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
Assistant Professor of Microbiology
Perelman School of Medicine
Philadelphia, PA

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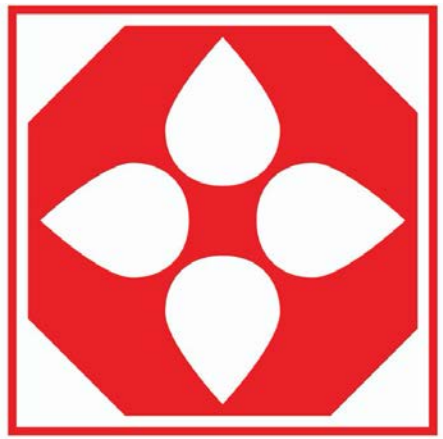

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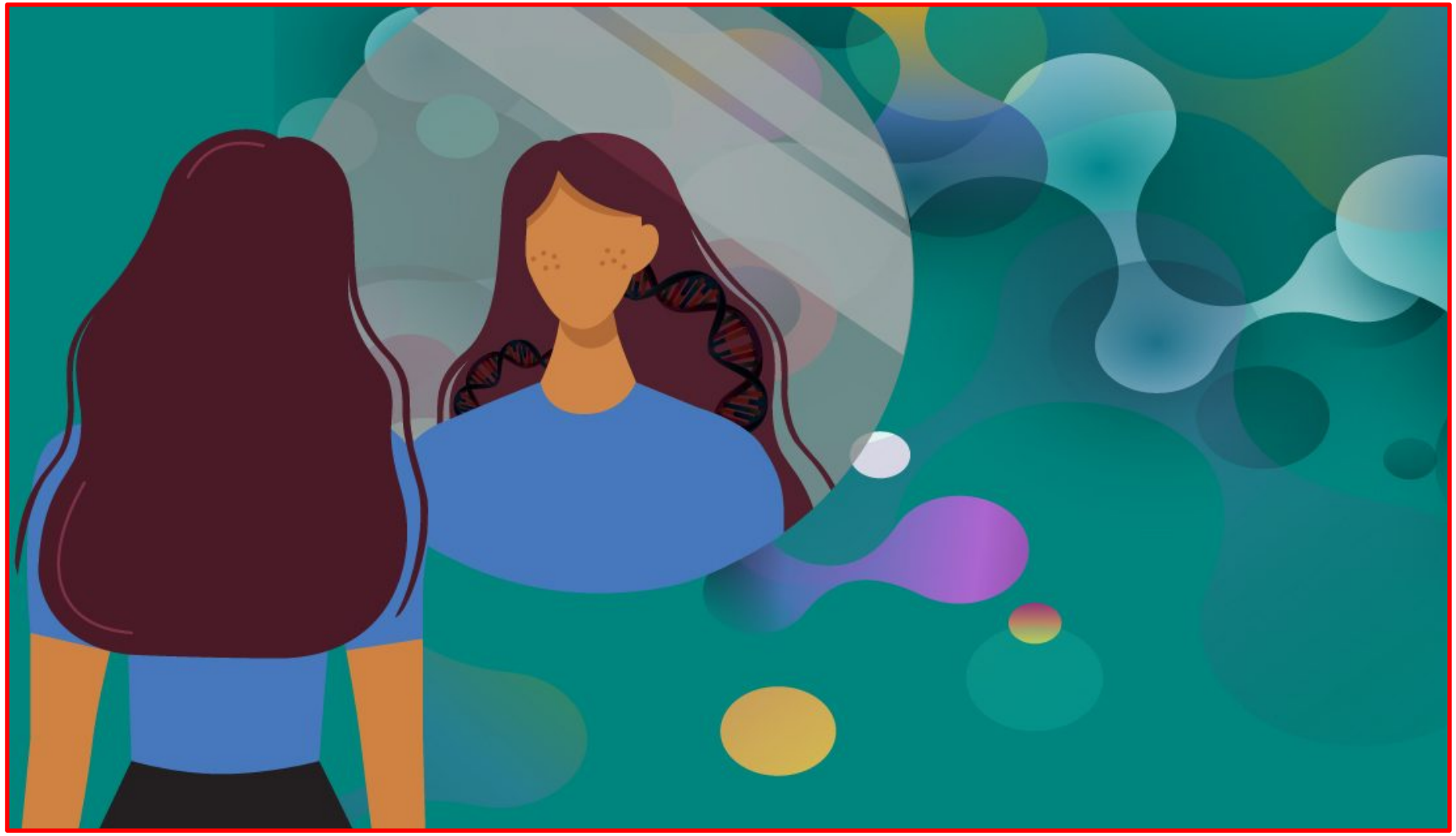
The Future of CAR-T Therapy: Can CAR-T Cure CLL?

Joseph A. Fraietta, Ph.D.
University of Pennsylvania

Cancer Therapy (Problem 1):
The Enemy is Ourselves



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Cancer Therapy (Problem 2):
Cancer-Specific Immune Cells are Very Rare, if Present at All

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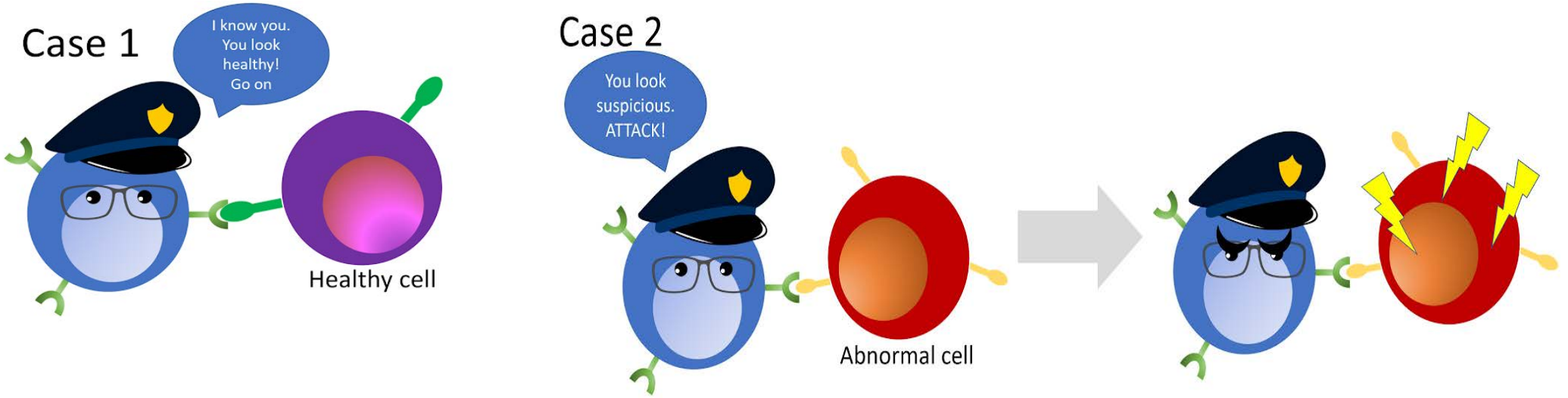
Immunology 101:
Antigen and T cell basics

- 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).



