BASIC MECHANISM OF TUMOR IMMUNE SUPPRESSION

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DISCLOSURE

National Institute
of Allergy and
Infectious Diseases

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GOALS

- Understand that immune suppression is one of the hallmarks of all cancers.
- Be familiar with common cellular and molecular mechanisms of immune suppression.
- Recognize that the pervasive nature of cancer immune suppression creates ample opportunities for immunotherapy.

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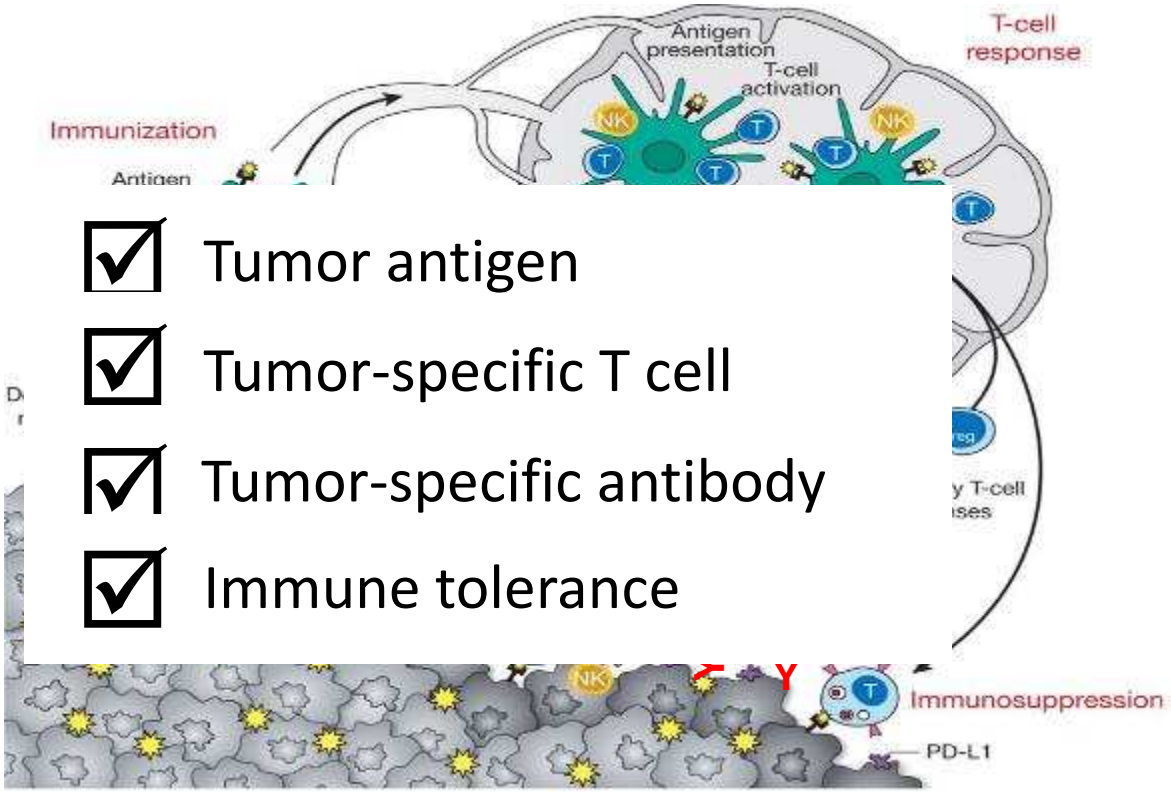
IMMUNE SYSTEM DOES CARE ABOUT CANCER

ANSWERS FROM THE HALF-CENTURY QUEST



- ☑ Tumor antigen
- ☑ Tumor-specific T cell
- ☑ Tumor-specific antibody
- ☑ Immune tolerance

I Mellman *et al. Nature* **480**, 480-489 (2011)

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NEW ONCOLOGY PARADIGM IN 2015:
TREATING THE IMMUNE SYSTEM, NOT THE CANCER

Chimeric Antigen Receptor

Magic Bullet

Checkpoint blockade

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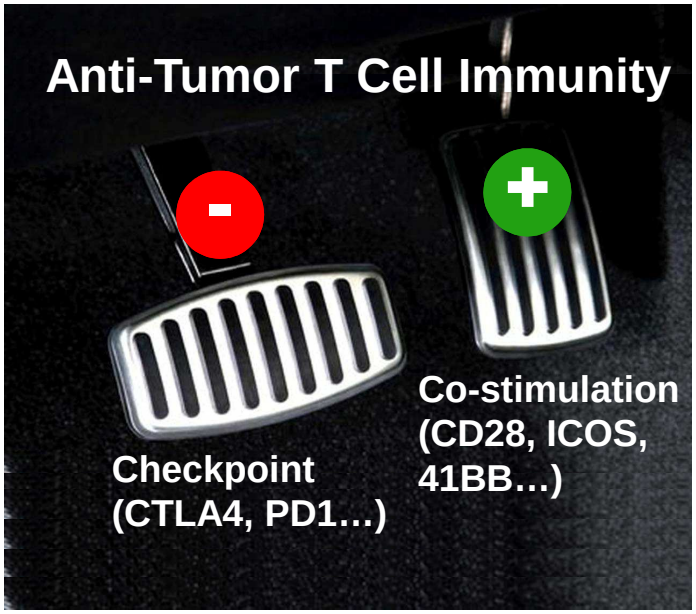
Z Li et al (2013) Exp Hematol Oncol

