Mechanisms of immune “escape” & immune inhibition

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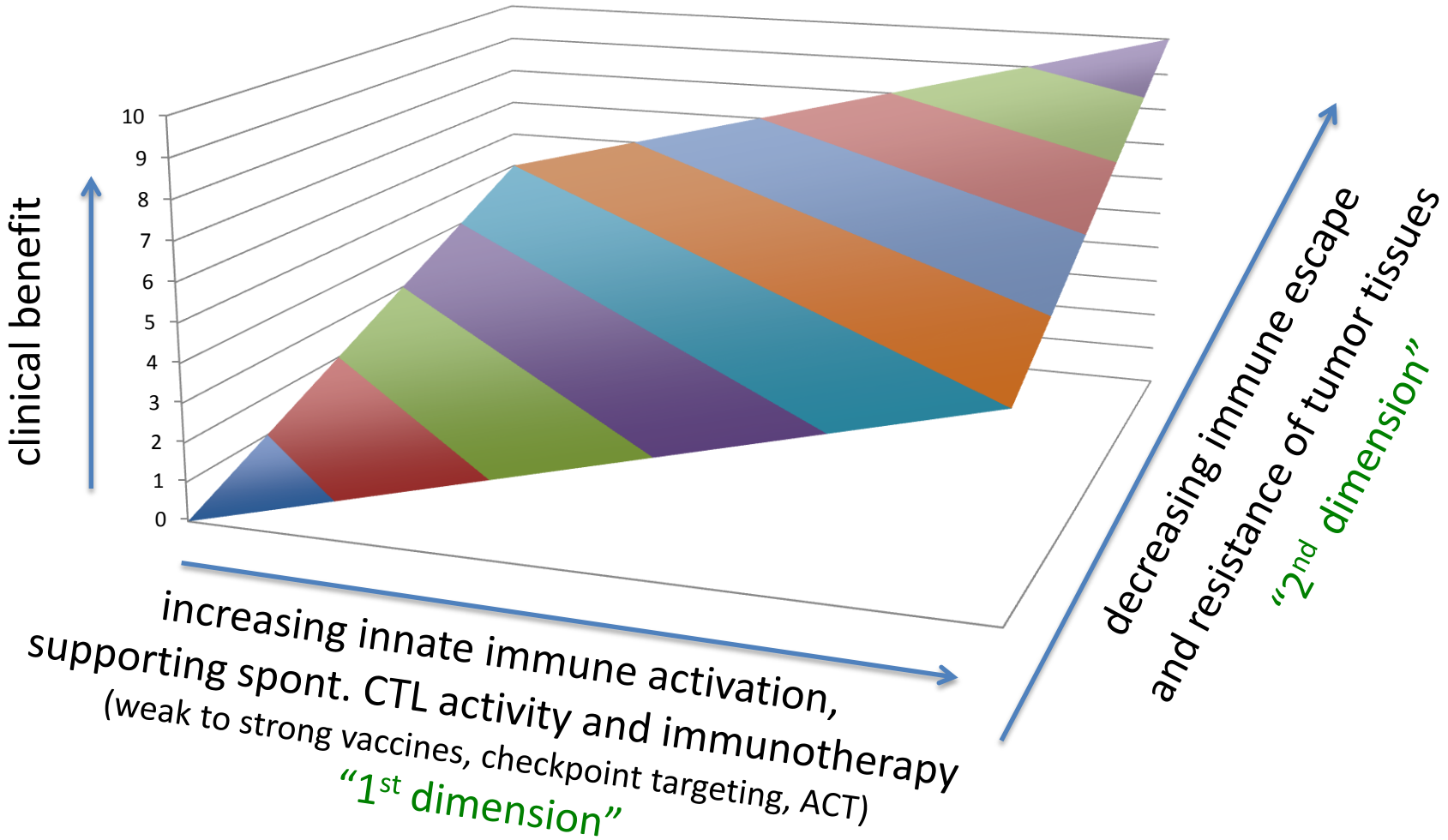
Therapy of cancer patients:

