Immunotherapy on the Horizon: Re-directed T cells as therapy

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Advances in Cancer Immunotherapy-MA SITC education event

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HARVARD MEDICAL SCHOOL

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Disclosures

- All cell therapies are currently investigational and not FDA-approved
- Speaker is inventor on patents related to engineered cell therapies; patents held by University of Pennsylvania and some of these are licensed to Novartis
- Speaker is a consultant for various cell therapy companies (Agenus, Juno, Intellia, Neon, Unum, TCR2 and WindMIL), none of which will be discussed

Learning Objectives

- Describe the rationale for cell-based immunotherapy
- Identify the scientific basis of T cells engineered with chimeric antigen receptors and T cell receptors
- Explain the mechanisms and types of toxicities that can be expected with T cell therapies, along with current management strategies

Immunology has offered hope for curing cancers for 100 years

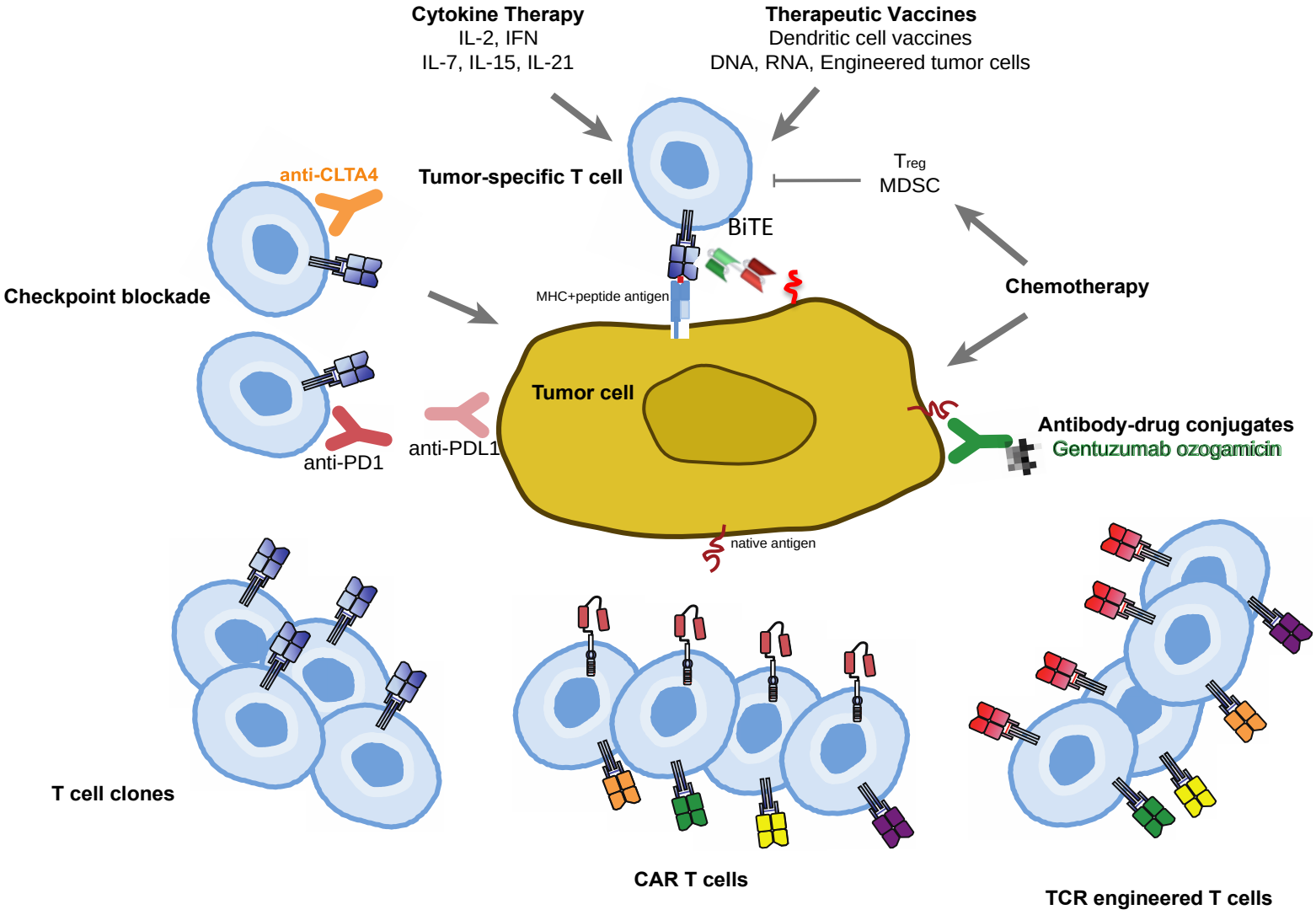
Why was it so hard? TOLERANCE

- Low affinity of T cell receptors (central tolerance)
- Inhibitory effects of tumor environment (stronger peripheral tolerance)
- (Trafficking of T cells into tumor?)

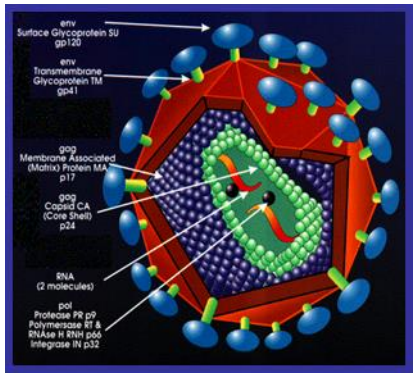
What is different now?

- Genetic engineering of T cell receptors to increase affinity
- Bypassing T cell receptor by using chimeric antigen receptors
- Blocking inhibitory molecules of tumor microenvironment

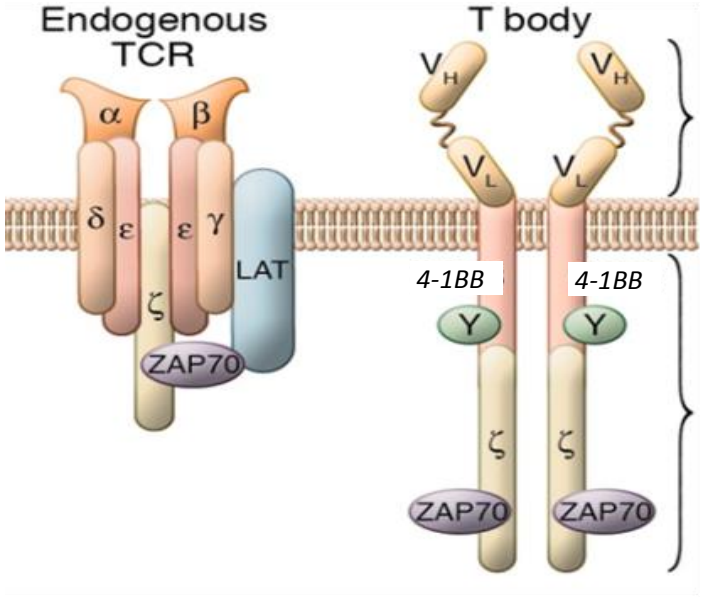
Approaches to overcome tolerance



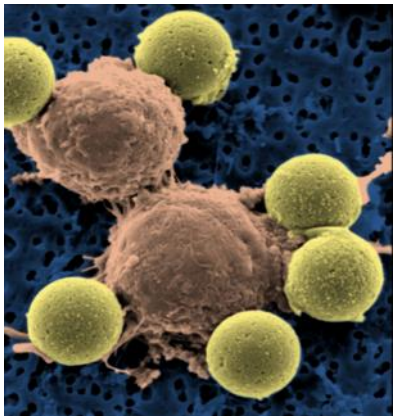
To engineer a T cell, you need…



A gene delivery system (lentiviral vector)



