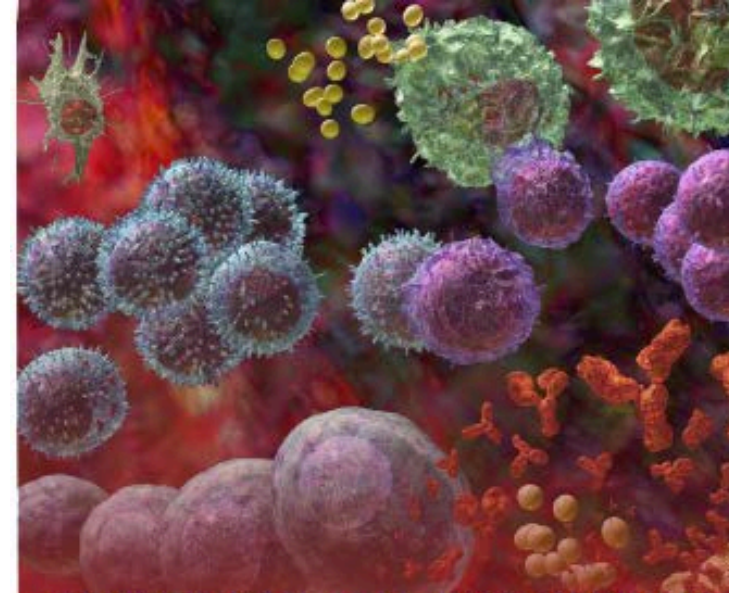


**The promise of T cell engineering  
CD19 CAR therapy  
A prologue to immune regenerative medicine  
Vast potential, patience, public education**

Academies' Cell Therapy Workshop  
Washington, October 13, 2016

Michel Sadelain, MD, PhD  
Director, Center for Cell Engineering  
Immunology Program, Sloan Kettering Institute  
Departments of Medicine and Pediatrics  
Memorial Sloan Kettering Cancer Center  
New York, NY



**CENTER FOR CELL ENGINEERING**

*Cell Engineering is part of the future to finding effective therapies to cure cancer and allied diseases*



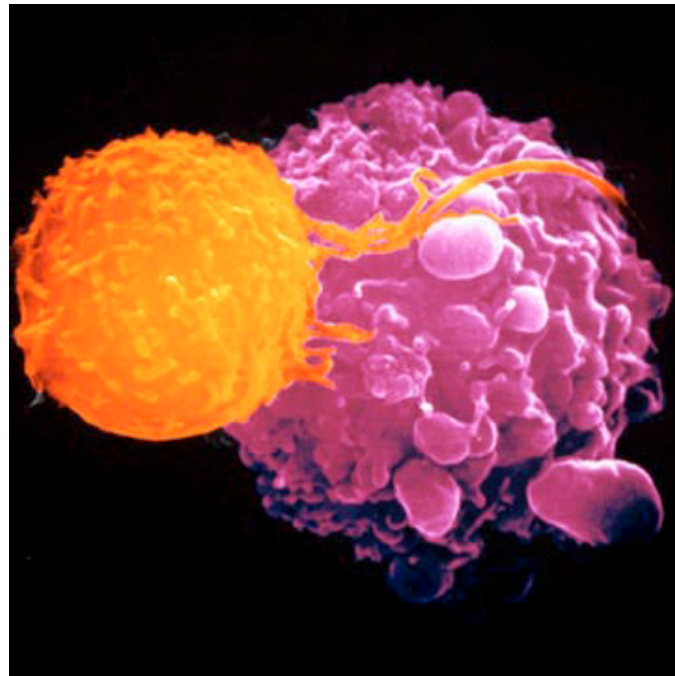
Memorial Sloan-Kettering  
Cancer Center

# The rise of engineered T cells as cancer drugs

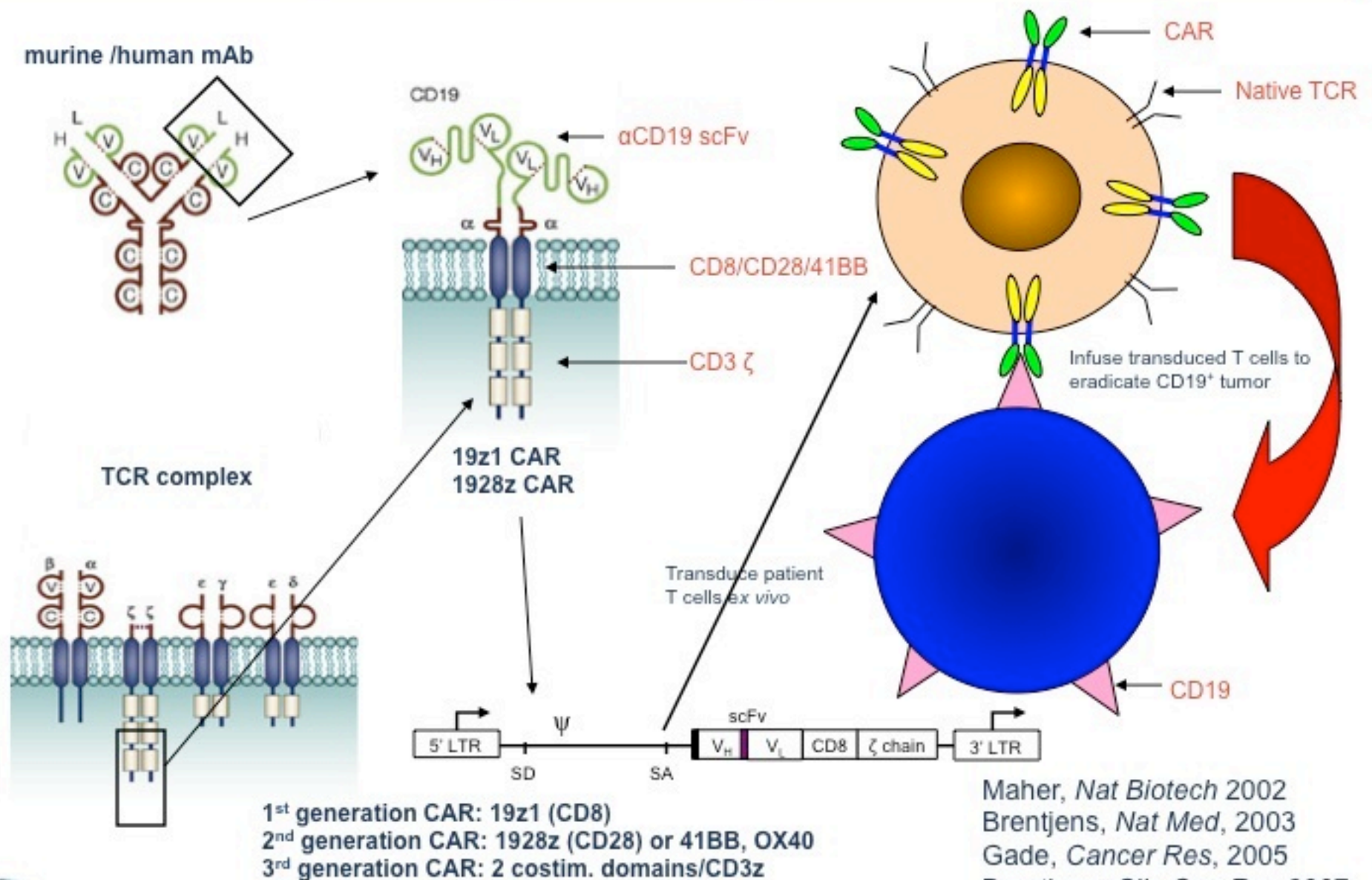
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- A major limitation of most existing cancer therapeutics is the lack of specificity or curative potential.
- Engineered T cells offer the prospect of combining specificity, potency and persistence from an optimized “living drug”.