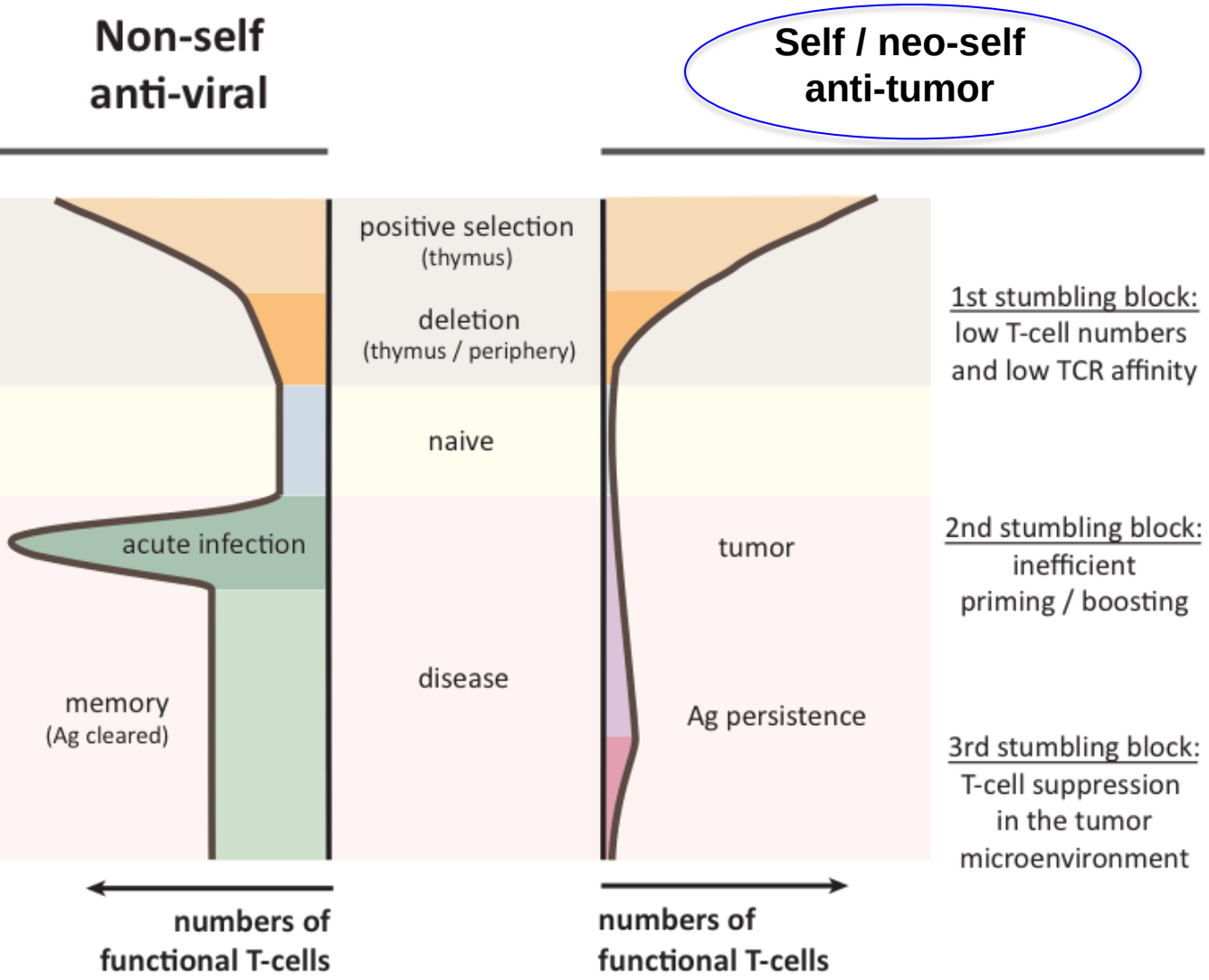
Clinical benefit

depends on CD8 T cells and tumor resistance



The three main stumbling blocks for anti-cancer T cells

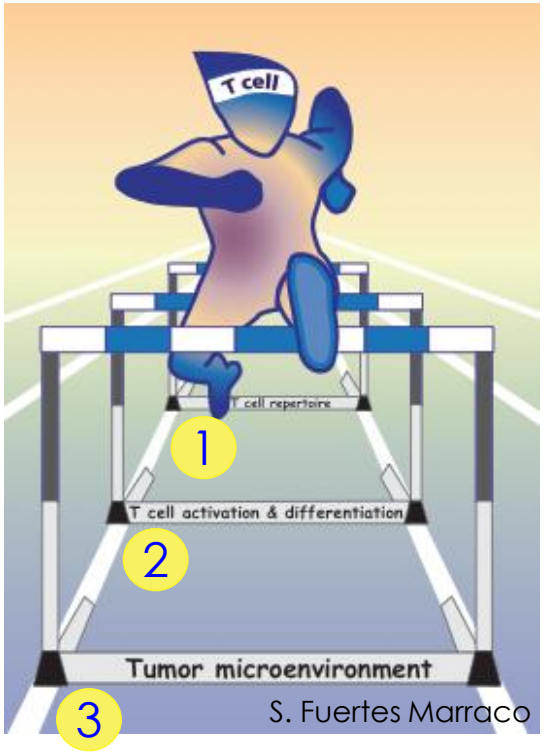
A scientific “check-list” for T cell based immunotherapy of cancer patients



1st stumbling block:
low T-cell numbers
and low TCR affinity

2nd stumbling block:
inefficient
priming / boosting

3rd stumbling block:
T-cell suppression
in the tumor
microenvironment



Baitsch, Speiser et al, Trends in Immunology, 2012; 33:364

Mechanisms of immune “escape” & immune inhibition

A major focus of tumor immunologists is on
mechanisms in the tumor microenvironment

Basic immunology, and other fields of immune research is more strongly focused on
systemic immune activation and inhibition

Extrinsic mechanisms of hyporesponsiveness of anti-cancer T cells

Apart from the three main stumbling blocks highlighted in this review, T cell extrinsic mechanisms play major roles in the hyporesponsiveness of anticancer T cells. Here, we list such mechanisms of tumor cells (I) and their microenvironment (II).

