IMMUNOTERAPIA: razionale e basi biologiche

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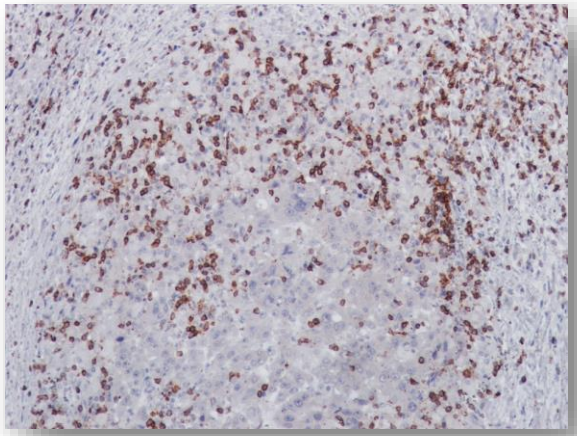
Cancer Immunotherapy:
the unique strategy of targeting tumor immunity



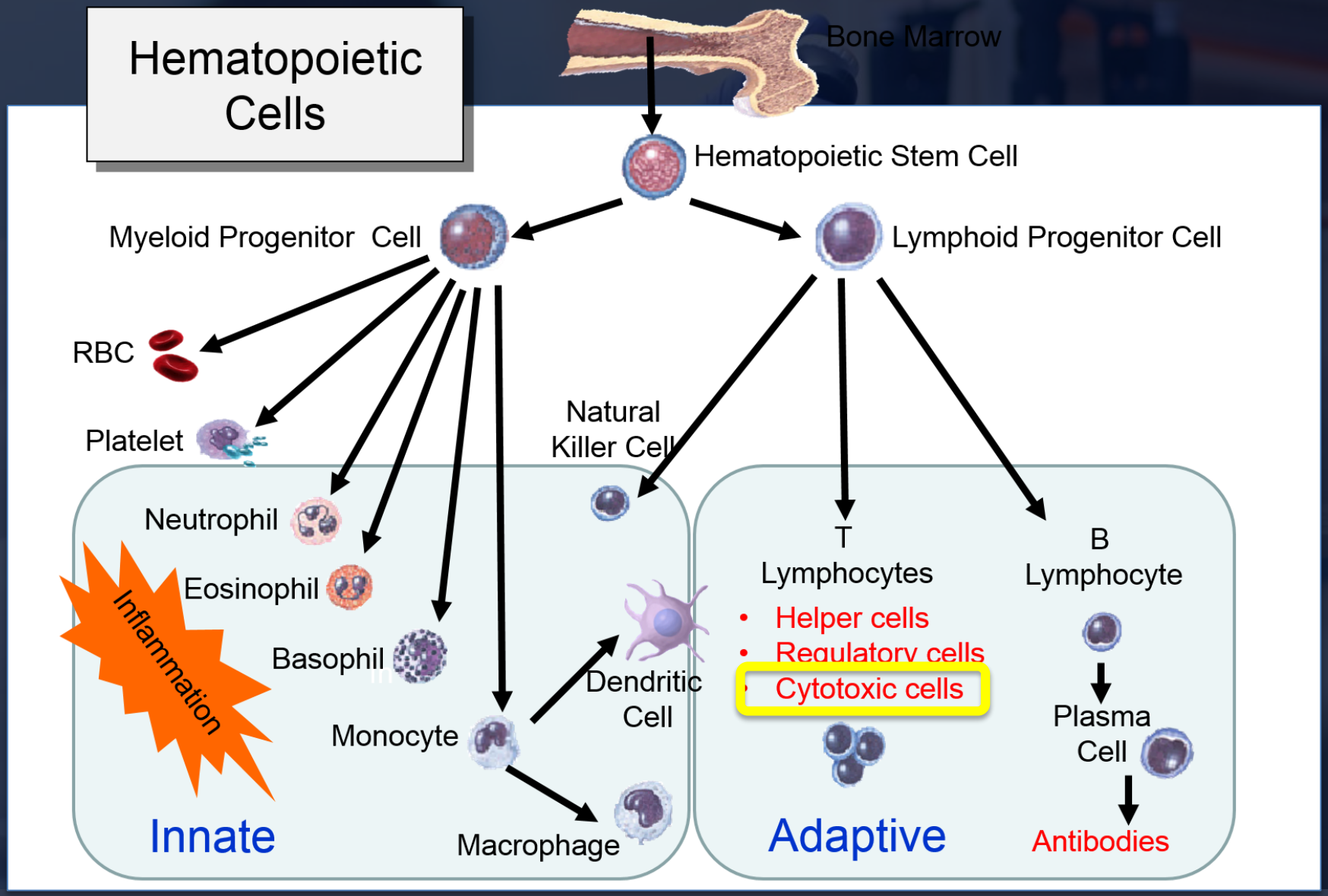
The immune system protects us from tumor through the same pathways utilized to fight pathogens

SPECIFICITY
Immune responses can finely recognize "aberrant" cells from normal cells

MEMORY
Once established, immunity can provide long-term protection

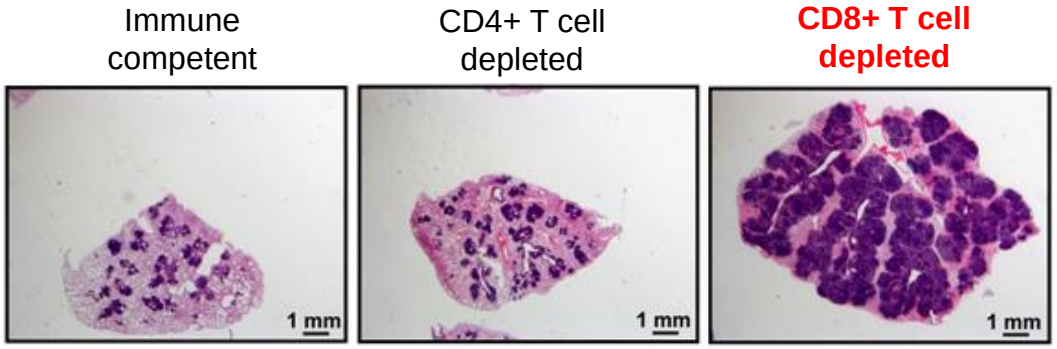
INTRINSIC THERAPY
Based on endogenous immunity, cancer immunotherapy may work in all tumor histologies

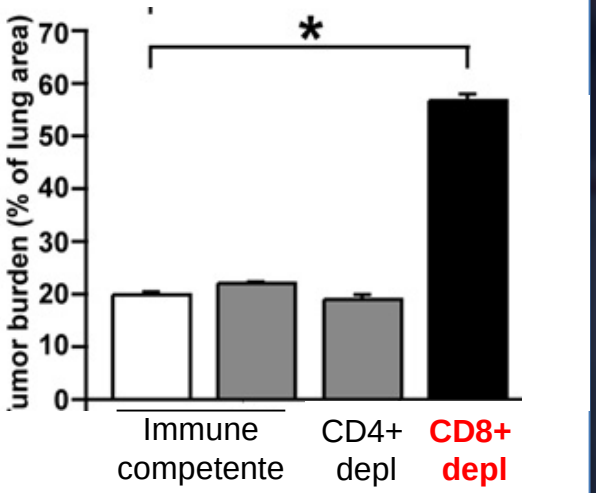
The complex network of anti-tumor immunity

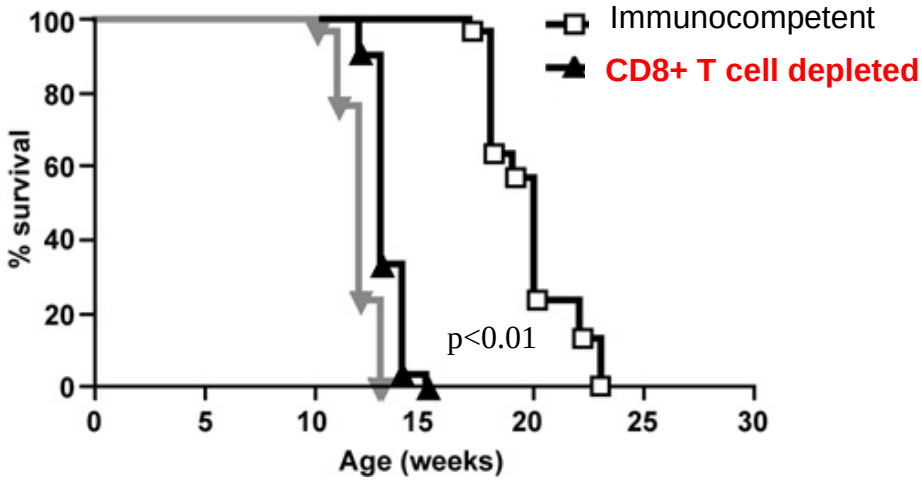


Kidd et al., Nature Biotech 2015

Tumor infiltrating CD8+ T cells control tumor growth in aggressive murine lung carcinoma

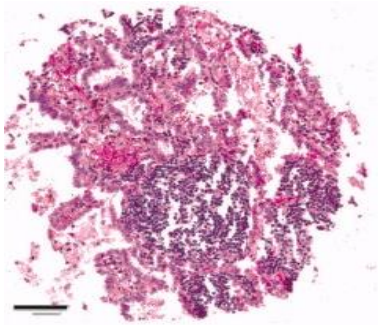




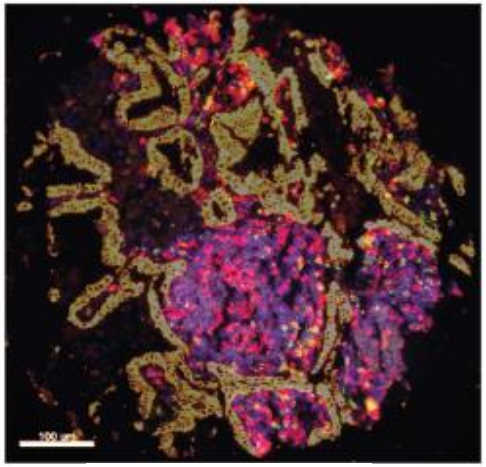


Ganesan et al., J Immunol 2013

Positive prognostic value of tumor infiltrating CD8 T cells



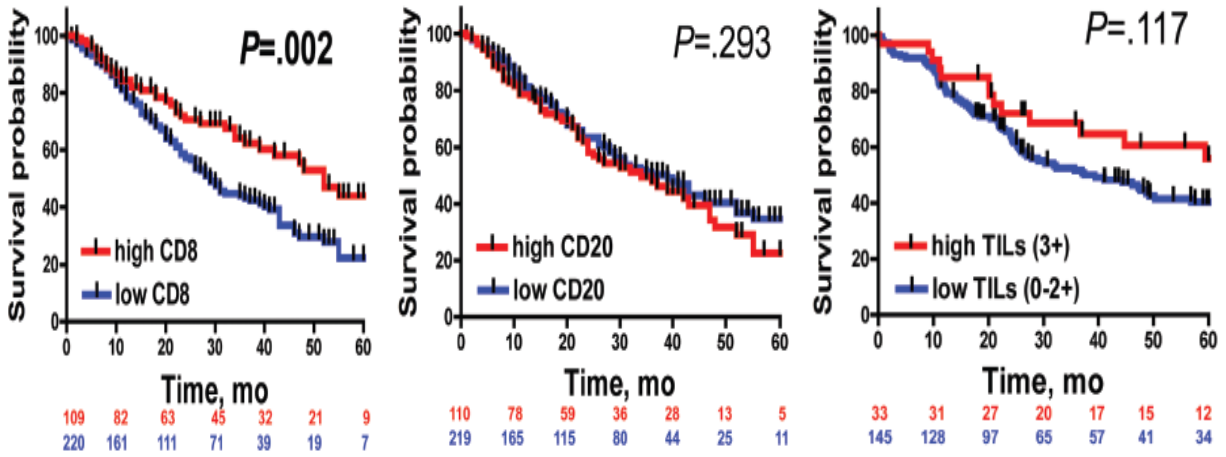
Hematoxylin & Eosin



DAPI/CK/CD3/CD8/CD20

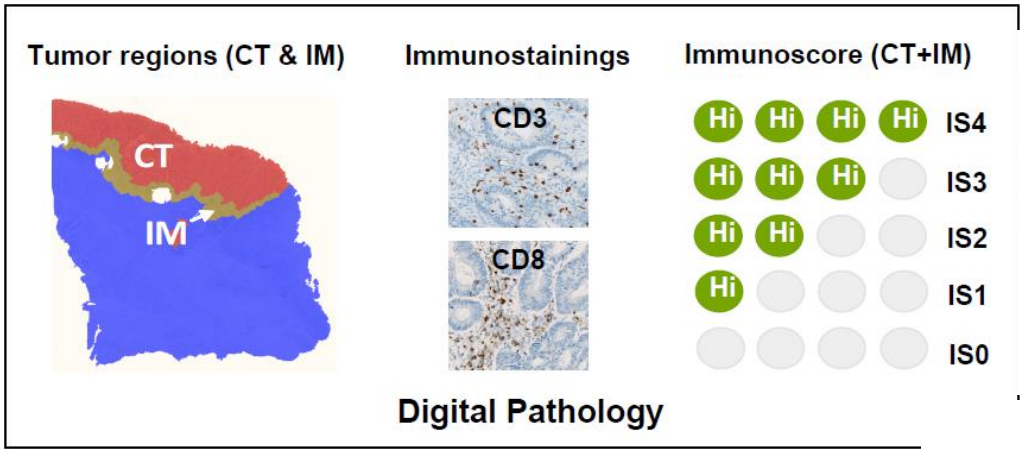
Confirmed by Djenidi et al., J Immunol 2015
and Donnem et al., Clin Cancer Res 2015

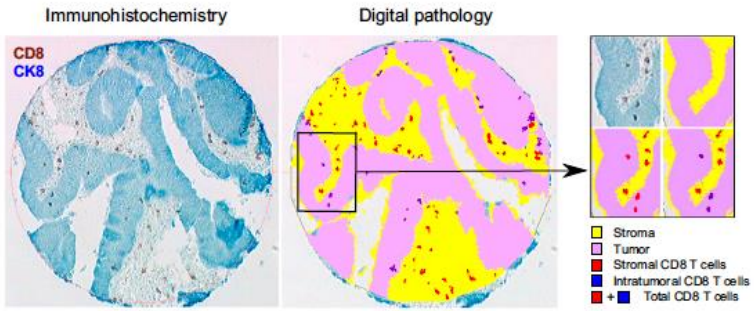
NSCLC

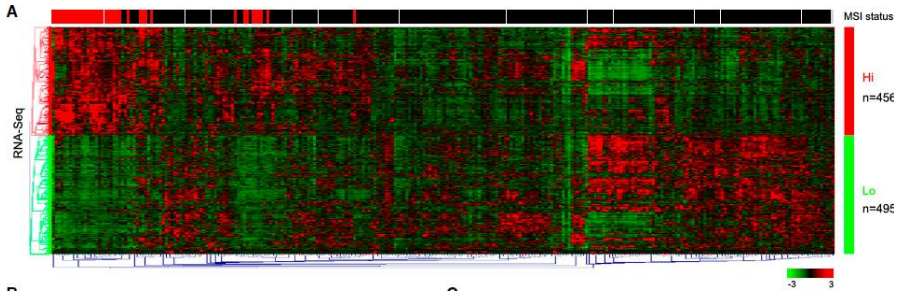


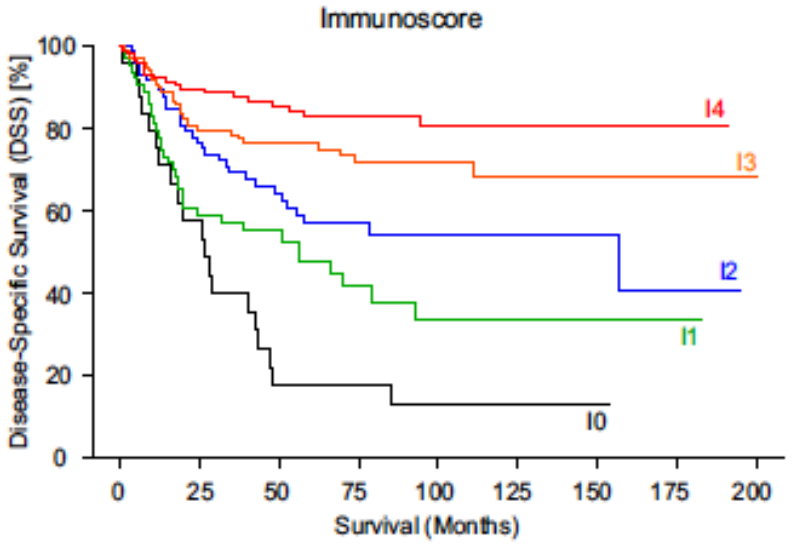
Schalper et al., J Natl Cancer Inst 2015

