SERVIZIO SANITARIO REGIONALE
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ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

New Drugs in Hematology

President:
Pier Luigi Zinzani
Co-President: Michele Cavo
Honorary President: Sante Tura

Bologna,
Royal Hotel Carlton
May 9-11, 2016

# CAR T cells

**Carl June**

**May 9, 2016**

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

Penn Medicine
Center for Cellular Immunotherapies


# Disclosures of: *Carl June*

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Novartis | xx | | | | | | IP licensure / Royalty |
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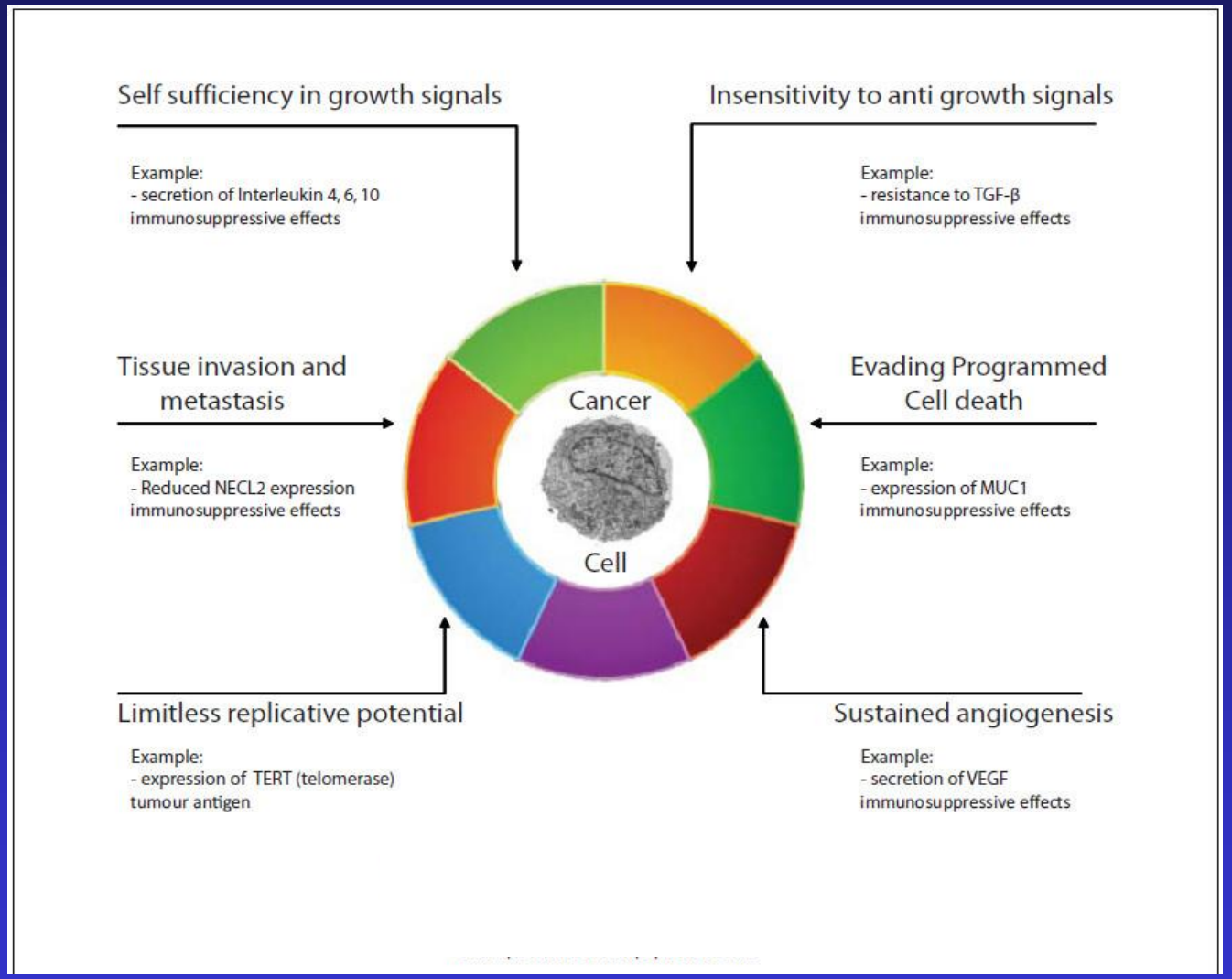
# Topics

- New CAR designs
- CD19 CARs for lymphoma
- BCMA CARs for myeloma
- Combination immunotherapy:

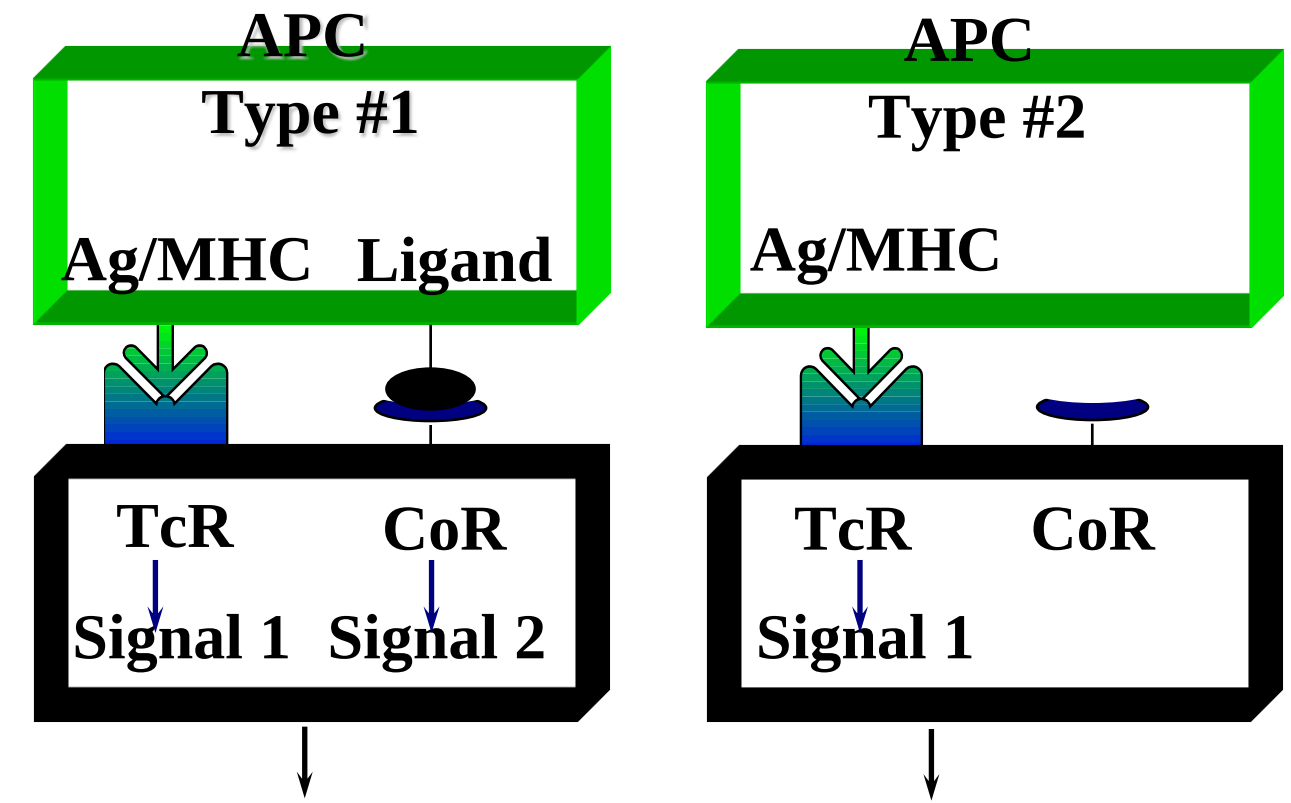
  => CARs meet checkpoints

# Hallmarks of Cancer: Immune Escape and Tolerance




Tesniere, et al. *Discovery Med* (2009)
Hannahan and Weinberg. *Cell* (2000)