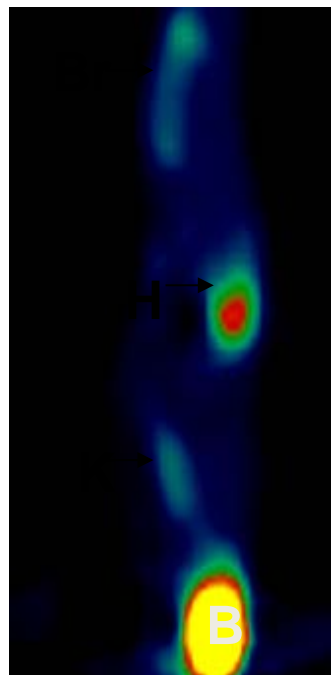
- Safety
  - Efficacy
- ↕
- Potency
  - Specificity
  - Long-acting



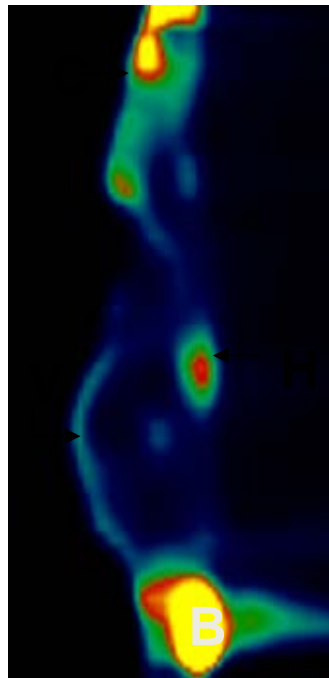
# CAR targeted T cells to increase anti-tumor functions



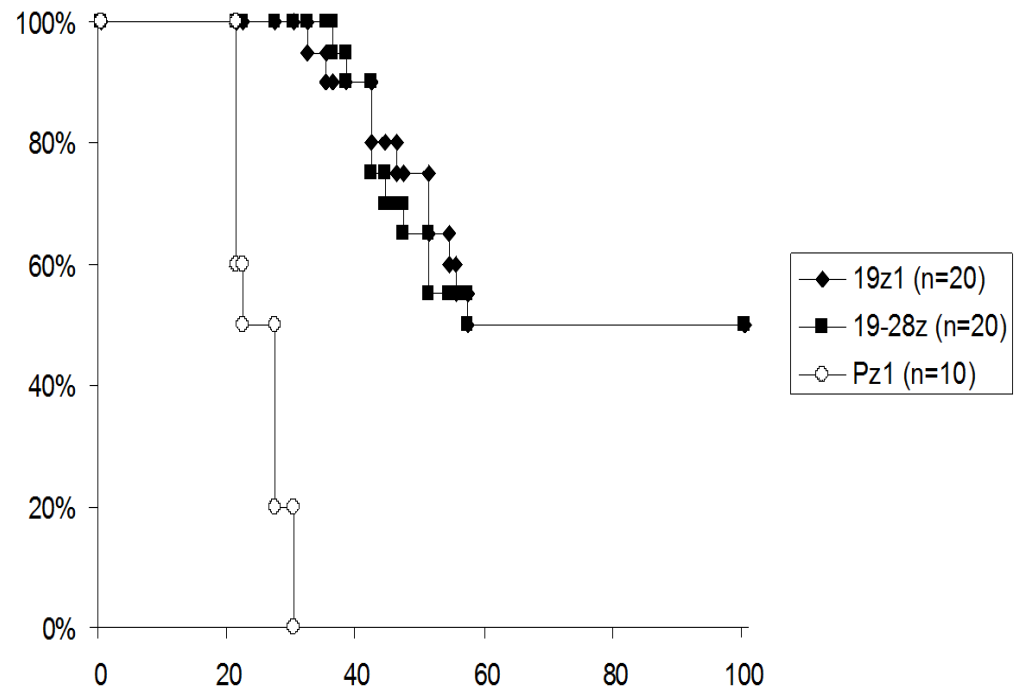
# Human CD19 CAR-targeted peripheral blood T cells eradicate systemic B lymphoma and ALL in mice



