EDIT-202, an AsCas12a and SLEEK™ gene-edited iPSC-derived NK cell therapy maintains prolonged persistence, high cytotoxicity, and enhanced in vivo control of solid tumors


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INTRODUCTION

• EDIT-202 is an engineered NK cell product under development to address the unmet need for treating solid tumors.
• Natural killer (NK) cell-based immunotherapy is a promising therapeutic approach for solid tumors because of its intrinsic tumor-killing capacity, minimal treatment-related toxicities, and ability to be administered to patients as an off-the-shelf therapy.
• NK cell effector function is diminished by a lack of functional persistence and tumor-intrinsic immunosuppressive mechanisms, such as the production of the pleotropic cytokine transforming growth factor beta (TGF-β). Furthermore, the ability of NK cells to exert antibody-dependent cellular cytotoxicity (ADCC) is impaired once CD16 is cleaved off NK cell activation. These biological limitations can be overcome with powerful editing tools that enable multiplexed gene editing of cells.
• EDIT-202 cells have been engineered with EDITas’ proprietary AsCas12a and the SLEEK gene editing tool to knock in CD16 and mibl-15 and knock out CISH and TGFβ2R. This prolongs persistence, enhances ADCC, and resists TGF-β-mediated immunosuppression in the tumor microenvironment.

RESULTS

• iPSCs were edited with an engineered AsCas12a to knock in CD16 and mibl-15 using the SLEEK™ method. Simultaneously, iPSCs were also edited with AsCas12a to knock out CISH and TGFβ2R. iPSC clones were selected and differentiated into NK cells. Surface expression of CD16 and mibl-15 by EDIT-202 cells was shown by flow cytometry (Fig. 1).
• In vitro persistence was measured by culturing wild-type (WT) and EDIT-202 cells in basal media without supporting cytokines for 21 days (Fig. 2).
• A fluorescent lactate dehydrogenase (LDH) release assay using SKOV3-3, FaDu, or A549 tumor cells was performed to assess 2D cell tumor killing (Fig. 3). CD16 shedding was analyzed by extracting NK cells from the 2D killing assay after 48 hours and running flow cytometry (Fig. 4).
• A 3D tumor spheroid killing assay using Incucyte® imaging of NucLight®-Red–tagged SKOV-3 cells was used to determine NK cell cytotoxicity (Fig. 5 and 6).
• Non-obese diabetic (NOD) severe combined immunodeficient (scid) gamma (NSG) mice were inoculated intravenously with 0.125 × 10⁶ 15Rα expression compared with WT

OBJECTIVE

To characterize and evaluate the anti-tumor efficacy of EDIT-202, an induced pluripotent stem cell (iPSC)–derived natural killer (NK) cell therapy that has CD16 and membrane-bound interferon-15 (mibl-15) knockin and in cytokine-inducible SH2-containing protein (CISH) and transforming growth factor β receptor 2 (TGFβR2) knocked out using EDITas’ proprietary engineered, highly active, and highly specific AsCas12a and SLEEK™ technology.

METHODS

• Number of independent experiments: 1.
• Number of mice per group: 5; ****

CONCLUSIONS

• EDIT-202 had significantly higher levels of CD16 and mibl-15 compared with WT NK cells, indicating that our SLEEK™ technology is a robust method for editing iPSCs.
• EDIT-202 had prolonged cytokine-independent persistence in vitro compared with WT NK cells, indicating that the mibl-15 knock-in in EDIT-202 cells is sufficient for survival and maintenance.
• CD16 showed significantly higher ADCC-mediated cytotoxicities against ovarian SKOV3-3, head and neck FaDu, and lung adenocarcinoma A549 tumor cells. Activated EDIT-202 induced significantly higher levels of IFN-γ.
• EDIT-202 cells had upregulated and continuous expression of CD16 after tumor exposure, which enabled the cells to significantly induce serial killing of SKOV-3 tumor cells compared with WT NK cells. EDIT-202 serial killing capacity was not affected in the presence of immunosuppressive TGF-β.
• In an in vivo SKOV3-3 solid tumor model, EDIT-202 + TRA treatment led to a significant reduction in lung tumor burden compared with TRA only and resulted in complete tumor clearance in multiple mice.
• When combined with TRA, EDIT-202 significantly increased survival over TRA only treatment in the solid tumor SKOV-3 model. At Day 100, 100% of 1× 10⁶ EDIT-202 + TRA treated mice were alive, whereas there was 0% survival with TRA only.
• These data support the development of EDIT-202 as a potential allogeneic cell-based medicine for treating solid tumors.

REFERENCES


DISCLOSURES


ACKNOWLEDGMENTS

This work was funded by Editas Medicine. The authors would like to thank all their Editas Medicine colleagues for helping with the work, and present their thanks to A. G. A. for providing expert assistance with the science. This work was supported by the Charité Medical School, with financial support from Editas Medicine in accordance with Good Practice Guidelines (GPP).

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