CAR-T Immunotherapy

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The Fifth Pillar of Cancer Therapy

Surgery	Radiotherapy	Chemotherapy	Precision Therapy	Immunotherapy
Ancient Times – Present	1890s – Present	1940s – Present	1998 – Present	1997 – Present

Cancer Immunotherapy has been hailed as the 'fifth pillar' of cancer treatment. At the forefront of this 'fifth pillar' is CAR-T cell Immunotherapy, which is personalized to each patient using their own T cells. CAR-T cell Immunotherapy aims to improve the immune system's intrinsic capabilities to identify and attack cancer cells while leaving healthy cells undamaged.

Source: National Institute of Allergy and Infectious Diseases/NIH

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IMMUNOTHERAPY

What is Immunotherapy

Immunotherapy is a type of cancer treatment designed to boost the body's natural defenses to fight the cancer. It utilizes the natural defenses made by the body in order to battle cancer.

Significantly improves the immune systems capability of finding and destroying cancer cells.

Completely stops or slows down the growth and the spread of cancer cells in the human body.

Prolonging remissions as CAR-T cells can remain in the body.

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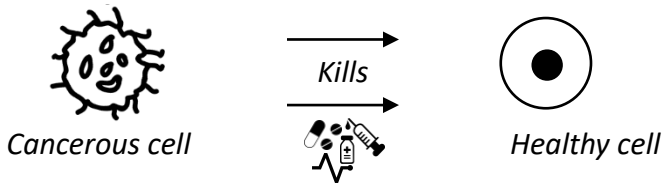
Chemotherapy VS Immunotherapy

Chemotherapy

Efficacy = Low

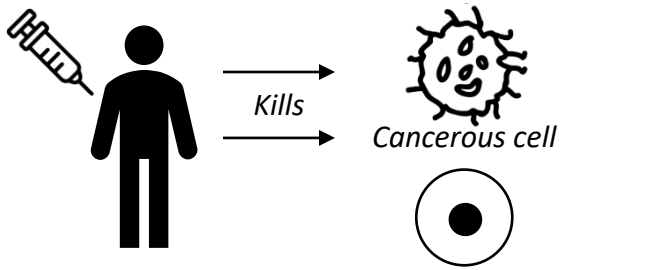


Side Effects

Post Treatment Protection

Immunotherapy

Efficacy = High



Side Effects

Post Treatment Protection

***Chemotherapy**: Side effects occur from drugs attacking all cells in the human body.*

***Immunotherapy:** Side effects result from an overstimulated or misguided immune response.*

***Chemotherapy**: Its effect is long-term as the drugs continue to stay in the body.*

***Immunotherapy:** Yields long-term protection against cancer, as the immune system is trained to recognize and fight against cancer cells.*

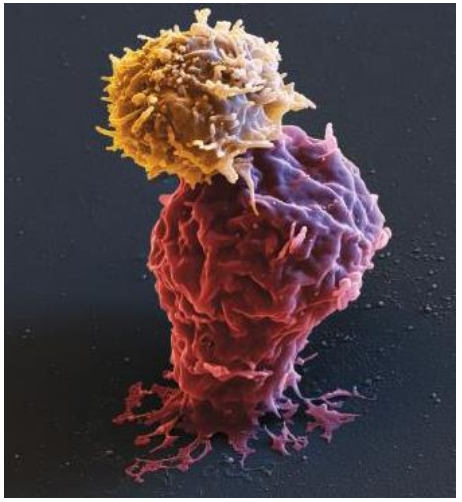
***Chemotherapy**: Needs multiple cycles to occur over several months/years.*

***Immunotherapy:** Cell-based immunotherapies (e.g CAR-T cell) typically require a single injection, however other immunotherapies may require multiple injections.*

CAR-T Cell

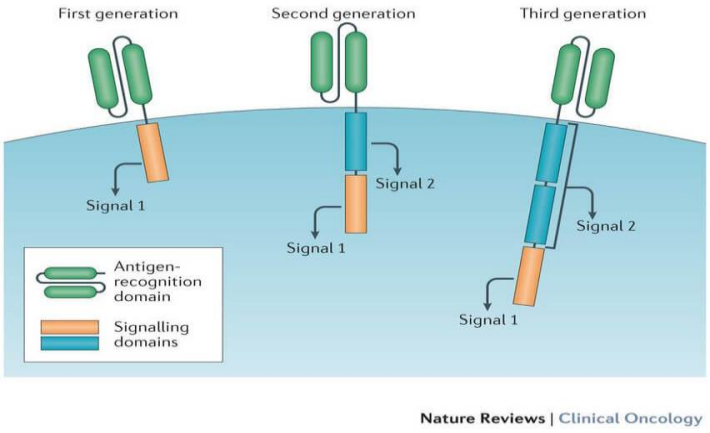
What is CAR-T?

