



Immunoterapia

Licia Rivoltini, MD

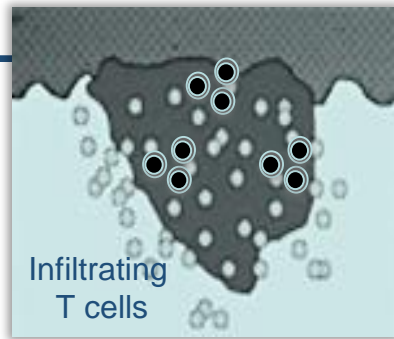
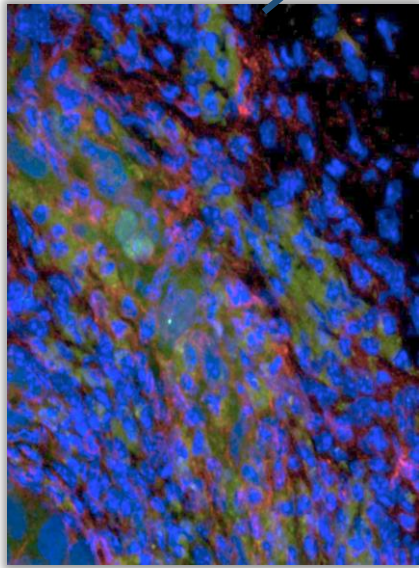
**Unità di Immunoterapia dei
Tumori Umani**

**Fondazione IRCCS
Istituto Nazionale dei Tumori
Milano**

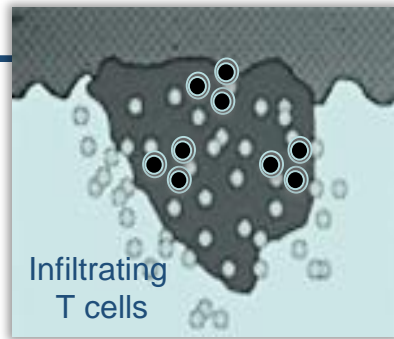
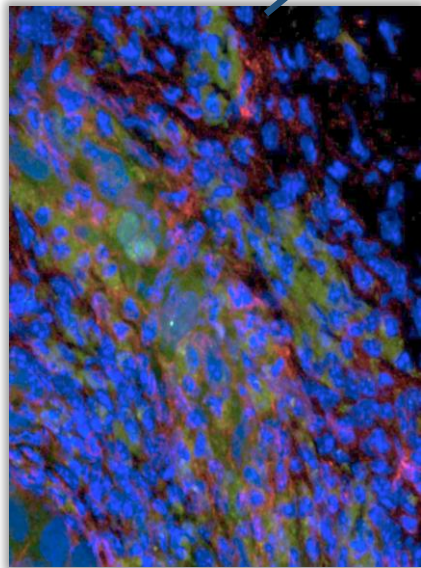
CARCINOMA DEL POLMONE
NON MICROCITOMA:
QUALI NOVITA' PER IL 2016?

VERONA
8-9 APRILE 2016
Hotel Leon d'Oro

Cancer lesions are infiltrated by tumor-specific cytotoxic T cells



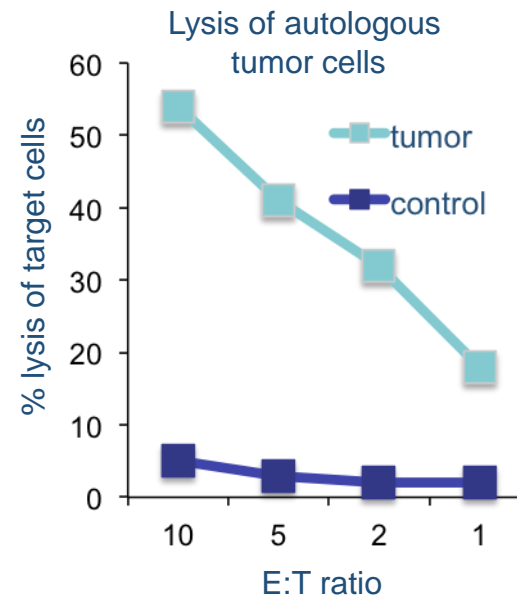
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Lymphocyte growth factors



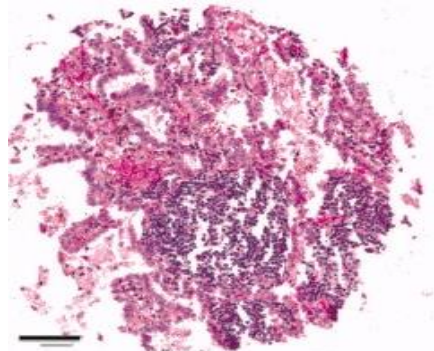
CD8+ T cells



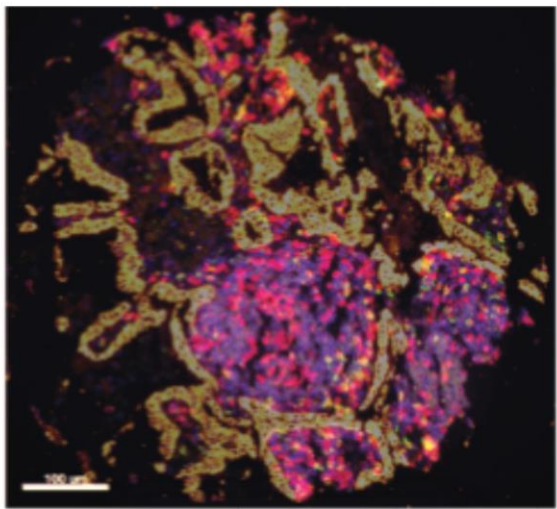
Lysis of:

- **autologous tumor**
- allogeneic tumors of the same histotype
- allogeneic tumors of different histotype

Positive prognostic value of tumor infiltrating CD8 T cells



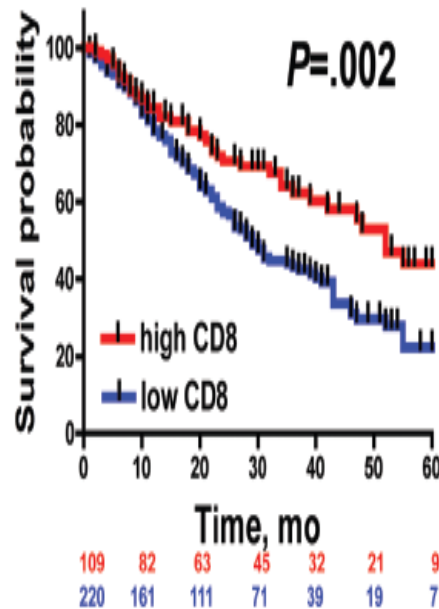
Hematoxylin & Eosin



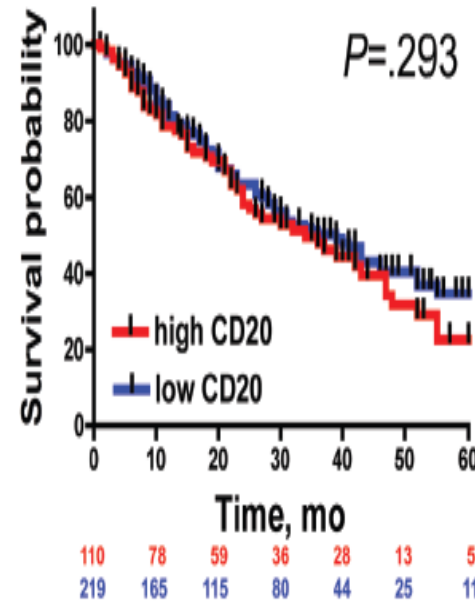
DAPI/CK/CD3/CD8/CD20

NSCLC

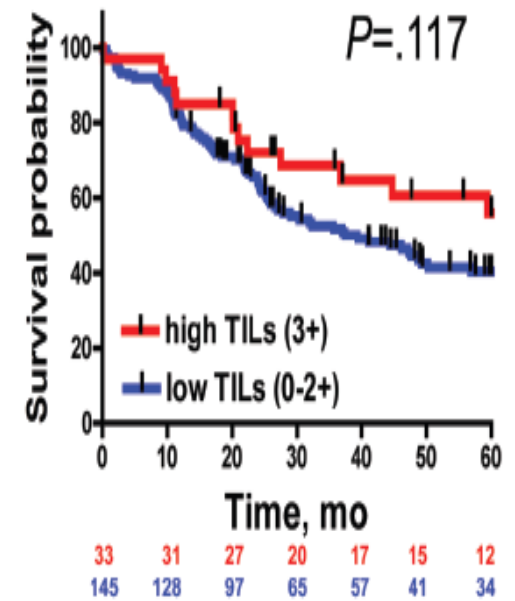
CD8 T cells



B cells

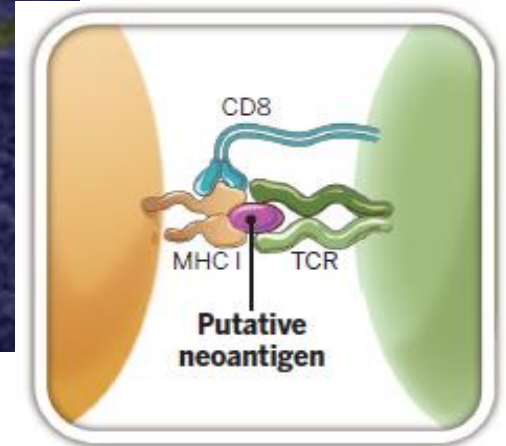
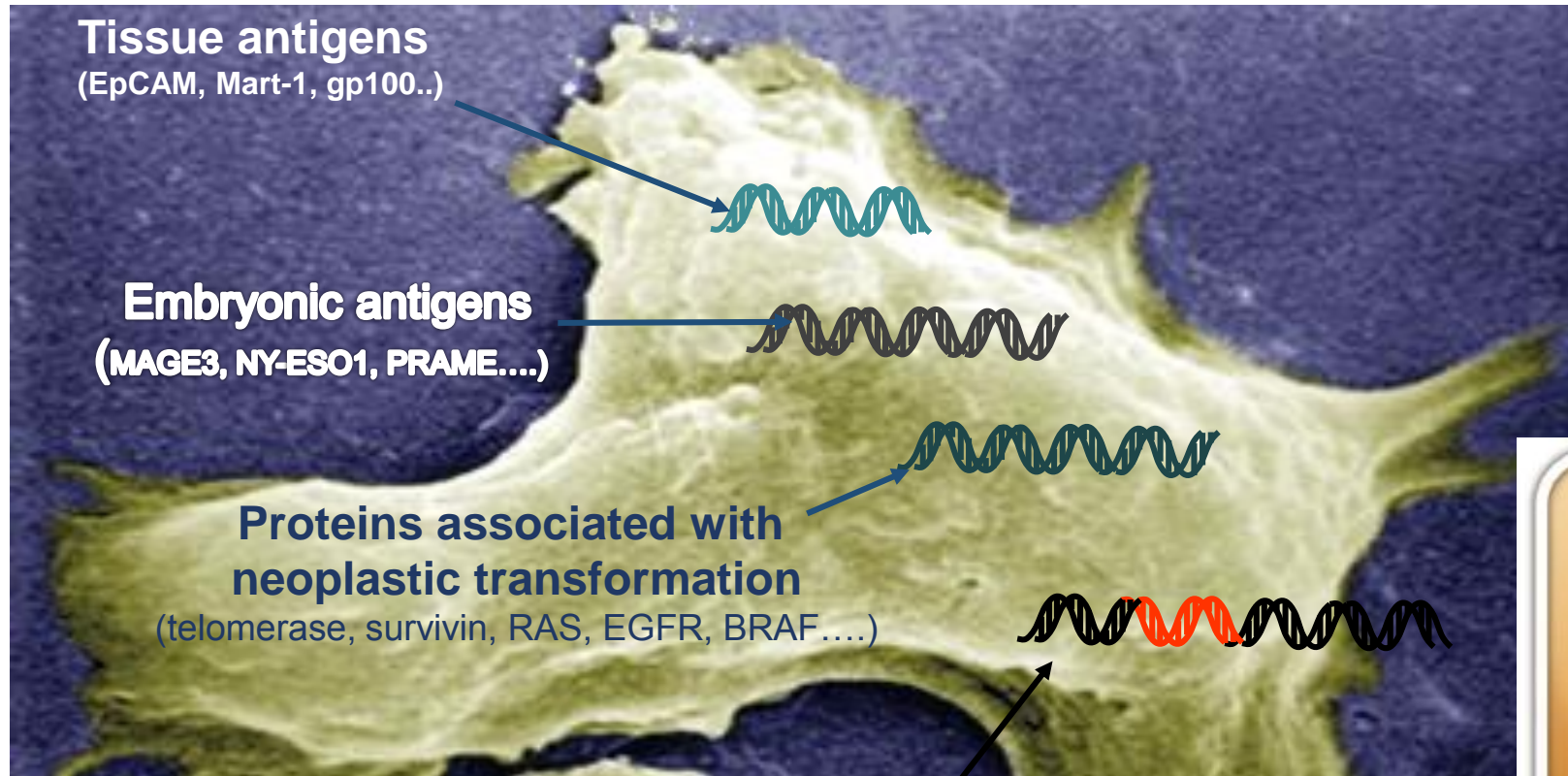