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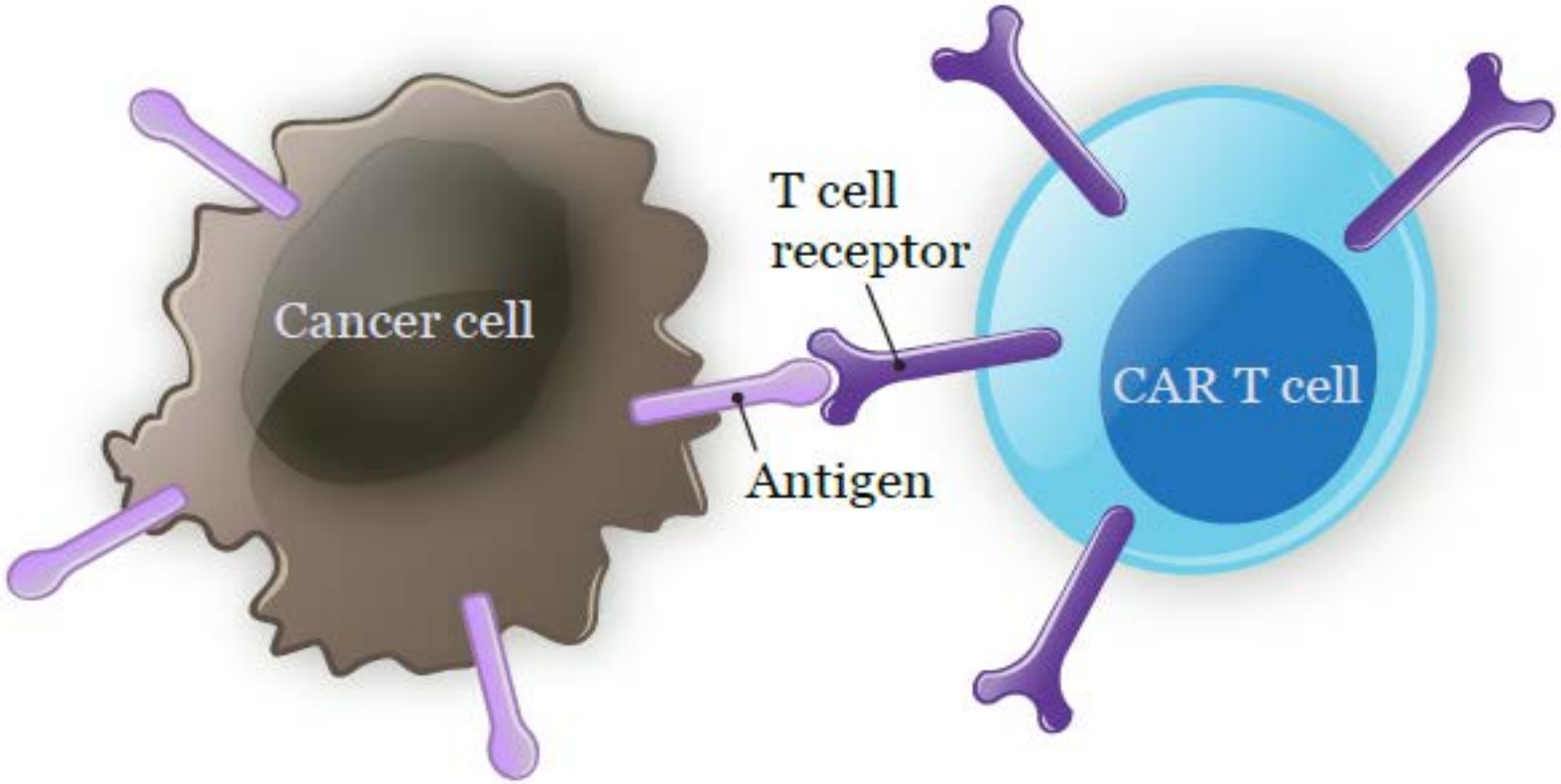
Why are CAR T cells Referred to as “Living Drugs” Engineered to Fight CLL and other Cancers?

- 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



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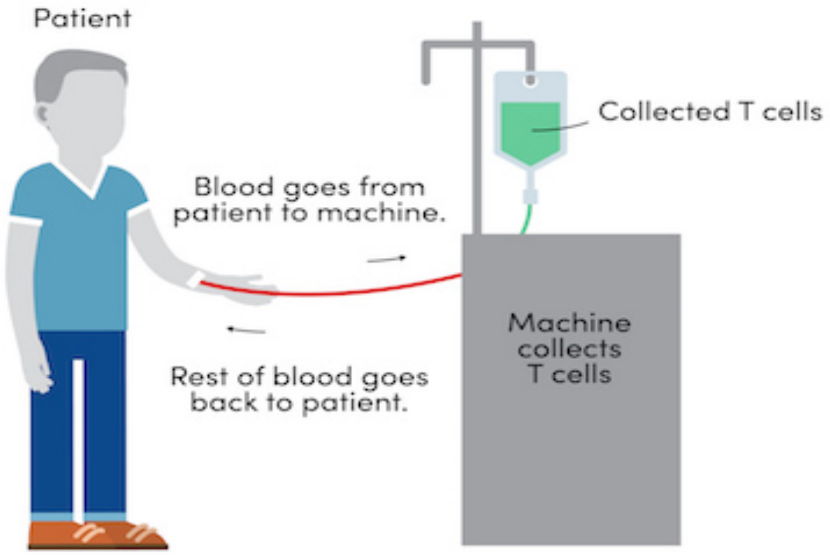
What is the CAR T cell Treatment Process like for Patients?

- 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.



