CAR-T cells
What are they? What is the future?

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Objectives:

- History of Cancer and Treatment
- What are CAR-T cells?
- What is the rationale behind CAR-T cells?
- What makes cancer cells a good CAR-T cell target
• Cancer is 2nd leading cause of death in the world, second to cardiovascular disease.
• 1/2 of men and 1/3 of women in the U.S. will develop cancer in their lifetime.
• The word CANCER came from a Greek words karkinos to describe carcinoma tumors by a physician Hippocrates (460–370 B.C)
• Cancer developed when normal cells in a particular part of the body begin to grow out of control. These cells continue to grow, divide and re-divide instead of dying and for new abnormal cells.
History of Cancer and Treatment:

- Human bone cancer was found in mummies in ancient Egypt 1600 B.C.
- Oldest recorded case of breast cancer-1500 B.C.
- Cancer develops from normal cells due to damage of the cellular DNA. Most of the time when DNA is damaged, the body is able to repair, unfortunately with cancer cells, damaged DNA is not repaired but replicated.
5 Pillars of Cancer Treatment:
Immunotherapy in Cancer:

- The human’s immune system is capable of noticing differences in protein structure and recognizing foreign and neoplastic cells.

- Tumor develop multiple resistance mechanisms to escape immune recognition and subsequent target destruction:
  - local immune evasion
  - induction of tolerance
  - systemic disruption of T-cell signaling

- Immunotherapy utilizes the body’s own immune system in various mechanisms to repair, stimulate, or enhance the body’s natural response.

Types of Immunotherapy:

- **Vaccination:**
  - spileucel-T, Calmette-Guerin (BCG), talimogene, laherparepvec (T-vec)

- **Cytokine Therapy:**
  - Interleukin, Interferons

- **Monoclonal Antibodies:**
  - Bispecific T-cell engagers (BiTE), checkpoint inhibitors: PD-1, PDL-1, CTLA-4 inhibitors

- **Adoptive Cellular Therapy:**
  - Chimeric antigen receptor T-cell therapy.

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Adoptive Cellular Therapy

- First studied in melanoma patients in 1980’s
  - Main barriers included:
    - Difficulty in culturing & manufacturing of tumor infiltrating lymphocytes
    - Immune tolerance to self-antigens
    - Requirement for major histocompatibility complex (MHC) presentation of antigens.
Cancers evade the host immune system by a number of different mechanisms.

Immunotherapy has been effective in certain types of cancers for decades but its use has been limited in scope and by toxicity.

- Allogeneic donor stem cell transplantation for hematologic malignancies
- IL-2 therapy for malignant melanoma and renal cell carcinoma
What is a CAR-T cell?

- A rapidly emerging immunotherapy approach to treating cancer is called adoptive cell transfer (ACT): collecting and using patients’ own immune cells to treat their disease.
- There are severe types of ACT: TILs, TCRs and CARs. The one that has advanced the furthest in clinical development are CAR-T cell therapy.
What is a CAR-T cell?:

- CARs are engineered proteins composed of two distinct functional components. The first consists of an antibody fragment or target binding domain that allows CARs to recognize targets that are present on the surface of cancer cells.

- The second provides signals that rapidly and powerfully activate the T cell to attack and kill cancer cells.
**What are Chimeric Antigen Receptors (CAR) and CAR T-cells?**

CAR = transmembrane receptor that contains:

1. Extracellular domain: Antibody domain (scFv) against a tumor antigen
2. Transmembrane domain
3. Intracellular domain:
   - **First generation CARs**: CD3ζ (T cell coreceptor necessary for T cell activation)
   - **Second generation CARs**: CD3ζ + either CD28 or 4-1BB (costimulatory domain)
   - **Third generation CARs to come**: CD3ζ + two costimulatory domains (CD28, 4-1BB, OX40, ICOS, CD27)

**CAR T-cells** = T cells transfected with DNA encoding a CAR, so the CAR is expressed on the T cell surface
What Makes a Cancer a Good CAR T-cell Candidate?

