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## **NEW TECHNOLOGY IN CANCER THERAPY: CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY**

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**Abstract**— *Our paper will explore the process and applications of Chimeric Antigen Receptor T-cell (CAR-T) Therapy. T-cells are one of the most important cell types in the human body's immune system due to their ability to identify and destroy threatening foreign cells in the body. We will discuss how cancer cells are able to disguise themselves as the body's domestic cells and are therefore left to replicate without regulation. CAR-T therapy addresses this by removing T-cells from the patient's body and genetically engineering them to express a single chain antibody fragment that can recognize and destroy cancer cells. Once returned to the bloodstream these cells will then be able to eradicate the cancer cells. The paper will also address why CAR-T cell therapy is considered a "living" therapy. We will describe how the lifespan of CAR-T cell therapy can be extended even longer by learning to use specific T-cells with a high capacity for replication.*

*Our paper will also evaluate the safety and cost effectiveness of CAR-T therapy, concluding whether or not the treatment is sustainable and what it would take to reach that point. Specifically, our paper will discuss a CAR-T product called U-CART19, which expanded CAR-T therapy to allogeneic cells for treatment of leukemia. The paper will explore the benefits, disadvantages, and research surrounding U-CART19 and other similar products. We will also discuss how mass producing this therapy allows for a standard of quality control to be established with more consistency and allows the therapy to be prepared in advance, which would make it more sustainable and immediately available for more patients.*

**Key Words** – Antigen, CAR-T, Chimeric, Lymphoma, Receptors, T-cell

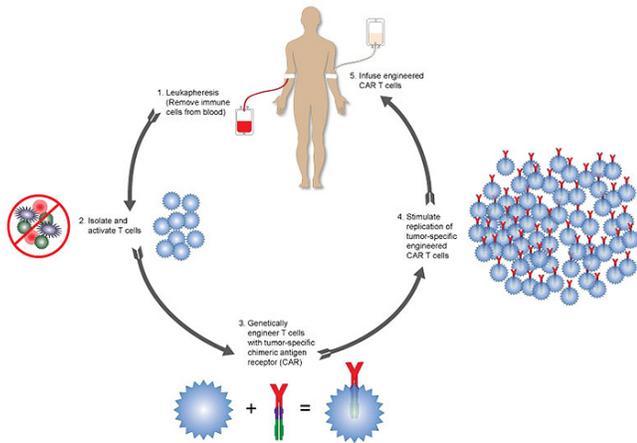
### **HISTORY OF LYMPHOMA TREATMENTS AND EXPLANATION OF CAR-T THERAPY**

The medical community has been studying, and subsequently treating, blood-related cancers since the **University of Pittsburgh, Swanson School of Engineering**  
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coining of Hodgkin's disease – and the more prevalent variation, non-Hodgkin's lymphoma – in the mid-18th century. Despite this early discovery, it took another eighty years for treatment to become widespread after World War II. Treatment initially utilized the derivatives of nitrogen-based mustard gas. From there, treatment quickly transitioned into the use of alkylating agents where it remained until the advent of chemotherapy. Though the discovery of chemotherapy led to higher rates of remission, it also led to higher chance of cytotoxicity, meaning the new treatments harmed healthy cells. Additionally, the remission rate for those treated with second-line chemotherapy was only 12% [1]. As can be seen from this brief overview, treatment for blood-related cancers was all but stagnating from its inception through the turn of current century. Remission rates were low, and many treatments caused devastating collateral damage to the body.

