail and in response to immunotherapeutics.

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