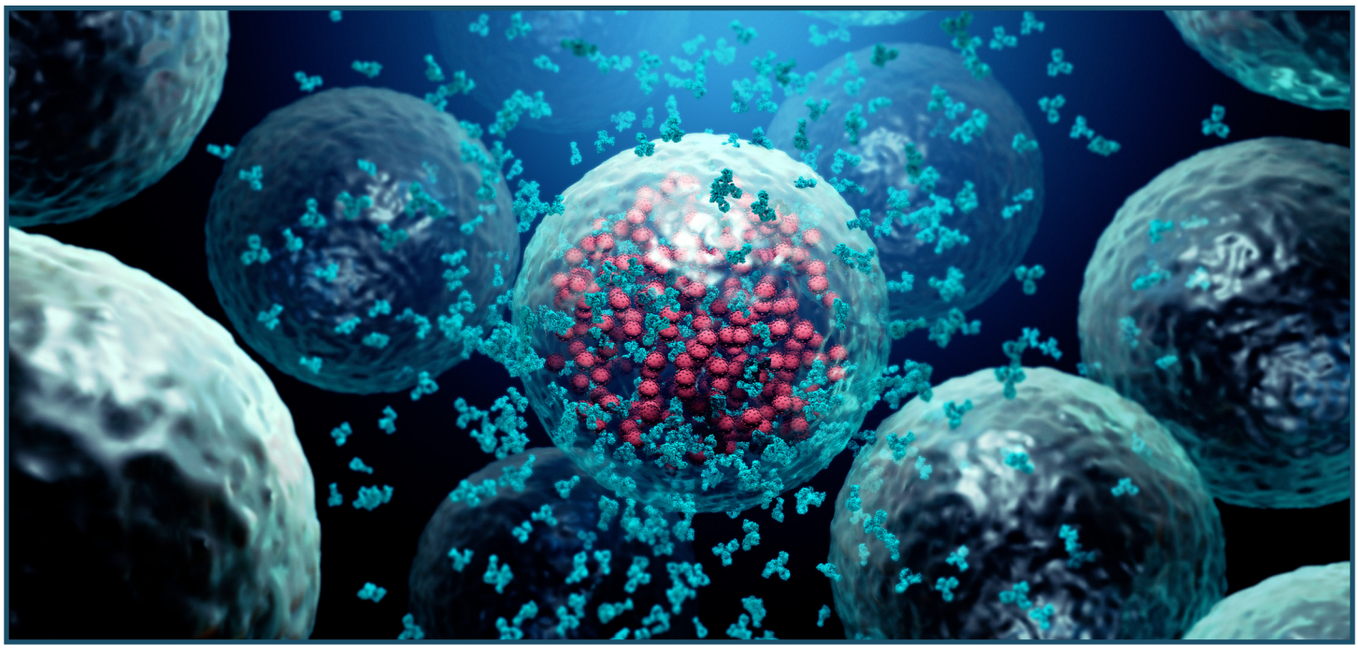

What Are Car T Cell Therapies?

Cellular therapies promise to revolutionize personalized medicine. These therapies offer new approaches for treating, and possibly curing, previously intractable diseases. One of the most consequential cellular therapies is the chimeric antigen receptor T cell (CAR T) therapy.

CAR T cell therapies first became available to patients in 2017. That year, the FDA approved KYMRIAH® (tisagenlecleucel) and YESCARTA® (axicabtagene ciloleucel) for the treatment of certain B-cell cancers, ushering in a new era in the fight against these diseases. A third CAR T cell therapy TECARTUS® (brexucabtagene autoleucel) was approved in 2020.

What makes these therapies so special? It all starts with the T cell and its central role in adaptive immunity.

What is a T Cell?

T cells were named so because they mature in the thymus and belong to a class of white blood cells known as lymphocytes. Functionally, T cells are the hub around which the adaptive (or acquired) immune system revolves. It is our adaptive immune system that provides highly specific and durable protection against bacteria, viruses, and other microbes with which we come into contact. It is also what makes vaccines effective at preventing diseases like influenza and chickenpox.

There are many different types of T cells, each with their own functions, but they almost all operate through a common set of molecular machinery. One of the most important of these is the T cell receptor (TCR). TCRs allow T cells to recognize specific antigens, which are structures or molecules that elicit an immune response.

