



Is CAR-T Cell Immunotherapy a Good Strategy for T-Cell Acute Lymphoblastic Leukemia?

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Editorial

T-cell Acute Lymphoblastic Leukemia (T-ALL) is an aggressive hematologic cancer that arises from the malignant transformation of T-cell progenitors and occurs in about 15% of pediatric and 25% of adult ALL cases. However, unlike B cell derived B-ALL in which the chimeric antigen receptor modified T cells (CAR-T cells) have been proven clinically successful in treating refractory, relapsed patient settings, there is few report for CAR-T cell therapy in T-ALL.

CAR contains three basic elements—the extracellular antigen binding domain, transmembrane domain, and cytoplasmic signaling domain. First-generation CAR featured a single signaling domain most commonly derived from the CD3 component of TCR (T cell receptor)/ CD3 complex. Second or third-generation CAR was designed by including additional signaling domains, such as CD28 and/or 4-1BB, that potentiate T-cell effector functions and activate co-stimulatory pathways, resulting in upregulation of genes encoding anti-apoptotic proteins and increased cytokine secretion. With this strategy, a complete remission for B-ALL patients who received CD19-targeting CAR-T cell therapy was achieved with up to >90% success rates [1].

The success in B-ALL treatment mainly contributed to using the B-ALL marker of CD19. The human CD19 antigen is a 95 kd transmembrane glycoprotein belonging to the immunoglobulin (Ig) superfamily, and expressed on follicular dendritic cells and B cells. In fact, it is present on B cells from earliest recognizable B-lineage cells during development to B-cell blasts, including B-ALL [2]. Thus, CD19 makes itself a perfect target for CAR-T cell therapy although B cell aplasia becomes a must occur side effect due to normal B cell elimination as well. However, the situation in T-ALL is quite complicated because T-ALL is a highly heterogeneous disease despite considerable efforts to identify immunophenotypic abnormalities have been made since 1990s [3].

Among those markers that have been characterized, CD7 is a very interesting molecule with therapeutic target potential for T-ALL. CD7 is a transmembrane glycoprotein which appears early in T cell ontogeny and is expressed by most T cells in the periphery. In our lab, we have observed that CD7 expression was missing in a subpopulation of ~10% mature human T cells and majority of those cells were CD4+, which is consistent with previous reports [3]. We also found that CD7 negative status lasts during the ex vivo expansion. Meanwhile, it has been demonstrated that the CD7- / CD8+ population seems to be a more persistent and stable population of effector cells [4]. One of the most important features for CD7 is that the expression level of CD7 increased ~75% in T-ALL cells comparing to the normal CD7+ T cells [5]. Therefore, CD7 is thought a best marker for T-ALL.

However, if CAR-T technology is pursued in this disease setting, the following two major challenges must be overcome. 1) most T cells, including CD7+ normal T cells, may be eliminated and resulted in severe immunodeficiency. In contrast, in B-ALL, monthly i.v. administration of Ig can compensate the loss of normal B cells; 2) the malignant T cells are not suitable to prepare CAR-T cells. Accordingly, to develop a clinically feasible CAR-T platform for T-ALL, we will preferably select CD7 as the target for above mentioned reason. In addition, CD7 negative normal T cells will be used to generate anti-CD7-CAR-T cells if the normal CD7- T cell is available in the patient. In this ideal scenario, CAR-T cells will kill the CD7+ T-ALL cells, and some adoptive memory anti-CD7-CAR- T cells may persist and provide essential cellular immunity for the patient. Furthermore, as long as the patient has some normal CD7- T cells, manufacturing of anti- CD7- CAR-T cells may not be an insurmountable obstacle because during the ex vivo expansion of CAR-T cells, the CD7+

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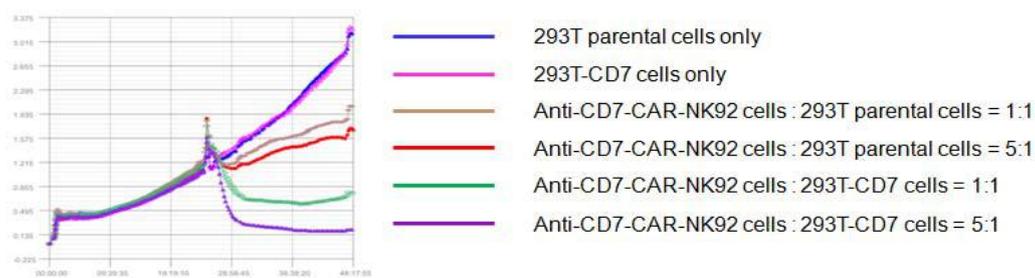


Figure 1: Anti-CD7-CAR-transduced NK92 cells could specifically and potently kill CD7 over expressed 293-T cells.

CD7 gene was stabilized into 293T cells. Anti-CD7-CAR-NK92 cells were incubated with either 293T parental cells or CD7 over expressed 293T-CD7 cells in a effector : target ratio of 1:1 or 5:1 respectively. The killing efficacy was monitored by xCELLigence RTCA DP (ACEA Biosciences) in real time manner, and the curve represented the target cell growth pattern.

T-ALL cells may be killed and CD7- normal cells with anti- CD7 CAR integrated will be selectively expanded. However, the patient may have insufficient normal CD7- T cells before or after *ex vivo* expansion. In this case, NK92 cell line may be the first choice to make an anti-CD7-CAR-NK cells to kill CD7+ T-ALL cells. Natural killer (NK) cells are critical for antiviral and anti-cancer immunity [6]. The central role of NK cells in immunity makes them an attractive subject of research and therapeutics. But autologous or allogeneic peripheral NK cells are also CD7+ cells, and hard to be transduced by viral vehicle. Thus, the activated NK cell line NK- 92 which has been proven highly cytotoxic against a broad spectrum of malignant cells [7], and can be grown in batch culture and under GMP conditions, make it a good candidate for anti-CD7-CAR driven cell therapy strategy. Although about ~70% of NK92 cells are CD7 positive, after the anti-CD7-CAR is stabilized in NK92 cells, only CD7 negative anti-CD7-CAR-NK cells survive because all CD7+ NK92 cells will be killed during the culture. We have established stable anti-CD7-CAR-NK cells which exhibited potent anti-CD7+ tumor cell efficacy (Figure 1). Recently, Silva et al reported that they used the CRISPR/Cas9 system to disrupt the CD7 gene in T cells prior to retroviral transduction with CD7-CAR. The CD7 gene was successfully disrupted in 90% of T cells, minimizing fratricide of CD7-CAR-T cells, and leading to a robust T cell expansion, similar to that of control T cells transduced with an irrelevant CAR, which may support the feasibility of using CD7-CAR-T cells for the targeted therapy of acute myeloid and lymphoid leukemia [8].

Future clinical trials may experience new challenges, including cytokine storm, neurotoxicity, and other common adverse events occurred in B-ALL CAR-T therapy, or insufficient clinical efficacy regarding CAR-NK therapy due to poor persistence of NK92 cells. However, CAR-T and/ or CAR-NK cell therapy may provide a new hope for those refractory/ relapsed T-ALL patients.

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