Background Patients with tumors characterized by high antigen diversity have shown increased response rates to immune checkpoint inhibitors. It follows that modulation of the cancer immunopeptidome offers a new therapeutic strategy to generate de novo anti-tumor T-cell responses and overcome current challenges of existing IO therapeutics. ERAP1 and ERAP2 represent a novel category of therapeutic targets in IO that can be manipulated to drive detection of cancer cells through modulation of the cancer antigen repertoire. We have previously described the preclinical development of the First-in-Class (FIC) ERAP1 inhibitor, GRWD5769, which has now entered Phase I clinical trials. ERAP2 has a distinct substrate specificity suggesting that inhibition of ERAP2 will generate a different cancer antigen repertoire thereby providing an opportunity to increase the number of responding patients and deepen existing responses. Here, we describe activities to validate ERAP2 as a target for the treatment of cancer and develop FIC inhibitors.

Methods ERAP2 rs2248374 is a loss-of-function variant whereby a premature stop codon causes nonsense-mediated RNA decay of the ERAP2 transcript. The association of ERAP2 rs2248374 with cancer progression and survival was determined through analysis of The Cancer Genome Atlas (TCGA) database. ERAP2 inhibitors were characterized in a suite of assays such as enzyme assays, crystallography, CETSA and functional antigen presentation assays. Importantly, the impact of modulating ERAP2 function on the immunopeptidome was assessed using a classical proteomic pipeline.

Results The presence of rs2248374 provides a significant 5-year survival advantage in several TCGA cancer types and an overall survival advantage across all cancers for patients who are homozygous for this single nucleotide polymorphism (SNP). Strikingly, patients with urothelial bladder carcinoma showed significant dose-dependent increases in survival based on the number of copies of the rs2248374 ‘knock-out’ SNP. A screening cascade has been established to optimise FIC ERAP2 small molecule inhibitors. As a result, potent and selective lead compounds with good ADME and PK properties have been identified. Modulation of ERAP2 function in human cancer cells leads to qualitative and quantitative changes in the cancer immunopeptidome that is distinct from ERAP1 inhibition.

Conclusions ERAP2 is a genetically-validated target for human cancer and member of an emerging category of therapeutic targets in the antigen presentation pathway that can alter the visibility of cancer through generation of novel cancer antigens. Current efforts are focused on optimizing our lead FIC ERAP2 inhibitors and validating ERAP2 inhibition in human and mouse cancer models.

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