

CAR T-Cell and Other Immunotherapies

Celebrating a Second Chance at Life
Survivorship Symposium

July 11-17, 2020



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July 15, 2020

Celebrating a Second Chance at Life
The Growing Role of CAR T-Cell Therapy



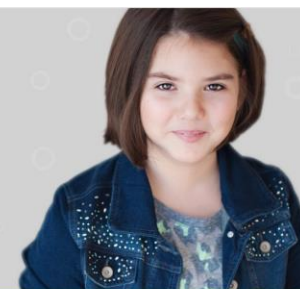
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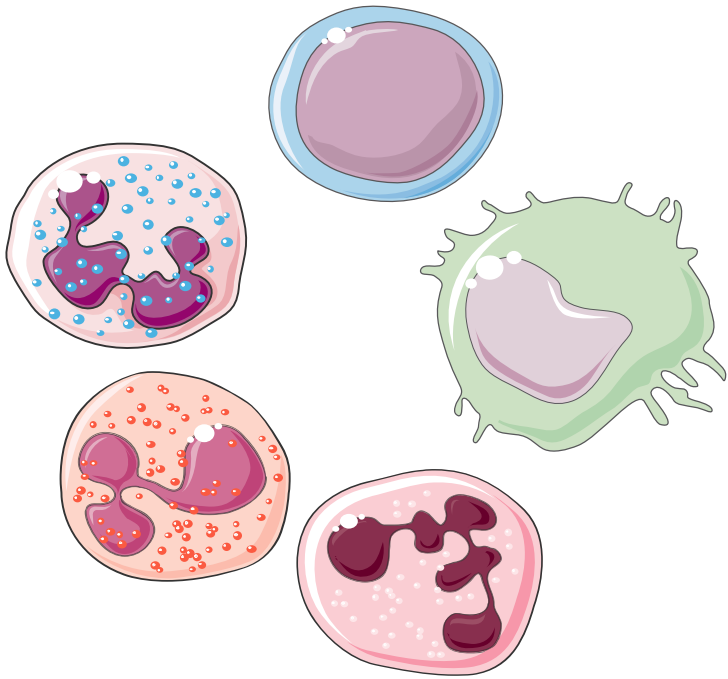
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Outline

- Overview of the Immune System
- How the Immune System Fights Cancer
- What is a CAR T-cell?
- Overview of the CAR T-cell Patient Journey
- What happens after CAR T-cells?
 - Side Effects
 - Follow-up/Expectations
- CAR T-cell Trials

Overview of the Immune System

Immune System Basics



White Blood Cells

Our Immune System is Important

1. Fights off infections (bacteria, parasites, viruses, fungus) and learns from it
2. Helps survey for things that shouldn't be there, ie. are not "self"
3. Recognizes when "self" may have gone awry, ie. cancer
4. Fights cancer if it is recognized

Innate vs Adaptive Immune Response



Neutrophil



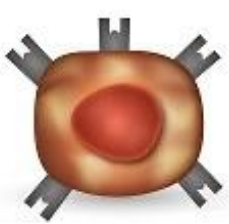
Eosinophil



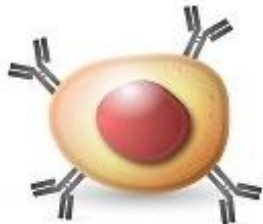
Basophil



Monocyte



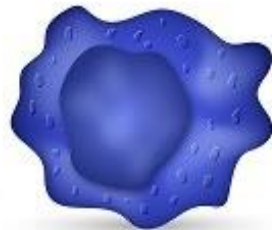
T Cell



B Cell



Natural killer



Macrophage

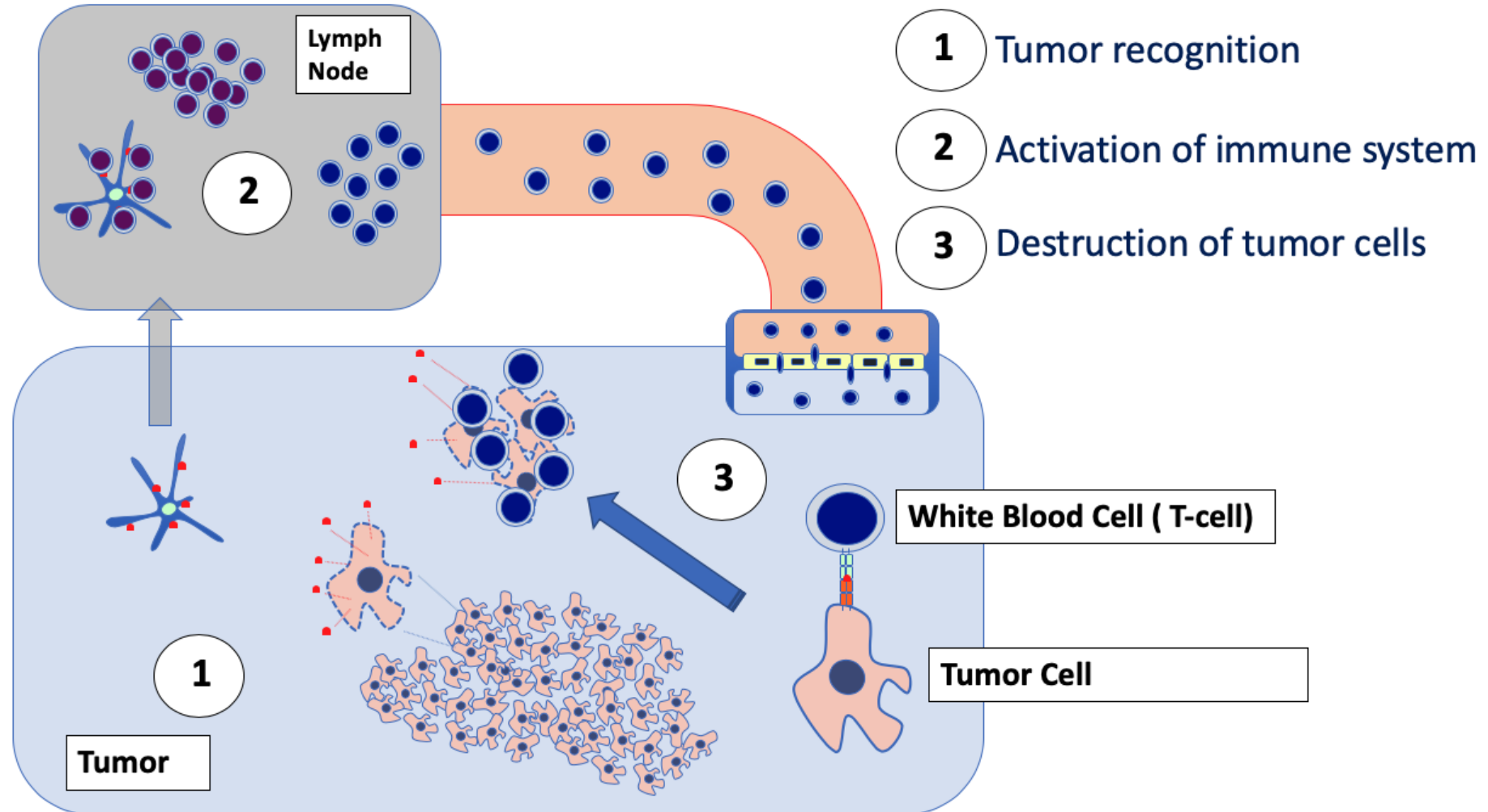
- The innate immune system helps to recognize foreign invaders and immediately kills them.
- The **adaptive immune** system is highly targeted but takes time to learn what is good and bad.
- Once the adaptive immune system learns, it can remember what it has seen for the rest of your life