CD4 T cells



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

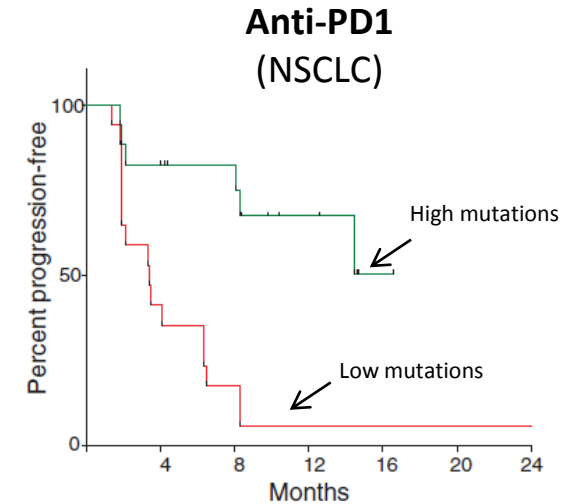
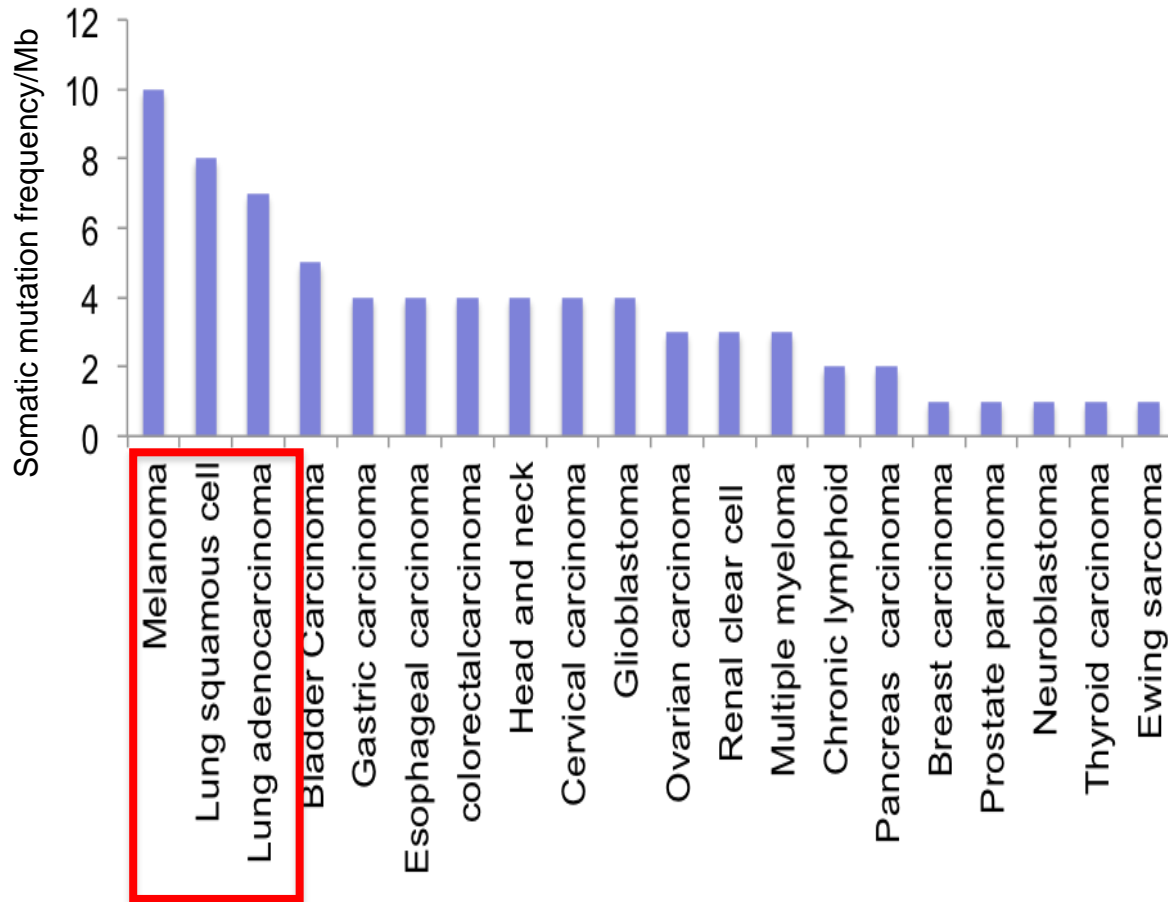
Tumor antigens recognized by T cells



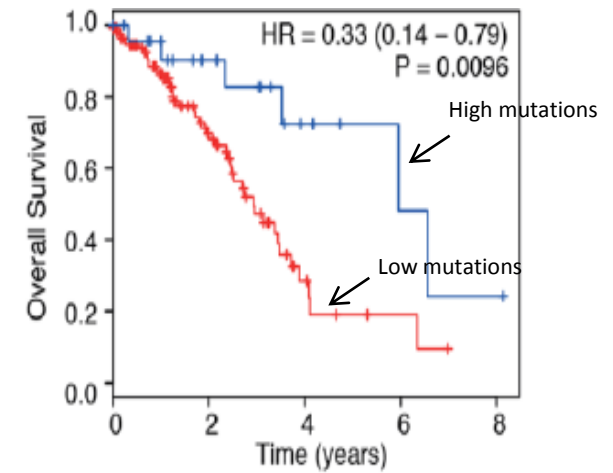
Unique mutated antigens or **NEO-ANTIGENS**

(non-synonymous mutations due to genetic instability)

