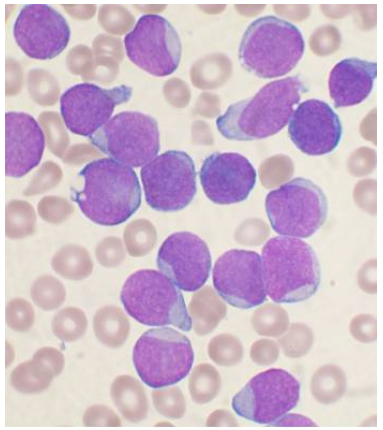


HIV-virus Inspires Effective Anti-Leukemia Therapy

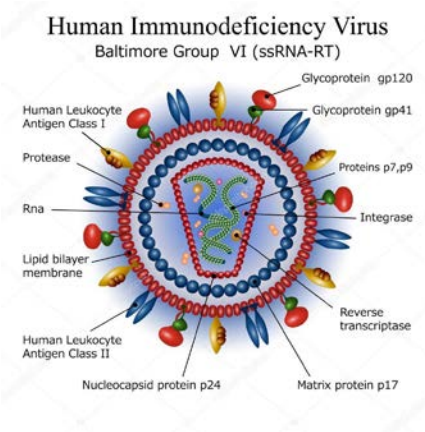
Nirali N. Shah, MD

Associate Research Physician

Pediatric Oncology Branch

National Cancer Institute

December 1, 2017



Disclosures

- None

Educational Objectives

- Provide an overview of CAR therapy
- Review the current state of the art for CAR therapy in ALL
- Discuss limitations to CAR therapy

