# The advantages of CAR-NK cell therapy and its current curative efficiency in different tumors

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**Keywords:** Neural Network, Prediction Model, Big Data.

**Abstract:** Power load forecasting is very important for power dispatching. Accurate load forecasting is of great significance for saving energy, reducing generating cost and improving social and economic benefits. In order to accurately predict the power load, based on BP neural network theory, combined with the advantages of Clementine in dealing with big data and preventing overfitting, a neural network prediction model for large data is constructed.

## 1. Abstract

The tumor is one of the most concerning diseases in the world. Around one-sixth of deaths are caused by cancer or related diseases. However, there has been no cure or good diagnosis methods for such a disaster yet. The current treatment methods are basically surgery and chemotherapy. The pain and side-effects of such treatment are so serious that many patients even cannot tolerate the whole process. Besides, the high possibility of recurrence cause that patients may not be able to fully recover. With the arrival of industrialization, which makes productivity improvement, people start to encounter more carcinogens so that the cancer incidence rate increases year by year. More and more voices pursuit a new type of cancer therapy. Researchers shift their focus towards immunotherapy. As one of the immunotherapies, the chimeric antigen receptor-engineered T (CAR-T) cells have shown impressive success in hematological cancer treatment. However, the drawbacks of CAR-T cell therapy are also clear. The risk of GvHD, the possibility of cytokine release syndrome, and the complicated and time-consuming production process of CAR-T cells are some of the major potential risks. Natural killer cell, another immune cell that can be used for immunotherapy, attract researchers' attention due to several advantages in the potential application. This review mainly focuses on the comparison between CAR-T cell therapy and chimeric antigen receptor-engineered natural killer (CAR-NK) cell therapy and the current curative effect of CAR-NK cell therapy on different types of cancers to illustrate that CAR-NK cell therapy can be a good substitute for CAR-T cell therapy for better cancer therapy application.

## 2. Keywords

CAR-T, CAR-NK, Immunotherapy, Cancer

## 3. Introduction

Cancer is one of the biggest death causes in the world. Millions of people have died because of different types of cancer. In recent two hundred years, the cancer incidence rate continues to increase, especially in low-income countries. Because of the economic transition, people have more chances to encounter cancer-causing materials, or carcinogens [1]. The situation is so alarming that people turn pale at the mention of cancer. The cure methods are not very effective now. Recurrence is one of the major issues that threaten patients' lives after surgery or chemotherapy treatment [2]. However, cancer is indeed curable either by early discovery or by appropriate treatment [3].

Cellular immunotherapy is a new approach to utilize hosts' own immune systems to treat cancer. The non-genetically-modified lymphokine-activated killer (LAK) therapy or tumor-infiltrating lymphocytes (TIL) therapy only has limited benefits in clinical trials, so immune cells, like T cells and NK cells, are engineered to express CARs for better recognition and cancer-killing ability [4]. CD8+ cytotoxic T cells and NK cells are two types of immune cells that can check and kill the malignantly transformed cells through very similar cytotoxic mechanisms. Various researchers have shown a huge success of CAR-T cell therapy in treating hematological cancers, more and more scientific researchers shift their interest toward CAR molecule engineered NK cells and the effectiveness of the CAR-NK cell therapy [5].

This article demonstrates the reason why CAR-NK cell therapy can attract researchers' attention from CAR-T cell therapy. Superior safety, easier construction, stronger ability against solid tumors, and feature as ready-to-use medicine are four main types of benefits of using CAR-NK cell therapy. This article also takes B-cell acute lymphoblastic leukemia, lung cancer, and breast cancer as examples of both hematological and solid cancers to prove the tumor-killing ability of CAR-NK cell therapy.

## 4. Adoptive Cell Therapy

Adoptive cell therapy (ACT) is a type of therapy that can utilize the patient's own immune cell. After being extracted from the patient's body, those cells can be activated, proliferated, selected, and mediated for re-infusion back to the patient's body to control or eliminate tumor cells. CAR-T and CAR-NK immunotherapies are sub-types of ACT. Chimeric antigen receptors (CAR) are engineered artificial receptors that can both specifically recognize antigens on tumor cells and stimulate the bound cell.

