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A novel KIR3DL2-directed CAR T-cell therapy for cutaneous and systemic T-cell lymphomas

Federico Mario Aletti, MD[1,a]; Jinsheng Weng, MD, PhD[1]; Cao Cuong Le, PhD[1]; Matthew D. Richard, BSc[1]; Abdur Rehman, PhD[1]; Selin Kolsuz, MD[1]; Xiaoyun Cheng, MBBS[1]; Sridevi Patchva, MBBS[1]; Yongfu Tang, PhD[1]; Chun-Yen Lin, PhD[1]; Jingjing Cao, BSc[1]; Kamini Singh, PhD[1]; Swati Mohapatra, PhD[1]; Karan L. Chohan, MD[1]; Shiv G. Rawat, PhD[1]; Jinsong Wei, BSc[1]; Faezeh Darbaniyan, PhD[1]; Fuliang Chu, PhD[1]; Jingwei Liu, MD[1]; Neeraj Saini, MD[1]; Michael R. Green, PhD[1]; Francisco Vega, MD, PhD[1]; Swami P. Iyer, MD[1]; Rafael Casellas, PhD[1]; Sattva S. Neelapu, MD[1]

[1] University of Texas MD Anderson Cancer Center, Houston, TX, USA

Corresponding author
[a] Federico Mario Aletti, MD, University of Texas MD Anderson Cancer Center, Houston, TX, USA
Email: faletti@mdanderson.org

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Abstract

Background

Chimeric antigen receptor (CAR) T-cell therapy targeting pan-B-cell antigens has achieved unprecedented clinical efficacy in B-cell malignancies. However, extending this approach to T-cell malignancies by targeting pan-T-cell thymic antigens (e.g. CD5 and CD7) has been challenging due to the risk of T-cell aplasia and fratricide. To address these limitations, we developed a CAR targeting killer cell immunoglobulin-like receptor, three Ig domains and long cytoplasmic tail two (KIR3DL2/CD158k), a post-thymic antigen with limited expression in NK and T cells but highly expressed in cutaneous T-cell lymphomas (CTCL), particularly Sézary syndrome (SS) and transformed mycosis fungoides. Elevated KIR3DL2 expression has also been reported in up to 38% of peripheral T-cell lymphomas (PTCL), including hepatosplenic T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, enteropathy-associated T-cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, extranodal NK/T-cell lymphoma, nasal type, and PTCL not otherwise specified.

Methods

We generated a novel anti-KIR3DL2 monoclonal antibody and designed single-chain variable fragment (scFv)-based CAR constructs with different spacer and signaling domains. CAR-transduced primary T cells were tested in various in vitro and in vivo functional assays.

Results

Peripheral blood mononuclear cell phenotyping in 15 healthy donors confirmed restricted KIR3DL2 expression in NK cells and terminally differentiated CD8 T cells (Fig. 1A). Lentiviral transduction yielded high and stable CAR expression in primary T cells (Fig. 1B). Anti-KIR3DL2 CAR T cells exhibited selective cytotoxicity against HUT-78 (SS cell line) and KIR3DL2-expressing HH (CTCL cell line) but not against isogenic KIR3DL2-negative cell lines. Cytolytic activity was sustained at effector-to-target ratios as low as 1:10 and across repeated tumor rechallenges (Fig. 1C and data not shown). Anti-KIR3DL2 CAR T cells also showed increased degranulation, proliferation, and

cytokine release compared to donor-matched activated untransduced T cells upon co-culture with target cells (Fig. 1D-F). NSG mice treated with anti-KIR3DL2 CAR T cells, but not control T cells, exhibited sustained tumor eradication and increased survival in two different cell line-derived xenograft models (HH-KIR3DL2+ and HUT-78) and one PTCL patient-derived xenograft model (Fig. 2A-E and data not shown).