Tumor Free



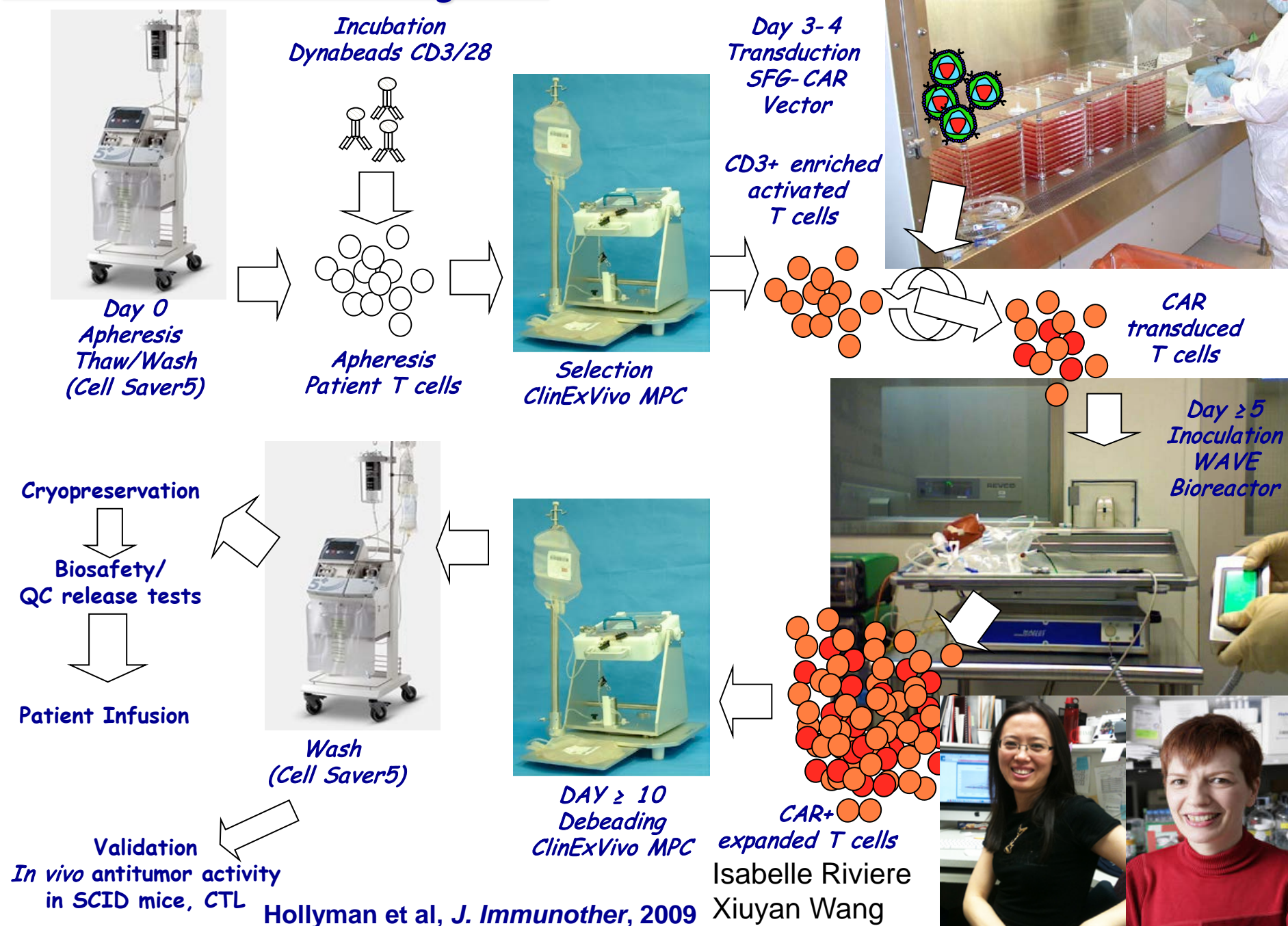
Untreated  
4 weeks



Brentjens et al, *Nat Med*, 2003



# CAR T cell Manufacturing Flow



# Relapsed, chemo-refractory adult ALL

## Summary of Clinical Outcomes (MSKCC, ASH 2015)

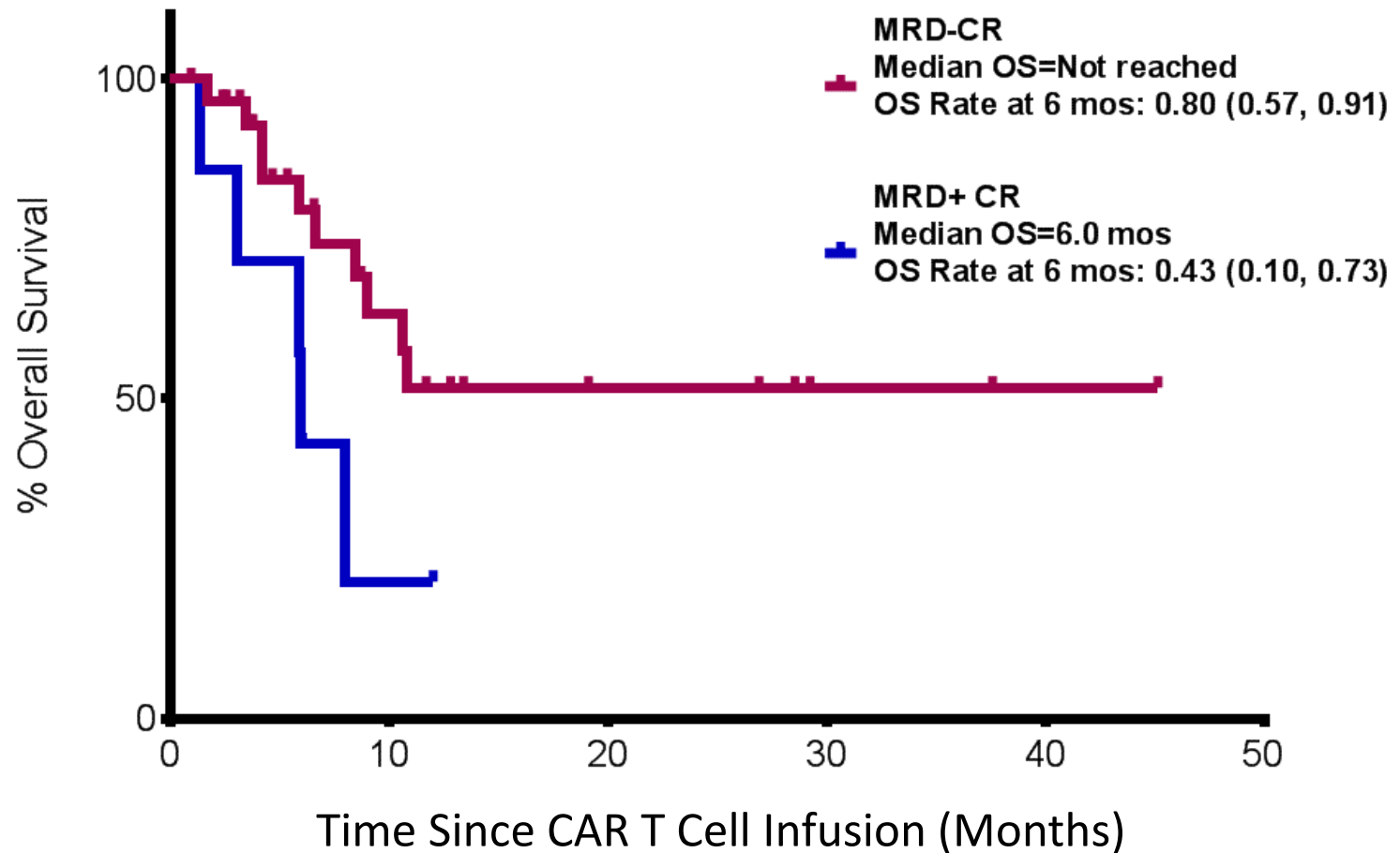
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	<b>Number of Patients N=45 (%) [95% CI]</b>
Overall CR Rate	37/45 (82%) [68 – 92]
Morphologic disease ( $\geq 5\%$ blasts)	18/24 (75%) [53 – 90]
Minimal disease ( $< 5\%$ blasts)	19/21 (91%) [70 – 99]
Overall MRD Negative CR Rate*	30/36 (83%)
Mean Time to CR (SD)	22 days (9.4)

