

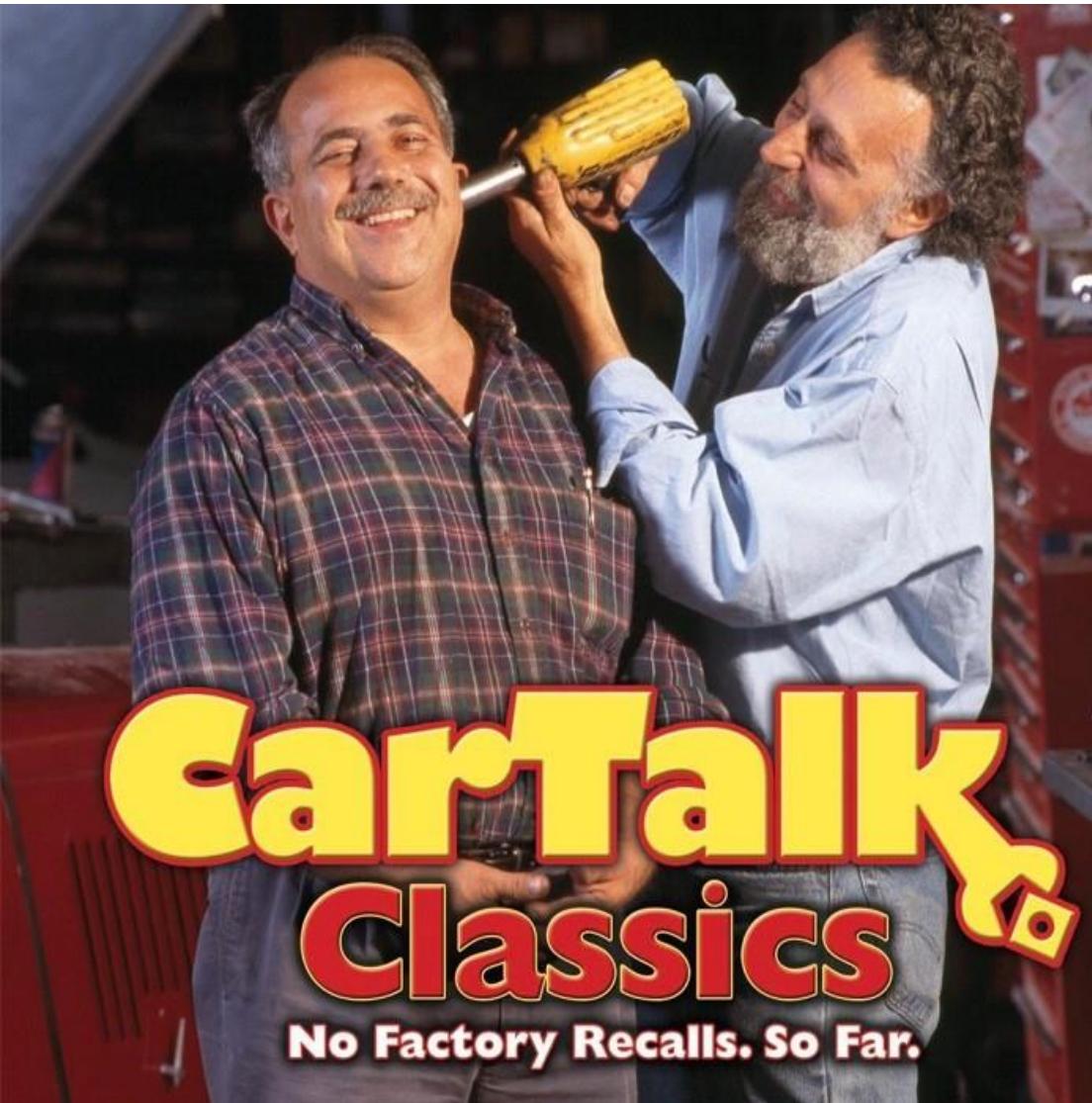
# “CAR Talk”

*Chimeric Antigen Receptor (CAR) T-Cell Therapy  
Driving Progress In The Fight Against Cancer*



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# Car Talk - NPR Classic Show



-Tom and Ray Magliozzi (aka “Click and Clack, the Tappet Brothers”)

-Two self-proclaimed “MIT nerds” who abandoned engineering careers to focus on their “fix it yourself” garage business.....

-Later appeared on a local radio program, and became nationally known as NPR hosts, featured every Saturday morning (for over 30 years, ending in 2018)

-Many loyal followers loved their mixture of wit, corny humor and expert automotive advice

-They ended each episode with the comment, *“well now you’ve wasted an otherwise perfectly good hour listening to Car Talk”*

*I hope to put this hour to good use....*

*....and I have no financial disclosures or  
other conflicts of interest*

# Objectives

- Understand the rationale for and components of CAR T-Cell Therapy
- Summarize the two major complications of CAR T-Cell Therapy and their appropriate management
- Appreciate the potential mechanisms underlying failure of CAR T-Cell Therapy