WHAT EVERYONE IS TALKING ABOUT



Checkpoint blockade against PD-1 pathway is broadly effective against advanced cancers:

Melanoma
Lung cancer
Bladder cancer
Renal cell carcinoma
Head and neck cancer
Triple negative breast cancer
Lymphoma *etc.*

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CAUTION AGAINST CHECKPOINT BLOCKERS

- Clinical experience remains limited
- > 50% patients do not benefit
- No effective biomarkers to separate R from NR
- Unclear of optimal clinical use

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It Takes An Army

PRINCIPLES OF ANTI-TUMOR IMMUNITY

Immunity

Mature dendritic cells

Co-stimulatory molecules (CD28, ICOS, 41BB etc.)

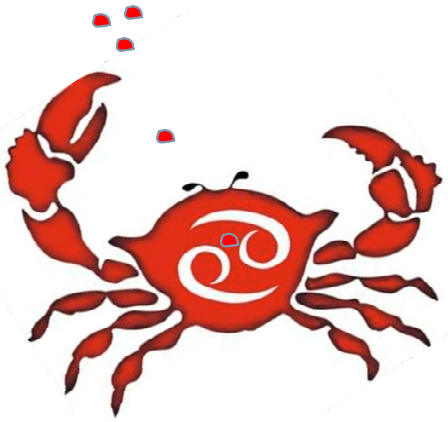
Effector T cells

Effector antibodies

IFN-γ etc.

Anti-tumor

Antigen presentation



Tolerance

Immature dendritic cells

Immune checkpoints (CTLA4, PD-1 etc.)

Regulatory T and B cells

Myeloid suppressor Cells (MDSCs, Mϕ)

TGF-β etc.

Pro-tumor

PRINCIPLES OF CANCER IMMUNOTHERAPY

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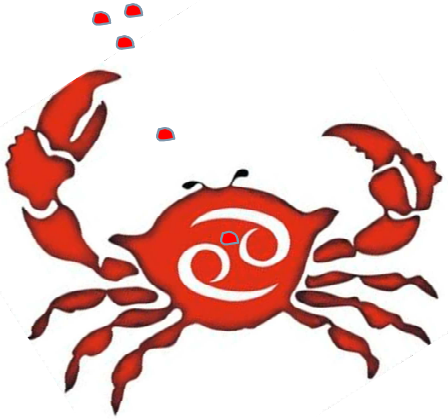

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TUMOR IMMUNE SUPPRESSION

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SUPPRESSION ≠ EVASION

Evasion

Loss of antigens

Loss of antigen-presentation machineries (e.g., MHC, TAP)

Immune shield

Suppression

Immature dendritic cells

Immune checkpoints (CTLA4, PD-1 etc.)

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TGF-β etc.

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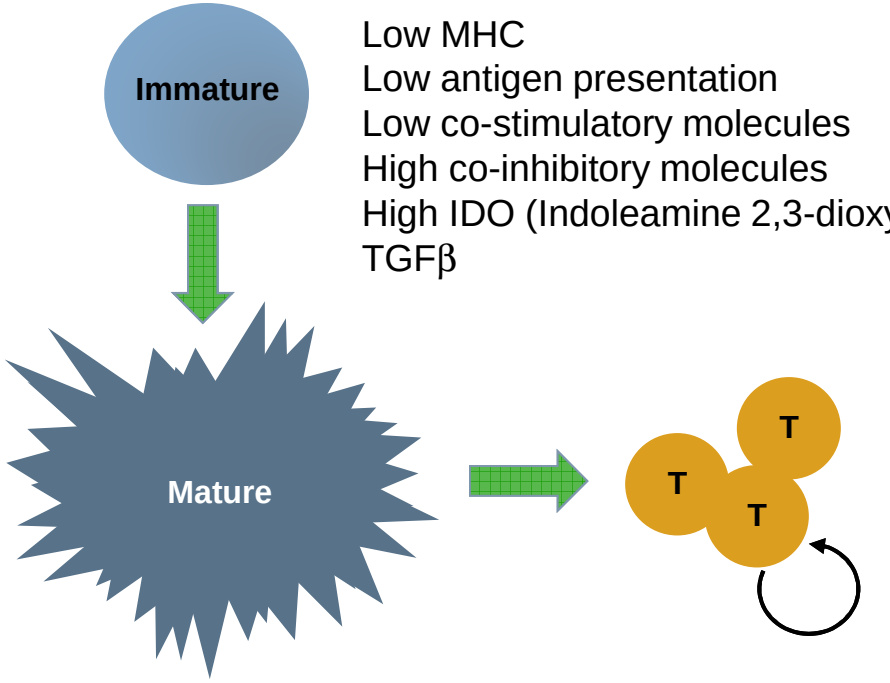
IMMATURE (TOLEROGENIC) DC