# Lafferty and Cunningham Model of Immunologic Tolerance: 1975



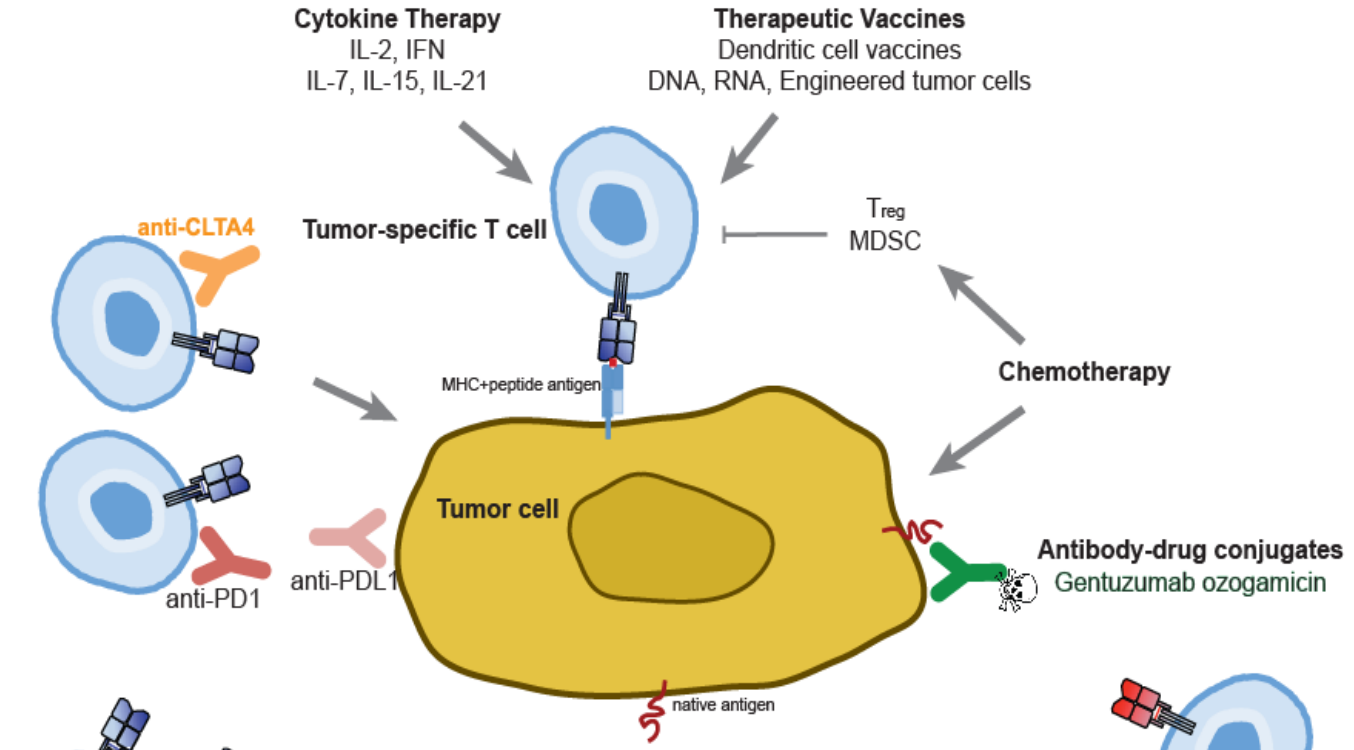

**Potential outcomes:**
**Clonal expansion**
**Effector functions**

**Potential outcomes:**
**Anergy**
**T cell death**

# Approaches to Overcome Self Tolerance: ACT and Checkpoint Therapies

**Checkpoint Therapies**

**ACT Therapies**



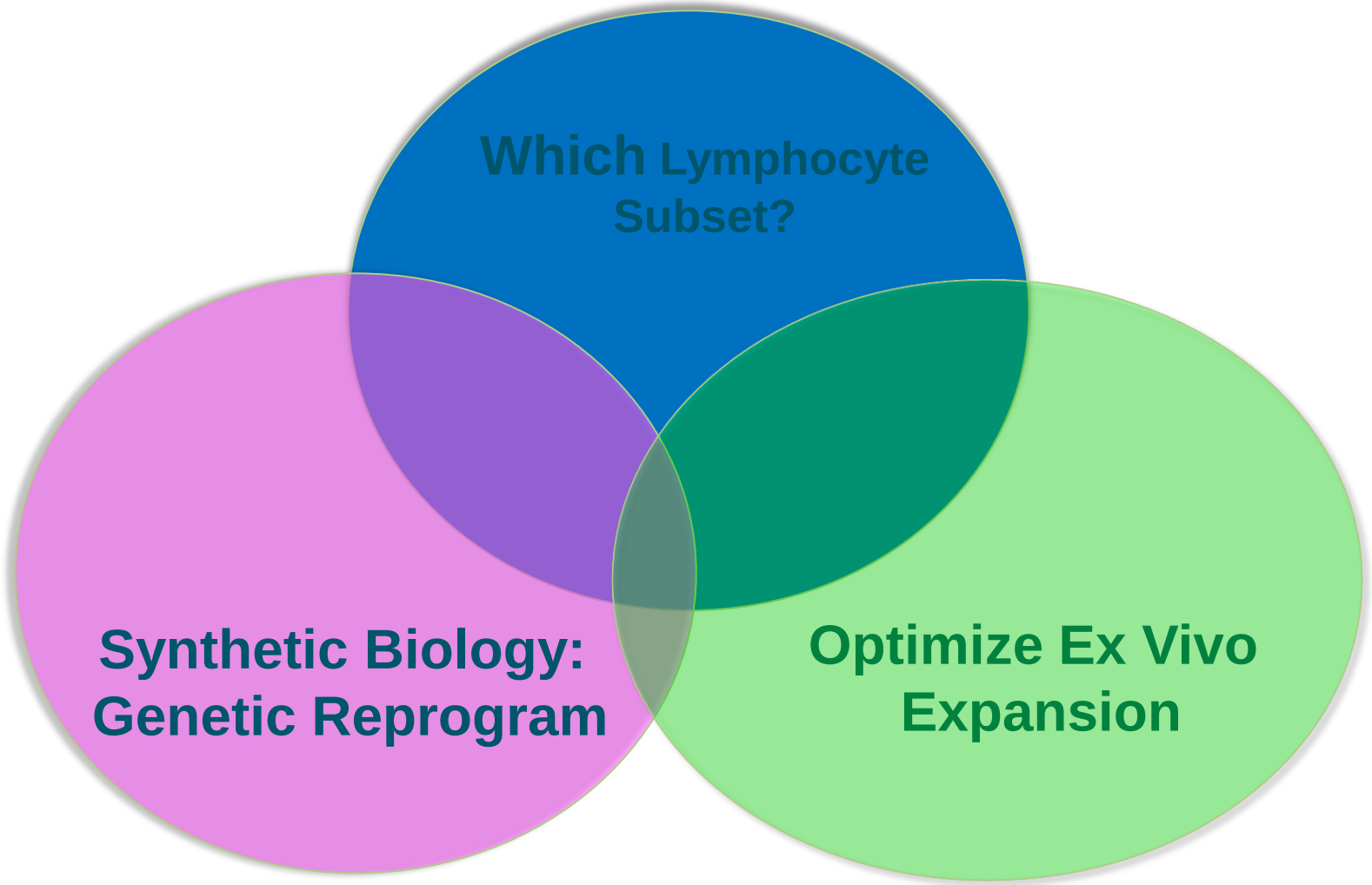

**TILs**

**CAR T cells**

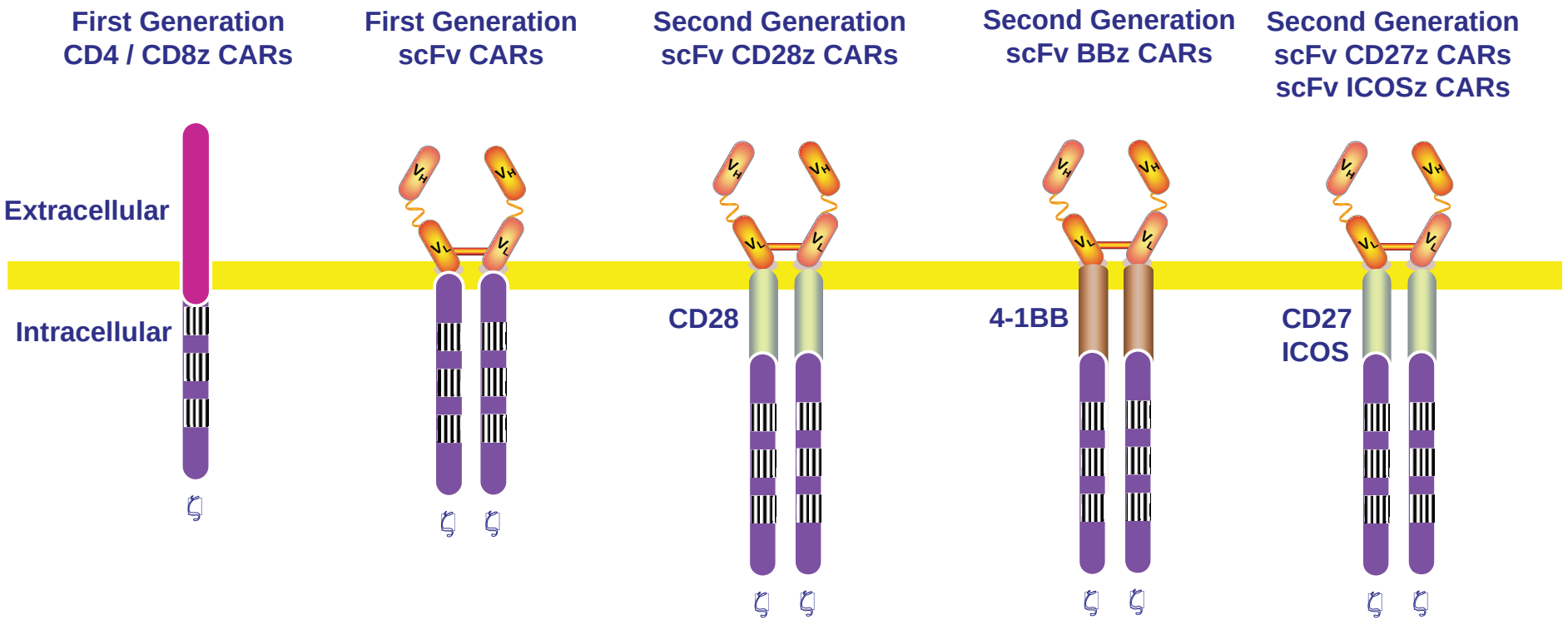
**TCR T Cells**

Maus MV et al. Blood. 2014;123:2625.

# Essential factors for augmenting adoptive immunotherapy



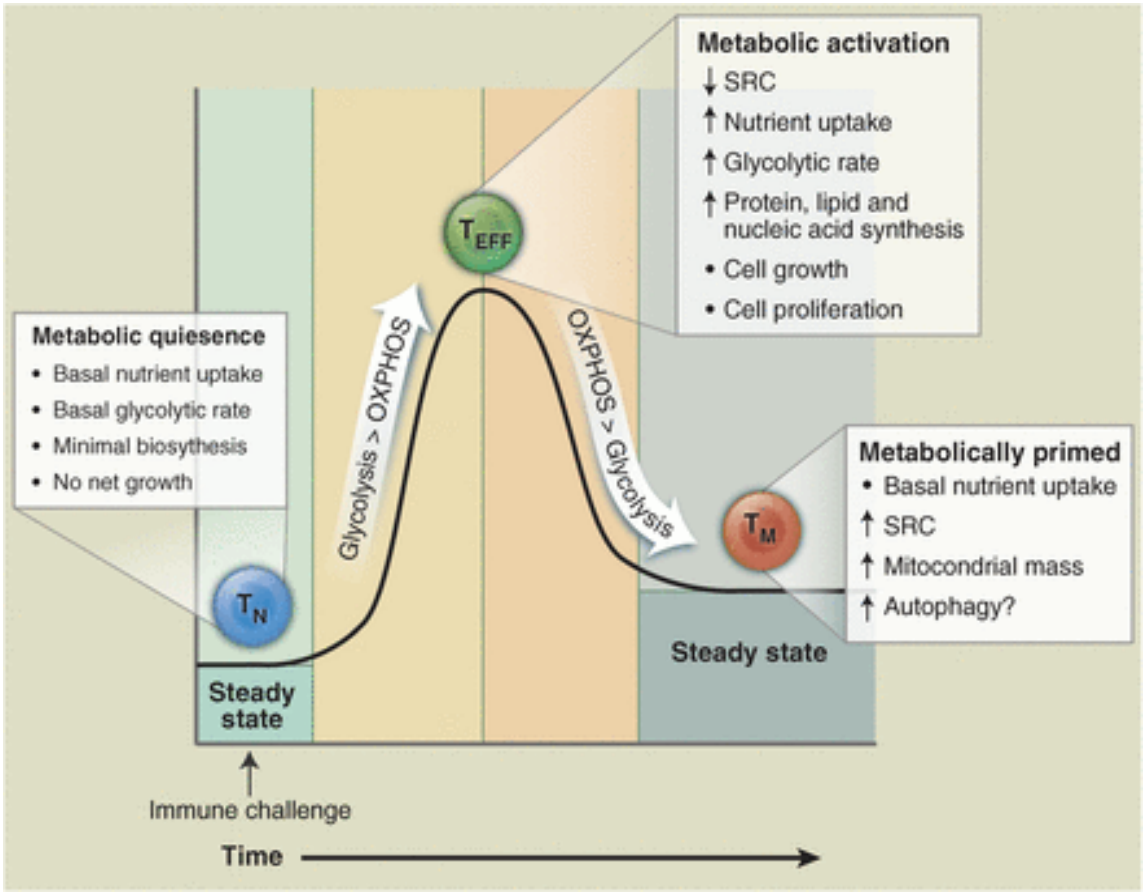
# Using Synthetic Biology to Overcome Tolerance
# Creation of Bi-specific CAR T cells




