Society for Immunotherapy of Cancer (SITC)

Basic Mechanisms of Tumor Immune Suppression

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Presentation originally prepared and presented by
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Society for Immunotherapy of Cancer

Disclosures

- UbiVac – Salary

- Providence/UbiVac – Receipt of Intellectual Property Rights/Patent Holder

- Perkin Elmer, AstraZeneca/Janssen, Nodality, 3M, Argos Therapeutics, Immunophotonics, Definiens – Consulting Fees

- Bristol-Myers Squibb, Janssen, Viralytics – Contracted Research

- UbiVac, UbiVac-CMV, Insys Therapeutics – Ownership Interest (Stocks, Stock Options or Other Ownership Interest *Excluding Diversified Mutual Funds*)

- Immunophotonics – Options

Outline: Basic Mechanisms of Tumor Immune Suppression

1. **Cancer Immunoediting Hypothesis**
2. **Cell Surface Molecular Mechanisms**
   - PD-L1
   - LAG3
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

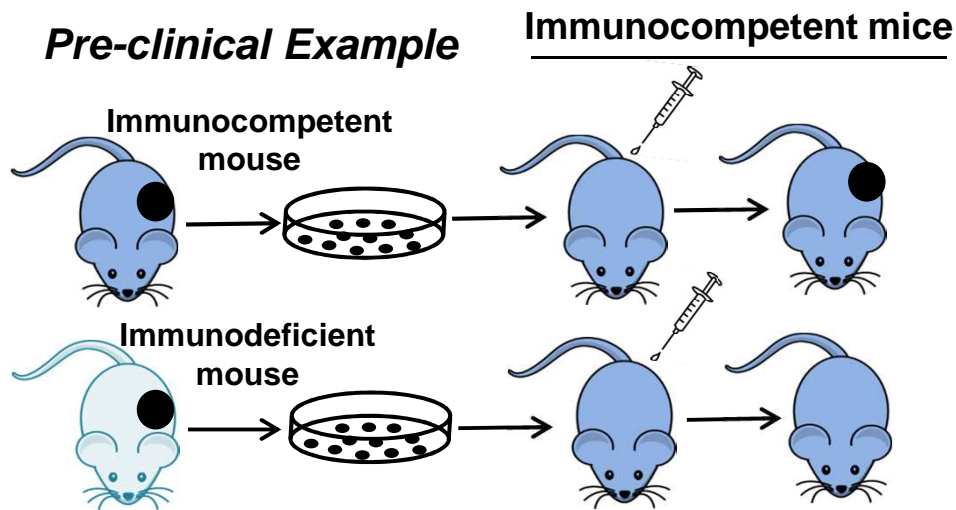Holtzhausen, A. et al. *Frontiers in Immunology.* 2014. 5: 438.
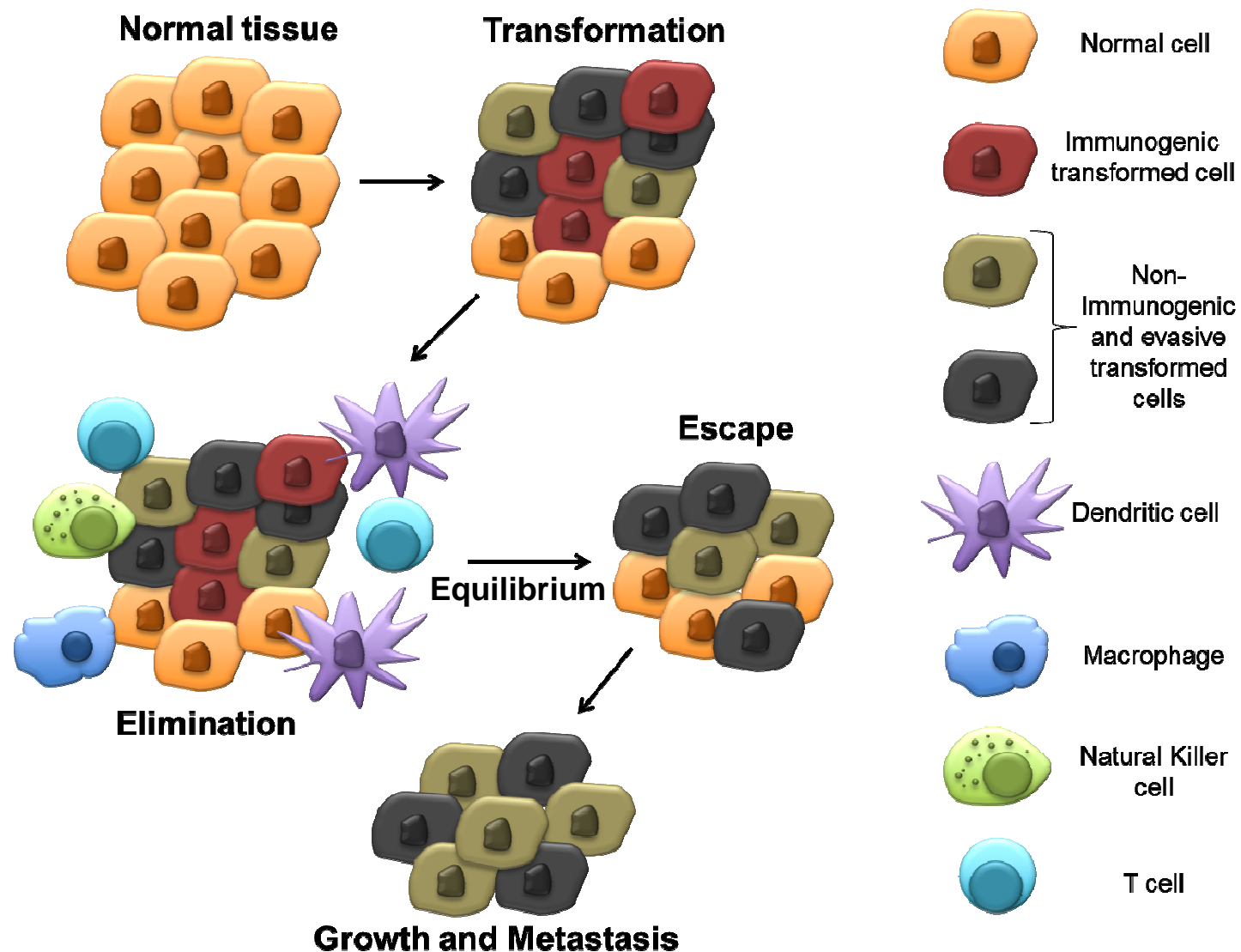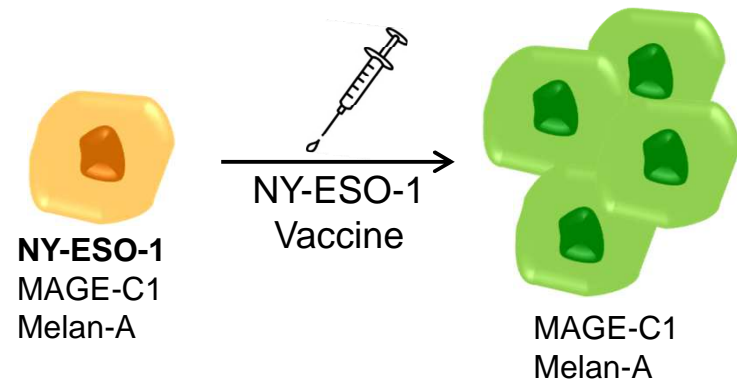
Cancer Immunoediting – the 3 E's