The c
Sever
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immu
cells

SCIENCE/TECH

Revolutionary Treatment Uses HIV to Reprogram Cells Into Fighting Cancer

Dec 10, 2012 04:50 PM By Makini Brice

HEALTH

An Immune System Trained to Kill Cancer

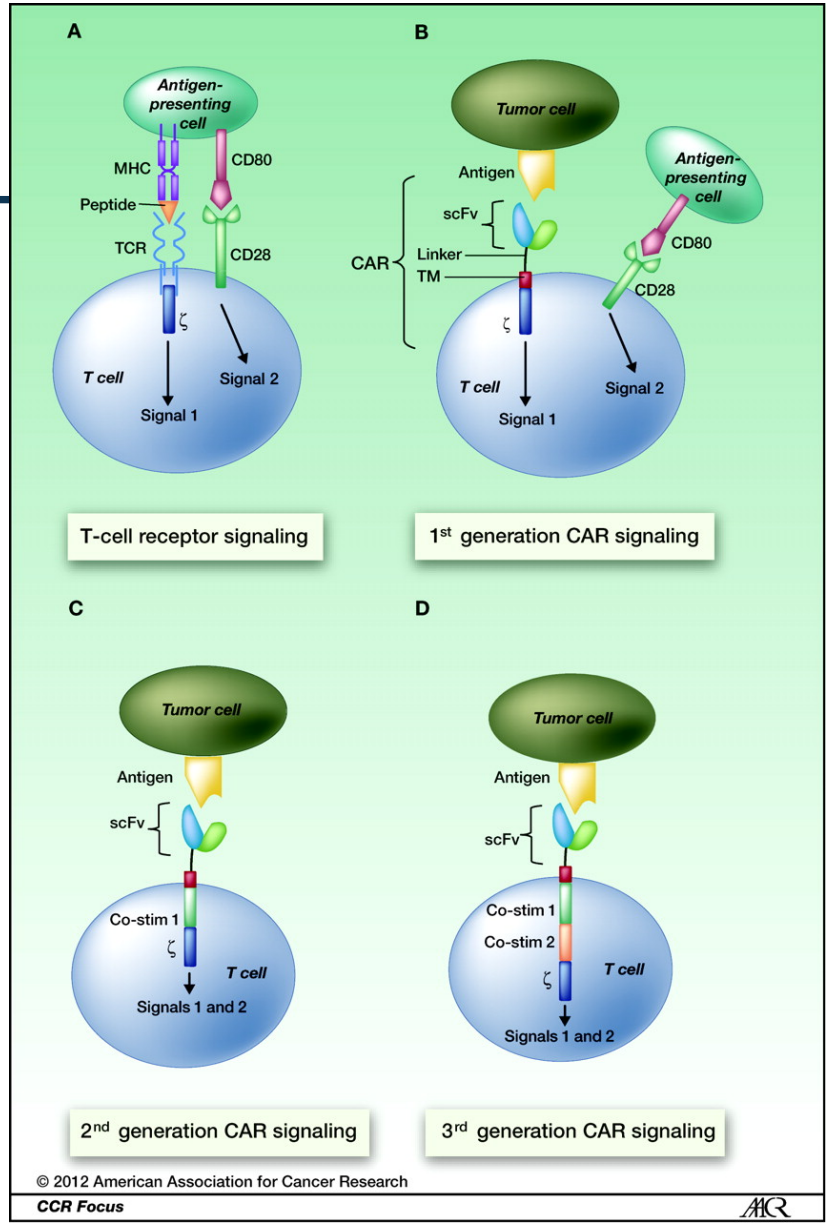
By DENISE GRADY SEPT. 12, 2011

How HIV Became a Cancer Cure

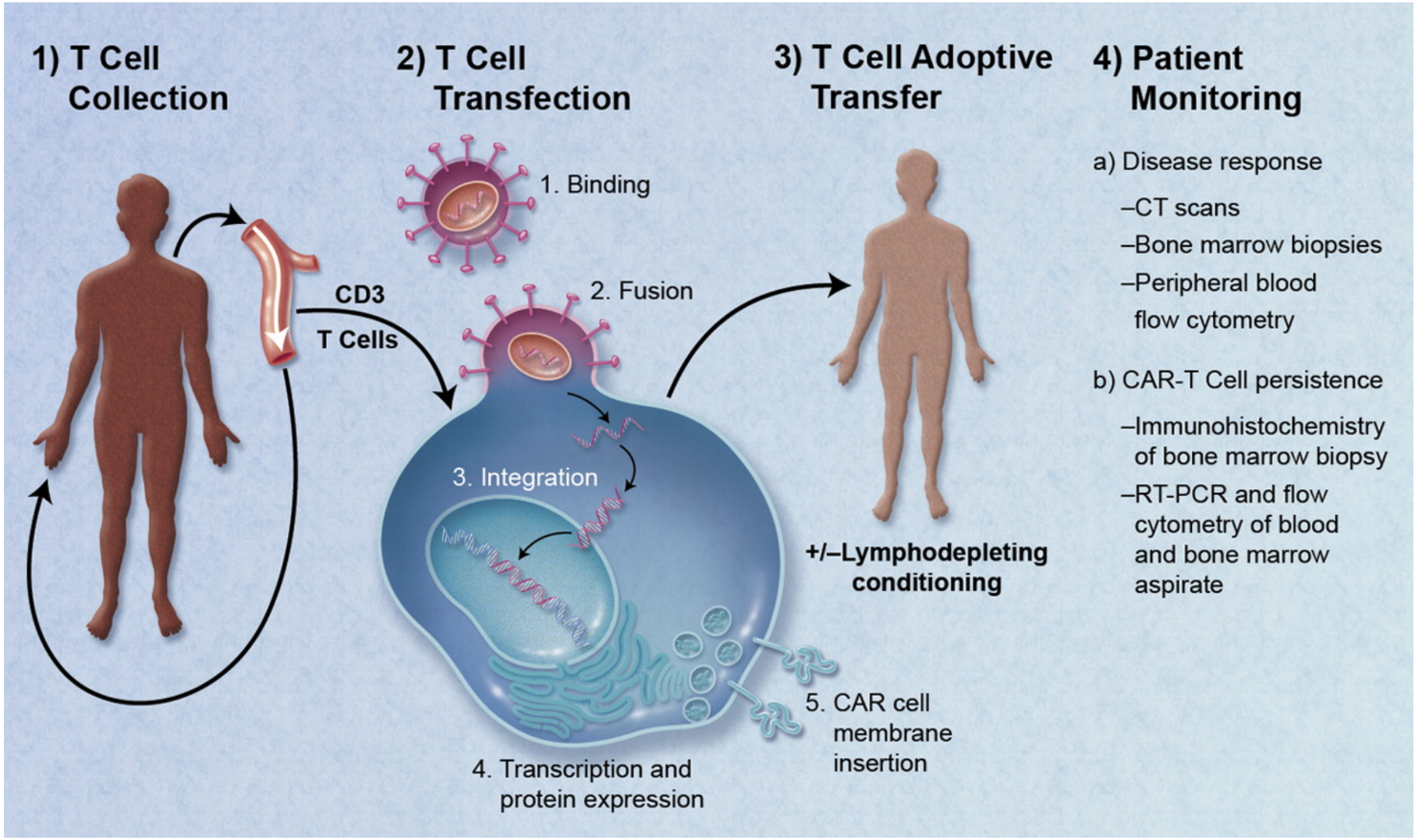
The immunologist behind the revolutionary new treatment set to win approval from the FDA.

