

“Targeting leukemia by CD1c-restricted T cells specific for a novel lipid antigen”

Background and Description of Invention. Acute leukemia comprises a heterogeneous group of hematological disorders characterized by blood and bone marrow accumulation of immature and abnormal cells derived from hematopoietic precursors. Current therapy for acute leukemia is based on poly-chemotherapy and allogeneic Hematopoietic Stem Cell Transplantation (HSCT). A major cause of treatment failure in HSCT is post-transplant re-growth of residual leukemia blasts that survive the conditioning regimen. Donor-derived T cells transferred into patients may induce a beneficial Graft Versus Leukemia (GVL) reaction capable of maintaining remission, but grafted T cells are also capable of killing patient cells in non-hematopoietic tissues inducing detrimental Graft Versus Host Disease (GVHD). To overcome this problem and improve the efficacy of the HSCT, herein, the inventors propose a new immunotherapy strategy taking advantage of an immune recognition of specific tumor-associate lipid antigens in order to selectively target T cell responses against malignant hematopoietic cells. More specifically, the present invention is an immunotherapy-based platform based on TCR having antigenic specificity for CD1c molecules associated with a self-lipid, named as methyl-lysophosphatidic acids (mLPAs), for treating leukemia. CD1c is frequently expressed by AML and B-ALL. TCR is able to recognize mLPA a specific antigene for selectively killing leukemia cells in CD1c restricted manner.

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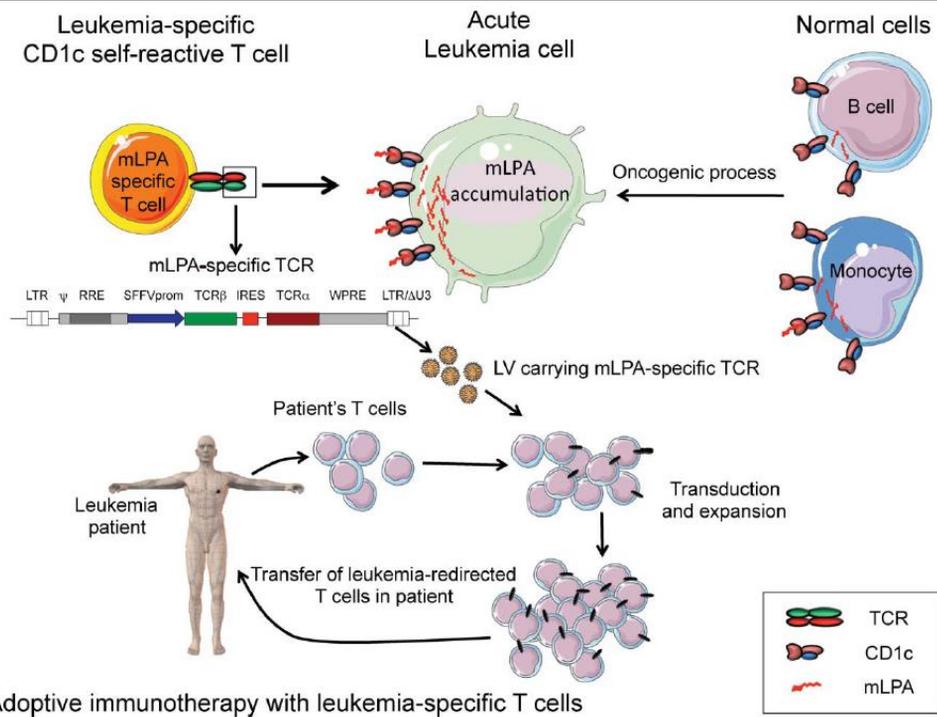


Figure 1. Targeting leukemia by CD1c-restricted T cells specific for a novel lipid antigen. Representative scheme of the immunotherapy-based platform: T cells from acute leukemia patients are expanded and transduced ex vivo with the LV carrying mLPA-specific TCR genes, which redirects T cells against the leukemia target upon adoptive transfer into the patients.

Stage of Development. The immune system contains T cells that recognize lipid antigens presented by the non-polymorphic, MHC class I-related family of CD1 molecules. CD1-restricted T cells can respond to different foreign lipid antigens derived from pathological bacteria and can also recognize endogenous self-lipid molecules. T cells that recognize self-lipids presented by CD1c are relatively abundant among circulating T cells in healthy individuals and might become activated by host antigen in autoimmune disease and cancer. Importantly, lipid-specific T cells can control cancer cell growth and kill transformed hematopoietic cells, but little is known about their self-lipid antigen specificity and potential anti-leukemic effects. In this respect, the inventors have identified the methyl-lysophosphatidic acids (mLPAs), a novel self-lipid antigens that stimulates CD1c auto-reactive T cells to destroy tumor cell lines and primary leukemia cells (*Lepore M. et al., A novel self-lipid antigen targets human T cells against CD1c(+) leukemias. J Exp Med. 2014; Lepore M. et al., Targeting leukemia by CD1c-restricted T cells specific for a novel lipid antigen. Oncoimmunology 2014; Dellabona P. et al., Group 1 CD1-restricted T cells and the pathophysiological implications of self-lipid antigen recognition. Tissue antigens 2015*). The inventors reported that blasts, derived from pediatric and adult patients affected by primary acute myeloid or B-cell acute leukemia, express CD1c molecules and that mLPAs accumulate in leukemia cells, but are poorly present in normal hematopoietic cells. mLPA-specific TCRs efficiently kill *in vitro* CD1c⁺ primary acute leukemia blasts, poorly recognizing non-transformed CD1c-expressing cells.

Potential Applications and Competitive Advantages. The mLPA-specific TCRs may be used for adoptive immunotherapy, for cell therapy, for the treatment of leukemia, for the prevention of leukemia relapse following hematopoietic stem cell transplantation (HSCT) (at present no therapy is available) and improvement of efficacy of HSCT.

Harnessing CD1c self-reactive T cell responses is an attractive option for adoptive immunotherapy of leukemia especially in the context of HSCT for the following reasons:

- The restricted CD1c expression on hematopoietic cells minimizes the risk of Graft Versus Host Disease (GVHD);
- The lack of CD1 polymorphisms permits to use allogeneic CD1 self-reactive T cell to treat any leukemia patient;
- Since more than 50% of AML cases expresses CD1c molecules and are recognized by mLPA-specific T cells, the frequency of patients that could benefit from this adoptive T cell immunotherapy would be relevant;
- Different from MHC-restricted protein antigens, lipid antigens are unlikely to undergo structural changes under the immune-mediated selective pressure, reducing the risk for leukemia immune escape.

We seek a potential commercial partner with a strong expertise in cancer adoptive immunotherapy to further explore the clinical use of lipid-specific T cells for the treatment of leukemia.

For further information on this project please contact:

Business Contact

Paola Vella

Head, Office of Biotechnology Transfer
San Raffaele Hospital and Scientific Institute

Tel: +39 02 2643 4281

Fax: + 39 02 2643 8138

E-mail: vella.paola@hsr.it

Scientific Contact

Drs. Giulia Casorati & Paolo Dellabona

Experimental Immunology Unit
San Raffaele Hospital and Scientific Institute

Tel: +39 02 2643 4727

Fax: + 39 02 2643 4786

E-mails: dellabona.paolo@hsr.it; casorati.giulia@hsr.it