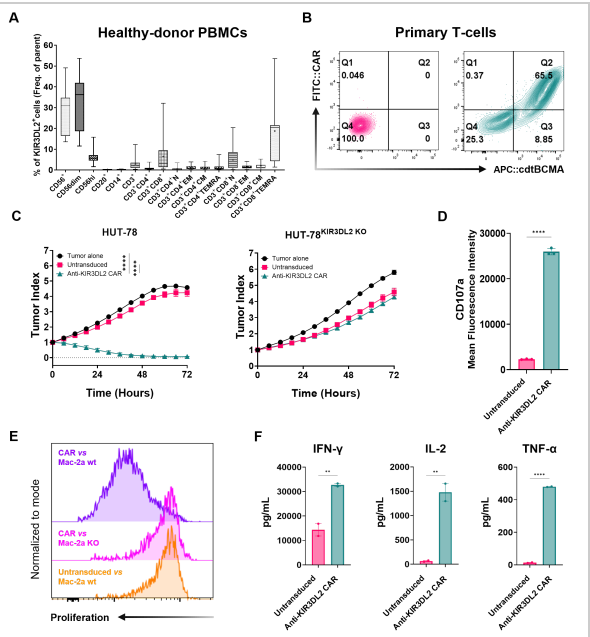


Figure 1. A) Peripheral blood mononuclear cells (PBMCs) isolated from 15 different healthy donors were analyzed by flow cytometry using an anti-KIR3DL2 monoclonal antibody (mAb). N, naïve (CD45RA$^+$CD62L$^+$); EM, early memory (CD45RA$^-$CD62L$^-$); CM, central memory (CD45RA$^-$CD62L$^+$); TEMRA, terminally differentiated effector memory (CD45RA$^+$CD62L$^-$). **B)** Anti-KIR3DL2 CAR was lentivirally transduced into primary human T-cells and binding of CAR to recombinant human KIR3DL2 protein with His tag was detected by flow cytometry with anti-His mAb staining. The transduction marker cdtBCMA (truncated BCMA lacking intracellular domain) was detected by anti-BCMA mAb staining. **C)** Target cells HUT-78 (left) and isogenic KIR3DL2-knockout (KO) HUT-78 (right) were lentivirally transduced to express eGFP and co-cultured *in vitro* in triplicate wells with or without expanded untransduced control T-cells or anti-KIR3DL2 CAR T-cells at 1:2 effector to target ratio (E:T). Live tumor cell quantification was performed using Incucyte Live-Cell Imaging and Analysis (Sartorius) by monitoring eGFP+ cells. Mean ± SD of fold change in live tumor cells from baseline (Tumor Index) over time is shown for each condition. **D)** Anti-KIR3DL2 CAR T-cells and donor-matched activated untransduced T-cells were co-cultured with HUT-78 at 1:2 E:T ratio in presence of anti CD107a mAb and monensin. Degranulation was estimated through CD107a mean fluorescence intensity on CD3$^+$ untransduced or CAR-positive cells after 6 hours. **E)** CellTrace™ Far Red-stained anti-KIR3DL2 CAR T-cells and donor-matched activated untransduced T-cells were co-cultured with Mac-2a wild-type (wt) or their isogenic KIR3DL2-knockout counterpart at 1:1 E:T ratio. Proliferation was estimated as decrease in CellTrace™ Far Red fluorescence intensity on CD3$^+$ untransduced or CAR-positive cells after 96 hours. **F)** Anti-KIR3DL2 CAR T-cells and donor-matched activated untransduced T-cells were co-cultured with HUT-78 at 1:1 E:T ratio. Cytokine release was assessed by multiplex assays (Meso Scale Discovery) from culture supernatants after 48 hours. IFN-γ, interferon-gamma; IL-2, interleukin-2; TNF-α, tumor necrosis factor alpha.

Figure 1.

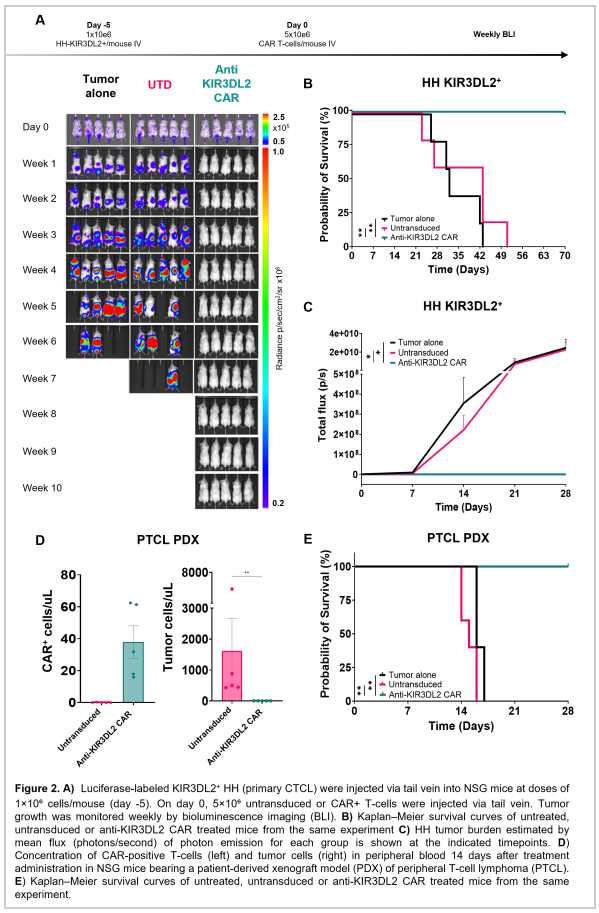


Figure 2. A) Luciferase-labeled KIR3DL2$^+$ HH (primary CTCL) were injected via tail vein into NSG mice at doses of 1×10^6 cells/mouse (day -5). On day 0, 5×10^6 untransduced or CAR+ T-cells were injected via tail vein. Tumor growth was monitored weekly by bioluminescence imaging (BLI). **B)** Kaplan–Meier survival curves of untreated, untransduced or anti-KIR3DL2 CAR treated mice from the same experiment **C)** HH tumor burden estimated by mean flux (photons/second) of photon emission for each group is shown at the indicated timepoints. **D)** Concentration of CAR-positive T-cells (left) and tumor cells (right) in peripheral blood 14 days after treatment administration in NSG mice bearing a patient-derived xenograft model (PDX) of peripheral T-cell lymphoma (PTCL). **E)** Kaplan–Meier survival curves of untreated, untransduced or anti-KIR3DL2 CAR treated mice from the same experiment.

Figure 2.

Conclusion

Our preclinical findings support KIR3DL2-directed CAR T cells as a potentially safe and effective therapy for several T-cell lymphomas. If successfully translated to the clinic, this approach could address a significant unmet need for patients with relapsed/refractory disease and historically poor prognosis.

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