CAR T Cell Therapy for Cancer: What have we learned so far?

Terry J. Fry, M.D.
Outline

• Brief History of Immunotherapy
• Development of CAR Concept
• Clinical CART experience
• Future of CART therapy
Coley’s Toxin: The beginnings of Immunotherapy

William Coley, MD
New York Cancer Hospital (later to become part of MSKCC)
Bone Sarcoma Surgeon
Took care of Elizabeth Dashiell, friend of JD Rockefeller, Jr, who died as a teen of aggressive bone cancer

19th century treatments based on theory that postsurgical infections improved chance for survival from cancer.

“Coley’s Toxins”
Learning from Exceptional Responders

“Nature often gives us hints to her profoundest secrets…”
(W. Coley, 1882-1936)
T cell Activation

Basic Science and Translation: Report of Tumor Rejection following anti-CTLA4 Treatment

Enhancement of Antitumor Immunity by CTLA-4 Blockade

Dana R. Leach, Matthew F. Krummel, James P. Allison

One reason for the poor immunogenicity of many tumors may be that they cannot provide signals for CD28-mediated costimulation necessary to fully activate T cells. It has recently become apparent that CTLA-4, a second counterreceptor for the B7 family of costimulatory molecules, is a negative regulator of T cell activation. Here, in vivo administration of antibodies to CTLA-4 resulted in the rejection of tumors, including preestablished tumors. Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells.

Clinical Response in Melanoma: NCI Surgery Branch anti-CTLA4 Trial

July, 2003

Complete resolution of 2 subcutaneous nodules, 31 lung metastases and 0.5 cm brain metastasis.
Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer

Matthew D. Hellmann,1,2,5,4,17,* Tavi Nathanson,5 Hira Rizvi,3 Benjamin C. Creelan,6 Francisco Sanchez-Vega,7,8 Arun Ahuja,6 Ai Ni,6 Jacki B. Novik,5 Levi M.B. Mangarin,10 Mohsen Abu-Akeel,10 Callian Liu,10 Jennifer L. Sauter,11 Natasha Rekhtman,11 Eliza Chang,5 Margaret K. Callahan,1,2,4 Jamie E. Chaft,1,2,3 Martin H. Voss,1,2 Megan Tenet,3 Xue-Mei Li,12 Kelly Covello,12 Andrea Renninger,12 Patrik Vitzka,12 William J. Geese,12 Hossein Borghaei,13 Charles M. Rudin,1,2,3 Scott J. Antonia,6 Charles Swanton,14,15 Jeff Hammerbacher,5,16 Taha Merghoub,1,2,4,10 Nicholas McGranahan,14 Alexandra Snyder,1 and Jedd D. Wolchok1,2,4,10
The prevalence of somatic mutations is low in many cancers
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Redirecting Specificity for Adoptive Cell Therapies: Synthetic Immunology

Advantages of CAR
- Specific for a surface antigen
- Free of MHC restriction
- Signals for full activation are self-contained

Adapted from Lee et al, Clin Can Res, 2012
Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

Communicated by Michael Sela, July 13, 1989 (received for review June 18, 1989)
Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19


1Surgery Branch, 2Metabolism Branch, and 3Laboratory of Pathology, National Cancer Institute, Bethesda, MD, and 4Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, MD

A

CD79a

B

CD79a

C

B cells/μL

Weeks after T cell infusion

BLOOD, 18 NOVEMBER 2010 • VOLUME 116, NUMBER 20
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Initial Experiences with CD19 CAR T cells

70-90% of patients achieve remission

CD19 CARs: original CARs: 
multiple variants, comparable efficacy in early phase trials

Sadelain, *JCI*, 2015
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

CD22 targeted CART achieves MRD Negative Remission in Relapsed/Refractory ALL

Haso…Orentas, Blood 2013
Haso….Fry, ASH 2013
Fry/Shah et al., Nature Medicine 2017
CD22 BBz CAR: Relapse associated with CD22 modulation

Duration in Continuous Remission

Days post CD22 CAR T-Cells

Subject ID

Duration in Continuous Remission

Pre-CD19/CD22 CAR
Post-CD19 Pre-CD22 CAR
Post-CD19/CD22 CAR

Shalabi.....Fry, Shah, Hematologica, 2017
Manufacturing Details Matter

<table>
<thead>
<tr>
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<th>CD3/CD28 enriched</th>
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<tr>
<td>Transduction efficiency</td>
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High B-cell blast

Starting apheresis

Post CD4/CD8 selection

Final product

Post-infusion

IL-6 (pg/ml)

Ferritin (mcg/L)

*, p = 0.018

*, p = 0.0007
Importance of Correlative Science

![Graphs and images depicting changes over time and frequency per 100 cells.

Vector Copy Number and CBL Clone Per 100 Cells

Days Post Infusion:

WBC, ALC, Ferritin, CRP levels over time.

Frequencies per 100 cells at various days post infusion.

Gene regions and lengths:

CBL (length 101,874bp) chr11:119143577

Pre-Treatment, Day 30, Day 90 images of patient.

3LTR, EF1a-CD22-CAR, 5LTR genetic intervals.

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Patterns of Failure after CAR T cell Therapy

- Poor T cell Expansion
- Lack of CAR Persistence

CAR Failure

- CD22
- CD19

CAR expansion
Remission
CAR Persistence

Leukemic Resistance
Multispecific CAR Targeting

Co-administration

Co-expression

Bispecific Constructs
Development of an Active CD19/CD22 Bivalent CAR

Haiying Qin
Nature Medicine, 2017
Molecular Therapy Oncolytics, 2018
Clinical Activity of TanCAR: Bivalent CD19/22-CAR

Hossain et al, ASH 2018, Abstract 490.
Translation

Signal Integration

Trial Planned CHCO and UCH for early 2020
Leukemic evolution in the context of targeted Immunotherapy can be complex

Jacoby et al., Nature Communications, 2016

Gardner et al., Blood, 2016
Patterns of Failure after CAR T cell Therapy

- Poor T cell Expansion
  - Lack of CAR Persistence

- CD22

- CD19
  - CAR expansion
  - Remission
  - CAR Persistence

- CAR Failure

- Leukemic Resistance
**Chimeric Receptors are Not the Same as the native TCR**

- Affinity for antigen is ~1000 fold higher in CARs
- 10 ITAMs per receptor
- CAR contains in-line co-stimulatory signaling
- Unknown if CAR activation results in organized synapse
- Distance between cells variable with CARs
- CD4/CD8 co-receptors not recruited by CARs
Signaling through the mCD19-28z CAR leads to prolonged Zap70 phosphorylation and decreased phosphorylation of Erk relative to TCR.
CAR-mediated anti-leukemic potency inferior to TCR

CAR-OTI Dose: 50,000/mouse
So, what have we learned?

- Single antigens comparable to CD19 will be difficult to find
- Details of CAR T cell products matter
- Antigen modulation as well as more complex patterns of cancer resistance will frequently emerge
- Current CAR formats do not fully recapitulate T cell biology
- As synthetic receptors, the ability to modify is almost endless
  - Binding domains, signaling domains, multiplexing

COST of and ACCESS to complex therapeutics will be a challenge
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Patients and Families