# Design of CAR T Cells

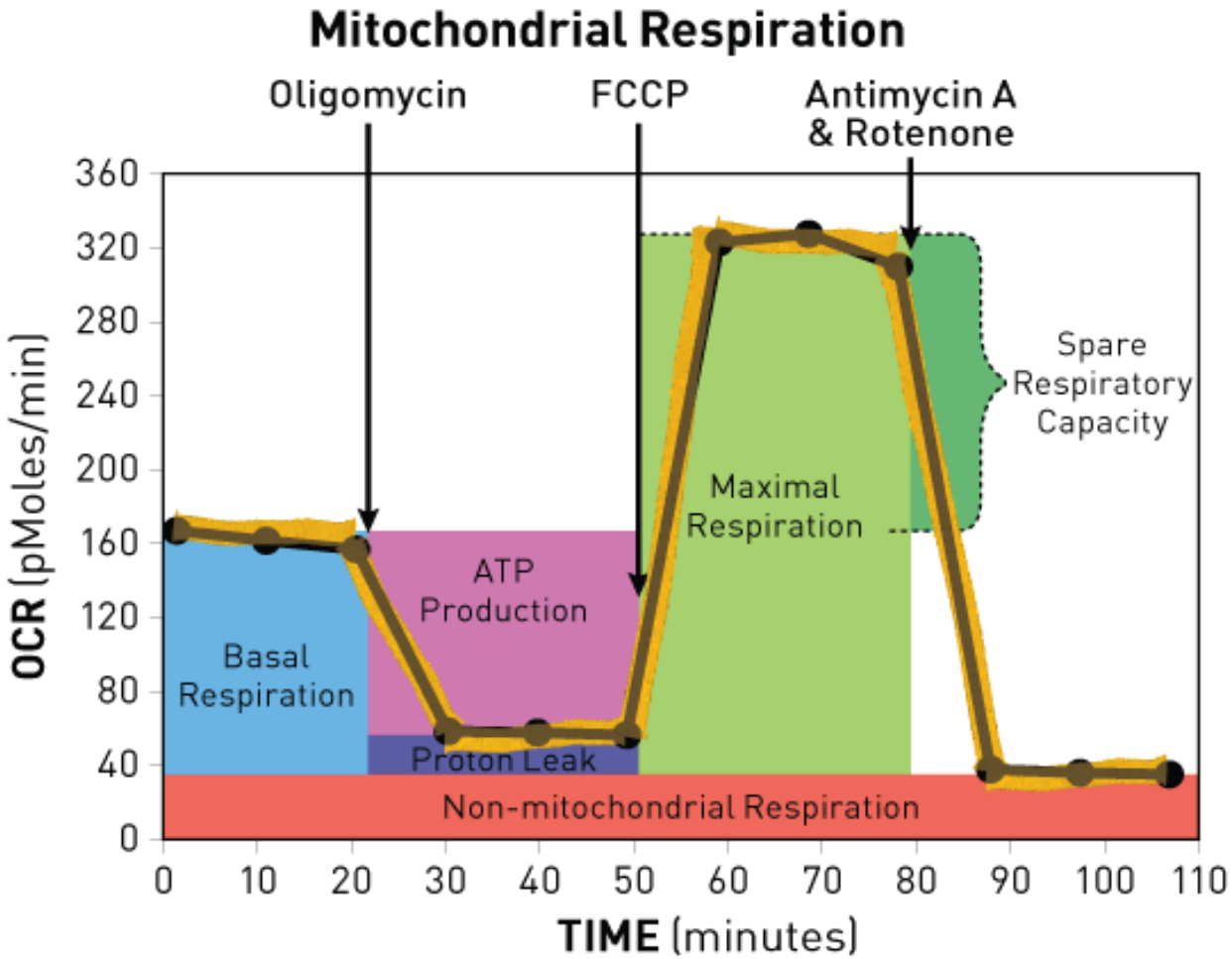
# Metabolic Features of Natural T cells

## Higher Spare Respiratory Capacity memory T cells



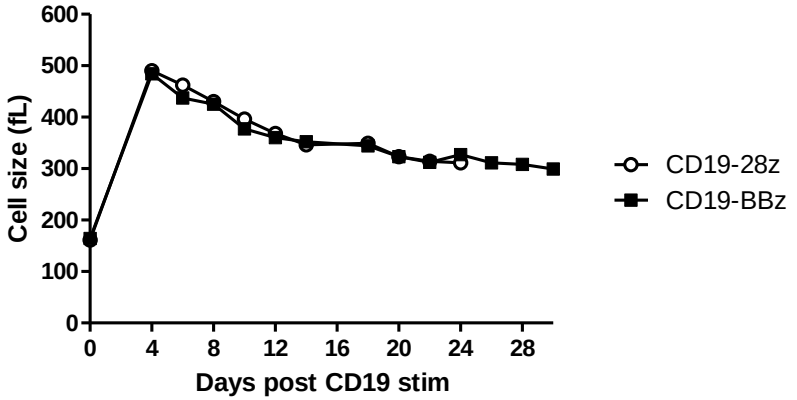

Pearce EL, Science 2013

## Seahorse assay

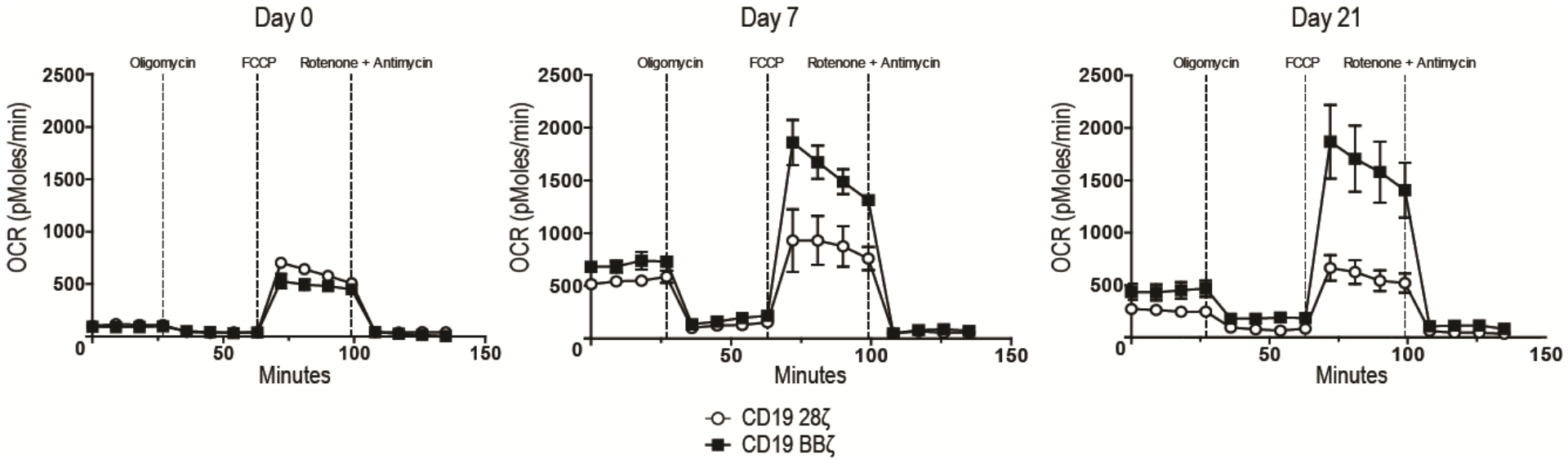


# Oxygen consumption profiles of CAR T cells

## *Cytosolic signaling domain has differential effects on cell volume and oxygen consumption*

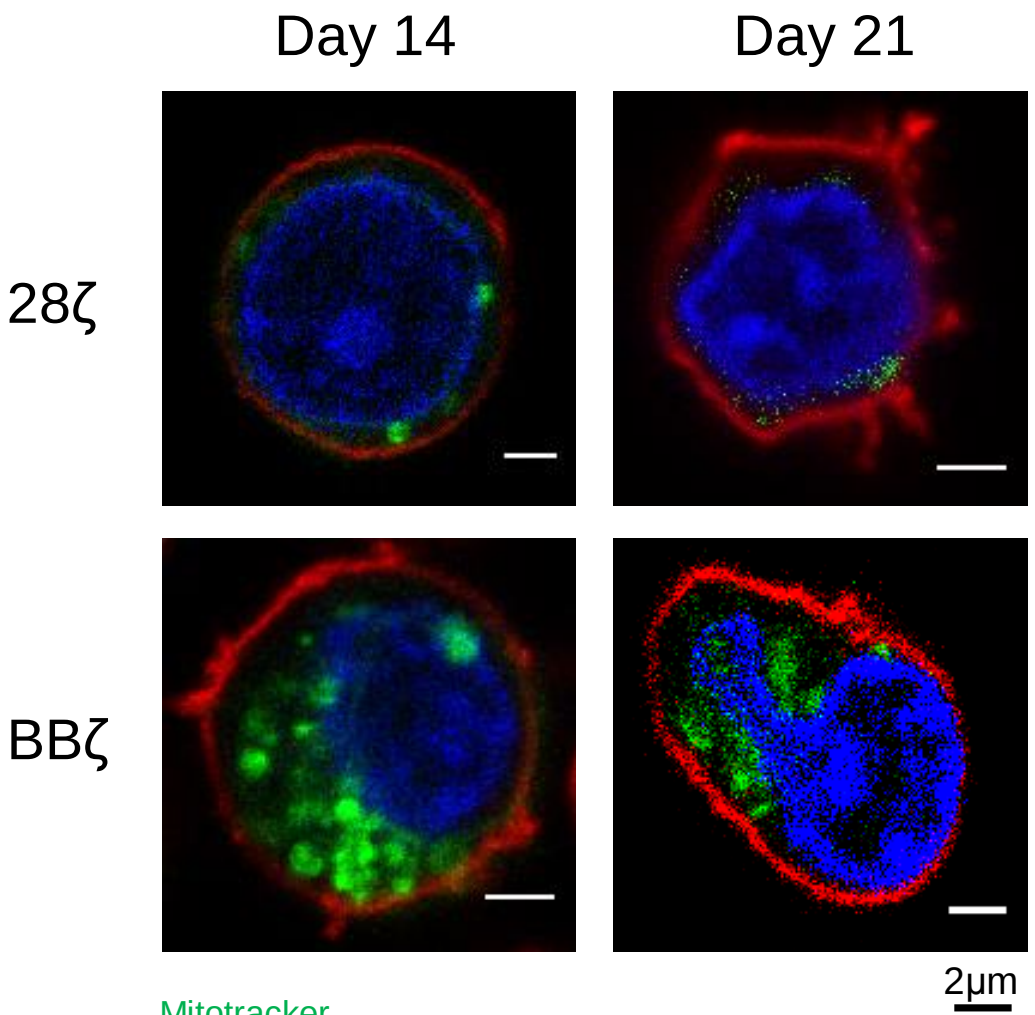


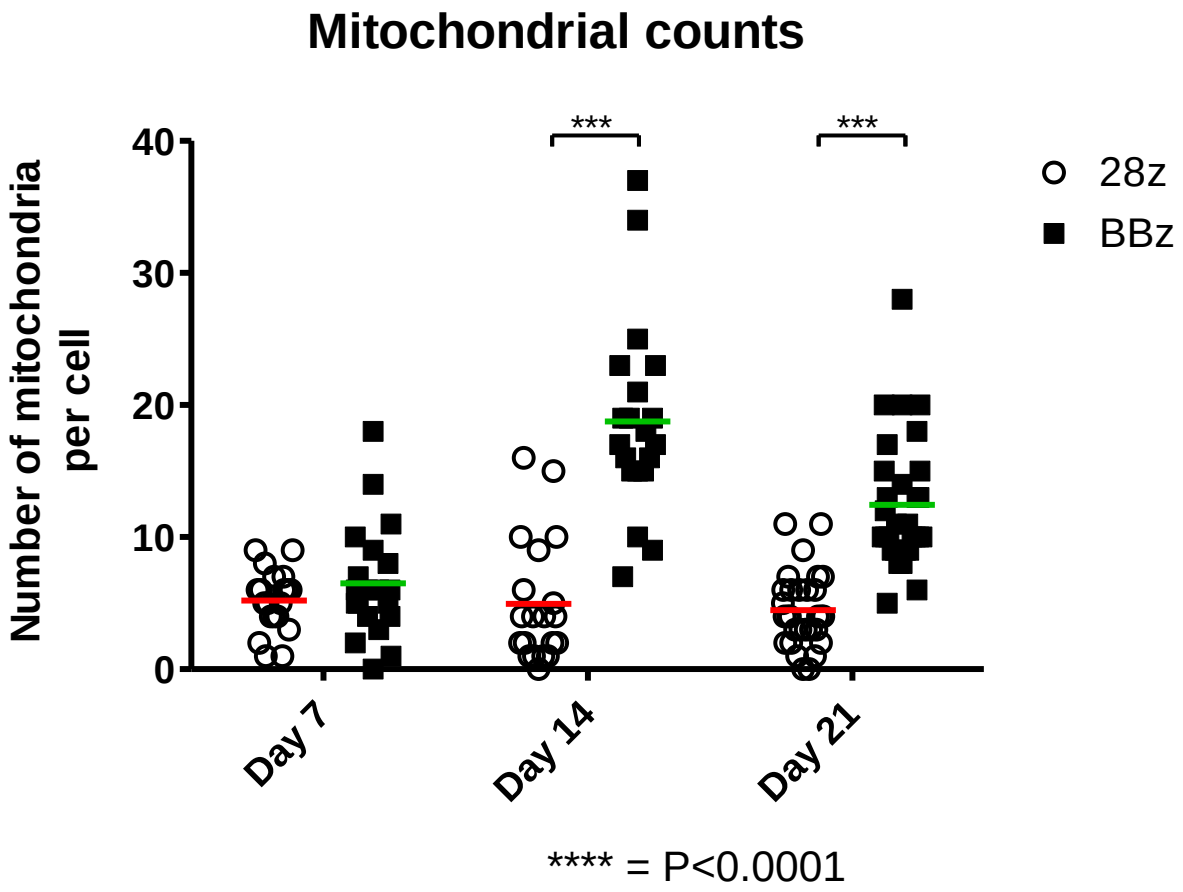

Kawalekar et al, Immunity 44: 380, 2016



# Increased mitochondrial biogenesis in 4-1BBζ CAR T cells

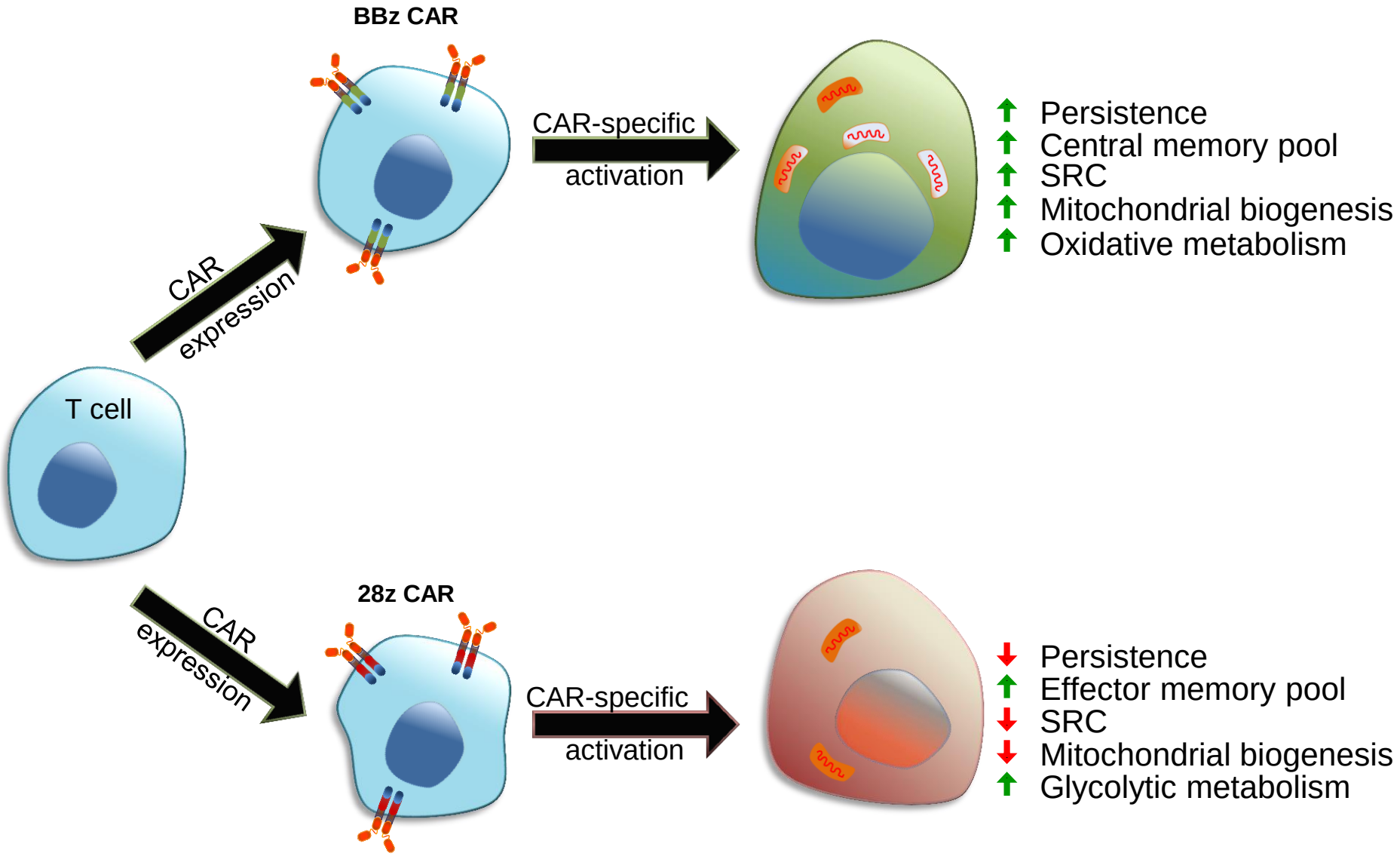
## *CD8+ T cells: confocal microscopy*




Kawalekar et al, Immunity 44: 380, 2016

# CAR Signaling Domains Program Cells for Metabolic Fitness



# CAR T Cells: they are bionic!

- CAR scFv or TCR can reprogram specificity of T cells for tumor target. Specificity is important to avoid toxicity
- CAR signaling domains can reprogram T cell metabolism. This can enhance survival in tumor microenvironment and effector function:
  - CD28 domains: enhance glycolysis via “Warburg” effect. This leads to enhanced effector function and decreased persistence
  - 4-1BB domains: enhance mitochondrial biogenesis, and are associated with enhanced persistence
  - ICOS domains: enhanced persistence and cellular respiration in CD4 CAR T cells

# CAR T Cell trials: Examples at Penn and Novartis

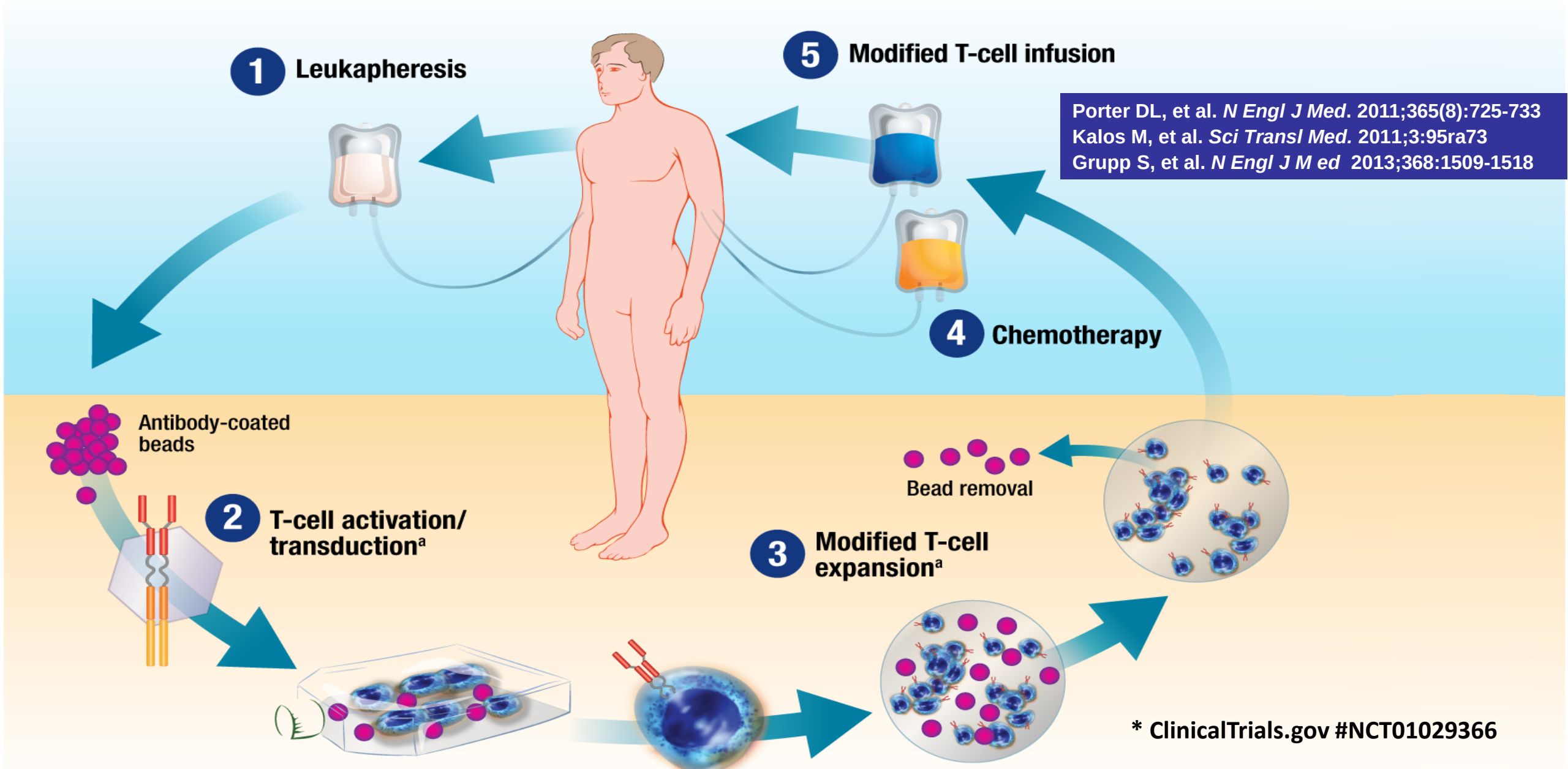
