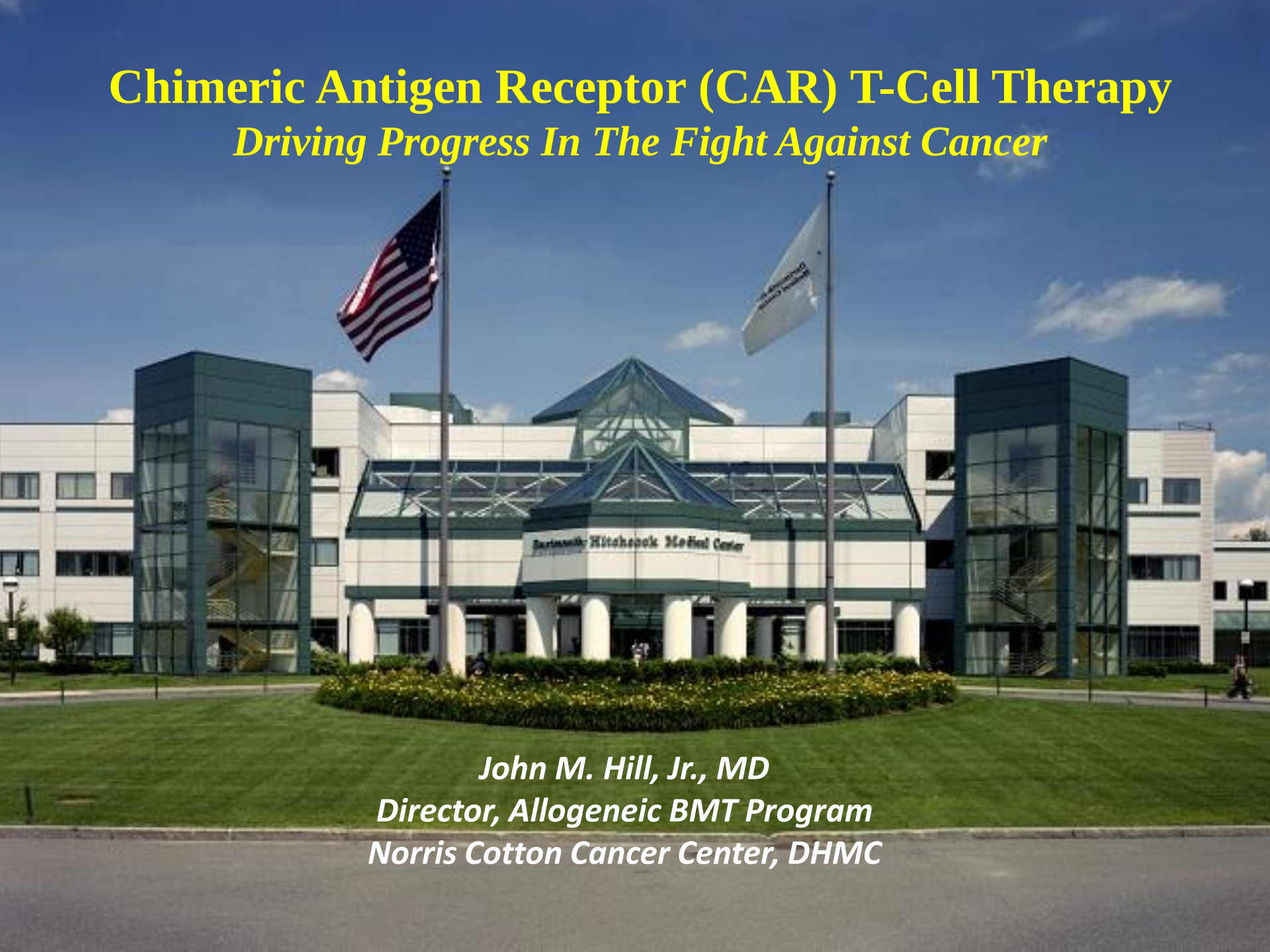
Chimeric Antigen Receptor (CAR) T-Cell Therapy

Driving Progress In The Fight Against Cancer



John M. Hill, Jr., MD
Director, Allogeneic BMT Program
Norris Cotton Cancer Center, DHMC

Objectives

- **Understand the rationale for and components of CAR T-Cell Therapy, and what factors constitute an appropriate candidate**

- **Recognize 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 (Cellular) 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**
- **Conclusion / Questions**

Index Patient: *Emily*

Age 5

-Diagnosed with Acute Lymphoblastic Leukemia (ALL)

-Treated with conventional ALL induction therapy

-Successful attainment of remission

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)

