History of immunotherapy and CAR T-cells

Immunotherapy and adoptive cell transfer

One of the most promising fields in cancer research is immunotherapy – manipulating the existing immune system to specifically attack tumors. Research on how to use the body's immune system to fight cancer (immuno-oncology) is rapidly increasing and provide new possible options for cancer treatment. The majority of immunotherapy involves the lymphocytes: B cell and T cells (Figure 1). T cells destroy infected or cancerous cells and help control the immune response. B cell produce antibodies, which alert the immune system to destroy foreign pathogens. These cells already exist in the body to help defend against diseases, where immunotherapy's goal is to increase the efficiency and efficacy of these defenses.

How to make CAR T-cells

Development

The first step in the creation of CAR T-cells is to obtain cells from the patient through apheresis (Figure 2). Subpopulations of cells are isolated and genetically engineered through either transduction, transfection, or electroporation to specifically target the tumor. Transduction involves transfer of DNA using a viral vector, while transfection use chemical based methods to transfer DNA. Electroporation utilizes electrical pulses to temporarily open up pores on cell membrane to introduce DNA. In order to increase the efficacy of the CAR T-cells treatment, cells are expanded ex *vivo*.

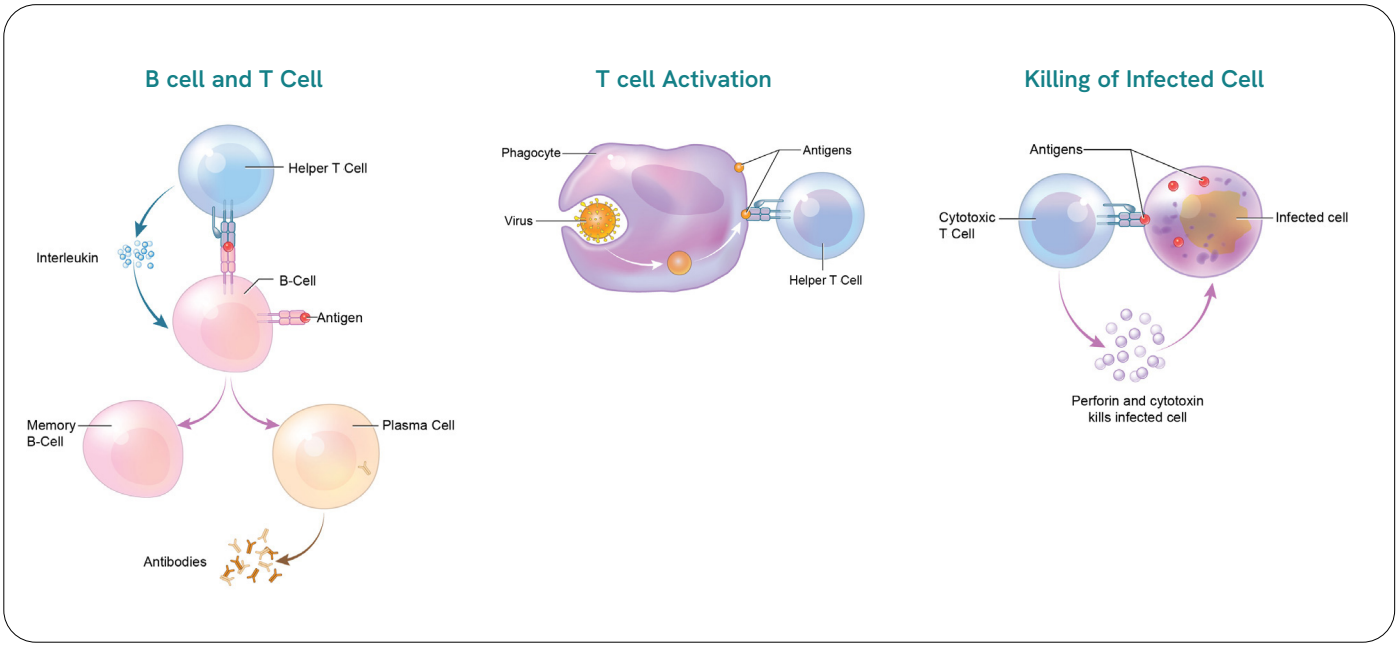

Figure 1.

Functionality testing

Genetically modified T cell are then tested for functionality to ensure they were engineered properly. Cell number and viability are also checked at this stage via accurate methods of live-dead cell counting.

Infusion

Once it is confirmed that the cells are functional and viable, they are then infused back into the patient. One important advantage in the use of CAR T-cells is that they are able to expand and persist in the patient post-infusion, thereby increasing the impact of the treatment on the patient. Additionally, CAR T-cells in some cases can remain in the body for months post-infusion, increasing the amount of time the cells can attack the tumor.

As CAR T-cells therapy becomes more widely used, this process has become more streamlined, decreasing the amount of time between obtaining cells and subsequent infusion. Whereas it used to take several weeks, some labs have successfully produced viable cells in less than 7 days. This undoubtedly is an improvement for the patients hoping to be treated using CAR T-cells therapy, as the wait time for their treatment to be ready is steadily decreasing.