Immunoscore is an independent prognostic histological parameter in CRC



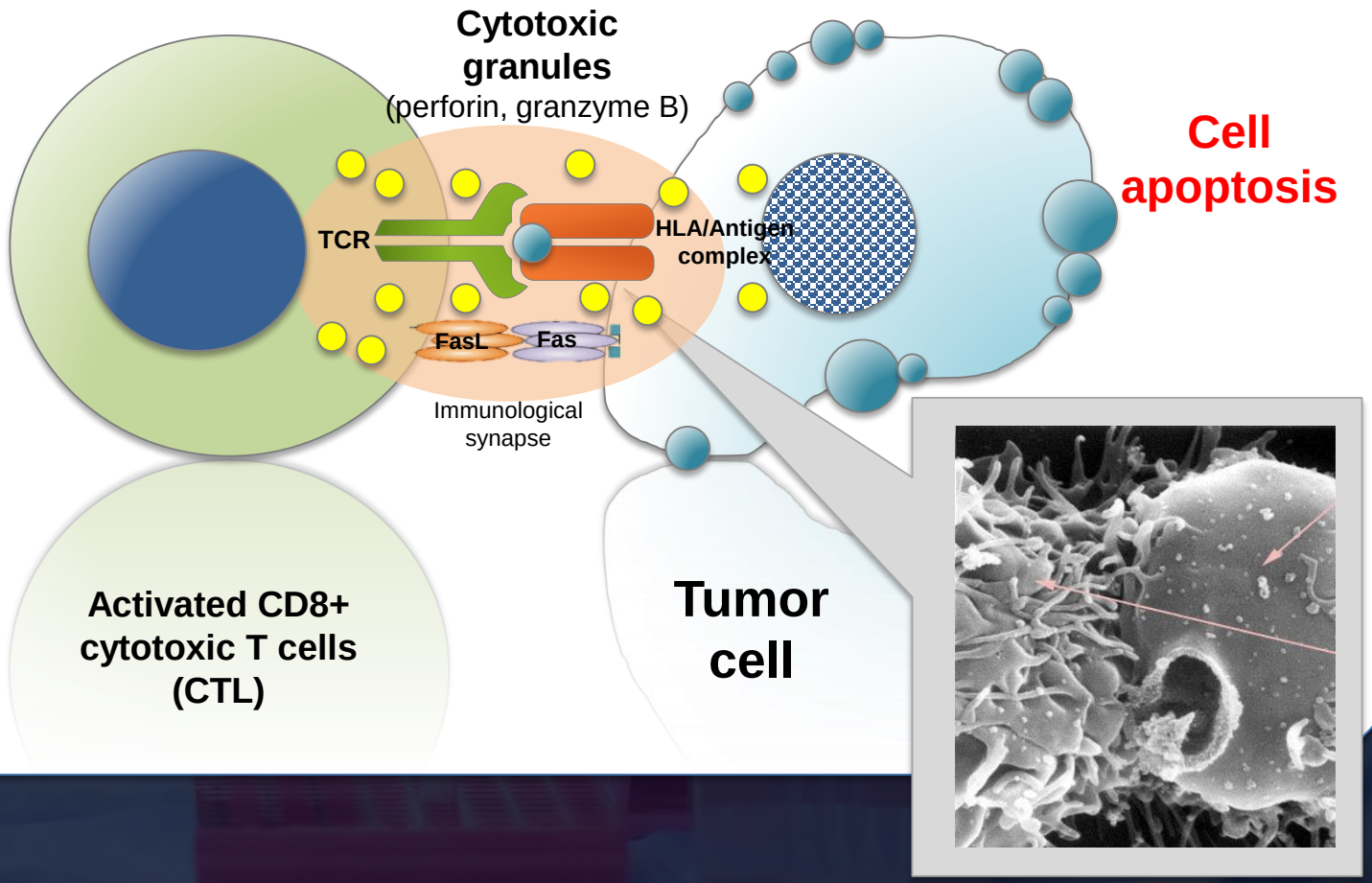






Mlecnik et al., ….and J Galon, Immunity 2016

Pathways of tumor cell killing by CD8+ T cells



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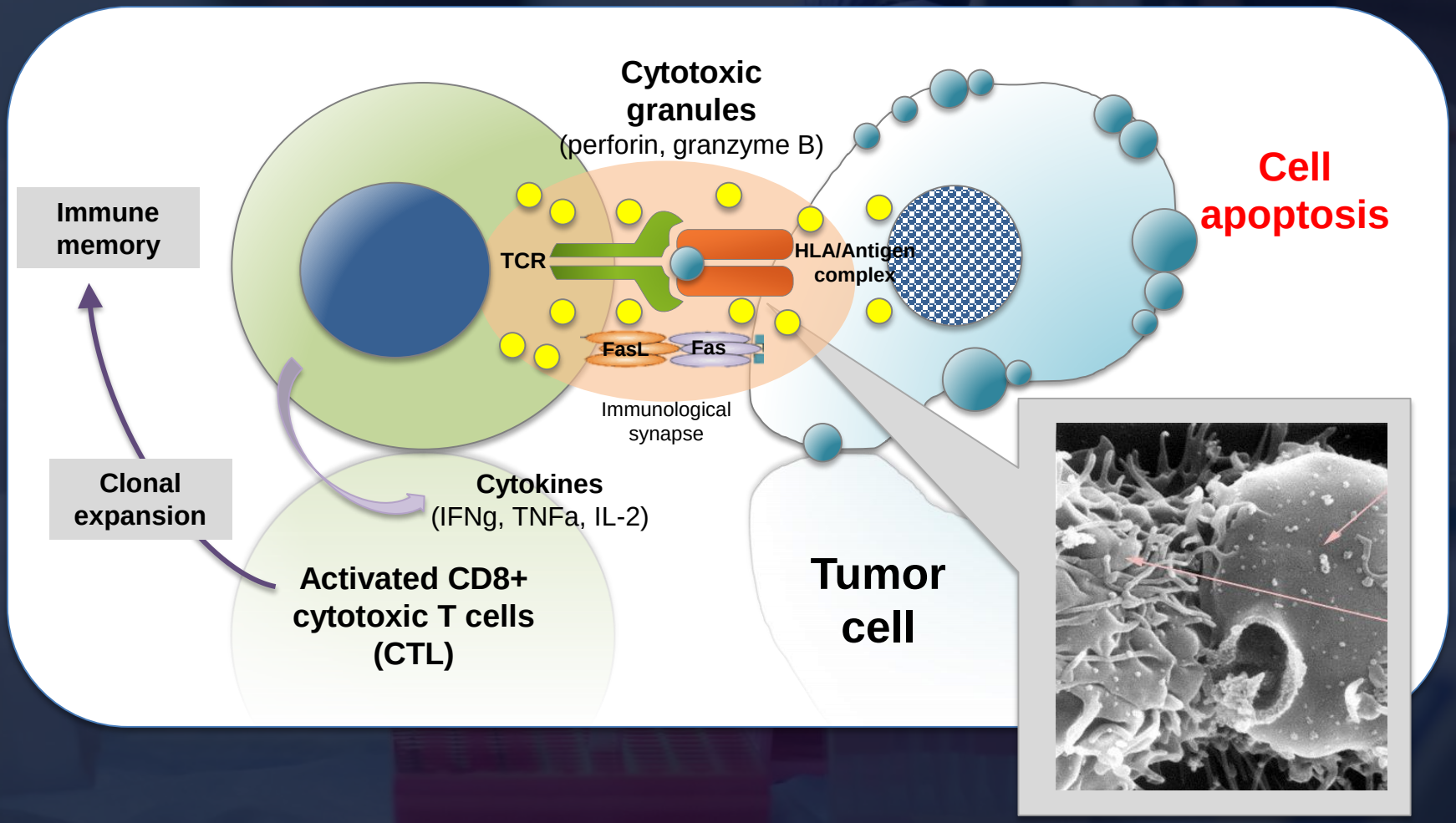
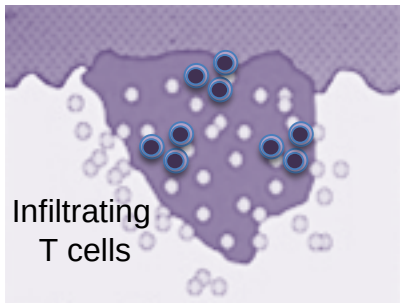
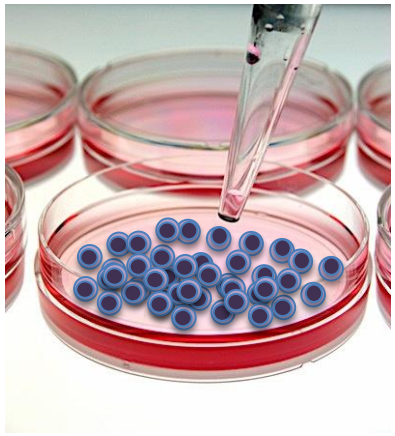


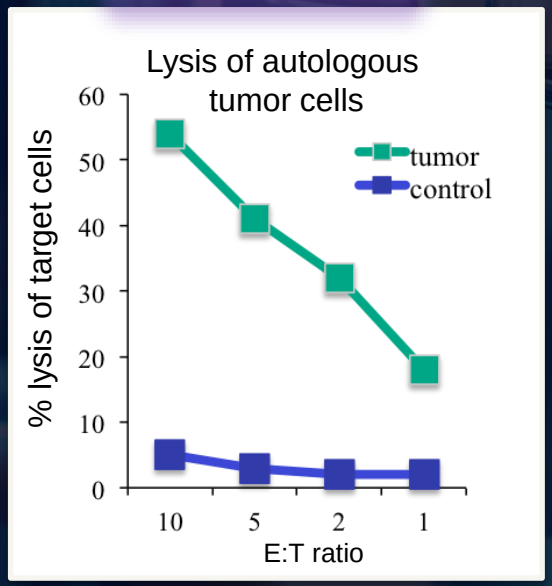
Cancer lesions are infiltrated by tumor-specific CD8+ cytotoxic T cells



Interleukin 2

CD8+ T cells





Lysis of: autologous tumor, common tumors same histotye, common tumor different histotype

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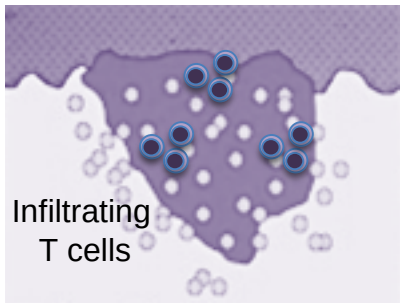

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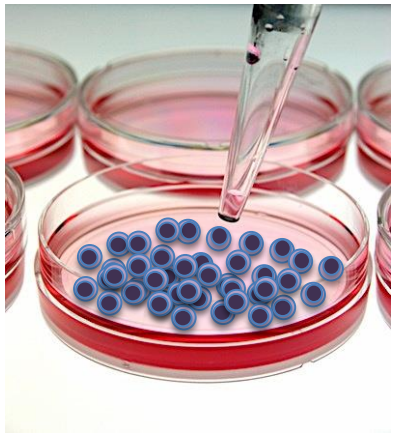
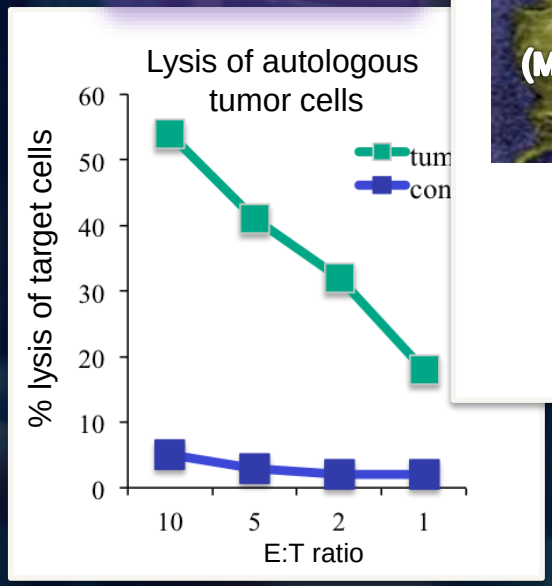


CD8+ T cells



Lysis of: autologous tumor, common tumors
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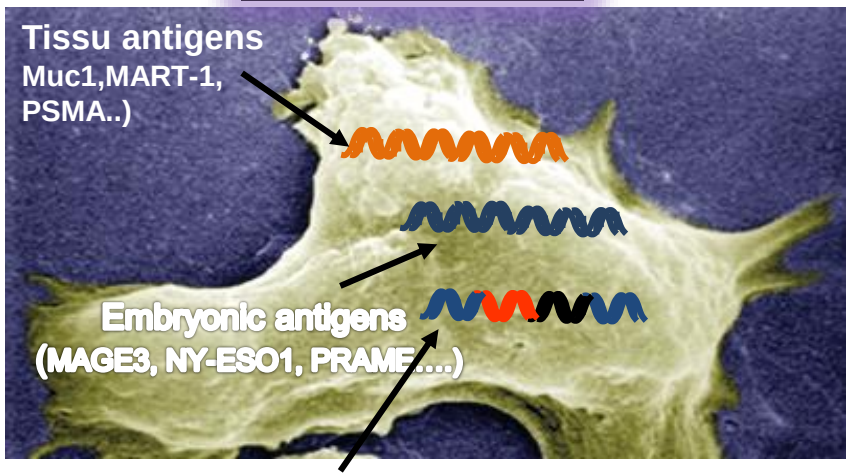
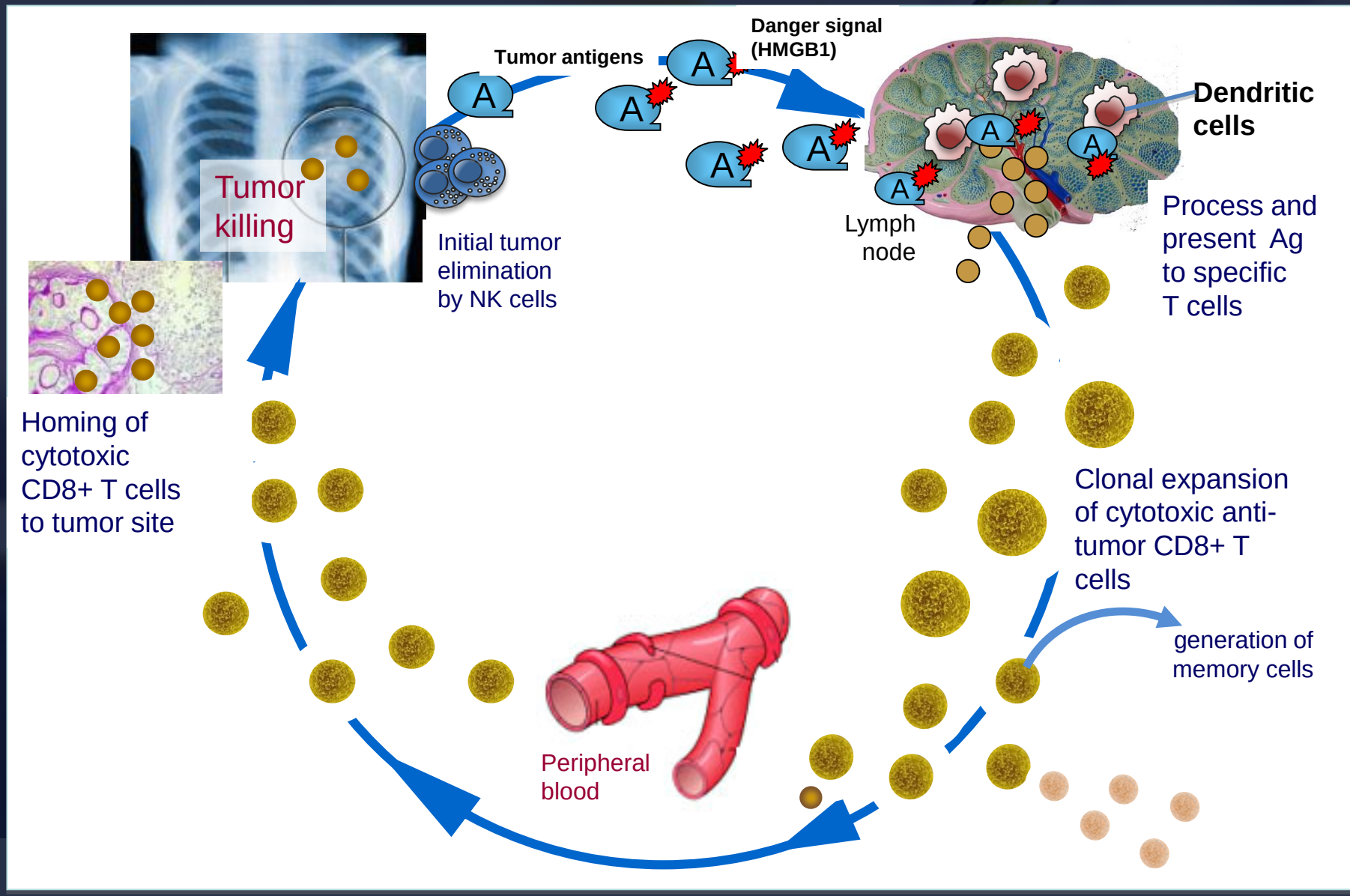
Tumor Antigens

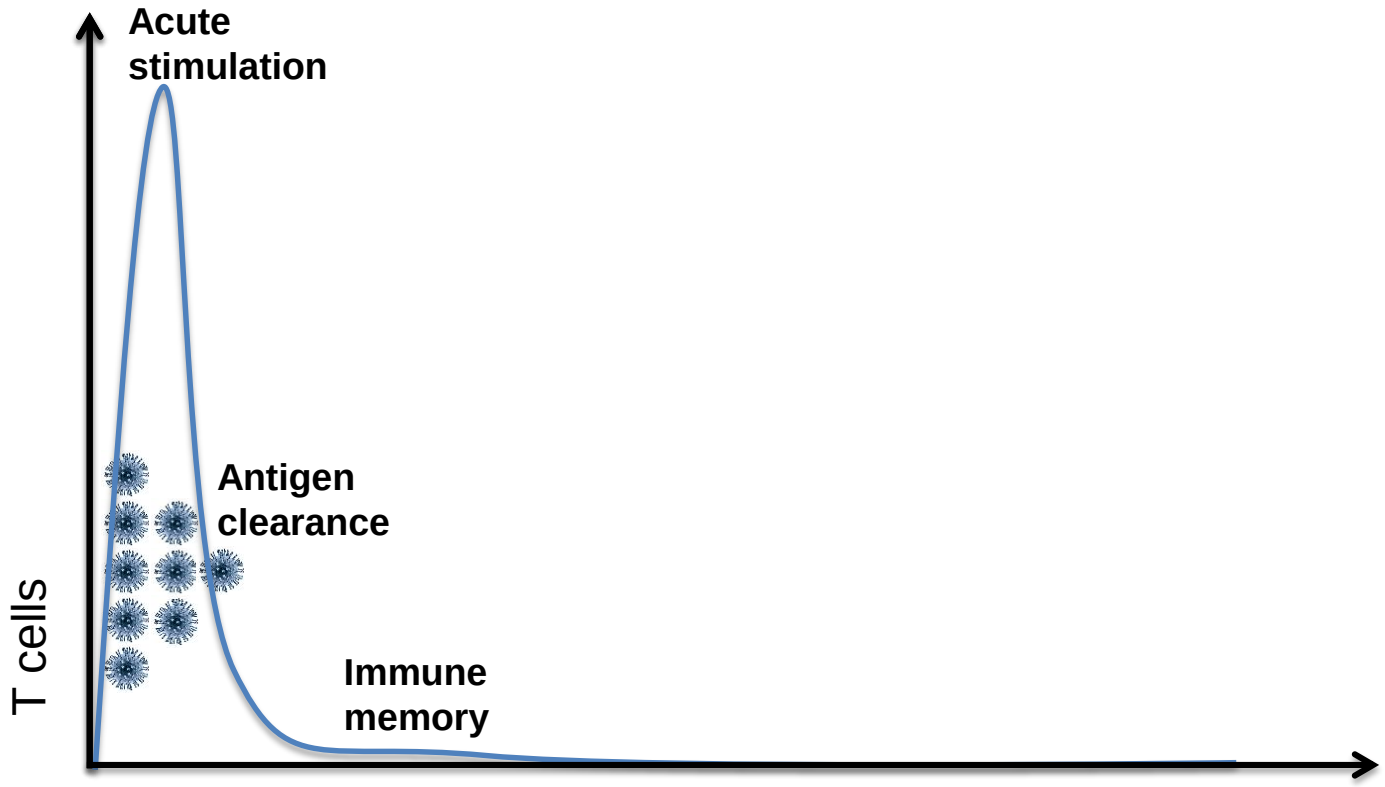


Unique mutated antigens or
NEO-ANTIGENS
(non-synonimous mutations
due to genetic instability)

Chronic tumor-mediated immune hyperstimulation: the Tumor Immunity Cycle



In cancer, like in chronic infections, antigen persistency leads to T cell exhaustion



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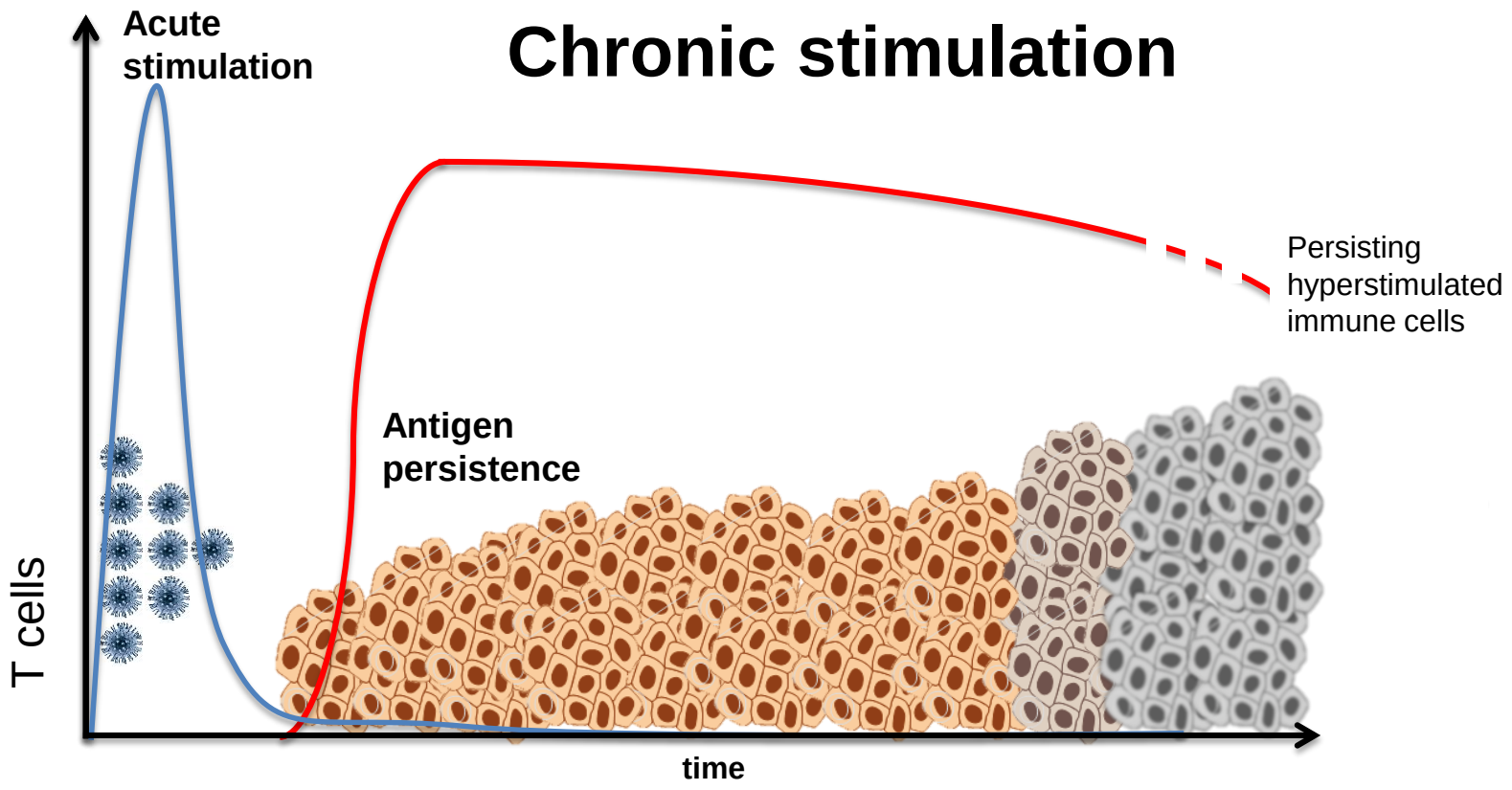

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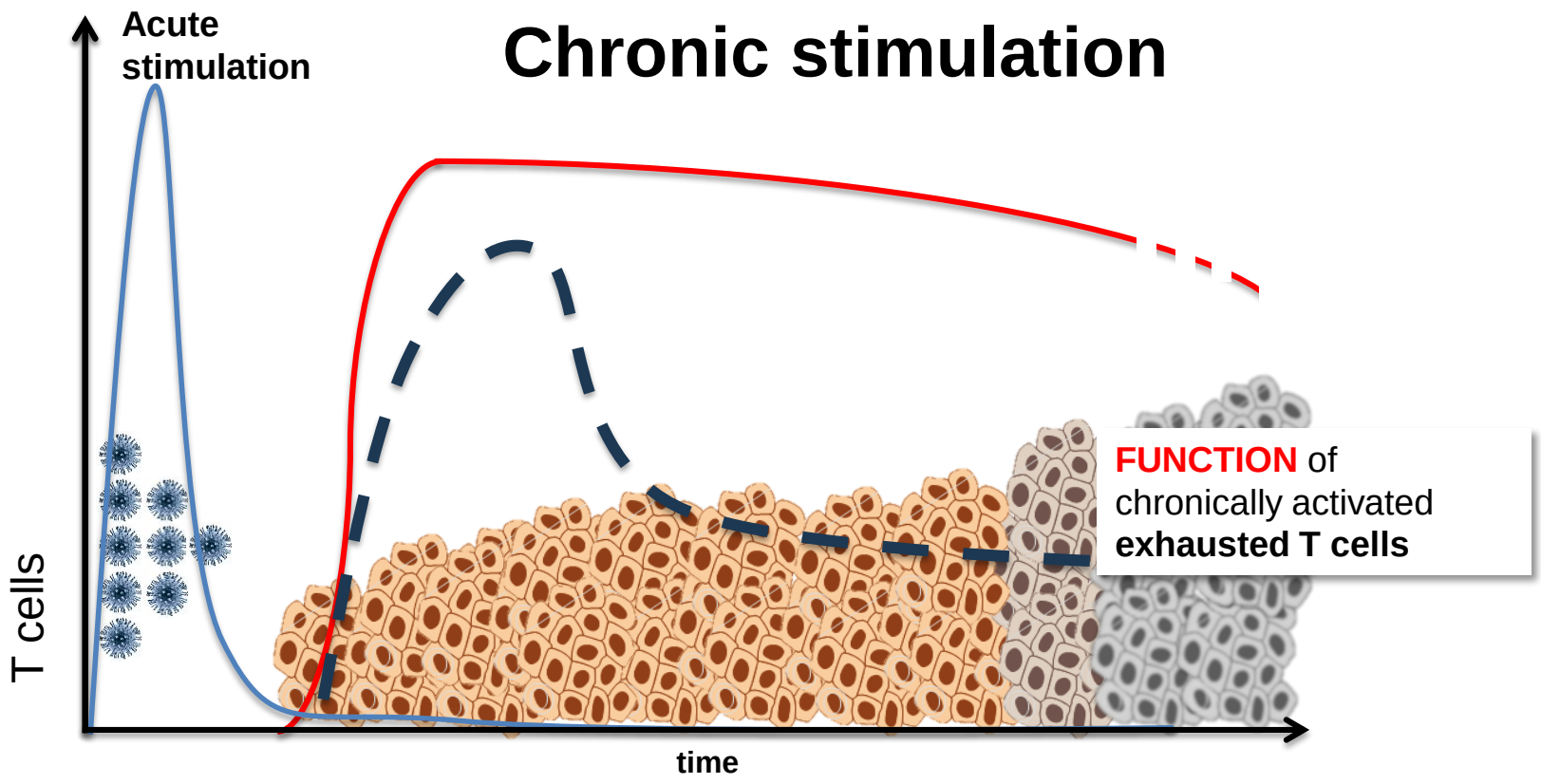