- **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

Immunocompetent mice

Immunocompetent mouse

Immunodeficient mouse

Clinical Example

NY-ESO-1
MAGE-C1
Melan-A

NY-ESO-1 Vaccine

MAGE-C1
Melan-A

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.

T Cell Mechanics

T-cell receptor: antigen/MHC


CD28 B7

CTLA-4 B7

IL-2

Vaccine?

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**
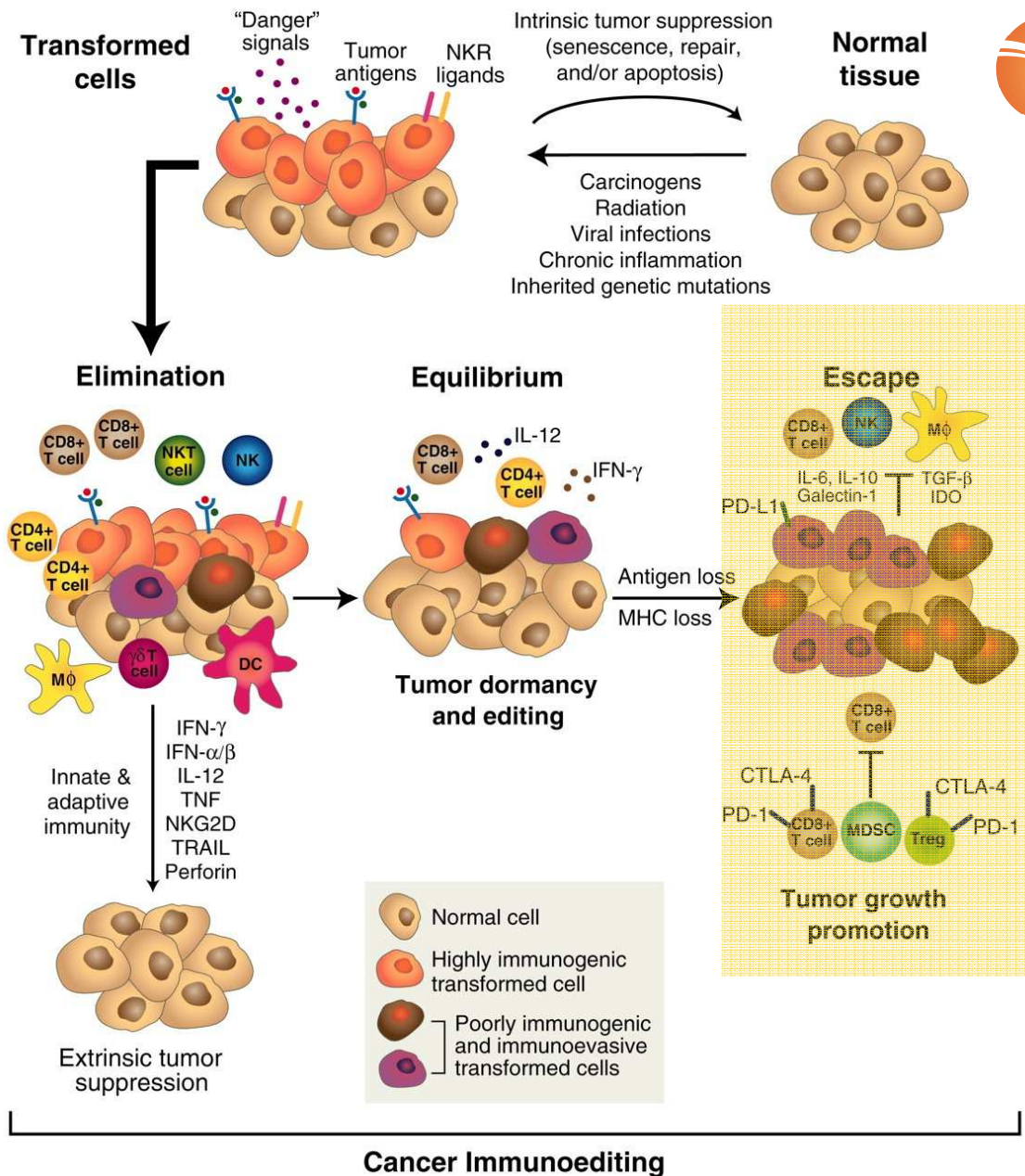
Colon Cancer - TILs
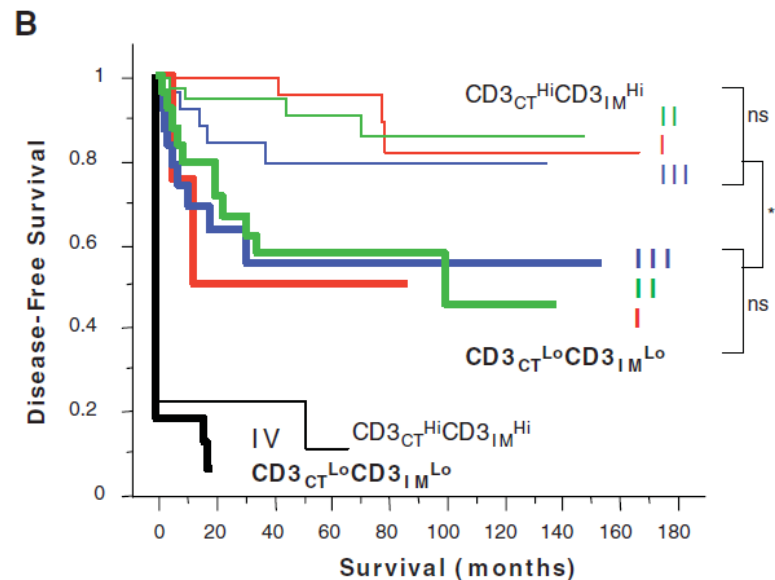
Melanoma – Mutational Load
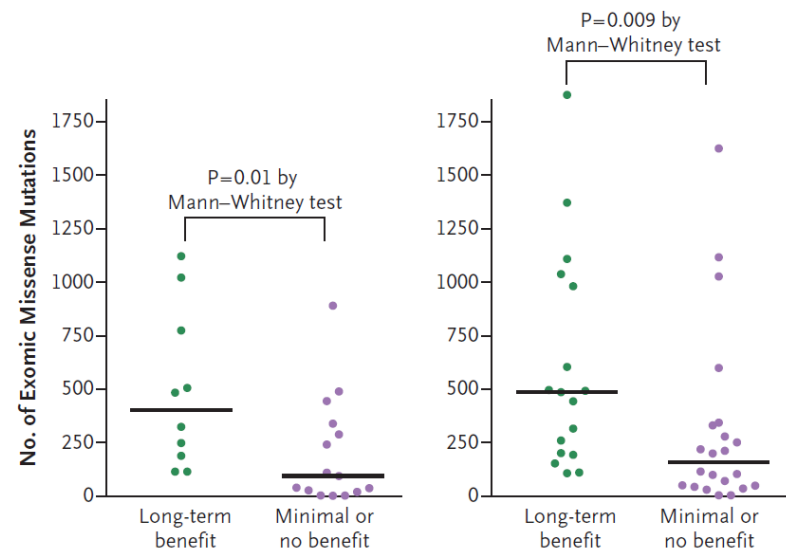
Galon, J. et al. *Science*. 2006. 313: 1960.

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

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The cancer immunoediting concept.

