The Future of CAR-T Therapy: Can CAR-T Cure CLL? November 17, 2020
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Speakers

**Welcome:** Patty Koffman, Co-founder and Communications Director, CLL Society

**Moderator:** Brian Koffman, MDCM (retired), DCFP, FCFP, DABFP, MSEd
Executive Vice President and Chief Medical Officer, CLL Society

**Speaker:** Joseph A. Fraietta, PhD
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The Future of CAR-T Therapy: Can CAR-T Cure CLL?

Joseph A. Fraietta, Ph.D.
University of Pennsylvania
Cancer Therapy (Problem 1):
*The Enemy is Ourselves*
Cancer Therapy (Problem 2): Cancer-Specific Immune Cells are Very Rare, if Present at All
Immunology 101: Antigen and T cell basics

- Your immune system helps your body fight infections and other diseases, such as cancer.
- Antigens are substances that activate (turn on) your immune system.
- Antigens are found on the surface of some things made inside your body, such as cells, bacteria, and viruses.
- T cells help your immune system tell which antigens don’t belong in your body. T cells are a type of white blood cell (lymphocyte).

Case 1: I know you, you look healthy! Go on.
Case 2: You look suspicious, ATTACK!
Healthy cell → Abnormal cell
Why are CAR T cells Referred to as “Living Drugs” Engineered to Fight CLL and other Cancers?

• The immune system we are born with is often not equipped to win the battle against cancer

• A patient’s own T cells can be engineered to make artificial receptors (CARs) allowing them to seek out and destroy tumors
What is the CAR T cell Treatment Process like for Patients?

- If CAR T cell treatment is right for you, your care team collects your T cells with a process called apheresis.

- Your blood goes through a machine that separates and collects your T cells. The rest of the blood goes back into your body.

- We send your collected T cells to a lab where CAR “hooks” are attached to them. This turns them into CAR T cells.

- Before you get your CAR T cells back, you will get chemotherapy to prepare your body for treatment.

- When your CAR T cells come from the lab, we put them back in your body by infusion into a vein. This happens in the hospital.
Let’s Look at Each Step: Collection

T cell Collection
Some of your T cells are collected from your blood. The T cells are then sent to a lab to be genetically modified (takes 2-4 hours)
Let’s Look at Each Step: Engineering/Modification

**T cell Modification**

While your T cells are being genetically modified into CAR T cells, you will have your pretreatment evaluation and pretreatment testing (takes 3-4 weeks).

1. Leukapheresis
2. T-cell activation/transduction*
3. Modified T-cell expansion*
4. Chemotherapy
5. Modified T-cell infusion

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* Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.
Let’s Look at Each Step: Conditioning

Lymphodepleting Chemotherapy (also called conditioning)

Once your CAR T cells arrive at the center, you will get chemotherapy to get your body ready for them (given about 3 days before your infusion)
Let’s Look at Each Step: Infusion

CAR T cell Infusion
Your CAR T cells will be infused into your bloodstream. This might be done in the Cellular Immunotherapy Unit or in the hospital (takes 5-30 minutes)
What are the Responses to CAR T cell Therapy in CLL?

• CAR T cell therapy can be dramatically effective for many patients with relapsed/refractory CLL who have run out of effective treatment options.

• The first 2 patients that we treated at the University of Pennsylvania remain in remission more than 10 years later, with no detectable evidence of CLL by any measure.

• In some patients, the CAR T cells eradicated 7 and a half pounds of tumor!

• Just over 50% of CLL patients respond, and between 25% and 35% of patients achieve a complete remission.

• Among these patients, the relapse rate is low.
What are the Side Effects Associated with CAR T cell Therapy in CLL?

- Most patients who respond to CAR T cell therapy develop some degree of cytokine release syndrome (CRS). It can be mild to severe and treatment options are available.

- Some patients experience neurologic toxicity that can lead to confusion, delirium, aphasia, seizures, etc.
  - In most cases, with supportive care, neurologic toxicity resolves spontaneously after a few days or up to a couple of weeks.