# Outline

- **Background**

- Evolution of (T-Cell) Immunotherapy*

- Rationale for a more “tumor-specific” approach*

- **CAR T-Cell Therapy**

- Basics, Specific Steps and Overview*

- Diagnosis and Management of Toxicities*

- Clinical Trials Review and Outcomes*

- When CARs Stall → Pot'l Barriers/Pitfalls*

- **Initiating CAR T at a Cancer/Tertiary Care Center**

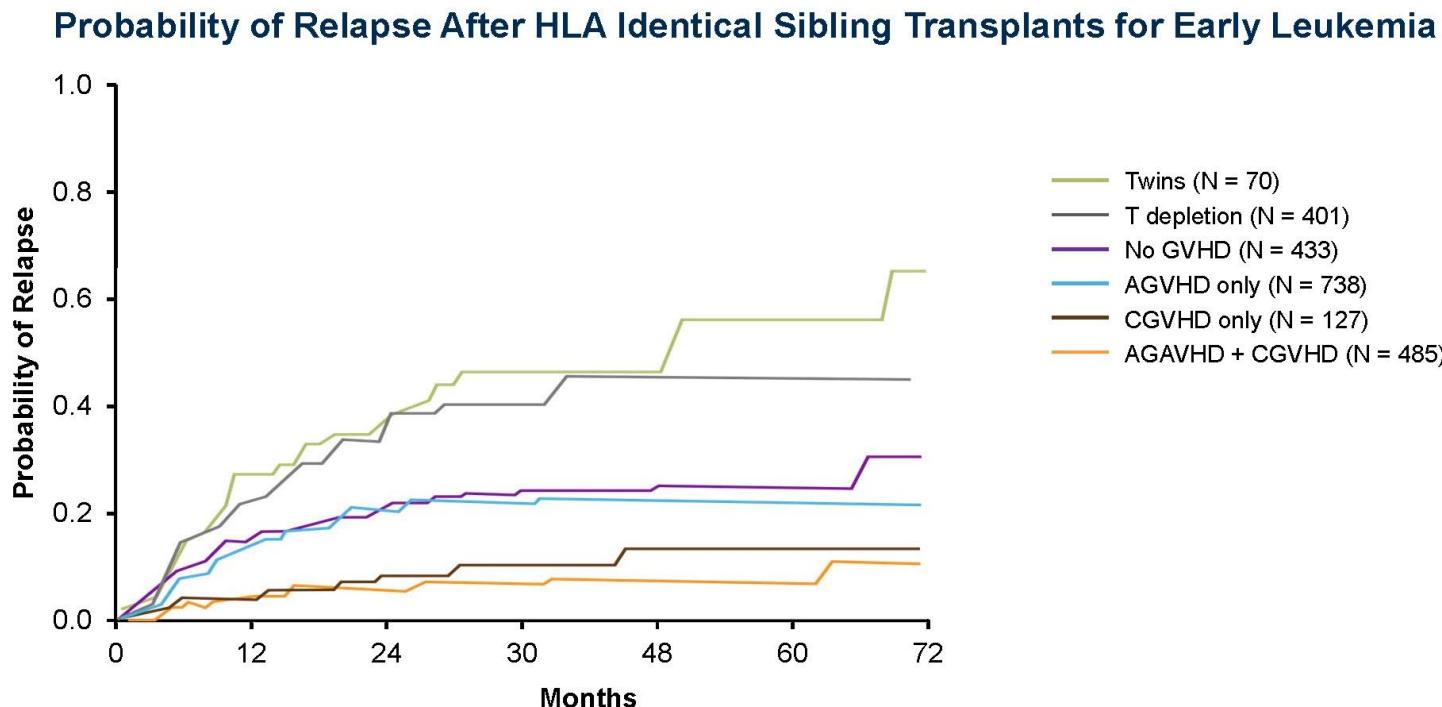
- **Future Considerations**

# Background

## ***Evolution of T-Cell Immunotherapy***

- Autologous vs Allogeneic HSCT – 2 distinct therapies
  - Auto** – High-dose chemotherapy with stem cell rescue ->
    - “*chemo does the work*” (*if chemo-sensitive disease*)
  - Allo** - Conditioning to minimize risk for graft rejection ->
    - once engrafted, the “donor T cells do the work”*
- **Adoptive Immunotherapeutic benefit** of donor T-cells
- Combines chemotherapy and immunotherapy
- Appreciation for GvT effect as ***curative*** component
- **Efficacy of donor lymphocyte infusions (DLI) provided rationale for T-cell therapy**

# Evidence of Graft-vs-Tumor Effect Supporting Allogeneic HSCT



Source: Bunn HF, Aster JC. Pathophysiology of Blood Disorders.  
www.accessmedicine.com.

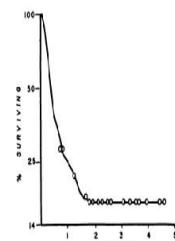


# Timeline of Advances in Immunotherapy

## Allogeneic BMT

### One Hundred Patients With Acute Leukemia Treated by Chemotherapy, Total Body Irradiation, and Allogeneic Marrow Transplantation

By E. Donnall Thomas, C. Dean Buckner, Meera Banaji, Reginald A. Clift, Alexander Fefer, Nancy Flournoy, Brian W. Goedell, Robert O. Hickmon, Kenneth G. Lerner, Paul E. Neiman, George E. Sole, Jean E. Sanders, Jack Singer, Mary Stevens, Rainer Storb, and Paul L. Weiden



## Donor Lymphocyte Infusions

### Donor Leukocyte Infusions in 140 Patients With Relapsed Malignancy After Allogeneic Bone Marrow Transplantation

By Robert H. Collins, Jr., Ofer Shpilberg, William R. Dobyski, David L. Porter, Sergio Giralt, Richard Champlin, Stacey A. Goodman, Steven N. Wolff, Wendy Hu, Catherine Verfaillie, Alan List, William Dalton, Nadine Ognoskie, Angela Chetrit, Joseph H. Antin, and John Nemunaitis

#### RAPID COMMUNICATION

### Donor Leukocyte Transfusions for Treatment of Recurrent Chronic Myelogenous Leukemia in Marrow Transplant Patients

By H.J. Kob, J. Mittelmüller, Ch. Clemm, E. Hofer, G. Ledderose, G. Brehm, M. Hein, and W. Wimanns

## Autologous BMT

1950

1960

1970

INF- $\alpha$

## Tumor Infiltrating Lymphocytes

## Rituximab (Anti-CD20)

## Sipuleucel-T

## Brentuximab Vedotin (Anti-CD30)

## Blinatumomab

## CAR T Therapies

## Checkpoint Inhibitors

*Tumor Specificity Increases Over Time*



# Background

## Rationale for CAR T-Cell Therapy

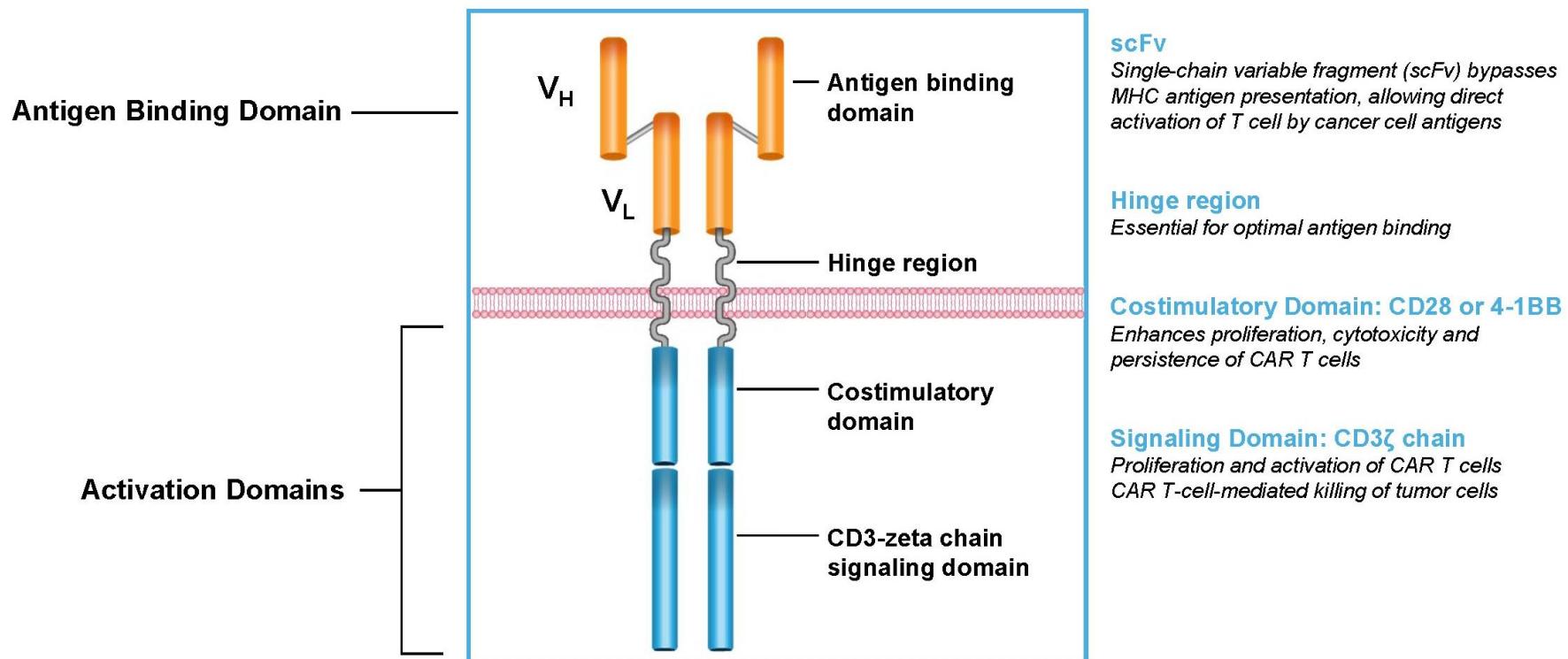
- *Despite our ability to treat leukemia, lymphoma and other cancers, sometimes to the point of extended relapse-free survival, these diseases often gain resistance to chemotherapy*
- *Thus, the need has arisen for novel therapies, including T-Cell Immunotherapy to directly target cancer cells*
- *CAR T-Cell Therapy -> designed to target a unique antigen (epitope) on a cancer cell*