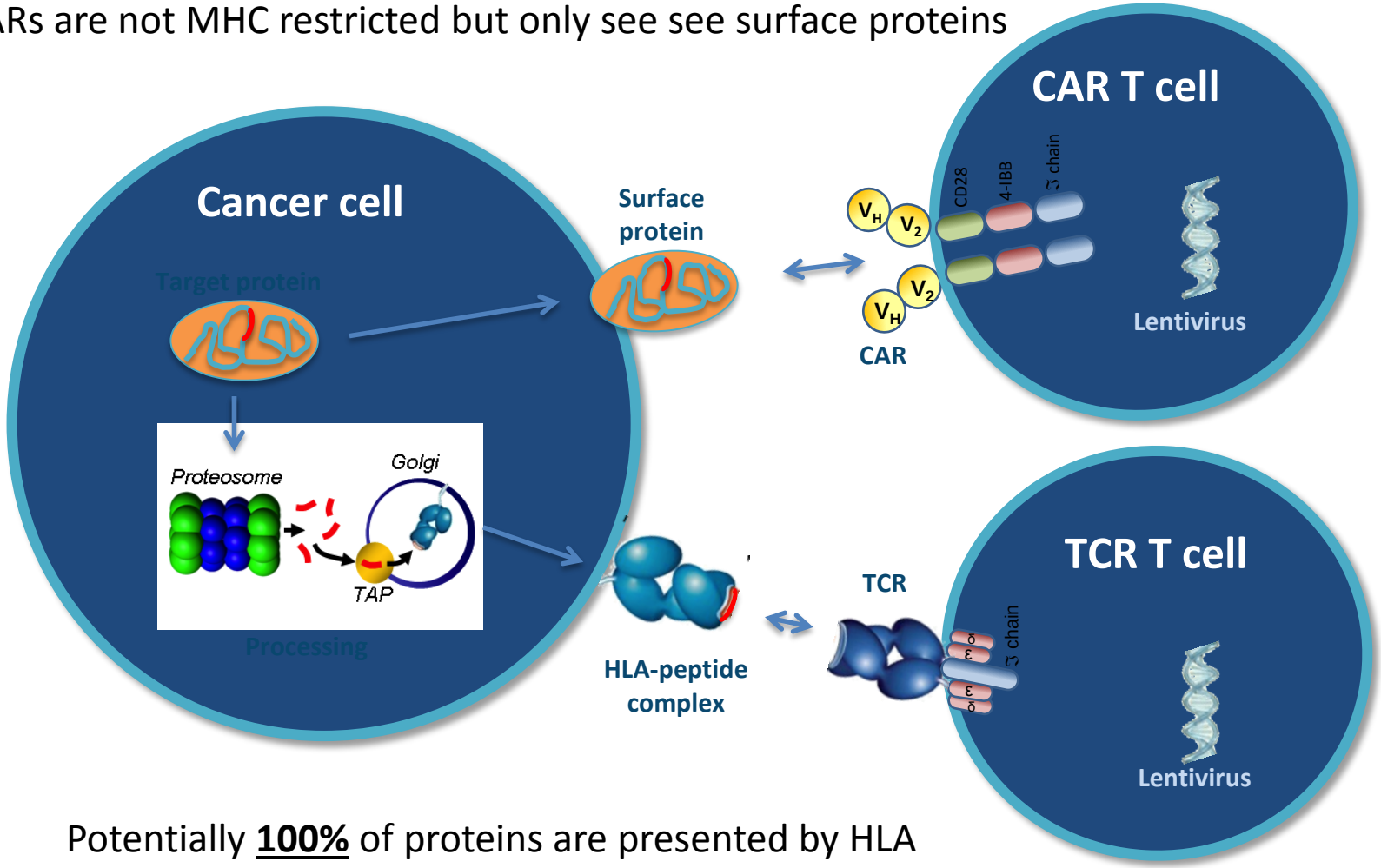
An antigen receptor (natural ligand, TCR or CAR)



Ex vivo culture system (anti-CD3/28 beads)