Neoantigens are the target of effective antitumor immune responses

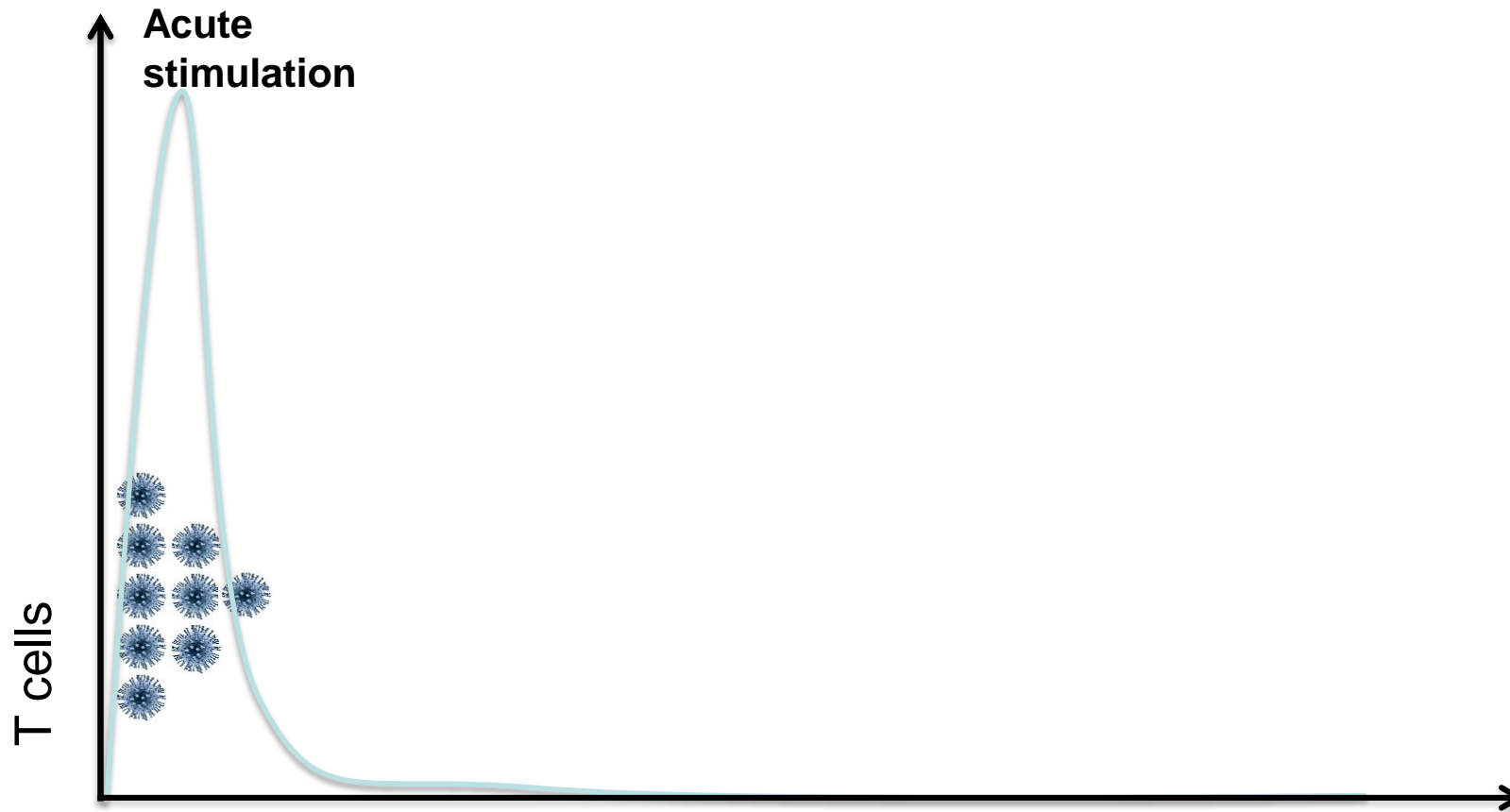


Rizvi et al. Science , 2015

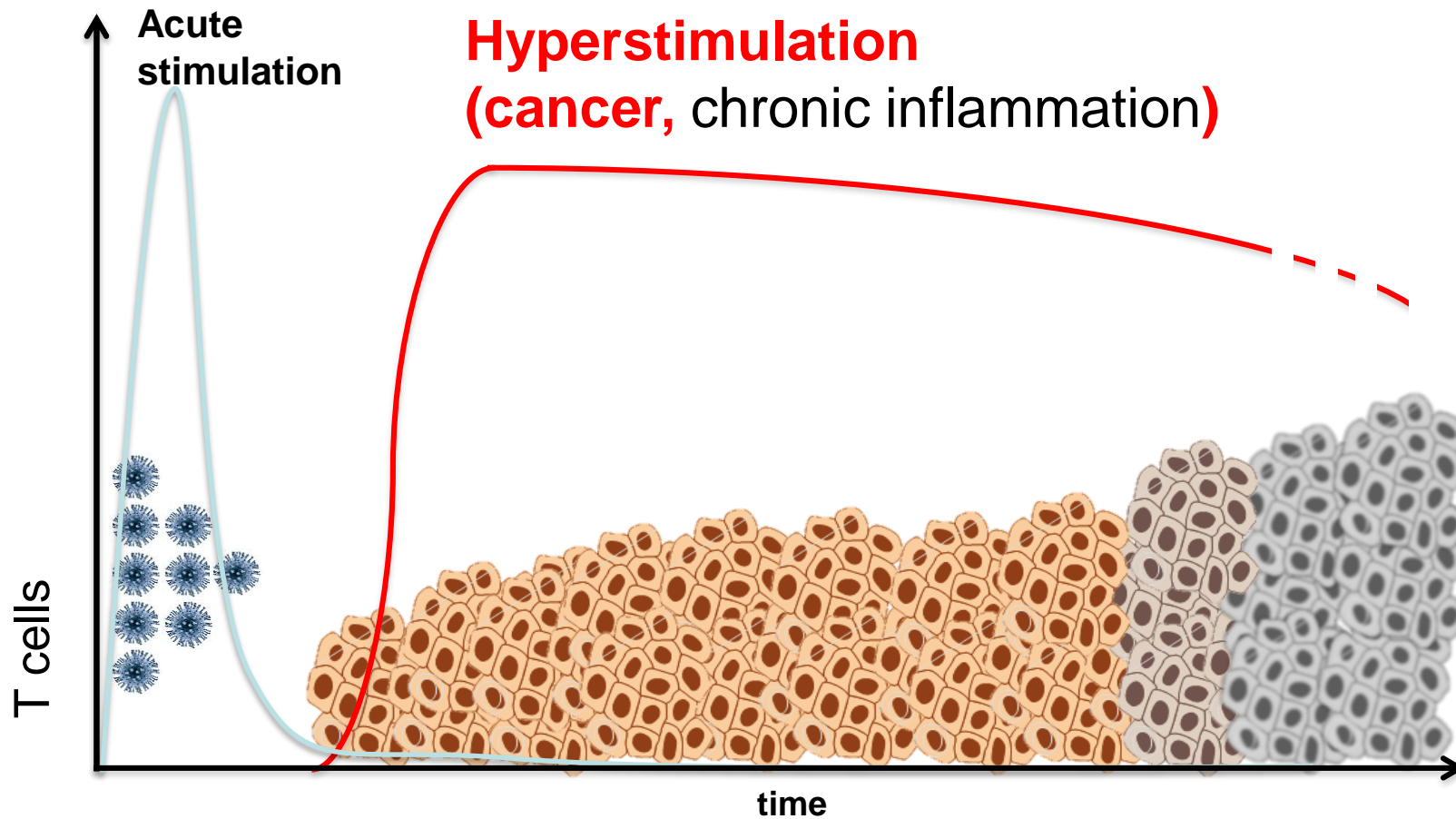


McGranahan et a., Science 2016

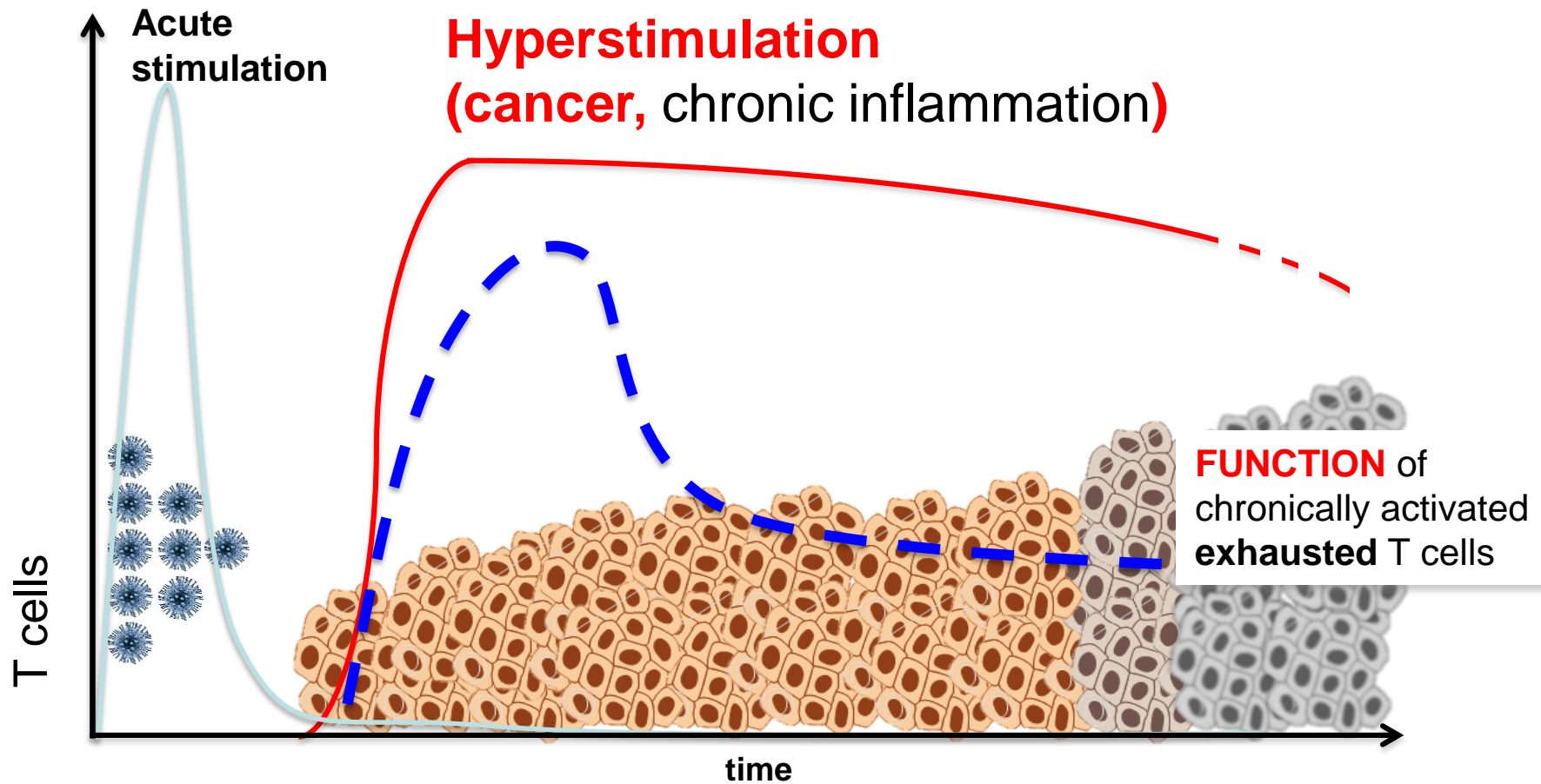
In cancer, like in chronic infections, antigen persistency leads to T cell exhaustion



