ImmunoRad

The INTERNATIONAL CONFERENCE ON IMMUNOTHERAPY RADIOTHERAPY COMBINATIONS

Paris, September 21, 2018

Adaptive T cell immunity: from the basics to the clinic

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T cell responses against solid tumors

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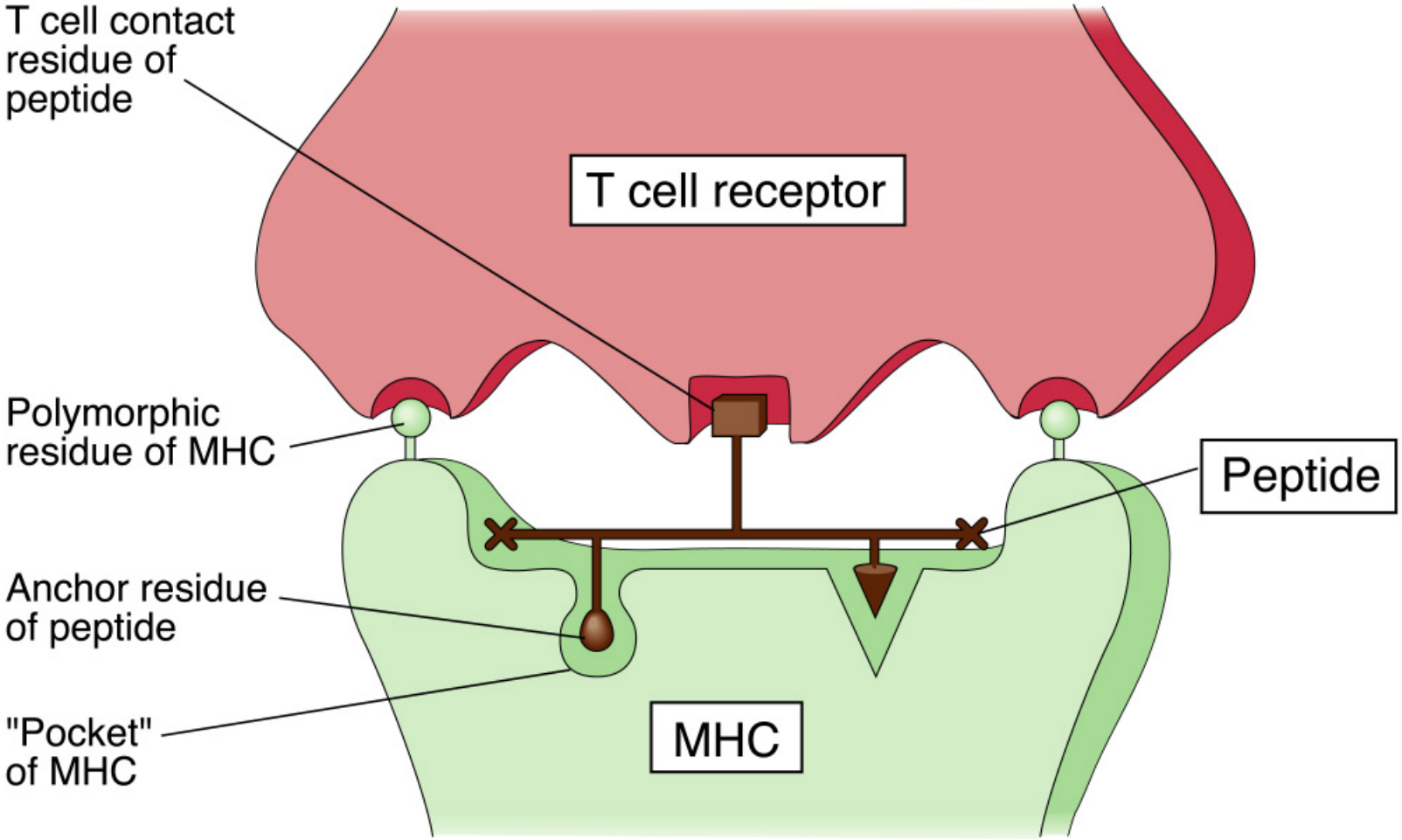
T Cell recognition of a peptide-MHC complex

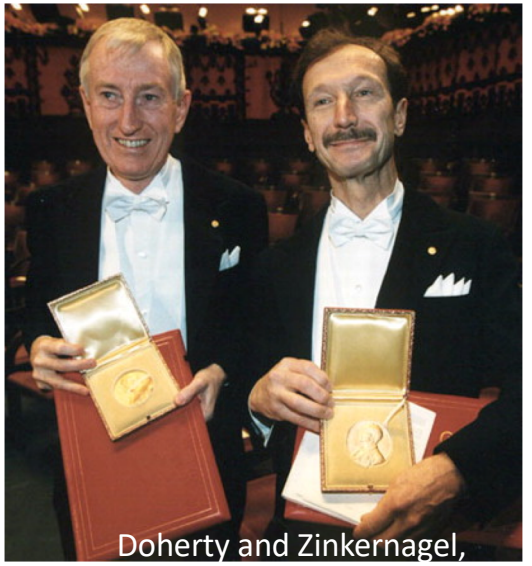


From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 4-1

An historical perspective

In 1973, Zinkernagel and Doherty discover the phenomenon of MHC restriction of antiviral responses. (MHC structure solved in 1987)

In late 1982 and early 1983 groups led by Jim Allison, Ellis Reinherz, and John Kappler and Philippa Marrack, identified the TCR protein.


Doherty and Zinkernagel,

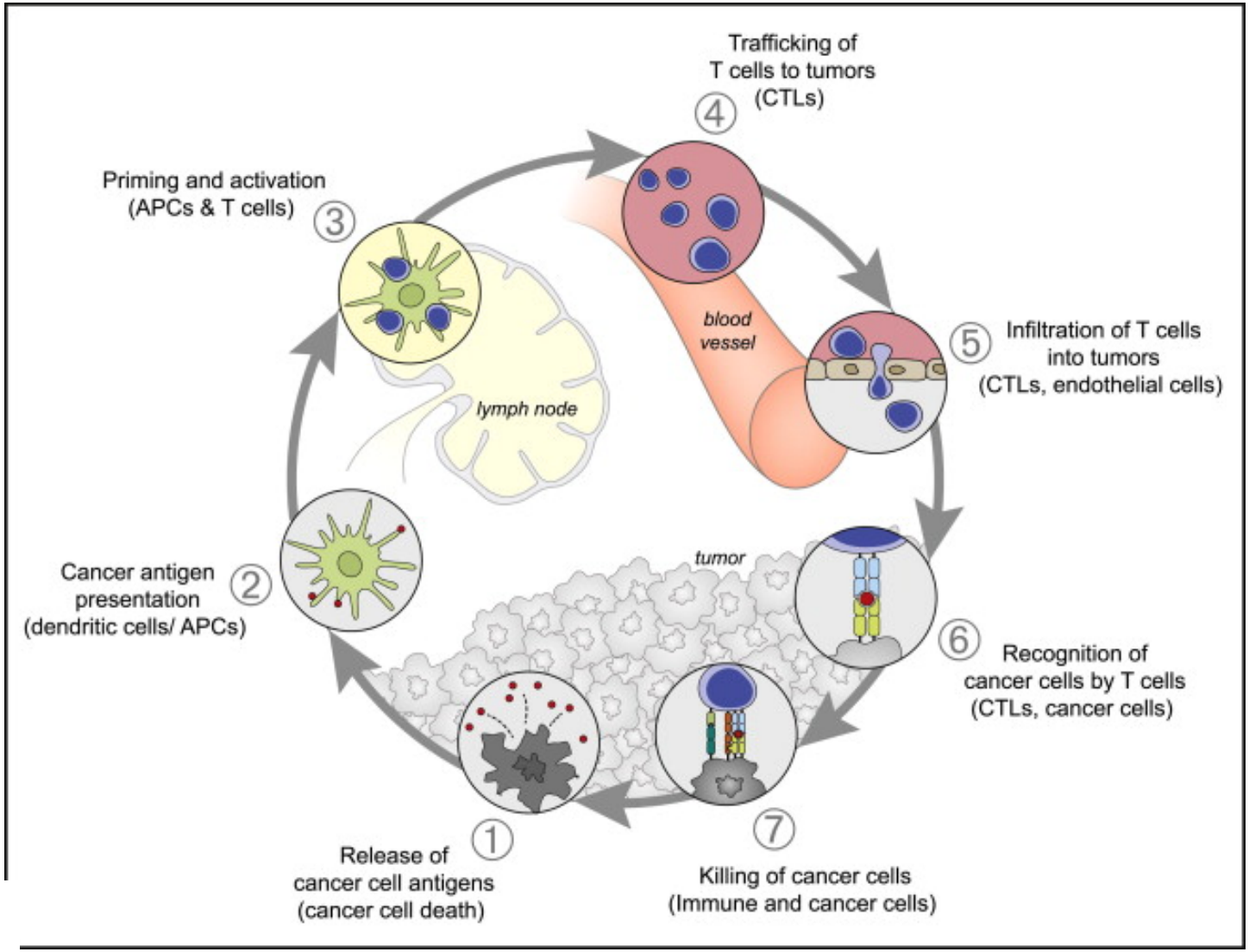
In 1984 Steve Hedrick and Mark Davis (as postdoctoral fellows) identified a cDNA clone for mouse TCR–beta chain and Tak Mak the human TCR –beta chain (Nature articles). Later M. Davis identified the alfa chain.

In 2002 first two clinical trails in human of adoptive T cell therapy (Dudley, Morgan, Rosenberg, NIH)

In 2008 first patient treated with TCR engineered T cell (Rosenberg, S NIH)

"T-cells are a living drug, as they have the potential to persist in our body for our whole lives."

Critical issues in T-cell therapy of solid tumors



Daniel S. Chen, Ira Mellman **Oncology Meets Immunology: The Cancer-Immunity Cycle**
http://dx.doi.org/10.1016/j.immuni.2013.07.012

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Solid Tumors from an immunological perspective

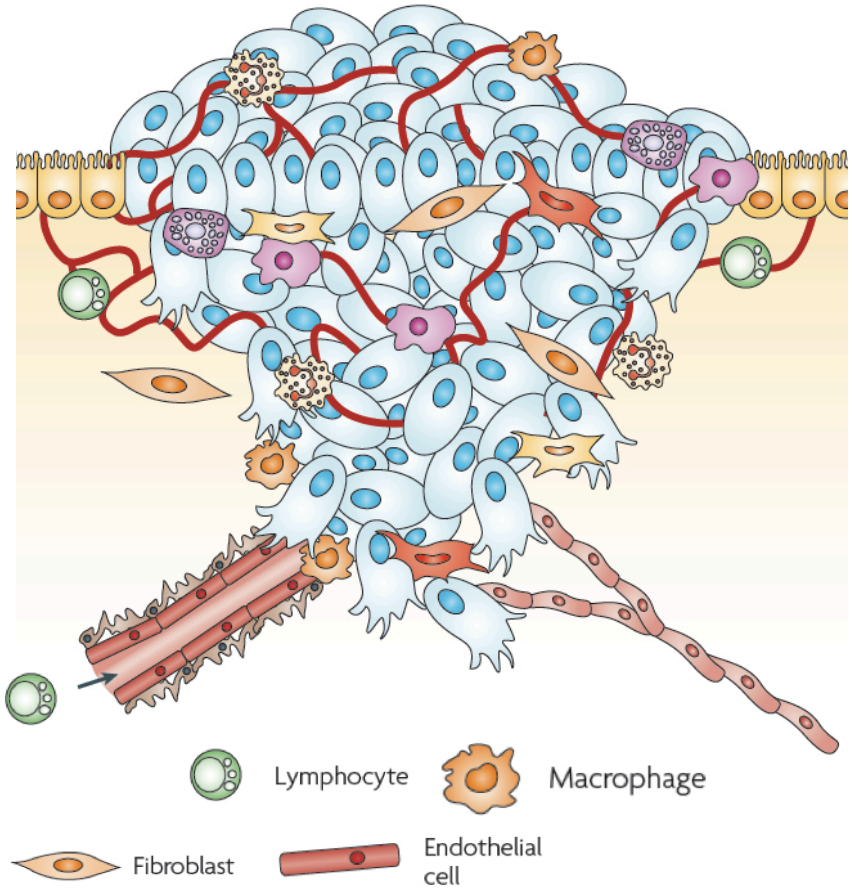
Arise from “self”
(central tolerance)

Often lack pro-inflammatory signals
(peripheral tolerance)

Are diverse
(intra and inter-tumoral variations)

Are immunologically smart

Are not “just” Tumor: the stroma



Adjusted from Joyce & Pollard, Nature Reviews Cancer 2009

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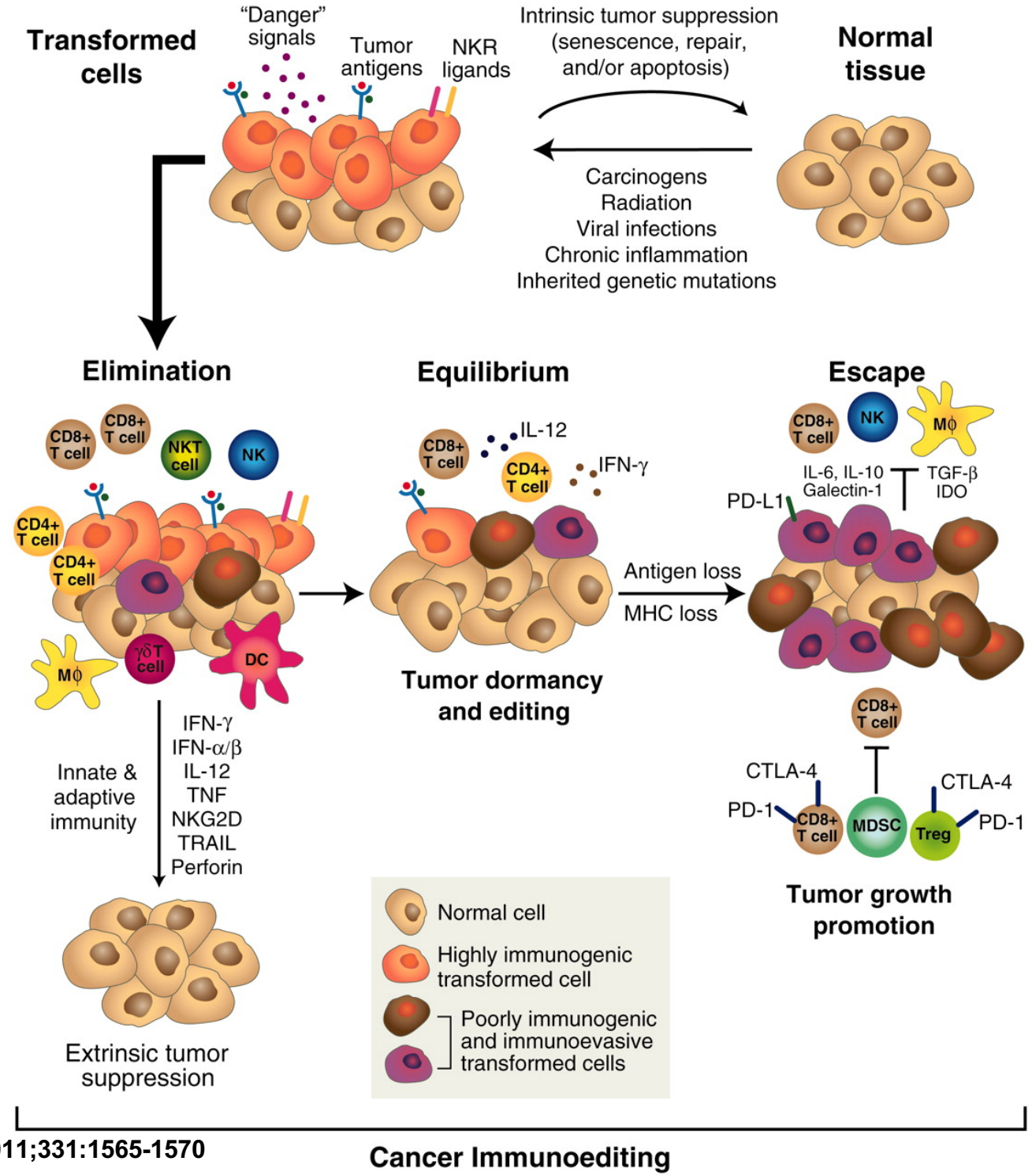
The 3Es of immunotherapy and immunoediting



R D Schreiber et al. Science 2011;331:1565-1570

Tumour Immunonity/immunotherapy: possible?