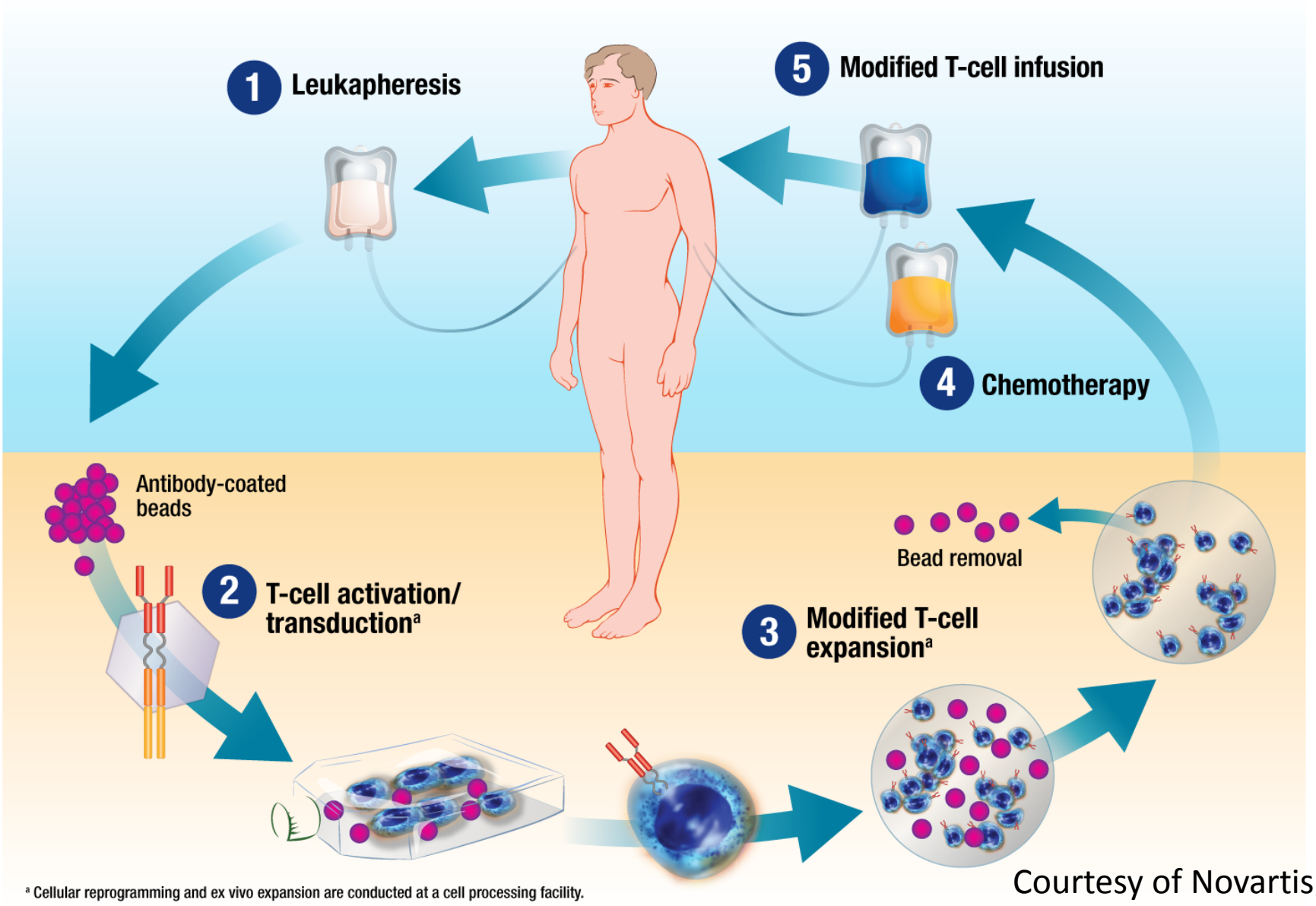
Antigen recognition: TCR vs CAR

CARs are not MHC restricted but only see see surface proteins



Potentially **<u>100%</u>** of proteins are presented by HLA

Overview of T cell Therapy



Courtesy of Novartis

T cells re-directed with higher-affinity TCRs

- Most self-directed natural TCRs have very low affinity, are probably not effective
- MART-1 TCR: on-target toxicity

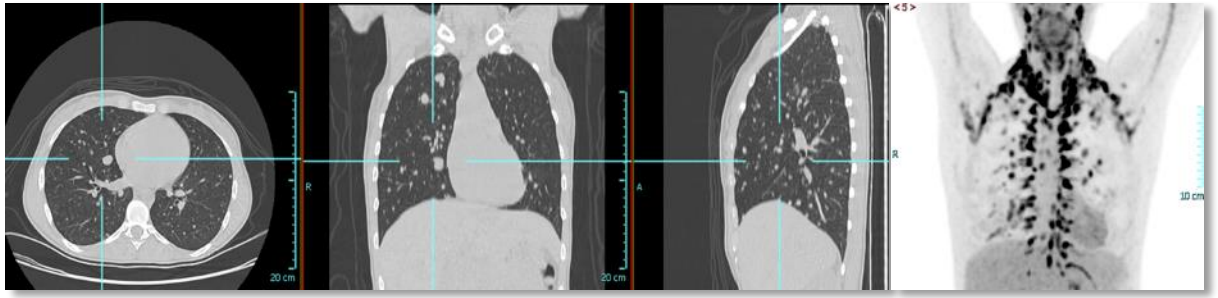
  (Johnson et al, Blood 2009)
- MAGE-A3 TCR: off-target toxicity

  (Linette et al Blood 2013, Cameron et al, STM, 2013)
- NY-ESO-1 TCR: responses!

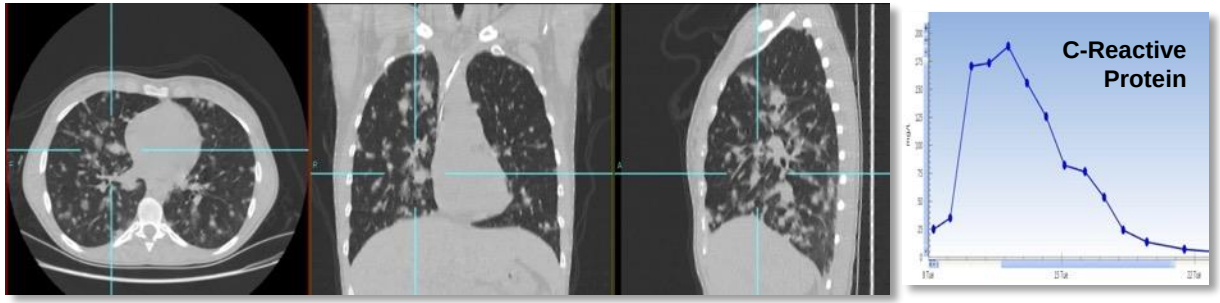
PHASE I/II STUDY IN SYNOVIAL SARCOMA

RADIOGRAPHIC PSEUDOPROGRESSION AND RESPONSE OF LUNG METASTASES LEADING TO COMPLETE RESPONSE

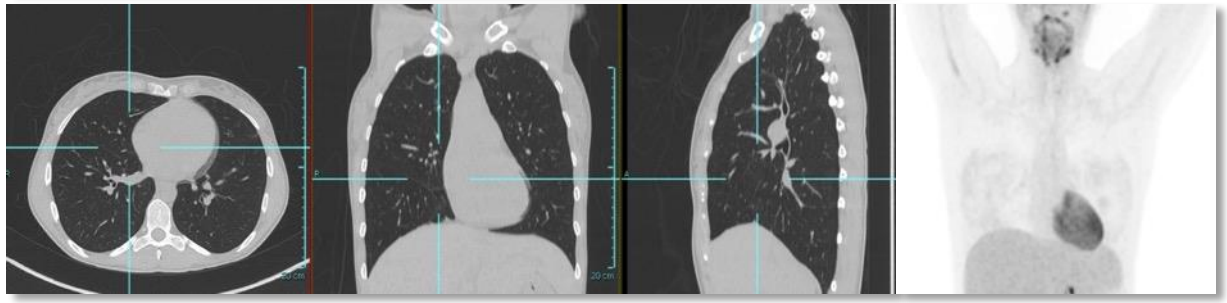
Baseline:
Bilateral miliary metastatic disease



Day +2:
Pseudoprogression due to immune infiltration



Day +101:
Complete Response



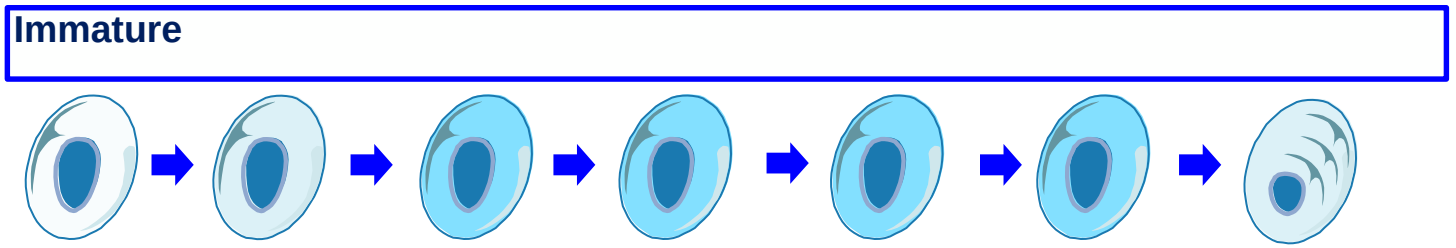
Source: AACR April 2015; Adaptimmune

Issues in CAR design

- What antigen to target?
  - Is it on the surface of the tumor? Is it a tumor driver or otherwise essential? Is it on any normal tissues?
  - Is there a patient population who could benefit?
- What mode of gene transfer?
- What signaling domains to include in CAR?
- What culture system to use for T cells?

