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Clinical Grade Manufacture of CYAD-101, a NKG2D-based, First in Class, Non-Gene-edited Allogeneic CAR T-Cell Therapy

Alexandre Michaux [1], Sébastien Mauën, Eytan Breman, Marie-Sophie Dheur, Laure Twyffels, Laura Saerens, Céline Jacques-Hespel, Emilie Gauthy, Sophie Agaugué, David E Gilham, Panagiota A Sotiropoulou

Affiliations

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Abstract

Allogeneic chimeric antigen receptor (CAR) T holds the promise of taking this therapeutic approach to broader patient populations while avoiding the intensive manufacturing demands of autologous cell products. One limitation to delivering an allogeneic CAR T is T-cell receptor (TCR) driven toxicity. In this work, the expression of a peptide to interfere with TCR signaling was assessed for the generation of allogeneic CAR T cells. The expression of a truncated CD3ζ peptide was shown to incorporate into the TCR complex and to result in blunted TCR responses. When coexpressed with a natural killer group 2D (NKG2D) CAR, the allogeneic T cells (called CYAD-101) failed to induce graft-versus-host disease in mouse models while maintaining antitumor activity driven by the CAR in vitro and in vivo. Two clinical grade discrete batches of CYAD-101 cells were produced of single donor apheresis resulting in 48 billion CAR T cells sufficient for the entire dose-escalation phase of the proposed

clinical trial. The 2 batches showed high consistency producing a predominantly CD4+ T-cell population that displayed an effector/central memory phenotype with no evidence of exhaustion markers expression. These clinical grade CYAD-101 cells secreted cytokines and chemokines in response to ligands expressing target cells in vitro, demonstrating effector function through the CAR. Moreover, CYAD-101 cells failed to respond to TCR stimulation, indicating a lack of allogeneic potential. This bank of clinical grade, non-gene-edited, allogeneic CYAD-101 cells are used in the alloSHRINK clinical trial (NCT03692429).

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