Colour-enhanced scanning electron microscope image of a CAR-T cell (beige colour) attacking a leukaemia cell (red colour). The binding of the CAR T cell to the tumour cell initiates an immune defence against the cancer cell.



Source https://www.ascopost.com/media/14008111/49_image.jpg

CAR receptor on T cells



Nature Reviews | Clinical Oncology

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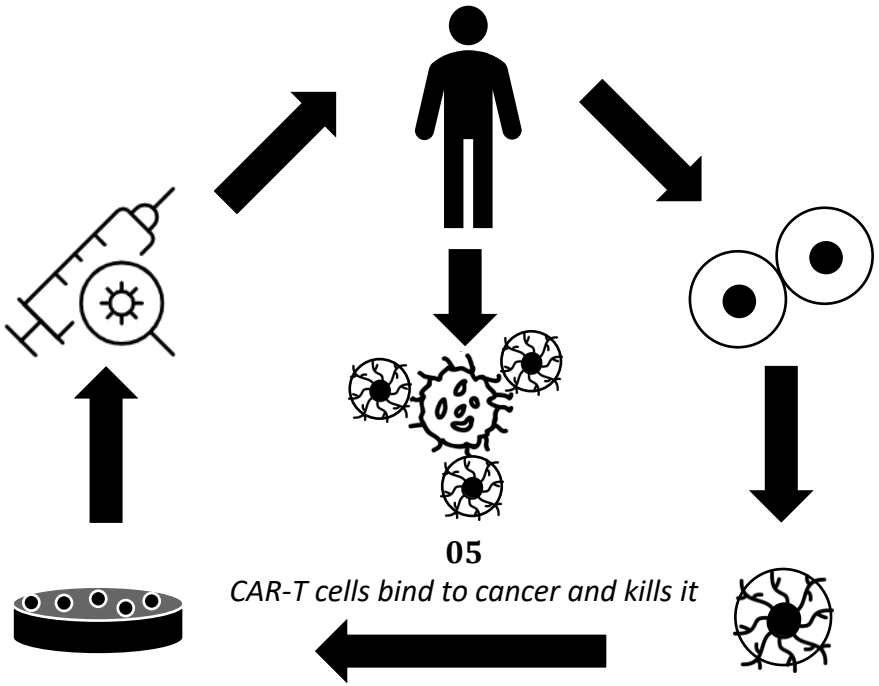
Autologous CAR-T Treatment



01
Extraction of White Blood Cells, including T cells (Leukapheresis)

02
A gene encoding a Chimeric Antigen Receptor (CAR) is transferred into the T cell.

03
Multiplication of T cells

04
Pre-treatment conditioning and infusion of CAR-T cell

05
CAR-T cells bind to cancer and kills it

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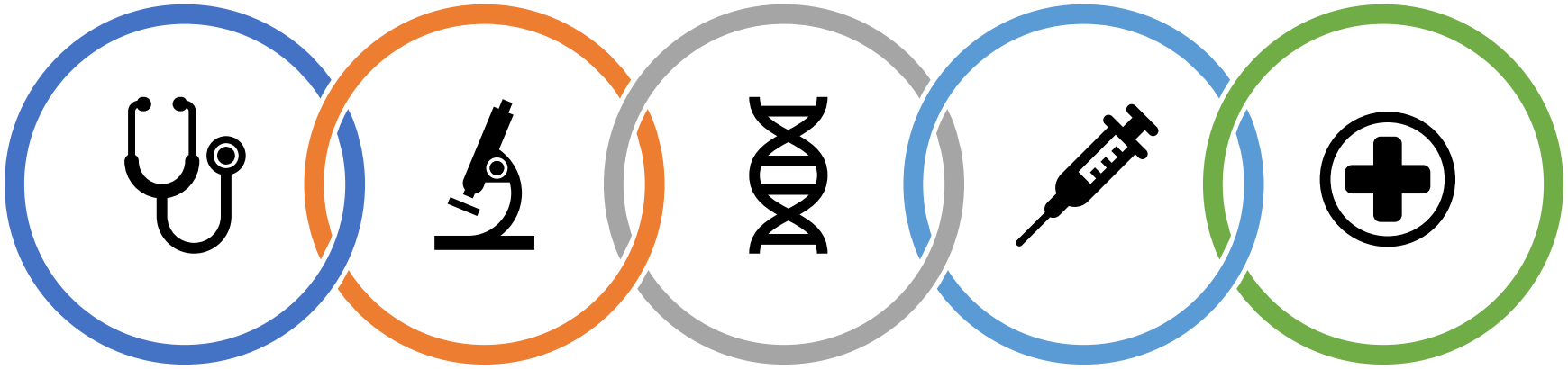
CAR-T Cell Therapy Process Flow



