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Immune Escape – Targeting Immune Suppression as a Therapeutic Option

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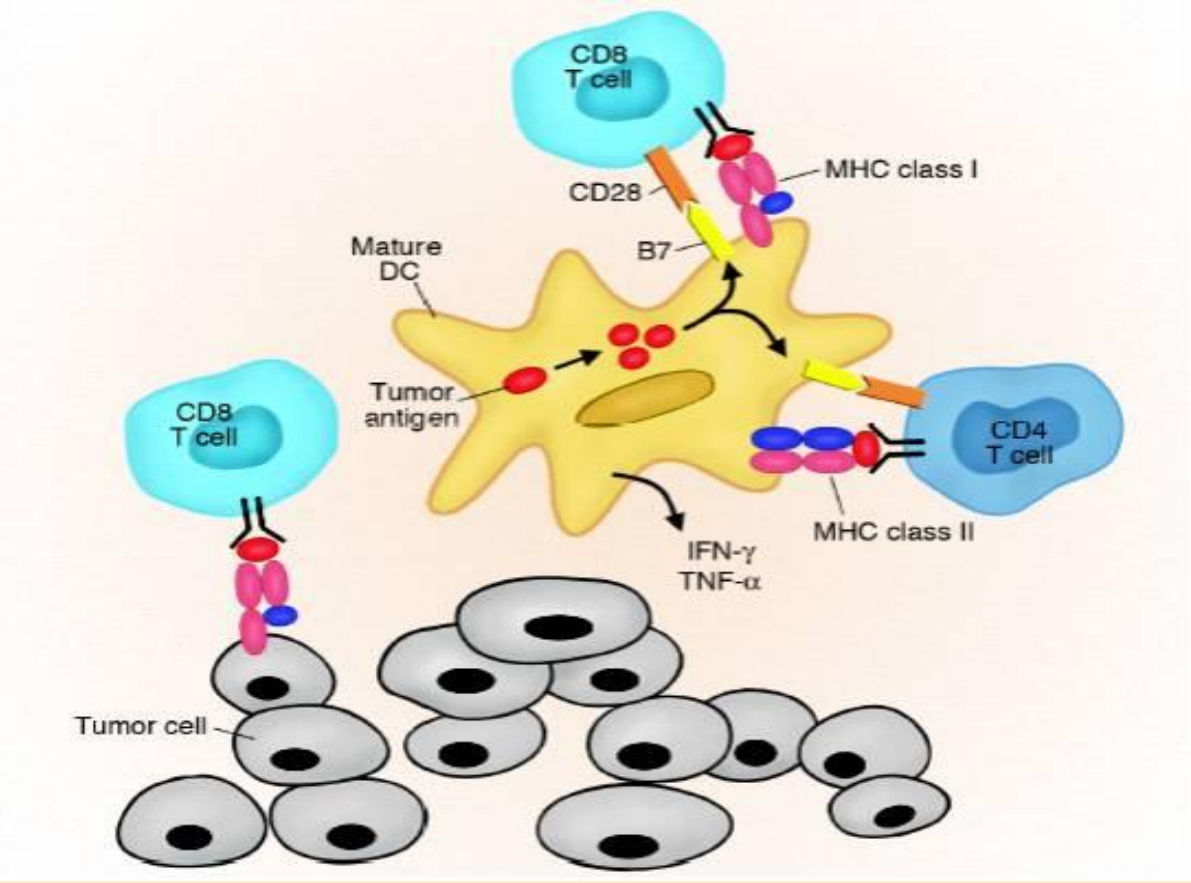
1. IMMUNE ESCAPE IN CANCER

