SITC Lecture Tumor Immunology 101: A Navigation Guide to the New Field of Immuno-oncology

T cells: How do they work and how can we use them to combat cancer?

Jeffrey S. Weber M.D. Ph.D.
Donald A. Adam Comprehensive Melanoma Research Center
Moffitt Cancer Center

Disclosures

- I have accepted honoraria for advisory boards and DSMBs from BMS, Merck, GSK, Celldex and Genentech of less than $10,000 dollars per year
- I am on the SABs of Lion Biotechnologies and Celldex and receive honoraria from both
- My institution, but not me personally, receives funds from BMS, Merck, GSK and Genentech for the performance of trials
- I am not a member of any speaker's bureau
- I have no other relevant disclosures

The immune system and cancer

- The immune system evolved over time as a means of protection against infection, chiefly bacterial
- Immunity consists of different mechanisms of protection- innate and adaptive
- Both cells and molecules can function in the immune system

What are the different parts of the immune system?

- The “innate” immune system: our first line of defense. Innate immunity is pre-existing and ready to respond to infection and inflammation: a “booby trap”
- Macrophages and neutrophils are examples of “innate” immune cells
- Innate immunity is not educated, nor is it selective - kill first, ask questions later

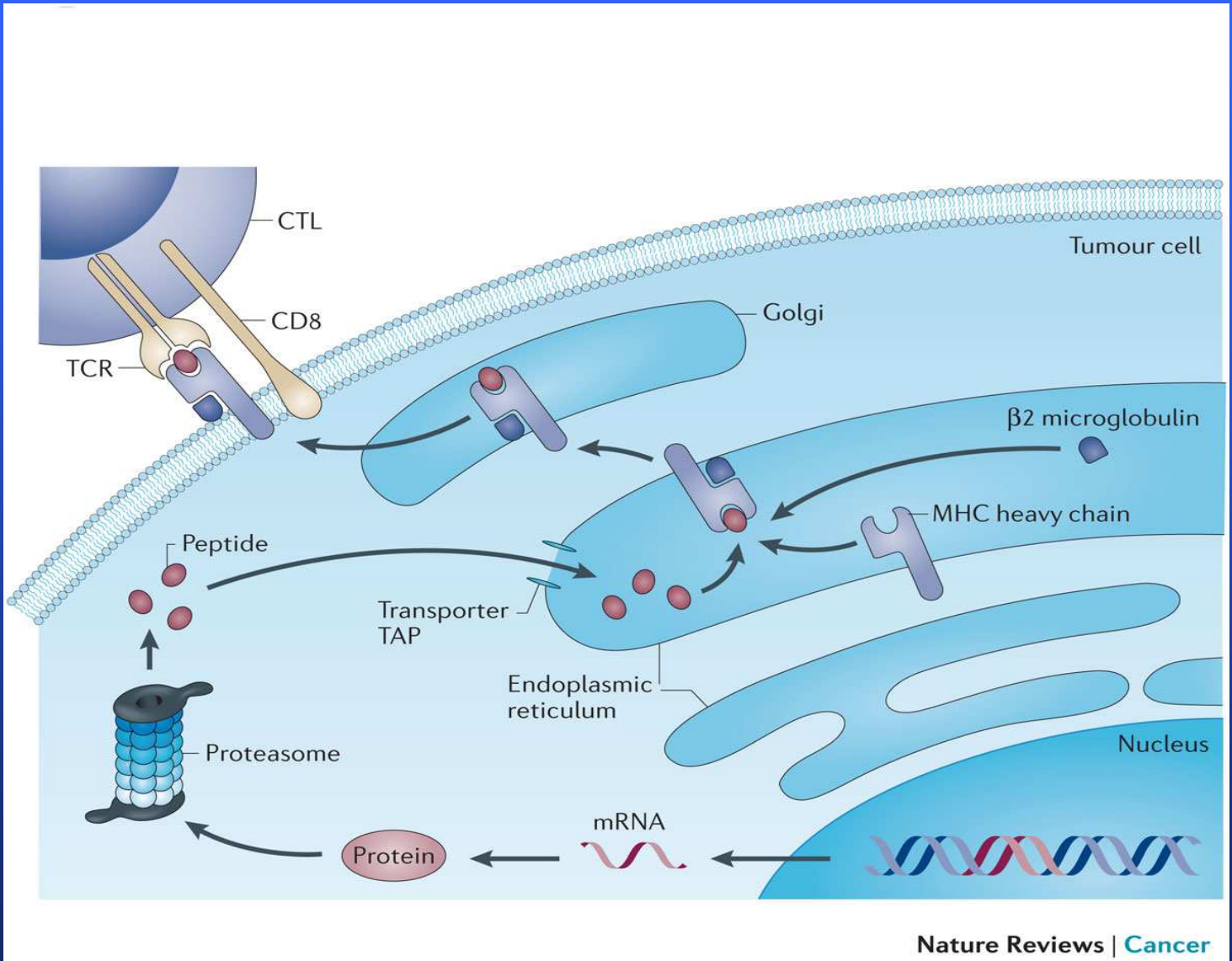
What are the different parts of the immune system?

- “adaptive” immunity is the other side of the coin from “innate” immunity
- Adaptive immune cells are B and T cells
- They are “educated” in that they can “learn”
- That means they have “memory” and recall prior exposure to bacteria or other stimuli
- Adaptive immune cells are “specific” and have a selective, not general action

Why does immunity work well against infection, not so against cancer?

- Cancer cells are all derived from normal cells and often differ in expression of normal genes
- Cancer cells evolve quickly to lose antigens that can be recognized by the immune system
- Cancer cells produce suppressive cytokines and other substances that decrease immunity, and ectopically express PD-L1 that suppresses T cells
- Patients sick with cancer who have received chemotherapy can’t mount immune responses

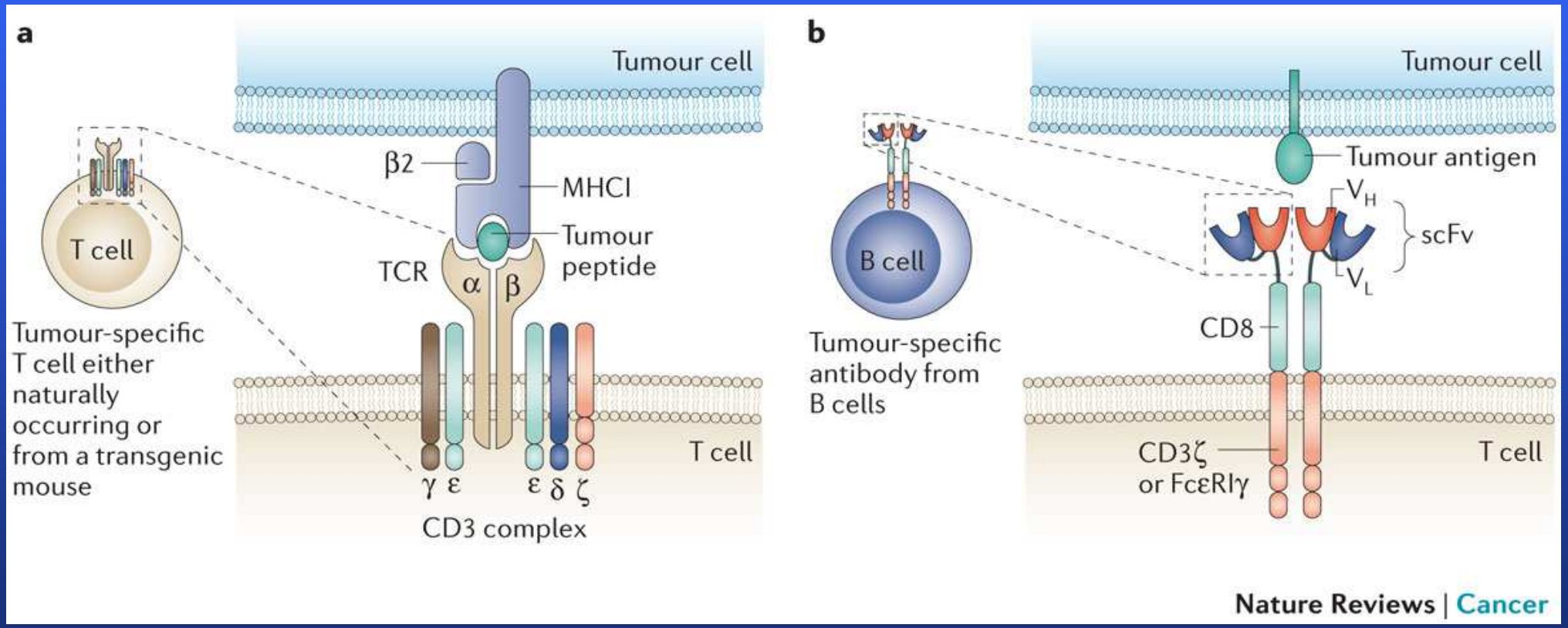
T cells recognize antigens processed and presented in the context of MHC molecules at the cell surface – “signal 1”



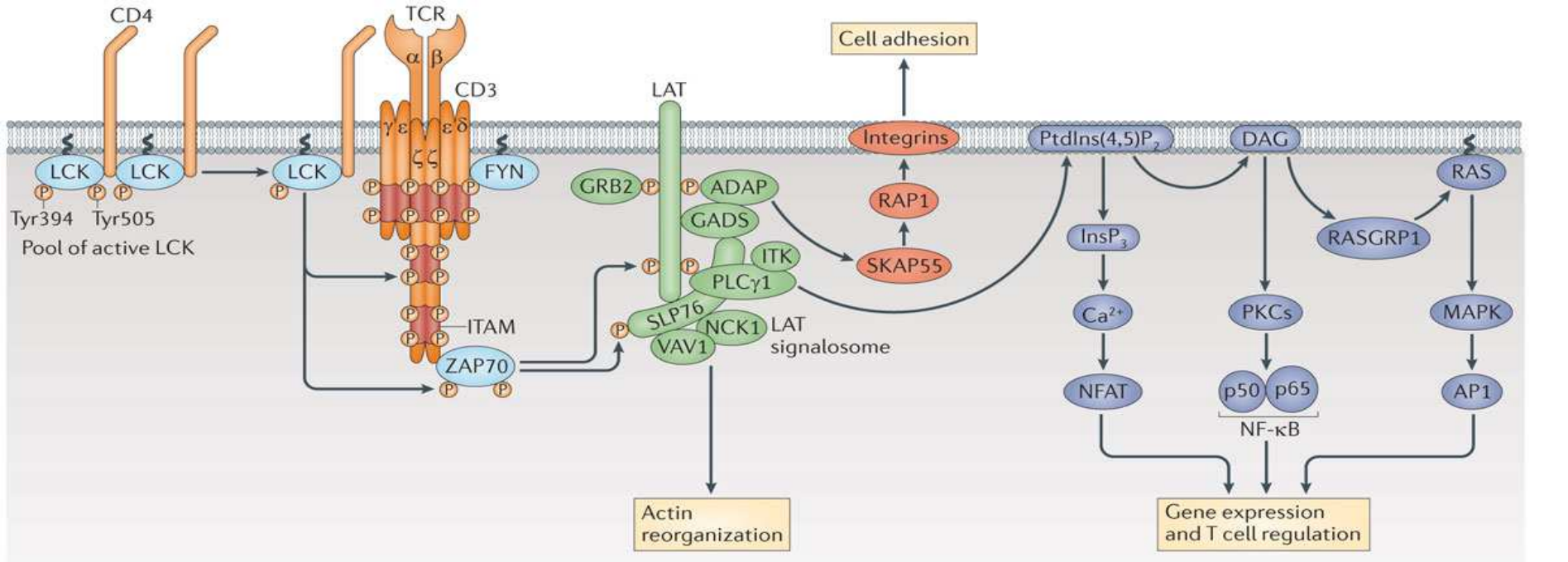
Signaling by T cells

- MHC-peptide binding to the T cell receptor (TcR) is “signal 1”
- CD28 on the T cells binding to B7.1 or B7.2 on the APC is “signal 2”
- There are multiple agonist or antagonist pairs of receptor-ligands that then interact to regulate the T cells
- One T cell can interrogate many possible targets