Patient Evaluation and Selection

- *Relapse/refractory confirmation*
- *Referral to panel of CAR-T cell experts*
- *Application Assessment and Approval*

T cells Evaluation & Selection

- *Leukapheresis (extraction of the Patients T cells)*
- *PBMC Isolation*
- *Cryopreservation and shipping for manufacturing*

Genetic Re-engineering & Expansion

- *Patient's T cells are engineered wit chimeric antigen receptors (CARs)*
- *The number of the cancer killing CAR-T cells are expanded*
- *Cryopreservation*
- *Shipment of the CAR-T cells to the Hospital*

Treatment

- *Pharmacy receipt and product check*
- *Conditioning therapy is administered*
- *Patient Identity confirmation and product match*
- *CAR-T cell Infusion*

Post Treatment & Recovery

- *Strict discharge plan provided to the patient*
- *Patient monitoring for late-onset adverse effects*
- *Alternative Treatment for non-responses*

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Potential Side Effects

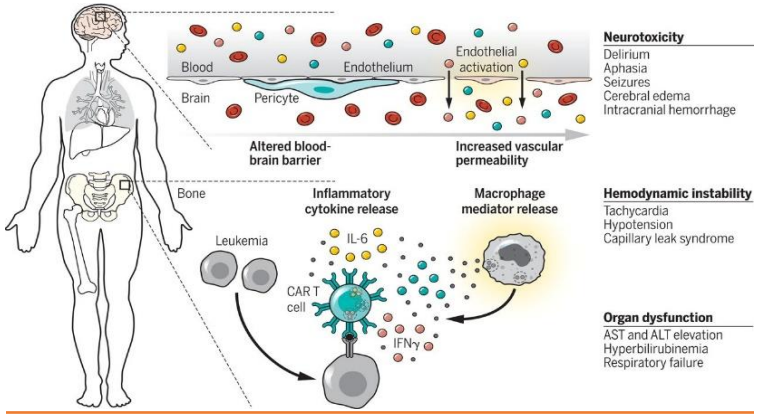

Table 1: Strategies to overcome current clinical challenges associated with CAR-T cell therapies.

Issue	Strategy	Expected Outcome
Cytokine release syndrome	Tocilizumab, siltuximab, JAK kinase inhibitors, corticosteroids	Blocking IL-6 effects rapidly reverses fevers, hypotension, and hypoxia
Development of anti-CAR idiotypic antibodies to murine scFvs	Use humanized scFv	Longer persistence of CAR-T cells
Lack of persistence of CAR T cells	Understand mechanisms of signalling domains that impart increased longevity; use sorted memory or stem cells	Long-term persistence of CAR T cells when desired by clinical situation
Relapse owing to loss of CD19 epitope	Target CD22 and CD19	Combinatorial surface targeting prevents escape

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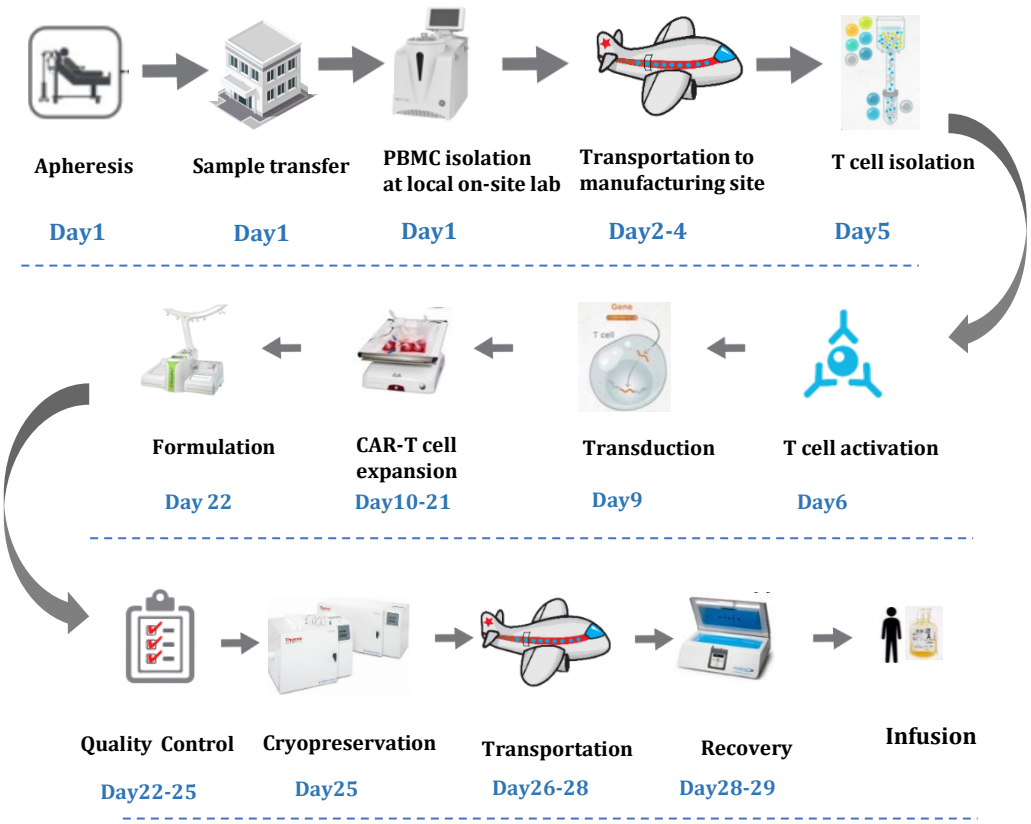
CAR-T cell Production Flow



