

# New Targets of CAR-T Therapy for B-cell lymphoma

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**Abstract.** B-cell lymphoma is a kind of hematologic malignancy with high morbidity and mortality, which is usually treated by chemoimmunotherapy followed by an autologous transplant. But the traditional therapy usually leads to relapse and refractory. Now FDA has approved four CAR-T cell products that all target CD19 to give relapsed or refractory patients another chance to control cancer. These achievements may thank the CD19, but the CD19 also leads to some problems including the off-tumor effect and antigen escape that result in off-tumor effects and relapses. These problems prevent CAR-T therapy from being widely used in treating B-cell lymphoma. To solve these problems, new targets should be discovered. Scientists have already done a lot of exploration in this area. To give the scientists some directions, this paper will briefly introduce the two problems, the characteristics that are required for the ideal targets, and some ideal future targets which are understudy now.

**Keywords:** Targets, CAR-T Therapy, B-cell lymphoma.

## 1. Introduction

Lymphoma includes Hodgkin lymphoma (HL) and Non-Hodgins's lymphoma (NHL), starting in lymphocytes (mainly B lymphocytes and T lymphocytes). Ten percent of lymphomas are HL characterizing Hodgkin Reed-Sternberg cells on histology which all originate from B lymphocytes. NHL accounts for the other 85% of lymphomas and 85% of NHL are B-cell malignancies. So, most of the lymphoma is B cell lymphoma [1].

Among hematological malignancies, NHL is the most common worldwide, which sits in the sixth position among the highest mortality rate malignancies and ranks seventh in the most prevalent cancer in the United States. NHL accounts for 4% of cancer diagnoses in the US. The probability of survival for patients suffering from NHL is 72.7 percent from 2010 to 2016. [1] In 2020, the incidence rate is 0.98 per 100,000 and mortality rate is 0.26 per 100,000 for HL [2].

Two of the standard therapies that treat the newly diagnosed B-cell lymphomas, Chemotherapy and stem cell transplantation, have been popular for a long time but they usually cause relapses leading to a low survival rate. To address the issue, Chimeric antigen receptor T cells (CAR-T) were developed to improve the outcomes and increase the survival among patients suffering refractory or relapsed B-cell lymphoma [3].

Now four CAR-T therapies have been approved to treat B-cell lymphomas. All of them have improved the patient's outcome [4]. However, the refractor to CAR-T treatment still suffers from some thorny issues like relapses after an initial response, as well as the side effects. The side effects and relapses are due to insufficient specificity and antigen loss of the target CD19 [3]. With the development of CAR-T cell products, now they possess mature CAR structure, preparation, and clinical protocols, but the four FDA-approved Car-T products only have one target CD19 [4]. To Find new targets for CAR-T therapy may be a key to solve the problem [5]. This paper will describe the mechanism of the off-tumor effect and relapses of CD19 CAR-T therapy, and summarize the characteristics required for an ideal target. In addition, the advantages and limitations of some ideal targets currently under study will be introduced.

## **2. The side effects and relapses of CD19 CAR-T therapy and the characteristics required for an ideal target**

### **2.1. Off-tumor effects and the specificity of the tumor**

Due to its extensive coverage on the surface of B-cell lymphoma, CD19 has been chosen as the antigen that is most frequently expressed during CAR-T treatment. However, there needs to be more than just good coverage to be a perfect target. Both healthy and malignant B-cells express CD19, despite the fact that it is mostly found on B-cells and seldom on non-B-cells. This might result in the most hazardous adverse effect of CAR-T treatment, called off-tumor, which is brought on by the CAR-T cells' indiscriminate assault due to their subpar antigen specificity [6]. Normal B cells will be eliminated by the CAR-T cells in the off-tumor impact, which causes long-term B cell aplasia. Thankfully, hypogammaglobulinemia brought on by CD19-ablated B cells may be treated with intravenous immunoglobulin replacement treatment [3].

To become an ideal target, the target needs to express only on the cancer cells consistently but rarely express on healthy cells and CAR-T cells. Now the new targets under study only have high coverage and lineage specificity. In the future antigens in the cancer cells should receive more attention as candidates for the target. Those antigens, as an identification of the cancer cell, are the results of gene mutation in the form of peptide/HLA complex [3].

### **2.2. Relapses and bispecific CAR-T cells**

After receiving CD19 CAR-T treatment, roughly 30% of B-cell NHL patients relapsed because of CD19 loss [7]. The antigen loss usually happens in two ways: gene mutation, which leads to the decrease of CD19 expression or selective expansion of CD19 negative malignant cells [8]. Then the CD19 CAR-T cells lose their target and cancer may relapse.

Bispecific CAR-T therapy came up to tackle this problem. It can recognize two different antigens simultaneously [3]. Compared to targeting a single antigen, the therapy targeting dual-antigen exhibits synergistic effects, which is equivalent to double insurance for the risk of antigen loss. When a target is lost, the other target could still express due to the low risk of losing dual-antigen. But the off-tumor toxicity also increases because of the expanding recognition scope [7].

