

1131

GRWD5769: A FIRST-IN-CLASS INHIBITOR OF ERAP1, GENERATING NOVEL CANCER ANTIGENS TO DRIVE DE NOVO ANTI-TUMOR T CELL RESPONSES

¹Peter Joyce*, ¹Andrew Leishman, ²Asolina Braun, ¹Mitul Patel, ¹Michael Pinggera, ¹Jessica Sette, ¹Kate Anderton, ³Edd James, ¹Valeriya Shunina, ²Anthony Purcell, ⁴Nicola Temette, ⁵Jason Shiers, ¹Martin Quibell, ⁴Wayne Paes, ¹Tom McCarthy. ¹Grey Wolf Therapeutics, Oxford, UK; ²Monash University, Melbourne, Australia; ³University of Southampton, Southampton, UK; ⁴University of Oxford, Oxford, UK; ⁵Signature Discovery, Nottingham, UK

Background Immune checkpoint inhibitors (ICI) have changed the cancer treatment paradigm, yet significant unmet need remains. Clinical data demonstrates increased antigen presentation diversity, genomic instability, tumor mutational burden and HLA diversity are all factors that improve clinical response to ICI.^{1,2,3} Further, the effectiveness of ICI is limited by the permanent exhaustion of pre-existing cytotoxic T cells, caused by chronic cancer antigen stimulation.⁴ Endoplasmic reticulum aminopeptidase 1 (ERAP1) trims peptides loaded into classical and nonclassical MHC Class I.⁵ In cancer, knockout or inhibition of ERAP1 changes a proportion of the antigen repertoire, generating and up-regulating cancer antigens.^{6,7} This leads to the activation of de novo anti-tumor T cell responses, causing tumour growth inhibition and bypassing a key resistance mechanism in immuno-oncology (IO), T cell exhaustion. We report the preclinical development, characterisation and mechanistic analysis of the first-in-class ERAP1 inhibitor, GRWD5769.

Methods Immunopeptidomics was used to assess the impact of ERAP1 inhibition on the cancer antigen repertoire, thus determine proof of mechanism. T cell receptor (TCR) repertoire sequencing, RNAseq and immunohistochemistry established the ability of ERAP1 inhibition to drive a differentiated T cell response in syngeneic mouse models and primary human immune cell co-cultures.

Results Extensive analysis of the immunopeptidomes of diverse cancer cell lines robustly showed that GRWD5769 modulates the cancer-related antigen repertoire across genotypes and cancer-type backgrounds. Novel or upregulated neoantigens generated by ERAP1 inhibition are conserved across cancer cell types and genetic backgrounds. ERAP1 inhibition diversified the TCR repertoire, up-regulated prognostic immune gene markers in the tumor, including markers for recently activated (thus non-exhausted) T cells, and drove infiltration of T cells into syngeneic mouse model tumours. ERAP1 inhibition is efficacious across syngeneic models, including different mouse strains. Importantly, the effects of ERAP1 inhibition on the T cell response correlate with efficacy. Further, ex vivo human T cell co-cultures demonstrate that novel and upregulated neoantigens generated by ERAP1 inhibition drive tumour cell killing.

Conclusions Grey Wolf Therapeutics' first-in-class, ERAP1 inhibitor clinical candidate, GRWD5769, drives novel anti-tumor T cell responses through neoantigen creation, circumventing T cell exhaustion, a key resistance mechanism in IO. GRWD5769 has completed GLP toxicology studies, has a very good safety profile and clear path forward to first patient dosed. Extensive biomarker development has resulted in development of proof of mechanism and proof of principle biomarkers that will be used to establish the activity and efficacy of GRWD5769 in patients in 2023.

REFERENCES

1. Rizvi N, Hellmann MD, Snyder A, *et al.* Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;**348**(6230):124–128.
2. Chowell D, uc G T Morris LGT,2 3, Grigg CM *et al.* Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy. *Science* 2018;**359**(6375):582–587
3. Chowell D, Chirag Krishna, Federica Pierini *et al.* Evolutionary divergence of HLA class I genotype impacts efficacy of cancer immunotherapy. *Nature Medicine* 2019;**25**(11):1715–1720
4. Oliveira G, Stromhaug K, Klaeger S, *et al.* Phenotype, specificity and avidity of antitumour CD8+ T cells in melanoma. *Nature* 2021;**596**:119–125
5. Shastri N, Nagarajan N, Lind KC, *et al.* Monitoring peptide processing for MHC class I molecules in the endoplasmic reticulum. *Curr Opin Immunol*. 2014;**26**:123–127.
6. James E, Bailey I, Sugiyarto G, *et al.* Induction of protective antitumor immunity through attenuation of ERAAP function. *J Immunol*. 2013;**190**(11):5839–5846.
7. Manguso RT, Pope, HW, MD Zimmer *et al.* In vivo CRISPR screening identifies Ptpn2 as a cancer immunotherapy target. *Nature* 2017;**547**(7664):413–418

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.1131>