# Society for Immunotherapy of Cancer (SITC)

## Basic Mechanisms of Tumor Immune Suppression

Jeffrey A. Sosman
Vanderbilt-Ingram Cancer Center

Advances in Cancer Immunotherapy™ - Nashville
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Preparerd and presented in part by
Brent Hanks, MD, PhD
Duke University Medical Center

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Society for Immunotherapy of Cancer

# Disclosures

Consulting Fees:

- Merck & Co.
- Genentech

Research Support

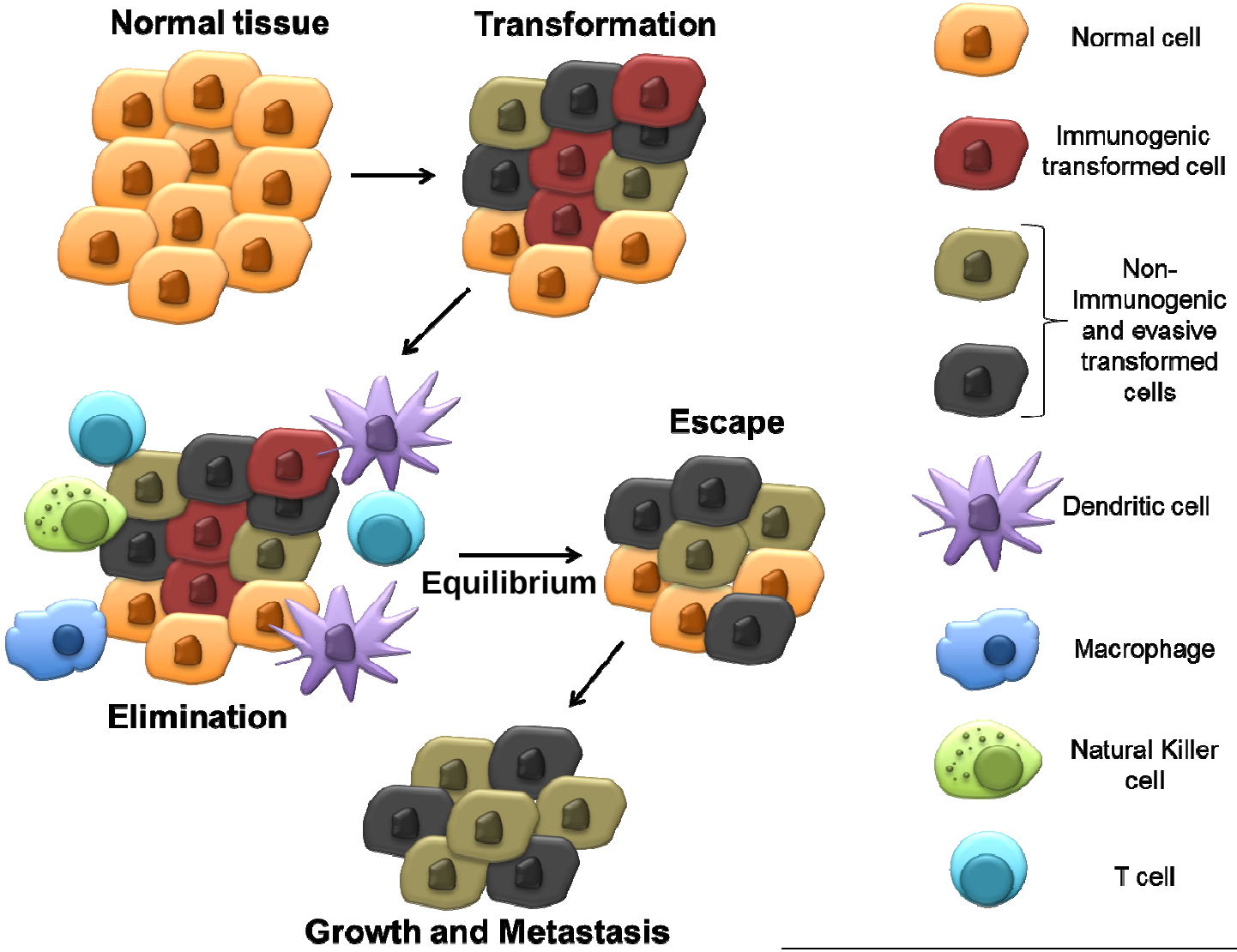
- Glaxo Smith Kline
- Bristol Myers Squibb

I will be discussing the use of products for non-FDA approved indications

# Outline: Basic Mechanisms of Tumor Immune Suppression

1. **Cancer Immunoediting Hypothesis**
2. **Cell Surface Molecular Mechanisms**
   - PD-L1
   - LAG3
   - TIM3
3. **Soluble Molecular Mechanisms**
   - TGF-β
   - IL-10
   - IDO
4. **Cell-dependent Mechanisms**
   - Tregs
   - TAMs
   - MDSCs
   - Tolerized DCs

# Cancer Immunoediting: The Interplay between the host Immune System and the Developing Tumor




Holtzhausen, A. et al. *Frontiers in Immunology*. 2014. 5: 438.

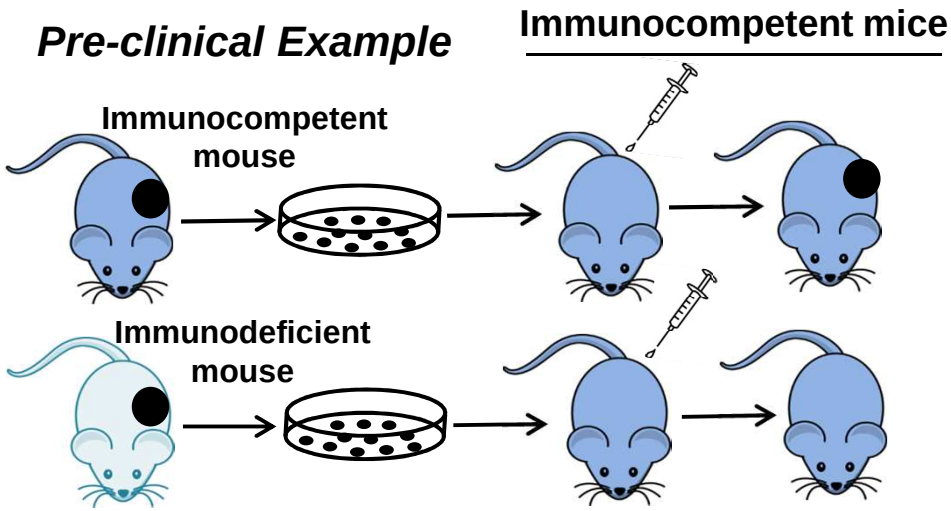
# Cancer Immunoediting – the 3 E's

- **Elimination Phase:** The immune system protects the host against tumor formation by selectively destroying the more immunogenic cancer cells.

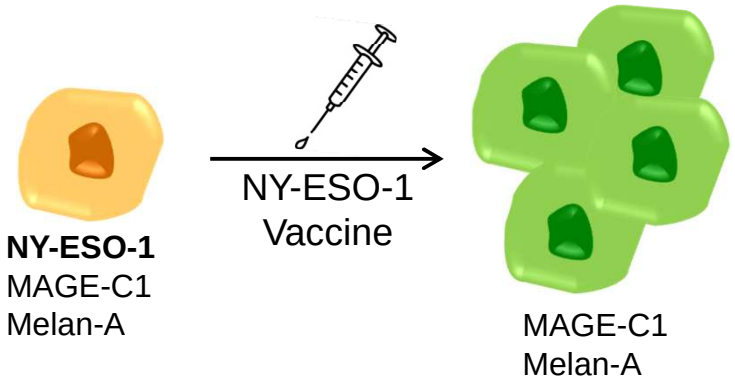
- **Equilibrium Phase:** The immune system prevents tumor cell outgrowth while "sculpting" the immunogenicity of the tumor. Many genetic alterations occur during the Equilibrium phase referred to as immunoediting.

  1. **Defective antigen presentation**
     - Downregulation in antigen presentation machinery (e.g. MHC class I)
     - Downregulation of antigen expression

***Pre-clinical Example***




***Clinical Example***




Schreiber, R. et al. *Science.* 2011. 331: 1565.

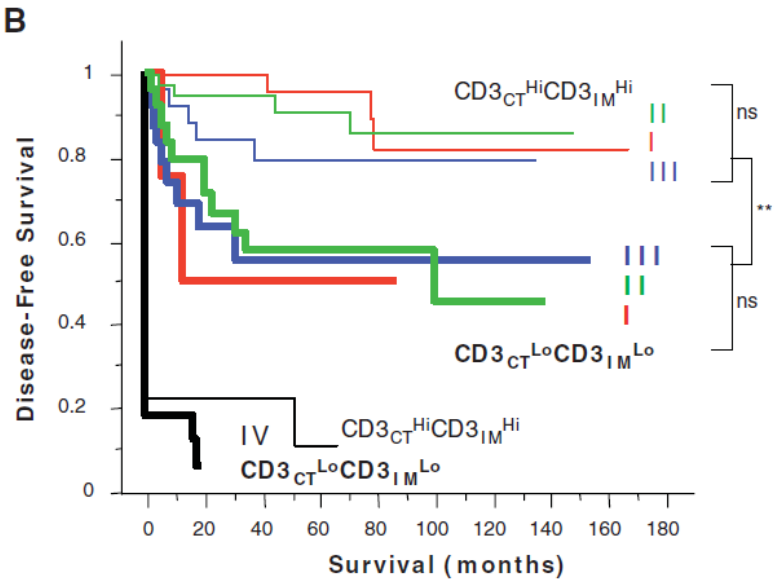
Mittal, D. et al. *Curr Opin Immunol*. 2014. 27: 16.
Von Boehmer, L. et al. *Cancer Immunol*. 2013. 13: 12.

