LEUKEMIA & LYMPHOMA SOCIETY®

CAR T-CELL THERAPY AND BLOOD CANCERS

Keren Osman, MD
Associate Professor
Director, Cellular Therapy Service
Bone Marrow and Stem Cell Transplant
Tisch Cancer Institute
Mount Sinai School of Medicine
New York, NY

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WELCOMING REMARKS

CAR T-CELL THERAPY AND BLOOD CANCERS

Lizette Figueroa-Rivera, MA
Sr. Director, Education & Support
The Leukemia & Lymphoma Society

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SPEAKER

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DISCLOSURES

CAR T-CELL THERAPY AND BLOOD CANCERS

Keren Osman, MD
Participation in Advisory Board for Kite, A Gilead Company.

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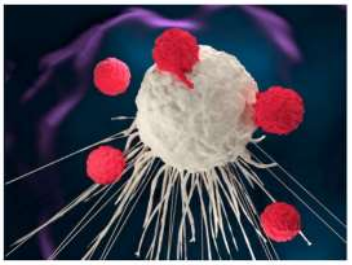
What is CART Therapy?

CAR T-cell therapy is a type of cancer therapy that uses a patient's own modified white blood cells to kill cancer cells.



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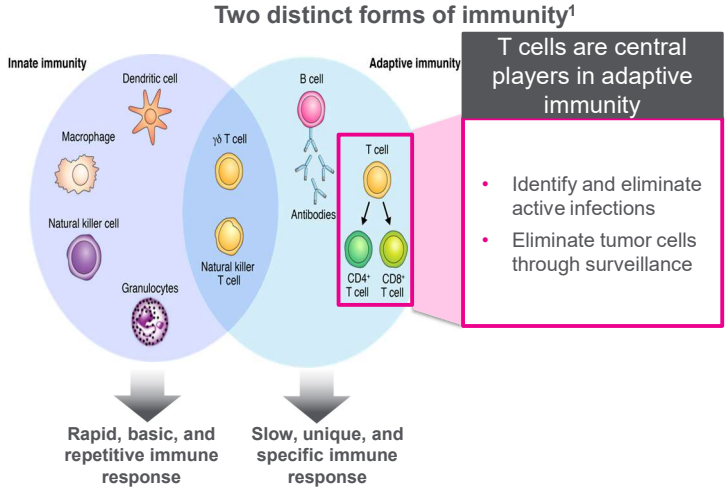
Role of the Immune System in Cancer Control/Eradication



1. Sharpe M, Mount N. *Dis Model Mech*. 2015;8:337-350.

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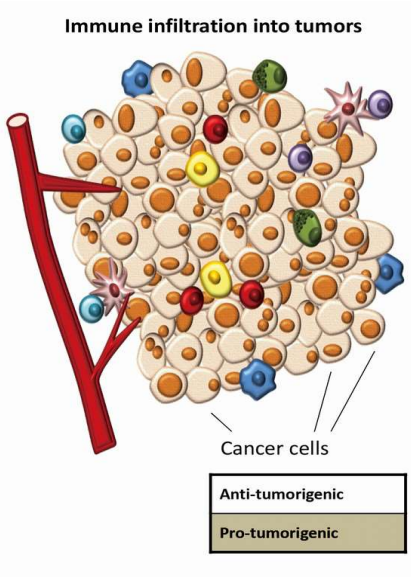

Immune Cell		Roles in cancer
	Dendritic cell (DC)	Release cytotoxic cytokines Antigen presentation to T cells
		Suppress T cell functions Promote tumor growth and progression
	T cell (CD8+, CD4+)	Directly lyse cancer cells Release cytotoxic cytokines
		Release tumor promoting cytokines
	Treg	Restore homeostasis to reduce chronic inflammation
		Suppress anticancer immune responses Stimulate inflammatory cytokine production
	Macrophage	Release cytotoxic cytokines Antigen presentation to T cells
		Promote angiogenesis, tumor proliferation, chemotaxis, invasiveness, and metastasis
	Myeloid derived suppressor cell (MDSC)	Limited
		Suppress T cell functions Recruit immunosuppressive immune cells
	NK cell	Release cytotoxic cytokines Directly cytotoxic to cancer cells
		Limited

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Approaches to Overcome Cancer Tolerance

- Considerations for T Cell Therapy
  - 1kg of tumor = 10^{12} cells
  - Killing machinery needs to be = tumor burden
- Failure to address critical mass of tumor may explain previous clinical trials and their disappointing results
- Two potential solutions:
  - Infuse a large # of T cells
  - Infuse a small # of cells which are programmed to proliferate

