A NOVEL PERIPHERAL BLOOD MONONUCLEAR CELL HUMANIZED MOUSE MODEL FOR PRECLINICAL EFFICACY AND TOXICITY EVALUATION OF CHIMERIC ANTIGEN RECEPTOR T-CELL IMMUNOTHERAPY

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Background Chimeric antigen receptor T (CAR T)-cell therapy has emerged as a revolutionary treatment for certain hematological malignancies. While several CAR T therapies showed an efficacious response in selected patients, wider adoption of the therapy is challenged due to toxicity which can be life-threatening, and high relapse potentials (~50%). Clinically we are unable to predict CAR T-cell therapy-associated toxicities and efficacy and thus, need to be addressed and modeled at the individual level. Here, we developed a novel peripheral blood mononuclear cell (PBMC)-humanized mouse model to assess the efficacy and toxicity of CAR T-cell therapy simultaneously. This model reflects individual donor variations recapitulating observed clinical levels of toxicity and efficacy.

Methods NSG™ variants, including NSG™-MHC I/II-double knock-out mice that show delayed graft-versus-host disease, were humanized using human PBMCs. PBMC-humanized mice were treated with autologous CAR T-cells targeting CD19, and efficacy, toxicity, and CAR T-cell expansion were assessed. To evaluate these parameters in the presence of tumors, humanized mice were injected with luciferase-tagged human B-cell lymphoma Raji tumor cells.

Results Autologous CD19 CAR T-cell treatment in highly humanized mice showed significant mortality compared to the PBS treatment. When the humanization level was optimized by adjusting the number of PBMCs, the humanized mice showed great efficacy by reducing the target cells in the blood and spleen, and significant human cytokine release, including IFN-γ, IL-10, IL-6, IL-3, and RANTES. This model measures differential toxicity, human cytokine release, and CAR T-cell expansion in different PBMC donors, suggesting that the model can address the individual difference. In the presence of tumor, CAR T-cell treatment induced significantly higher human cytokines (IL-10: ~12,000 pg/mL, IL-6: ~850 pg/mL), as well as greater CAR T-cell expansion, compared to the mice without the tumor.

Conclusions In summary, we have developed a novel humanized mouse model to test the preclinical efficacy and toxicity of CAR T-cell immunotherapy. The assay is rapid that can be completed in 12-16 days. The model captures donor variability, and CAR T dose-response, in both efficacy and toxicity, such as cytokine release and body weight loss. Our novel humanized mouse model can potentially be used to predict an outcome in the clinic at the individual level.

Ethics Approval The Jackson Laboratory Institutional Animal Care and Use Committee and institutional review board approved all protocols used.