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

2. 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
Advantages of CAR-T cell Therapy:

- Circumvent immune tolerance of T-cell & MHC restriction
- Limited off-target effects
- Specific to certain types of cancers
- Rapid onset of action
- Potential long-term control

CAR-T cell therapy overview:

1. **Extraction:** At the hospital, a machine separates the patient’s white blood cells, including T cells, from the rest of their blood. The resulting bag of cells is shipped to a manufacturing facility for reprogramming.

2. **Reprogramming:** In the approved CAR-T therapies, a viral vector delivers a gene encoding a chimeric antigen receptor, or CAR, into the T cells.

3. **Multiplication:** The engineered cells, now known as CAR T cells, are multiplied in a bioreactor.

4. **Preparation:** The patient receives chemotherapy to lower their white blood cell numbers and make room for the incoming CAR T cells.

5. **Treatment:** The CAR T cells are infused into the patient’s blood, where they proliferate and detect and destroy cancer cells.
CAR-T cell design - 3 generations

- Schematic representation of the different generations of CARs (1G, first generation, 2G, second generation, 3G, third generation). The scFv is highlighted in green, while the different component of TCR signal transduction machinery are highlighted in red (CD3 ζ chain/ZAP70), blue (CD28/PI3K) and yellow (4-1BB or OX40/TRAF).
Anti-CD19 CAR T-cell Pharmaceutical Trials: B-ALL

Novartis – ELIANA
- N=63* (16 patients did not get their infusion)
- Pediatric/young adult B-ALL
- MRD negative CR rate 83%
- PFS:
  - 6 month – 75%
  - 12 month – 64%

Buechner J, et al. EHA 2017:a181763

Juno - ROCKET
- N=51 (30 morphologic; 21 MRD+)
- Adult B-ALL
- JCAR015 (co-stimulatory domain CD28)
- CR rate
  - Morphologic: 77%
  - MRD positive: 90%
- 6 month OS:
  - Morphologic: 57%
  - MRD positive: 73%

Park JH, et al. ASCO 2016:a7003
# Anti-CD19 CAR T-cell Pharmaceutical Trials: DLBCL

## Kite – ZUMA-1
- N=101 (DLBCL 77; PMBL/tFL 24)
- Refractory
- ORR=82%, CR rate 54%
  - DLBCL: ORR = 82%, CR rate 49%
  - PMBL/tFL: ORR = 83%, CR rate 71%
- Month 6: 36% in ongoing CR
  - DLBCL: 31% in ongoing CR
  - PMBL/tFL: 63% in ongoing CR

## Novartis – JULIET
- N=85* (43 patients discontinued before infusion)
- Relapsed or refractory
- ORR=59%, CR rate 43%
- Month 3: 37% in an ongoing CR

## Juno
- N=14 (13 DLBCL)
- Relapsed or refractory
- ORR=82%, CR rate 73%
- No longer term data yet available

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Neelapu SS et al, ICML 2017, a28

Schuster SJ et al, ICML 2017

Abramson JS et al, ASH 2016, a4192
FDA Approval in DLBCL
CAR T-cells versus other available therapies: Refractory DLBCL

- SCHOLAR-1 is a meta-analysis conducted by Kite of available treatment trials for patients with refractory DLBCL
  - ORR 26%
  - CR 8%
  - Median OS 6.6m
- When compared with SCHOLAR-1, treatment on ZUMA-1 resulted in a significantly higher response rate, CR rate and OS

Neelapu SS et al, ICML 2017, a28
Cytokine Release Syndrome (CRS):

- **Cytokine release syndrome** (CRS), a systemic inflammatory response caused by cytokines released by infused CAR T cells can lead to widespread reversible organ dysfunction. ... Pharmacologic management is complicated by the risk of immunosuppressive therapy abrogating the antimalignancy activity of the CAR T cells.
CRS toxicity by organ system:

**Neurologic:**
- Headaches
- Changes in level of consciousness
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial nerve palsy
- Seizures