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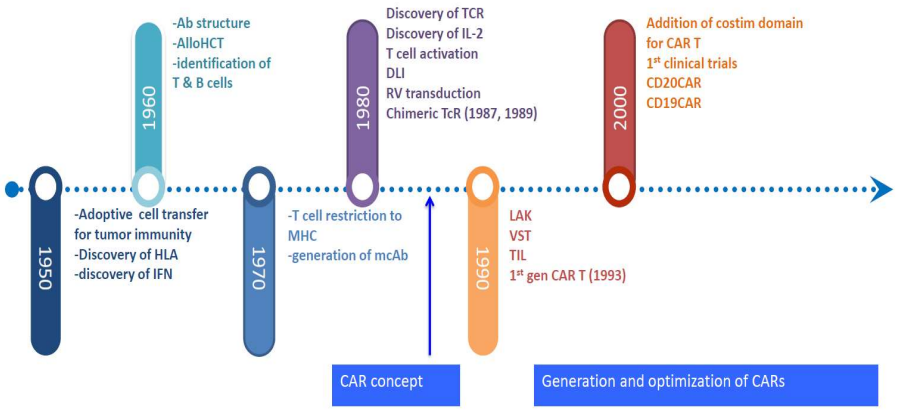
Development of Adoptive Cellular Therapy



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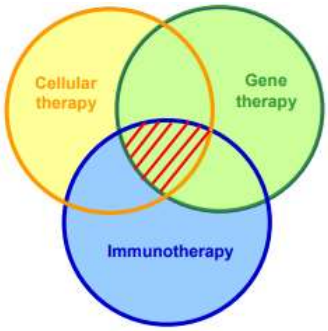
CART Cells are at the Intersection of Three Innovative Technologies



Cellular therapy
Using the patient's own T- cells as therapy

Gene therapy
Insertion of genes into a patient's cells, thereby causing these cells to produce a new therapeutic protein (CAR)

Immunotherapy
Harnessing the patient's own immune system (T- cells) to treat his/her disease

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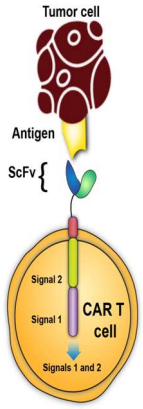
Goal: Harness the Power of a Patient's Own Immune System to Target and Attack Cancer Cells

Chimeric antigen receptor (CAR) T cell therapy is a class of immunotherapy that involves engineering patient's own immune cells with a goal of[1,2]:

- **Helping a patient's own T cells to recognize tumor cells as foreign**
- **Expanding a patient's own T cells**
- **Reactivating a patient's own T cells to attack target cells**



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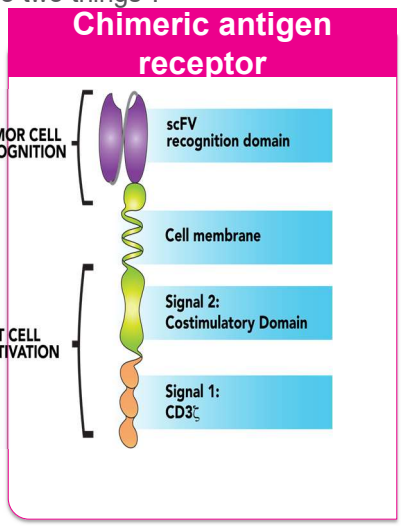
CARs are Composed of a Tumor Recognition Domain and a T cell Activation Domain

CARs are fusion proteins designed to do two things[1]:

1. **Target** cancer cells by engineering a recognition domain (commonly an antibody fragment [scFV]) on the T cell surface

2. **Activate** the CAR T cell by signaling through the CAR's intracellular signaling domain with the goal of
   - Proliferation & activation of the T cell
   - CAR T cell-mediated apoptosis of tumor cells



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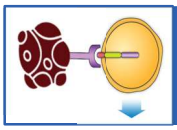
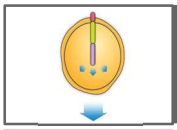
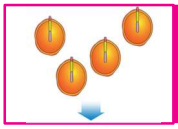
CAR T Cell Therapy is Designed to:



Recognize — CAR T cells recognize their target



Signal — This binding causes signaling through the two CAR intracellular domains



Activate & proliferate — Activated CAR T cells are now capable of rapid proliferation

Induce tumor cell apoptosis — Activated CAR T cells can induce apoptosis of target-expressing cells

- 1. Camicia R, et al. *Molecular Cancer.* 2015;14:207.

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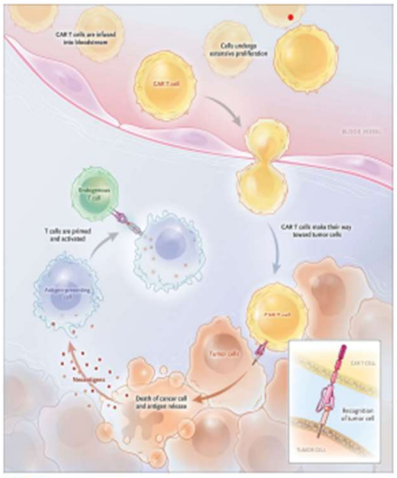
CAR T Cells Traffic to Tumor and Proliferate Extensively after Infusion



