explained

HOW DOES CAR T CELL THERAPY WORK?

By engineering immune cells to effectively attack cancer cells, researchers established a new paradigm for cancer therapy.

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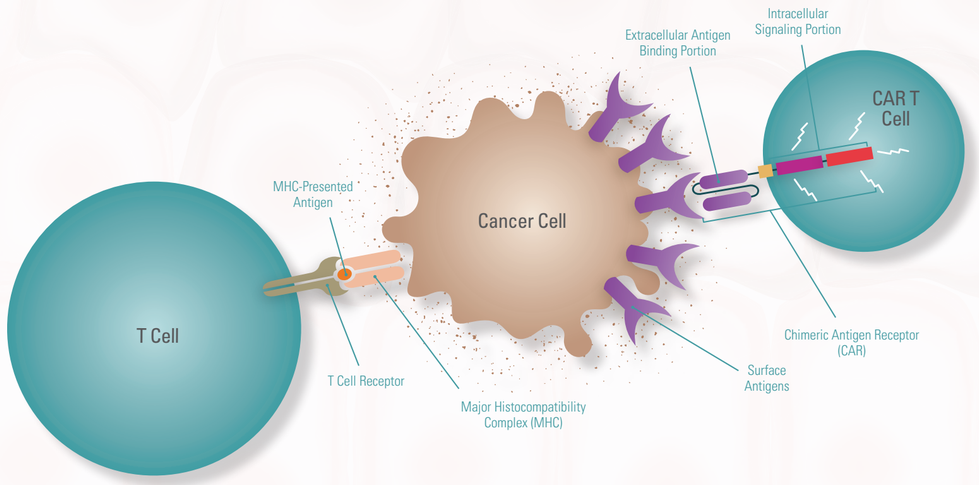
Treating cancer traditionally relies on chemotherapeutic chemicals, radiation energy sources, or surgical procedures to eliminate cancer cells. More recently, researchers developed strategies to boost the ability of the body's immune system to detect and kill cancer cells from the inside. One such cancer immunotherapy, chimeric antigen receptor (CAR) T cell therapy, emerged as a promising addition to the arsenal against cancer. From initial drug design to treatment protocols, researchers are finetuning CAR T cell therapy to improve outcomes for cancer patients.

1 What are CAR T cells?

As white blood cells involved in the immune system's response to foreign substances, T cells patrol the body for cells housing viral pathogens or cancer-causing genetic mutations (1). T cells express receptors that bind to antigens loaded onto the major histocompatibility complex (MHC), a protein complex on the surface of the infected or cancer cell that helps the immune system detect the invader (2,3). Upon binding to the MHC-presented antigen, the T cell initiates cytotoxic pathways that trigger the aberrant cell's death (2,3). However, in order to evade the immune system, cancer cells can alter gene expression or protein function to downregulate MHC on the cell surface, preventing T cells from recognizing and effectively clearing them (3,4).

Due to specific genetic mutations or changes in gene expression, cancer cells can uniquely express certain antigens on their surface (5). Scientists modify T cells with CARs, synthetic proteins that bind to these antigens, enabling T cells to access cancer cells through a back door (2,3). The extracellular portion of the CAR binds to a cancer cell surface antigen, anchoring the T cell to its unsuspecting target (2,3,6). The intracellular portion of the CAR transmits and amplifies a signal that activates the T cell's cytotoxicity, killing the cancer cell (2,3,6).