Human CD19 Expression by Hematopoietic Cells (*Opportunities for CART19 Intervention*)

Normal: Pro-B | Pre-B | Immature B | Naïve B | Germinal Center B | Memory B | Plasma Cell



Acute Lymphoblastic Leukemia (ALL)

Chronic Lymphocytic Leukemia (mutated)

Malignant:

Chronic Lymphocytic Leukemia (CLL) (unmutated)

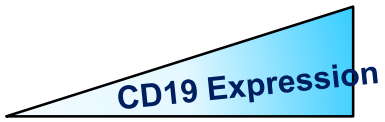
Mantle Cell Lymphoma

Multiple Myeloma (MM)

Follicular Lymphoma

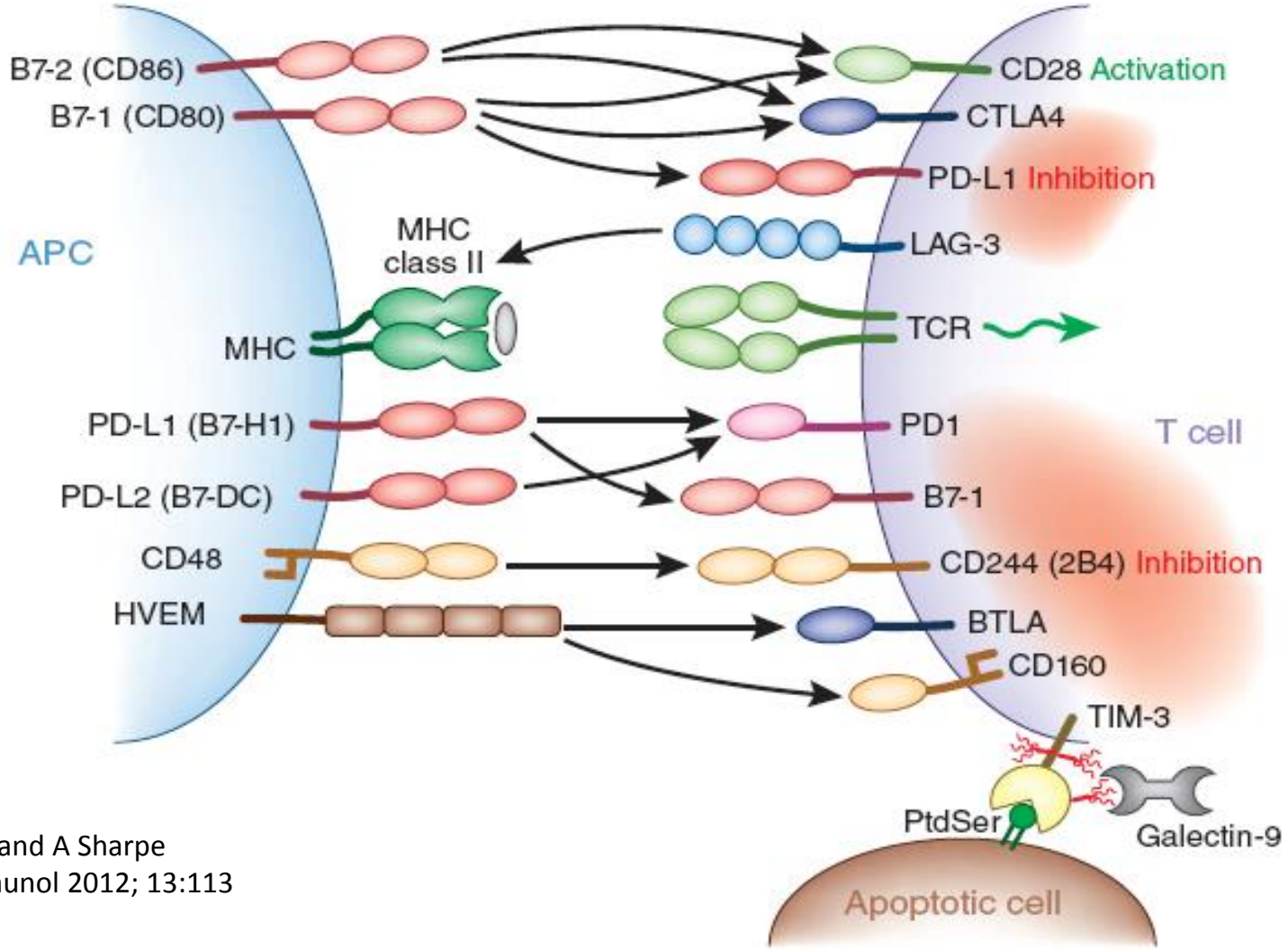
Waldenstrom's Macroglobulinemia

Diffuse Large B-Cell Lymphoma



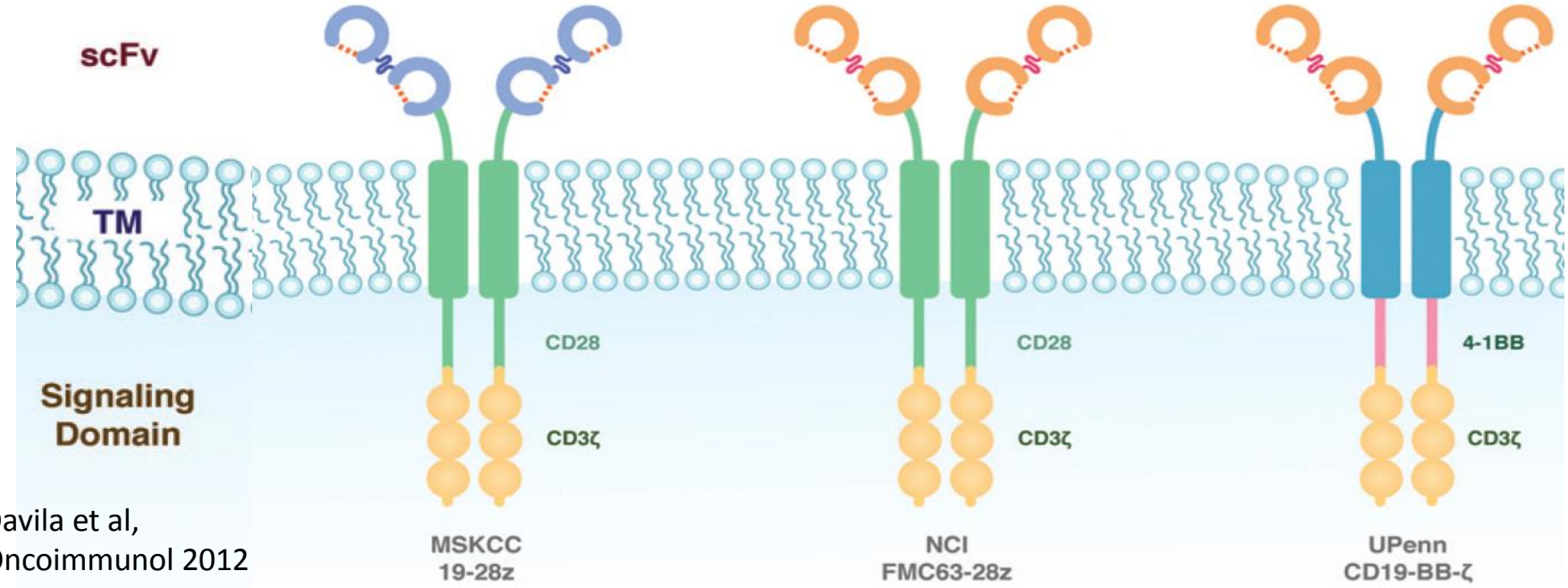
Adapted From: J Rubenstein, M.D., Ph.D.