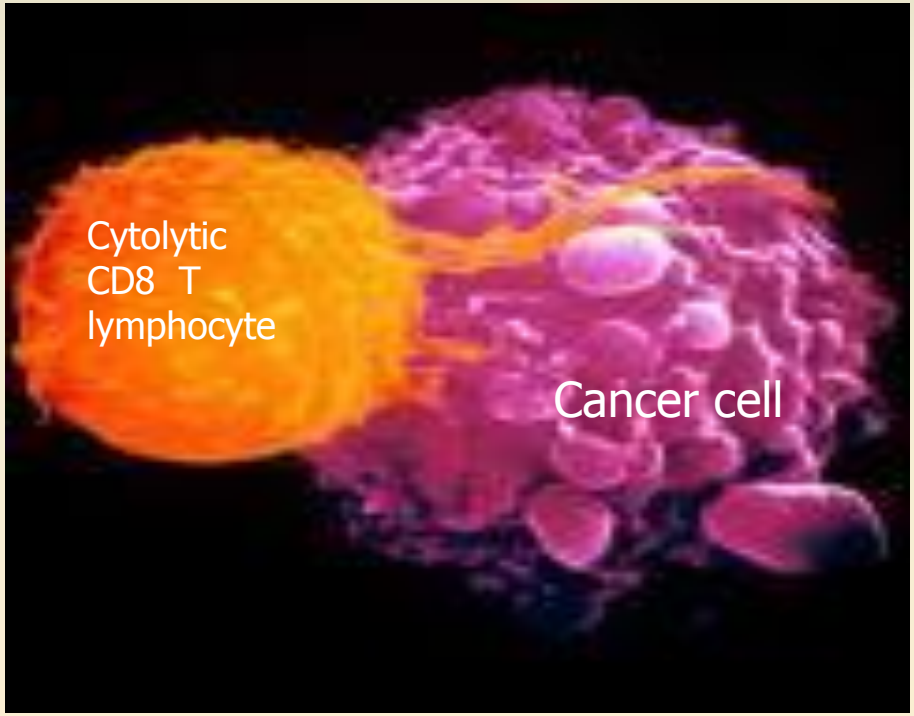
2. TARGETING IMMUNE ESCAPE

IMMUNE ESCAPE

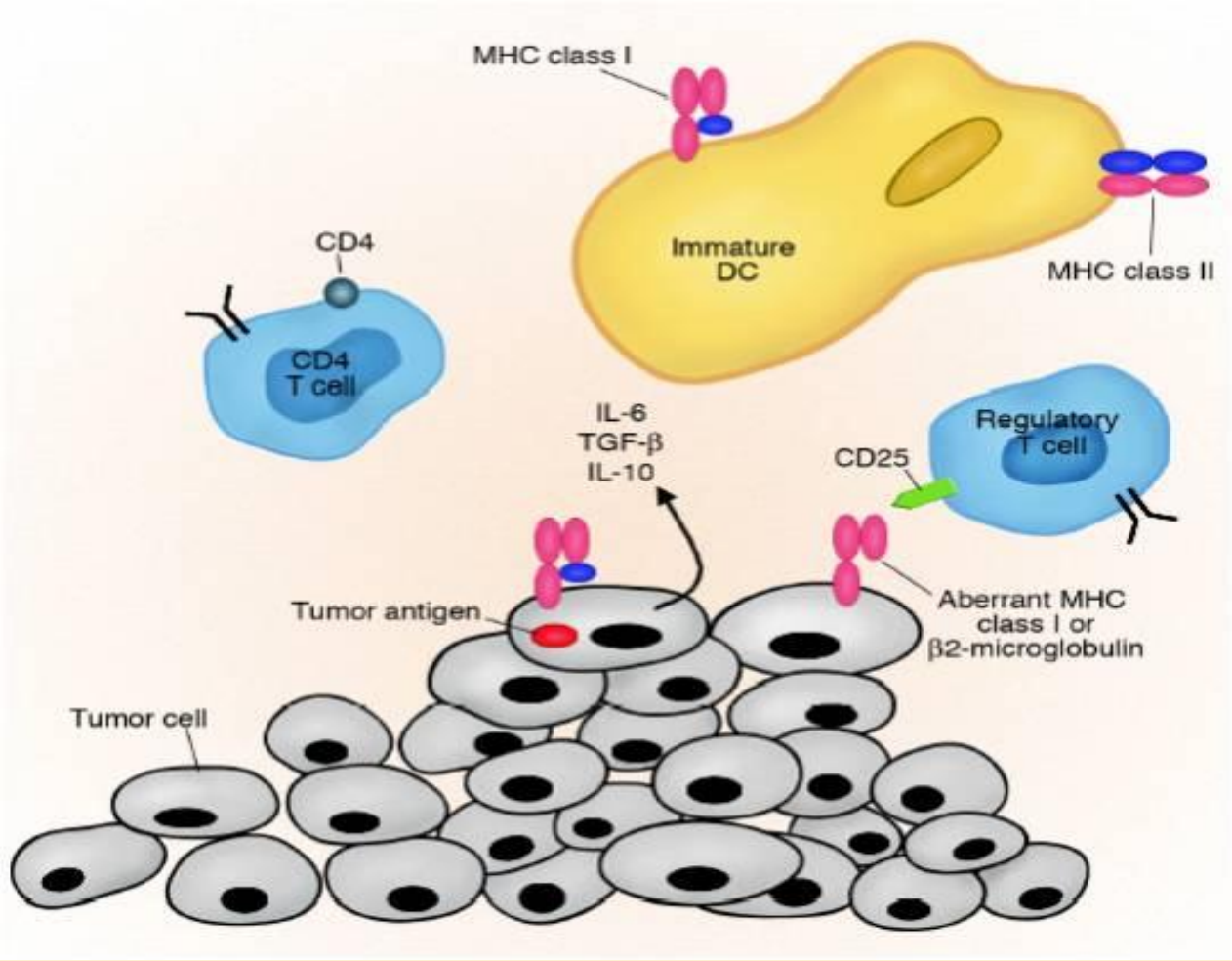
Antigen-presenting cells play a key role in initiation of adaptive anti-tumor immune response