June CH, Sadelain M. N Engl J Med 2018;379:64-73

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Ideal CAR Target

Tumor antigen that is present on all, or most, of the cancer cells and is necessary for that cancer cell's survival

Tumor antigen that is not present on normal healthy cells such that immune attack on those normal healthy cells would lead to unacceptable toxicity

A Good CAR T-cell Candidate

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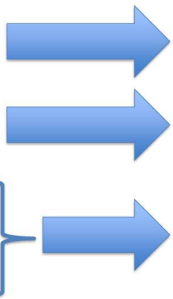
CD19 = Good CAR T-cell Tumor Antigen

- University of Pennsylvania
  - Costimulatory molecule: 4-1BB
- National Cancer Institute
  - Costimulatory molecule: CD28
- Memorial Sloan Kettering
  - Costimulatory molecule: CD28
- Fred Hutch Cancer Center
  - Costimulatory molecule: 4-1BB



- Novartis: tisagenecleucel or Kymriah
- Kite: axicabtagene ciloleucel or Yescarta
- Juno:
  - CD28: JCAR015
  - 4-1BB: JCAR017 or lisocabtagene ciloleucel

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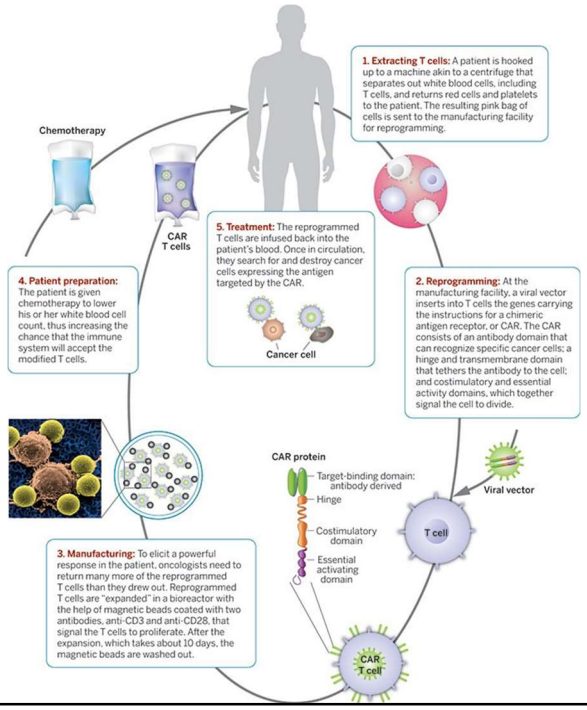

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FDA Approved CAR-T products

FDA-Approved CAR T-Cell Therapies

Generic Name	Brand Name	Target Antigen	Targeted Disease	Patient Population
Tisagenlecleucel	Kymriah	CD19	B-cell acute lymphoblastic leukemia (ALL)	Children and young adults with refractory or relapsed B-cell ALL
			B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Axicabtagene ciloleucel	Yescarta	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
			Follicular lymphoma	Adults with relapsed or refractory follicular lymphoma
Brexucabtagene autoleucel	Tecartus	CD19	Mantle cell lymphoma (MCL)	Adults with relapsed or refractory MCL
			B-cell acute lymphoblastic leukemia (ALL)	Adults with refractory or relapsed B-cell ALL
Lisocabtagene maraleucel	Breyanzi	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Idecabtagene vicleucel	Abecma	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma
Ciltacabtagene autoleucel	Carvykti	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma

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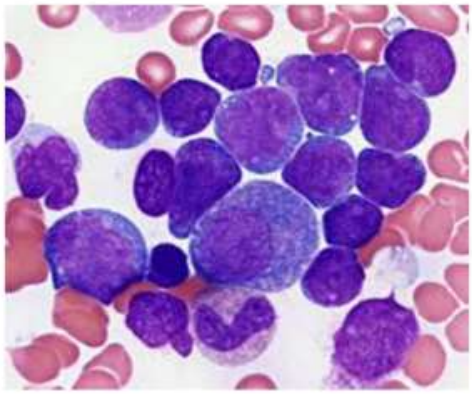
CAR T- Cell Therapy in B-Cell Acute Lymphoblastic Leukemia (B-ALL)



Atlas of Genetics and Cytogenetics in Oncology and Hematology

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Eliana Study in Children

- Single arm, open-label, multi-center, global phase 2 study
  - 107 pts screened, 88 enrolled, 68 treated
- Dose of Tisagenlecleucel: 2-5 x 10^6 CAR-T cells/kg
  - Conditioning chemo: Flu 30 mg/m2 x 4days + Cy 500 mg/m2 x 2 days
- Response rates: Complete Remission/Complete Remission with incomplete hematologic recovery **CR/CRi: 81%** (CR 60% + CRi 21%)
- **Tisagenlecleucel approved for treatment of patients up to age 25 with B-ALL that is refractory or in 2nd or later relapse**