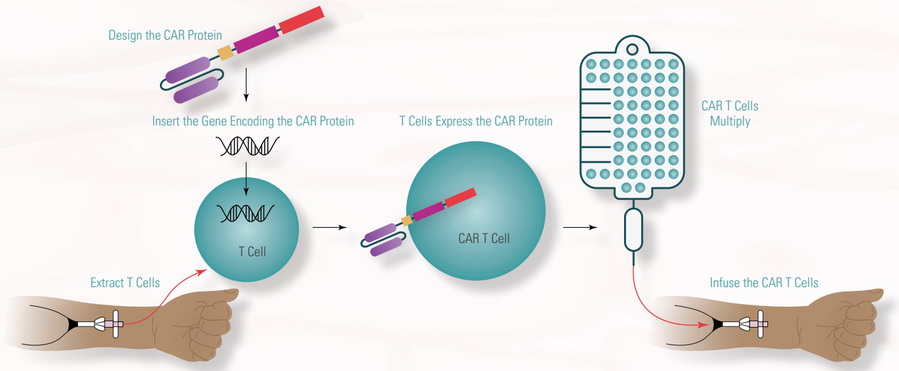


2 How do scientists engineer CAR T cells?

To make a CAR T cell, scientists must first design the CAR protein. The intracellular portion usually derives from natural signaling domains that activate T cell cytotoxicity, although the number and type of domains can vary (7). Researchers tailor the extracellular portion to bind to a specific surface antigen on a cancer cell (7). They employ a variety of methods, including protein engineering, computational modeling, and high throughput screening, to develop CARs with sufficient affinity and selectivity for the target antigen, stability, and ability to activate the T cell (7).

To incorporate the CAR into T cells, scientists identify the gene that provides the instructions for making the CAR protein. Using various genetic engineering approaches, they insert the gene into T cells extracted from a patient's blood, causing the cells to express the CAR protein (6). Scientists grow these CAR T cells in the lab to generate millions of them to infuse into the patient (6). While the exact number of CAR T cells a patient receives depends on how many are initially retrieved and how efficiently the modified cells multiply, one FDA-approved CAR T cell therapy requires 0.2 to 5 million CAR T cells per kilogram of patient weight (8).

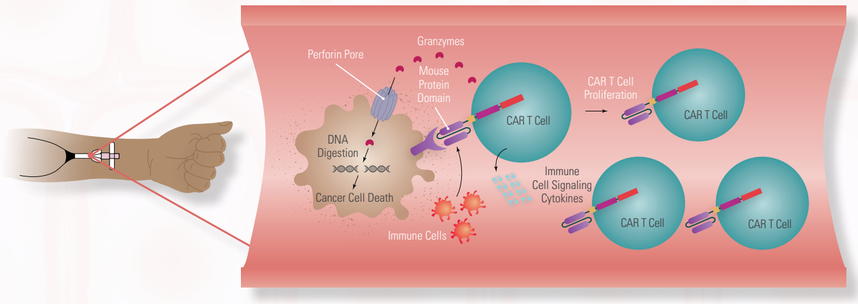
Researchers are also interested in manufacturing CAR T cells from healthy T cell donors rather than cancer patients. As the process of creating CAR T cells can take weeks, using donor cells provides a stored inventory of CAR T cells that are immediately available when cancer patients need them (6,9). Additionally, as combatting cancer can leave patient T cells exhausted, T cells from healthy donors may be able to kill cancer cells more effectively than those from cancer patients (10,11). However, donor-derived T cells may recognize the recipient's healthy cells as foreign and attack them (10). Researchers use gene editing techniques such as CRISPR/Cas9 to eliminate receptors involved in recipient cell recognition from donor T cells (10). Once CAR T cells from patients or healthy donors find themselves inside the body, their journey toward treating cancer begins.



3 What happens when CAR T cells enter the body?

CAR T cells injected into the body circulate in the bloodstream, hunting down cancer cells that present their complementary antigens. Once a CAR T cell hones in on its target, it binds to the antigen and launches its cytotoxic mechanisms at the cancer cell. The T cells release perforin proteins that poke holes in the membrane of the cancer cells and granzyme enzymes that use those holes to enter the cell (12,13). The granzymes activate a cascade of enzymes that causes DNA digestion, leading to cell death (12,13). CAR T cells can also harness T cells' natural ability to release cytokine chemical messengers to activate other immune cells to support their attack against cancer (12,13,14).

