ABSTRACT FORM

to be sent by e-mail to the Organising Secretariat (alice.trovato@achelois.eu) by **September 8h, 2022**

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ABSTRACT TITLE: DONOR-UNRESTRICTED TARGETING OF CD1C-EXPRESSING LEUKEMIA BY T AND INKT CELLS ENGINEERED WITH LIPID-SPECIFIC TCR

ABSTRACT TEXT (max 2500 characters – including spaces)

Background

Disease recurrence is the major unmet clinical need of acute leukemia following treatment by chemotherapy and allogeneic stem cell transplantation. Adoptive cell therapy (ACT) with allogeneic donor-derived T cells can control disease recurrence by inducing a beneficial Graft-versus-Leukemia (GvL) reaction. However, grafted alloreactive T cells can cause a detrimental graft-versus-host disease (GvHD), prompting the search for new donor-unrestricted strategies targeting malignant cells. Leukemia blasts express CD1c antigen-presenting molecules, which are recognized by T cell clones specific for the CD1c-restricted leukemia-associated methyl-lysophosphatidic acid (mLPA) lipid antigen. Because CD1c molecules are identical in all individuals and expressed only by mature leukocytes, and mLPA is highly enriched in malignant cells, we propose a donor-unrestricted ACT strategy with T or iNKT cells redirected against $CD1c^+$ acute leukemia. iNKT cells promote GvL reaction without eliciting GvHD and modulate immunosuppressive myeloid cells in the tumor microenvironment (TME) through their TCR. Hence, we envision to generate bi-specific iNKT cells armed with a universal mLPA-specific TCR to dual target leukemia cells and the immunosuppressive myeloid TME.

Methods

To assess the feasibility of ACT for acute leukemia with CD1c-restricted mLPA-specific T and iNKT cells, we identified the lead mLPA-specific TCR to use for human T and iNKT cell transduction and we tested the efficacy and the safety of mLPA-specific ACT in vitro and in vivo in immunodeficient mouse xenografts.

Results

We could generate mLPA-specific T cells that killed in vitro several different CD1c$^+$ acute leukemia cells, but not normal circulating CD1c$^+$ cells. The adoptive transfer of DN4.99 TCR-transduced T cells delayed the progression of 3 models of leukemia xenograft in NSG mice, an effect that is boosted by mLPA-cellular immunization with monocyte-derived DCs. We are now assessing whether the transfer of an optimized mLPA-specific TCR into iNKT cells can further improve efficacy and safety of this strategy. We have established a protocol to isolate, transduce and expand human primary iNKT cells that can efficiently kill leukemia targets expressing CD1c and/or CD1d in vitro.

Conclusions

Our results highlight a novel approach for ACT of acute leukemia with T or iNKT cells engineered to recognize malignant cells by the transfer of a lipid-specific TCR that works across MHC-barriers like a CAR.

KEYWORDS: please select 2 of the following keywords

- ☒ Adoptive Cell Therapy
- ☐ Cancer Metabolism
- ☐ Emergency myelopoiesis
- ☐ Growth-Arrested State
- ☐ Melanoma
- ☐ Metastasis
- ☐ Microbioma
- ☐ Neoadjuvant therapy
- ☐ PDX/Preclinical models
- ☐ Tumor and Stromal targeting
- ☐ Tumor resistance
- ☐ Cancer Dormancy
- ☐ Clinical trial
- ☒ Engineered Lymphocytes
- ☐ Immunotherapy
- ☐ Metabolic Alteration
- ☐ Metastasis Niche
- ☐ Myeloid Infiltrate
- ☐ Organoids
- ☐ Personalized medicine
- ☐ Tumor stroma and senescence

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