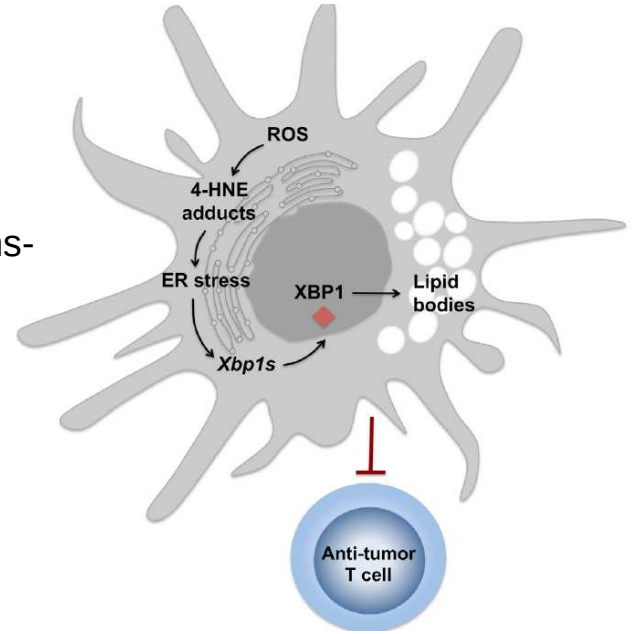
Low MHC
Low antigen presentation
Low co-stimulatory molecules
High co-inhibitory molecules
High IDO (Indoleamine 2,3-dioxygenase)
TGFβ

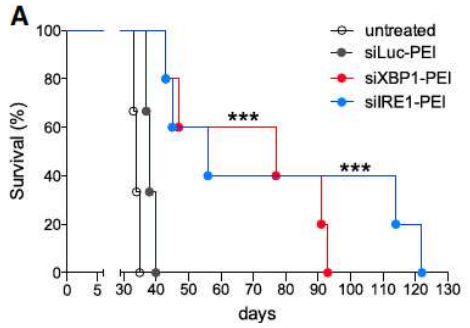
Prostate, breast, renal, liver, lung cancer, HNSCC, myeloma, leukemia, neuroblastoma. melanoma, glioma, etc

A.H. Enk, H. Jonuleit, J. Saloga, J. Knop (1997) Dendritic cells as mediators of tumor-induced tolerance in metastatic melanoma Int J Cancer, 73:309–316