## **3. Ideal future targets for CAR-T therapies of B-cell lymphoma**

### **3.1. Targets of single-target CAR-T therapy**

#### **3.1.1 CD30**

Although HL is one of the most treatable cancers, which the majority of patients with HL are cured after the first-line therapy, 15% of the patients relapse after an initial response or be refractory. The first-line therapy for HL is high-dose chemotherapy, and then, if the first-line therapy fails, autologous stem cell transplantation will follow up. The high morbidity and mortality make the prognosis of the relapse of refractory HL patients a bad one. CAR-T therapy gives them another chance to survive. CD30 is universally expressed in the Reed-Sternberg cells, which makes it an effective target for CAR-T therapy. Carlos A et al. conducted 2 parallel phase I/II studies at independent 2-center on refractory or relapsed HL patients who were treated with CD30 CAR-T therapy after different lymphodepletion regimens. The 1-year ORR and CR rates among the 41 patients were 72 and 59 percent, respectively, while the PFS was 41 percent. There are no notable changes in the lymphodepletion regimens, and the 1-year OS was 94%. This information demonstrates the clinical effectiveness of CD30 CAR-T treatment in HL. The data on safety is also amazing. Grade 3+ adverse events are the most common toxicities. There is no neurologic toxicity and the cytokine release syndrome was all grade 1 in the observed 10 patients. The study shows that patients who got refractory or relapsed HL have a high rate of durable responses to the CD30 CAR-T therapy with excellent safety [9].

### 3.1.2 BAFF-R

B cell activating factor receptor (BAFF-R) is an appealing target for CAR-T therapy due to the fact that it is a B lineage marker which has high expression only on the B-cells. It has been proved that the BAFF-R still expresses when the CD19 was absent after CD19 CAR-T therapy. BAFF-R signaling activates nuclear factors, making it a driver of B cell proliferation and survival. Increased BAFF-R expression may relate to the progression of B cell lymphoma. This crucial feature causes BAFF-R expression down-regulation, which may further lead to limiting the B-cell tumors to evade the CAR-T. So, it is unlikely that the antigen loss emerges from BAFF-R CAR-T therapy. Qin et al. conducted a trial on the mouse model that simulated the human B-cell lymphoma and the lymphoma cells with CD19 loss caused by CD19 CAR-T therapy to test the effectiveness of BAFF-R-CAR-T therapy under these circumstances. The BAFF-R-directed CAR T cell shows a great response to both CD19 positive or negative B-cell lymphoma, which can be a complementary therapy for CD19 loss patients. Also, combining dual targeting of CD19 and BAFF-R can emerge as hot research topics in the future. But the trial also has some limitations. The possible mechanism of resistance against this therapy requires a further clinical trial to confirm and the side effects would not be detected because the model mice were immunodeficient [10].

## 3.2. Research status

### 3.2.1 CD19/CD22

There have been studies on CD19/CD22 dual-targeted CAR-T cells in order to deal with the antigen escape of CD19. Targeting both CD19 and CD22 at the same time possibly reduces the likelihood of antigen-loss events. High levels of CD19 and CD22, which are usually co-expressed in B-Cell lymphoma cells, create a good foundation for the dual-targeted CAR-T cells. Wei et al. conducted a trial on 24 patients who had relapsed/refractory B-cell lymphoma to measure the effectiveness and safety of the dual-targeted CAR-T therapy. The result shows it is likely a prudent, effective anti-lymphoma cell-based targeted immunotherapy. The side effect of the therapy could be well tolerated. The mostly observed side effects are 1/2 CRS, and grade 4 happened on only one patient. No patients developed neurotoxicity [7].

Also, the responses to the dual-targeted therapy are durable which means no relapse emerges. In Wei's study, the responses to said therapy could last more than 2 years without consolidation therapy and the CR could be retained for no more than 21.6 months as soon as the patients achieved CR. In addition, the response of the therapy is more rapid than CD19 CAR-T therapy, in which the time they need to reach the CR is one month and three months, respectively. In the 16 eligible patients in the study, only three patients relapsed, and all of the relapses are not due to antigen loss [7].

### 3.2.2 CD19-OR-CD20

CD19 and CD20 are both expressed specifically on malignant B cells. There are a lot of clinical data to prove their efficacy in the role as the target for CAR-T therapy. If the target cells express either CD19 or CD20, CD19-OR-CD20 CARs can eliminate the malignant B cells. Although the broad recognition capability of dual-targeted CAR-T may result in increasing off-tumor toxicity, CD19-OR-CD20 CARs would not have this concern due to the same off-tumor toxicity. Meanwhile, similar to other dual-targeted CAR-T, it can also avoid the antigen escape relapsing because they can target CD20 that still express when the CD19 is down-regulated and the simultaneous loss of two antigens is an almost impossible event. But since the its special manufacturing technology, the target may have antigenicity which could lead to an autoimmune response resulting in the elimination of CAR-T cells. CD19-OR-CD20 CARs require more clinical trials for further research [8].

## 4. Conclusions

The choice of the CAR-T therapy's target for B-cell lymphoma has been a hot topic in recent years. Uncertain target might result in relapses or off-tumor effects. High coverage and high specificity just

for B-cell lymphoma cells are required in an ideal target. Also, it should be stable to be continuously expressed to avoid antigen loss. But targets that meet these conditions at the same time are too difficult to find. Therefore, the antigen inside the cells and the bispecific CAR-T cells are researched to address these problems. Right now, the understudied targets do fantastically in the studies and demonstrate their potential to be used for more than only treating relapsed or refractory B-cell lymphomas. This passage is to give some inspiration to the scientists who are studying the new targets for CAR-T therapy and to help find the direction.

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