# Natural Line of Defense: Update on Immunotherapy in Hematologic Malignancies

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TOPA

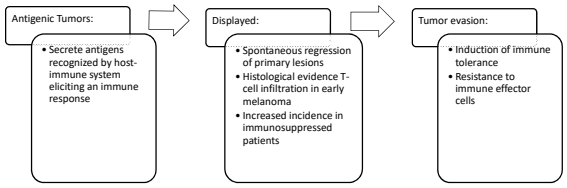
## Conflict of Interest

- I have no professional/financial disclosures to report

## Objectives

1. Review the principles of immunotherapy in the treatment of hematologic malignancies
2. Discuss chimeric antigen receptor (CAR) T-cell targets and current treatment strategies integrating recent data on patterns of response and mechanisms of resistance
3. Summarize novel immunotherapy approaches in development for treatment of hematologic malignancies
4. Evaluate common toxicities of immunotherapy and highlight the pharmacists' role for ensuring safe immunotherapy treatment

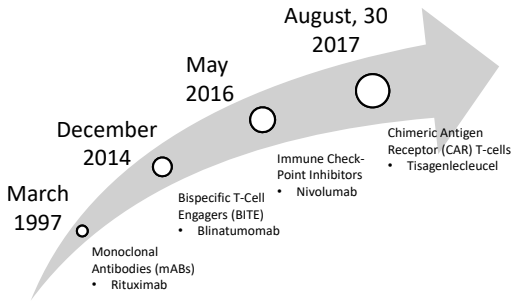
## Immunogenicity of Cancer




- Immunotherapy has eradicated hematologic malignancies with allogeneic hematopoietic cell transplant (allo HCT)
  - Use of alloreactive T-cells to control recipient malignancy
  - Also target non malignant cells and cause graft versus host disease (GVHD)
  - Limitations to extending allo HCT to wider ranges of hematologic conditions

Guerry D et al. J Invest Dermatol. 1993 Mar;100(3):342S-345S.
Welniak LA et al. Annu Rev Immunol. 2007;25:139-170.

## Immunotherapy Agents



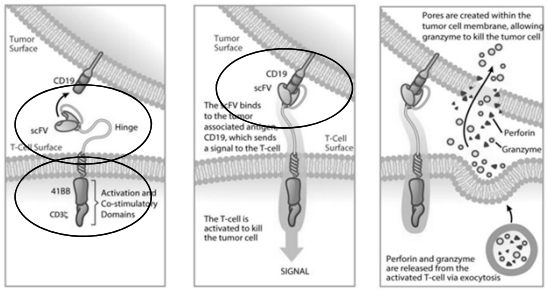

## Chimeric Antigen Receptor (CAR) T-cells

## CAR T-Cell

- First CAR T-Cell discovered in 1989
- Autologous T-lymphocytes genetically modified to combine the advantage of:
  - Human leukocyte antigen (HLA)- independent antigen recognition
  - Cytotoxic ability of T-cells

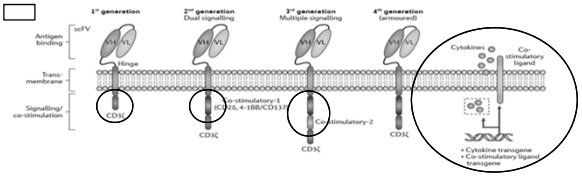
Namuduri M et al. Expert Rev Hematol. 2016 Jun;9(6):511-3.
https://am.asco.org/immunotherapy-approaches-expanding-hematologic-malignancies

## CAR T-cells in Action




http://blogs.shu.edu/cancer/files/2015/11/CD19-CAR.jpg

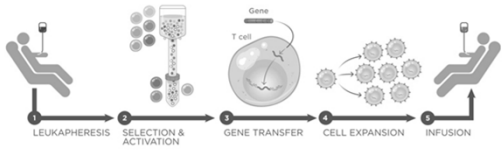
## CAR T-cell Development




- 1st Generation: Single-chain variable fragment of an antibody specific for tumor antigen linked to the intracellular signaling domain of the TCR
  - Lacked significant antitumor activity most likely due to inadequate t-cell persistence
- 2nd/3rd Generation: added 1 (CD28/4-1BB) or 2 (CD28/4-1BB /OX40) co-stimulatory domains
  - Most display significant clinical activity
- 4th Generation: "armored CAR" combine a second-generation CAR with the addition of various genes, including cytokine and co-stimulatory ligands, to enhance the tumoricidal effect
  - Early in clinical testing

Batlevi CL et al. Nat Rev Clin Oncol. 2016 Jan;13(1):25-40.
Till, B et al. Blood. 2008;112, 2261–2271.
Wang, J. et al. Hum. Gene Ther. 2007; 18, 712–725.
Pegram, HJ et al. Cancer J. 2014; 20, 127–133.