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

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
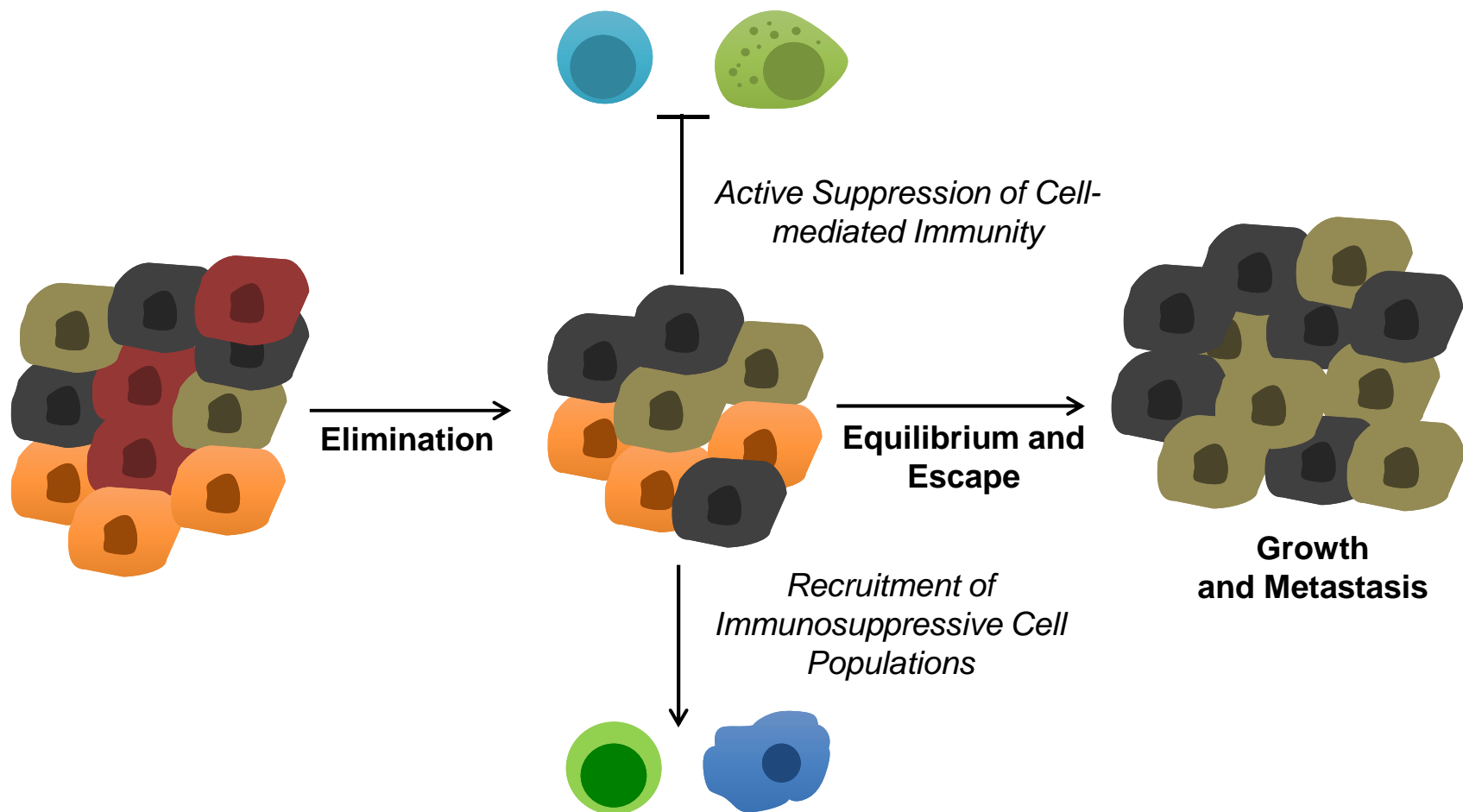
Outline: Basic Mechanisms of Tumor Immune Suppression

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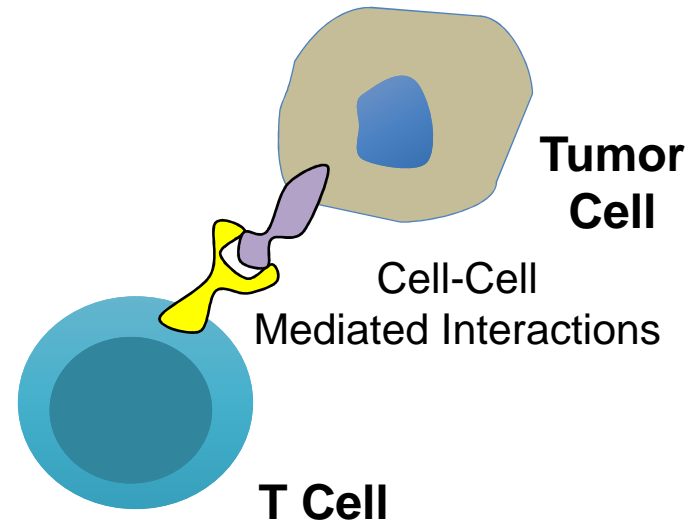   - PD-L1