1. Buechner J, et al. *Haematologica*. 2017;102(suppl 2) [abstract S476];
2. Maude SL, et al. *N Engl J Med*. 2018;378:439-448;

20

Outcomes with CART19 Therapy in Children and Adults with Relapsed/Refractory B-ALL

Reference	CAR	Population	Response
Maude et al. NEJM 2018	PENN 4-1BB	ALL (peds/adults) N=71	CR: 81% 6mo EFS & OS: 73% & 90% 12mo EFS & OS: 59% & 76% 11% proceeded to alloHSCT after CAR T cells
Park J et al. ASCO 2017, Abstract 7008	MSKCC CD28	ALL (adults) N=53	CR: 84.6% MRD-CR rate: 66.6% 39% proceeded to alloHSCT after CAR T cells.
Turtle et al. JCI 2016	Seattle 4-1BB Defined CD4/CD8 composition	ALL (adults) N=30	CR=93% MRD-CR rate: 86% 1 pt proceeded to alloHSCT after CAR T cells
Lee et al. Lancet 2015	NCI CD28	ALL (peds/adults) N=21	CR=67%

Now FDA approved for both adults and children with relapsed or refractory ALL

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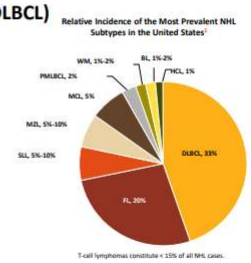
CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- **Diffuse Large B-Cell Lymphoma (DLBCL)**
- Mantle Cell Lymphoma (MCL)
- Follicular Lymphoma
- Marginal Zone Lymphoma



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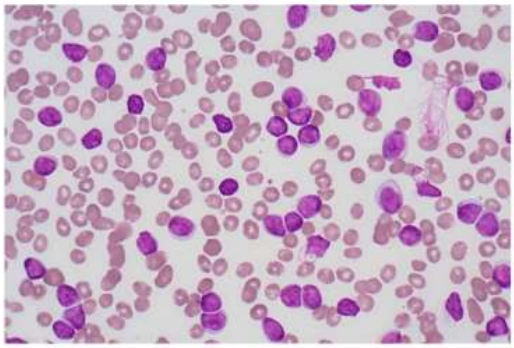
CAR T-Cell Therapy in Chronic Lymphocytic Leukemia (CLL)



Increased numbers of mature lymphocytes
in peripheral blood

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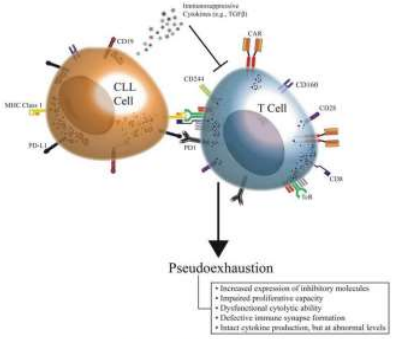
Improving CLL Therapy with CAR T-cells



Fraietta JA, Schwab RD, Maus MV. Semin Oncol. 2016 Apr;43(2):291-9.

CAR T cell therapy is promising for relapse/refractory CLL patients. Complete and durable remission of CLL is possible in patients treated with CAR T cells but further investigations are necessary to understand and possibly predict how patient specific factors influence the outcome of this treatment.

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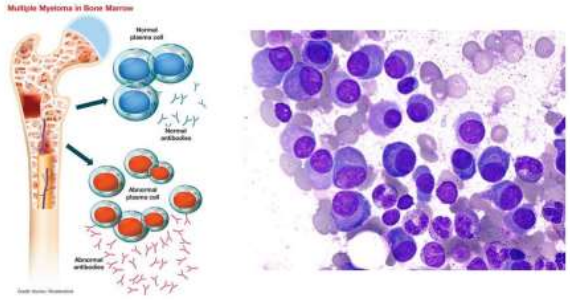
CAR T- Cell Therapy in Multiple Myeloma (MM)



Clinician Reviews. 2018 January;28(1):16-18,20-21

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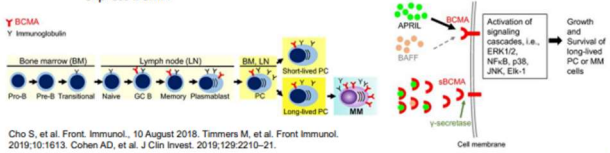
B-Cell Maturation Agent= BCMA

- Functions to maintain long-lived plasma cell homeostasis
  - Essential in regulating B-cell maturation and differentiation
- Highly expressed on malignant plasma cells in MM
  - Increased expression associated with progression of disease
- BCMA shed from the surface of plasma cells leads to soluble BCMA (sBCMA) detectable in circulation
- Higher concentrations of sBCMA associated with poorer outcomes
  - Low level expression on healthy differentiated B-cells; no other normal cells/tissues express BCMA



Cho S, et al. Front. Immunol., 10 August 2018. Timmers M, et al. Front Immunol. 2019;10:1613. Cohen AD, et al. J Clin Invest. 2019;129:2210–21.

