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## CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY

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*Abstract-Cancer has long been a deadly disease that can affect any person, and to this day researchers are still learning about exactly what causes this uncontrolled cell growth. Immunotherapy offers a new option for people who do not respond well to most other types of cancer treatment. A new technology in this field is Chimeric Antigen Receptor T-cell (CAR-T) therapy. This breakthrough technology is FDA approved for combating B-cell precursor acute lymphoblastic leukemia (ALL), a form of lymphoid leukemia. ALL is the most common type of malignant cancer in children in the U.S and is the most common cause of cancer death in children. ALL has two subtypes, T-cell and B-cell. T-cells (also known as thymus cells), and B-cells (bone marrow or bursa-derived cells), are the major cellular components of the adaptive immune response. The B-cell subtype of the disease causes uncontrolled cell division of B-cells and occurs in most children diagnosed with ALL. CAR-T therapy involves isolating T-cells from the patient's blood and genetically engineering them to express a new chimeric receptor on their cell membranes. The chimeric receptor helps the T-cell identify and attack B-cells by recognizing the CD19 protein found on the cell membrane of both malignant and healthy B-cells to limit the disease's capability to spread. After the T-cells have been genetically altered, the T-cells are cultured in a process known as adoptive cell therapy before being reintroduced to the patient's bloodstream. By harnessing the power of the human immune system, immunotherapy and genetic engineering have given researchers new tools such as CAR-T cell therapy to combat B-cell ALL. The potential to expand this technology to additional treatments now offers new hope for patients afflicted with a wide range of diseases.*

*Key terms- Acute Lymphoblastic Leukemia (ALL), B-cells, Chimeric Antigen Receptor T-cell (CAR-T) therapy, Immunotherapy, T-cells*

### INTRODUCTION: THE FUTURE OF CANCER TREATMENT

Cancer for years has carried with it a well-established reputation as a dangerous and devastating disease. According to the American Cancer Society, there will be an estimated 1.7 million new cancer cases and over 600,000 cancer deaths in the United States in 2019 [1]. Almost everybody in America knows somebody who has been affected with this terrible disease. When someone reveals that they have cancer, an image comes to mind of somebody with the classic characteristics of a cancer patient. Hair loss, loss of strength, and long stays in the hospital are all life-changing events that we expect a cancer patient to be forced to endure. These common side-effects are primarily the result of the brutal chemotherapy regimen and radiation therapy that have led the way in cancer treatment since the 1940's. While chemotherapy has saved lives, it offers little hope when initial treatments are unsuccessful. Since then, there has been limited progress in the common methods used to treat cancer. Now, however, promising new areas of research are offering new hope to patients who have not achieved remission after chemotherapy alone. Such areas include immunotherapy, which harnesses the power of the human immune system to fight disease. Immunotherapy takes advances made in gene editing and puts them to use to specifically engineer the immune system on a cell by cell basis. Gene editing, specifically a method known as CRISPR came to prominence in the late 2000s and since then has provided powerful tools in medicine. As with all engineering technologies, sustainability must be called into question. In public health, sustainability can apply to reducing patient cost, increasing effectiveness of medications which in turn reduces time spent in the hospital, and ensuring that the technology contributes positively to the long-term health of society [2]. CRISPR is offering sustainable solutions to a range of industries including food and medicine. In the food industry, challenges arise from the growing population in that more people means the world needs more food. Genetically modified organisms,

or GMO's, while controversial do offer a sustainable solution by making crops more resistant to changing weather or pests. In medicine, CRISPR is being used to cut down on negative side effects of some aggressive treatments such as chemotherapy and radiation, as well as reducing hospital stays and providing more affordable options of treatment. The impacts of these technologies have wide reaching benefits in industry and medicine. In our paper, we will focus generally on one of these alternatives, immunotherapy, and explore in detail a specific therapy that has arisen from this area of study: Chimeric Antigen Receptor T-cell (CAR-T) Therapy.