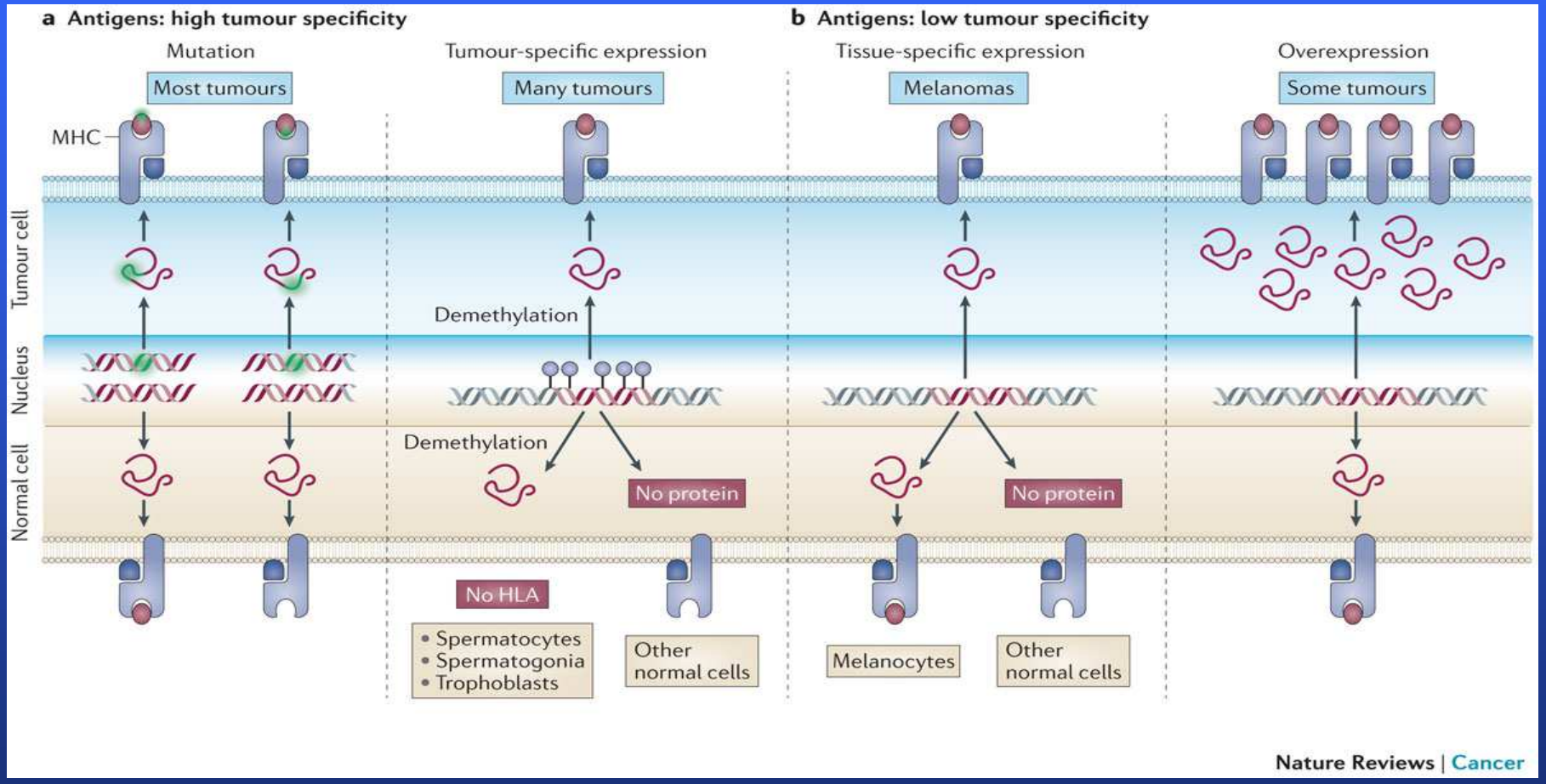
T cells have a two chain α β TcR structure and complex with other molecules (CD3) to transduce signals intra-cellularly



T cell receptor engagement is optimal at a “synapse” where the T cell and the target come together in apposition