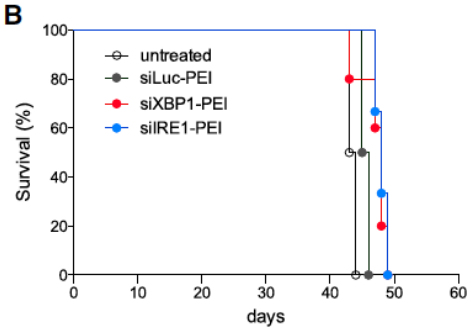
TUMOR-DCs PROMOTE OVARIAN CANCER

4-HNE: unsaturated aldehyde 4-hydroxy-trans-2-nonenal





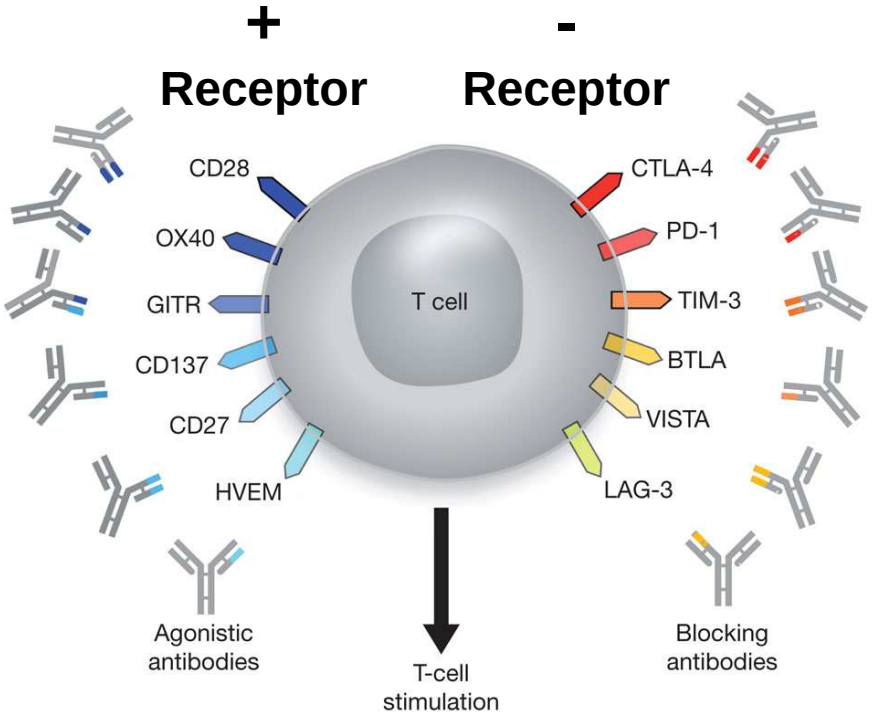
+T,B cells



-T,B cells

Cubillos-Ruis et al. (2015) ER stress sesonr XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. Cell, 161:1527-1538

IMMUNE CHECKPOINTS



Tolerance
Exhaustion
Deletion

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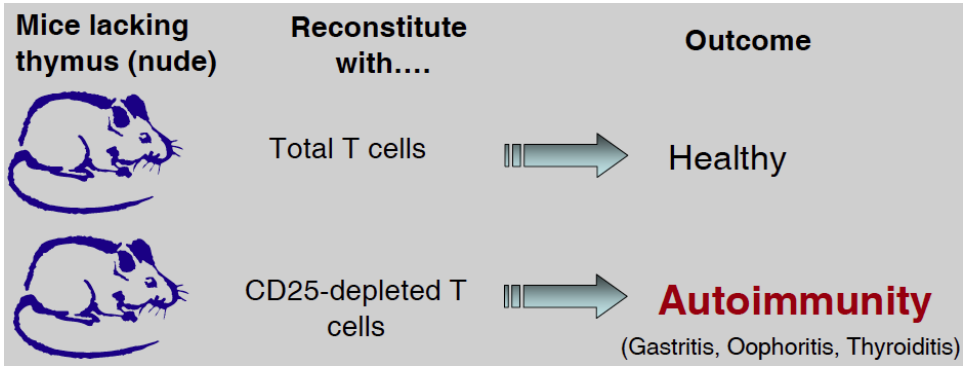
Nature 480, 480–489 (22 December 2011)

REGULATORY T CELLS

- **1970/1980** “Supppressor” T cells proposed but discredited
- **1990s** $CD4^{+}CD25^{+}$ “Regulatory T cells” by Shimon Sakaguchi



- **Early 2000s** Discovery of Treg master transcription factor ***Foxp3*** (Brunkow et al. Nat Gen 2001; Bennett et al, Nat Gen 2001; Wildin et al., Nat Gen 2001; Chatila et al., JCI 2000)

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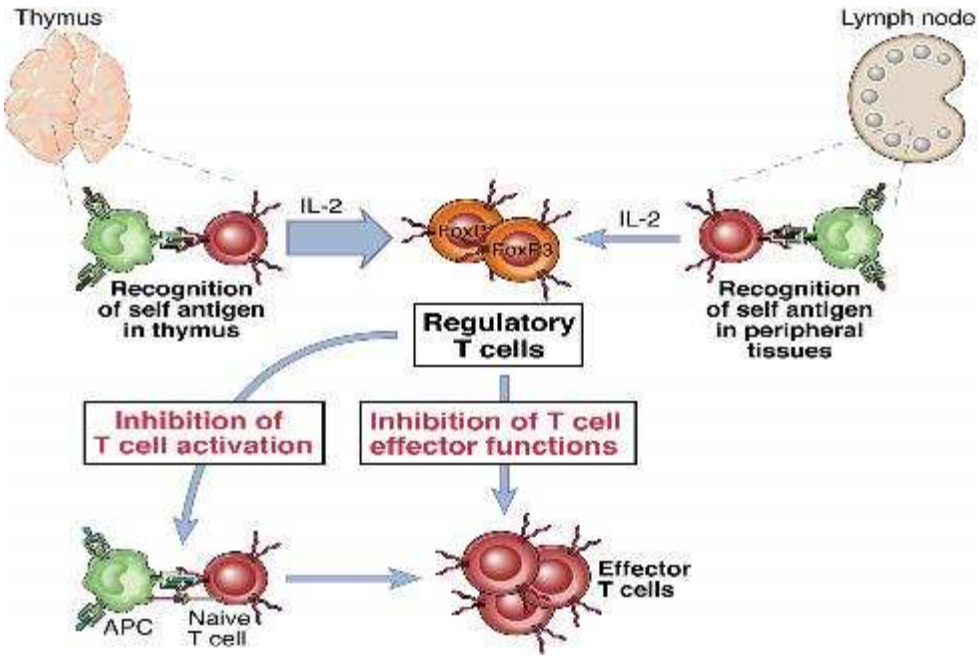
REGULATORY T CELLS