"It would be as difficult to reject the right ear and leave the left ear intact, as it is to immunize against cancer."

W.H.Woglom, *Cancer Research* (1929)

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Which is the ideal Ag to be targeted?

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Candidate target antigens for T cell treatment

should preferably fulfill the following criteria

- be selectively expressed in tumors and not in normal tissues (tumor specificity; neo-antigens, oncoviral and cancer germline antigens);
- be related to oncogenesis (tumor addiction); true driver mutations cover only a fraction of the total number of mutations (estimated at most at 15%), and only a small fraction of mutations constitutes predicted T cell epitopes (about 1%);
- be able to evoke a T cell response (immunogenicity).

Nature of tumor-associated antigens

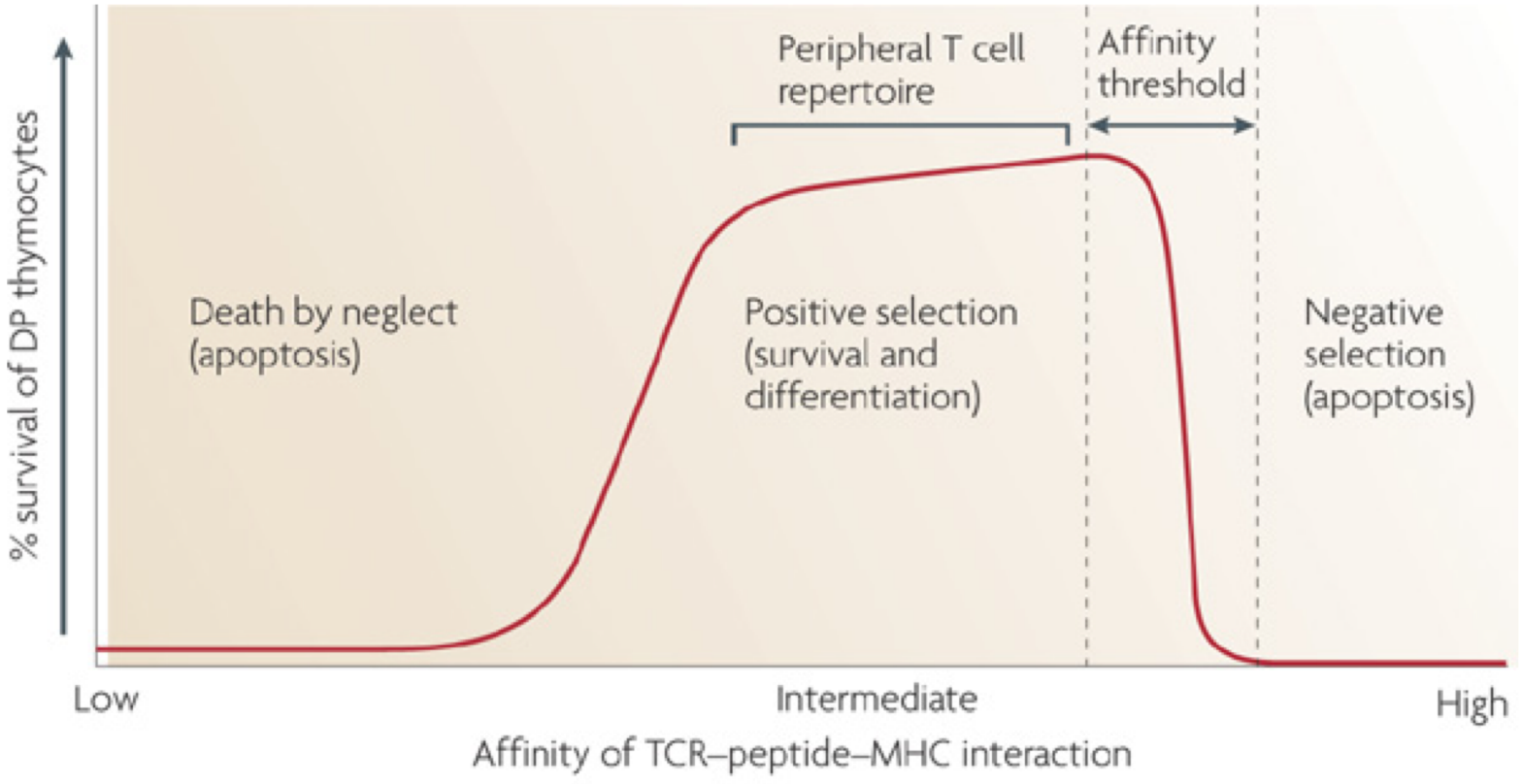
TABLE 17–1 Tumor Antigens

Type of Antigen	Examples of Human Tumor Antigens
Products of mutated oncogenes, tumor suppressor genes	Oncogene products: Ras mutations (~10% of human carcinomas), p210 product of Bcr/Abl rearrangements (CML) Tumor suppressor gene products: mutated p53 (present in ~50% of human tumors)
Unmutated but overexpressed products of oncogenes	HER2/Neu (breast and other carcinomas)
Mutated forms of cellular genes not involved in tumorigenesis	Various mutated proteins in melanomas recognized by CTLs
Products of genes that are silent in most normal tissues	Cancer/testis antigens expressed in melanomas and many carcinomas; normally expressed mainly in the testis and placenta
Normal proteins overexpressed in tumor cells	Tyrosinase, gp100, MART in melanomas (normally expressed in melanocytes)
Products of oncogenic viruses	Papillomavirus E6 and E7 proteins (cervical carcinomas) EBNA-1 protein of EBV (EBV-associated lymphomas, nasopharyngeal carcinoma)
Oncofetal antigens	Carcinoembryonic antigen on many tumors, also expressed in liver and other tissues during inflammation α-Fetoprotein
Glycolipids and glycoproteins	GM_2, GD_2 on melanomas
Differentiation antigens normally present in tissue of origin	Prostate-specific antigen in prostate carcinomas CD20 on B cell lymphomas

CML, chronic myelogenous leukemia; CTL, cytotoxic T lymphocyte; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; MART, melanoma antigen recognized by T cells.

T cells are generated in the thymus

- *positive and negative selection*



Nature Reviews | Immunology

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Which is the affinity of tumor-specific TCR?

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Which is the affinity of tumor-specific TCR?

T cells specific for mutated self antigens/product of oncovirus

High affinity

T cells specific for non mutated self antigens-TCR affinity

Low affinity

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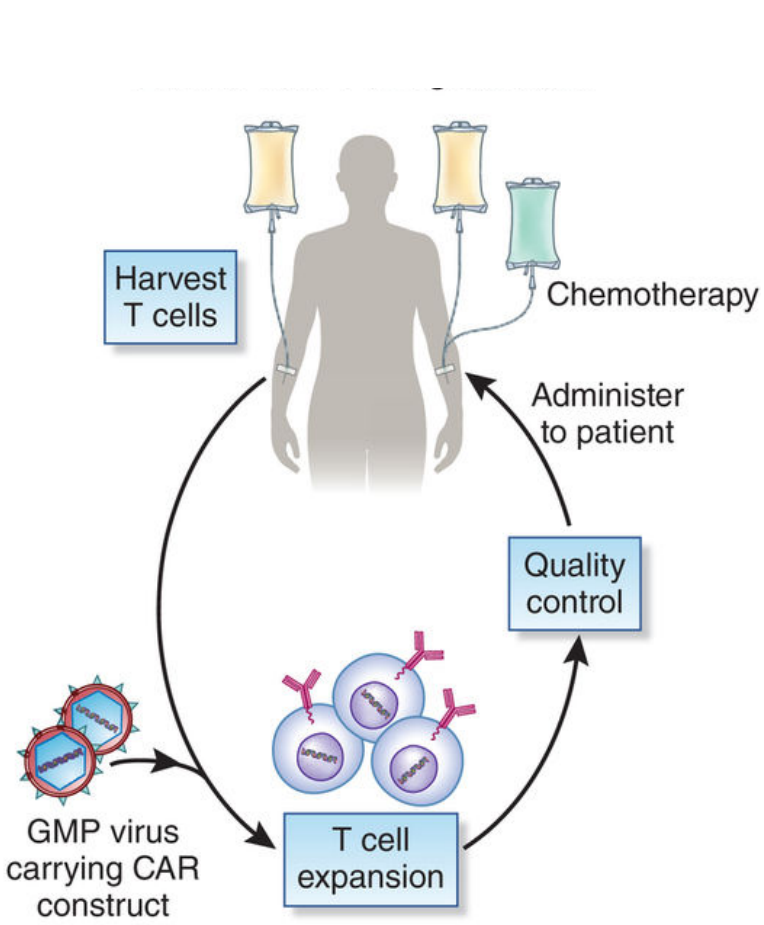
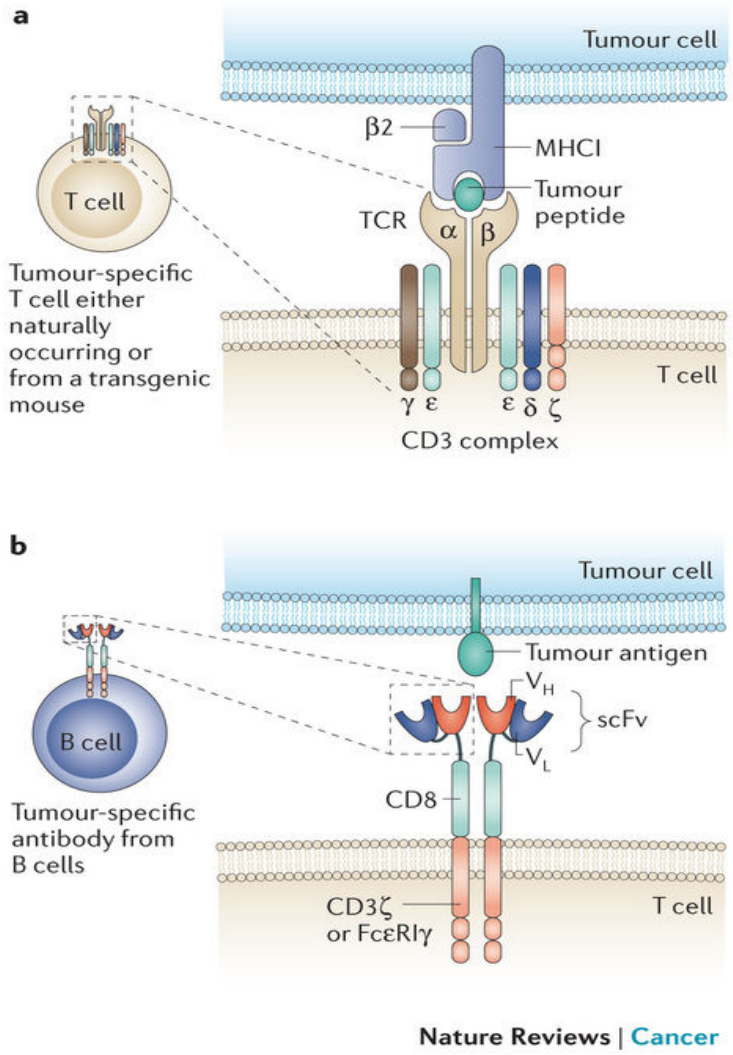
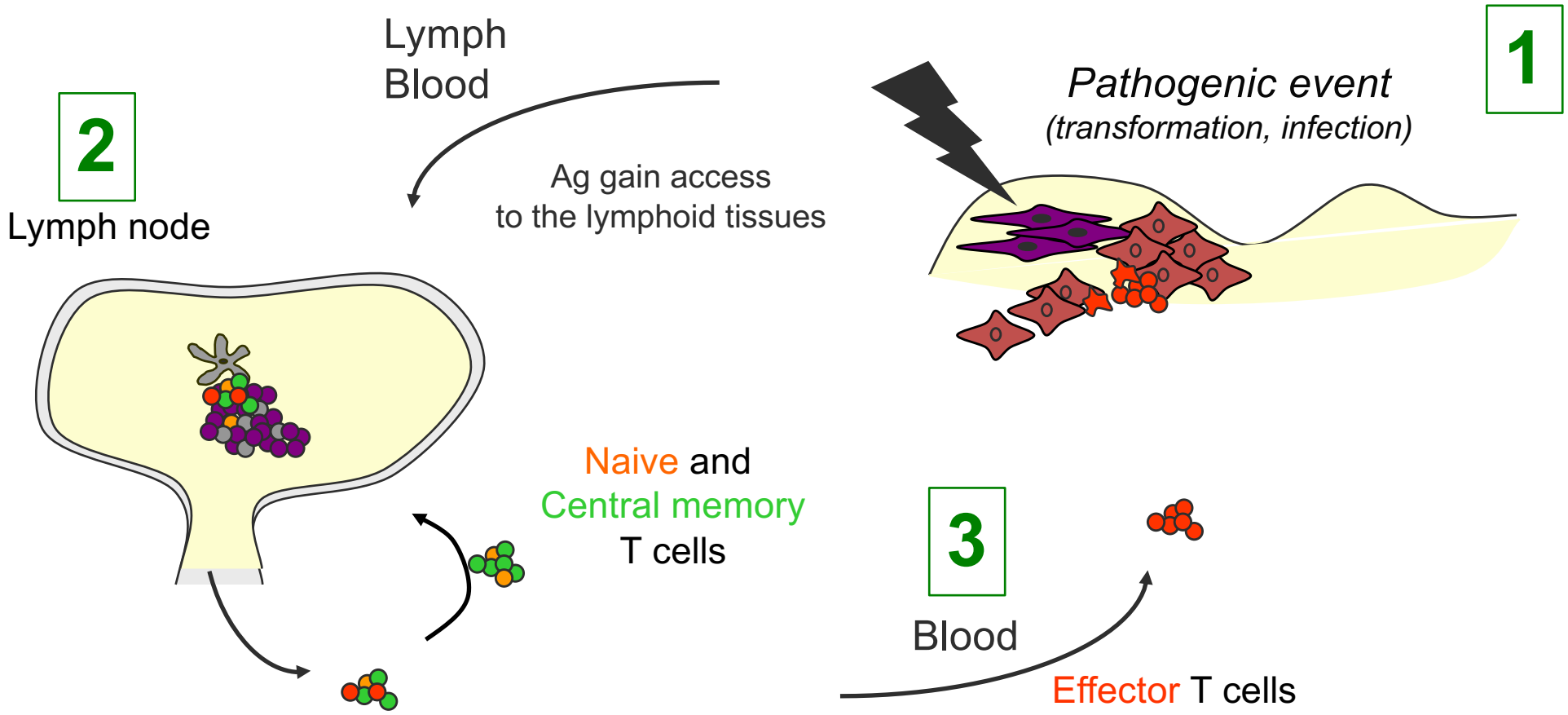
T cells engineering: TCR and CAR