What does this map demonstrate?

This map illustrates how Vamos Biotech operates the production of CAR-T cell in the laboratory. The patient's Peripheral Blood Mononuclear Cells (PBMC) will be harvested by the apheresis in a hospital, where an employee transfers the PBMC sample to their laboratory through either a cooler bag or a dry shipper. In a local on-site laboratory, PBMC will be isolated then put into cryopreservation. The transportation of the isolated PBMC will be arranged urgently to the cell manufacturers of T cell activation and lentivirus transduction. After lentiviral transduction, the CAR-T cells will expand in numbers in a small bioreactor until there is the required amount. Following this, the CAR-T cells will be preserved in a freezing reagent for transportation and long-term preservation. Prior to the CAR-T cells being released for clinical use, a serial of QC tests will undergo, such as the cell viability, endotoxin, bacteria, fungi, CAR+ rate, and the percentage of TCM. After the tests are completed, the CAR-T cells will be transferred to a hospital using a cooler bag or dry shipper depending on the travel distance. After recovery in the hospital, the cells are ready for infusion.

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Cryopreservation process

Below is the cryopreservation process for the delivery to oversea laboratories. It is the delivery via Cryogenic storages. The crucial factors are provision of reliable liquid nitrogen storage with controlled temperatures, and x-ray proof material.

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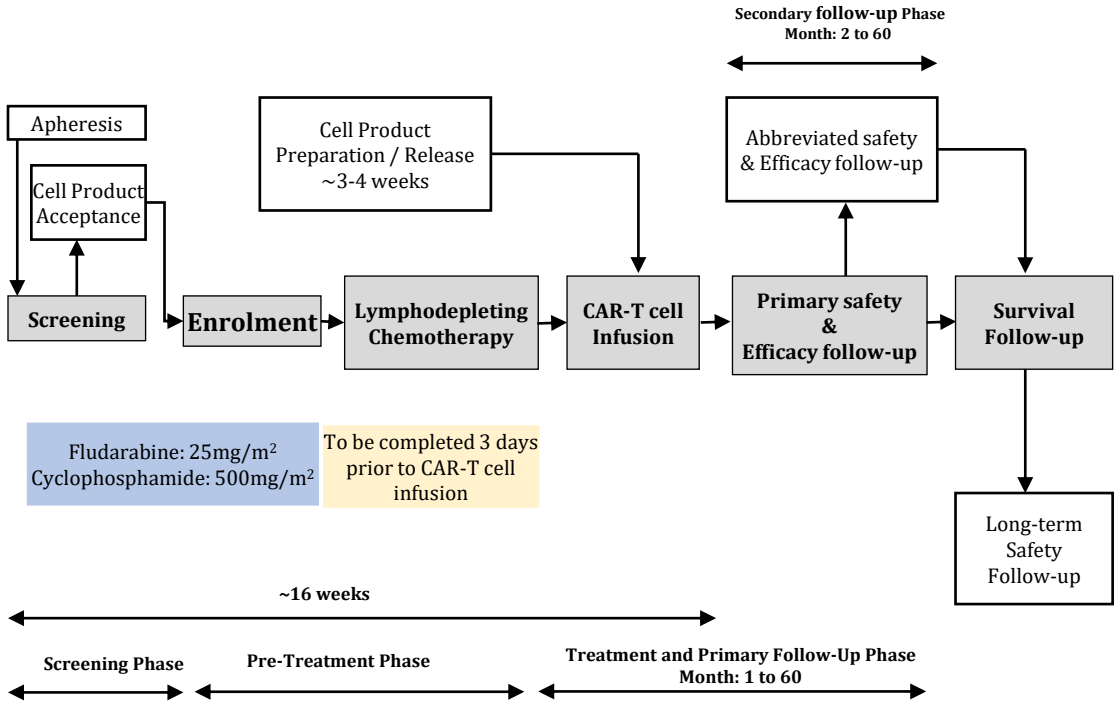
CAR-T cell Treatment Process



What is our treatment process?