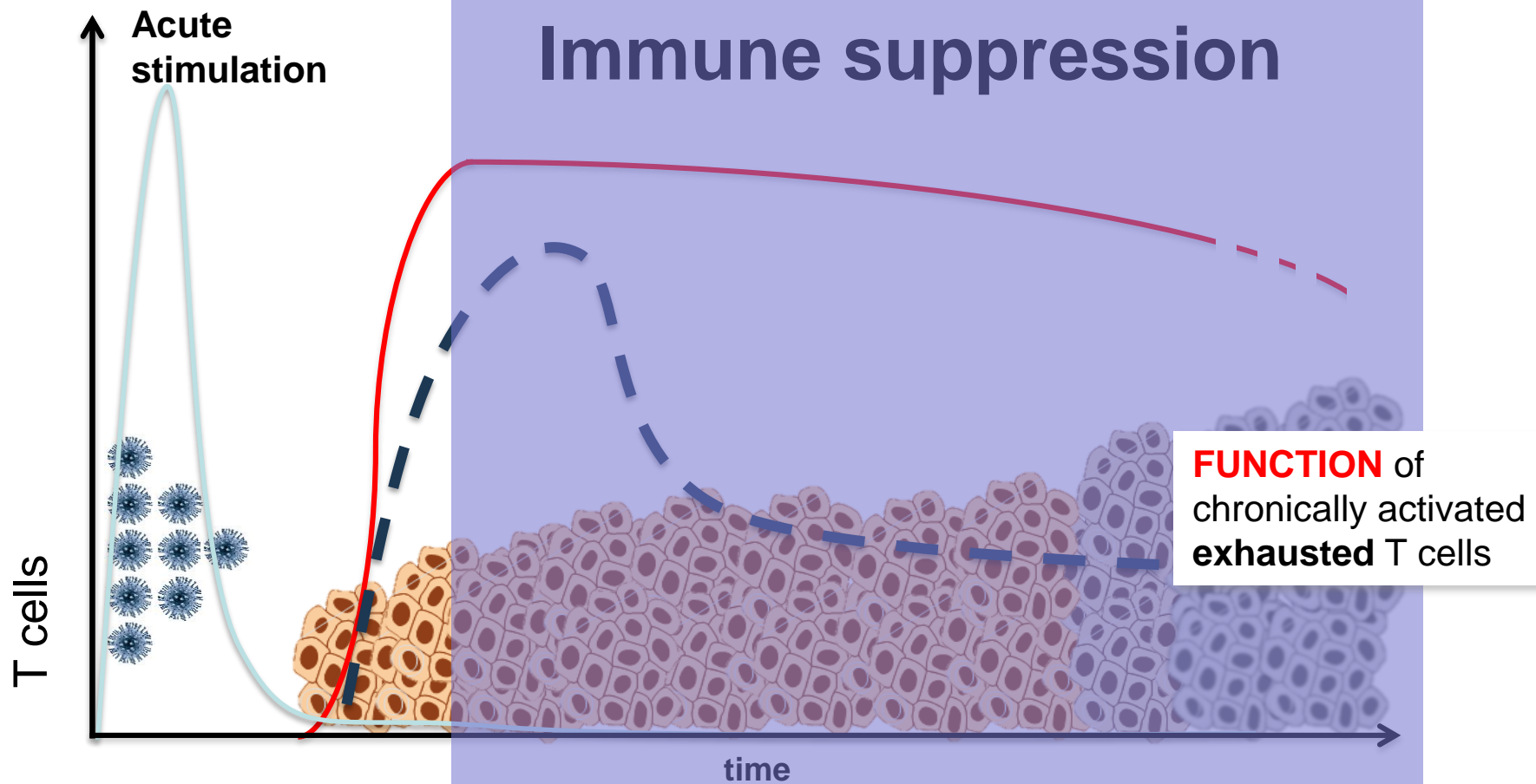
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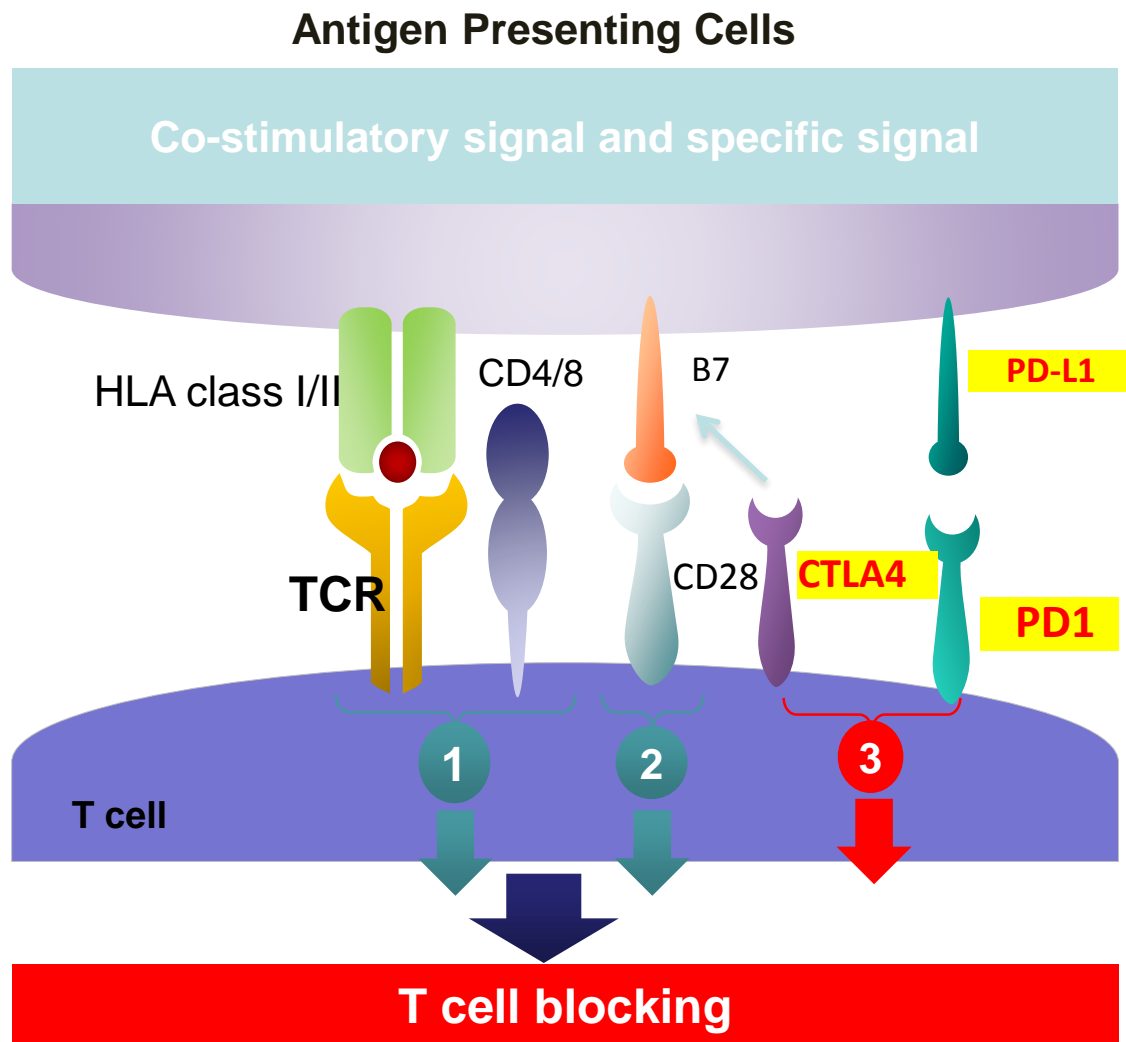
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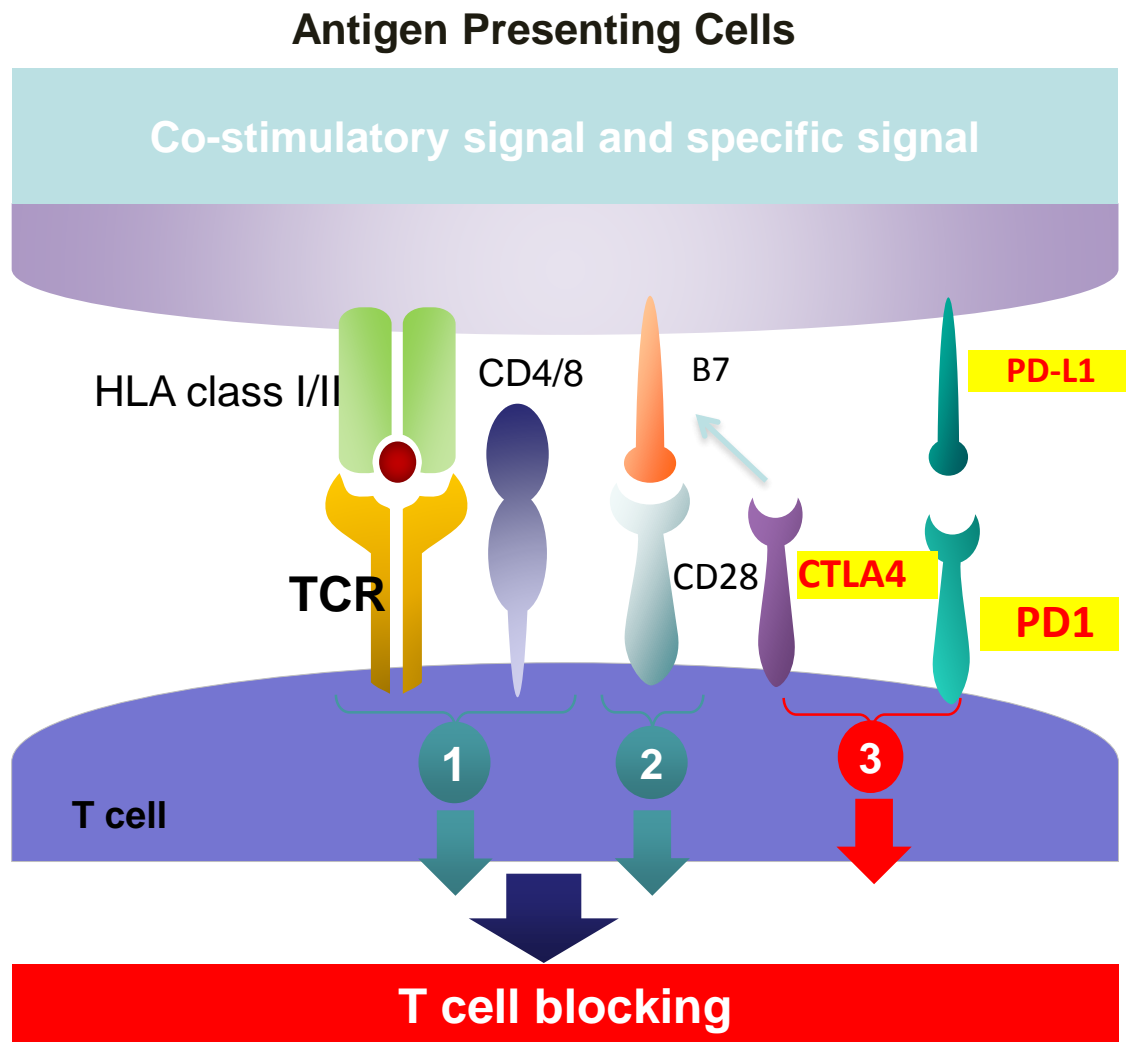
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T cell activation induces the expression of immune checkpoints



T cell activation induces the expression of immune checkpoints



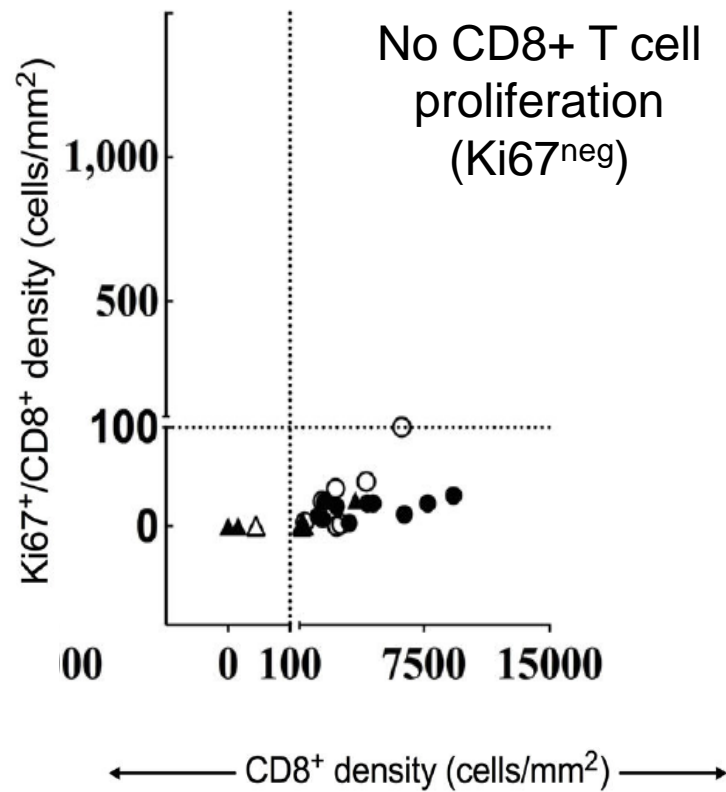
Immune checkpoints

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

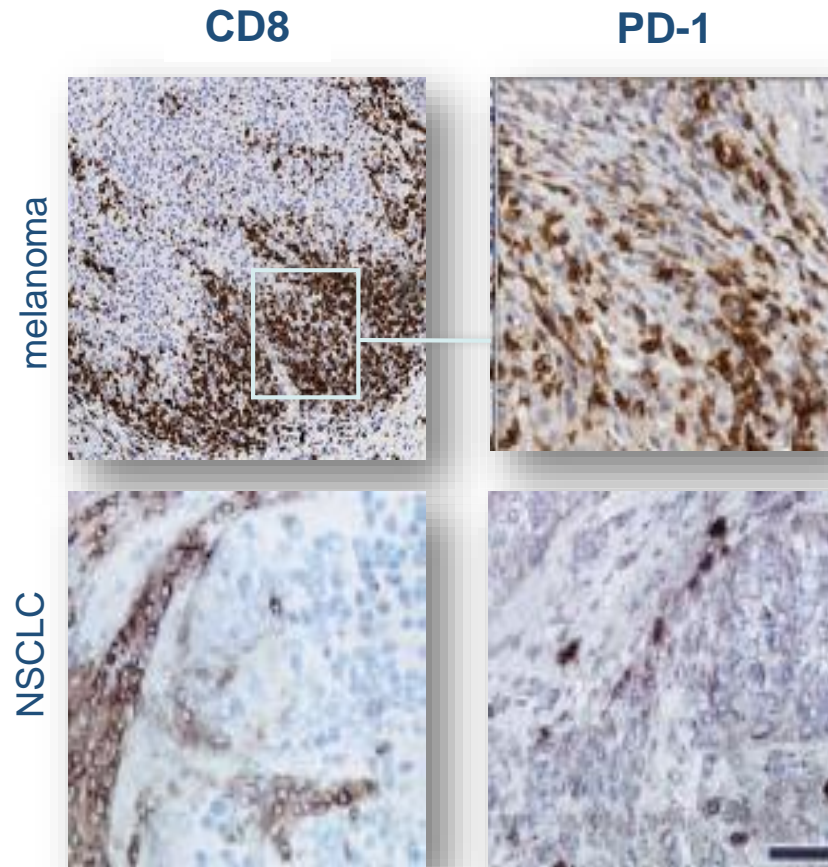
In a reversible fashion

**Immune checkpoint
expression is the
unavoidable consequence
of T cell activation**

Immune checkpoints are upregulated in tumor infiltrating T cells: a clear sign of persistent activation