### 4.1 CAR-T Cell Therapy and CAR-NK Cell Therapy

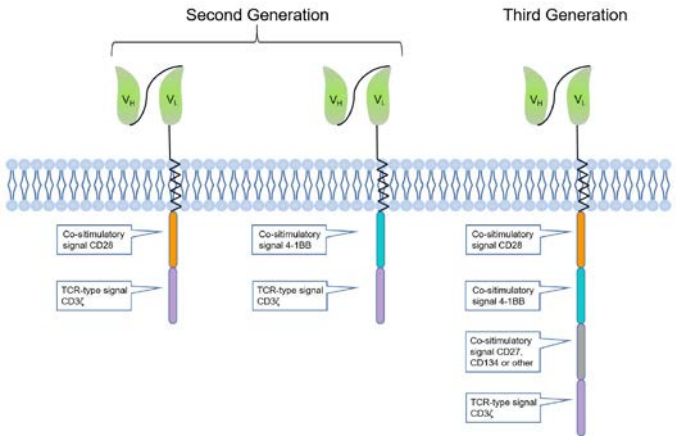


**Figure 1.** The common construction of second and third generation of CAR molecules [8]

ScFV regions are labeled $V_H$ and $V_L$. Transmembrane domains are shown as zigzag lines.

CAR-T cell therapy has a wide application area. It can be used to treat AML, ALL, Melanoma, and etc., but the most effective treatment majorly focuses on hematological malignancies [9]. After the huge success of CAR-T cell therapy in the treatment of hematological cancers, more and more scientific researchers shift their interest toward CAR molecule engineered NK cells and the effectiveness of the CAR-NK cell therapy [5]. Discovered in mouse spleen and human peripheral blood, natural killer cells have first been recognized as cytolytic effect lymphocytes [10]. Natural killer (NK) cells belong to white blood cells and share the same progenitor, lymphoblast, with T cells and B cells. The natural killer cell is a type of immune cell that uses perforin and granzyme, which can express similar cytotoxic effects as killer T cells, to kill cancer cells, virus-infected cells, allogeneic cells, and etc. However, unlike T and B cells using adaptive or antigen-specific immune systems, natural killer cells have the system called "missing-self" by detecting recognition proteins like MHC to determine whether the target cells are self-cells and whether they should release granzymes to lyse

the target cells [11]. By adding a CAR molecule, the NK cells are able to bind with tumor antigens more easily. With third-generation CAR molecule, besides the single-chain fragment variable (scFV) region can help the recognition process, multiple stimulation domains can open different activation pathways to help more efficiently release cytokines and chemokines to influence the immune response and kill tumor cells by using perforin and granzyme-related pathways.

### 4.2 Comparison between CAR-T and CAR-NK

Comparing to the T cells and other immune cells, NK cells have several specific features that allow NK cells to be a very attractive focus for the therapy using genetically engineered immune cells. [12]

Firstly, CAR-NK therapy has superior safety comparing to CAR-T therapy. NK cells have a short life span inside the body. The research uses deuterium-labeled glucose to detect the NK cells and reports that NK cells have a turnover time of around 4% per day, which means a doubling time/half-live of the order of 1-2 weeks [13]. Due to the short life span of the NK cells, the CAR-NK therapy has a lower chance to make toxicity to normal cells, which is a big off-target problem of CAR-T cell therapy. In addition, in a clinical trial where 11 patients received 3 different dosages of CAR-NK cells, none of them show the development of major toxic effects [14]. CAR-NK cells are less likely to result in a cytokine release syndrome because NK cells mainly release interferon-gamma; CAR-T cells, on the other hand, can release so many types of cytokines, such as IL-1a, IL-10, IL-15, etc., which can more easily lead to cytokine release syndrome [4].

Secondly, due to the wide range of recognition of the NK cells and the natural tumor cells killing ability, NK cells can be more efficient than CAR-T therapy in eliminating tumor cells. In both cases, CAR-T cells or CAR-NK cells can recognize potential tumor cells by scFV region on the CAR molecule binding with antigens on tumor cells' surface. Besides the CAR-guided mechanism, NK cells themself have the natural ability to search and suppress tumor cells. CAR-NK cells can be activated by receptors like NKG2D or DNAM-1 and possess cytotoxicity; CAR-NK cells are also able to go through the CD16-mediated antibody-dependent cell-mediated cytotoxicity to kill cancers [4, 15]. For those tumor cells that do not have the CAR-targeted receptors, CAR-NK therapy definitely has a stronger effect than CAR-T therapy. For some of the T cell-related tumors, NK cells are also a better choice for treatment.