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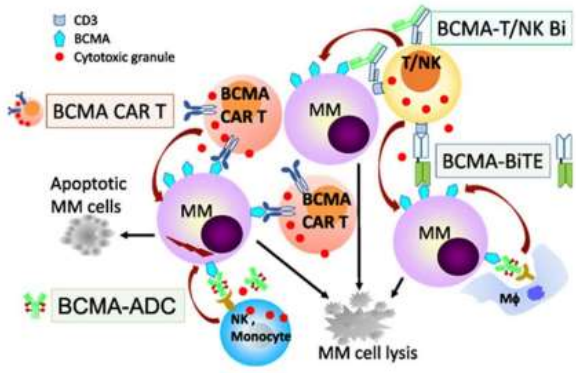
BCMA based Therapies in Multiple Myeloma



Cho S., Anderson KC., Tai Y. Front. Immunol., 10 August 2018.

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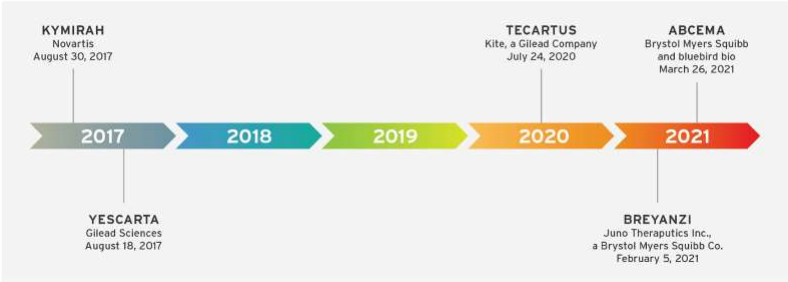

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CAR T-cell Toxicity

- Cytokine Release Syndrome (CRS)
  - Caused by activation/expansion of CAR T-cells and increased levels cytokines like IL-6, IL-15, INF-γ, GM-CSF and others
    - Monocytes and macrophages are a source of some of these cytokines
  - Onset: 1-3 days
  - Duration: 3-5 days
  - Risk variable but gr3+ up to 20-30%
- Neurotoxicity
  - Mechanism less well understood
    - Clinically associated with tumor burden, CAR T-cell expansion, cytokine levels, early and high grade CRS
    - Biologically associated with markers of DIC, endothelial activation and breakdown of the blood brain barrier
      - CAR+ and CAR- T-cells and inflammatory cytokines are found in the CSF
  - Onset: 5-7 days
  - Duration: 5-10 days
    - Fully reversible except in cases of fatal cerebral edema
  - Risk variable but gr3+ in up to 30-40%

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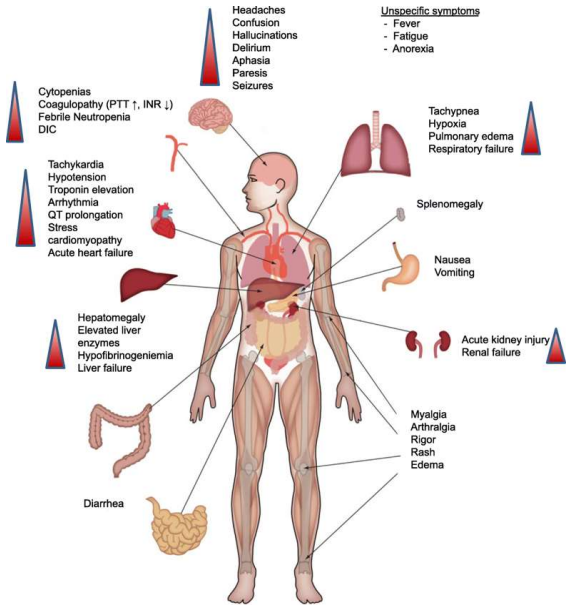
CRS



Heterogeneous presentation flu like symptoms to severe life threatening symptoms

Risk Factors:
1.Type of therapy
2.Burden of underlying disease
3.Nature of the CAR construct (CD28 co-stimulation)
Disease burden is most imprtatnt predictor
Administered dose of T cells also important and the strength of T cell actovation and degree of T cell expansion

**** Degree of CRS does NOT correlate with response the CAR-T therapy

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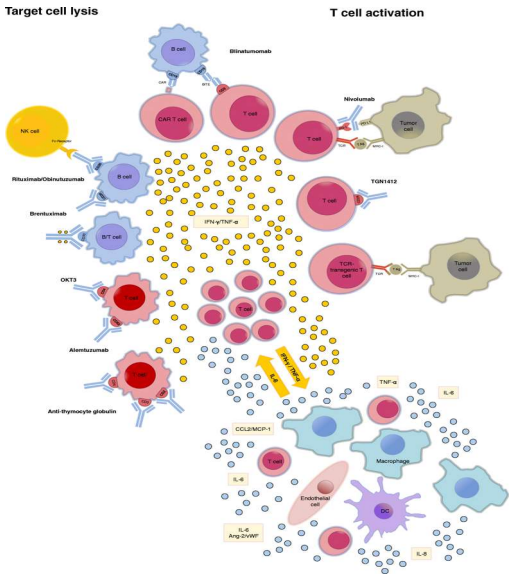
Mechanism of CRS