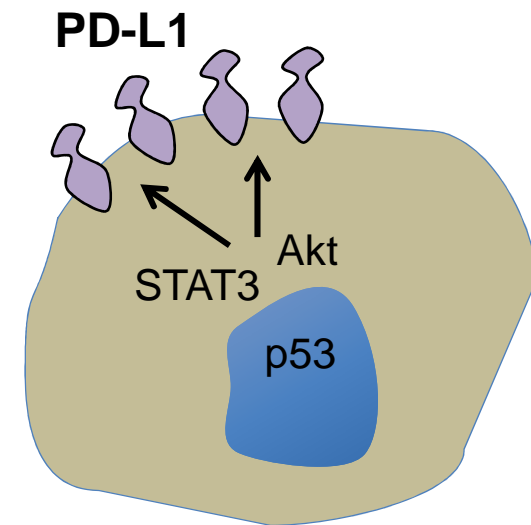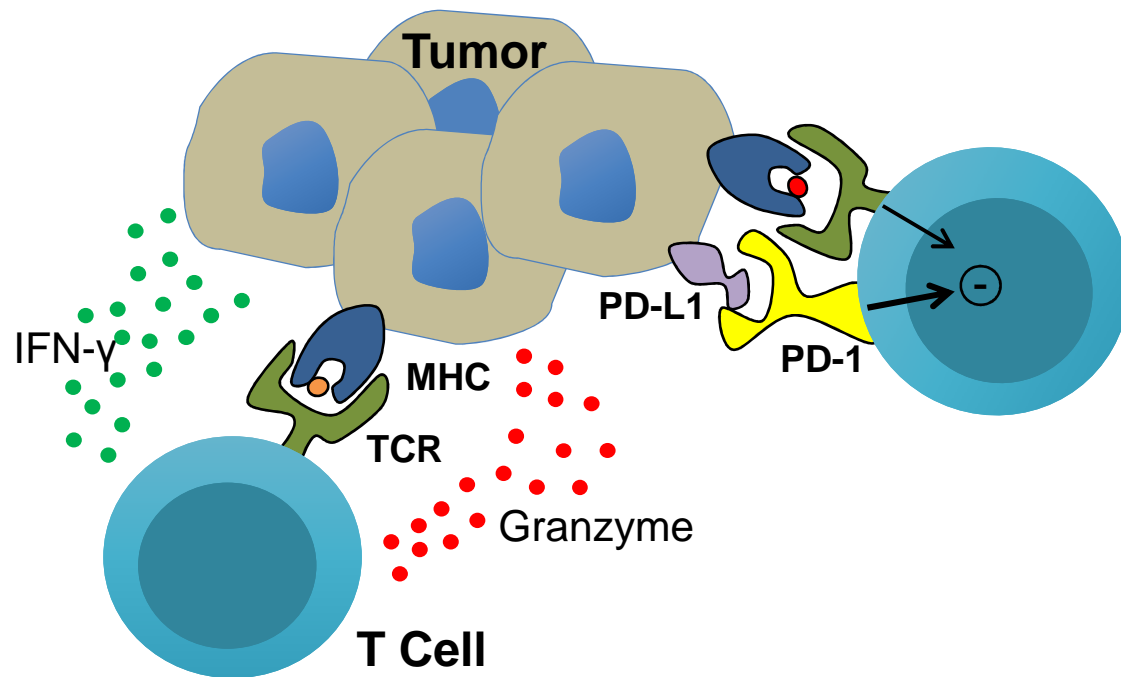   - LAG3
3. **Soluble Molecular Mechanisms**
   - TGF-β
   - IL-10
   - IDO
4. **Cell-dependent Mechanisms**
   - Tregs
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   - MDSCs
   - Tolerized DCs