I. Mechanisms of tumor cells (reviewed in [81])

- Antigen loss: shedding of surface antigens, MHC downregulation, alterations of the antigen presenting machinery affecting peptide trimming, transport or MHC binding
- Production and release of immunosuppressive factors, e.g., IDO, prostaglandin (PG)E2, transforming growth factor (TGF)-β, IL-10, granulocyte–macrophage colony-stimulating factor (GM-CSF)
- Overexpression of antiapoptotic molecules, e.g., BCL-2, FLIP
- Expression of Fas ligand or its release in microvesicles inducing T cell apoptosis
- Secretion of soluble Fas or DcR3 binding Fas ligand on T cells and preventing apoptosis [82]

II. Factors in the tumor microenvironment

Regulatory T cells (Tregs): (reviewed in [83])

Tregs may inhibit anticancer T cells by

- Induction of T cell apoptosis via cell–cell contact
- Disruption of T cell metabolism due to transfer of cAMP via gap junctions
- IL-2 consumption via CD25
- Blocking of Th1 responses due to production of IL-10 and TGF-β

Tolerogenic DCs (reviewed in [84])

- Downregulation of MHC-II and the co-stimulatory molecules CD80 and CD86
- Induction of T cell apoptosis due to IDO expression
- Shifting T cell responses from Th1 to Th2 polarization due to IL-10 secretion

Tumor associated macrophages (M2) (reviewed in [85])

- Blocking of Th1 responses due to production of IL-10 and TGF-β
- Recruitment of naive T cells, Th2 cells and Tregs due to production of chemokine CC ligand (CCL)17, -18 and -22

Myeloid-derived suppressor cells (reviewed in [86,87])

- Shifting T cell responses from Th1 to Th2 polarization due to IL-10 production
- Arg-1 and inducible NO synthase (iNOS) activity: Arginine depletion and production of reactive oxygen species (ROS) and reactive nitrogen oxide species (RNOS)
  - → Loss of antigen recognition due to TCR nitration
  - → Nitrosylation of signaling proteins and prevention of their phosphorylation
  - → Decreased IL-2 production due to instable mRNA
  - → Blocking of TCR signaling due to CD3-ζ chain downregulation
  - → Enhanced T cell apoptosis
- Blocking T cell activation due to depletion of cysteine
- Blocking T cell migration due to loss of CD62L expression

Lymphoid-like reticular network

- Recruitment of lymphoid-tissue inducer (LTi) cells by tumors expressing CCL21 and consequent formation of a lymphoid-like stroma within tumors favoring a tolerogenic microenvironment [88]

Cancer-associated fibroblasts (reviewed in [89])

- Secretion of factors supporting tumorigenesis and metastases, e.g., epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF)
- Secretion of chemokines attracting tumor-promoting immune cells, e.g., chemokine CXC ligand (CXCL)14

Baitsch, Speiser et al, Trends in Immunology, 2012; 33:364

Mechanisms of immune attenuation in metastases

CTLA-4, PD-1 and further inhibitory receptors

(Tim-3, Lag-3, 2B4, BTLA, TIGIT, VISTA, KLRG-1, CD160)

Regulatory T cells (“Treg”): CD4+CD25+FoxP3+ T cells

Myeloid derived suppressor cells (MDSC)

Th2 polarization of $CD4^+$ T cells, ILCs and NKT cells (IL-4, -5, -13)