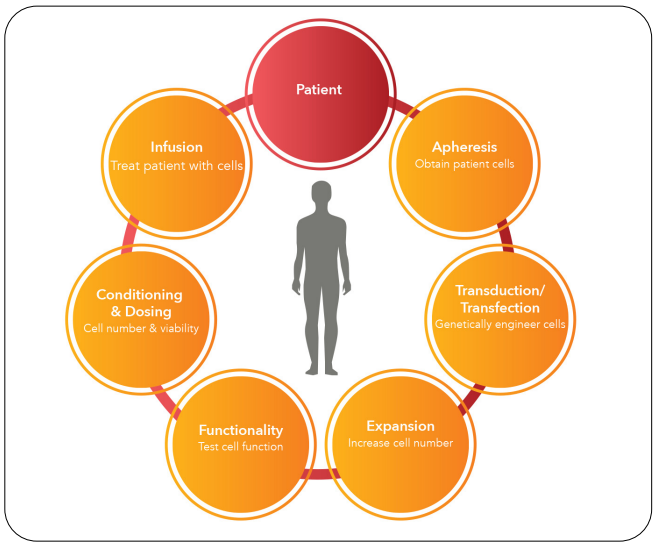

Figure 2.

Structure of a CAR T-cells

The current generation of CAR T-cells (Figure 3) contains fragments of synthetic antibodies designed for a target antigen as well as signaling and co-stimulatory domains (e.g. CD19, CD22, CD3, or CD28). The choice of co-stimulatory domains can affect the overall function of the CAR T-cells and the ability of the receptor to recognize and bind to the antigen on the tumor cell. CD19 is a popular domain because it is found on the surface of both malignant and healthy B cells[3]. It is also not only highly expressed in B cell malignancies, but also never expressed outside of the B cell lineage[2]. In 2011, a CAR T-cells therapy targeted to CD19 was first used to successfully treat chronic lymphoblastic leukemia[4]. Loss of endogenous B-cells after CAR T-cells therapy is often managed via intravenous immunoglobulin replacement therapy, similar to the treatment used for patients with genetic deficiencies in their B-cells[2].

Current medical use

CD19 CAR T-cells therapy was approved by the FDA in 2017 for liquid tumors, specifically acute lymphoblastic leukemia in children and advanced lymphomas in adults[5]. Currently there are only three FDA approved CAR T-cells treatments, all for use with liquid tumors: Tisagenlecleucel (Kymriah™), Axicabtagene ciloleucel (Yescarta™) and Tocilizumab (Actemra®). A Phase I clinical trial into the use of CAR T-cells in solid tumors, specifically mesothelioma and malignant pleural disease, is expected to be completed in 2020[6]. Due to the continued studies on safety and efficacy, as of 2019, treatment with CAR T-cells therapy is limited to patients who have relapsed or refractory disease and are not currently enrolled in a clinical trial. As CAR T-cells therapy is currently still in development, there are potentially serious, even deadly, side effects. This is in part why, even though CAR T-cells therapy has proven to be effective, the FDA has only approved it for limited uses.

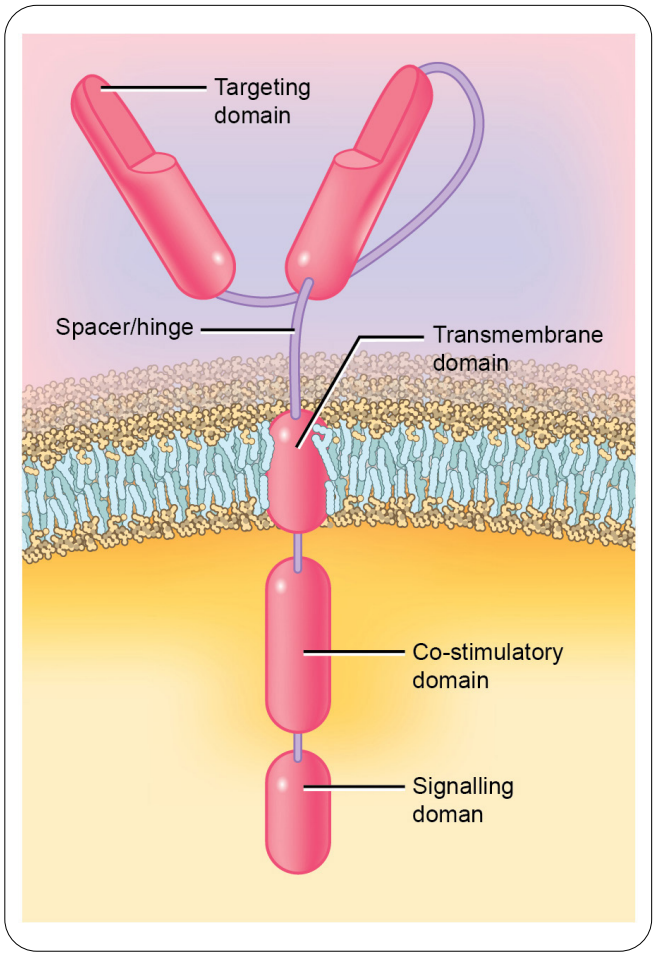

Figure 3.

Looking ahead

Efficacy of CAR T-cells therapy has greatly improved since the first generation was developed in the early 1990s. The 2017 FDA approval demonstrates the progress of the therapy, but there is a wealth of information yet to be gathered. While the therapeutic potential for this type of immunotherapy is great, so is the risk of adverse events. One of the major challenges in the use of CAR T-cells therapy is the occurrence of dangerous and potentially lethal side effects such as Cytokine-Release Syndrome (CRS). CRS is a life-threatening toxicity effect that is the most common complication seen in CAR T-cells therapy. In fact, it has been reported in 57-97% of patients in clinical trials[7]. Researchers are currently working to improve the design to decrease and eventually overcome these clinical challenges.

References

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