CIRM Webinar: CAR-T Cell Immunotherapy - Challenges and Opportunities Using Mature or Stem Memory T Cells, March 18th, 2015
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Primary Factors Influencing CAR T Cell Potency

- Manufacturing process
- Patient pre-conditioning regimen
- **CAR Design**
T Cell Receptor eACT

The diagram illustrates the process of T cell receptor engineering (eACT) for targeting cancer. It shows the integration of TCR (T Cell Receptor) α and β chains into the cell membrane, enabling the cell to recognize and respond to cancer-associated proteins. The diagram highlights the steps of peptide processing, assembly of peptides with MHC (Major Histocompatibility Complex), and the subsequent cytolytic activity and cytokine release from the TCR-engineered T cell.
Chimeric Antigen Receptor eACT
Evolution of the CAR Field: a 25 Year Odessey

Gross, 1989
Ab-TCR CAR

1989

Irving & Weiss, 1991
CD8ζ, CAR: proof of concept
Romeo & Seed, 1991
CD4ζ, CAR: anti-HIV

1991

Eshhar, 1993
scFv-CAR

Stancovski; Hwu; Gross, 1993
Anti-tumor CAR

1993

Roberts, 1994
1st gen anti-HIV CARs: preclinical study
CD4ζ, scFv-based CAR

1994

Kershaw, 2000
Clinical trial with 1st gen anti-folate receptor CAR
Lamers, 2006, 2007
Clinical trial with 1st gen CAR anti-CA-IX CAR

1995

Walker, 1996
Clinical trial with 1st gen anti-HIV CAR: CD4ζ

1996

Alvarez-Vallina & Hawkins, 1996
scFv-CD28
Krause, 1998: scFv-CD28;
Finney, 1998: 2nd gen scFv-CAR

1997

Roberts, 1995
US 5712149 2nd gen CAR

2010

Kochenderfer, 2010
Clinical trial with 2nd gen CAR (α-CD19)
CAR Design - 1st Generation

Essential features

I: TM & extracellular domain

- **Spacer/Fc domain**
  - Distance between T cell and target cell plasma membranes at immunological synapse (TCR-pMHC complex formation) ~ 135 Å
  - Requirement for/length of spacer (e.g. IgG Fc domain) is CAR scFv-epitope specific

- **Hinge**
  - Provides appropriate flexibility for CAR-target epitope binding
  - Derived from members of Immunoglobulin Superfamily (IgSF)
  - Potential for covalent homodimer formation via conserved Cys

- **Transmembrane domain (TM)**
  - Derived from IgSF TM proteins that participate in immunological synapse; independent of other proteins for surface expression

II: Signaling domain

- Cytoplasmic domain of TCR CD3ζ chain provides essential signal 1 via ITAM adaptors
Role of Co-stimulatory Receptors

**Concept of Signal 2**

- **Signal 1**: TCR-pMHC
  - TCR/CD3ζ ITAMS

- **Signal 2**: Co-signaling receptors
  - Stimulatory
  - Inhibitory

- **Costimulatory receptors regulate**
  - **Memory-effector T cell subsets**
  - Proliferation and survival
  - Polarization of effector T cells

- **Two major superfamilies**
  - Ig superfamily
    - CD28, CD2/SLAM, B7, TIM, CD226
  - TNFR superfamily
Role of Costimulatory Receptors in Regulation of Human T Memory, Expansion & Survival

- Subset expansion, survival
- Subset conversion
- Effector function

Farber et al., Nat Rev Immunol 2014 14:24
CD28 Family of Co-signaling Receptors

B7H2
B7.1, B7.2

B7H2
B7.1, B7.2

B7H2

B7H1, B7DC

HVEM

APC

T cell

CD28
Lck, PI3K

CTLA4
SHP2

ICOS
PI3K

PD-1
SHP2

BTLA
SHP1, SHP2

CD160

GPI-linked
CD28 Costimulatory Function

- Constitutively expressed on naïve & memory subsets
  - Naïve, Tscm, Tcm, Tem
  - Ligands induced on APC –EARLY

- Naïve T cells
  - Essential for naïve T cell activation

- Major prosurvival and proliferative role
  - Induces IL-2 production and T cell proliferation
  - Protects against antigen-induced cell death and anergy

- Memory subsets
  - Major role in Tcm expansion; CM→EM conversion

- Acts as a TCR signal amplifier
  - Mitogenic activity requires TCR, CD3ζ, Zap70
    - No TCR-pMHC independent activity in response to natural ligand
TNFR Superfamily of Co-signaling Receptors

TNFR SF counter-receptors: TNF homology domain
41BB Costimulatory Function

- Expression induced during late phase of T cell activation
  - Transiently induced on activated T cells (GITR-dependent?)
  - CD137L induced on APC
  - Induced on Tcm cells by IL-15 and IL-2 in vitro

- No role in naïve T cell priming

- Drives CD8 Tcm expansion/maintenance
  - TCR activation-/antigen-independent expansion – unlike CD28
  - Does not induce IL-2
  - Proximal signaling pathways distinct from TCR/CD3, CD28 & ICOS
  - Distal pathways partially overlapping
  - More dramatic impact on CD8s compared to CD4s
CAR Design: Second Generation

Inclusion of Co-stimulatory Domain

- Drives temporal association of CD3ζ signal 1 and costimulatory signal 2
- Compensates for lack of costimulatory ligand expression on non-hematologic solid tumors, and down-regulation of costimulatory receptors on T cells
- Enhances T cell persistence, expansion and anti-tumor activity in setting of hematologic malignancies, despite expression of costimulatory ligands
  - Kowolik et al., 2006 Cancer Res 66: 10995 [CD28-CAR vs 1st gen in mouse]
  - Savoldo et al., 2011 J Clin Invest 121: 1822 [CD28-CAR vs 1st gen in human]
As expected, anti-tumor activity 2nd gen CARs dramatically superior to 1st gen ζ only.

No significant difference in anti-tumor activity of different 2nd gen CAR T cells.

No significant difference in blood frequency of 2nd gen CAR T cells @ 3 weeks.

Impact of costimulatory (and other) domains on CAR T cell effector functions, memory subset formation/survival in blood & tumor under investigation.


Folate receptor (FR)-specific CARs:
- FR-ζ
- FR-CD27ζ
- FR-41BBζ
- FR-CD28ζ
Kite/NCI Study of anti-CD19 CAR in Relapsed/Refractory B-Cell Malignancies

- Phase 1/2 study investigating safety, feasibility, and efficacy
  - DLBCL, PMBCL, CLL, Indolent NHL
- Refractory/recurrent disease incurable by standard therapy
- Evolving treatment protocol (conditioning/dosing)
- 10-day manufacturing process → reduced to ~ 1 week

Kochenderfer Blood 2012; Kochenderfer JCO 2014; Kochenderfer ASH 2014
Streamlined and Rapid eACT™ Manufacturing Process for anti-CD19 CAR T Cells (KTE-C19)

- Apheresis product shipped to CMO
- Lymphocyte enrichment
- Retroviral vector transduction of CAR gene
- T cell activation with anti-CD3 Ab
- T cell expansion
- Harvest, cryopreserve product
- Ship product; ready for bedside use

- Single T cell stimulation of PBMC in human serum-free media
- Streamlined process amenable to cGMP
- Progenitor Cell Therapy (PCT) to manufacture clinical supply
- Kite developing additional clinical and commercial manufacturing facilities
- Transportation logistics in place for KTE-C19 multi-center clinical trial
Kite/NCI Phase 1/2
Memory Subset Composition of 10-Day Product

- CAR+ Tcm present at ~40% in 10-day product for 13/15 patients
- Peak frequency CAR+ T cells in blood observed at day 7-17 post transfer
- Impressive clinical response
  - 8 CR, 4 PR, 1 stable, out of 13 evaluable patients
- Potential for reconstitution normal B cells
  - Retreat if necessary
- Extensive immunophenotypic analysis of patient product and blood samples underway

Adapted from: Kochenderfer et al., 2014 JCO
Kite/NCI Study of anti-CD19 CAR in Relapsed/Refractory B-Cell Malignancies: Phase 1/2

- 32 adult patients enrolled (29 evaluable); largest dataset of anti-CD19 CAR in lymphoma

<table>
<thead>
<tr>
<th>Tumor Type (n evaluable)</th>
<th>Overall Response Rate</th>
<th>Complete Response Rate</th>
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<tbody>
<tr>
<td>Any (29)</td>
<td>76%</td>
<td>38%</td>
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<tr>
<td>DLBCL/PMBCL (17)</td>
<td>65%</td>
<td>35%</td>
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<td>CLL (7)</td>
<td>86%</td>
<td>57%</td>
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<tr>
<td>Indolent NHL (5)</td>
<td>100%</td>
<td>25%</td>
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- 16 patients still in response; 12 ongoing > 1 year
- 3 patients were re-treated after progression; all in ongoing response (17+ to 52+ months)
Complete Response in Patient with Chemotherapy Refractory PMBCL

Primary Mediastinal Large B-Cell Lymphoma

- Primary refractory
- Progressed on R-CHOP, R-ICE, and R-GDP
- Referred for progressive liver and other abdominal lymphoma

Ongoing Complete Response 15+ months

Prior to treatment

9 months post-treatment

Scans from Dr. Rosenberg NCI
Patient with Refractory DLBCL

Prior to treatment

6 months post-treatment

Scans from Dr. Rosenberg NCI
# Kite’s CAR & TCR Product Pipeline

## Program Indications

<table>
<thead>
<tr>
<th>Program</th>
<th>Indication</th>
<th>Pre-IND</th>
<th>Phase 1</th>
<th>Phase 2/3</th>
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<td>Anti-CD19 CAR</td>
<td>B Cell Malignancies</td>
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<td>KTE-C19 CAR</td>
<td>NHL (DLBCL)</td>
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<td>NHL (MCL)</td>
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<td>Neo-antigen</td>
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<td>SSX2</td>
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<td>Amgen Multi-Target CAR Collaboration</td>
<td>Heme Malignancies/ Solid Tumors</td>
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*Targets and target # undisclosed*

## Blood Cancers

- NHL (DLBCL)
- NHL (MCL)
- CLL
- ALL

## Solid Tumors

- Glioblastoma
- Various tumors
- Cervical / Head & Neck Cancer
- Various tumors
- Various tumors
- Various tumors
- Various tumors

*Pivotal studies in 2015*
Kite CAR T Cell Product Development

• Key attributes of optimal CAR T cell product
  - Robust CAR expression
  - Minimal tonic signaling
  - Efficient multifunctional T cell activation in response to antigen
  - Durability of response and/or ability to retreat
  - Relatively straightforward manufacturing process

• Manufacturing process
  - KTE-C19: streamlined, rapid process
  - In addition, developing new processes for eACT products

• CAR Design
  - High throughput characterization and selection of optimal TM/hinge/spacer domains
  - Rational selection of costimulatory domain

• Next generation eACT
Next Generation eACT

Endow CAR with Novel Properties

Deliver Immune Enhancers

Overcome tumor microenvironment

Increase rate and durability of anti-tumor response

Control Safety/Dosing

Eliminate Immune Inhibition

Improve safety profile