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CRISPR/CAS9 GENE-EDITED ALLOGENEIC CAR-T CELLS TARGETING CD33 SHOW HIGH PRECLINICAL EFFICACY AGAINST AML WITHOUT LONG-TERM HEMATOPOIETIC TOXICITY

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Background CD33 is the most consistently expressed antigen in AML, with high levels and homogeneous expression observed in malignant AML cells from most patients, including those with relapsed disease. Normal myelomonocytic cell lineages and a percentage of hematopoietic progenitors also express CD33, and the extreme myeloablation caused by the CD33-targeted antibody-drug conjugate (ADC) gemtuzumab ozogamicin reinforced concerns about targeting this antigen with more potent agents such as T-cell engaging bispecific antibodies and CAR-T cells. We have shown previously that allogeneic CRISPR/Cas9 gene-edited CAR-T cells targeting CD33 with TRAC disruption to reduce GvHD and B2M disruption to reduce allogeneic host rejection could eliminate tumors in xenograft models of AML.

Methods Given that off-target activity of the toxin could contribute to the myeloablation seen with CD33-targeted ADCs, we created in vitro and in vivo models to examine reconstitution of the myeloid compartment following treatment of CD33-targeted allogeneic CAR-T cells.

Results Although co-culture of CD34+ stem cells in vitro with our CD33-targeted allogeneic CAR-T cells did significantly deplete the cell population, colonies still formed after removal of the CAR-T cells as the presumably CD33-negative stem/progenitor cells expanded and differentiated. A similar phenomenon was observed in vivo with CD34 humanized mice bearing an AML tumor (THP-1 cells) and treated with the CD33-targeted allogeneic CAR-T cells. The CAR-T cells completely eradicated the THP-1 tumor but did not lead to long-term myelosuppression or B cell aplasia.

Conclusions Thus, allogeneic CRISPR/Cas9 multiplex gene-edited CD33-targeted CAR-T cell therapy may be both efficacious and tolerable in AML.

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