What is a CAR?

- Chimeric Antigen Receptor
- Customized receptor
  - Extracellular antigen-binding domain
  - Intracellular signaling domain of T cells
- Retains the functionality of a T-cells with the antigen recognition properties of antibody



Process of Making CAR T-Cells



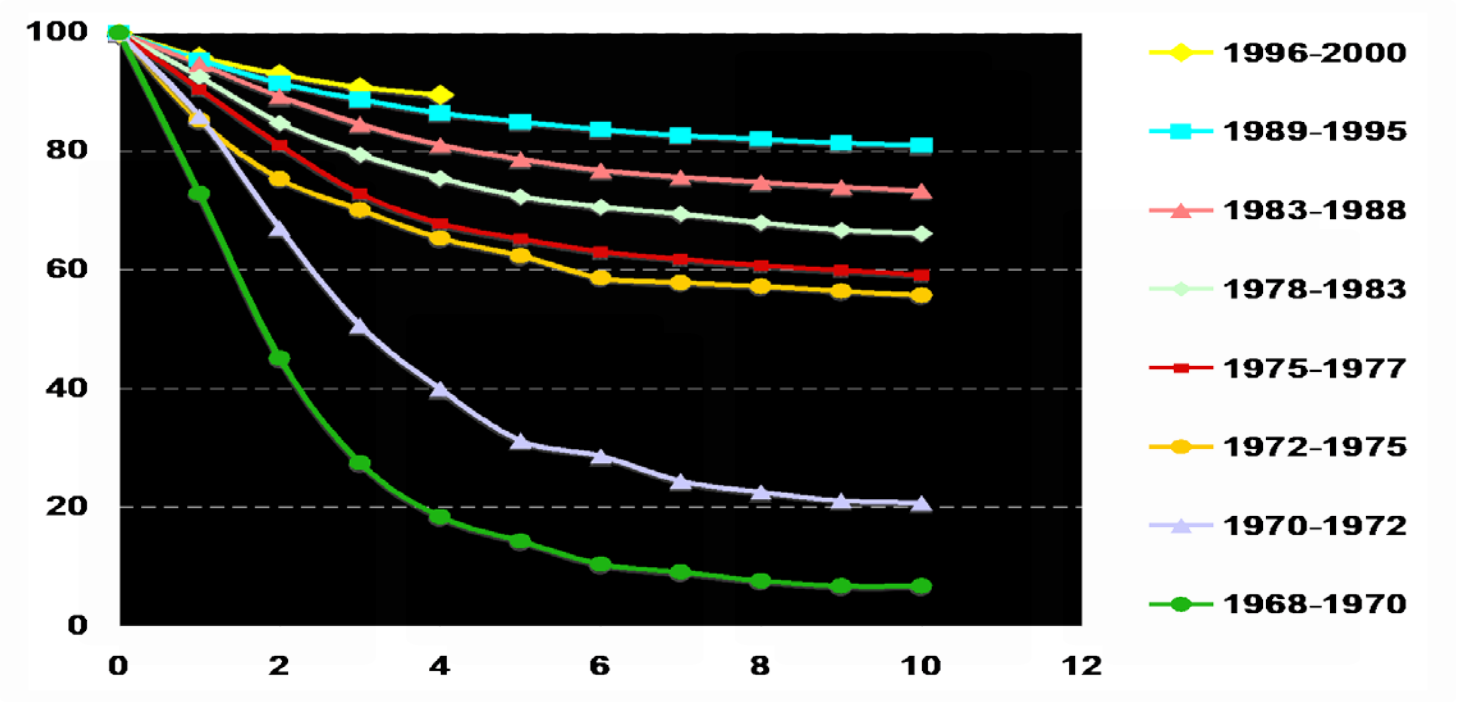
Role for HIV?

