Personalized Medicine

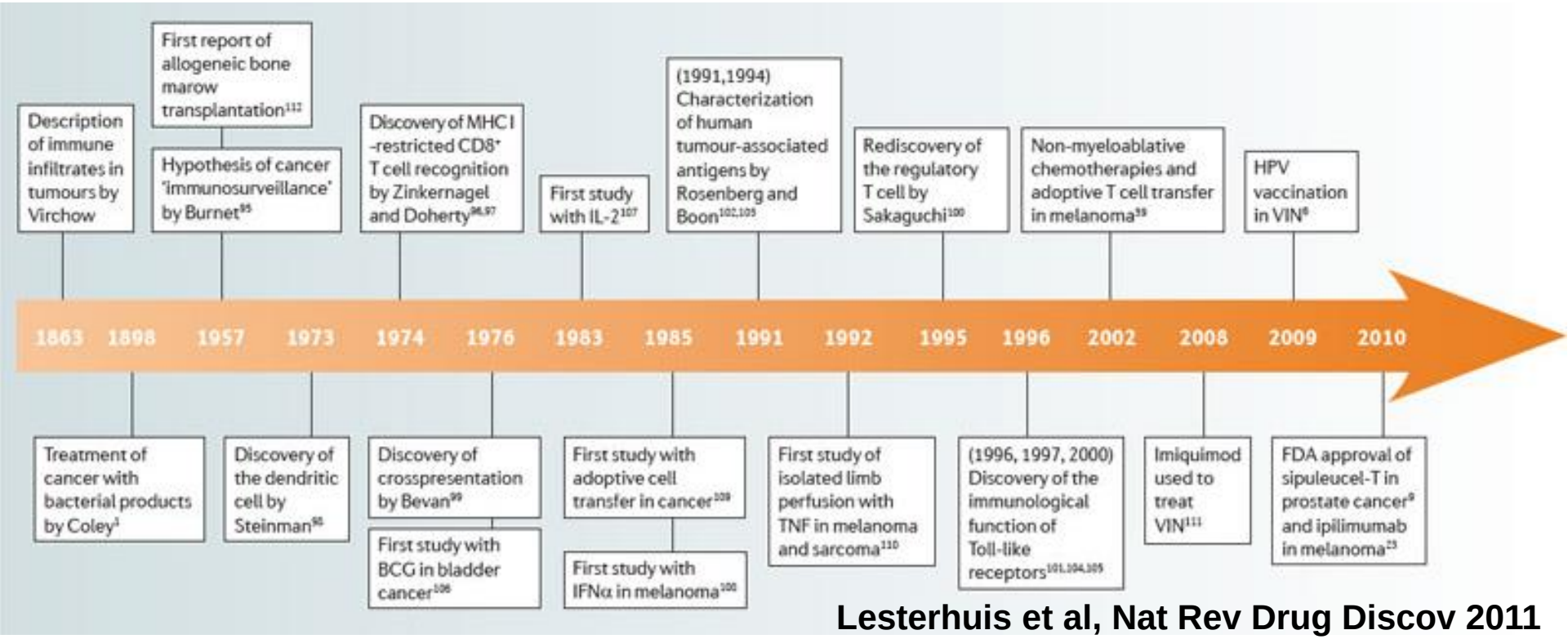
Delivering precision immunotherapy

Carl June, M.D.

University of Pennsylvania

September 27, 2014

Abridged history of cancer immunotherapy



Lesterhuis et al, Nat Rev Drug Discov 2011

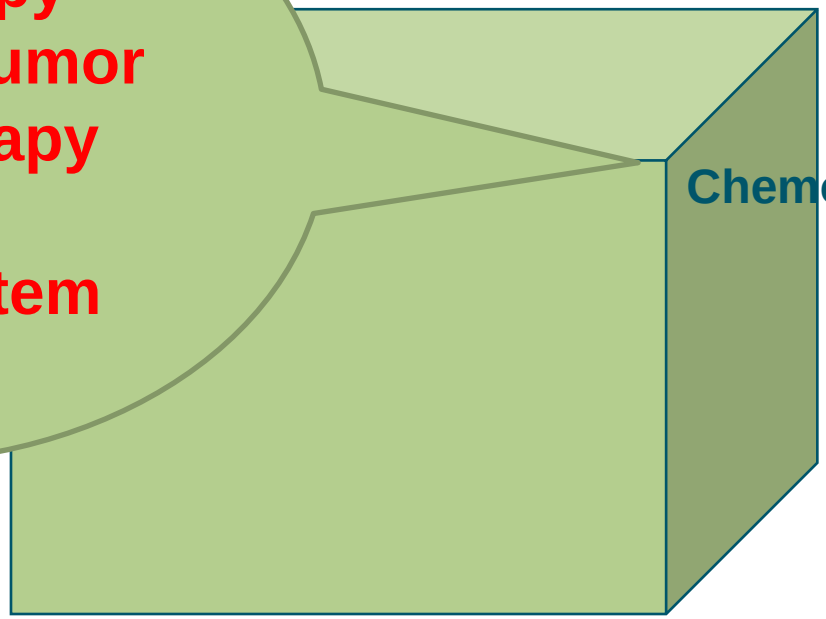
2011: Ipiliumumab shows overall survival benefit in melanoma

2012-2014: PD1 and PD-L1 blockade has benefit in melanoma, NSCLC, renal cell

2011-2014: CAR-modified T cells show durable remissions in B cell ALL and CLL

Combinatorial Cancer Immunotherapies: Many possibilities

- **Chemotherapy targets the tumor**
- **Immunotherapy targets the immune system**



Targeted Small Molecule Drugs

Chemotherapy

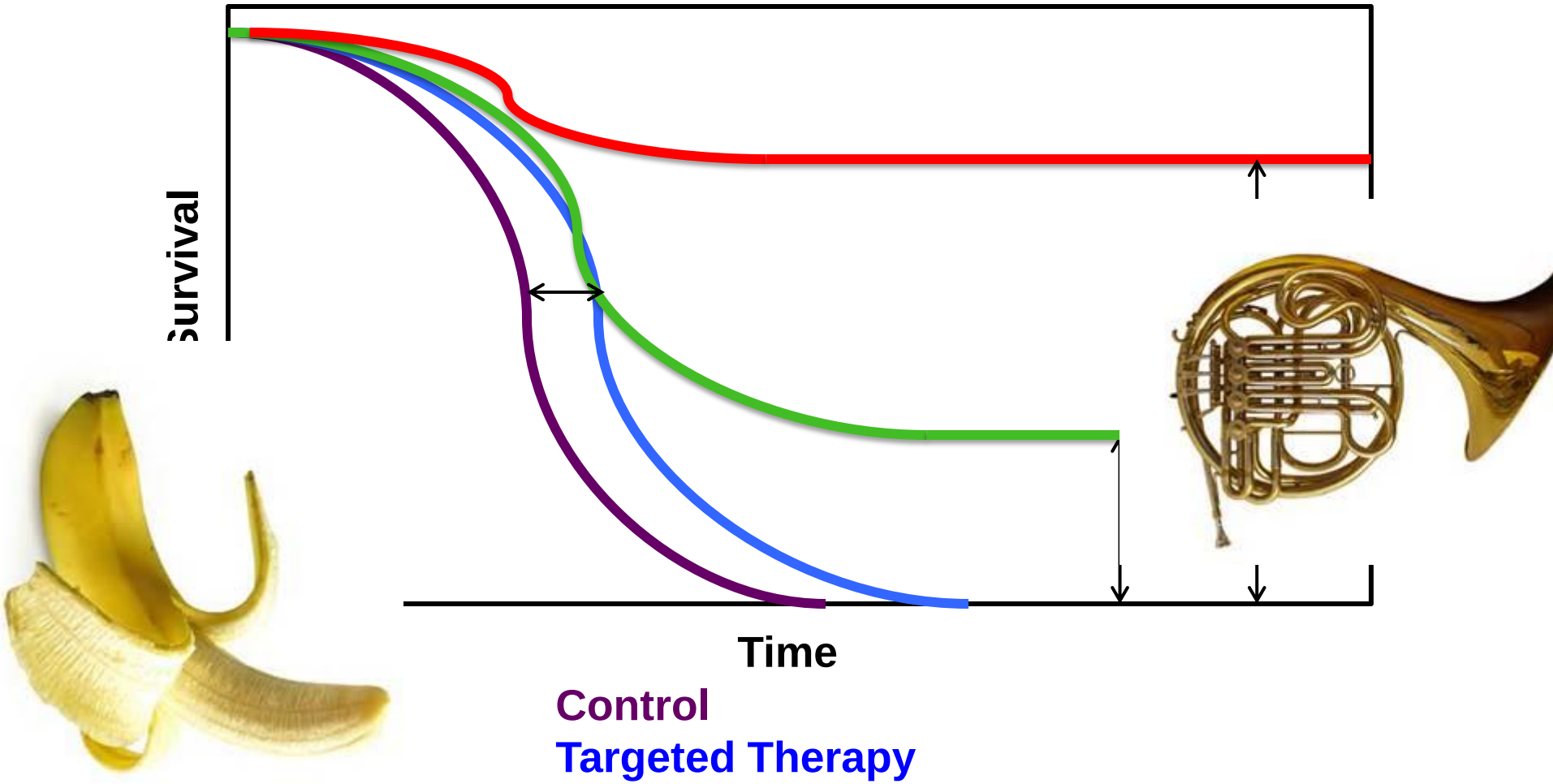
Radiation

Antibodies

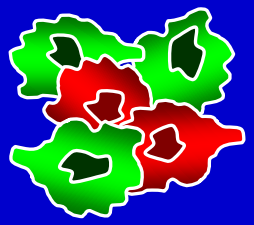
Cell Based Therapies

Clinical Trial Design Issues

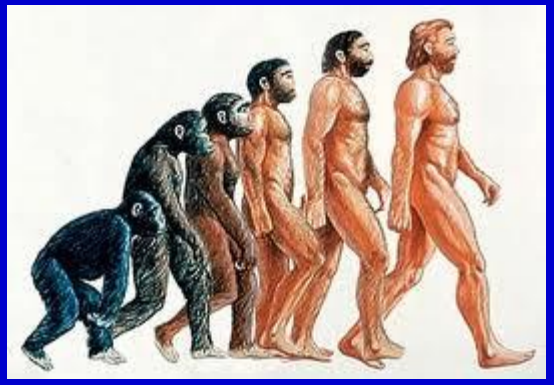
Improving Survival with Combination Therapy



T Cell Immune Surveillance of Cancer

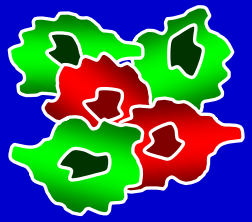


Evolutionary Biology

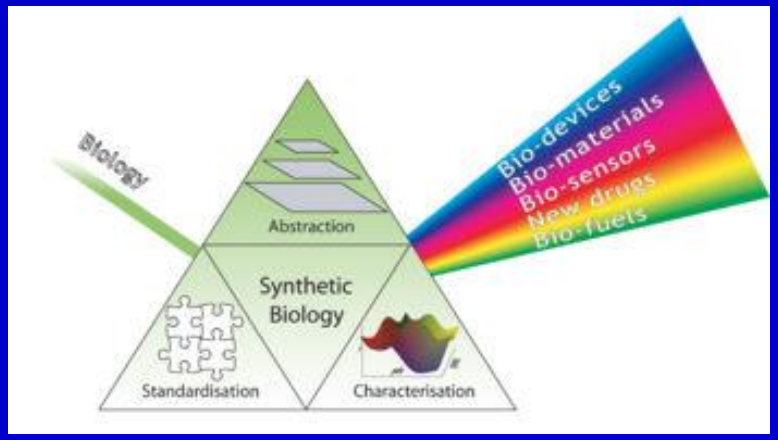


T cell response — Elimination — Immunoediting — Escape → Tolerance

Tumor



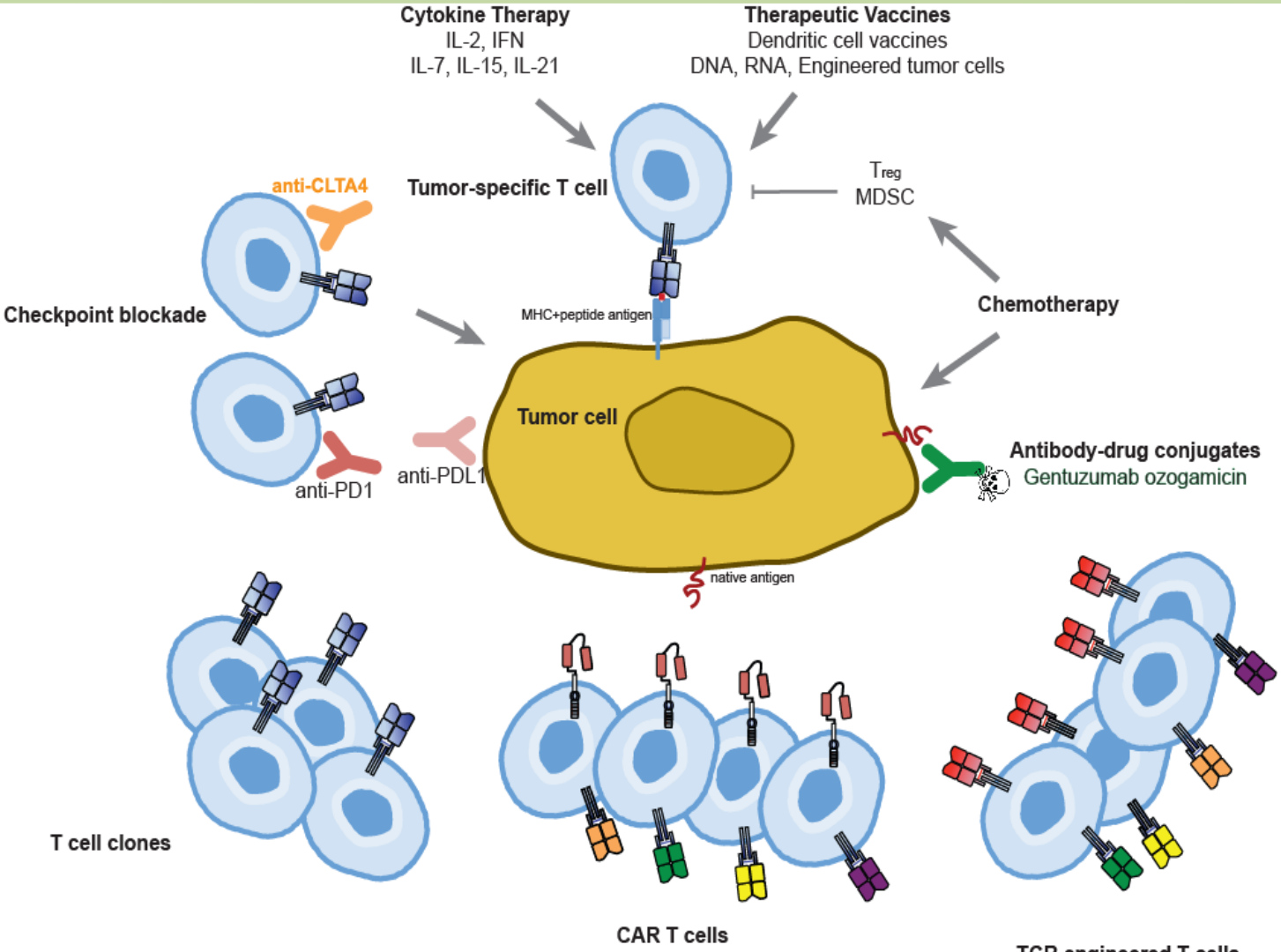
Synthetic Biology



T cell response — Elimination — Immunoediting — Engineered T cells → **Tumor elimination**