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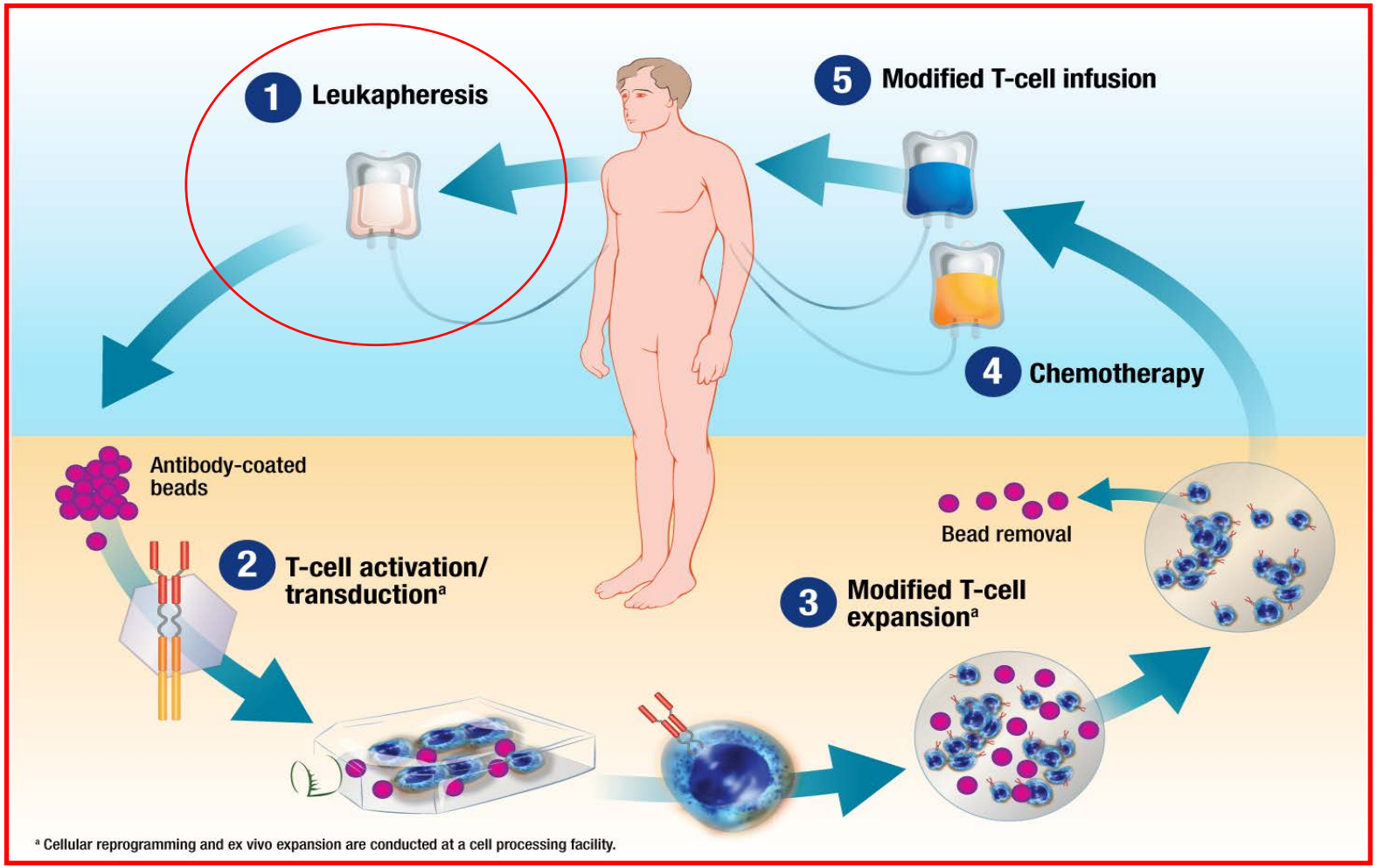
Let's Look at Each Step: Collection

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)



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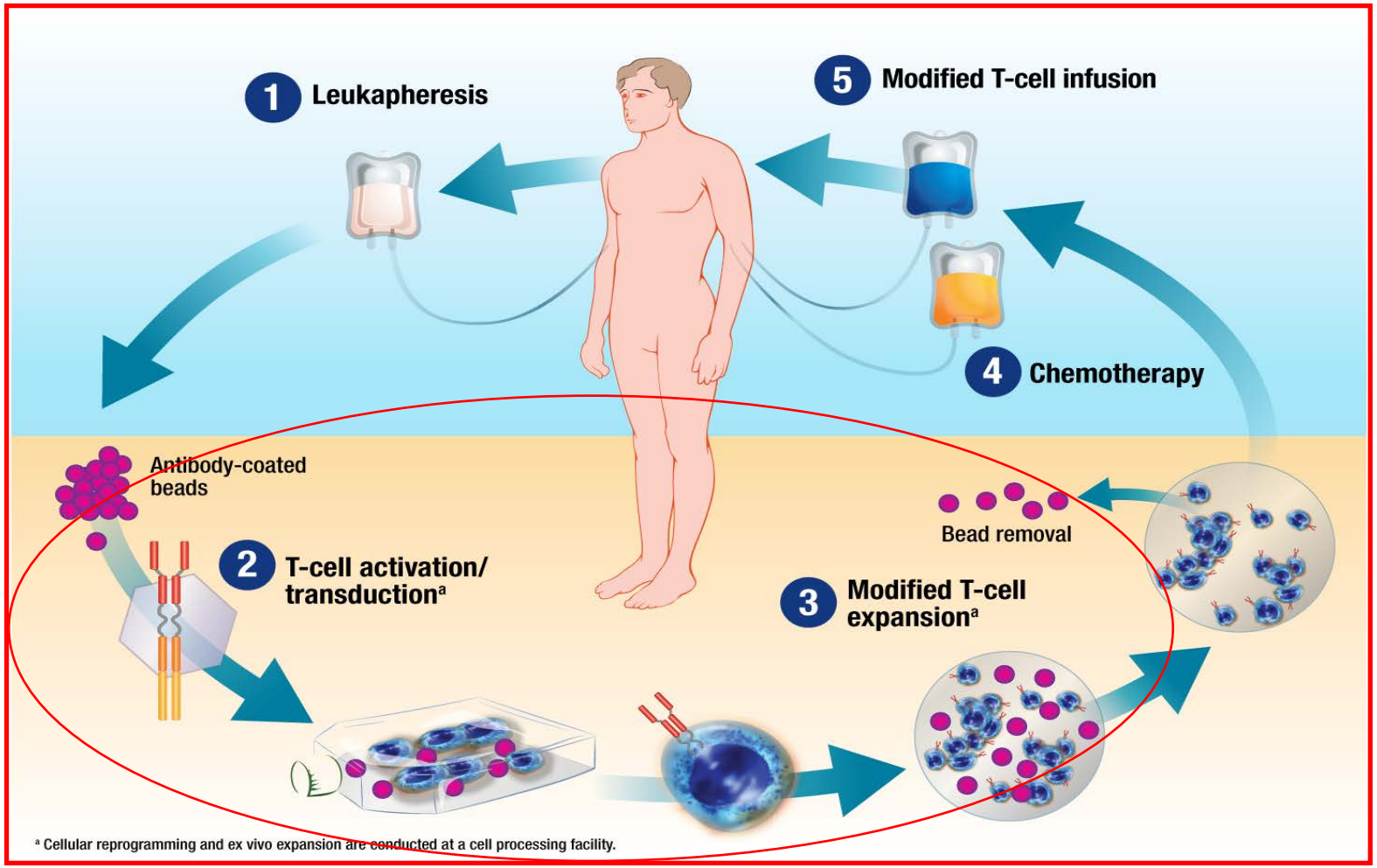
Let's Look at Each Step: Engineering/Modification

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)