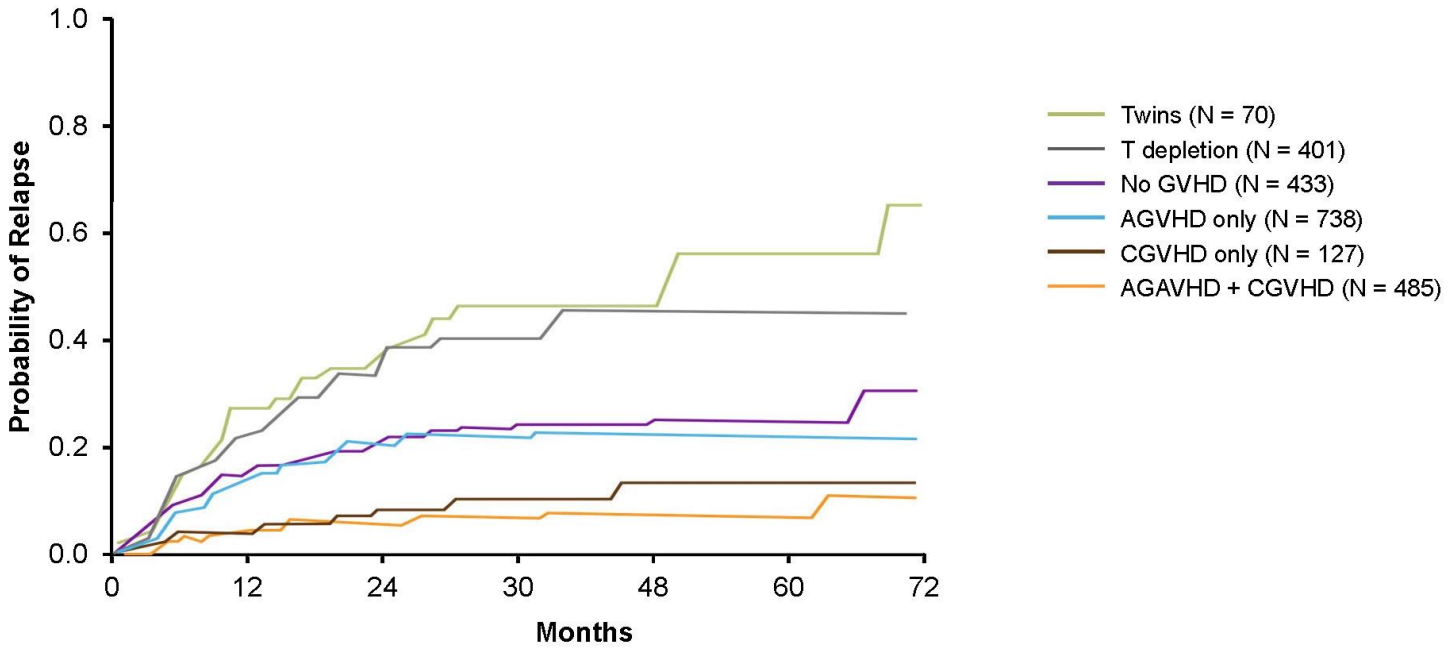
Allo - Conditioning to minimize risk for graft rejection ->

--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

Probability of Relapse After HLA Identical Sibling Transplants for Early Leukemia



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

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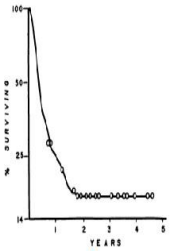
Timeline of Advances in Immunotherapy

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. Goodell, Robert O. Hickman, Kenneth G. Lerner, Paul E. Neiman, George E. Sale, 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. Drobyski, 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. Kolb, J. Mittermüller, Ch. Clemm, E. Holler, G. Ledderose, G. Brehm, M. Heim, and W. Wilmanns

Autologous BMT

Tumor Infiltrating Lymphocytes

INF-α

IL-2

Rituximab (Anti-CD20)

Sipuleucel-T

Brentuximab Vedotin (Anti-CD30)

