Immune checkpoint blockade unleashes Mucosal Associated Invariant T (MAIT) cells in tumor microenvironment of NSCLC patients

Pakhi Birla¹, Boyang Zhang², Jiajia Zhang¹, Ananya Gulati³, Lansaoi Yang⁴, Ramona Johnson¹, Alex Lee¹, Kellie Smith¹, Cynthia Sears¹, Fyza Shaikh¹, Franck Housseau, and Drew Pardoll¹

¹Johns Hopkins University School of Medicine, ²Stanford Univ., ³Johns Hopkins Univ., ⁴Johns Hopkins Bloomberg Sch. of Public Hlth.

Mucosal associated invariant T (MAIT) cells are innate like T-cells that recognise non-peptide metabolite antigens presented on monomorphic MHC related-1 (MR1) making them an attractive off the shelf tool for cancer immunotherapy. In this study, we investigate the function of MAITs in the tumor microenvironment of neoadjuvant anti-PD1 treated lung cancer patients (NCT02259621). Paired single cell RNA/TCR sequencing analysis revealed an oligoclonal expansion of MAITs comprising of canonical TRAV1-2 and non-canonical MAITs TRAV1-2. TCR capture from canonical MAIT clonotypes confirmed their in vitro recognition of 5-OP-RU, a bacteria derived riboflavin derivative. However, the nature of antigens recognised by non-canonical MAITs remains poorly understood. On mining transcriptional profiles of MAITs, we observed a high clonal amplification of canonical MAITs whereas the non-canonical clonotypes expressed a strong activation/exhaustion gene signature. This suggests that both these MAIT populations recognise different types of antigens, are differentially activated, and respond to immune checkpoint blockade (ICB), the non-canonical MAITs being highly dysfunctional. Using bacterial 16S RNA amplicon and metagenomics sequencing, we seek to identify microbial and metabolomic signatures associated with MAIT activation and response to ICB. Our findings will provide further insights into the nature of ligands recognised by MAITs and the mechanisms associated with MR1 dependent recognition and killing of tumor. Investigating the role of unconventional T-cells in response to ICB has the potential to reveal new tumor-associated antigens which could open up avenues for innovative combination immunotherapies.