- Retroviruses, in particular lentivirus, are particularly skilled at entering T-cells
- Used to introduce genetic material into a T-cell which is then incorporated into the host cell genome
- Modified virus used to introduce anti-leukemia targeted antigen recognition properties

Childhood ALL

- Most commonly diagnosed childhood cancer
- 2900 cases/year
- Relapsed refractory disease remains a therapeutic challenge
- Outcomes in the AYA population remain poor

Improved Survival by Study Era

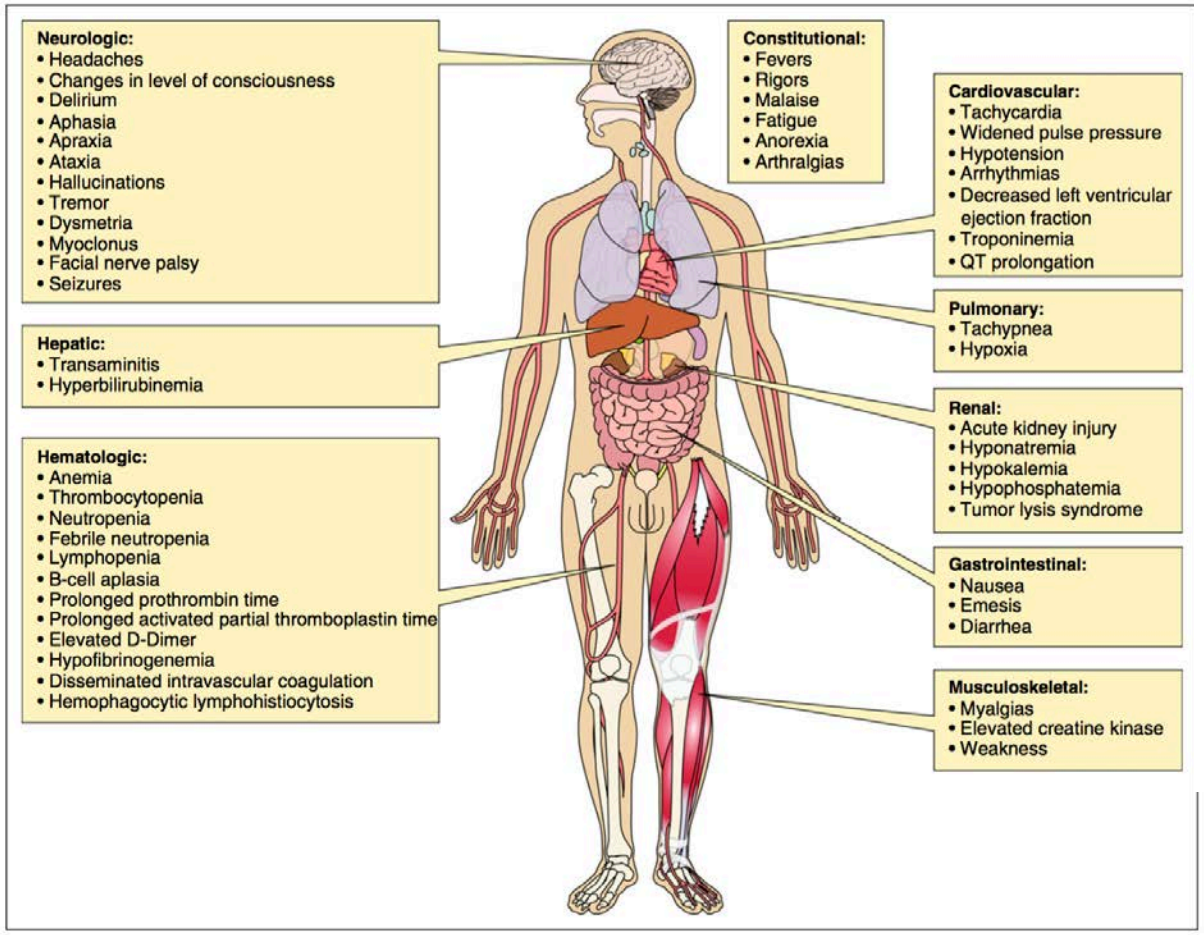


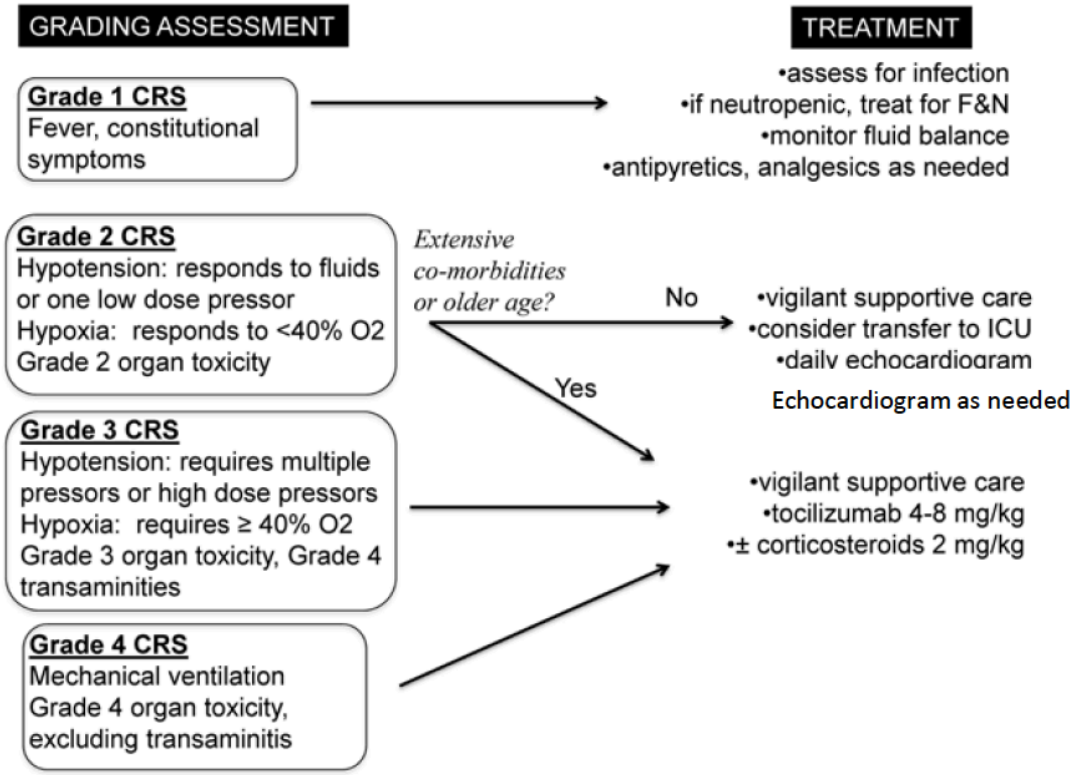
Data courtesy of GH Reaman, H Sather, Children's Oncology Group

CD19 CAR

- CD19 is a B-cell marker