From Abbas, Lichtman and Pillai. Cellular and Molecular Immunology 6th ed, 2007

REGULATORY T CELLS

2010

Microenvironment and Immunology

Cancer Research

Selective Depletion of Foxp3^{+} Regulatory T Cells Improves Effective Therapeutic Vaccination against Established Melanoma

Katjana Klages[1], Christian T. Mayer[2], Katharina Lahl[3], Christoph Loddenkemper[4,5], Michele W.L. Teng[6], Shin Foong Ngiow[6], Mark J. Smyth[6], Alf Hamann[7], Jochen Huehn[1], and Tim Sparwasser[2]

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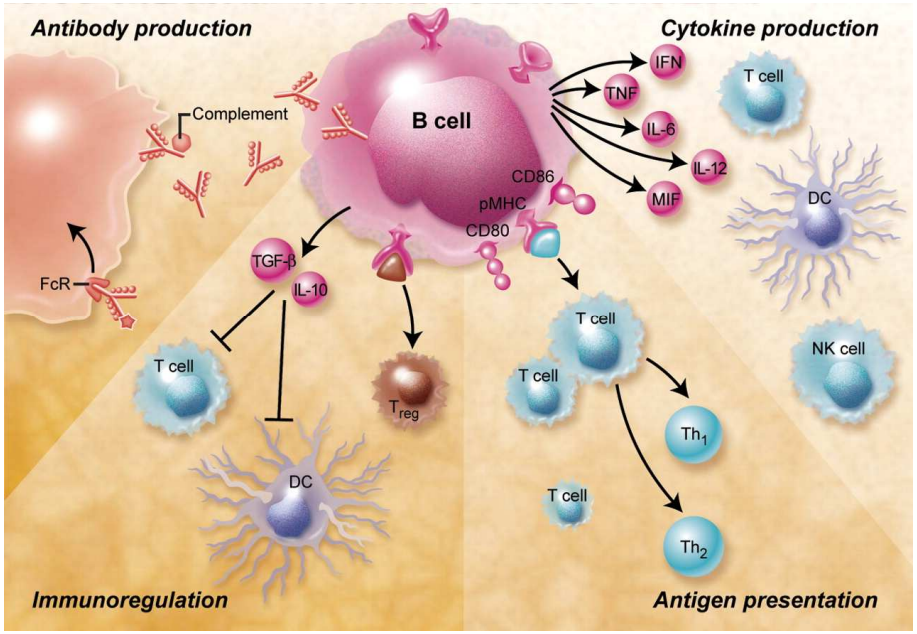
REGULATORY B CELLS



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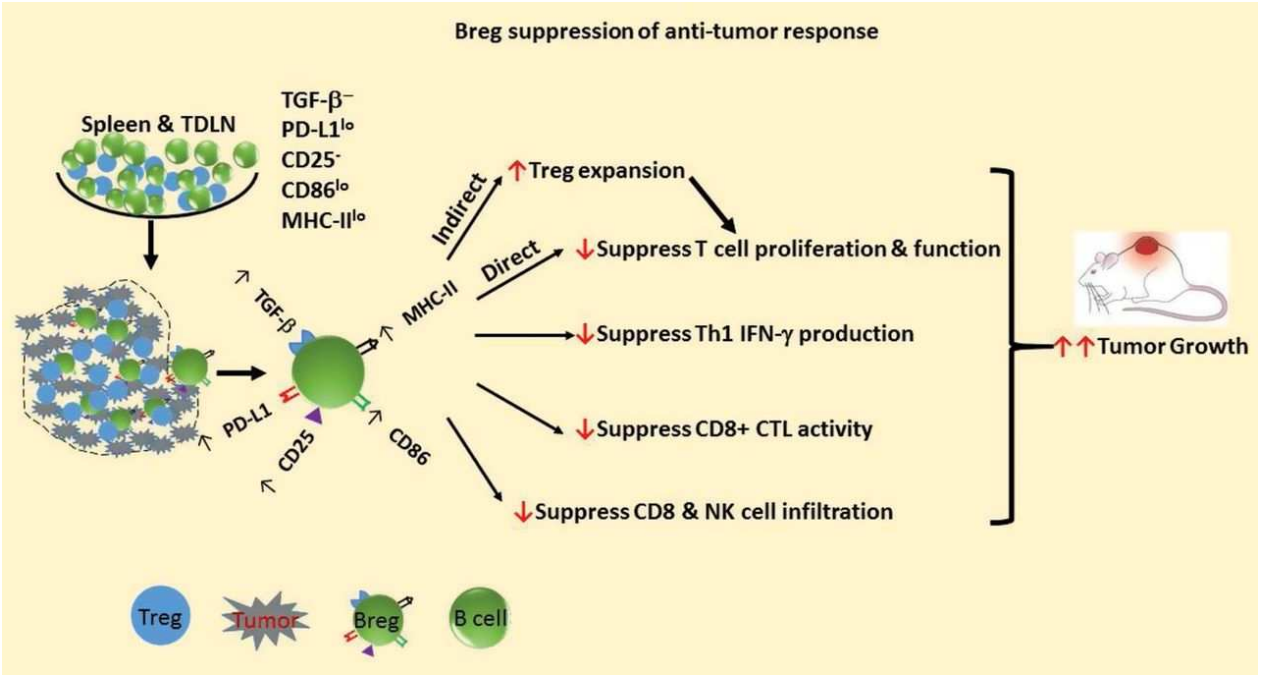
December 3, 2009; Blood: 114 (24)