Blinatumomab

CAR T Therapies

Checkpoint Inhibitors

1950 1960 1970 1980 1990 2000 2010 2015

Tumor Specificity Increases Over Time

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Background

Rationale for CAR T-Cell Therapy

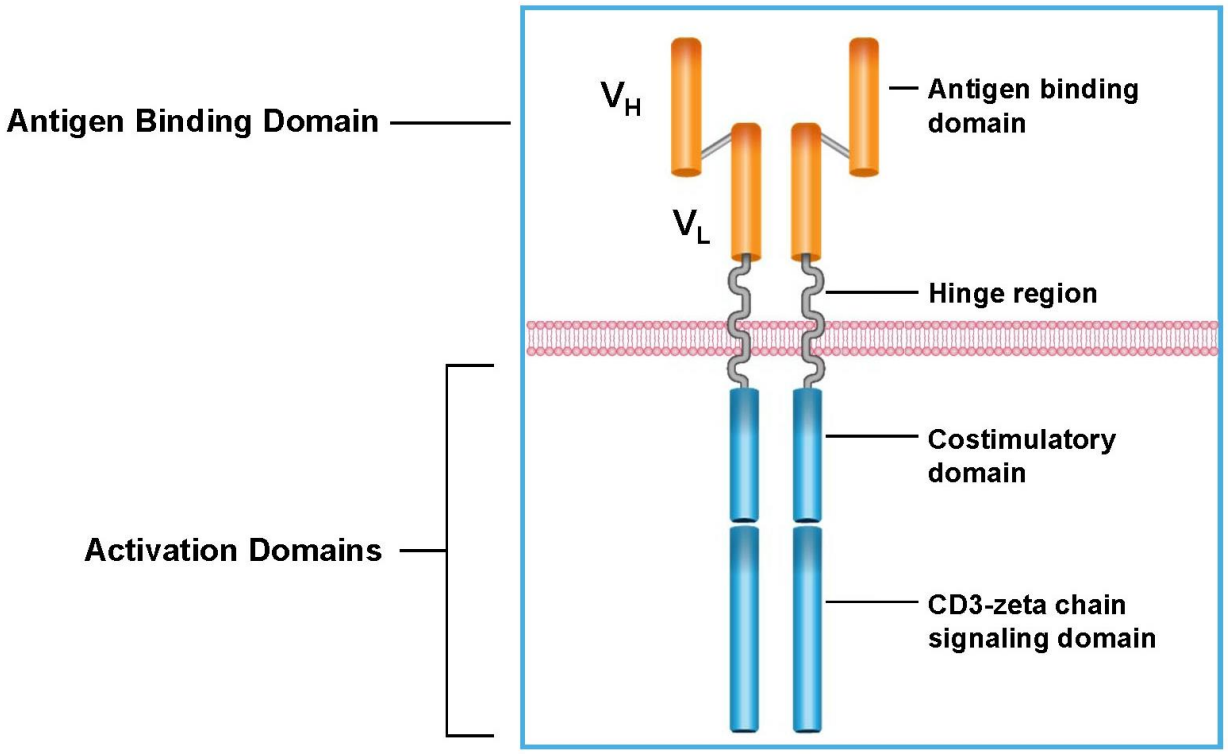
- *Despite our ability to treat leukemia, lymphoma and other **cancers**, sometimes to the point of extended relapse-free survival, these diseases **often gain resistance to chemotherapy***
- *Thus, the **need** has arisen **for novel therapies,** including **T-Cell Immunotherapy** to **directly target 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:** Five (5) CAR T products now being utilized for the treatment of R/R Lymphomas, B-cell ALL, Myeloma

Chimeric Antigen Receptors



scFv
Single-chain variable fragment (scFv) bypasses MHC antigen presentation, allowing direct activation of T cell by cancer cell antigens

Hinge region
Essential for optimal antigen binding

Costimulatory Domain: CD28 or 4-1BB
Enhances proliferation, cytotoxicity and persistence of CAR T cells

Signaling Domain: CD3ζ chain
Proliferation and activation of CAR T cells
CAR T-cell-mediated killing of tumor cells

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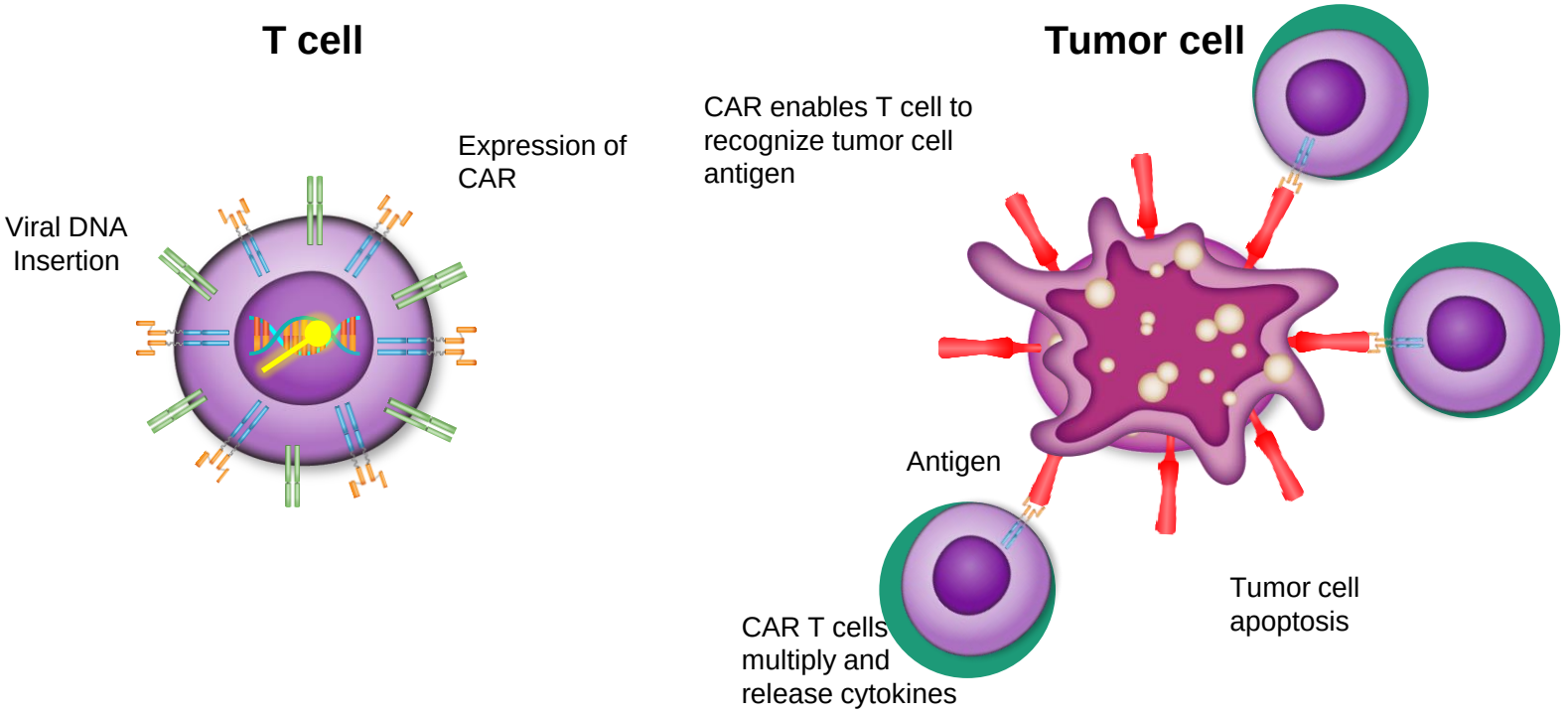
CAR T-Cells: Mechanism of Action



