# The Current Status of Chimeric & Adoptive T cell transfer therapy

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# Disclosures

Patent on ICOS signaling for cancer immunotherapy

# Learning objectives (Part 1)

Forms of Adoptive T cell transfer therapy

1) Naturally arising tumor-specific T cells called:

-Tumor Infiltrating Lymphocytes (TILS)

1) Gene-engineered T cells via

-T cell receptors (TCRs)

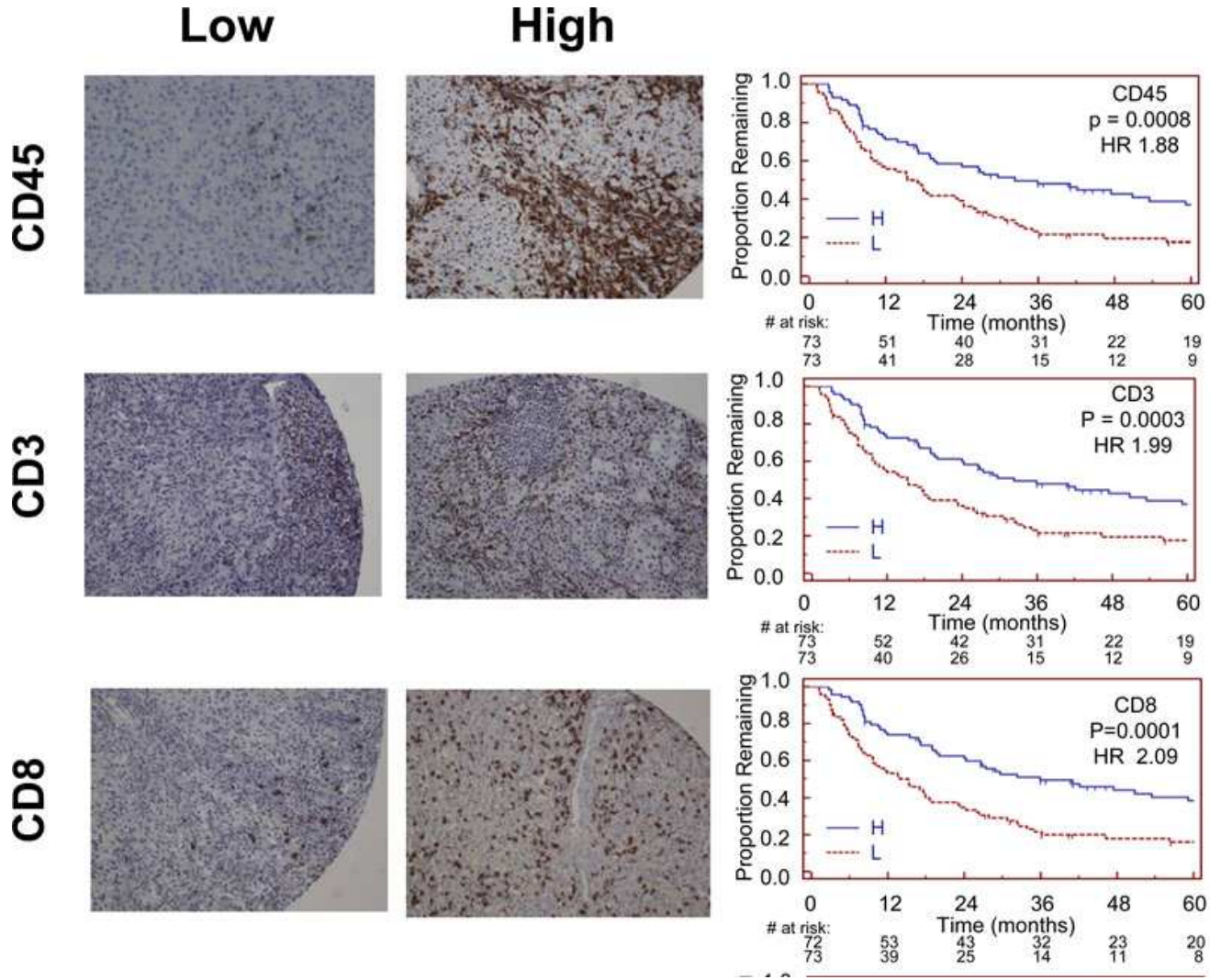
-Chimeric antigen receptors (CARs)

# Learning objective (Part 2)

Determinants for successful ACT therapy

1) Host Preconditioning
2) T cell properties
3) Antigen – self, neo-antigen, etc.
4) Side effects/treatment outcome

# T cell immune responses in human malignancies is good

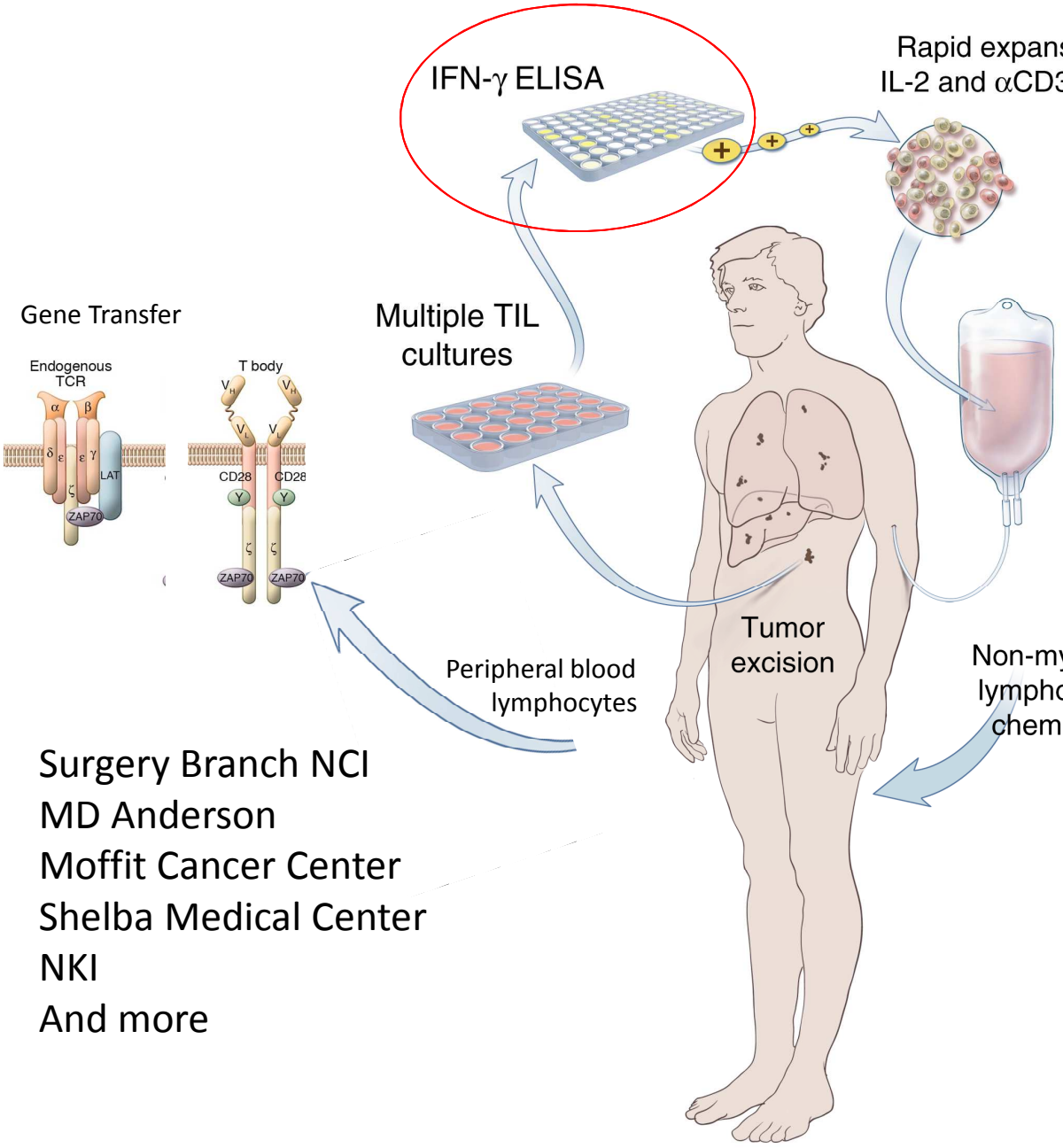



Erdag, G. et. al. Cancer Research 2012

# Advantages of ACT

1) Administer many and selected T cells with avidity for tumor antigen
2) These T cells can be manipulated to have desired function and/or memory phenotype
3) Patient can be properly prepared for infusate
4) T cells can be modified to possess any desired antitumor property via TCRs or CARs