Thirdly, comparing with CAR-T cells, whose T cells are normally extracted from peripheral blood from the patients, NK cells can have varied sources for making CAR-NK cells. For example, besides the isolation of peripheral blood mononuclear cells, isolation of cord blood, irradiation of cells in NK92 cell line, and even differentiation from induced pluripotent stem cells (iPSCs) can be the possible sources to extract the interested NK cells [16]. iPSCs can also first be genetically engineered by CAR-gene transduction to carry the CAR molecules and then to be induced to differentiate into CAR-NK cells [16].

Finally, CAR-NK cells are ready-to-use biological medicines. Some clinical trials have shown that patients have a good tolerance to infusion of allogeneic NK cells and do not express Graft vs Host Disease (GvHD), which is one of the major concerns of CAR-T therapy [17]. As a result, biomedical industries can produce CAR-NK cells in batches from healthy donors as reserved resources for potential patients. In comparison, CAR-T therapy requires patients' own T cells so that the CAR-T therapy cannot have the well-engineered CAR-T cells in advance, and preparing the CAR-T cells after the diagnosis of the disease would waste time for the patients.

## 5. Current situation of CAR-NK cell therapy in different types of caner

**Table 1.** Preclinial study of CAR-NK in different tumors. [20]

| Target | Tumor Type | NK source | CAR construction |
|---|---|---|---|
| CD19 | B-ALL | PB-NK | CD28+CD3ζ |
| CD19 | B-cell malignancies | NK-92 | CD3ζ |
| EGFR | Breast cancer | PB-NK/NK-92 | CD28+CD3ζ+oHSV |
| HER2 | Breast cancer/GBM | NK-92 | CD28+CD3ζ |
| PD1 | Lung cancer | NK-92 | NKG2D-41BB |

### 5.1 B-cell Acute Lymphoblastic Leukemia (B-ALL)

B-cell Acute Lymphoblastic Leukemia is a malignant tumor disease when hyperplasia of immature B cell precursor happens in the patients' bone marrow. While bone marrow is the position where hematopoiesis takes place, B-ALL can suppress the normal hematopoietic function. B-ALL normally affects children, but it can also be diagnosed in adults [18]. With the innovation of biomedical technology and the improvement of clinical medical treatment, the survival rates are around 90%, but the relapsed and chemotherapy-refractory disease still makes 5-year survival rates of the adult patients are lower than 60% [18].

With more and more new CD-19 CAR-T therapy medicines are on the biomedical market, such as the products from NOVARTIS or FOSUNKite, CAR-T therapy shows a wonderful therapeutic effect in leukemia treatment to the public. In a research at the University of Pennsylvania, 30 patients consisted of children and young adults are treated with CAR-T cell therapy [19]. The CAR molecules were designed with 4-1BB as costimulatory domain and CD3ζ as TCR-type signal domain [19]. Finally, the patients show a complete response at around 90%; however, patients did express some side-effects, B-cell aplasia, and cytokine-release syndrome.

As long as CAR-NK cells also use CAR molecules, even the same signal domains, CAR-NK cell therapy should present the same or similar effects as CAR-T cell therapy in B-ALL treatment. FMS-like tyrosine kinase 3 (FLT3) is a typical target in B-ALL treatment because of the overexpression of FLT3 in abnormal B cells. By constructing a CAR molecule with an scFV region specifically targeting FLT3 and typical signal domains of CD28 and CD3ζ, NK cells irradiated from the NK92 cell line can be engineered with FLT3-specific CAR to improve the recognition ability [18]. In the test of mouse model carrying SEM B-ALL, CAR-NK cells express a notable anti-leukemia ability and no obvious B-cell aplasia and cytokine-release syndrome [18]. To further improve the safety of CAR-NK cell therapy, an inducible caspase-9 gene can also be engineered into the CAR-NK cells' genome as a suicide switch for inhibition of the further cytotoxic effects beyond tumor cell targets [18].