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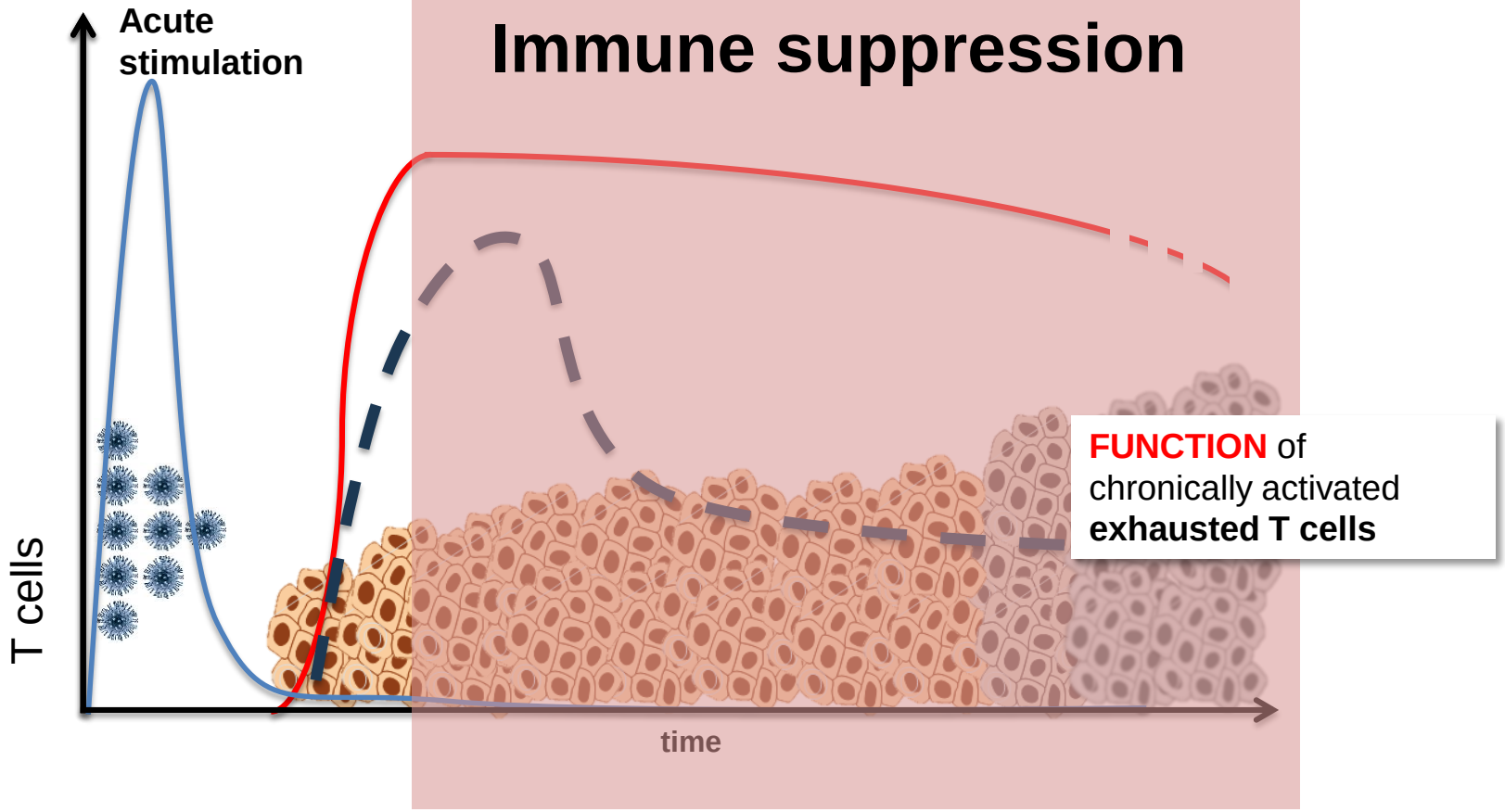
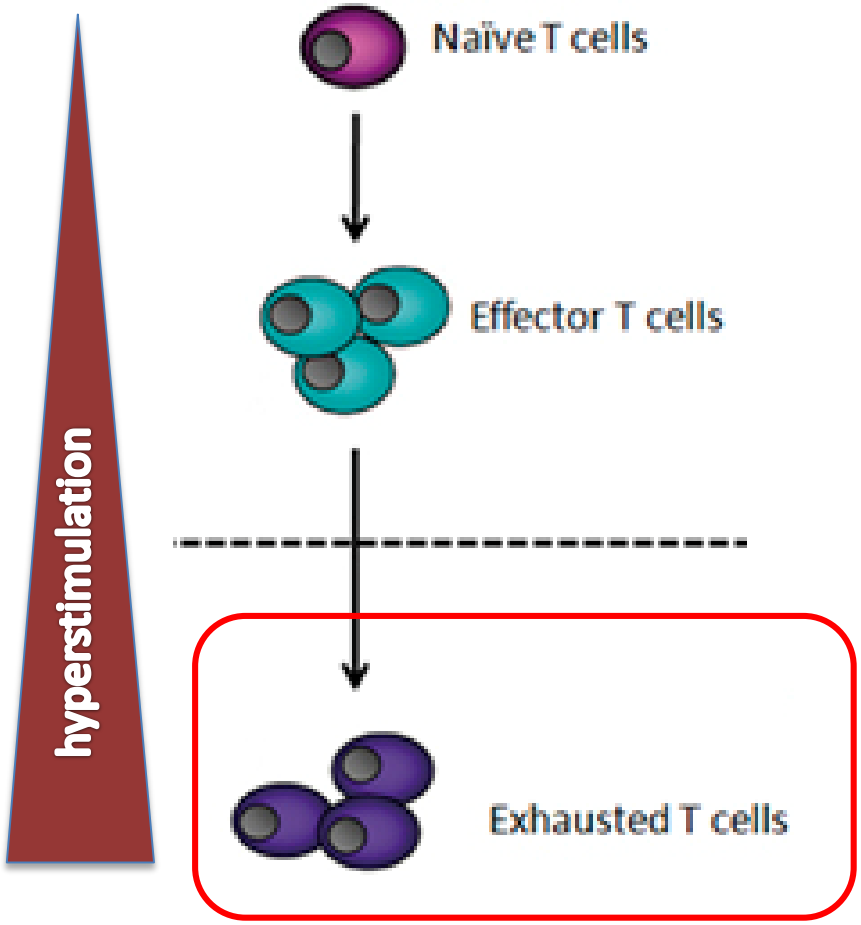
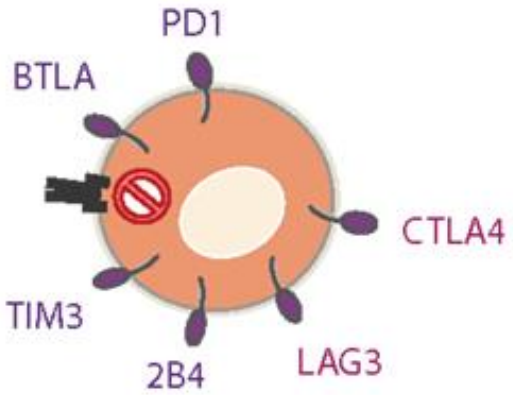


Chronic antigen stimulation induces **T cell exhaustion**

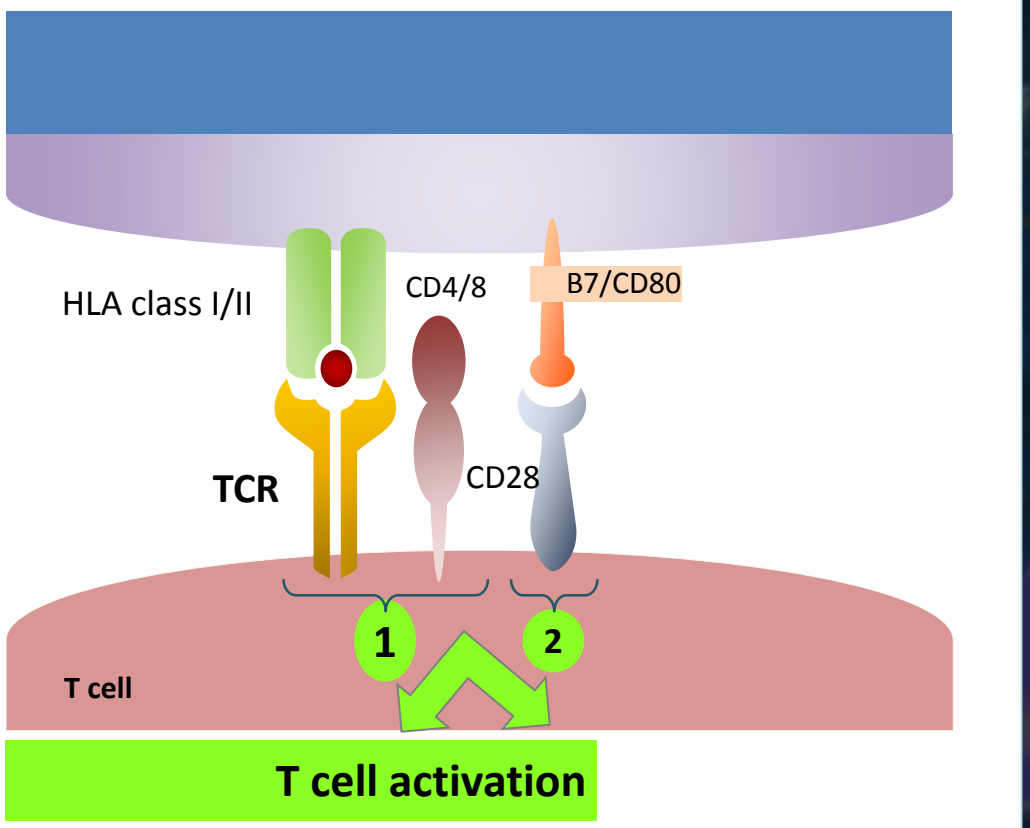


"Exhausted"
(chronic infection & cancer)



Progressive up-regulation of inhibitory receptors
(immune checkpoint)

T cell activation induces the expression of immune checkpoints



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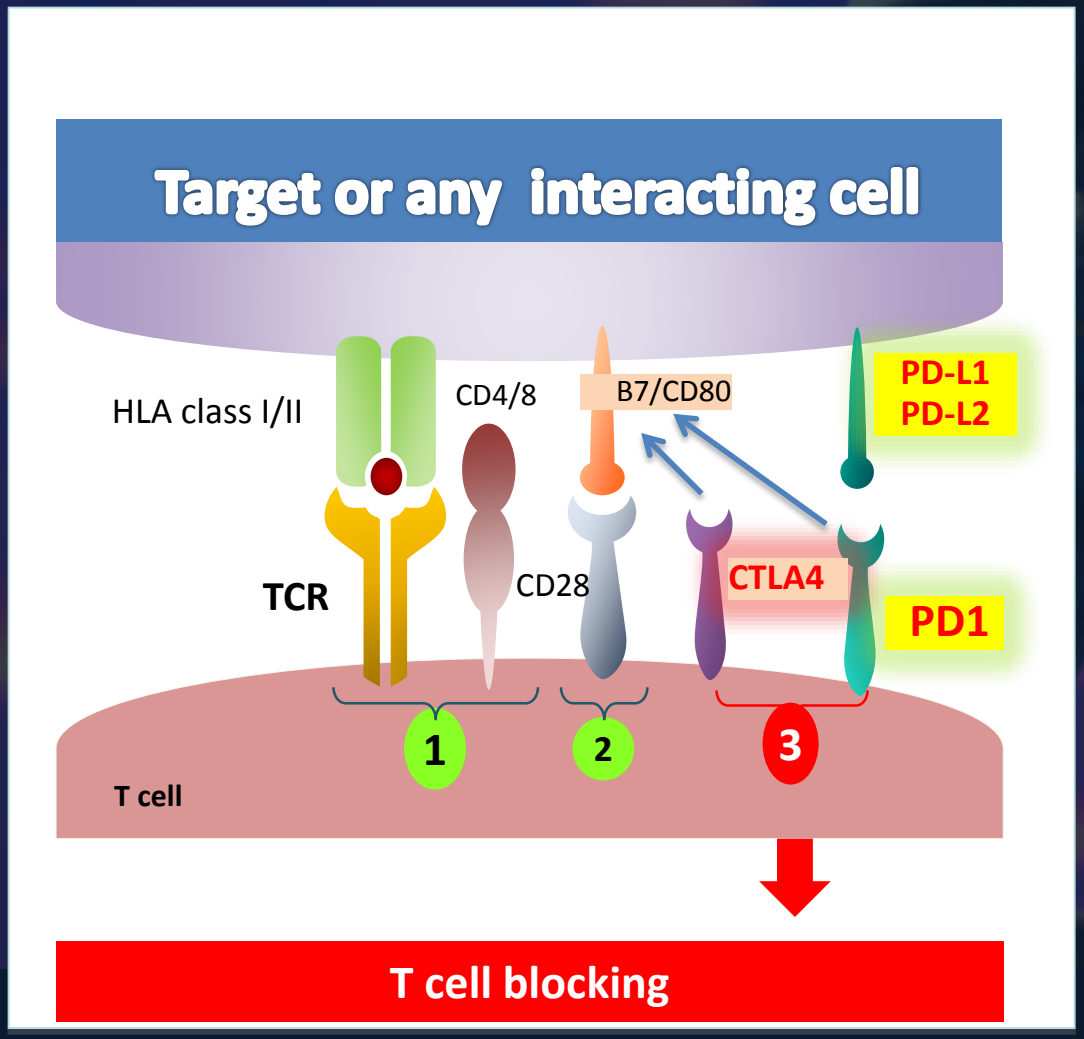

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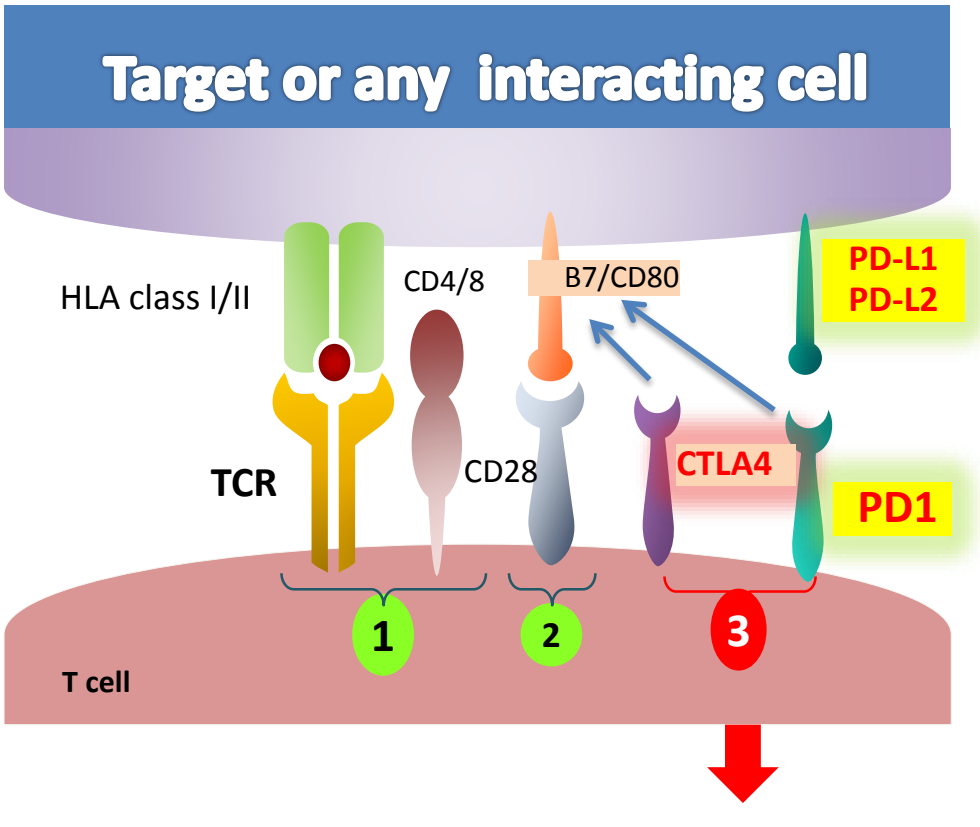


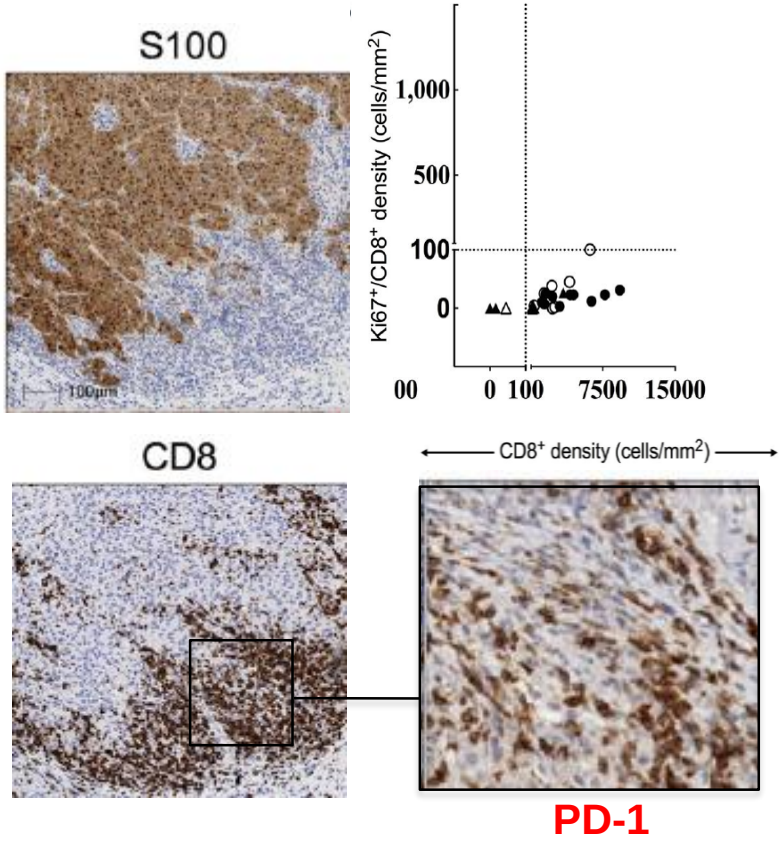
Immune checkpoints

- Stop of proliferation
- Reduced glucose consumption
- Inhibition of cytotoxicity and cytokine release
- Blocking of antibody production

In a reversible fashion

Immune checkpoint are upregulated in all antitumor effector cells (T cell, NK cells, B cells)

Immune checkpoints are upregulated in tumor infiltrating T cells



Tumeh et al., Nature 2014

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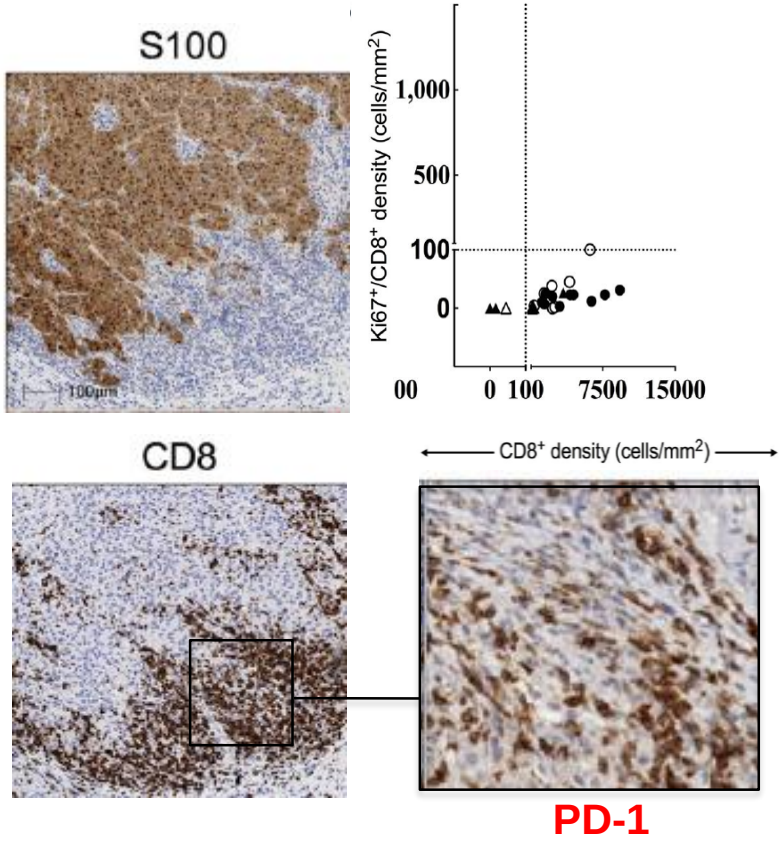