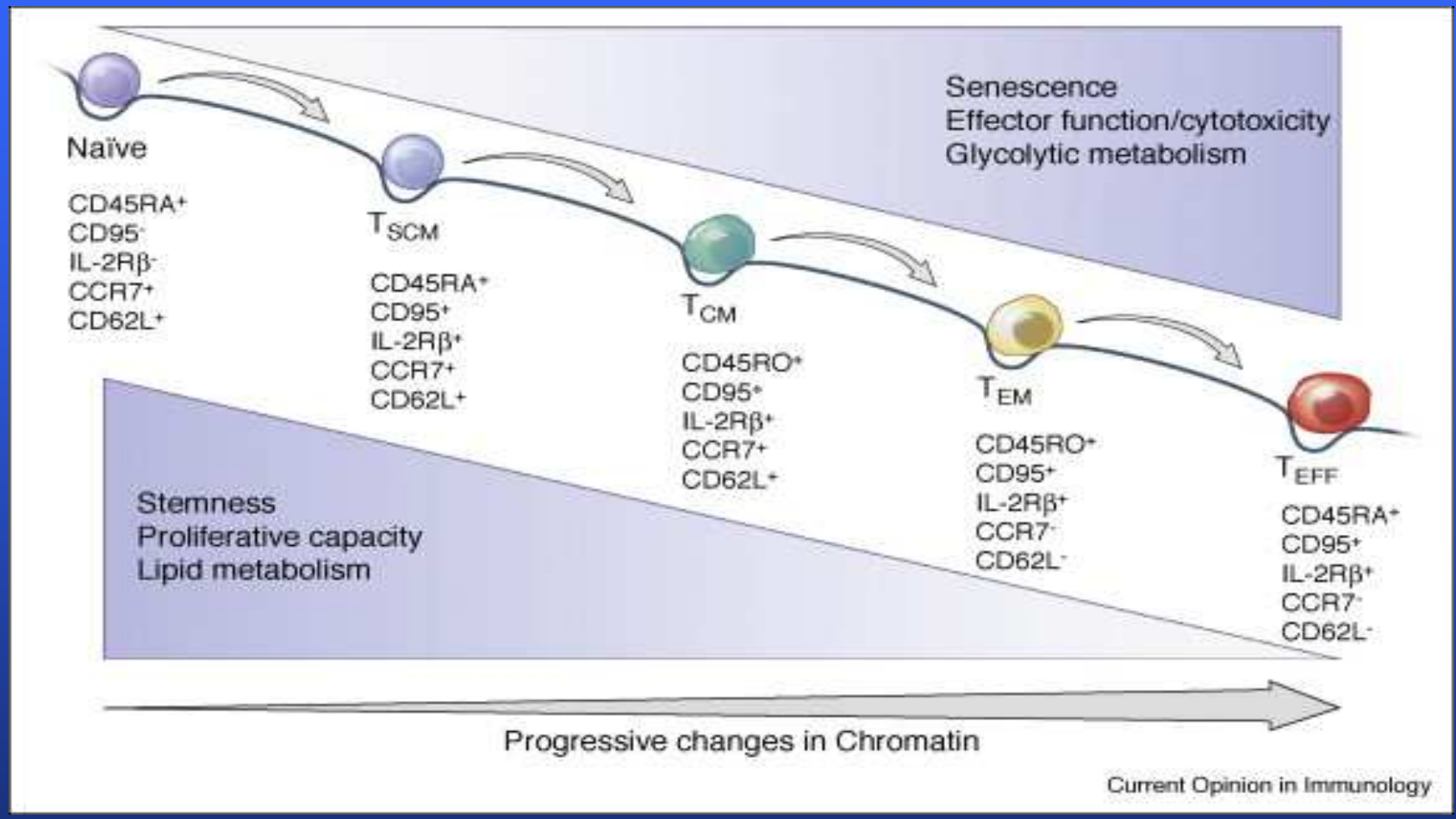


Antigens recognized by T cells fall into distinct categories



There are also viral specific tumor antigens

T cells mature along a fixed pathway to become effector cells

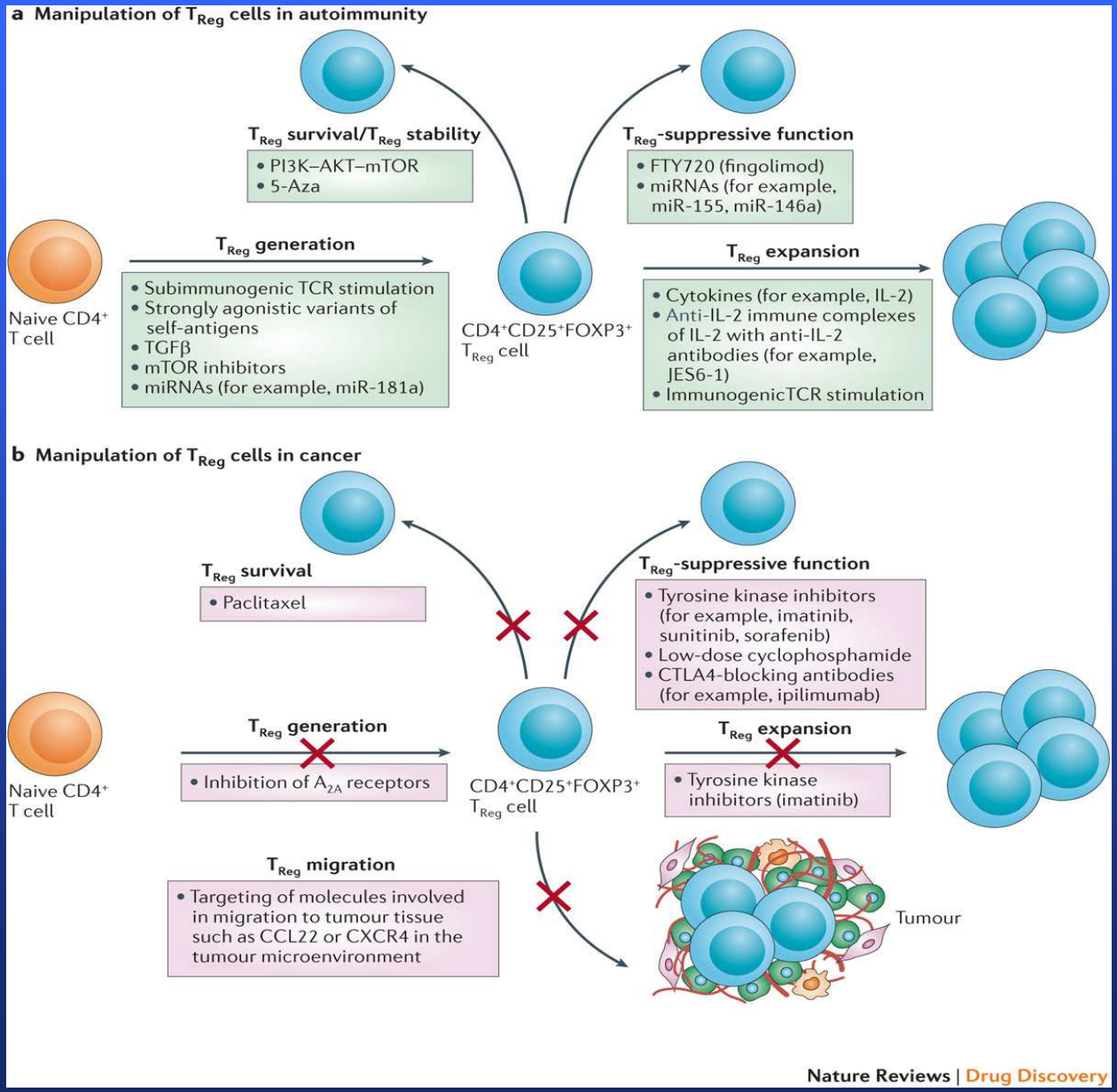


The progressive differentiation CD8 + T cells is largely a unidirectional process. The differentiation of cells proceeding efficiently in mainly one direction has been analogized to a ball rolling down a hill, with the gradual loss of potential. ...

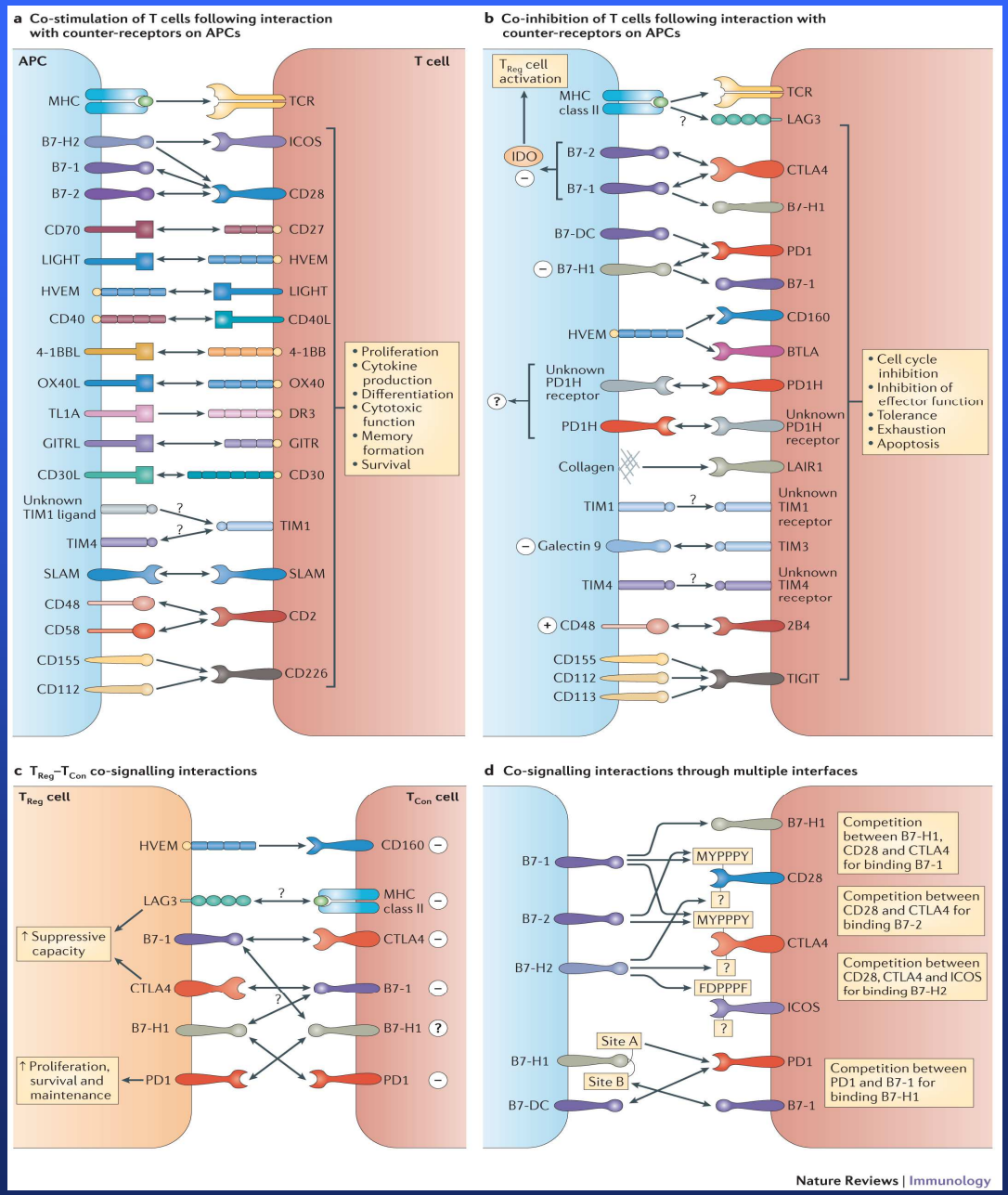
Nicholas P Restifo , Luca Gattinoni **Lineage relationship of effector and memory T cells**

Current Opinion in Immunology, Volume 25, Issue 5, 2013, 556 - 563

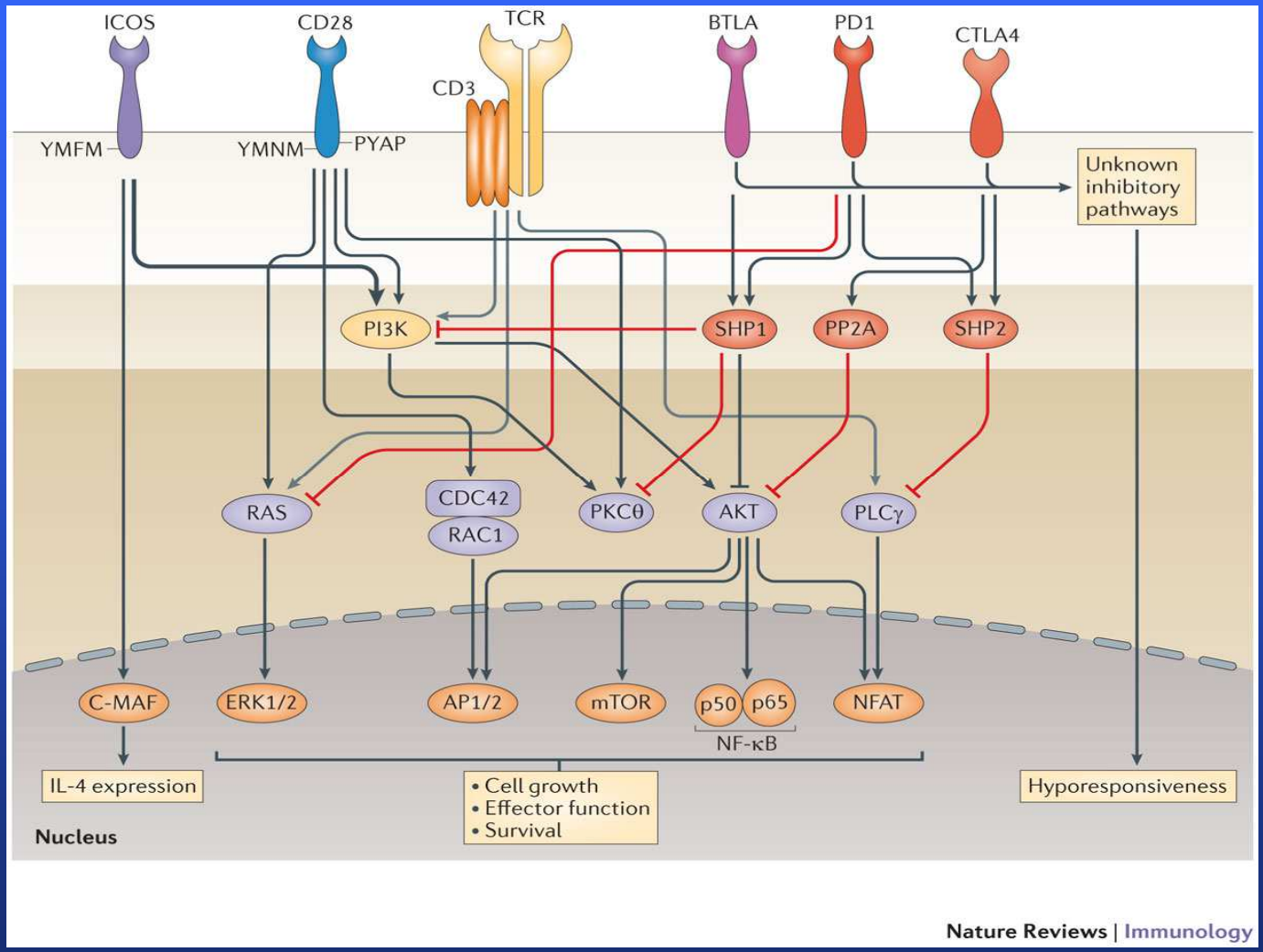
T cells can also take on suppressive roles as regulators