Adaptive Immune System

How the Immune System Kills Cancer

Working Together The Innate and Adaptive Immune System Fight Cancer

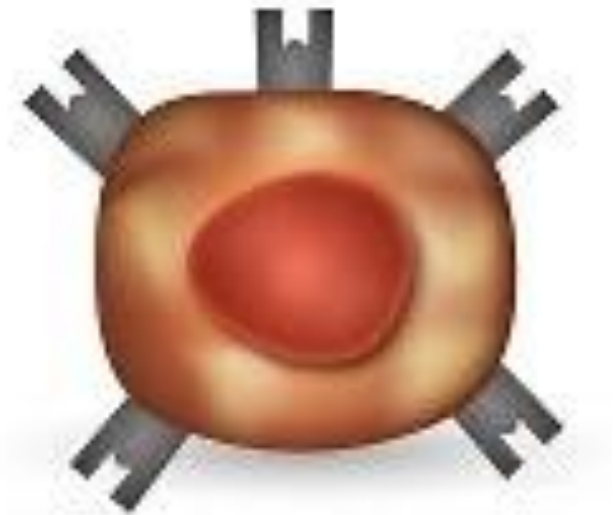
How the Immune System Fights Cancer



T-cells: The Generals of the Immune System

T-cells Oversee the Immune Response

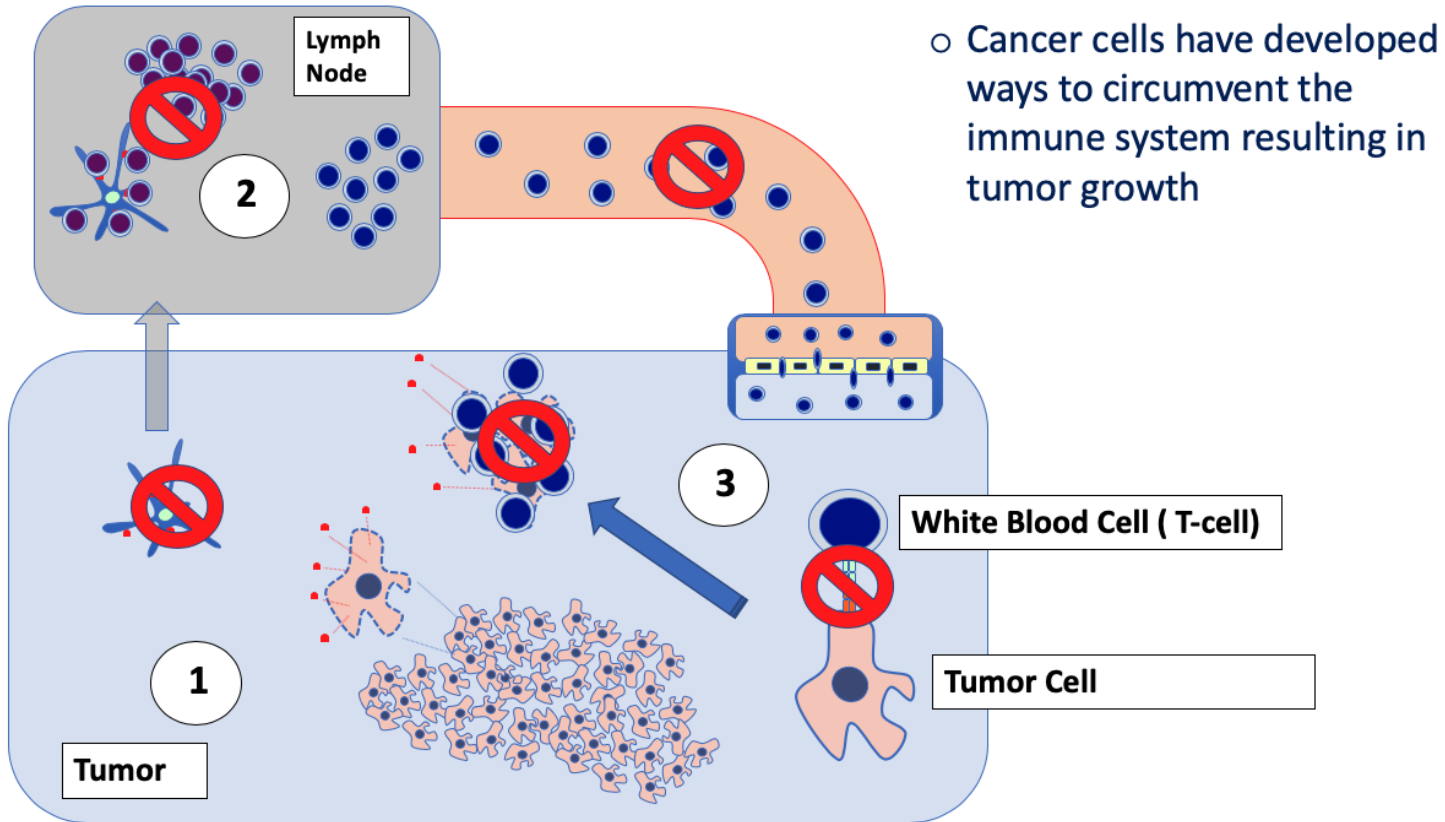
- T-cells are part of the **adaptive immune** response
- They talk to the innate immune cells and **learn when there are danger signals**
- Recognize foreign invaders or abnormal “self” (cancer) and kill off infected/abnormal cells
- When they go awry can cause autoimmune disease or graft vs host disease



T Cell

How Cancer Evades the Immune System

How Cancer Evades the Immune System



- Cancer can hide the signals that say it shouldn't be there.
- Cancer can prevent the immune system from activating.
- Cancer can resist killing by the immune system.

What happens when the immune system doesn't recognize cancer as bad?

- We have options!
 - Cancer immunotherapies (immune checkpoint blockade, vaccines, etc.)
 - Bone marrow transplant using someone else's immune system (cell therapy)
 - Re-program the immune system to target what it can't/won't see (gene therapy)
 - Viruses (adenovirus, lentivirus, retrovirus)
 - Gene editing (CRISPR, TALENs, ZFNs)
 - Transposon systems (ancient viruses hopping around our genome)
 - Temporary expression of new genes

What Are CAR T-Cells?

