Chimeric antigen receptor T (CAR-T) cell therapeutics have been successful at driving remissions in several B cell malignancies, but their efficacy against most tumor types remains limited. An emerging strategy to increase CAR-T efficacy against solid tumors is to arm CAR-T cells with additional transgenes encoding immunomodulatory payloads such as IL-12, that weaken the tumor and its supportive microenvironment, and enhance the anti-tumor effector functions of T cells. However, several clinical trials investigating the use of armed T cell therapeutics have demonstrated that immunomodulatory payload arming necessitates stringent payload expression control to prevent systemic payload exposures, which can limit therapeutic efficacy and persistence, and simultaneously drive toxicity and severe adverse events.

Methods Here we report the repurposing of a native T cell gene regulatory node, that operates post-transcriptionally to prevent effector cytokine expression in quiescent T cells, as a cellular engineering platform that conditionally affects transgenic payload expression exclusively in activated CAR-T cells. We have applied this cellular engineering platform develop aTnMuc1 CAR-T cells armed conditionally with IL-12. TnMuc1 is a hypoglycosylated variant of MUC1, an antigen expressed by many Adenocarcinomas but not by healthy cells.

Results Our anti-TnMuc1 CAR-T cells armed conditionally with IL-12 dramatically outperformed cognate unarmed aTnMuc1 CAR-T cells in vitro and in vivo. anti-TnMuc1 CAR-Ts armed conditionally with IL-12 exhibit very low levels basal IL-12 expression in quiescent states, and efficiently cleared tumors at low CAR-T doses in multiple preclinical Adenocarcinoma models; cognate unarmed anti-TnMuc1 CAR-T cells were unable to clear these tumors at any dose level. Additionally, tumor-bearing mice dosed with anti-TnMuc1 CAR-T cells armed conditionally with IL-12 demonstrated no weight loss and had low serum IL-12 levels.

Conclusions These data demonstrate the utility of applying a native T cell gene regulatory mechanism to produce highly efficacious, conditionally armed CAR-T cells. Based on the results of our preclinical data, we are advancing anti-TnMuc1 CAR-T cells armed conditionally with IL-12 for clinical trials to confirm these results in humans.