| Institution | CAR | Target Indication |
|---|---|---|
| UPENN<br>CHOP | CART19 | CLL, ALL, DLBCL, Follicular Lymphoma, Myeloma |
| UPENN | CART BCMA | Myeloma |
| UPENN | CART Mesothelin | Pancreatic cancer, ovarian cancer, mesothelioma |
| UCSF | CART<br>Mesothelin plus<br>CART19 | Pancreatic cancer |
| UPENN | CART cMet | Triple-negative breast cancer |
| UPENN<br>UCSF | CART EGFRviii | Glioblastoma |

# Cummulative Patient Safety: Years of Genetically Modified T cells

## University of Pennsylvania (as of Dec 2014)

| Trial | Engineered T Cell | # Patients Infused | Safety (Patient-Years) |
|---|---|---|---|
| Sangamo ZFN (HIV) | Ad5/35 zinc finger nuclease | 12 | 49.1 |
| CD4z CAR (HIV) | Retroviral CAR | 44 | 690.6 |
| Takara (HIV) | Retroviral MazF | 5 | 4.4 |
| VirxSys VRX496 (HIV) | Lentiviral antisense HIVenv | 20 | 161.9 |
| Adaptimmune (HIV) | Lentiviral gag TCR | 2 | 6.6 |
| Adaptimmune Myeloma and Sarcoma | Lentiviral NY-ESO1 TCR | 21 | 54.3 |
| Novartis CART19/CTL019 | Lentiviral 19:BBz CAR | 151 | 246.3 |
| | | | |
| | **Total** | **255** | **1213** |

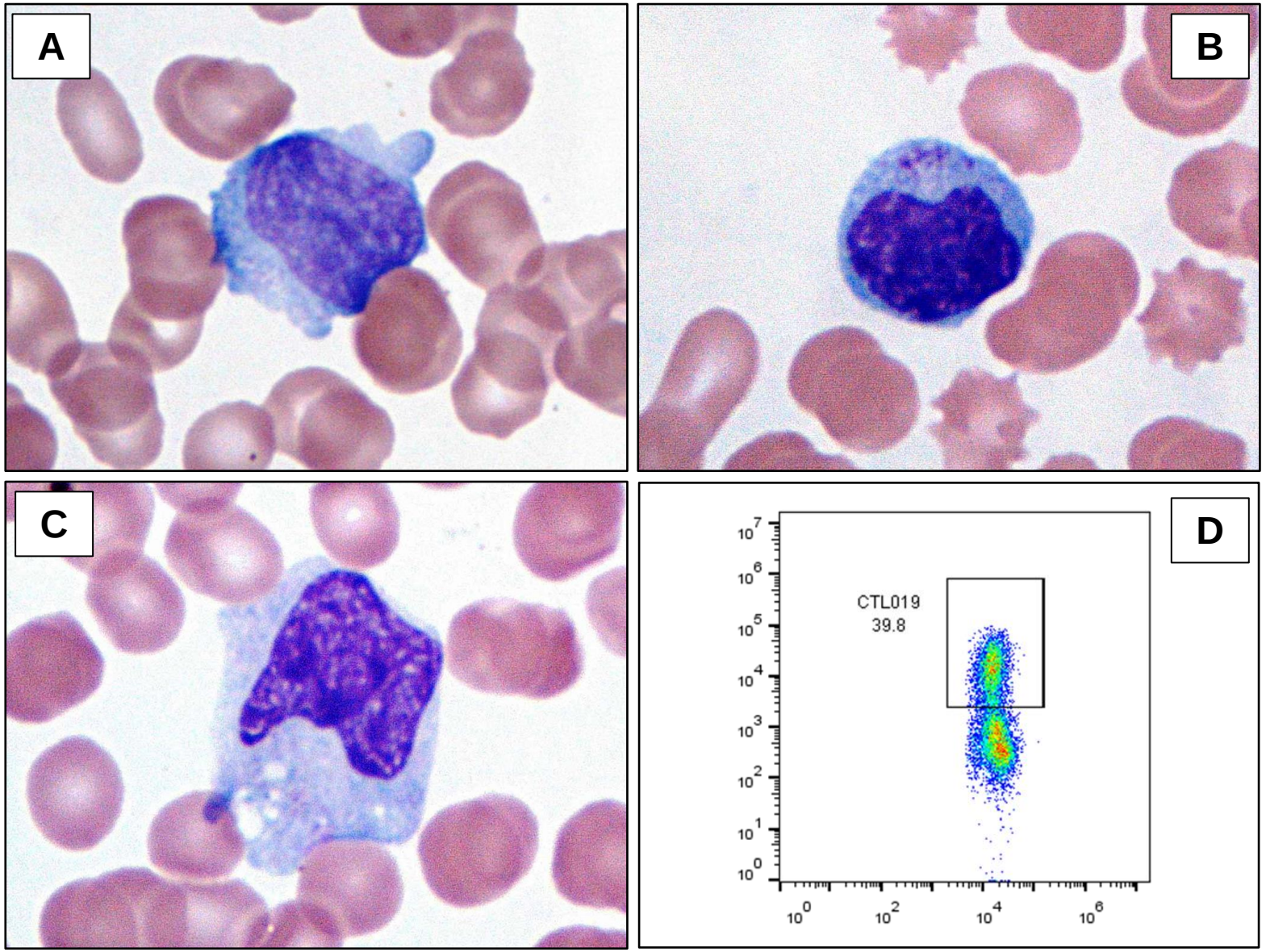
# Adult Chronic Leukemia Study Overview*




Porter DL, et al. *N Engl J Med*. 2011;365(8):725-733
Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73
Grupp S, et al. *N Engl J M ed* 2013;368:1509-1518

* ClinicalTrials.gov #NCT01029366

# Circulating CTL019 in CLL: diagnostic challenge!




- Recognition of CAR T cells can be a challenge
- In CLL: CAR T or Richter's transformation?