Tumor Cell

Cell-Cell Mediated Interactions

**T Cell**

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.

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Naiyer A. Rizvi,[1,2]*† Matthew D. Hellmann,[1,2]* Alexandra Snyder,[1,2,3]* Pia Kvistborg,[4] Vladimir Makarov,[3] Jonathan J. Havel,[3] William Lee,[5] Jianda Yuan,[6] Phillip Wong,[6] Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[2,3,5]‡

G — All Tumors
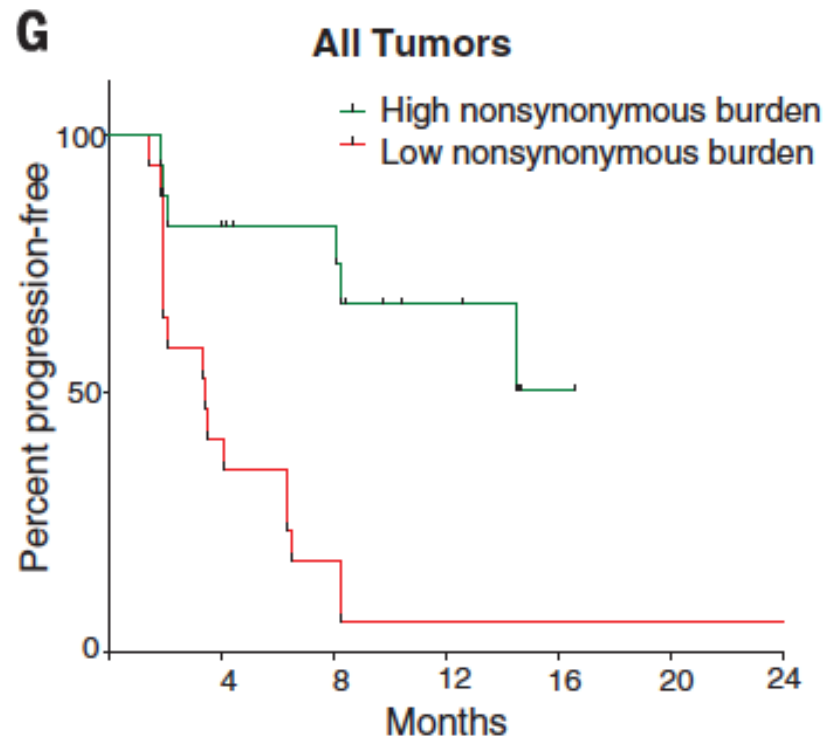
Hypothesis: PD-1 Blockade works in patients with most "mutated" / "immunogenic" cancers.