# What Is CAR T-Cell Therapy?

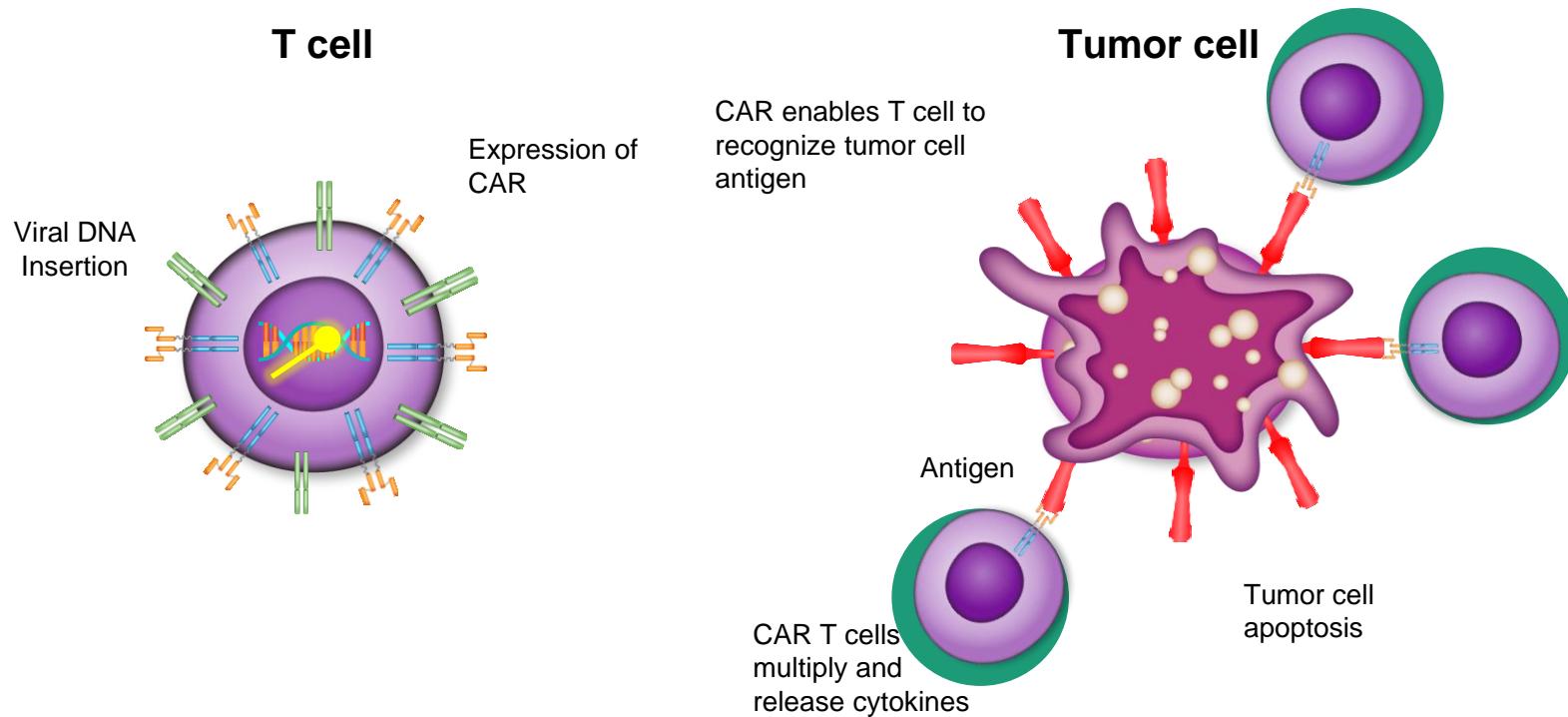
## Chimeric Antigen Receptor (CAR) T Cells

- ***Genetically modified T cells*** designed to recognize a specific tumor antigen (eg, CD19 on B-cell NHL or B-ALL)
- ***Autologous*** T cells -> collected, modified in the lab, then re-infused back into the patient to attack cancer cells
- CAR T cells are considered “***a living drug***” since they are meant to persist indefinitely (with cont’d anti-CA benefit)
- This therapy has led to complete and ***durable remissions*** for many patients with previously resistant disease
- **FDA approved:** ***Yescarta*** and ***Kymriah*** – Two CAR T products being initiated with DHMC’s CAR T-Cell Program