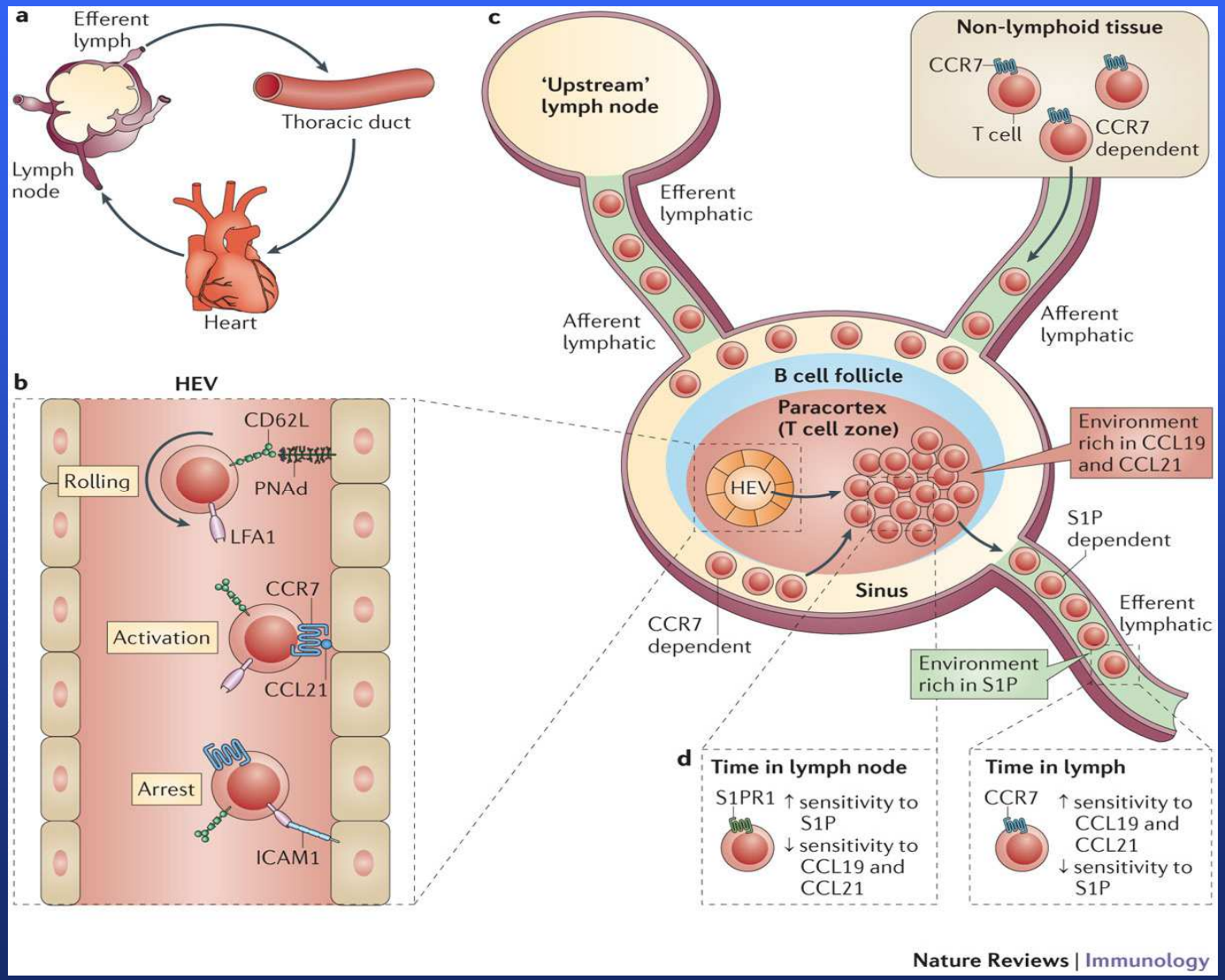
There are many “accelerators” and “brakes” on T cells



Checkpoint proteins and activators signal via phosphatases



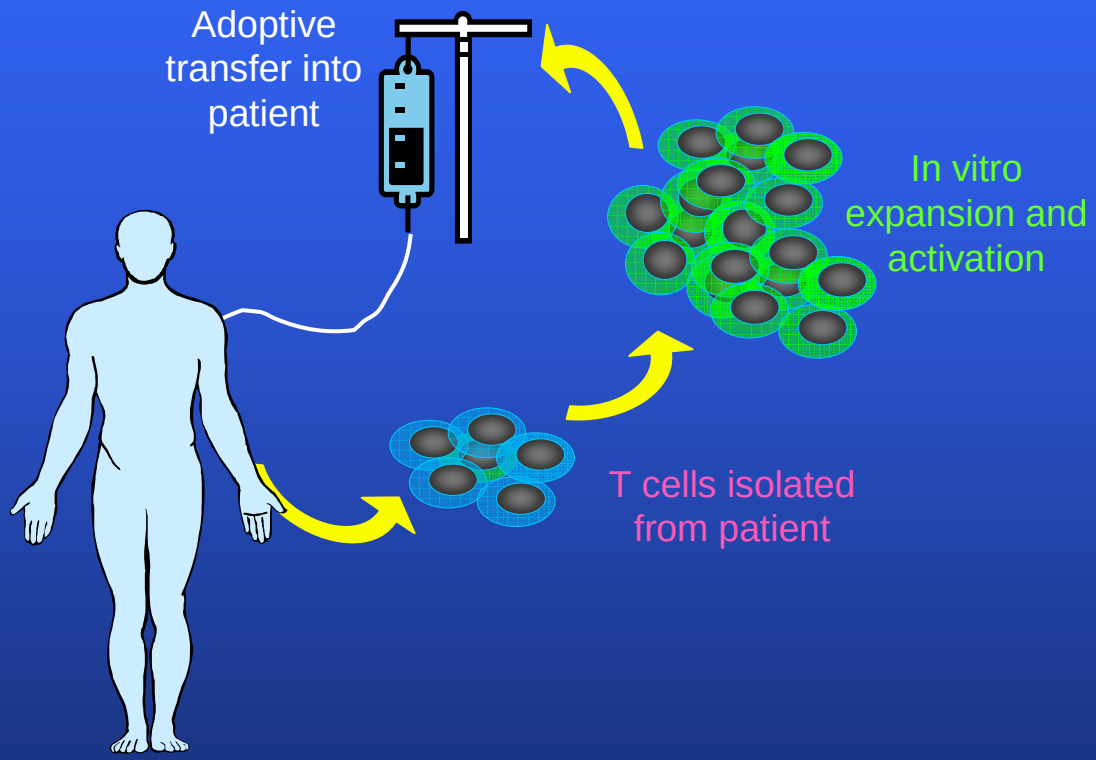
T cells circulate constantly within the lymphatics



So, how do we translate this information to an anti-cancer therapy?

- Adoptive cell therapy
  - TIL
  - T cell clones
  - Transduced TcR T cells
  - Chimeric antigen receptor T cells (CAR)
  - NK/NKT cells

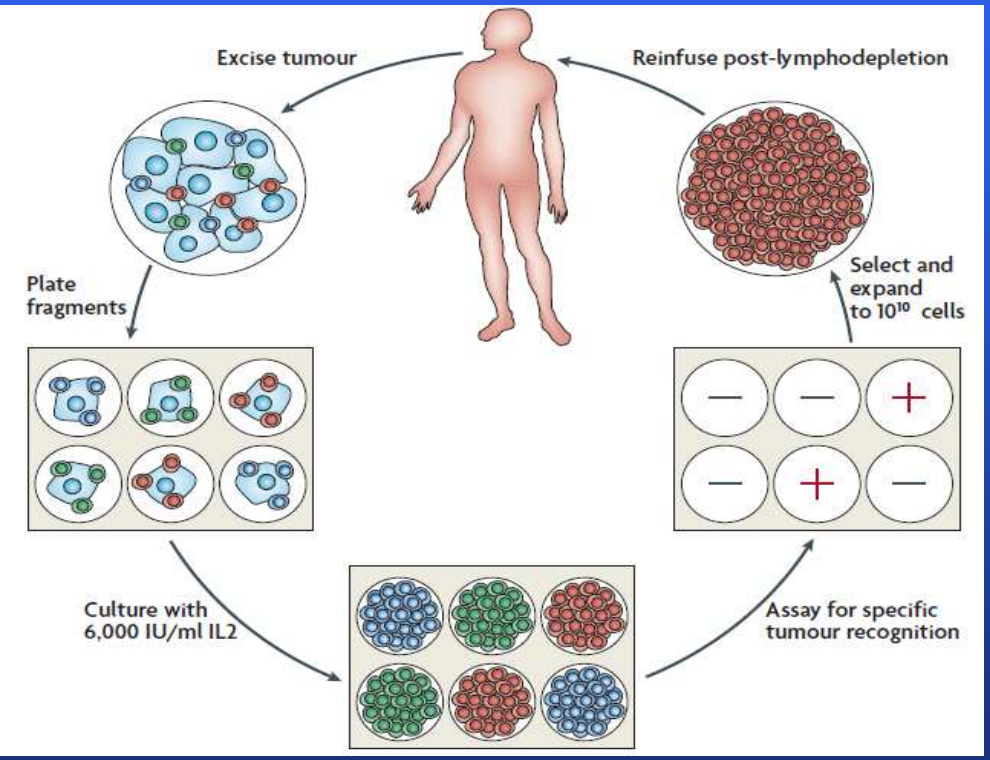
What Is Adoptive Cell Therapy for Cancer?



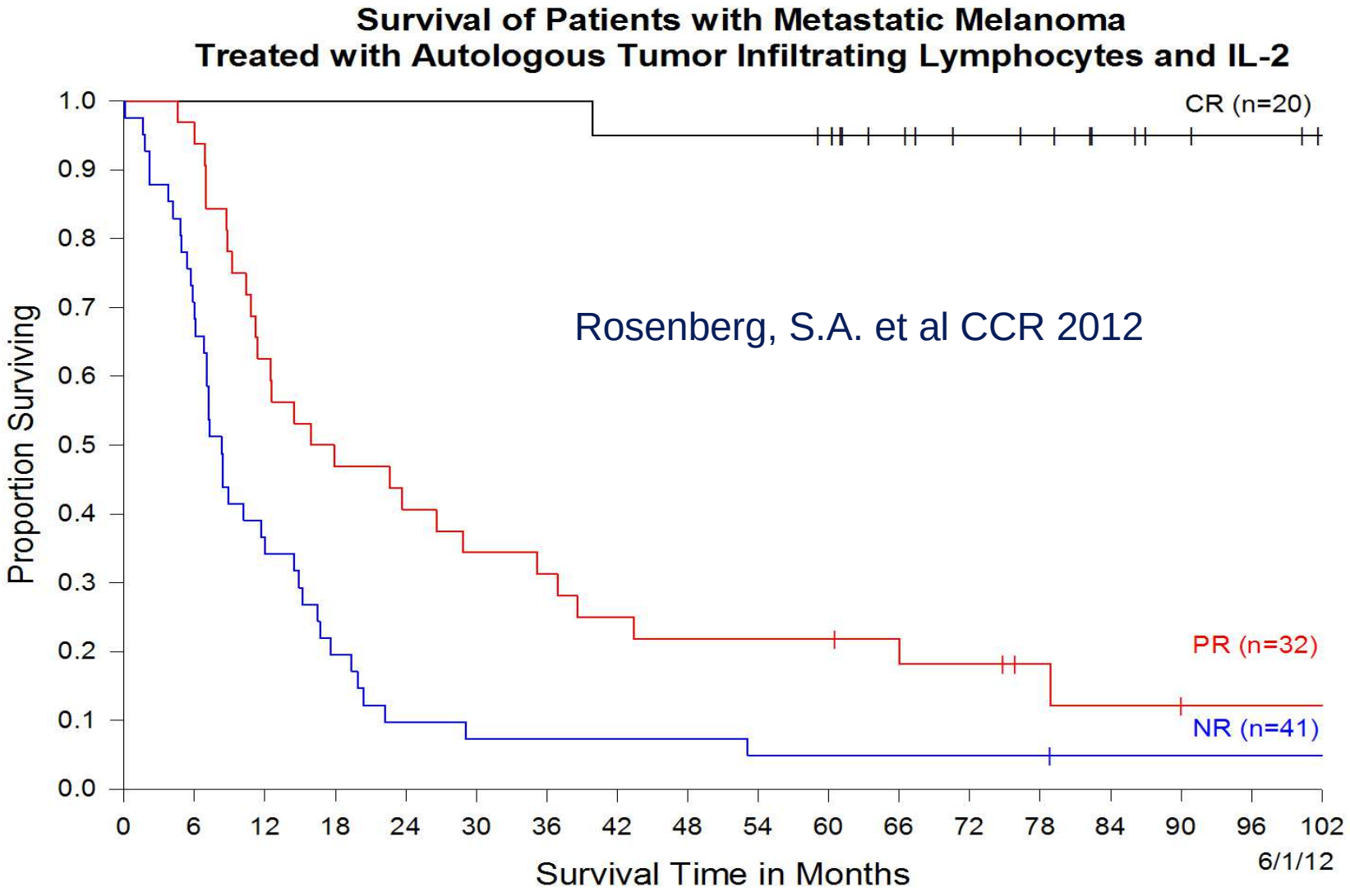
- T cells are isolated from tumor infiltrating lymphocytes or peripheral blood
- Ex vivo enrichment and expansion of antigen-specific effector T cells utilizing
  - IL-2, anti-CD3, feeder cells, and/or antigen-pulsed DCs
- T cells are reintroduced back to patient

Yee C. *2009 ASCO Educational Book*. Alexandria, VA: American Society of Clinical Oncology. 2009;511-515.

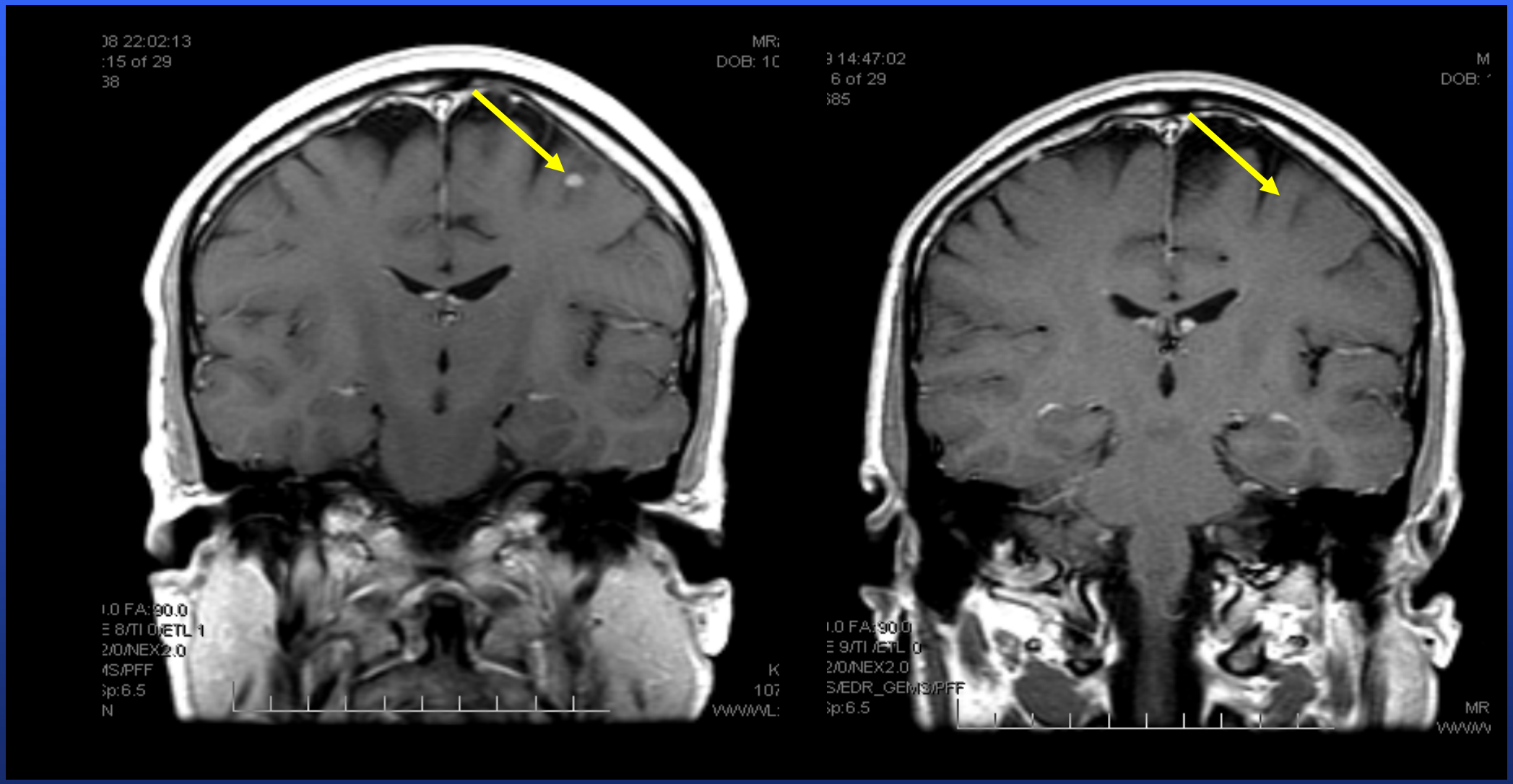
TIL Therapeutic Regimen



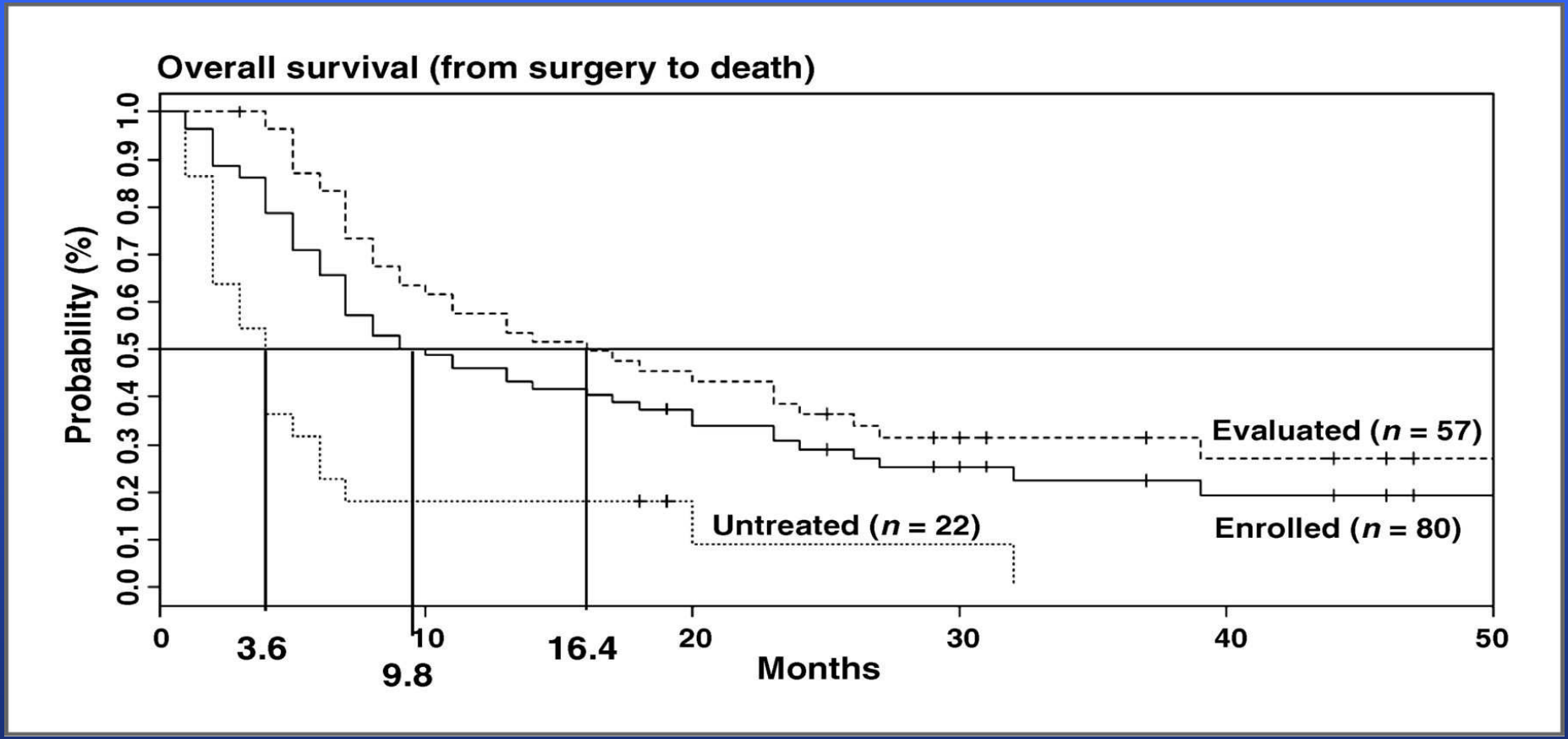
- Lymphocytes with anti-tumor activity (TILs) migrate into tumor during tumor growth
- TILs are isolated from tumor, grown *ex vivo* to great numbers, and infused back into patient
  - TILs are cultured *ex vivo* away from suppressive *in vivo* influences, enabling administration of highly activated cells with strong anti-tumor effector functions
- Patient is preconditioned with non-myeloablative chemotherapy to remove all suppressive influences prior to infusion of *ex vivo* cultured TILs to enhance therapeutic outcome


Survival of Patients with Metastatic Melanoma
Treated with Autologous Tumor Infiltrating Lymphocytes and IL-2
CR (n=20)
PR (n=32)
NR (n=41)
Rosenberg, S.A. et al CCR 2012
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
42
48
54
60
66
72
78
84
90
96
102
Survival Time in Months
6/1/12

Response of Brain Metastasis to TIL Therapy



Overall survival in enrolled patients: use of young TIL at Sheba Medical Center.



