

## BATF and IRF4 Cooperate to Counter Exhaustion in Tumor-Infiltrating CAR-T Cells

Researchers at the La Jolla Institute for Immunology have discovered that two transcription factors, BATF and IRF4, cooperate to counter T cell exhaustion in tumor-infiltrating lymphocytes. As such, the researchers have generated BATF- and IRF4-overexpressing CAR-T cells that cooperate with IRF4 and lead to the generation of long-lived memory T cells that control tumor recurrence.

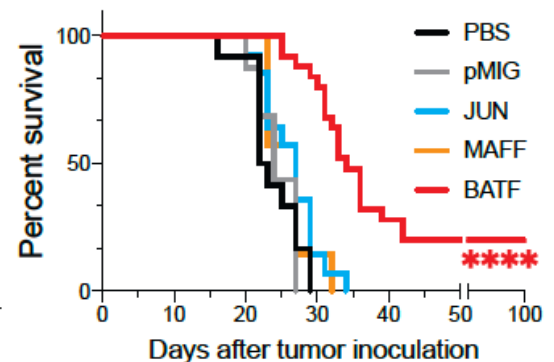
CD8<sup>+</sup> T cells that infiltrate solid tumors and are exposed to prolonged antigen stimulation in the absence of adequate co-stimulation enter a hyporesponsive, “exhausted” state in which they do not effectively destroy tumor cells. Both the effector and exhaustion responses of CD8<sup>+</sup> T cells are initiated by TCR signaling, in which the transcription factor NFAT plays a pivotal role. Recent attention has focused on two downstream targets of NFAT - NR4A and TOX. Previous research shows that restoring NFAT interaction with its binding partner AP-1 prevents CD8<sup>+</sup> T cell exhaustion.

Similar to NFAT, BATF can contribute both to effector function and exhaustion, depending on the biological context. Here, researchers at LJI show that the overexpression of BATF and IRF4 in CAR-T cells leads to a marked increase in the survival and expansion of tumor-infiltrating cells, increases the ability of the CAR TILs to produce cytokines and granzymes after stimulation, and reduces their expression of inhibitory cell surface receptors and the exhaustion-associated transcription factor TOX. In fact, tumor-bearing mice that had previously received BATF-transduced CD8<sup>+</sup> T cells and rejected the tumor developed long-lived memory T cells that controlled tumor recurrence.

### ADVANTAGES:

- Leads to an increased survival and expansion of CAR TILs
- Increases ability of CAR TILs to produce cytokines and granzymes
- Reduces CAR TIL expression of inhibitory cell surface receptors and exhaustion factors

*BATF- and IRF4-overexpressing CAR-T cells counter exhaustion within the tumor microenvironment*



*Mice transfected with BATF-overexpressing CAR-T cells showed increased survival compared to controls*