# Cancer Immunoediting – the 3 E's

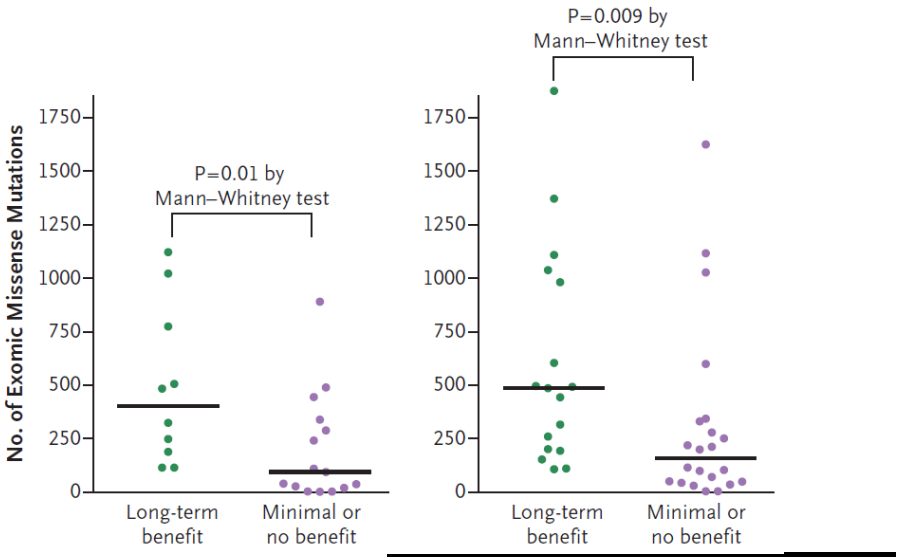
- Defective antigen processing and presentation alone does not explain the relationship observed between tumor-infiltrating lymphocytes (TILs) and prognosis for many solid tumors; evidence of clinical activity in several immunotherapy clinical trials

- This mechanism also fails to explain the existence of high mutational loads in cancers that fail to respond to anti-CTLA-4 antibody immunotherapy /
- **Mutations not "THE" critical checkpoint for anti-CTLA4**

## Colon Cancer - TILs




## Melanoma – Mutational Load



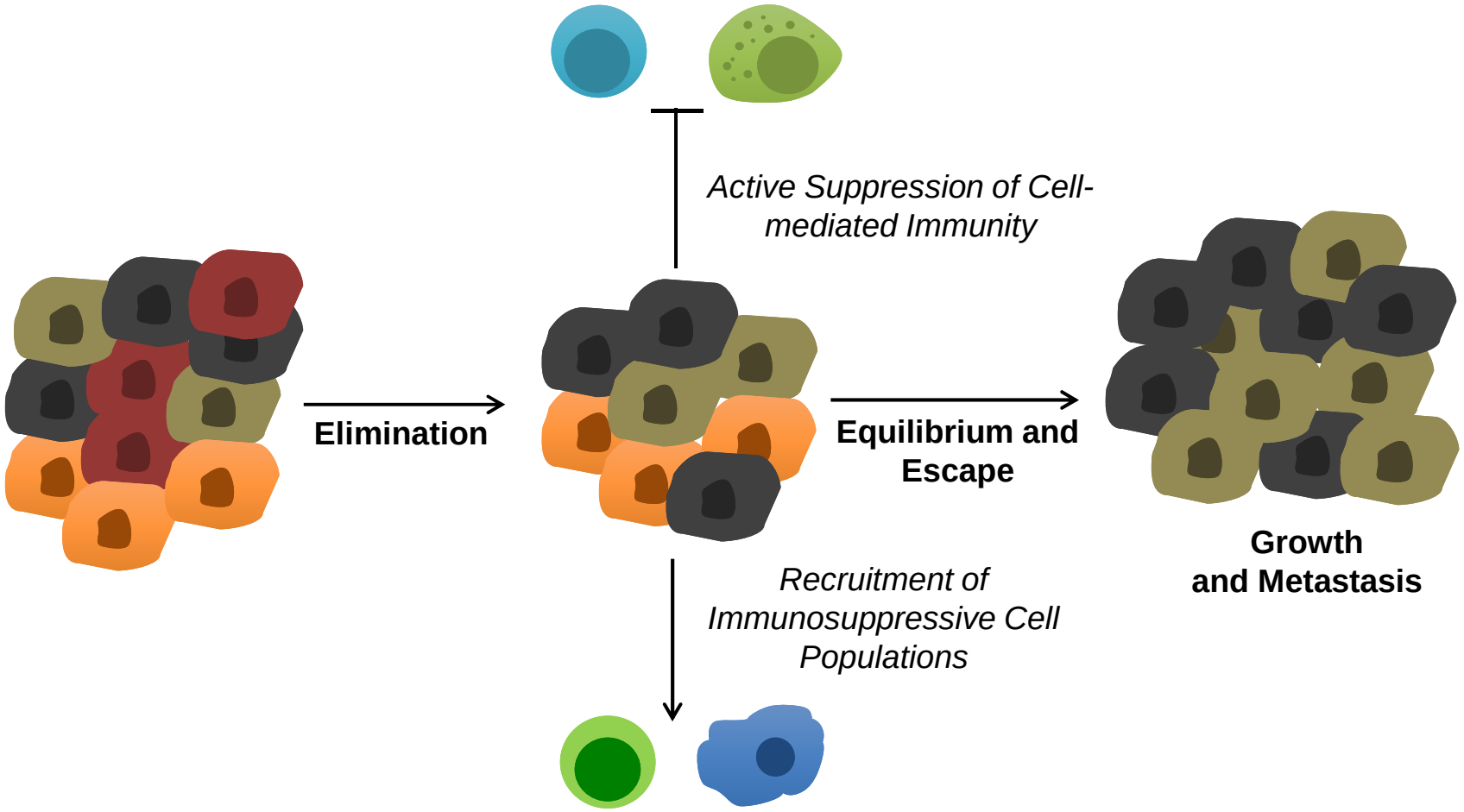

Galon, J. et al. *Science*. 2006. 313: 1960.

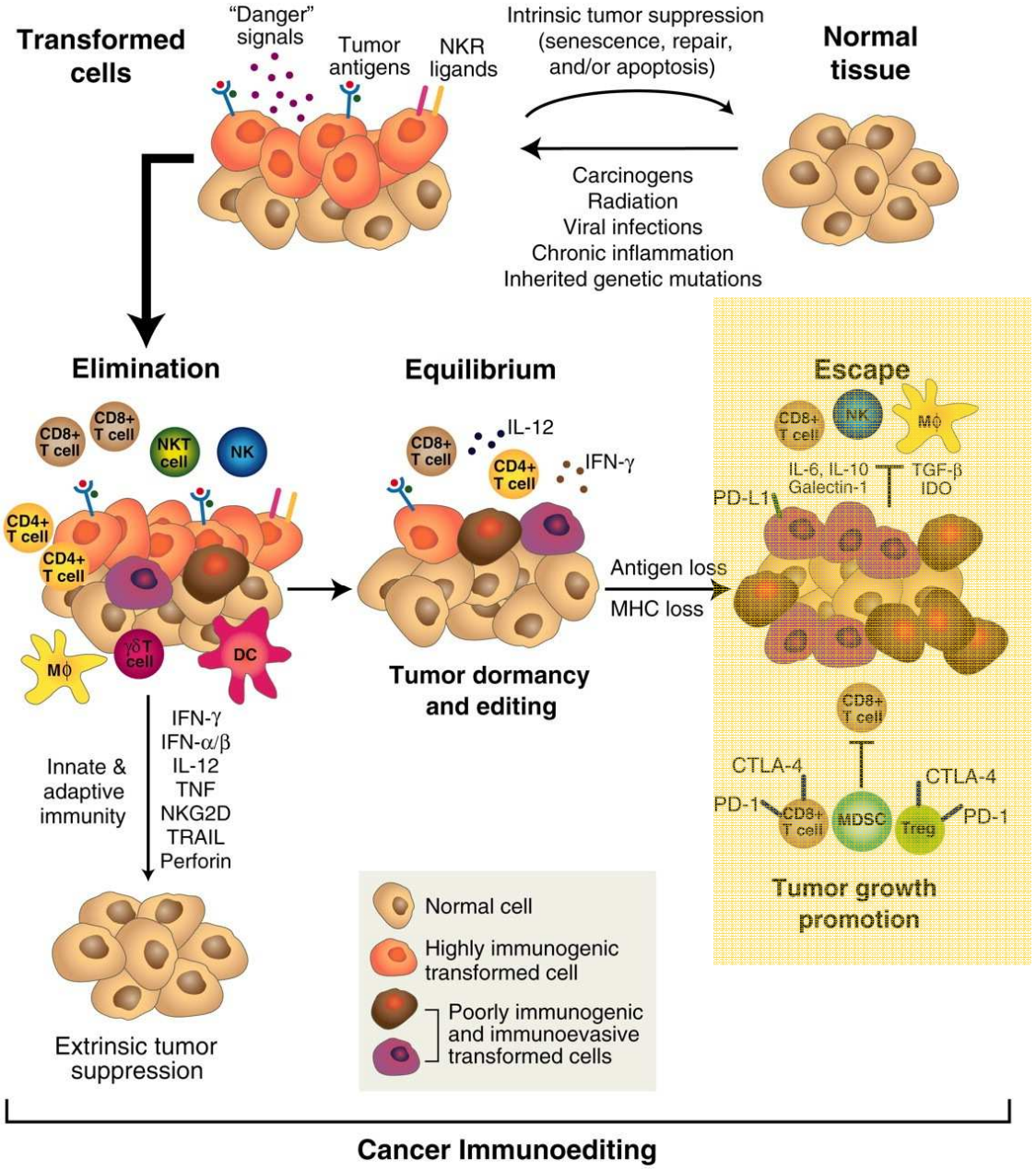
Snyder, A. et al. *NEJM.* 2014. 271: 2189.