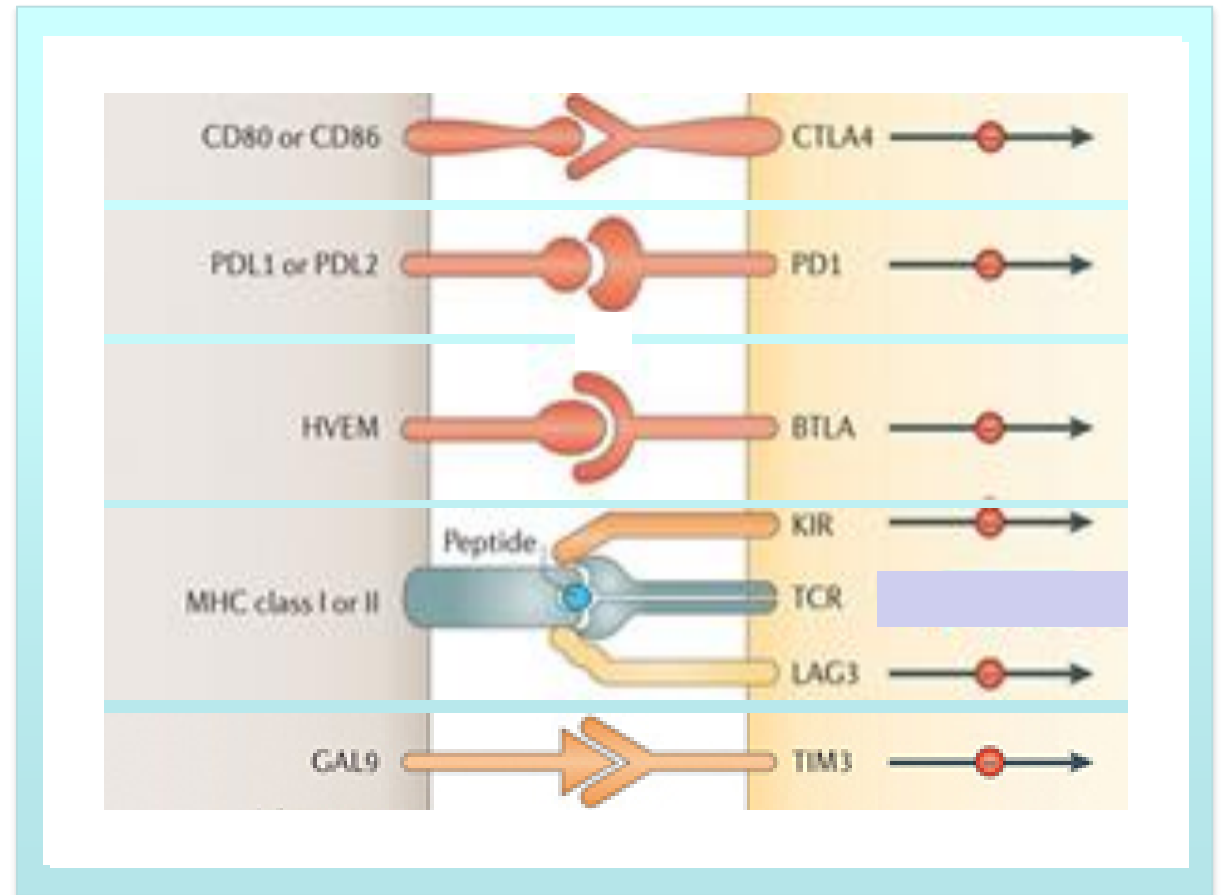
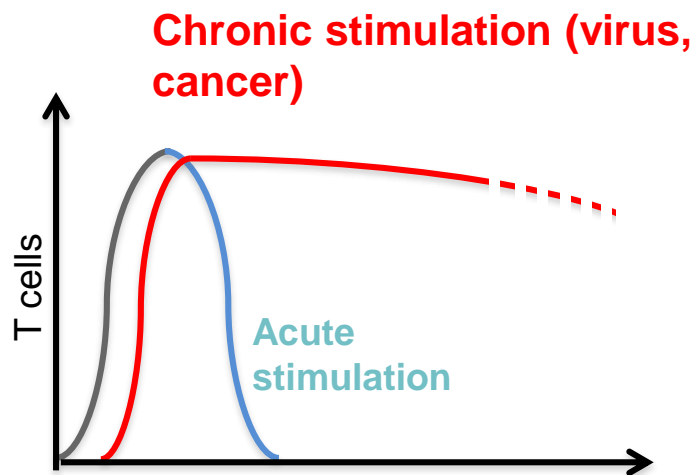


Tumeh et al., Nature 2014



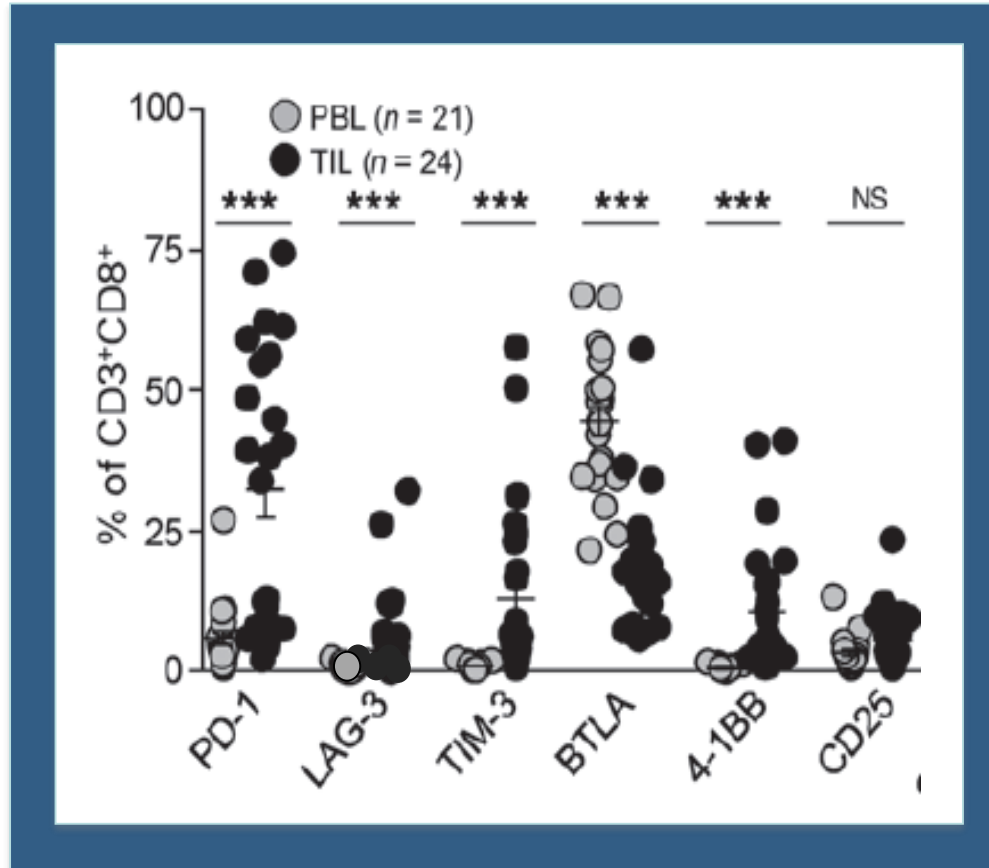
Konishi, Clin Cancer Res 2004

In cancer, persistent immunostimulation up-regulates the expression of immune checkpoints