# Chimeric Antigen Receptors



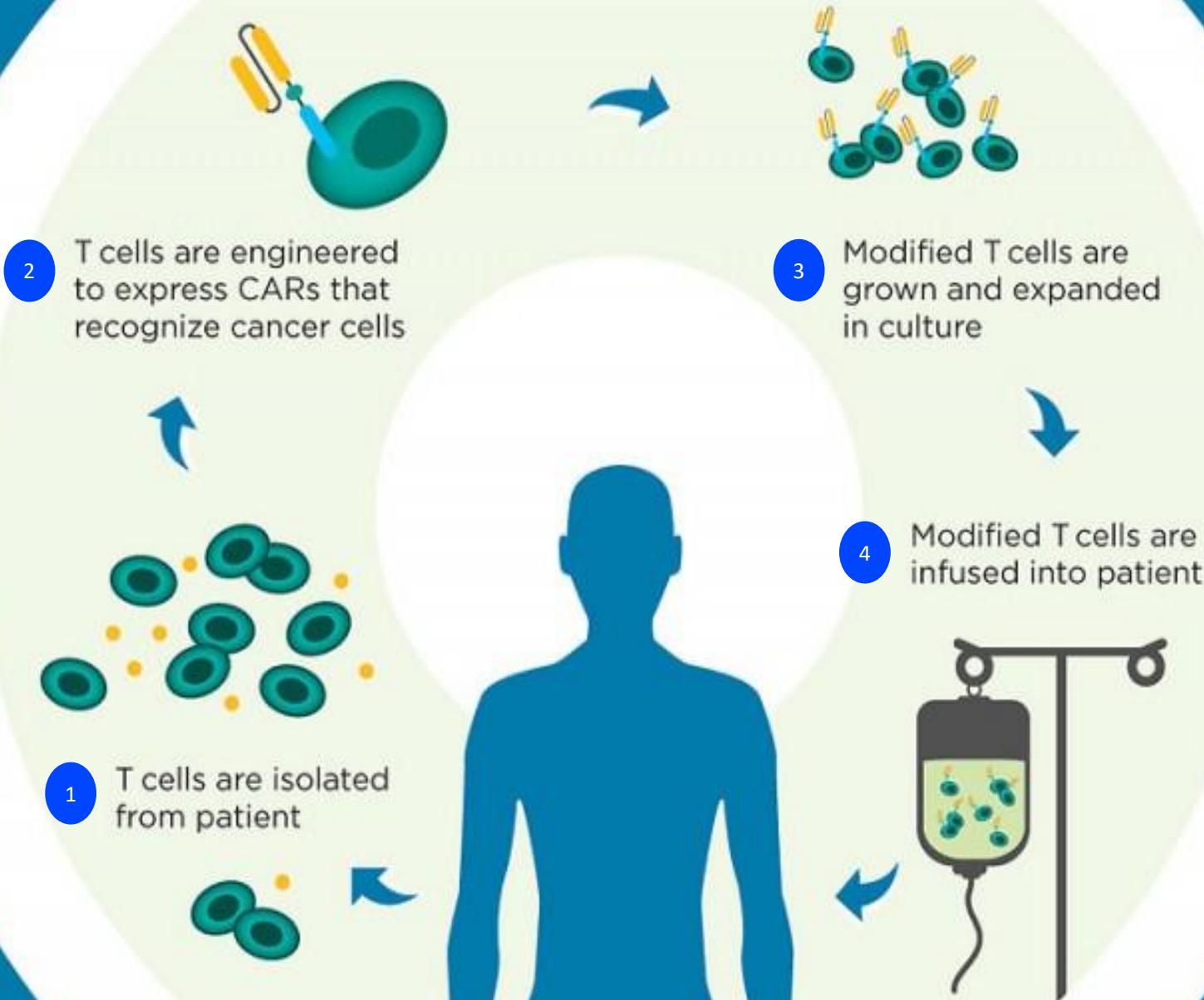
# CAR T-Cells: Mechanism of Action



# Summary of CAR T-Cell Therapy

1. Leukapheresis to procure patient's T-cells
2. Genetic modification (transduction)
3. Ex-vivo expansion
- \**17-21 day turnaround time for CAR T-cell delivery*
4. Consideration for “bridging” chemotherapy
5. Lymphodepletion chemotherapy (Flu/Cy)
6. Re-infusion of genetically modified CAR T-cells
7. Patient monitoring and supportive care for post-infusional CAR T related toxicities [eg, Cytokine Release Syndrome (CRS) and Neurotoxicity (ICANS)]

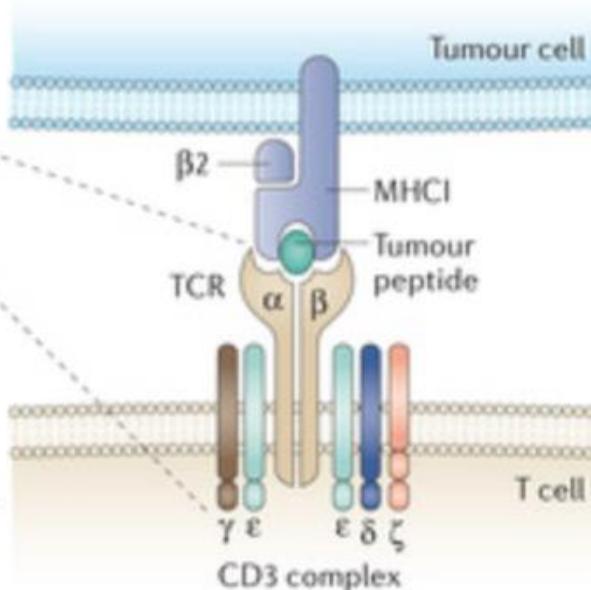
# Overview of CAR T-Cell Therapy



# Chimeric Antigen Receptors (CAR) Greatly Simplify the Activation of T-Cells so They Can Kill Cancer Cells

Normal T-Cell Receptor (TCR)

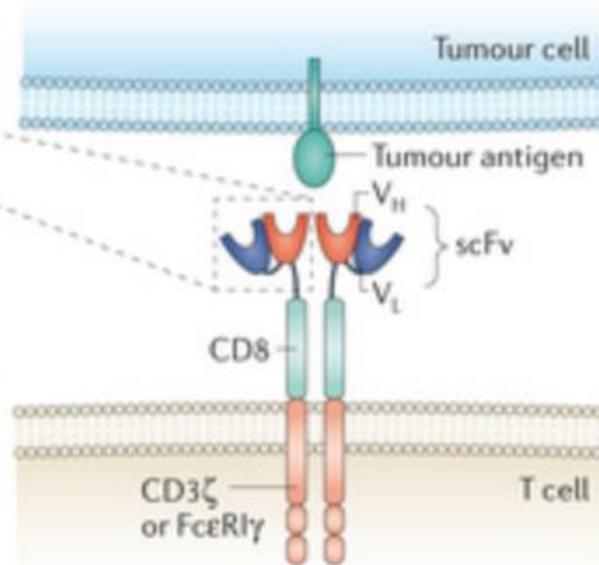
a  
T cell  
Tumour-specific T cell either naturally occurring or from a transgenic mouse



T-Cell Activation

Chimeric Antigen Receptor (CAR)

b  
B cell  
Tumour-specific antibody from B cells



Nature Reviews | Cancer

T-Cell Activation

# Advantages of CAR T-Cell Therapy

- Infused at a single point in time
- *Living therapy*, since CAR T cells continue to multiply in the patient's body
- MHC-indep't Ag recognition (so universal appl'n)
- Active for both CD4+ and CD8+ T cells
- Rapid generation of tumor specific T cells
- Capable of rapid proliferation and persistence
- Minimal risk for graft-versus-host disease (GVHD)

# Index Patient: *Emily*

**Age 5**

-Diagnosed with Acute Lymphoblastic Leukemia (ALL)

-Told by one provider “you have the *good* type of ALL”

-Treated with conventional ALL induction therapy

-Successful attainment of remission



# Index Patient: *Emily*

**Age 7**

- Relapsed and failed ALL salvage treatments
- NOT a candidate for allogeneic stem cell transplant
- Out of standard options:  
Hospice planned
- However, a new protocol was starting: CAR T-cell therapy (she would be the first patient)
- In April 2012, Emily became the first pediatric patient in the world to receive CAR T-cell therapy

(CHOP: Children's Hospital of Philadelphia)



# Complications of CAR T-Cell Therapy

- Acute infusional toxicity – rare, but reported
- Constitutional symptoms
- Tumor lysis syndrome – variable, dep on tumor burden
- **Cytokine Release Syndrome (CRS)\***
  - Often needing mgt by expert multidisciplinary team
  - May require ICU transfer for pressors + ventilatory support
- Cardio-Pulmonary / Renal
- GI-Hepatic / Musculo-skeletal
- Cytopenias / Infection / **Neurologic**
- Macrophage activation syndrome (MAS) or HLH (severe form)
- **Neurologic toxicity\***
  - CRES (*CAR T Encephalopathy Syndrome*) or
  - ICANS (*Immune Effector Cell Associated Encephalopathy Syndrome*)
- B-cell aplasia and Hypogammaglobulinemia / Infection

*\*Acute, life-threatening, yet generally manageable (resolved by day +30)*

# CRS: Clinical Signs and Symptoms

- Malaise, headache; ***post-infusion fever (hallmark)***
- ***Hypoxia***
- ***Hypotension / Sepsis / Capillary Leak Syndrome***
- Azotemia
- Transaminitis, hyperbilirubinemia
- Coagulopathy; HLH/MAS
- ***Neurologic / MOSF***
- ***An acute inflammatory disorder driven by CKs (IL-6)***
- ***Median time to onset: 2-3 days; med dur'n: 7 days***
- ***Tocilizumab (IL-6Ri) = mainstay of therapy***
- ***Alternative agent: Siltuximab (anti-IL-6 Mo.Ab)***
- ***Declining serum IL-6 and CRP indicate improvement***

Organ System	CRS - Symptoms and Findings
Constitutional	Fever + / – rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
Gastro-intestinal 	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia + / – bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	<b>Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, altered gait, seizures</b>

Lee DW, et al. *Blood*. 2014;124(2):188-195.