•*Nature Reviews Cancer* **13**, 525–541 (2013)

T cell therapy of solid tumor: an anatomical perspective



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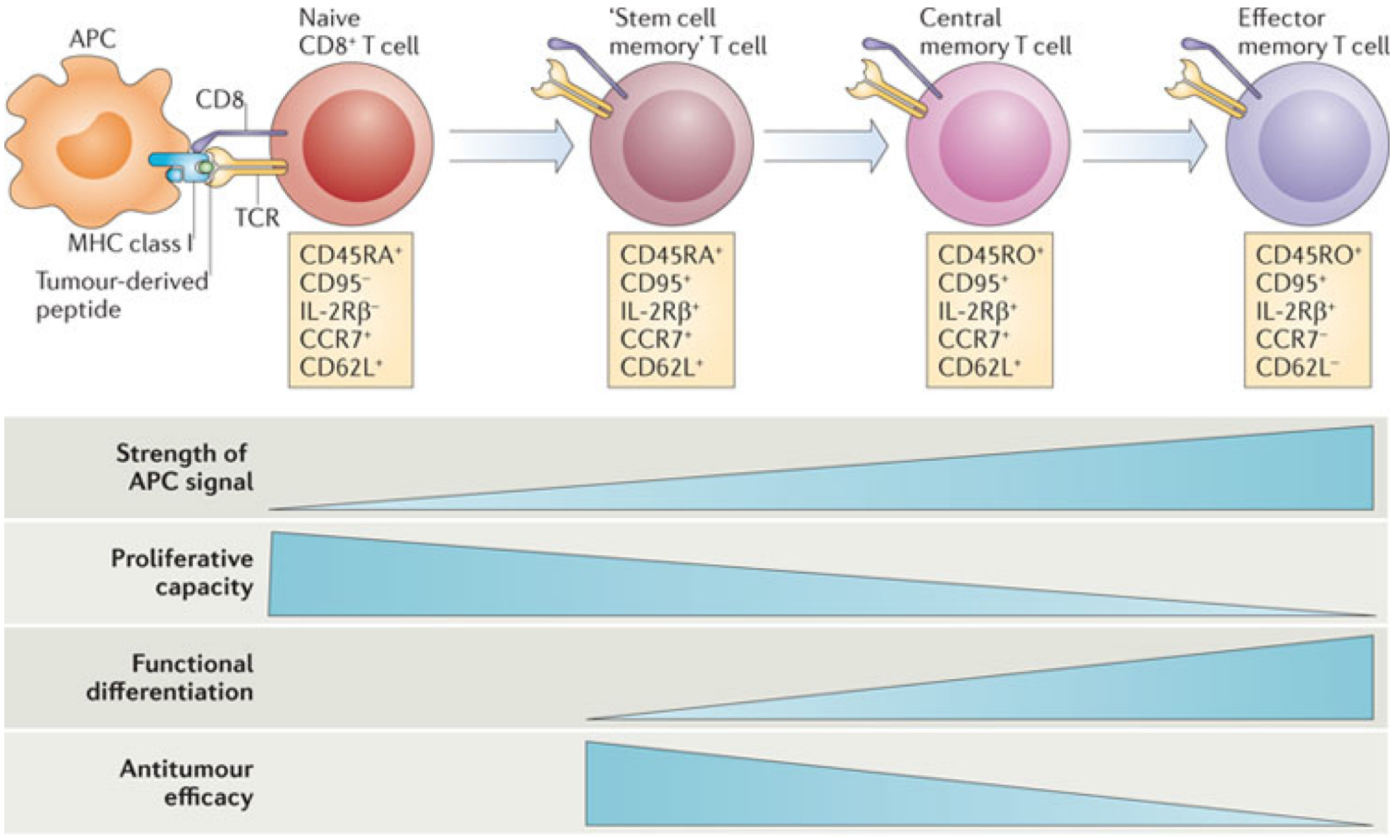
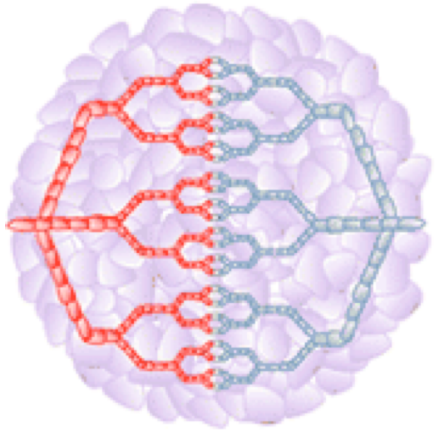
Understanding and exploiting T cells

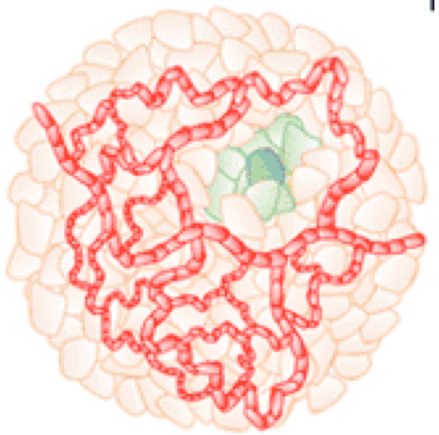


Nicholas P. Restifo, Mark E. Dudley & Steven A. Rosenberg
Nature Reviews Immunology 12, 269-281 (April 2012)

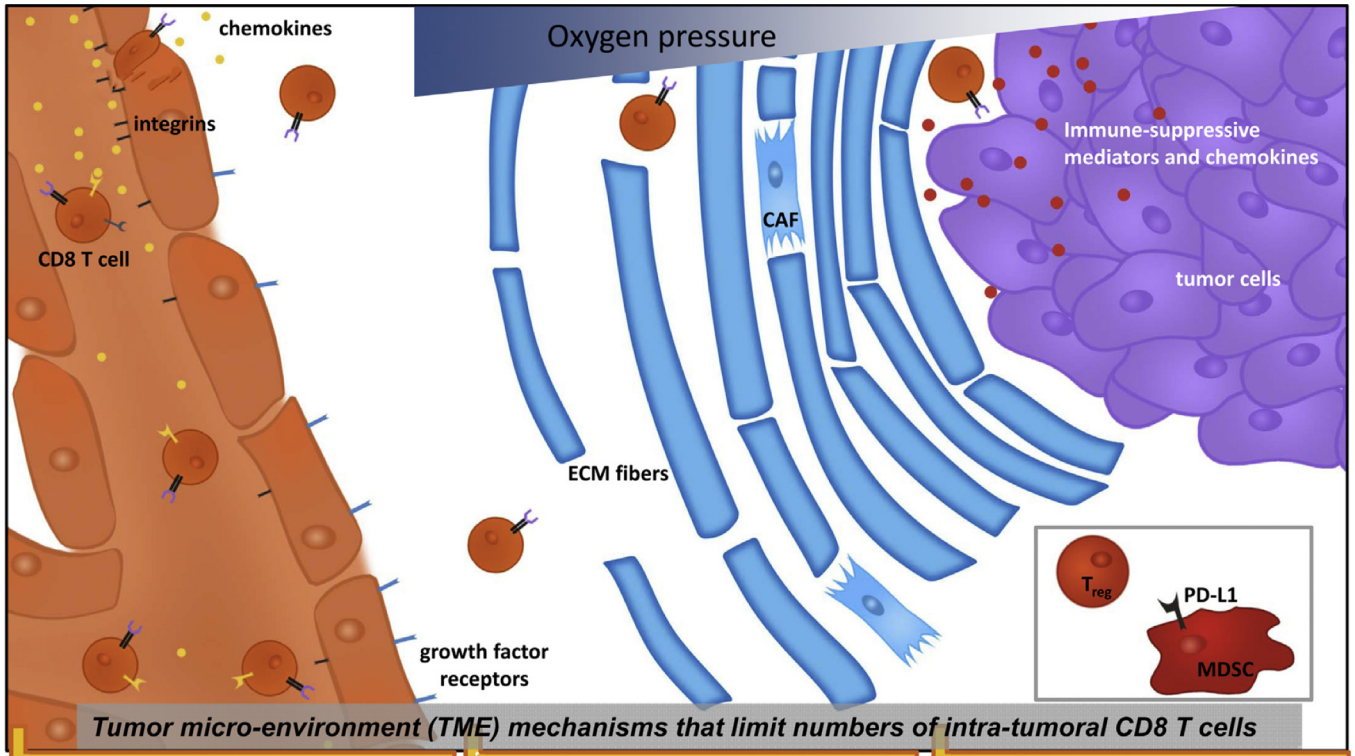
The Tumor vasculature and the TME limit intra-tumoral infiltration



Normal vasculature



Tumor vasculature

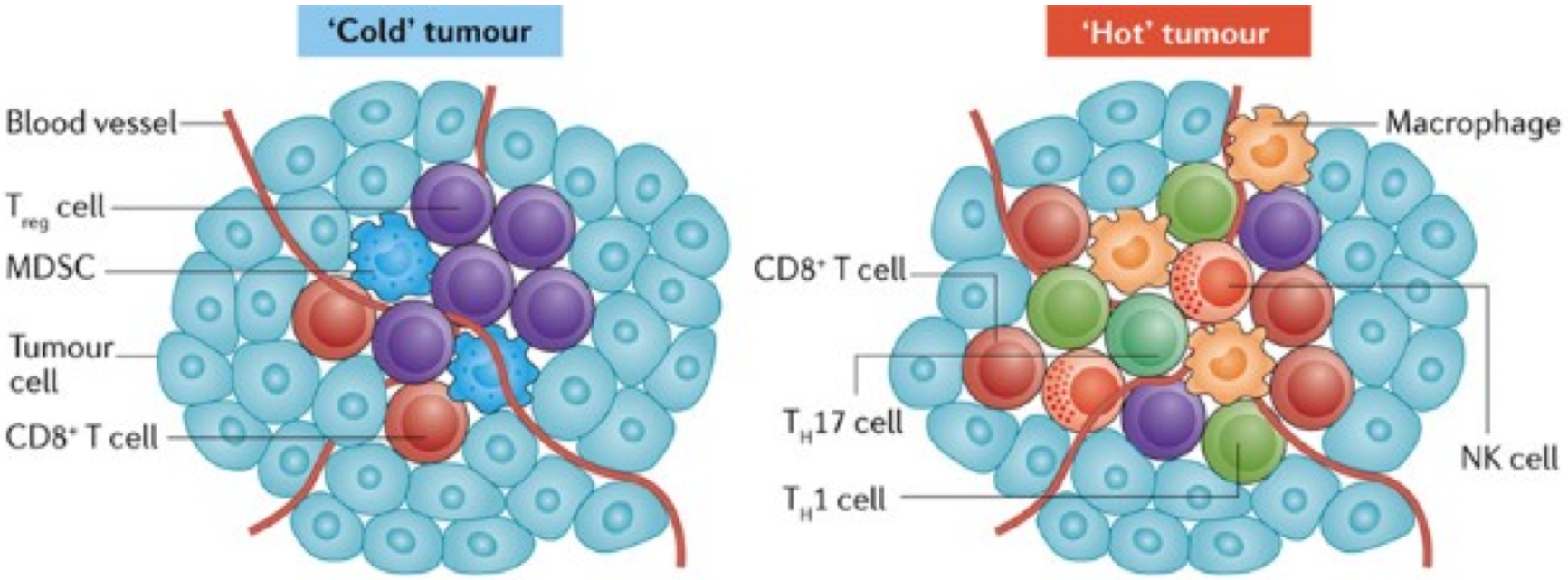


Tumor micro-environment (TME) mechanisms that limit numbers of intra-tumoral CD8 T cells

Attraction and entry of T cells	Migration of T cells	Local activation of T cells
• Limited availability of chemokines (CCL2, CXCL9, 10) • Limited expression of adhesion molecules (ICAM1) • Phenotype of endothelial cells to disengage CD8 T cells (PDL1, B7H3, ET(B)R, FasL)	• Increased density of ECM • Shielding of tumor cells (CXCL12) • Enhanced recruitment and activation of Tregs and MDSC (CCL3)	• Induction of abnormal vessels (HIF) • Limited activation of CD8 T cells related to Nanog and TGFβ; limited activation of DC (VEGF) • Enhanced recruitment and activation of Tregs and MDSC (via PD-L1)

TCR-engineered T cells to treat tumors: Seeing but not touching?
Seminars in Immunology, Volume 28, Issue 1, 2016, 10–21 Reno Debets, Emmanuel Donnadieu, Salem Chouaib, George Coukos

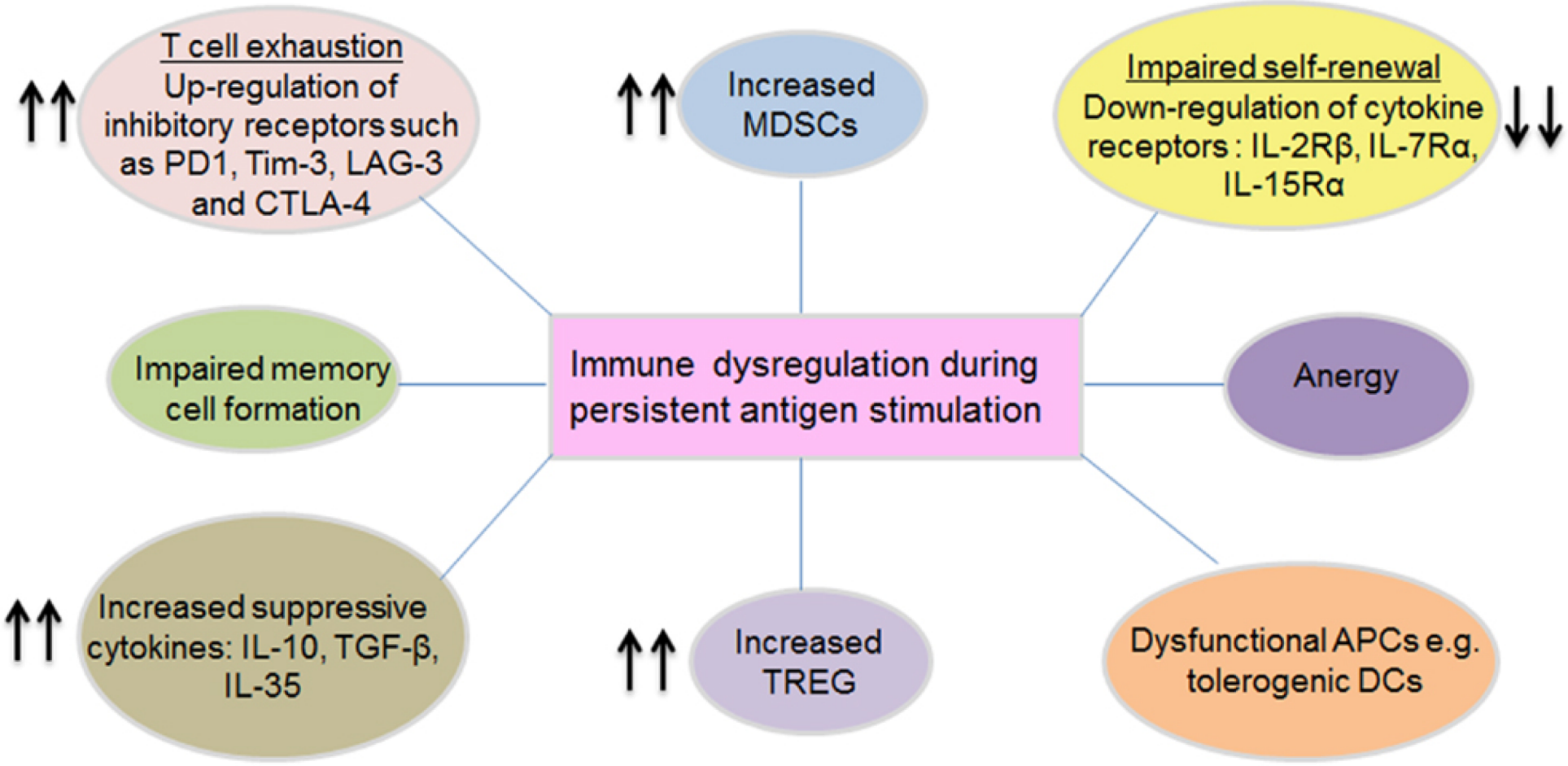
Intra-tumoral infiltration/T cell representation: a critical issue



