A novel library of optimal affinity KRAS mutation-specific T cell receptors associated with multiple HLAs, in combination with a PD1-41BB armoring and enhancement costimulatory switch receptor

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Background

- Activating mutations in the Kirsten rat sarcoma (KRAS) gene are highly prevalent oncogenic driver mutations in human cancers associated with transgene-induced and aggressive tumor growth [1].
- M240 K114Q (mKRAS) is estimated to be present in >300,000 patients with high prevalence found in prostate (81.72%), colorectal (13.78%) and non-small cell lung cancer patients (23.82%) [2].
- mKRAS variants elicit T cell responses, with G012(G201R), G12V (Q61R) and G12D (Q61K) being the most common [3].

- Despite the recent approval for targeted therapies targeting G12C mutations (Kisun) the primary need for further efficacious immunotherapies remains.

- Using our ‘End-to-End Platform’ to develop best-in-class TCR-T cell therapy [4] we are building a library of optimal affinity mKRAS-specific T cell receptor (TCRs) that recognize multiple mutations and other human leukocyte antigen (HLA) alleles. These TCRs are further combined with PD1-41BB armoring and enhancement costimulatory switch receptor (CSR) to address the challenges in hostile tumor microenvironments (TME) [5].

Here we show our development approach and predictive data for our mKRAS library (G012(G201R)/G12V/G12D).

High-throughput TCR generation delivers multiple, unique candidate TCRs

- T cells of multiple healthy donors were primed using dendritic cells (pDC/HLA-A11:181 priming), acquiring diverse TCR repertoire for comprehensive high-throughput functional screens rapidly identified five unique candidate TCRs for in-depth characterization.

In-depth testing to select optimal TCRs for specificity, sensitivity and safety

- TCR-PD1-41BB-transduced GBM T cells were co-cultured with target cells loaded with either mKRAS-G012(G201R) or G12V peptide or HLA-A02 positivity, with wildtype cells used as controls.
- PD1-41BB-transduced T cells were co-cultured with target cells loaded with either mKRAS-G12D or G12V peptide or HLA-A02 positivity.
- mKRAS variants were represented in GBM T cells.
- TCR-PD1-41BB-transduced GBM T cells were co-cultured with target cells loaded with G12V or G012(G201R) peptide in the presence of inhibitors for HLA-A02 positivity.

Conclusions

- Our high-throughput TCR generation process with early functional screens delivers multiple, unique mKRAS G012(G201R)-specific lead candidate TCRs.
- Proprietary vetoing algorithm allows selection of optimal affinity TCRs with exclusive mKRAS-G012(G201R) specificity, high peptide sensitivity with strong tumor cell recognition and a favorable safety profile (25 TCR).
- mKRAS-G012(G201R)-specific TCRs combined with PD1-41BB CSR and enhanced T cell functions to develop best-in-class TCR-T therapies to address the challenges of a hostile TME and improve patient outcomes.
- Our multi-dimensional library of mKRAS-specific 25 TCRs targeting multiple mutations and HLAs alleles, are in improve outcomes for a broad global population suffering from difficult-to-treat solid tumors.

References

[8] Nakanishi K et al., Clin Cancer Res. 2022;28(8):1482