REGULATORY B CELLS



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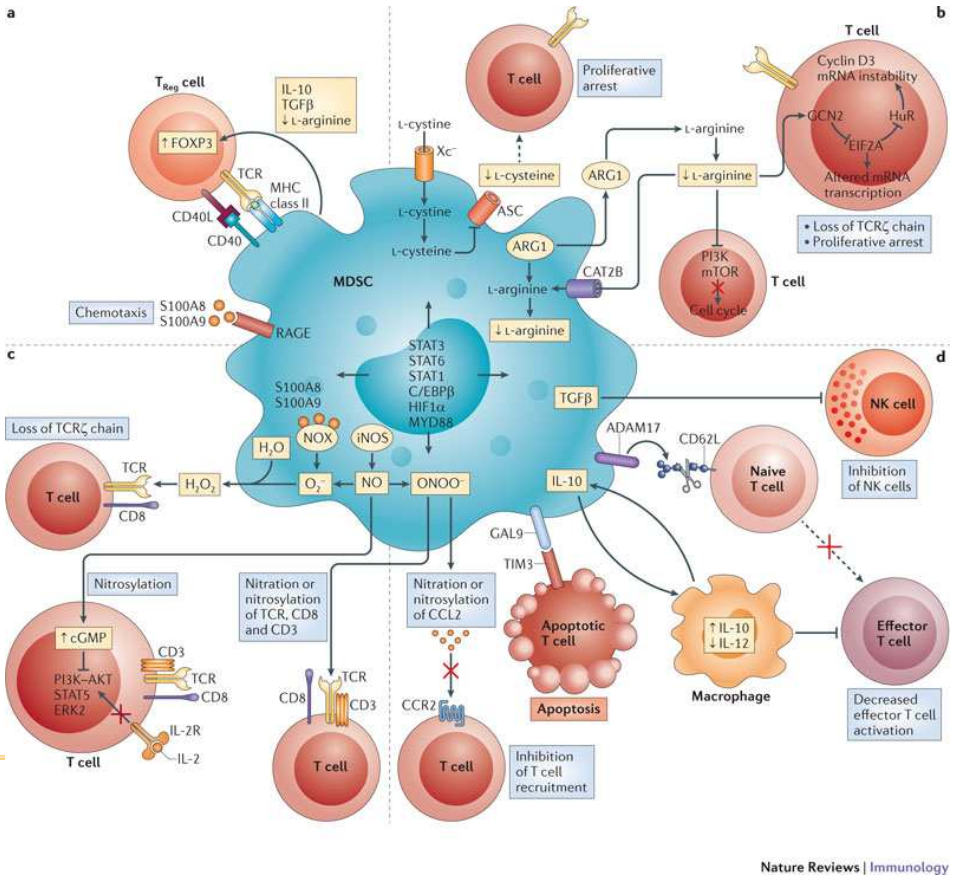
December 3, 2009; Blood: 114 (24)

MYELOID-DERIVED SUPPRESSOR CELL (MDSC)



Nature Reviews Immunology 12, 253-268 (April 2012)

