Background Autologous chimeric antigen receptor (CAR) T cell therapies have revolutionized the treatment of B cell malignancies, leading to long-term remission in 30-40% of certain patient populations. Despite the promising clinical efficacy of CAR T cells in hematologic malignancies, major limitations hinder their widespread application, including challenges for patient access, complex manufacturing, and high cost.

Methods To overcome these challenges, we have developed VivoVec, a surface-engineered lentiviral vector-based platform harboring a CAR transgene that is being developed for off-the-shelf use for the generation of CAR T cells in vivo. To achieve specific and efficient in vivo T cell transduction, VivoVec particles are pseudotyped with the Cocal fusion glycoprotein and an anti-CD3 single chain variable fragment (scFv), and we have previously shown that these first-generation particles generate CAR T cells in vivo that mediate antitumor activity.

Results We have advanced the VivoVec platform through incorporating costimulatory molecules into the particle surface, in addition to the anti-CD3 scFv and Cocal fusion glycoprotein. These second-generation VivoVec particles exhibit enhanced T cell binding and activation, resulting in increased transduction and greater numbers of CAR+ T cells in vitro. In addition, CAR T cells generated with second-generation VivoVec particles exhibited a less-differentiated, central memory-like phenotype and enhanced CAR-antigen-specific polyfunctionality, including cytokine production, proliferation, and tumor cell killing. Finally, in a humanized NSG mouse model of B cell malignancy we observed that second-generation VivoVec particles generated greater numbers of CAR T cells in the blood, resulting in enhanced antitumor activity at lower doses compared to first-generation particles. Our results indicate that incorporation of costimulatory molecules onto the surface of VivoVec particles increases both the overall number and functionality of the resulting CAR T cells, greatly augmenting VivoVec mediated CAR T cell generation and antitumor activity in vivo.

Conclusions Overall, these data demonstrate that second-generation VivoVec particles efficiently generate large numbers of highly functional CAR T cells able to mediate durable tumor control in a preclinical model of B cell malignancy. VivoVec particles have the potential to overcome many of the limitations associated with the current class of CAR T cell therapies.