# Cancer Immunoediting – the 3 E's

**2. Upregulation of active immune suppressive mechanisms**

- Better explains tumor expression of immunogenic antigens and existence of tumor antigen-specific T cell populations
- Consists of both Molecular Mechanisms and Cell-dependent Mechanisms






## *The cancer immunoediting concept.*

R D Schreiber et al.
Science 2011,
331:1565-1570

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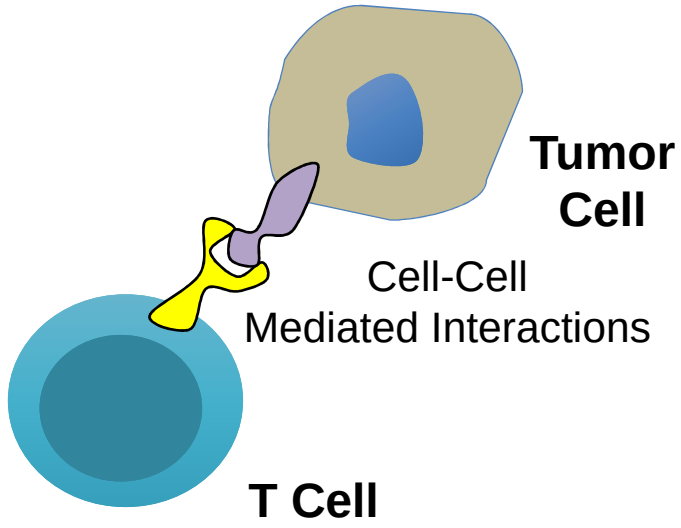
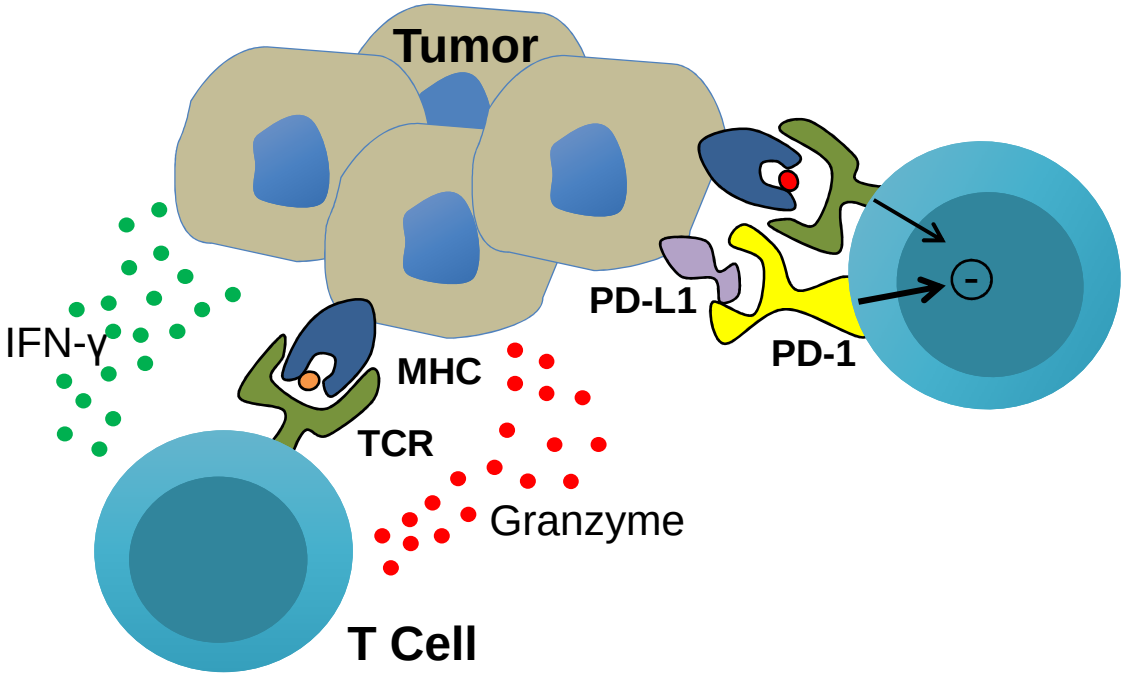
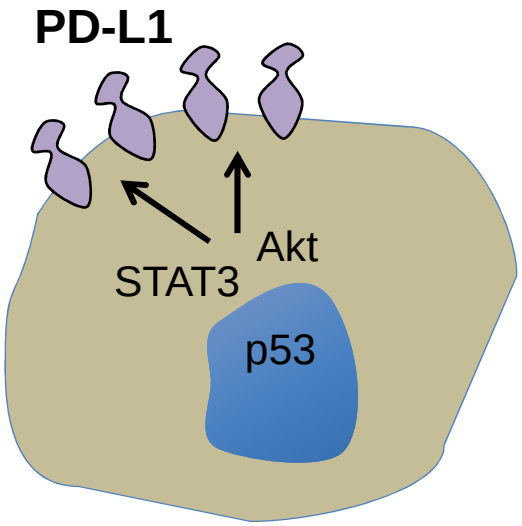


# PD-1 : PD-L Inhibitory Pathway

- PD-1 signaling promotes T cell tolerization by inhibiting downstream activation signals
- PD-1 expression is upregulated by activated and exhausted T cell populations
- T cell surface PD-1 receptor binds to and is activated by PD-L1 and PD-L2
- Many tumor tissues express PD-L1 allowing for the suppression of T cell activation
- Tumor PD-L1 expression is regulated via two general mechanisms:
  1. Adaptive immune resistance: upregulated by IFN-γ in peripheral tissues
  2. Innate immune resistance: oncogenic signaling pathways



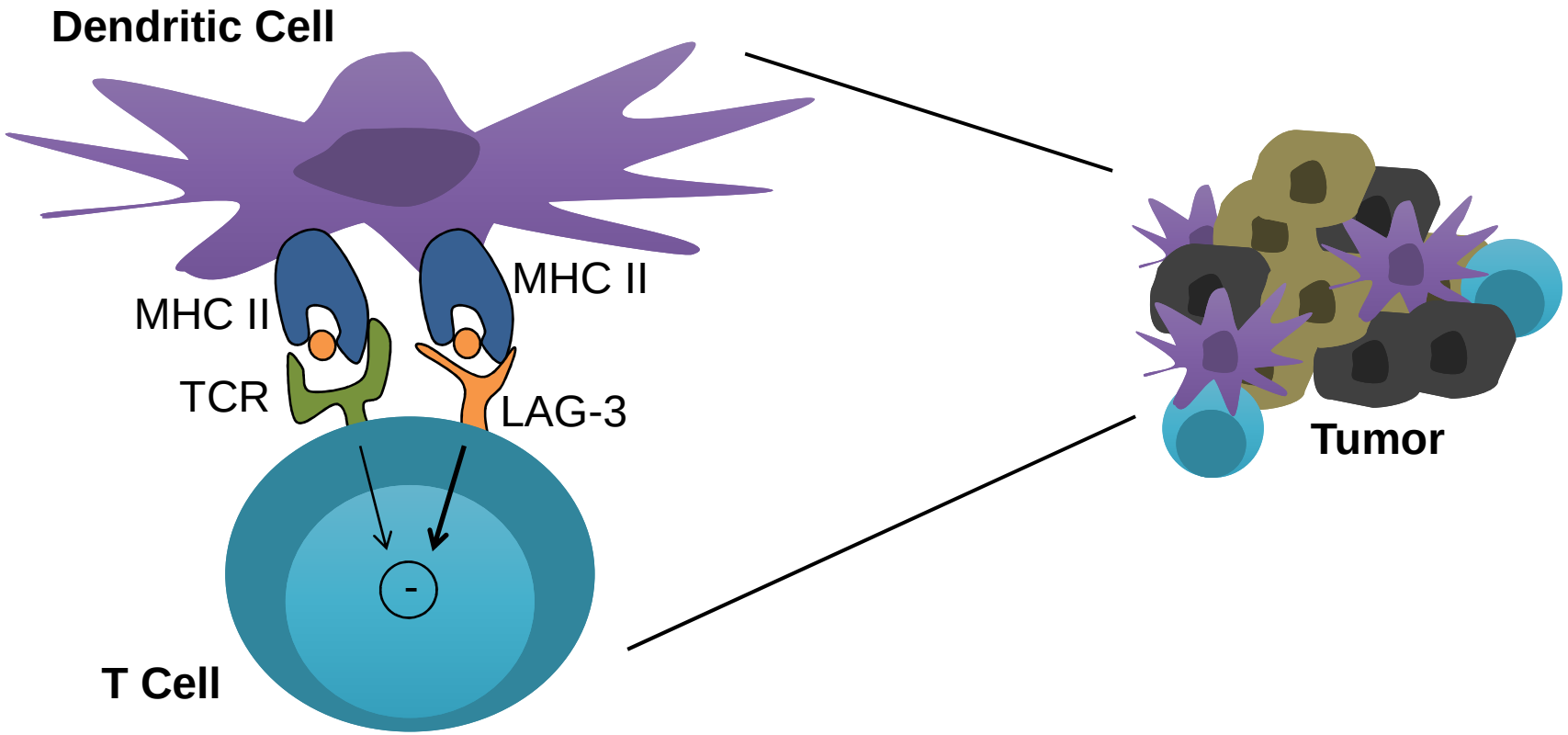




Francisco, L. et al. *Immunol Rev.* 2010. 236: 219.