**Hepatic:**
- Transaminisits
- Hyperbilirubinemia

**Hematologic:**
- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile neutropenia
- Lymphopenia
- B-cell aplasia
- Prolonged prothrombin time
- Prolonged activated partial thromboplastin time
- Elevated D-Dimer
- Hypofibrinogenemia
- Disseminated intravascular coagulation
- Hemophagocytic lymphohistiocytosis

**Constitutional:**
- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Arthralgias

**Cardiovascular:**
- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fraction
- Triclonia
- QT prolongation

**Pulmonary:**
- Tachypnea
- Hypoxia

**Renal:**
- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

**Gastrointestinal:**
- Nausea
- Emesis
- Diarrhea

**Musculoskeletal:**
- Myalgias
- Elevated creatine kinase
- Weakness
CRS:

- **Fever** is usually the first symptom, may occur within a few hours after infusion up to a week later. Temp to 104 F po.
- Rigors, malaise, headaches, myalgias and anorexia are common.
- **Cardiac**: tachycardia associated with fever is common. With more severe CRS, hypotension, arrhythmias, and decreased cardiac ejection fraction can occur.
- **Pulmonary**: pulmonary edema, hypoxia, dyspnea, and pneumonitis, which can be severe enough to require mechanical ventilation.
**Renal:** Acute renal injury following CAR T-cell infusion is multifactorial and almost always reversible. Reduced renal perfusion is often the most important cause of renal injury. Reduced renal perfusion can be caused by cytokine-mediated vasodilation, decreased cardiac output, or intravascular dehydration due to insensible losses from high fevers. TLS and drug effect from medications such as antibiotics are other possible causes of renal injury. Electrolyte disturbances, such as hyponatremia, hypokalemia, and hypophosphatemia are not uncommon.

**Hepatic:** Elevations in serum transaminases and bilirubin can occur during CRS, and should return to normal with reduction of CRS. Diarrhea, colitis, nausea, and abdominal pain.

**Hematologic:** Cytopenias are a common occurrence following CAR T-cell infusion. Grade 3-4 anemias, thrombocytopenia, leukopenia, neutropenia, and lymphopenia.
CRS con’t:

- **Infectious Disease:** patients become neutropenia and lymphopenic. They are at high risk for opportunistic infections.
- **Neurologic:** include headaches, confusion, alterations in wakefulness, hallucinations, dysphasia, ataxia, apraxia, facial nerve palsy, tremor, dysmetria, and seizures.
Tocilizumab

• Tocilizumab is an IL-6 receptor antagonist that is used to treat rheumatologic disorders.

• While not approved for this use by the Food and Drug Administration, it has effectively treated CRS-related toxicities in clinical trials, and is now widely used off-label for toxicity following CAR T-cell infusions. Tocilizumab can effectively lessen or abrogate the CRS-related toxicities following CAR T-cell infusions.

• Experience with treating ALL patients with tocilizumab demonstrated that complete remissions still occur when patients receive tocilizumab to treat CRS caused by CAR T cells. Some concern still exists that tocilizumab might subtly impair the depth or duration of anti-malignancy responses caused by CAR T cells; formal studies of the impact of tocilizumab on antimalignancy outcomes have not been performed. In addition, most published experience with tocilizumab is with ALL. **Tocilizumab might impair the efficacy of CAR T cells against lymphoma or other malignancies even if it does not impair the activity of CAR T cells against ALL.**
CAR-T Cell Toxicity: Cytokine Release Syndrome

**Grade 1 CRS**
Fever, constitutional symptoms

**Grade 2 CRS**
Hypotension: responds to fluids or one low dose pressor
Hypoxia: responds to <40% O₂
Organ toxicity: grade 2

**Grade 3 CRS**
Hypotension: requires multiple pressors or high dose pressors
Hypoxia: requires ≥ 40% O₂
Organ toxicity: grade 3, grade 4 transaminitis

