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UCART20x22: First allogeneic dual CAR T-cell therapy for the treatment of B-cell malignancies

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Abstract:

Autologous CAR T-cell therapies have been transformative in the treatment of selected blood cancers. Despite this remarkable success, common mechanisms of resistance, such as tumor antigen escape, tumor heterogeneity and weaker CAR activity with low levels of antigen, emphasize the need to further optimize CAR T-cell therapies. In addition, there is a need to develop allogeneic "off-the-shelf" therapies that are readily available at the time of treatment decision. To address these challenges, we generated UCART20x22, the first allogeneic dual CAR T-cell targeting two well-validated antigens in B-cell malignancies, CD20 and CD22. Using *in vitro* cytotoxic and proliferation assays, we demonstrated that UCART20x22 displays strong activity against tumor cell lines with diverse CD20/CD22 antigen combinations, as well as increased activity against cells presenting both targets simultaneously. The specific activity of dual UCART20x22-cells persists overtime against tumor cells expressing both antigens (CD20, CD22) or only one. We also developed a pre-clinical model carrying subcutaneous lymphoma tumors expressing different antigen combinations in one single mouse. In this model, dual CAR T-cells provide efficient *in vivo* clearance of tumor cells expressing one or two antigens (CD20 and/or CD22) in a dose dependent manner, starting at a low dose of $1x10^6$ CAR T-cells. Using a disseminated model of lymphoma with different combinations of antigen-expressing tumor cells, we demonstrated robust efficacy and persistence of UCART20x22 cells in the bone marrow. Furthermore, we used primary Non-Hodgkin Lymphoma patient samples expressing diverse CD22 and CD20 antigen levels to demonstrate that UCART20x22 displays robust and specific cytotoxic activity as well as IFNγ release in all tested combinations. Besides efficiently targeting two commonly expressed antigens in B-cell malignancies, UCART20x22 incorporates TALEN® mediated TRAC and CD52 specific gene editing to prevent Graft-vs-Host Disease and improve persistence in the presence of alemtuzumab (an anti-CD52 monoclonal antibody that can be used as part of a lymphodepleting regimen). These attributes allow the production of allogeneic CAR T-cells from healthy individuals that can be administered at the time of treatment decision. In summary, we show an efficient first in class allogeneic dual CAR T-cell product candidate with demonstrated *in vitro* and *in vivo* properties to overcome antigen escape in B-cell malignancies.

Author Disclosure Information:

B. Aranda-Orgilles: ; Cellectis Inc. ; Cellectis Inc. **I. Chion-Sotinel:** ; Cellectis SA. ; Cellectis SA. **S. Grudman:** ; Cellectis Inc. ; Cellectis Inc. **B. Mumford:** ; Cellectis Inc. ; Cellectis Inc. **C. Dixon:** ; Cellectis Inc. **R. Galetto:** ; Cellectis SA. ; Cellectis SA. **A. Gouble:** ; Cellectis SA. ; Cellectis SA. **L. Poirot:** ; Cellectis SA.
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