Immunotherapy

- A type of cancer treatment that helps your immune system fight cancer

Gene Therapy

- A type of treatment that uses genetic engineering to reprogram cells to do what we want them to
 - CAR = Chimeric Antigen Receptor

Cellular Therapy

- A type of cancer therapy that uses a specific kind of immune cells to fight cancer
 - CAR-T = T-cells



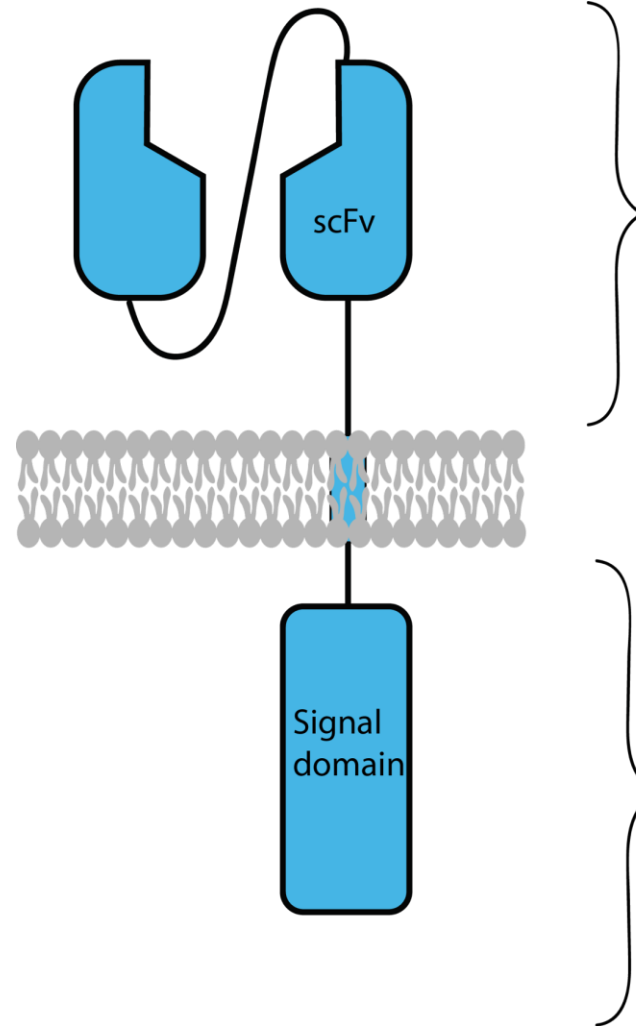
HARVARD MEDICAL
SCHOOL



MASSACHUSETTS
GENERAL HOSPITAL
CANCER CENTER

What are CAR-T Cells?

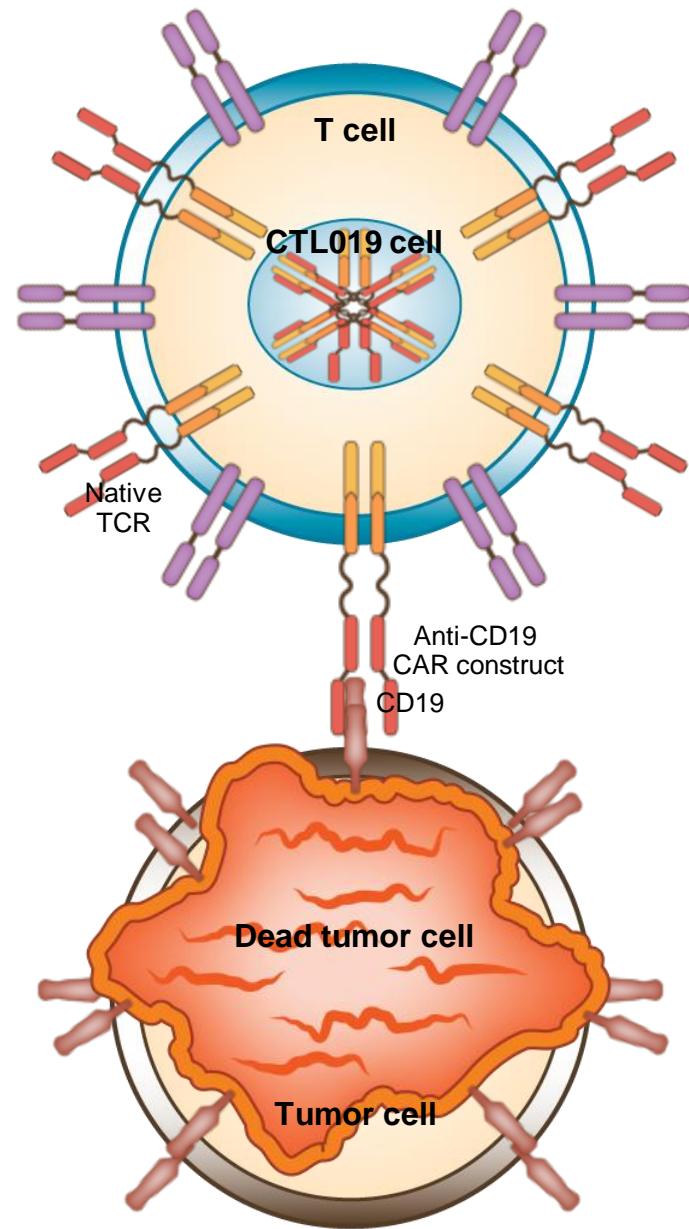
Outside (cancer)



How a
CAR-T cell sees

Inside (T-cell)