In recent years, a new form of therapy termed chimeric antigen receptor T-cell (CAR-T) therapy has emerged as an option to be used in tandem with, or as alternative to, the traditional treatment methods. This new form of therapy works to stimulate the patient's own immune system in hopes it will target cancerous cells. Cancerous cells multiply in an unregulated manner in the human body because the body's domestic T cells – a type of immune cell – are unable to identify the cells as foreign and threatening. CAR-T therapy uses the principles of genetic engineering to allow T cells to recognize these cancerous cells as a threat and destroy them. In order to accomplish this, the patient first undergoes pheresis, where blood is taken intravenously and white blood cells are isolated from the blood. From there, a technique called flow sorting column separation is used to extract T cells from the rest of the blood. The cells are then genetically modified to produce chimeric antigen receptors (CARs). The chimeric antigen receptors have a single chain antibody fragment, expressed along with signaling elements that were previously expressed on the T cell receptors. Most regularly, the CD19 antigen is used for hematological malignancies like leukemia and lymphoma [2]. These

antigen-presenting cells are now able to recognize cancerous cells as threatening and destroy them. Lastly, the cells are stimulated for reproduction to ensure they will continue to target cancerous cells within the body. The modified cells are then infused back into the bloodstream with the hope they will eradicate the leukemia or lymphoma cells [3]. Figure 1 shows a visual representation of this process.



**FIGURE 1 [2].**

**Process of removing, modifying, and reinserting T cells**

The earliest treatments for these diseases are vastly different from that of the CAR-T cell therapy that is being studied now. Cancer treatment is something that has had a big impact on the health community and still serves to be an area that needs more research. While CAR-T therapy is still a recent discovery, it shows that the cancer research is headed in the right direction and that big strides are being taken. The importance of this research cannot be understated, and hopefully CAR-T therapy will continue to grow and solve many of the health problems that we struggle with now. These include not only cancer, but other diseases that result from an immune system failure, such as HIV. CAR-T therapy is one of the newest forms of treating these diseases, yet it could end up being the most effective. This means that research, trials, and implementation could lead to eventually saving the lives of many.

**THE BENEFITS OF CAR-T THERAPY**

CAR-T therapy is still in its early stages, and the full range of effects have yet to be discovered; however, this new form of treatment has already shown improvements over traditional methods via increased remission rates and decreased side effects and recovery times. Furthermore, CAR-T is a 'living therapy', meaning that the engineered T cells are active in the body long after initial reinfusion due to

the high replicative capacity of central and stem memory T cells extracted from the patient's body. This capacity for reproduction and the efficiency of T cells is sometimes improved even further during the genetic editing phase of the process. Because CARs are specifically active for cell-surface molecules, they overcome the constraints of other types of antigen-expressing cells, meaning that the body does not try to revert the engineered T cell back to its original state. This means the engineered T cells will remain in the body longer to continue combatting cancerous cells. While they remain in the body, the tumor will be unable to metastasize, and the therapy as a whole will have a longer active life. Additionally, CAR-T therapy can also be used to insert genes that improve the efficacy of the T cells. When the cells are removed from the patient and being edited to express the CARs, they are also often edited to prevent apoptosis, stimulate reproduction, and remodel the microenvironment of the cancerous tumor to inhibit growth [2]. This will allow T cells to be used for much more than just the original purpose. Because these T cells can be edited to have a range of jobs within the body, they will be able to fight off many different diseases and perform other beneficial functions for the patient.

Naturally, the ultimate goal of any cancer treatment plan is to cure the afflicted party. While it is not being touted as a cure to blood-related cancers, CAR-T therapy has led to a drastic increase in the remission rates discussed in the previous section. This is clear to see in the case of Kymriah, the first FDA approved CAR-T therapy aimed at leukemia patients age twenty-five or younger. During clinical trials, this new therapy saw 80% of patients go into remission [4]. When compared with the measly 12% mentioned above, it is obvious that T-cell treatment has made great improvements in the effectiveness of cancer treatments. A prime example of these improved remission rates is the clinical trial for the chimeric antigen receptor NCT01626495. In this trial, more than 85% of the treated patients reached a complete response as their best clinical outcome, meaning they show an absence for all detectable cancers [5]. This astounding number continued to be the benchmark for the other tests investigated by the team of Hartmann, Schüßler-Lenz, and Bondanza. The success rate of CAR-T therapy is slowly increasing and giving more patients the ability or hope to be able to use this therapy in their own lives. As success rates continue to grow this treatment will likely be able to reach more people and improve their chances of survival.