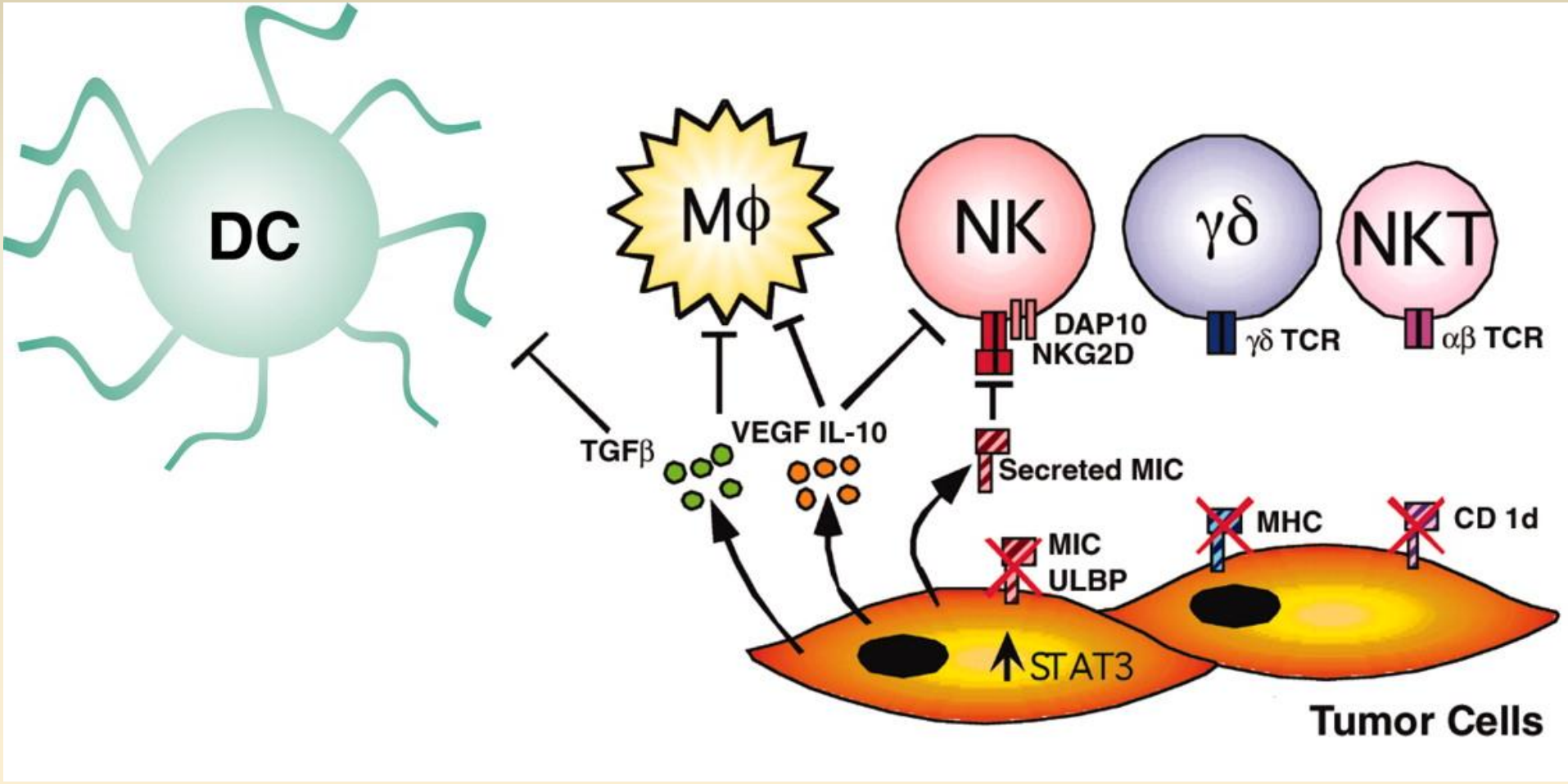
Presentation of tumor antigen to CD8+T lymphocyte results in T cell-mediated tumor cell lysis