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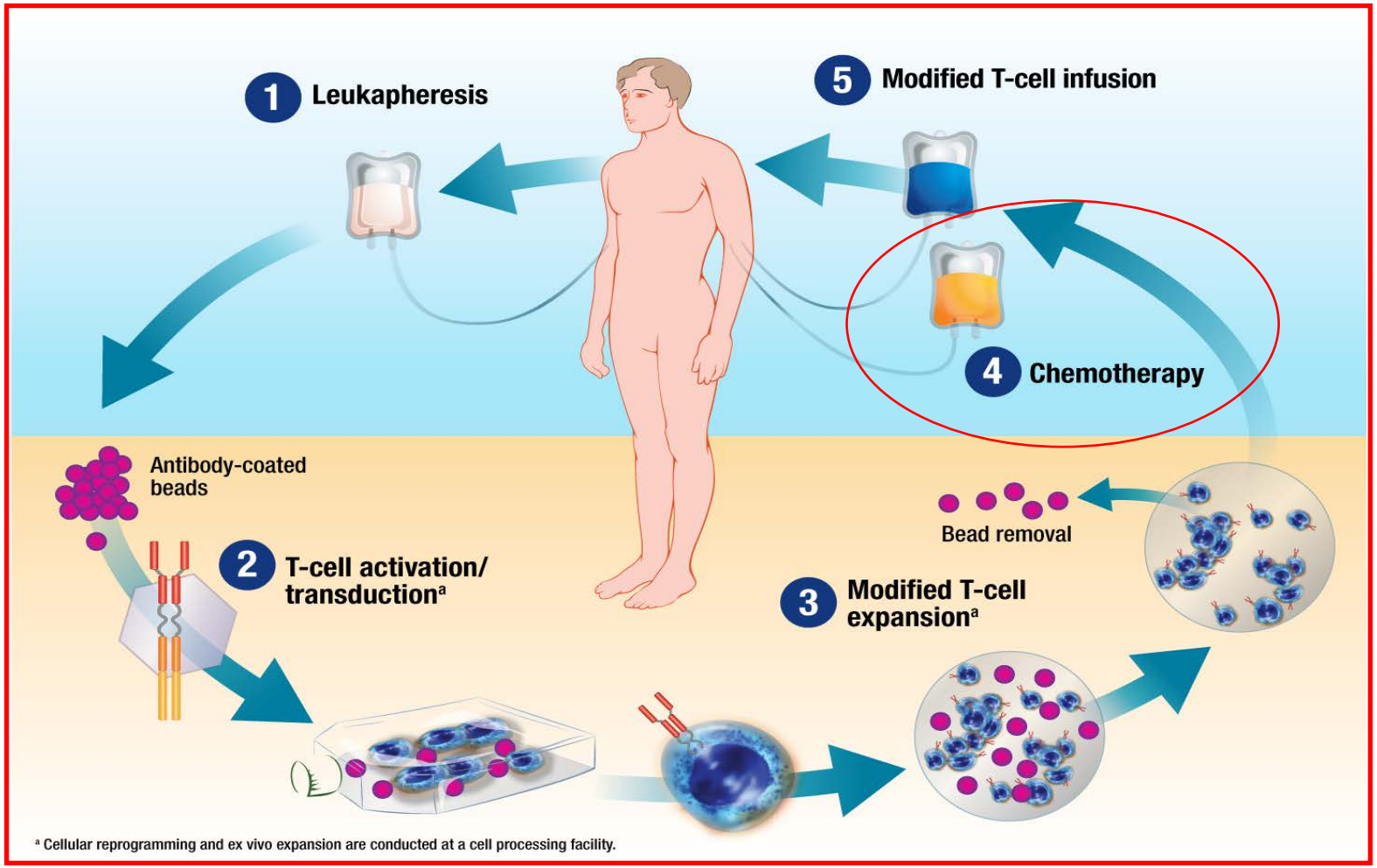
Let's Look at Each Step: Conditioning

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)



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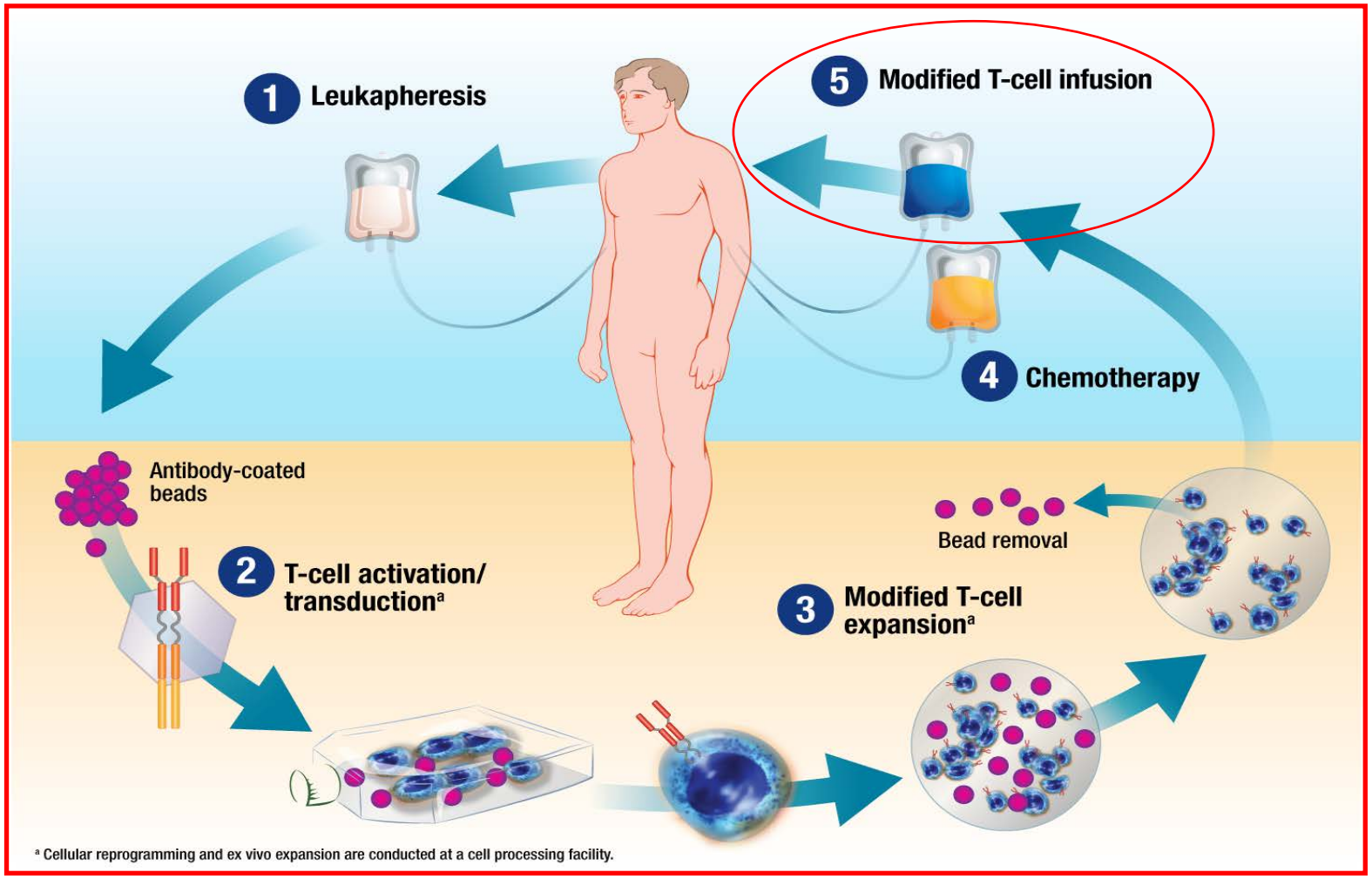
Let's Look at Each Step: Infusion

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)