- First used to target CLL (chronic lymphocytic leukemia)
- Associated with cytokine release syndrome
- First child treated in 2012
- Several centers had simultaneous clinical trials

Cytokine Release Syndrome



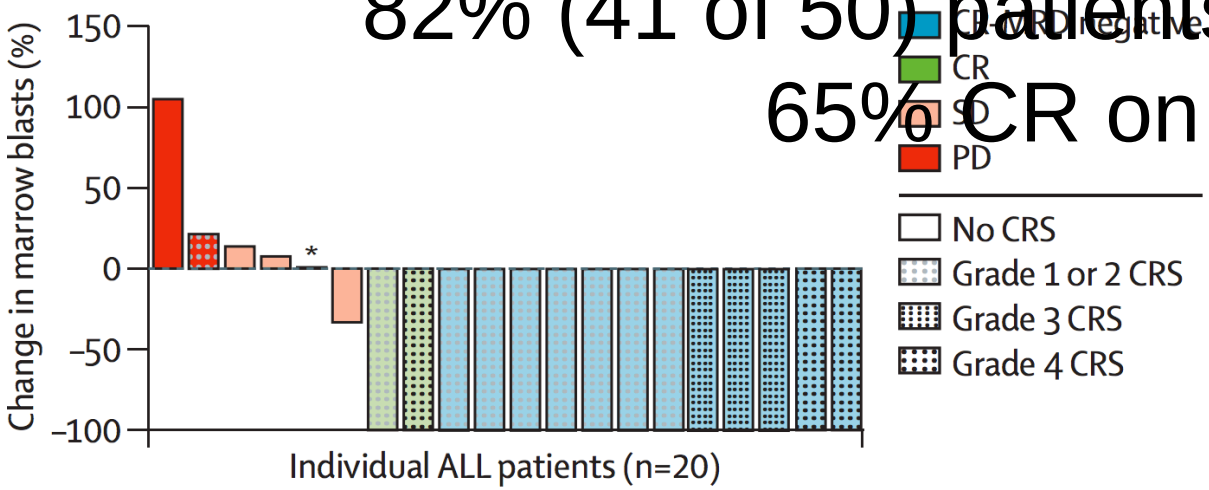


Lee/Mackall Blood 2014
Brudno/Kochenderfer Blood 2017

CD19 CAR Clinical Updates

T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial

Daniel W Lee, James N Kochenderfer, Maryalice Stetler-Stevenson, Yongzhi K Cui, Cindy Delbrook, Steven A Feldman, Terry J Fry, Rimas Orentas, Marianna Sabatino, Nirali N Shah, Seth M Steinberg, Dave Stroncek, Nick Tschernia, Constance Yuan, Hua Zhang, Ling Zhang, Steven A Rosenberg, Alan S Wayne, Crystal L Mackall