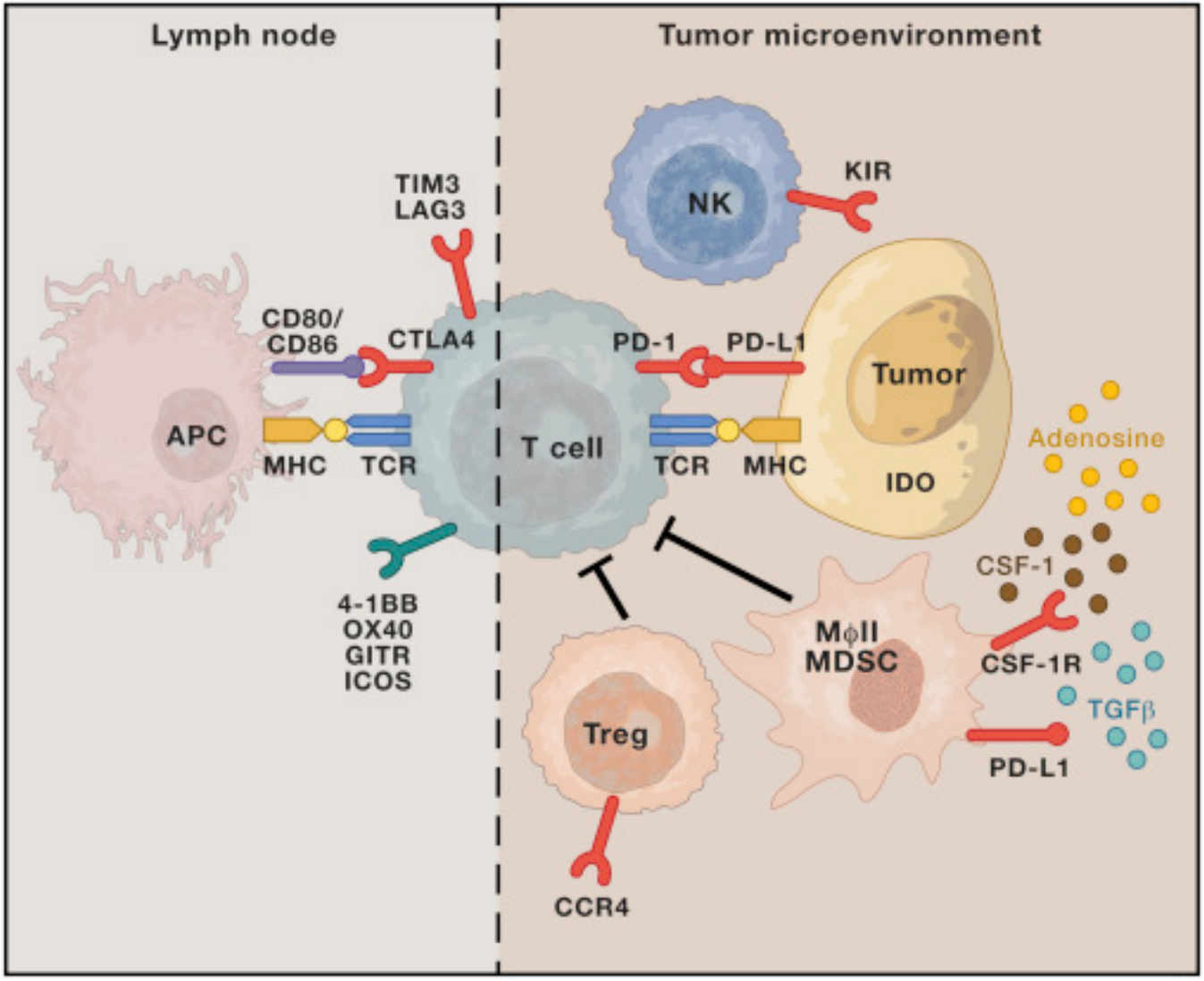
- Efficacy of IT
- Efficacy of Immune checkpoint blockers

Modified from Nagarsheth, Nat Rev Immunol 2017

Mechanisms of tumor escape



Mechanisms of tumor escape



Padmanee Sharma, Siwen Hu-Lieskovan, Jennifer A. Wargo, Antoni Ribas

Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy http://dx.doi.org/10.1016/j.cell.2017.01.017

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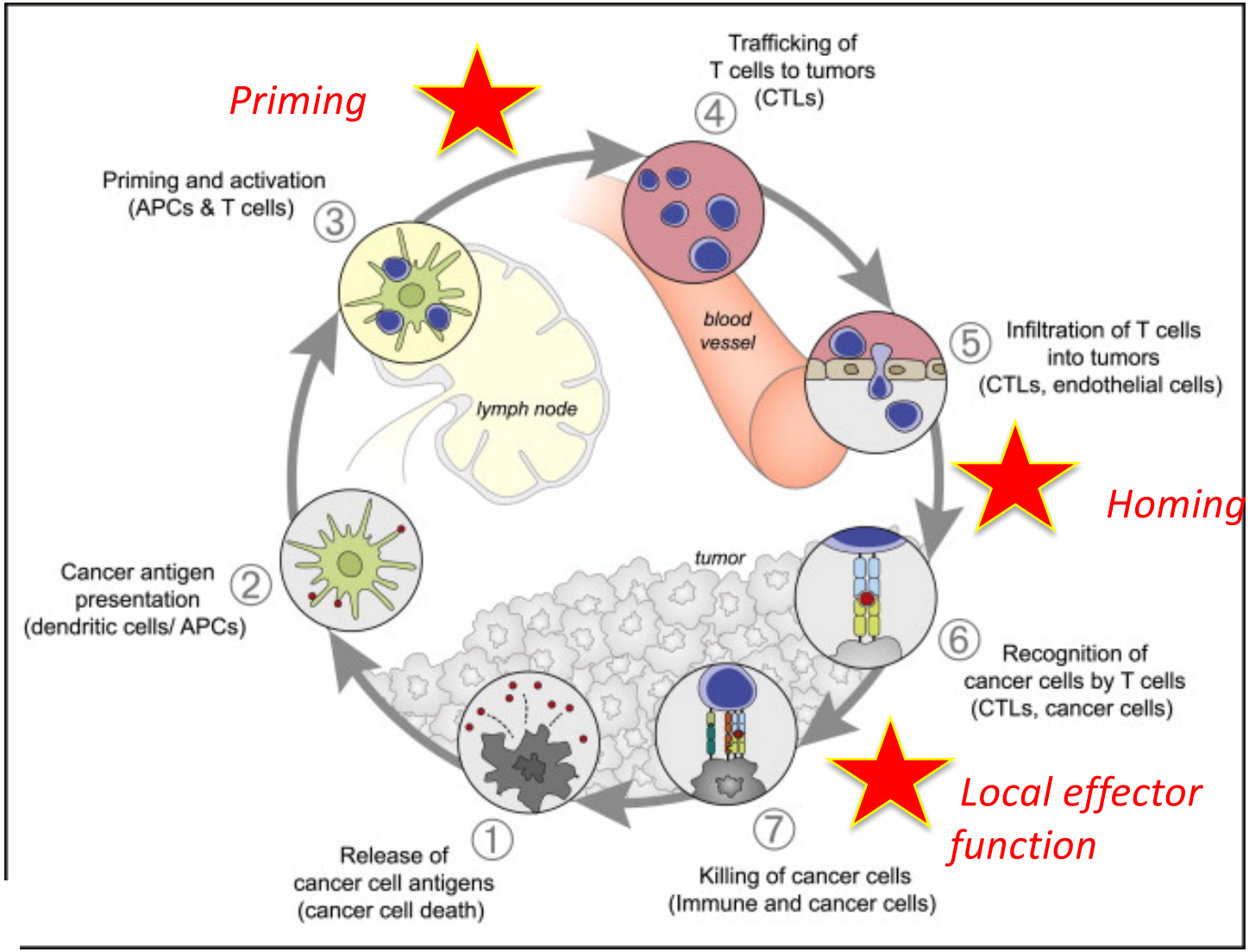
Critical issues in T-cell mediated tumor rejection



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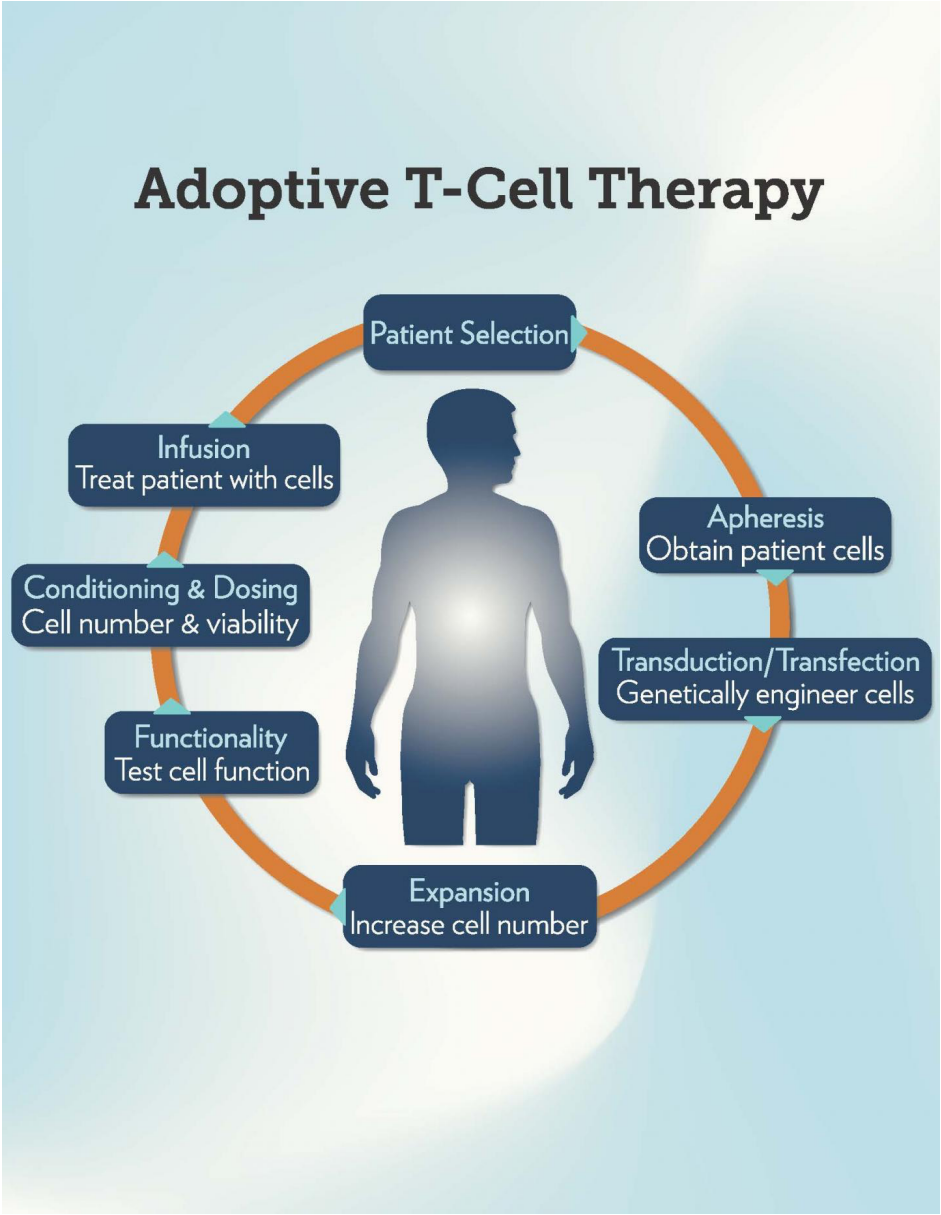
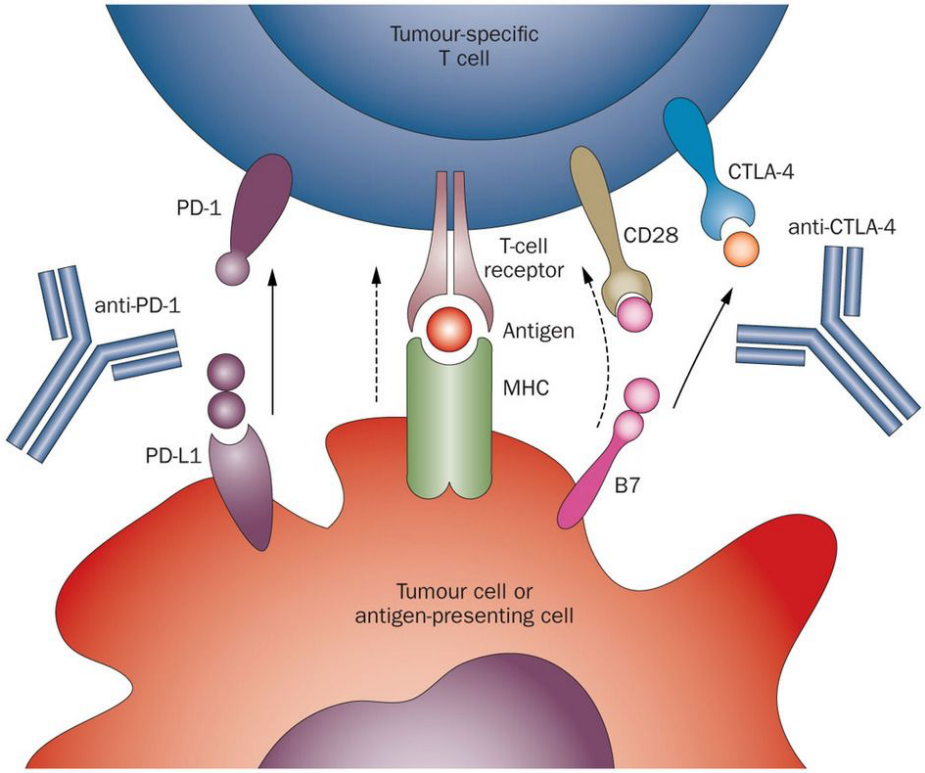
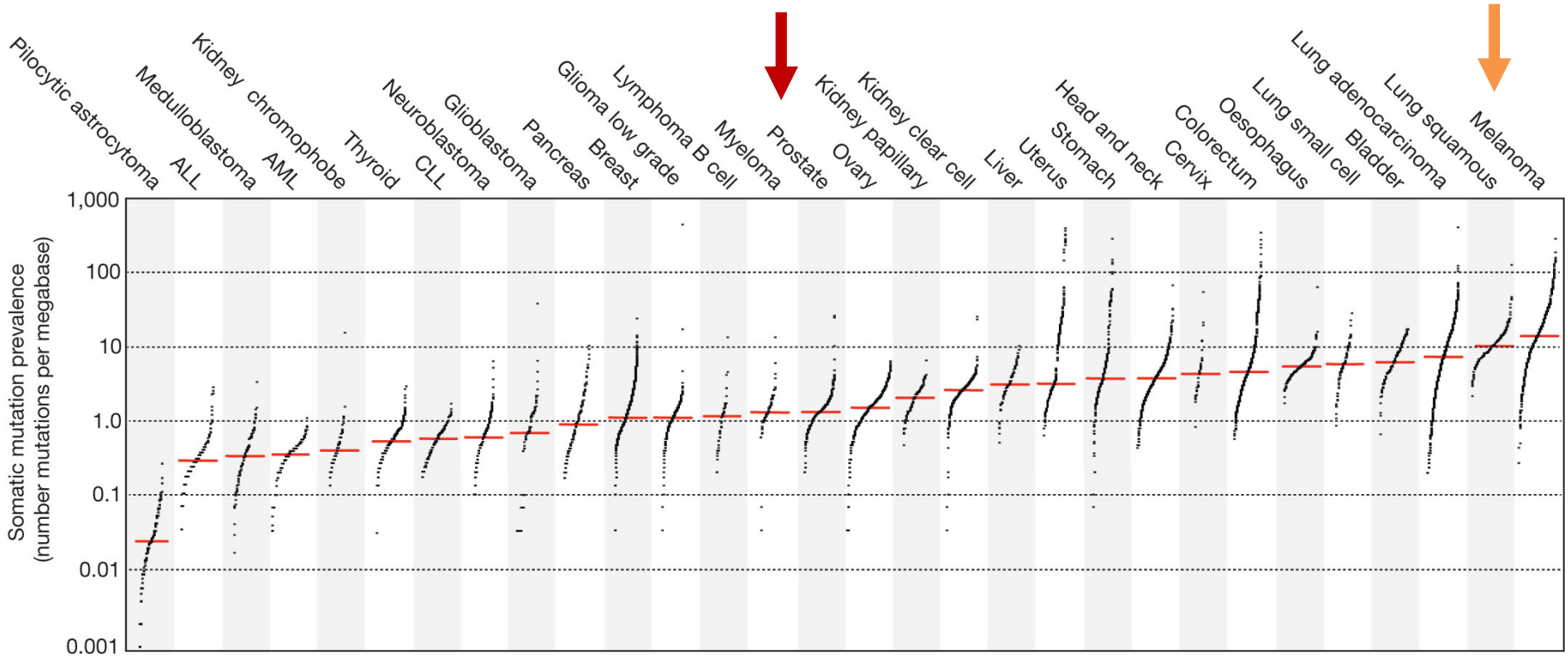