T cells Express Multiple Co-Receptors



G Freeman and A Sharpe
Nature Immunol 2012; 13:113

Comparing CD19 CARs for Leukemia



Davila et al, Oncoimmunol 2012

JCAR 015 (MSKCC)

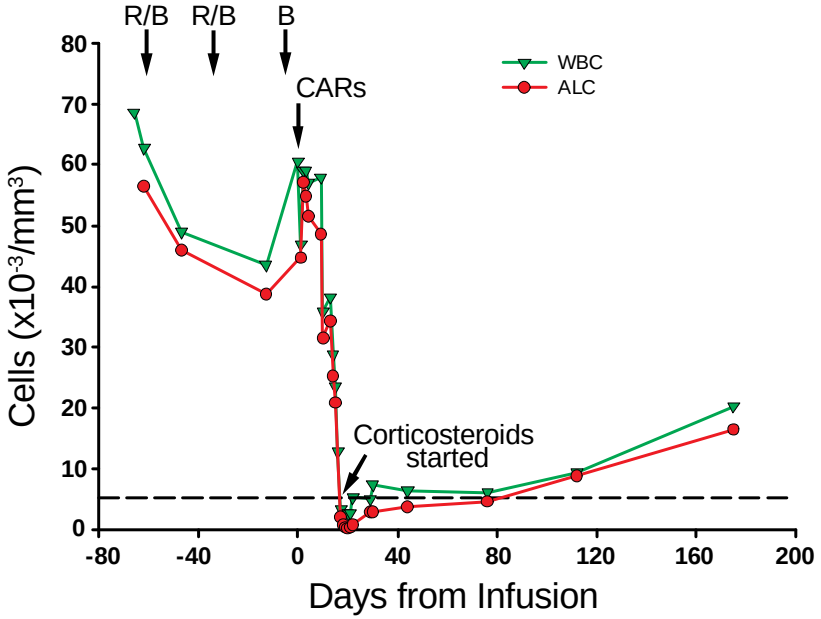
KTE-C19 (NCI)

Novartis CTL019
JCAR 017 (Seattle)

Vector	Retroviral[1]	Retroviral[2]	Lentiviral[3]
Expression	~30 Days	~30-60 Days	>4 years
	[1]Brentjens Blood 2011 and Science Trans Med, 2014	[2]Kochenderfer Blood 2012; Kochenderfer JCO 2014; Lee, Lancet Oncology 2015	[3]Porter NEJM 2011; Science Trans Med, 2011 , 2015