Tumor cells form immunosuppressive microenvironment promoting **immune escape**



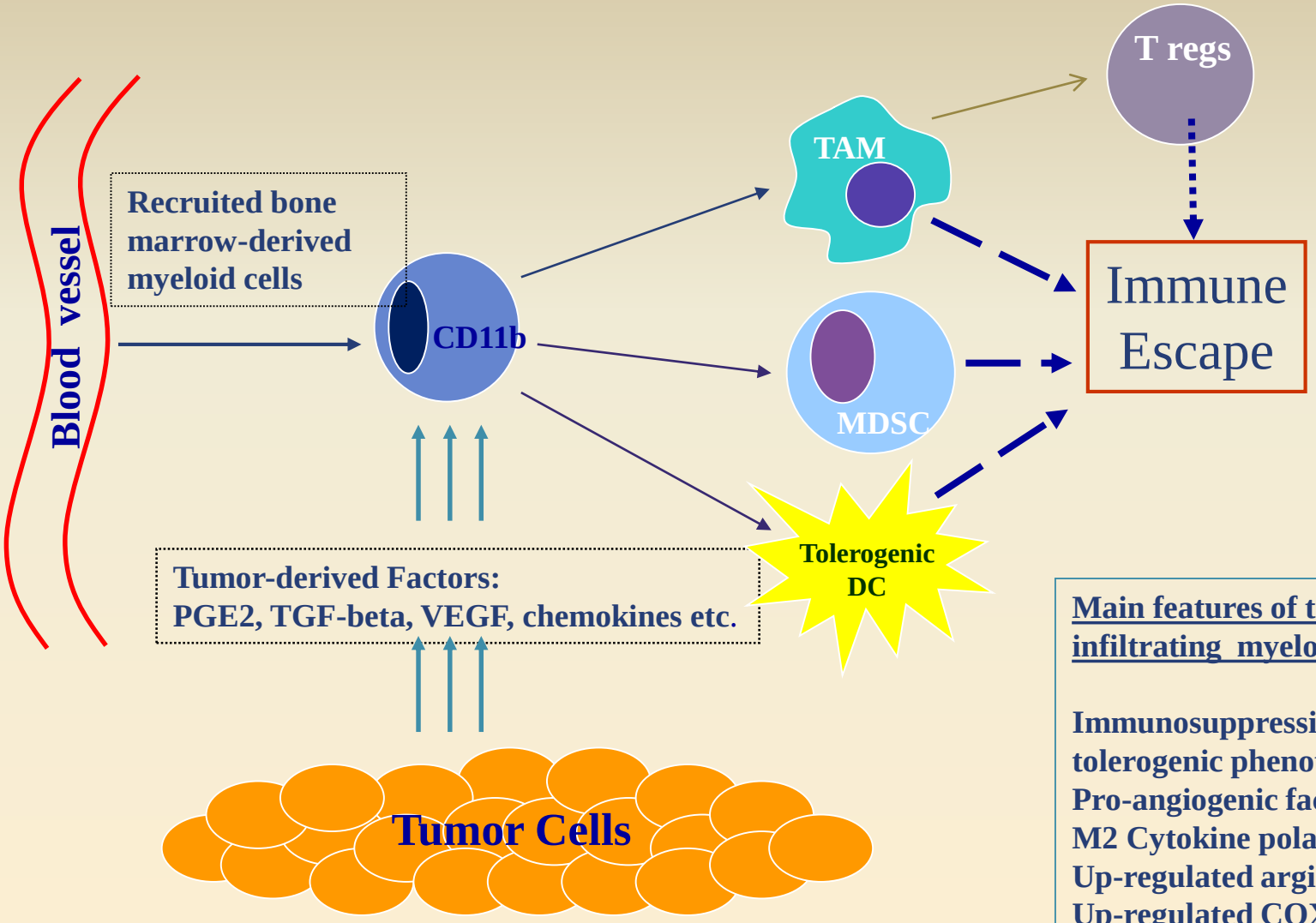
Immune escape 2



Tumor cells can avoid activating innate responses by producing inhibitory cytokines and down-regulating or secreting ligands for activating receptors

Major players in tumor-induced immune escape:

- Myeloid-derived suppressor cells (**MDSC**)
- Tumor-associated macrophages (**TAM**)
- Regulatory T cells (**T regs**)