Tumor

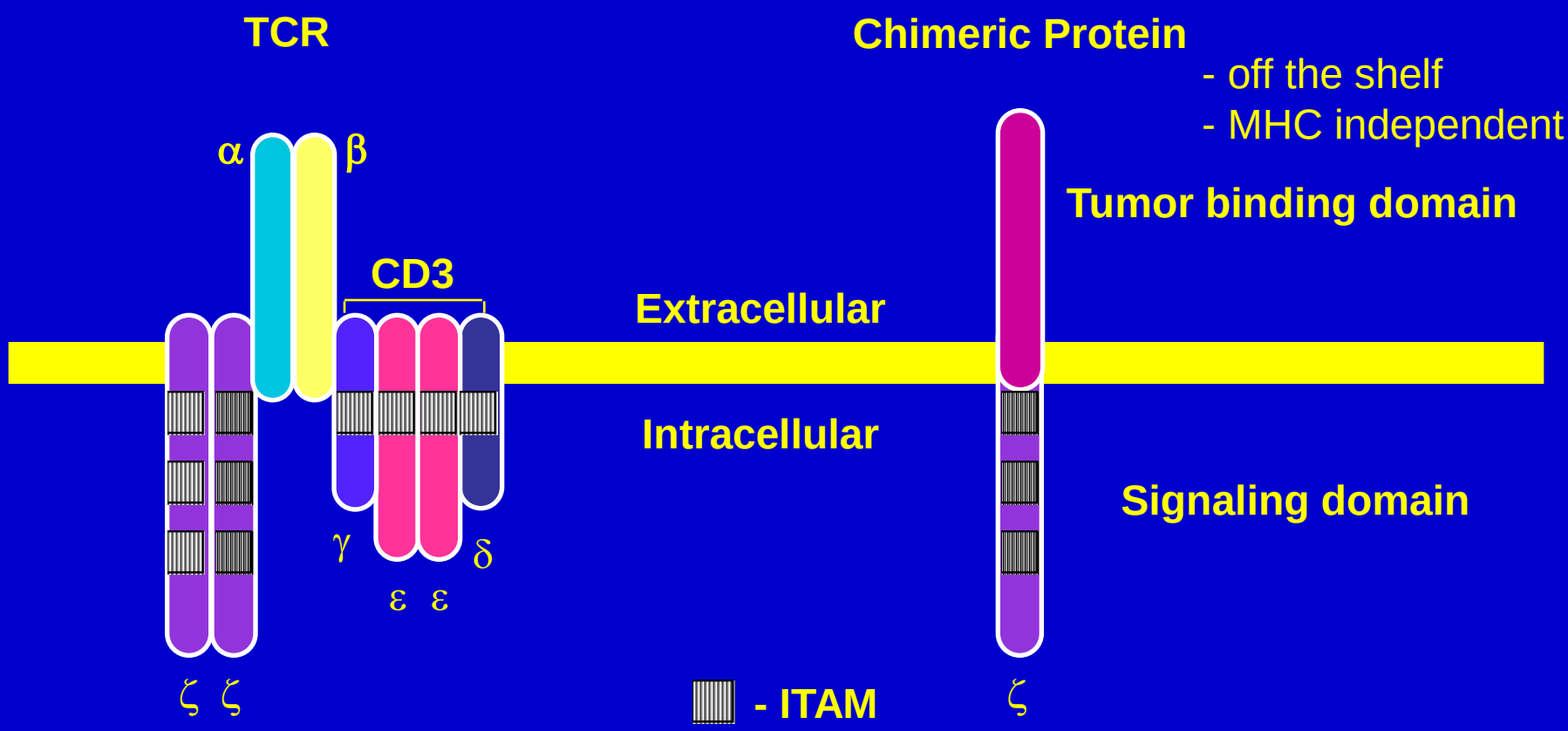
Approaches to Overcome Tolerance



Maus MV et al. Blood. 2014;123:2625-2635.

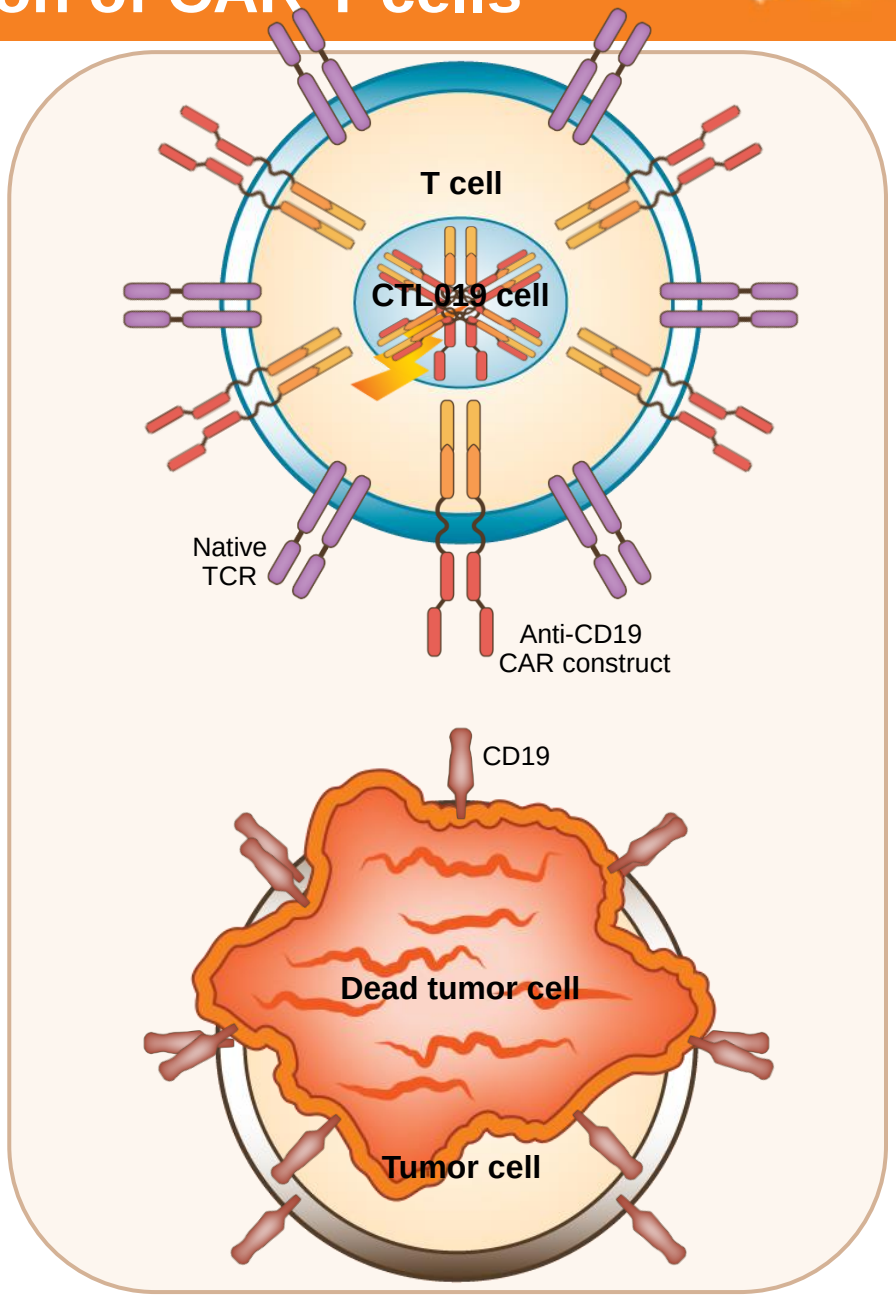
Using Synthetic Biology to Overcome Tolerance
Creation of Bi-specific T cells

TCR heterodimer approach "CAR" or T body approach



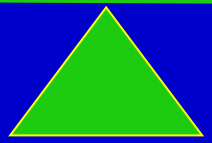
Redirecting the Specificity of T cells – Proposed Mechanism of Action of CAR T cells

- Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity[1,2]
- CART19 therapy takes advantage of the cytotoxic potential of T cells thereby killing tumor cells in an antigen-dependent manner[1,3]
- Persistent CART19 cells consist of both effector (cytotoxic) and central memory T cells[3]
- T cells are non-cross resistant to chemotherapy
- Responses are cytolytic: no swelling!



1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

Engineered CARs and TCRs: which is "better"?



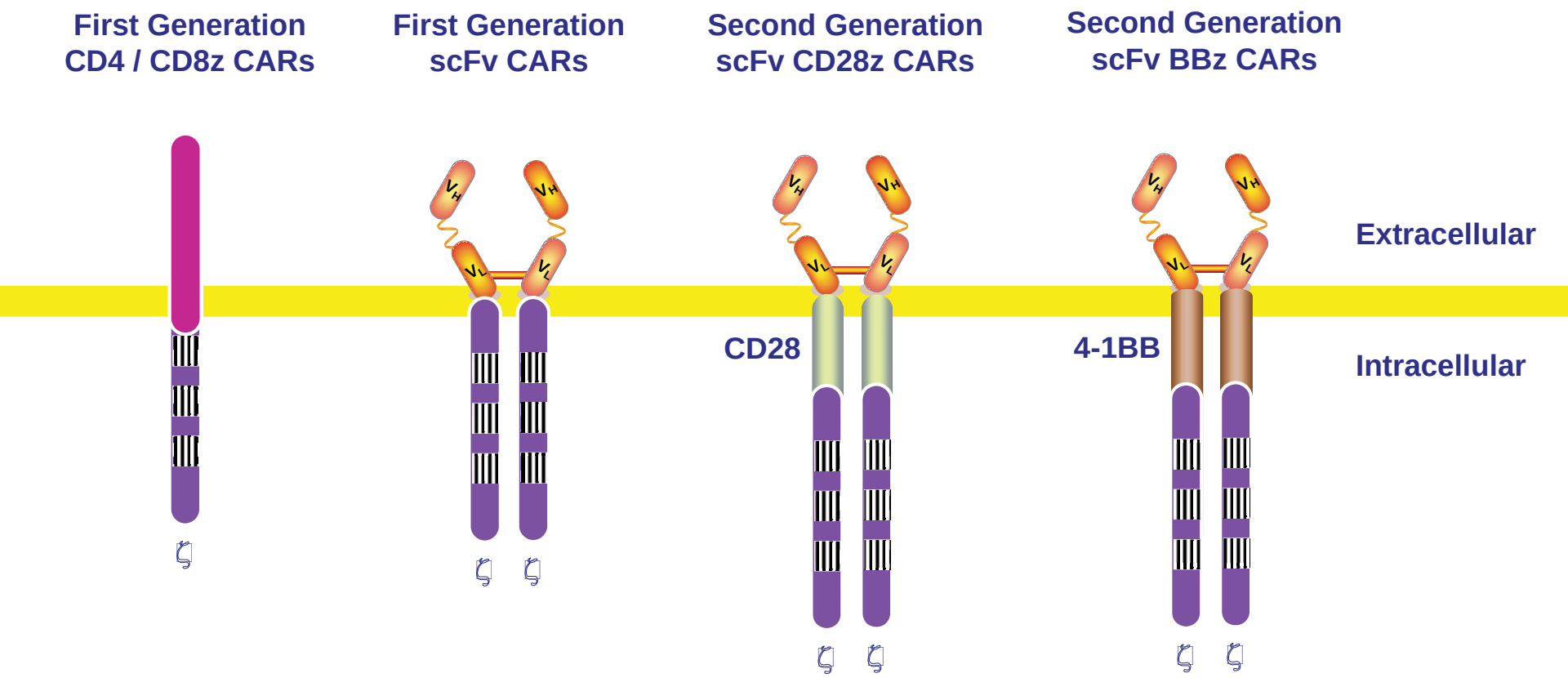
TCR

1. Sensitive signal amplification derived by evolution
2. Low avidity
3. Targets intracellular proteome
4. Requires MHCI expression and HLA matching on tumor cell
5. Life long persistence (14 yrs)
6. Toxicity difficult to predict…

CAR

1. Signal amplification derived by synthetic biology
2. Avidity controllable
3. Targets only surface structures
4. MHC independent: "off the shelf"
5. Decade long persistence

Design of CAR T Cells



Irving & Weiss, 1991
Letourneur, 1991
Romeo, 1991

Eshhar, 1993

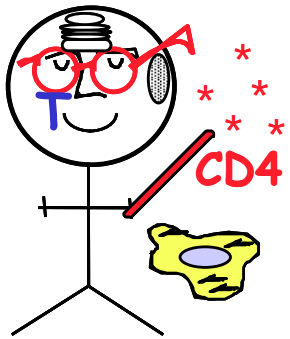
Roberts, 1995
Finney, 1998
Maher, 2002

Imai, 2004
Milone, 2009
Carpenito, 2009

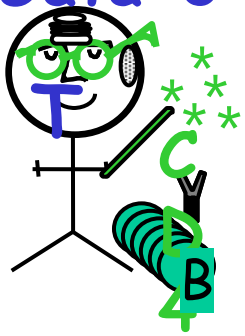
Tolerance is Controlled by CD4 Cells
Four Types of CD4 T Cells

T-bet

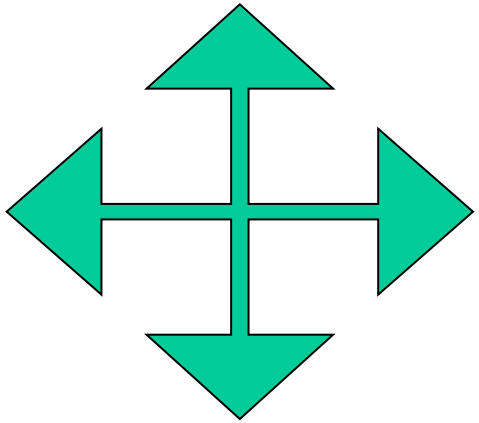
Th1:
Fight
Intra-cellular
Pathogens
And cancer!