\*Assessed among those patients who achieved CR and evaluable for MRD analysis (n=36)

# Overall Survival

## By MRD Status After CAR T Cell Treatment



# Science

20 December 2013 | \$10

Breakthrough of the Year

## Cancer Immunotherapy

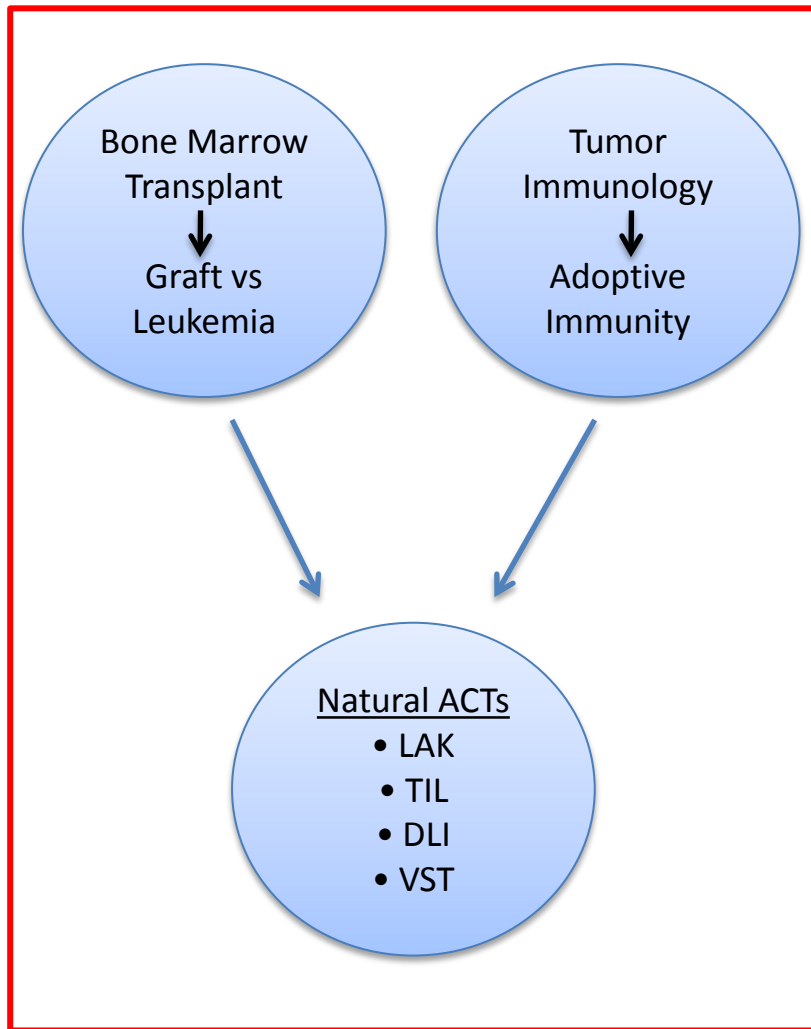
T cells on the attack

AAAS

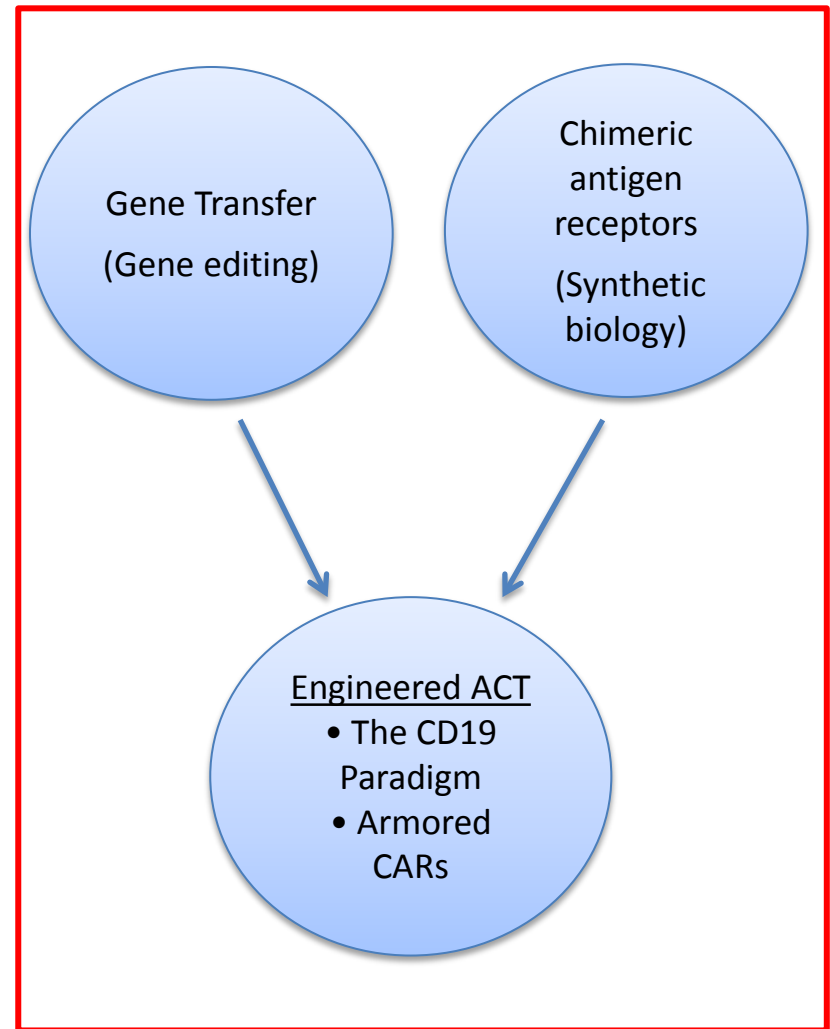




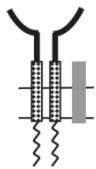
## Define and Isolate Natural T Cells



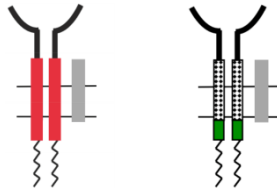
## Design and Manufacture T Cells



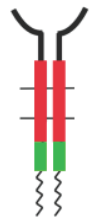
1<sup>st</sup> gen



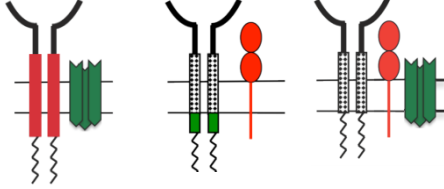
2<sup>nd</sup> gen