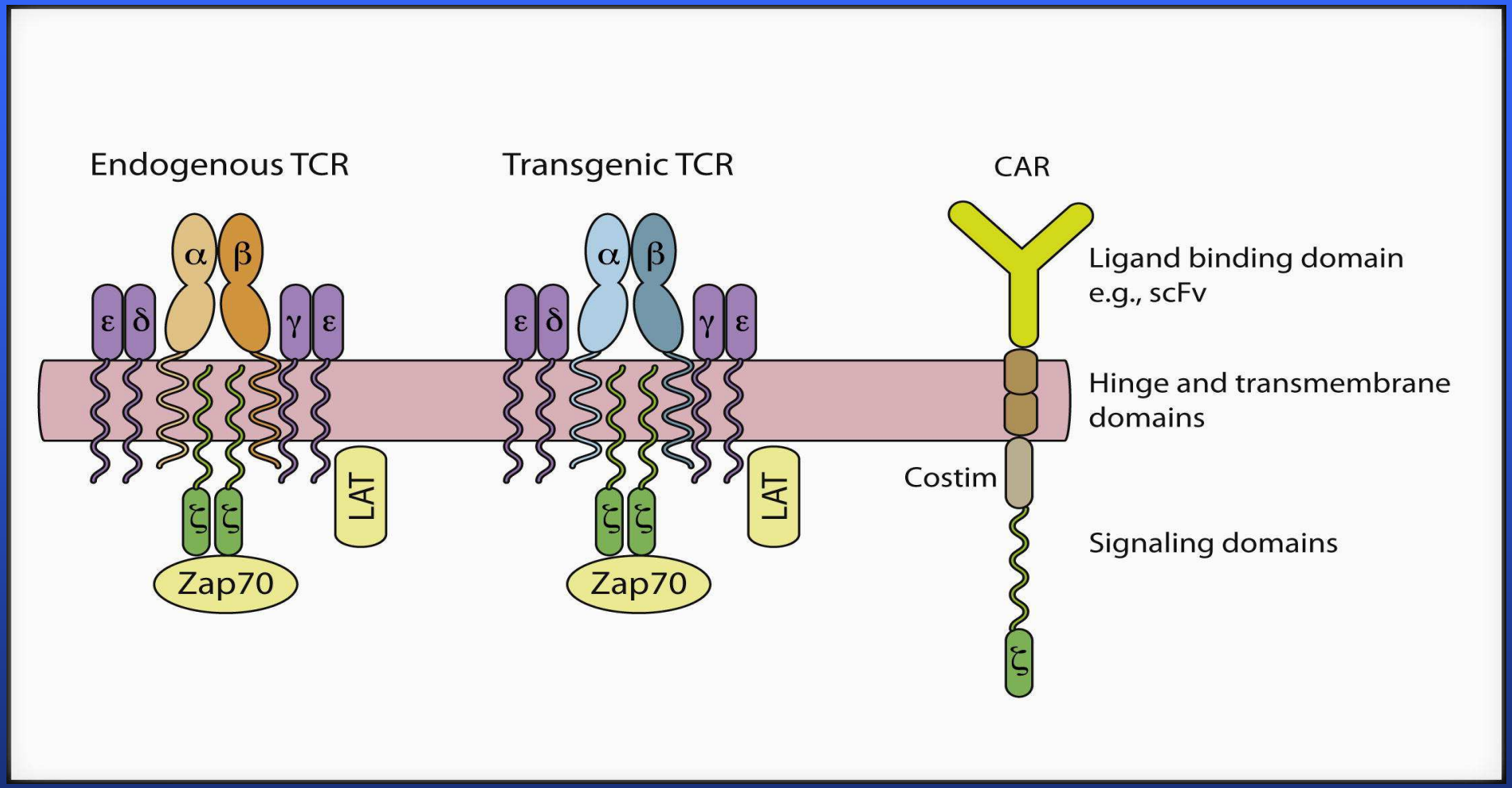
Besser M J et al. Clin Cancer Res 2013;19:4792-4800