# Adoptive T cell transfer therapy approach




**$10^{11}$**
**Both CD4 and CD8**
**Bolus IL-2**

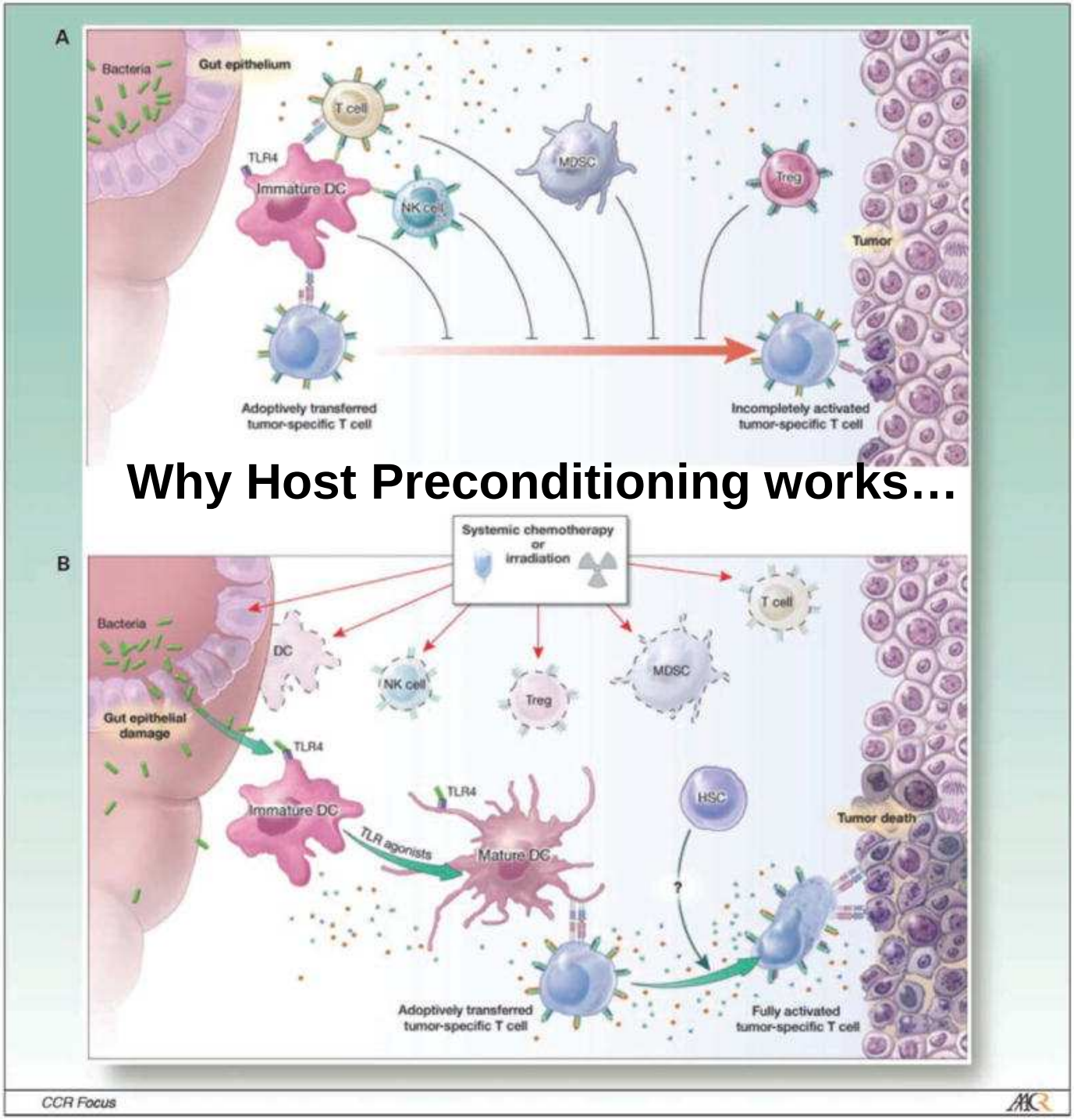
Lymphodepletion prior to ACT improves T-cell immunotherapy in patients with melanoma – with a response rate of >50% and with a higher persistence of transferred T cells (Dudley in Science 2002; Dudley et. al., J. Clin. Oncol. 2005).

**Cyclophosphamide (30 mg/kg twice)**
**Fludarabine (25mg/kg 5x)**

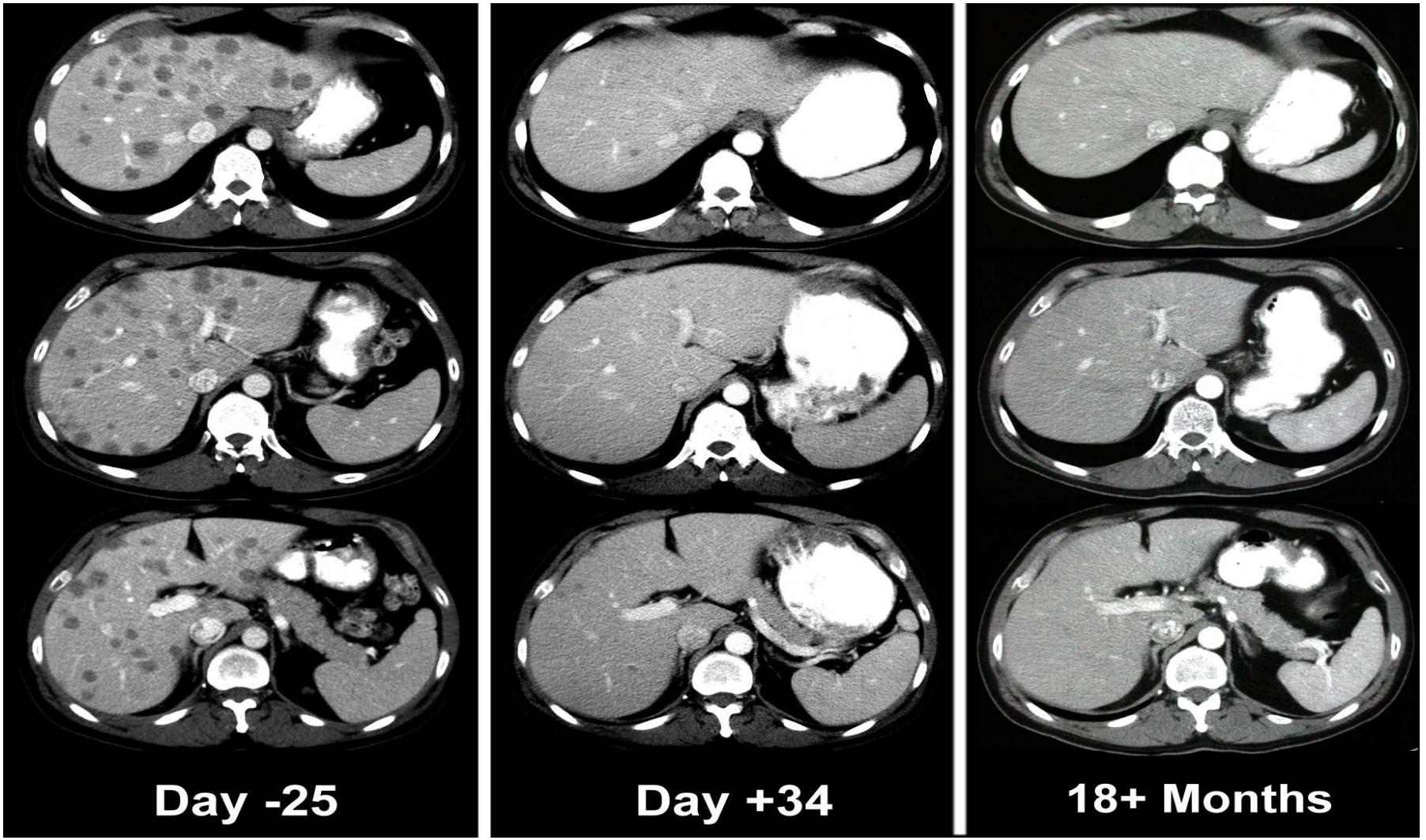
Surgery Branch NCI
MD Anderson
Moffit Cancer Center
Shelba Medical Center
NKI
And more


**Riddell S, et. al. Science 1992**
**Dudley M, et. al. JCO 2005**
**Levine B, et. al. PNAS 2002**
**Johnson L, et. al. Blood 2009**
Offringa, R, Science, 2006
June, C.H. JCI, 2007
Zhang, Y, Plos Pathogens 2010