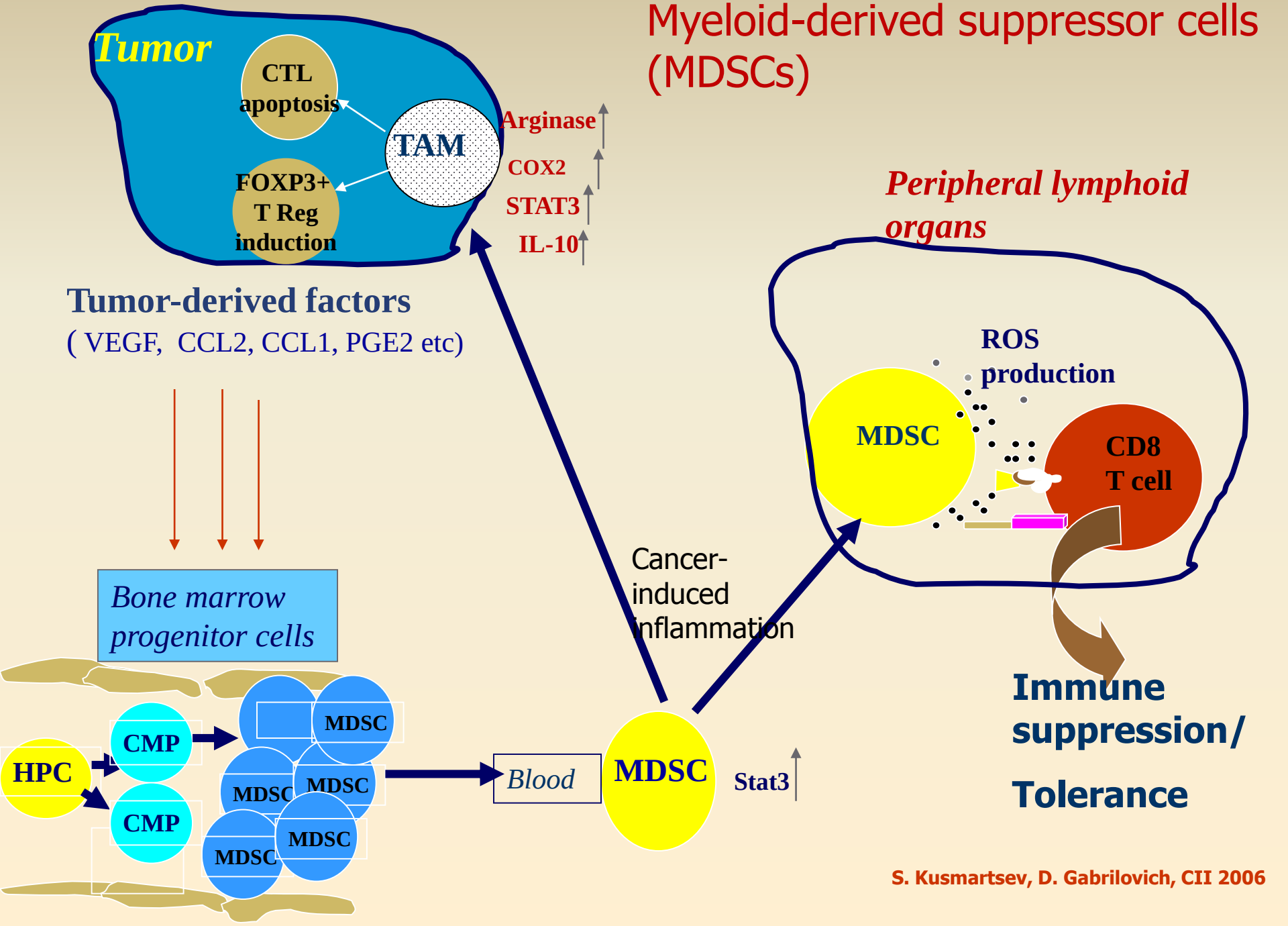


Main features of tumor-infiltrating myeloid cells:

Immunosuppressive and tolerogenic phenotype
Pro-angiogenic factors
M2 Cytokine polarization
Up-regulated arginase
Up-regulated COX-2

J. Vieweg and S.Kusmartsev, 2009

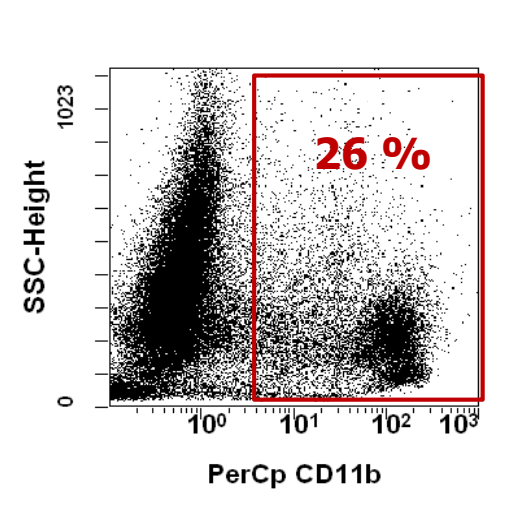
Myeloid-derived suppressor cells (MDSCs)



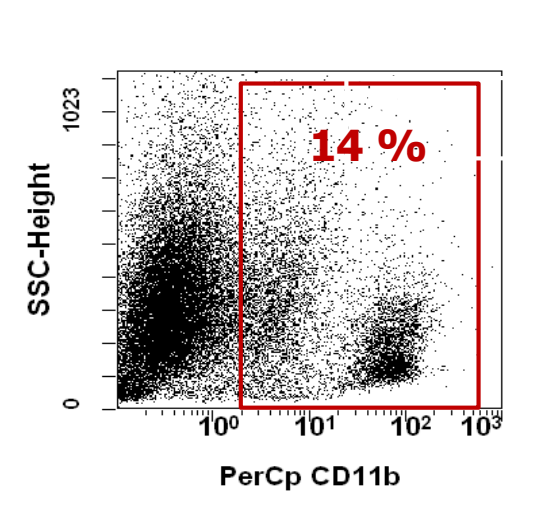
S. Kusmartsev, D. Gabrilovich, CII 2006

Human bladder tumor cells implanted into immunodeficient mice attract myeloid cells such as MDSC

SW780 tumor



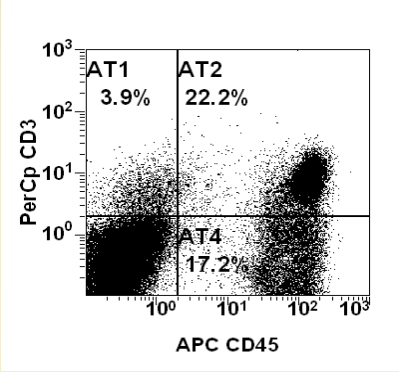
Urothel 11 tumor



Tissue

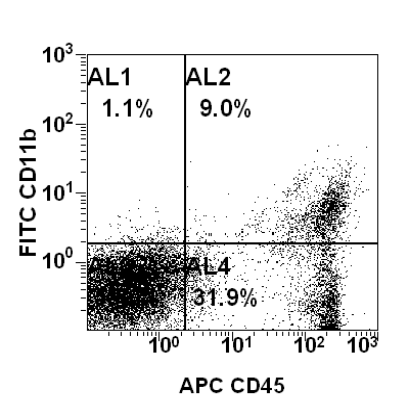
Tumor-infiltrating immune cells in human kidney cancer