Adoptive T-Cell Therapy
Patient Selection
Apheresis
Obtain patient cells
Transduction/Transfection
Genetically engineer cells
Expansion
Increase cell number
Functionality
Test cell function
Conditioning & Dosing
Cell number & viability
Infusion
Treat patient with cells


Tumour-specific
T cell
PD-1
CTLA-4
CD28
anti-CTLA-4
T-cell
receptor
anti-PD-1
Antigen
MHC
PD-L1
B7
Tumour cell or
antigen-presenting cell

PC has a low prevalence of somatic mutations

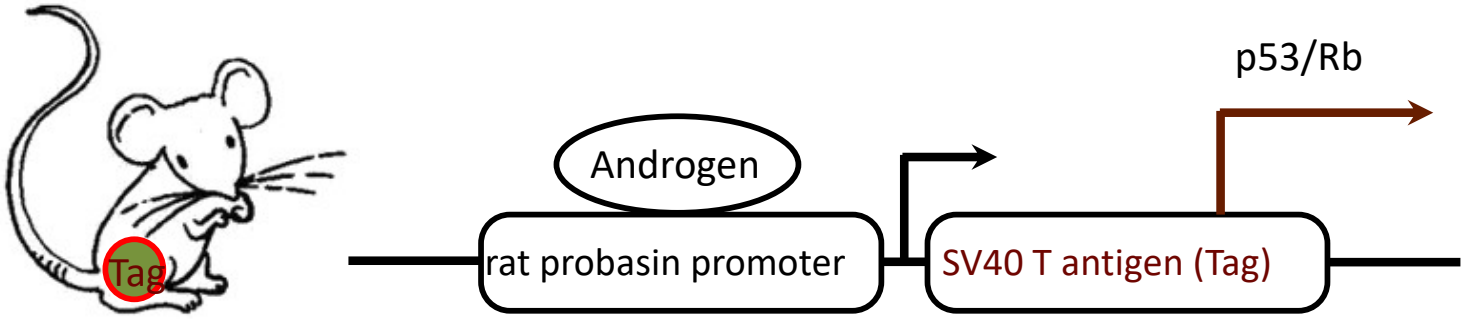
The prevalence of somatic mutations across human cancer types.



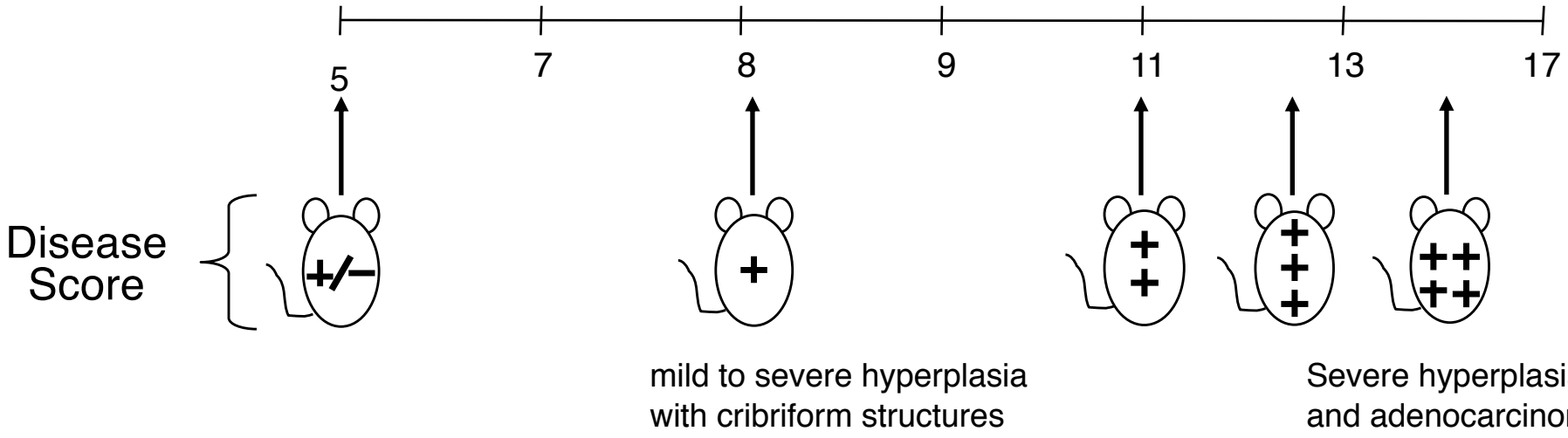
LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

TRAMP

- TRansgenic Adenocarcinoma of the Mouse Prostate -

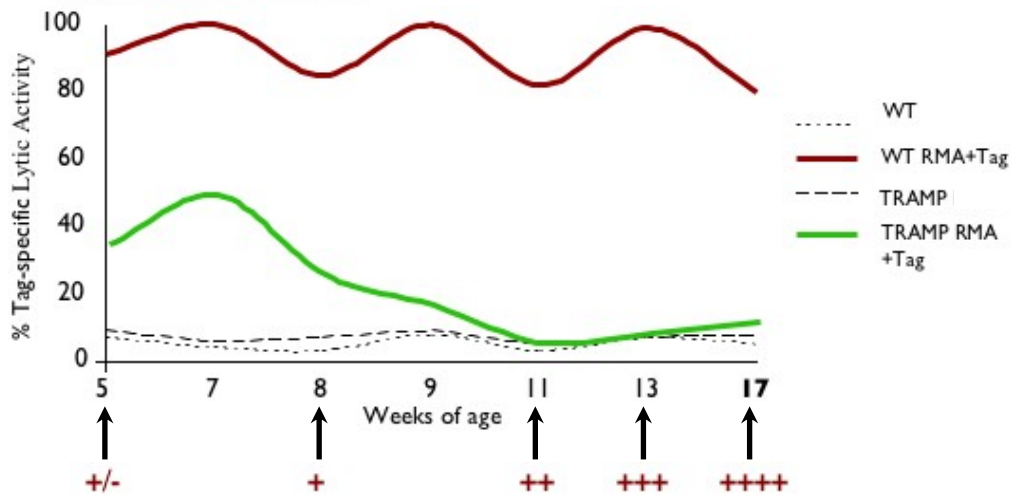


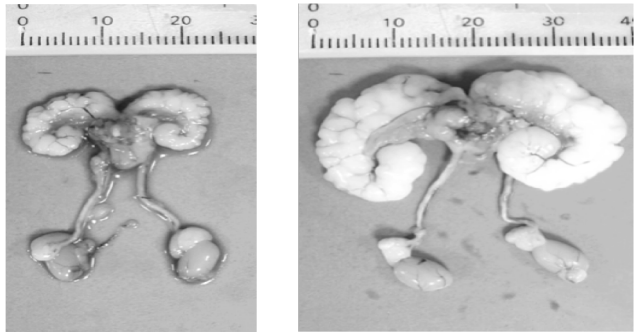
Autochthonous prostatic epithelium tumor development at puberty (*Greenberg, N. 1995)*



Degl'Innocenti et al. Eur J Imm, 2005

Central and peripheral T cell tolerance in TRAMP mice





Degl'Innocenti et al. Eur J Imm, 2005

- **Central tolerance:** T antigens are expressed in the thymus: deletion high affinity T cells
- Progressive **peripheral tolerance** to Tag is observed, role for CD8+ suppressor cells (Bellone's group)

- **Immunotherapy mostly fails:**

Active (vax), adoptive immunotherapy (ag-expanded cells, TCR redirected T cells)

T reg, MDC inhibition/deletion

Delay on tumor growth, no effect of long-term survival

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…..and prolong overall survival

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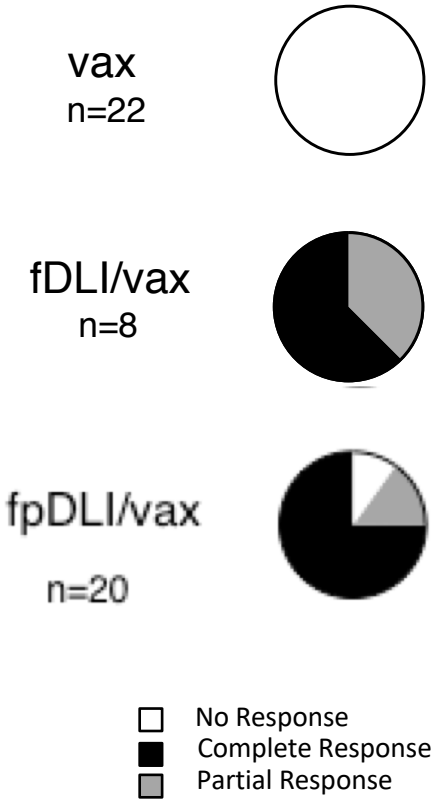