Paulos, Restifo et. al. Clinical Cancer Research 2007

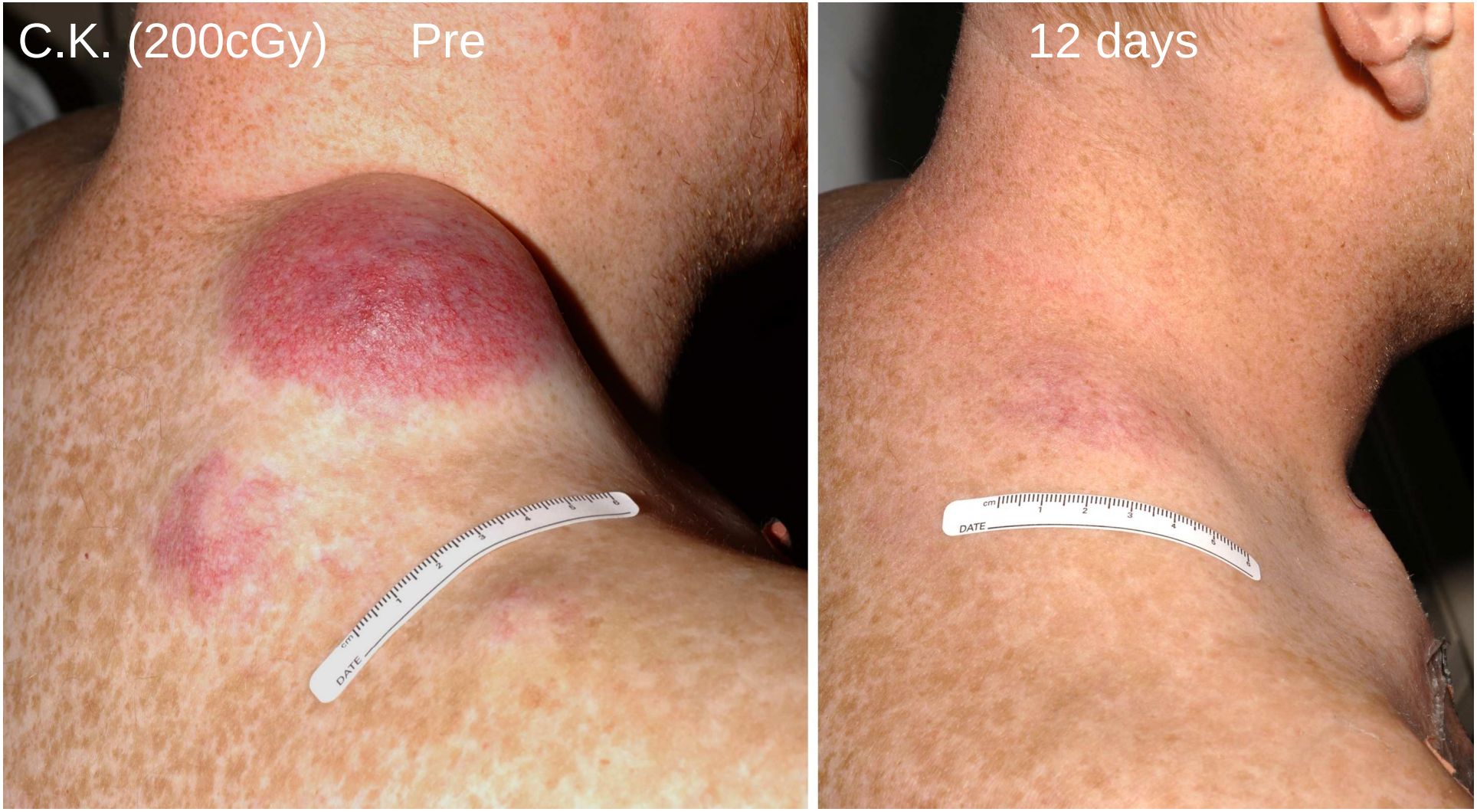


# TILs mediate regression of melanoma




Dudley ME, et. al., NRC 2003

**……at various sites and quickly!**

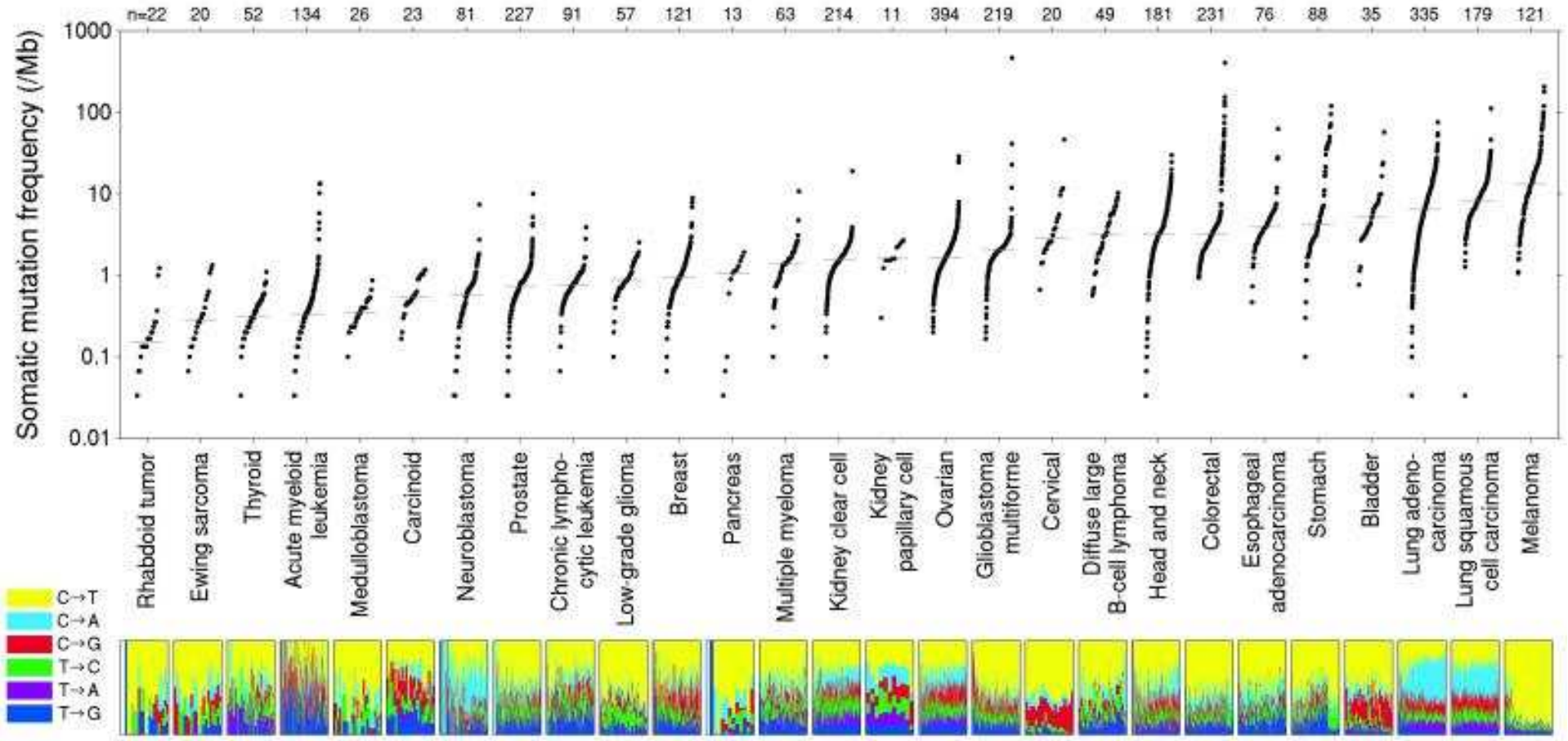



Dudley ME, et. al., NRC 2003

# Vitiligo after successful therapy with TIL

Dudley ME, et. al., NRC 2003

# Mutations in cancer cells can serve as “neoantigens” recognized by the immune system




MS Lawrence et. al., Nature. 2013 Jul 11; 499(7457): 214–218.

# Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells

**Paul F Robbins, Yong-Chen Lu, Mona El-Gamil, Yong F Li, Colin Gross, Jared Gartner, Jimmy C Lin, Jamie K Teer, Paul Cliften, Eric Tycksen, Yardena Samuels & Steven A Rosenberg**

*Nature Medicine* **19**, 747–752 (2013) doi:10.1038/nm.3161 **14 May 2013**

This simplified approach for identifying mutated antigens recognized by T cells avoids the need to generate and laboriously screen cDNA libraries from tumors and may represent a generally applicable method for identifying mutated antigens expressed in a variety of tumor types.