On Target Effects: binding to bispecific Ab on CAR-T receptor

Activation of Bystander immune cells and NON immune cells such as endothelial cells

Activation of bystander cells causes massive cytokine release

Cytokines trigger a chain reaction due to activation of innate immune cells such as macrophages and endothelial cells
Endothelial cells are the source of IL-6: leads to further cytokine release

Capillary leak, hypotension, coagulopathy

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Cytokine Release Syndrome (CRS) and Neurologic Toxicities

- Two common and potentially serious cytokine-associated toxicities arising from CAR T cell therapy

CRS

- Mediated by high levels of inflammatory cytokines, such as IL-6[1]
- Symptoms include fever, tachycardia, hypotension, and hypoxia[2]

Neurologic Toxicities

- Toxicities are associated with high CAR T cell levels and/or high cytokine levels[3,4]
- Symptoms include confusion, tremor, aphasia, encephalopathy, and seizures[1]

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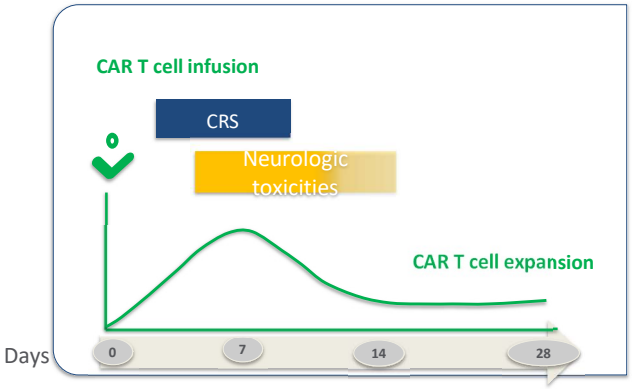
Onset and Resolution of CRS and Neurologic Toxicities

- May occur within minutes or hours but generally appear within days or weeks[1]
  - Coincide with maximal T cell expansion[1]
- Generally reversible in most patients; rare cases of long-term symptoms and fatalities[1]
- There are multiple protocols and published guidelines describing the grading and management of CRS and neurologic toxicities.[1-3]



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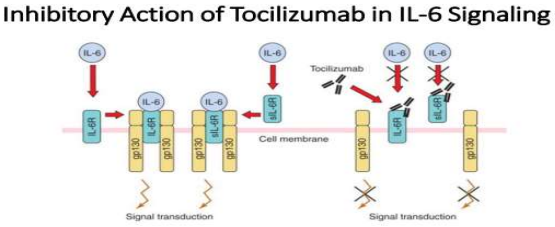
Management of Severe CRS

Management of Grade 3/4 CRS*

- Treat with tocilizumab, a humanized monoclonal antibody targeted against the IL-6 receptor that works by blocking the activity of IL-6



Norihiro Nishimoto, Toru Mima, in *Rheumatoid Arthritis*, 2009

- Consider corticosteroids as a second immunosuppressive agent if CRS symptoms are severe or if the patient does not improve or stabilize after tocilizumab dosing
- Management of Grade 3/4 CRS may vary according to institutional procedures, clinical trial protocols, published guidelines, and prescribing information.

- *Management of Grade 3/4 CRS may vary according to institutional procedures, clinical trial protocols, published guidelines, and prescribing information.
- CRS=cytokine release syndrome; IL-6=interleukin 6.
- 1. Lee DW, et al. *Blood*. 2014;124(2):188-195. 2. Neelapu et al. *Nature Review Clin Oncol*. 2017 [Epub ahead of print] 3. Brudno et al. *Blood*. 2016

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Mechanism of Neurotoxicity

- Pathophysiology remains unclear:
  - Diffusion of cytokines into central nervous system
  - Trafficking of T cells into central nervous system
- CSF is usually positive for CAR T cells
- MRI of brain is usually negative
  - Reversible white matter changes and cerebral edema have been rarely observed
- EEG is either non-focal with generalized slowing or might show non-convulsive seizure pattern

Maude et al. NEJM 2014; Davila et al. SciTrMed 2014; Lee et al. The Lancet 2015; Turtle et al. JCI 2016; Kochenderfer et al. JCO 2015; Turtle et al. JCI 2016; Gust et al. Cancer Disc. 2017

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Management of Neurologic Toxicities: General Principles

- Q4h neurological assessments, such as an MMSE, completed by bedside nurse
- Immediate notification to provider of change in neurological status
- Safety measures: seizure precautions, one-to-one observation if needed, NPO if unable to swallow, airway monitoring, transfer to ICU if airway compromised
  - Continuous pulse oximetry and telemetry for non-communicative patients
- Re-education/reinforcement to family that most neurological symptoms are temporary and reversible