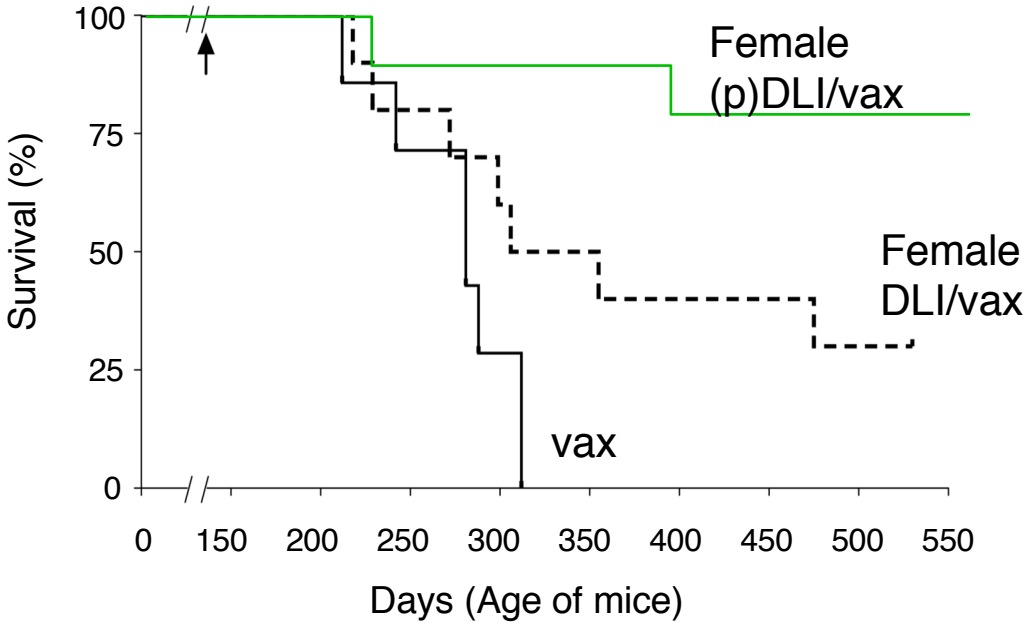

Hess Michelini, Cancer Res. 2010 Hess Michelini and Manzo, Cancer Res. 2013

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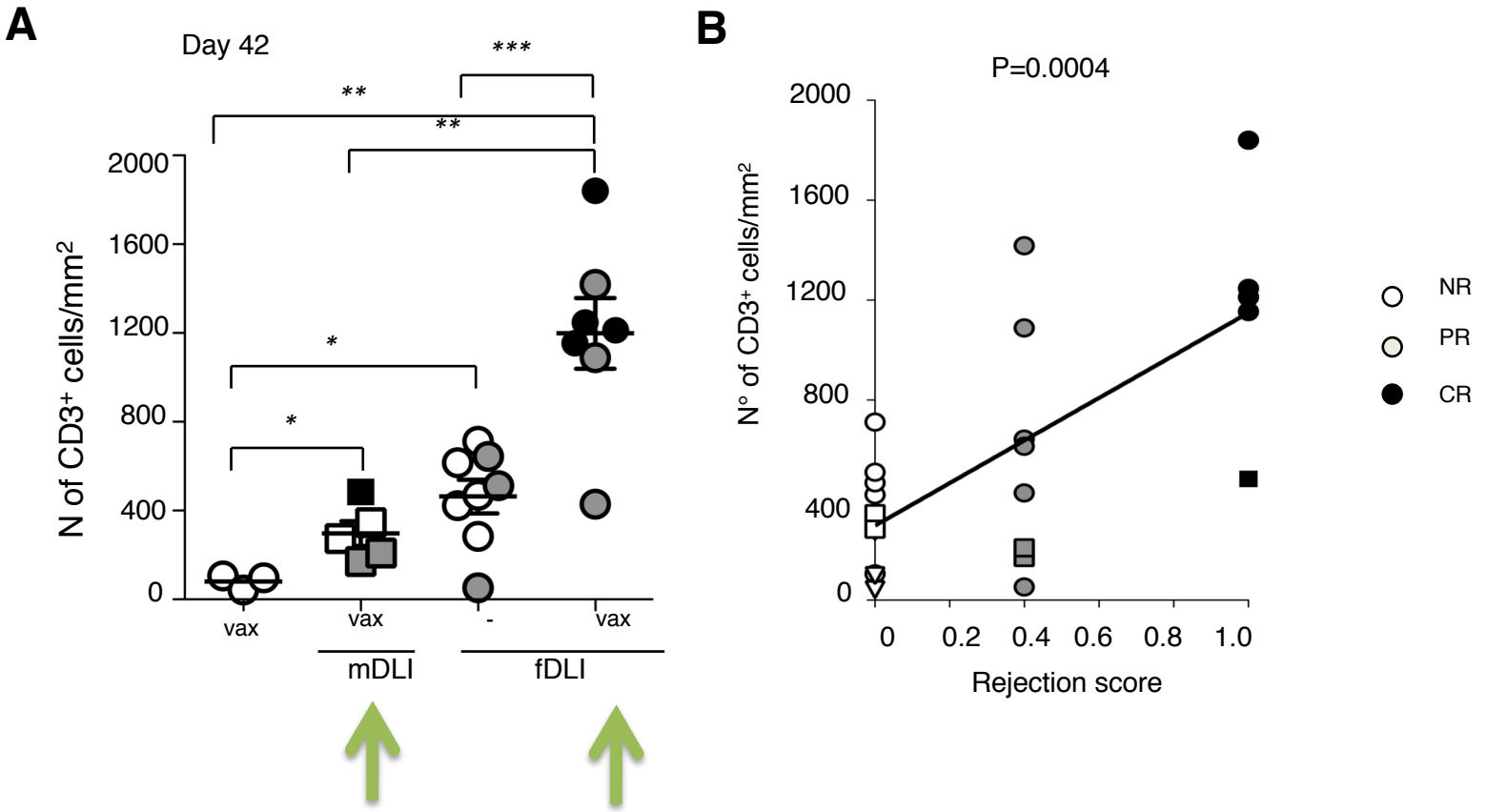
Allo/Y-directed T cell responses grant optimal tumor infiltration

DI ID Scientific Retreat 2017



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Dual targeting: the tumor and the stroma

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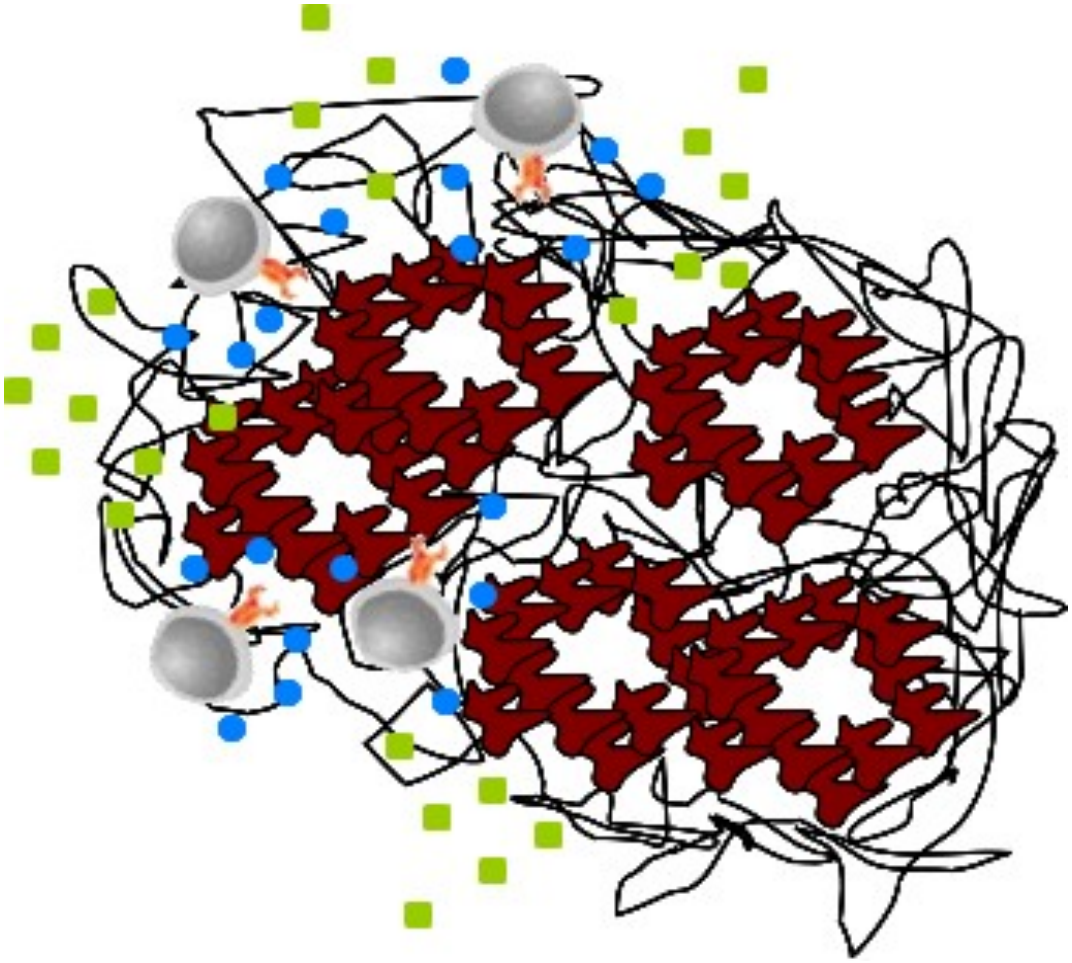

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Autologous TCR redirected T cells to recapitulate the allogenic effect

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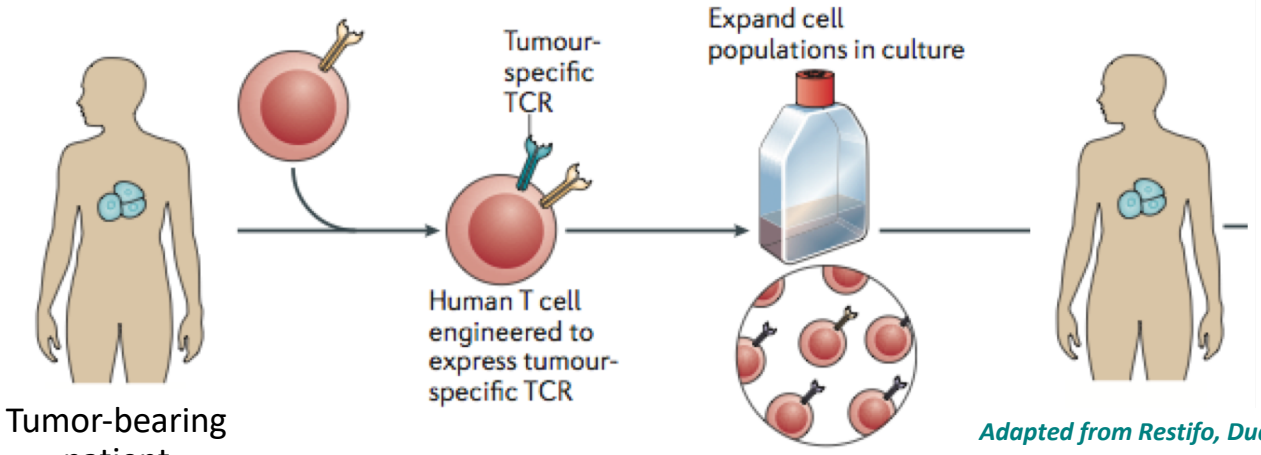
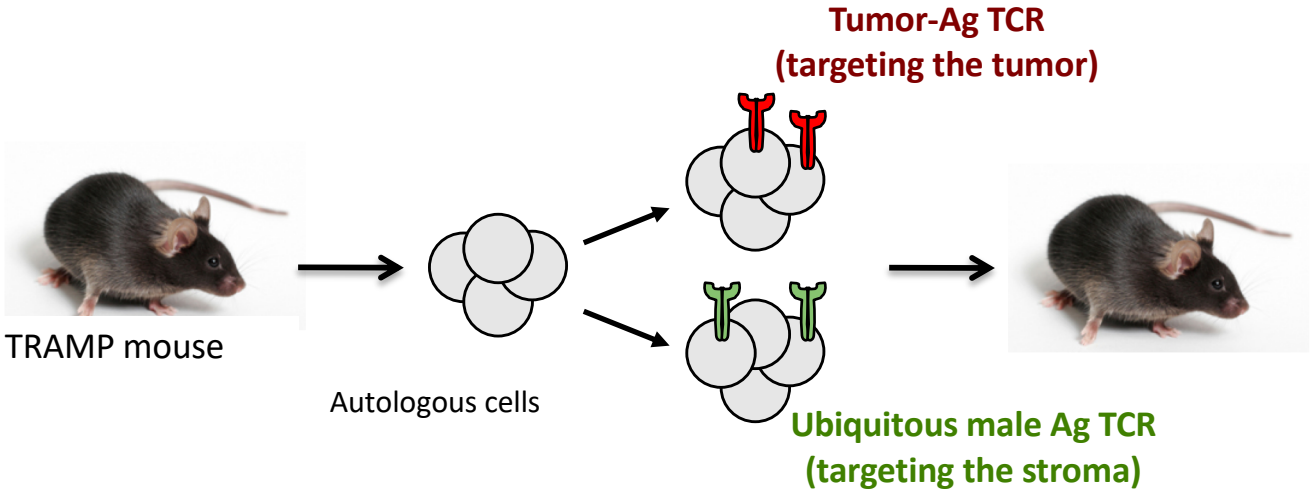
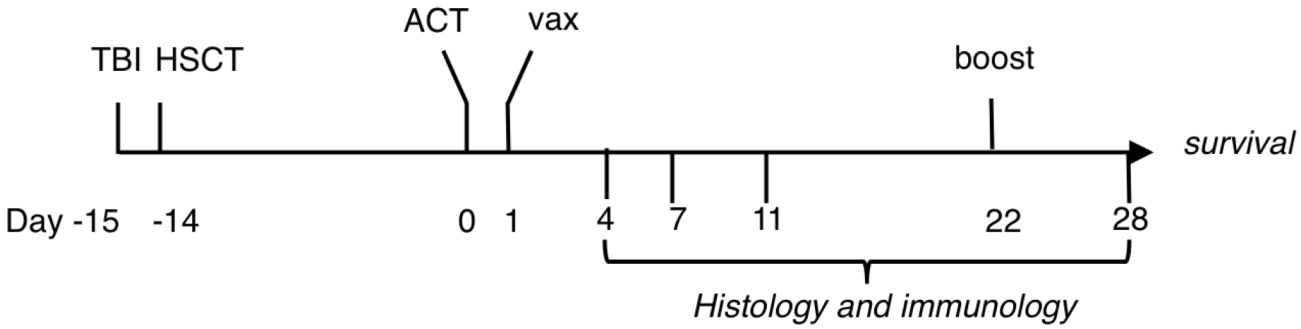
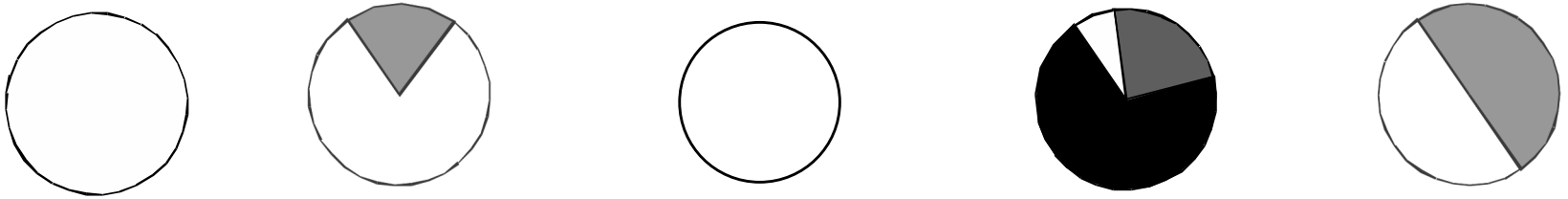


Adapted from Restifo, Dudley & Rosenberg, 2012



Combined TCR-redirected ACT precipitate acute tumor debulking





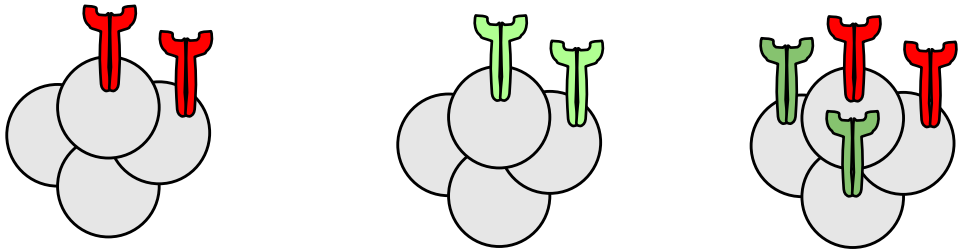
CTR (mock)
(n=7)

Tumor +mock
(n=5)

Allo/Y +mock
(n=5)

Tumor+Allo/Y
(n=12)

TagIY 2-3x
(n=6)



No Response
Complete Response
Partial Response

Manzo and Sturmheit et al, Cancer Res. 2017

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Dual Targeting ACT promotes superior tumor infiltration….