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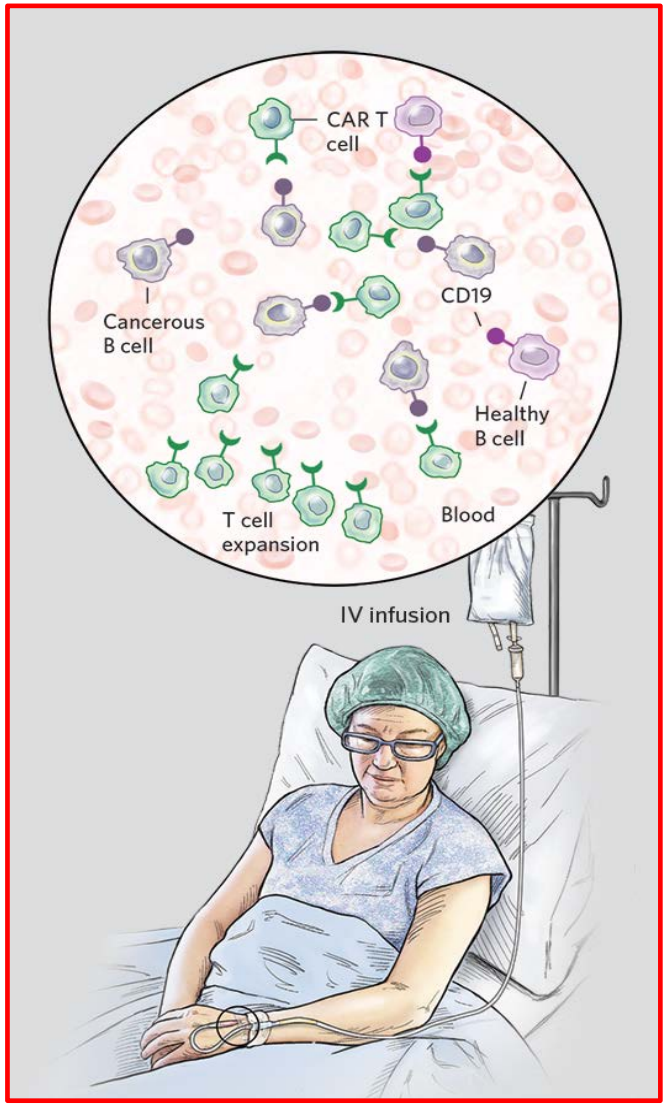
What are the Responses to CAR T cell Therapy in CLL?

- 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.



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What are the Side Effects Associated with CAR T cell Therapy in CLL?

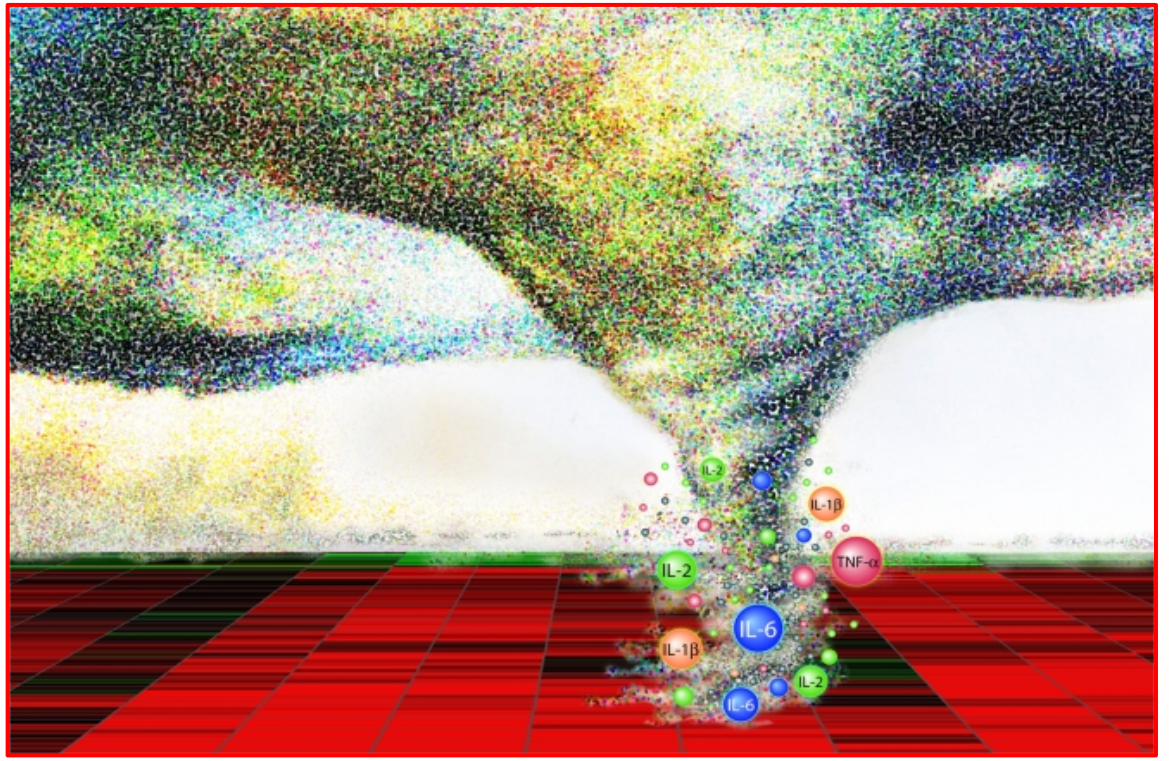
- Most patients who respond to CAR T cell therapy develop some degree of cytokine release syndrome (CRS). It can be mild to severe and treatment options are available.

- 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)



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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