Gata-3



Th2:
Fight
Extra-cellular
Pathogens



ROR-γT

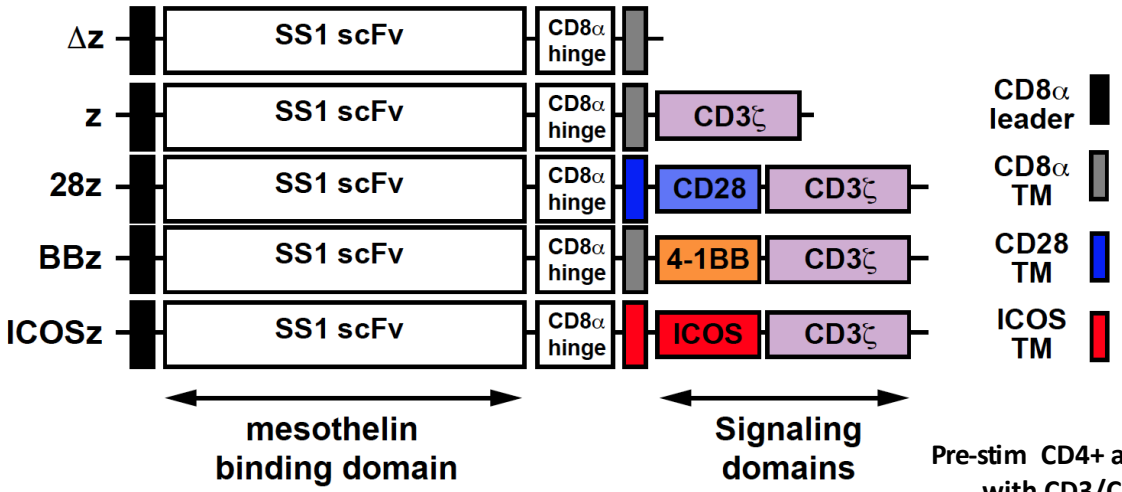
Th17:
Chronic
Inflammation
& autoimmunity

FoxP3

CD4
Treg

Treg: Silences
Or Kills Effector T Cells
Accumulate at Tumor

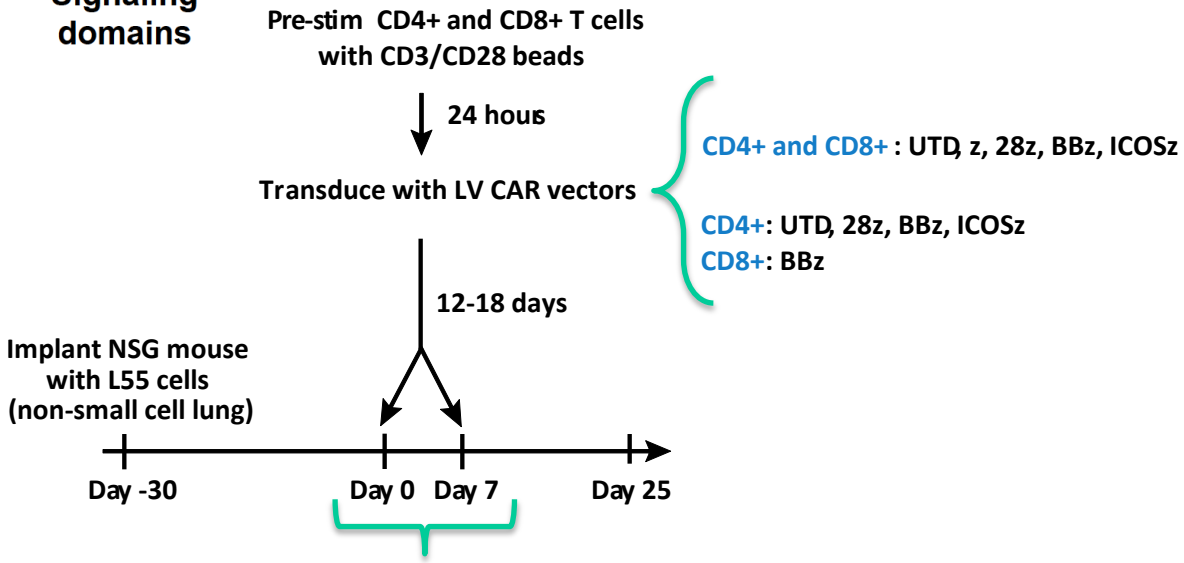
Role of ICOS based CARs in enhancing T cell persistence in NSG mice bearing solid tumor xenografts



Key Points

- ICOS-based CARs program bipolar T_H17/T_H1 cells with augmented effector function and in vivo persistence.
- The expression of selected CAR endodomains can program T cells for their subsequent differentiation fates and effector functions.

Sonia Guedan, PhD



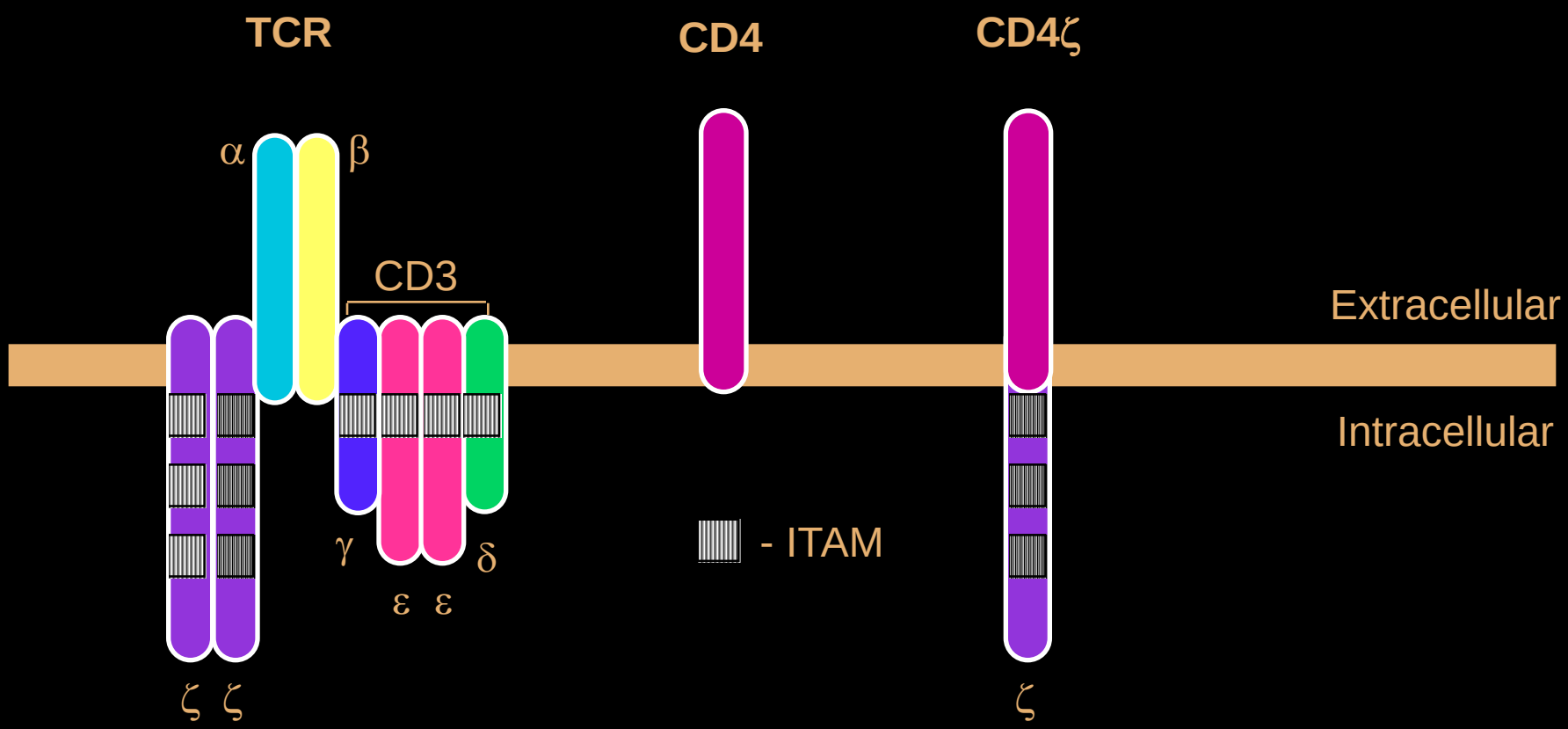
Two doses of redirected $CD4^+$ and $CD8^+$ T cells:
$10x10^6$ T cells per dose, 60-70% CAR^+

ICOS-based CARs can reprogram bipolar Th17/Th1 cells: Conclusions

- Redirection of $CD4^+$ T cells with an ICOS-based CAR enhanced persistence of $CD4^+$ T cells compared to CD28 or 4-1BB based CAR T cells
- Redirection of $CD4^+$ T cells with an ICOS-based CAR significantly increased the persistence of $CD8^+$ T cells redirected with CD28 or 4-1BB-based CAR
- The use of selected CAAR endodomains can program T cells for subsequent differentiation fates

Sonia Guedan, Blood 2014; 124: 1070-80

The First "CAR" Trial: CD4ζ Chimeric Antigen Receptor for HIV



Irving, B.A., and A. Weiss. Cell 1991; 64:891-901
Mitsuyasu et al, Blood 2000;96:785-93
Walker RE et al. Blood. 2000;96(2):467-74
Deeks SG et al. Mol Ther. 2002;5 788-97

CD4zeta CARs: persistence and safety

Infusions of CD4z modified T cells results in long term (>decade) persistence at stable levels of ~0.5% of T cells.

37 of 39 patients have CD4z persistence in PBMC up to 11 years post infusion.

No integration near oncogenes or tumor suppressor genes

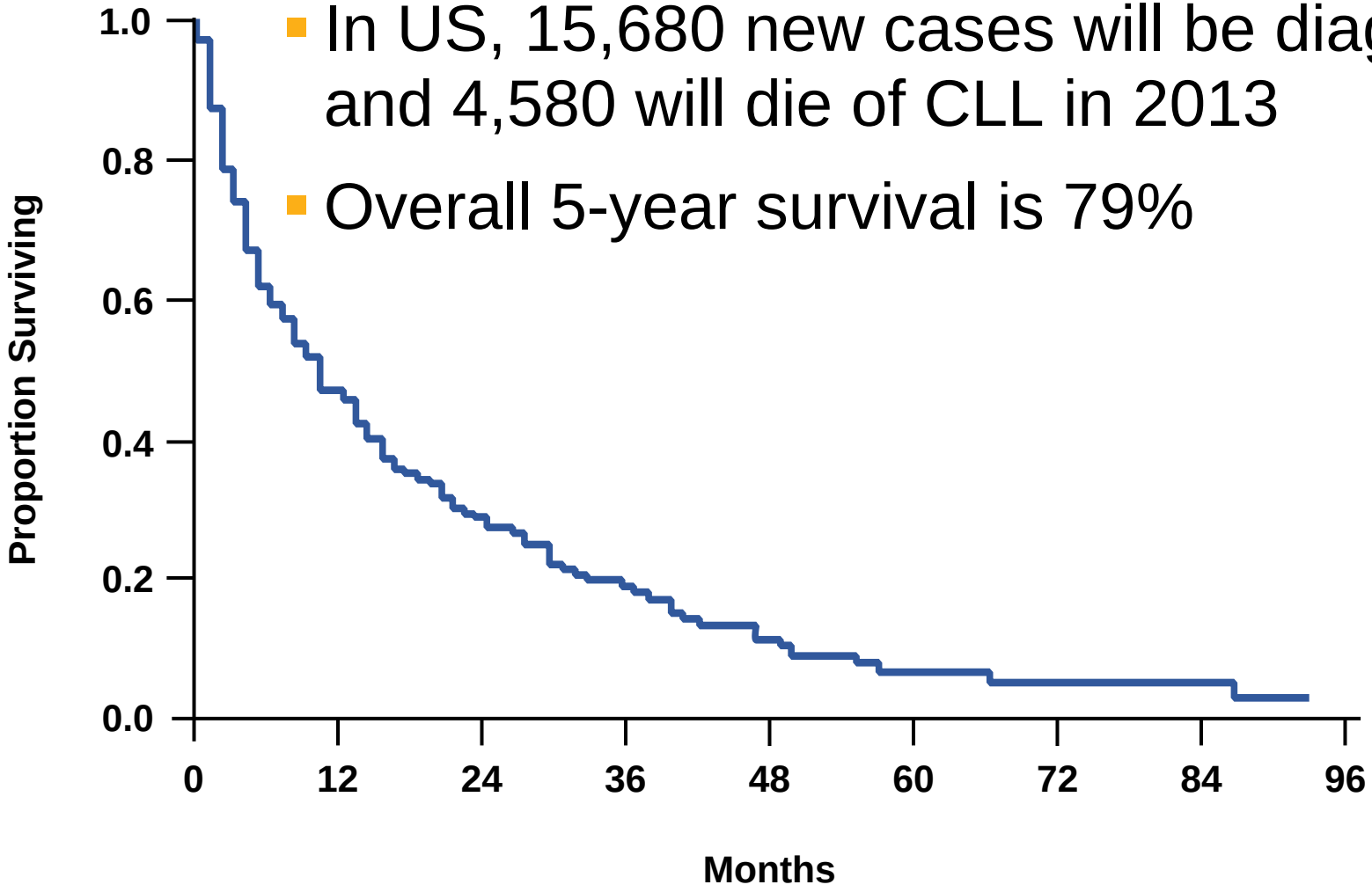
No SAE in >568 years of patient followup