Pardoll, D.M. *Nat Rev Cancer*. 2012. 12: 252.

# LAG3: lymphocyte activation gene 3

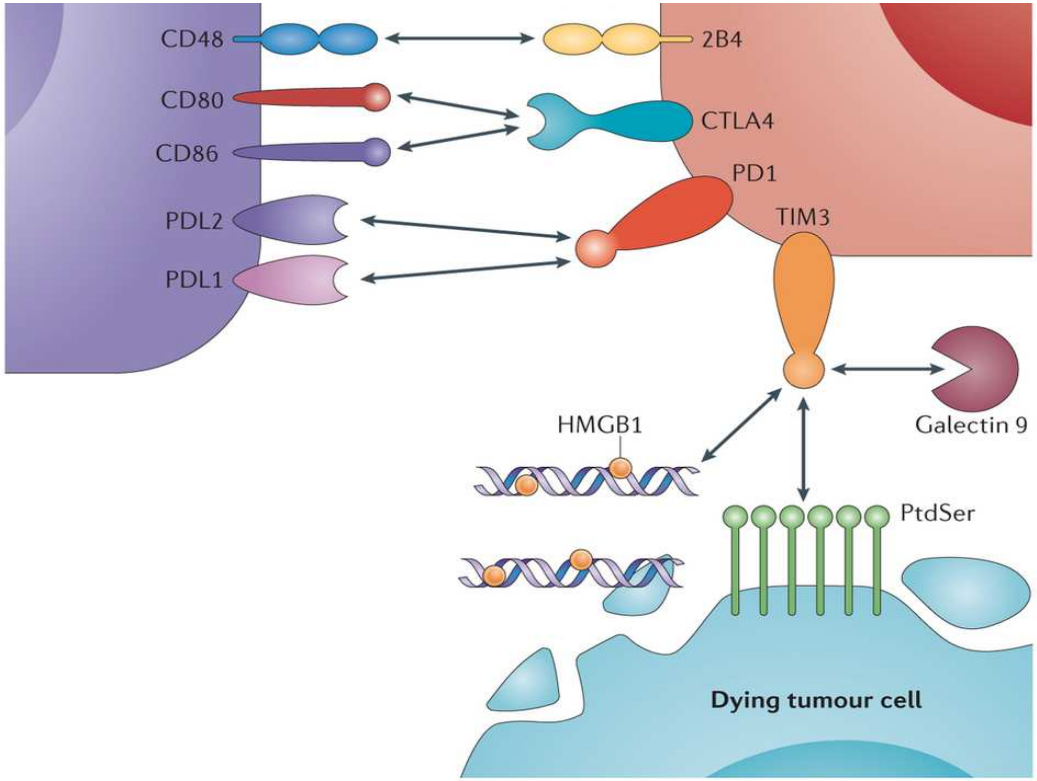
- Upregulated by activated and exhausted T cells
- Negative co-stimulatory receptor that suppresses T cell activation
- Expressed by regulatory T cells; promote regulatory T cell-mediated immune suppression
- Binds to MHC II molecules with high affinity on the surface of tumor-infiltrating DCs and macrophages




Nguyen, L. and Ohashi, P. *Nat Rev Immunol.* 2015. 15: 45.
Driessens, G. et al. *Immunol Rev.* 2009. 229: 126.

# TIM3: T cell Ig domain and mucin domain 3

- **T cell immunoglobulin domain and mucin domain 3 (TIM3).**
- **Its ligands include galectin 9, phosphatidylserine (PtdSer) and high-mobility group box 1 protein (HMGB1).**
- **PtdSer and HMGB1 are shown emanating from dying tumour cells.**
- **A stressed tumour cell could also upregulate these TIM3-binding partners**




Nature Reviews | Immunology

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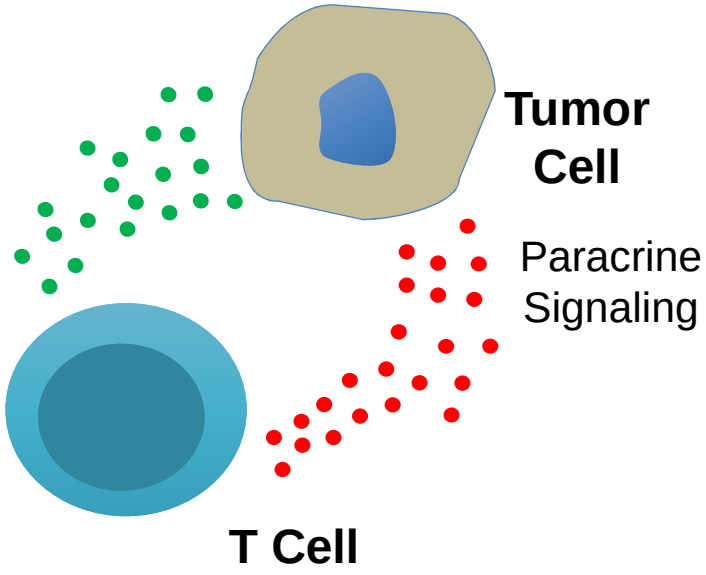
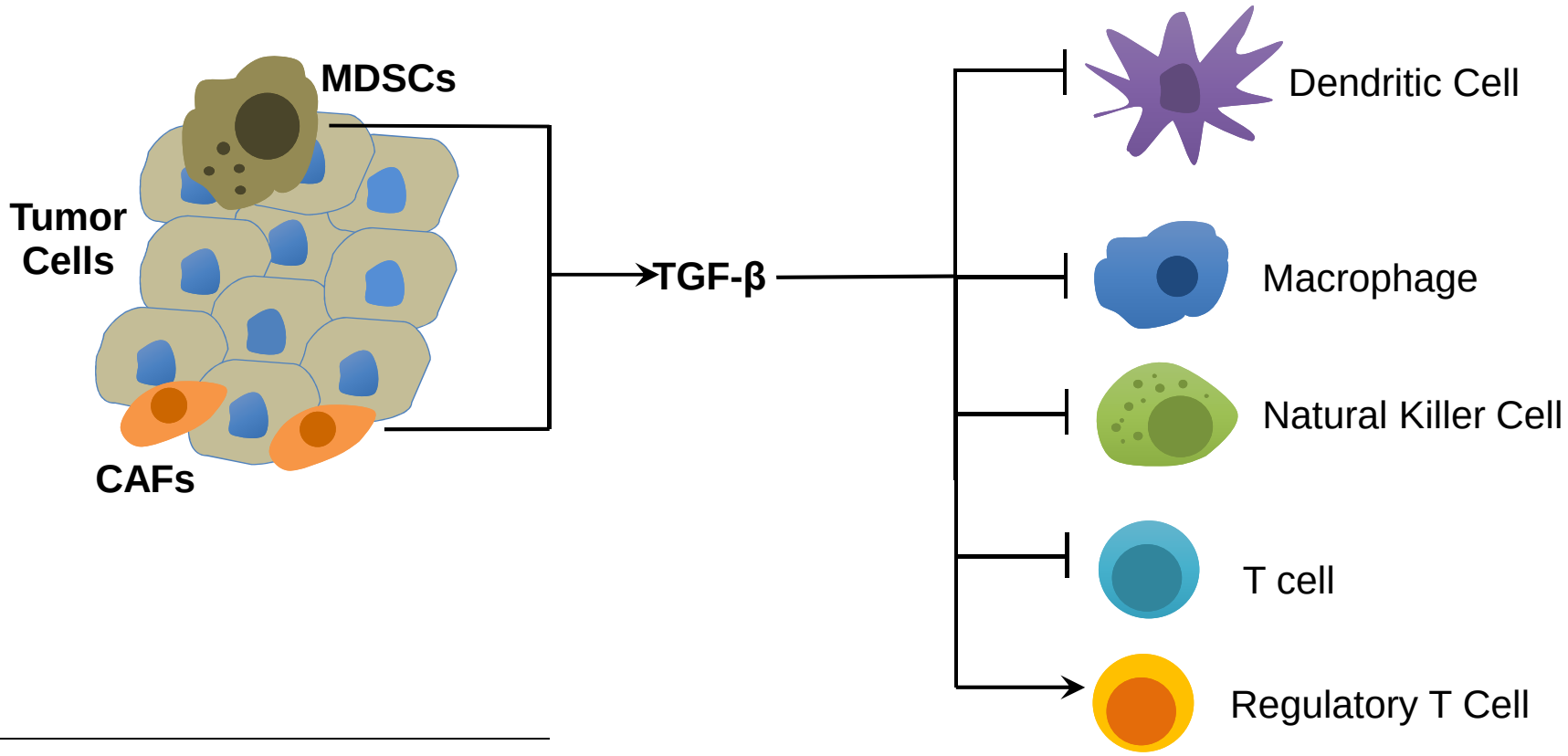