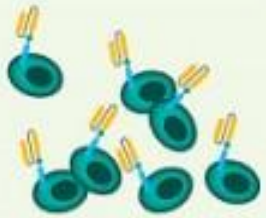
Summary of CAR T-Cell Therapy

1. Screening: R/R dz; fxn'l status; comorbidities; <75y; inf'n
2. Leukapheresis to procure patient's T-cells
3. Genetic modification (transduction) – in outside lab
4. Ex-vivo expansion (off site)

**17-21 day turnaround time for CAR T-cell delivery*

5. Consideration for "bridging" chemotherapy
6. Lymphodepletion chemotherapy (Flu/Cy)
7. Re-infusion of genetically modified CAR T-cells
8. 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



2 T cells are engineered to express CARs that recognize cancer cells

3 Modified T cells are grown and expanded in culture

4 Modified T cells are infused into patient

1 T cells are isolated from patient

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 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: 2-4 days; med dur'n: 7 days*
- *Tocilizumab (IL-6Ri) = mainstay of Rx; 2nd-line: steroids*
- *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	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, altered gait, seizures

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

CRS Grading Assessment: Summary

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
*Fever**	≥38°C	≥38°C	≥38°C	≥38°C
WITH				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
*AND/OR***				
Hypoxia	None	Requiring low-flow nasal cannula*** or blow-by	Requiring high-flow nasal cannula***, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

*Fever is defined as temperature ≥38°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°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 ≤6L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6L/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, 02 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 ≥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 – generally **steroids** (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*** (variable efficacy): 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) – gen. favorable efficacy***

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 unarousable 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. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>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 hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local cerebral edema on neuroimaging †	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

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)

FDA Approved CAR T-cell Products

CAR T Agents:

- Axicabtagene ciloceucel (***Yescarta***) – Lg B-cell NHL, FL
- Tisagenlecleucel (***Kymriah***) – Lg B-cell NHL, B-ALL (<25y)
- Brexucabtagene autoleucel (***Tecartus***) – MCL, B-ALL (>18y)
- Lisocabtagene maraleucel (***Breyanzi***) – Lg B-cell NHL
- Idecabtagene vicleucel (***Abecma***) – Multiple Myeloma
- Ciltacabtagene autoleucel (***Cilta-cel***) – Myeloma

-not yet approved (currently under FDA priority review)

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/m2 + Cy 500 mg/m2 (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

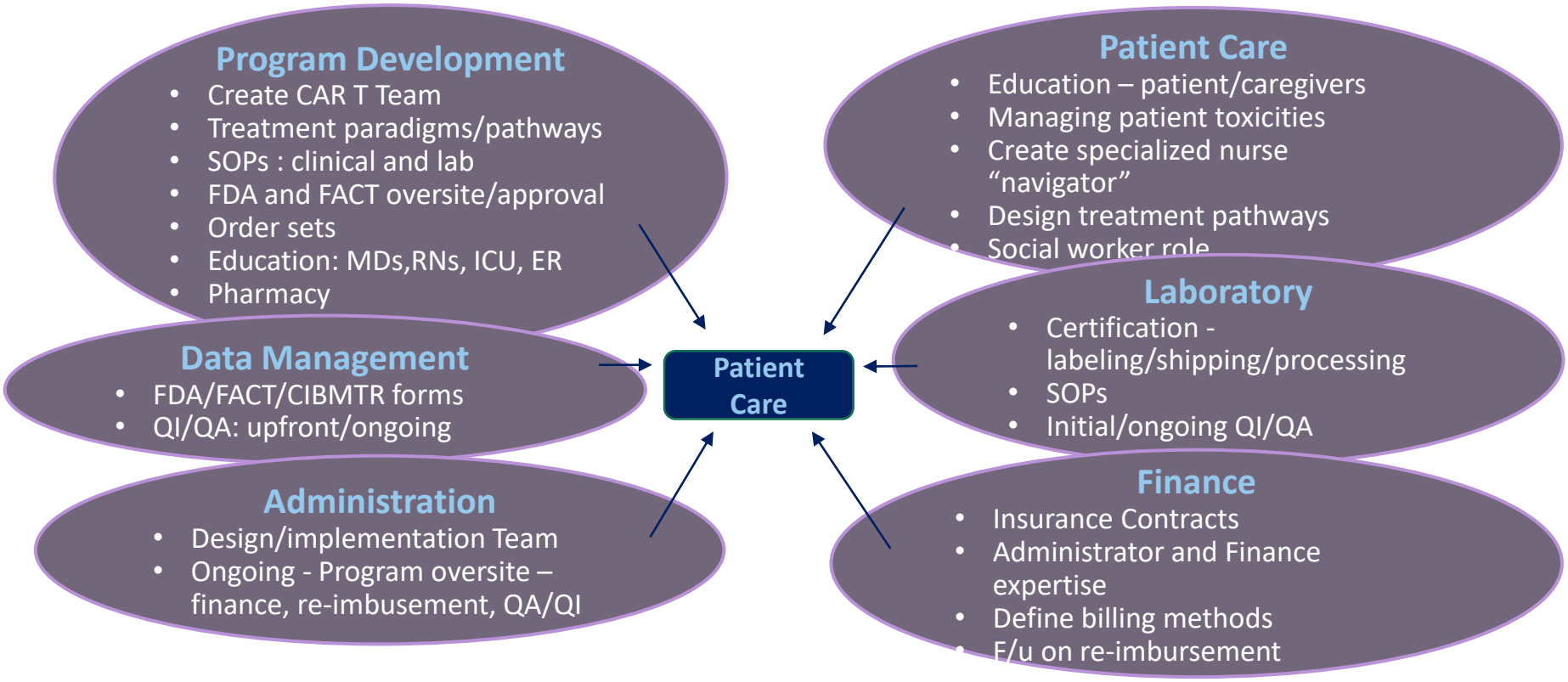
- Phase 2, single-cohort, 25 center, global study
- 75 pedi/young adult pts with CD19+ R/R B-cell ALL
- Overall 3 mo remission rate: 81% / MDR not reached
- **EFS/OS at 6, 12 mo -> 73/90% (6m), 50/76% (12m)**
- **Grade 3-4 CRS/ICANS: 77/40% (*no cerebral edema*)**
- **2 deaths** attributed to Kymriah: 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 2nd/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 ≥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



Implementation of CAR T at DHMC

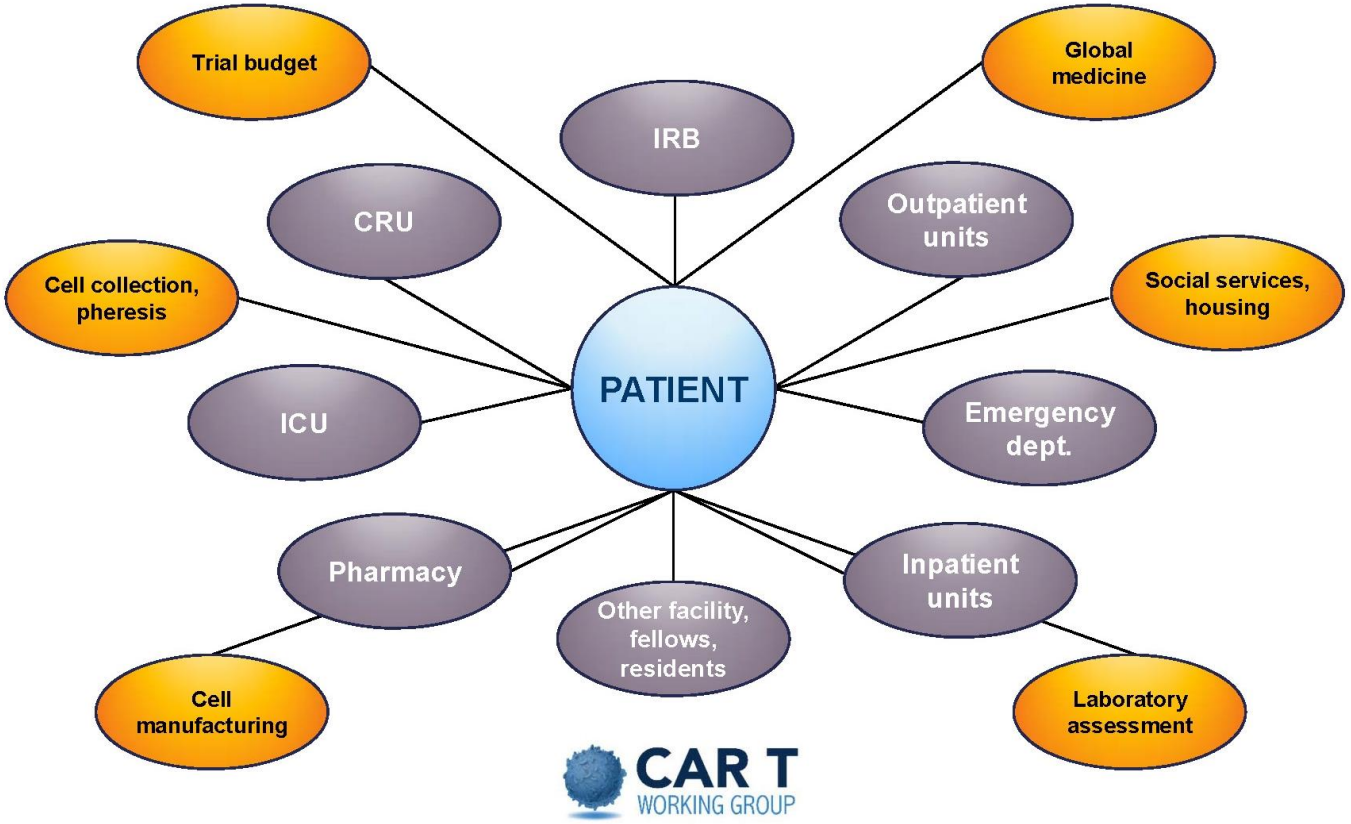
NCI-Designated Cancer Center / FACT Accredited BMT Program

Timeline

- Discussion with Senior Leadership, NCCC (2-3 years)
- Contract negotiations / agreements (1-2 years)
- Clinical Pathways, SOPs, Order Sets
- **Implementation of REMS Training / Knowledge Assess't**

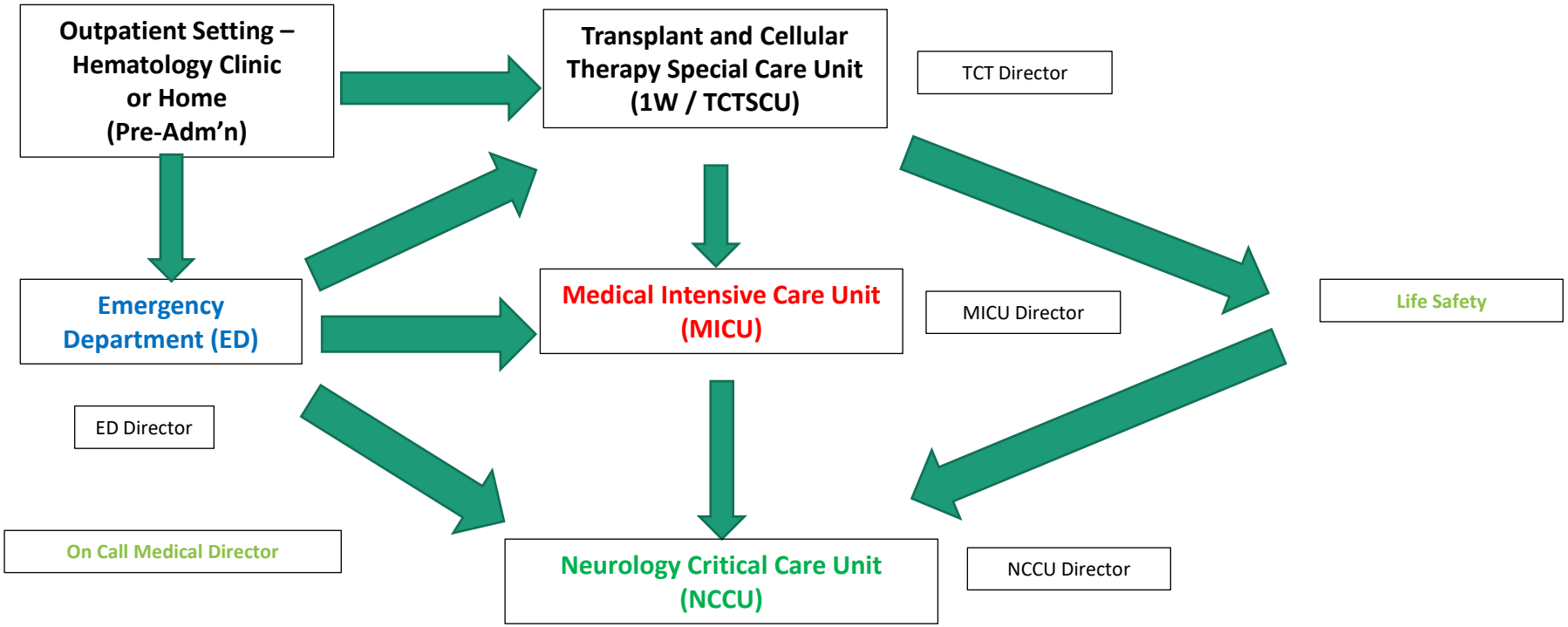
  Risk Evaluation and Mitigation Strategy
- In-depth review of CAR T-Cell Therapy standards – done with priority Sections within DHMC
- Compliance with drug dispensing guidelines, accurate documentation, adverse event reporting + audit readiness
- **Discussions / modifications related to COVID pandemic!**
- **April 2020: *Start of CAR T-Cell Therapy* (1st CAR T Pt)**

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



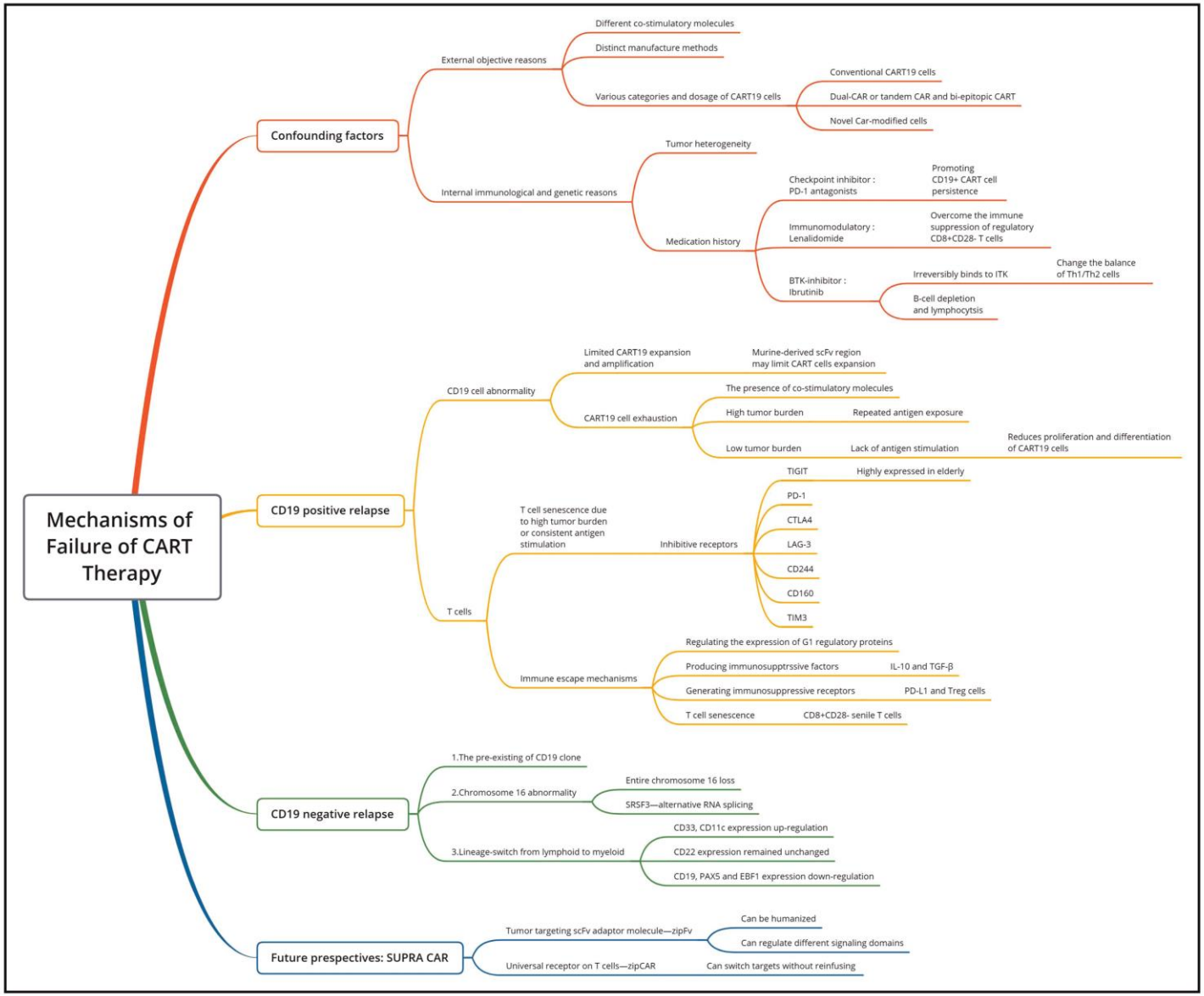
DHMC CAR T-Cell Therapy:

Transfer Algorithm for Escalation of Patient Care

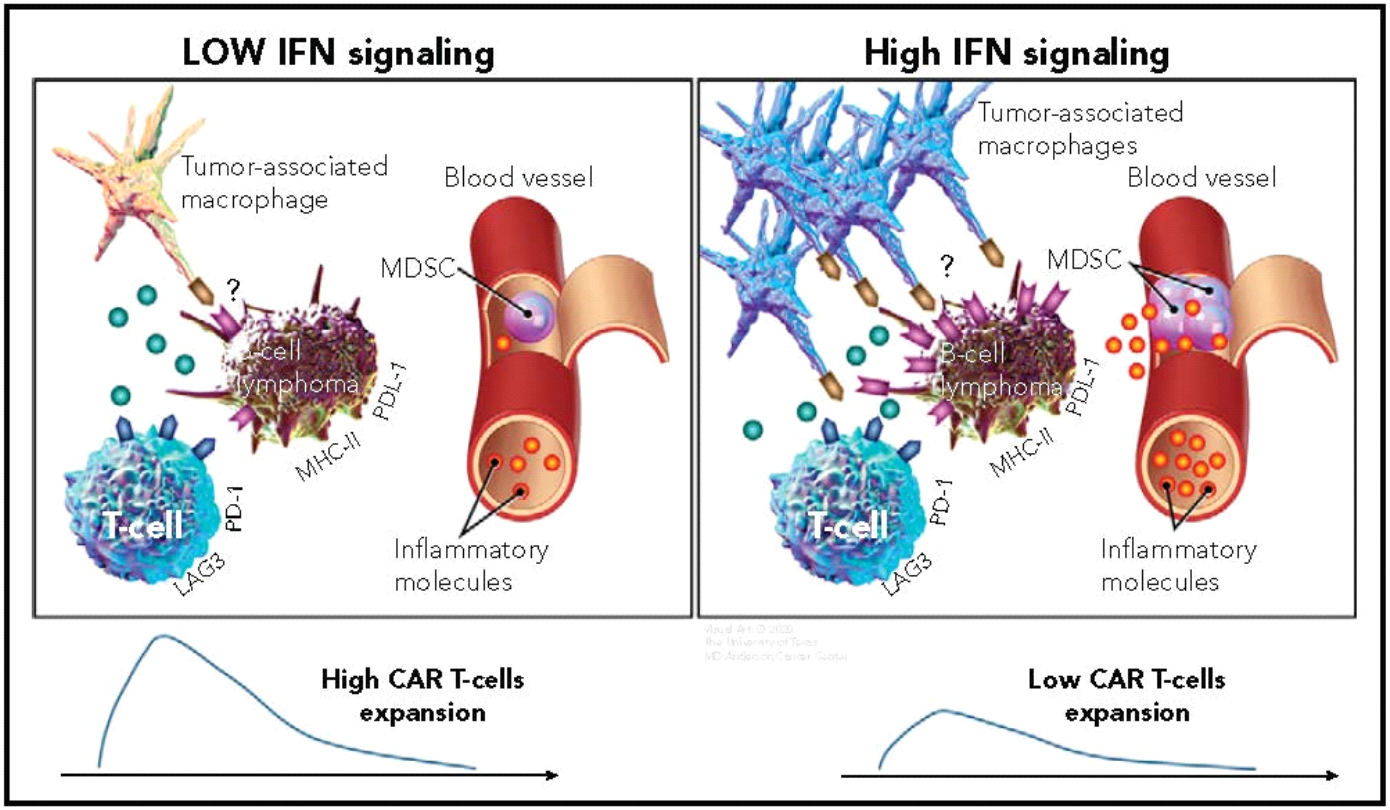


Why CARS Stall….
Potential Barriers and Pitfalls

- Inadequate T-cell collection
- Failed CAR production / *ex-vivo* expansion
- T-cell ***exhaustion*** (d/t repeated Ag exposure)
- T-cell ***senescence*** (d/t inhib rec expr'n: PD-1)
- Ag Escape (CD19 neg relapse)
- Failure of response (CD19+ relapse)
- Hypogammaglobulinemia (c/w B-cell loss)
- COST issues (400-500k per procedure)!!



The mechanism of relapse after the treatment for R/R B-cell hematological cancer with CART19 cells.



Compared with B-cell lymphomas with low IFN signaling (*left*), high tumor IFN signaling (*right*) is associated with a higher number of tumor-associated macrophages, a higher level of systemic inflammatory molecules, and in-creased expression of immune checkpoint ligands, such as PD-L1 and MHC class II on tumor cells, which could inhibit T cells via PD-1 and LAG-3, respectively. Both high tumor IFN signaling in the tumor microenvironment and high levels of monocytic MDSCs in the circulation are associated with lower CAR T-cell expansion and a lower rate of durable responses.

Ongoing CAR Trials in Solid Tumors

	No. of Clinical Trials	Targets Currently Being Investigated
Astrocytoma	7	HER2, EGFRvIII, IL13Rα2
Glioblastoma	7	HER2, EGFRvIII, IL13Rα2, NY-ESO
Breast	13	HER2, EpCAM, cMET, Mesothelin, ROR1, MUC1, CEA, CD70, CD133, NY-ESO
Colorectal	9	CEA, EGFR, MUC1, HER2, CD133,
HCC	11	Glypican-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

www.clinicaltrials.gov. Search term "chimeric antigen receptor." Accessed May 18, 2017.

CAR T WORKING GROUP

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 >9 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 relapsed and/or refractory 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.

Questions