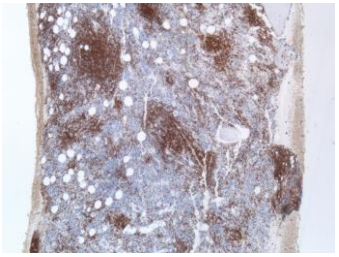
Examples of Clinical Responses: CLL

UPN 02

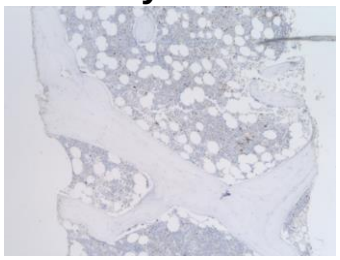


UPN 01

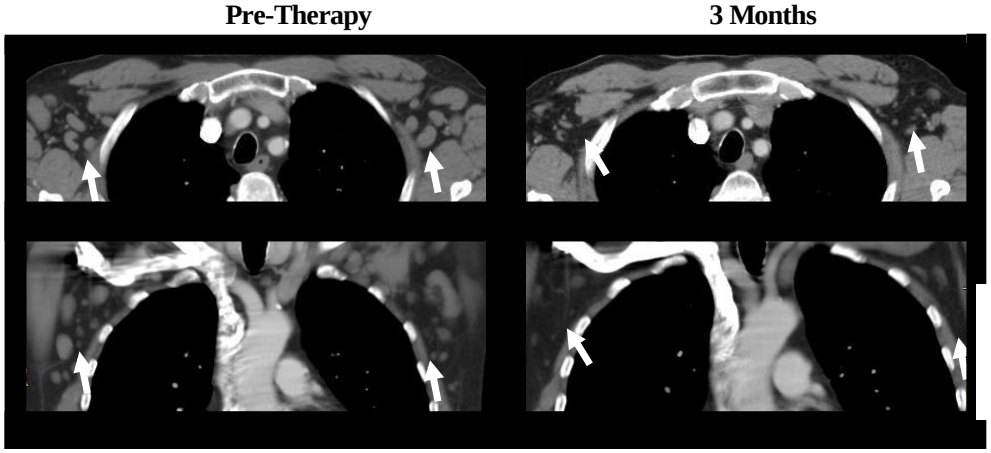
Day -21



Day 177



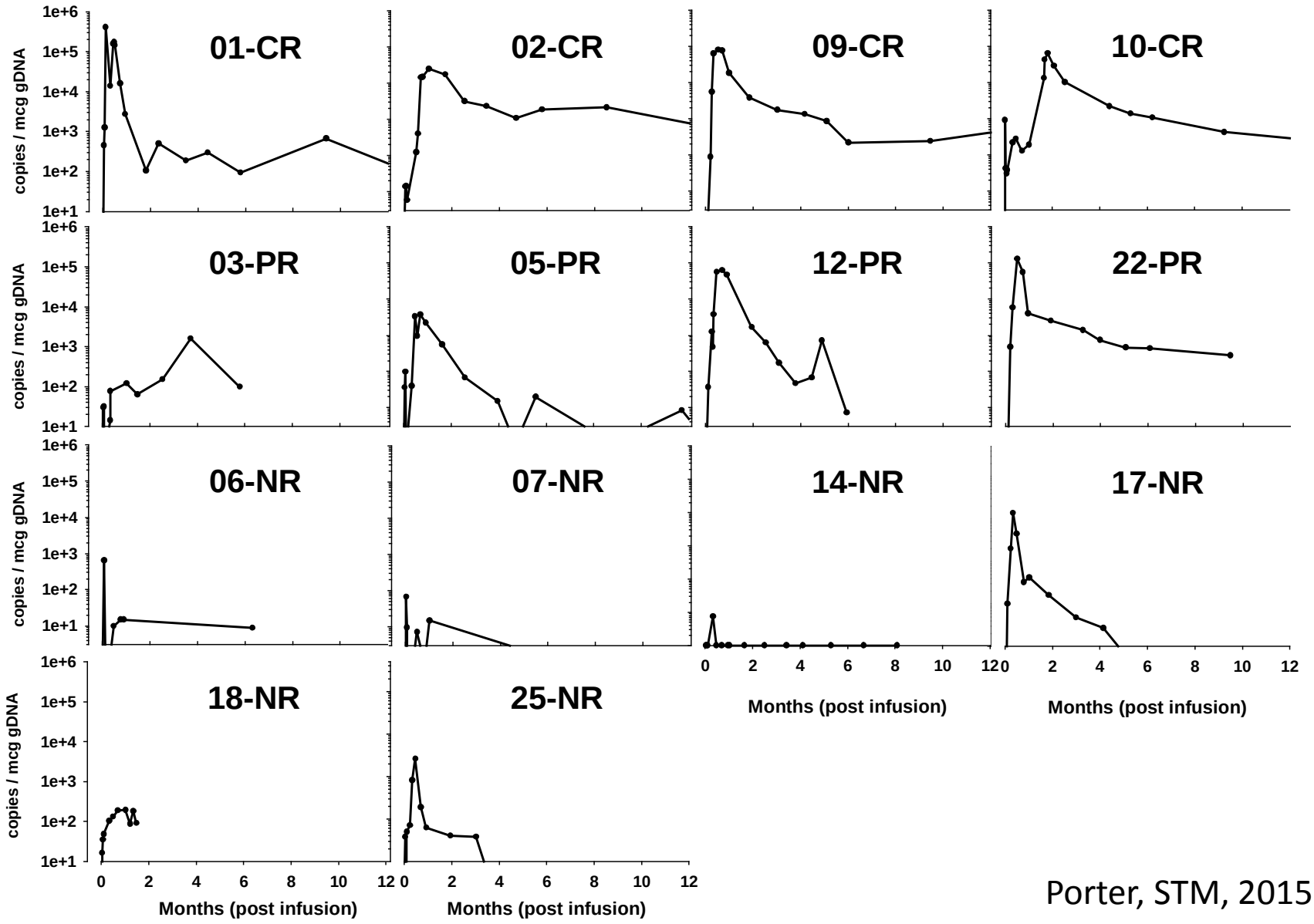
UPN 03



Porter NEJM 2011
Kalos STM 2011

Long term persistence in CLL patients with durable remission

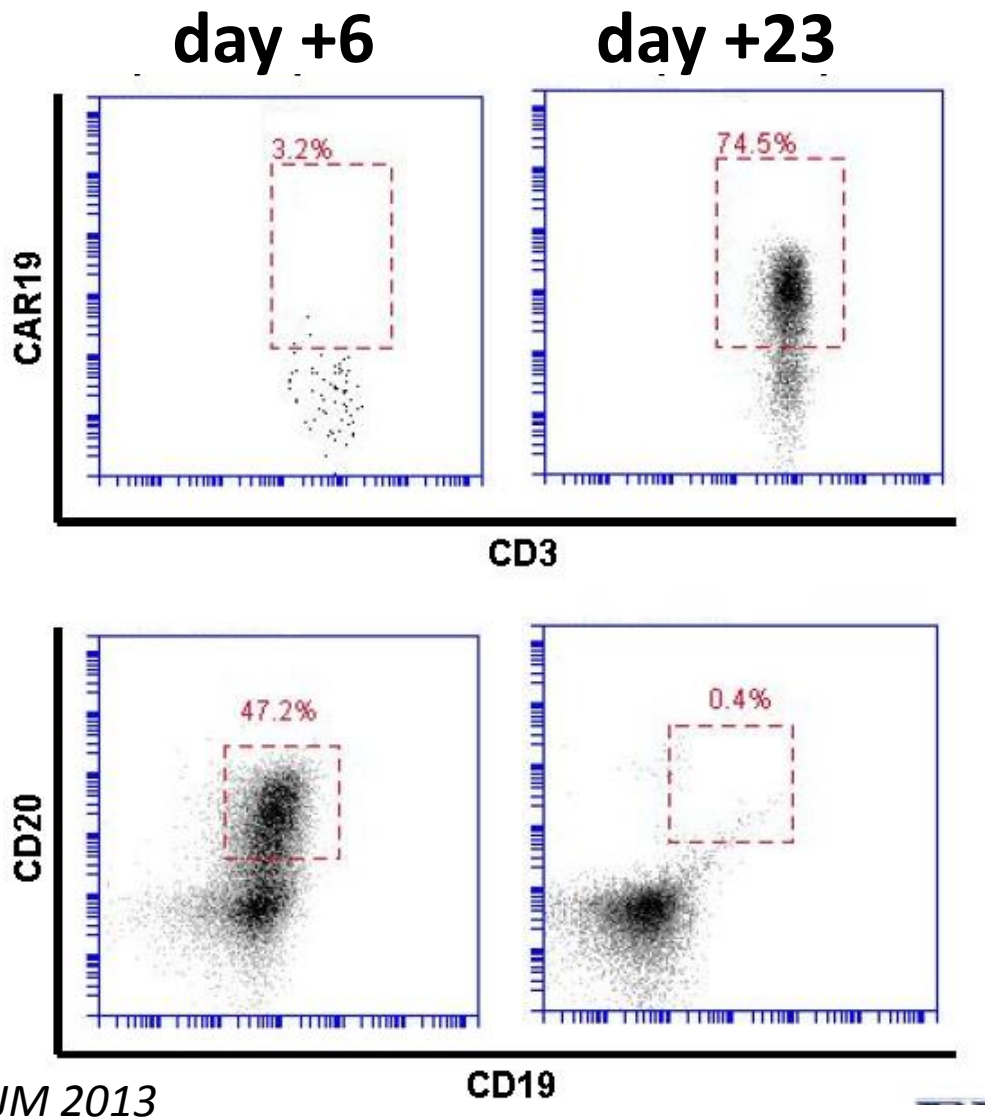
Persistence for first year after infusion