Although CAR-T therapy now has many clinical trials to support its effective tumor suppression ability, CAR-NK relatively is in the inception phase, so there is a small number of clinical trials registered in ClinicalTrial.gov. Two clinical trials (NCT00995137, completed Phase I; NCT01974479, Phase II) targeting B-ALL tested CAR-NK cells with CD8αTM+4-1BB+CD3ζ design [20]. Both trials extracted NK cells resources from peripheral blood mononuclear cells. The first trial is hosted by St. Jude Children's Research Hospital recruiting 14 patients who are less or equal to 10 years old and have >5% blasts in the bone marrow. The second trial, on the other hand, recruited 20 patients who are 0 months to 80 years old and have persistent disease. Both clinical trials are still in the closing phase, so there is no current result about how CAR-NK cell therapy affects the progression of tumor cells of B-ALL in vivo.

### 5.2 Lung cancer

Although CAR-T cell therapy achieve huge success in the cancer of the blood, it showed very limited effects on solid cancers. In comparison, CAR-NK cell therapy may be a good candidate to improve the killing ability of adoptive cell therapy in solid cancers because tumor cells are sensitive to antigen-specific CAR-NK cells.

Lung cancer is one of the carcinomas with highest incidence rate and the highest fatality rate. It is very hard to cure so it becomes one of the biggest life-threaten solid cancers. Around 85% of lung cancers are non-small cell lung cancers (NSCLCs) [21]. With current traditional therapy methods, NSCLC patients typically receive surgery, chemotherapy, or irradiation. Immunotherapy is a new approach in NSCLC treatment. CAR-NK has already shown a very fruitful result for a possibility of a cure for NSCLC. NSCLC tissues express a relatively high level of B7-H3, an immune checkpoint molecule [22]. As a result, a CAR-NK cell can be constructed by CAR-NK-92MI cells carrying a CAR molecule with an anti-B7-H3 scFV region [23]. With the recognition ability of the anti-B7-H3 CAR molecule, the usage of CAR-NK shows an obvious regression of the volume of tumor cells and a significant extension of survival time both in vitro and in vivo [23].

An inhibitory receptor, PD1, plays an important role for cancer cells to suppress the ability of patients' immune systems. Even though NK cells naturally have the ability to combine with and kill the tumor cells, PD1 can inactivate the immune cells so that tumor cells can get away with the supervision of the immune system. Aiming at the PD1 receptor, a CAR molecule with an anti-PD1 region can help NK cells to kill the tumor cells. Researchers designed a chimeric costimulatory converting receptor (CCCR) as a PD1-NKG2D-41BB construct [24]. This type of design, combined with NK-92 cells, shows a significant improvement in reducing the volume of human lung cancer H1299 cells [24]. NK cells can actually be engineered with interested CAR molecules to reveal the strong power of anti-tumor ability to make pyroptosis, even if solid tumors have a microenvironment that can suppress the immune system.

When treating lung cancer with CAR-NK cell therapy, nanotechnology can also get involved. The usage of nanotechnology can generate a platform to image the cancer cell target for better analysis. A theranostic nanoplatform contains nanoparticles and IR-1048 dye in a nanostructure [25]. While the IR-1048 dye can actually go into the lipid bilayer, the nanoparticles suspend on the surface of the tumor cells for better computed tomography (CT) image [25]. While CAR-NK therapy can be used to eliminate the lung cancer cells after the synergistic photothermal therapy, the nanoplatform can provide feedback for better treatment.

### 5.3 Breast Cancer

Breast cancer is an uncontrolled proliferation phenomenon when mammary epithelial cells are influenced by multiple carcinogens. The exact pathogenic cause still remains unclear. At the early stage of breast cancer, lumps will accumulate in patients' breasts and nipples will discharge, but at the late stage, metastasis will occur and impact various organs to threaten patients' lives. Breast cancer is cancer with the top incidence rate among females in the US [26], so although the treatment outcome is good with the development of modern biomedical technology, triple-negative breast cancern and breast cancer brain metastases are still hard to treat with surgery or chemotherapy.

Triple-negative breast cancer (TNBC) constitutes around 15% of the total types of breast cancer. TNBC is very hard to treat mainly because there is no clear antigen target on the surface of the TNBC cells. However, researchers recently found that 50% to 85% of TNBC patients express tissue factors (TF), also known as CD142, in the TNBC cells so that TF can be a target for TNBC treatment [27]. With a clear target, a CAR molecule that aims at TF can be engineered and attached to the NK cells. Researchers construct TF-CAR-NK cells with co-expression of CD16 and the Fc receptor so that NK cells can efficiently find TNBC cells and take the antibody-dependent cellular toxicity (ADCC) [27]. In the preclinical research, TF-CAR-NK cells showed a very impressive effect of cytotoxicity on TNBC cells. The effect of TF-CAR-NK cells can also be boosted by TF-targeting antibody-like immunoconjugate to further reduce the volume of TNBC but there is no huge difference between the two [27]. The potential of CAR-NK therapy to a great extent depends on the target of the TNBC cells and the design of the CAR molecules. Although TNBC is very hard to cure, CAR-NK cell therapy provides an option with the possibility to cure TNBC and other types of breast cancer. Patients may not need to recourse to surgery which resects the whole breasts.

Metastasis is a common feature of breast cancer. Breast cancer brain metastases (BCBMs) are one of the metastases of breast cancer. Unfortunately, no method now has been developed to treat the

BCBMs so that there is still high mortality in such patients. EGFR protein, as an important role of cellular survival, is selected and discovered as a commonly expressed of BCBM by assessment of immunohistochemical [28]. As a result, the EGFR-CAR molecule can be constructed as a guide for NK cells to treat BCBMs. In the modern immunotherapy field, a combination of different therapies. Engineered oncolytic virus (OV), oHSV-1 is a type of cancer gene therapy method, so the combination therapy of both oHSV-1 and EGFR-CAR-NK cell is a potentially effective way of BCBM treatment. The EGFR-CAR-NK cell therapy alone can increase the secretion of interferon-gamma (IFNγ) to strengthen the ability to kill BCBM cells; meanwhile, the oHSV-1 gene therapy alone has the ability to lyse the BCBM cells [29]. However, researchers use the combination methods to treat breast cancer cell line MDA-MB-231, the cytotoxic level increases; the combination therapy can also elongate the survival time of the tumor-bearing mice [29].

## 6. CAR-NK Bottlenecks and Perspectives

For both hematologic cancer and solid cancer, CAR-NK cell therapy shows a wonderful treatment result comparing its former method CAR-T cell therapy. CAR-NK cell therapy is still not perfect that does not need any improvement. In the current situation of CAR-NK cell therapy, there are very limited clinical trials so that the result of usage of CAR-NK cell therapy is still not stable. There are also a few limitations of CAR-NK cell therapy.

First, the CAR-NK cells have a relatively short lifespan in vivo. Although it is safer due to the less chance of GvHD, the patients need more often injection of the CAR-NK cells. Second, before being treated with CAR-NK cells, patients need radiotherapy first to reduce the immunity for better treatment result of CAR-NK cell therapy, so the side-effects of radiotherapy should also be considered as a limitation of CAR-NK cell therapy. Third, the regulatory T cells and myeloid-derived suppressor cells in the microenvironment of solid tumor cells can still inhibit the performance of CAR-NK cells. Last but not least, most current researches use the NK92 cell lines as the resources of the NK cells. The more useful resources like peripheral blood mononuclear cells, isolation of cord blood, and iPSC still lack enough researches to prove the real status of CAR-NK cells from such resources.

In the future, researchers can test more of the different NK cells from various resources to find the most suitable resource for clinical trials, analyze the life-span in vivo to reduce the time of treatment cycle, or design better CAR molecules to restrain the negative effect of the cancer microenvironment. Despite the bottlenecks of CAR-NK cell therapy, the emergence of CAR-NK is still revolutionary and encouraging. With the huge success of former CAR-T therapy, CAR-NK therapy does illustrate multiple benefits as a cancer treatment, so it will lead us to a new time of immunotherapy due to potential effects on solid cancer treatment.

## 7. Conclusion

Multiple researchers have shown the benefits of CAR-NK cell therapy. It is relatively safe because of the low risk of cytokine release syndrome and GvHD. The decent effectiveness due to NK cells' natural killing ability is also another benefit of CAR-NK cell therapy. The CAR-NK cell therapy also has many resources of NK cells be better production. The ready-to-use feature of CAR-NK cells makes CAR-NK cell therapy a good application for real clinical treatment. Besides the benefits of using NK cells, the current experiments reveal enough curative efficiency against both hematological and solid cancers.

The technology of CAR-NK cell therapy is still immature so it still has quite a lot of drawbacks and uncertainty. Overcoming the microenvironment by new CAR molecule design may be the next step of the development of CAR-NK cell therapy. More clinical trials should be established as projects for better repeatability and certainty of experimental results.

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