# CRS Grading Assessment: Summary

<i>CRS Parameter</i>	Grade 1	Grade 2	Grade 3	Grade 4
<i>Fever*</i>	$\geq 38^{\circ}\text{C}$	$\geq 38^{\circ}\text{C}$	$\geq 38^{\circ}\text{C}$	$\geq 38^{\circ}\text{C}$
<b>WITH</b>				
<i>Hypotension</i>	<b>None</b>	<b>Not requiring vasopressors</b>	<b>Requiring a vasopressor with or without vasopressin</b>	<b>Requiring multiple vasopressors (excluding vasopressin)</b>
<b>AND/OR**</b>				
<i>Hypoxia</i>	<b>None</b>	<b>Requiring low-flow nasal cannula*** or blow-by</b>	<b>Requiring high-flow nasal cannula***, facemask, nonrebreather mask, or Venturi mask</b>	<b>Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)</b>

\*Fever is defined as temperature  $\geq 38^{\circ}\text{C}$  not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

\*\*CRS grade is determined by the most severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of  $39.5^{\circ}\text{C}$ , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

\*\*\* Low-flow nasal cannula is defined as oxygen delivered at  $\leq 6\text{L}/\text{minute}$ . Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at  $>6\text{L}/\text{minute}$ .

# Index Patient: Emily

- Relapsed/refractory ALL
- Undergoing CAR T-cell therapy
- Received CAR T-cell infusion
- Developed grade 4 CRS
- High fevers, multiple pressors, on ventilatory support in ICU
- Her CAR T providers appealed to Pharmacy/Rheumatology Staff for Tocilizumab *off-label* use. She was given one dose and *within hours she was recovering from the CRS!*
- But, still a long course ahead....



# CRS Management

- Management of CRS is **based on clinical parameters**, not laboratory values
  - Ferritin, CRP, serum cytokines should only be used to support the diagnosis
- CRS can be fairly well managed with **high level of clinical surveillance, fluids, O<sub>2</sub> and vasopressors**
  - CRS requires continuous monitoring, often in an ICU setting
- The IL-6 receptor antibody **Tocilizumab** is the **consensus first line treatment for CRS**
  - For Grade  $\geq 2$  CRS or persistent Grade 1 (refractory fever or recurrent >3d):  
**Tocilizumab 8mg/kg IV for up to 3 doses in a 24h period (max 4 doses total)**
- **Second line treatment** for CRS varies by protocol and / or institutional guidelines
  - **Steroids** effective, but lymphotoxic: Dex 10-20 mg IV q6h or M-pred 1g IV qd
  - The IL-6 antibody **Siltuximab** (under investigation): 11 mg/kg IV once (q3 wks)

# CRS Management: Monitoring and Supportive Care

## **Close hemodynamic monitoring is imperative**

- Vital signs should be checked every 2 to 4 hours
- CBC with differential and comprehensive metabolic panel should be drawn twice daily
- Monitor CRP daily
- Monitor uric acid, lactate and ferritin

## **Full infectious work-up and rapid implementation of anti-infective agents upon first signs of fever**

- Fever should be managed with acetaminophen; avoid corticosteroids or NSAIDs
- If a patient is neutropenic and febrile, blood cultures should be drawn, and broad spectrum antibiotic therapy should be initiated
- Infectious diagnoses should be aggressively pursued by imaging and cultures to avoid missing infections concurrent with CRS

## **Hypotension must be recognized early and managed aggressively**

Keep MAP>65 and always consider another IVF bolus a liter at a time

Patients with hypotension that is not fluid responsive should receive vasopressors and be evaluated for cardiomyopathy by echo

## **CRS requires close cardiac monitoring and ICU notification**

Cardiac events have been associated with CRS including myocardial ischemia and death

Patients with CRS should be monitored with ECGs and echocardiograms

Tachycardia is common in the setting of CRS and medications to slow sinus tachycardia should be avoided

## **Cytopenias should be managed with transfusion support**

## **Growth factors are controversial (may exacerbate CRS)**

# Neurotoxicity (ICANS): Clinical Signs/Symptoms

- Diminished attention (*often insidious onset*)
- Impaired handwriting
- Bradyphrenia, confusion
- Language disturbance / dysphasia -> aphasia
- Agitation, tremors
- Seizures / incontinence (-> *status epilepticus*)
- Somnolence / Stupor
- ***Cerebral edema*** -> coma -> death
- ***Median time to onset: 4d / med. duration: 17d***
- ***May be precipitated by Tocilizumab (under debate)***  
-leads to increase in unbound IL-6 (including CNS)
- ***IV Steroids: mainstay of therapy (Dex or M-pred)***
- ***Anakinra (IL-1R antagonist) – under investigation***

## Encephalopathy Assessment Tools for Grading of ICANS/CRES

ICE (Currently used at DHMC)	Points
Orientation: orientation to year, month, city, hospital	4
Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points	3
Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1
Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle")	1
Attention: ability to count backwards from 100 by 10	1

### Grading of ICANS with ICE Grading Scale

*ICANS = Immune Effector Cell Associated Encephalopathy Syndrome*

*ICE=Immune Effector Cell Encephalopathy*

GRADE	TOTAL SCORE
No impairment	10
Grade 1	7-9
Grade 2	3-6
Grade 3	0-2
Grade 4	0 due to patient unarousable and unable to perform ICE assessment

# ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is <b>unarousable</b> and unable to perform ICE)
Depressed level of consciousness §	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. <b>Stupor or coma.</b>
Seizure	N/A	N/A	Any clinical <b>seizure</b> focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening <b>prolonged seizure</b> (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings ‡	N/A	N/A	N/A	Deep focal motor weakness such as <b>hemiparesis or paraparesis</b>
Elevated ICP/cerebral edema	N/A	N/A	Focal/local <b>cerebral edema</b> on neuroimaging †	Diffuse <b>cerebral edema</b> on neuroimaging; <b>decerebrate or decorticate posturing</b> ; or <b>cranial nerve VI palsy</b> ; or <b>papilledema</b> ; or <b>Cushing's triad</b>

**ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.**

N/A indicates not applicable. / **Mainstay of therapy: STEROIDS -> Dex 10 mg IV q6h or M-Pred 1g daily**

\*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 will be classified as grade 4 ICANS if unarousable.

§ Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading. **CTCAE: Common Terminology Criteria for Adverse Events**

†Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

**Cushing's triad: Clinical triad of bradycardia, systolic HTN and slowed resp'ns (due to impaired brainstem function)**

# Yescarta (Axicabtagene Ciloleucel)

- A CD19-directed CAR made by Kite/Gilead
- The first FDA approved CAR T therapy for adults with R/R Lg B-Cell Lymphoma after >2 lines of systemic Rx
- Approval supported by data from the ZUMA-1 pivotal trial
- Background to ZUMA-1: *SCHOLAR-1 Study*
  - a retrospective, international multi-institutional study for patients with refractory Lg Cell Lymphoma (n=636)
  - demonstrated a very poor prognosis for this pt subset
  - ORR: 26% / CR rate: 7% / Median OS: 6.3 months
  - results of SCHOLAR-1 study thus provide a benchmark for assessing the efficacy of new therapies in this high-risk patient population (R/R NHL); *Blood 2017;130: 1800*

# Axicabtagene Ciloleucel (**Yescarta**) CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma: **ZUMA-1 Trial**

**Neelapu, et al. NEJM 2017; 377: 2531**

- A multi-center, single-arm, phase 2 trial
- Pts with Diffuse Large B-cell Lymphoma + variants  
*-Transformed FL and Primary Mediastinal B-cell Lymphoma*
- Chemo-refractory disease (n=111)  
*-stable or progressive disease or relapse*
- Based on historical data, pts had limited options  
**(SCHOLAR-1 study: pts with refractory Lg BCL-> ORR 26% / CR 7%)**  
ZUMA-1 trial at a median follow up of 15.4 months:  
**ORR=89/108 (82%) / CR=63/108 (58%)**  
-2 treatment-related deaths (1 HLH; 1 cardiac arrest)

# Long-term F/U of ZUMA-1 Trial (Yescarta)

(Locke, et al. Lancet Oncology 2019; 20: 31)

## **Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma**

- Phase 2: 101 pts assessable at 27.1 months
- LD Cond: Flu 30 mg/m<sup>2</sup> + Cy 500 mg/m<sup>2</sup> (days -5,-4,-3)
- Yescarta target dose: 2x10e6/kg CAR T cells
- **Toxicities: Grade 3-4 CRS: 11%/Grade 3-4 ICANS: 32%**
- At 2y f/u, MS not yet reached + no new Rx-rel'd deaths
- **After 1 dose of CAR T -> 2y PFS: 39% / 2y OS: 51%**
- Pts in PR/CR at 90d -> likelihood of CR at 2y: 75%

# Tisagenlecleucel (Kymriah):

CD19-directed CAR made by Novartis

## Maude, et al. NEJM 2018; 378: 439 → ELIANA Trial

- Phase 2, single-cohort, 25 center, global study
- 75 pedi/young adult pts with CD19+ R/R B-cell ALL
- Overall 3 mo remission rate: 81% / MDR not reached
- **EFS/OS at 6, 12 mo -> 73/90% (6m), 50/76% (12m)**
- **Grade 3-4 CRS/ICANS: 77/40% (*no cerebral edema*)**
- **2 deaths** attributed to Kymriah: delirium, encephal'y
- Kymriah detected in pts up to 20m (c/w persistence)
- **FDA approved** for patients up to 25 yrs with B-cell precursor ALL that is refractory or in 2<sup>nd</sup>/later relapse

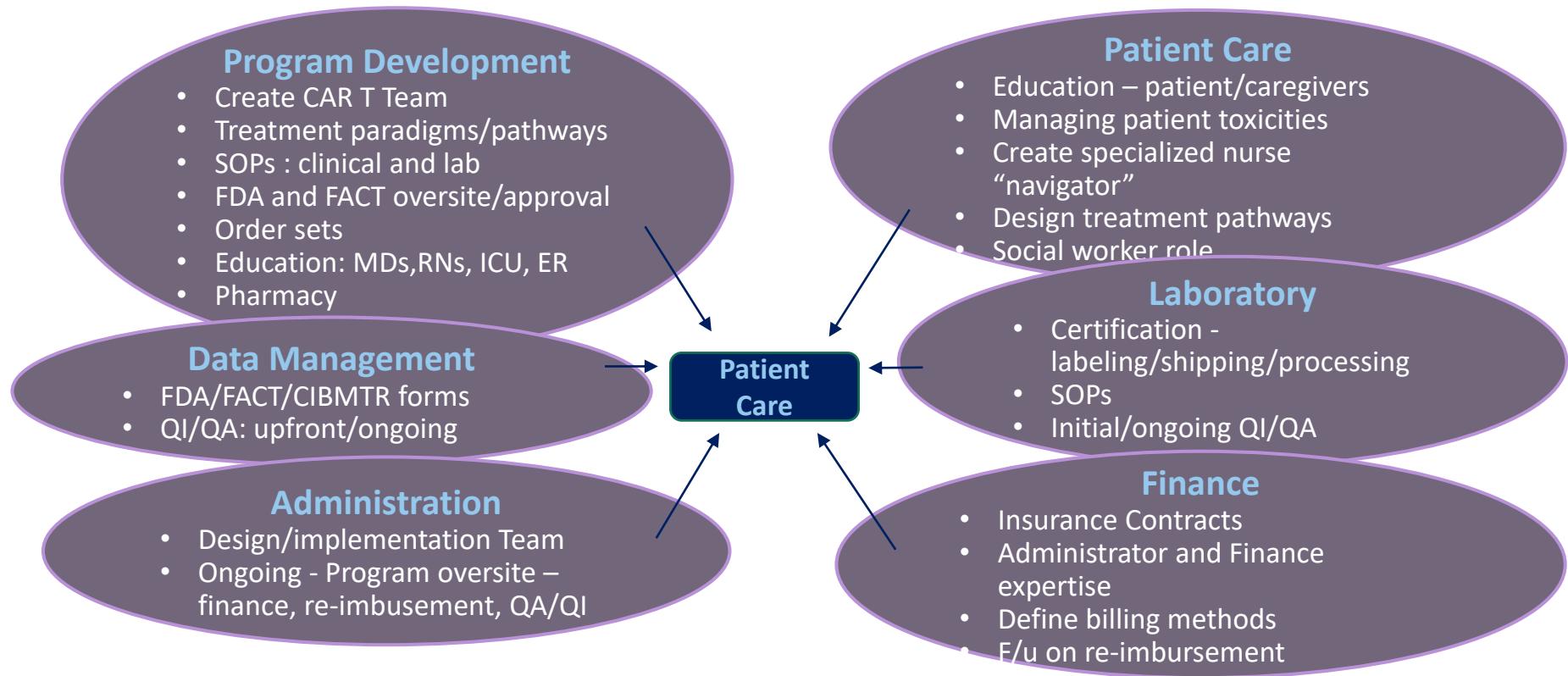
# Tisagenlecleucel (Kymriah):