# TGF-β: Transforming Growth Factor-β

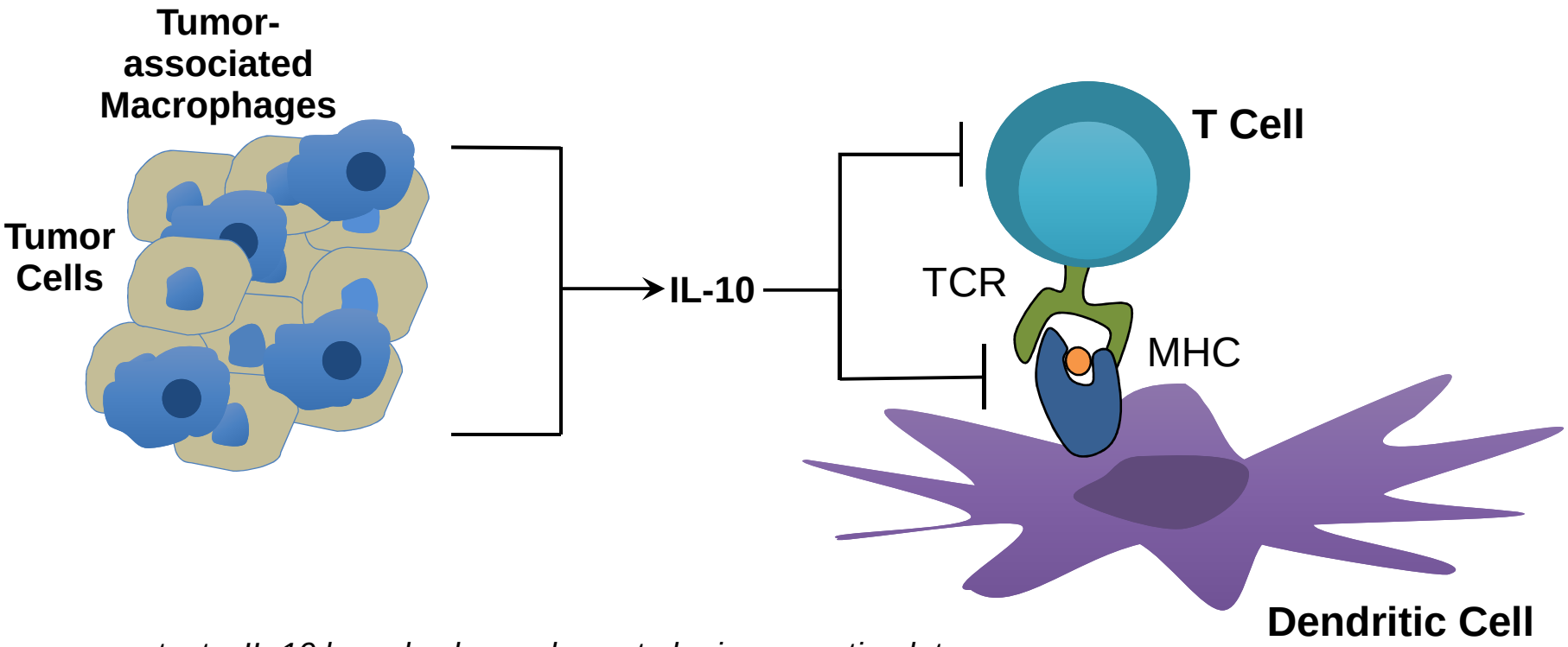
- TGF-β is a soluble cytokine expressed by several tumor types in addition to cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) in the tumor microenvironment
- TGF-β potently suppresses the proliferation and activation of $CD8^+$ cytotoxic T cells, $CD4^+$ T helper cells, and Natural Killer (NK) cells while promoting the differentiation of regulatory T cells




Flavell, R. et al. *Nature Rev Immunol*. 2010. 10: 554.
Hanks, B.A. et al. *J Clin Inves*. 2013. 123: 3925.

# IL-10

- IL-10 is expressed by a variety of cell types within the tumor microenvironment including macrophages, $CD4^+$ T cells, and regulatory T cells
- IL-10 suppresses the activation, proliferation, and effector function of naïve T cells while also suppressing the function of antigen-presenting cells such as dendritic cells; promotes regulatory T cell function
- IL-10 enhances the expression of TGF-β and its receptor



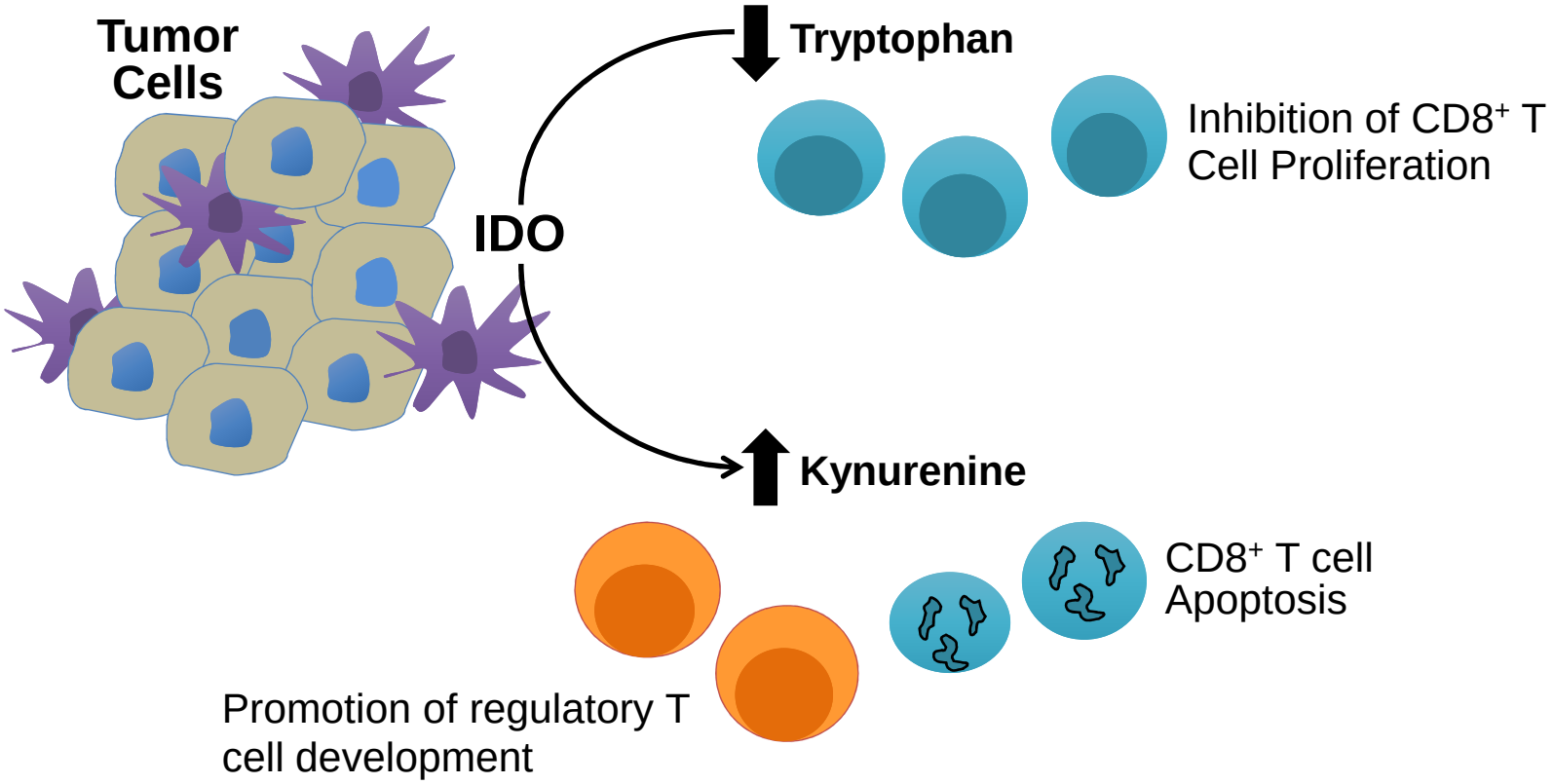

** In some contexts, IL-10 has also been shown to be immunostimulatory*


Ruffell, B. et al. *Cancer Cell.* 2014. 26: 623.
Mittal, S. and Roche, P. *Curr Opin Immunol.* 2015. 34: 22.

Mocellin, S. et al. *J Leukocyte Biol.* 2005. 78: 1043.