Science 9 May 2014:
Vol. 344 no. 6184 pp. 641-645
DOI: 10.1126/science.1251102

**REPORT**

## Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Eric Tran[1], Simon Turcotte[1]*, Alena Gros[1], Paul F. Robbins[1], Yong-Chen Lu[1], Mark E. Dudley[1]†, John R. Wunderlich[1], Robert P. Somerville[1], Katherine Hogan[1], Christian S. Hinrichs[1], Maria R. Parkhurst[1], James C. Yang[1], Steven A. Rosenberg[1]‡

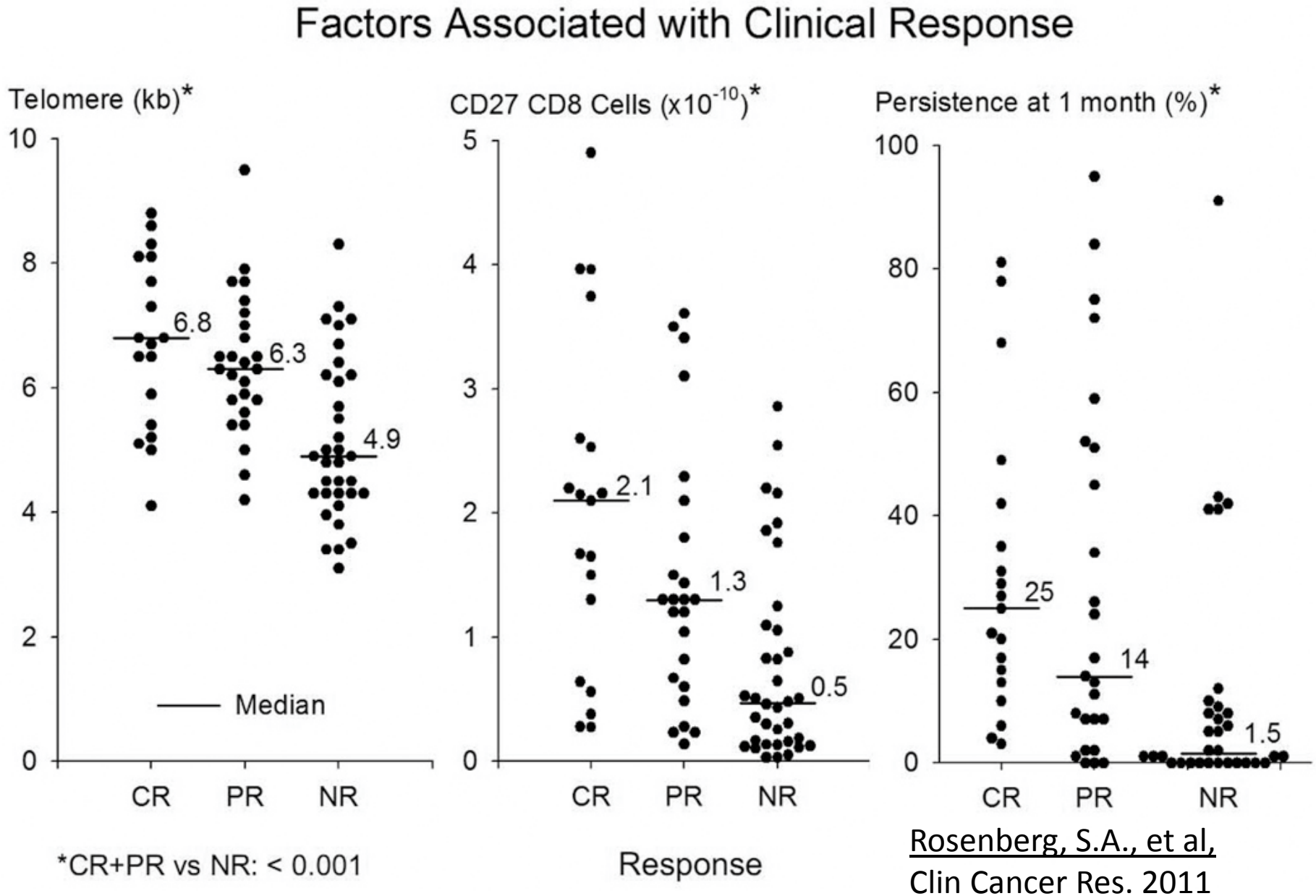
New York Times

## DURABLE COMPLETE RESPONSES IN HEAVILY PRETREATED PATIENTS

| Treatment | *n* | PR, *n* (duration, months) | CR, *n* (duration, months)* | OR† |
|---|---|---|---|---|
| No TBI | 43 | 16 (84, 36, 29, 28, 14, 12, 11, 7, 7, 7, 7, 4, 4, 2, 2, 2) | 5 (>86, >84, >83, >82, >69) | 49% |
| 2 Gy TBI | 25 | 8 (14, 9, 6, 6, 5, 4, 3, 3) | 5 (>73, >70, >65, >62, >59) | 52% |
| 12 Gy TBI | 25 | 8 (21, 13, 7, 6, 6, 5, 3, 2) | 10 (>53, >50, >49, >49, >44, >43, >43, >43, >42, 19) | 72% |

*20 CRs: 19 ongoing at 42–86 months. †52 responding patients: 42 had prior IL-2 therapy, 22 had prior IL-2 and chemotherapy. Abbreviations: CR, complete response; IL, interleukin; OR, overall response; PR, partial response; TBI, total body irradiation.

## Transferred T cells Persist Long Term in Patients




Rosenberg, S.A., et al,
Clin Cancer Res. 2011
Jul 1; 17(13): 4550–4557.

# Lessoned learned from ACT Trials

1. Successful ACT is contingent upon the selection and proper expansion of Tumor-infiltrating T cells from cancer patients (Melanoma and Cervical Cancer)

2. Persistence of the T cells is critical and correlative to patient survival

3. Less differentiated T cells with memory responses are ideal

4. $CD4^+$ and $CD8^+$ T cells are both needed to mediate durable immunity in mouse and human.

# Problems using TILs in the clinic

1) Collection of tumor-reactive T cells from the tumor and subsequent expansion can be difficult and requires specialized team.

2) TIL can not be generated from all patients

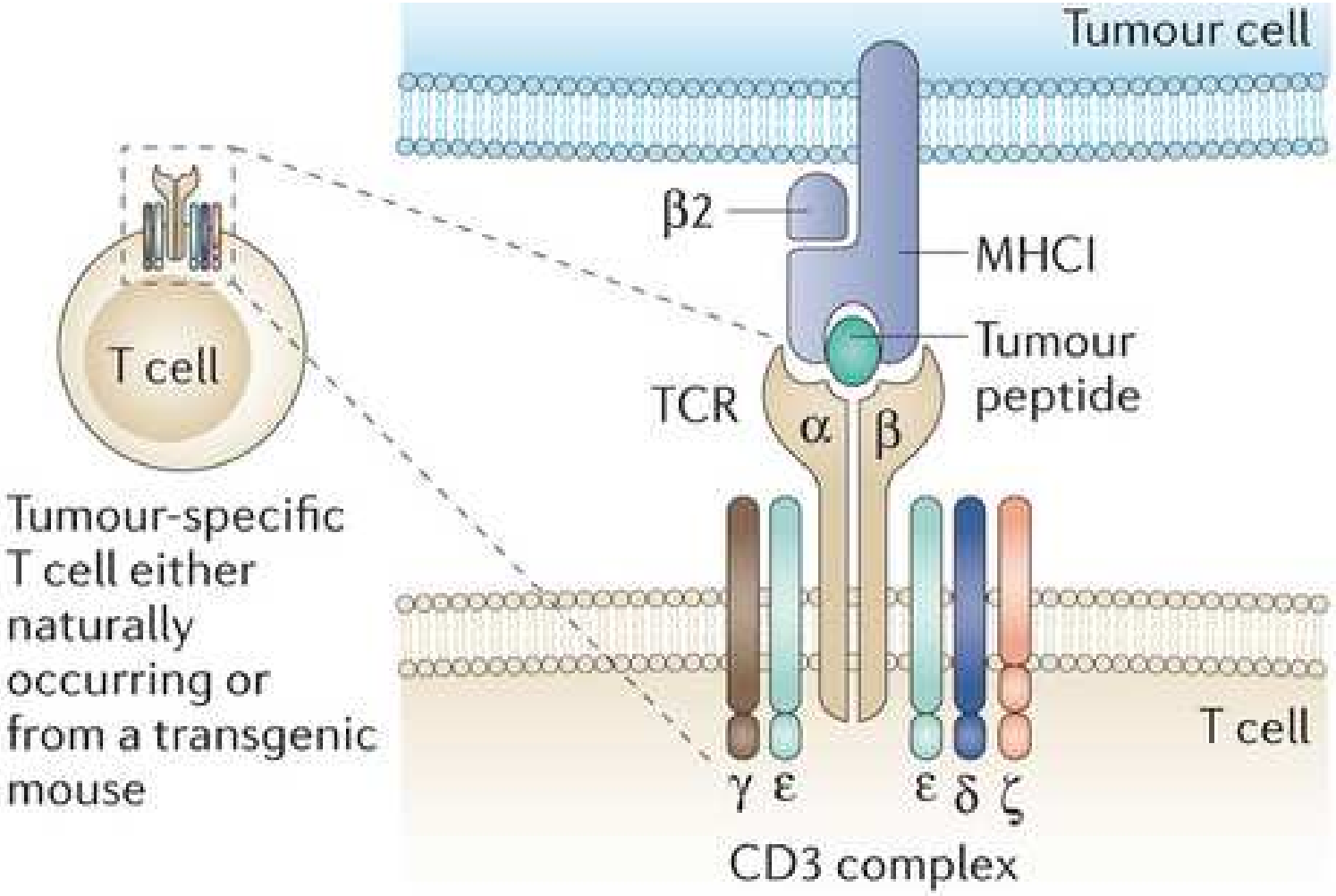
3) Surgical removal of tumor is not always possible

**SOLUTION:**

**GENETIC REDIRECTION OF T cells with TCRs the recognize tumor**

-what is a TCR?