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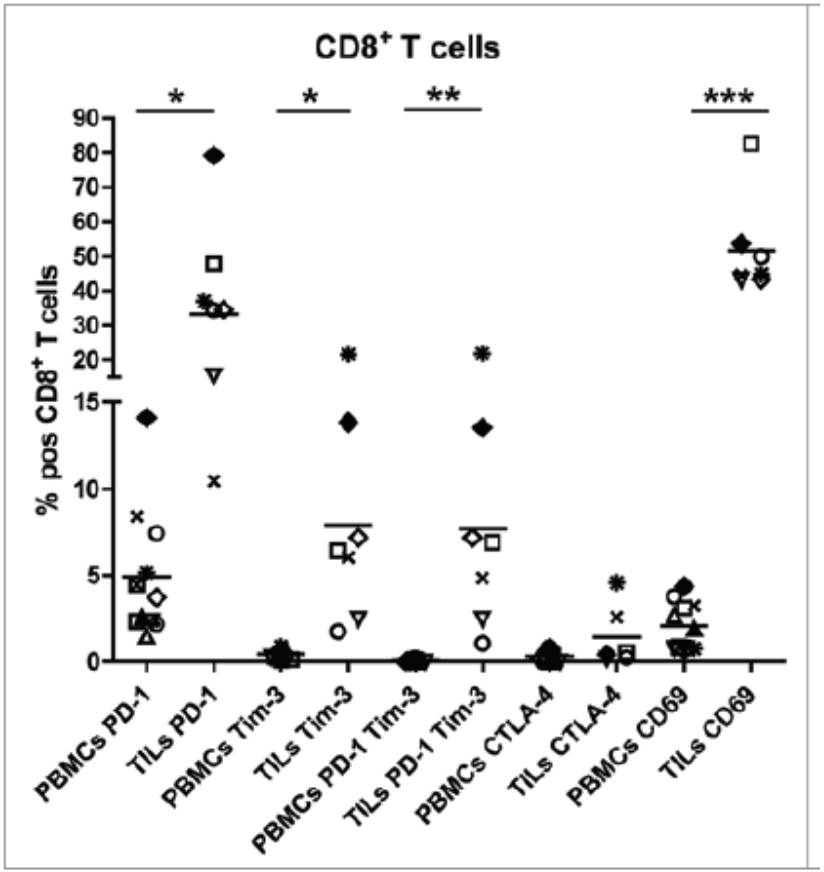
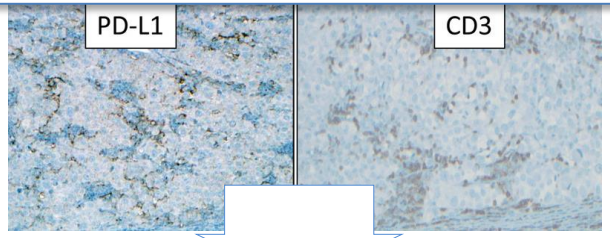


Gentles et al., OncoImmunol 2015

Checkpoint ligands are highly upregulated in in tumor microenviroment

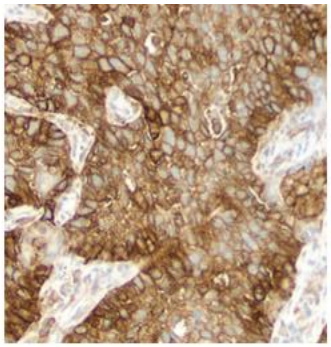
ADAPTIVE IMMUNE RESPONSE
(activated CD8+ T cells)



Inducible expression due to local inflammation

- cytokines and chemokines
- IFN produced by T cells

PD-L1 in tumor cells



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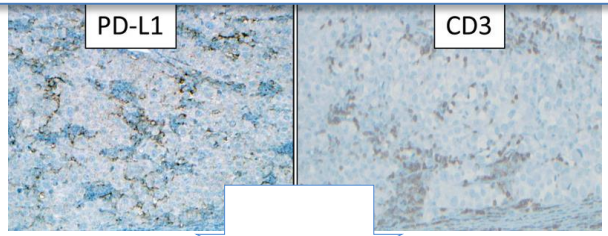
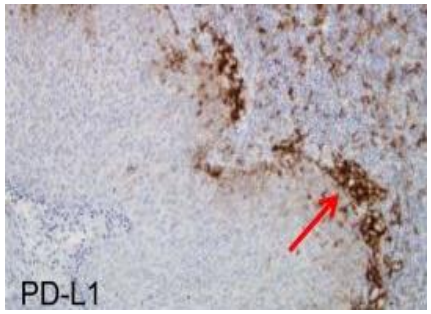
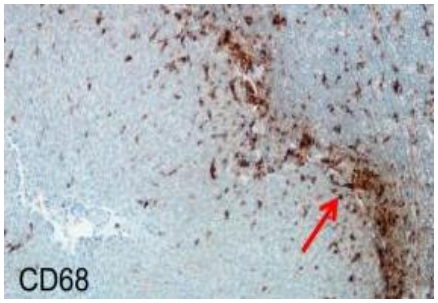


PD-L1 in stroma cells

PD-L1 in tumor infiltrating stroma (myeloid) cells





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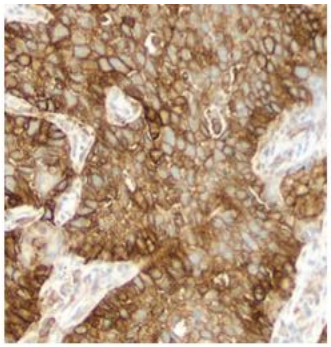

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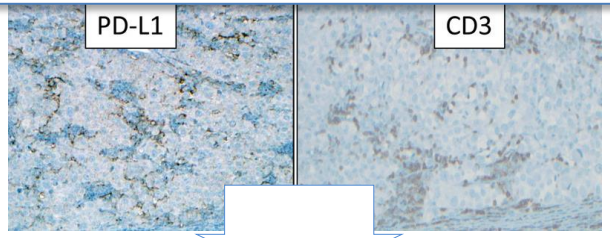

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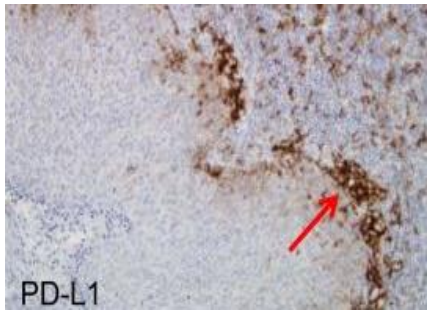
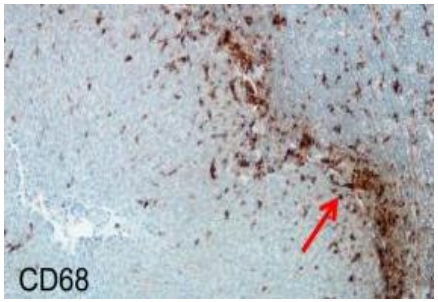




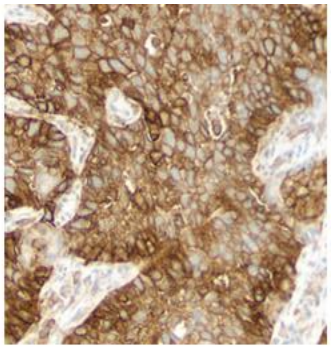
Inducible expression due to local inflammation

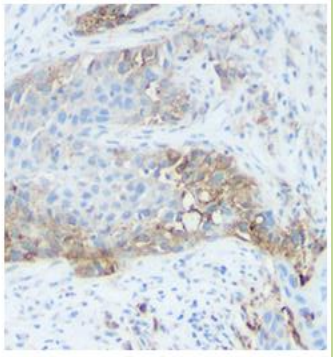
- cytokines and chemokines
- IFN produced by T cells

Constitutive expression due to oncogenic pathways

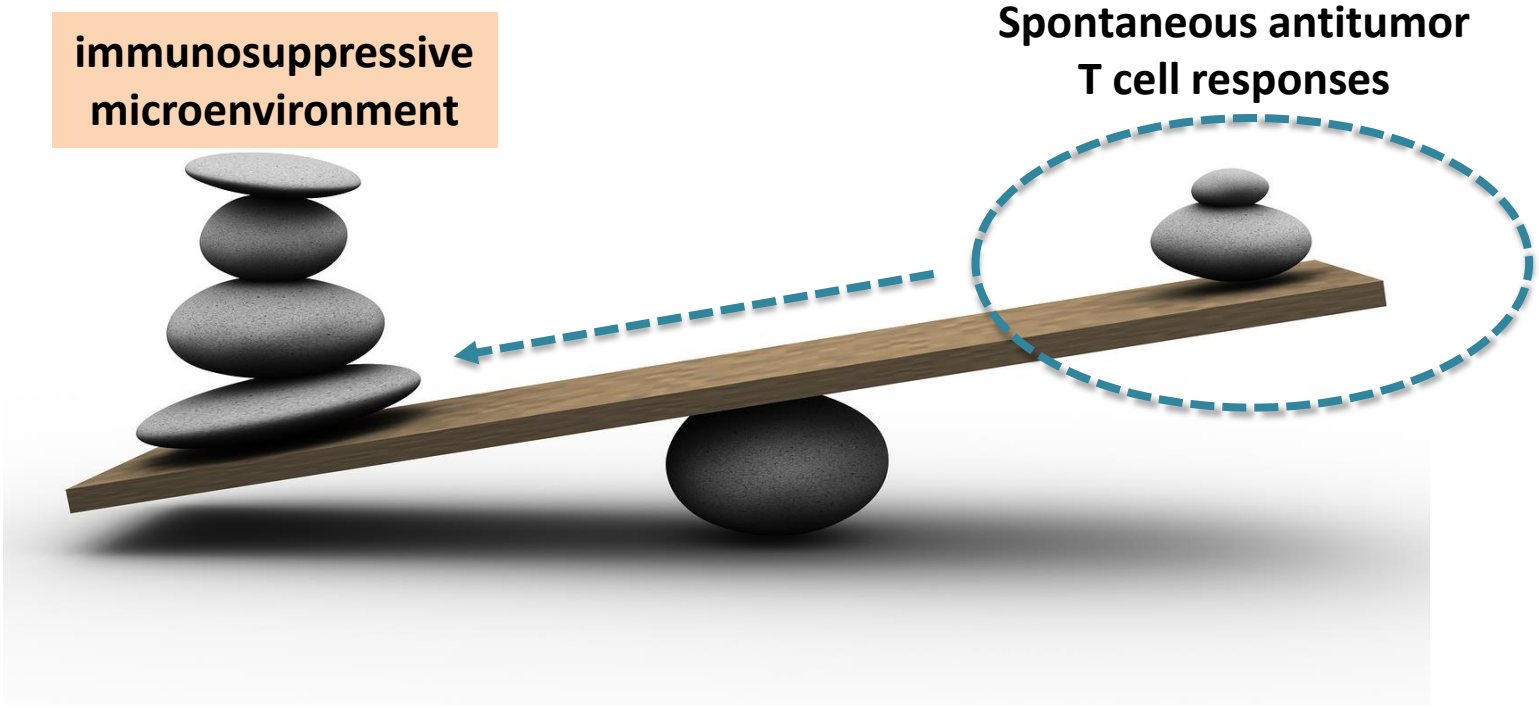
- HIF1a-hypoxia
- VHL
- EGFR activation
- AP-1 signaling
- PTEN loss
- PI3K/AKT/mTOR

PD-L1 in tumor cells





Strategies to boost anti-tumor immunity



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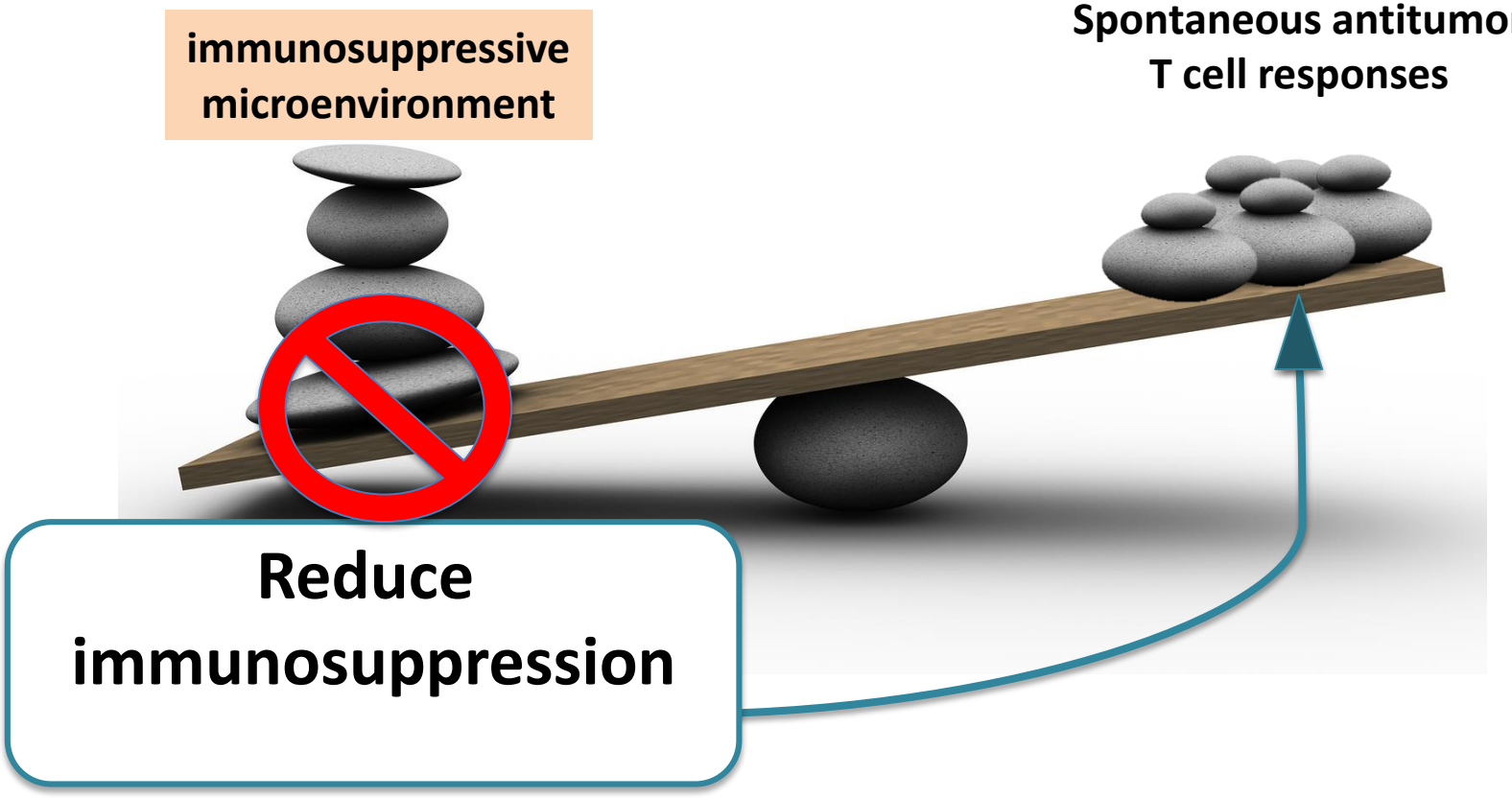
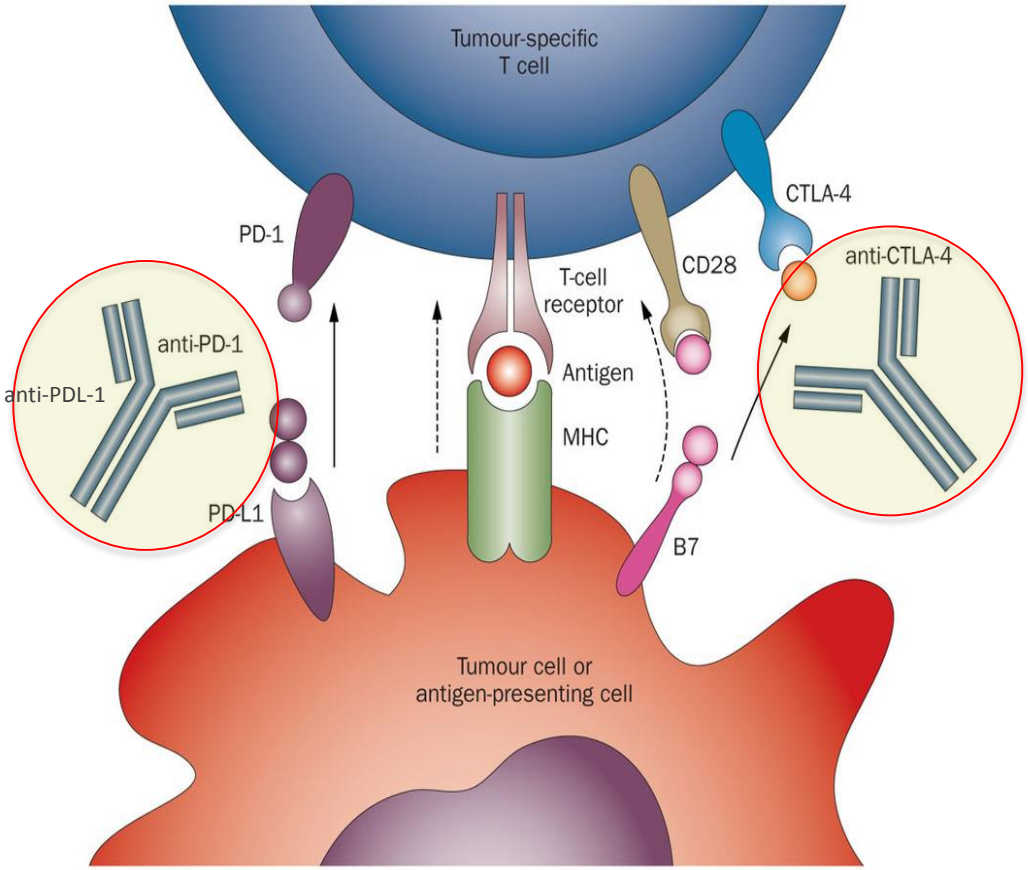


The effect of
Immune checkpoints inhibitors



Nguyen et al., Nature Rev Immunol 2015

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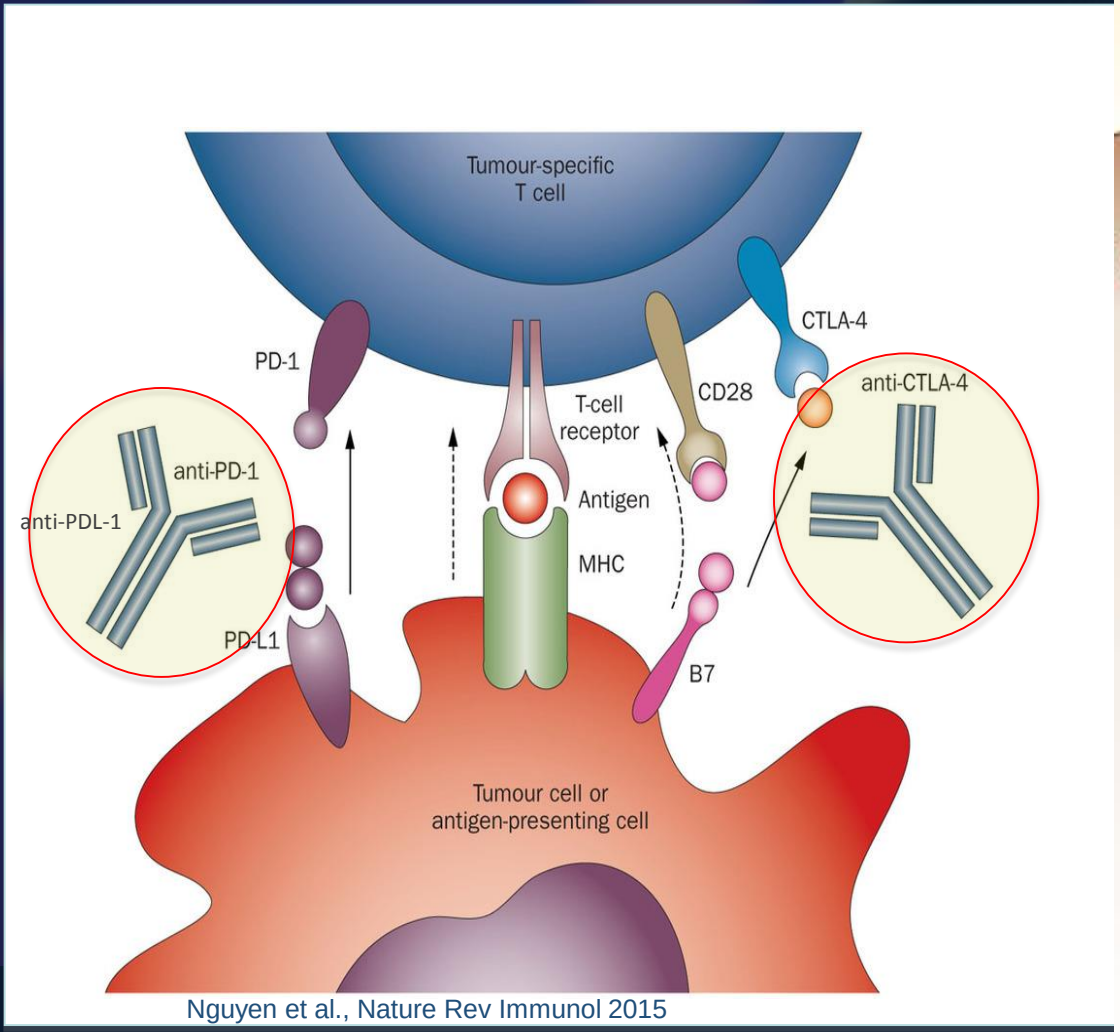