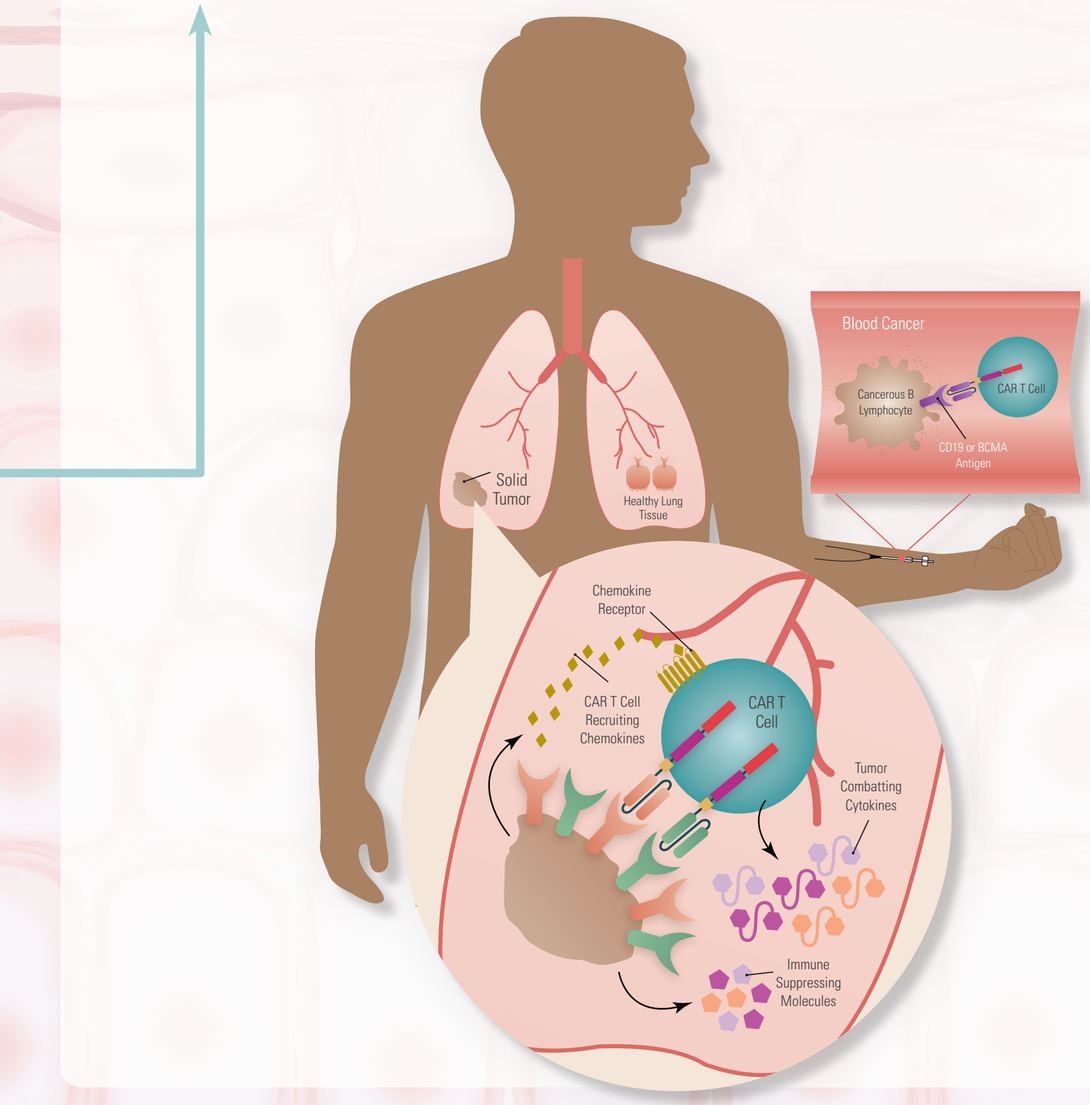
Binding to the cancer cell cues the CAR T cell to begin proliferating inside the body, creating a renewable therapy that could last years (15,16). However, the lifespan of CAR T cell therapy can be cut short if the immune system detects the CAR protein as foreign and degrades the CAR T cells (16). The source of the CAR protein plays a role in immune recognition since the extracellular portion often derives from a well characterized but unfamiliar mouse antibody (7). Researchers at the National Cancer Institute found that swapping a CAR's antigen binding domain from a mouse to a human version yielded higher levels of CAR T cells over time, suggesting that CARs made up of human protein fragments may better avoid immune-based degradation (17).



4 What types of cancer respond to CAR T cell therapy?

All six FDA-approved CAR T cell therapies treat blood cancers such as leukemia, lymphoma, and myeloma (6). These CAR T cells bind to the cluster of differentiation 19 (CD19) antigen or B cell maturation antigen (BCMA), which are robustly and selectively expressed on B lymphocyte white blood cells (6,18,19). Scientists have had less success identifying similar antigen targets on solid tumors such as those found in brain and lung cancer. Different tumors, or even individual cells within a single tumor, may express antigens nonuniformly (6,20). These antigens often exist at low levels on healthy cells, which can side track the CAR T cell's cytotoxicity (21). The unique environment of a solid tumor also secretes immune suppressing molecules that can disarm T cells and presents physical barriers that block CAR T cell penetration (6,20).