Bagg, Wasik et al

# CTL019 Phase I Trial for r/r CLL: 5 yr follow up
# Summary of patient baseline characteristics

*N= 14 patients, protocol 04409 (NCT01029366)*

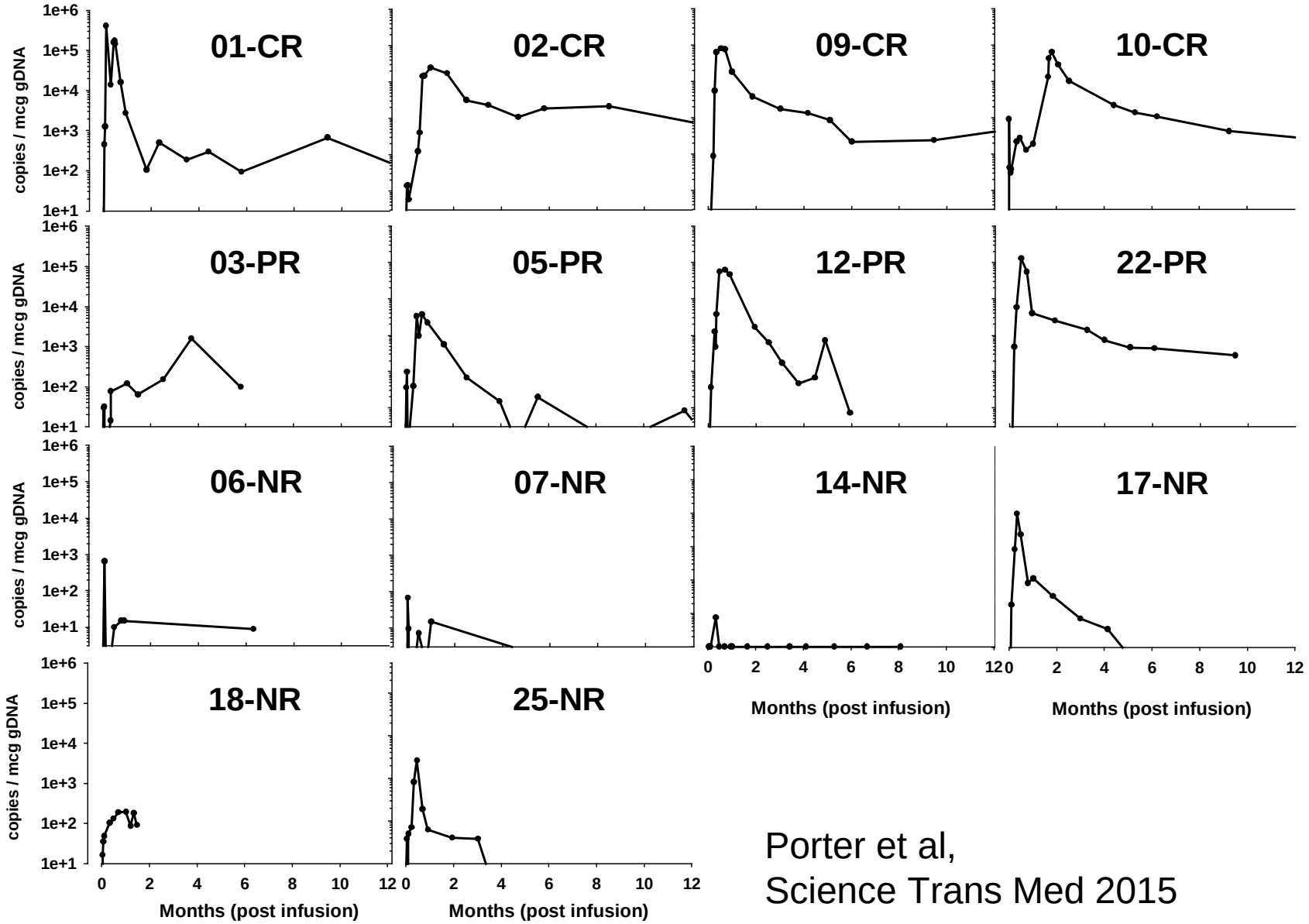
| Characteristics | Statistics, N(%) |
|---|---|
| N | 14 |
| Age at infusion in years | |
| Mean (SD) | 66.9 (8.1) |
| Median (range) | 66 (51-78) |
| Gender | |
| Male | 12 (85%) |
| Female | 2 (14%) |
| Number of prior therapies | |
| Mean (SD) | 5.3 (2.8) |
| Median (range) | 5 (1-11) |
| P53 or 17p deletion | |
| No | 8 (57%) |
| Yes | 6 (43%) |
| IGHV mutation | |
| No | 9 (64%) |
| Yes | 4 (29%) |
| Unknown | 1 (7%) |

- Overall response rate: 57%
- CR 4/14 (28%)
- PR 4/14 (28%)
- NR 6/14 (43%)

**Porter et al, Science Trans Med 2015**

# Long term persistence and expression of CTL019 in CLL is associated with durable remission

***Persistence for first year after infusion***




Porter et al,
Science Trans Med 2015

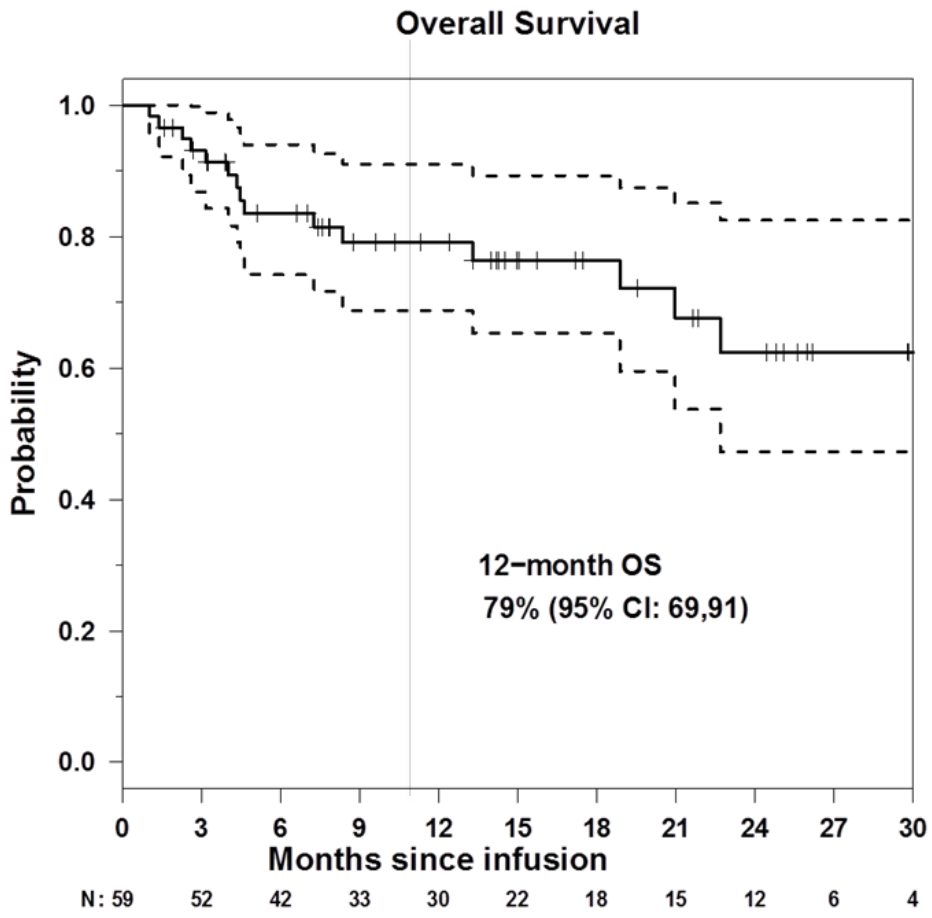
# Key CAR-T Results: Pediatric/Young Adult ALL

| | CTL019 (anti-CD19) | JCAR017 (anti-CD19) | JCAR018 (anti-CD22) | KTE-C19 (anti-CD19) |
|---|---|---|---|---|
| **Trial [sponsor]** | Phase I/IIa, NCT01626495 / CHP959 [Univ of Pennsylvania] | Phase I/II, NCT02028455 / PLAT-02 [Seattle Children's Hospital] | Phase I, NCT02315612 [National Cancer Institute] | Phase I, NCT01593696 [National Cancer Institute] |
| **Patient population** | 4-24 yrs*, ≥2nd r/r ALL (**N=59**), ≥2nd relapse or refractory (majority refractory to multiple prior therapies) [*enrolled adults too; efficacy data here is for pediatric cohort only] | 1-26 yrs, r/r ALL (N=37, **evaluable N=32**); majority (>75%) have had 1 or 2 relapses; ~2/3 have had transplant | 7-22 yrs, r/r ALL, (**N=9, 7 assessed**) all had undergone ≥1 prior alloHSCT and had been previously treated with a CAR-T | 4-27 yrs, r/r ALL or NHL (**N=46 infused**; ALL n=45, DLBCL n=1). Prior transplant history not stated. |
| **Dosing** | Varied lymphodepleting chemotherapy regimens used. Target dosing **$10^7$-$10^8$ cells/kg**. Median 4.3x$10^6$ cells/kg infused | Varied lymphodepleting strategies used 4 dose levels: 5x$10^5$-1x$10^7$ cells/kg; MTD **5x$10^6$ cells/kg** better risk-benefit profile with much lower **5x$10^5$ cells/kg** dose | Induction chemotherapy with fludarabine 25 mg/$m^2$ days -4,-3,-2 and cyclophosphamide 900 mg/$m^2$ on day -2 Lowest dose: **3x$10^5$ cells/kg** (6 pts treated). Next dose: **1x$10^6$ cells/kg** (3 pts treated) | Initial 21 pts and all w low burden: low-dose chemo: fludarabine (25 mg/$m^2$/day days -4 to -2) and cyc (900 mg/$m^2$ day -2) High disease burden: high-dose individualized chemotherapy regimen Dose-finding: 1x$10^6$ or 3x$10^6$ cells/kg; **MTD was 1x$10^6$ /kg** |
| **Response rate** | **CR 93%** (55/59) at 1 month, median f/u 12 mo | **CR 91%** (21/22) as of Sept 2015 data cut-off; CMR 91% (85% MRD-negative) | (Preliminary data) **2/7 pts had MRD-negative CR** (1 at each dose), 2 with SD, 3 with PD, 2 pts too early to assess | **CR 60%** |
| **Response durability** | 18 pts in remission >1 yr, 13 without further therapy | Longest CR: 7 mos | In the 1 MRD-negative CR pt, sustained at 2 mo (relapsed at 3 mo) | Longest CR 28 mo (in pt with primary refractory ALL) Median LFS 17.7 mo (45.5% probability of LFS at 18 mo), based on 20 pts who achieved MRD-negative CR |
| **Persistence of CAR T cells** | Detectable 3 yrs or longer | 3 mos | In the 1 MRD-negative CR pt, 19% CAR T cells in bone marrow at 2 mo | 68 days |
| **Safety** | sCRS in **27%** (8/30) among early (N=30) cohort/ CRS (all grades) 88% of larger pediatrics cohort (N=59). Severe AEs: **43%** (13/30) neurotoxicity; self-limiting. 3 CRS-related deaths among adult pts (none among pediatric pts) | CRS **27%** (n=22) **18%** (n=22) neurotoxicity. No deaths reported | Max CRS was gr 2; no dose-limiting CRS. At lowest CAR-T dose, 1 pt had gr 3 diarrhea. No deaths reported | sCRS 7/46 (**15%**); grade 3/4 neurotox 3/46 (**7%**); no permanent neurocognitive decline No deaths reported. |

# 93% CR rate for r/r ALL after CTL019

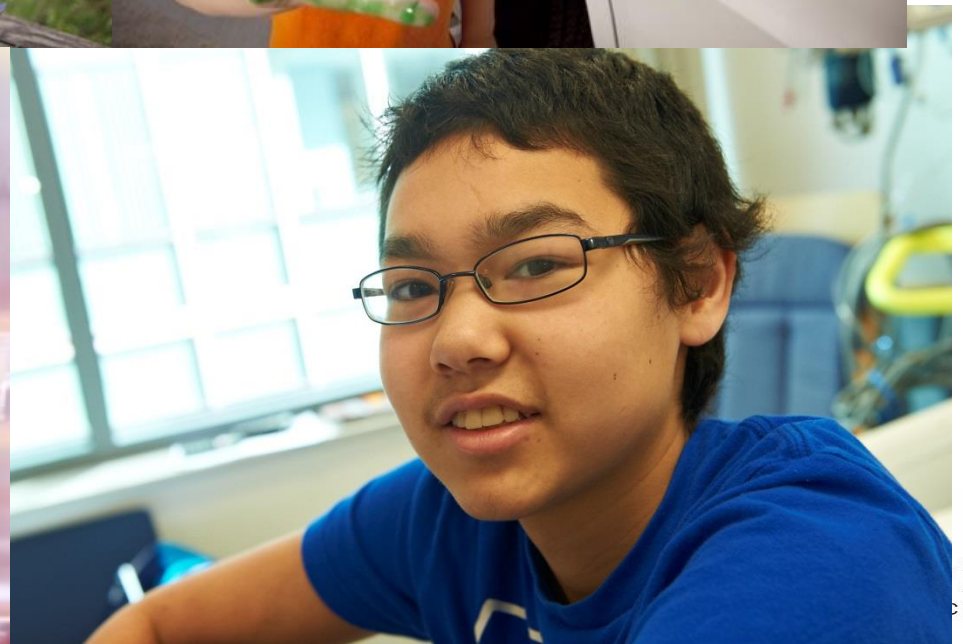
>200 patients with CLL, ALL, NHL, MM have gotten CTL019

- 59 r/r pediatric ALL pts:
  55 in CR at 1 mo (93%)
  median f/u 12 mo
- 6 went to subsequent transplant, 1 to DLI
- 6 mo RFS: 76% (95%ci 65-89%)
  12 mo RFS: 55% (95%ci 42-73%)
- No relapses past 1 year
- 18 patients in remission beyond 1 year