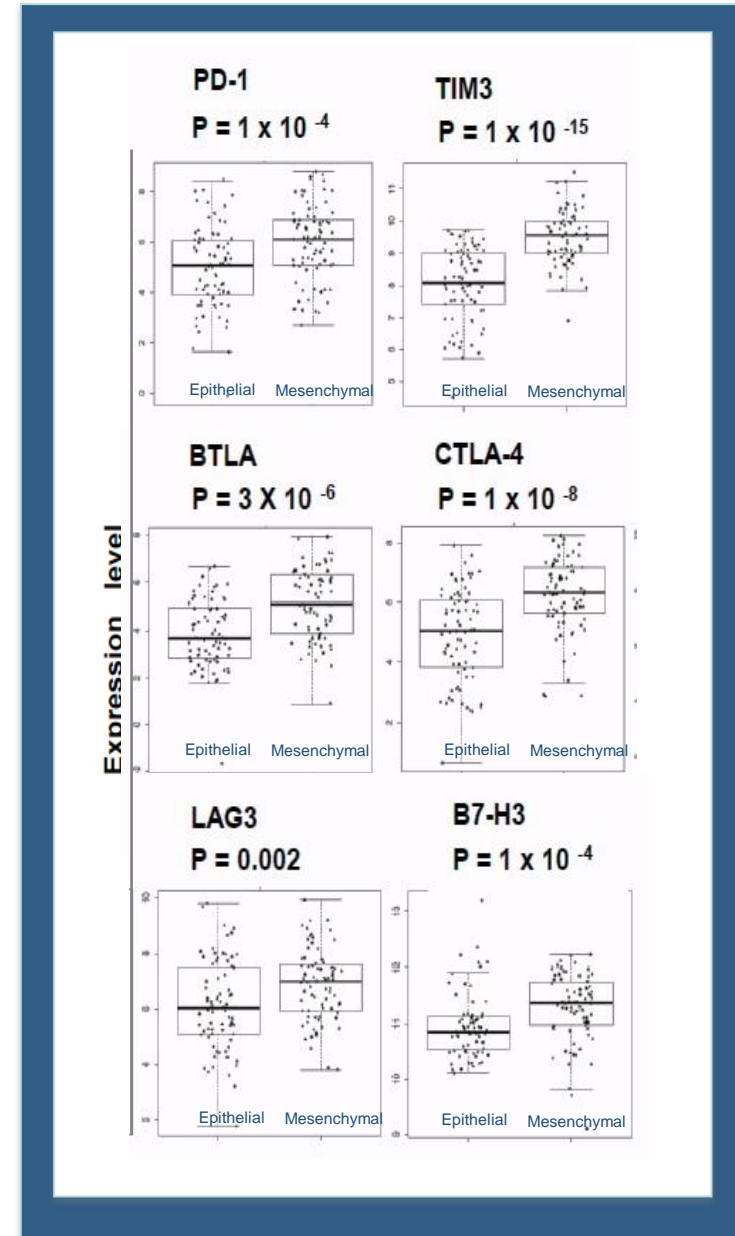


Multiple immune checkpoints in tumor microenvironment

Melanoma



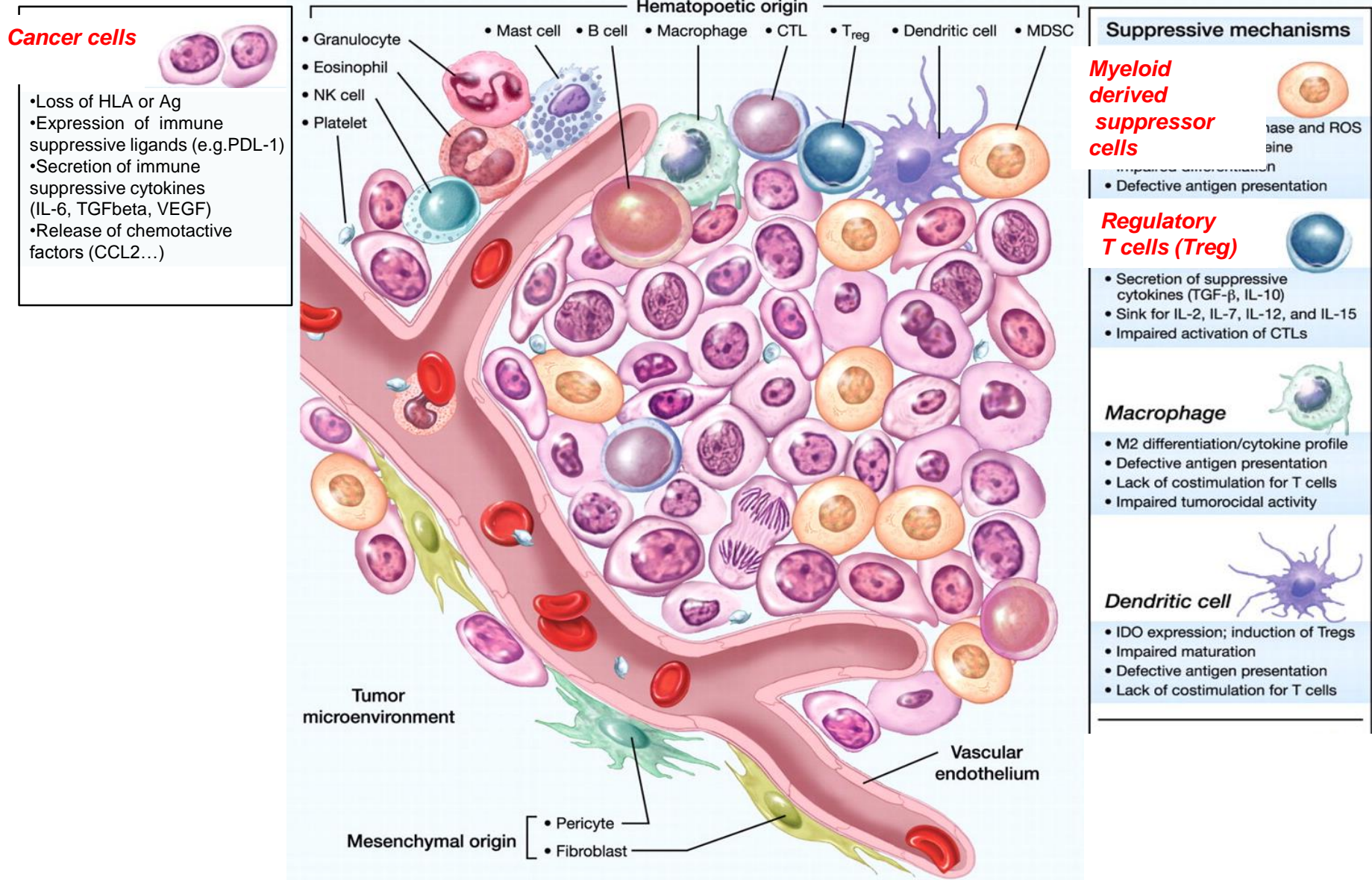
Gros et al., J Clin Invest 2014



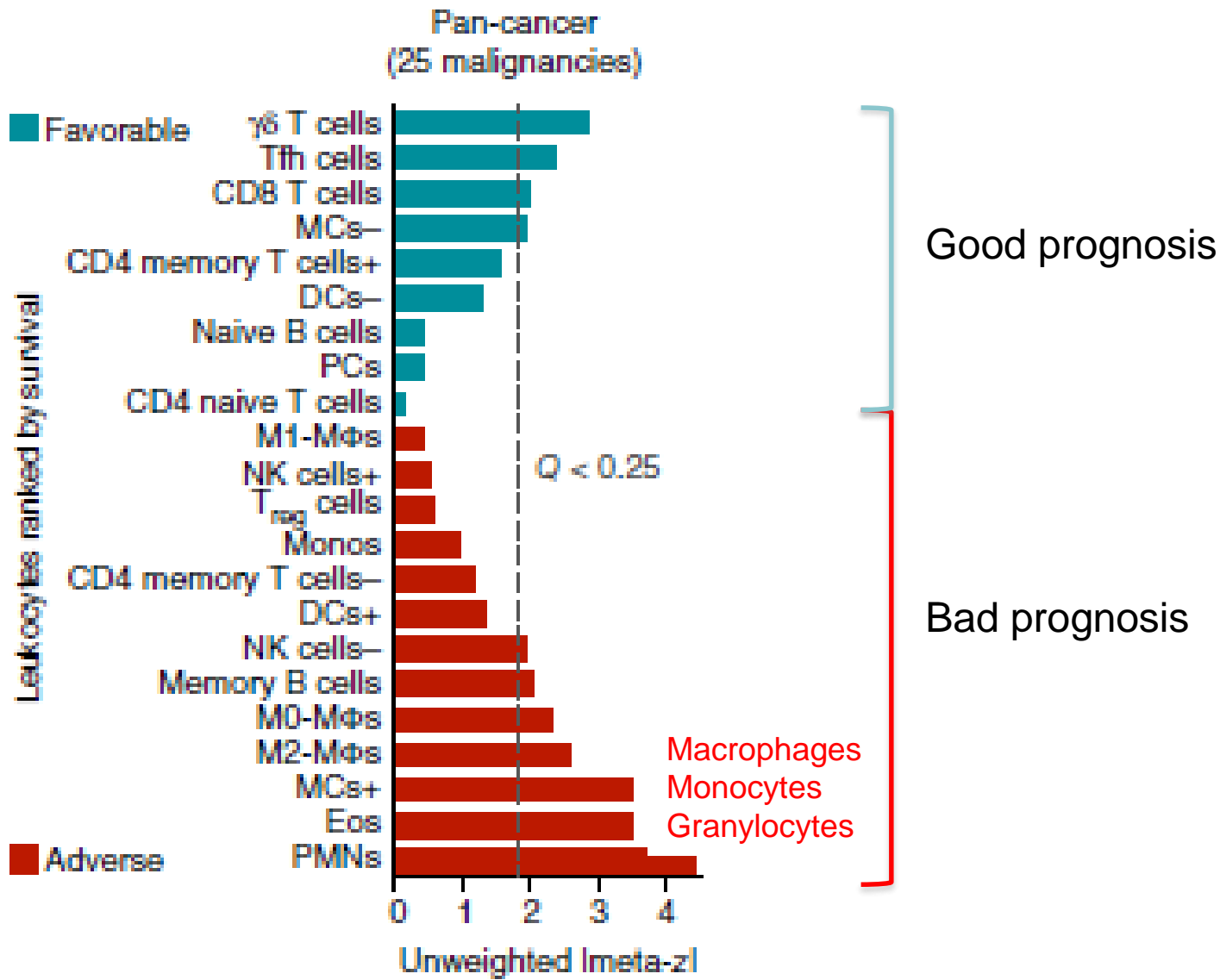
NSCLC

Lou et al., Clin Cancer Res 2016

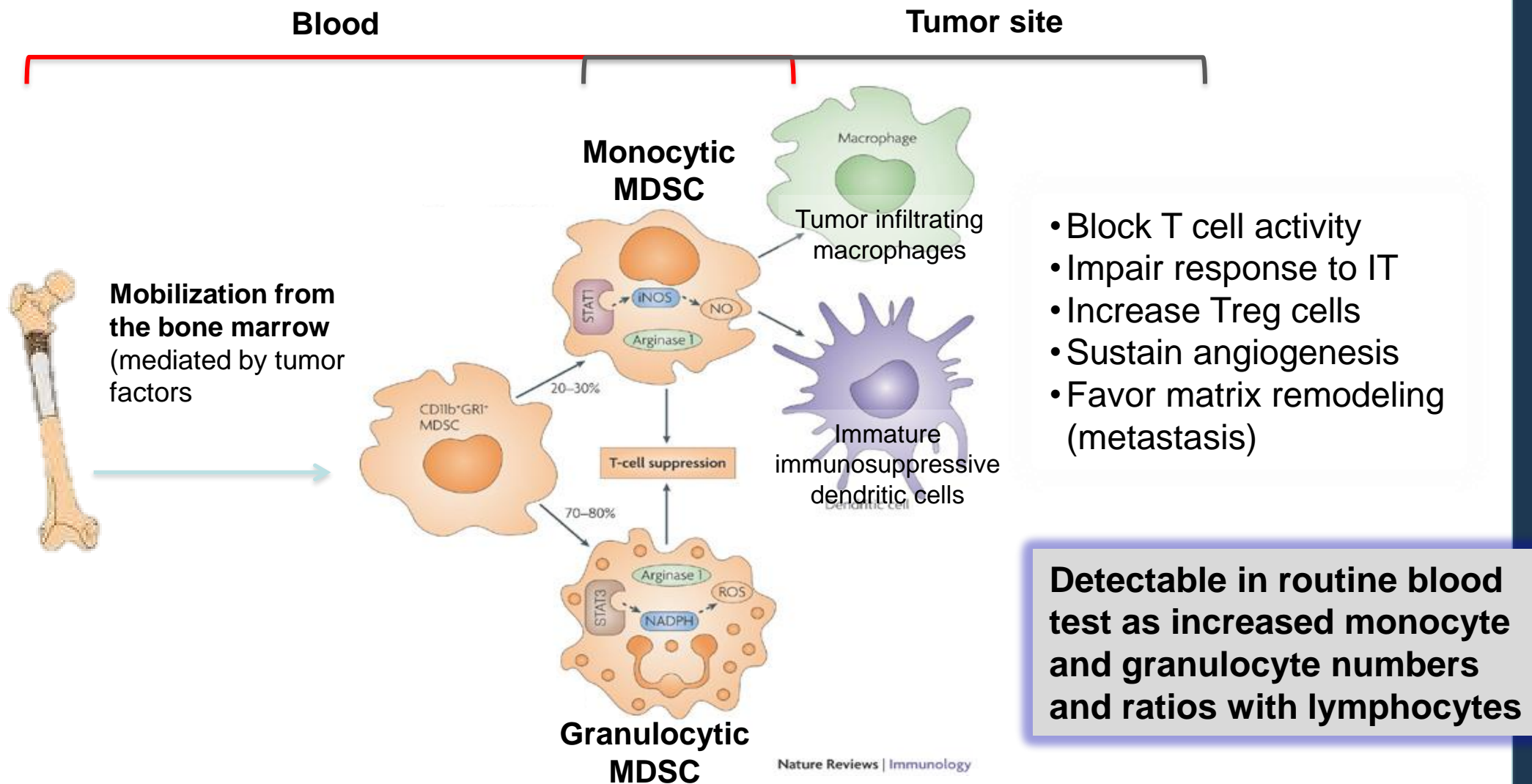
Accumulation of immunosuppressive cells and pathways at tumor site



The accumulation at tumor site of myeloid components is associated with poor prognosis



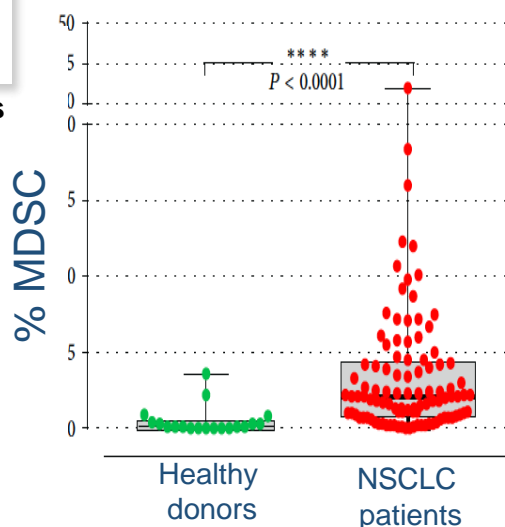
Accumulation of myeloid derived suppressor cells (MDSC) in melanoma patients



Accumulation of myeloid derived suppressor cells (MDSC) is a negative prognostic factor in NSCLC patients

NSCLC patients
BLOOD

CD14⁺HLA-DR^{neg} cells
CD15⁺ cells

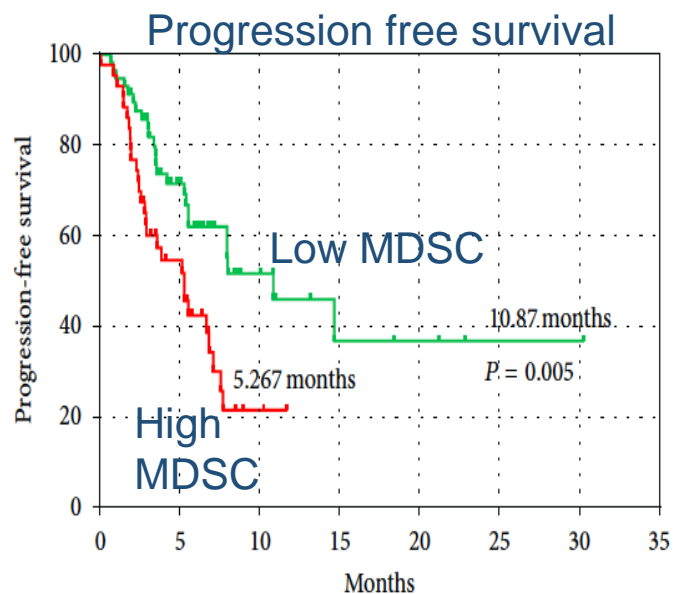
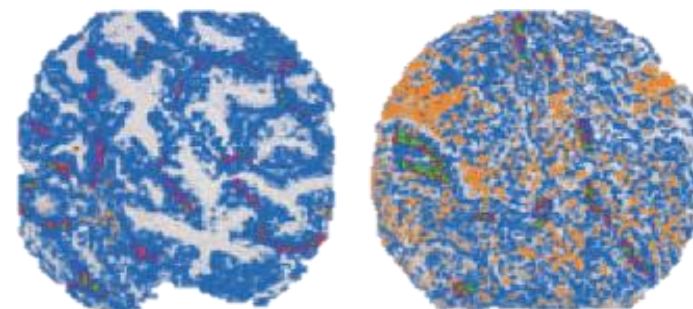


