THE USE OF SMALL MOLECULE INHIBITORS TO TARGET NOVEL PATHWAYS IN EXHAUSTED T CELLS FOR IMMUNO-ONCOLOGY THERAPEUTIC INTERVENTION

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Background The ability to reverse exhaustion in CD8+ T cells holds great promise for therapeutic intervention in oncology. Indeed, treatment with therapeutics targeted at checkpoint inhibitors, such as Nivolumab (anti-PD-1), have shown great promise in the treatment of a subset of individuals and tumour types. However, pre-clinical success does not always translate to success in clinical trials and resistance to these approaches is prevalent. As such, there is a pressing need to develop novel approaches that target alternative pathways for use alone or potentially in combination with checkpoint inhibitor modulation. A secondary need is the requirement for advanced assays that accurately recapitulate the pathways and cell phenotypes prevalent in the tumour environment.

Methods Here we describe the characteristics of an *in vitro* human T cell exhaustion assay whereby *in vitro* stimulated T cells phenotypically and functionally recapitulate the exhausted T cells found within the tumour microenvironment. We also demonstrate the effect of checkpoint blockade as well as small molecule inhibition of a novel target on the exhausted T cell phenotype.

Results In this assay, exhaustion can be partially but not fully reversed by treatment with anti-PD-1 alone. In addition, we demonstrate the effect of a small molecule inhibitor targeting IKZF3, a transcription factor shown to be upregulated in T cell exhaustion, on reversing T cell exhaustion alone and in combination with checkpoint inhibitor blockade.

Conclusions These assays and approaches enable investigation into the ability of compounds to influence reversal of T cell exhaustion where anti-PD-1 treatment does not fully reverse the exhausted phenotype and offers the ability to test combination therapy approaches.

Acknowledgements This work was aided by the valuable input and insight of Professor Stephen Anderton.

Ethics Approval The study obtained ethics approval from West Midlands – Black Country Research Ethics Committee under IRAS project ID 270936. All donors gave informed consent before taking part.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.251>