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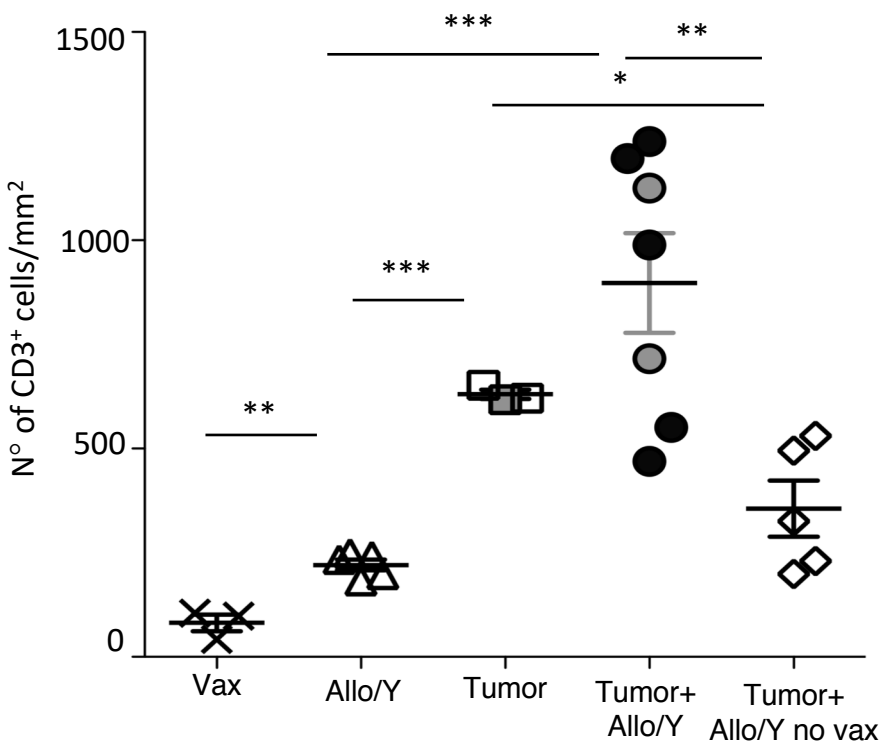


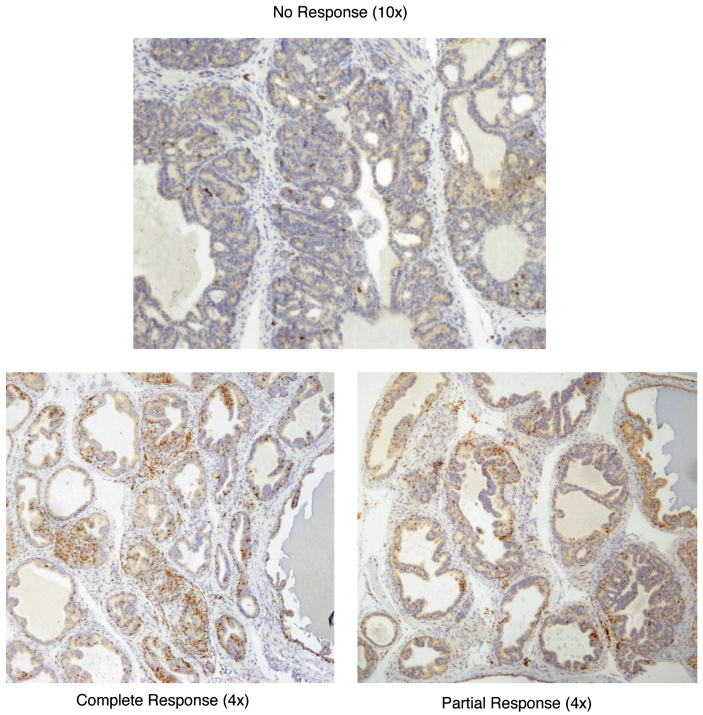
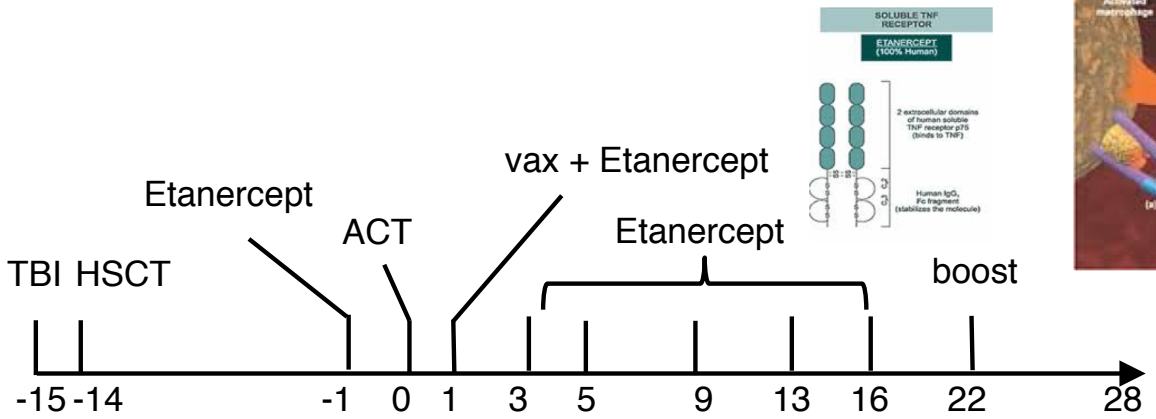
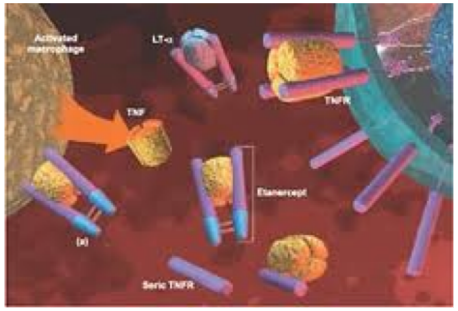


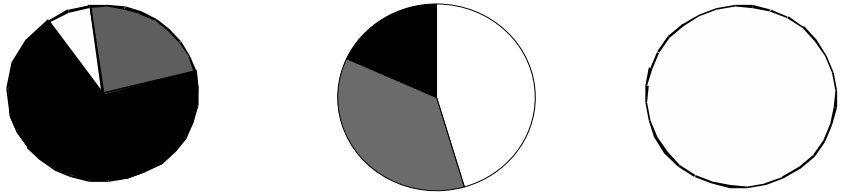
Figure S6

TNF-α is critical for ACT- induced tumor debulking





Histology and immunology



Tumor+Allo/Y

Tumor+Allo/Y+ Ethanercept

Mock+ Ethanercept

Manzo and Sturmheit et al, Cancer Res. 2017

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Tumor Vessel-Targeted TNF-α

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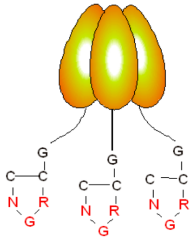
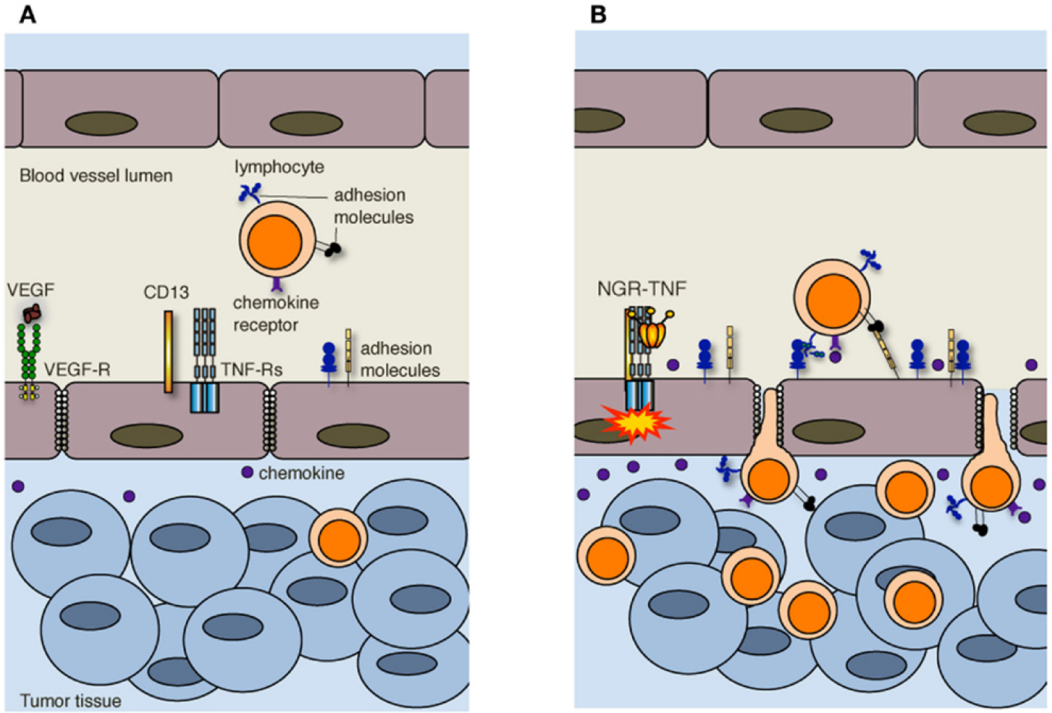
CNGRC *Binds CD13 isoform expressed in tumor vessels*



Currnis et al Nat Biotechnol (2000)
Currnis et al (2005)
Corti et al Blood (2008)
Corti et al Med Res Rev. (2012)

A. Corti *M. Bellone*



Calcinotto and Bellone,J Immunol. 2012
Bellone M, Calcinotto A, Corti A – Oncoimmunol. 2012

NGR-hTNF is in phase III trials

TNF-α promotes ACT- induced tumor debulking

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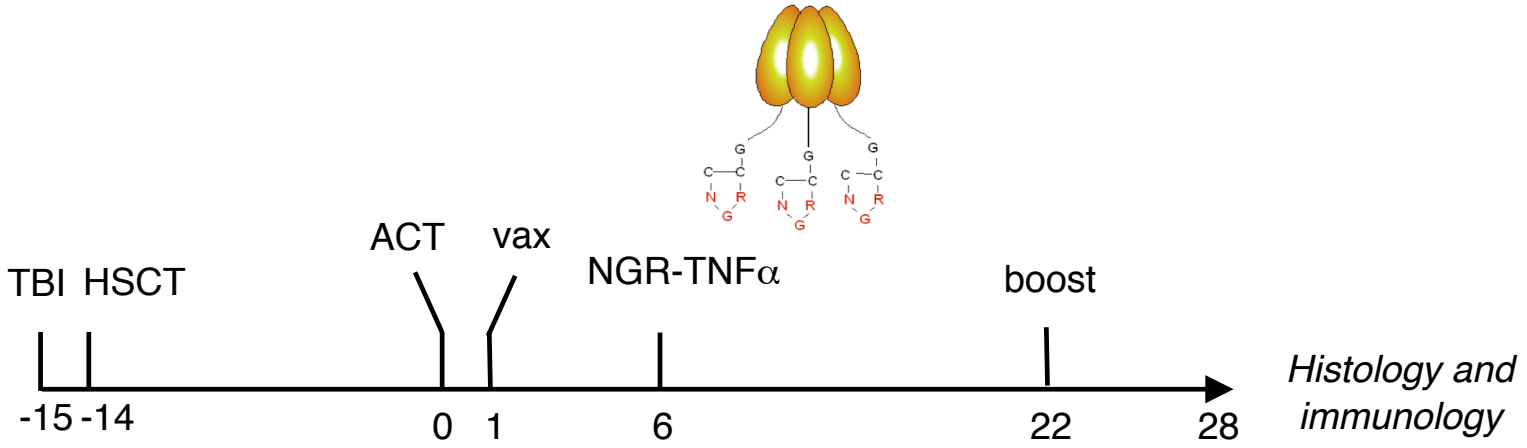

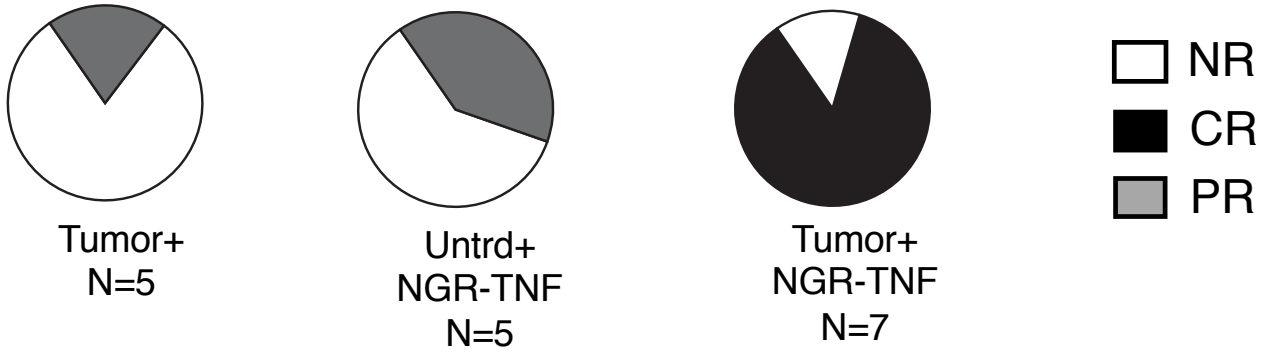

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NGR-TNF promotes ACT therapeutic efficacy

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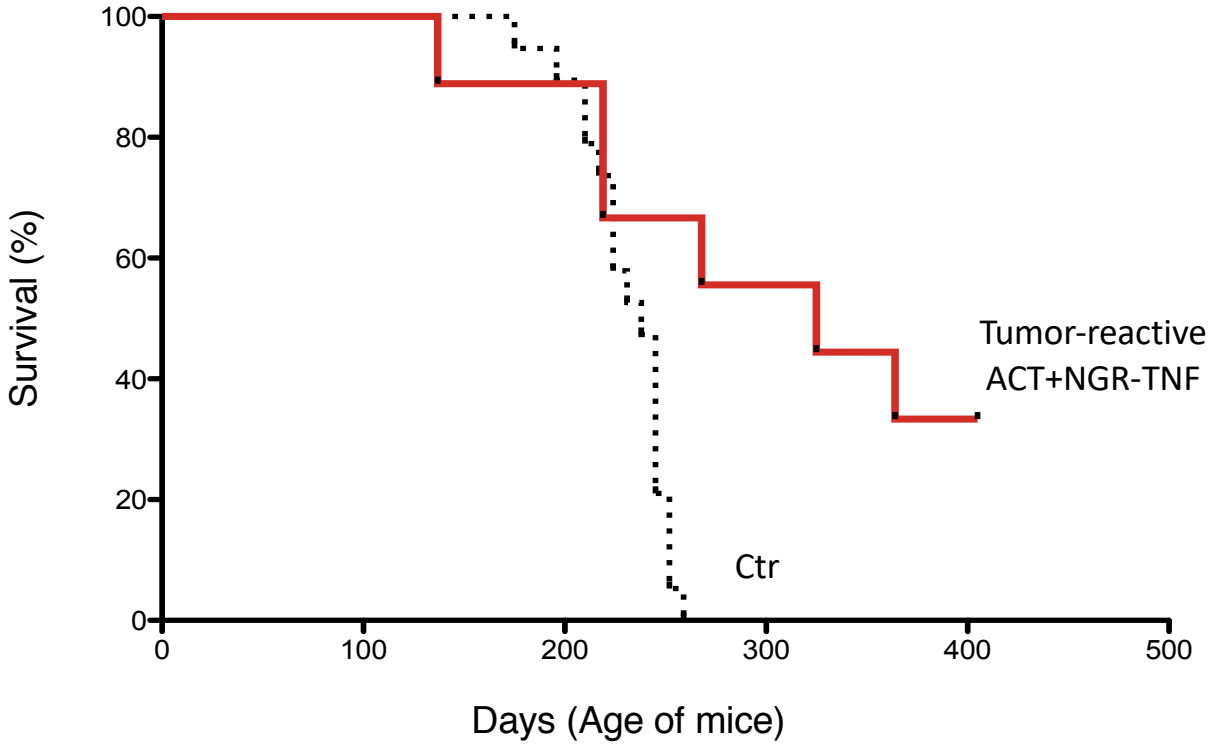
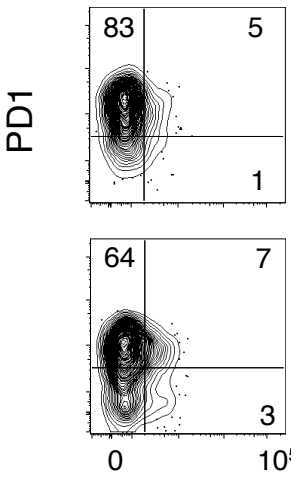
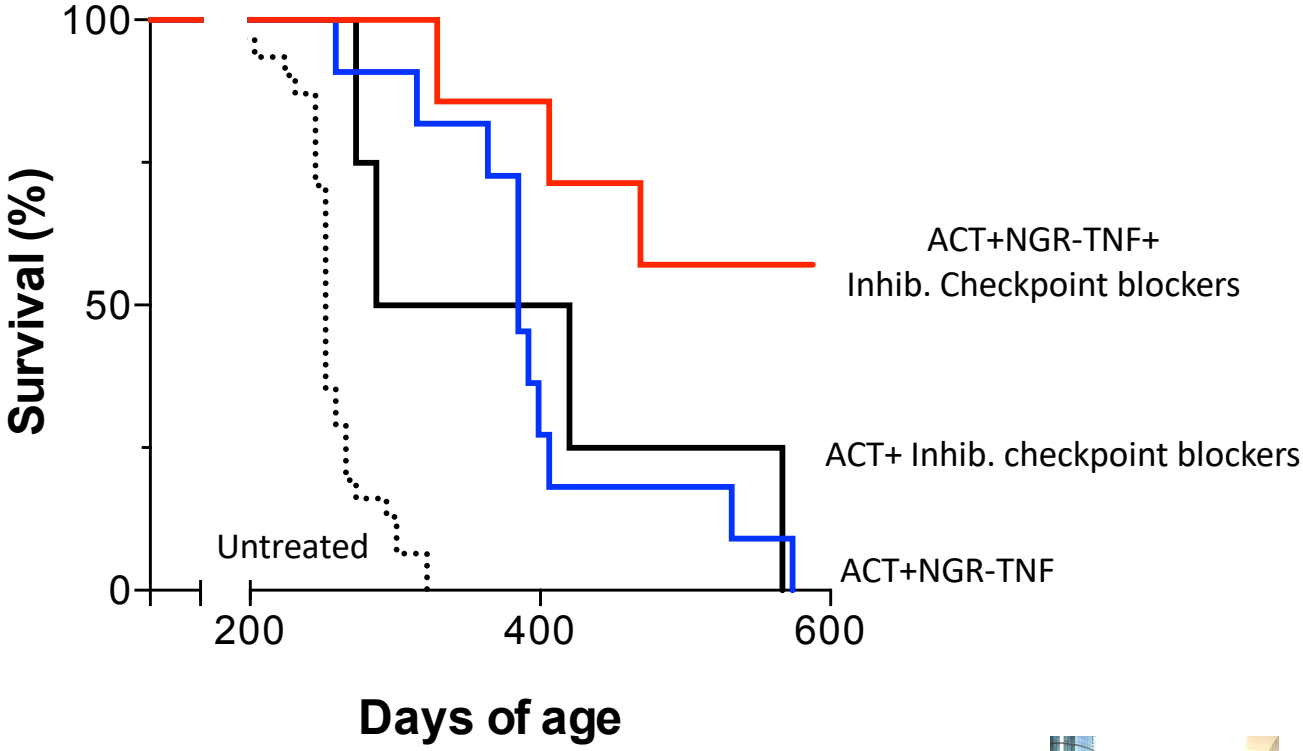