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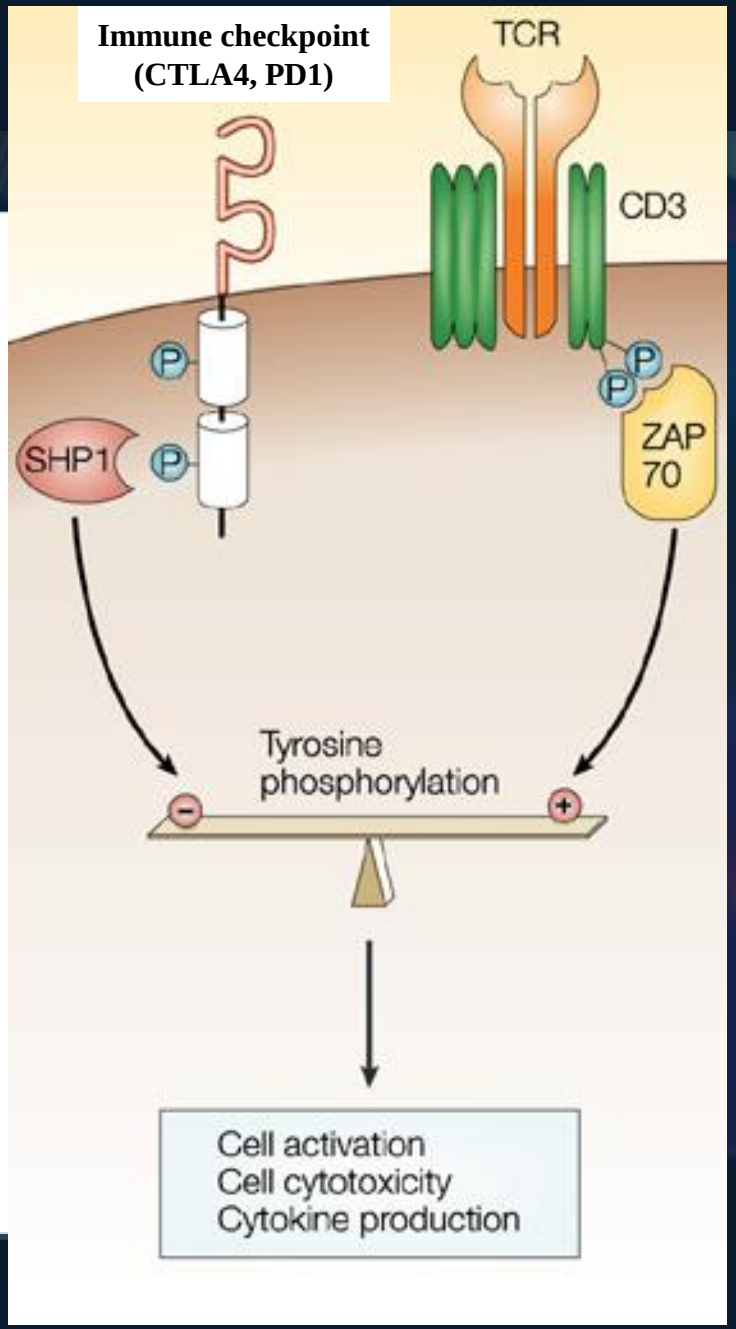

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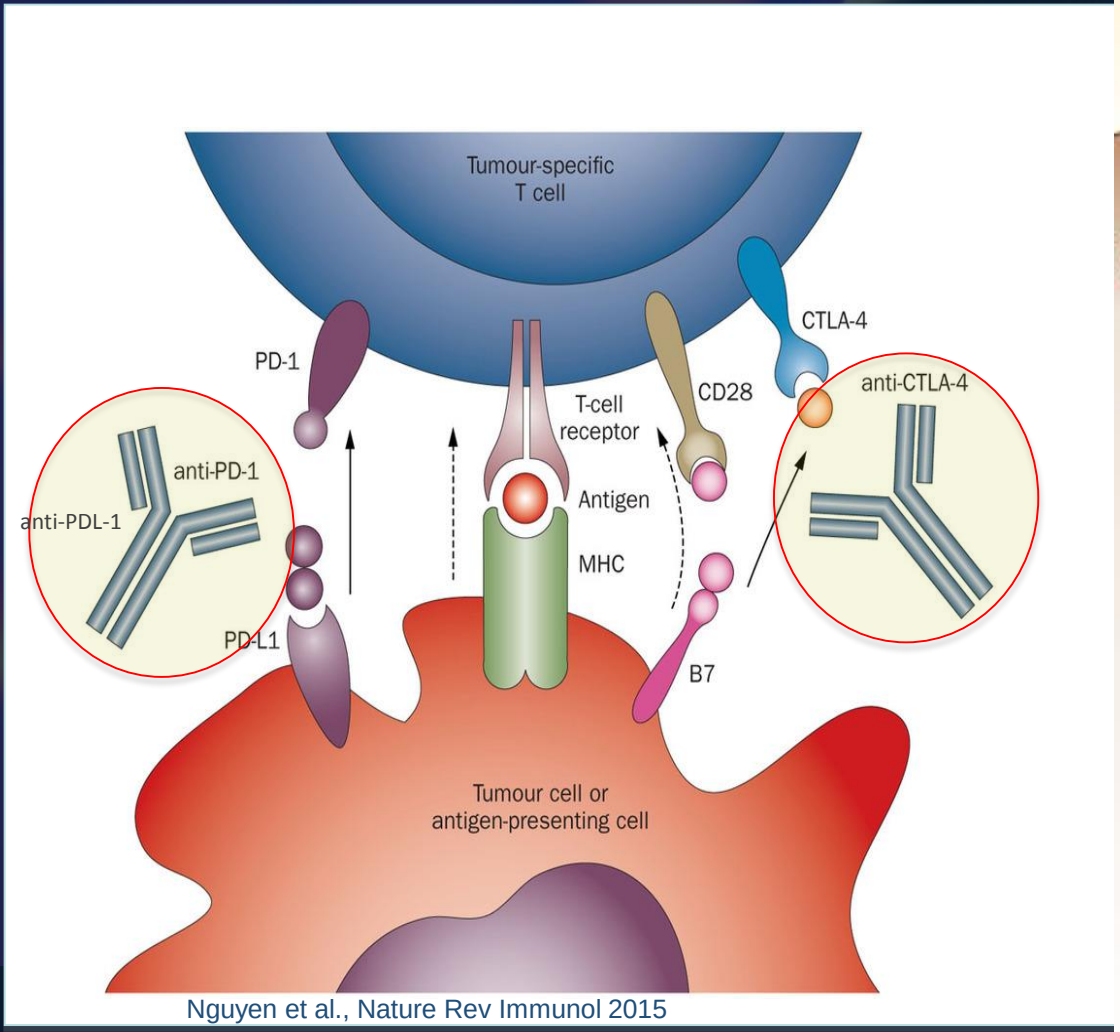

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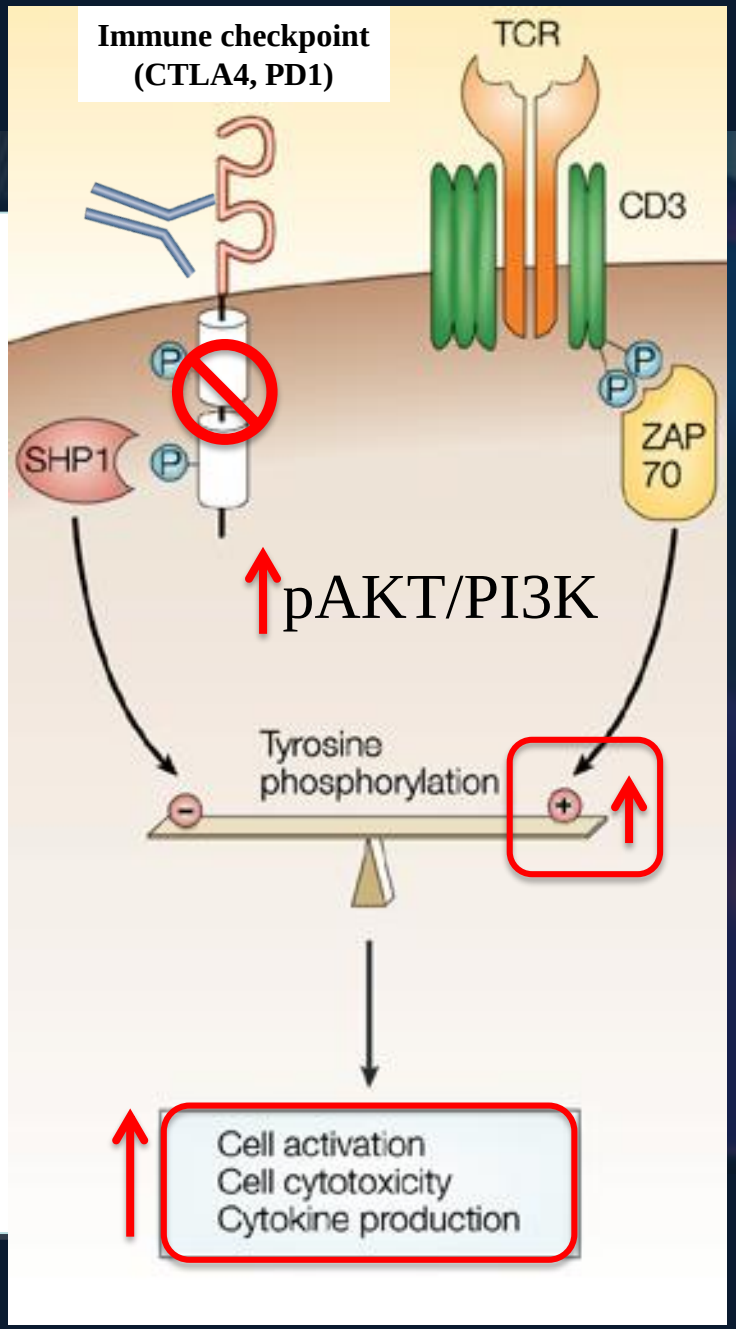
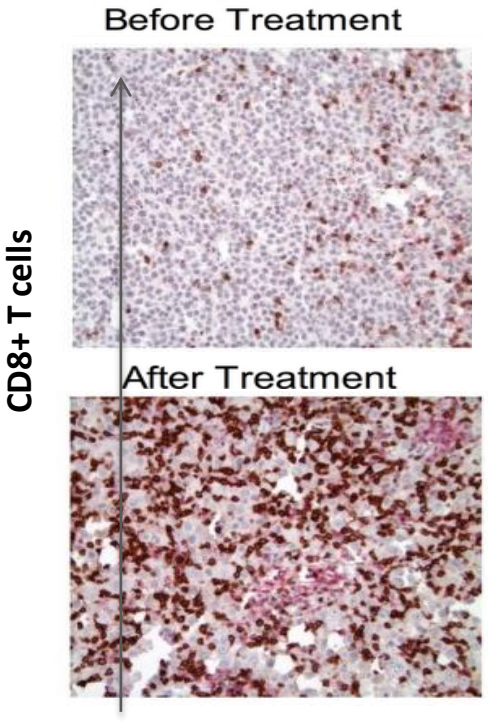


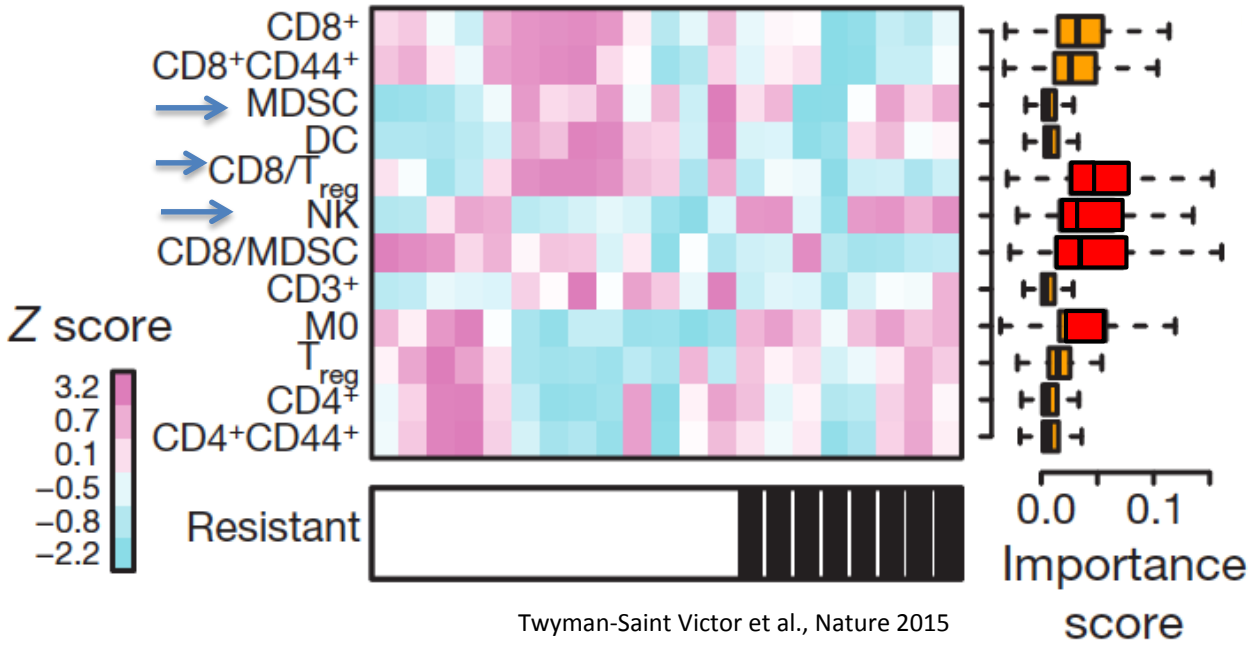
Immune checkpoint inhibitors rescue T cell activation and reduce immunosuppression

PD-1 blockade in melanoma



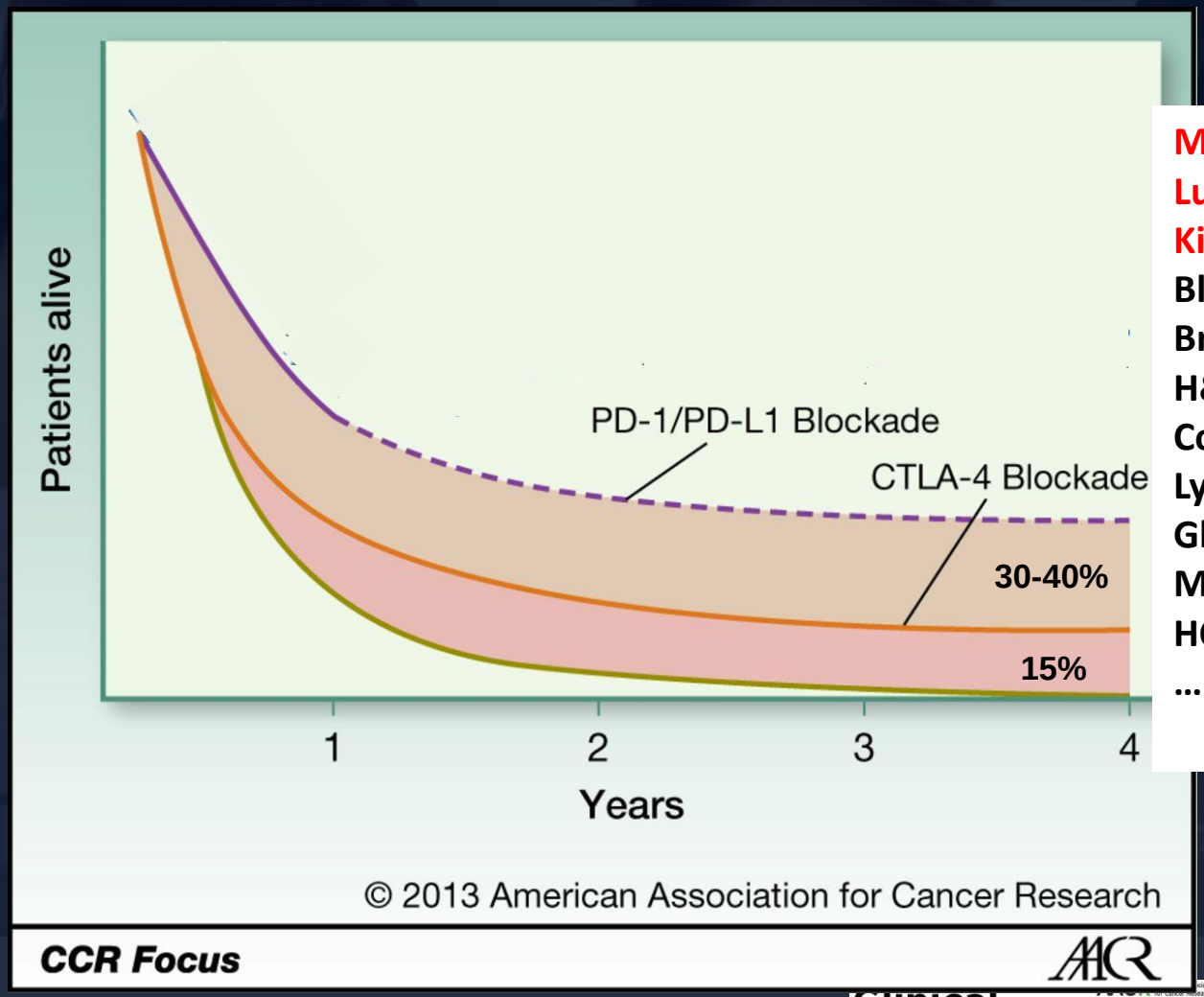
Tumeh et al, Nature 2014

CTLA4 blockade in melanoma



Twyman-Saint Victor et al., Nature 2015

Immune checkpoint inhibitors improve overall survival of cancer patients (immune memory)

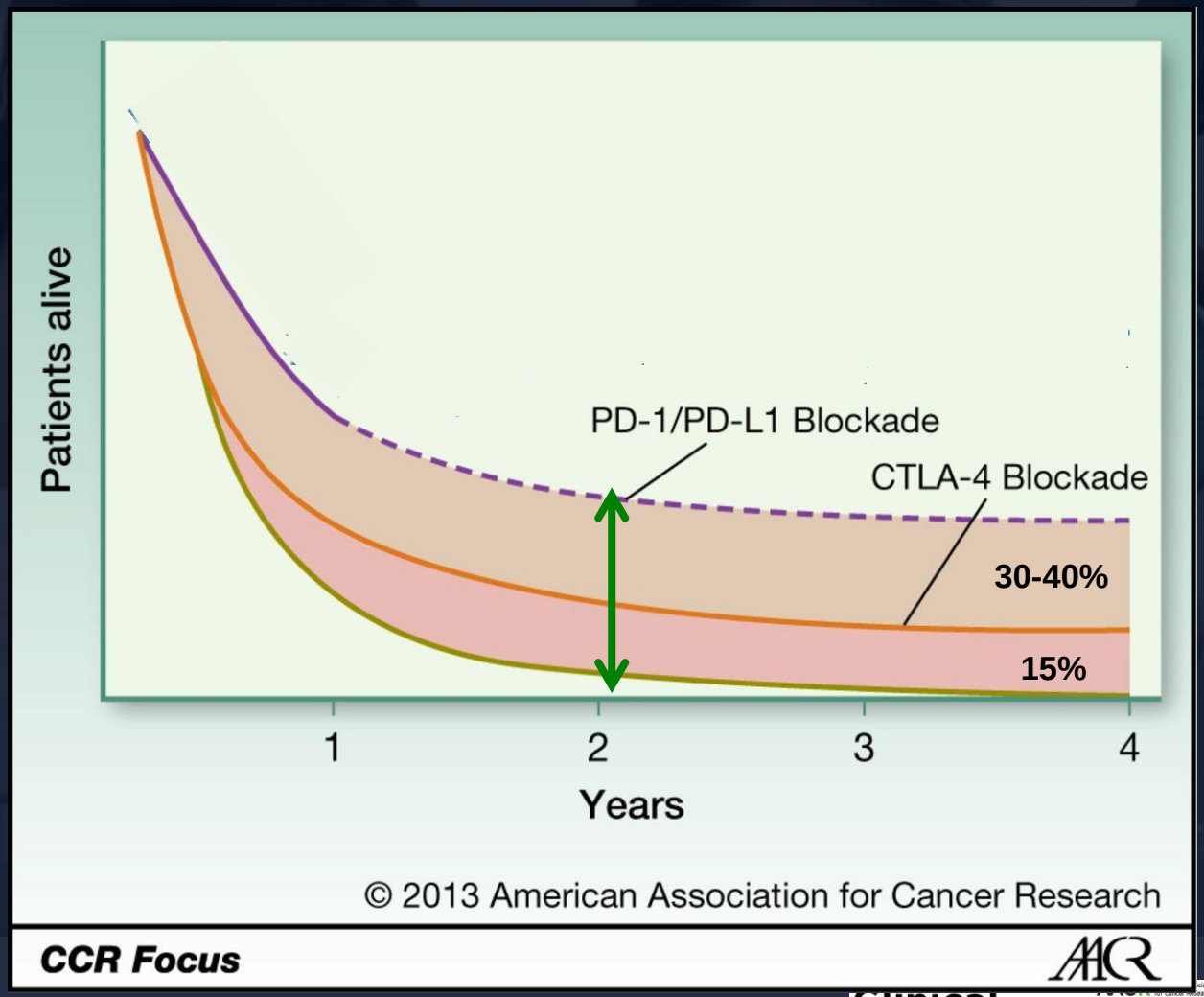


Melanoma
Lung cancer
Kidney cancer
Bladder cancer
Breast cancer (triple negative)
H&N cancer
Colorectal cancer (MSI)
Lymphoma
Glioblastoma
Myeloma
HCC
……..