# Some of Dr Grupp's Pediatric Leukemia Patients





# White House Visit to UPENN
# Vice President Biden: Moonshot Discussions,  Feb 2016

Penn Medicine

the cure is within
ABRAMSON CANCER CENTER

# Vatican Conference, April 2016

## Convegno internazionale promosso dal pontificio consiglio della cultura

# Vatican Conference, April 2016

## Convegno internazionale promosso dal pontificio consiglio della cultura

## Pope Francis and Nick Wilkins, ALL pt# 15


Penn Medicine

# Determine Efficacy and Safety of CTL019 in Pediatric Patients with Relapsed and Refractory B-cell ALL (ELIANA)

**US sites**

- Children's Hospital of Philadelphia
- Cincinnati Children's Hospital
- University of Wisconsin
- Children's Medical Center of Dallas/UTSW
- Children's Mercy Kansas University
- Oregon Heath & Science University
- Stanford University
- University of Minnesota
- Children's Hospital Los Angeles
- University of Michigan
- Duke University

**Ex- US**

**(Canada, Australia, EU, Japan)**

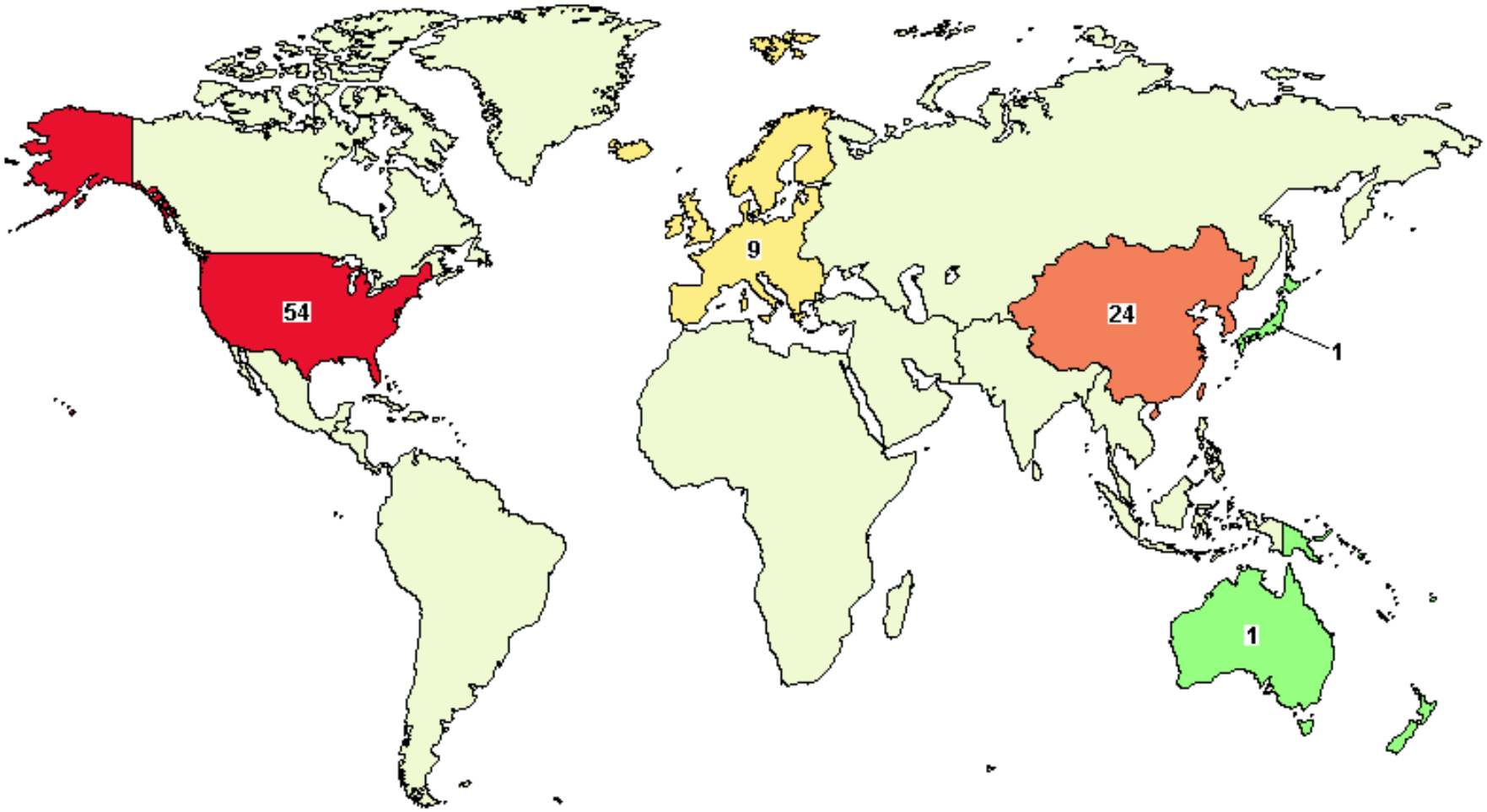
- Royal Children's Hospital (Australia)
- Hospital St. Justine (Canada)
- Ghent University (Belgium)
- Oslo Univ. Hospital (Norway)
- Kyoto (Japan)

Clinicaltrials.gov NCT02435849

Protocol closed to enrollment

NOVARTIS

# CAR T Cell Trials Are Now Global



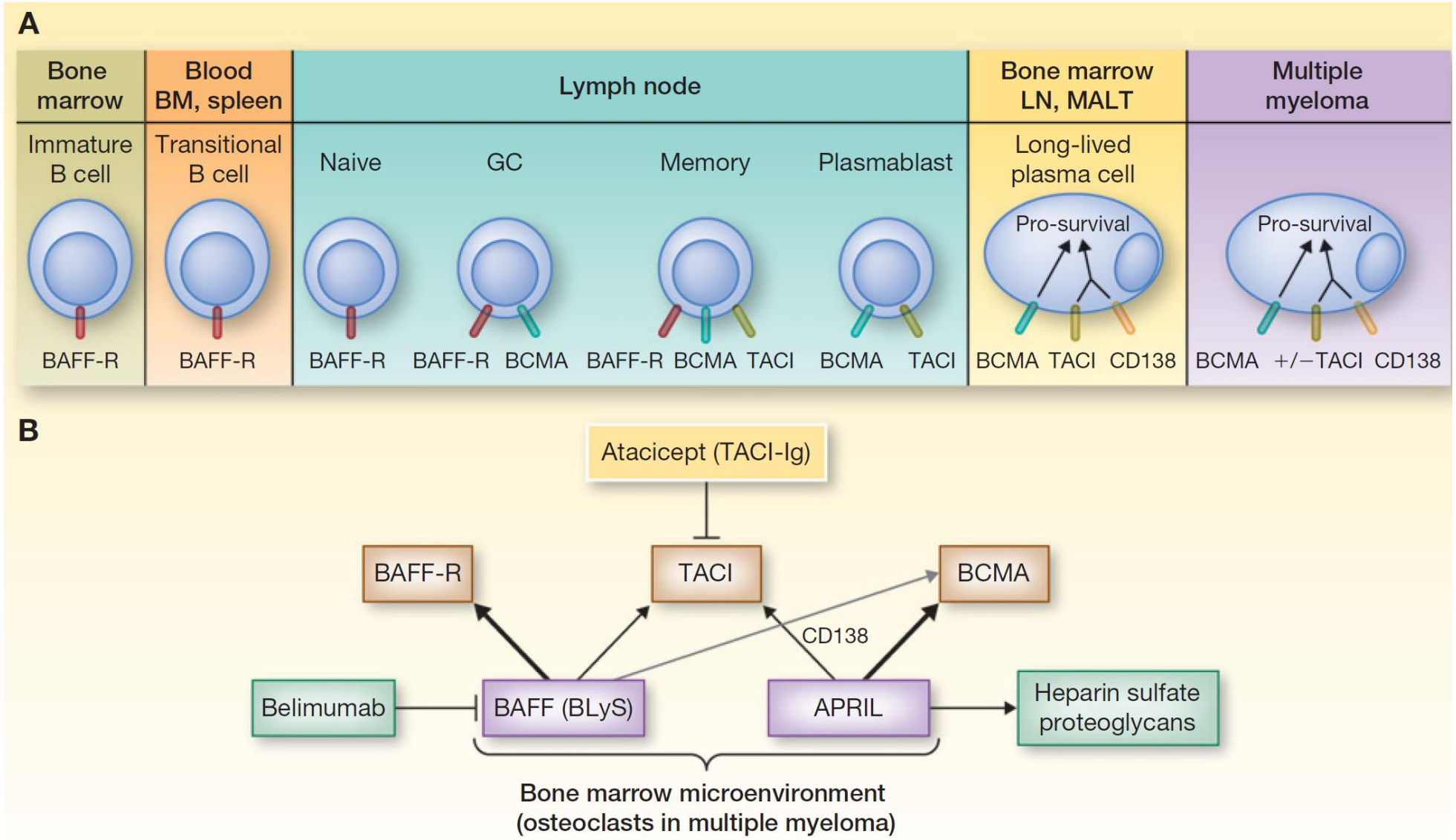

Clinical trials.gov search term “chimeric antigen receptor”
88 trials ongoing as of December 10, 2015

# Moving beyond leukemia: CAR T for myeloma*

| Institution | CAR | Protocol Title |
|---|---|---|
| **NCT02135406 UPENN** | CART19 | Pilot Study of Redirected Autologous T Cells Engineered To Contain Anti-CD19 Attached To TCRζ And 4-1BB Signaling Domains Coupled With Salvage Autologous Stem-Cell Transplantation (ASCT) In Multiple Myeloma Patients With Early Relapse/Progression After Initial ASCT |
| **NCT02215967 NCI** | CART BCMA | A Phase I Clinical Trial of T-Cells Targeting B-Cell Maturation Antigen for Previously Treated Multiple Myeloma |
| **NCT02546167 UPENN** | CART BCMA | Pilot Study of Redirected Autologous T Cells Engineered To Contain an Anti-BCMA scFv Coupled To TCRζ And 4-1BB Signaling Domains in Patients With Relapsed and/or Refractory Multiple Myeloma |
| **NCT02658929 NCI / Bluebird Bio** | CART BCMA | A Phase 1 Study of bb2121 in BCMA-Expressing Multiple Myeloma |
| **NCT01886976 Chinese PLA General Hospital** | CART 138 | Clinical Study of Chimeric CD138 Antigen Receptor-modified T Cells in Relapsed and/or Chemotherapy Refractory Multiple Myelomas |

*** clinicaltrials.gov**

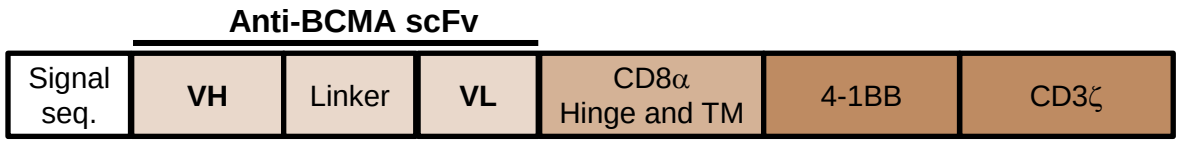
# BCMA (B-cell maturation antigen)