NSCLC patients
Tumor site

Low MDSC

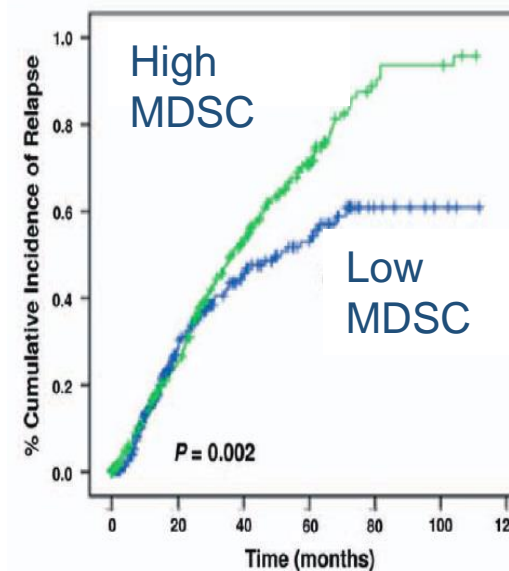
High MDSC

CD14⁺CD163⁺
CD14⁺ CD68⁺
CD66⁺



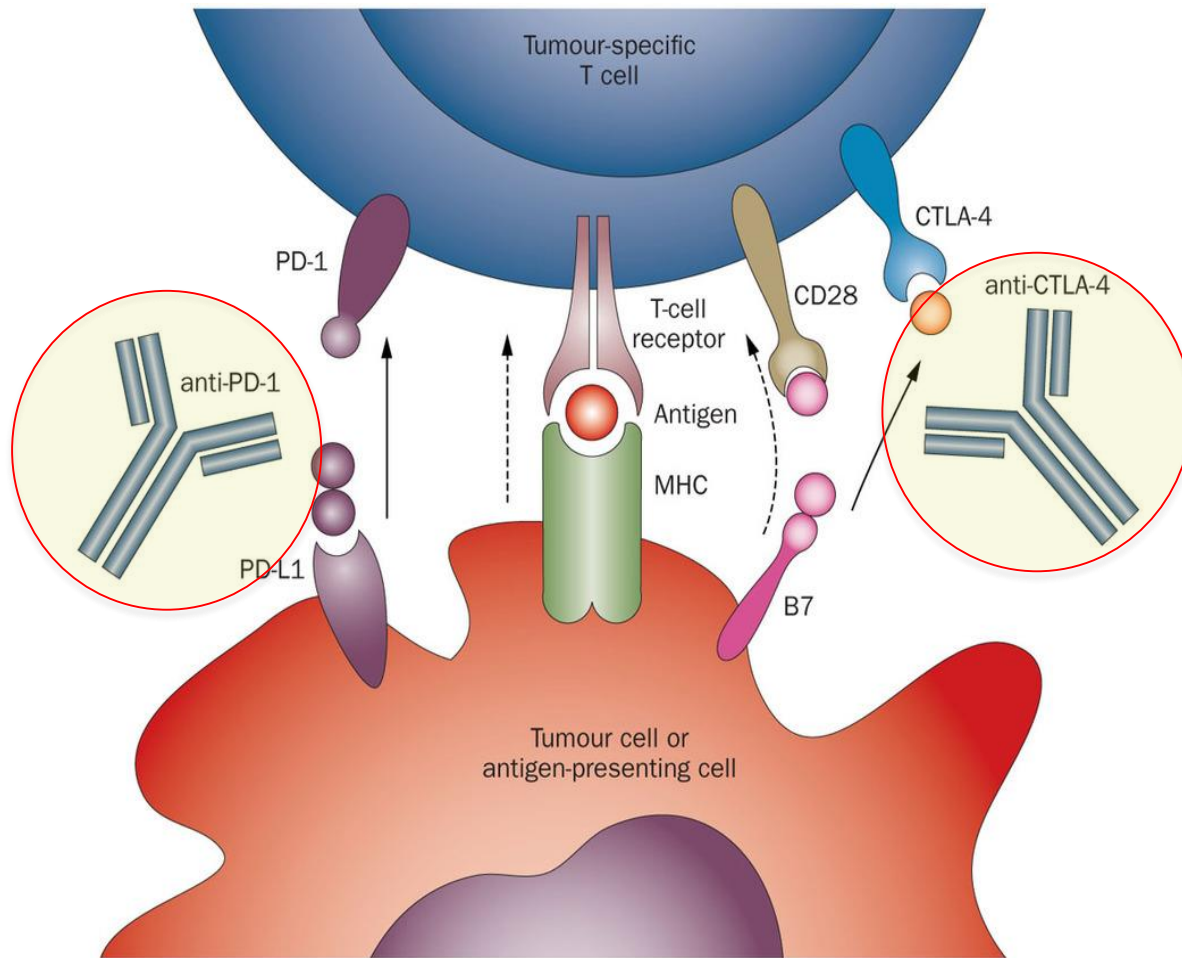
Vetsika et al., J Immunol Res 2014

Incidence of relapse



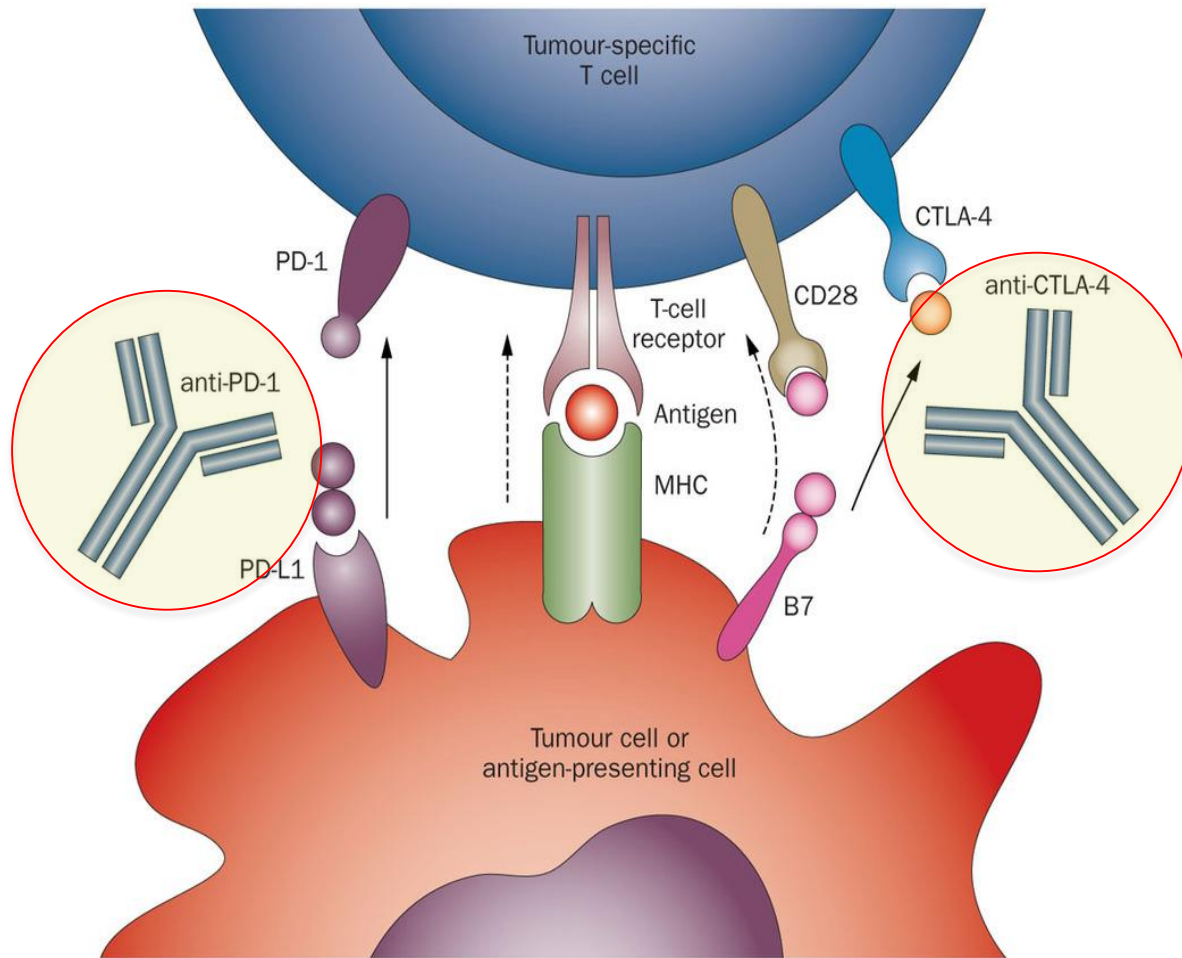
Ilie et al., Cancer 2012

Immune checkpoints inhibitors enhance anti-tumor T cell responses



Nguyen et al., Nature Rev Immunol 2015

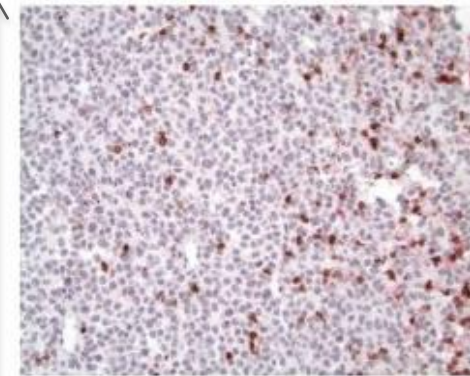
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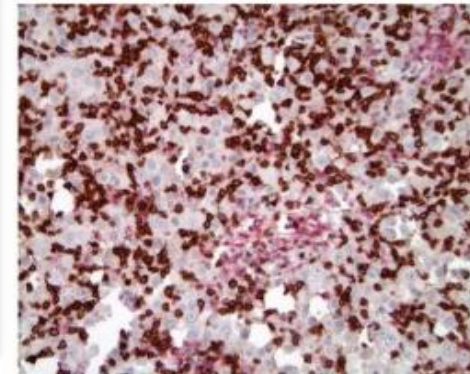
Nguyen et al., Nature Rev Immunol 2015

PD-1 blockade

Before Treatment



After Treatment



CD8+ T cells

Tumeh et al, Nature 2014

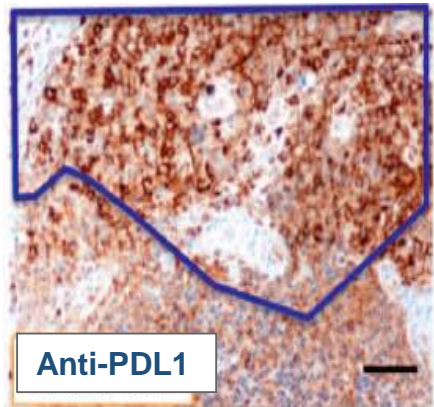
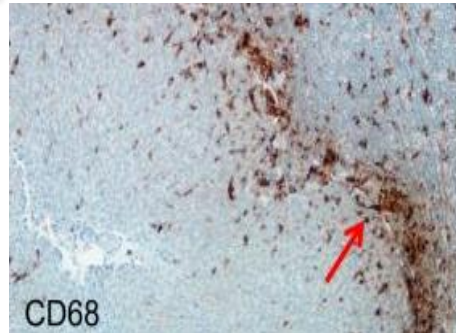
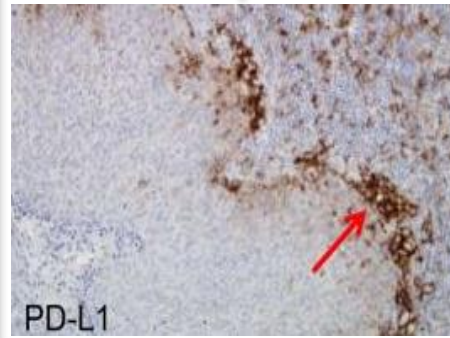
Checkpoint ligands (PDL-1) are broadly expressed in tumor microenvironment: a target to reduce immunosuppression by infiltrating myeloid cells