In addition to the promising remission rates, CAR-T therapy also has notably fewer side effects than the traditional batch of cancer treatments. That is not to say that CAR-T therapy is free of collateral damage entirely (those will be discussed in the following section), but it does not cause some of the most harmful symptoms that often result from chemotherapy and radiation therapy. Some of the most common effects associated with chemotherapy include hair loss, kidney problems, dry mouth/sore throat, "chemo brain"

– mood changes and lack of concentration – and easy bleeding or bruising [6]. Radiation therapy often causes symptoms such as tooth decay, muscle pain or stiffness, lymphedema, shortness of breath, and a type of permanent lung scars called radiation fibrosis [7]. These devastating side effects can often cause just as much harm and disruption to a patient’s life and body as the cancer itself. CAR-T therapy causes none of these side effects, meaning that it does significantly less collateral damage to the body of a cancer patient. This can result in shorter hospital stays and an increased quality of life for the patient while he or she recovers. Many of these patients are willing to try any sort of treatment in an attempt to help diminish their cancer. Often, the side effects are not the most important part, but rather the effectiveness of the treatment. Now, with the option of CAR-T therapy, patients will have the ability to choose a treatment that is not only effective in combatting cancerous cells, but will also have significantly fewer side effects than other typical treatments.

Due in part to the minimal harm CAR-T therapy imparts on the body, it has a recovery time that is much shorter than other cancer treatment plans. In this sense, recovery time discussed refers to the time it takes the body to recover from the treatment and all side effects to dissipate. Even after a patient’s cancer has gone into remission, the symptoms that person experiences can continue to linger. Naturally, CAR-T therapy having less side effects means this overall recovery time is much shorter. Typically, CAR-T therapy has a recovery time of about two or three months [8]. Chemotherapy has a recovery time of twice as long, between 3 and 6 months, and radiation therapy can have effects that persist for years in the body [9,10]. Even the maximum recovery time in the range for CAR-T therapy is a fraction of the time that a patient would spend recovering from chemotherapy or radiation therapy. Objectively speaking, CAR-T therapy has improved over traditional treatments by allowing patients to continue their lives after cancer more quickly than ever before.

As can be seen, CAR-T therapy offers many crucial benefits. It has a high remission rate, few side effects, and a quick recovery time. The goal of cancer treatments is to rid the patient of cancer and allow them to return to their normal life. CAR-T remission rates are promising and can hopefully reach a large amount of people. Not only is the effectiveness of the therapy impressive, but, along with its limited side effects and quick recovery time, CAR-T is a viable option for the most effective and smallest risk therapy available to patients. CAR-T therapy will be able to help patients and allow them to return to the lifestyle they had before cancer overtook their lives.

## **THE DRAWBACKS OF CAR-T THERAPY**

Despite the great advancements CAR-T therapy has made in treating leukemia and lymphomas, it is by no means

a miracle cure. CAR-T therapy is, in its current form, unsustainable as the standard treatment method for blood-related cancers. In this sense, sustainability is referring to the just how possible it actually is for patients to be treated with CAR-T therapy. As it stands, patients attempting this therapy face serious physical, economical, and health-related barriers that hinder the possibility of this being adopted as the new typical treatment plan. Though collateral damage to the body is significantly reduced when compared to other treatment plans, CAR-T therapy can cause its own side effects, such as Cytokine Release Syndrome and neurological complications. Cytokine Release Syndrome is an illness that can occur during and after CAR-T therapy due to a large amount of cytokine being exposed to the patient’s body. Cytokine is a substance released by cells of the immune system and can accidentally be released in a quantity much larger than normal from the engineered T cells due to their stimulation to rapidly reproduce. Cytokine Release Syndrome causes effects such as nausea, fever, hypotension, and hypoxia that can range from flu-like to deadly due to the weakened physical state of a cancer patient. Luckily, this disease can be treated and even fully reversed as long as the patient’s body is strong enough, which successful CAR-T therapy will help make a reality [4]. Additionally, the patient can experience serious neurological events during the reinsertion of the modified T cells as the body’s reaction to what it perceives to be a foreign threat. These may only be mild reactions, such as drowsiness, agitation, and loss of balance; however, the treatment may also cause seizures that can lead to encephalopathy or aphasia [4]. Encephalopathy is a term referring to any disease, damage, or malfunction of the brain, and aphasia is the loss of the ability to understand or express the spoken word. These are extreme responses to treatment, but they can have lasting and devastating effects on a person’s life, even if the cancer does go into complete remission. Also, due to the fact that this therapy is so young, the side effects are still being discovered and studied. Knowledge of all the possible long-term effects on the body are not yet known, and the therapy could be potentially dangerous in ways researchers are not yet aware of. While many are willing to treat the cancer and think about the side effects later, these effects are factors that still need to be discussed and considered when weighing the benefits and drawbacks of CAR-T cell therapy.

The longer CAR-T therapy continues, the more severe the negative side effects can become and may even ultimately lead to the premature death of the patient. After initial treatment, the body may trigger an autoimmune response and reject the modified T cells being inserted. This happens in a similar manner to the way that a person has an allergic reaction to harmless material such as pollen. The body registers the influx of the modified cells as a foreign attack and deploys white blood cells to neutralize them [11]. This can cause its own issues within the body. Now the T cells must not only combat the cancerous tumor, but also the

patient's body itself. This not only limits the effectiveness of the CAR-T therapy but may also send the patient into life-threatening anaphylactic shock [11]. If this occurs, the effectiveness of the CAR-T therapy is severely hindered. Many of the modified T cells may be eradicated before they are able to attach to the tumor. The polar opposite effect may also occur, and the T cells could eliminate the tumor too quickly. Most people would not consider the speedy elimination of a cancerous mass a bad thing, but the sudden loss of a large number of cells can cause metabolic issues. This rapid eradication is referred to as tumor lysis syndrome and can cause issues such as hyperuricemia – high levels of uric acid in the bloodstream – and hyperkalemia – high levels of potassium in the bloodstream [11]. In the case of Juno Therapeutics, several of the mentioned side effects led to the deaths of multiple CD19-CAR test subjects. Three separate deaths were reported in the study resulting from severe levels of neurotoxicity [11]. CAR-T therapy is new and comes with the same risks as any other medical advancement in its early stages. Though it shows promise as a leukemia and lymphoma treatment (as previously explored), it comes with its own set of side effects that can be deadly in their own right. There is the potential to better CAR-T cell therapy to limit these side effects and perfect the effectiveness of the product, but until then, extended treatment side effects still remain a major barrier to a completely effective treatment.

Unfortunately, CAR-T therapy is also very expensive, further limiting its sustainability. It is estimated that patients being treated with this therapy should expect additional fees of about \$30,000 to \$36,000, before the costs from drug expenses. As previously discussed, CAR-T therapy also increases the chances of cytokine release syndrome, which can itself cost up to \$56,000 to treat. One of the CAR-T therapies that has been approved by the FDA, tisagenlecleucel, is estimated to cost between \$478,777, for patients that have not suffered from cytokine release syndrome, and \$531,813 for those who have [12]. Obviously, this is not the type of money that the average person has stuffed under their mattress, and paying for this treatment can seriously financially cripple a patient. As with most medical expenses, there are insurance policies that help to cover the cost of the treatment; however, the fact that CAR-T therapy is such a recent advancement makes it an unknown quantity for insurance companies. Most firms are hesitant to offer insurance for this treatment simply because they do not know how expensive the outcome could be. There are companies that are preparing policies for FDA approved CAR-T therapy treatment plans, but most patients are currently reviewed on a case-by-case basis [8]. This makes it much easier for an insurance company to deny a claim since there is no binding agreement covering this new type of therapy. Without any insurance, the full burden consisting of hundreds of thousands of dollars is leveled squarely at the patient already fighting for his or her life.