## **IMMUNOTHERAPY**

In order to achieve an in depth understanding of immunotherapy, one must have an understanding of the processes within the immune system. The human immune system is essential for survival and is the body's natural defense from harmful influences in the environment. The immune system must differentiate between its own cells and foreign bodies in order to do its job of protecting the body while not damaging healthy tissue. This differentiation is made possible by proteins found on the cell membranes called antigens. Antigens are divided into two subtypes, hetero-antigens and autoantigens. Hetero-antigens are produced by foreign bodies such as microorganisms or viruses, while autoantigens represent tissues made by the human. Antigens bind to receptor molecules on the surface of a complementary lymphocyte that is produced in the body's immune response. Lymphocytes and their production will be further discussed with the topic of Acute Lymphoblastic Leukemia. Immunotherapy is unlike most other common categories of cancer treatment such as chemotherapy or surgery. Essentially it is a form of treatment which the patient's immune system is altered in a way to help fight cancer cells. This treatment uses substances made by the body that are often altered in the laboratory to improve the function of the immune system and assist in it either stopping or slowing the production and spread of cancer in the body [3]. This could quite possibly be one of the most important parts of this type of therapy. For this type of therapy, the cells are taken from the person's own body which is much better for the environment than using drugs or other techniques that can involve production in factories that can lead to runoff in drinking water and emissions from these factories. "A 2014 global review of pharmaceuticals in the environment, commissioned by Germany's environment ministry, found that of the 713 pharmaceuticals tested for, 631 were found above their detection limits. They are found all over the world — in 71 countries across all the United Nations' five regional groups" [4]. Also, many of these drugs that are taken come out in the urine and feces of people and animals who takes these drugs, but these cells were already part of the body and are just being reintroduced after being genetically modified [4].

Various forms of immunotherapy focus on different parts of the human immune system to treat different types of diagnosed cancer. As discussed previously the focus of this paper is CAR-T cell therapy which is a form of immunotherapy, however there is a multitude of other methods in this field of cancer treatment. Some focus on assisting the immune system to detect cancer cells which are often unable to be distinguished regularly enabling them to be destroyed by the immune system itself. Common immunotherapies used include monoclonal antibodies and tumor-agnostic therapies, T-cell therapy, nonspecific immunotherapy, and oncolytic virus therapy [3]. In order to understand the concept of immunotherapy completely descriptions of some of the various divisions of the treatment are necessary. One example is oncolytic virus therapy. This therapy has just recently been approved by the U.S. Food and Drug Administration for the first time in 2015 [3]. Much like CAR-T therapy it is newer in the development of immunotherapy cancer treatments. Genetically modified viruses are used to kill cancer cells in the body. This is done by injecting the virus into the cancerous tumor. The virus then enters the cell, multiplies, and kills the cancer cell. The death of the cancer cell causes the release of antigens that triggers the immune system to then target the cancer cells on its own [5]. This is just one showing how immunotherapy can be harnessed to fight cancer. Another well-known altering of the immune system to fight disease is vaccines. Vaccines work by imitating an infection and allowing the immune system to adapt. This adaptation is a result of the production of T-lymphocytes to fight the imitation infection. Once the infection subsides the body is left with B-lymphocytes that will be effective in fighting off the now familiar disease [6]. Just as vaccines work to adapt the human immune system to combat disease and infection, immunotherapy and specifically chimeric antigen T-cell therapy, alters the immune system to fight Acute Lymphoblastic Leukemia. This is a very basic example of how the immune system can be edited to become more resilient to disease, but it represents the same basic principle as CAR-T therapy. The immune system is an incredibly powerful tool that has been a deciding factor in the success of the human race. However, sometimes the body can play tricks on itself as in cancer where the danger is not a foreign body, but a mass of cells that the immune system sees no issue to because they do not recognize them as an outside threat to the body. This is where gene editing comes into play. With a little help, the immune system can be engineered to see that these cancer cells are not in fact friendly at all. Researchers in immunotherapy are simply using one of the most powerful systems in nature to their advantage, and the results so far are promising.