=> Gene modified T cells are “safe” as a platform

Scholler et al. *Science Translational Medicine 4:132Ra153, 2012*

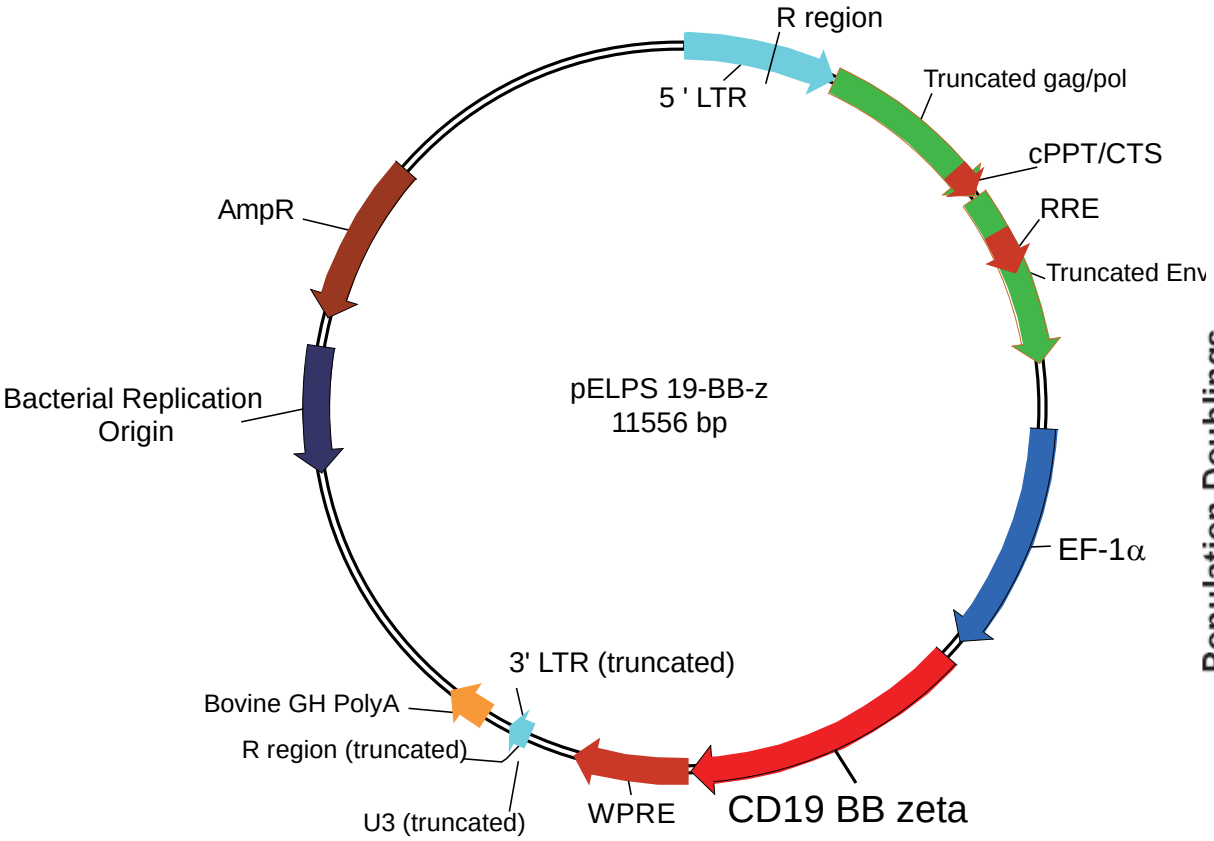
Median OS of fludarabine-refractory CLL is 10 months

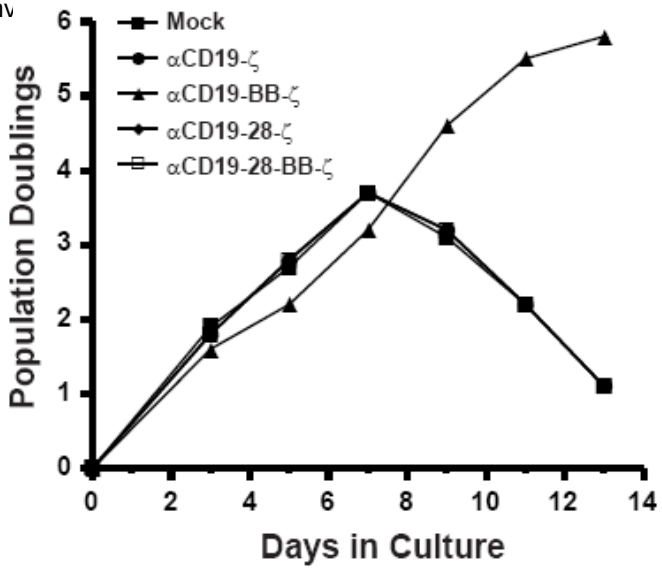
- In US, 15,680 new cases will be diagnosed and 4,580 will die of CLL in 2013
- Overall 5-year survival is 79%

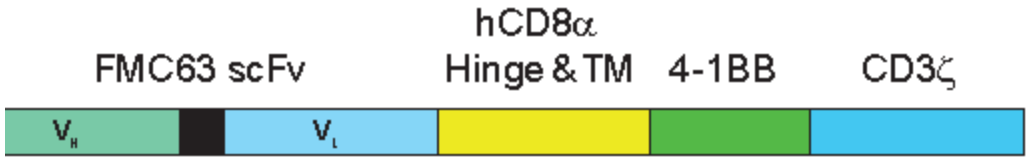


Brown J R Hematology 2011;2011:110-118, from Keating et al, 2002 Leuk Lymphoma 43:1755–1762 ©2011 by American Society of Hematology

Design of CART19: Choice of 4-1BB Signaling Domain Promotes CAR T Cell Proliferation/Survival



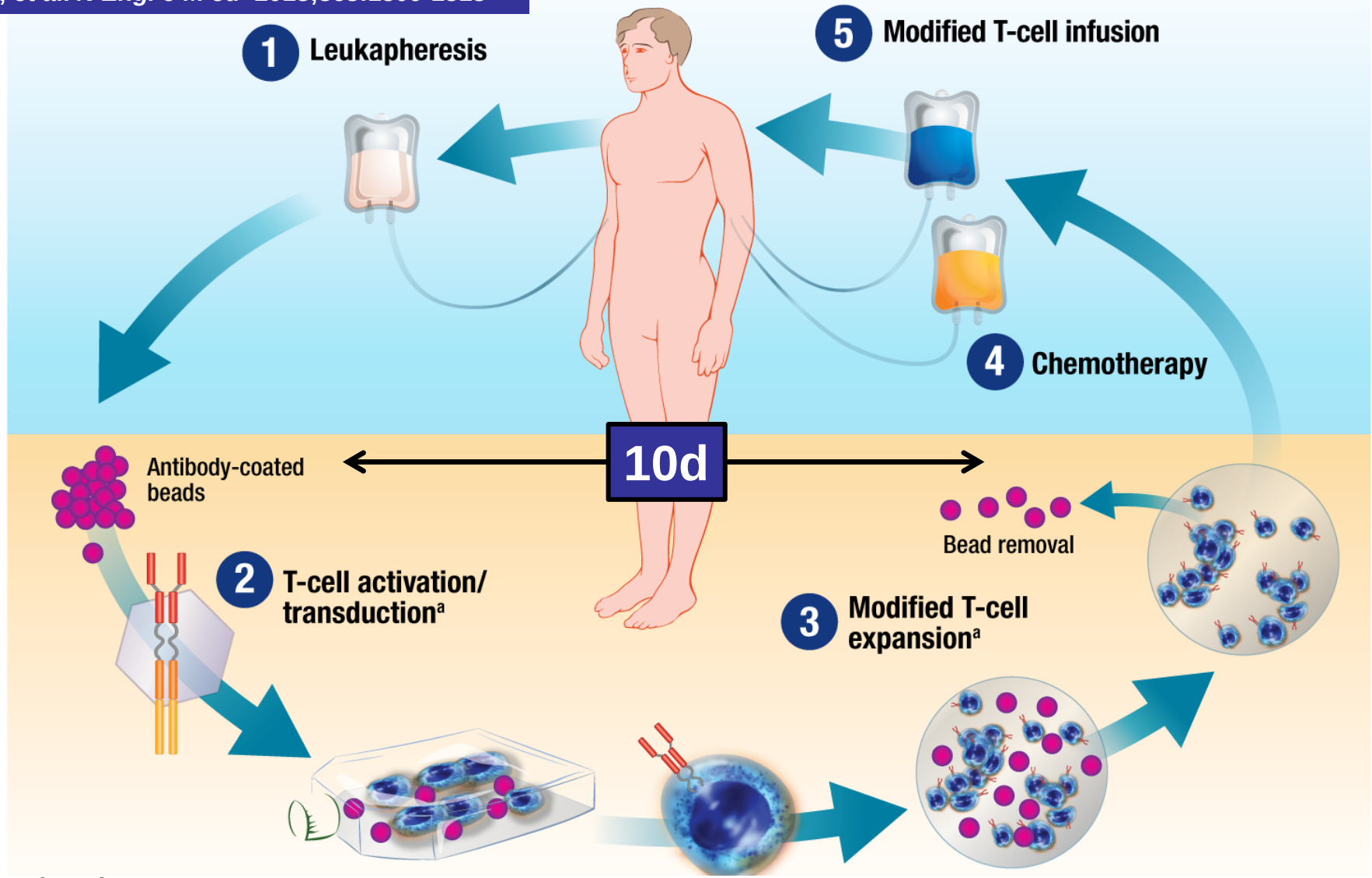




Finney et al. J Immunol 2004
Imai et al. Leukemia 2004
Milone, et al. Mol Ther 2009
Carpenito, et al. PNAS 2009

CART19 CLL Study Overview*

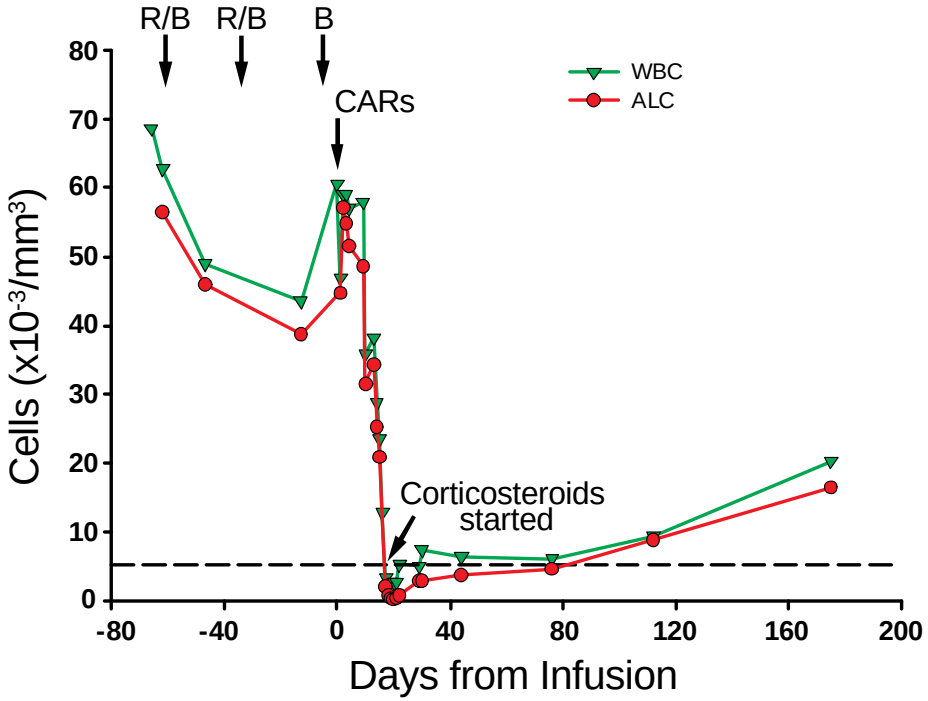
Porter DL, et al. *N Engl J Med*. 2011;365(8):725-733
Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73
Grupp S, et al. *N Engl J M ed* 2013;368:1509-1518



* ClinicalTrials.gov #NCT01029366

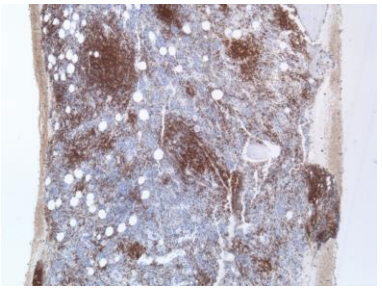
Examples of Clinical Responses

UPN 02

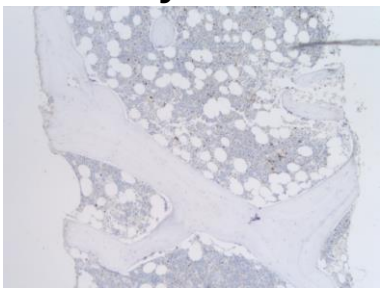


UPN 01

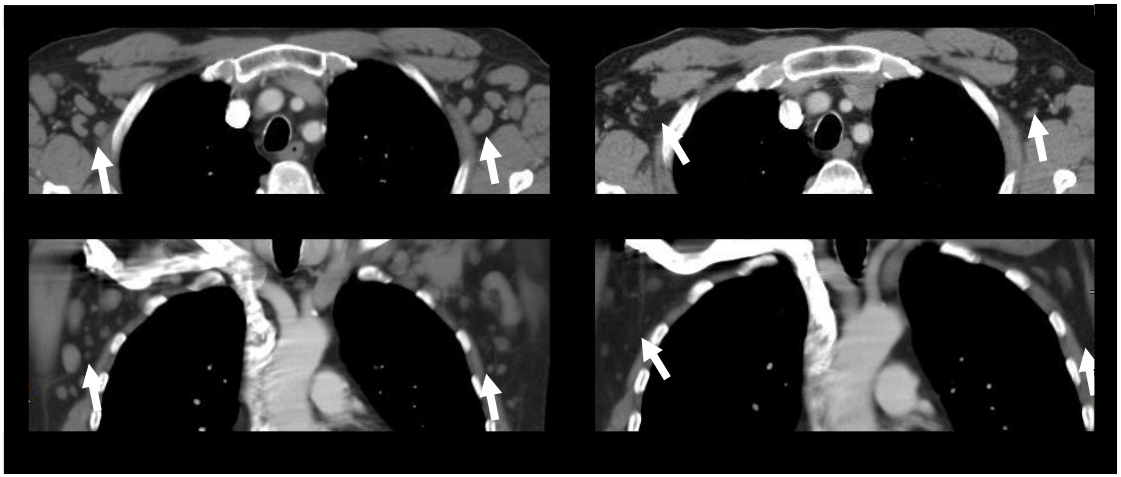
Day -21



Day 177

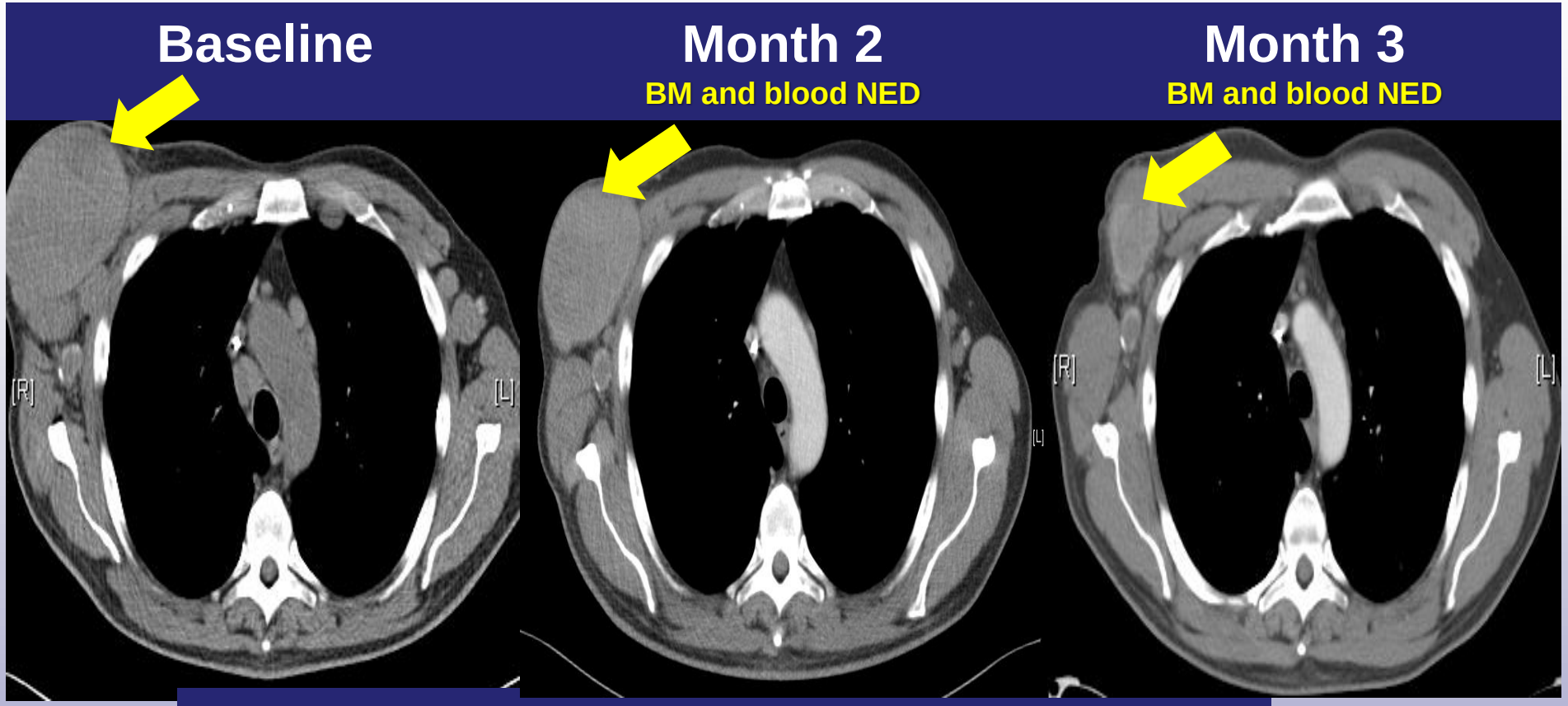


UPN 03



David Porter, MD
N Engl J Med
365:725, 2011

Kinetics of Response in Advanced CLL



UPN #18: 10 prior therapies, transformed CLL, del(17p), ibrutinib resistant, XRT resistant