Patrick A. Ott et al. Clin Cancer Res 2013;19:5300-5309

Clinical Cancer Research

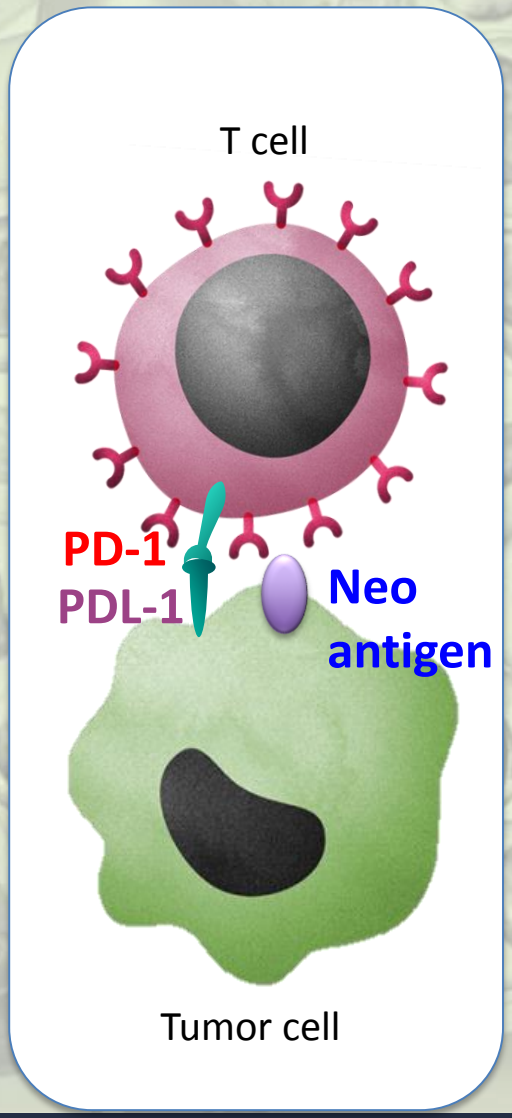
Predictive factors of response?



Patrick A. Ott et al. Clin Cancer Res 2013;19:5300-5309

Clinical Cancer Research

Multifactorial biomarkers of clinical response to PD-1 blockade

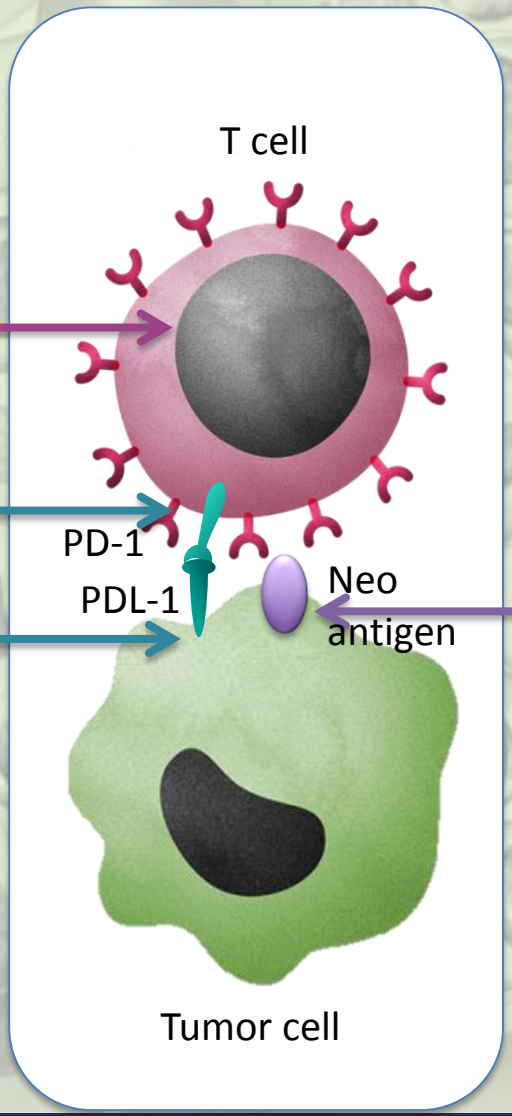


"Immunogenic" tumors are more likely to respond to PD-1 blockade

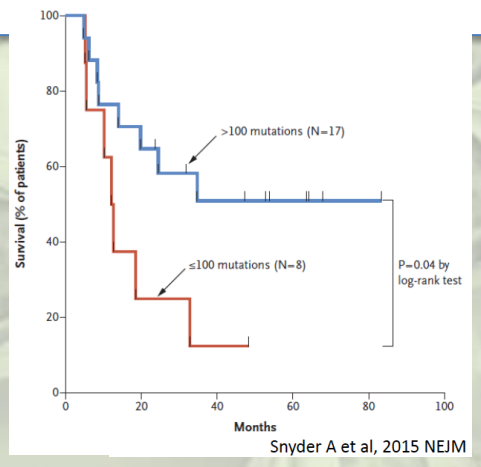
HIGH level of T cell infiltrate

HIGH level of PD-1 expression in T cells

HIGH level of PD-L1 expression in tumor cells (and stroma)



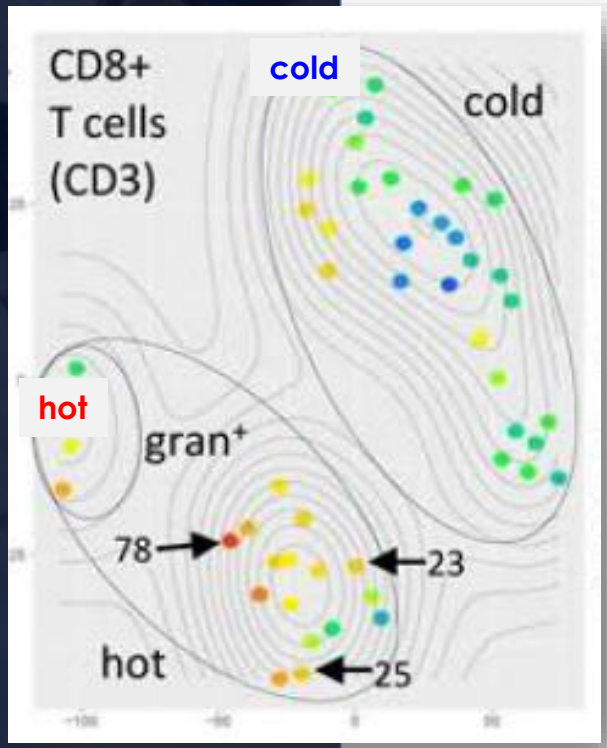
HIGH level of tumor antigens (**neo-antigens**)



Snyder A et al, 2015 NEJM

"HOT and cold" tumors respond differently to PD-1 blockade

(the example of NSCLC)



Lizotte et al , J Clin Invest 2016

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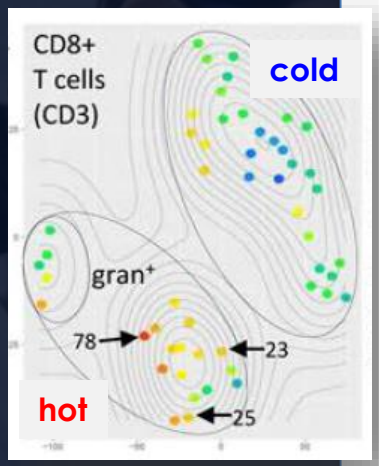
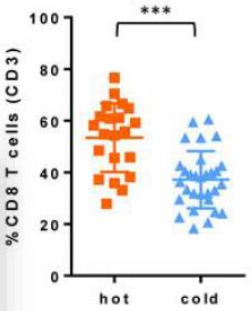
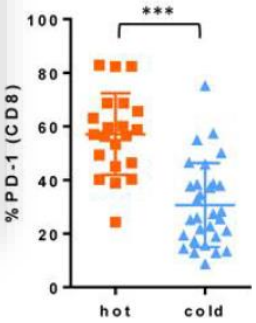


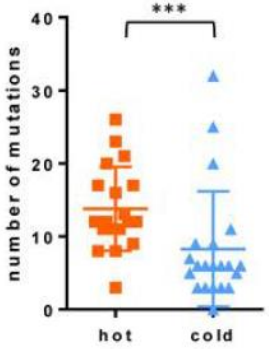
CD8+ T cells

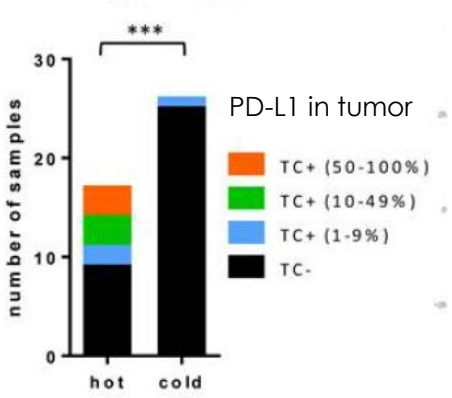


CD8+ PD-1+ T cells



Mutational load
(neoantigens)





Lizotte et al , J Clin Invest 2016

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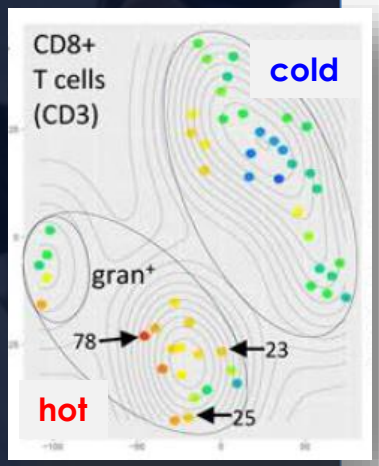
(the example of NSCLC)



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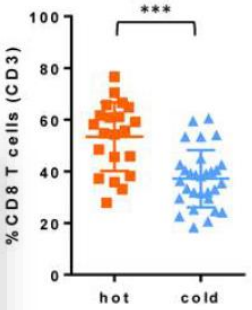
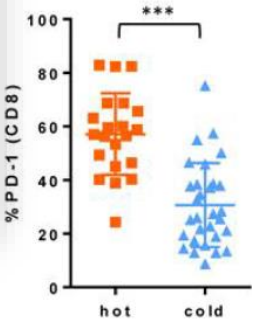


CD8+ PD-1+ T cells



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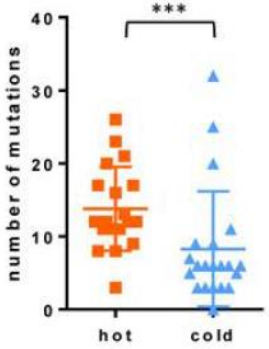
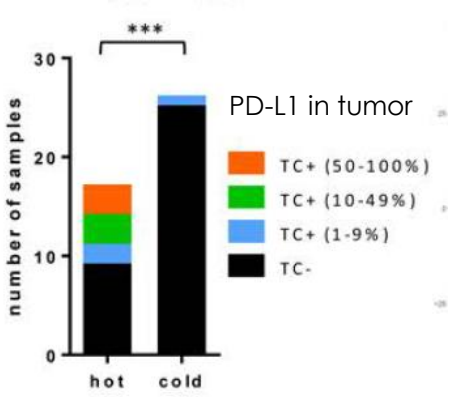
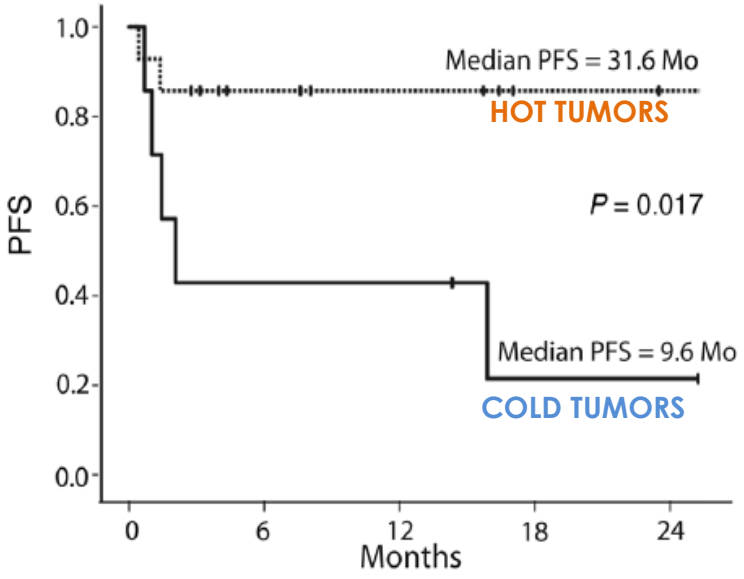




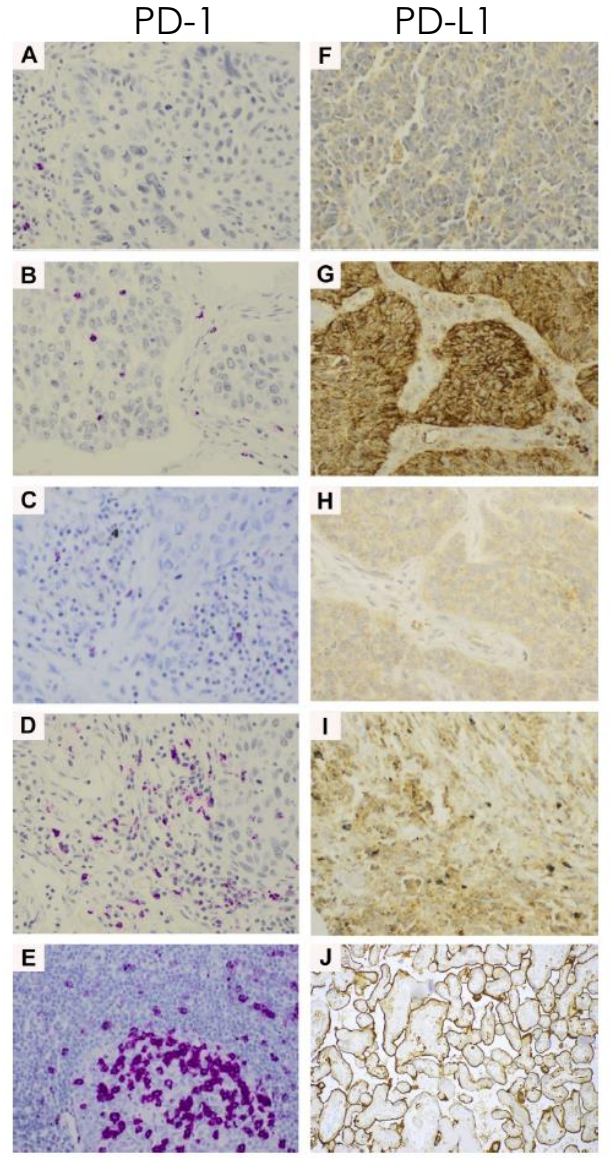
PD-1 blockade



Lizotte et al , J Clin Invest 2016

Daud et al , J Clin Invest 2016

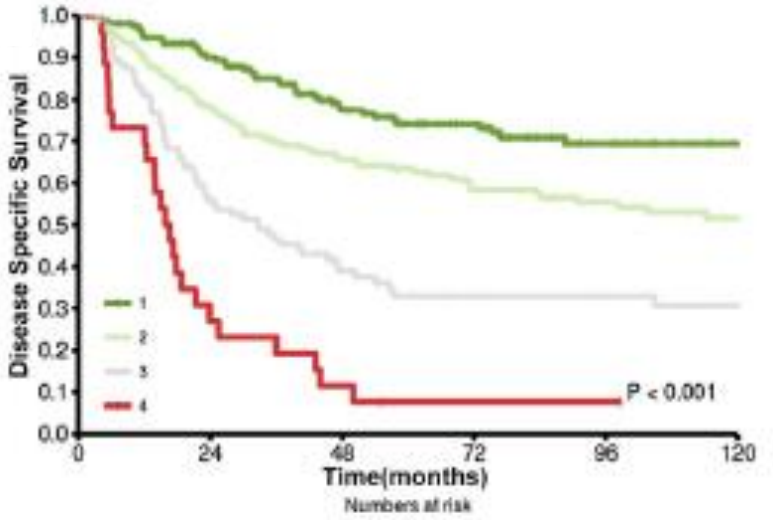
A novel TNM- IMMUNOSCORE in NSCLC integrating PD-1 and PD-L1 expression



TNM-Immunoscore

	PD-Immunoscore	
	Low + Low	Other
Pstage I	64% (n=75)	74% (n=161)
Pstage II	34% (n=53)	63% (n=128)
Pstage IIIA	8% (n=29)	31% (n=50)

5 year survival:
1: <10%
2: 10-40%
3: 40-70%
4: >70%

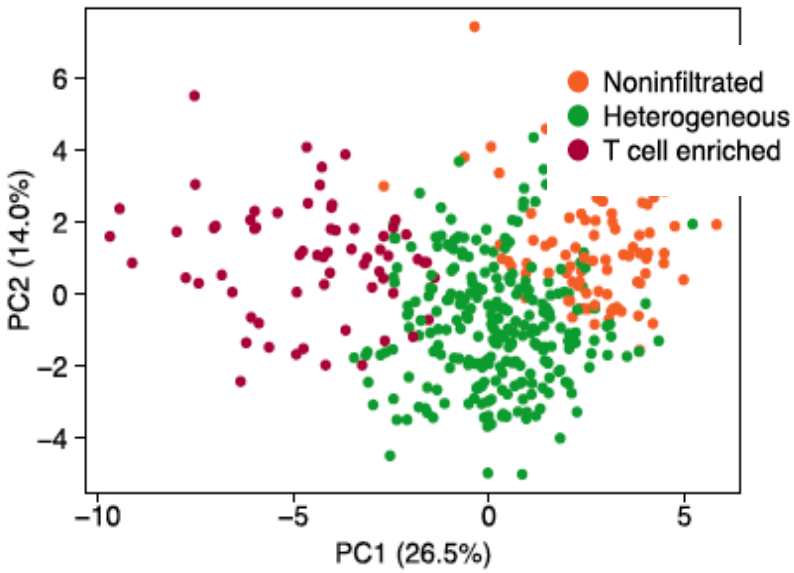


N=536 SNSCLC patients patients

Paulsen et al , Clin Lung Cancer 2016

T cell enriched RCC responds to Immunotherapy

T cell enriched tumors are infiltrated by highly immunosuppressed cells independently of the tumor stage and grade



Şenbabaoğlu *et al. Genome Biology* (2016) 17:231

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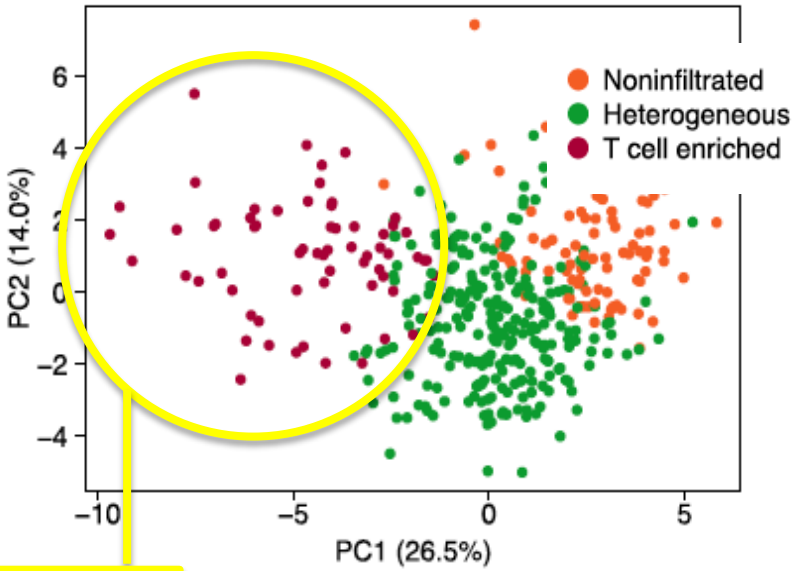
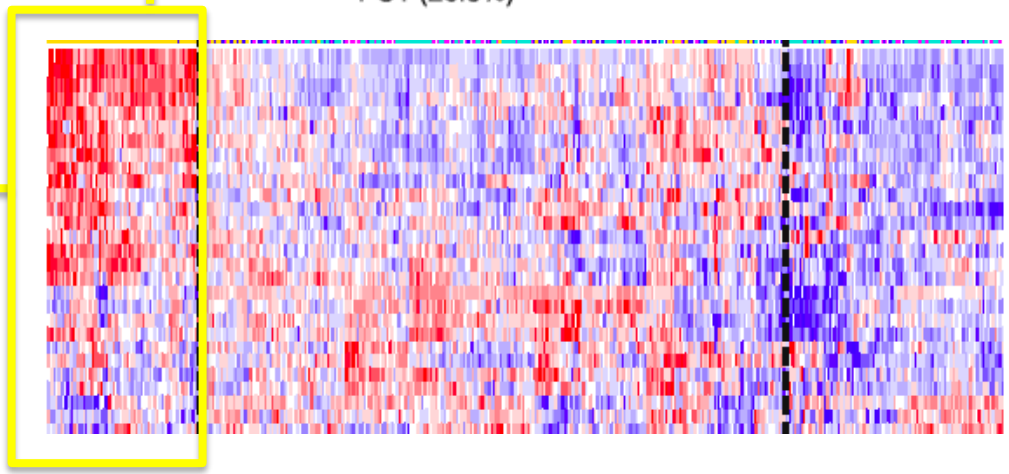
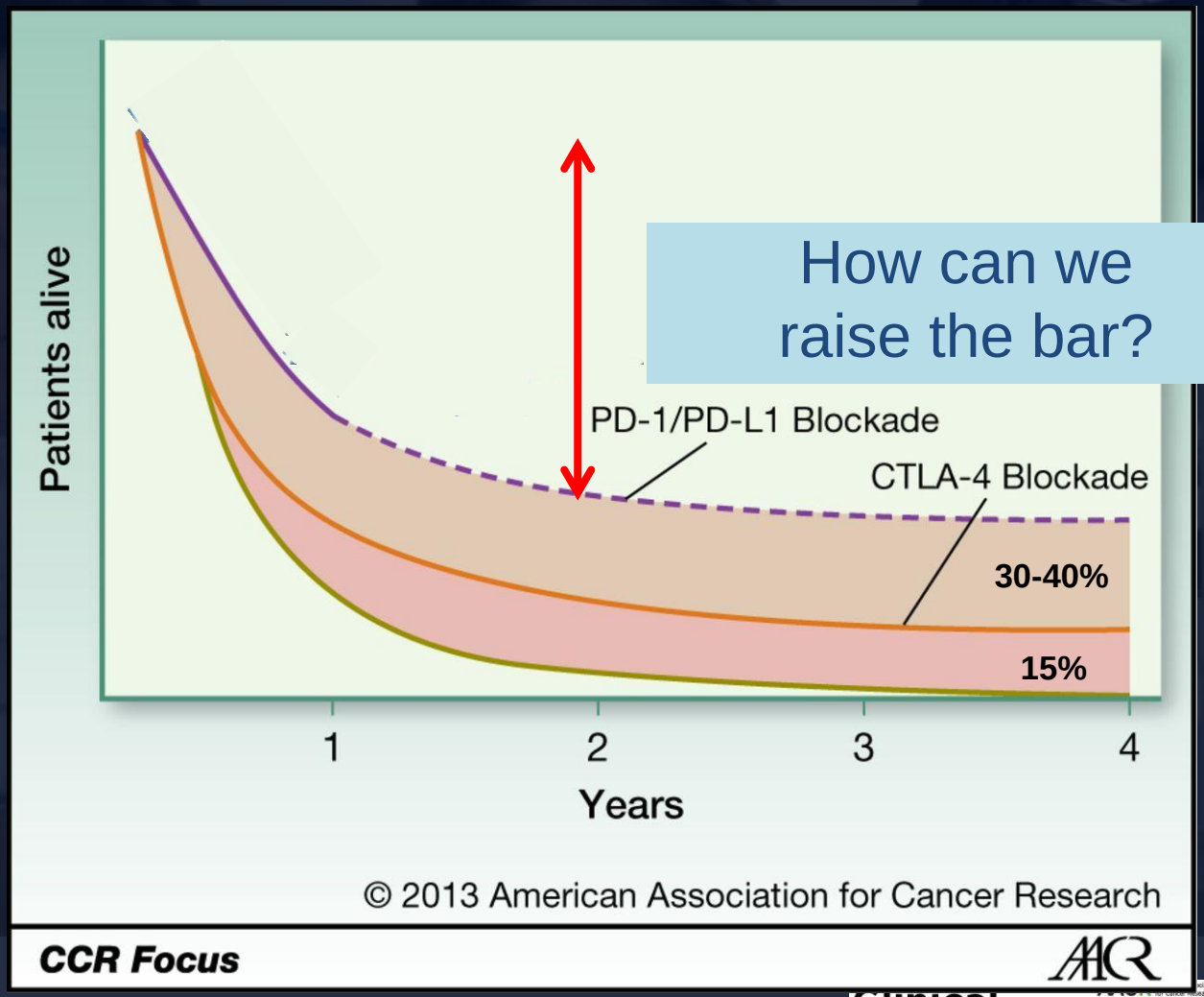