## **GENE EDITING**

Immunotherapy could not be possible without effective methods of engineering the genome within individual cells. Engineering the genome can be described as specifying the specific genetic makeup of an organism. Undesirable traits can be changed and replaced with a more suitable code for the researcher's purpose. This is a tremendous breakthrough in the field of medicine. Gene editing has allowed the field of immunotherapy to explode with promising research. With this powerful tool of gene editing, researchers can quickly change the fundamental genetic information within a cell. Genetic engineering has been implemented for the purpose of studying gene functions or genetics of human diseases. Perhaps the most exciting result of this technology is the field of personalized medicine that is immunotherapy. Currently, the most effective method of genetic engineering is clustered regularly interspaced short palindromic repeats (CRISPR) [7]. In this technique, researchers first design, then synthesize short RNA molecules that correspond to a specific DNA sequence [7]. The RNA will then be introduced into the cell and match up with the pre-determined portion of DNA. Specific genetic sequences can then either be silenced or removed completely depending on the desires of the researcher. The possibilities of this process are quite literally endless as there are billions of combinations possible within even a single genome. Some of the most relevant applications of this technology include industry, research, and medicine.

The highest potential for impactful use of this technology is that in research and medicine. Specifically, CRISPR's use in immunotherapy opened the door to personalized therapies that can be engineered to limit side-effects or to specifically target a group of cancer cells. In doing this, CRISPR is offering a sustainable future in cancer treatment. The average cost of chemotherapy with a good insurance plan is more than \$4000 per year [7]. Along with additional hospital costs, the total bill could end up over \$30,000 for less than a year of treatment [7]. As CRISPR becomes more mainstream, the cost of treatments that use this technology will offer well needed relief to expensive traditional chemotherapy. While CRISPR puts a tool in the hands of researchers that has never been possible. It is important that we do not get blinded by the innovation of the technology and seriously consider the ethical implications of what is possible with increasing technology. Is it responsible to change the genetic makeup of an organism that has been evolving for millions of years? Essentially what once took a million years of natural selection can now be accomplished with enough funding and a talented researcher. As research continues using CRISPR, it is important to keep in mind the purpose at hand and not let commercial interests deter ethical actions.

CRISPR is also offering a sustainable future for the food industry. CRISPR can be used to make cultures of bacteria

more resistant to viral infections that could ruin an entire batch of yogurt, resulting in major loss of productivity and revenue, or worse, impacting human health. In this way, the industry is being geared toward sustainable practices that will allow long term success in business and economics. The population of the earth doubled from 3 billion in 1959, to 6 billion in 1999 [8]. The food industry has been struggling to find new ways to feed a growing population. Genetically modified organisms offered a solution but were met with much protest from the public as concerns rose about the safety of these foods. GMO's involve combining genomes of multiple organisms to achieve a wanted trait in a crop [8]. CRISPR offers a more natural solution as they are using the cut and paste technology to alter specific aspects of the organism's genome, not combine it with other organisms. Not only is this a more natural approach, but it also offers a more efficient and cost-effective method that does not require a PhD in biology to understand. The most accessible technique involves blasting the cells of a plant with CRISPR coated pellets that pierce the tissue, delivering the desired genes [8]. Moving forward, one such specific problem that researchers are currently addressing with the help of CRISPR is a type of cancer called acute lymphoblastic leukemia (ALL).

## **ACUTE LYMPHOBLASTIC LEUKEMIA**

The main problem that our technology addresses is a type of leukemia known as B-cell precursor Acute Lymphoblastic Leukemia (ALL). ALL is a type of cancer that causes uncontrolled cell growth of lymphocytes. These lymphocytes more commonly known as white blood cells, are essential to the human immune system. There are two primary types of lymphocytes, B-lymphocytes and T-lymphocytes, both of which originate from stem cells in bone marrow. T-Cells differentiate from B-Cells in that they have matured in the thymus, a specialized primary lymphoid organ of the immune system, and actively kill foreign bodies. B-cells act as the memory of the immune system, storing antibodies from past infections that will be used to more easily fight off the same infection should it come around later in life. Both cells work by bonding to antigens which are foreign bodies and microorganisms within the body. In adults approximately twenty to thirty percent of white blood cells are made up of lymphocytes [3]. The number of healthy blood cells is often reduced as well as the overproduction of the lymphocytes blocks the normal development of these healthy cells. This results in numerous detrimental effects on the human body including lower healthy blood cell count. Other effects also depend on the form of treatment used for the cancer.