Porter, STM, 2015

Rapid Induction of Remission in pre-B ALL

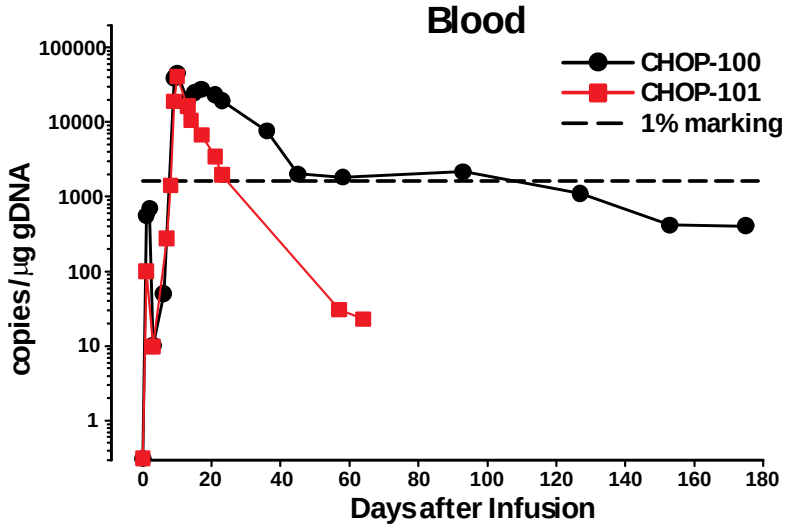
Marrow

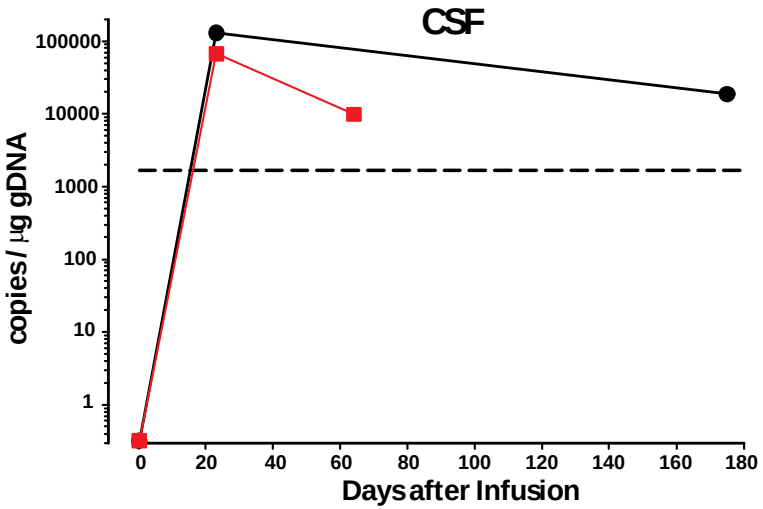


- **Deep remission induced in 23 days**
- **No chemotherapy was given**
- **Status: CR (12+)**
- **MRD <0.01% cells**

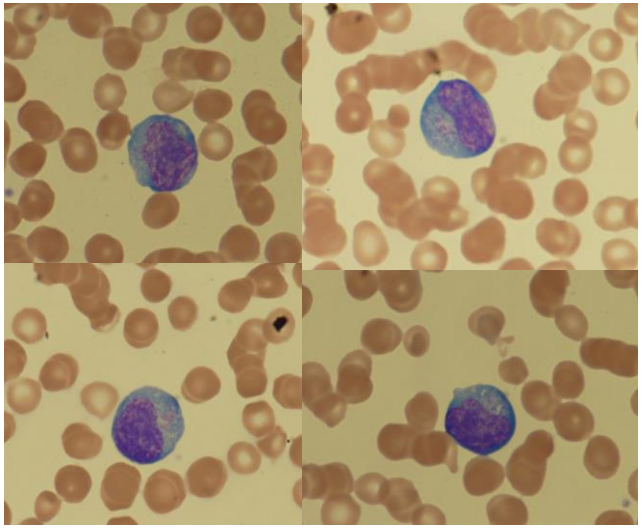
Stephan Grupp, NEJM 2013

Trafficking of CAR T to CNS in ALL

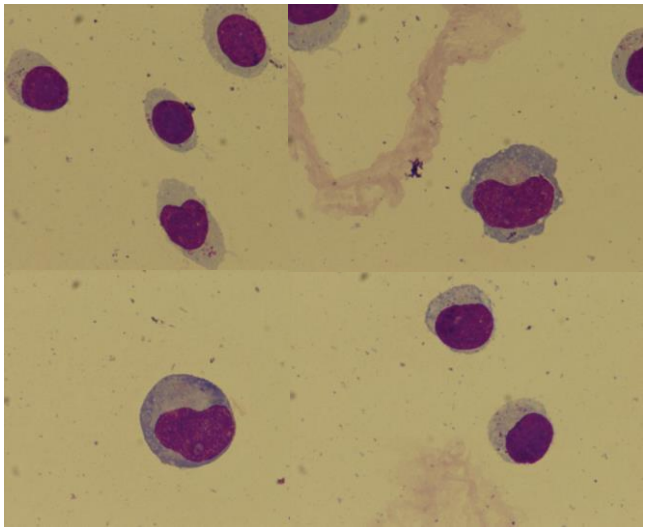




Blood
Day 10

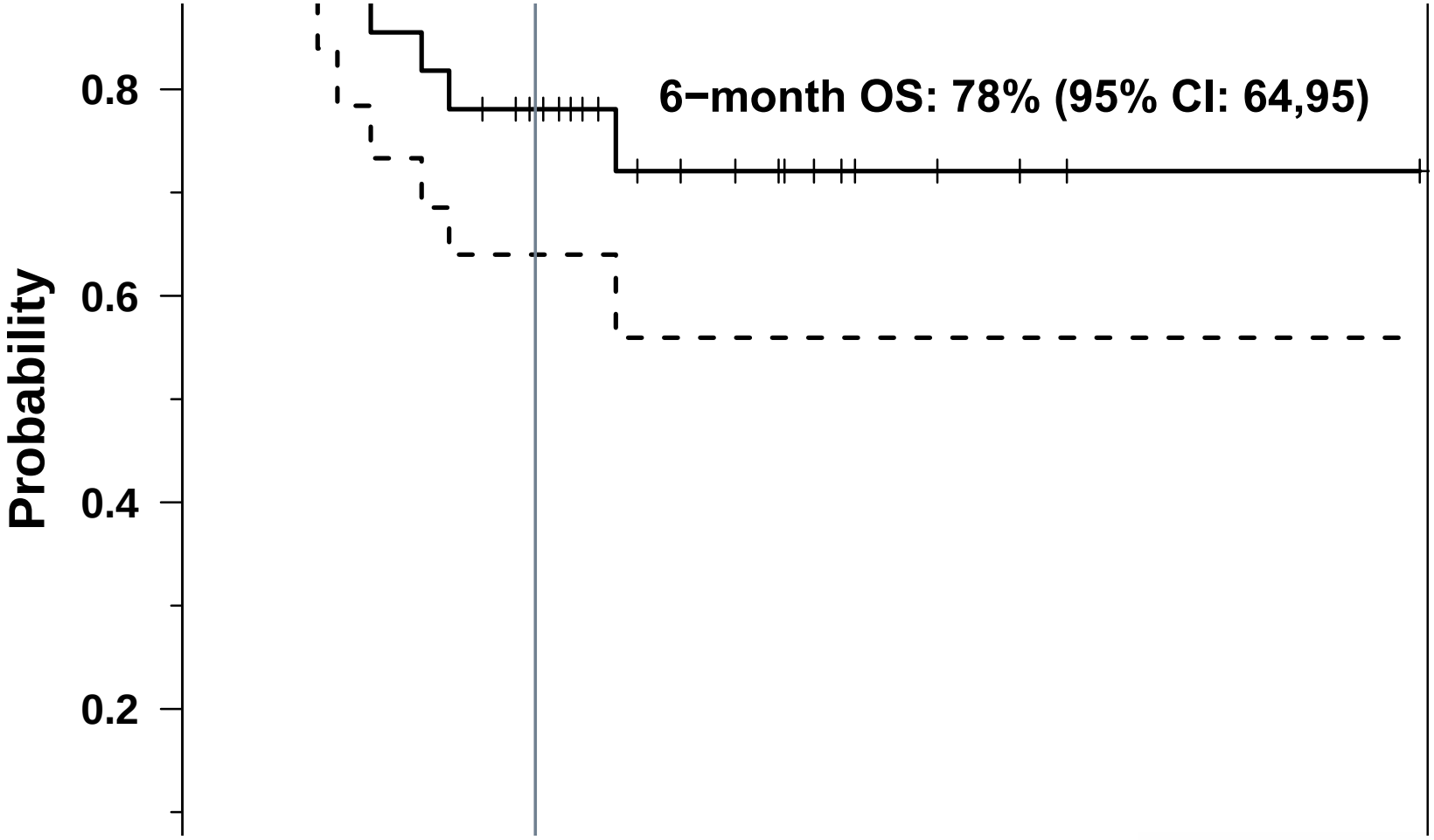


CSF
Day 23



Stephan Grupp, NEJM 2013

OS in relapsed/refractory ALL



Maude, Frey et al. NEJM 2014;371:1507-1517.