Indoleamine dioxygenase (IDO, tryptophan ↓), arginase I

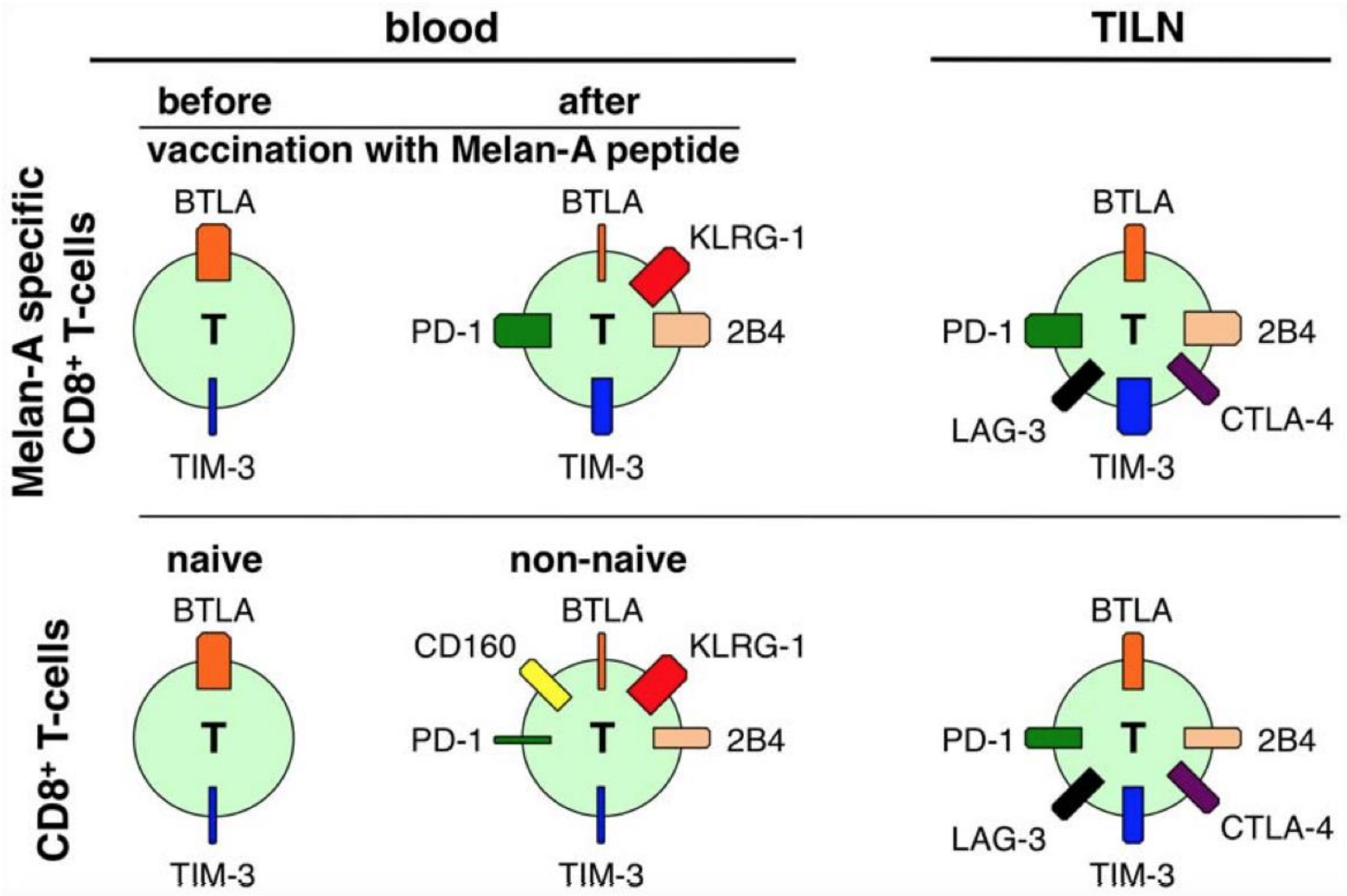
Prostaglandin E_2, cyclooxygenase-2

VEGF, TGF-β, IL-10, IL-35

Fas, TRAIL

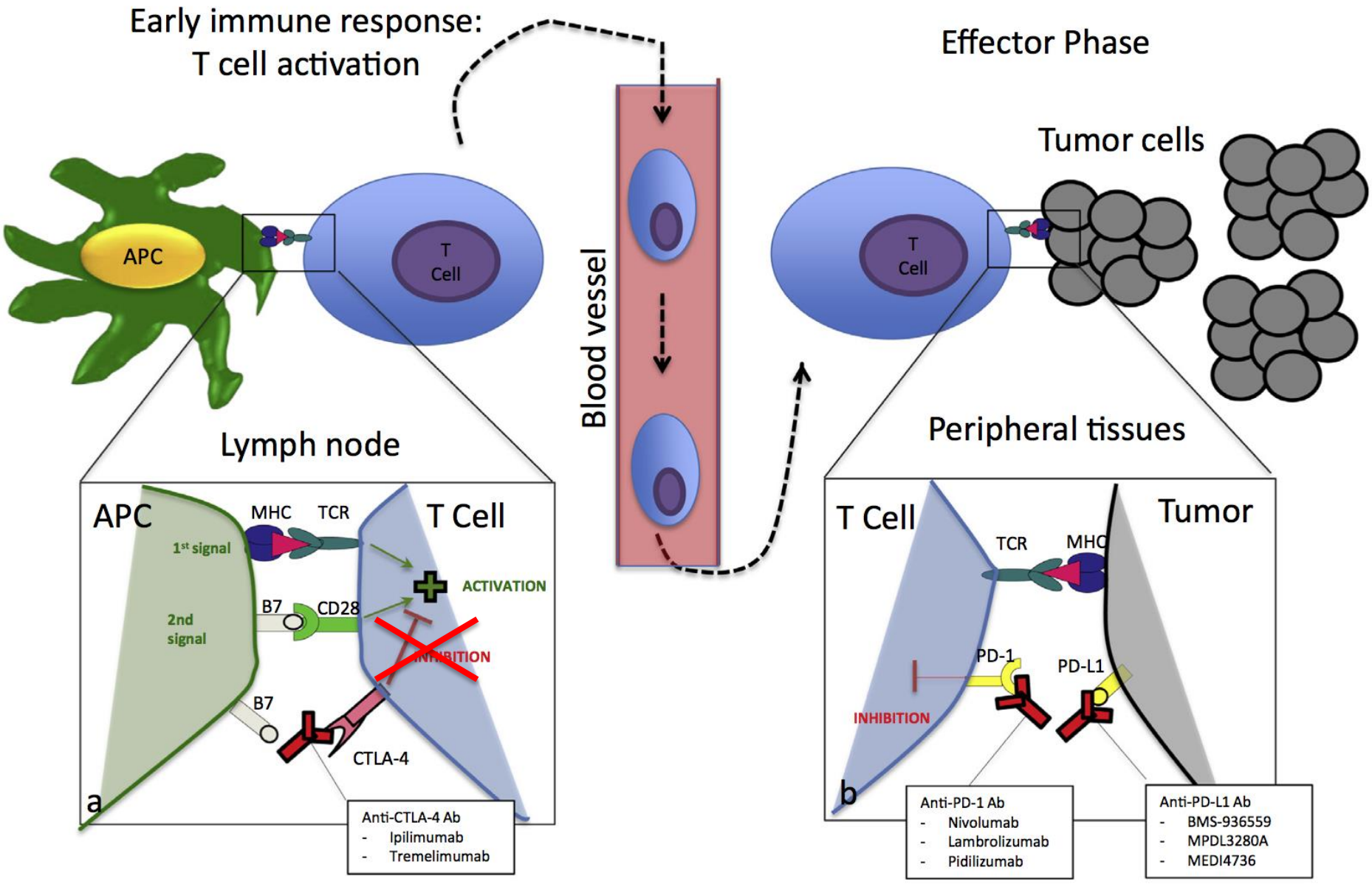
MHC ↓, antigen ↓ on tumor cells

Schematic representation of inhibitory receptor co-expression according to differentiation status and physical location