Before the infusion of CAR-T cell back into the patient's body, all patients will receive a low dose of chemotherapy in order to weaken the tumour burden and eliminate part of the lymphocytes (a type of white blood cell) in the body. This treatment is beneficiary due to it assisting in keeping the side effects under control.

Following this, infusion will of CAR-T cell will take place, then a safety measurement and efficacy follow up in order to ensure the survival and long-term safety of the patient.

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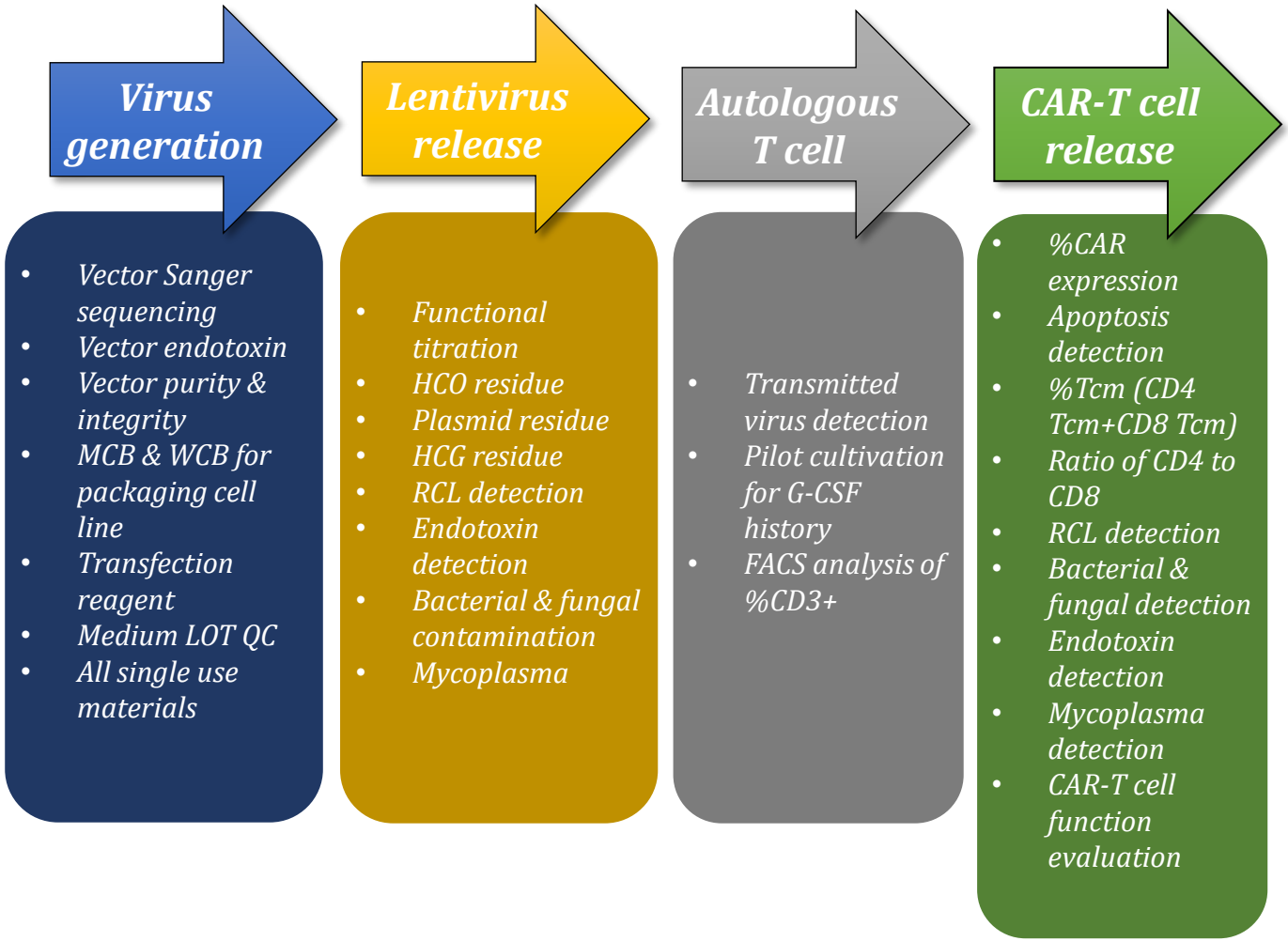
Quality Control at Laboratory



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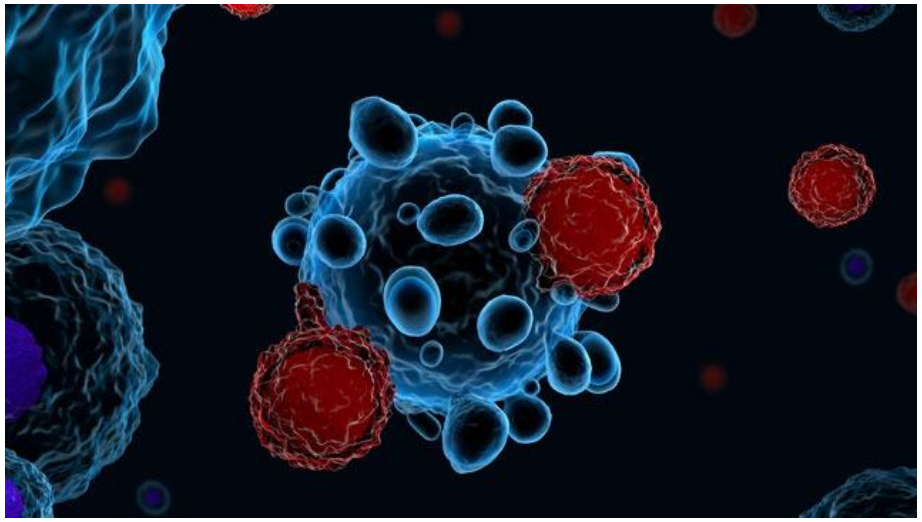
Available CAR-T cell Immunotherapies



Option 1

CAR-T cell type : CD-19/22/BAFF-R.
Indications : Paed and Adults.
Relapsed/refractory of B cell-Acute Lymphoblastic Leukemia (ALL TYPES)

Option 2

CAR-T cell type : CD-19/79b
Indications : Relapsed/refractory Non-Hodgkin Lymphomas (NHL): DLBCL

Option 3

CAR-T cell type : BCMA
Indications : Multiple Myelomas

Option 4

CAR-T cell type : CD-30
Indications : Hodgkin Lymphoma Hodgkin; Anaplastic Large cell Lymphoma

Frequently Asked Questions

What are the major Adverse effects (AE)?

The major AEs of CAR-T cell therapy are:

1. *Cytokine Release Syndrome (CRS): this typically occurs in the first week after CAR-T cell infusion. Most patients will have mild CRS; however, more severe CRS (grade 3 or 4) is less common and is avoidable with better patient management prior to CAR-T cell therapy (treat early rather than later and treat when the tumour burden is low). CRS is easily treated using Tocilizumab.*

2. *Neuro-toxicity: this typically occurs in the second week after CAR-T cell infusion. Neuro-toxicity is less common (20-40%), and mostly mild (grade 1or 2). Diagnosis are empirical, treatment is supportive as it will resolve spontaneously.*

3. *Leucopoenia: This occurs in all patients due to the conditioning chemotherapy administered prior to CAR-T cell infusion. It will resolve spontaneously though may be prolonged up to a month in some patients.*

In conclusion, rare life-threatening AEs arising of CRS or Neuro-toxicity can be treated with steroids or Cetuximab, both drugs however will completely abrogate the effect.

Frequently Asked Questions (2)

What is the role of CAR-T cell in the treatment of Leukemia and Lymphomas?

Current standard of care for Leukaemia and Lymphomas in general proceed as follows:

- *Initial induction-consolidation to reduce the number of cancer cells using chemo and targeted/antibody therapies. This treatment (+ maintenance chemo for up to 24 months for ALL) may suffice for most patients. High risk patients however may relapse after the therapy is stopped.*

- *Potentially **curative** therapy should therefore follow initial induction therapy. Bone marrow transplant BMT (aka HSCT) was the only known curative therapy.*

The advent of CAR-T therapy is changing this standard, and is increasingly offered upfront after induction therapy for these patients:

1. *High risk patients (older age, unfavourable cytogenetics, CNS disease, slow responder/relapsed).*
2. *High risk patients who are likely to relapse after BMT.*
3. *Patients who fail to achieve deep remission (MRD negative or PET negative) after induction. In this setting, CAR-T cell is often used as a bridge to BMT.*
4. *Patients without donor option or who are NOT fit for BMT (old age, comorbidities).*
5. *Patients who are unwilling to accept the high risk of transplant related morbidity & mortality associated with BMT.*
6. *Lastly, in many SE Asian countries, BMT is simply NOT available as a treatment option.*

Frequently Asked Questions (3)

When is the optimal timing to administer CAR-T cell in the treatment of relapsed/refractory Cancers?