- MMSE=mini-mental status exam; ICU=intensive are unit; NPO=nothing by mouth (nil per os); q4h=every 4 hours.
- 1. Lee DW, et al. *Blood*. 2014;124(2):188-195. 2. Neelapu et al. *Nature Review Clin Oncol*. 2017 [Epub ahead of print] 3. Brudno et al. *Blood*. 2016

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Other Complications of CAR-T Cells

- B Cell aplasia
  - Immunoglobulin replacement required to keep Ig > 500
- Long term cytopenias
- Encephalopathy
  - Unclear pathogenesis
  - Self limiting
  - No long term complications
  - CAR T cells in CSF in all patients

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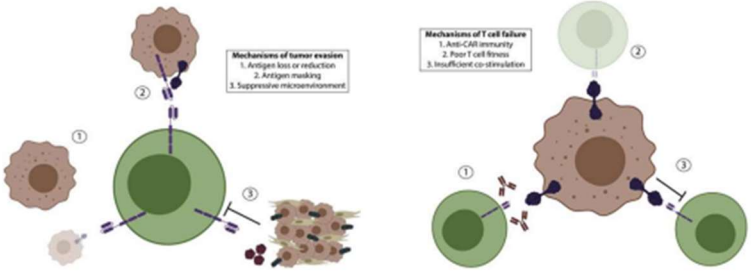
Why Doesn't CAR T-Cell Therapy Always Work?

- Leukemia relapse after CAR T-cells could be classified into 2 distinct types:
  - Loss of the CD19 target antigen on the surface of leukemia cells
  - Loss of CD19 CAR T-cells in blood (short persistence)



1. Grupp et al NEJM 2013; 2. Sotillo E, et al. *Cancer Discov*. 2015; 3. Jacoby E, et al. Nat Commun. 2016; 4. Turtle et al. JCI 2016
5. Nathan Singh N et al. Seminars in Cancer Biology, Volume 65,2020, Pages 91-98

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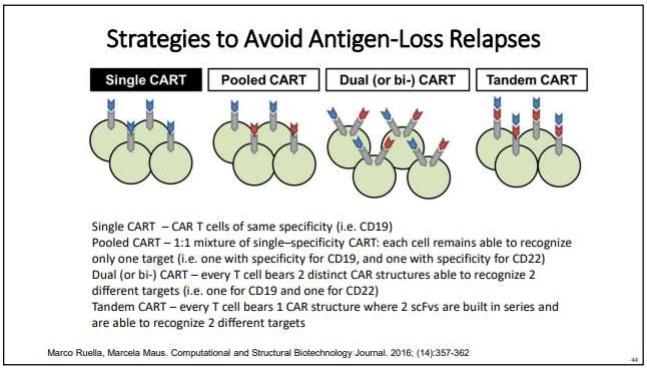
What is the future of CARTs?



Strategies to overcome relapse after CART therapy by using new types of CART

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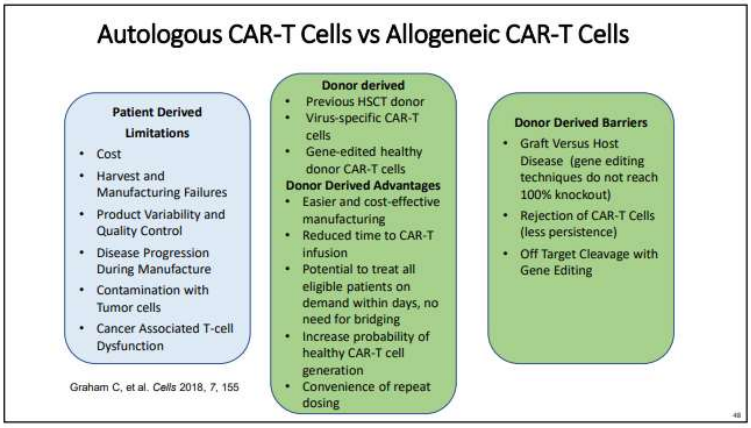

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Currently there are over 400 clinical trials with CARTs in the United States

- Lung Cancer
- Breast Cancer
- Osteosarcoma
- Ovarian Cancer
- Hepatocellular Cancer
- Glioblastoma
- AML
- Melanoma
- HIV
- Pemphigus
- Myasthenia Gravis
- Lupus
- Neuromyelitis optica
- Systemic sclerosis
- Sjogren's syndrome

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Who should be referred for commercial CAR T-cell therapy?