How a CAR-T
knows what to do



Approved CAR T-cells

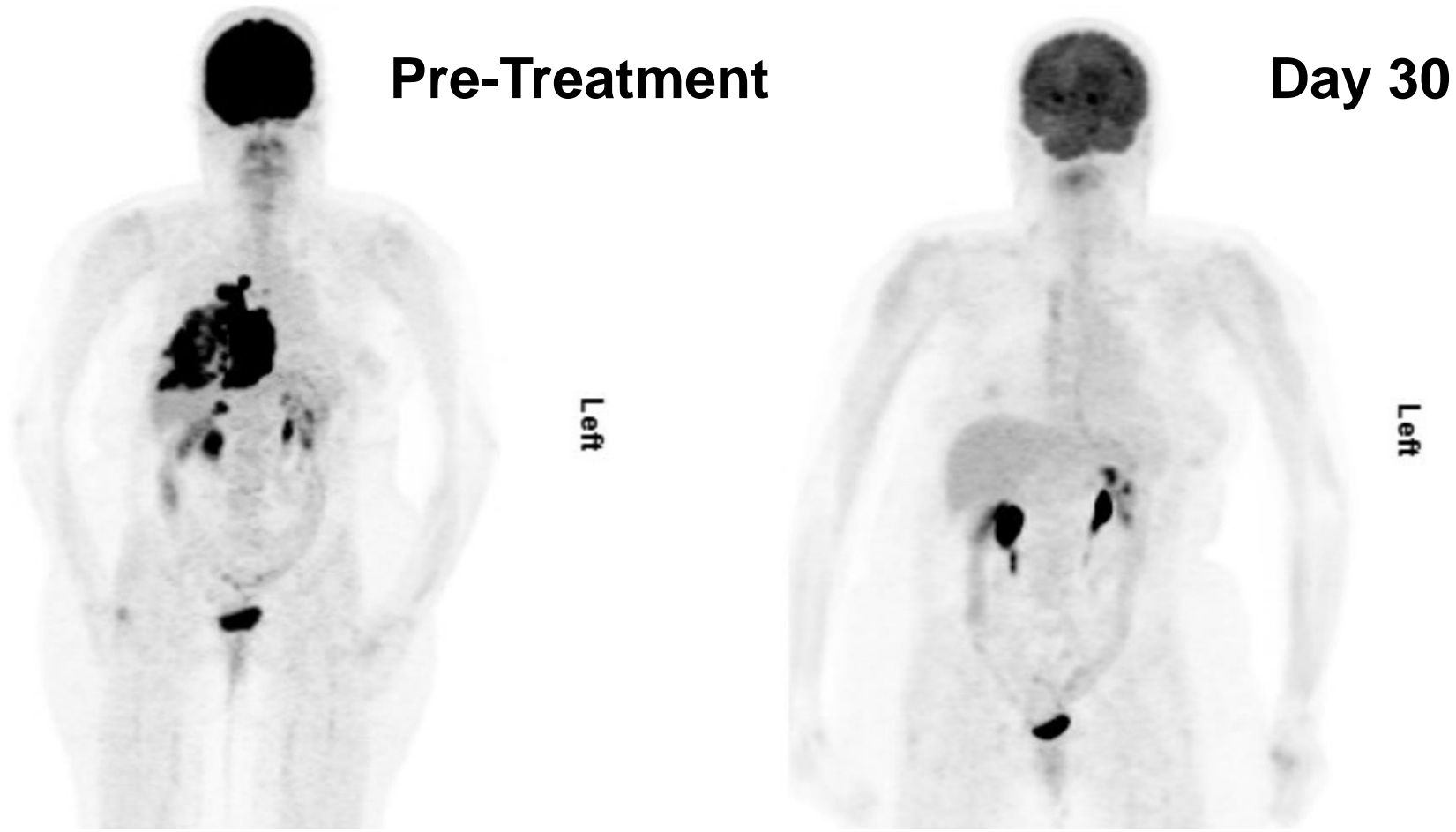


1. Pediatric and young Adult B-ALL
2. Relapsed/refractory diffuse large B-Cell lymphoma

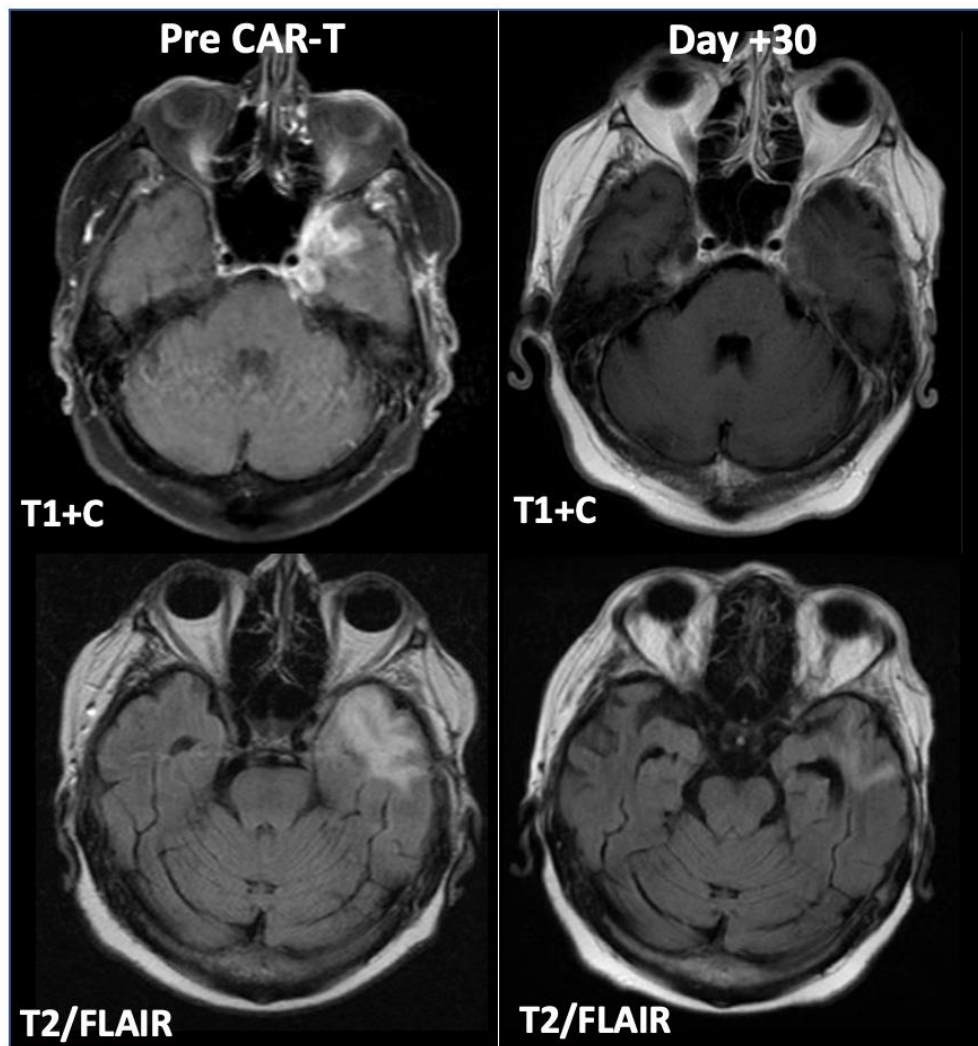


1. Relapsed/refractory diffuse large B-Cell lymphoma

CAR T- Cell Responses - Systemic

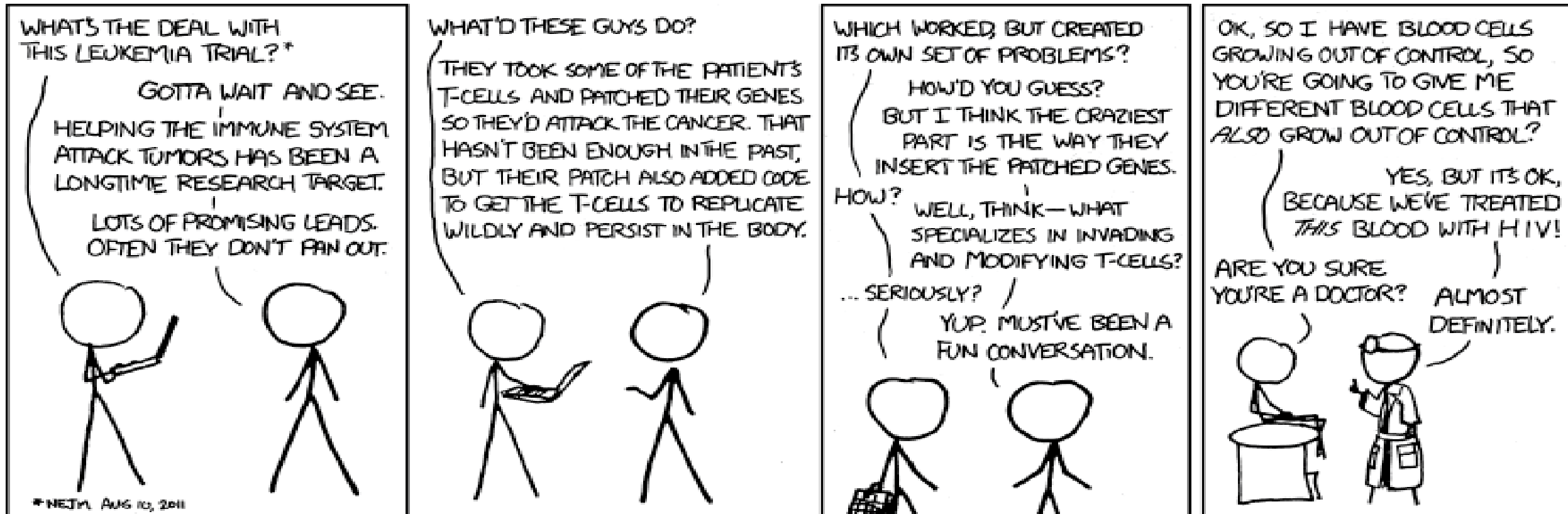


CAR-T Responses – Central Nervous System (CNS)



CAR T-Cells have shown efficacy in SECONDARY CNS lymphoma however are not approved for PRIMARY CNS lymphoma. Clinical trials are underway.

Cancer Gene Therapy?