## Car T-Cell Generation & Administration




1. Leukoapheresis of patients peripheral blood mononuclear cells (PBMCs)
2. T cells are activated and selected by incubation with anti-CD3 and anti-CD28 paramagnetic beads
3. Activated T-cells transduced with retro/lentiviral vectors carrying the CAR construct
4. Cells expanded 1,000 fold over a 1-2 week period
5. CAR T-cells infused into patient over 1-2 day period

Batlevi CL et al. Nat Rev Clin Oncol. 2016 Jan;13(1):25-40.
https://www.junotherapeutics.com/our-science/scientific-platform/Car T-Cell Process

## CD 19 Antigen

- Attractive target due to:
  - Presence in the vast-majority of b-cells
    - 95% of NHL
  - Expressed throughout b-cell development
    - Wider range of b-cells to target than with CD20
    - Immature progenitor cells may be cause of relapse in mature b-cell malignancies
  - Depletion restricted to lymphoid system
    - B-cell aplasia not necessary life-threatening
- Most investigations conducted in CD19 positive hematologic malignancies such as:
  - B-cell Acute Lymphoblastic Leukemia (B-ALL)
  - Chronic lymphocytic lymphoma (CLL)
  - Follicular Lymphoma (FL)
  - Diffuse Large B-cell Lymphoma (DLBCL)
  - Mantle Cell Lymphoma (MCL)

Ghorashian S, et al. Br J Haematol 2015;169: 463-478.
Kim SJ. Korean J Hematol. 2011; 46: 211-213.
Kim SM,et al. Blood 2014; 124: 1622.

## Car T-cells

- Advantages in hematologic malignancies:
  - Established cell surface antigens
  - Less invasive tumor sampling
  - Natural homing of t-cell to malignancy site
    - Blood, bone marrow, lymph nodes
- Studied in heavily pretreated, relapsed, refractory and post- allogeneic transplant patient population
  - 100 trials were registered with ClinicalTrials.gov with the search term "chimeric antigen receptor,"
    - United States, Europe, China, Japan, and Australia

Im A et al. J Hematol Oncol. 2017 Apr 24;10(1):94.

**Acute Lymphoblastic Leukemia (ALL)**

| Reference | Number/Age | Complete Remission Rates |
|---|---|---|
| Brentjens RJ et al. | 5 adults | 100% |
| Grupp SA et al. | 2 children | 100% |
| Davila ML et al. | 16 adults | 88% |
| Lee DW et al. | 20 children | 70% |
| Maude S et al. | 25 children<br>5 adults | 90%<br>100% |
| Frey NV et al. | 12 adults | 89% |
| Park JH et al. | 27 adults | 89% |

Brentjens RJ et al. Sci Transl Med, 2013;5 (177):177ra138.
Grupp SA et al. N. Engl. J. Med. 2013; 371,1509-1518.
Davila ML et al. Sci Transl Med. 2014;6(224):224ra25.
Lee DW et al. Lancet. 2015; 385, 517–528. A382.
Maude S.L et al N. Engl. J. Med. 2014; 371, 1507–1517.
Frey NV, et al. ASH. 2014; Paper 76315
Park JH et al. ASH. 2014; Paper 76573

## ELIANA Trial- Efficacy

- Global Phase II trial reporting on 63 pediatric/young adults
  - CD19+ R/R B-cell ALL with ≥5% bone marrow lymphoblasts by morphology
  - Median follow-up 6.4 months
- 83 % (52/63) achieved CR or CRi within 3 months
- Relapse free probability after remission
  - @ 6 months 75% @12 months 64%
- Survival probability
  - @ 6 months 89% @12 months 79%

CRi: CR with incomplete blood count recovery

Buechner J, et al. European Hematology Association Annual Meeting. Abstract S476. Presented June 24, 2017.