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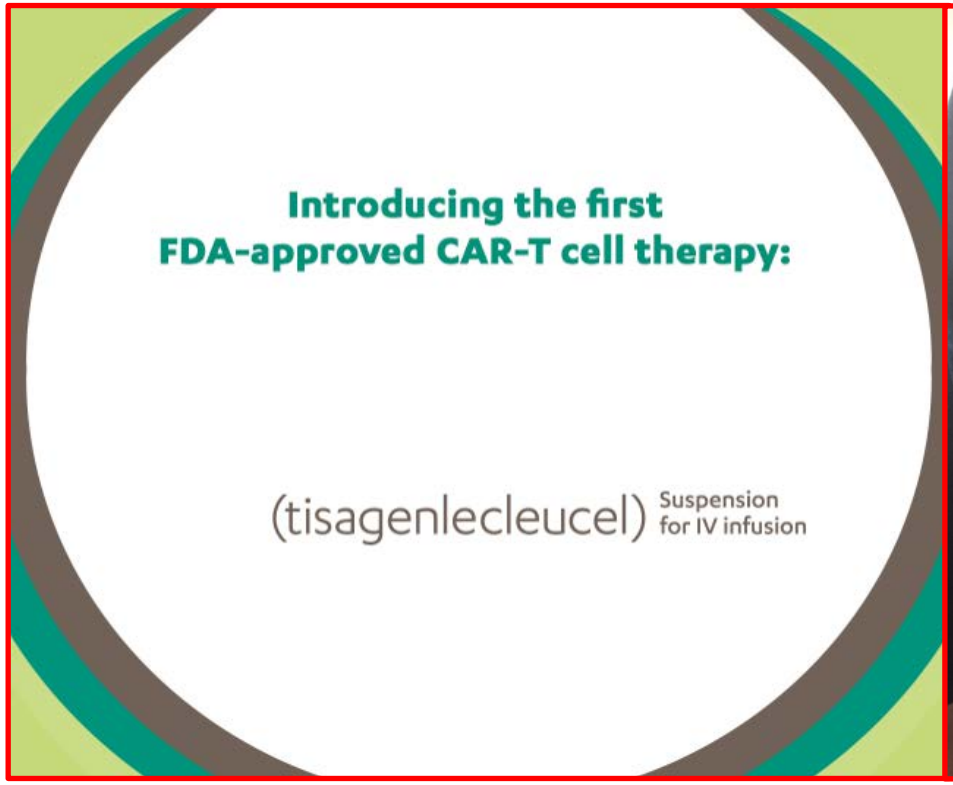
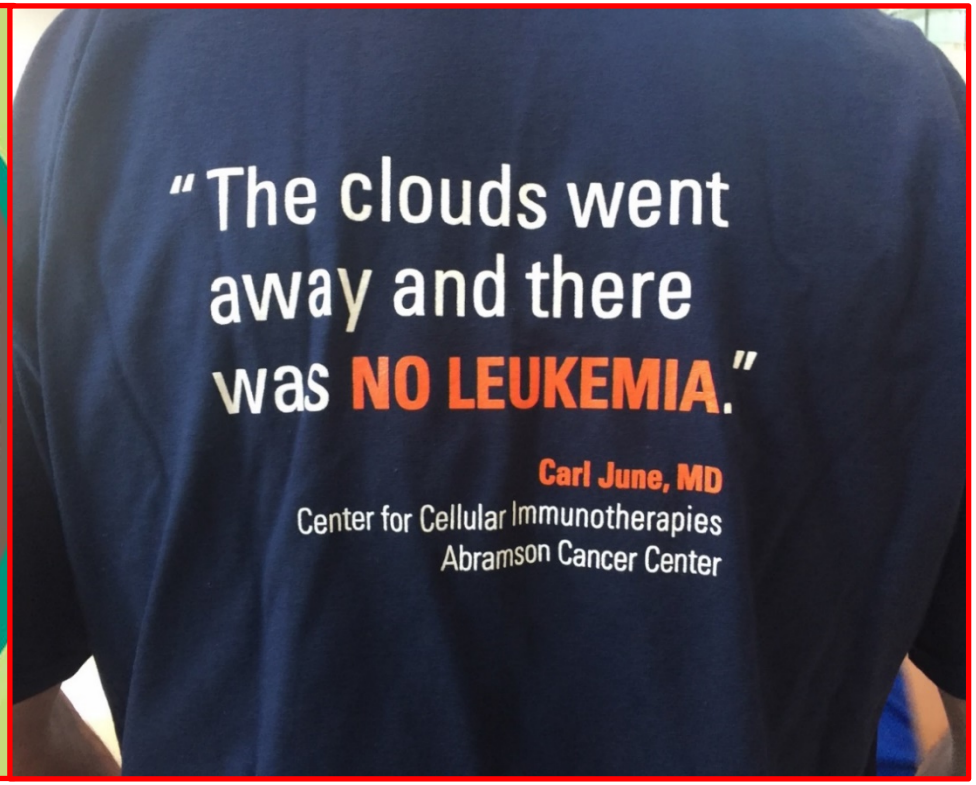
What is the Current Status of FDA-approved CAR T cell Therapy for CLL?

- **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).**





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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.

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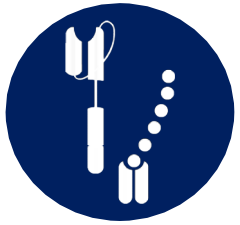
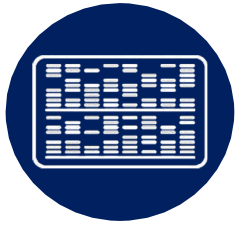
Is There Any New Promising Research in CAR T cell Therapy for CLL? What's on the Immediate Horizon for this Approach?

Rational Drug Combinations with CAR T cells for CLL



Controllable CAR T cells for CLL



Biomarker-driven CAR T cell Therapy for CLL

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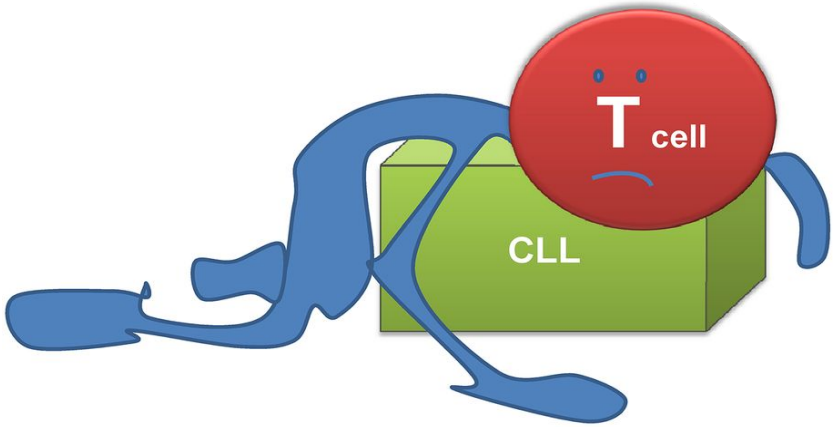
Targeting CD19 with CAR T cells: Success Sometimes Has Limits

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 <u>26% complete response rate in CLL</u>***

- **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

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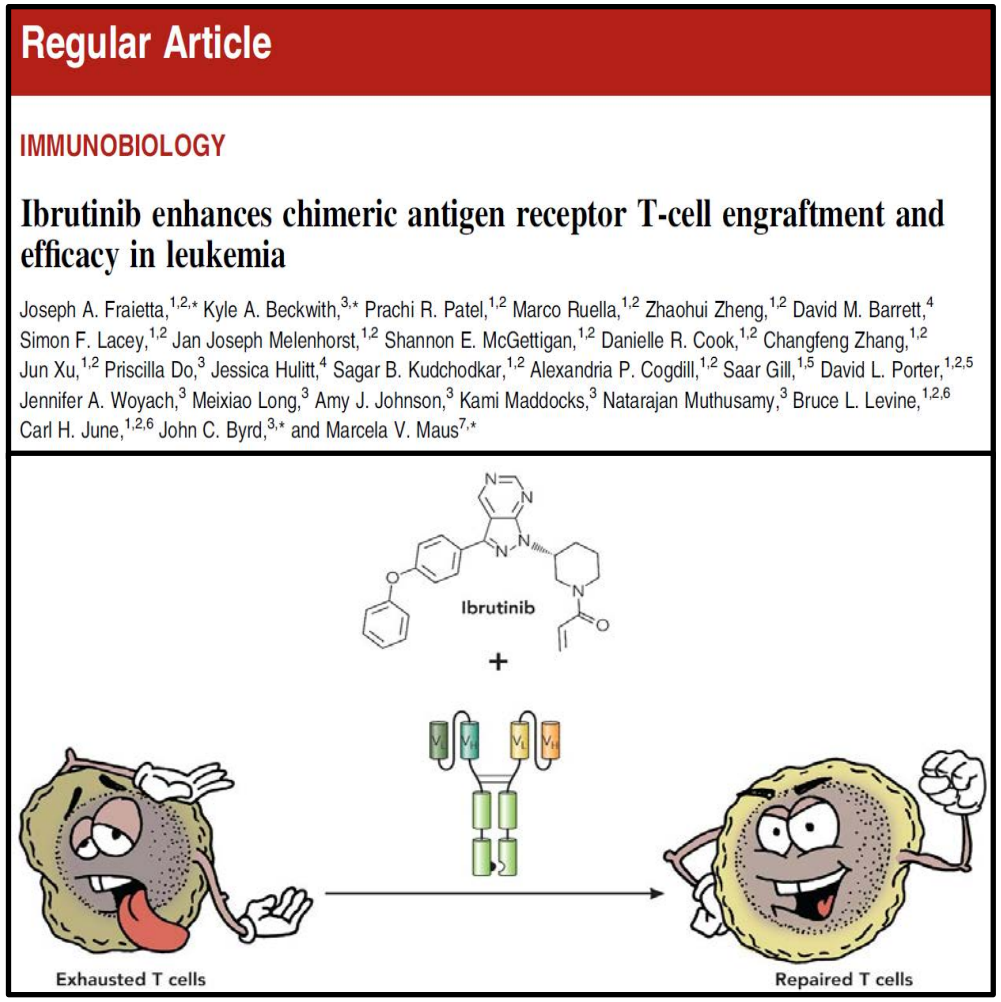
Research Highlight: Rational Drug Combinations with CAR T cells for CLL