CD19-directed CAR made by Novartis

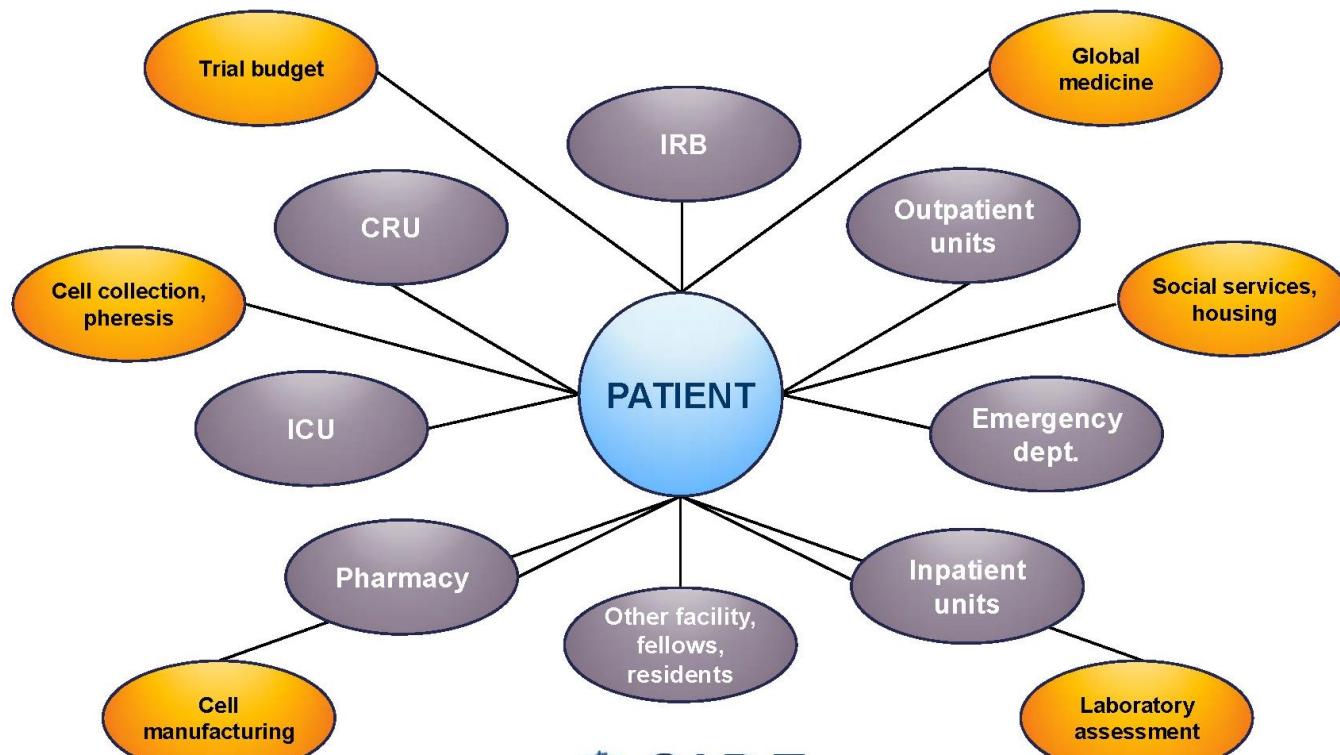
## Schuster, et al. NEJM 2019; 380: 45 → JULIET Trial

- International, phase 2 study – R/R DLBCL (n=93)
- **Overall RR: 52% -> 40% CRs / 12% PRs**
- **1 yr RFS: 65% (79% among pts with a CR)**
- **Grade 3-4 CRS: 22% / Neurologic: 12%**
- **No deaths attributed to Kymriah/CRS/cerebral edema**
- **FDA approved** for adult patients with R/R large B-cell lymphoma after  $\geq 2$  lines of systemic therapy
- ***Not indicated*** for treatment of patients with **Primary CNS lymphoma (PCNSL)**

# Initiating a CAR T Program at a Cancer Center Associated with a Tertiary Care Medical Center



# Best Practices: Ensure Crosstalk Between Clinical, Nursing, Financial, and Coordination Teams



# Implementation of CAR T at DHMC

**NCI-Designated Cancer Center / FACT Accredited BMT Program**

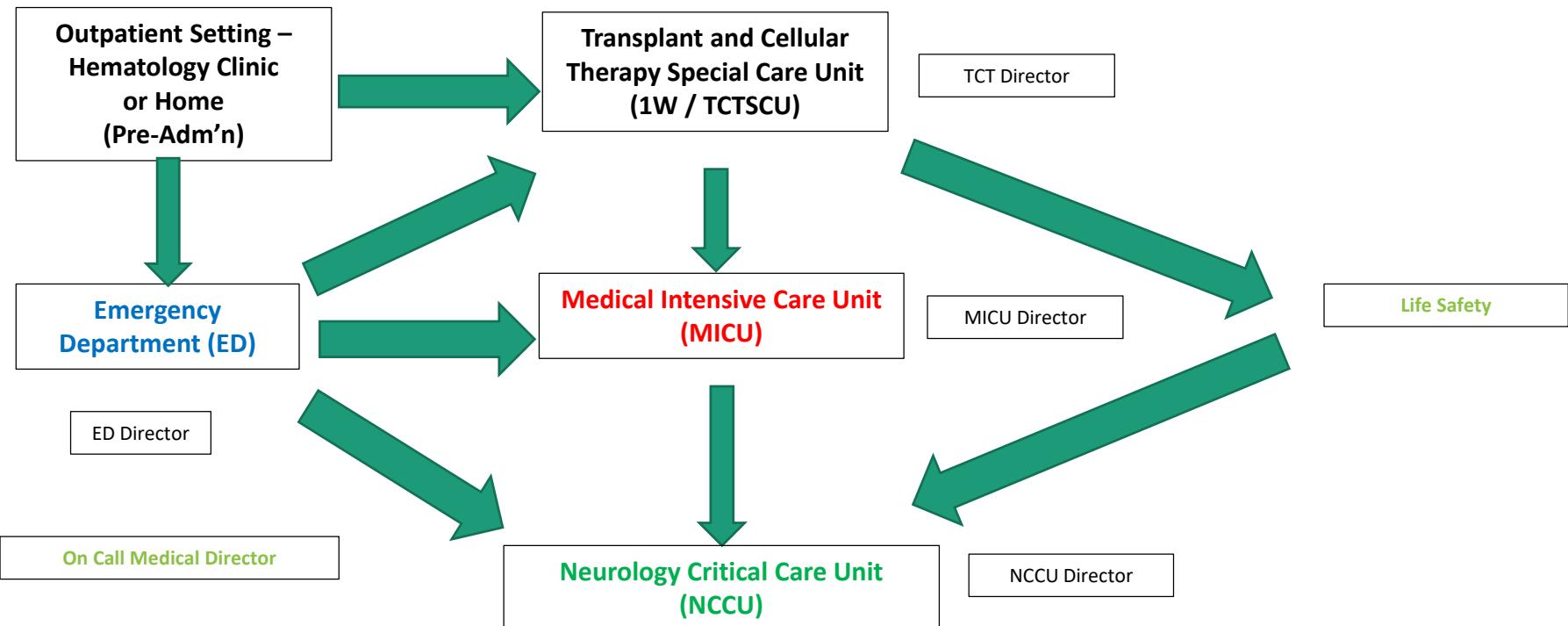
## Timeline

- Discussion with Senior Leadership, NCCC (2-3 years)
- Contract negotiations -> finalized (Novartis; Kite)
- Clinical Pathways, SOPs, Order Sets completed
- **Implementation of REMS Training / Knowledge Assess't**

### ***Risk Evaluation and Mitigation Strategy***

- In-depth review of CAR T-Cell Therapy standards – done with priority Sections within DHMC
- Compliance with drug dispensing guidelines, accurate documentation, adverse event reporting + audit readiness
- Mock drills of clinical cases with multi-disciplinary team
- **CAR T-Cell Therapy goal: 1-2 patients/month**

# DHMC CAR T-Cell Therapy: *Transfer Algorithm for Escalation of Patient Care*



# Why CARS Stall....

## Potential Barriers and Pitfalls

- Inadequate T-cell collection
- Failed CAR prod'n / *ex-vivo* expansion
- T-cell exhaustion or lack of persistence
- Antigen Escape (CD19 neg relapse)
- Failure of response (CD19+ relapse)
- Hypogammaglobulinemia (c/w B-cell loss)
- COST issues (400-500k per procedure)!!