**Maus and June, Clin Cancer Res 2013**

# CART-BCMA Cells for Multiple Myeloma

## clinicaltrials.gov NCT02546167




Adam Cohen

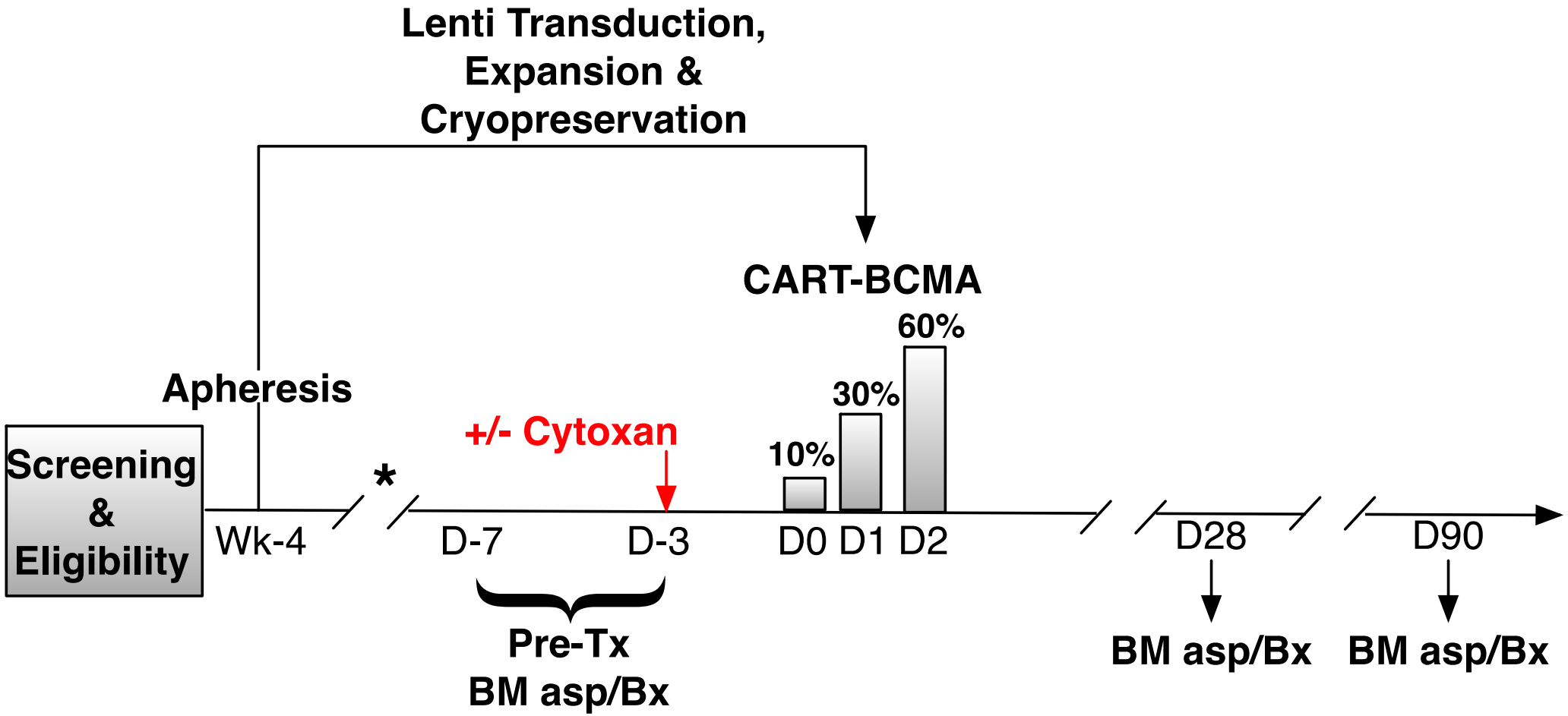
Michael Milone

- **Pilot, first-in-human, 3+3 dose-escalation study**
- **n=12-18 rel/ref MM patients (≥ 3 priors)**
- **Primary obj: Safety**

| Cohort | Lymphodepleting chemo | CART-BCMA cell dose |
|---|---|---|
| -1 | - | 1 to 5 x $10^7$ |
| 1 (n=3-6) | - | 1 to 5 x $10^8$ |
| 2 (n=3-6) | Cytoxan 1.5 g/$m^2$ | 1 to 5 x $10^7$ |
| 3 (n=3-6) | Cytoxan 1.5 g/$m^2$ | 1 to 5 x $10^8$ |

# CART-BCMA Cells for Multiple Myeloma

## Overall Study Design



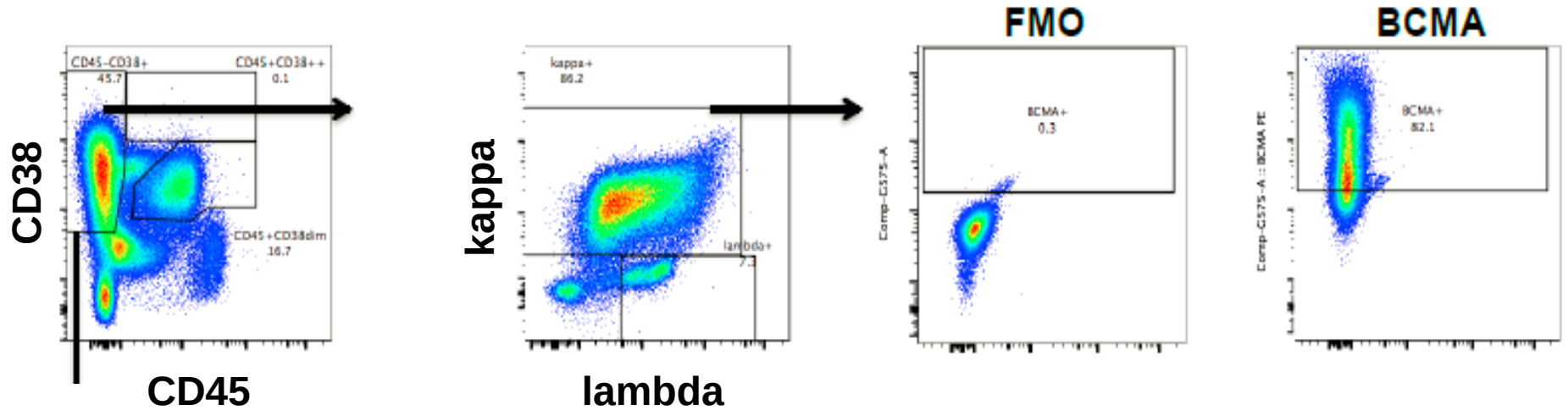

* Patients may receive therapy during manufacturing to maintain disease control

# CART-BCMA Cells for Multiple Myeloma

## Subject #1

- **66M, IgG kappa MM dx'd April 2006**
  - **11 prior lines, progressing on last therapy**
  - **Pre-treatment bone marrow bx:  70% MM cells**
    - **FISH:  gain CCND1, del17p, loss of MAF (16q)**
    - **NGS: mutations in *NRAS, TP53, TP53***

**Pre-treatment marrow**

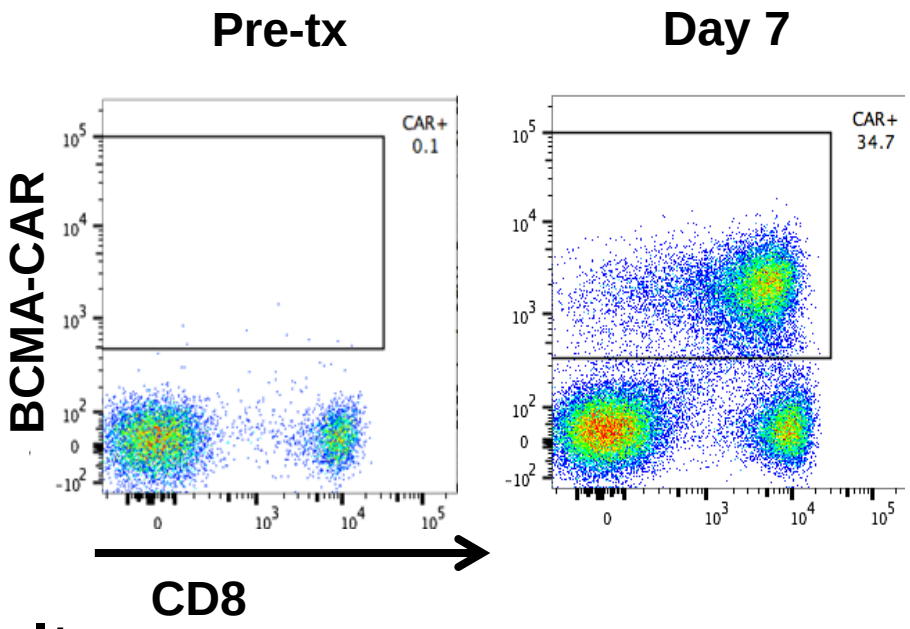


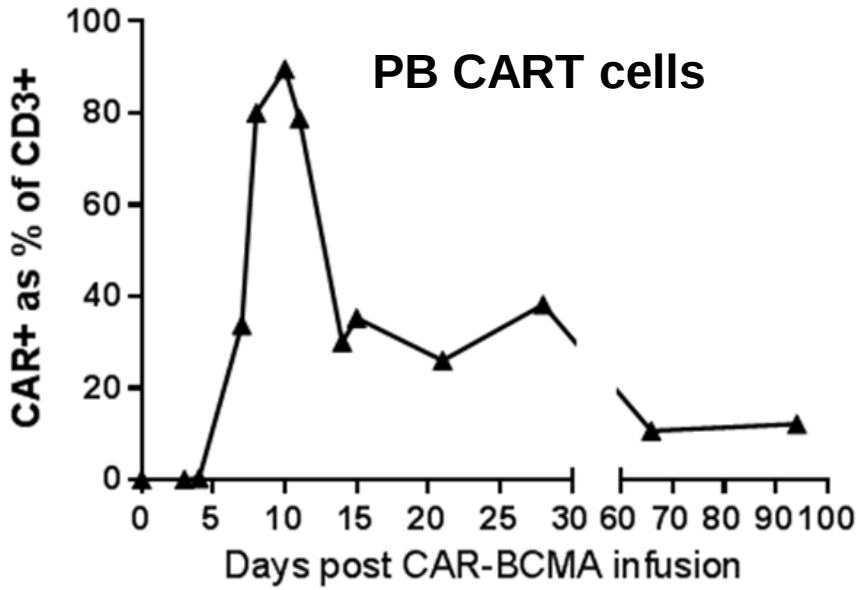

**Interim results**

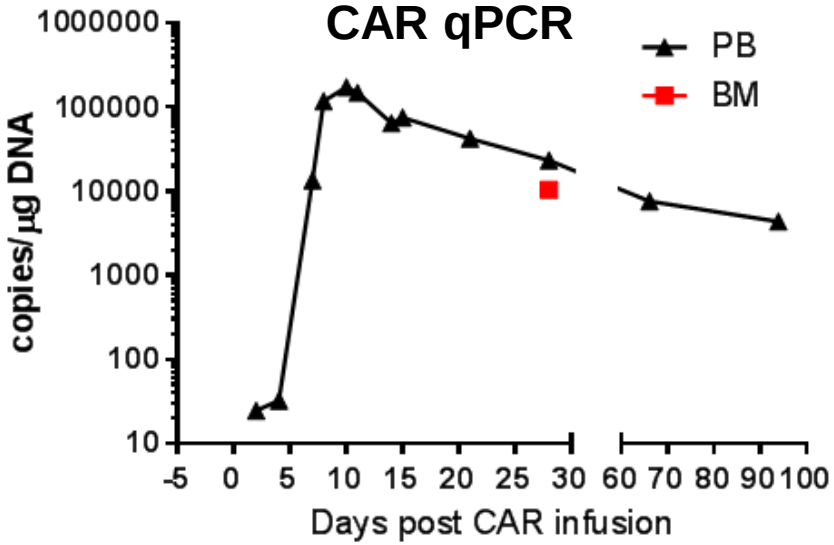
# CART-BCMA Cells for Multiple Myeloma

## Subject #1

- **2 x $10^8$ CART-BCMA cells**
  **=> no lymphodepletion**
- **Grade 3 CRS→ responded to tocilizumab**
- **Robust CART-BCMA expansion and persistence: similar to CART19**