- **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**

Fraietta, JA et al., *Blood* 127, 1117–1127 (2016)

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Research Highlight: Biomarkers for CAR T cell Therapy of CLL

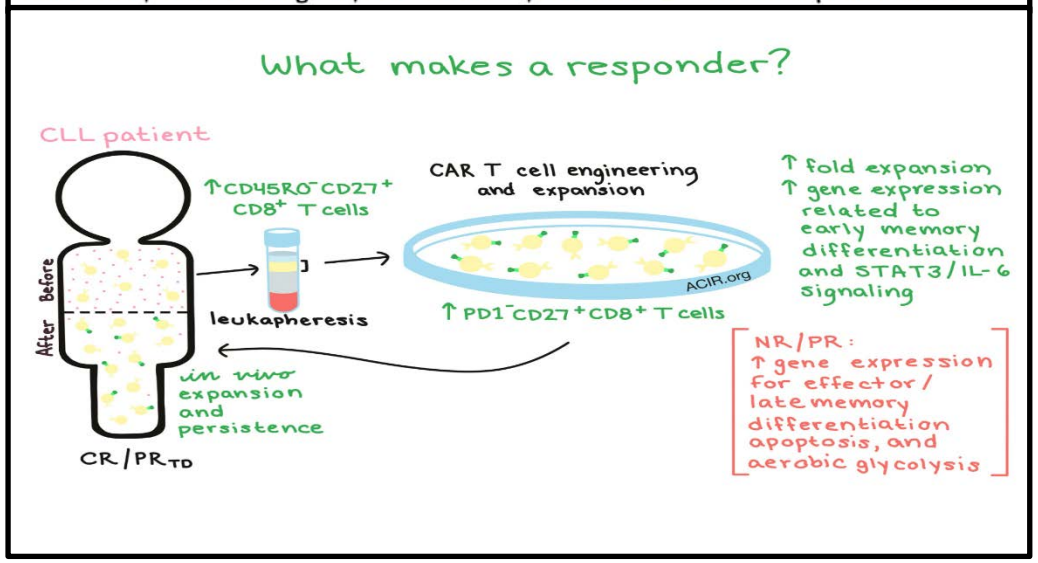
nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0010-1

Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia

Joseph A. Fraietta[1,2,3], Simon F. Lacey[1,2,3,9], Elena J. Orlando[4,9], Iulian Pruteanu-Malinici[4], Mercy Gohil[2], Stefan Lundh[2], Alina C. Boesteanu[2], Yan Wang[2], Roddy S. O'Connor[2], Wei-Ting Hwang[5], Edward Pequignot[2], David E. Ambrose[2], Changfeng Zhang[2], Nicholas Wilcox[2], Felipe Bedoya[2], Corin Dorfmeier[2], Fang Chen[2], Lifeng Tian[2], Harit Parakandi[2], Minnal Gupta[2], Regina M. Young[2], F. Brad Johnson[1], Irina Kulikovskaya[2], Li Liu[2], Jun Xu[2], Sadik H. Kassim[4], Megan M. Davis[1,2], Bruce L. Levine[1,2], Noelle V. Frey[2,6], Donald L. Siegel[1,2,7], Alexander C. Huang[3,8], E. John Wherry[3,8], Hans Bitter[4], Jennifer L. Brogdon[4], David L. Porter[1,6], Carl H. June[1,2,3] and J. Joseph Melenhorst[1,2,3]*



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**

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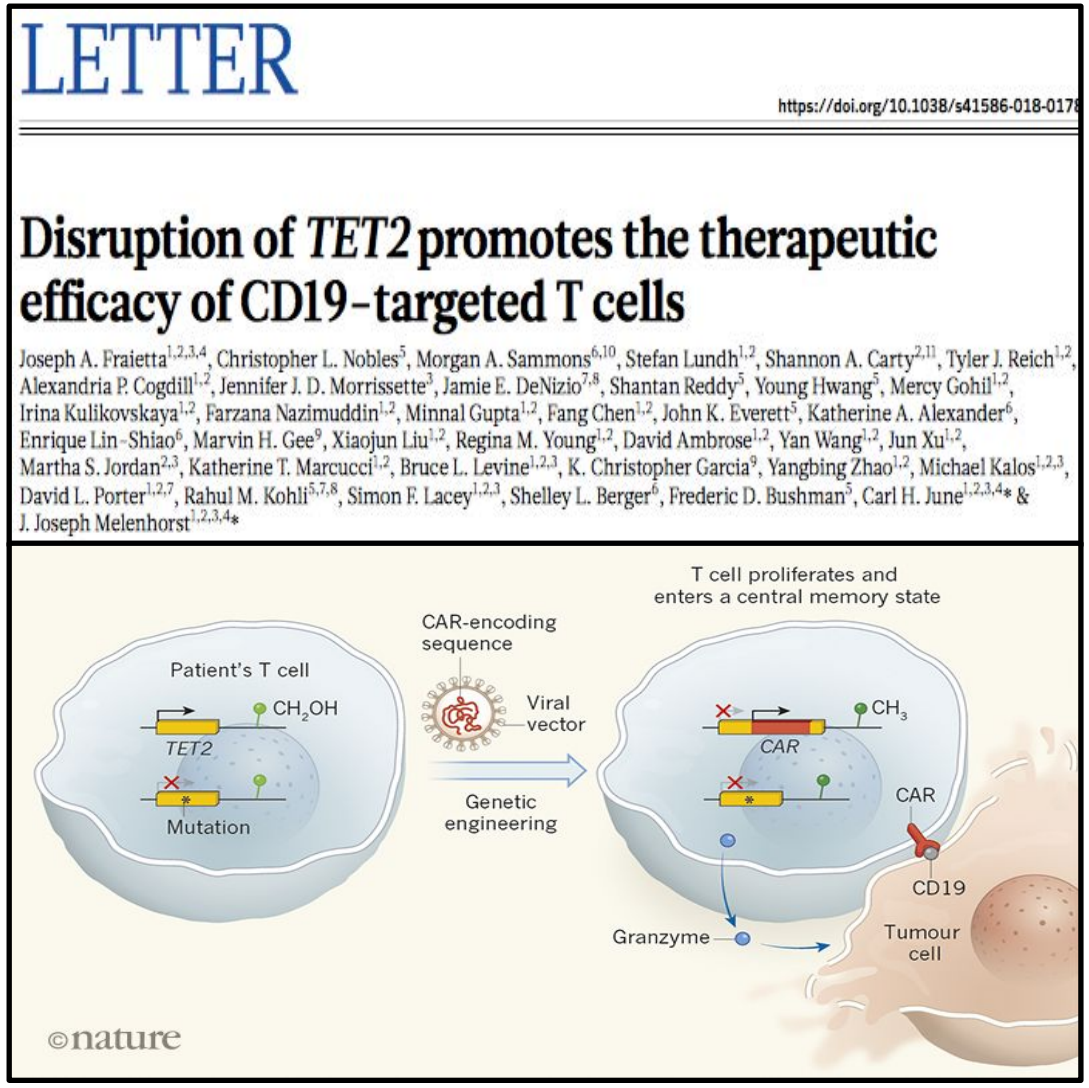
Research Highlight: Complete Remission Driven by a Single Cell