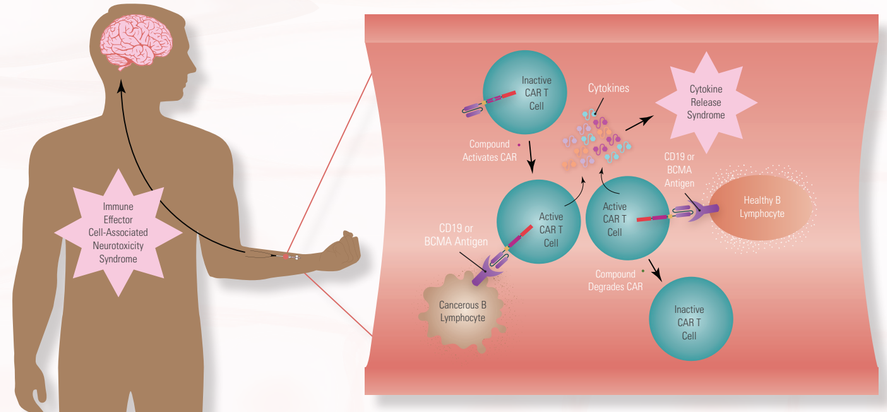
Researchers are exploring strategies to overcome these obstacles and expand the range of cancers that CAR T cell therapy can treat. They developed T cells that express two CARs that each bind a distinct antigen. The CAR T cell may initiate cytotoxicity if either antigen is present, allowing it to target heterogenous tumors, or only if both antigens are present, allowing it to better discriminate between cancerous and healthy tissues (20,22). Researchers also engineered CAR T cells to release cytokines that combat tumors' immunosuppressive mechanisms and express receptors for chemokines, immune cell recruiting molecules released from tumors, to enhance infiltration into solid tumors (16,23,24).



5 What are the side effects of CAR T cell therapy?

While T cell production of cytokines can enhance the activity of CAR T cells, it also creates the risk for cytokine release syndrome (CRS) during CAR T cell therapy. CRS occurs when CAR T cells overwhelm the bloodstream with cytokines, producing a dangerous inflammatory response that can cause a high fever, low blood pressure, and other potentially life-threatening symptoms (6,25). Cytokines may also play a role in immune effector cell-associated neurotoxicity syndrome (ICANS), another possible side effect of CAR T cell therapy characterized by neurological impairments such as confusion, seizure, and slurred speech (6,25). Both healthy and cancerous B lymphocytes express CD19 or BCMA antigens, so current CAR T cell therapies for blood cancers can kill off normal white blood cells, impairing the body's ability to fight infection (6,18,19).

While clinicians can manage some of these side effects with drugs, researchers want to reign in CAR T cell toxicity by designing cells where activity can be switched on and off by various stimuli (21). For example, researchers at the University of California, San Francisco designed a CAR in which two components assemble to form a functional protein only in the presence of a small molecule (26). Similarly, researchers at the Dana-Farber Cancer Institute and Massachusetts General Cancer Center engineered a CAR protein that degrades upon interaction with a chemical compound (27). Researchers can turn CAR T cells on or off by administering these exogenous drugs, providing a form of control over CAR T cell dosage that may reduce side effects (21).



Putting the CAR T before more chemotherapy

CAR T cell therapy is still in its infancy with its first FDA approval in 2017 (6). At present, many oncologists approach CAR T cell therapy as a last resort for treating cancers after more established forms of treatment have failed (6). Chemotherapy remains the first line of defense against blood cancer, but in two recent clinical trials, researchers found that patients with non-Hodgkin lymphoma who received CAR T cell therapy as a second line treatment showed better prognoses than those who underwent a standard regimen involving additional rounds of chemotherapy (6,28,29). In another ongoing clinical trial, researchers are assessing the efficacy of CAR T cell therapy in children and young adults with acute lymphoblastic leukemia whose cancer did not respond to initial chemotherapy (6,30). These studies will help determine whether some patients may benefit from undergoing CAR T cell therapy earlier. With efforts to optimize CAR T cell manufacturing, extend CAR T cell lifespan in the body, translate CAR T cell advances to solid tumors, and improve CAR T cell safety underway, CAR T cell therapy will continue to cement itself as a new frontier in cancer treatment.

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