## **EVALUATION OF THE THERAPY OVERALL**

There are a variety of positive and negative outcomes associated with CAR-T therapy. However, CAR-T therapy provides a new opportunity for patients to have a higher chance of remission. Through critical assessment of the benefits and drawbacks, it is clear that CAR-T therapy can be massively beneficial and has many advantages over traditional treatment methods. For example, the FDA approved CAR-T treatment, Kymriah, increased remission rates from traditional methods by 68% [4]. Although there are risks associated with CAR-T therapy, there are severe risks associated with all forms of cancer treatment, as previously discussed. Although all treatment methods pose great risk to the health of the patient, CAR-T therapy seems to provide the opportunity of remission at a much higher rate than that of the traditional treatments. CAR-T cell therapy is allowing patients to effectively rid the body of cancer cells while, in most cases, also minimizing the patient's recovery time and exposure to side effects. This is attractive because of the likelihood that patients will be able to return to their regular lifestyle soon after their treatment is completed.

As previously stated, one of the major issues researchers are discussing is the high cost of CAR-T therapy and whether this is a practical treatment method for most people. However, CAR-T therapy is in its infancy stage, and it is still unclear how most insurance companies will go about reimbursing patients for this form of cancer treatment. Further, the high cost of treatment could also be diminished as the therapy progresses and is perfected for mass use [12]. Currently, researchers are still working on determining the best way to mass produce this therapy, and once a solution is found for production, the costs do have the potential to greatly decrease.

CAR-T therapy has an excellent recovery process. Patients who undergo CAR-T therapy will be in recovery for much less time than patients who undergo any other type of cancer treatment therapy. When comparing recovery time against that of other forms of cancer treatment, one will see that some patients are in recovery for years, while CAR-T cell therapy can have a recovery period of as short as a few weeks. Additionally, CAR-T therapy minimizes hospital stays not only due to the shorter recovery time, but also because the actual process of CAR-T therapy is less time consuming than other forms of treatment. Patients can spend months in chemotherapy, whereas the entire process of CAR-T therapy only takes around twenty-eight days on average. This therapy is even faster than some other forms of T cell therapy, like blinatumomab, which takes at least twelve weeks [11]. It's effectiveness and timeliness are two large factors when discussing the benefits of this therapy. Patients want to return to their normal life as quickly as they can, and with CAR-T therapy, that may become a reality.

While there are some areas where CAR-T therapy struggles, it does show great promise. This research is new, and the technology is still very much in its early stages. With more research and adaptations to the product over time, the risk may become even lower than it currently is. While at first glance, it may seem that CAR-T therapy poses too great of a risk to patients, is too expensive, or is too much of an unknown quantity to be worth its use, the drawbacks of this therapy are minimal compared to the potential that CAR-T treatments hold for the medical community. Through more research and trials, it is probable that many of the CAR-T obstacles we face now will be alleviated. Overall, this therapy is something that should eventually be implemented in hospitals and used to help more patients. While it does still need more work, it has the potential to save many lives with its effectiveness and help patients return quickly and safely to their regular lives.

## **FUTURE PROSPECTS OF THE THERAPY**

### **Becoming Sustainable**

Although CAR-T therapy has made great strides in the treatment process of cancer, it also holds great potential for improvement. Namely, CAR-T therapy must become a sustainable treatment method for blood-related cancers. As previously mentioned, sustainability here means creating a treatment method that can be utilized commonly for patients without serious medical and financial burdens. As has been previously discussed, CAR-T therapy remains an expensive process that few can afford. This is one of the largest obstacles for making a therapy that can be widely used and, therefore, sustainable. One method of achieving this sustainability is through the standardization of CAR-T therapy. When T cells are standardized, it means they are capable of responding to cells of a different body than the one they originated in. This is achieved by adding a specialized CAR that allows the T cells to bond to foreign cancer cells the same way they would with cancer cells from the donor [13]. This would drastically reduce its cost of therapy as the T cells would already be extracted and modified, essentially eliminating half of the tasks required with each individual patient. Additionally, the highly-specialized nature of CAR-T therapy would become moot and T cells would be available in the same way blood donations currently are. Once this is accomplished, CAR-T therapy will be more easily accessible for any patient without the requirement of their own T cells and significantly more affordable. This increased ease of access will then bring the treatment closer to the sustainability defined above. One company, Cellectis, is developing T cell products that can be mass produced in the manner just described. One of their most successful attempts is a T cell product called UCART-19, which utilizes CAR-T therapy principles [14]. UCART-19 is improving upon traditional CAR-T therapy by