The NEW ENGLAND JOURNAL of MEDICINE

ALL: Mechanisms of Resistance to CART-19

- In pediatric and adult ALL, there is a >90% CR at 1 month
- To date, there have been 15 relapses in the first 50 patients given CART19:
  - No patient has relapsed beyond year
  - 15 patients have relapsed
  - **Early relapses associated with loss of B cell aplasia (n=5)**
  - **Late relapses are associated with target loss (CD19 negative leukemia, n=10)**

Grupp, et al. *NEJM 2*013.
Maude, et al. NEJM 2014.

Common toxicities with CAR 19

- Cytokine release syndrome
  - Characterized clinically by fever, hypotension, sepsis-like picture
  - Clinical lab elevations in C-reactive protein, ferritin, may have other lab evidence of organ damage (DIC, transaminitis, AKI, etc.)
  - Severe CRS is very similar to HLH/MAS
  - Mechanism related to high levels of circulating IL-6, IFN gamma
  - Managed primarily with anti-cytokine therapy
- Neurological toxicity
- B cell aplasia – on-target effect

CRS Grading

Grade	Description of Symptoms
1 Mild	Not life-threatening, require only symptomatic treatment such as antipyretics and anti-emetics (e.g., fever, nausea, fatigue, headache, myalgias, malaise)
2 Moderate	Require and respond to moderate intervention: • Oxygen requirement < 40%, or • Hypotension responsive to fluids or low dose of a single vasopressor, or • Grade 2 organ toxicity (by CTCAE v4.03)
3 Severe	Require and respond to aggressive intervention: • Oxygen requirement ≥ 40%, or • Hypotension requiring high dose of a single vasopressor (e.g., norepinephrine ≥ 20 µg/kg/min, dopamine ≥ 10 µg/kg/min, phenylephrine ≥ 200 µg/kg/min, or epinephrine ≥ 10 µg/kg/min), or • Hypotension requiring multiple vasopressors (e.g., vasopressin + one of the above agents, or combination vasopressors equivalent to ≥ 20 µg/kg/min norepinephrine), or • Grade 3 organ toxicity or Grade 4 transaminitis (by CTCAE v4.03)
4 Life-threatening	Life-threatening: • Requirement for ventilator support, or • Grade 4 organ toxicity (excluding transaminitis) (by CTCAE v4.03)
5 Fatal	Death

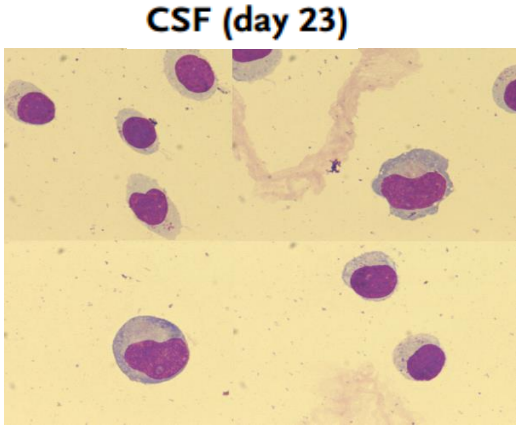
Adapted from (Lee 2014)

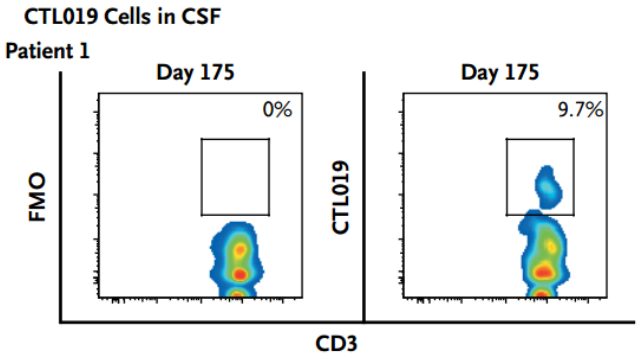
HLH/MAS

- Macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH).
- Characterized by high fevers, hepatosplenomegaly, liver dysfunction, coagulopathy, hypofibrinogenemia, and profound hyperferritinemia.
  - Often elevated C-reactive protein (CRP), soluble interleukin-2 receptor (sIL-2R), triglycerides, and variable transaminases
- Histological evidence of macrophage and hemophagocytosis noted on bone marrow biopsy at peak of CRS.
- Resolves with tocilizumab and/or cessation of CRS.

Neurological Side Effects

- Can occur in the presence or absence of CRS
- Symptoms include confusion, delirium, expressive aphasia, obtundation, myoclonus, seizure-like activity and frank seizure
- In some instances neurologic symptoms may be the earliest sign of sCRS
- Symptom onset can be early (day 5-7) with/without CRS or delayed even after the resolution of CRS
- Mechanism and management evolving; usually transient
- More responsive to steroids than anti-cytokine therapy





Rare/Theoretical Toxicities with engineered T cells

- On-target
- Off-target (cross-reactivity)
- Bystander innate cells (i.e. systemic CRS)
- Allergy
- Autonomous signaling/GvHD
- Integration site oncogenesis
- Replication competent virus

Present status of CD19 CAR T cells for ALL and NHL

Penn/Novartis data:
Pediatric ALL: ORR 93%, n=59
DLBCL: ORR 47% at 3 months, n=15
FL: ORR 77%, n=13

Race for Registration: CD19 CARs for ALL in pediatrics and adults, and NHL

Ongoing Phase II trials

New targets for 2nd generation CARs (similar design as anti-CD19)

- Hematologic malignancies
  - AML (CD123, CD33)
  - Hodgkin's (CD30)
  - Multiple myeloma (BCMA – bluebird, Novartis)
- Solid tumors
  - Glioblastoma (EGFRvIII)
  - Mesothelin (ovarian, mesothelioma, lung)
  - Prostate (PSMA)
  - Melanoma (cmet)

Hurdles for solid tumors

- Specific antigen targets
  - What's a dispensable cell or tissue?
  - How to survey in pre-clinical setting?
  - How will you measure it on a per-patient/per-tumor basis?
- T cell trafficking
  - How will you measure it? How many is enough?
- T cell persistence
- Inhibitory microenvironment
  - Are CAR T cells as sensitive to inhibition by PD1/TIM3/LAG3 as normal T cells? Does the signaling domain matter?

Take home points about CAR T cells

- Living drugs
  - Highest PK typically at day 7-14
- Long-lived cells (PK of months/years!)
- Traffic everywhere (including CNS)
- Make bioactive cytokines/engage other cells
  - Cytokine release syndrome, macrophage activation syndrome
- Activity (on target and off target) occurs anywhere and at time of peak expansion
- Multiple different CAR designs; new ones to reduce toxicity and extend to other tumors are on the horizon