3<sup>rd</sup> gen



2<sup>nd</sup> gen – armored (CL)

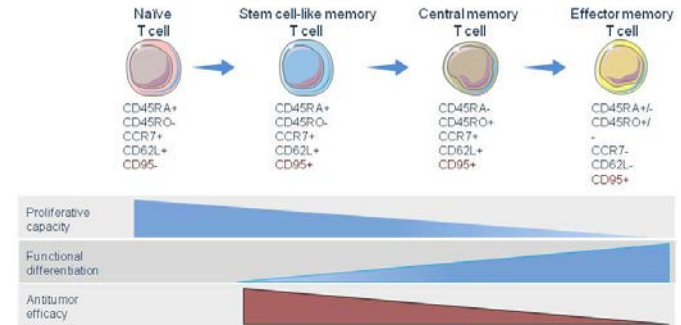


- 2<sup>nd</sup> gen CARs
- CAR + X (armored CARs)

Introduction

## Adoptive transfer of T cells for cancer immunotherapy

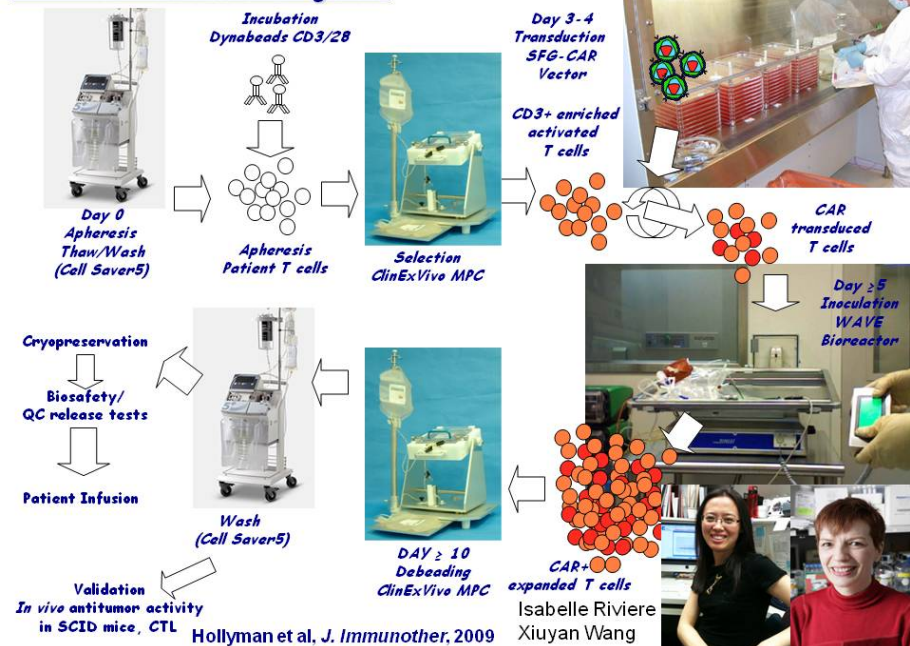
- Differentiation of memory T cells:



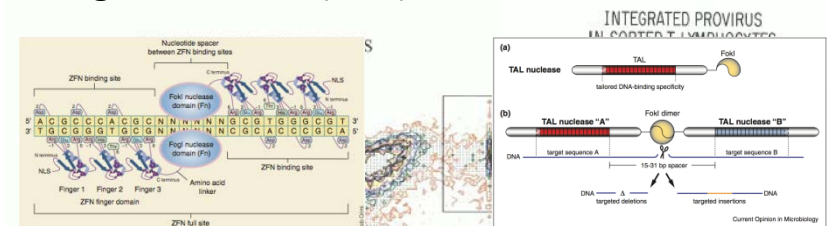
(Adapted from Restifo NP et al, Nat Rev Immunol, 2012)

- CD4/CD8 ratio (defined composition)
- T cell subset (eg TCM)

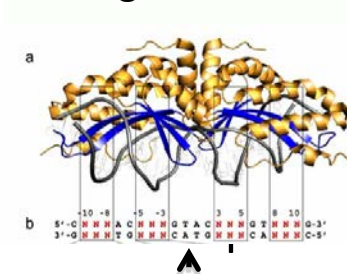
## CAR T cell Manufacturing Flow



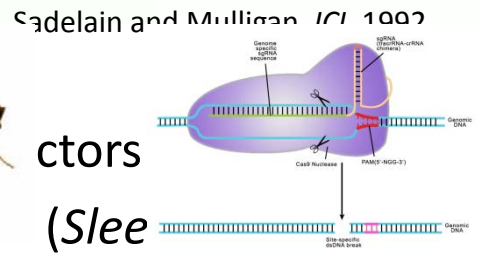
## Zinc-finger nuclease (ZFN) TALE nuclease (TALEN)



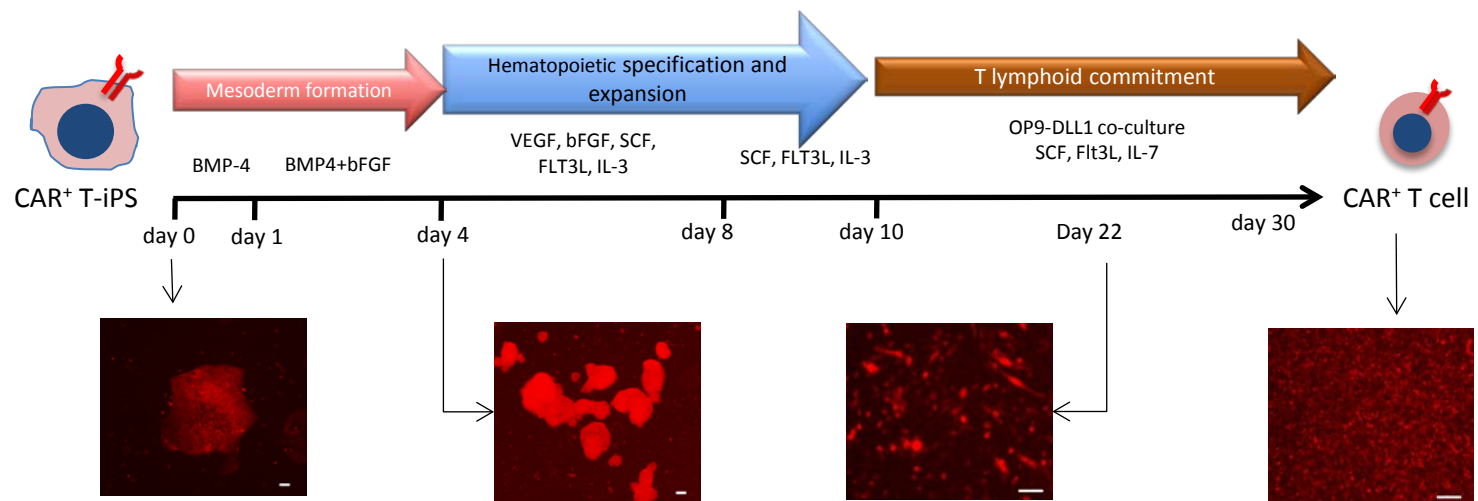
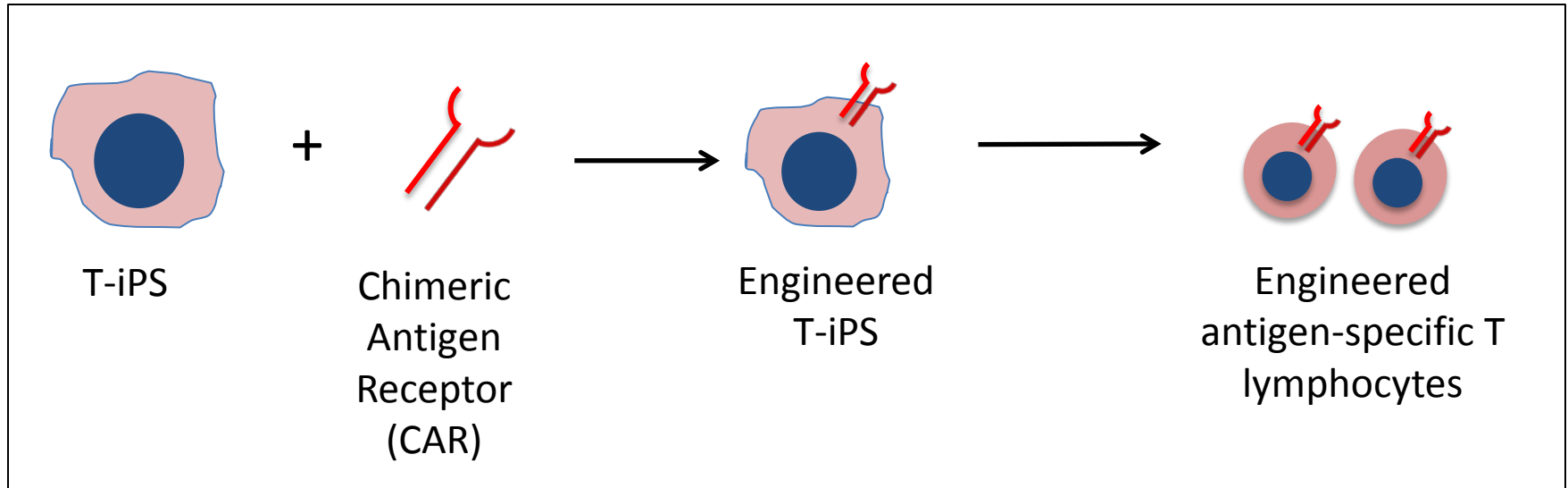
## Meganuclease



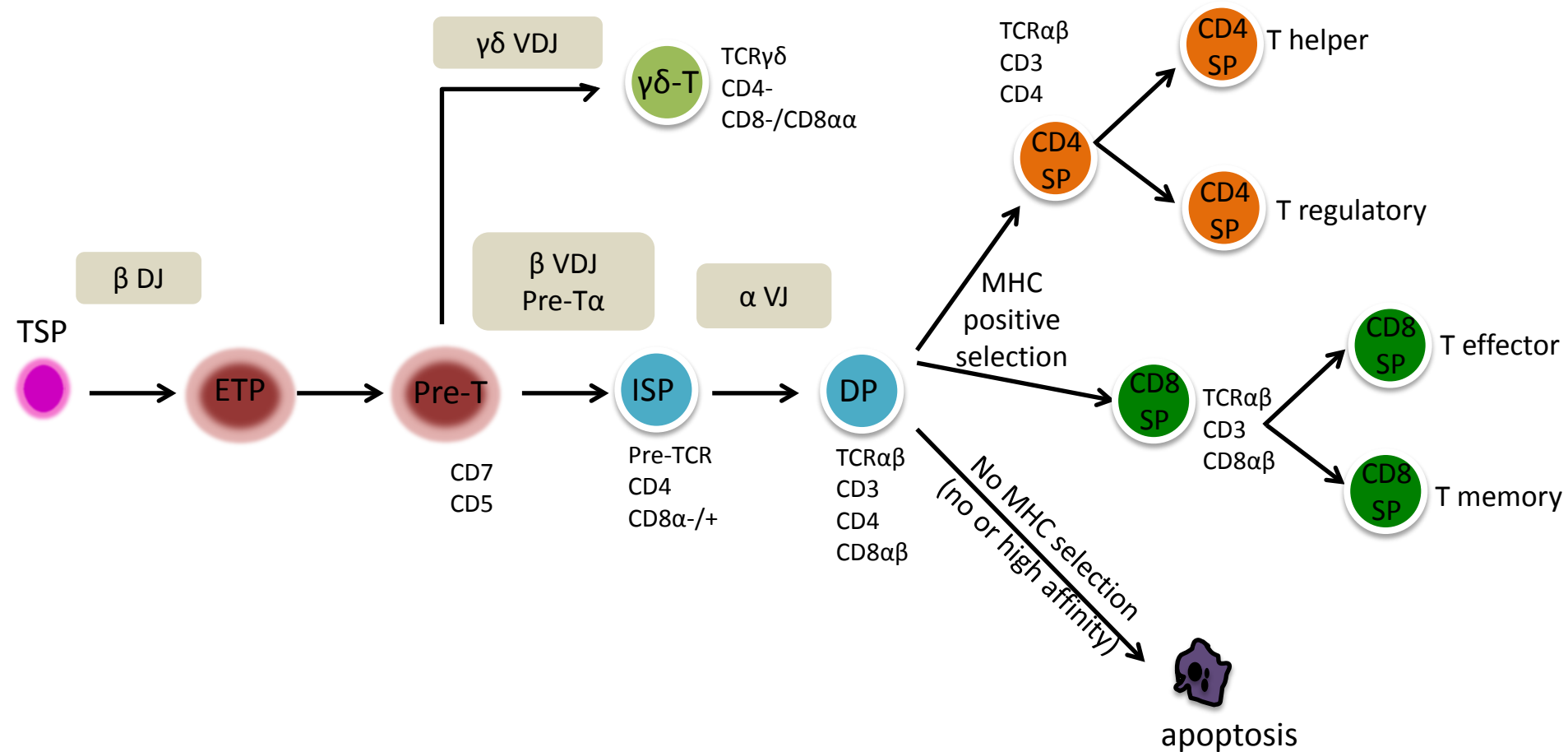
## CRISPR-Cas9



# T-iPS-derived CAR-targeted T cells



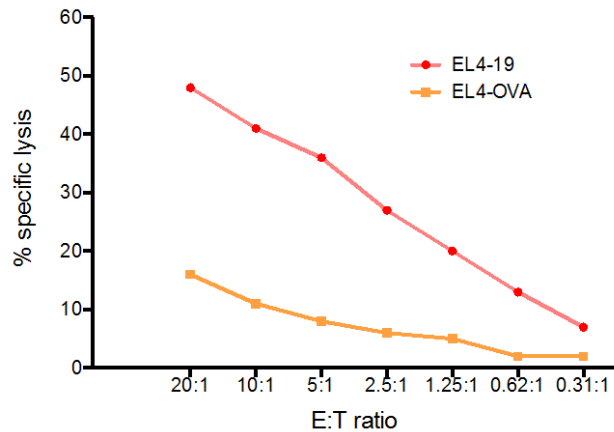
# How T cells are made (in the thymus)



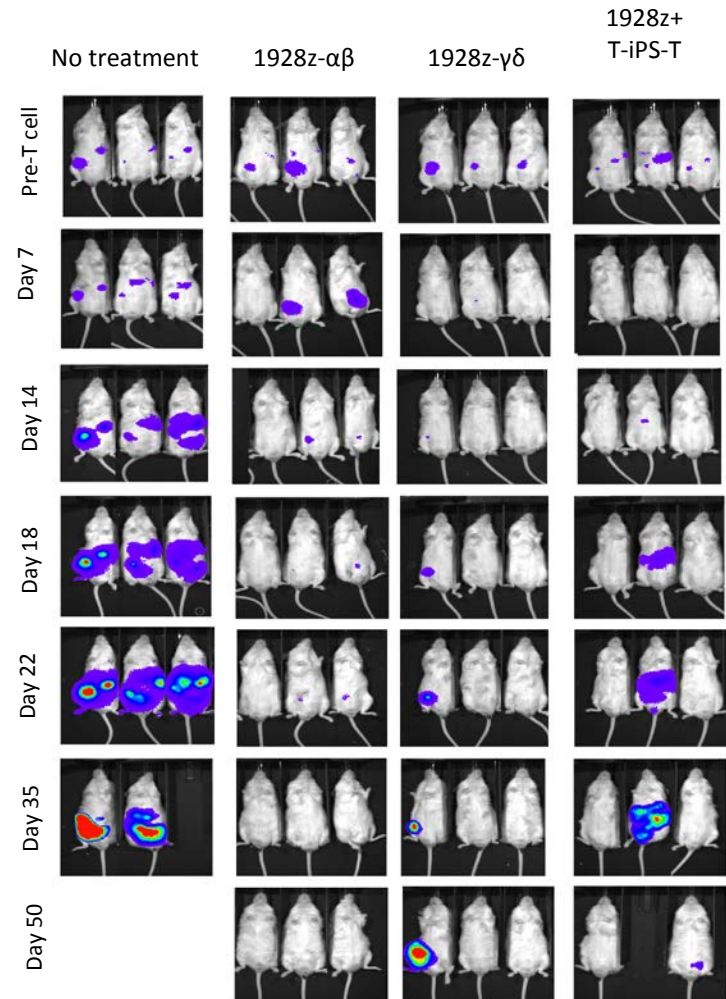
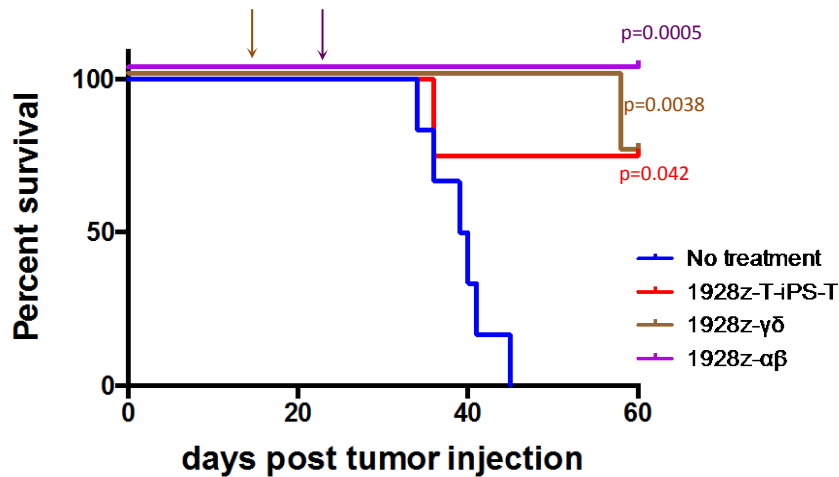


# 1928z-T-iPS-T cells lyse CD19+ tumor cells in vitro and in vivo

## In vitro

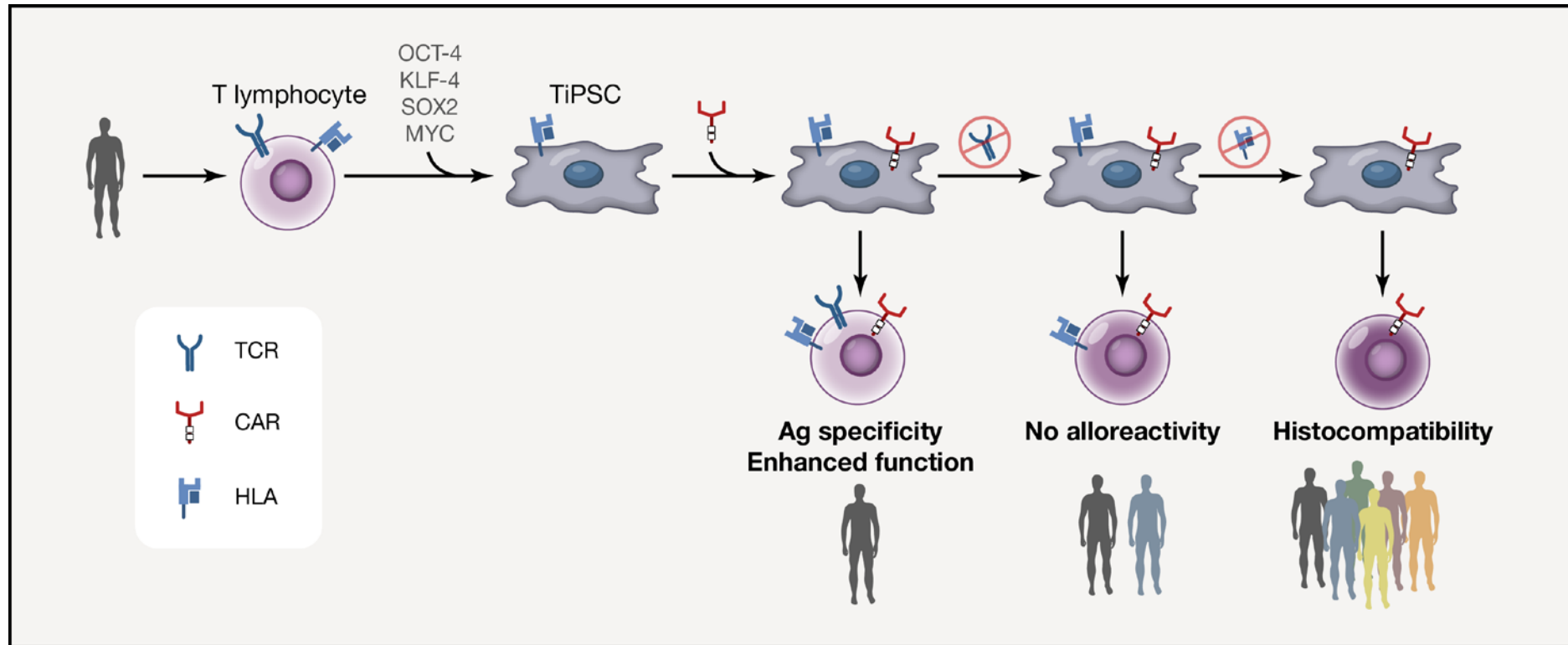


## In vivo

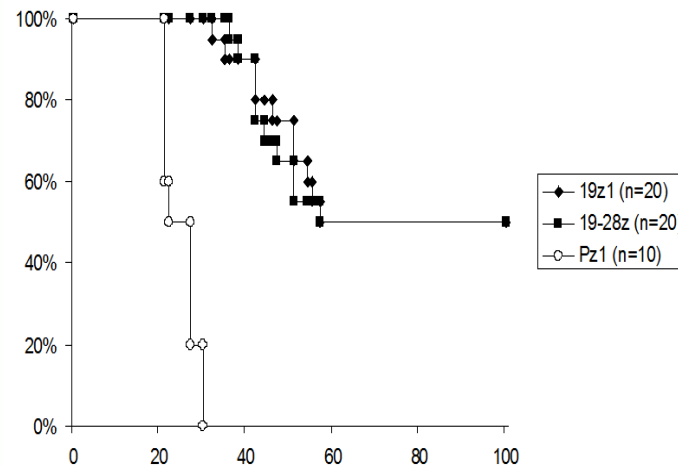
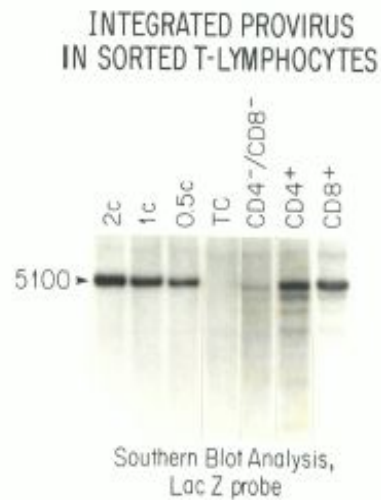


CD19+ Raji-FFLuc i.p.

# A perspective for large-scale generation of potent histocompatible therapeutic T cells



# From idea to proof-of-concept to clinical benefit CD19 CAR therapy 1992-2013



Mouse T cell Engineering  
Sadelain and Mulligan, 1992



CD19 CAR therapy POC  
Brentjens et al, 2003



Clinical trials  
FDA Breakthrough design., 2014





# Public education and network building

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