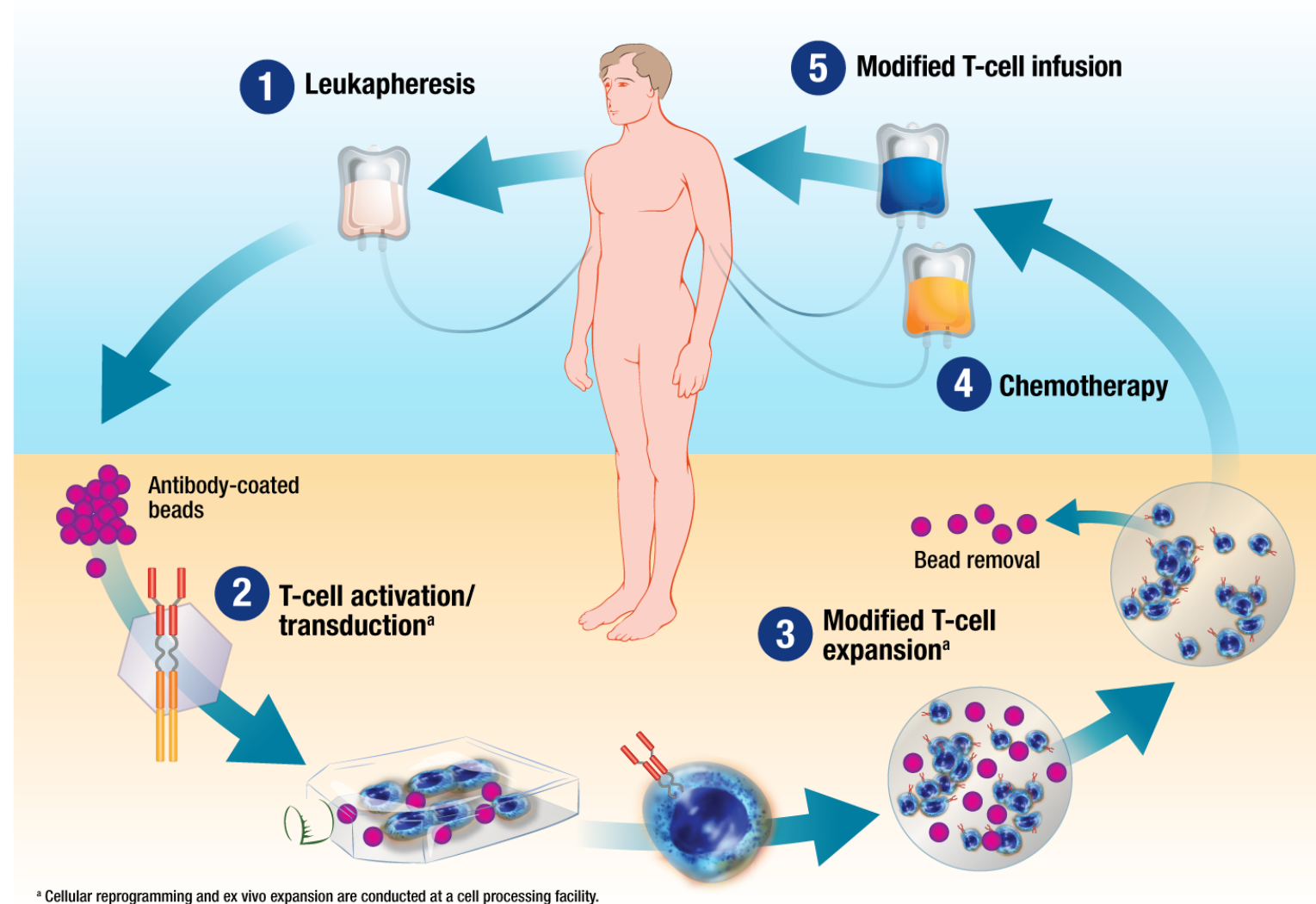


Overview of the CAR T- Cell Patient Journey

Overview of CAR T-Cell Therapy

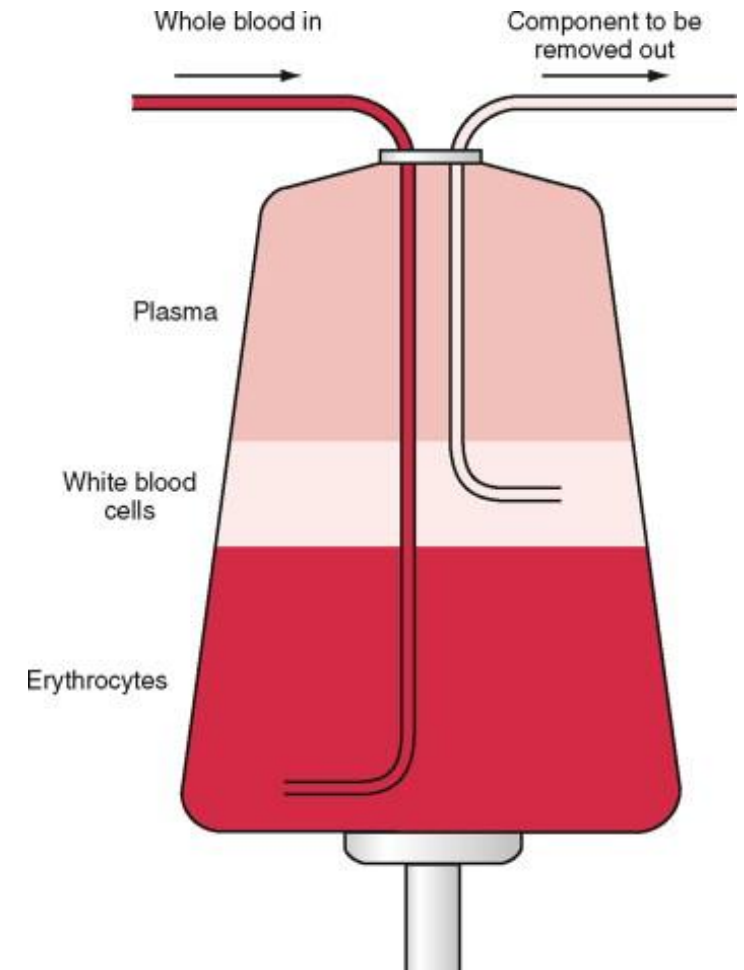
**Clinical Care –
Patient
Perspective**

**Manufacturing –
Product
Preparation**

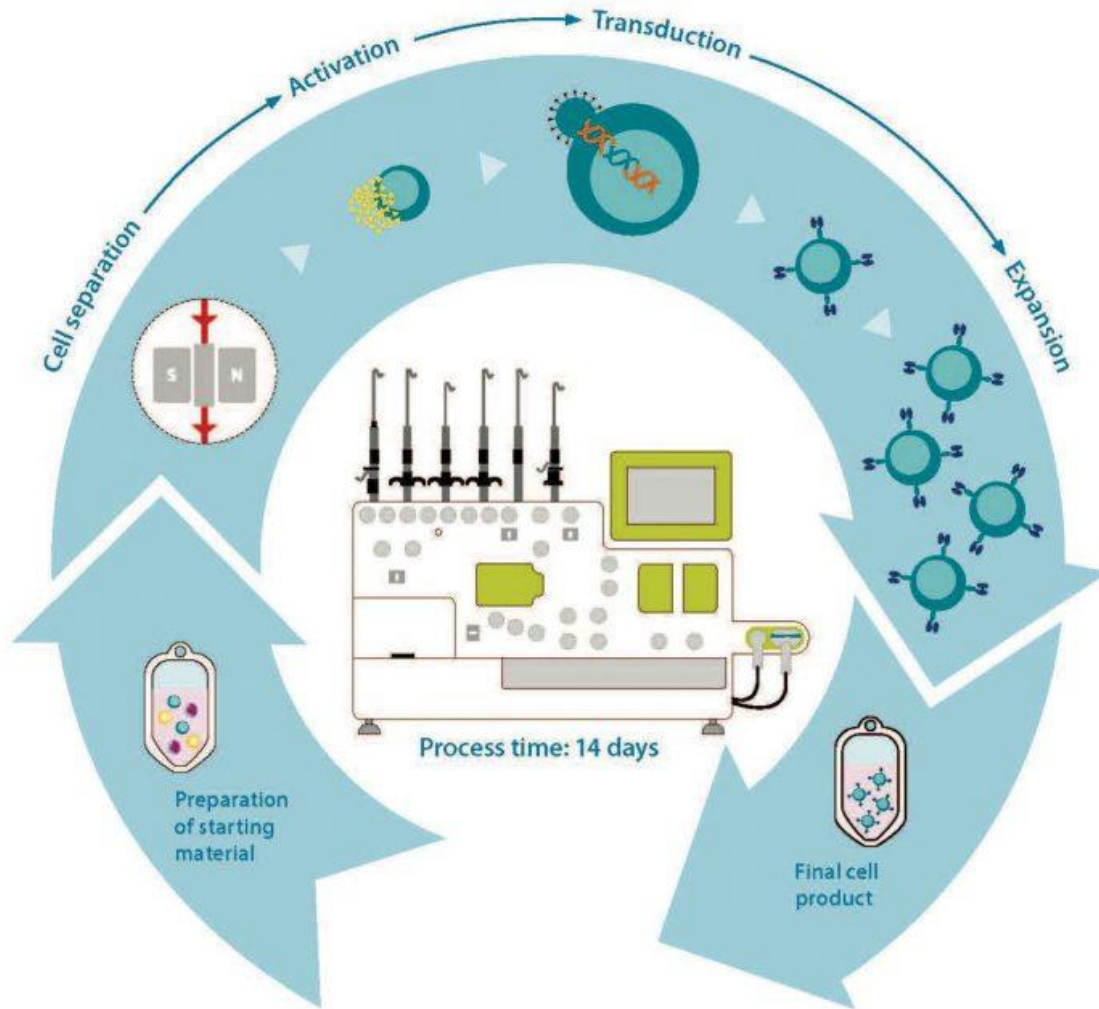


Leukapheresis

- Process by which we separate the immune cells (T-cells) from a patient's blood



Cell Manufacturing: Activation/Expansion



What happens with T- Cell Manufacturing?

- Your cells may be further purified
- Your T cells are activated so they start to grow
- The cells are "transduced" to insert the new genetic material into the cells.
- The "transduced cells" start to divide rapidly carrying the new genetic material with them
- The cells are again purified and undergo extensive testing

Lymphodepletion (Low dose chemotherapy)

- Now that we've made a new sports car it's time to clear the highways.
- Lymphodepleting chemotherapy (usually cyclophosphamide and fludarabine) primes your body to receive the CAR T-cells.
- It "depletes" the immune cells in your body as to create more "space" for the CAR T-cells to survive and expand within your body.
- Once infused the CAR T-cells can grow >1,000x inside your body in order to fight the cancer.
- In most cases this involved 3 days of chemotherapy followed by 48 hours of rest before your CAR T-cell infusion.
- The symptoms of your chemotherapy should be mild as these are lower dosages than you have likely received in the past.
- This can be done as an inpatient or outpatient.

CAR T-Cell Infusion

- Your CAR T-cells are usually frozen for transport and are thawed at the treating center.
- They are typically infused via a central line and can be in a bag or a vial.
- Infusions usually take less than 30 minutes.
- CAR T-cell infusions can occur as an inpatient or an outpatient.