For patients with relapsed &/or refractory Leukaemia and Lymphomas, and without transplant option, their prognosis are grave. We prefer they be treated earlier with CAR-T cell than leaving it late after repeated re-induction/salvage chemo. There are several advantages to using CAR-T cell therapy earlier:

1. *Patients are more likely to be healthy enough to undergo treatment.*

2. *Disease is likely to remain sensitive to chemotherapy, thus enabling lower tumour burden to be achieved. High tumour burden before CAR-T cell treatment is associated with adverse effects, especially CRS.*

3. *Avoid negative consequences of prolonged exposure to chemotherapy, such as myelodysplasia, secondary cancers.*

4. *Patients who have never been exposed to chemotherapy will have better T cells and higher blood T cell counts for the production of CAR-T cells.*

***It is worth bearing in mind CAR-T cell is NOT another salvage therapy, it is intended to achieve durable remission**. We have lost too many patients in the past who never had the opportunity for CAR-T cell; they strongly deserve a shot at a potentially curative therapy.*

Case study

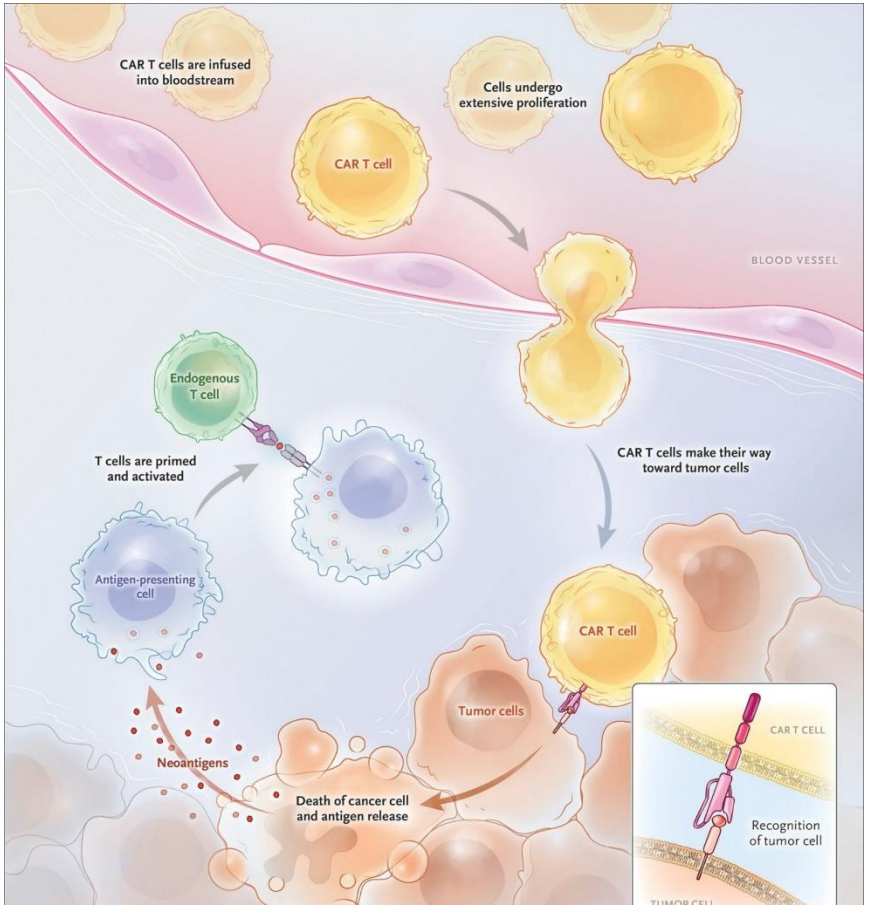
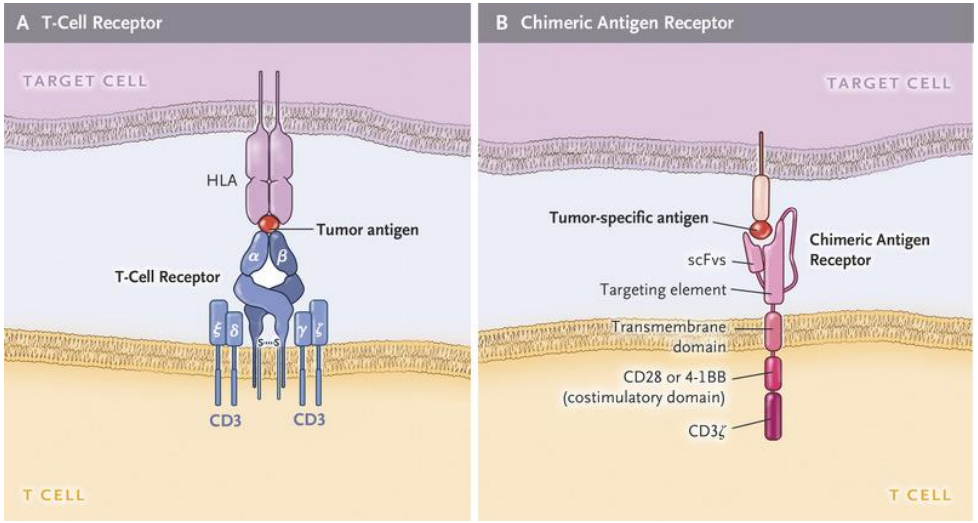