## ELIANA Trial- Safety

- Cytokine Release Syndrome (CRS)
  - 78% of pts (21% grade 3; 27% grade 4); no CRS-associated deaths occurred
- Neurotoxicity
  - 15% (grade 3 neuropsychiatric AEs) with no grade 4 events and no cerebral edema reported
- Deaths:
  - 2 within 30 days of infusion
    - ALL progression, n=1; cerebral hemorrhage, n=1
  - 9 more than 30 days after infusion
    - ALL relapse/progression, n=6; HHV-6 encephalitis, pneumonia, systemic mycosis, n=1 each

Buechner J, et al. European Hematology Association Annual Meeting. Abstract S476. Presented June 24, 2017

## Tisagenlecleucel (Kymriah™)

- First gene therapy approved in the United States by the FDA
  - "Breakthrough therapy status"
- One-time treatment of relapsed/refractory B-cell precursor ALL patients up to 25 years old
- REMS which include elements to assure safe use (ETASU)
- Requires specially certified centers for treatment
  - Available at 20 centers in September
  - 32-35 centers by end of 2017

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm

## Pricing

- Cost: $475,000
- Pay for Performance deal
  - First of its kind with CMS
  - Free of charge in children on Medicaid with no response after 1 month
- Patient assistance program
  - Co-pay discounts, travel assistance, free treatment
- P&T implications
  - Regulated as a drug
  - Available prescribing information

http://fortune.com/2017/08/31/novartis-kymriah-car-t-cms-price/

**Non Hodgkin's Lymphoma (NHL)**

| Reference | Number/Age | Complete Remission Rates |
|---|---|---|
| Sauter CS et al. | 6 adults | 100% |
| Schuster SJ et al. | 8 adults | 38% |
| Kochenderfer JN et al. | 11 adults | 55% |
| Turtle CJ et al. | 9 adults | 11% |

**Chronic Lymphoblastic Leukemia (CLL)**

| Reference | Number/Age | Complete Remission Rates |
|---|---|---|
| Porter DL et al. | 23 adults | 22% |
| Kochenderfer JN et al. | 4 adults | 25% |
| Park JH et al. | 7 adults | 29% |

Sauter, C. S. et al. Blood.2014; 124, a677.
Schuster, SJ et al. Blood. 2014; 124, a3087.
Kochenderfer, JN et al. J. Clin. Oncol.2015;33, 540–549.
Turtle, CJ. et al. J. Blood. 2014; 124, a384.
Porter, DL et al. Blood. 2014; 124, a1982.
Kochenderfer, JN et al. Blood. 2012; 119, 2709-2720.
Park, JH et al J. Clin. Oncol. 2014;32 (5s Suppl.), a7020.

## Car T-cell Clinical Trial Design

- Numerous distinctions between trials by various groups including:
  - scFvs derived from separate hybridomas
  - Disparate signaling domains (CD28 vs. 4-1BB)
  - Genetic modification methodology
  - Dose/preparative regimen prior to cell infusion
    - Prime t cells for expansion
  - T-cell dose

Namuduri M et al. Expert Rev Hematol. 2016 Jun;9(6):511-3.

## Car T-cell Lessons

- Cells work where drugs fail
  - Capable to clear CNS disease
  - Durable remissions are possible
- No GVHD in post-allogeniec patients
- Response correlates with in vivo expansion of cells and presence of CRS
  - Not degree of CRS

Im A et al. J Hematol Oncol. 2017 Apr 24;10(1):94.
Sadelain M. J Clin Invest. 2015 Sep;125(9):3392-400
Yang X et al. Blood. 2014 Jun 12; 123(24): 3750–3759.

## Car T-cell Persistence

- Benefit of ongoing disease surveillance
- Disadvantage of long-term B-cell aplasia
  - Surrogate marker for persistence
- Optimal duration unknown
  - May vary based on antigen target
  - Documented up to 4 years after infusion in CLL patients
- Complex picture
  - Linked to co-stimulatory domains and cell culture system

Maus MV et al. Clin Cancer Res. 2016 Apr 15;22(8):1875-84.