This data supports hypothesis

B Fox CFDA

The NEW ENGLAND JOURNAL of MEDICINE

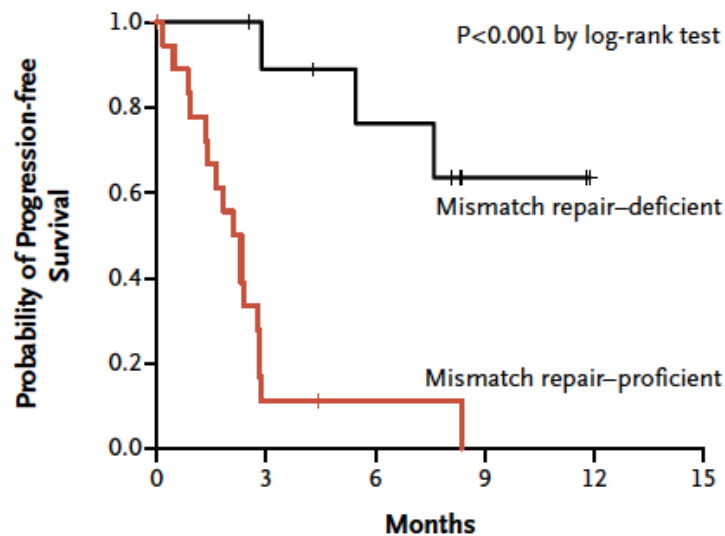## PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring,
A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower,
A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg,
A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood,
N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish,
J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

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PD-1 Blockade in "high mutated" / "immunogenic" cancers. **Still not enough CRs…**

A **Progression-free Survival in Cohorts with Colorectal Cancer**

P<0.001 by log-rank test

Mismatch repair–deficient

Mismatch repair–proficient

B **Overall Survival in Cohorts with Colorectal Cancer**

P=0.03 by log-rank test

Mismatch repair–deficient

Mismatch repair–proficient

B Fox CFDA
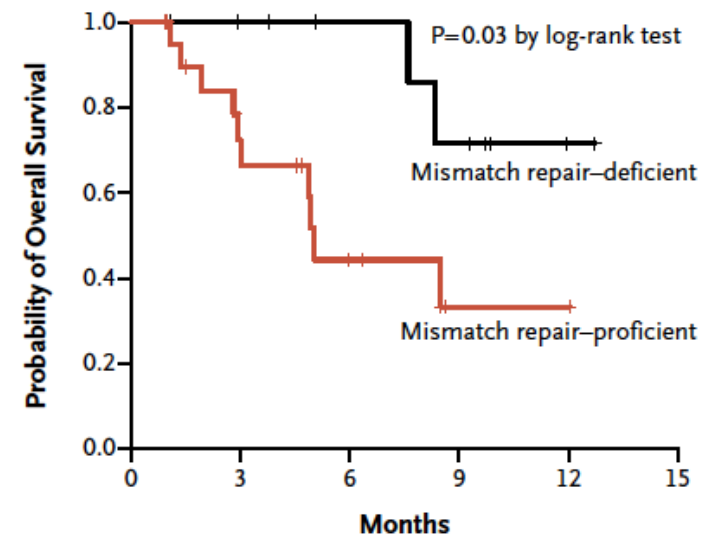
This article was published on May 30, 2015,