**Tumor regression mediated by T cells recognition via the T cell receptor (TCR)**



# APPROACH: TCR gene therapy for the treatment of cancer

**ADVANTAGE to TIL:**

1. Off the shelf
2. Less invasive
3. Introduce desired and new tumor spec.
4. Multiple cancers
5. Can vaccinate against infused T cells to drive engraftment and function

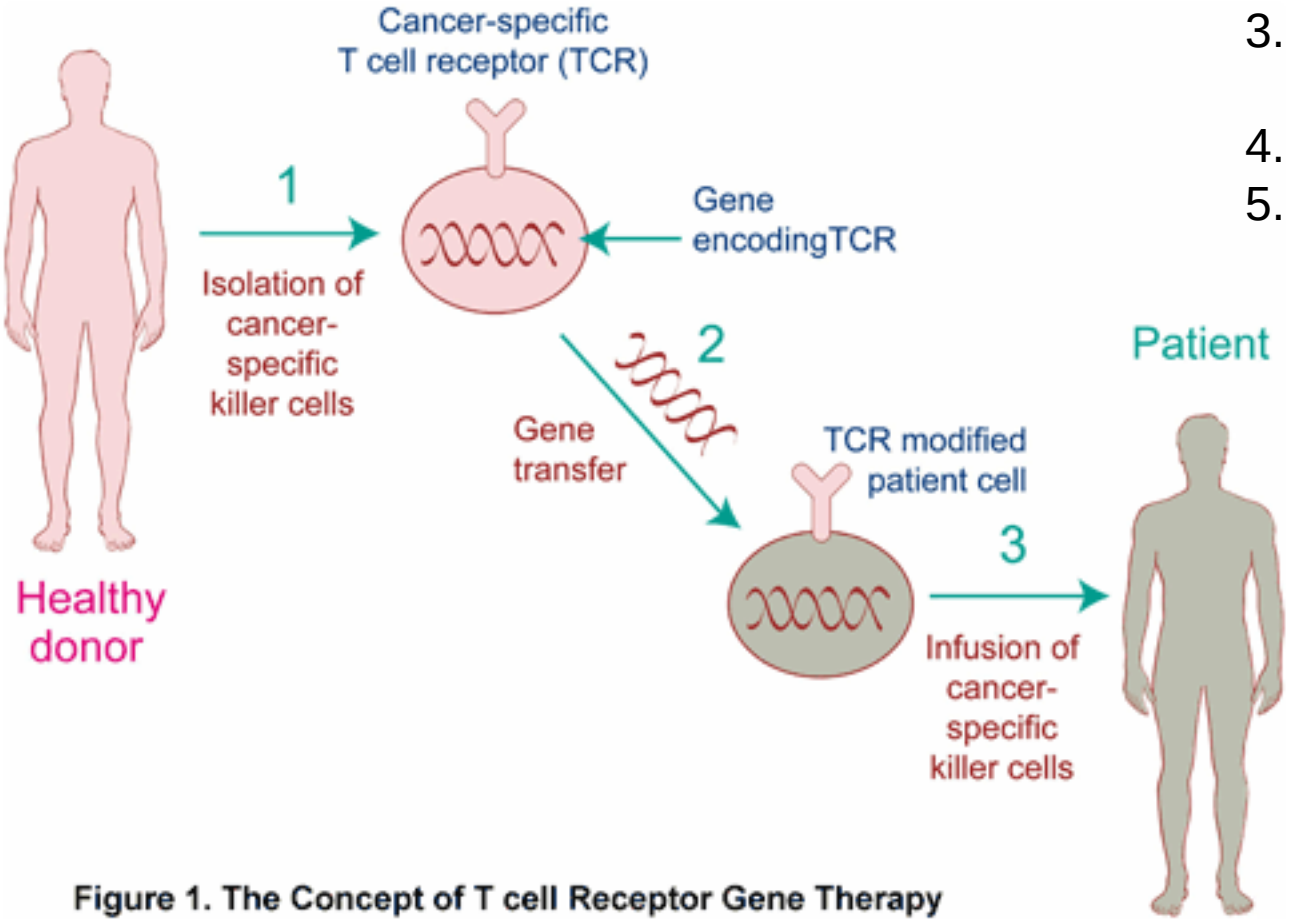
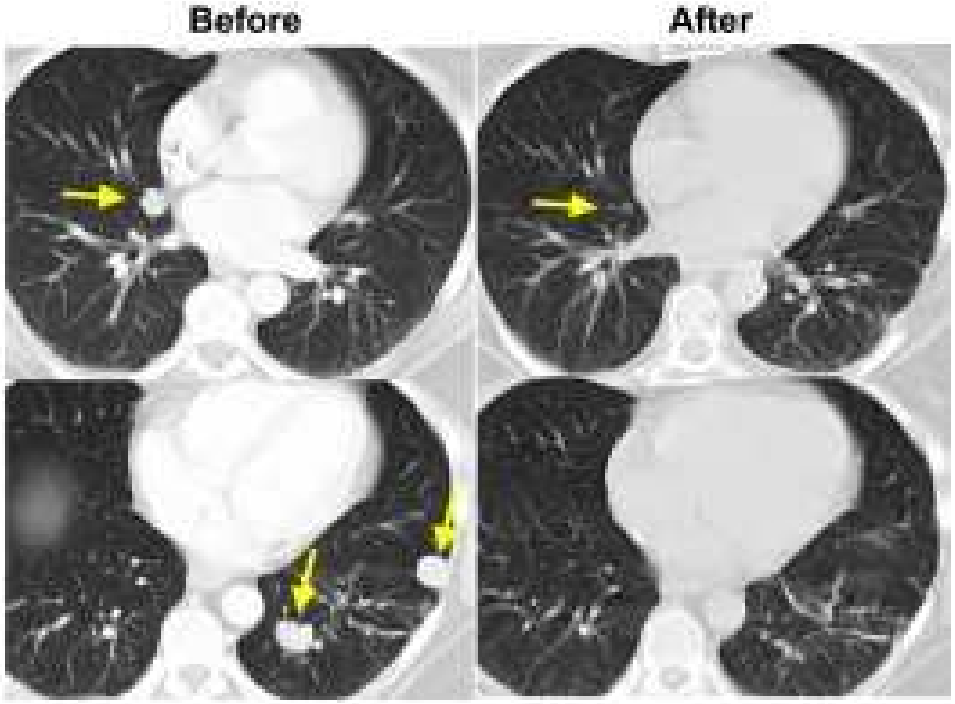
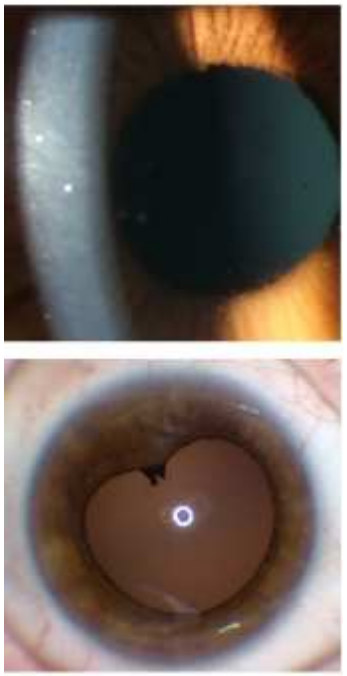
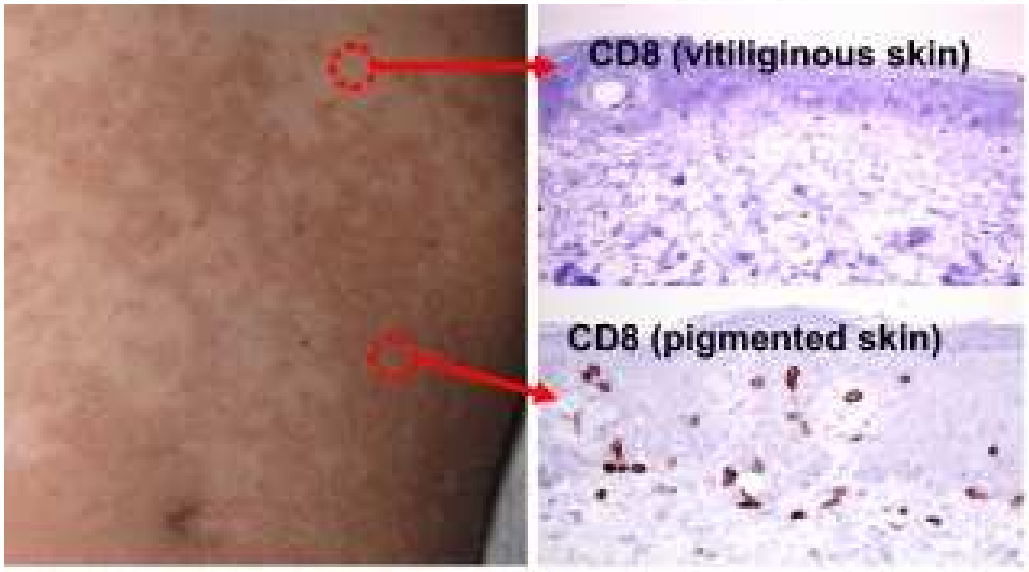