Clinical Cancer Research

Adoptive therapy of mutation specific CD4 TIL cells in cholangiocarcinoma

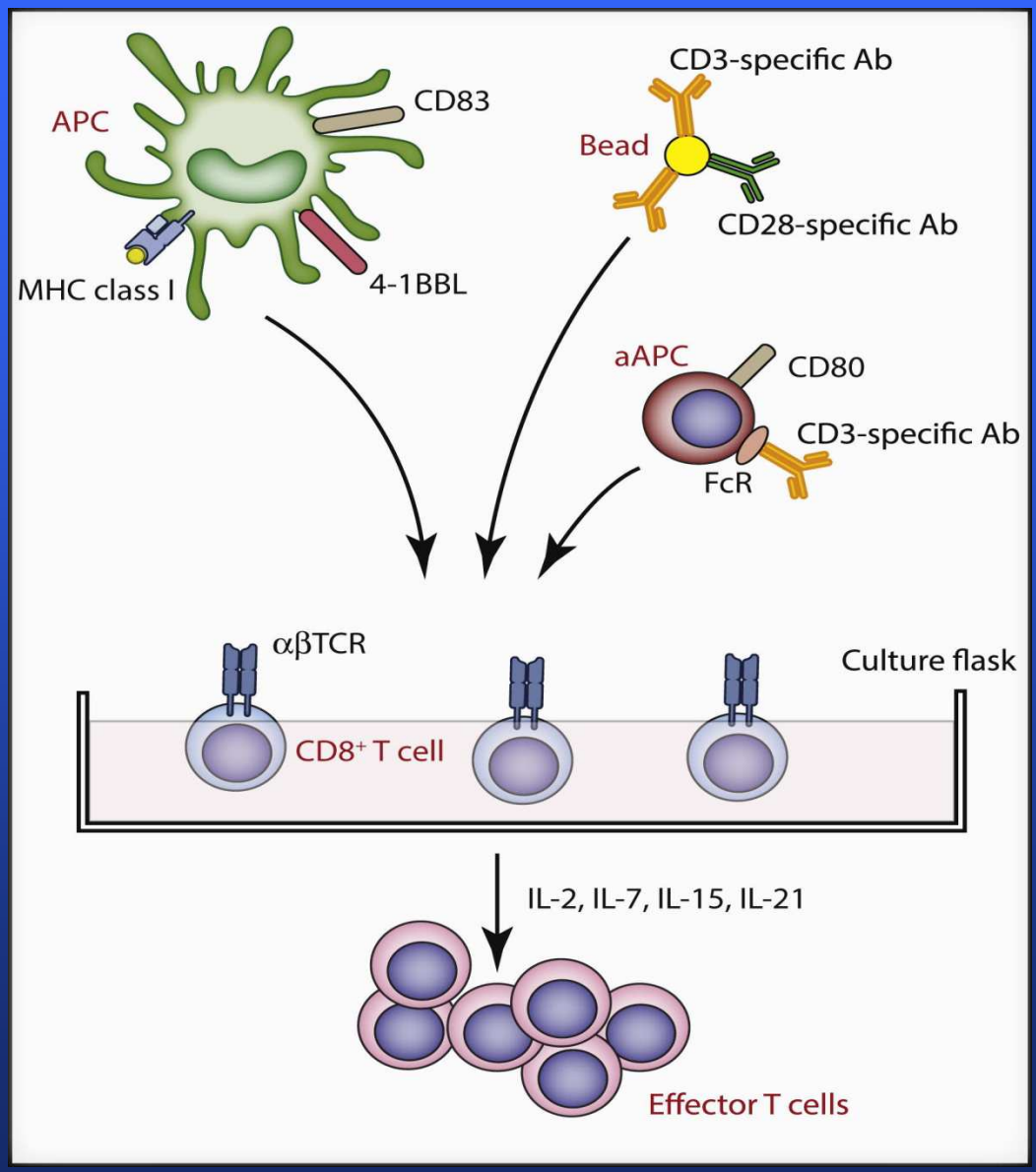
Tran, E. et al Science 2014

T cells, Transgenic T cells, and CARs



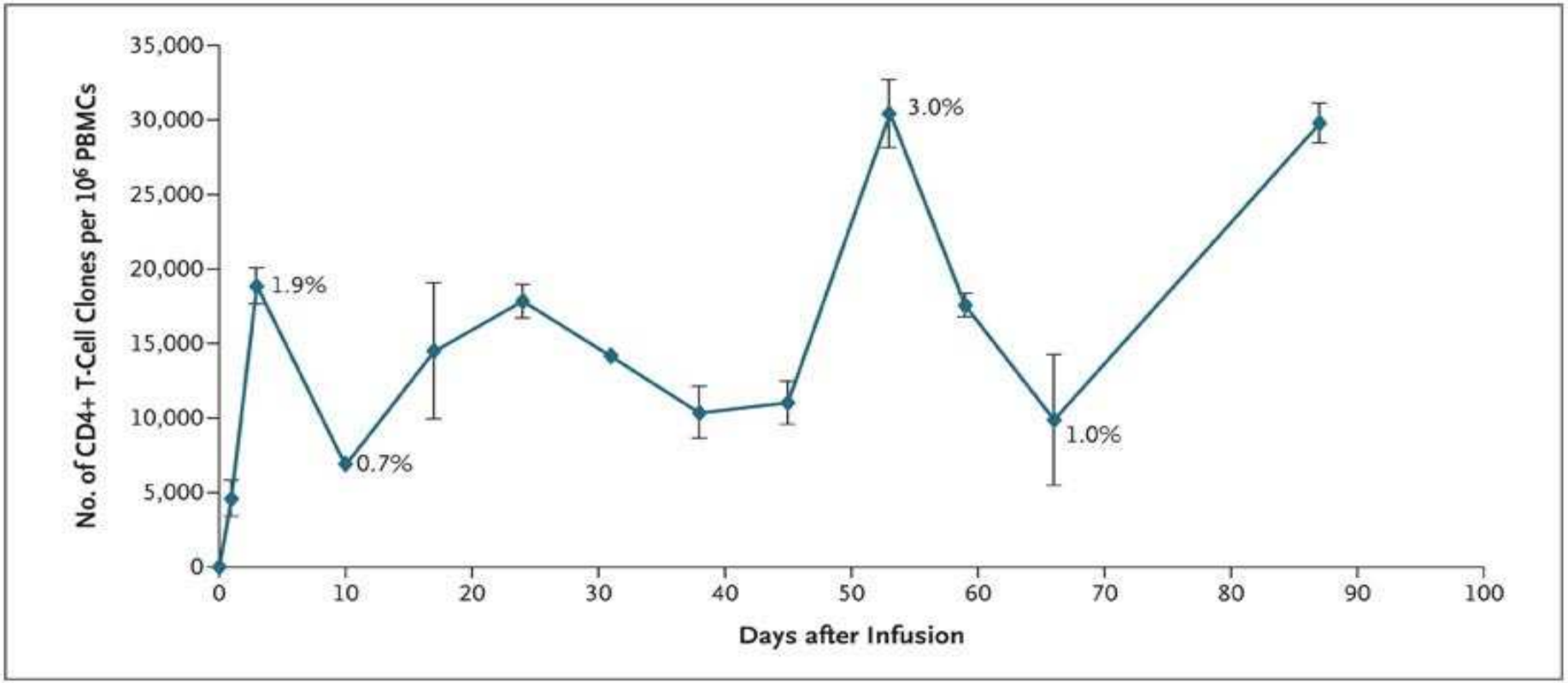
Immunity 2013 39, 49-60DOI: (10.1016/j.immuni.2013.07.002)

Different ways to grow and propagate T cells

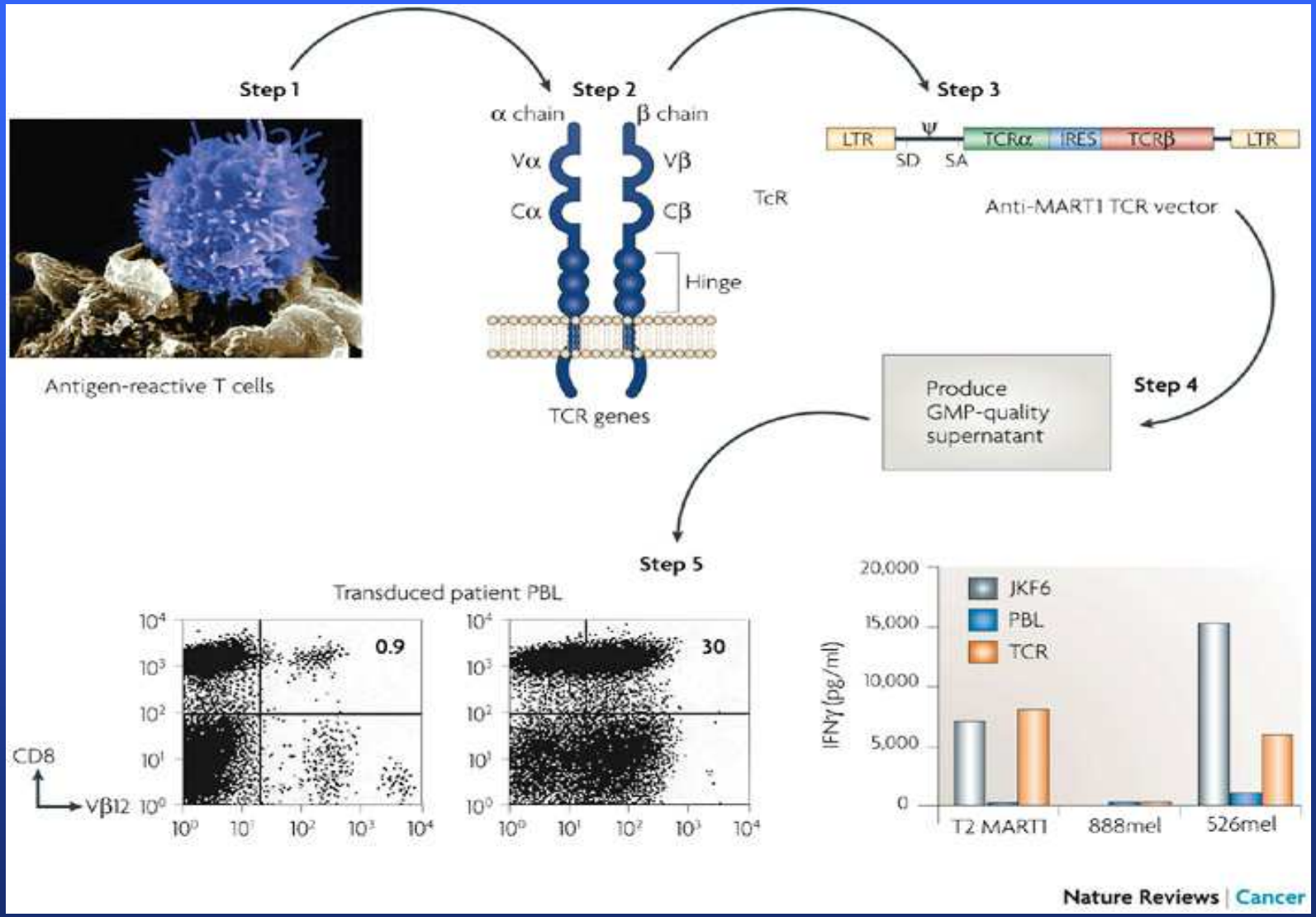


Immunity 2013 39, 49-60DOI: (10.1016/j.immuni.2013.07.002)