## CAR T Cell Response and Resistance

- ALL has high response rates and relapse rates
  - 25-50% will relapse with CD-19 negative disease
  - CD-19 positive relapse occurs when cells no longer present
- CLL has lower response and relapse
  - Less intrinsically active T-cells
- NHL falls in the middle
  - Target downregulation not as apparent as a mechanism for resistance
- Therefore, need different strategies to improve efficacy and prevent resistance

Sadelain M. J Clin Invest. 2015 Sep;125(9):3392-400
Im A et al. J Hematol Oncol. 2017 Apr 24;10(1):94.

## Car T-cell Resistance: ALL CD-19 Negative disease

- Selective pressure by CAR T-cells yields antigen escape variants
  - Not seen in NHL or CLL
- Dual Antigen Targeting
  - Targets include CD12 and CD22
  - 2 antigens would mean that escape of CAR T-cell–mediated destruction would require simultaneous mutations in two genes

Sadelain M. J Clin Invest. 2015 Sep;125(9):3392-400

## Dual Antigen Targeting

- Increased antitumor function compared with a T-cell expressing a single CAR
- Multiple co-stimulatory domains may result in:
  - Lower vector titers
  - Lower expression of CAR at cell surface
  - Decreased functionality due to requirement of accessory signaling apparatus proximal to cell the membrane

Maus MV et al. Clin Cancer Res. 2016 Apr 15;22(8):1875-84.

## *CAR T-Cell HEADLINES*

## "ASCO 2017: CAR T Cell Therapy Shows Incredible Results in Myeloma"

https://www.myelomacrowd.org/asco-2017-car-t-cell-therapy-shows-incredible-results-in-myeloma/

## BCMA- Plasma cell specific antigen

- Phase 1 clinical trial in China
  - 33/35 pts with response (14 CRs)
    - 5 patients followed out 12-14 months still in remission
- Bluebird Bio/Celgene Phase 1
  - 11 patient, dose-finding, 78% ORR
  - Expanded to CRB-401 2-part, non-randomized, open label, multi-site Phase 1 study of bb2121 in adults with relapsed/refractory multiple myeloma (MM)
  - Enrolling at 7 sites in US

https://www.myelomacrowd.org/asco-2017-car-t-cell-therapy-shows-incredible-results-in-myeloma/

## "CRISPR Turbocharges CAR T Cells, Boosts Cancer Immunotherapy"

http://www.genengnews.com/gen-news-highlights/crispr-turbocharges-car-t-cells-boosts-cancer-immunotherapy/81253925

## CRISPR/Cas9

- Custom genome editing technology used for removing, adding or altering sections of the DNA sequence
- Consists of 2 key molecules
  - Cas9 Enzyme
    - Acts as a pair of molecular scissors that can cut 2 strands of DNA to remove or add DNA
  - Guide RNA
    - Small piece of pre-designed RNA sequence within a longer RNA scaffold. Scaffold binds to DNA and the pre-designed sequence "guides" Cas9 to right spot in genome to cut

http://www.genengnews.com/gen-news-highlights/crispr-turbocharges-car-t-cells-boosts-cancer-immunotherapy/81253925
https://www.yourgenome.org/facts/what-is-crispr-cas9

## CRISPR/Cas9

- After Cas9 makes cut in DNA the cell uses natural repair mechanisms to fix
- Preliminary work of CAR T-cells designed with technology report:
  - Uniform CAR expression
  - Enhanced T-cell potency
  - Delayed T-cell differentiation and exhaustion
  - Potentially safer and more effective cells
- "off-target"effects
  - More specific guide RNA, single strand Cas9 enzyme

https://www.yourgenome.org/facts/what-is-crispr-cas9
Eyquem J et al Nature. 2017 Mar 2;543(7643):113-117.