Figure 1. The Concept of T cell Receptor Gene Therapy

# The power of gene transfer with TCRs in melanoma patient






PROS:
Objective response rates in **30%** of pt

CONS:
Less effective the TIL perhaps, as not multiple antigen receptors

Off target effects to MART+ on normal tissue, such as eye and skin (**90%!!!**)

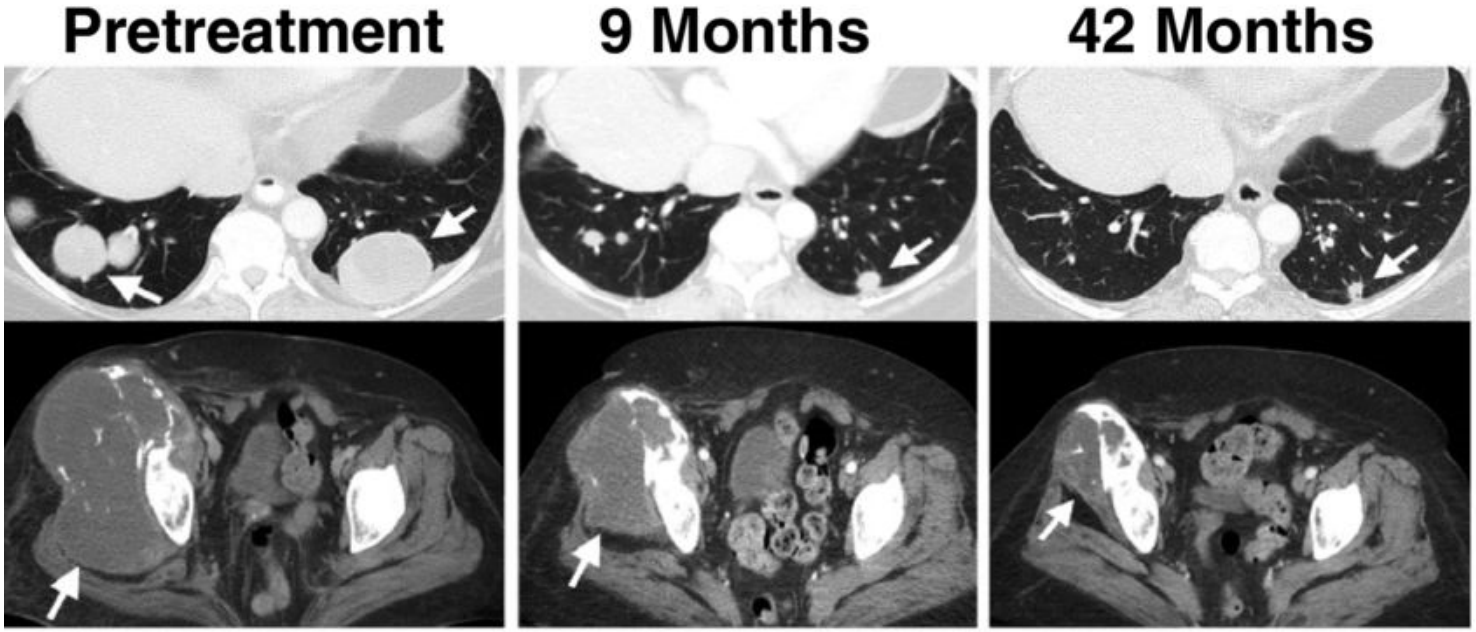
Johnson, L, et. al, Blood 2009

# What is the ideal antigen to target?

-Self/tumor-specific – off target!
-Tumor-restricted – on target, no off target
-Perhaps mutated antigen, glycosylated antigen

**Examples of on-target ag:**
Cancer/testis (CT) antigens
-normal expression restricted to testis, ovary and trophoblasts
-not on adult somatic tissues
-CT antigen expression in a variety of tumors

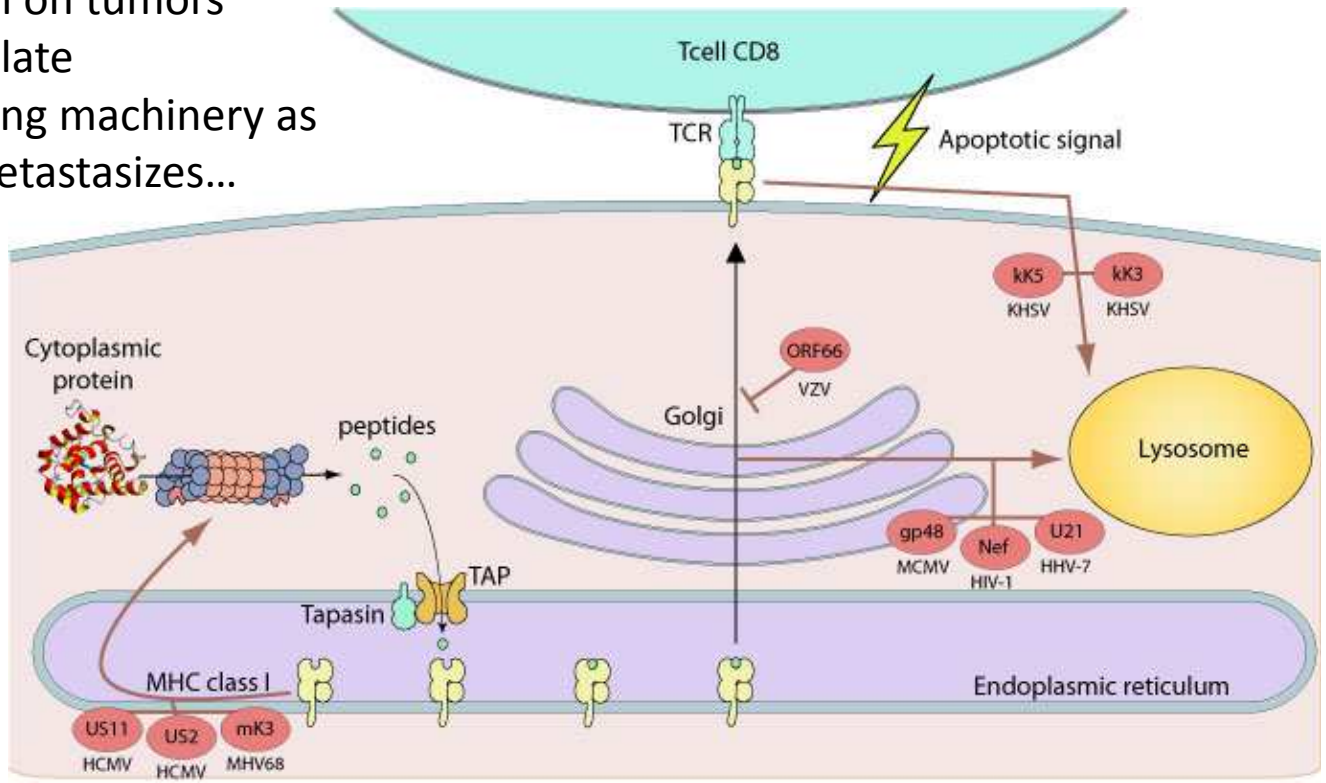
**NY-ESO-1** is expressed in melanoma, synovial sarcomas and other maligancies