David Porter, MD

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

CART19 CLL: Generalities on First 3 Treated Patients

- All 3 patients had Chronic Lymphocytic Leukemia (CLL)
  - ✓ Late stage incurable leukemia
  - ✓ 3.5-7 pounds of tumor/patient
- Each infused CAR T cell or its progeny

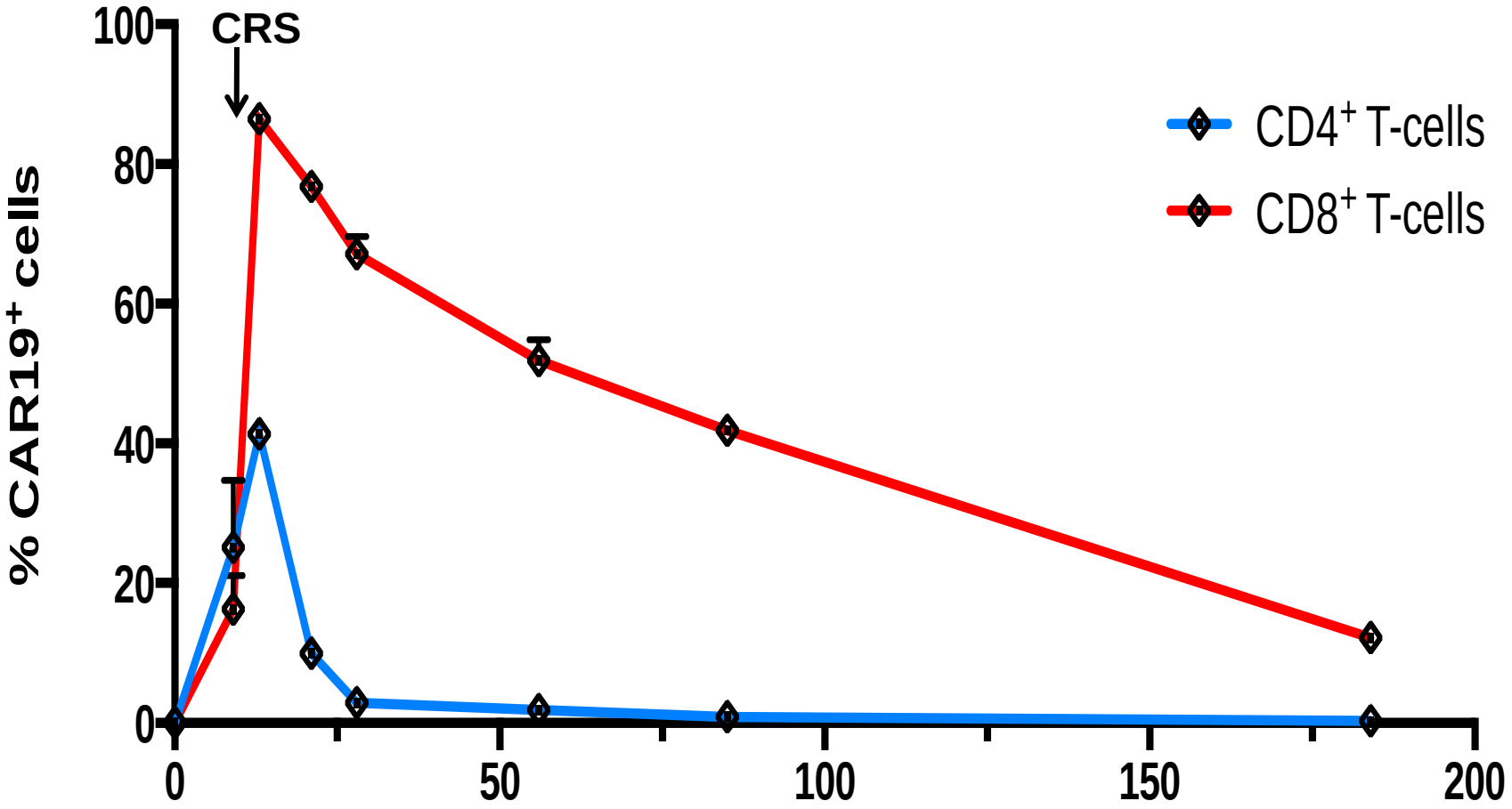
  killed more than 1000 tumor cells: CARs are “Serial Killers”
- Remissions durable to date
- Sustained antibody delivery with a single infusion

  of engineered T cells (beyond 3+ yrs)

Porter, D.L. et al.. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia New England Journal of Medicine 365:725-733.

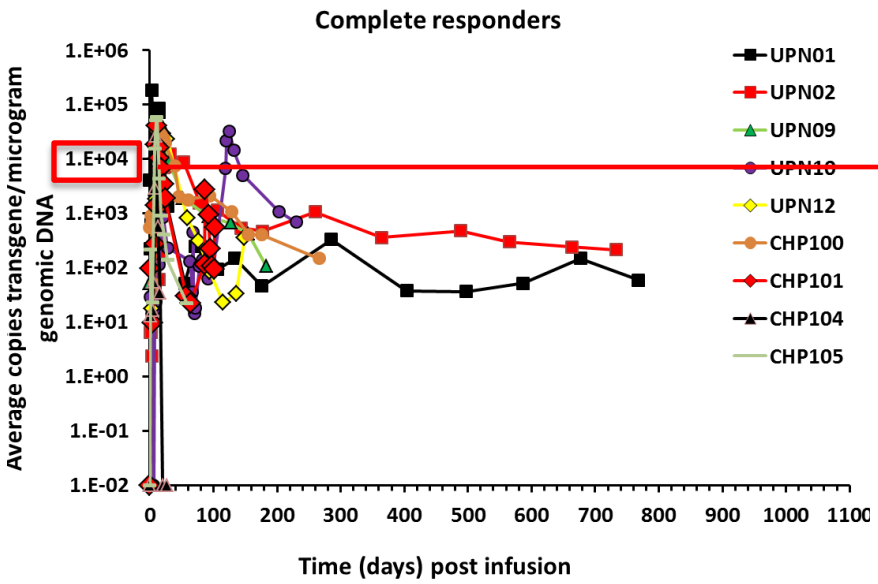
Kalos, M., et al . 2011. T cells expressing chimeric receptors establish memory and potent antitumor effects in patients with advanced leukemia. Science Translational Medicine 3:95ra73.

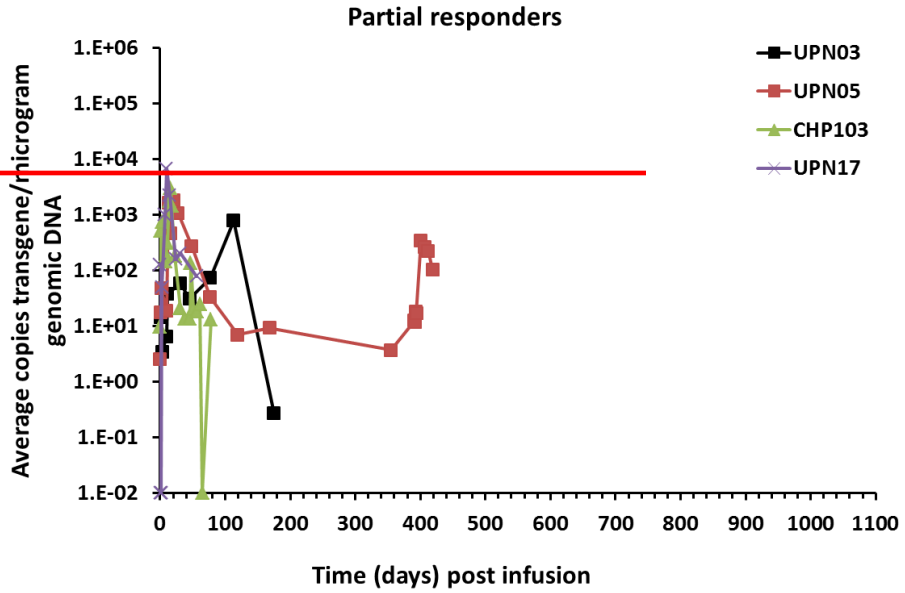
CTL019 cell expansion and persistence in CLL



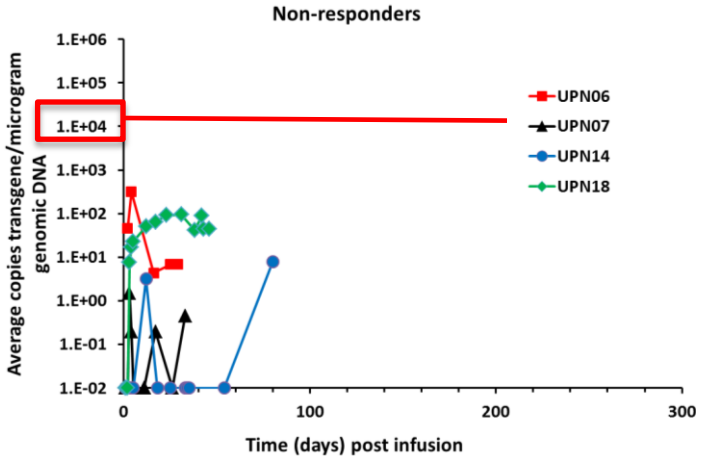
YD Mahnke & DE Ambrose

Predictive Biomarker: Magnitude of peripheral CTL019 cell expansion distinguishes responders





c.a. 6% of total mononuclear cells



04409, 959 cohorts

Q-PCR analysis
CTL019 cells/microgram genomic DNA

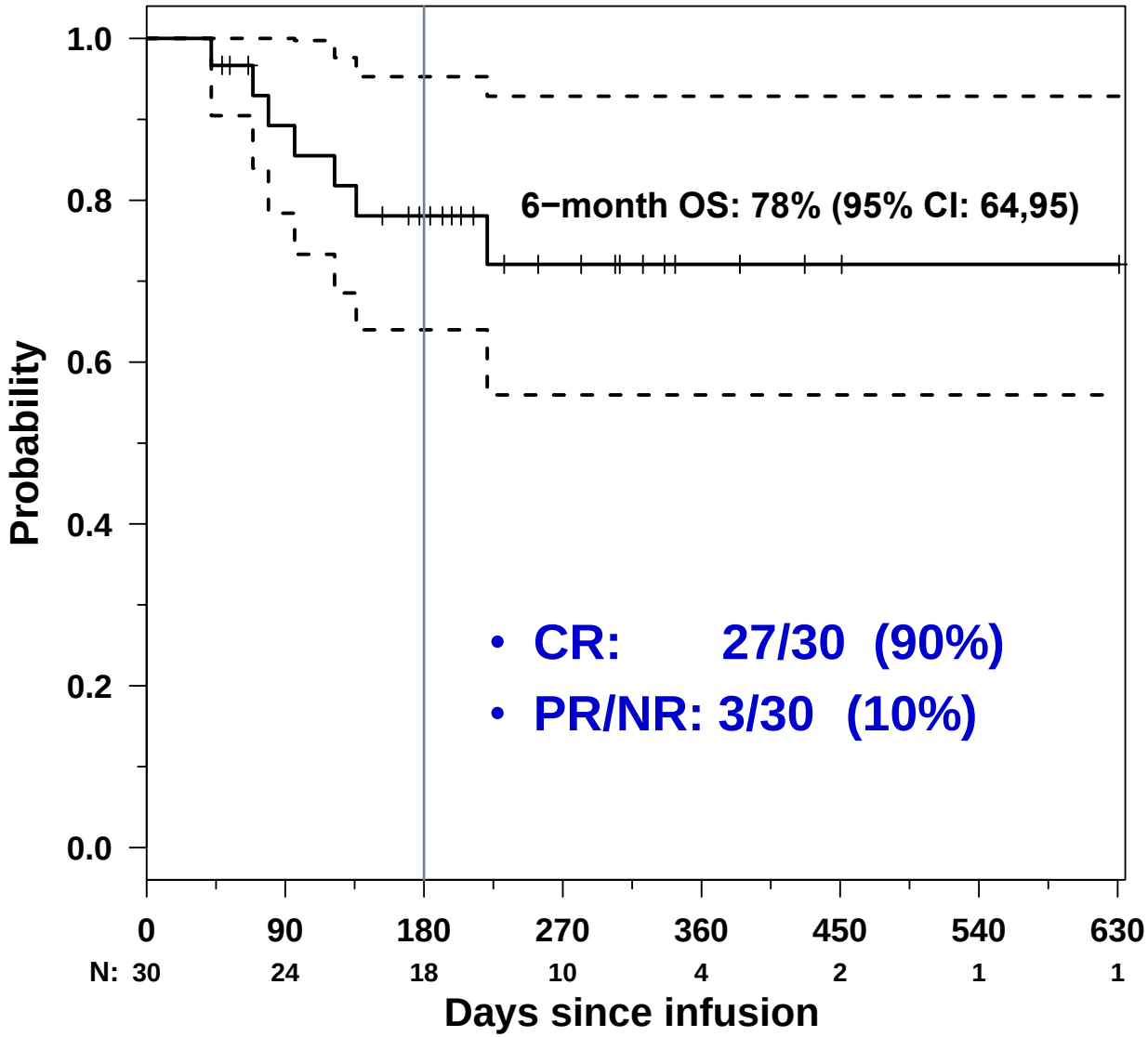
Micheal Kalos, PhD

Perelman School of Medicine
University of Pennsylvania

Clinical Update of Pediatric and Adult ALL Patients Treated with CART19

	Pediatric Cohort N=25	Adult Cohort N=5	Total N=30
Sex			
Female	11 (44%)	1 (20%)	12 (40%)
Male	14 (56%)	4 (80%)	18 (60%)
Age at Infusion	11 (5, 22)	47 (26, 61)	14 (5 ,61)
Median (range)			
Race			
African American	1 (4%)	1 (20%)	2 (6.7%)
Asian	2 (8%)		2 (6.7%)
Caucasian	21 (84%)	4 (80%)	25 (83.3%)
Pacific Islander	1 (4%)		1 (3.3%)
Post Allogeneic Transplant			
Yes	18 (72%)	0 (0%)	18 (60%)