Tumor-infiltrating T lymphocytes

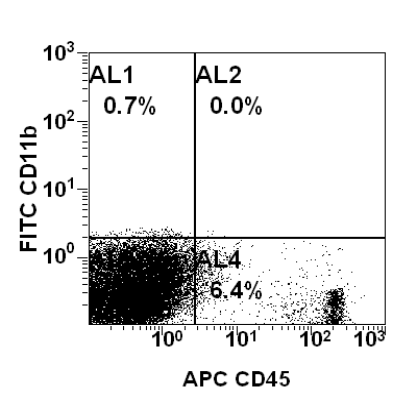


Tumor-infiltrating myeloid cells

RCC, Tumor tissue

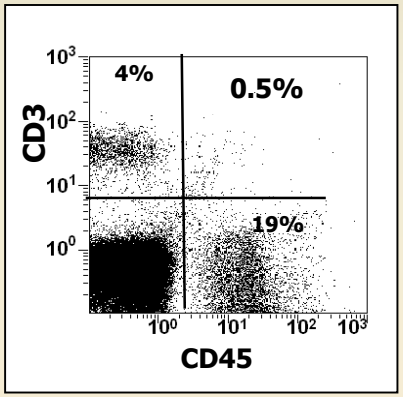


Normal kidney



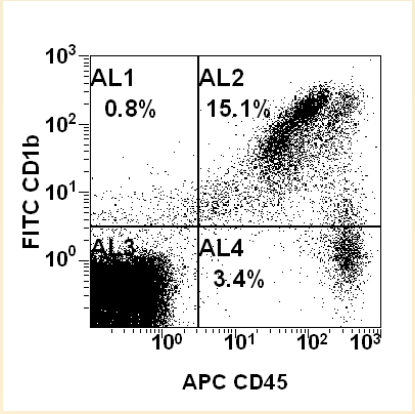
Tumor-infiltrating immune cells in human bladder cancer