PD1
T cells
Cytotoxic cells
CD8 T cells
Th1 cells
aDC
CTLA4
Treg cells
B cells
NK CD56bright cells
Th2 cells
NK CD56dim cells
Tgd cells
PDL1
Tfh cells
T helper cells
Tcm cells
Angiogenesis
pDC
NK cells
Tem cells
iDC
Macrophages
Mast cells
DC
Th17 cells
Neutrophils
Eosinophils



Şenbabaoğlu *et al. Genome Biology* (2016) 17:231

Mechanisms of resistance to immune checkpoint inhibitors



Patrick A. Ott et al. Clin Cancer Res 2013;19:5300-5309

Clinical Cancer Research

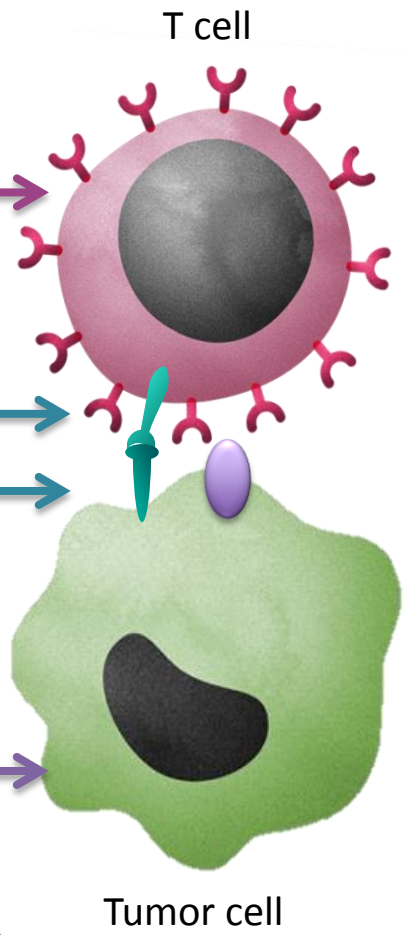
"COLD" tumors are infiltrated by immunosuppressive cells

LOW level of T cell infiltrate

LOW level of PD-1 in T cells

LOW level of PD-L1 in tumor cells (and stroma)

LOW level of tumor antigens (neo-antigens)



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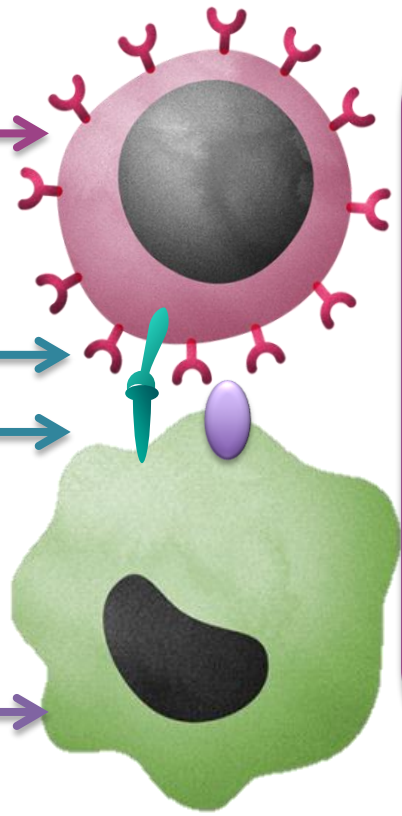
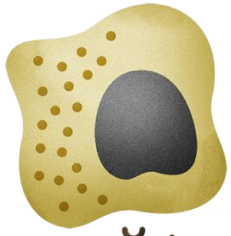
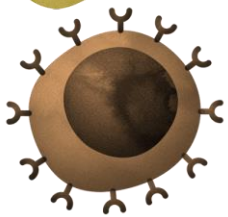


Immunosuppressive immune components

Myeloid-derived suppressor cells

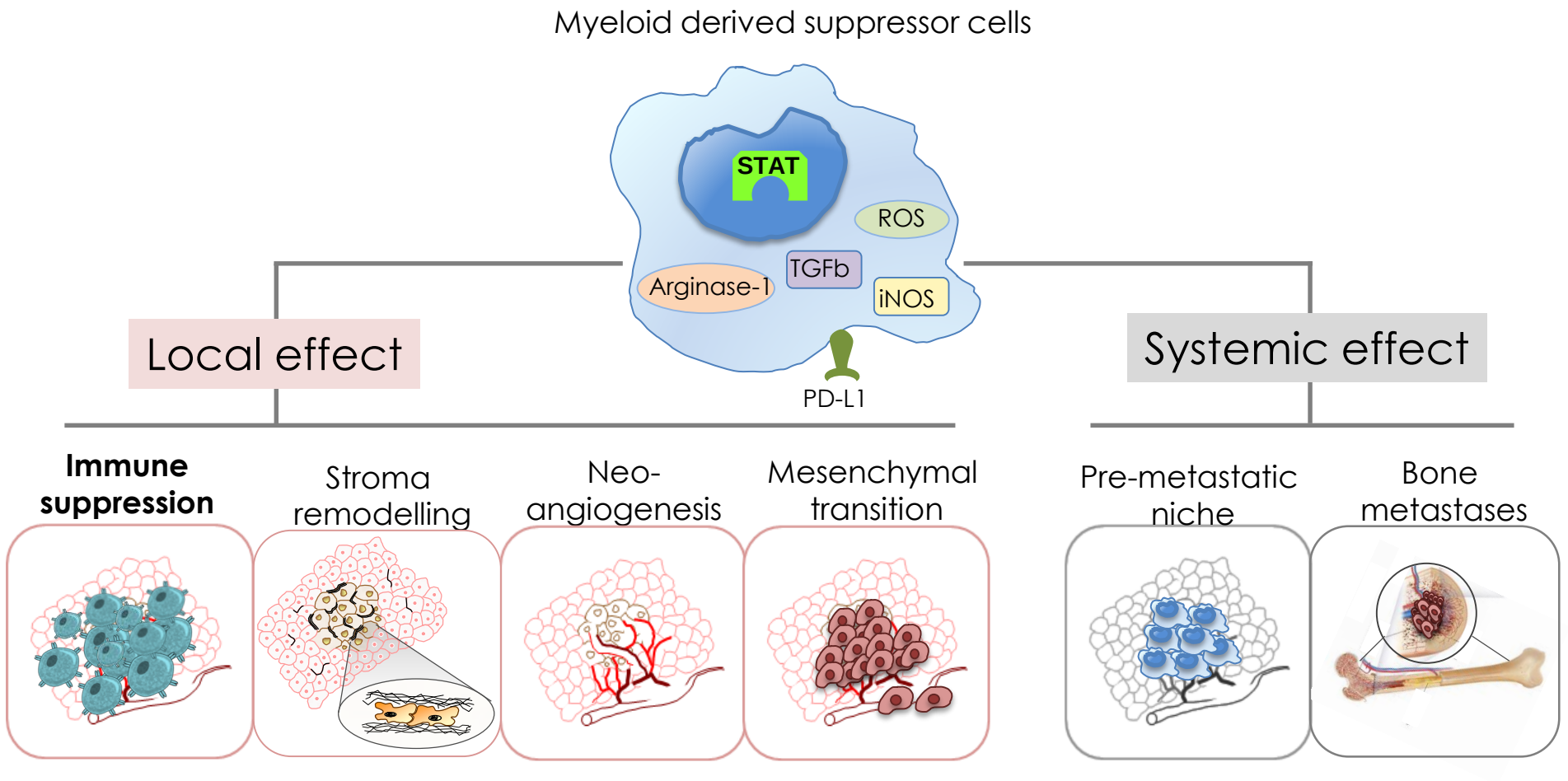


Tumor associated macrophages

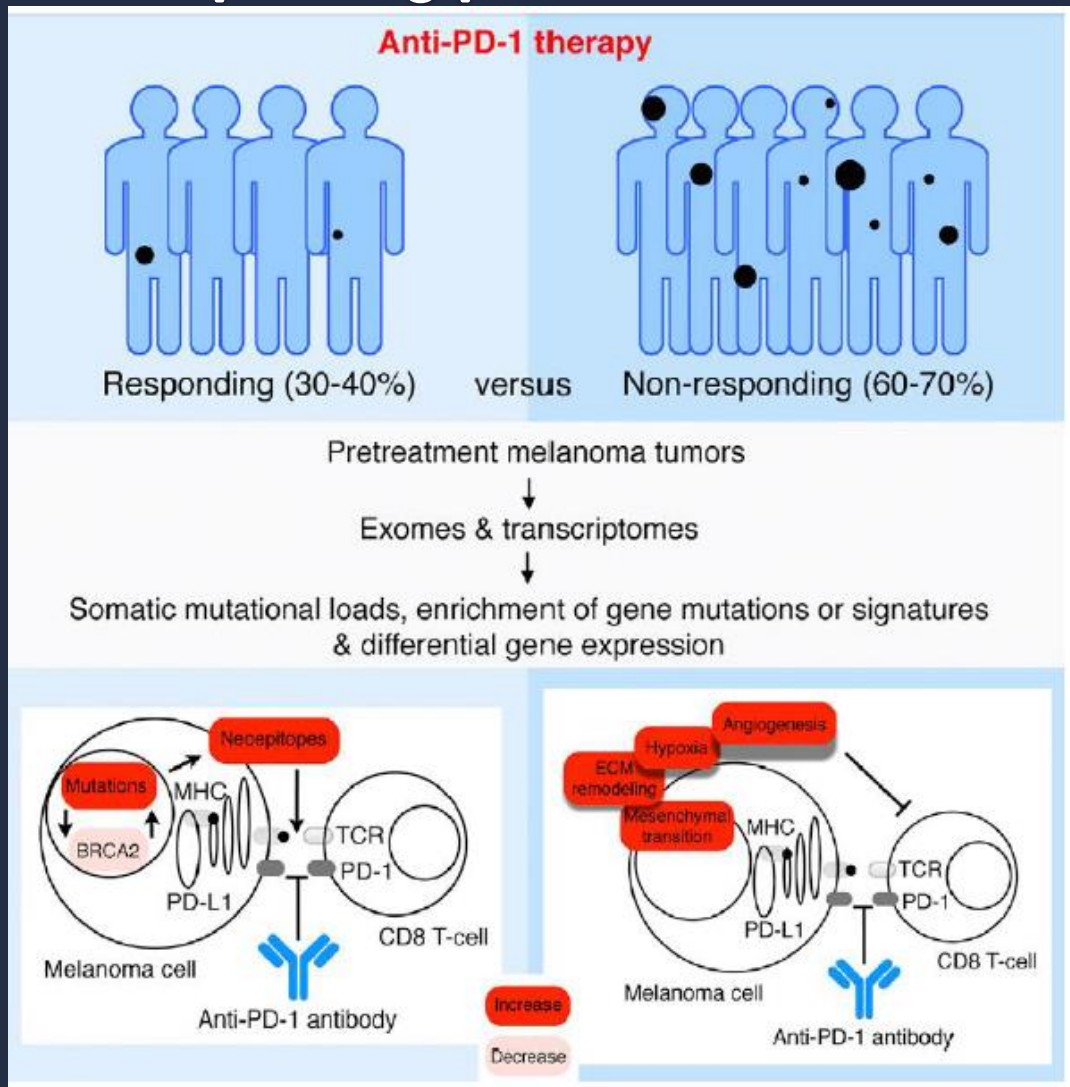


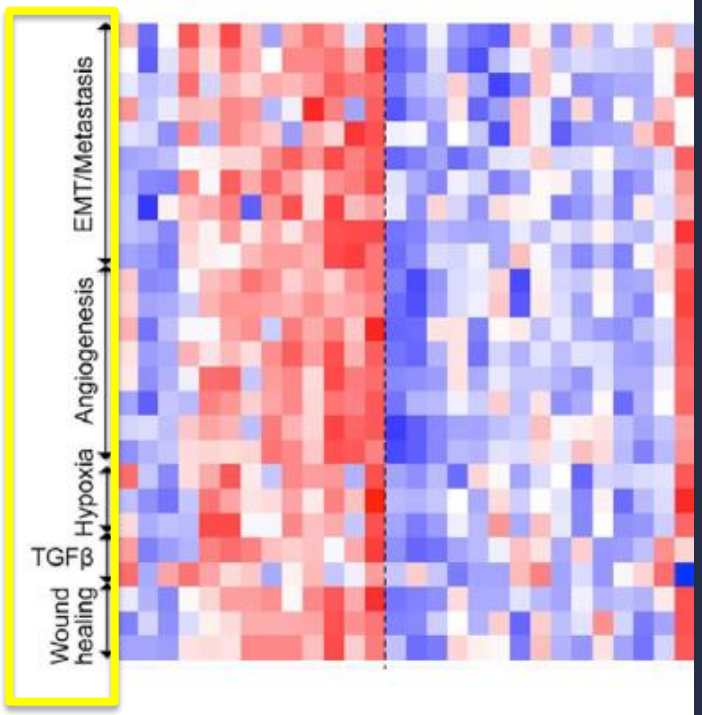
Regulatory T cells

Myeloid-derived suppressor cells: the best tumor allies



A myeloid-associated wound healing signature characterizes non responding patients

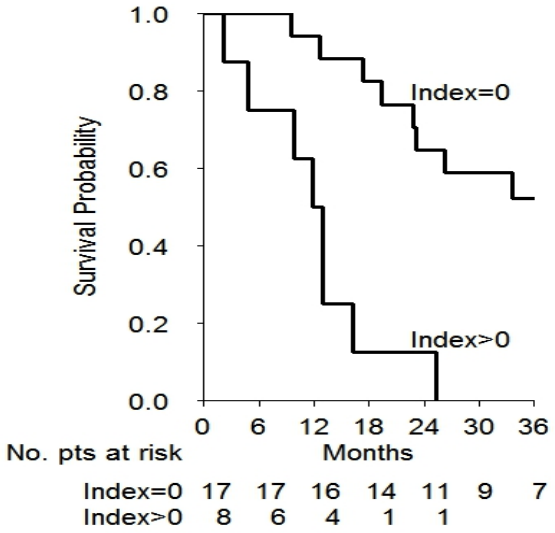




Hugo et al 2016 Cell

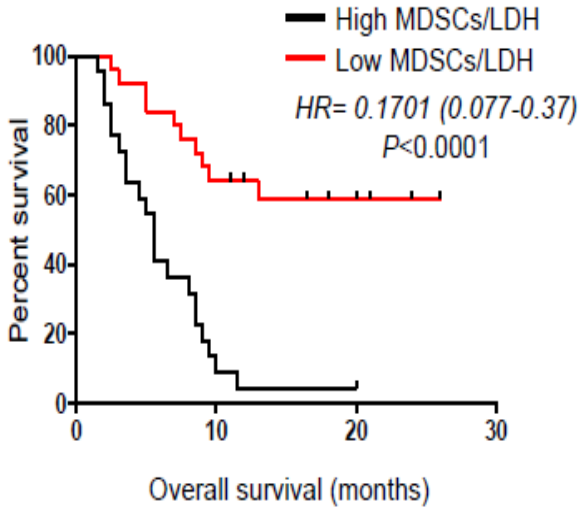
Myeloid cells:
a circulating predictive marker of resistance to IT?

Myeloid Index Score



Rivoltini et al., manuscript in prep

Monocytic MDCS



Sade-Feldman et al., Clin Cancer Res 2016

Myeloid cells: a circulating predictive marker of resistance to IT?

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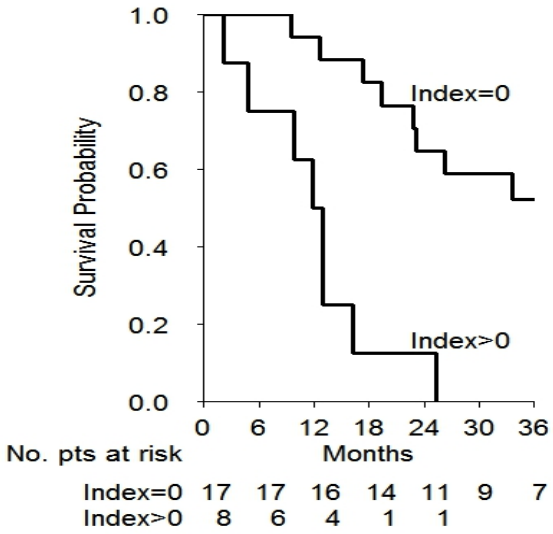

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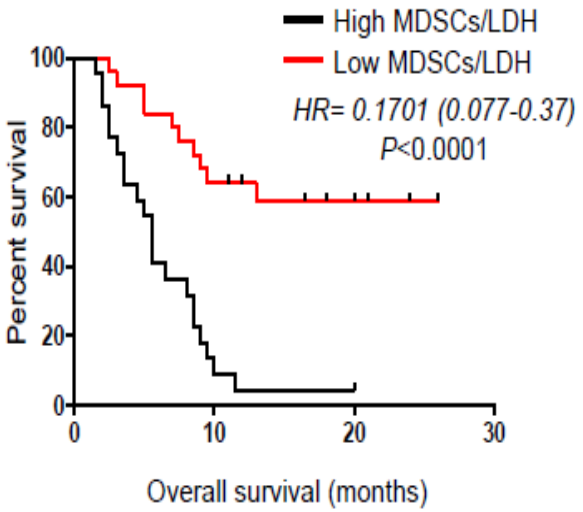
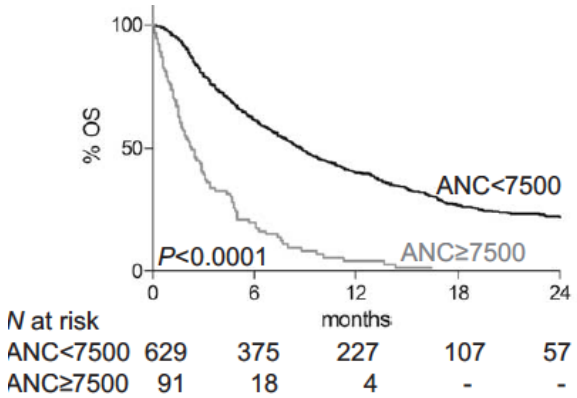
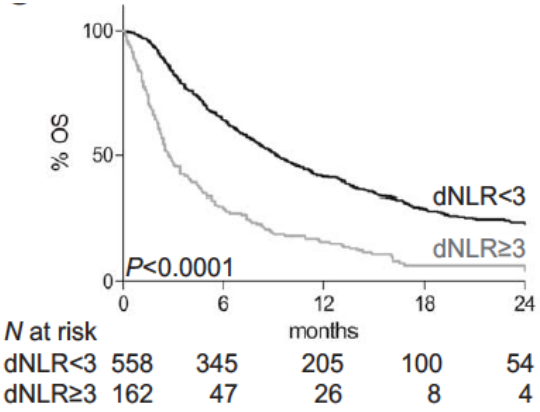