**No off target responses. 1 CR and 11 OR in sarcoma patients!!!**
Robbins, P et.al CCR Mar 2014

# Problems with TIL and TCR gene ACT therapy

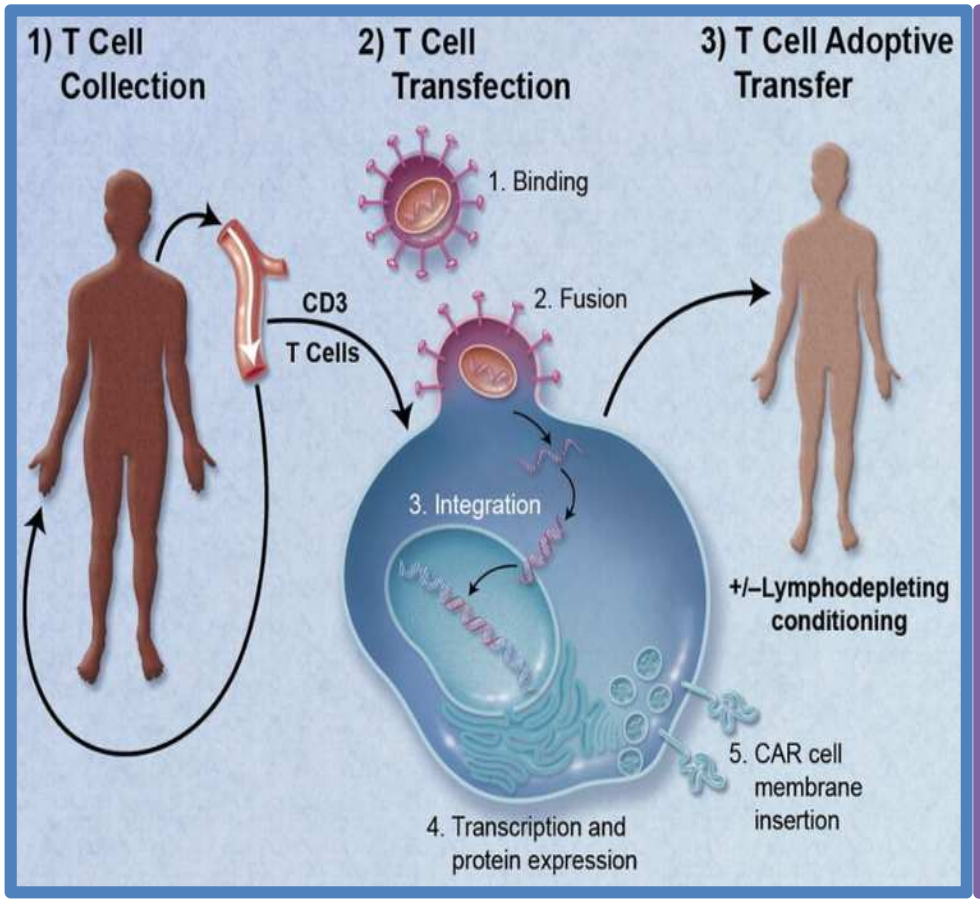
1) Not all cancers will express target antigen
2) Antigen loss can happen on tumors
3) MHC I and II down-regulate
4) Loss of antigen processing machinery as cancer progresses or metastasizes…

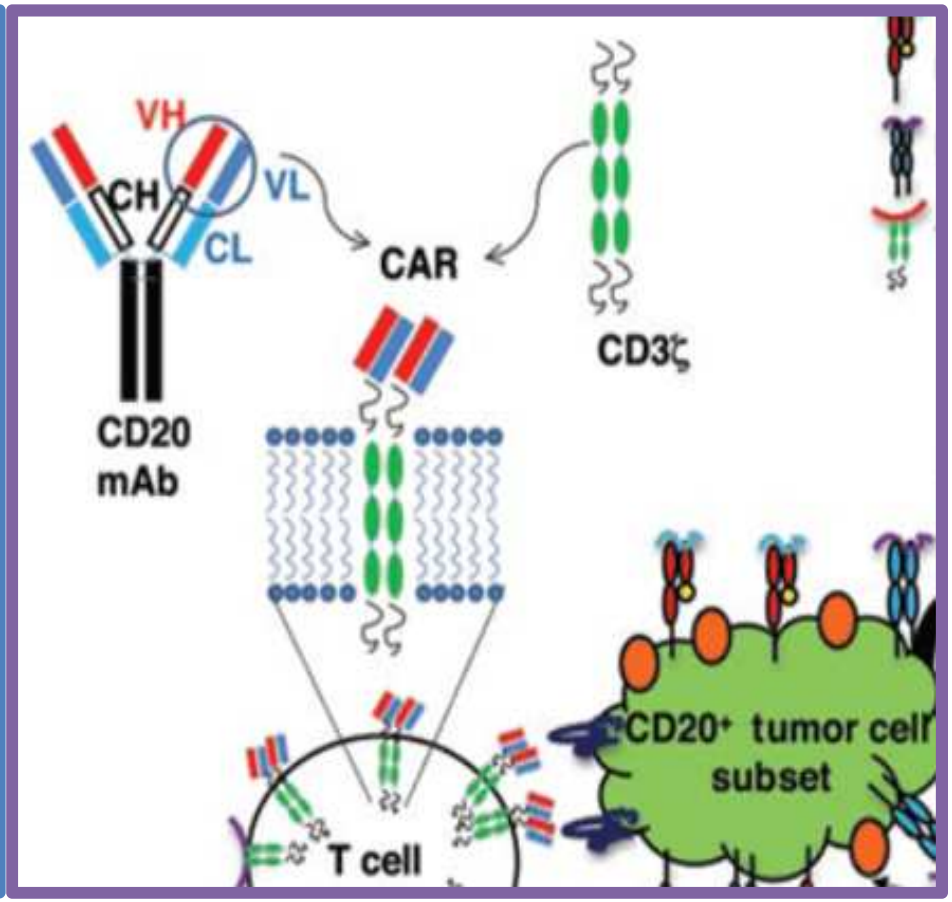



Vitale et. al. CCR 2006, Han et. al. CCR 2008

**Potential SOLUTION:** Chimeric antigen receptors are man made and can be used to directly target whole tumor antigen on human cancer!!!