# IDO: Indoleamine 2,3-dioxygenase

- IDO is expressed by dendritic cells, macrophages, and tumor cells
- IDO catalyzes the conversion of the essential amino acid tryptophan to kynurenine
- Suppresses T cell proliferation/activation and promotes T cell apoptosis
- Promotes regulatory T cell differentiation and activation



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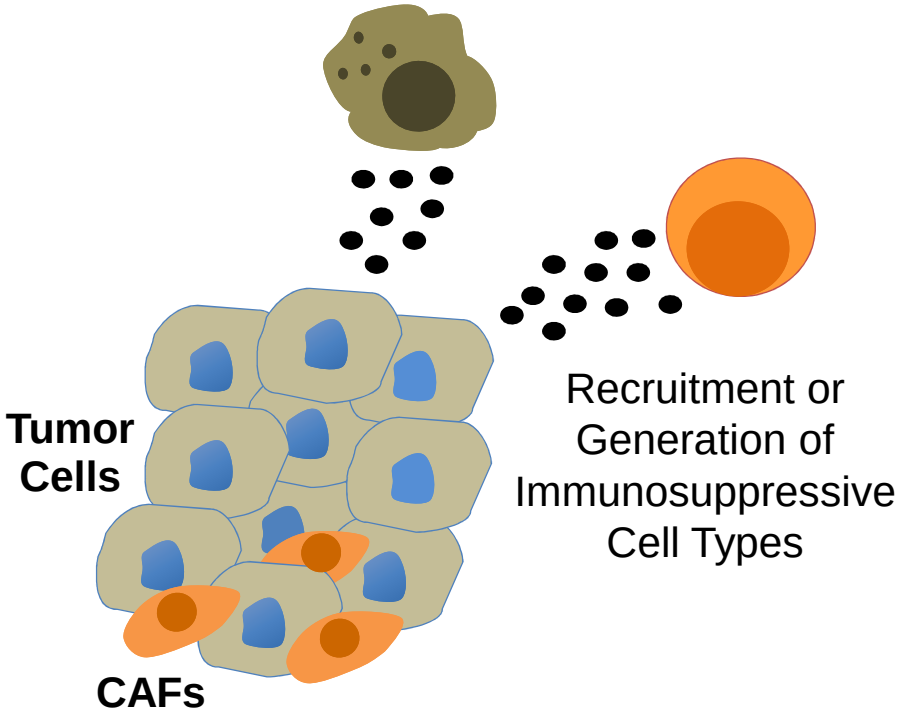
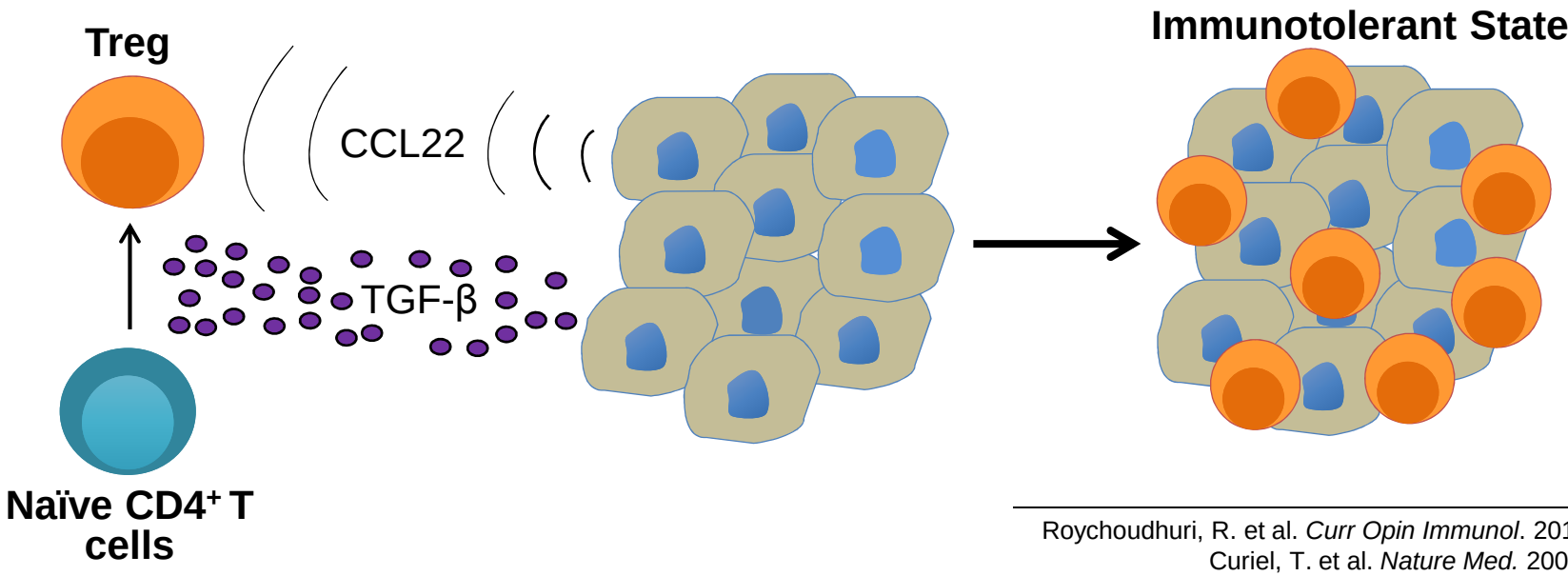


# Tregs: Regulatory T Cells

- $CD4^+$ $FoxP3^+$ Tregs play a critical role in maintaining peripheral tolerance
  - FoxP3 is a transcription factor that drives the genetic program of Tregs
  - A defect in the FoxP3 gene leads to the development of a lethal autoimmune disease in humans
- Tregs mediate effector T cell suppression via cell-cell contact-dependent mechanisms (CTLA-4, PD-L1) and the production of soluble cytokines (TGF-β, IL-10)
- Low $T_{effector}$/Treg ratios are associated with a poor prognosis in multiple cancer types
- TGF-β and IDO promote the differentiation and activation of Tregs within the tumor microenvironment
- Tumors also recruit Tregs to the tumor bed via expression of soluble chemokines

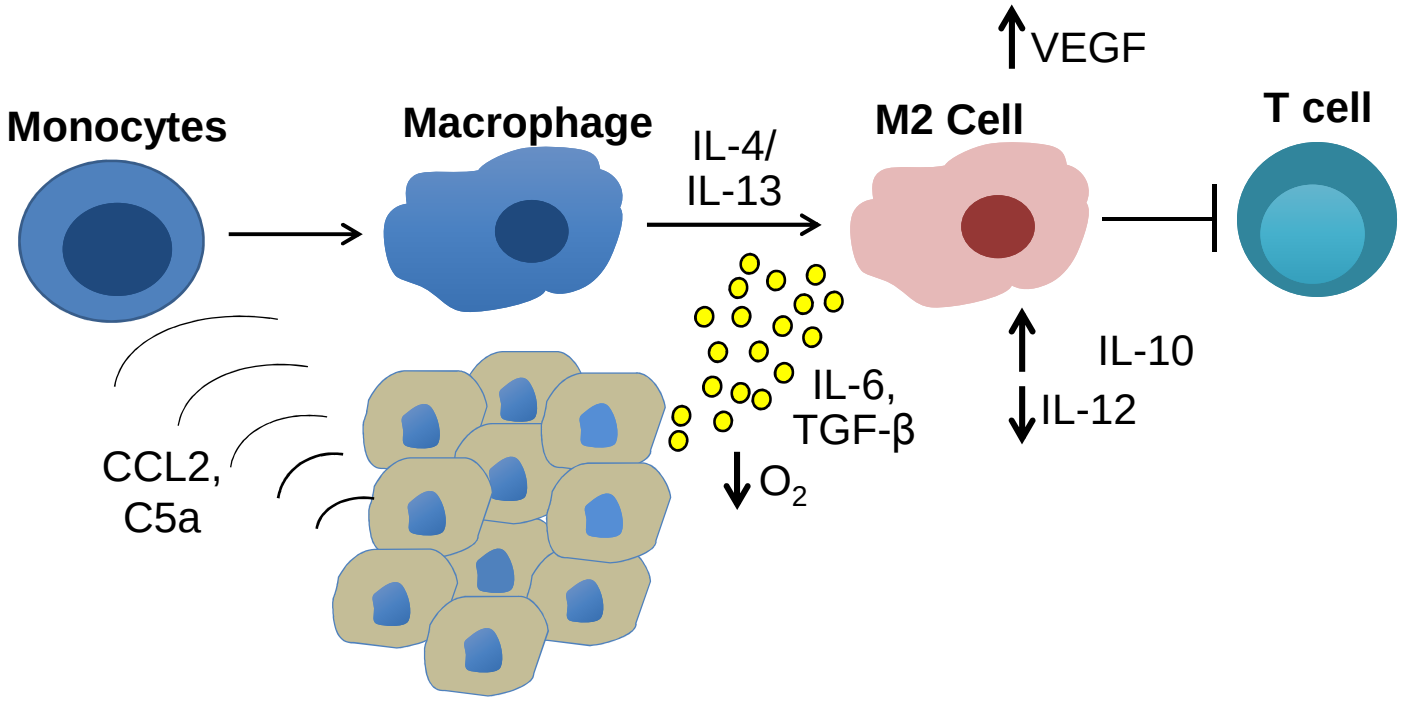



Roychoudhuri, R. et al. *Curr Opin Immunol*. 2015. 33: 101
Curiel, T. et al. *Nature Med.* 2004. 10: 942.