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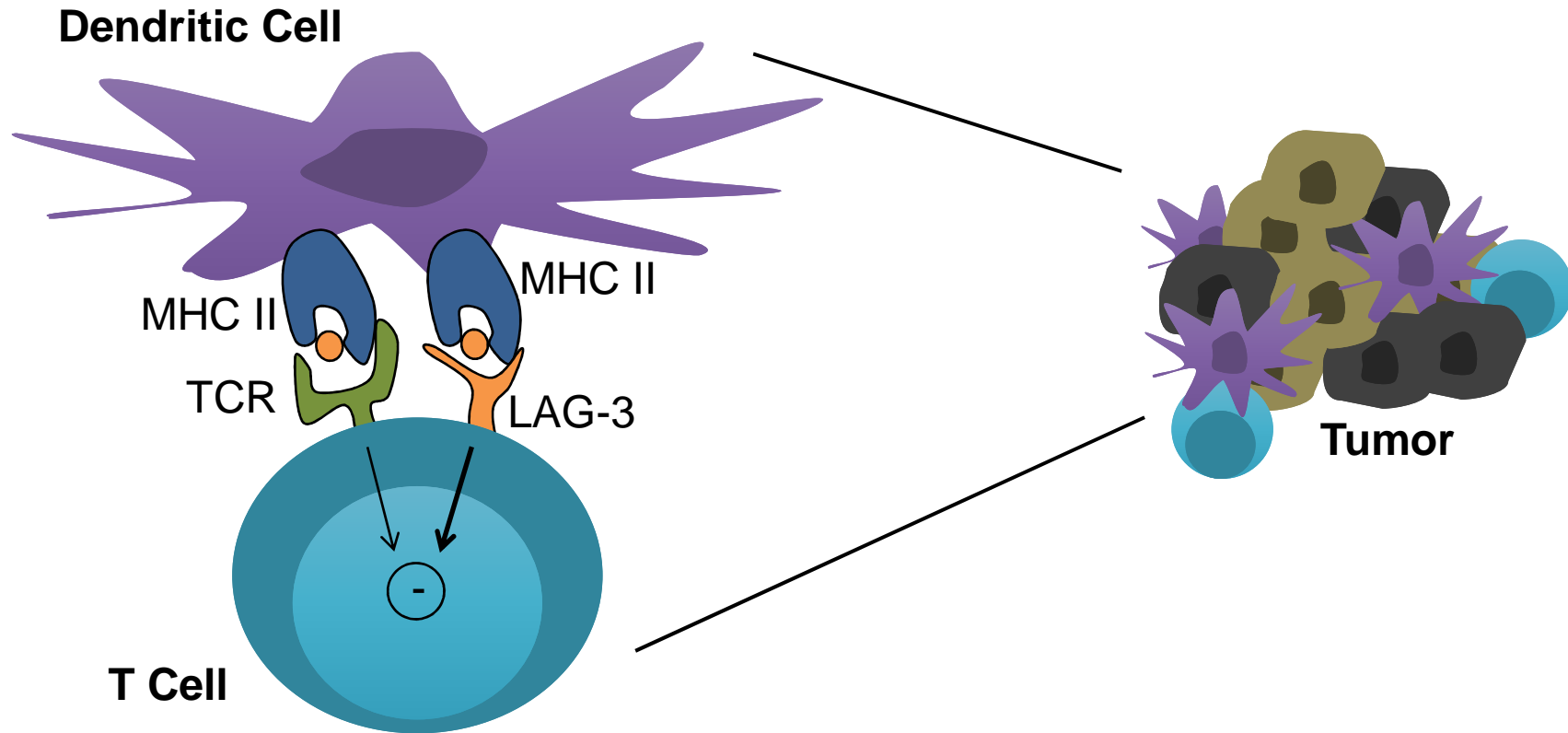
Nguyen, L. and Ohashi, P. *Nat Rev Immunol.* 2015. 15: 45.
Driessens, G. et al. *Immunol Rev.* 2009. 229: 126.
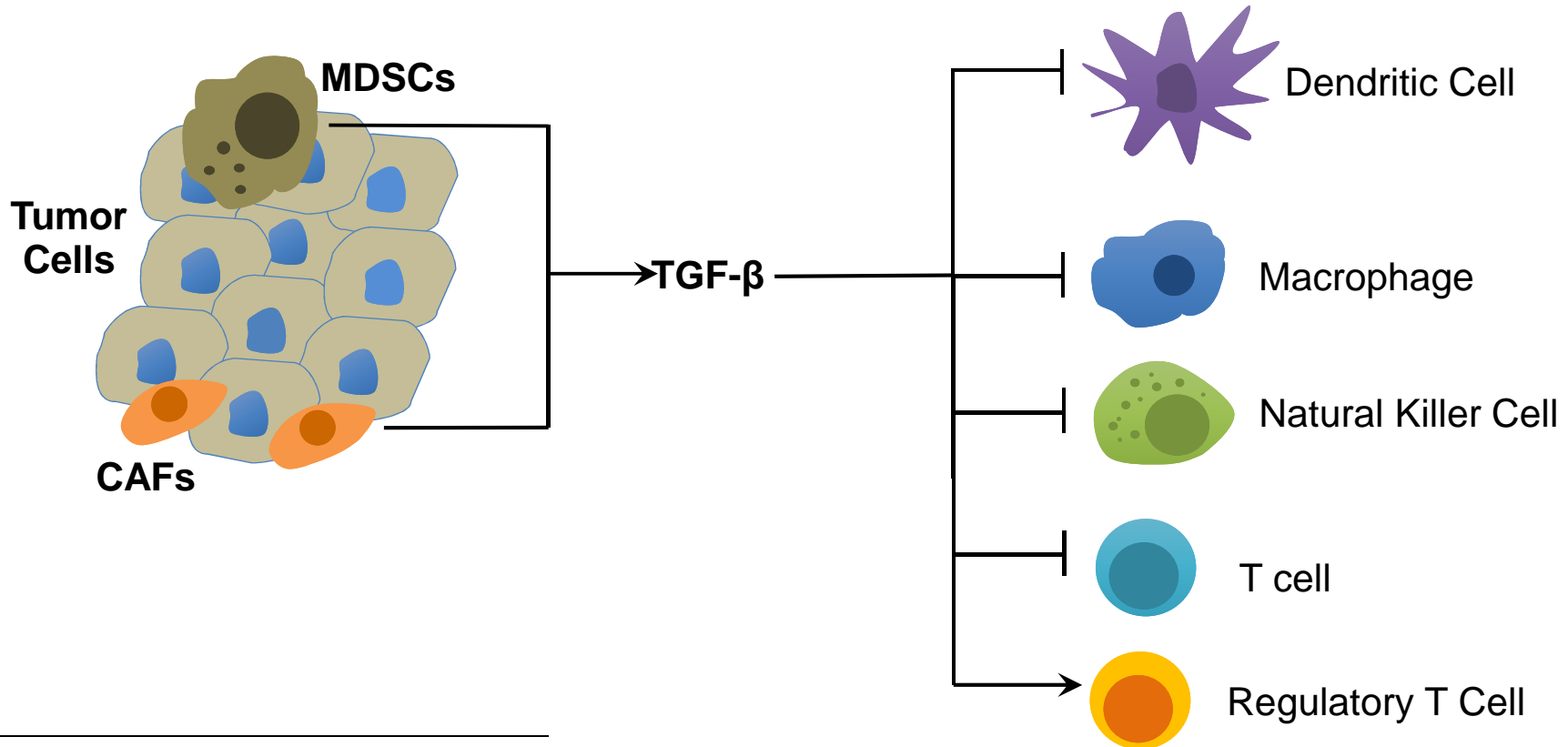
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Tumor Cell