Tumor-infiltrating T lymphocytes

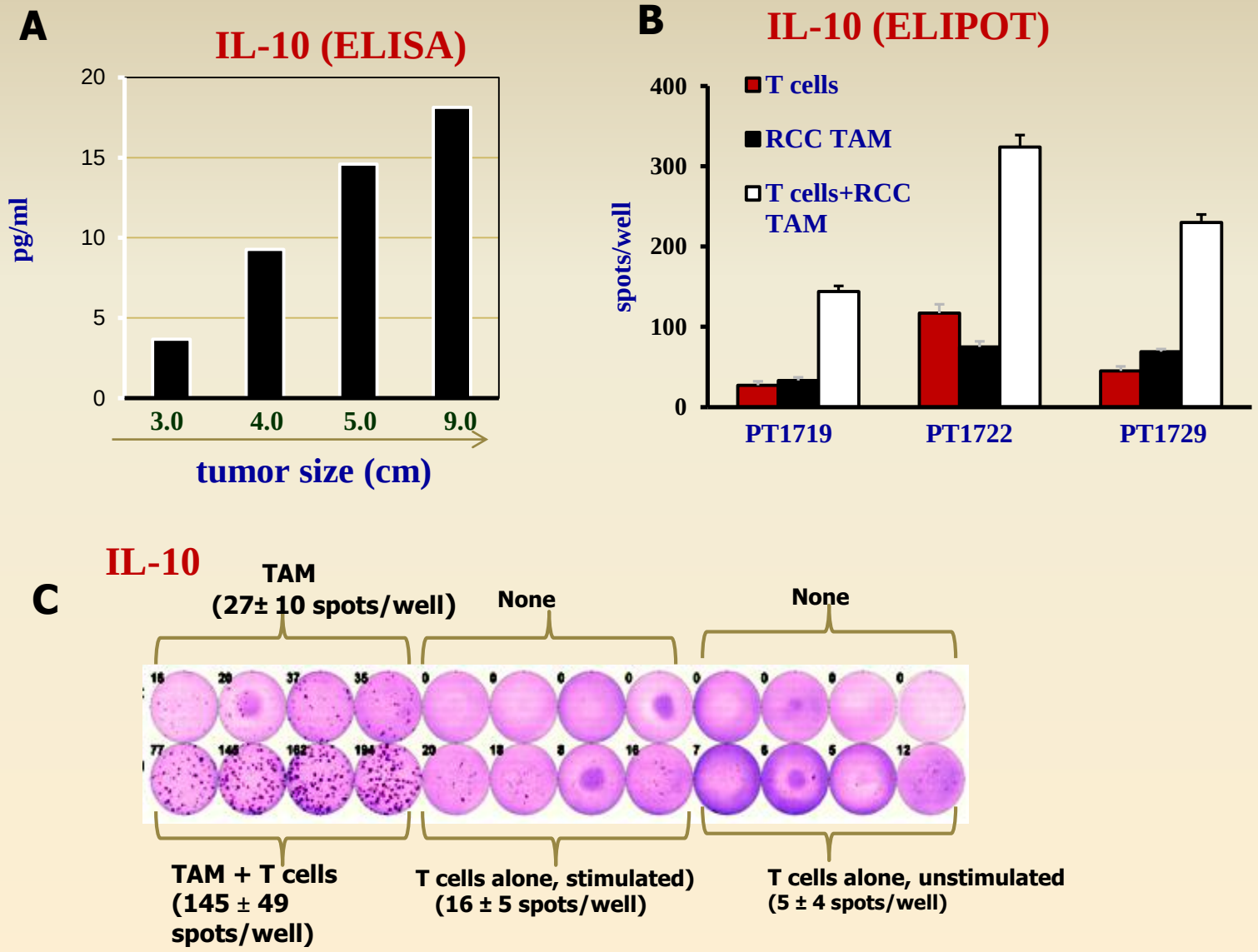


Tumor-infiltrating myeloid cells

Bladder, tumor tissue

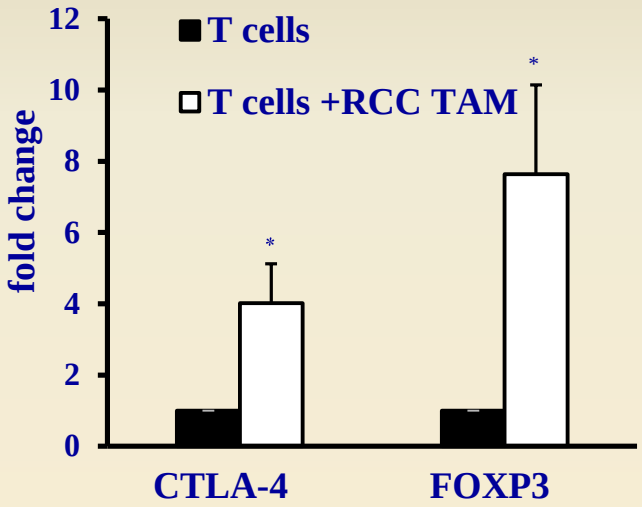


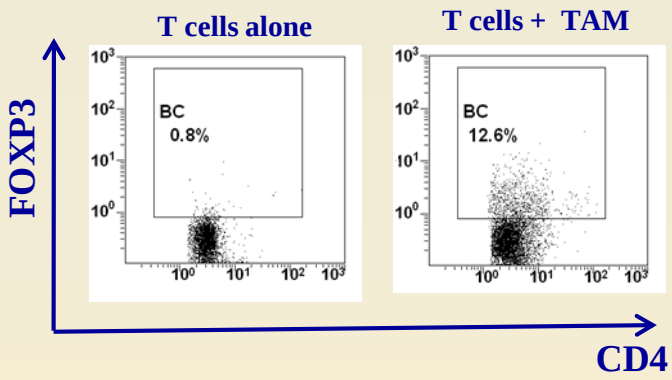
TAM induce production of immunosuppressive cytokine IL-10 in autologous T lymphocytes



Daurkin et al. , Cancer Res., 2011

TAM induce FOXP3 and CTLA-4 in autologous T lymphocytes





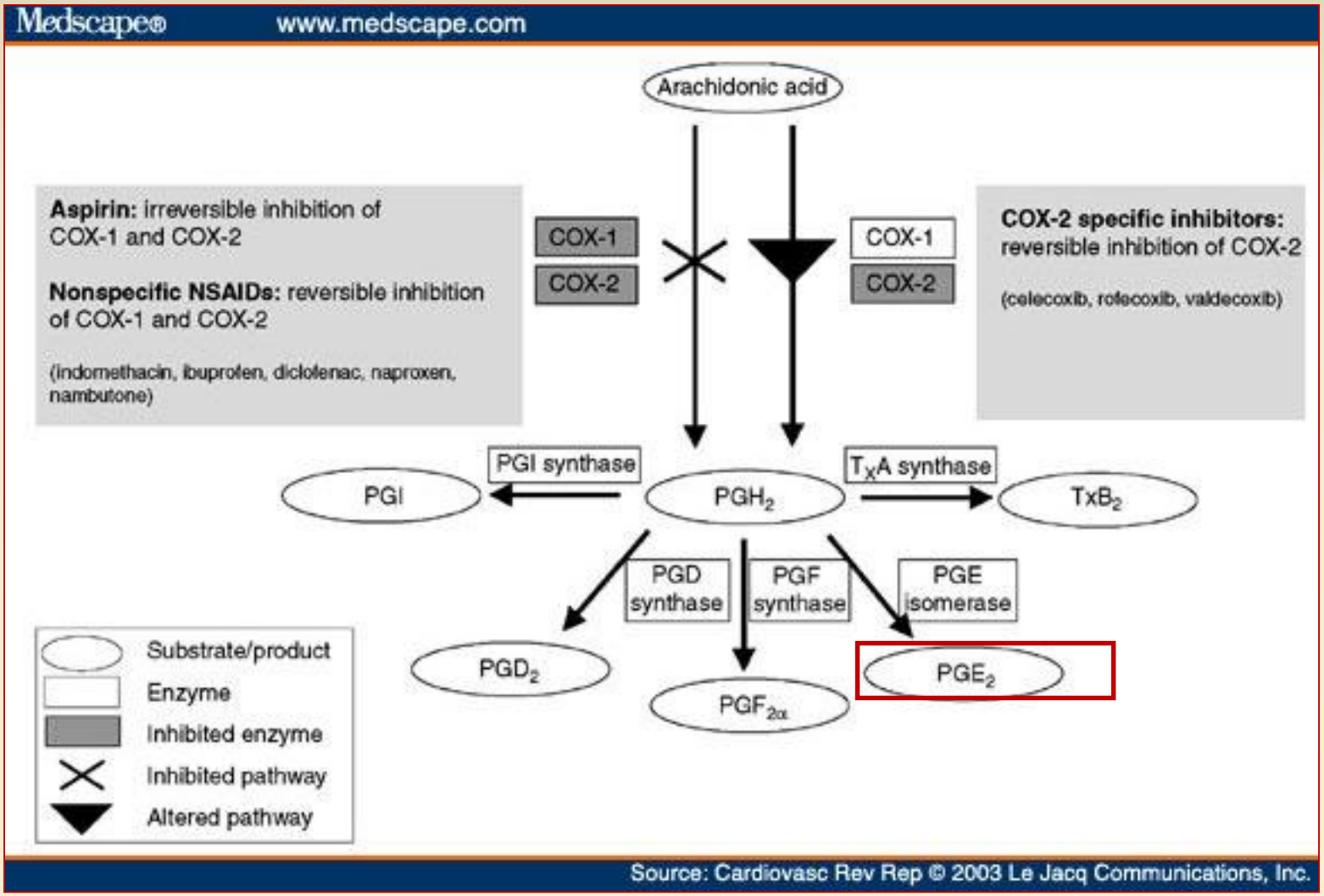
Daurkin et al. , Cancer Res., 2011

TARGETING IMMUNE ESCAPE

Potential Targets:

- Tumor metabolism
- MDSCs and TAMs
- Blockade of immunosuppressive receptors/factors
- T regs

Tumor metabolism: Enhanced production of PGE2 in tumors creates tumor-promoting inflammation and induces immunosuppressive cells



Effects of PGE2 on immune system

- PGE(2) selectively suppresses effector functions of macrophages and neutrophils and the **Th1-, CTL-, and NK cell-mediated type 1 immunity,** but it promotes Th2, Th17, and regulatory T cell responses.

- PGE(2) modulates chemokine production, inhibiting the attraction of "good" proinflammatory cells while enhancing local accumulation of **regulatory T cells cells and myeloid-derived suppressor cells.**

- Targeting the production, degradation, and responsiveness to PGE(2) provides tools to modulate the patterns of immunity to cancer.

Kalinski P, Regulation of immune responses by prostaglandin E2.
J. Immunology, 2012, 188 (1): 21-28

Elimination of MDSCs or T regs enhances anti-tumor immune response and inhibits tumor growth (selected pulications)

Fujita M et al**. COX-2 blockade suppresses brain tumors growth by inhibiting myeloid-derived suppressor cell.** Cancer Res. 2011, 71(7):2664-74.

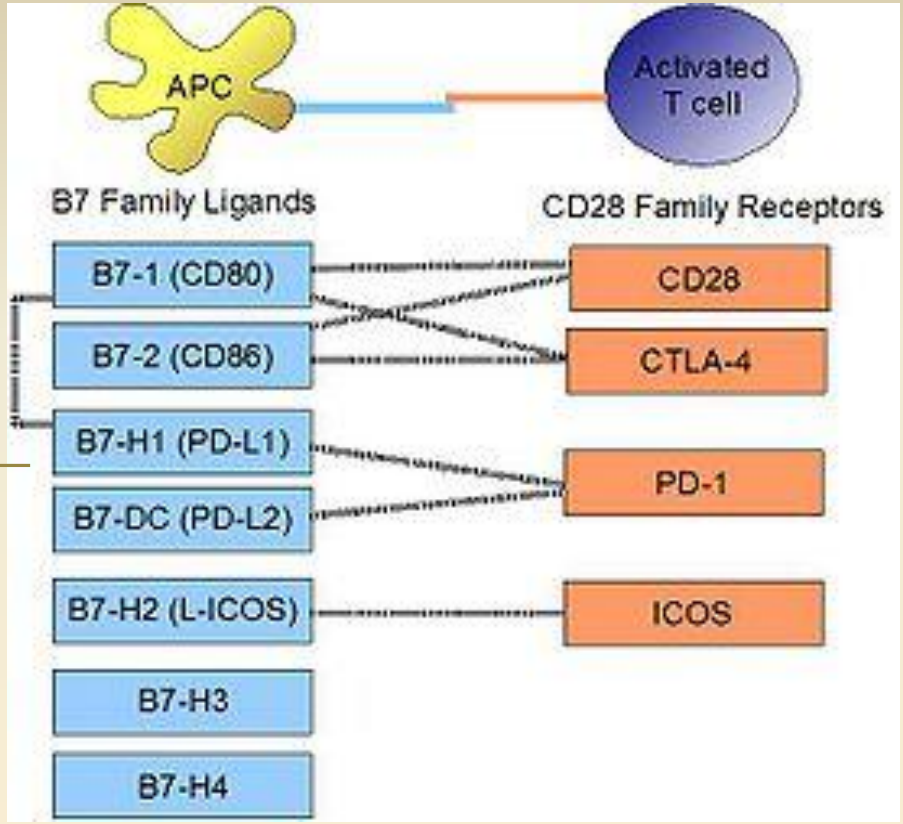
Kim K et al. **Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells.** PNAS, 2014, 111(32):11774-9.

Srivastava MK et al. **Myeloid suppressor cell depletion augments antitumor activity in lung cancer.** PLOS ONE**,** 2012;7(7):e40677.

Dannull J. et al. **Enhancement of vaccine-mediated antitumor immunity in cancer patients after depletion of regulatory T cells.**
J Clin Invest, 2005, 115(12):3623-33.

Fecci PE et al**. Systemic anti-CD25 monoclonal antibody administration safely enhances immunity in murine glioma without eliminating regulatory T cells.** Clin Cancer Res, 2006, 12(14):4294-305.

MDSC s and TAMs express PDL-1



Anti-PD1 antibody (Pembrolizumab) fom Pfizer blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This drug effective for melanoma treatment.

Summary

- Cancer cells form immunosuppressive microenvironment promoting ***immune escape***

- ***MDSCs, T regs and TAMs*** are major players in tumor-associated immune suppression and immune escape

- Blockade of cancer-related inflammation and tumor-associated immune suppression results in ***boosting of anti-tumor immune response and enhances efficacy of cancer immunotherapies***

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