FROM EXHAUSTION TO MEMORY: ALTERING T CELL FATE IMPROVES IMMUNOTHERAPEUTIC RESPONSES TO CANCER
Nicole Scharping*, Allison Cafferata, Maximilian Heeg, Quynhanh Nguyen, Ananda Goldrath. University of California San Diego, San Diego, CA, USA

Background In cancer, CD8+ T cells have the power to target and kill tumor cells with precision but often fail due to chronic activation from the immunosuppressive tumor microenvironment (TME), differentiating into a dysfunctional cell state known as exhaustion. In healthy tissues, T cells differentiate into tissue-resident memory cells (TRM) in response to infection, which remain lodged in tissues to provide protection from reinfection. When TRM cells are found in patient tumors, they correlate with improved responses to immunotherapy and patient outcomes. Understanding how to manipulate T cell fates to avoid exhaustion and favor TRM characteristics could benefit cancer immunotherapy.

Methods To explore differences between these cell states, we screened the core TRM gene expression signatures for genes downregulated as T cells differentiate to terminal exhaustion. Targets were then overexpressed in antigen-specific T cells and adoptively transferred into tumor-bearing mice for analysis.

Results We found many genes related to protein regulation were identified, including multiple E3 ubiquitin ligases with not well-described targets. When these genes are individually overexpressed in tumor-specific T cells, we found the transduced T cells express less inhibitory receptors and showed enhanced anti-tumor function: increased accumulation in the TME, upregulation of TRM markers, and polyfunctional cytokine production, which resulted in controlled tumor growth and increased mouse survival in multiple cancer models.

Conclusions These results highlight the understudied field of negative regulation of T cell function by protein degradation in T cell differentiation fate and function, and uncovers potential gene targets for immunocellular therapies to favor functional T cell fates in cancer.