# TAMs: Tumor-associated Macrophages

- Circulating monocyte recruitment maintains a population of resident TAMs within the tumor microenvironment (CCL2)

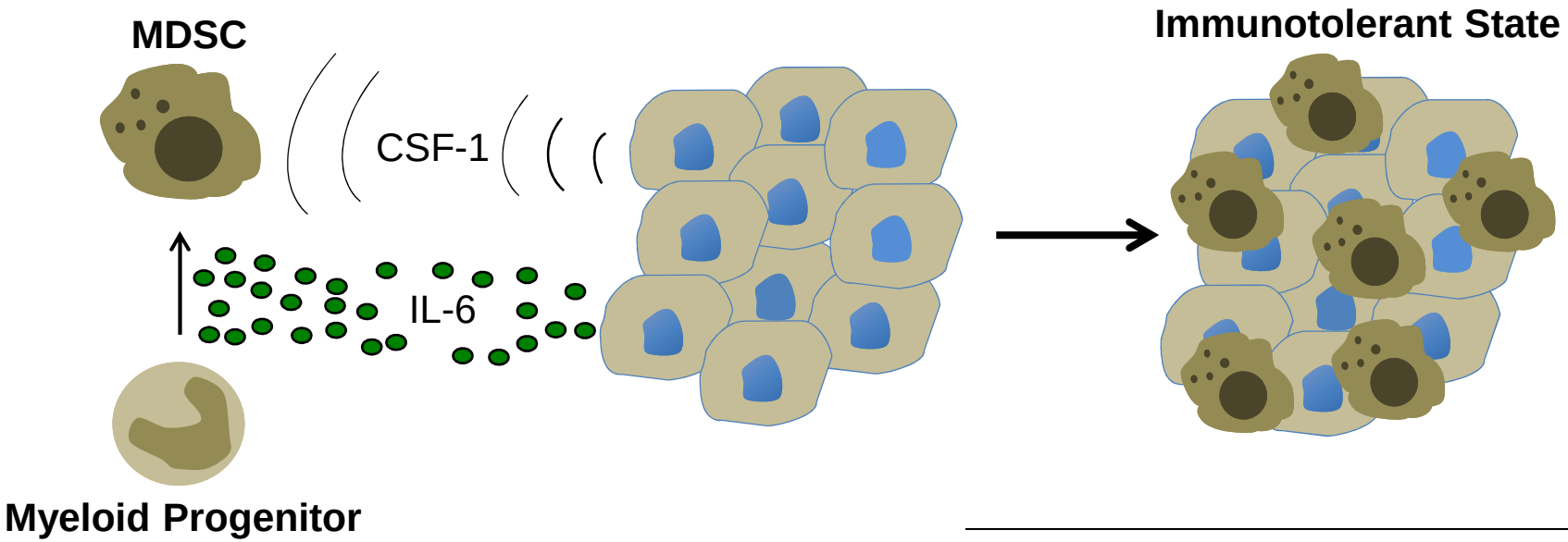
- Various signals within the tumor (cytokines, metabolic products) polarize macrophages to undergo a phenotypic switch (M2) to express several factors that suppress local immunity, promote angiogenesis, and promote tumor cell survival




Mantvani, A. and Allavena, P. *J Exp Med*. 2015. 212: 435.
Noy, R. and Pollard, J. *Immunity*. 2014. 41: 49.

# MDSCs: Myeloid-derived Suppressor Cells

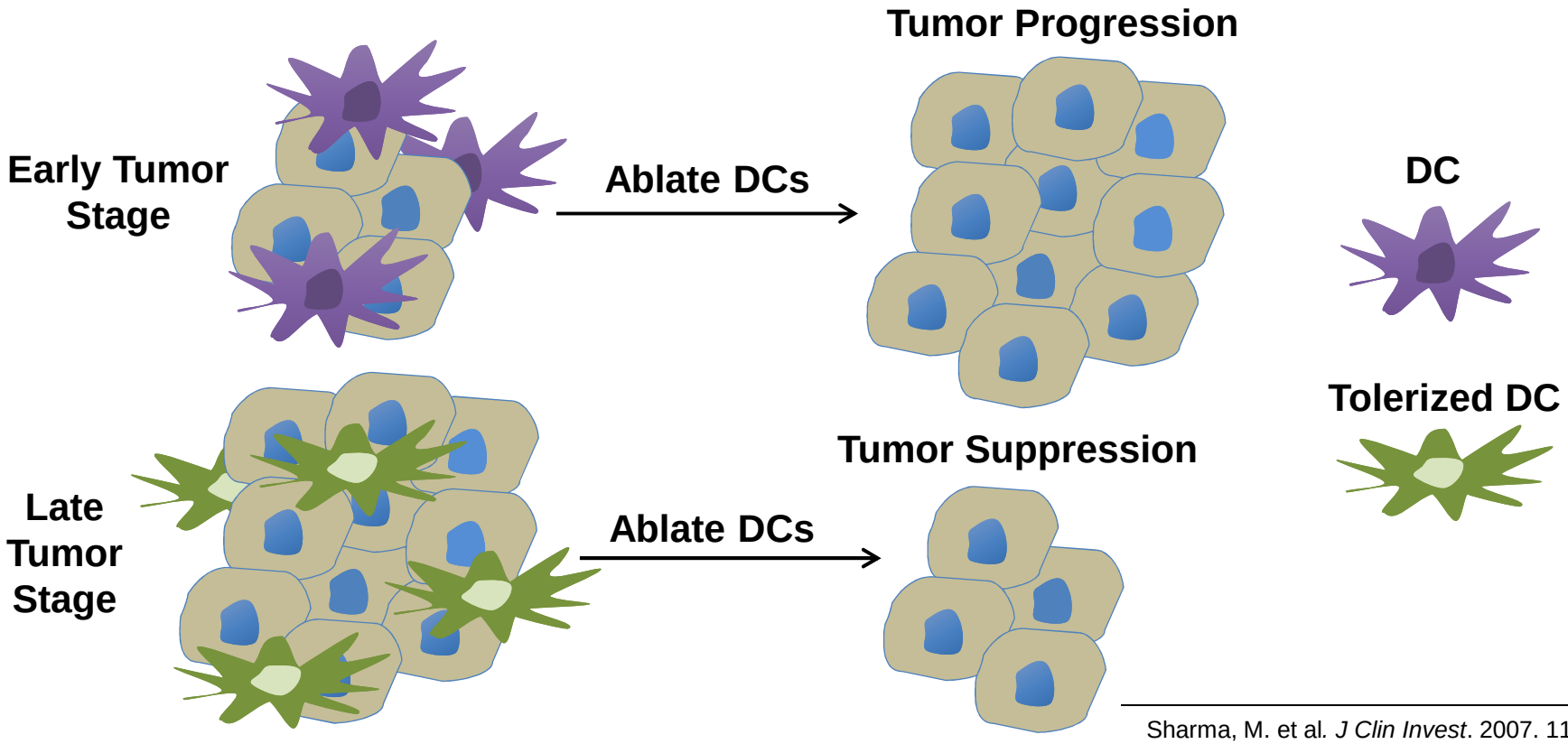
- MDSCs represent a heterogenous population of immature myeloid cells that develop due to defective differentiation in the bone marrow
- MDSC numbers expand in the setting of cancer and inflammation; tumor-mediated signaling via STAT3 (e.g. IL-6, VEGF) promotes MDSC expansion
- MDSCs are capable of suppressing T cell response via several mechanisms
  - In the setting of cancer, MDSCs upregulate the expression Arginase and iNOS (inducible nitric oxide synthase) to degrade arginine and generate NO and reactive oxygen species (ROS)
  - Express high levels of TGF-β




Cheng, P. et al. *J Exp Med*. 2008. 205: 2235.
Serafini, P. et al. *Sem Cancer Biol.* 2006. 16: 53.
Gabrilovich, D. and Nagaraj. S. *Nat Rev Immunol*. 2009. 9: 162.