# Newer CAR Models

- CAR T-cell therapy (BCMA) for Myeloma
- Bi-specific CARs (CD19, CD22) to prevent Antigen escape
- “Off-the-Shelf” CARs (*allogeneic*)
- Targeted CARs for solid tumors
- CAR NK Cell Therapy
- Next-generation CARs (eg, Armored CARs)
  - CAR T with constitutive production of CKs*
  - CAR T combined with checkpoint inhibitor*
- SEAKER cells: synth small molec.s (ON/OFF)

# Ongoing CAR Trials in Hematologic Malignancies

	Number of Clinical Trials			Targets Currently Being Investigated
	Total	Phase 1	Phase 2	
<b>Lymphoma</b>	105	89	44	
B-cell lymphoma	56	47	25	CD19, CD20, CD22, CD30
ALL	43	37	17	CD19, CD22, CD7
CLL	36	30	18	CD19, CD20, CD22
Non-Hodgkin lymphoma	67	58	29	CD19, CD30, CD22, CD20
DLBCL	24	20	14	CD19, CD20, CD22
MCL	16	14	11	CD19, CD20, CD22
FL	15	13	9	CD19, CD20, CD22
Burkitt lymphoma	14	13	5	CD19, CD20, CD22
Hodgkin lymphoma	11	9	3	CD19, CD30, NY-ESO
<b>Leukemia</b>	90	76		
B-cell leukemia	36	30	17	CD19, CD5, CD20, CD22, CD30, CD33, CD123, BCMA
AML	12	9	3	CD7, CD33, CD123
MM	13	11	4	CD19, BCMA, CD138, NY-ESO

# Ongoing CAR Trials in Solid Tumors

	No. of Clinical Trials	Targets Currently Being Investigated
Astrocytoma	7	HER2, EGFRvIII, IL13Ra2
Glioblastoma	7	HER2, EGFRvIII, IL13Ra2, NY-ESO
Breast	13	HER2, EpCAM, cMET, Mesothelin, ROR1, MUC1, CEA, CD70, CD133, NY-ESO
Colorectal	9	CEA, EGFR, MUC1, HER2, CD133,
HCC	11	Glycan-3 (GPC3), MUC1, EPCAM, NY-ESO
NSCLC	5	PD-L1, MUC1, ROR1, CEA, NY-ESO
Melanoma	3	cMET, GD2, CD70, NY-ESO
Mesothelioma	4	FAP, mesothelin
Neuroblastoma	8	GD2, CD171, NY-ESO
Ovarian	7	Mesothelin, CD70, HER2, CD133, CEA, NY-ESO
Pancreatic	13	Mesothelin, Prostate Stem Cell Antigen (PSCA), CD70, MUC1, HER2, CD133, NY-ESO
Stomach	8	EPCAM, CEA, MUC1, HER2, NY-ESO
Thoracic	5	MUC1, ROR1, PD-L1



# Index Patient: Emily Whitehead

## **Age 5**

-Diagnosed with  
Acute Lymphoblastic  
Leukemia (ALL)

## **Age 7**

-She relapsed and  
failed ALL available  
treatments

-In April 2012, at age 7,  
Emily became the first  
pediatric patient in the  
world to receive CAR T-  
cell therapy. (CHOP)

***Now 7 years in  
remission!!***



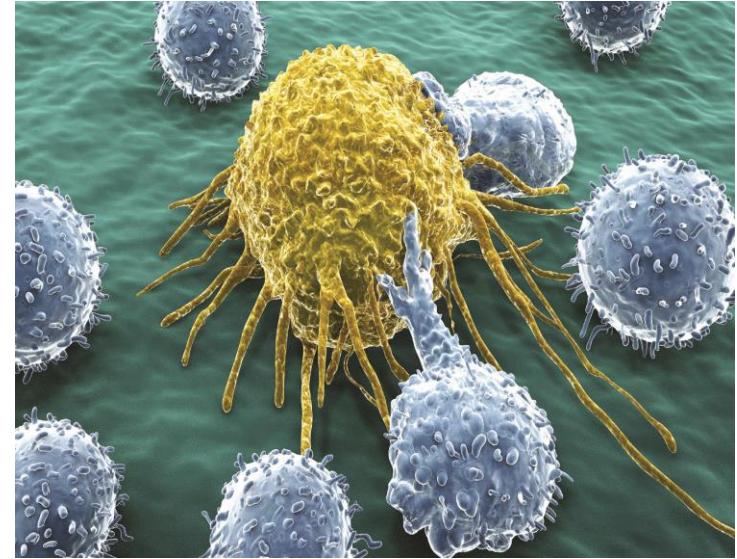
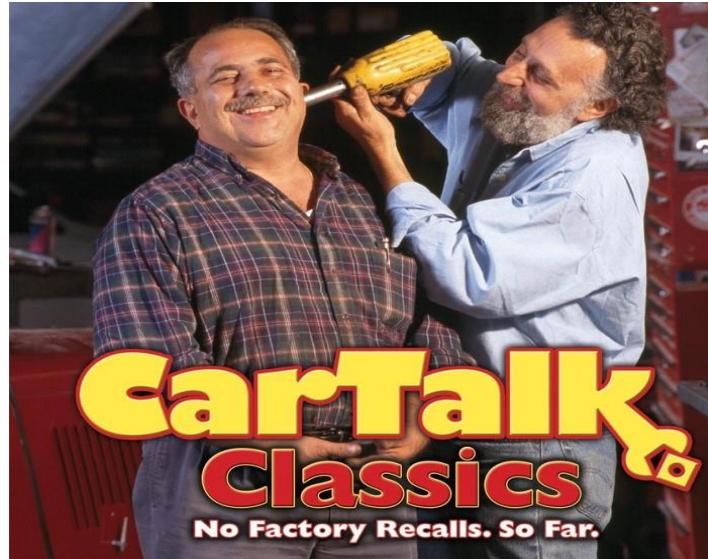
*"It is very inspiring to me  
to be 7 years cancer free  
and that my story is  
helping other patients  
from all over the world.  
Always remember to  
never give up and smile  
everyday!"*

Emily, Age 14  
May 2019

# Conclusions

- 1. CAR T-cell Therapy represents an innovative and promising adoptive immunotherapeutic modality for a select subset of cancer patients with resistant disease.***
- 2. While early data are encouraging, long-term follow-up efforts are needed to fully define and optimize benefit.***
- 3. A multi-disciplinary commitment is needed to successfully implement this complex and high-risk treatment at a cancer center associated with a major tertiary care medical center.***
- 4. Ongoing efforts to improve the efficacy, toxicity and financial support of this therapy will hopefully be realized in the next few years.***

*Well...now that you've wasted  
an otherwise perfectly good  
hour listening to my “CAR Talk”....*



*....I'll be glad to take Questions*