attempting to generalize its use for more than just one individual. Rather than just leukemia treatment, UCART-19 will be able to treat a variety of different health problems. UCART-19 is advertised as an “off-the-shelf” T cell product, where T cells are donated instead of taken from the patient [14]. This is especially helpful in cases where the patient does not produce enough of their own T cells, which is common when a patient has already gone through other treatment options like chemotherapy, or when treating pediatric patients. Donated T cells are stripped of the DNA identification markers that prohibit them from generalized use then genetically modified as previously stated [14]. Allogeneic, or genetically dissimilar, products like UCART-19 also provide an opportunity to standardize quality controls and make immediate treatment for a larger number of patients available. UCART-19 and similar products can also diminish the cost of treatment by standardizing the process of CAR-T therapy [14]. If this is implemented, the downside of the expensive cost of this treatment may become a nonfactor. While the therapy will still be fairly expensive, the price should continue to fall as this therapy continues to grow.

The next step in achieving this sustainability is understanding how to take the process from being specialized for each individual patient to standardized for every patient. Keir, Levinen, Miskin, and Wonnacott describe the “transition from flexible processes at single academic institutions to highly controlled processes that can be implemented across many collection, manufacturing, and treatment sites” as crucial in the implementation of CAR-T therapy at a practical level. [13]. The idea of commercial manufacturing is to extract source tissue and transport it to a manufacturing site for cell isolation, expansion, and harvesting to then be transported back to the clinic and delivered to the patient [13]. One of the major obstacles of this process is making certain that all of the institutions involved are communicating and adhering to the same set of standards. Effective coordination among the collection, manufacturing, and treatment sites involved is crucial to ensuring that the material is handled correctly and patients are appropriately scheduled throughout the therapeutic process. [13]. Another difficulty is making sure that the transportation from the clinic to the manufacturing site is organized and limits the number of mistakes that could be made. In order for commercial manufacturing to be successful, manufacturers and scientists need to have an immense amount of knowledge on CAR-T therapy and be confident in their understanding of the product and its process. Once the commercial manufacturing process is perfected, however, it will be greatly beneficial for patients. By commercially producing this product, companies will be able to make improvements to the product more successfully. They will also be able to have a completed product in a much shorter amount of time than would otherwise be possible. Most importantly, mass production will be able to ensure

uniform products. Having a standardized model for CAR-T therapy will allow doctors and scientists to predict how the modified T cells will react with the patient before insertion, ultimately reducing health risks and making the treatment more sustainable.

### **Further Trials and Research**

The process of standardization is also making CAR-T therapy safer by reducing the chance of human error related complications [14]. One of the most promising examples for the success of UCART-19 took place in 2015. Layla Richards, an eleven-month-old with aggressive acute lymphoblastic leukemia (ALL), had already been through multiple rounds of chemotherapy and undergone a bone marrow transplant without success. In the words of Layla's doctor, "She was out of T cells and out of options" on account of the fact that she was too young to have produced enough T cells for CAR-T therapy [15]. At the time, UCART-19 had never undergone human clinical trials, but Cellectis was asked to make an exception, called a compassionate-use exception, as UCART-19 was Layla's last option. Fortunately, UCART-19 was successful in Layla. She was able to be released from the hospital two weeks after treatment and was in complete remission less than eighteen months later. To this day, Layla is still in remission. Two weeks after the news of Layla's outcome was released, Cellectis was approved to begin human clinical trials, and soon after, the company began large-scale production of UCART-19, which continues successfully today as one of the many types of CAR-T therapy options [15]. They are now working towards researching the effects that this therapy has on patients and hope to have it as a viable therapy option soon. This therapy will be extremely helpful to all of the patients who do not have enough T cells to utilize other options. With more testing, this product could potentially save lives as a mass-produced treatment.