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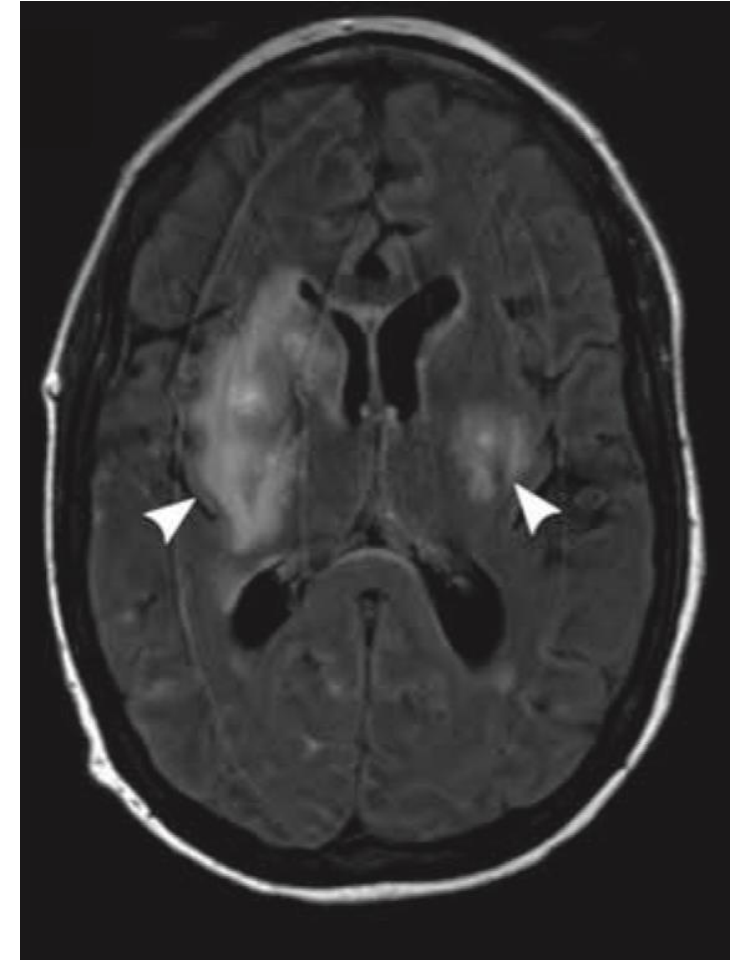
WHAT HAPPENS AFTER CAR T-CELL INFUSION?

Cytokine Release Syndrome (CRS)

- Typical onset 2-3 days, typical duration 7-8 days
- Can range in severity from low-grade constitutional symptoms to a high-grade syndrome associated with life-threatening multiorgan system failure.
- On a spectrum of excessive immune system activation and sometimes can be fatal.
- You do not need to have CRS in order to have a response from CAR T-cells.
- Largely driven by proteins in the blood called “cytokines” that are secreted and activate other parts of the immune system.
- The most important cytokine may be IL-6, and we therefore treat patients with a drug that blocks IL-6 called tocilizumab.

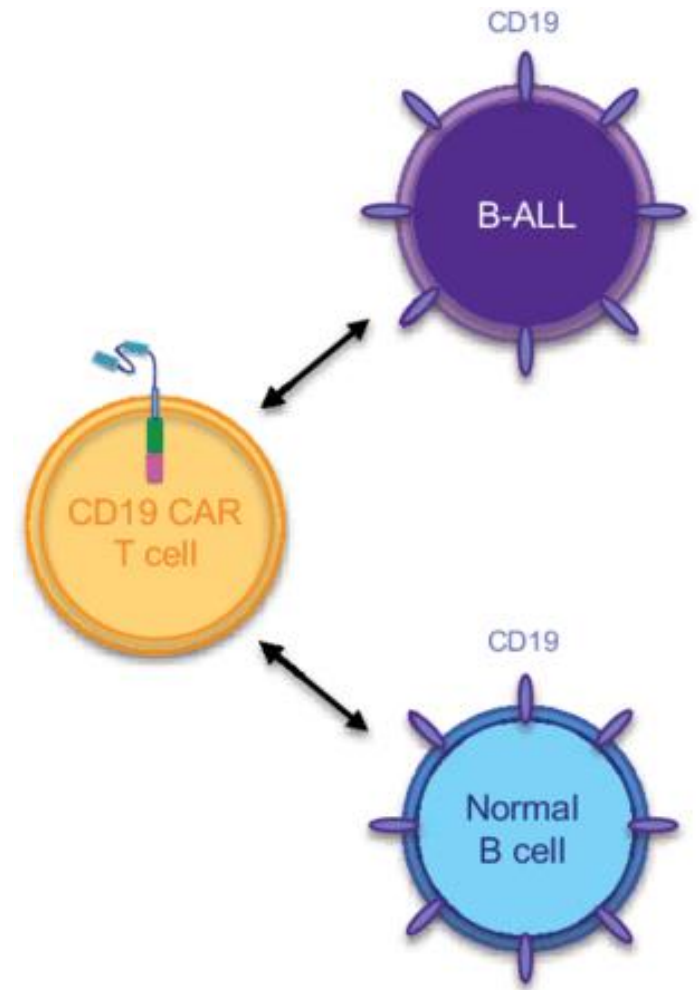
Neurotoxicity

- Typical onset 4-6 days, typical duration 14-17
- Toxic “encephalopathy” with symptoms of confusion and delirium, with occasional seizures and even rarer swelling in the brain.
- Some patients may just have headaches. Others may have difficulty speaking and even may enter a coma.
- Some patients need to be put on a ventilator to help them breath.
- Usually all of these symptoms are reversible.
- This is mainly treated with STEROIDS.
- We do not currently believe that steroids decrease the likelihood of having a response from your CAR-T cells.



Long-Term Side Effects

- B-Cell Aplasia
 - Because CD19 is expressed on bad and good B-Cells, the CAR T-cells will get rid of your normal B-Cells
- Hypogammaglobulinemia
 - B-cells usually make antibodies (like IgG) and therefore without them you may have low IgG levels
 - This can be treated by giving infusions of IVIG
- Cytopenias
 - Some patients also may have prolonged low blood counts from the chemotherapy and side effects of CAR T-cell therapy.
 - Your doctor will monitor these counts
- Because this is a new therapy the FDA requires patients to be followed for upwards of 15 years through a group called the CIBMTR.



Expectations after CAR T-Cell Therapy

- After discharge you will be followed as an outpatient.
- You are required to stay within 2 hours of the treating center for at least 30 days following your CAR T-cell treatment
- You will have blood work and exams performed to determine how well the therapy worked
- You may have repeat imaging and/or biopsies performed to re-stage your disease
- You will require medications to prevent infections for 6-12 months
- You may need blood transfusions and other medications to help your weakened immune system

Expectations after CAR T-Cell Therapy

- Patients can expect to go back to work/school approx. 1-3 months after their CAR-T cell therapy.
- You may experience fatigue following CAR T-cell therapy which should improve within 3-6 months.
- There are newer CAR T-cell therapies being studied in case the first CAR T-cell therapy does not work. There are also studies looking at combining special medications with CAR T-cells to improve how they work.
- Some patients who received CAR T-cells are now alive and cancer free almost 10 years from their initial treatment.

How Do CAR T-Cells Compare to Transplant?