**Grade 4 CRS**
Mechanical ventilation
Organ toxicity: grade 4, excluding transaminitis

- Vigilant supportive care
- Assess for infection

**Extensive co-morbidities or older age?**
- No
  - Vigilant supportive care

**Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed**

**Monitor cardiac and other organ function closely**

**ICU-level care (30%)**
- **Tocilizumab**
  - ± corticosteroids
### Cytokine Release Syndrome: Incidence

<table>
<thead>
<tr>
<th>Disease</th>
<th>Study</th>
<th>N</th>
<th>CRS</th>
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<tbody>
<tr>
<td>B-cell ALL</td>
<td>UPenn (CTL019)</td>
<td>53 pedi</td>
<td>91% any grade; 32% grade 3/4</td>
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<tr>
<td></td>
<td>UPenn (CTL019)</td>
<td>12 adults</td>
<td>92% grade 3/4; 27% grade 5</td>
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<tr>
<td></td>
<td>MSKCC (JCAR014)</td>
<td>46 adults</td>
<td>24% grade 3/4</td>
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<tr>
<td></td>
<td>NCI (KTE-C19)</td>
<td>20 pedi</td>
<td>75% any grade; 30% grade 3/4 (one cardiac arrest)</td>
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<tr>
<td>CLL</td>
<td>Fred Hutch (JCAR017)</td>
<td>27 adults</td>
<td>26% grade 3/4; 10% grade 5</td>
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<tr>
<td></td>
<td>NCI (KTE-C19)</td>
<td>4</td>
<td>0%</td>
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<tr>
<td></td>
<td>MSKCC (JCAR014)</td>
<td>7</td>
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<tr>
<td></td>
<td>UPenn (CTL019)</td>
<td>14</td>
<td>64% any grade; 43% grade 3/4</td>
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<td></td>
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<td>26</td>
<td>54% any grade</td>
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<td>NHL</td>
<td>NCI (KTE-C19)</td>
<td>9 (DLBCL/PMBCL)</td>
<td>80% any grade; 27% grade 3/4</td>
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<td>15 (DLBCL/iNHL)</td>
<td>67% any grade; 8% grade 3/4</td>
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<td></td>
<td>UPenn (CTL019)</td>
<td>22 (13 DLBCL, 6 FL, 2 MCL)</td>
<td>67% any grade; 8% grade 3/4</td>
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<tr>
<td></td>
<td>Fred Hutch (JCAR017)</td>
<td>28 (18 DLBCL, 6 FL, 4 MCL)</td>
<td>0%</td>
</tr>
</tbody>
</table>

**B-ALL**
- **ELIANA (Novartis/UPenn, CTL019)**
  - 47% grade 3 or 4 CRS
  - Morphologic dz: 44% grade 3 or higher CRS
  - MRD positive dz: 0% grade 3 or higher CRS

**DLBCL**
- **ROCKET (Juno/MSKCC, JCAR015)**
  - 44% grade 3 or higher CRS
  - 0% grade 3 or higher CRS
  - 1 cardiac arrest
  - 1 case of hemophagocytic syndrome

- **ZUMA-1 (Kite/NCI, KTE-C19)**
  - 13% grade 3 or 4 CRS
  - 2 grade 5 CRS
  - 1 cardiac arrest
  - 1 case of hemophagocytic syndrome
  - 43% got tocilizumab
  - 27% got steroids

- **JULIET (Novartis/UPenn/CTL019)**
  - 26% grade 3 or 4 CRS
  - 0% grade 3 or higher CRS (21% grade 1 or 2)
  - 21% grade 3 or higher CRS

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CAR T-cell Toxicity: Neurotoxicity

**Grade 1**
Mild confusion and dysphasia w/o impairment

- Vigilant supportive care
- Telemetry and cont O2 sat monitoring

**Grade 2**
Moderate confusion, dysphasia, somnolence interfering with iADLs; generalized seizure

- Corticosteroids (decadron 10mg IV q6prn)
- Neurologic evaluation

**Grade 3**
Severe confusion, dysphasia, somnolence interfering with self-care; multiple seizures despite intervention

- ICU-level care (30%)
- Corticosteroids (solumedrol 1g daily x3d + taper)