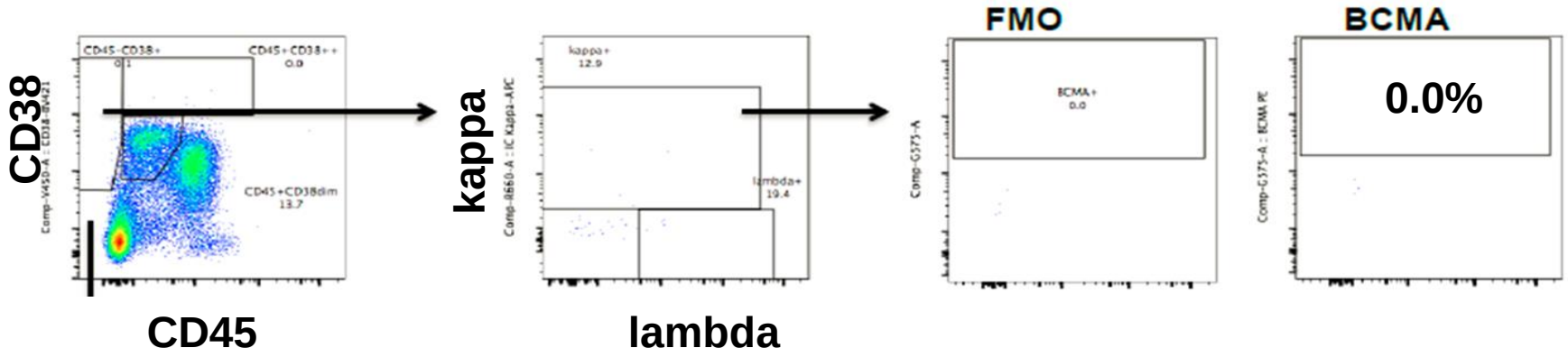



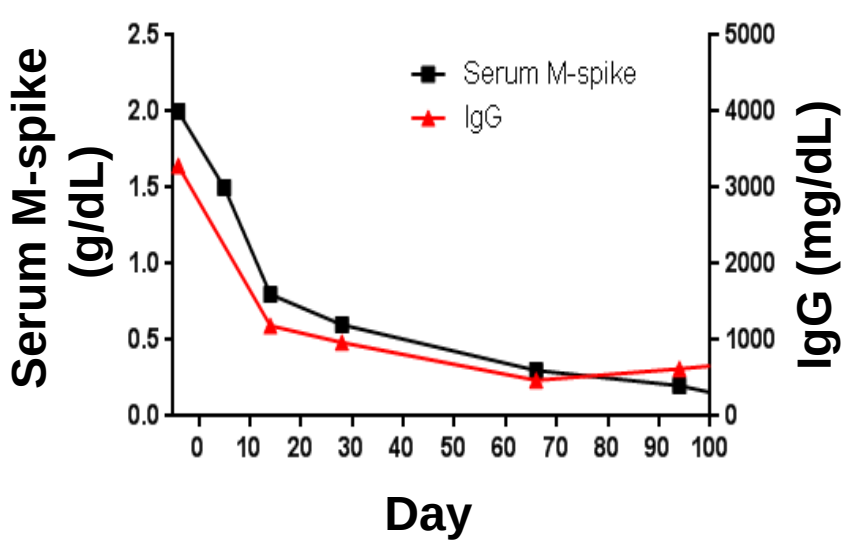

## Interim results

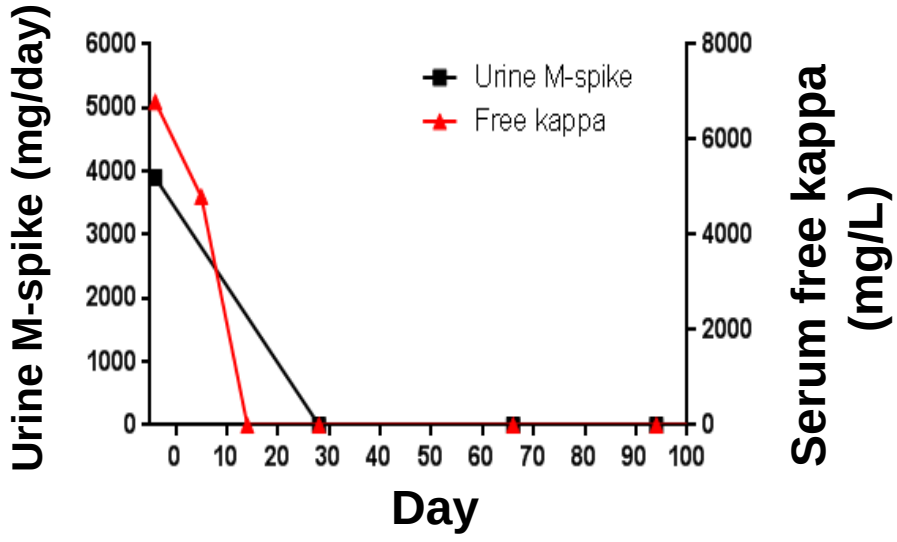
# CART-BCMA Cells for Multiple Myeloma: Response

## Subject #1

- Day 28 marrow:  negative for myeloma by IHC and flow
- Ongoing response (5+ months)



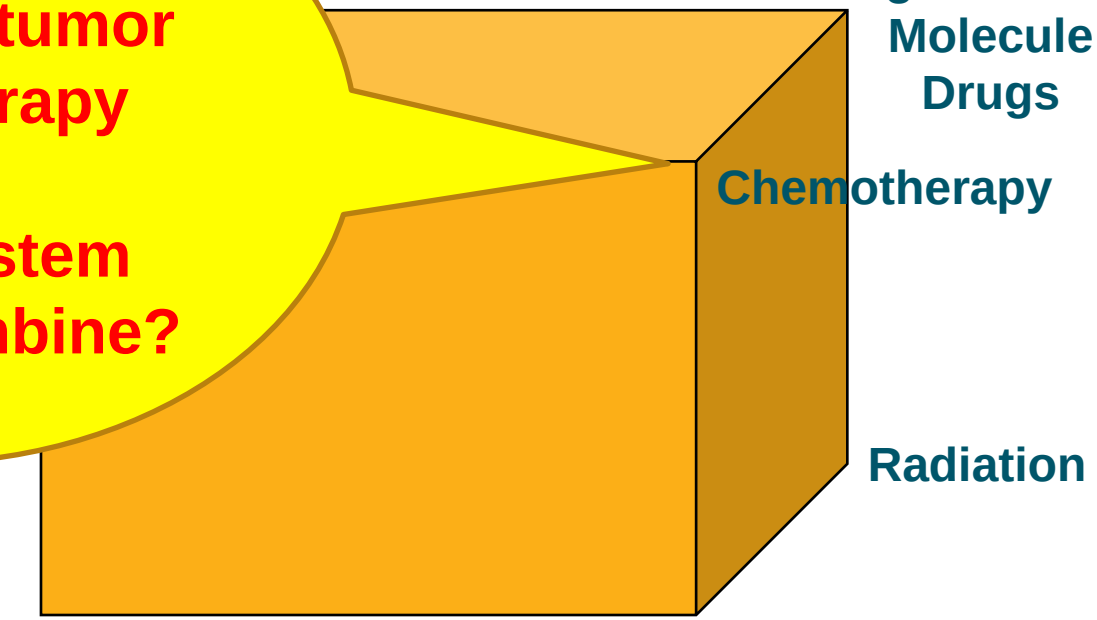



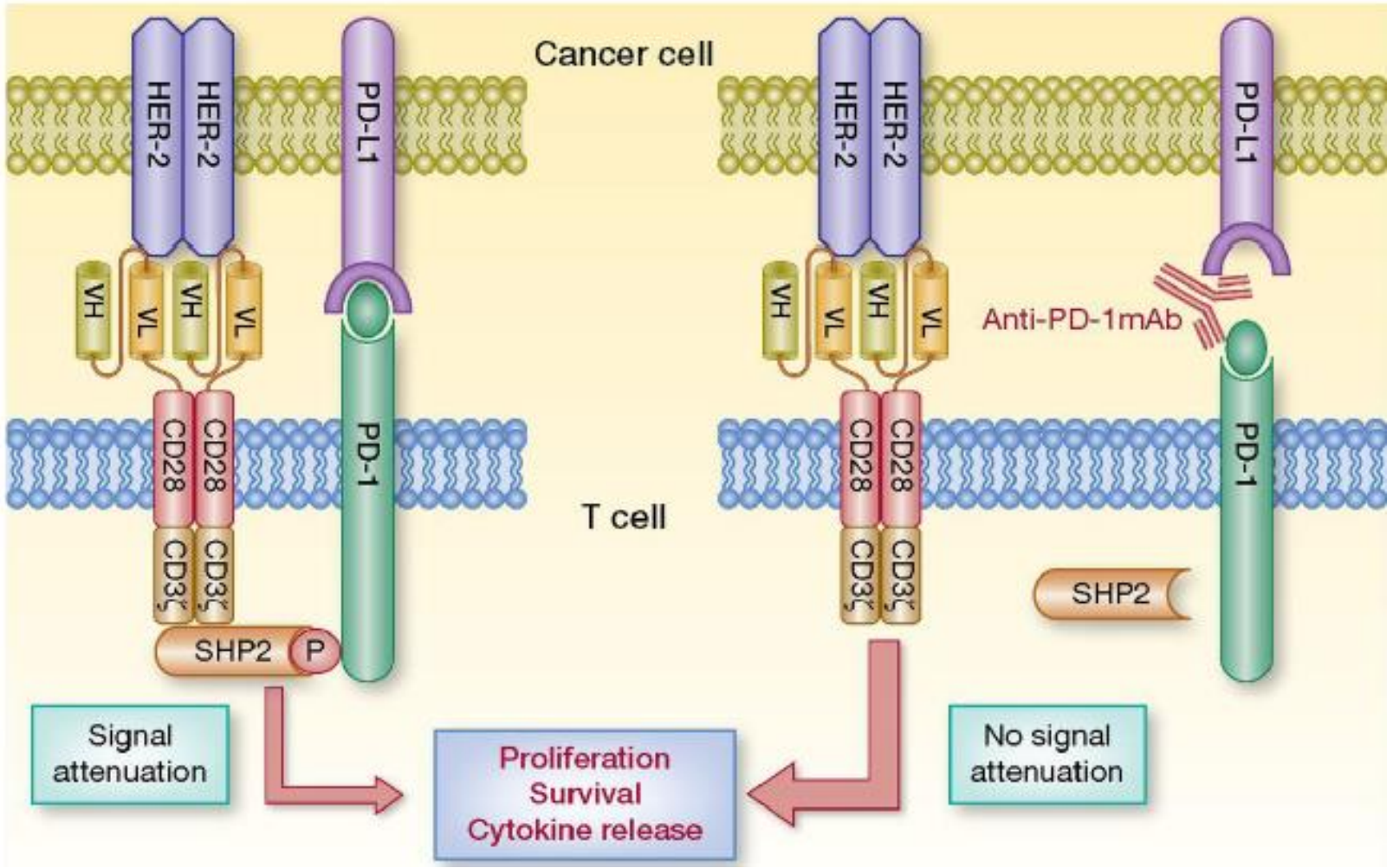

**Interim results**

# Combinatorial Cancer Immunotherapies: Many possibilities

- Chemotherapy targets the tumor
- Immunotherapy targets the immune system
- How to combine?

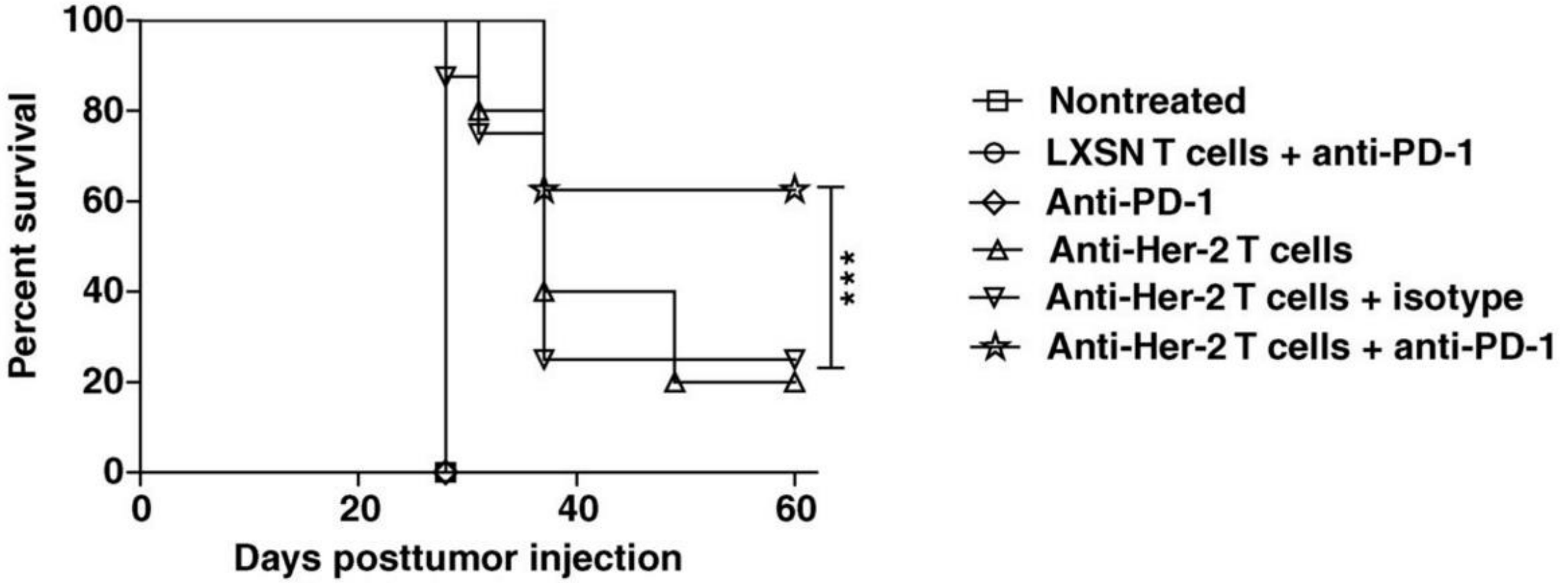


# CAR T Cells and Checkpoint Antibody Therapies Have Potential Synergism at the Synapse




Morales-Kastresana A. Better Performance of CARs Deprived of the PD-1 Brake. Clin Cancer Res. 2013;19(20):5546-8

# CAR T Cells and Checkpoint Antibody Therapies: Potential Synergism

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# Summary and Conclusions

- **Signaling domains in CAR T cells can influence persistence and metabolism**
- **Chimeric antigen receptor modified T cells directed against CD19 (CTL019) can achieve durable responses in patients with relapsed or refractory CD19+ follicular lymphomas.**
  - **All patients who achieved CR remain in CR.**
- **Single arm, open-label, multi-center, phase II study of efficacy and safety of CTL019 in relapsed or refractory follicular lymphoma is planned for 2016.**
- **Sequential administration of checkpoint antagonists and CAR T cells is feasible, and preliminary data suggests that this combination has activity**
- **CD19 and BCMA directed CAR T cells have promise for refractory myeloma**

# Colleagues and Patients: Thank you!


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