Local inflammation

- ◆ cytokine an
- ◆ chemokines
- ◆ IFN produced by T cells

Oncogenic pathways

- ◆ EGFR activation
- ◆ AP-1 signaling
- ◆ PTEN loss
- ◆ PI3K/AKT/mTOR



Taube et al., Science Transl Med 2012

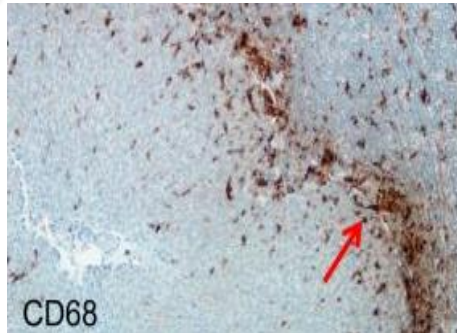
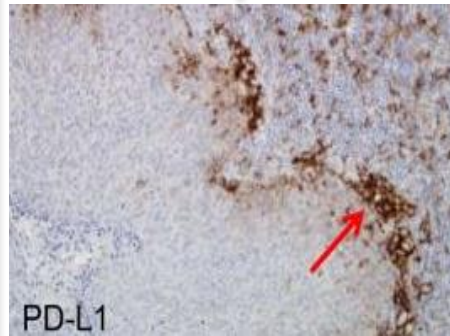
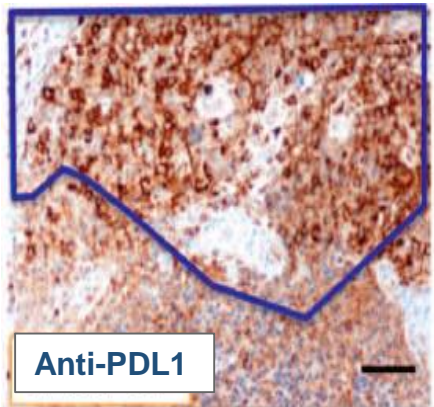
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Local inflammation

- ◆ cytokine and chemokines
- ◆ IFN produced by T cells

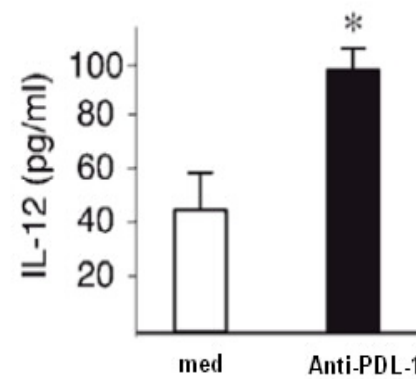
Oncogenic pathways

- ◆ EGFR activation
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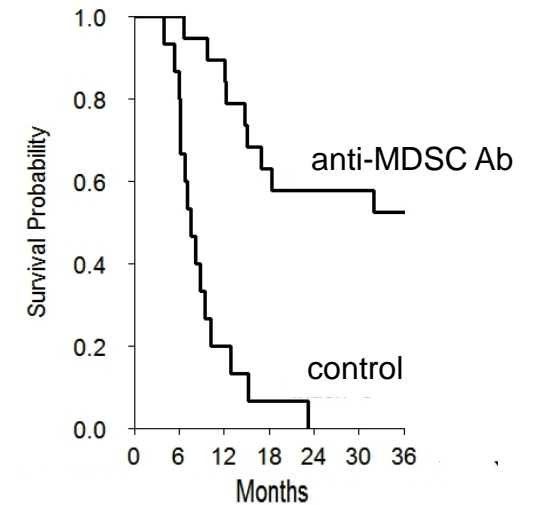
Taube et al., Science Transl Med 2012

PDL-1 blockade converts MDSC into antitumor immune cells (dendritic cells)



Highfill SL et al., Sci Transl Med. 2014

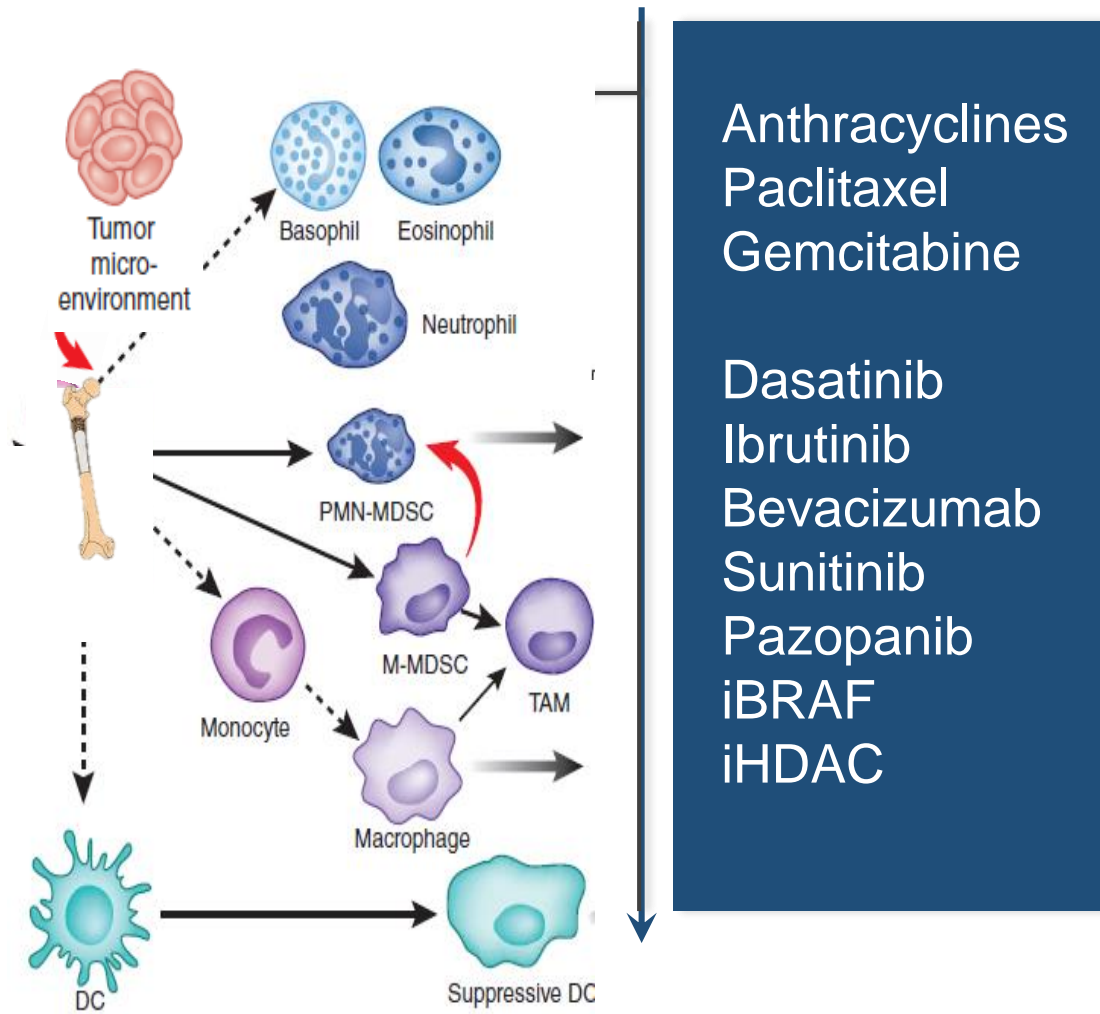
Blocking MDSC accrual increase therapy with anti-PD-1 Ab



Curiel et al., Nature Medicine 2003

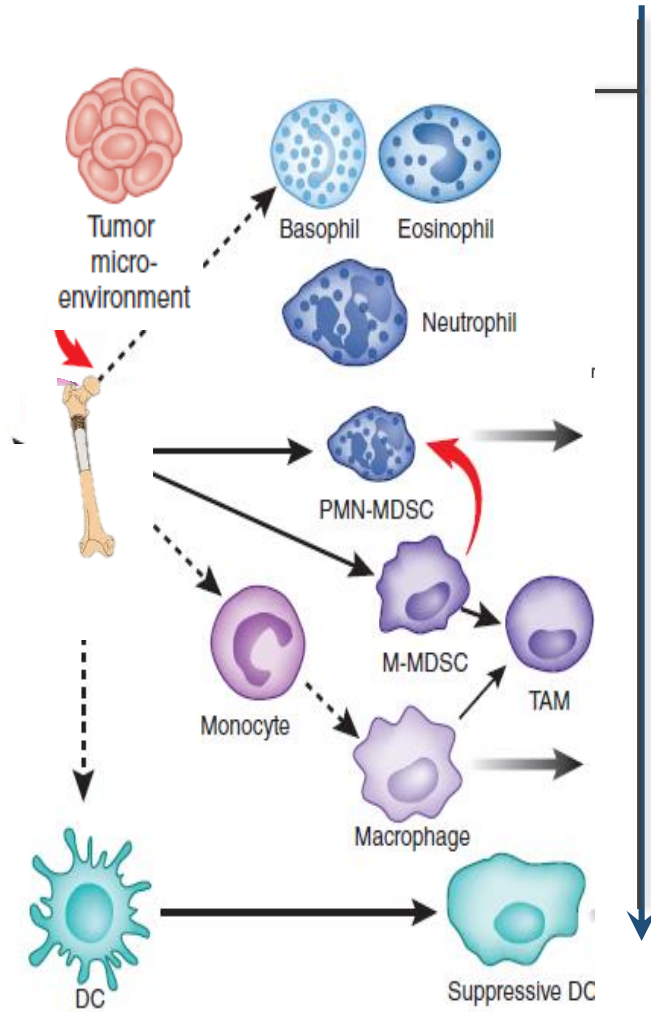
Immunomodulating properties of standard cancer therapies

Increased tumor antigenicity and T cell activation



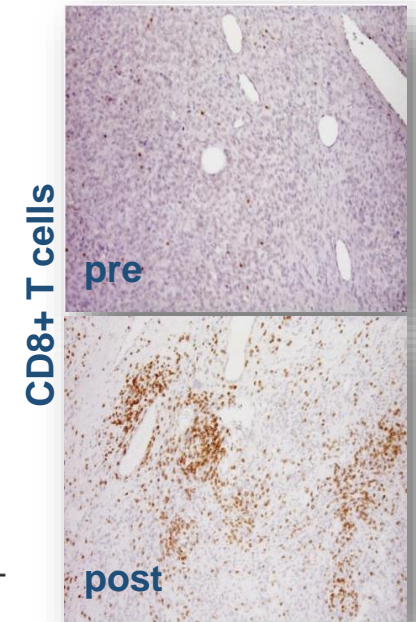
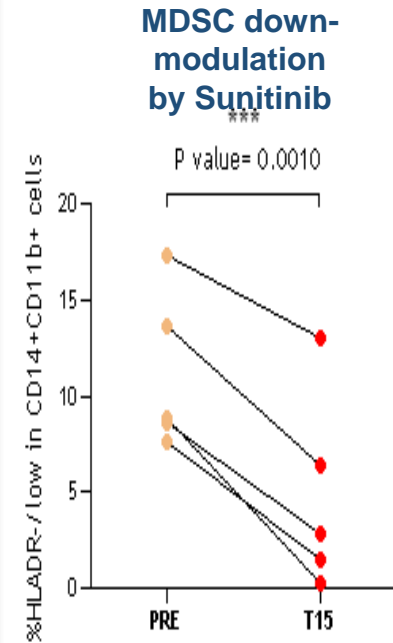
Immunomodulating properties of standard cancer therapies

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Anthracyclines
Paclitaxel
Gemcitabine

Dasatinib
Ibrutinib
Bevacizumab
Sunitinib
Pazopanib
iBRAF
iHDAC



To summarize

Lung cancer, as many other tumors, is immunogenic thanks to the high load of DNA mutations leading the generation of NEOANTIGENS

Tumor immunogenicity induces chronic stimulation and immunosuppression through overexpression of immune checkpoints and accrual of immunoregulatory cells (MDSC)

Frequency of neoantigens, as well as accumulation of immunosuppressive pathways, impact on patient prognosis and response to immunotherapy

Blocking immunosuppressive pathways, including immune checkpoints, allows the recovery of antitumor T cell immunity and immune-mediated disease control

Combination strategies can also be envisaged based on the immunomodulating properties of conventional cancer therapies