Summary of CART19 Efficacy in ALL (n=30)
Case mix on phase I: 25 pediatric and 5 adult
NEJM 2014 (in press)



Potential Roles of CAR T Cells for ALL

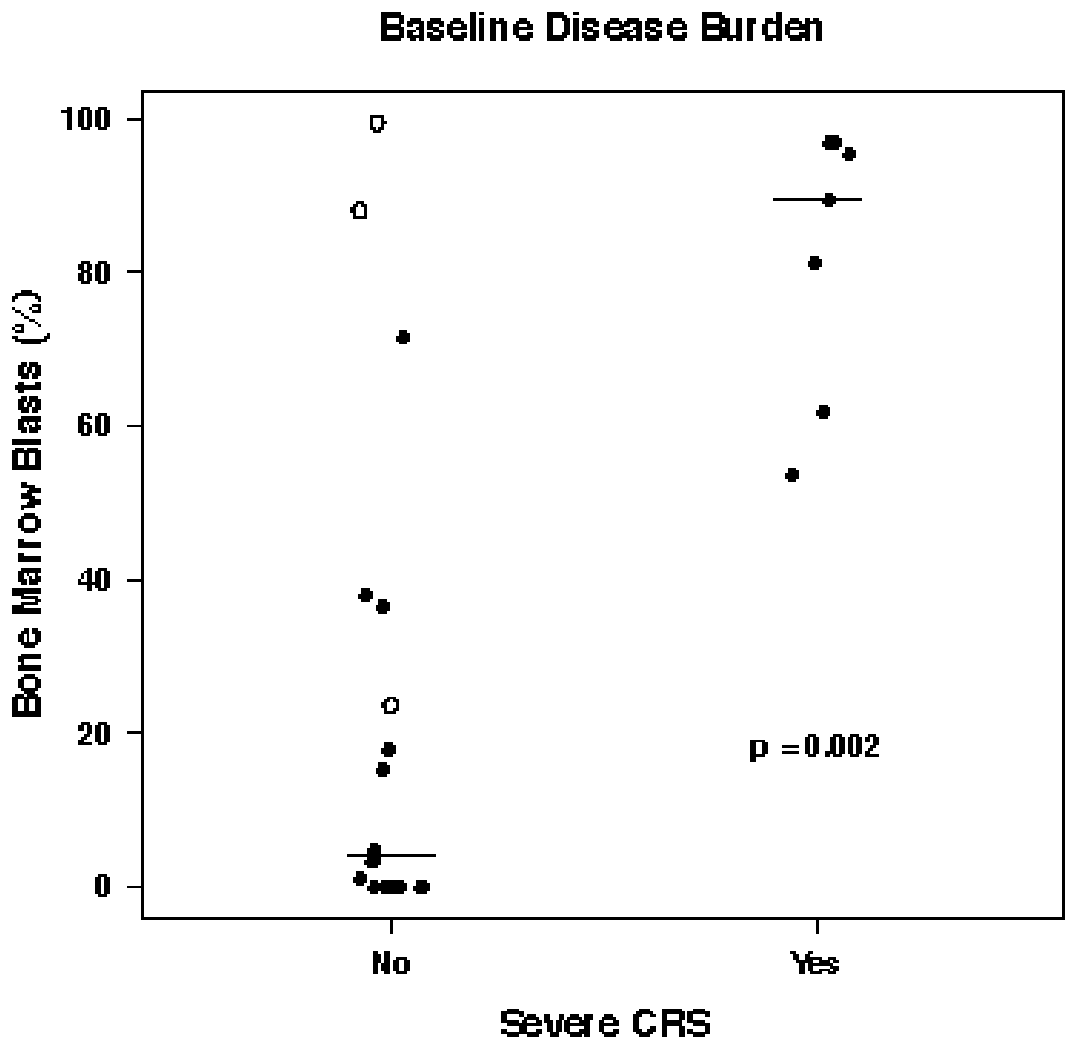
- Consolidate patients with MRD
- Reinduce remission
- Produce MRD (-) state prior to allo SCT
- “Bridge” to SCT
- Multicenter phase II trials in pediatric ALL (Novartis): NCT02228096
- With adequate persistence, CAR T cells may replace bone marrow transplants:

  - cancer “stem” cells can persist >1 decade

CART19 Toxicities

- **B cell aplasia**
  - **observed in all responding patients to date**
  - **managed with replacement therapy**
- **Tumor lysis syndrome (TLS)**
  - **may be delayed for 20 to 50 days post infusion**
- **Cytokine release syndrome (CRS)**
  - **reversible, on-target toxicity**
  - **Severity related to tumor burden: Treat MRD as outpatient?**
- **Macrophage activation syndrome (HLH / MAS)**
  - **elevated serum ferritin (>500,000 ng/ml), CRP, D-dimer**
  - **elevated cytokines: IL-6, IFN-gamma**
  - **Reversed with tocilizumab**

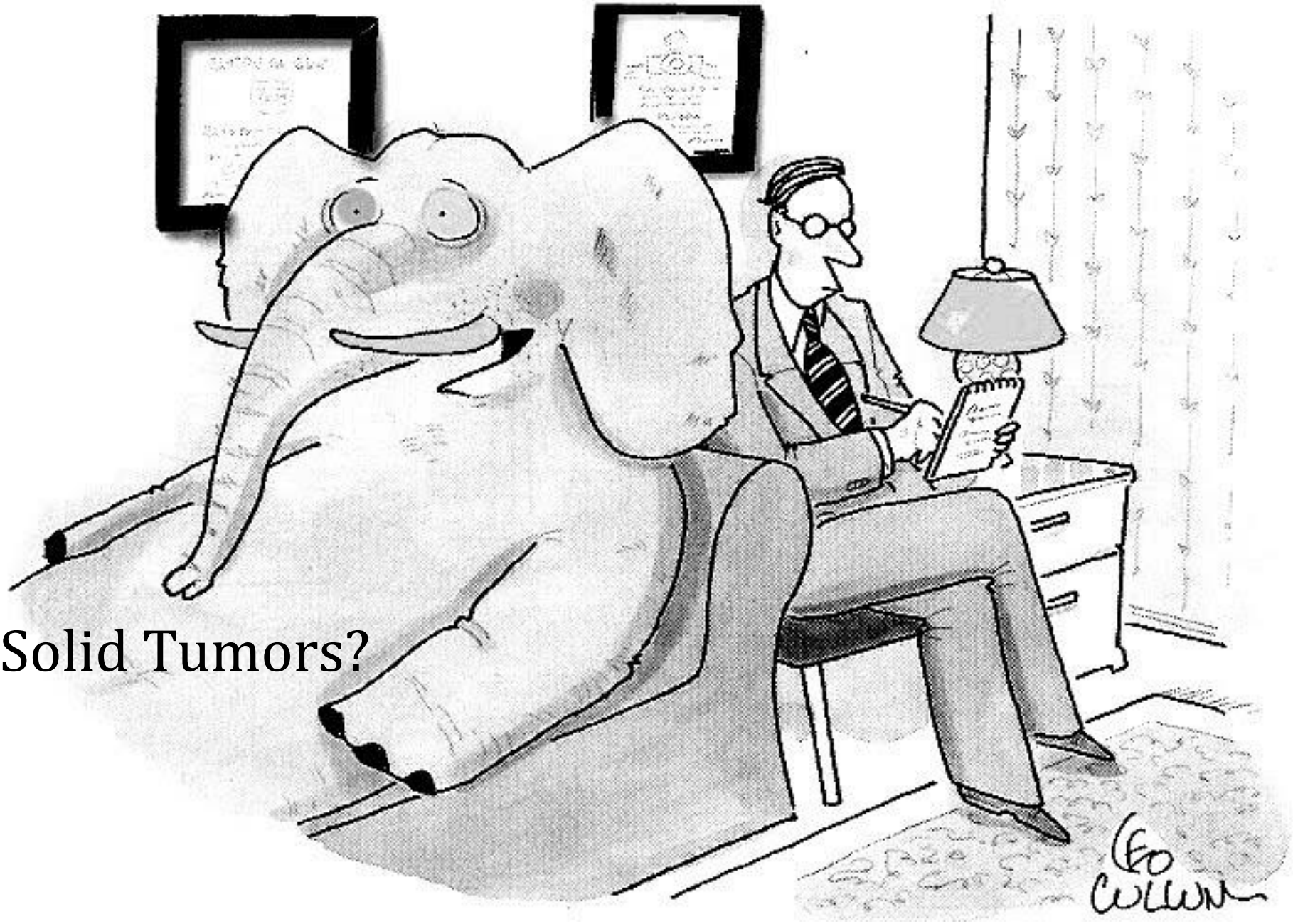
Disease burden is well-correlated with grade 4 CRS (r/r pre-B cell ALL)



Maude et al, NEJM 2014, in press

CARs in Development

Commercial CARs: Celgene, Juno, Kite, Novartis, Takara	
Academic Institute (US)	**Target(s)**
Fred Hutchinson Cancer Center	CD20, ROR1
Baylor College of Medicine	GD-2, Her2, CD30, kappa Ig
National Cancer Institute (NCI)	CD19, CSP4, GD-2, EGFRvIII , mesothelin, VEGFR2
Roger Williams Medical Center (RI)	CEA, PSMA
University of Pennsylvania	CD19, mesothelin, BCMA, EGFRvIII PSMA
Children's Mercy Hospital Kansas City	GD-2
Academic Institute (non-US)	**Target(s)**
Chinese PLA General Hospital	CD19, CD20, CD33, CD138, HER2
Christie Hospital NHS Foundation Trust	CD19
Peter MacCallum Cancer Centre, Australia	LewisY
University of Zurich	FAP