Absolute neutrophil count



Neutrophil to lymphocyte ratio

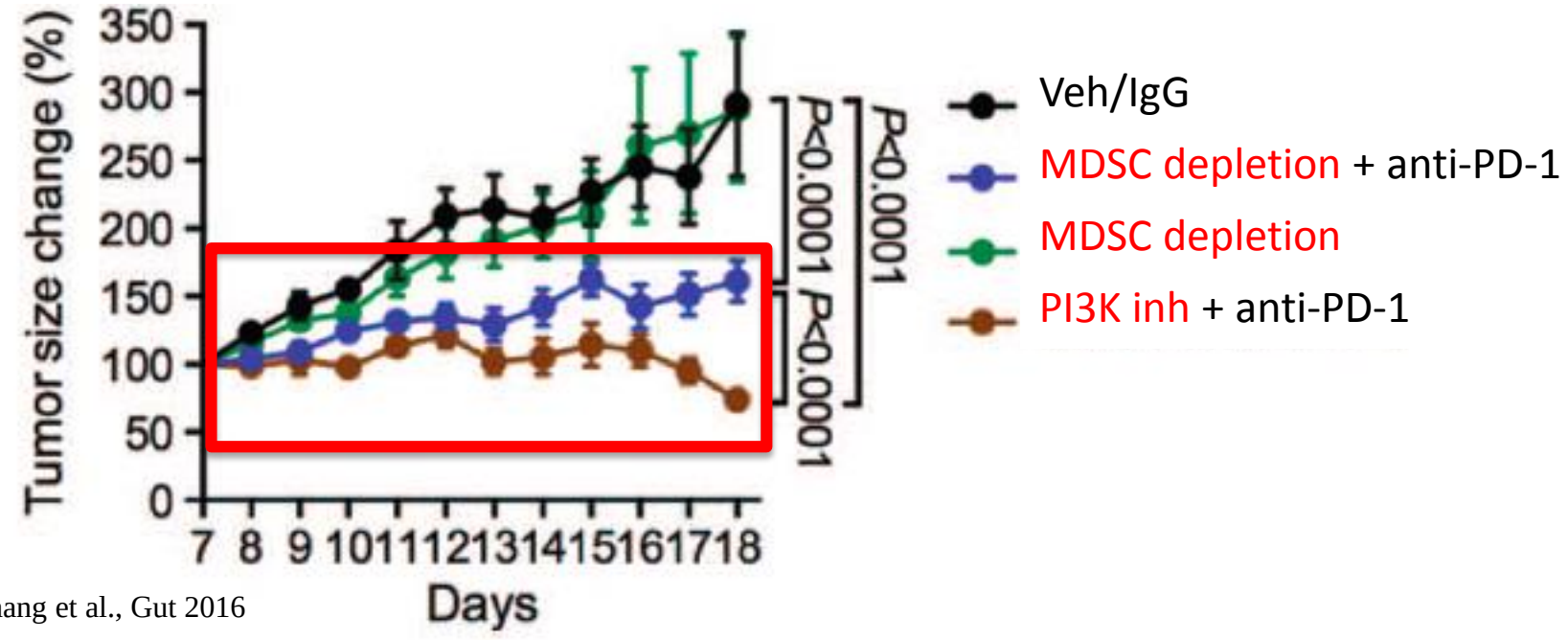


Rivoltini et al., manuscript in prep

Sade-Feldman et al., Clin Cancer Res 2016

Valpione et al-. Eur J Cancer 2015
Ferrucci et al., Ann Oncol 2015

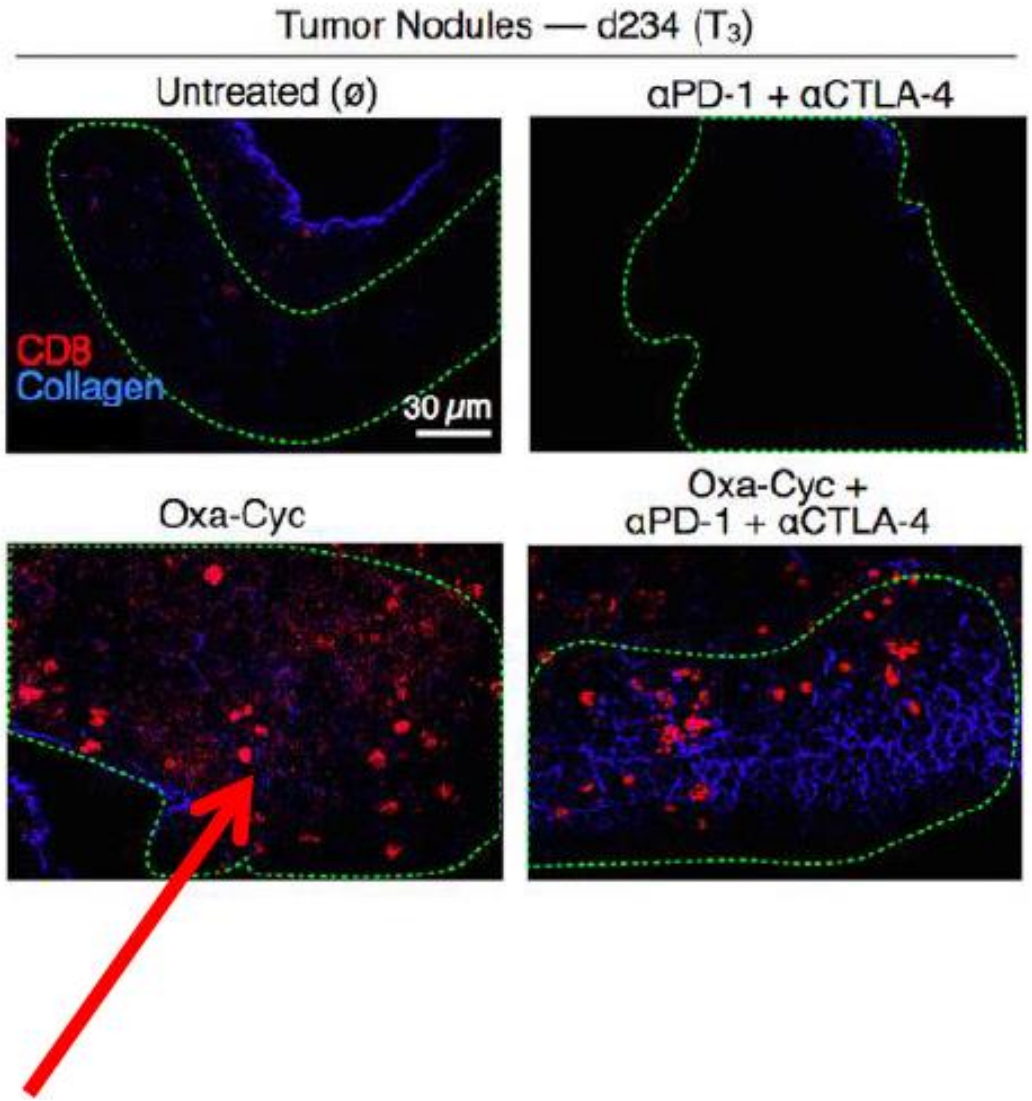
MDSC depletion is required to unleash the therapeutic efficacy of PD-1 blockade



Zhang et al., Gut 2016

Multiple examples in literature on the evidence that MDSC are associated with resistance to different types of immunotherapy and their removal by different means improves immune-mediated tumor control in both murine and clinical setting

Chemotherapy depletes MDSC and synergizes with immune checkpoint inhibitors



Pfirschke C et al 2016 Immunity

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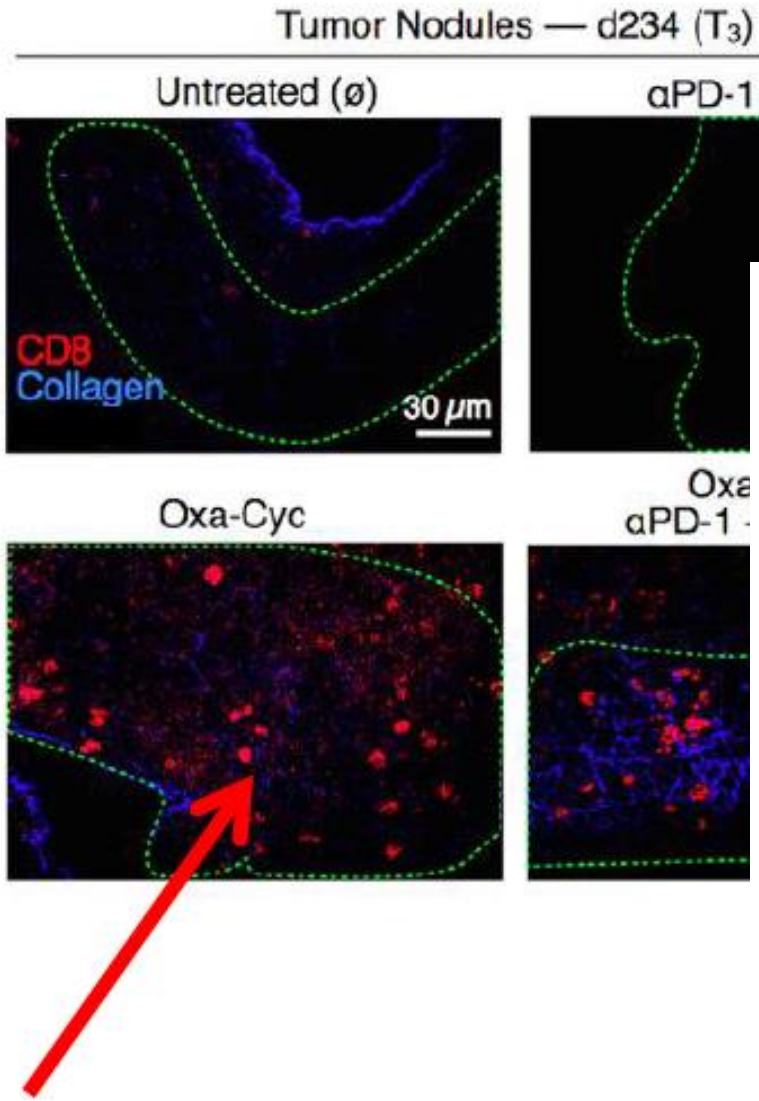
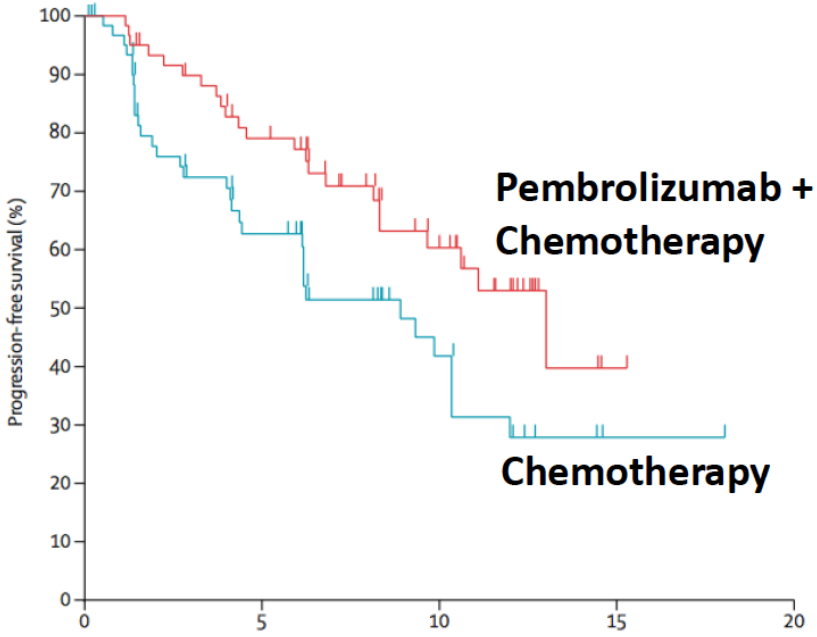


Pfirschke C et al 2016 Immunity

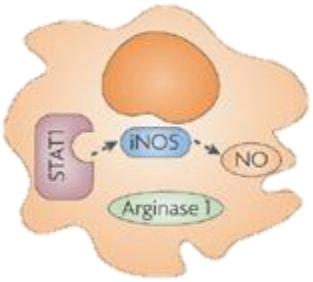
Chemotherapy + anti-PD-1 1st L NSCLC



Langer CJ, et al. Lancet Oncol. 2016

Immunomodulating properties of "non-immunological" cancer therapies

Myeloid derived suppressor cells



Anthracyclines
Gemcitabine
Fotemustine

Dasatinib
Ibrutinib
Bevacizumab
Sunitinib
Pazopanib
Axitinib
PI3Ki

Radiotherapy

IDOi
Anti-TGFb
Anti-CSF1R

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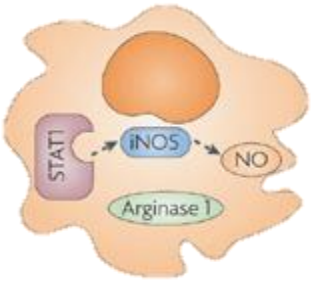

Anthracyclines
Gemcitabine
Fotemustine

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Bevacizumab
Sunitinib
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Axitinib
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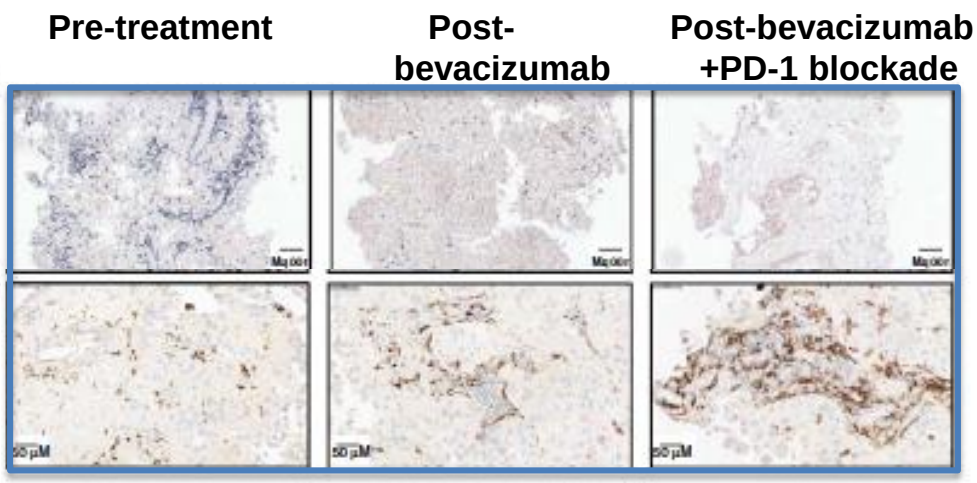
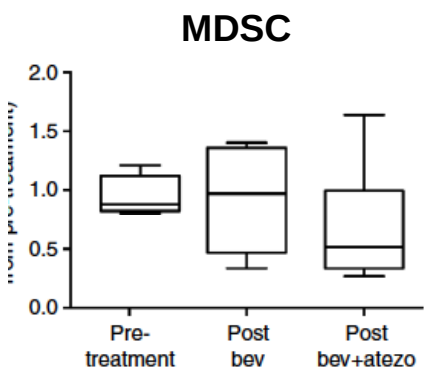
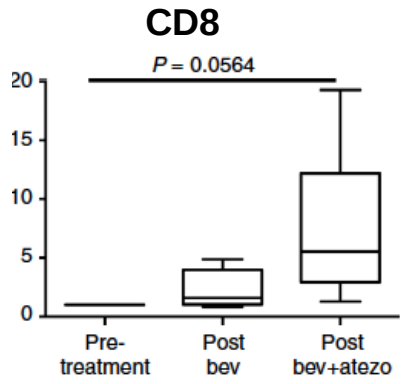
Radiotherapy

IDOi
Anti-TGFb
Anti-CSF1R



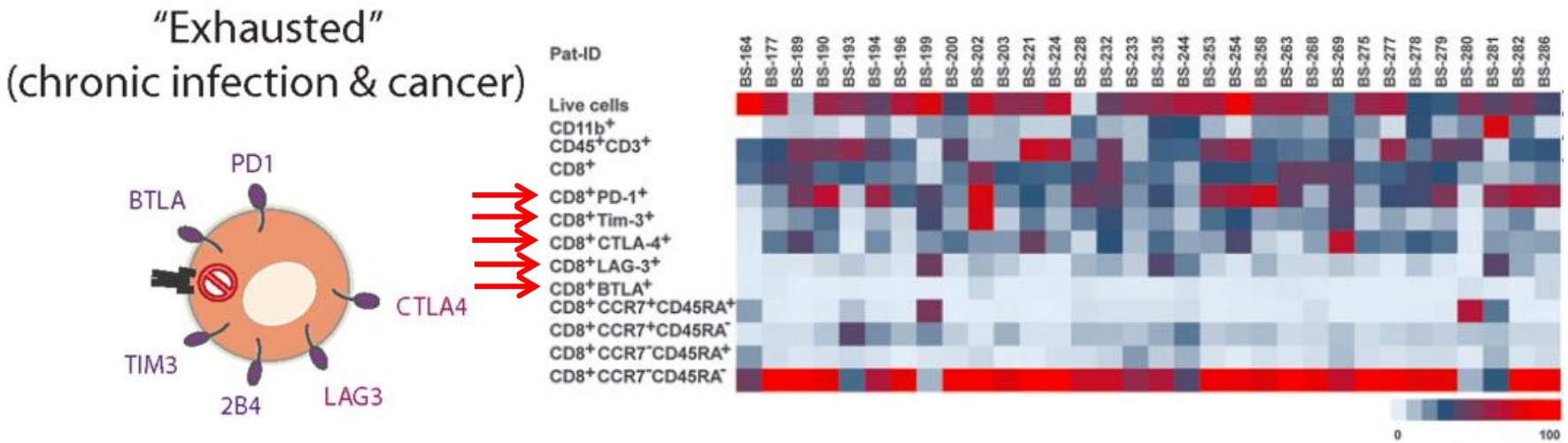




Wallin et al., Nature Communications 2016

Blocking additional immune checkpoints to further boost antitumor immunity

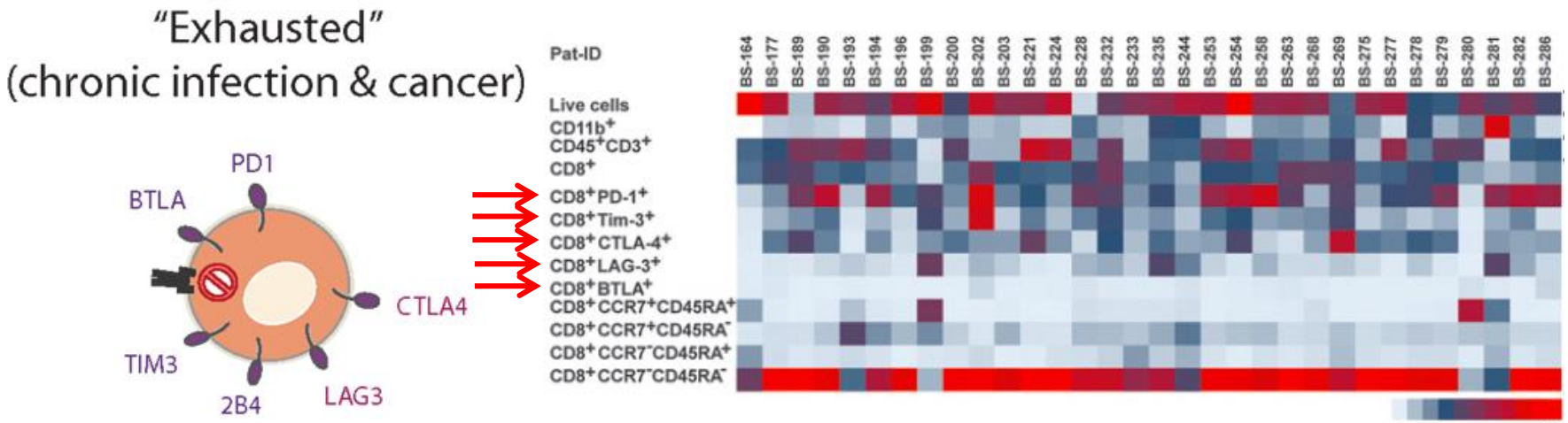
Thommer et al., Cancer Immunol Res 2015

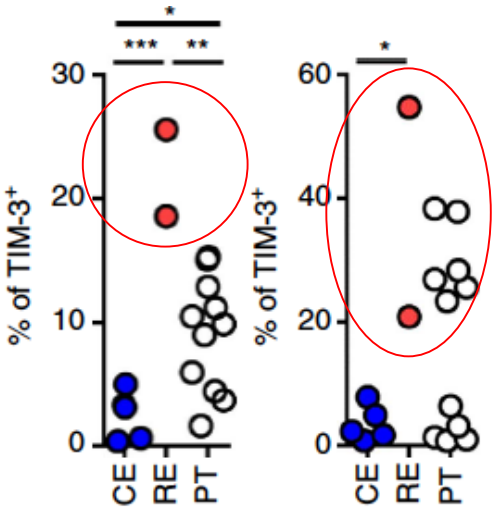


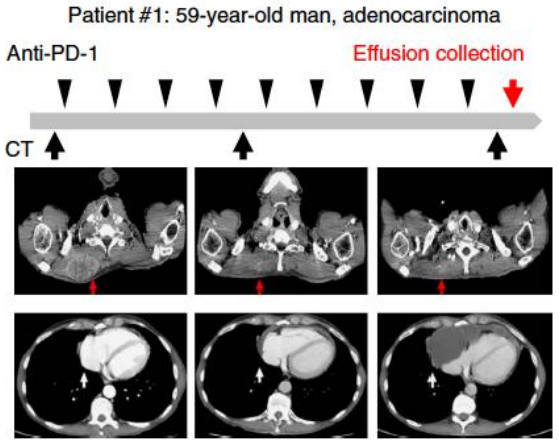
Koyawa et al., Nature Communications 2016

Blocking additional immune checkpoints to further boost antitumor immunity

Thommer et al., Cancer Immunol Res 2015







Koyawa et al., Nature Communications 2016

To summarize

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To summarize

- Tumor cells induce spontaneous immune responses mediated by CD8+ T cells and influencing disease course
- Inhibitory immune checkpoints restrain antitumor immunity, that can be unleashed by antagonist antibodies
- Predictive biomarkers of sensitivity to checkpoint blockade ("hot tumors") involve pre-existing level of T cell immunity, ligand expression by tumor cells, and lack of immunosuppressive pathways in tumor microenvironment
- To rescue "cold" resistant tumors, improved immunogenicity (increase CD8+ T cell infiltration and activation) and reduced immunosuppression (decrease MDSC) should be reached by combination therapies

Thank you