# Chimeric antigen receptors

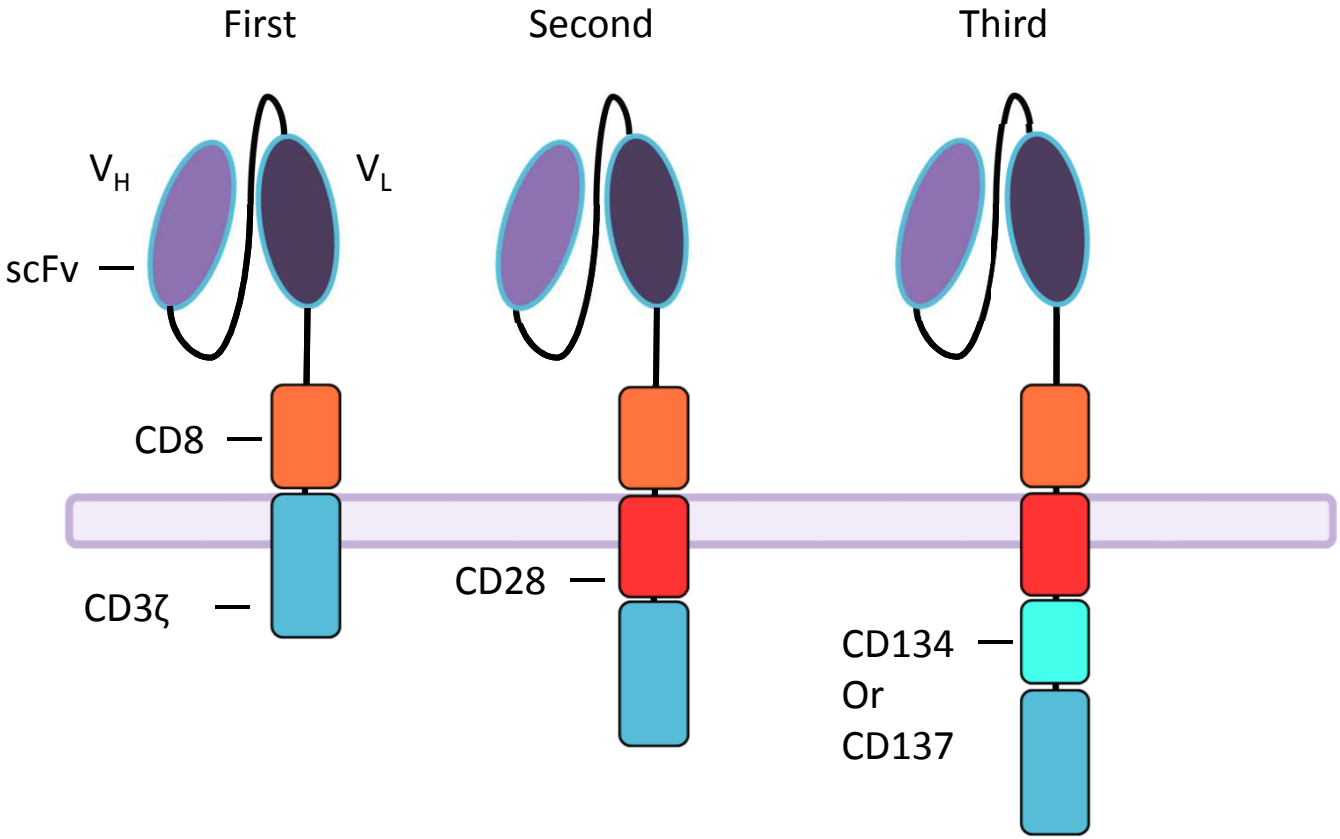



**Pros of CARs over TCR:**
**MHC-independent, antigen processing machinery not required, universal**

Ritz, Blood 2009 Herlyn, Mol. Therapy 2011

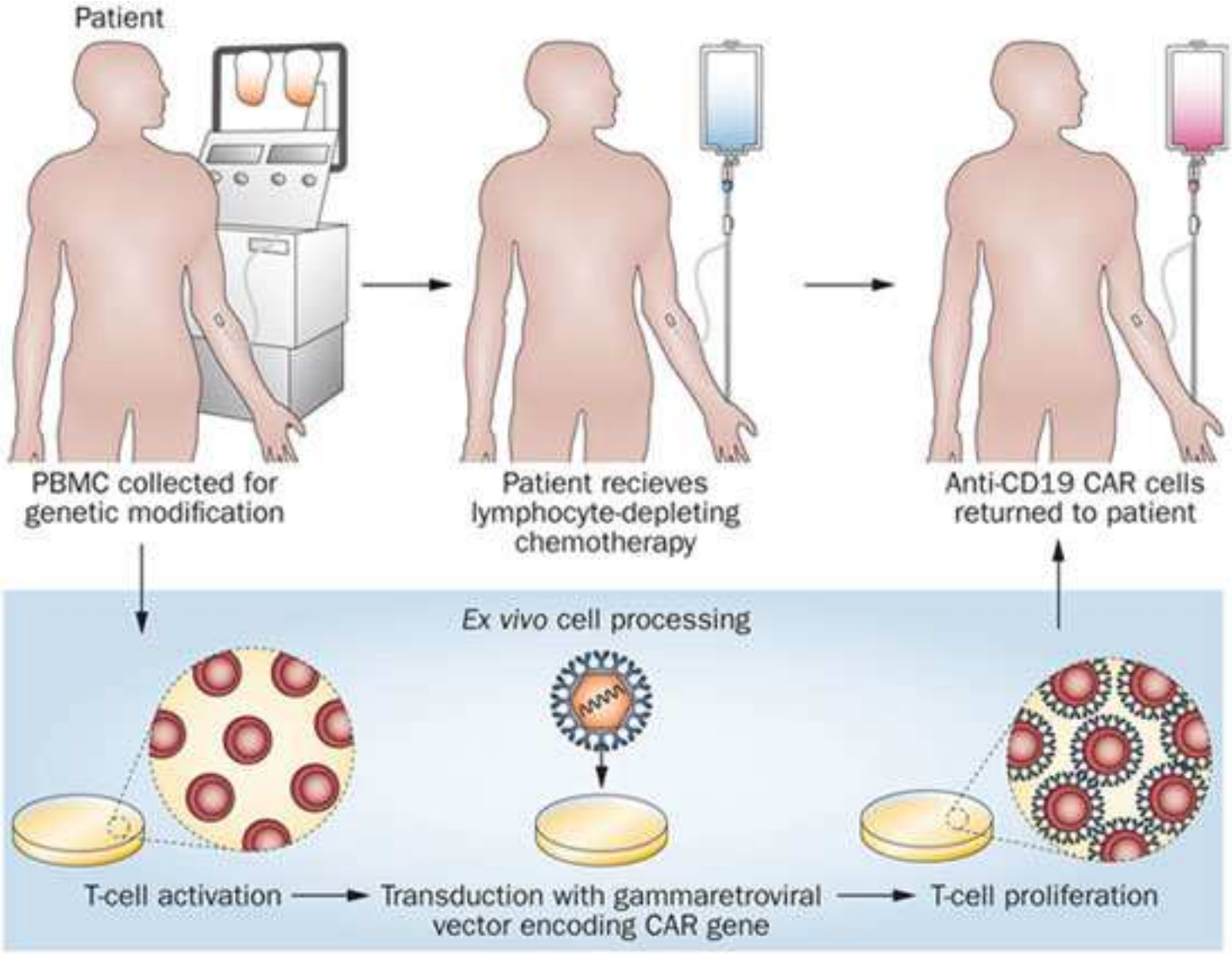
# Signal one, Signal two is needed: CARS the RUN!!!




T cells need two signals to expand logarithmically
-Second/third gen CARs have improved proliferation
-Engraft better and resist apoptosis
-Have greater and more robust effector function

**Nelson, et. al. Immunol Rev 2015**

# Schematic of anti-CD19 CAR T cell therapy




*Nature Reviews Clinical Oncology* **10**, 267-276 (May 2013)

# Clinical results w/ anti-CD19 CAR therapy

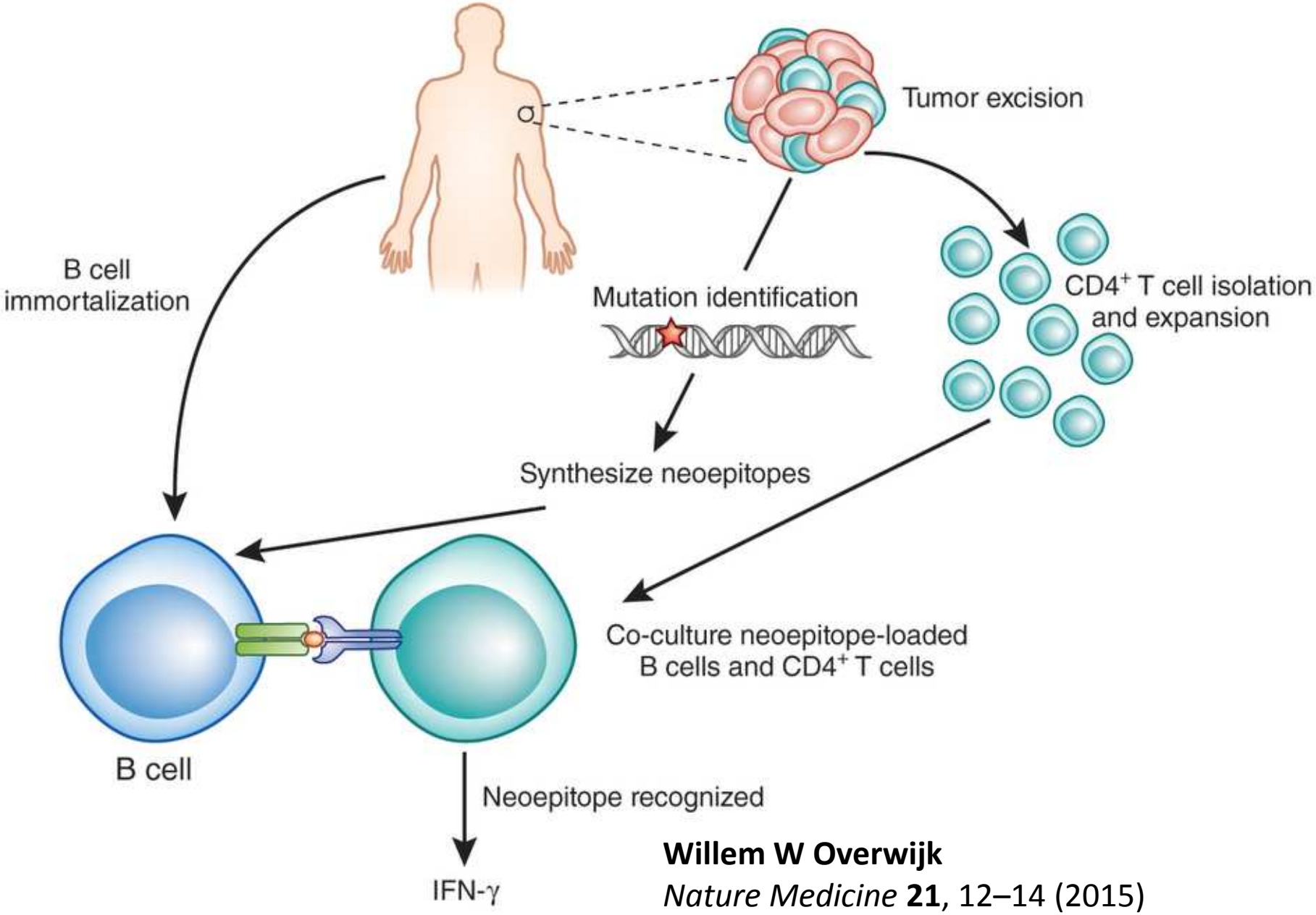
-90% Complete Remission Rate in ALL
-30% in CLL
-kills normal B cells
–does this contribute to outcome?
Requires IVIG infusion
Cytokine release syndrome (IL-6)

Antigen loss happens in relapsed patients

***Multiple reports at NIH, Upenn and MSKCC
Major company interest and going for FDA approval

Although this approach has been effective in hematological malignancies, it has yet to be effective in solid tumors. Why?

# Genomic medicine: Personalized Care!!!




**Willem W Overwijk**
*Nature Medicine* **21**, 12–14 (2015)

# Summary

TIL therapy represents a promising way to treat advanced refractory solid tumors and drive objective response rates of 50% in patients with melanoma and cervical cancer.

Gene transfer has potential, as it can generate T cells off-the-shelf where T cells that could not otherwise be made for the individual.

CAR strategies are attractive and have shown promise in patients with hemotological malignancies.

Harnessing mutations/neo-antigens could be an important advancement in treating solid tumors with next generation ACT clinical trials (based on NCI work!).

*All of these approaches are attractive and many companies are now spending considerable time and money developing this approach to treat patients with various malignancies!*