- FDA label very broad:
  - Relapsed/refractory HGBL, DLBCL, PMBL (axi-cel only) or tFL after 2 lines of systemic therapy
  - No primary CNS lymphoma
  - No upper age limit
  - No evidence that tumor must demonstrate CD19+
- Real world studies suggest that expansion beyond clinical trial criteria preserves efficacy without an increase in toxicity
  - Eligibility criteria will be center dependent
- Special considerations:
  - Can the patient wait: tumor burden and/or potential for organ function compromise
  - Performance status
  - Risk of bleeding
  - Cardiac, renal and/or pulmonary reserve
  - Prior history or current CNS involvement
  - History of autoimmune disease or neurologic conditions
- Timing matters! Best to refer at the time of relapse, before salvage chemotherapy

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Post-CAR T-cell Therapy Management and Concerns

- Patients remain within 2 hours of treating center for 4 weeks, and abstain from driving for 8 weeks, following CAR T-cell infusion due to a low risk of recurrent CRS and/or NT
- After this, patients should be monitored for:
  - Prolonged cytopenias – transfusions as indicated, G-CSF as needed for neutropenia
  - B cell aplasia (IgG levels) – replete with IVIg for levels <400
  - Relapse
  - Secondary malignancies
- Antibiotic (herpes virus and PJP) prophylaxis
  - Variable practices; we continue for at least 6m, at which time we measure the CD4 count and discontinue only if the CD4 count is >200
- Upon relapse, patients should be biopsied
  - Immunomodulatory therapies have had success in salvaging CAR T-cell relapses; can check for PDL1 on the tumor
  - Repeat CAR T-cell infusions have had limited testing in lymphoma and it is unclear if there is any role in this population

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Summary

CAR T cell Therapy leads to durable remissions in a large proportion of patients

Use of anti-CD19 CAR T-cells in the commercial/real world setting yields similar rates of response and toxicity as those who were reported on clinical trials

New indication for earlier steroid use to prevent severe CRS and NT shows no effect on RR

CD19 CART now FDA approved for Mantle Cell Lymphoma, Follicular Lymphoma, Adult ALL

BCMA CART approved for Multiple Myeloma

Clinical trials evaluating the use of CAR T-cells alone or in combination with other agents, in other malignancies, and versus standard of care therapies are ongoing

Allogeneic CAR T-cell therapy may overcome barriers to current FDA approved product

Timing of CART not yet well established

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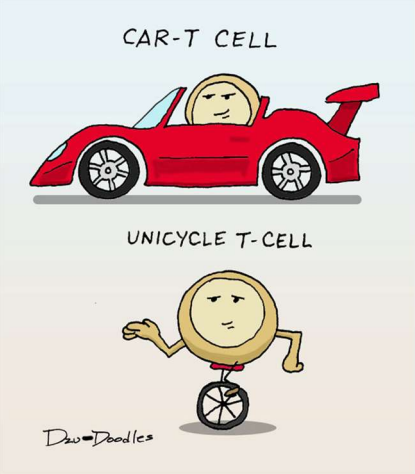
Thank You!



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ASK A QUESTION

CAR T-CELL THERAPY AND BLOOD CANCERS

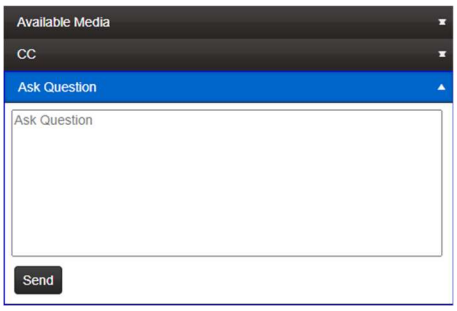
Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

Ask a question by web:

Click "Ask a question"
Type your question
Click "Submit"



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LLS EDUCATION & SUPPORT RESOURCES

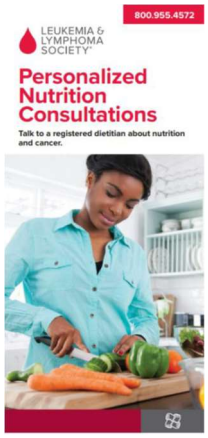
HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET
Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET
Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER

Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation



NUTRITION CONSULTATIONS

Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLS.org/Consult.

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LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit www.LLS.org/Chat

Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit www.LLS.org/EducationVideos

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org

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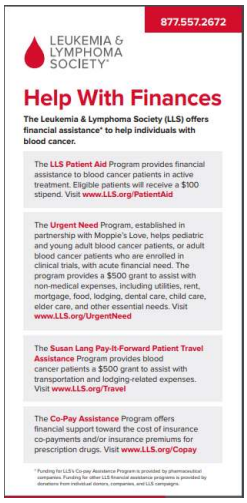
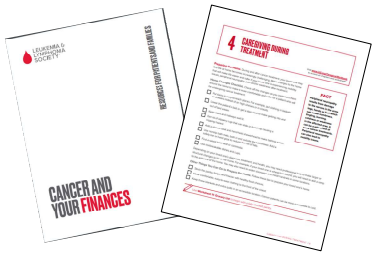


The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: **www.LLS.org/Finances**



To order free materials: **www.LLS.org/Booklets**

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