Baitsch, Speiser et al, PLoS One, 2012, 7:30852

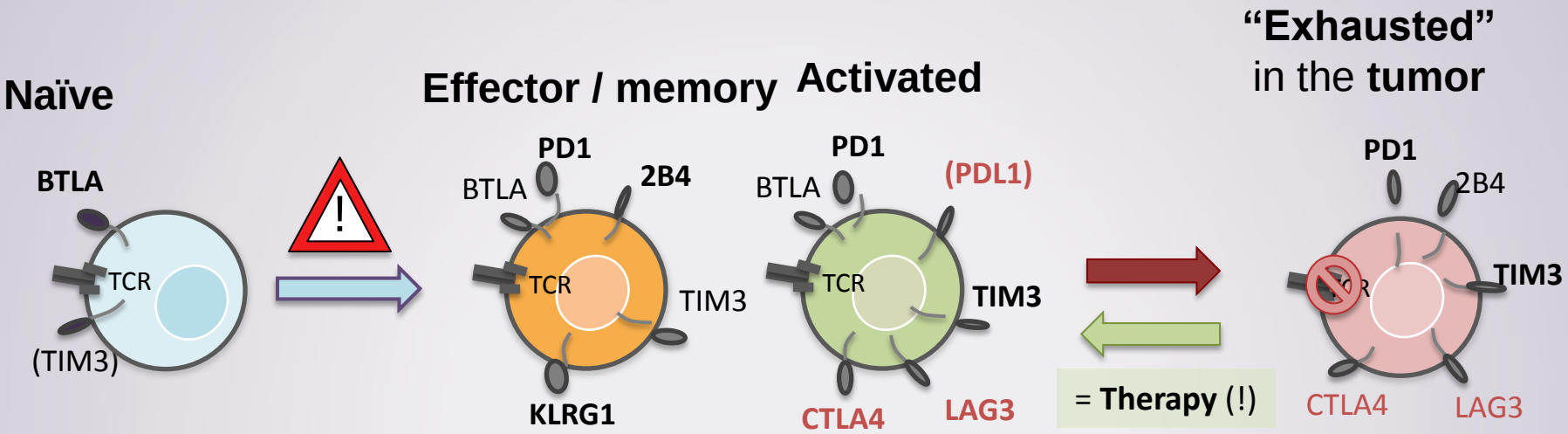
Mechanisms of CTLA-4 and PD-1/PD-L1 targeting



Kyi, C., and M.A. Postow. 2013. *FEBS Lett*. 588:368

exhaustion markers ? **Activation and differentiation status**

strongly impact on expression of inhibitory receptors (iRs)



Inhibitory receptor+ T cells are often:

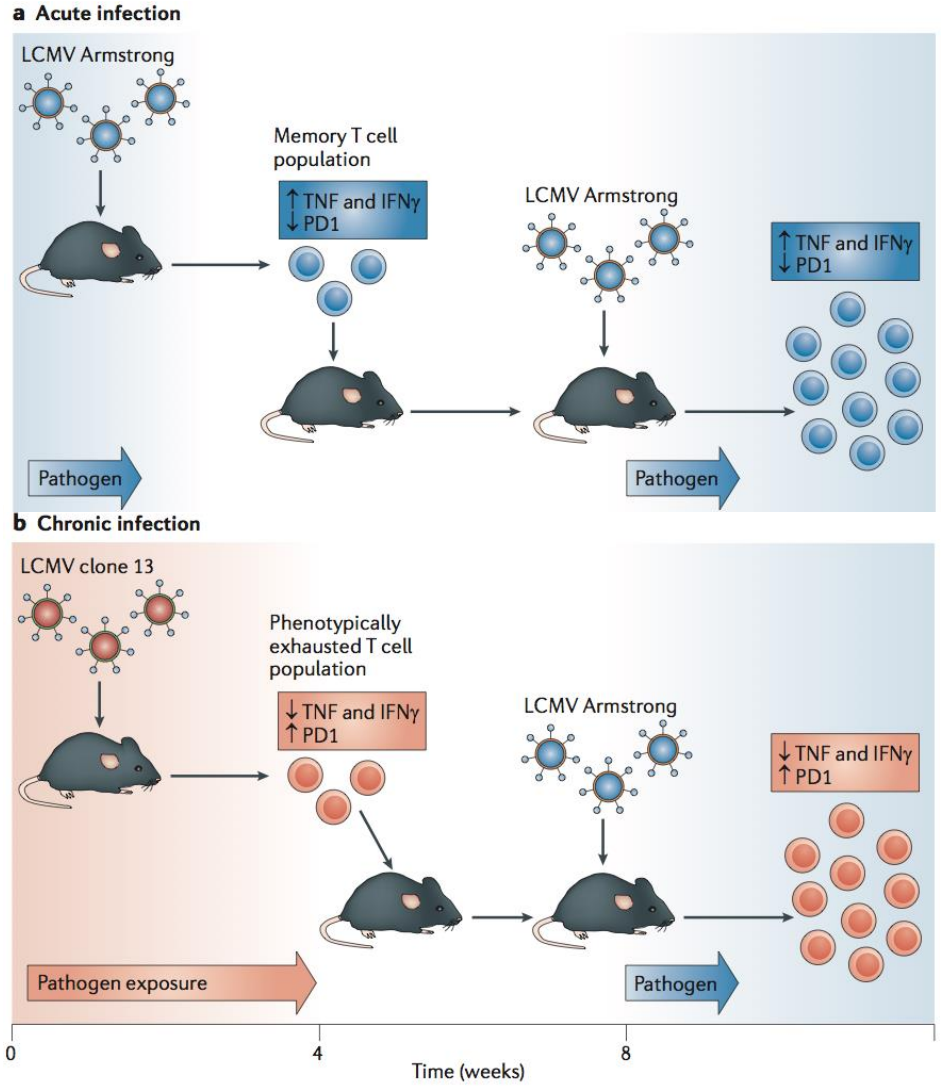
1. activated (except CD160, KLRG1, 2B4, BTLA)
2. differentiated (except BTLA)
3. functional. Reduced IFNγ/TNFα only in CTLA-4+ / CD160+ cells
   (as measured in absence of iR-ligands on APCs / targets)

- Analysis of T cell functions is important (albeit challenging)
- Phenotyping of iRs is not conclusive in absence of activation and differentiation markers

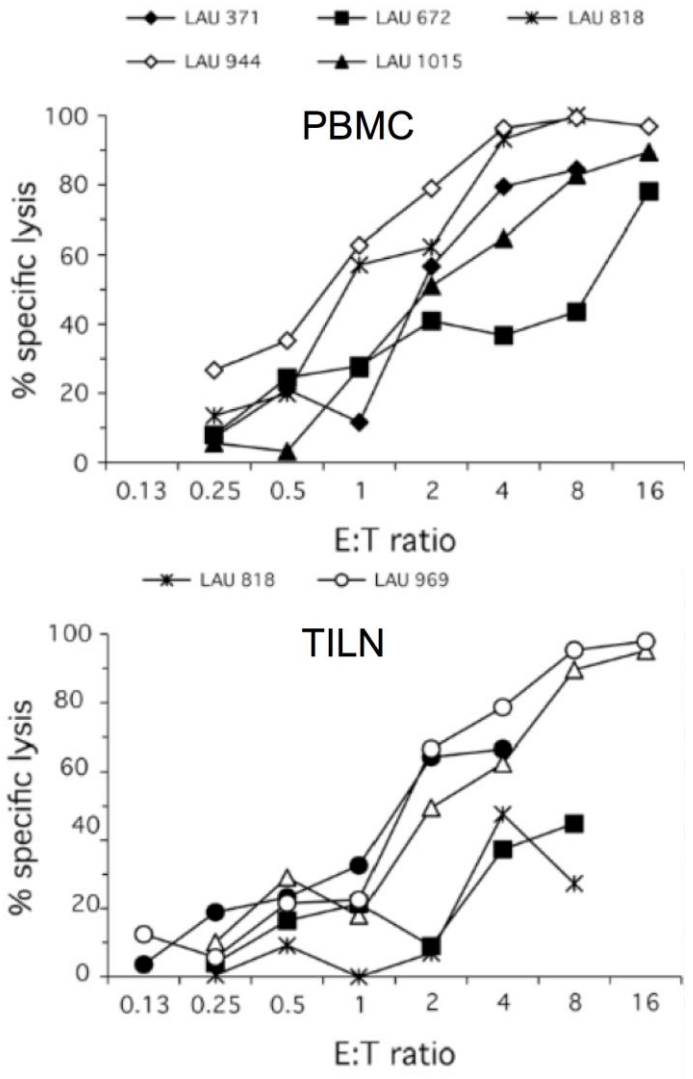
Legat, Fuertes Marraco et al, Frontiers Immunol 2013

Functional competence of “exhausted” CD8 T cells

Virus clearance in mice:



Cytotoxic capability in melanoma patients:

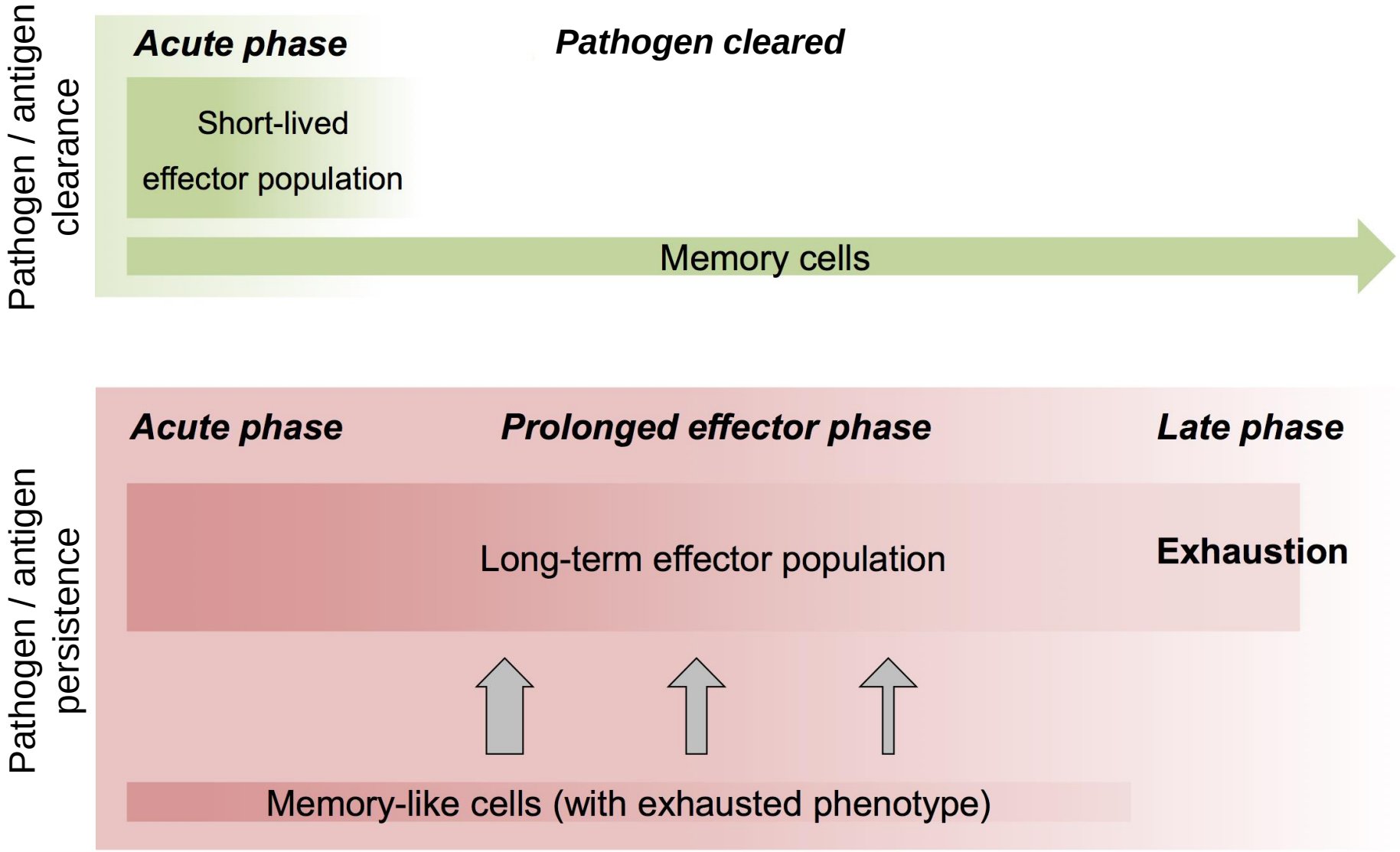


Utzschneider et al, Nature Immunology 2013; 14:603
Speiser et al, Nature Rev Immunology 2014. Epub ahead of print.

Mahnke / Devevre et al. OncoImmunology 2012; 1:467

Functionally adapted CD8 T cells

T cells in chronic infection and cancer (with "exhaustion" phenotype) can have comparable functional competence as effector T cells

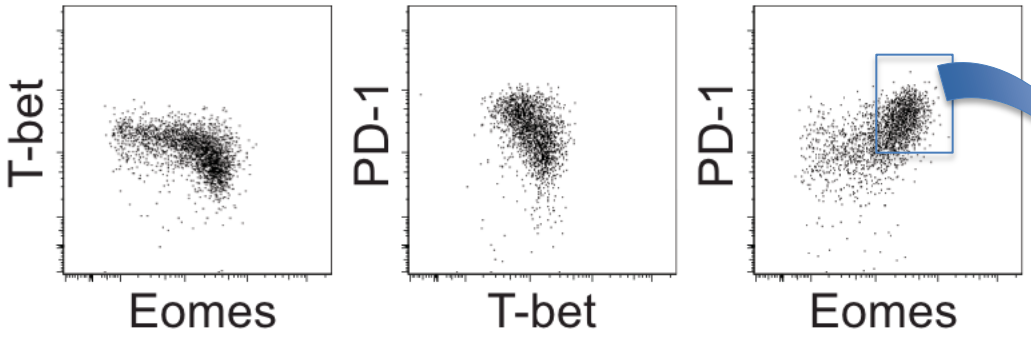


Speiser et al, Nature Rev Immunology 2014. Epub ahead of print. Adapted

Progenitor and Terminal Subsets of CD8$^+$ T Cells Cooperate to Contain Chronic Viral Infection