NEJM 2014
(not ITT)

Novartis sponsored global CD19 CAR registration trial ("ELIANA")

82% (41 of 50) patients achieved CR

65% CR on ITT

Lee et al. Lancet 2015

67% CR rate (ITT)

All responders with CRS

FDA Approval!!

FDA News Release

FDA approval brings first gene therapy to the United States

August 30, 2017

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

FDA News Release

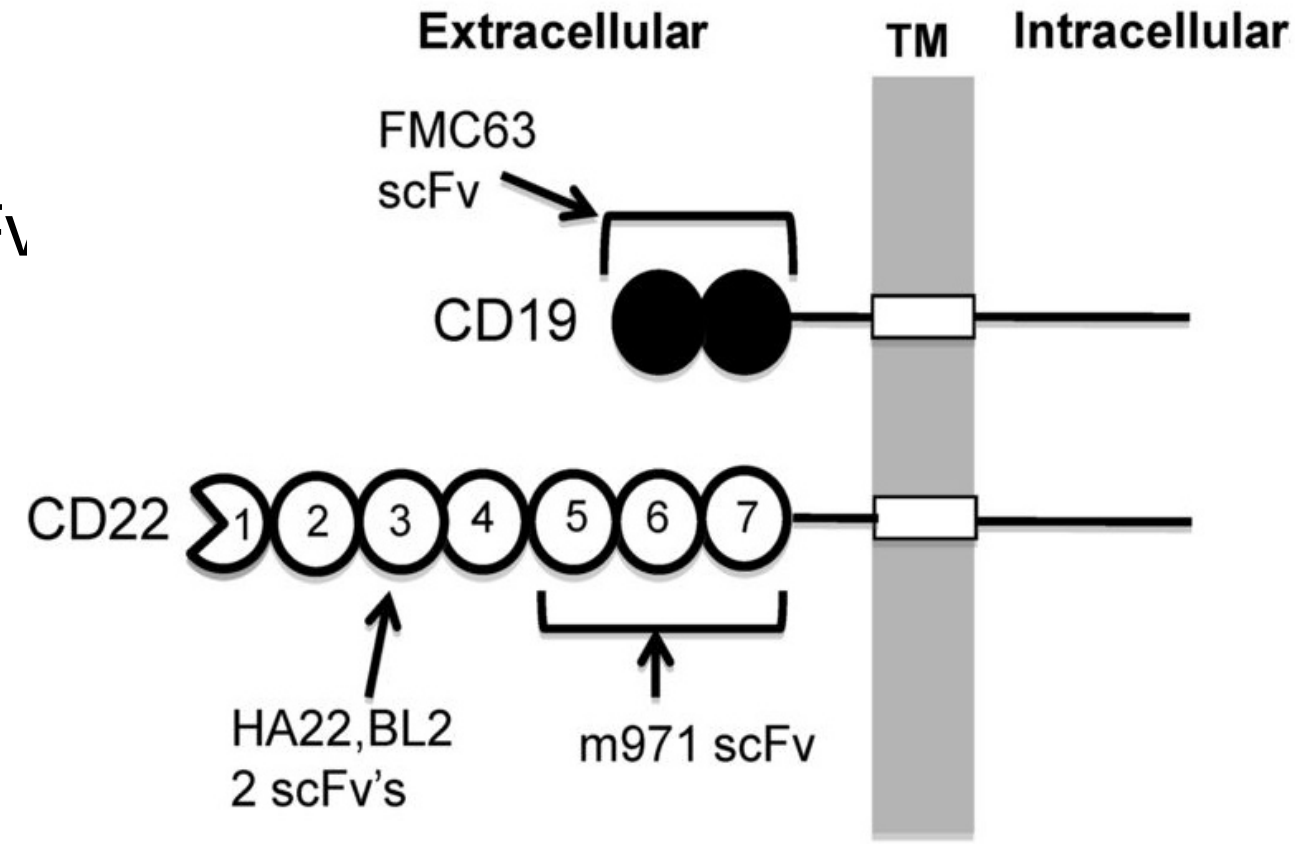
FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma

October 18, 2017

Will CD19 CAR be “THE” Answer?

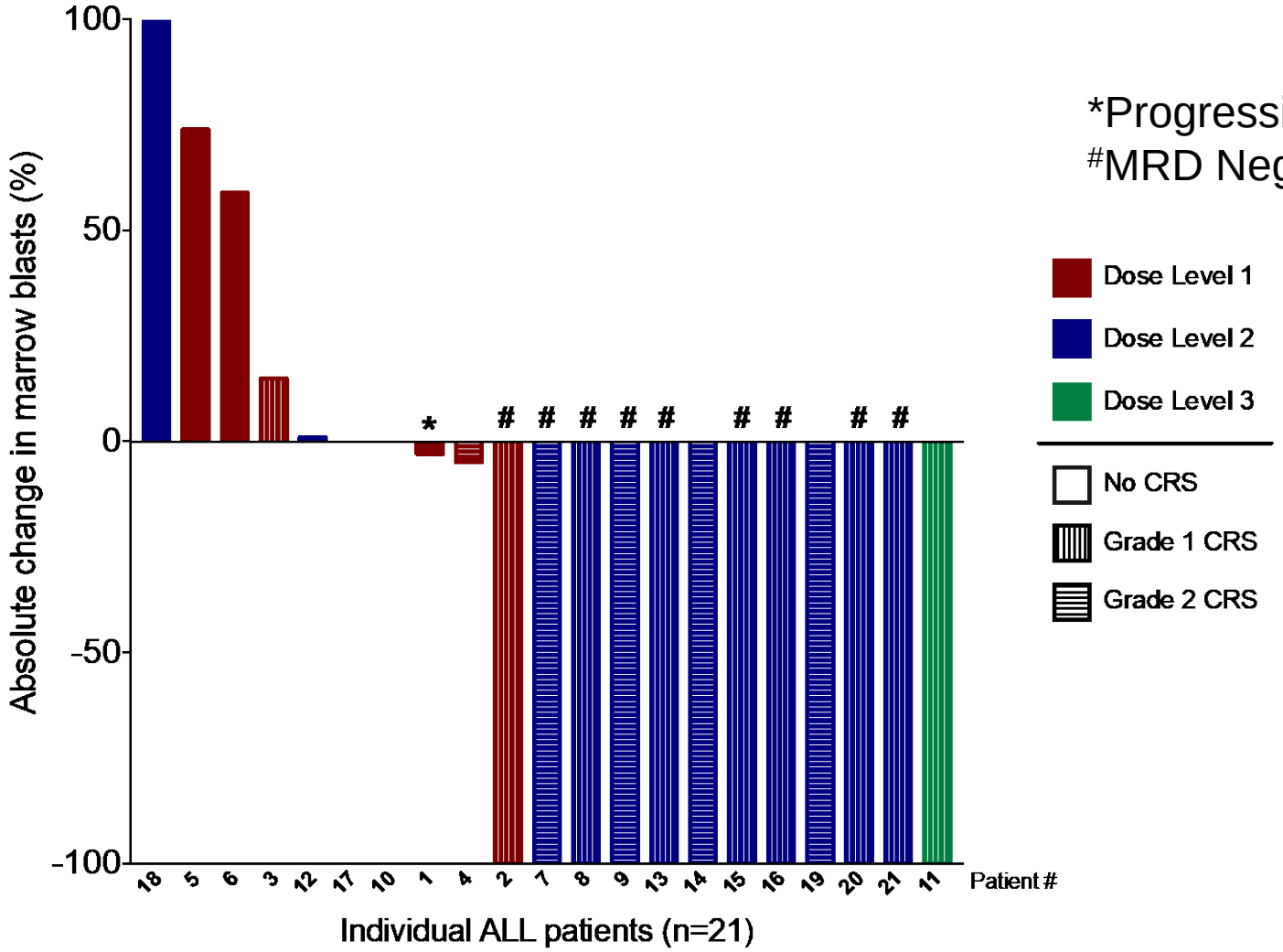
Anti-CD22 CAR Construct

- Second generation CAR
- Utilizes m971 anti-CD22 scFv
- 4-1BB/CD3-zeta signaling



Haso et al, *Blood 2013*

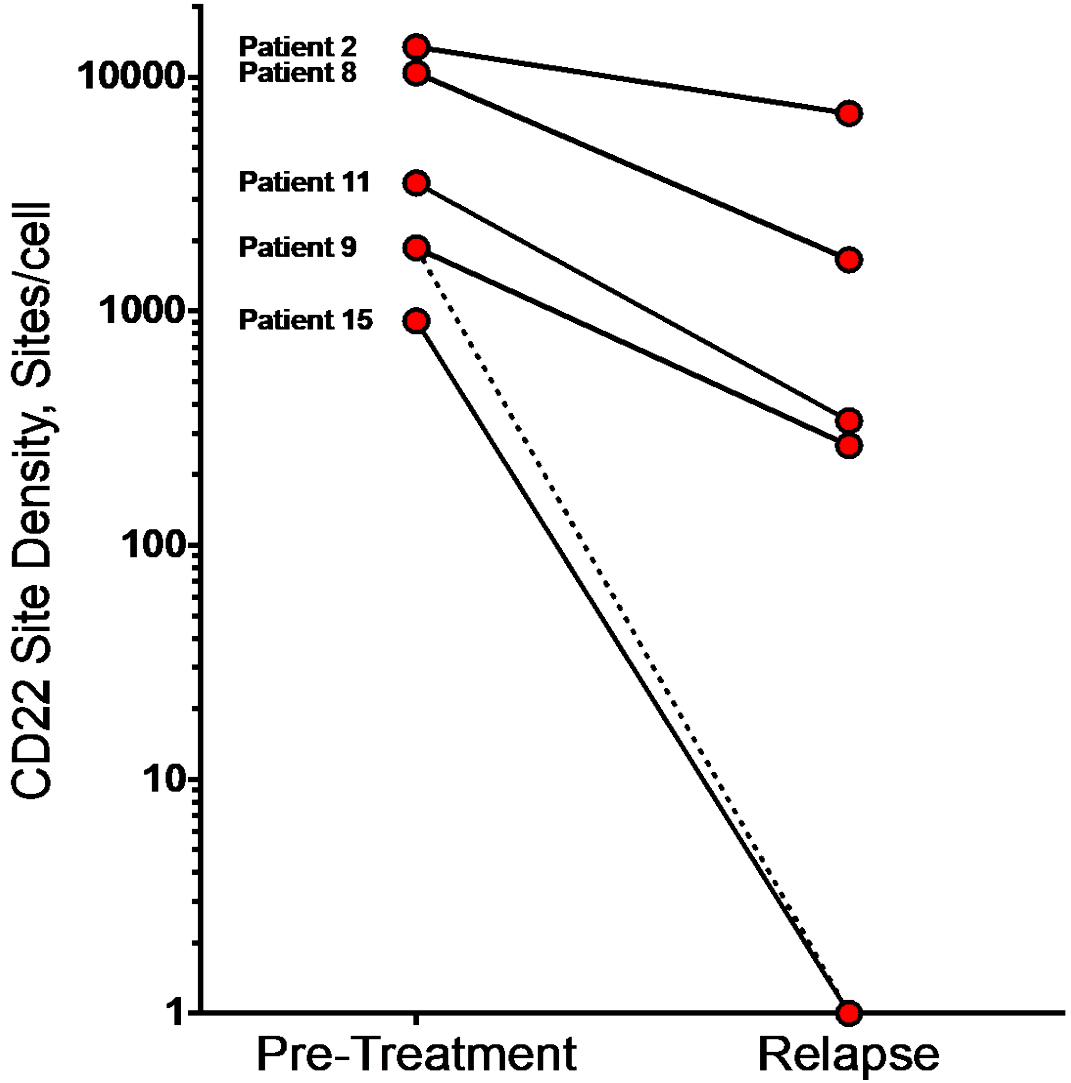
Phase I Study of Anti-CD22 CAR T-Cells: Dose-Dependent Response



*Progressive disease by peripheral blasts
#MRD Negative CR

Fry, Shah et al, *Nat Medicine 2017*

Relapse Remains a Problem



Fry, Shah et al, *Nat Medicine 2017*

Future Directions

- Simultaneous multi-antigen targeting
- Expanding to other disease subtypes and presentations
  - AML
  - Central nervous system disease
  - Lymphoma
- Solid Tumors and Brain Tumors
- Exploring Toxicity

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Photo credit: Marvin Joseph/The Washington Post
washingtonpost.com

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