LETTER

https://doi.org/10.1038/s41586-018-0178

Disruption of *TET2* promotes the therapeutic efficacy of CD19-targeted T cells

Joseph A. Fraietta[1,2,3,4], Christopher L. Nobles[5], Morgan A. Sammons[6,10], Stefan Lundh[1,2], Shannon A. Carty[2,11], Tyler J. Reich[1,2], Alexandria P. Cogdill[1,2], Jennifer J. D. Morrissette[3], Jamie E. DeNizio[7,8], Shantan Reddy[5], Young Hwang[5], Mercy Gohil[1,2], Irina Kulikovskaya[1,2], Farzana Nazimuddin[1,2], Minnal Gupta[1,2], Fang Chen[1,2], John K. Everett[5], Katherine A. Alexander[6], Enrique Lin-Shiao[6], Marvin H. Gee[9], Xiaojun Liu[1,2], Regina M. Young[1,2], David Ambrose[1,2], Yan Wang[1,2], Jun Xu[1,2], Martha S. Jordan[2,3], Katherine T. Marcucci[1,2], Bruce L. Levine[1,2,3], K. Christopher Garcia[9], Yangbing Zhao[1,2], Michael Kalos[1,2,3], David L. Porter[1,2,7], Rahul M. Kohli[5,7,8], Simon F. Lacey[1,2,3], Shelley L. Berger[6], Frederic D. Bushman[5], Carl H. June[1,2,3,4]* & J. Joseph Melenhorst[1,2,3,4]*

The minimum dose of CAR T cells needed to induce complete remission is 1 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!

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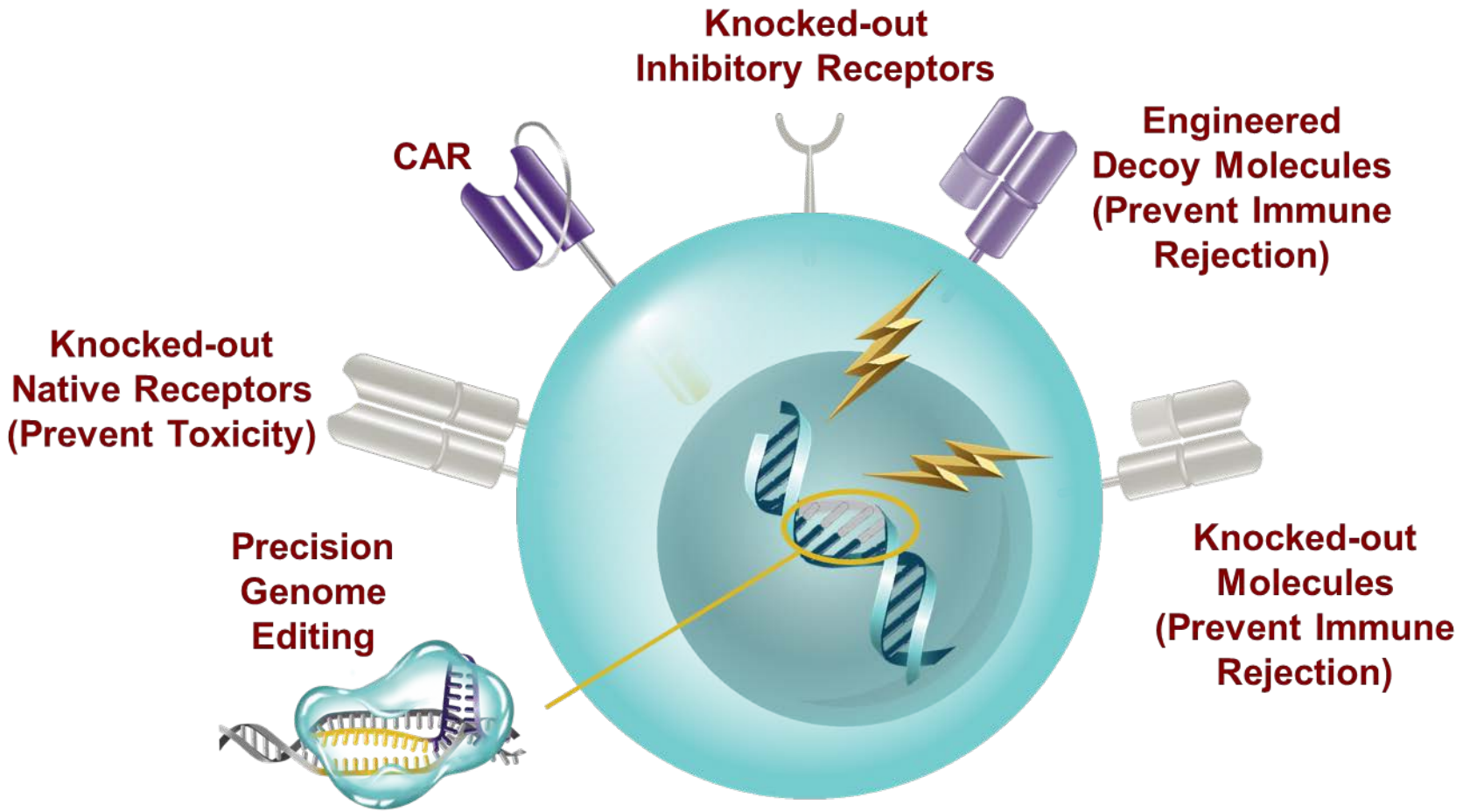
Research Goal: *Engineering Off-the-Shelf CAR T cells*

- 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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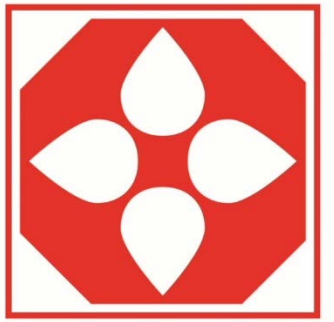

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