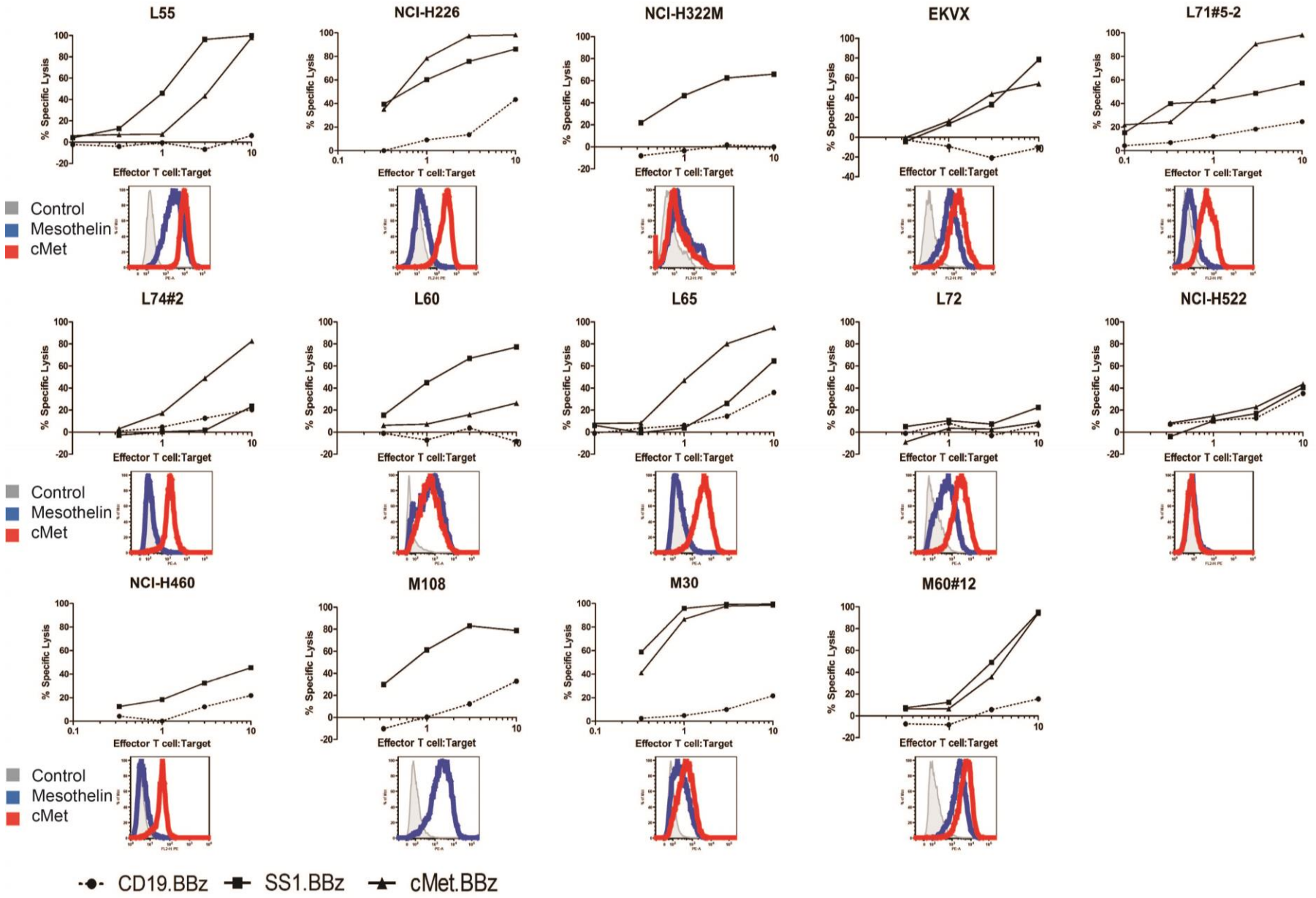


I'm right there in the room, and he doesn't even acknowledge me

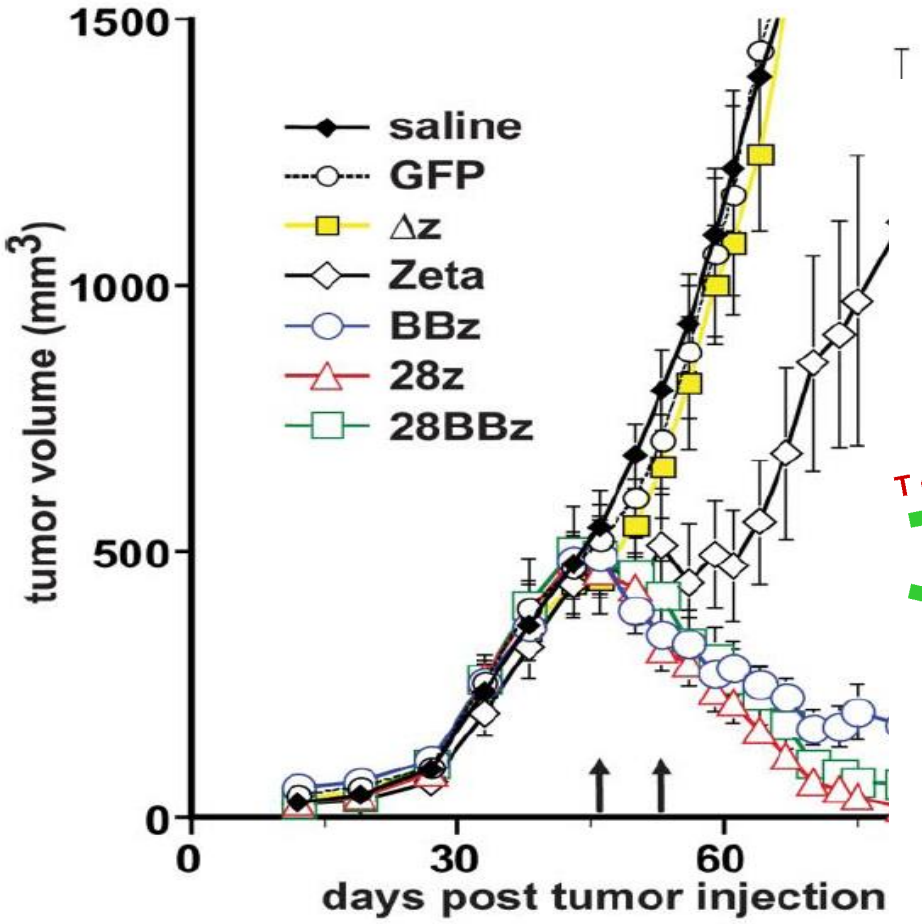
Beyond leukemia and lymphoma: engineered T cells for other cancers

- Numerous CARs targeting various surface molecules are being developed for many cancer histologies
- Examples:
  - EGFRviii for glioblastoma
  - PSMA for prostate cancer
  - Mesothelin for ovarian, pancreatic cancer and mesothelioma
  - Her2/neu (c-erB2) for breast and other carcinomas
  - FAP to target tumor stroma
- Key challenges and solutions

cMet and Mesothlin CAR T Cells Kill Most NSCLC Cells

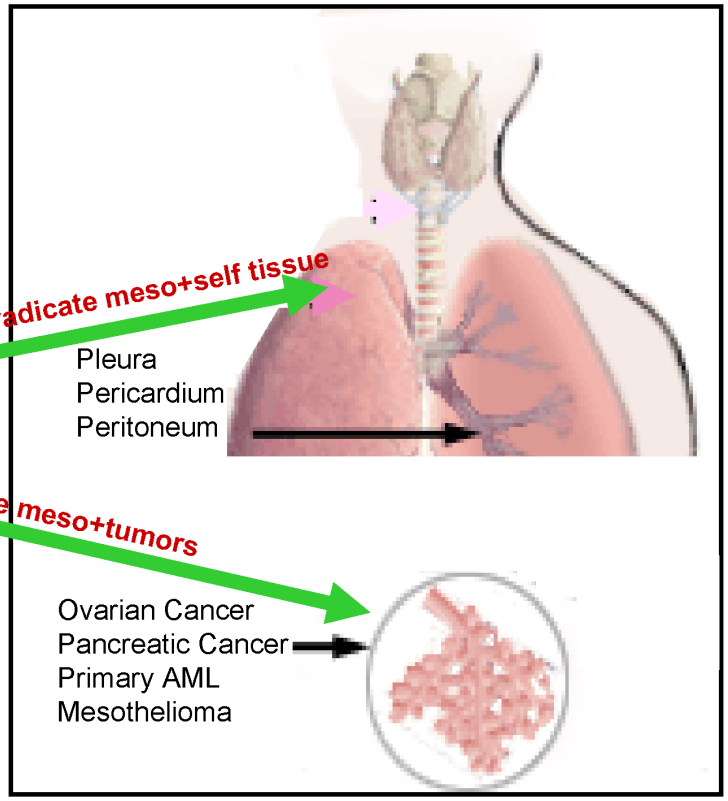


Anti-mesothelin CARs engineered with lentiviral vectors have potent anti-tumor effects in pre-clinical models



Carpenito, PNAS 2009

The potential bad news



NOVARTIS

Phase I Clinical Trial Of Autologous Mesothelin RNA CAR T Cells Administered Intravenously In Patients With Progressive Malignant Pleural Mesothelioma and Pancreatic Cancer: Demographics

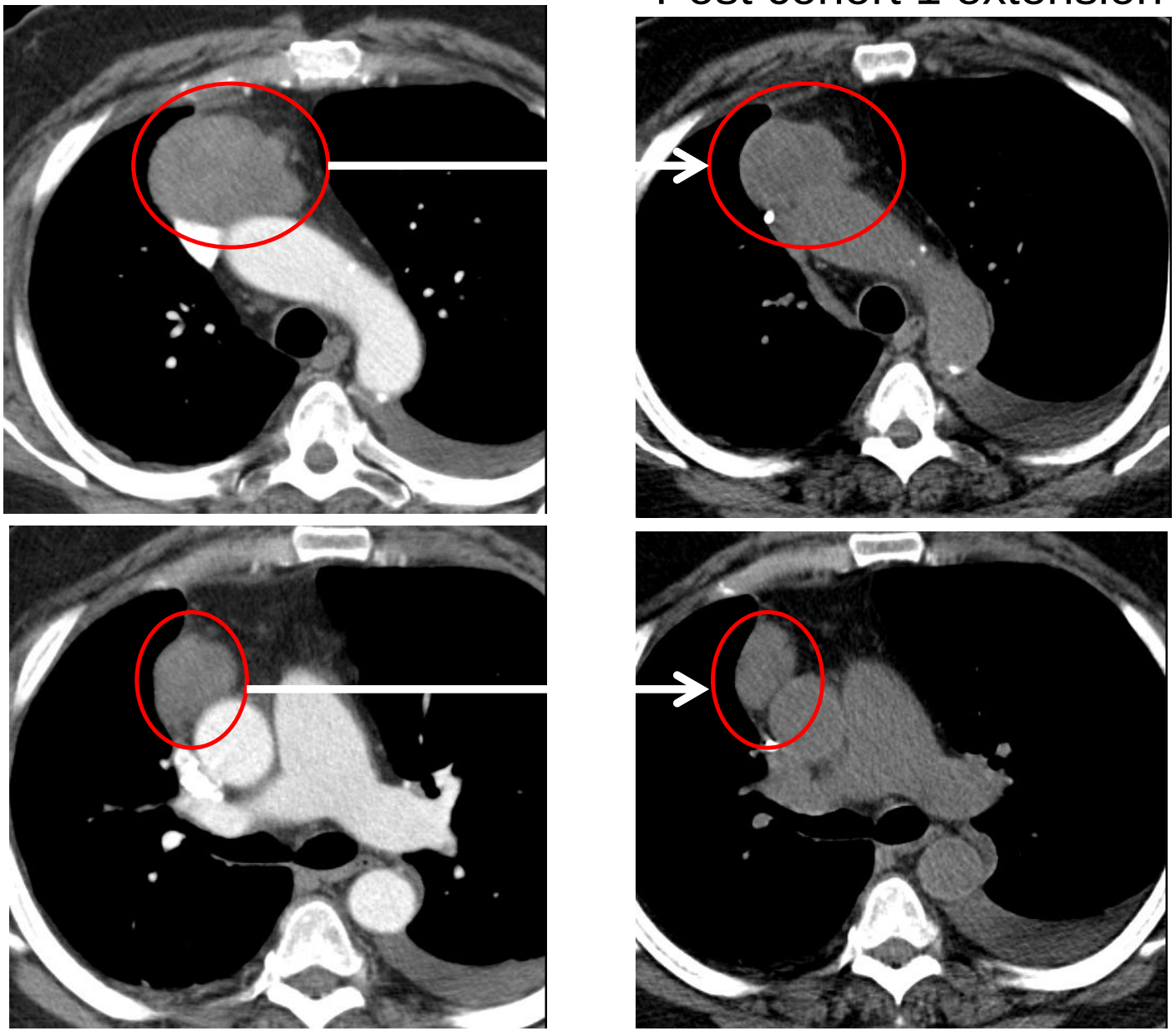
Subject	Age/sex	Disease	Prior therapies	Co-morbidities	Sites of disease at enrollment	Total infusions received and route of administration
17510-105	81/M	Malignant pleural mesothelioma	Pemetrexed/carboplatin (10 cycles) Pemetrexed (17 months) Intrapleural adenovirus-IFNα gemcitabine	asthma	Bilateral pleura, mediastinal and peritoneal lymph nodes	2 iv infusions (cohort 1); 1 iv infusion (cohort 2); total of 3 iv infusions
21211-101	75/M	Pancreatic adenocarcinoma	Gemcitabine/CDDP (3 cycles) Modified FOLFOX6 (9 cycles)	-DVT on LMWH -Abdominal infections -h/o AML s/p syngeneic BMT 5 yrs prior to enrollment	Abdominal mass, liver masses, peritoneal nodules, ascites, Right knee subcutaneous	8 iv infusions; 2 intratumoral injections; 1 intraperitoneal injection

Gregory Beatty, MD PhD and Andrew Haas, MD
Maus et al, Cancer Immunol Research, 2013

Mesothelioma Patient #3: Partial Response

Pre cohort 1 extension

Post cohort 1 extension

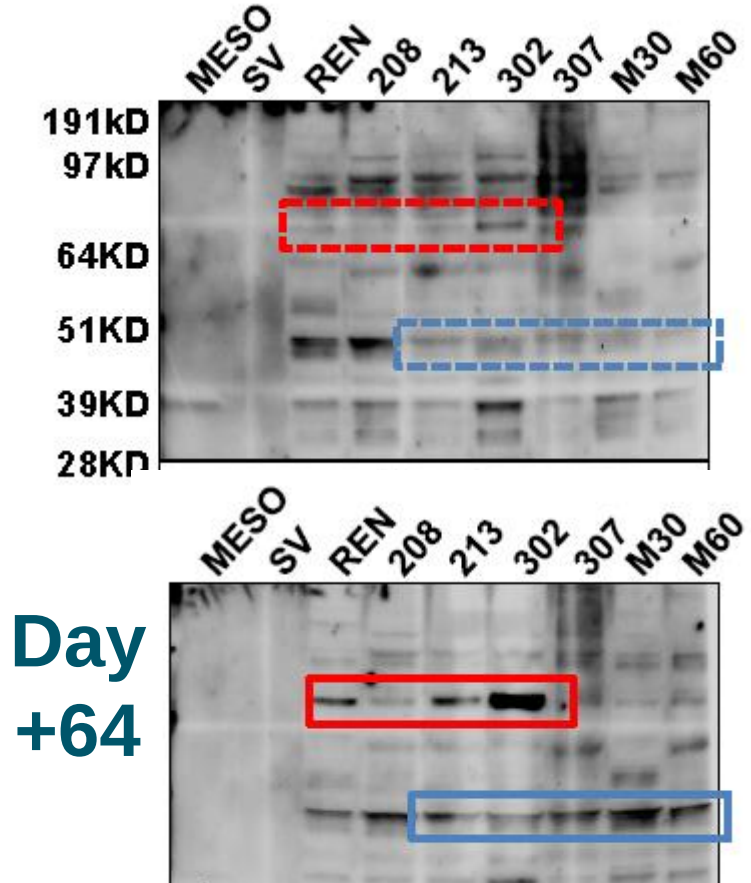


Estimated 57% decrease in volume

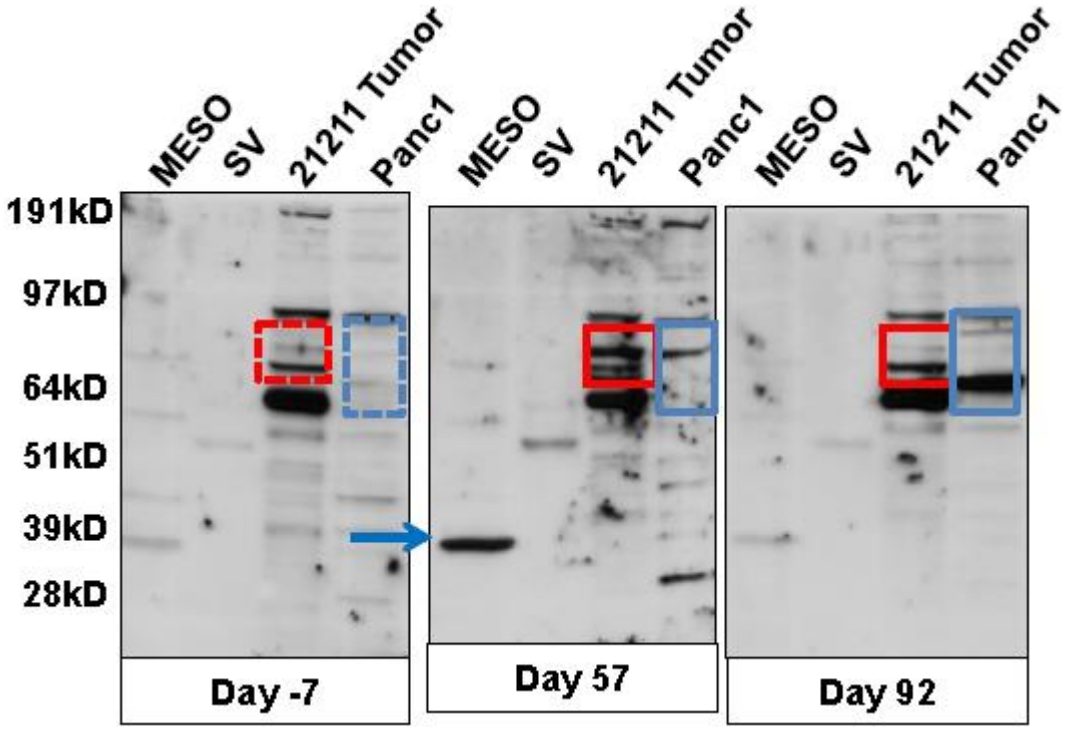
Vaccine Effect following RNA CAR Meso T Cell Infusions: cross priming?