Combining ACT with targeted cytokines and checkpoint blockade



TCR-redirected

Polyclonal

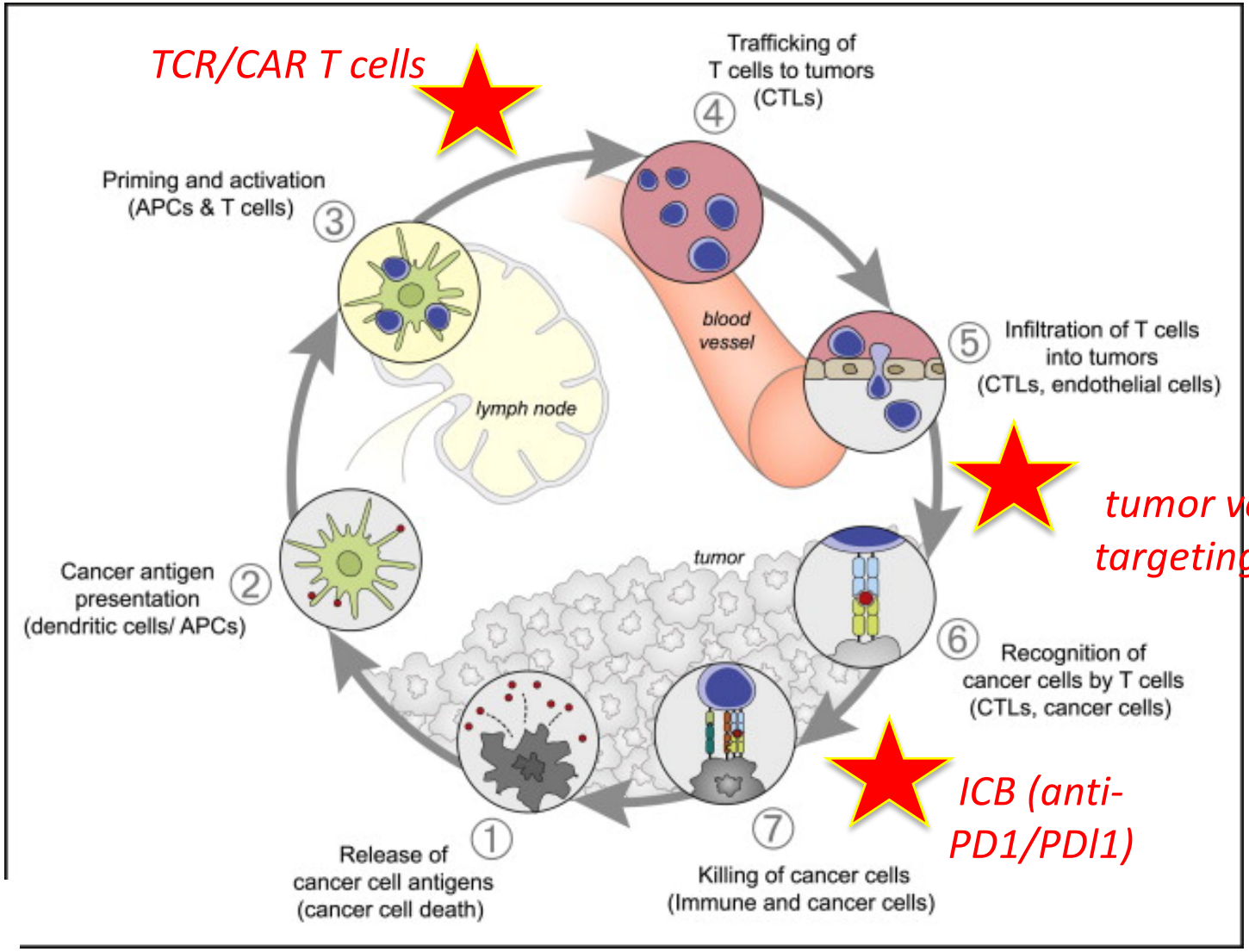


CANCER RESEARCH INSTITUTE

Elia et al., Unpublished

Matteo Bellone and Angela Rita Elia
Cellular Immunology Unit

Critical issues in T-cell mediated tumor rejection



Daniel S. Chen, Ira Mellman **Oncology Meets Immunology: The Cancer-Immunity Cycle**
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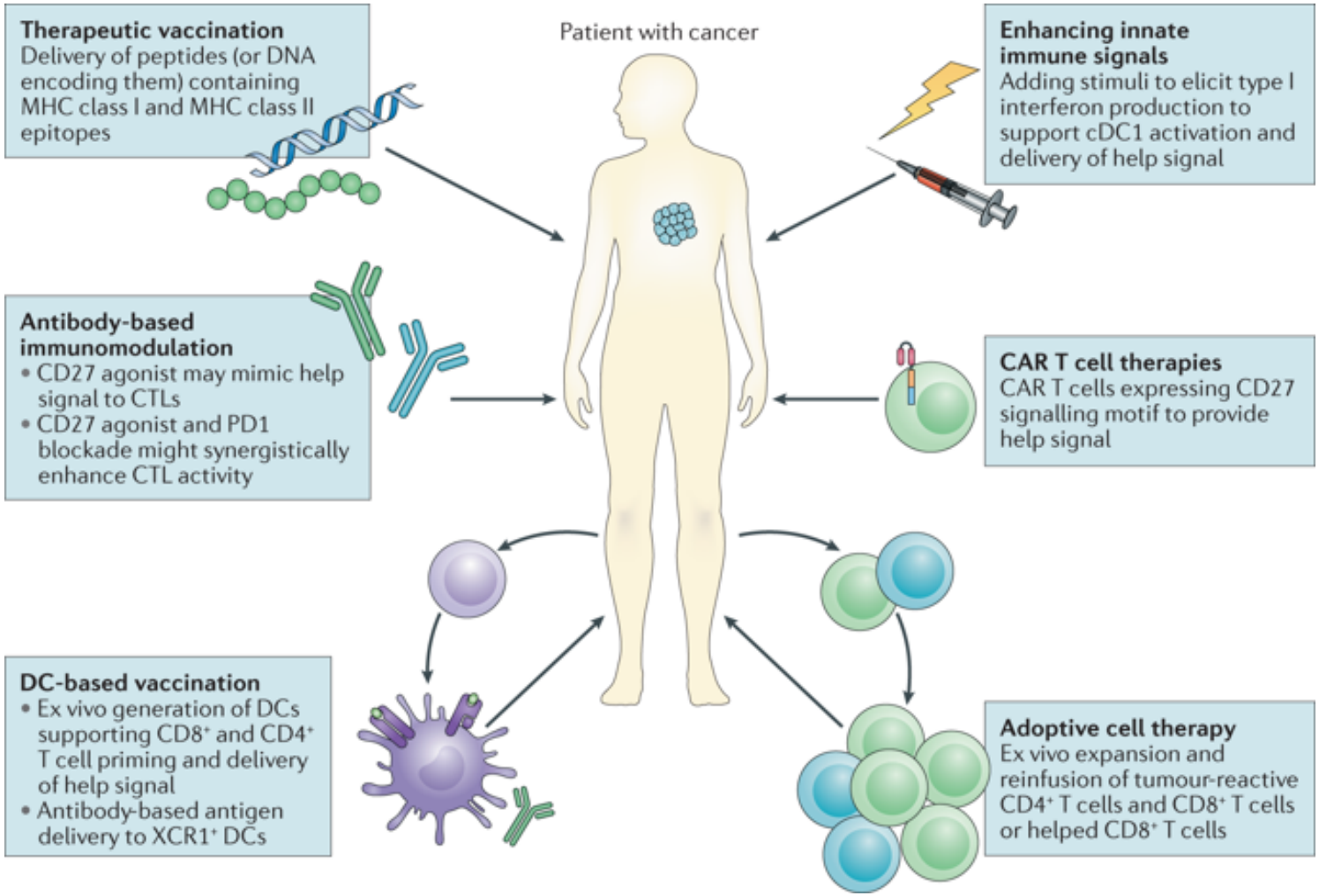
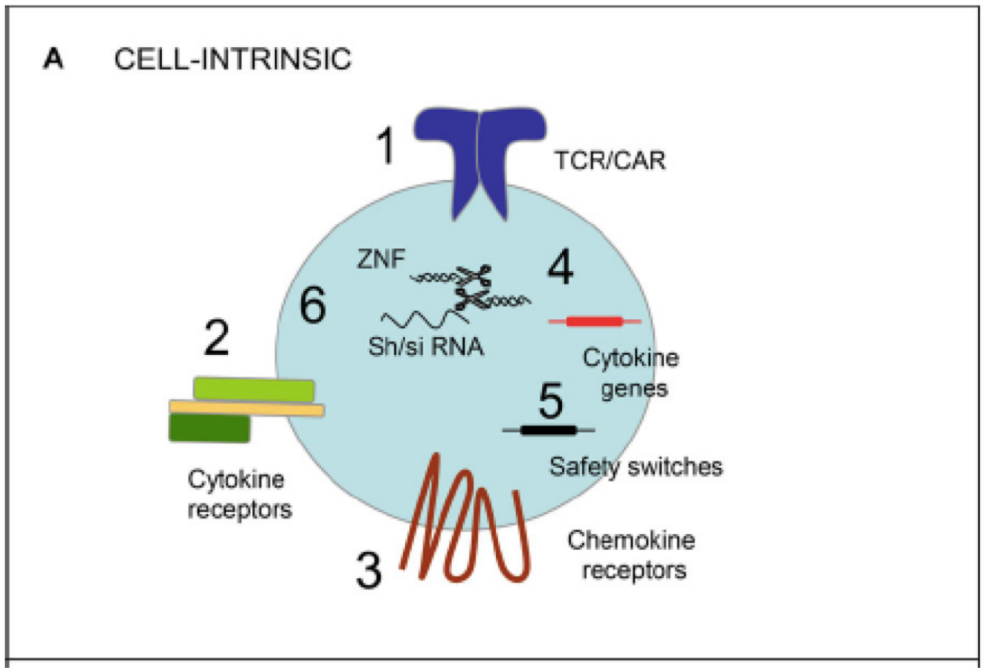
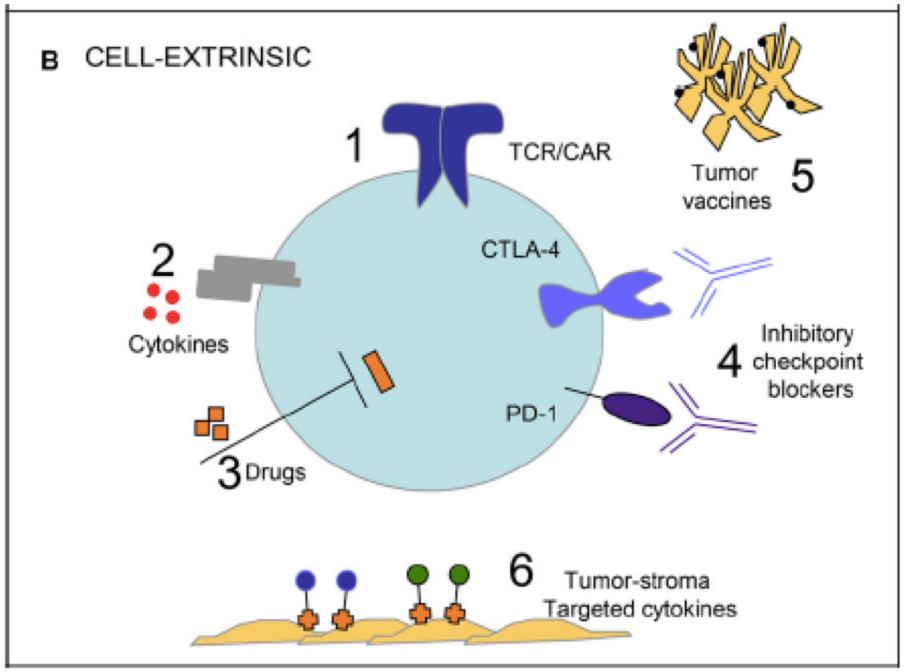


Borst, J et al. Nature Reviews Immunology (2018)

Future developments

Exploiting cell extrinsic and cell-intrinsic means





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Eur. J. Immunol. 2015. 45: 2457–2469

C. Bonini *M. Casucci* *P. Dellabona, G. Casorati* *M. Bellone* *A.Corti*

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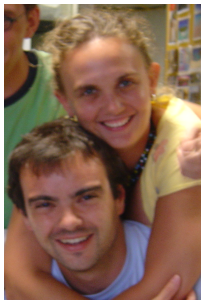
DIID Scientific Retreat 2017

Mondino's lab

Past and present



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