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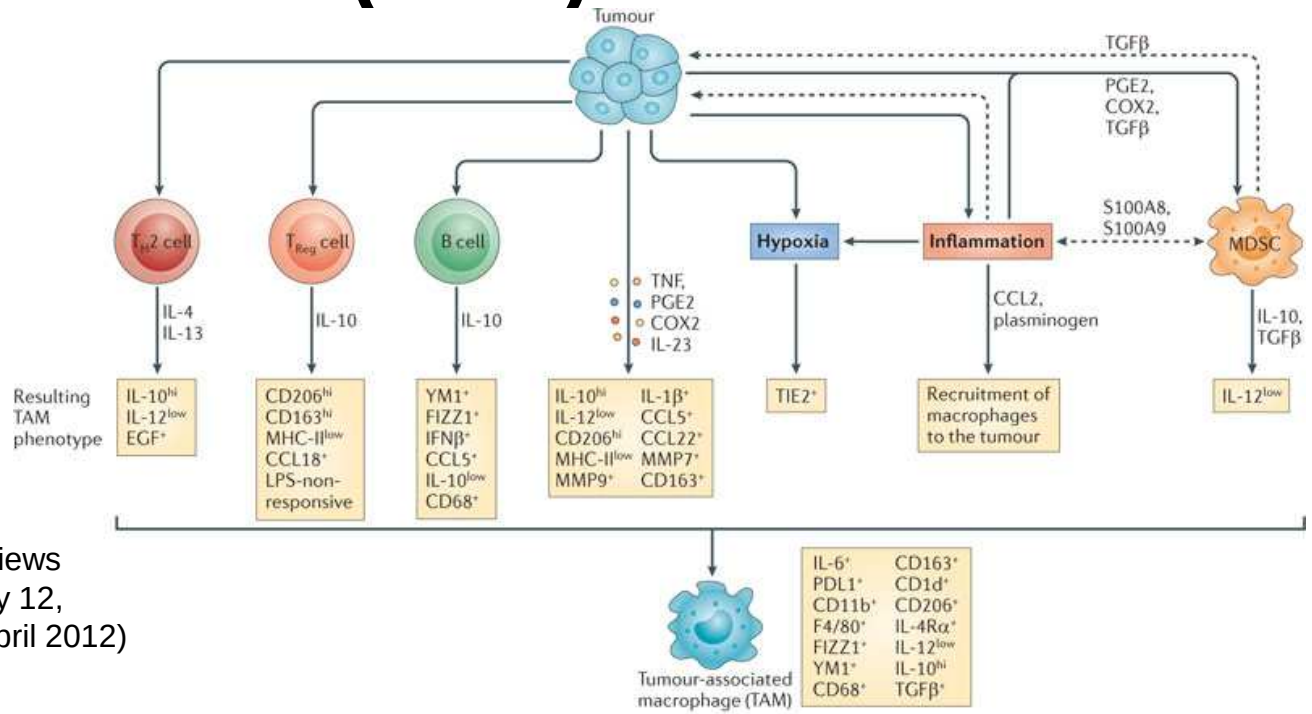
TUMOR-ASSOCIATED MACROPHAGES (TAM)



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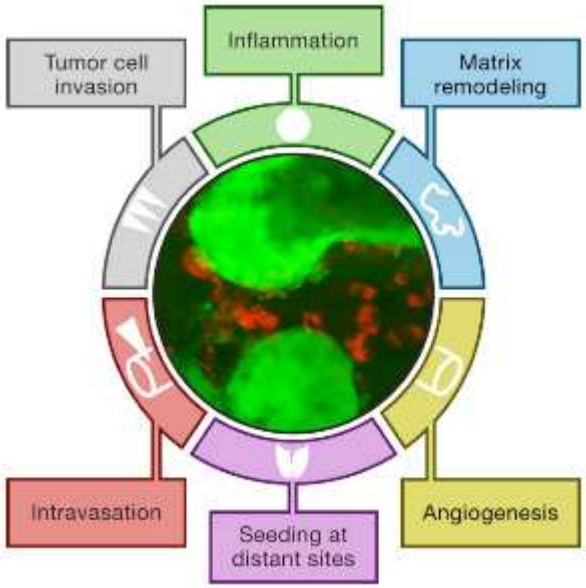
TARGETING MYELOID CELLS FOR TREATMENT OF CANCER