- Low white blood cell count (neutropenia)

- Low red blood cell count (anemia)

- B cell aplasia (e.g., CD19 and CD20 CAR T)
What does the Recovery Phase Look Like?

**Early Recovery (lasts 4 weeks after your infusion)**
You will have appointments daily or every few days. Your CAR T team will see how you’re doing and manage your side effects. You will stay in the hospital or nearby.

**Long-term Recovery (for about 100 days or longer after your infusion)**
You will have appointments every few weeks or months. Your CAR T team will see how you’re doing and manage your side effects.
What is the Current Status of FDA-approved CAR T cell Therapy for CLL?

• Right now, the FDA has approved CAR T cell therapy for adult patients with certain types of lymphoma and for children and young adults with acute lymphoblastic leukemia that haven’t responded to other forms of treatment.

• CAR T cell therapy is not yet FDA-approved for CLL, but ~30 clinical studies across the globe are currently recruiting patients (i.e., generally for treatment of relapsed/highly refractory disease).
How does CAR T cell Therapy Compare with other Treatments for CLL?

• Difficult to compare CAR T cell therapy with other treatments

• Used primarily in patients with multiply relapsed or refractory disease, and there are not many treatments for CLL in that category.

• In contrast to other treatments in CLL, CAR T cell therapy is a one-time treatment. Repeated dosing is not required.

• When CAR T cells are effective, they can induce deep clinical remissions even as assessed by deep sequencing, which can detect 1 in 1,000,000 CLL cells.

• Few treatments for CLL can induce deep sustained complete remissions.
Is There Any New Promising Research in CAR T cell Therapy for CLL? What’s on the Immediate Horizon for this Approach?

- Rational Drug Combinations with CAR T cells for CLL
- Controllable CAR T cells for CLL
- Biomarker-driven CAR T cell Therapy for CLL
Targeting CD19 with CAR T cells: Success Sometimes Has Limits

Why does CAR T cell Therapy Work Better in ALL than in CLL?

- **CD19 CAR T cell Efficacy:** >80-90% complete response rate in pediatric acute leukemia compared to 26% complete response rate in CLL

- Potential Reasons:
  - Tumor cell susceptibility to CAR T cells
  - Effect of prior therapy on T cells (i.e., chemotherapy)
  - Where the T cells have to go (bone marrow vs. lymph nodes)
  - Suppressive nature of CLL tumor cells
  - T cell defects
    - Age of T cells (old vs. young)
    - Exhausted (war-weary) T cells
    - T cells receptive to inhibitory signals

- The above factors alone or in combination may influence CAR T cell potency and effectiveness

Our research focuses on how to make CAR T cells work better for CLL patients
Research Highlight: Rational Drug Combinations with CAR T cells for CLL

**Ibrutinib administration results in:**

- Repaired T cells as a better “seed” population for CAR T cell therapy
- Better CAR T cell expansion when patients are pre-treated with this drug
- Synergy with CAR T cells when given together
Research Highlight: Biomarkers for CAR T cell Therapy of CLL

For the first time, we understand why CAR T cell therapy is highly effective in some patients and not others

- This allows us to:
  - Select CLL patients most likely to benefit from CAR T cell treatment and thus improve their quality of life
  - Understand how to alter the immune system to try to increase clinical responses in many more patients
Research Highlight: Complete Remission Driven by a Single Cell

Disruption of TET2 promotes the therapeutic efficacy of CD19–targeted T cells

Joseph A. Fiala et al.

Research Highlight: Complete Remission Driven by a Single Cell

• 78-year old man with chronic leukemia treated over many years with various forms of therapy (chemotherapy, antibody therapy)

• Relapsed with aggressive leukemia, despite multiple therapies

• Treated with CAR T cells

• His complete remission was driven by a single CAR T cell that expanded massively into an army of immune cells that wiped out his blood cancer

• He is still cancer-free 6 years later!
Research Goal: *Engineering Off-the-Shelf CAR T cells*

- CAR T cells can be gene-edited to be “universal” to treat more patients
- Eliminates issues associated with using a patient’s own and sometimes defective T cells
- Have cells readily available right away when patient is deemed eligible
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