Michael A. Paley,[1] Daniela C. Kroy,[2] Pamela M. Odorizzi,[1] Jonathan B. Johnnidis,[1] Douglas V. Dolfi,[1] Burton E. Barnett,[1] Elizabeth K. Bikoff,[3] Elizabeth J. Robertson,[3] Georg M. Lauer,[2] Steven L. Reiner,[4]* E. John Wherry[1]†

Subsets differing in Eomes expression, correlating with distinct functional properties



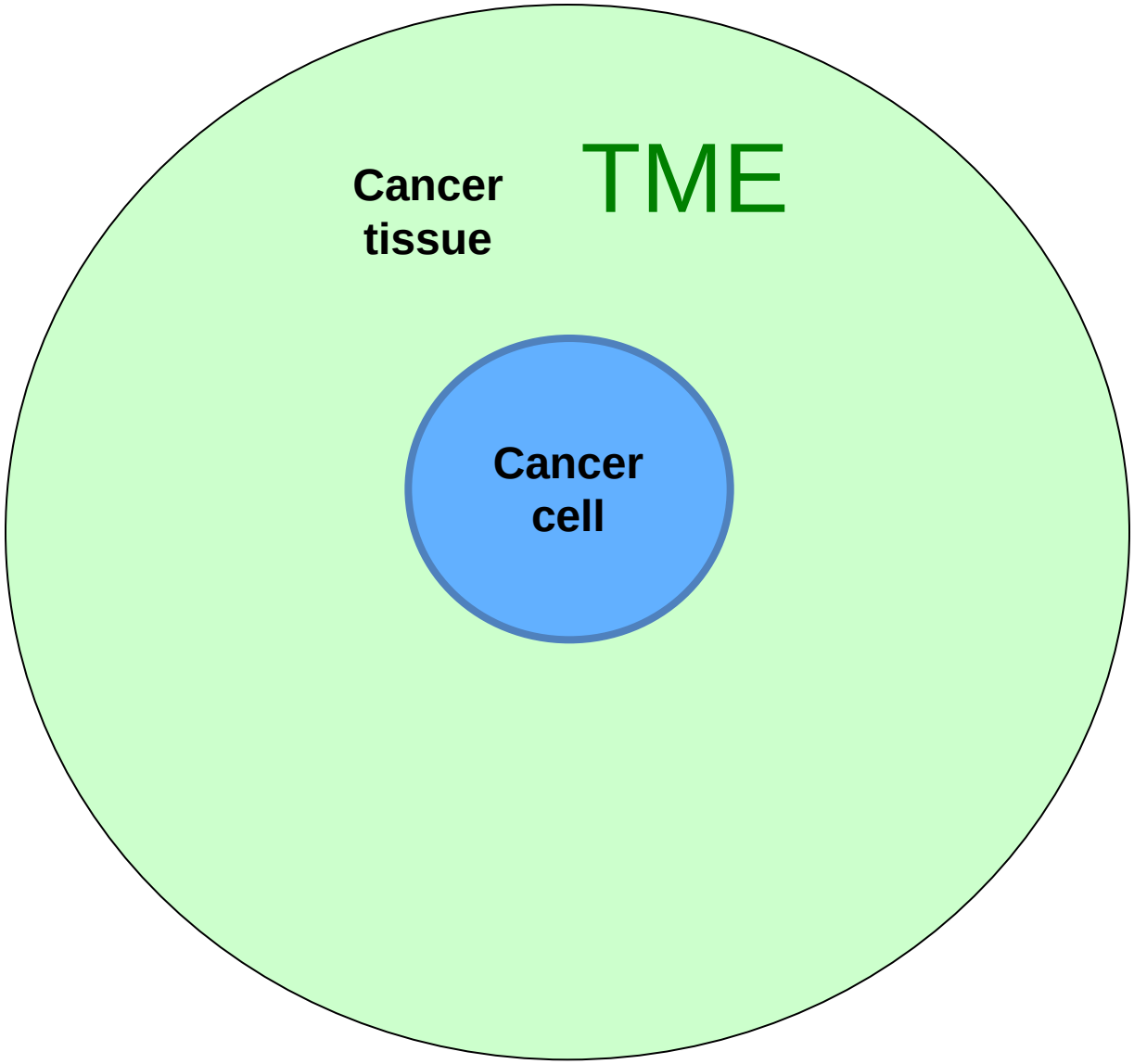
Flow cytometric analysis of T-bet, Eomes, and PD-1 expression in Db/gp33-specific CD8+ T cells, 21 days after LCMV clone 13 infection

T-bet^{hi} cells display low intrinsic turnover but proliferate in response to persisting antigen, giving rise to Eomes^{hi} (PD-1^{hi}) terminal progeny.

Genetic elimination of either subset results in failure to control chronic infection.

Paley et al, Science 2012. 338:1220

Driving malignant disease



The 2 backbones of malignancy:

1. Cancer cell-internal disease mechanisms

Cancer cells “specialize” (by mutation & selection) through the acquisition of cancer cell-internal drivers: