Corso di Biologia cellulare del Cancro 2020/21

Cancer immunoediting from immune surveillance to immune escape

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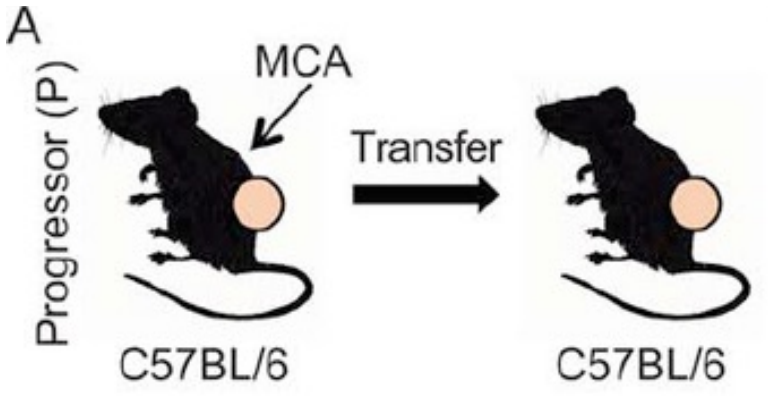
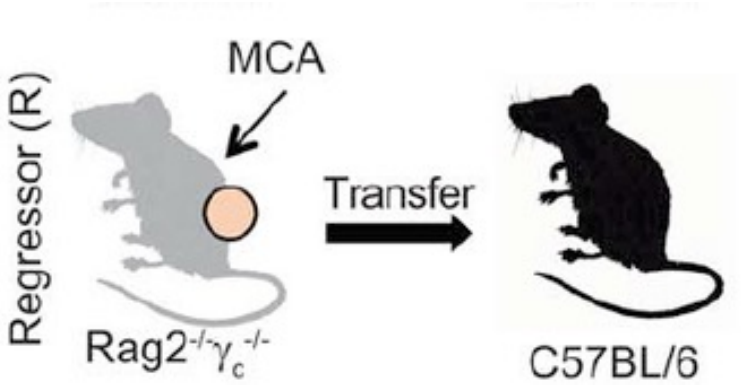
Immunological Surveillance



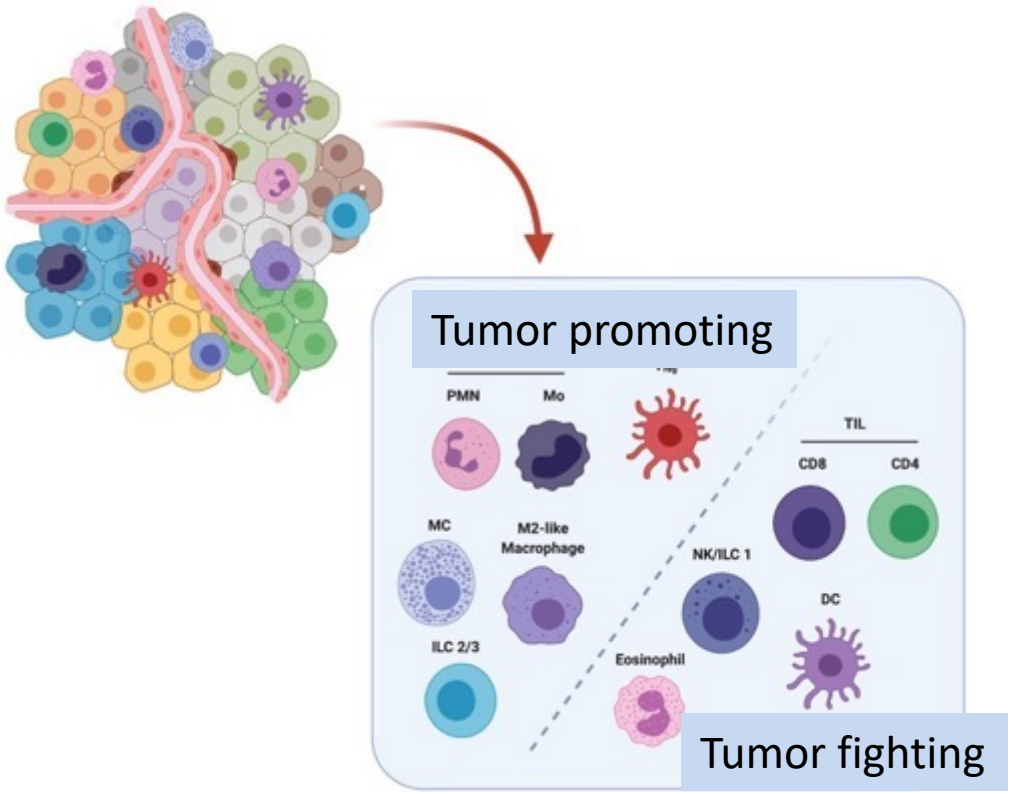
GROWTH



REJECTION

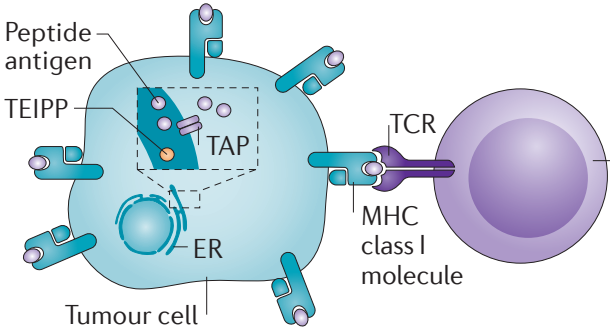
Dual role of the immune system in cancer

- Inflammation (by immune cells) can promote tumorigenesis
- The imune system has potent anti-cancer properties

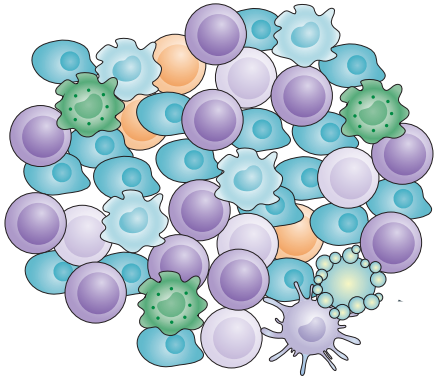


Generation of a tumor promoting/immuno suppressive environment

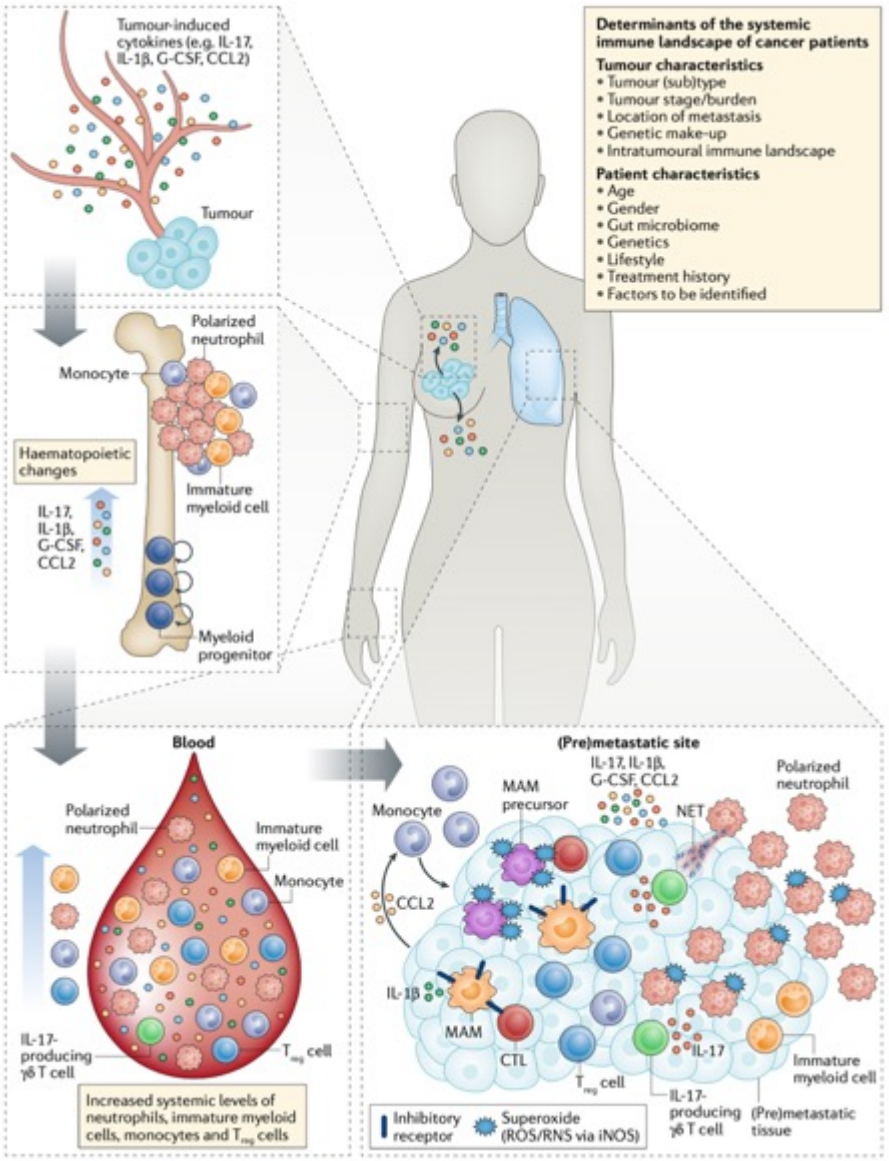
CELL AUTONOMOUS MODIFICATIONS



INFLAMMATION AND IMMUNE SUPPRESSIVE NETWORK



Immune cells in metastasis



- Tumor induced systemic inflammation is a key feature of disease progression associated to metastasis formation
- **IL-17,IL-1b, CCl2, G-CSF** reprogram hematopoiesis towards the myeloid lineage (monocytes, macrophages, neutrophils)

↓

Systemic accumulation of suppressive neutro and Treg

CCl2: drives accumulation of mono in the premetastatic niche

nature

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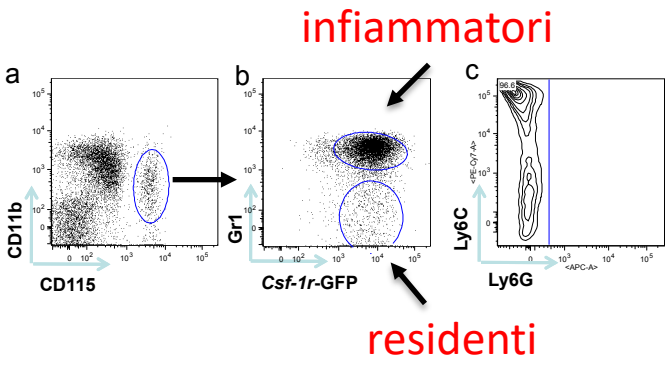
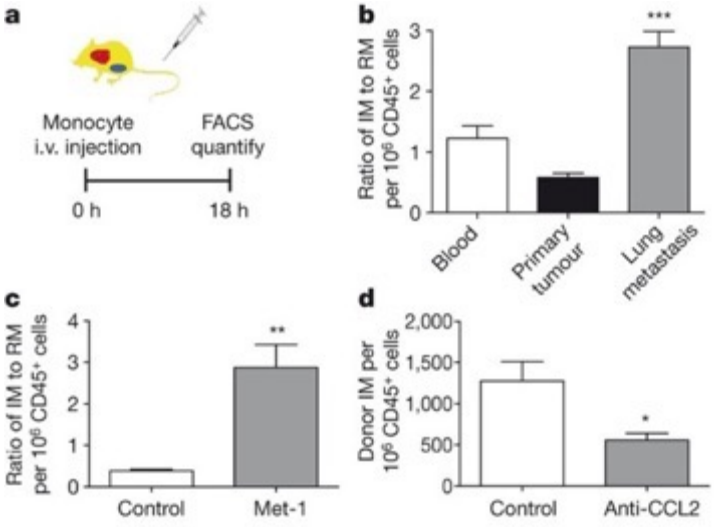
Published: 08 June 2011

CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis

Bin-Zhi Qian, Jiufeng Li, Hui Zhang, Takanori Kitamura, Jinghang Zhang, Liam R. Campion, Elizabeth A. Kaiser, Linda A. Snyder & Jeffrey W. Pollard ✉

Fluorescent monocytes csf1r-GFP





LETTER

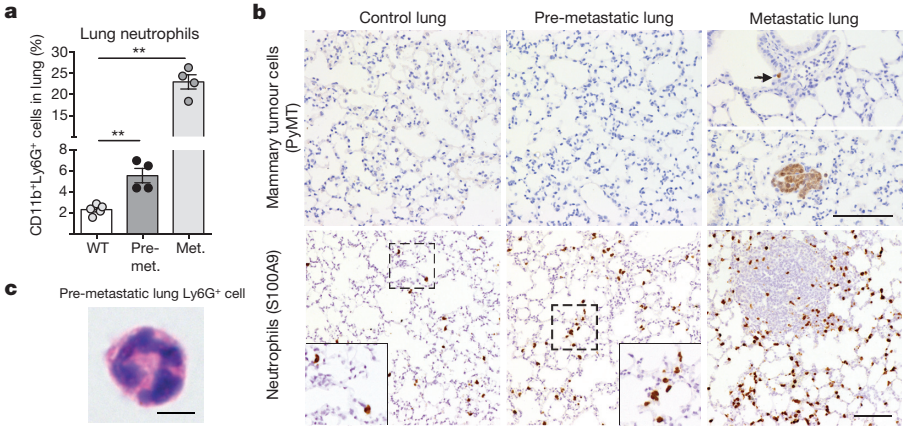
doi:10.1038/nature16140

Neutrophils support lung colonization of metastasis–initiating breast cancer cells

Stefanie K. Wculek[1] & Ilaria Malanchi[1]

MMTV-polyoma middle T antigen tumor model (spontaneous breast cancer model)

Question: leukocytes composition at distant sites favour metastatic growth? focus on neutrophils

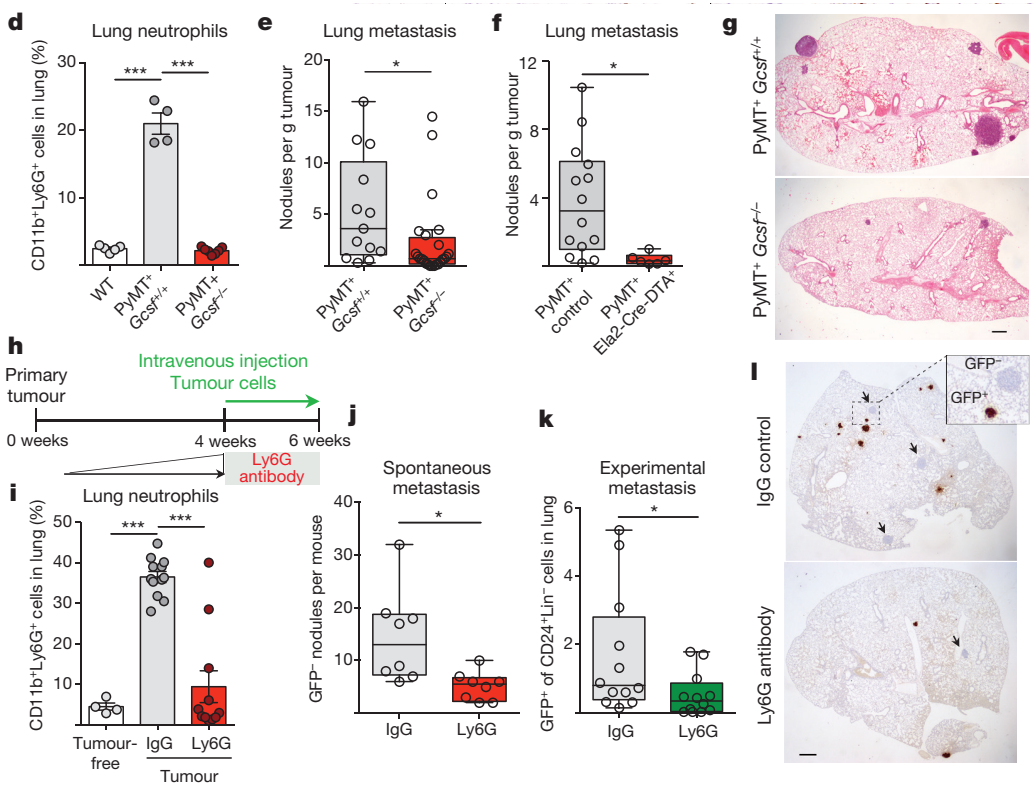


Neutrophils accumulate in the lung BEFORE arrival of cancer cells

Models of neutrophils deficiency: gcsf-null background

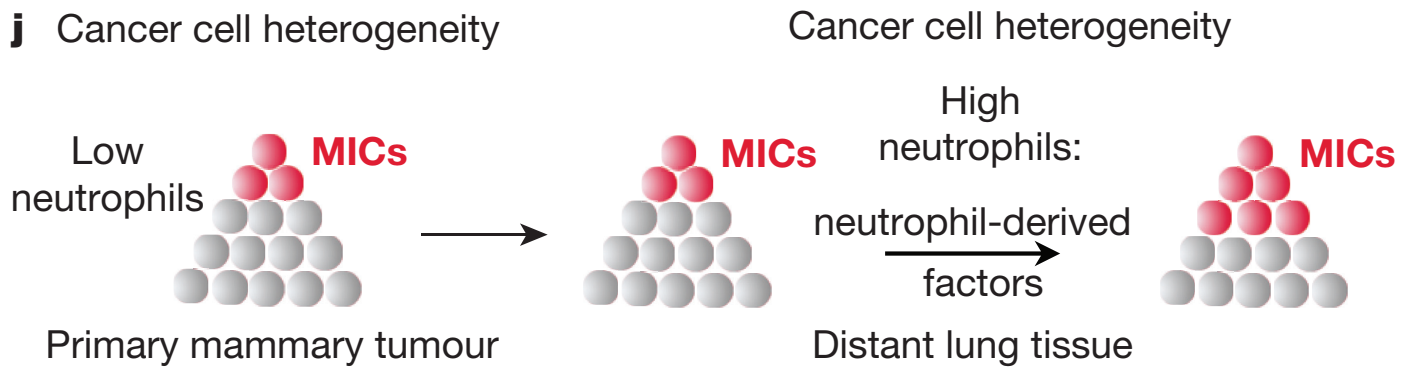
Second model of neutro depletion: Cre sotto promotore neutro specifico incrociati a difteria Toxic flozed

(elimino selettivamente i neutro)



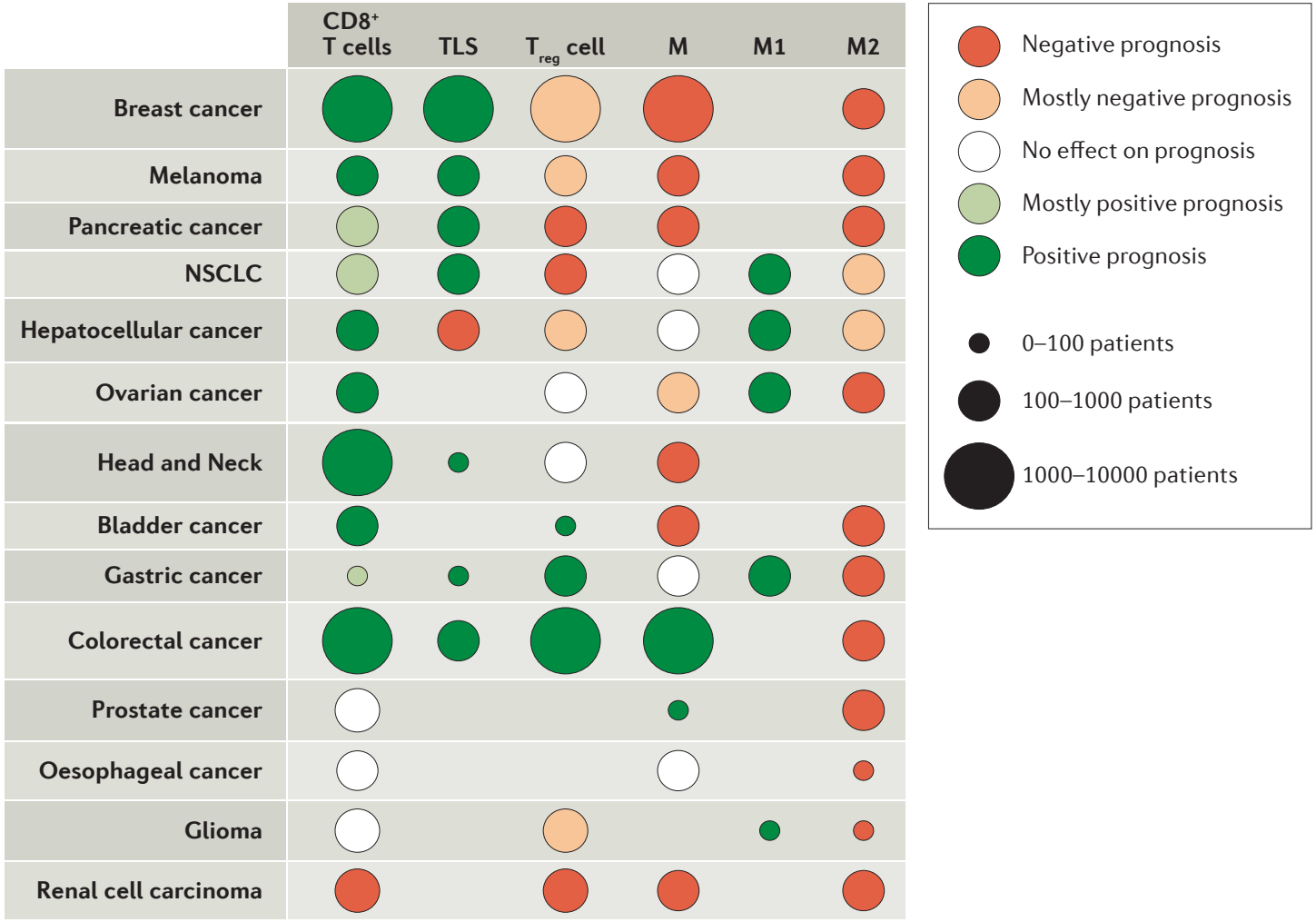
Rag- background, neutro depletion by antibodies

- Conclusions: neutrophils specifically support metastatic initiation. Neutro derived leukotrienes aid the colonization of distal tissues by expanding the sub-pools of cancer cells that retain tumorigenic potential



MIC: metastasis intiating cells

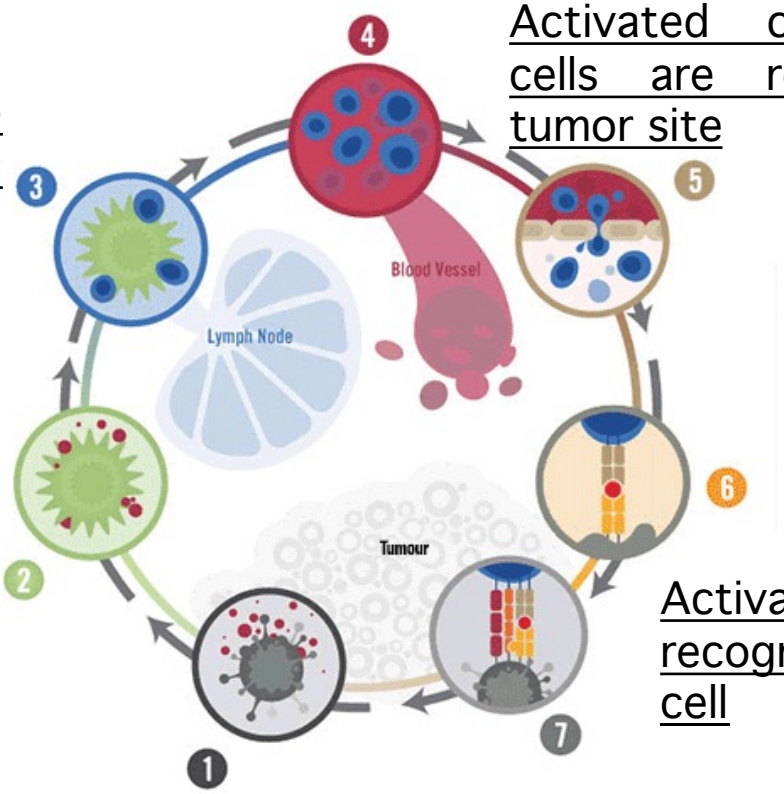
Effect of the immune infiltrate on the prognosis of patients



Cancer-immunity cell cycle and immunotherapy

Activated cytotoxic T cells are recruited at tumor site

APC present neo-Ags to cytotoxic T cells



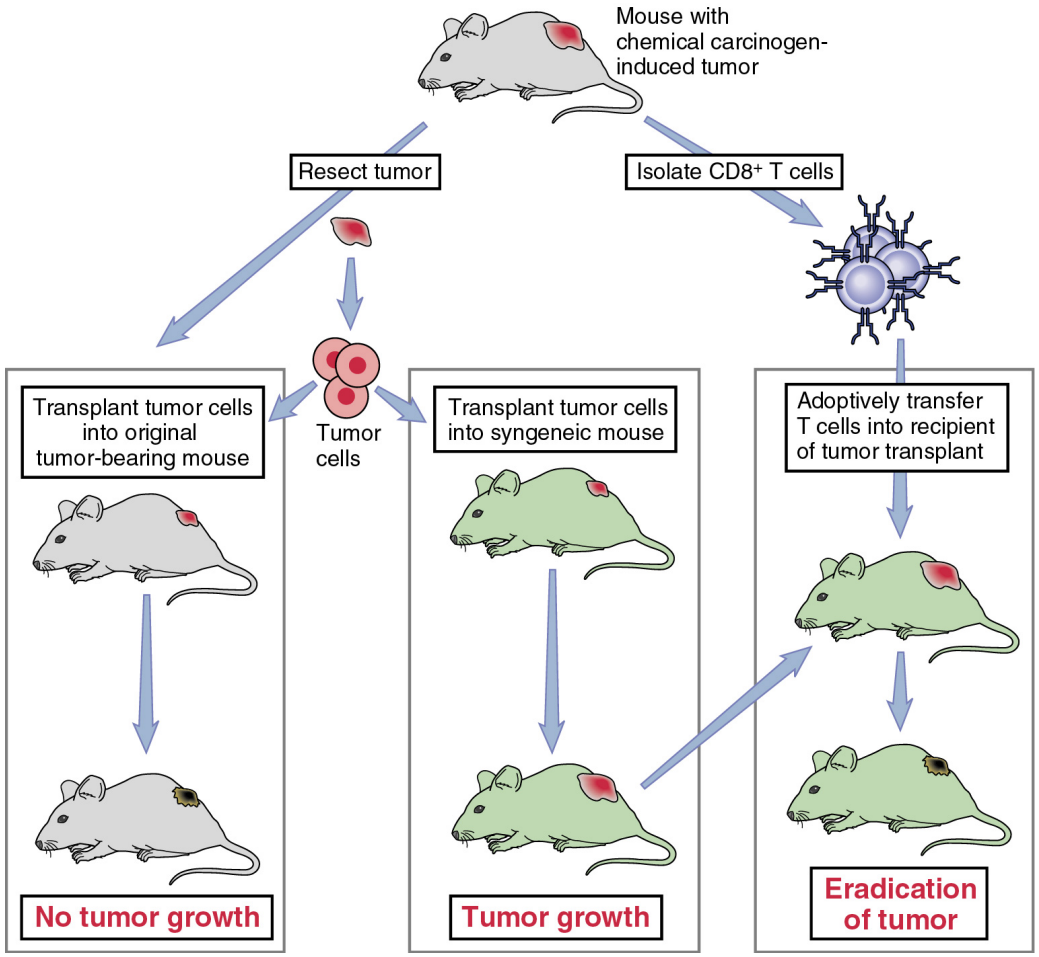
APC phagocyte apoptotic tumor cells and process the neo-antigens

Activated cytotoxic T cells recognize and eliminate cancer cell

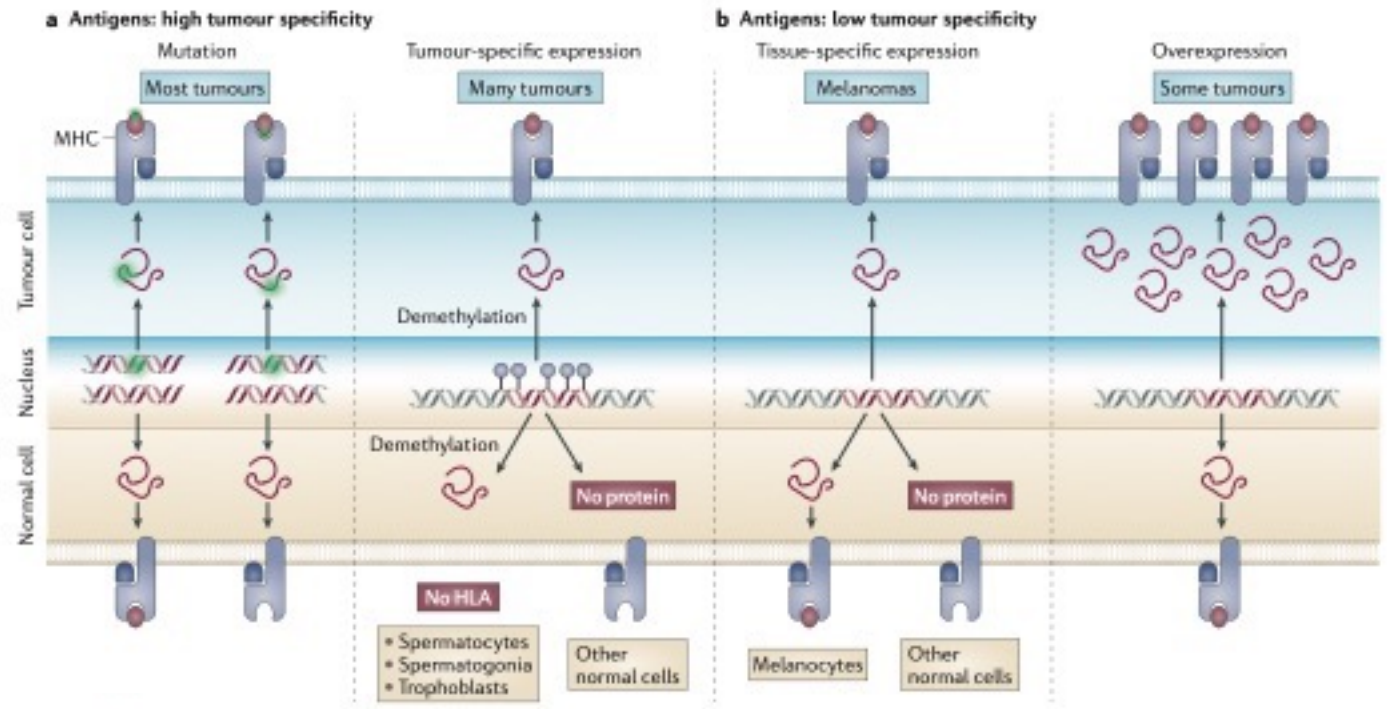
Mutations in cancer cells cause release of neo-antigens

Tumor Antigens
Discovery & Definition

Experimental Demonstration of Antigen-specific Tumor Immunity



What antigens are recognized by the immune response



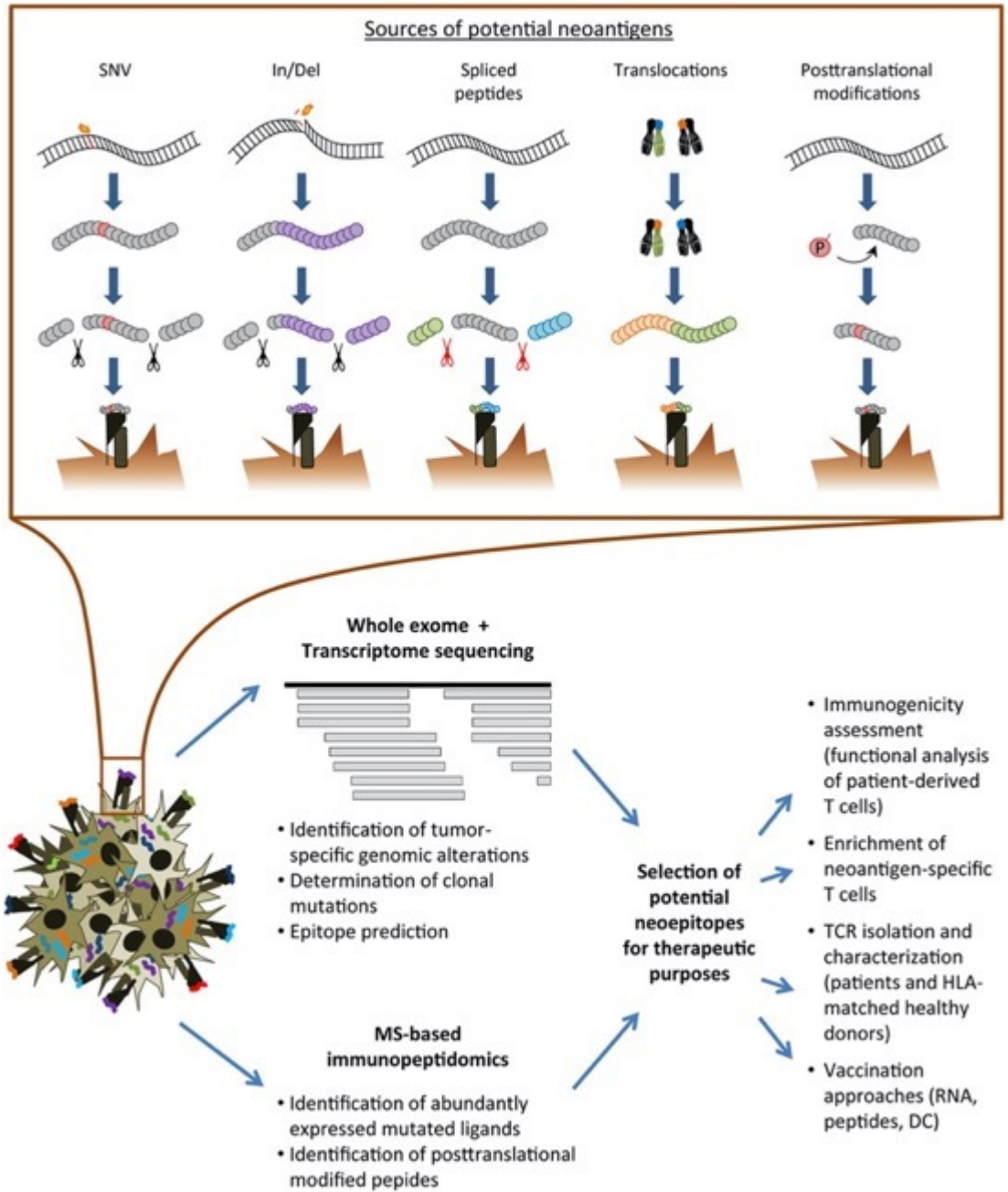
Point mutations that modify a peptide binding to MHC class-I, generation of new epitopes

Activation of genes not expressed in normal tissue, by demethylation

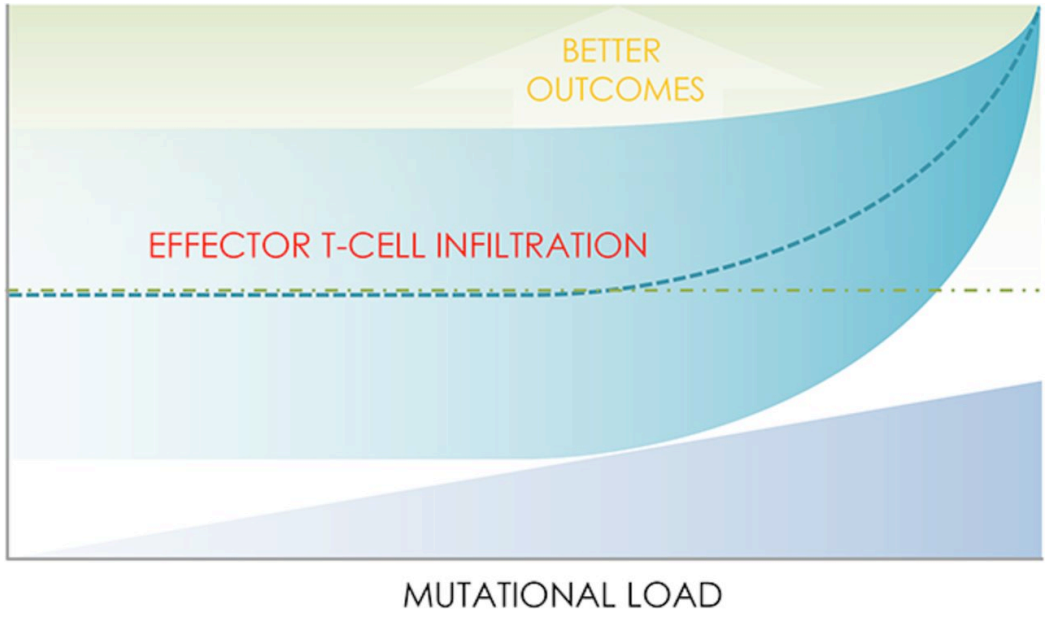
Tissue specific expression

Overexpression WT1:leukemia

Neoantigens: discovery and definition

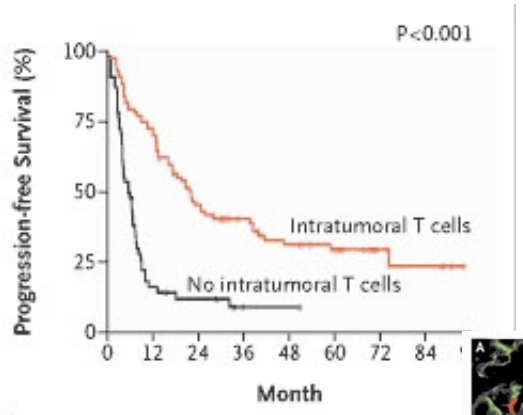


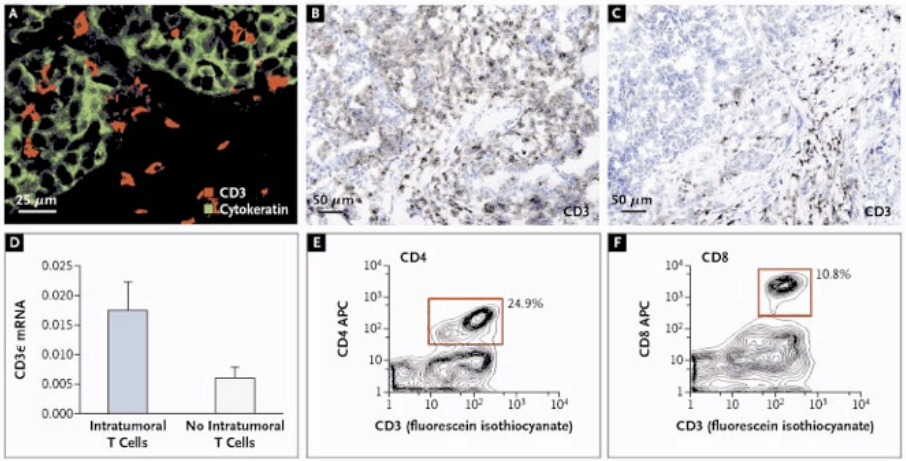
- More mutations → more neoantigens → more T cell infiltration



The presence of tumor antigens is demonstrated by the enrichment of T cells in antigenic tumors

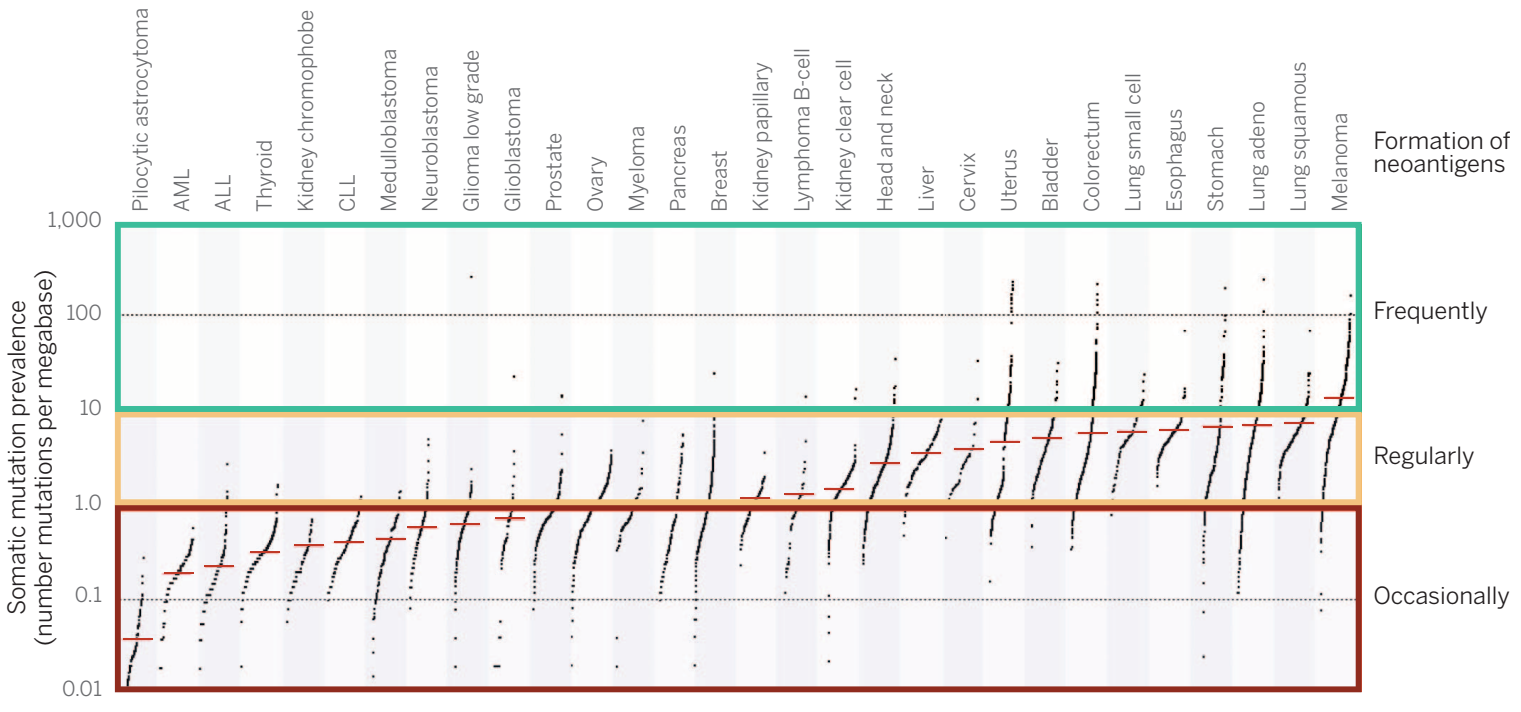
Tumor-infiltrating lymphocytes
correlation with survival
in ovarian cancer patients





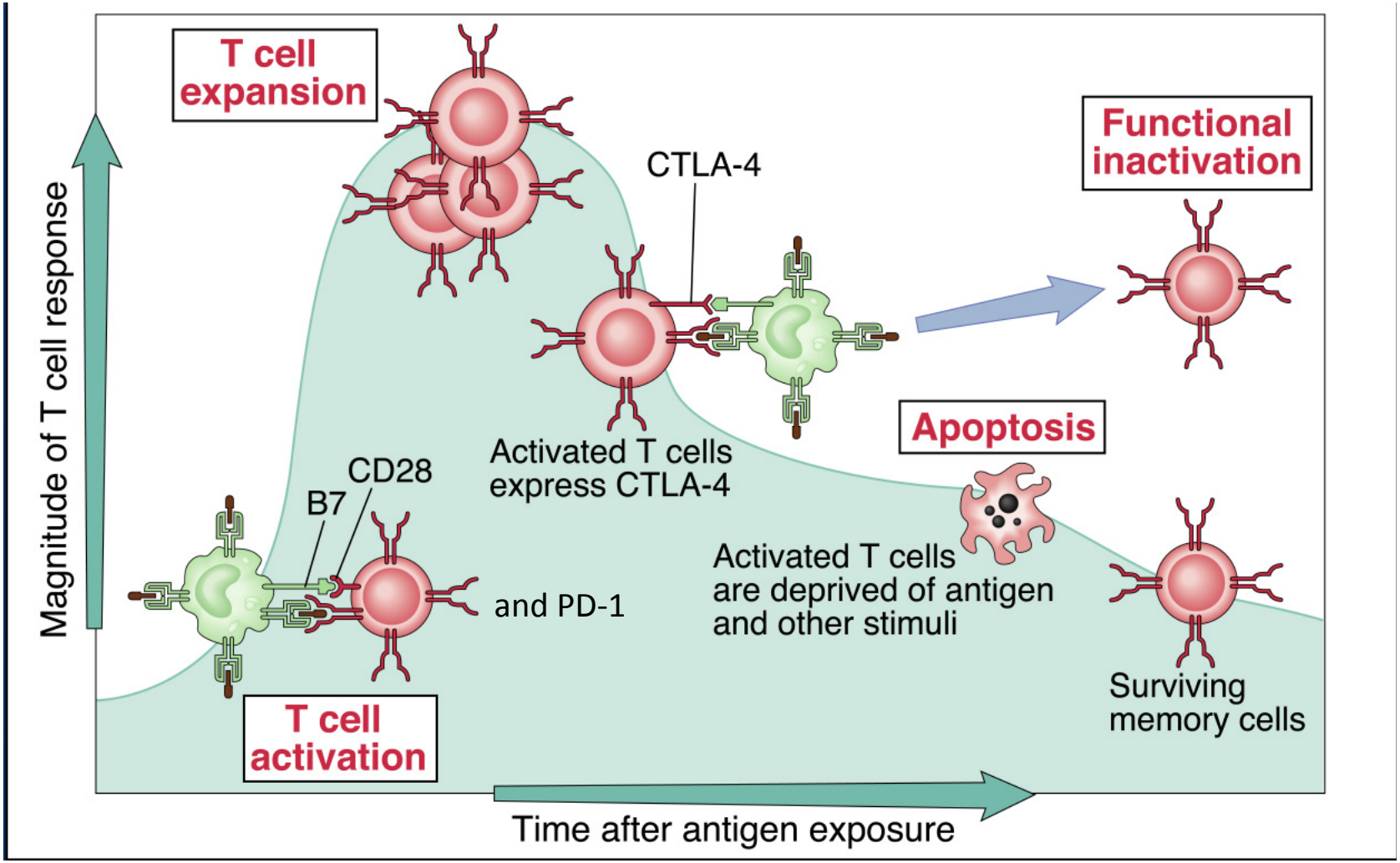
Zhang et al. NEJM 348:203, 2003

Frequencies of neoantigens across human cancers



"The genetic damage that on the one hand leads to oncogenic outgrowth can also be targeted by the immune system to control malignancies."

T cell activation is integrated with signals to restrain and dampen the immune response



The PD-1 inhibitory pathway

- PD-1 recognizes two ligands (PD-L1, PD-L2)
- Upregulated on T cells after activation
- Knockout of PD-1 leads to autoimmune disease (different manifestations in different strains)
- PD-1 expression in T cells suppress chronic infections

Exhaustion of CD8 T cells is reversible: the first report of PD-1/PD-L1 blockade to restore T cells responses in infection

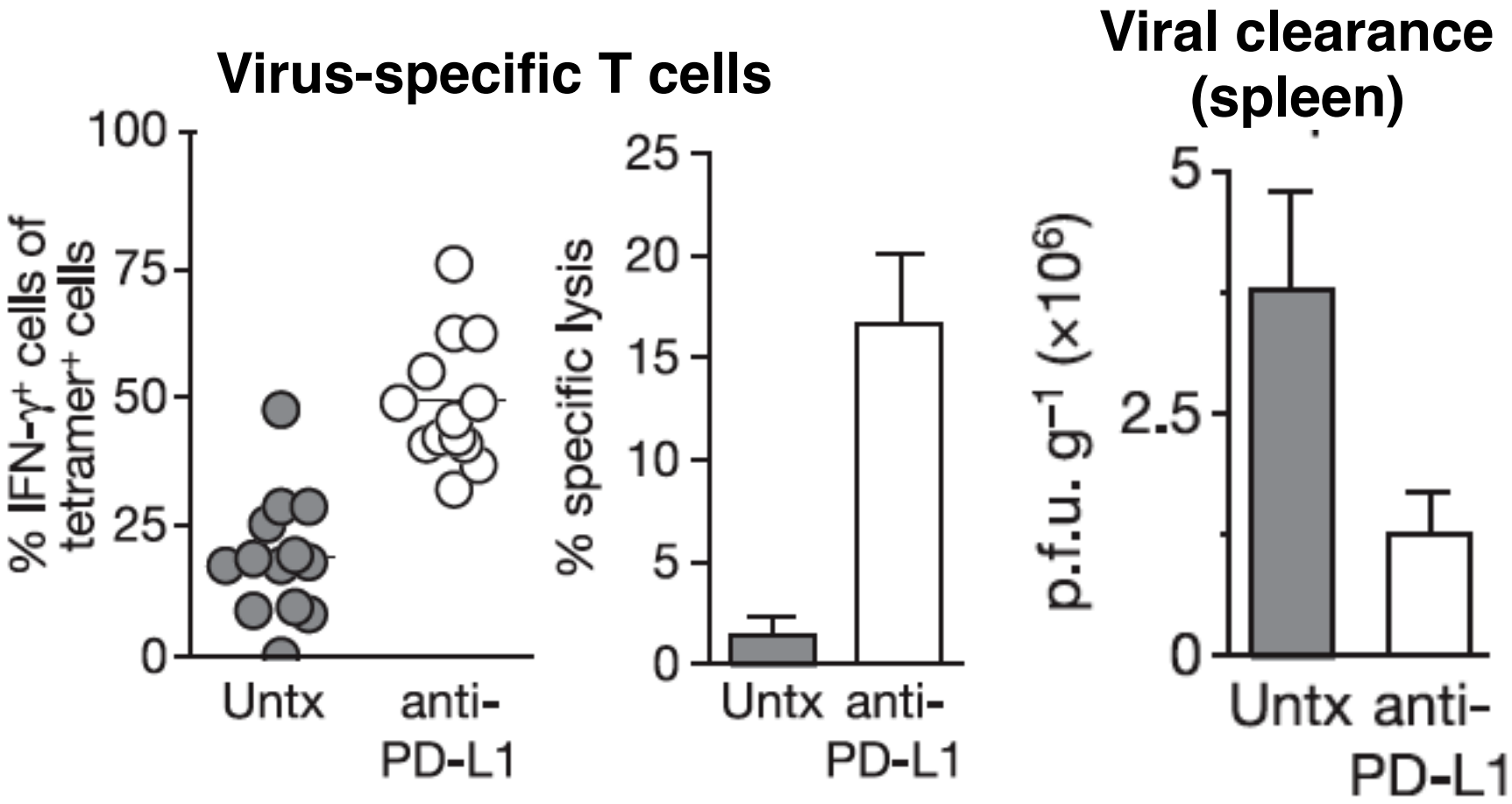
ARTICLES

Restoring function in exhausted CD8 T cells during chronic viral infection

Daniel L. Barber[1], E. John Wherry[2], David Masopust[1], Baogong Zhu[3], James P. Allison[4], Arlene H. Sharpe[5], Gordon J. Freeman[3] & Rafi Ahmed[1]

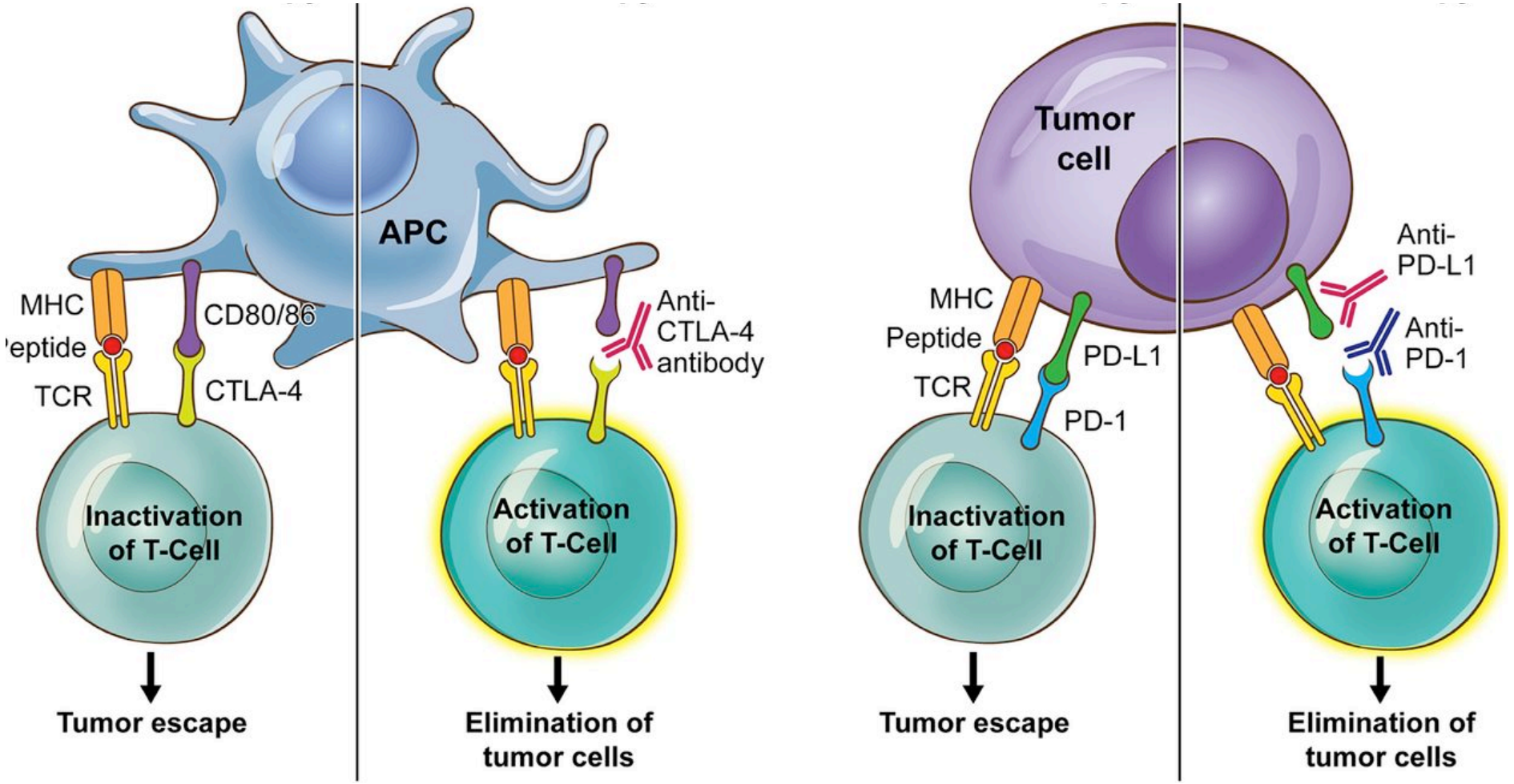
Functional impairment of antigen-specific T cells is a defining characteristic of many chronic infections, but the underlying mechanisms of T-cell dysfunction are not well understood. To address this question, we analysed genes expressed in functionally impaired virus-specific CD8 T cells present in mice chronically infected with lymphocytic choriomeningitis virus (LCMV), and compared these with the gene profile of functional memory CD8 T cells. Here we report that PD-1 (programmed death 1; also known as Pdcd1) was selectively upregulated by the exhausted T cells, and that *in vivo* administration of antibodies that blocked the interaction of this inhibitory receptor with its ligand, PD-L1 (also known as B7-H1), enhanced T-cell responses. Notably, we found that even in persistently infected mice that were

T cell exhaustion is reversible by blockade of inhibitory receptor

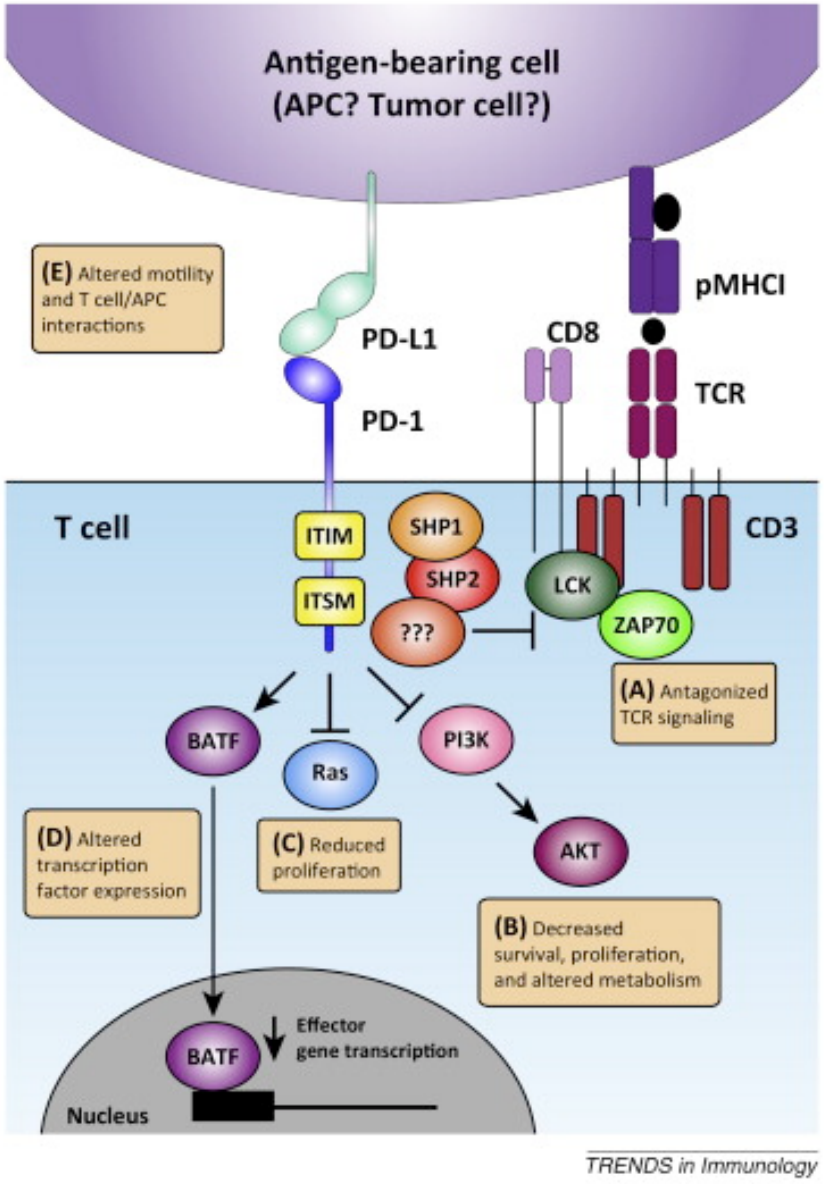


In chronic LCMV infection in mice, virus-specific T cells become paralyzed; express high levels of PD-1; function restored by blocking the PD-1 pathway. Barber et al (Ahmed lab) Nature 2006

PD-1/PDL1 blockade in cancer



Mechanism of PD-L1/PD-1 blockade



CANCER IMMUNOLOGY

Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer

Naiyer A. Rizvi,[1,2*†] Matthew D. Hellmann,[1,2*] Alexandra Snyder,[1,2,3*] Pia Kvistborg,[4] Vladimir Makarov,[3] Jonathan J. Havel,[3] William Lee,[5] Jianda Yuan,[6] Phillip Wong,[6] Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[2,3,5‡]