**Grade 4**
Life threatening confusion, somnolence, seizures requiring urgent intervention and mechanical ventilation

- ICU-level care (30%)
- Corticosteroids (solumedrol 1g daily x3d + taper)
- Mannitol, hyperventilation, hypertonic saline, cooling, surgical intervention

Cerebral edema

- ICU-level care (30%)
- Corticosteroids (solumedrol 1g daily x3d + taper)
- Mannitol, hyperventilation, hypertonic saline, cooling, surgical intervention

30-40%

10-30%
Neurotoxicity: Incidence

- **B-ALL**
  - ELIANA (Novartis/UPenn, CTL019) – **15%** grade 3 neurotoxicity
  - ROCKET (Juno/MSKCC, JCAR015)
    - Morphologic dz: **40%** grade 3 or higher neurotoxicity
    - MRD positive dz: **14%** grade 3 or higher neurotoxicity
    - In the phase 2, however, there were 4 deaths due to cerebral edema (grade 5 neurotoxicity) causing the study to be closed.

- **DLBCL**
  - ZUMA-1 (Kite/NCI, KTE-C19) – **28%** grade 3 or 4 neurotoxicity
  - JULIET (Novartis/UPenn, CTL019) – **13%** grade 3 or 4 neurotoxicity
  - Juno (MSKCC/Fred Hutch, JCAR017) – **14%** grade 4 neurotoxicity

CAR T-cell Therapy: A Multidisciplinary Coordinated Approach
CAR T-cells: Other diseases

- **Glioblastoma**
  - Tumor targets: IL-13 receptor α2 (50%) and EGFRIII
  - Phase 1 clinical trial of 1st generation CAR targeting IL-13Rα2 yielded transient responses in 2 patients
    - Case report of response following multiple intracranial infusions of anti-IL-13Rα2 CAR T-cells
  - Anti-EGFRIII CAR T-cells have only been tested in preclinical models; clinical trials are ongoing

- **Neuroblastoma**
  - Tumor target: GD2, CD171
  - Phase 1 clinical trials of 1st generation CAR have been mixed, but in one (anti-GD2) CR rate 27% in 19 patients

- **NSCLC**
  - Tumor target: EGFR, CEA
  - Phase 1 trial of 2nd generation CAR (4-1BB): n=11; RR 18% (all PRs)

- **Ovarian cancer**
  - Tumor target: Folate receptor α, Muc-16, mesothelin
  - Phase 1 trial of 1st generation CAR against folate receptor α: no responses

- **Prostate cancer**
  - Tumor target: PSA
  - Phase 1 trial of 1st generation CAR: n=5; ORR 40% (all PRs)

- **Renal cell carcinoma**
  - Tumor target: CAIX
  - Phase 1 trial of 1st generation CAR: no responses

- **Sarcoma**
  - Tumor target: HER2, NYESO1, GD2
  - Phase 1 trial of 2nd generation CAR against HER2: n=17, SD in 24%

- **Head and neck cancer**
  - Tumor target: ErbB
  - Clinical trials ongoing with 2nd generation CARs

- **Breast cancer**
  - Tumor target: HER2, CEA
  - Clinical trials ongoing with 2nd generation CARs
Conclusions:

• CAR T-cell therapy represents a new and innovative form of immunotherapy for the treatment of cancer
  – Now FDA approved for the treatment of pediatric and young adult r/r B-ALL
  – FDA approved for the treatment of adult refractory DLBCL
  – Ongoing investigation in other CD19+ diseases, multiple myeloma, and a variety of solid tumors

• Efficacy is dependent on finding the right tumor antigen and the right tumor microenvironment
  – CD19 and BCMA are the best targets to date

• Unique toxicity profile may limit availability/eligibility

• Further cellular engineering and/or combination studies may broaden the applicability of this therapy in the future
Challenges and Opportunities with CAR T Cells

- CAR T Cells are agnostic of genetics
- More patient specific
- NOT off the shelf
- Needs scaling up because of demand
• Thank you!

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