Approximately 4000 cases of Acute Lymphoblastic Leukemia are diagnosed every year in the United States with most cases being children and adolescents [9]. Of the total

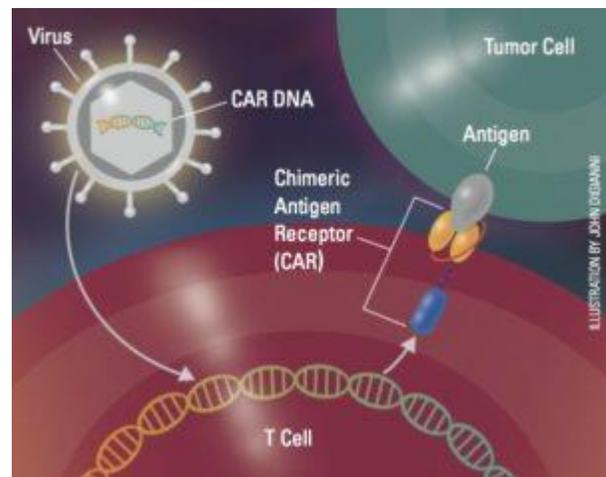
number of cases diagnosed per year, 75% are of the B-cell precursor [10]. The impact on families and children is substantial as Acute Lymphoblastic Leukemia is the most common form of childhood cancer and according to the American Cancer Society, 80% of ALL occurs in children [10]. The risk for developing ALL is highest in children under the age of 5, the risk then slowly declines until the mid-20's and begins to rise slowly again after age 50 [2]. Though there is no obvious reason why this disease occurs, there are several risk factors for developing ALL. Such risk factors include previous exposure to chemotherapy or radiation therapy, gender as men are more likely to develop the disease, and race with Hispanics and whites at a greater risk [1].

Several tests may be used to diagnose ALL. Doctors typically begin with a basic physical exam and health history, complete blood count in which blood is drawn and amounts of blood cells is checked, or a blood marrow biopsy. After detection of Acute Lymphoblastic Leukemia by a medical professional immediate treatment is required as this form of cancer can spread throughout the body and get much worse in a short amount of time. Treatment of ALL varies depending on whether the cancer affects B-Cell or T-Cell lymphocytes, the age of the patient, and how quickly the leukemia cell count drops after treatment. Children often have a better chance of remission than adults since their bodies can handle more aggressive treatments. Currently the main treatment used for treating ALL in both children and adults is long-term chemotherapy. Other treatment options included immunotherapy, stem cell transplants, radiation therapy, or surgery. The survival rates of childhood ALL ranges from 70 to 83 percent in developed countries with an overall cure rate of approximately 80 percent depending on how early the cancer was diagnosed and the treatments used [9]. For adults however, the survival rate is far less positive. A 2006 study reported that approximately 40 percent of cases resulting in successful [8]. The causes of this difference between children and adults can be attributed to a multitude of sources. Adults have been found to have an increased frequency of high-risk ALL and greater resistance to drugs during treatment. With new treatments developing such as Chimeric Antigen Receptor T-Cell Therapy, or CAR-T Cell Therapy, these numbers are expected to increase in the future for patients suffering from B-Cell Acute Lymphoblastic Leukemia as the technology progresses.

### **CAR-T CELL THERAPY**

ALL has devastating effects on families as it most often attacks young children. Exciting research in the field of immunotherapy is being done to address this problem. The most promising of such therapies is known as CAR-T cell therapy. CAR-T cell therapy is offered to patients who have experienced multiple relapses from chemotherapy and radiation therapy [11]. The therapy involves isolating T-cells

from the blood and genetically engineering them to express a new chimeric antigen receptor [11]. CRISPR as described in the above section is used to achieve this task. Specifically, the chimeric receptor is programmed to contain a binding site that is compatible with the CD19 protein expressed by malignant B-cells [11]. Once the engineered T-cells recognize the CD19 protein, it will self-replicate in order to better combat the invader, which in this case is a malignant B-cell. This is a specific example of just how useful the human immune system can be in fighting disease. Instead of worrying about creating enough engineered T-cells in a lab, the engineered T-cells will reproduce naturally within the body when they are reintroduced. The following image from the "Dana-Farber Cancer Institute" illustrates very broadly the processes involved in the therapy [11]. The first process shown on the left is the use of the gene editing tool CRISPR to edit the DNA of the T cell. The virus shown in the image contains a DNA sequence that will be added into the DNA of the T cell. After the DNA is altered, the cell will express the Chimeric Antigen Receptor that can then bind to the patient's tumor cells.



As they reproduce, they are increasing the number of cells that contain the engineered receptor. This is a huge benefit to CAR-T therapy as it allows the body to naturally fight off the cancer cells after the engineered T-cells have been introduced. The modified T-cells will kill any malignant B-cell that is expressing the CD19 protein. Prior to administering the therapy, patients will be prepped with lymphodepleting chemotherapy [11]. This serves one main purpose and that is to deplete the immune system so that once the modified T-cells are introduced back into the bloodstream, most of the T-cells in the body will be expressing the chimeric antigen receptor that allows them to recognize CD19 [11]. Essentially, the therapy aims to replace the T-cells in the body with engineered T-cells that can recognize and kill the malignant B-cells. It is important to have as many engineered

T-cells as possible because normal T-cells cannot recognize the malignant B-cells. This is since T-cells are not supposed to target the body's own cells. This is the biggest problem with cancer in general. The immune system does not recognize that there is a problem because all the malignant cells are created by the body. CAR-T cell therapy offers a logical approach to cancer treatment, use the power of the body's own immune system to fight the disease. This therapy is exciting due to its promising clinical data. In a study conducted by the Children's Hospital of Philadelphia treated 53 children with relapsed B-cell ALL with CAR-T therapy as described above. A complete remission (CR) was observed in 50 patients (94%) [10]. Although more effective in children, CAR-T has also shown activity in adults with relapsed B-cell ALL. In a study conducted by the Memorial Sloan Kettering Cancer Center, with the same process as the prior study mentioned, CR was observed in 88% of patients [10]. Obviously, more clinical data is needed to be sure about the therapy's efficacy. However, initial trials such as the ones mentioned above show true promise. So much promise in fact, that on August 30, 2017 the FDA approved a CAR-T cell therapy (tisagenlecleucel) for patients up to 25 years of age with B-cell ALL [7]. By no means is this a cure-all for cancer. However, these results show that CAR-T therapy has helped those that once would have had nowhere else to turn in terms of treatment options. It is the potential of the therapy that draws such intrigue. CRISPR was discovered as an effective genetic, "cut and paste tool", in 2012, meaning that the tool can be adopted by laboratories worldwide to allow research to proceed more quickly and economically [7]. Now, not even a decade later, there is already an FDA approved therapy showing that immunotherapy with the use of CRISPR can lead to actual results for people who are literally fighting for their lives.

Though the study results and data appear to be quite promising for most patients, there are a variety of known yet unidentified factors that contribute to either the efficacy of CAR-T therapy. Such factors include the "CAR design, the composition of the infused T cells, the tumor type and microenvironment, and recipient preconditioning regime" [12]. Just with almost any form of medical treatment CAR-T therapy has its drawbacks and side effects. However, currently it remains a promising new advancement in the field of cancer research and treatment. CAR therapy is also offering hope for reducing the cost of cancer treatment. For 60 years chemotherapy and radiation were the only prominent therapies that showed any real results in fighting cancer. It is exciting to think about where immunotherapy and CAR-T could lead the world of oncology in the next 60 years.

## **ISSUES FACING CAR-T THERAPY**

As with all aggressive cancer treatments, the side effects of CAR-T therapy can be severe. The most common side-

effect of the treatment is cytokine release syndrome (CRS). CRS is a combination of inflammatory symptoms that are a result of an overactive immune system [11]. Symptoms can be mild and flu-like, while more serious complications include hypotension, vascular leak, and multiorgan system failure [11]. Mild symptoms can be treated with corticosteroids while more severe cases can require hospitalization and may lead to death [11].

Another issue currently facing CAR T-Cell therapy is the low quantity of viable T-Cells in ALL patients. Patients at this point have undergone chemotherapy and radiation that has decreased their T-cell count. Also, the therapy requires removing T-cells from the patient's blood stream, further weakening their immune system. These factors put the patient at risk of infection from common bacteria and viruses such as influenza that can become deadly when coupled with a weakened immune system. Therefore, it is important that patients receive routine examinations and stay out of high population areas in order to decrease the risk of contracting one of these potentially deadly infections. The therapy itself can take up to several weeks to successfully modify the patient's T-cells before the treatment is ready to be administered [7]. During this time, it is difficult to keep the patient's condition stable

The last issue with this type of immunotherapy is that it can only be used against hematological malignancies. Doctors and researchers would like to be able to apply this technology to fighting solid tumors as well. The first problem in trying to fight these tumors is finding them. Unlike in cases of ALL these tumors rarely express one type of specific antigen so a type like CD19 used in ALL would not be able to be used to find this [13]. Researchers though have found a way around this. "Recently, to open the doors to targeting intracellular antigens with CAR T cells, Patel et al. (93) showed success in an in vivo myeloma study with a CAR/TCR hybrid that recognized the antigen NY-ESO-1 in the context of HLA-A2. These TCR-CARs were shown to effectively bind an HLA-A2+ T cell artificially engineered to express NY-ESO-1. TCR-CARs that recognize antigen in combination with MHC can thus recognize both extra- and intra-cellular antigens in the way that wild-type or modified TCRs can" [13]. Another problem against these types of tumors is that they must infiltrate the tumor. "Chemokine-receptor mismatch can prevent migrating lymphocytes from following a chemotactic gradient. Surface markers like selectins on endothelial cells that bind circulating lymphocytes and induce signaling cascades for subsequent extravasation into sites of inflammation are necessary, as are the corresponding receptors on T cells. Additionally, physical barriers such as cancer associated fibroblasts (CAFs) and abnormal vasculature at the tumor site can block T cell entry" [13]. However there have been some studies that have shown some new options to achieve this. Anti-angiogenic therapy targeting VEGF, CD276, or endothelin B receptor has been

shown to normalize tumor vasculature and can be used with genetically-engineered T-cells to increase infiltration in to the tumor [13]. There is hope that some studies will be able to come over this issue of infiltration, but there is also one more barrier to cross to be able to use these T-cells against solid tumors. These T-cells must be able to survive in the microenvironment of the tumor. "The glycolytic metabolism of tumor cells renders the environment hypoxic, acidic, low in nutrients, and prone to oxidative stress" [13]. Though there is also some promising research in this field which can even lead to the T-Cells being able to be used against solid tumors. "One approach designed to protect T cells from the oxidative stress inflicted by ROS in the TME was the design of a CAR T cell expressing catalase, an enzyme that reduces hydrogen peroxide to water and oxygen" [13]. The study showed that this can be successful it did not stop the cells from the many other problems that they faced in the tumor including low or no oxygen [13].

While these are significant issues and side-effects, they are expected as with any cancer treatment. The most common side-effect CRS can be treated in most cases successfully with a simple steroid. In most cases now, the steroid is being given to patients while they are receiving CAR-T therapy as a preventative measure against CRS [11]. Also, oncology nurses are being trained to recognize the symptoms of this side-effect as it seems to be common in the trials mentioned prior.

Overall, the side-effects from CAR-T cell therapy are no more severe than those of chemotherapy and radiation in most cases. It is a more natural treatment that often times allows for quicker recovery due to the fact that the CAR-T cells can remain in the body with no harm to the patient [11]. Even though CAR-T cell therapy might not be able to be used against all types of cancers, it is promising to see that the research is being done to find other applications of the technology.

## **CASE STUDIES OF CAR-T THERAPY**

Through the research and development of CAR-T therapy, it has so far proven be a promising new for of treatment for specific cancers. However, as previously stated in other sections, the technology is still not perfected and that this stage has had some negative results in a quantity of individual cases. In one of these cases an attempt was made to treat a patient with ERBB2 overexpressing tumors. ERBB2 is a member of the epidermal growth factor receptor family [13]. Overexpression of ERRBB2 is often associated with a more aggressive cancer. The patient in this case was a 39-year-old female who had undergone three different chemotherapy regimes with little success. Tumor progression occurred in the lungs and liver of the patient and required the application of a different form of treatment. After a preparation regime of two days cells transduced with the

ERBB2 CAR were injected intravenously. Within 15 minutes of the infusion the patient suffered from respiratory complications. As described by the report, the patient "remained severely ill with maximum intensive care unit support for the next 5 days at which time progressive hypotension and bradycardia as well as gastrointestinal bleeding resulted in cardiac arrest from which she could not be resuscitated" [14].

It is important to be aware of the age of this report as it occurred in 2010 and the development of this therapy has progressed greatly in that since that time. Also, this case is quite extreme in its outcome. However, it does show that the technology is still quite young and can cause detrimental effects on the patient just as another other form of aggressive cancer treatment can.

On the other end of the spectrum Chimeric Antigen T-cell therapy has often proven more successful than not. Had this fact not been true the technology never would be in the stage it is in today. An example of one of these many successful applications of CAR-T therapy is the study of a 53-year-old man with diffuse large B-cell lymphoma. Standard treatment for this disease is a chemotherapy regime with including a monoclonal antibody [15]. After completion of the chemotherapy his remission lasted only two months before the stage-3 cancer returned. The man eventually became a part of a clinical trial for CAR-T cell therapy and had his T-cells collected. After injection of the chimeric antigen receptor T-cells into his body, the patient suffered from typical side effects such as flulike symptoms. However, one year after the side effects subsided the patient had a complete response to the therapy, meaning there is no evidence of the disease remaining [15]. There is a multitude of stories just as this and there is bound to be more as this breakthrough cancer research technology develops in the future.

## **CONCLUSION: WHAT THE FUTURE HOLDS**

CAR-T cell therapy is offering patients with relapsed B-cell ALL a new option in terms of treatment. An option that was not even thought possible a decade ago. Specifically, CAR-T therapy will better serve to help children fighting the disease for a few reasons. Children make up 80% of all cases of B-cell ALL, which also happens to be the most common type of cancer inflicting children [10]. Also, the therapy is intensive in nature and children tend to respond better to the treatment than older patients [15]. CAR-T therapy is innovative in that not only does it change the way we can treat one specific type of cancer, it also changes how we think about fighting other more common cancers. To recap, CAR-T therapy is administered as a secondary treatment of B-cell ALL for patients who have experienced relapse from

traditional methods. T-cells are taken from the patient's blood and genetically engineered using CRISPR to express a chimeric antigen receptor. This receptor binds to the CD19 protein expressed by malignant B-cells within the body. Before the CAR-T cells are introduced back into the blood stream, the patient will undergo a round of lymphodepleting therapy to lower their white blood cell count in order to stimulate reproduction of CAR-T cells. CAR-T cells are introduced back into the blood stream where they will recognize CD19 protein on B-cells and kill them through the natural processes of the human immune system. CAR-T therapy is one of the most promising breakthroughs that has come from the research being done on immunotherapy. By understanding just how powerful the human immune system can be, researchers are offering new hope to patients suffering from a wide range of diseases.

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