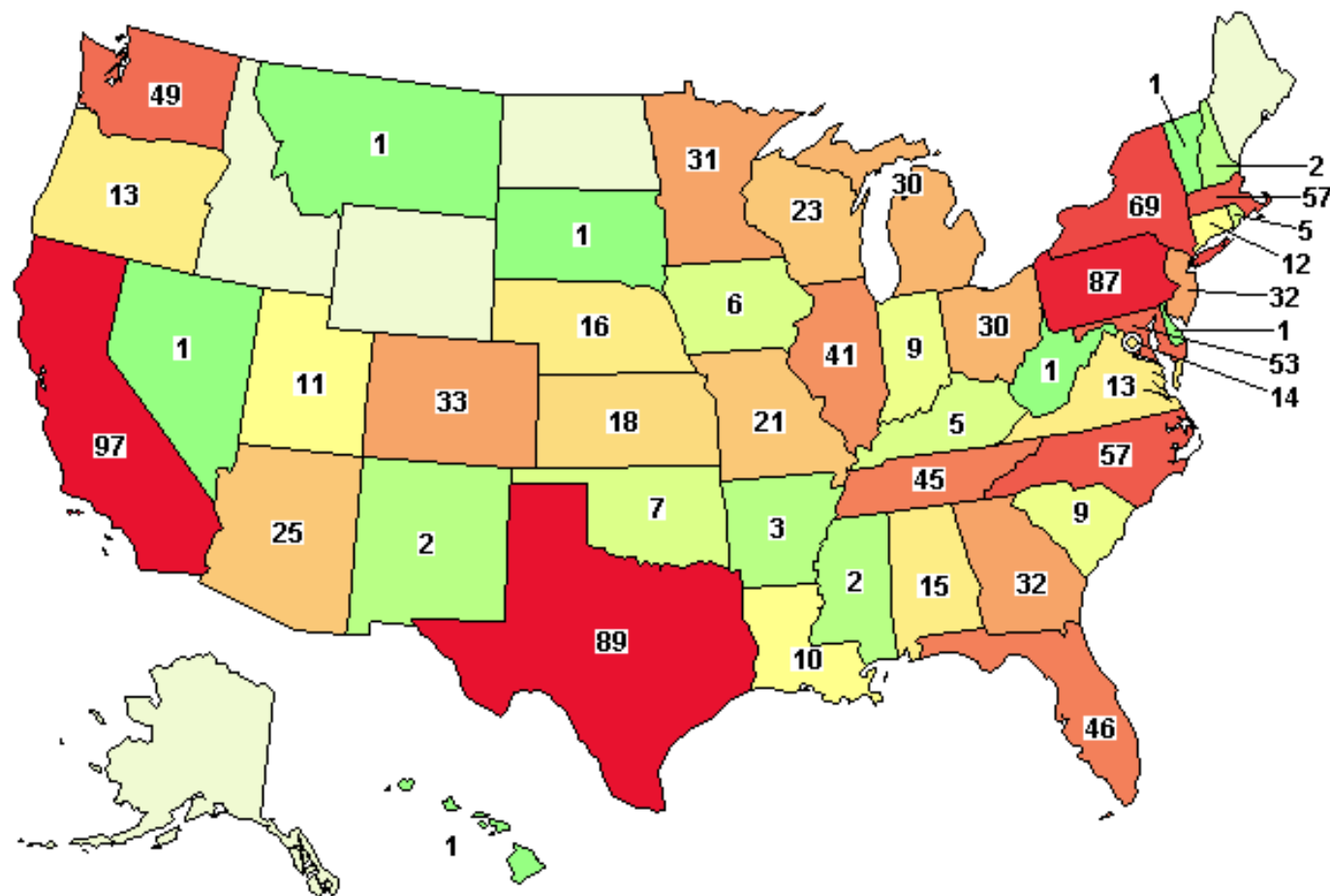
- The process for CAR T-cell therapy is very similar to an autologous stem cell transplant (transplant using your own cells).
- The side effects differ in that in addition to the side effects from chemotherapy, the CAR T-cells can cause cytokine release syndrome and neurotoxicity.
- Unlike allogeneic stem cell transplants (transplants using donor cells), CAR T-cells do not require long-term immunosuppression, and current versions do not have the risk of graft-vs-host-disease.
- CAR T-cells can be given before or after a patient has had a bone marrow transplant.
- Patients may have a bone marrow transplant after CAR T-cell therapy.

CAR T-Cell Therapy with COVID-19

- You may need to have COVID testing done before your chemotherapy and CAR T-cell infusion
- You may need to be tested for COVID if you have a fever
- You may not be able to have visitors with you in the hospital during your treatment
- You may not be able to bring visitors with you to appointments
- We may try to make as many visits virtual
- You should avoid crowded/public spaces and avoid people with symptoms before, during and after your treatment because of your weakened immune system

CAR-T CELL TRIALS

CAR-T Trials across the United States



Total Trials by date:

400 – 06/24/20

349 – 01/17/19

317 – 09/26/18

220 – 08/27/17

183 – 04/13/17

123 – 05/19/16

88 – 12/10/15

77 – 09/2015

<5 – 2010

Map as of 09/26/18

Search term:

“chimeric antigen receptor”

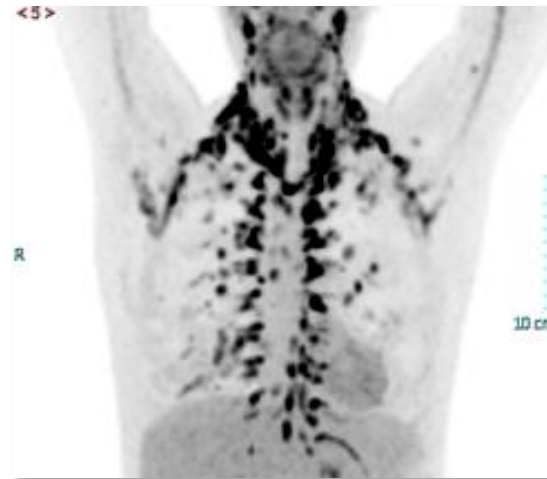
Jason Carter Clinical Trials Program

Clinicaltrials.gov

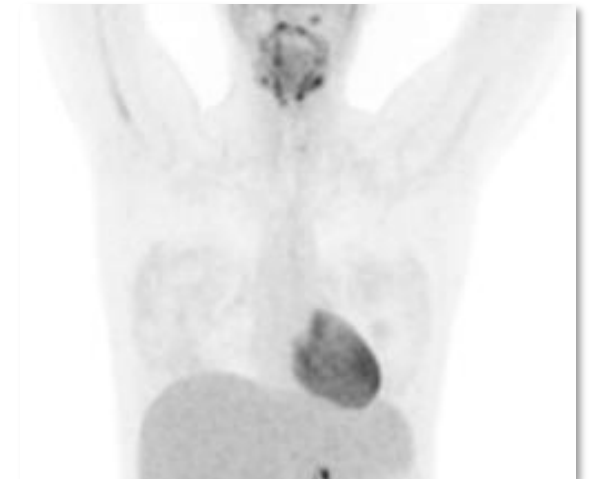
Future CAR T-Cells Coming Soon

- Mantle cell lymphoma
- Adult B-ALL
- Multiple Myeloma
- Other types of cell therapies:
 - Solid tumors such as melanoma

Before Cell Therapy



After Cell Therapy





Questions?



Celebrating a Second Chance at Life Survivorship Symposium

July 11-17, 2020

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