Figure 1. Chimeric Antigen Receptor (CAR) T cells Engrafting, Trafficking to Tumor, and Proliferating Extensively after Infusion.

After infusion, CAR-T cells leave the blood and travel to sites of tumor, where they identify and kill tumor cells. This can trigger extensive proliferation of CAR-T cells and the release of tumor antigens, which activates the immune system to recruit non–CAR-T cells, thus eliciting further antitumor responses in a process known as cross priming.

N Engl J Med 379;1 nejm.org July 5, 2018

Case study (2)



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CD19 CAR T CELLS

CARs are synthetic receptors that redirect the specificity, function, and metabolism of T cells (Fig. 2). CARs consist of a T-cell activating domain (typically including the zeta chain of the CD3 complex) and extracellular immunoglobulin-derived heavy and light chains to direct specificity.[16-18] These minimal structures, termed first-generation CARs,[9] recognize antigen independently of HLA but do not direct sustained T-cell responses, owing to their limited signaling capability.[19,20] Chimeric costimulatory receptors, which enhance proliferation and afford antiapoptotic functions in human primary T cells,[21] paved the way for dual-signaling CARs that could effectively direct the expansion of functional T cells on repeated exposure to antigen.[22] These receptors, termed second-generation CARs,[9] enabled the generation of the persistent "living drugs" that are the foundation of current CAR T-cell therapy.

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Case study (3)

Table 1. Responses to CAR T-Cell Therapy.*

Disease	Response Rate	Comments	Reference
	percent		
Leukemia			
B-cell acute lymphoblastic leukemia (in adults)	83–93	High initial remission rates; unresolved issue is whether CAR T-cell therapy is definitive therapy or should be followed by allogeneic hematopoietic stem-cell therapy	Park et al.,[35] Davila et al.,[36] Turtle et al.[37]
B-cell acute lymphoblastic leukemia (in children)	68–90	Approximately 25% of patients reported to have a relapse with CD19-negative or CD19-low leukemia; CD22 CAR T cells may improve survival among some patients with CD19 relapses	Maude et al.,[34] Maude et al.,[38] Fry et al.,[39] Lee et al.[40]
Chronic lymphocytic leukemia	57–71	Relapse is rare in patients who have a complete response; ibrutinib appears to increase response rates	Porter et al.,[41] Turtle et al.[42]
Lymphoma			
Diffuse large B-cell lymphoma	64–86	Approximately 40–50% of patients reported to have a durable complete response	Turtle et al.,[43] Kochenderfer et al.,[44] Schuster et al.,[45] Neelapu et al.[46]
Follicular lymphoma	71	At a median follow-up of 28.6 mo, the response was maintained in 89% of patients who had a response	Schuster et al.[45]
Transformed follicular lymphoma	70–83	A total of 3 of 3 patients with transformed follicular lymphoma had a complete response	Turtle et al.,[43] Schuster et al.,[45] Neelapu et al.[46]
Refractory multiple myeloma	25–100	B-cell maturation antigen CAR T cells; stringent complete response in approximately 25% of patients	Ali et al.,[47] Fan et al.,[48] Berdeja et al.[49]
Solid tumors			
Glioblastoma	ND	In case report from phase 2 study, complete response on magnetic resonance imaging after intravenous and cerebrospinal fluid administration of CAR T cells; response lasted 7.5 mo	Brown et al.[50]
Pancreatic ductal adenocarcinoma	17	In one patient with liver metastasis, CAR T-cell treatment produced a complete metabolic response in the liver but was ineffective against the primary pancreatic tumor	Beatty et al.[51]

* ND denotes not determined.

N Engl J Med 379;1 nejm.org July 5, 2018

Why Vamos?

Our Focus

We invent and produce new technology and new substances for treatment of cancers, viral infections, antibiotic resistant bacterial infections, and other incurable diseases.

Our Results

Our products achieve results in treatments of many incurable diseases for which treatments are not available or no results can be reached.

Our Prices

The costs of our cancer immunotherapies are the lowest in the industry and significantly lower compared to any other competitor, while at the same time, our results are second to none.

THANK YOU

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