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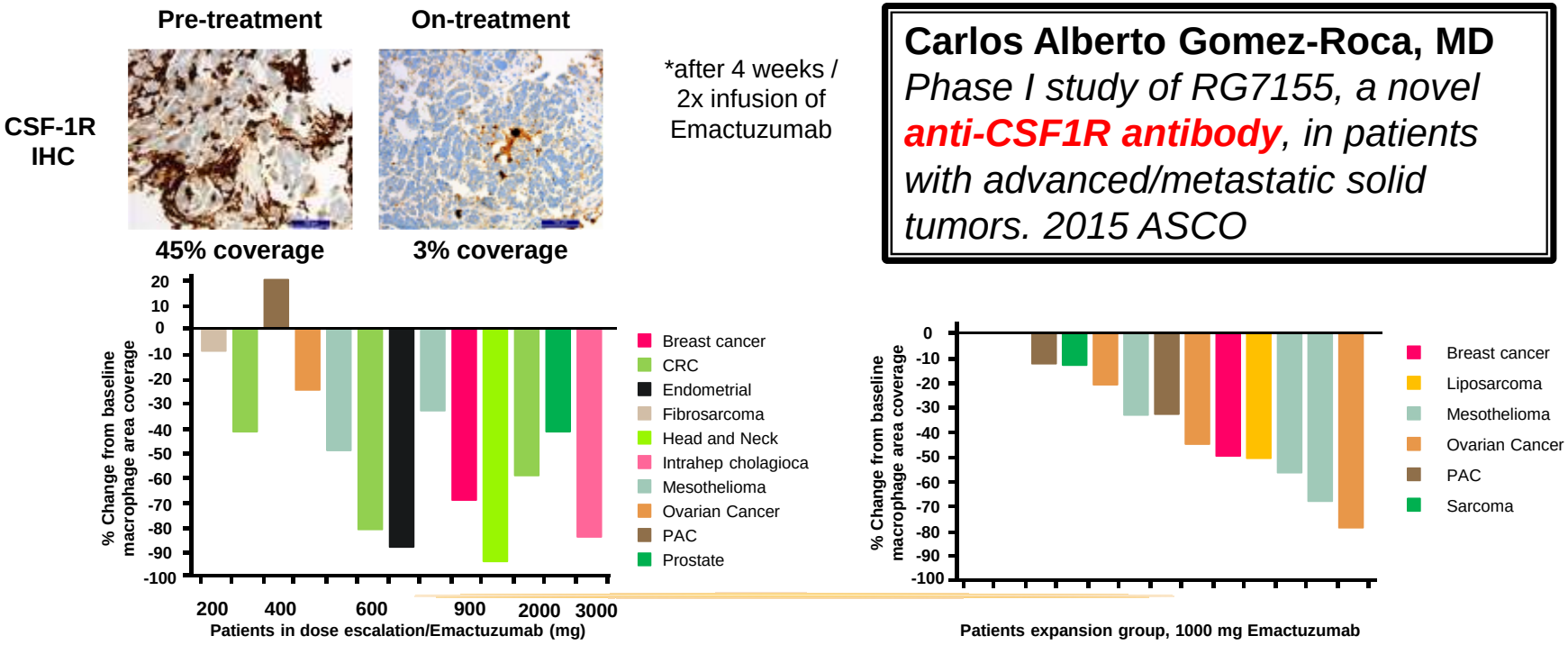
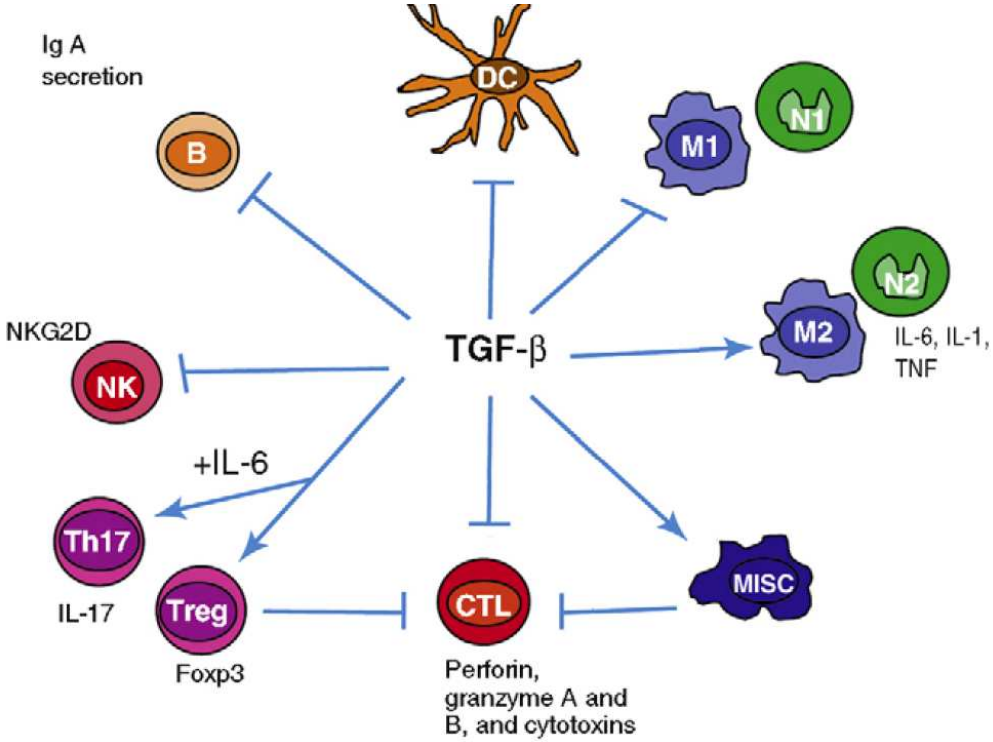
Condeelis and Pollard (2006) Cell

TARGETING MYELOID CELLS FOR TREATMENT OF CANCER



Carlos Alberto Gomez-Roca, MD
Phase I study of RG7155, a novel ***anti-CSF1R antibody****, in patients with advanced/metastatic solid tumors. 2015 ASCO*

TGF-β: A MASTER IMMUNE REGULATOR



Yang et al. (2010) Trends in Immunology

TAKE HOME MESSAGE

Immature dendritic cells

Immune checkpoints (CTLA4, PD-1 etc.)

Regulatory T and B cells

Myeloid suppressor Cells (MDSCs, Mϕ)

TGF-β etc.

Cancer immune suppression

- **Validation of tumor surveillance**
- **Opportunity for immunotherapy**

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