Allogeneic products like UCART-19 have been shown to be massively effective at treating relapsed chronic myeloid leukemia. This has sparked the birth of several trials inspecting the potential of CAR-T therapy uses with other forms of cancer [2]. For example, there are currently clinical trials exploring CAR-T treatment of advanced epithelial ovarian cancer, metastatic renal cell carcinoma, and neuroblastoma. Furthermore, researchers are beginning to explore the effect of antigen chains, other than CD19, on the effectiveness of CAR-T therapy [11]. Overall, the future for using CAR-T therapy is very promising, with the ability to reach many types of patients with many types of health obstacles [4]. However, because this form of treatment is so new, studies still need to be done with a larger number of patients, along with a variety of longitudinal studies.

Due to its success in cancer treatment, CAR-T therapy is now being explored to treat a number of other medical issues, specifically blood related autoimmune disorders.

Edward Berger, a researcher at the National Institute of Health, is exploring the possibility of a "functional cure" to HIV. More specifically, he is exploring the possibility of using T cells in order to keep the virus in check. Currently, research involves giving animals genetically programmed T cells to find and destroy cells where the simian version of HIV is being replicated [15]. While cancer treatment is something very prevalent today, an HIV epidemic is also an issue that the world faces. CAR-T therapy is currently focusing on cancer treatment, but it could soon have an even larger impact and work towards bettering patients with many other types of diseases. In addition to HIV related research, CAR-T therapy also holds promise for developing treatments, and possibly even cures, for other autoimmune diseases like diabetes, multiple sclerosis, and lupus [15]. Though this research has barely begun, it has shown promise that CAR-T therapy has the ability to adapt to the needs of many patients and many types of diseases.

Due to a lack of knowledge about CAR-T cell therapy in the pharmaceutical industry, it is difficult for research and products to be tested and manufactured. As this technology is growing, the pharmaceutical industry needs to further its knowledge on individual gene therapy products. This is not something that has been previously available to the public, which means there are not only the obstacles of testing the product, but a discussion also needs to be had on how to best manufacture and distribute this therapy. While some researchers may have theorized about the best way to do this, the pharmaceutical industry as a whole needs to determine how this therapy can become something that is accessible to all. Most companies are relying on external research for their knowledge on this subject because they have never worked with something such as CAR-T therapy before. Additionally, since the therapy is new, there are very few regulations, especially within the pharmaceutical industry, on how to handle this product [11]. It is also important for good distribution practice (GDP) to be strictly enforced. When CAR-T cells are being transported from the manufacturing site to hospitals, it is crucial to ensure that there are no patient-product matching mistakes. These challenges must be overcome if CAR-T therapy is to become a viable treatment plan for cancer patients in the future.

While testing is still necessary in order to learn more about these processes, in the European Union, CAR-T therapy is currently being used and marketed. Not only has CAR-T cell therapy been given this authorization, but so have eight other new advanced therapy medicinal products (ATMP). Three of these new products are classified as GTMPs, or gene therapy medicinal products. Two of these GTMPs on the market in Europe utilize genetically modified T cells that are similar to the products we see in the United States. Though only one type of gene therapy is available in the U.S. market, the number of trials and tests being done in the United States is much higher than in Europe [11]. This is in part due to Europe's lack of funding for clinical trials and

difficulty in accessing proper manufacturing supplies. It's hard to currently weigh the difference between the therapy in the United States versus therapy in Europe because of the issue of translation of technology and ideas from one continent to another. Still, the high number of clinical trials in the United States as well as the increasing approval across the Atlantic shows promise for the future of widespread CAR-T therapy.

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**Team 22**

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