Western blot analysis on autologous tumor cell line: induction of anti-tumor antibodies

Pt 17510-105

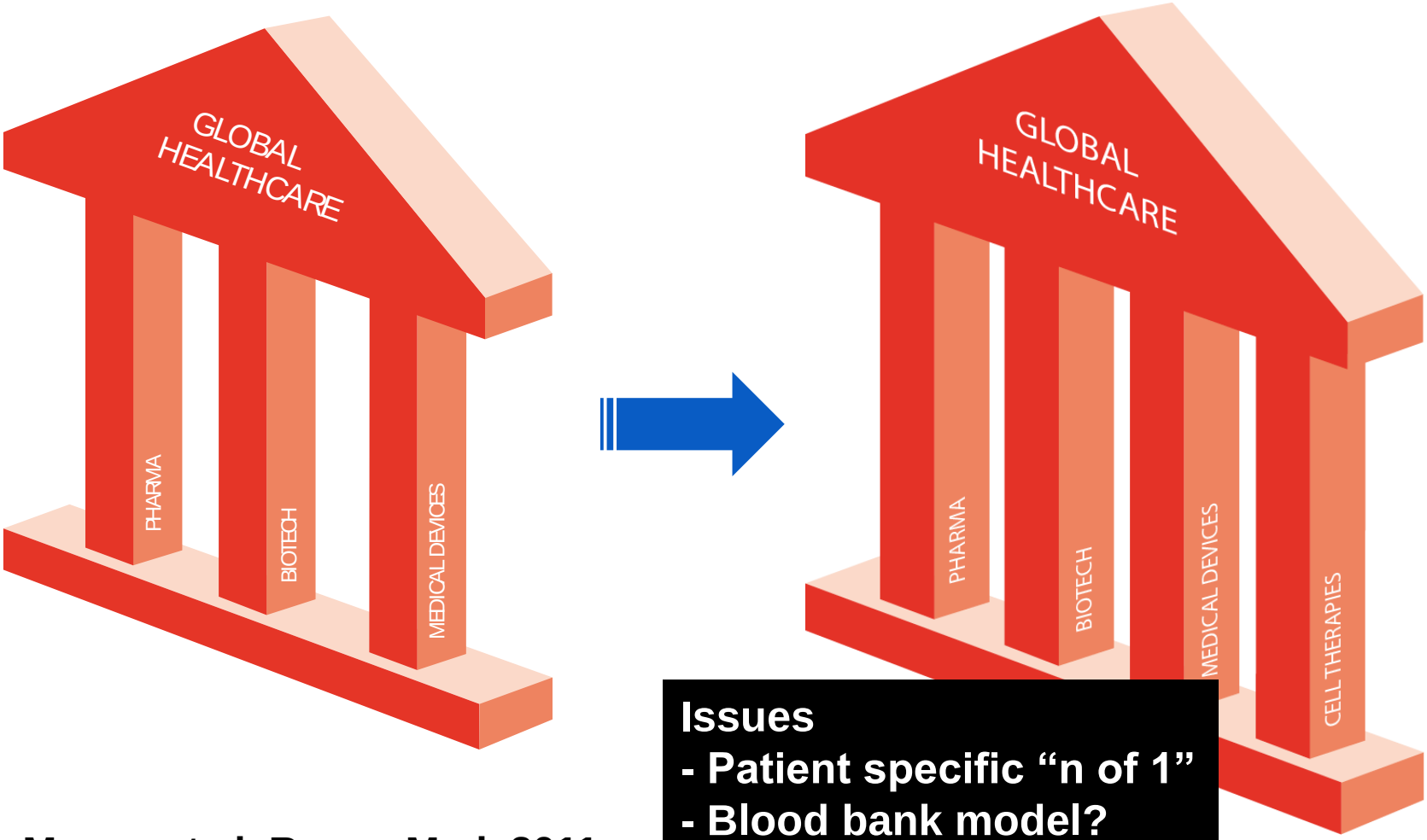


Pt 21211-101



Beatty et al. Cancer Immunol Res. 2014 2(2):112-120.

Health Care Challenges



Issues
- **Patient specific "n of 1"**
- **Blood bank model?**
- **Central manufacturing?**

Chris Mason et al, Regen Med. 2011
Levine and June, Nature. 2013

Cell Manufacturing Issues
Cell Cullture: “N of 1”

- Robotic and automated cell culture be required to move beyond botique. An engineering issue…

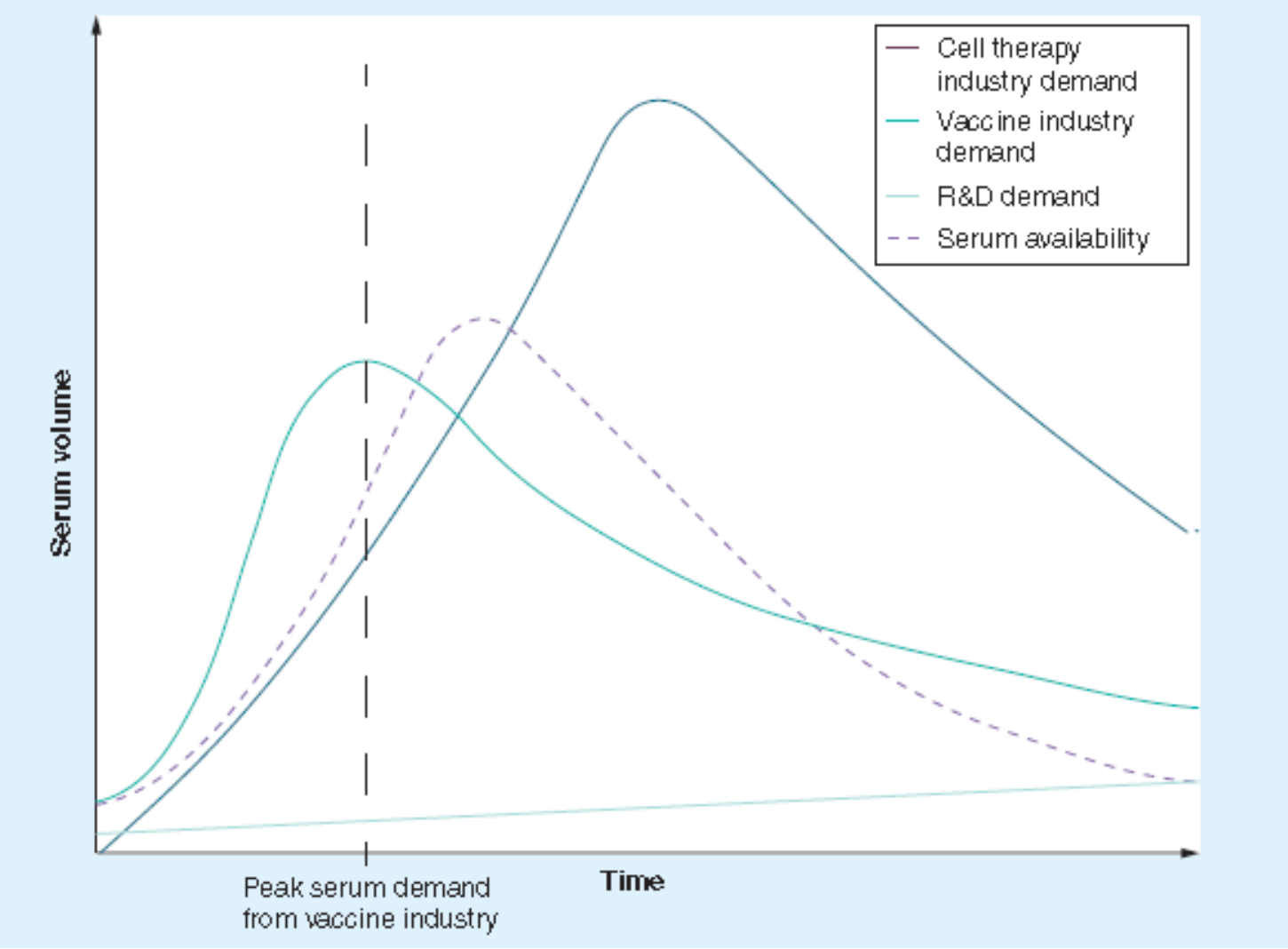
- Education of patients and physicians regarding specific issues with immune based therapy…

- Serum free is essential

Levine, B.L., and C.H. June. 2013. Perspective: assembly line immunotherapy. Nature 498:S17.

Peak Serum: Like Peak Oil?

Global supply of serum:



- **Brindley et al. 2012. Regenerative medicine 7:7-13.**

Allogeneic CART19 for Relapsed CD19+ Disease

***Kochenderfer et al. Blood 2013 :*122(25):4129**

- All pts with disease after allo-HSCT and prior DLI
  - N=10 (4 CLL, 4 MCL, 2 DLBCL)
- CARs manufactured from each patient's allo-HSCT donor
  - Matched sibling donor (6), Unrelated donor (4)
  - Cell dose: 0.4 – 7.8 x 10^6 CAR T/kg
- Results
  - 1 CR (CLL, URD) 9+ mo
  - 1 PR (MCL, URD) 3+ mo
  - 6 SD (1-11+ mo); 2 PD

  => No GVHD. Towards universal donors for CAR T cells?

Personalized “N=1” Cellular Therapies

Companies ponder how truly ‘personal’ medicines can get

Take it personally: Tailored drugs cost more.

Optimists are quick to cite Provenge as the crest of a wave of new therapies. "It has huge implications," says Ronald Levy, a co-founder of Idec Pharmaceuticals (which merged to form Biogen Idec in 2003). "There may be 50 other therapies who hope to follow in the Provenge example."

It has been a long, hard road since the start of efforts to make medicines from patients' own cells, says Brenner, and personalized therapies are still very much a work in progress. "It's twenty years on," Brenner says, "and we still only have Provenge."

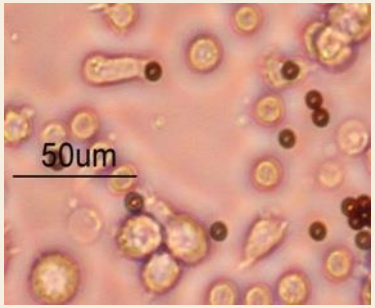
Monya Baker

Outscaling CAR manufacturing: robotic and automated cell culture

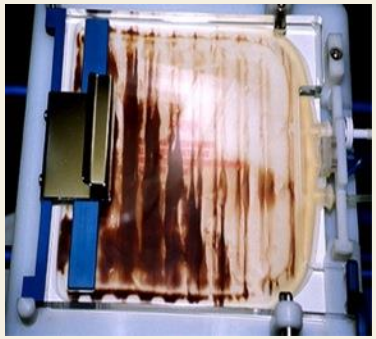
CAR: Sedan

CAR: CD19

Bead addition

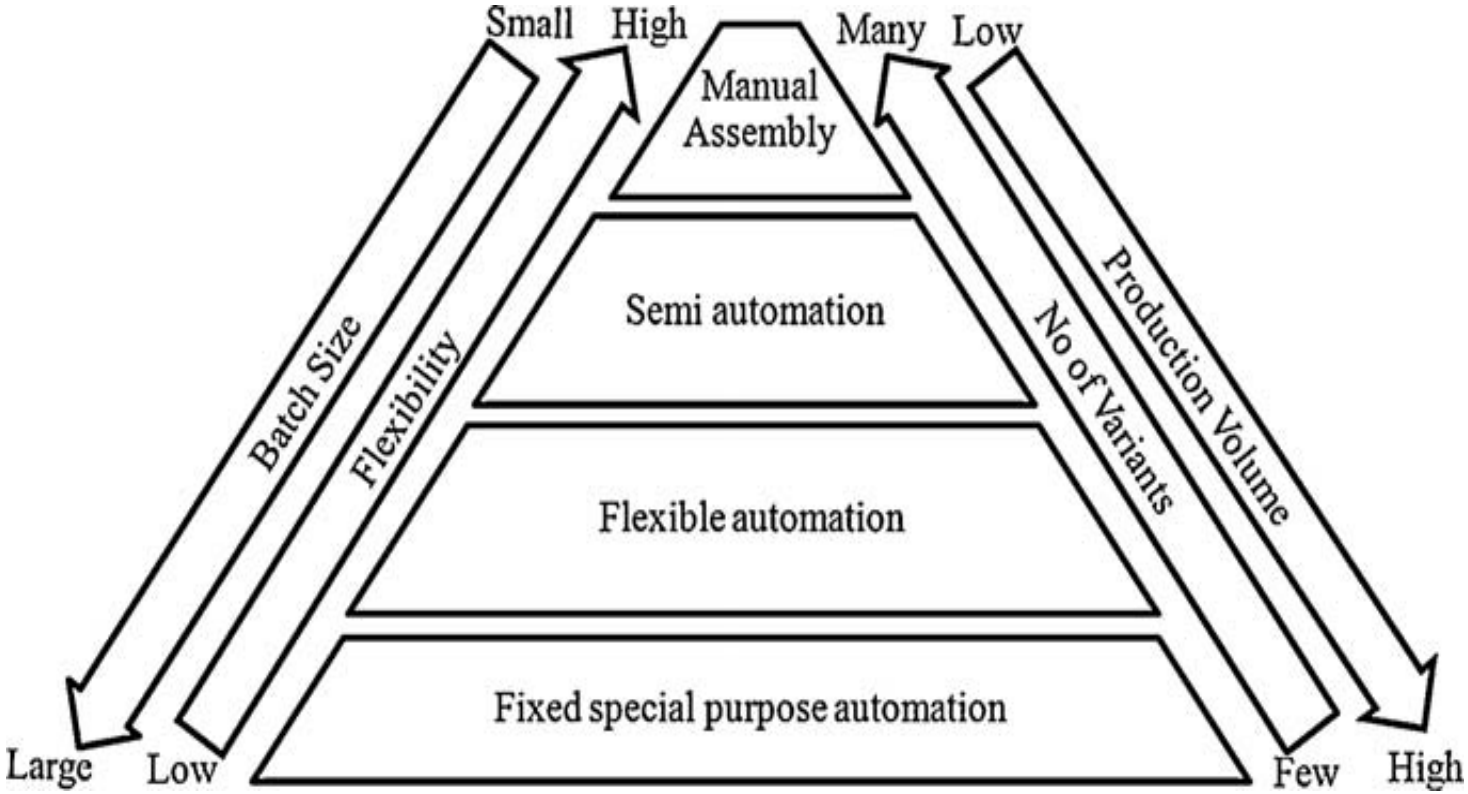


Bead removal



T-cell infusion

Robots and Automation: Lessons from Detroit



Volkswagen

Performance characteristics of assembly systems following different assembly principles (Heilala, J. Modular Reconfigurable Flexible Final Assembly Systems, Assembly Automation, 21/1: 20–28, 2001)

CAR Trials: Colleagues and Collaborators

ACC Translational Research

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Gregory Beatty
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ACGT ALLIANCE FOR CANCER GENE THERAPY
National grants for cancer research

The Leukemia & Lymphoma Society®
Fighting Blood Cancers