To a T cell, recognizing an antigen means recognizing a threat. Once an antigen is recognized, the TCR generates a signal inside the T cell that instructs the cell to begin the process of eliminating the threat. This may include recruiting neutrophils to ingest and dispose of large microbes, stimulating B cells to produce antibodies, or directly killing the cell attached to the antigen, just to name a few.

Given a T cell's capacity to target an antigen with high specificity and the ability of researchers to modify these cells to target an antigen of interest (e.g., a protein on the surface of a tumor cell), T cells have become an attractive choice in the fight against cancer.

Contact us today:
888.615.5111 | discover@nuventra.com

Nuventra PHARMA SCIENCES

Making a CAR T Cell

The concept behind CAR T cells is deceivingly simple—use a patient's own immune system to recognize and eliminate cancer cells. However, producing a CAR T cell is a complex and multi-step process. It starts with designing the CAR. The CAR, much like a native TCR, is a combination of protein domains that work in concert to identify the antigen of interest and then transmit a signal inside the T cell that will ultimately lead to the destruction of the cancer cell. The CAR typically includes an extracellular region for antigen recognition, a hinge/linker region, and an intracellular region for signal transmission.

Because the CAR does not exist naturally in a T cell, a gene that encodes the CAR must be introduced into the cell. Using a patient's own T cells that have been extracted using a process called leukapheresis, recombinant (i.e., engineered) viruses can be used to introduce the CAR gene into the cells. Once inside, the CAR gene integrates into the cell's DNA and promotes long-term expression of CAR proteins and their presentation on the T cell surface. Non-viral delivery methods are also possible.

Following introduction of the CAR, the CAR T cells are activated and expanded before returning them to the patient. Upon activation, CAR T cells can be induced to develop into specialized T cell subtypes by treating them with cytokines—a class of small proteins that are important for cellular signaling. This ability to differentiate T cell subtypes is important because certain subtypes of T cells (or mixtures of subtypes) may be better than others at killing tumors. Following activation, the cells are expanded, meaning that they are cultured under conditions that encourage cell division. After enough cells have been produced, the CAR T cells are concentrated to an infusible volume, frozen, and transported back to the clinic for injection into the patient.

One intriguing alternative to using a patient's own T cells is to develop what are known as "off-the-shelf" CAR T cells. While no off-the-shelf CAR T cell therapies have been approved yet, the idea behind them is straightforward even if its implementation is challenging. Off-the-shelf T cells would be isolated from donors who are genetically similar (but not identical) to the patient. The donor T cells would then be transduced with the CAR gene just as before but also modified via gene editing to eliminate expression of immunogenic proteins, such as their native TCRs.

This extra step reduces the risk of graft versus host disease, in which the donated T cells could attack the recipient's healthy cells. Ideally, off-the-shelf CAR T cells would shorten the time between diagnosis and treatment and reduce costs compared to autologous CAR T approaches. These and other potential advantages could make this "next generation" therapy another step forward in the battle against certain cancers.

Advantages of CAR T Cell Therapy

Before CAR T cell therapies came on the market, most patients with B-cell cancers relied upon chemotherapy and stem cell transplants. While the decision about an individual patient's treatment should remain with the patient and her/his health care provider, CAR T cell therapy does offer certain advantages that could make it an appealing choice. Among these are the potential for shorter treatment times, prolonged durability, and fewer side effects.

TREATMENT TIMES

CART T cell therapies require very short treatment times—generally a single infusion with less than 2 weeks of inpatient care. While stem cell transplants also typically require only a single infusion over a few hours, the full course of treatment, including preparatory work and recovery, can take months. Stem cell treatments that involve more than one infusion, known as tandem transplants, can take even longer. Chemotherapy treatment regimens typically also require months to complete, with multiple treatment cycles throughout (i.e., alternating periods of treatment and recovery, with generally 3 weeks set aside for recovery after each dose).