# Tolerized Dendritic Cells

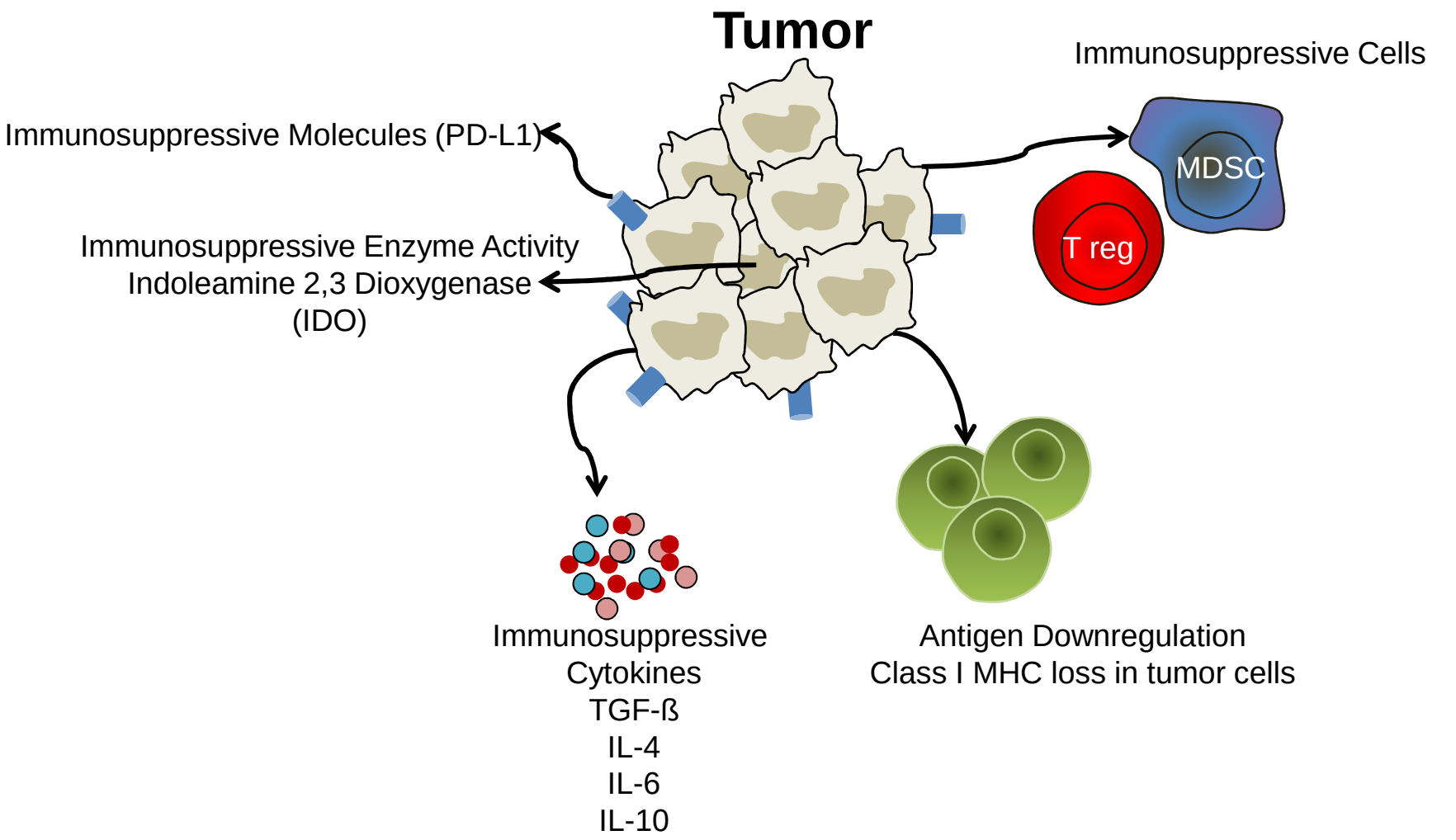
- Dendritic cells (DCs) play a key role in tumor immunosurveillance by priming tumor antigen-specific T cell responses and modulating their function
- DCs capable of promoting Treg generation and activation accumulate within both tumor tissues and nearby draining lymph node tissues
- Tolerized DCs potently suppress nearby effector T cell responses
- IDO seems to significantly contribute to the immunosuppressive function of tolerized DCs





Sharma, M. et al. *J Clin Invest*. 2007. 117: 2570.
Scarlett, U. et al. *J Exp Med*. 2012. 209: 495.
Hurwitz, A. and Watkins, S. *Cancer Immunol Immunother.* 2012. 61: 289.

# Tumor-Derived Immune Suppression




Weiner LM. *N Engl J Med* 2008

# Lessons and Take Home Messages

- The Cancer Immunoediting Hypothesis provides the intellectual framework for understanding the evolution of cancer-mediated immune suppression

- Developing cancers actively suppress the host immune system through a variety of mechanisms which are ultimately necessary for cancer progression

- Understanding these mechanisms of cancer-mediated immune evasion promises to lead to the identification of novel immunotherapeutic approaches which will likely involve combinatorial regimens

- Understanding which immune evasion mechanism is dominant for which individual cancer type or individual patient will facilitate the development of personalized immunotherapy regimens

Celebrating 30 Years of Advancing Cancer Immunotherapy Worldwide

SITC 2015

The Society for Immunotherapy of Cancer (SITC) Presents its

# 30th Anniversary Annual Meeting & Associated Programs

## **November 4 – 8, 2015** | National Harbor, Maryland

- **SITC 30th Anniversary Annual Meeting**
- **Workshop on New Perspectives for Target Antigens in the Changing Cancer Immunotherapy Landscape**
- **Primer on Tumor Immunology and Cancer Immunotherapy™**
- **Global Regulatory Summit**
  Organized in Collaboration with Regulators from Around the Globe
- **International Symposium on Cancer Immunotherapy: Featuring Today's Innovators, Tomorrow's Leaders**
  Organized in Collaboration with the World Immunotherapy Council
- **Biomarkers in Cancer Immunotherapy: Oasis or Mirage?**
  Organized in Collaboration with the SITC Annual Program Committee and the SITC Industry Committee
- **Immunotherapy Patient Forum for the Treatment of Melanoma, Leukemia, Lung and Genitourinary Cancers**
  Organized in Collaboration with the Global Resource for Advancing Cancer Education (GRACE) and the Melanoma Research Alliance (MRA)

***CME available!*** *The 30th Anniversary Annual Meeting, Workshop and Primer are jointly provided by the Annenberg Center for Health Sciences at Eisenhower and the Society for Immunotherapy of Cancer in collaboration with Postgraduate Institute for Medicine.*

### Conference Highlights

- Keynote address to be given by **Professor Tasuku Honjo**, *2015 Richard V. Smalley, MD Memorial Award Recipient*
- *Milestones in Immunotherapy* session featuring talks by Dr. James P. Allison, Dr. Cornelis J.M. Melief, Dr. Steven A. Rosenberg & Dr. Robert Schreiber
- Dedicated Early Career Scientist Activities & Awards
- Special 30th Anniversary Programming & Celebratory Events

Submit your abstract by July 9!

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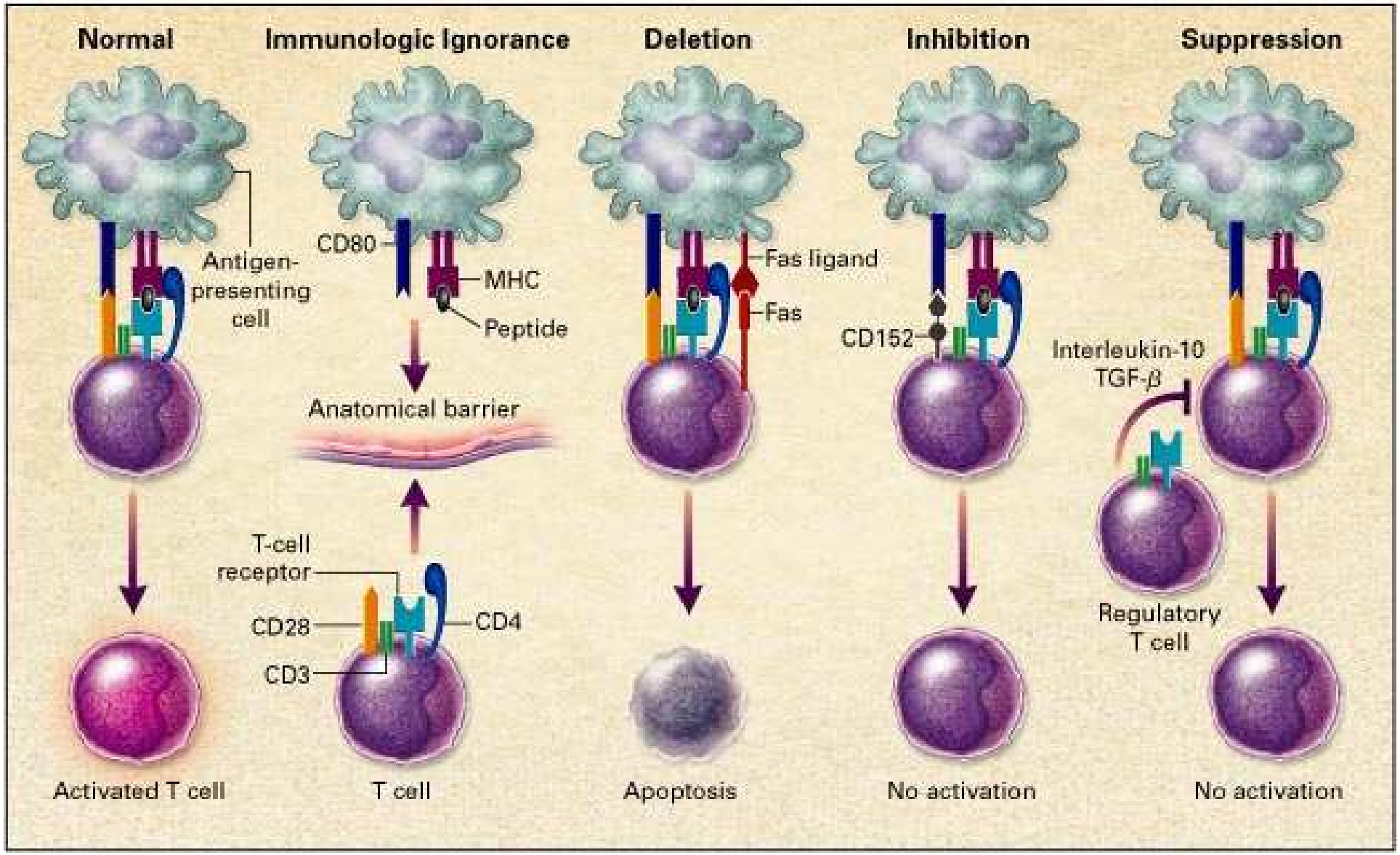
# Mechanisms of Immune Suppression



# T Cell Mechanics

**T-cell receptor: antigen/MHC**

**CD28 B7**


**CTLA-4 B7**

**Vaccine?**