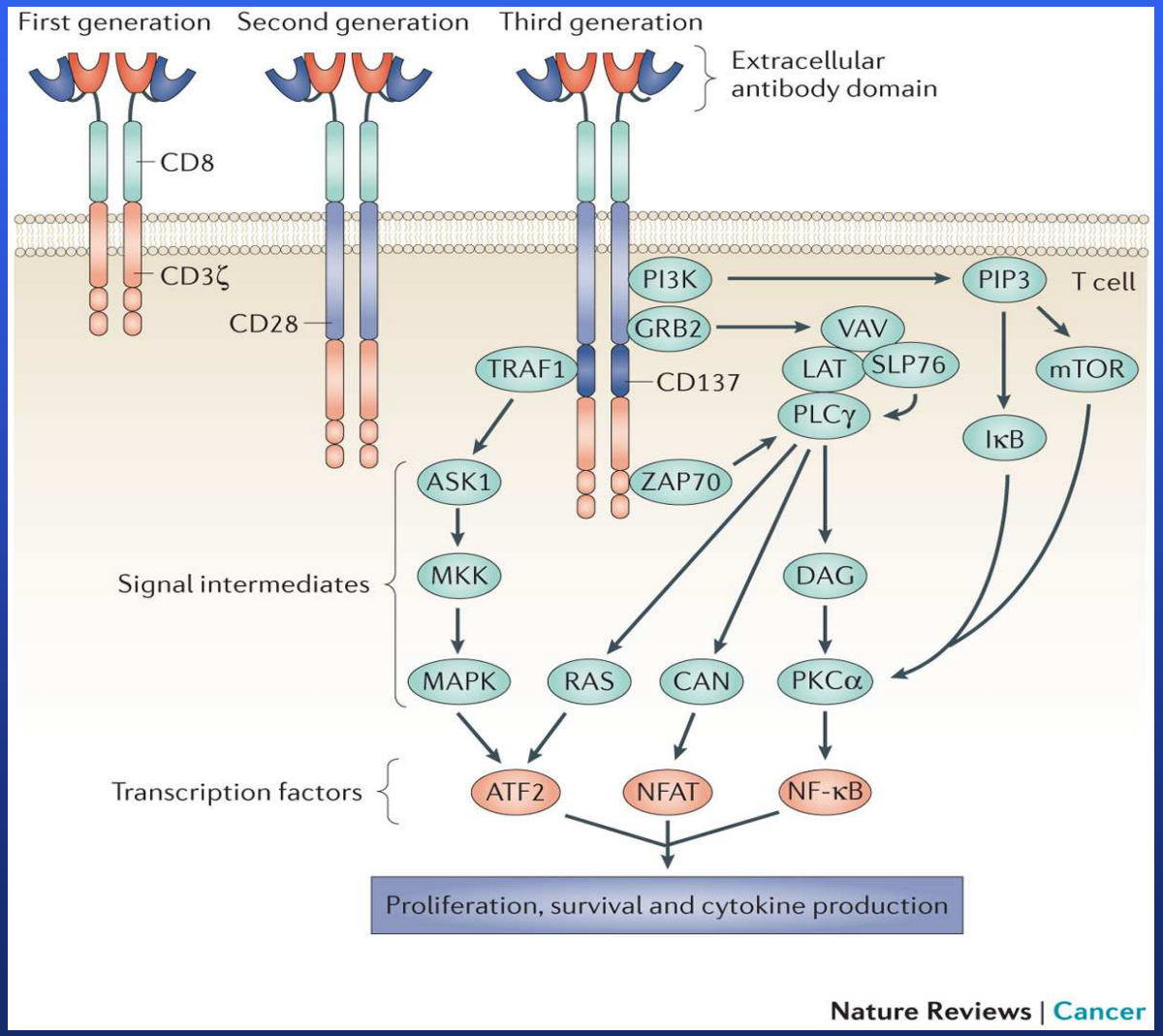
Persistence: NY-ESO-1 CD4 clones



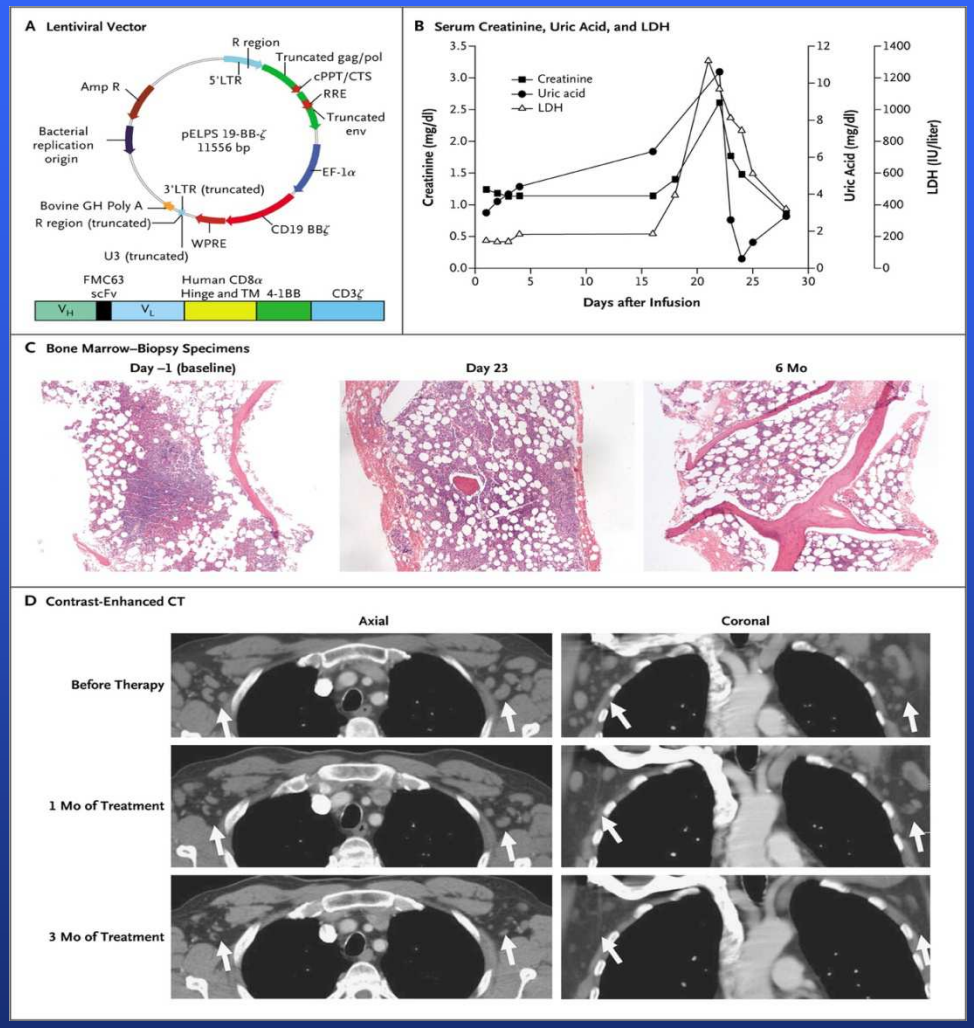
Transduced T cell receptor T cell therapy



Chimeric antigen receptor T cells (CARs) set off a complex signal cascade



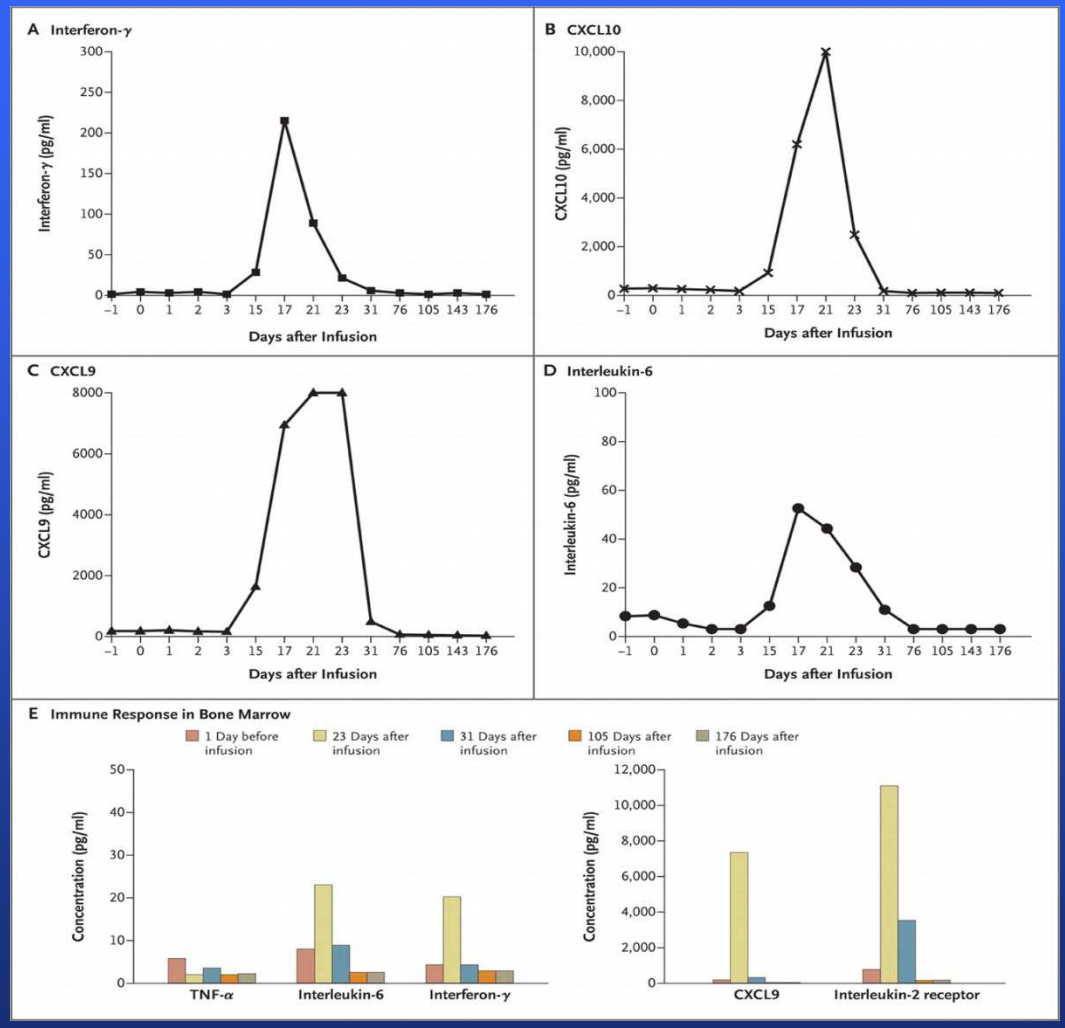
Clinical Response in a CLL Patient to a CD19 CAR



Porter DL et al. N Engl J Med 2011;365:725-733.

The NEW ENGLAND JOURNAL of MEDICINE

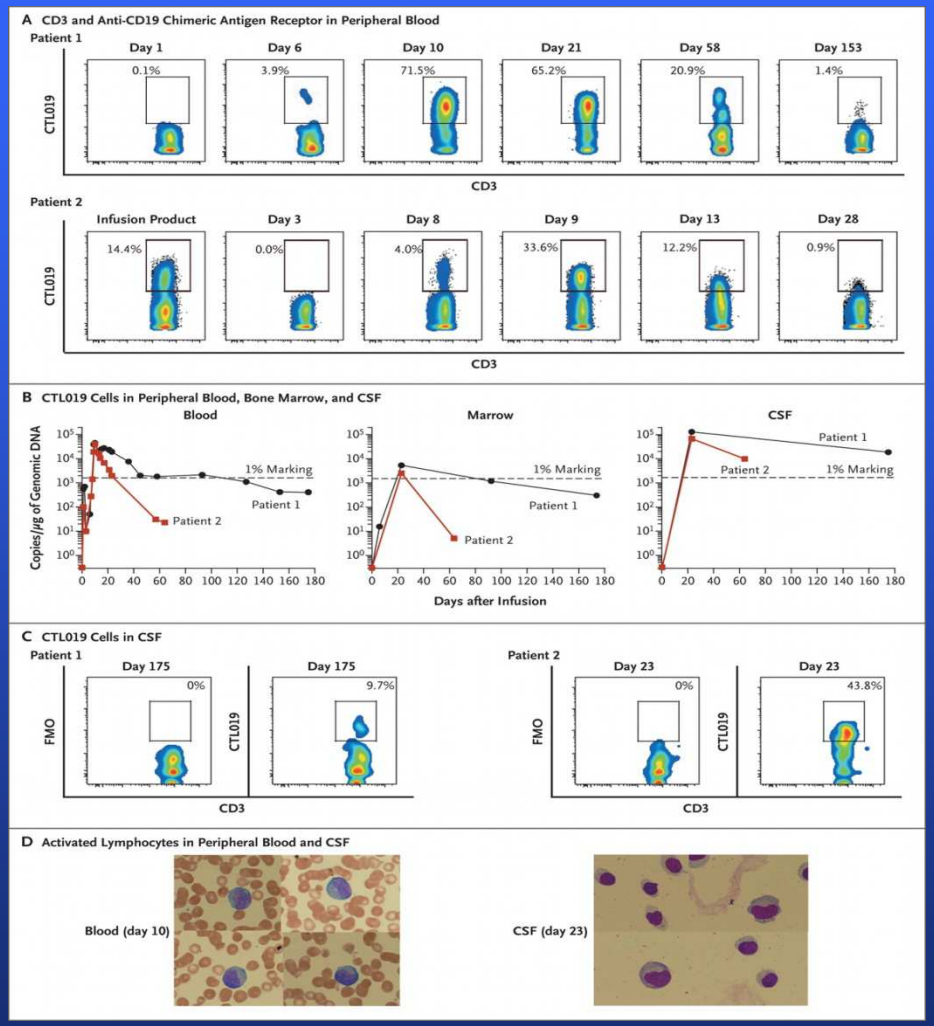
Serum and Bone Marrow Cytokines before and after Chimeric Antigen Receptor T-Cell Infusion in CLL



Porter DL et al. N Engl J Med 2011;365:725-733.

The NEW ENGLAND JOURNAL of MEDICINE

Expansion and Visualization of CTL019 CAR Cells in Peripheral Blood, Bone Marrow, and Cerebrospinal Fluid (CSF) of a treated ALL patient



Grupp SA et al. N Engl J Med 2013;368:1509-1518.

The NEW ENGLAND JOURNAL of MEDICINE

CARS: The good and the bad news

- There are 27 active trials in which CARs are being used against CD19
- Response rates are high in CLL, adult ALL, pediatric ALL
- Persistence of cells is important for therapy
- Cytokine storm featuring high levels of IL-6 complicate treatment
- CNS symptoms, high fevers and hypotension have been a problem

Conclusions:

- > 50% objective response rates have been seen after lympho-depleting conditioning regimen prior to adoptive cell transfer with TIL, and after CAR transfer without lymphodepletion
- Robust long-term persistence of the adoptively transferred cells seen
- Multiple homeostatic mechanisms regulate the number and functional status of T-cell lymphocytes in a normal host
- Lymphopenia creates selective advantage for some populations of T cells, eliminating regulatory T cells and competing cell populations (‘cytokine sinks’)
- Chimeric anti-CD19 T cell receptor transduced peripheral blood cells are very active in ALL, CLL, but have potential toxicity