## After Trial Deaths, Juno Pivots and Scraps Lead CAR-T Therapy

http://www.xconomy.com/seattle/2017/03/01/after-trial-deaths-juno-pivots-and-scraps-lead-car-t-therapy/

## Juno Therapeutics JCAR015

- ROCKET TRIAL
  - Phase II trial in relapsed/refractory adult ALL
- Canceled after 5/38 patient deaths
  - All 5 deaths due to cerebral edema, fatal toxicity not reported in prior CAR T trials
  - Initially thought to be due to fludarabine lymphodepleting conditioning
  - 2 more deaths after removing fludarabine
- Further investigation with JCAR015 discontinued
- Juno still investigating JCAR014, JCAR016, JCAR017, JCAR018

http://www.xconomy.com/seattle/2017/03/01/after-trial-deaths-juno-pivots-and-scraps-lead-car-t-therapy/

## CAR T-CELL Toxicity

## CAR T-Cell Toxicity

- Not associated with the infusion of the cells, rather with the expansion and persistence
  - Immune activation that is critical for response rates is also responsible for this therapy's most significant treatment-related toxicity
- Most notable toxicities:
  - CRS
    - Severe CRS
  - CNS toxicity
  - B-cell aplasia

Lee, DW et al. Lancet. 2015; 385, 517–528. A382.
https://am.asco.org/optimizing-outcomes-clinical-trials-car-t-cell-therapy-patients-all

## CAR T-Cell CRS

**Clinical CRS**

- Fevers
- Hypotension
- Capillary Leak syndrome
- Respiratory distress
- Neurologic disturbances

**Biochemical CRS (elevated)**

- Liver Function Tests
- Ferritin
- Triglycerides
- Hypo-fibrinogenemia
- Interferon-gamma
- Interluekin-6
- Soluble IL-2Rα
- IL-10
- C-Reactive Protein (CRP)

- Occurs within 1-3 weeks of infusion
- Incidence 18-100%
- Elevated CRP with clinical symptoms can be a biomarker for severe CRS, incidence 27-53%
- Risk Factors:
  - Higher disease burden at baseline
  - Higher cell infusion quantity
- Treatment
  - Supportive care
  - Tocilizumab- indication expanded
  - Steroids

Davila ML, et al. Sci Transl Med. 2014;6(224):224ra225.
Grupp SA, et al. N Engl J Med. 2013;368(16):1509–1518.
Hylton et al. Biol Blood Marrow Transplant 21 (2015) S355eS373
https://am.asco.org/optimizing-outcomes-clinical-trials-car-t-cell-therapy-patients-all
Hylton et al. Biol Blood Marrow Transplant 21 (2015) S355eS373

## CAR T-Cell Toxicity

**CNS Toxicity**

- Incidence as high as 50%
- Unknown if CAR T-cells cross into CNS, believe neurotoxicity secondary to an inflammatory state rather than direct affect on neural tissue
- Symptoms
  - Confusion, delirium, word-finding aphasia, coma, seizures
  - May require intubation for airway protection
- Most studies start seizure prophylaxis
  - Keppra 500 mg q12h

**B-cell Aplasia**

- Incidence 86-100%
- Can last for weeks to months
- Hypothesized as a surrogate marker for CAR T cell persistence
- IVIG replacement can supplement hypogammaglobinemia and reduce infection risk

Namuduri M et al. Expert Rev Hematol. 2016 Jun;9(6):511-3.

## Physician Driven Persistence Mechanisms

- "Suicide" switch
  - Incorporation of inducible suicide gene caspase-9 (iCasp9)
    - Cell containing iCasp9 can be depleted by administering a synthetic small molecule to dimerize iCasp9 promolecules and trigger apoptosis
  - Coexpression of protein for which a depleting antibody already exists such as CD20
    - Administer rituximab to "cure" toxicity
- None clinically tested, most investigators prefer to use pharmacologic interventions to manage toxicity versus ablate a potentially curative and expensive therapy

Maus MV et al. Clin Cancer Res. 2016 Apr 15;22(8):1875-84.

## FACT Pharmacist Responsibility

- Immune Effector Cells (IEC)
- Training :
  - An overview of hematology/oncology patient care, including the cellular therapy process, cytokine release syndrome, and neurological toxicities
- Development and implementation of guidelines or SOPs for pharmaceutical management of cellular therapy recipients
- Access to medications adequate to treat expected complications, including CRS
  - Tocilizumab available on a 24-hour basis
  - Dispensing it within 30 minutes of a request
- Complete continuing education including, not limited to:
  - Field of HPC transplantation
  - CRS and neurological toxicities

http://www.factwebsite.org/iecstandards/

## Natural Line of Defense: Update on Immunotherapy in Hematologic Malignancies

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