DURABILITY

While the durability of CAR T cell therapy is the subject of ongoing research, remission following CAR T cell therapy appears to be long lived in many patients and commonly lasts for several years. Like stem cell therapy, CAR T cell therapy may prove to be curative in at least some patients. Because CAR T cells persist in the body, these cells may continue to treat relapses long after the initial cancer becomes undetectable. By contrast, traditional chemotherapy is only effective at killing cancer cells during and shortly after administration. Relapses therefore require restarting chemotherapy (or an alternative regimen) to elicit an effect.

SAFETY

CAR T cell therapies do not require aggressive chemotherapy, and unless there is an elevation in cytokines following infusion, patients receiving CAR T cells do not typically require immunosuppression. This is an important safety advantage over both stem cell transplantation and chemotherapy. Sometimes the side effects of stem cell transplants and chemotherapy can be so severe that patients will opt out of treatment altogether, which worsens their prognosis.

Toxicity & Side Effects of CAR T Cell Therapy

While CAR T cell therapy can be a safer alternative to chemotherapy and even stem cell transplantation in certain patients, there are several common side effects of CAR T cell therapy that can pose serious risks and therefore warrant careful monitoring.

Cytokine release syndrome (CRS) is a common toxicity associated with CAR T cell therapy. CRS results from overproduction of inflammatory cytokines like tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6). These cytokines are produced when CAR T cells proliferate in the body, indirectly activating macrophages and other immune cells. Depending on the level of cytokine production, clinical outcomes can range from flu-like symptoms to life-threatening shock. To address this, drugs such as ACTEMRA® (tocilizumab), an IL-6 receptor antagonist, may be needed.

CAR T-cell-related encephalopathy syndrome (CRES) is another common side effect. This condition generally appears within a few days of infusion. Symptoms of CRES range from mild confusion and disorientation to fatal cerebral edema, and often include speech difficulties. A slightly broader neuropathological category, immune effector cell-associated neurotoxicity syndrome (ICANS), is often referenced in the literature. ICANS includes CRES and other neurological toxicities arising from CAR T and other therapies (e.g., other cellular immunotherapies, bispecific antibodies) that present similar immune-cell-mediated side effects.

Another potential side effect, termed "on-target/off-tumor" toxicity, occurs when CAR T cells attack non-tumor cells expressing the target antigen. For example, KYMRIAH, YESCARTA, and TECARTUS all target CD19, which is found on the surface of both normal and cancerous B-cells (albeit typically at much lower levels on normal cells). As a result, these therapies not only target cancer cells but can also deplete healthy antibody-producing B cells, making the patient more susceptible to infection. Next generation CAR T cells are being designed to minimize this effect, which should make these therapies safer in the future.

Other possible and significant side effects of CAR T cell therapy include (but are not limited to) infusion reactions, tumor lysis syndrome, cytopenias, cardiac toxicity, and hypogammaglobulinemia. While these and other side effects of CAR T cell therapy can be serious or even life threatening, most will either resolve on their own or can be effectively managed with drugs. In many cases, any side effects associated with CAR T cell therapy will be less burdensome than those with chemotherapy.

CAR T Cell Dose Selection and Dose Justification

Dose selection is one of the keys to an efficient and informative clinical trial. When it comes to dose selection, cellular therapies like CAR T cell therapy can appear more complicated than small molecule drugs however, many of the same principles apply. Because CAR T cells include novel transgenes that are distinct from a patient's own DNA, it is possible to measure these transgenes using a technique like quantitative PCR and to use these data to describe the cellular kinetics.

Using modeling and simulation (i.e., pharmacometric) techniques, cellular kinetics can be coupled with measurable pharmacodynamic responses to support appropriate dosages for clinical trials. These techniques can also be used to provide key support to the eventual product label and to the safe and effective use of the product once on the market. For a more detailed discussion on selecting optimal doses for cellular and gene therapies, please see our blog post titled, "Cellular and Gene Therapies: What Is My Optimal Dose?"

Conclusions

Cellular immunotherapies represent an exciting advancement in oncology and personalized medicine, but like all drugs and biologics, they are not without risk. Understanding these risks and being able to effectively navigate the developmental and regulatory hurdles that face these types of therapies is the key to getting your product approved. Nuventra understands the complexities behind developing cellular therapies, including CAR T therapies. If you are developing a cellular or other immunotherapy, contact us to learn more about Nuventra's experience and how Nuventra can help you make the most of your development program.