Paracrine Signaling
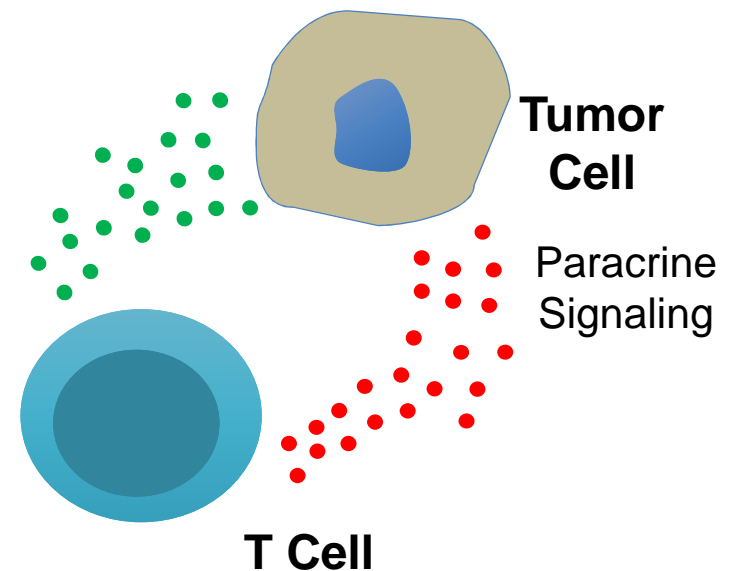
T Cell

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
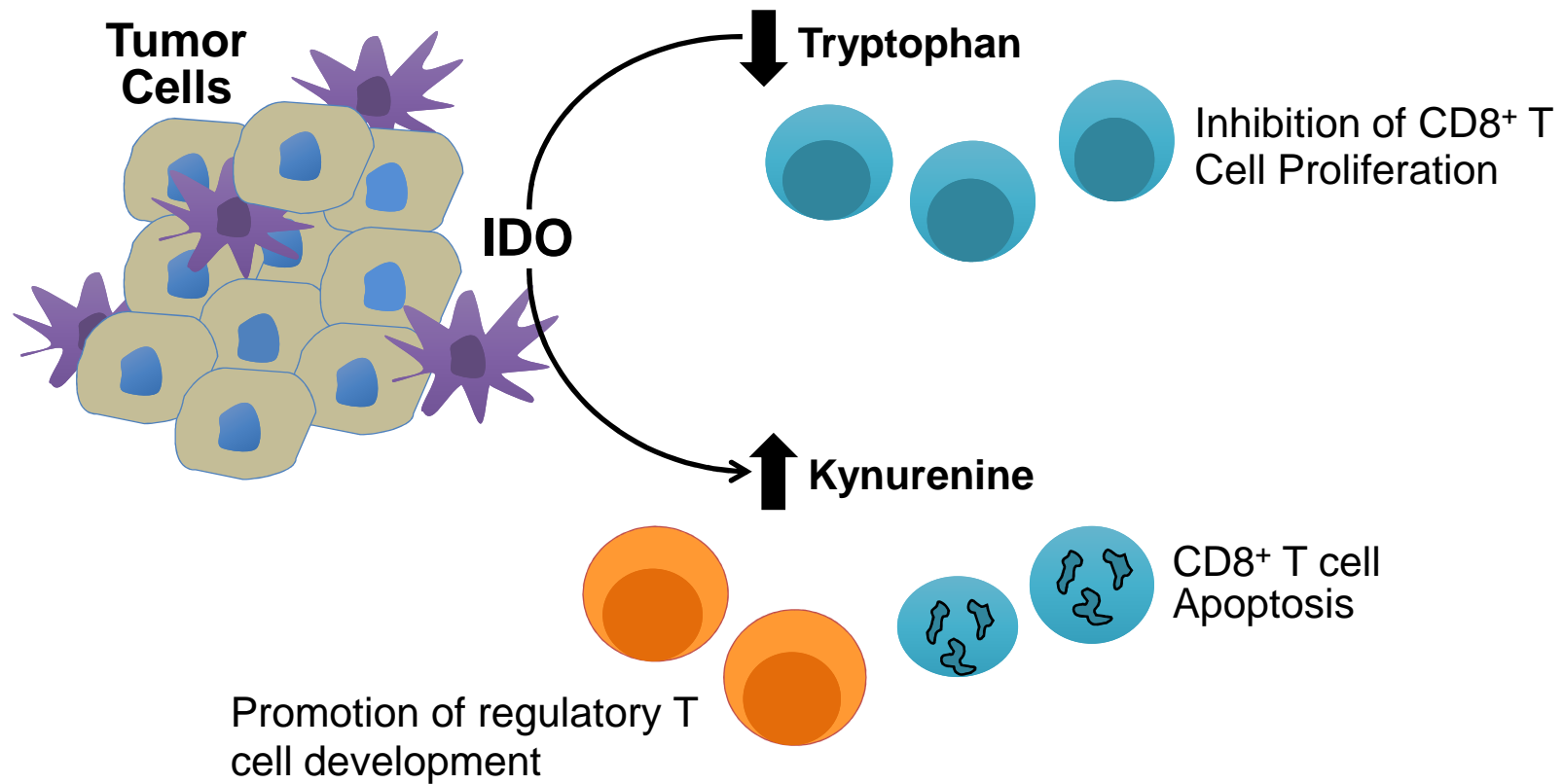
- IL-10 suppresses the activation, proliferation, and effector function of naïve T cells while also suppressing the function of antigen-presenting cells such as dendritic cells; promotes regulatory T cell function

- IL-10 enhances the expression of TGF-β and its receptor

Tumor-associated Macrophages

Tumor Cells

T Cell

IL-10

TCR

MHC
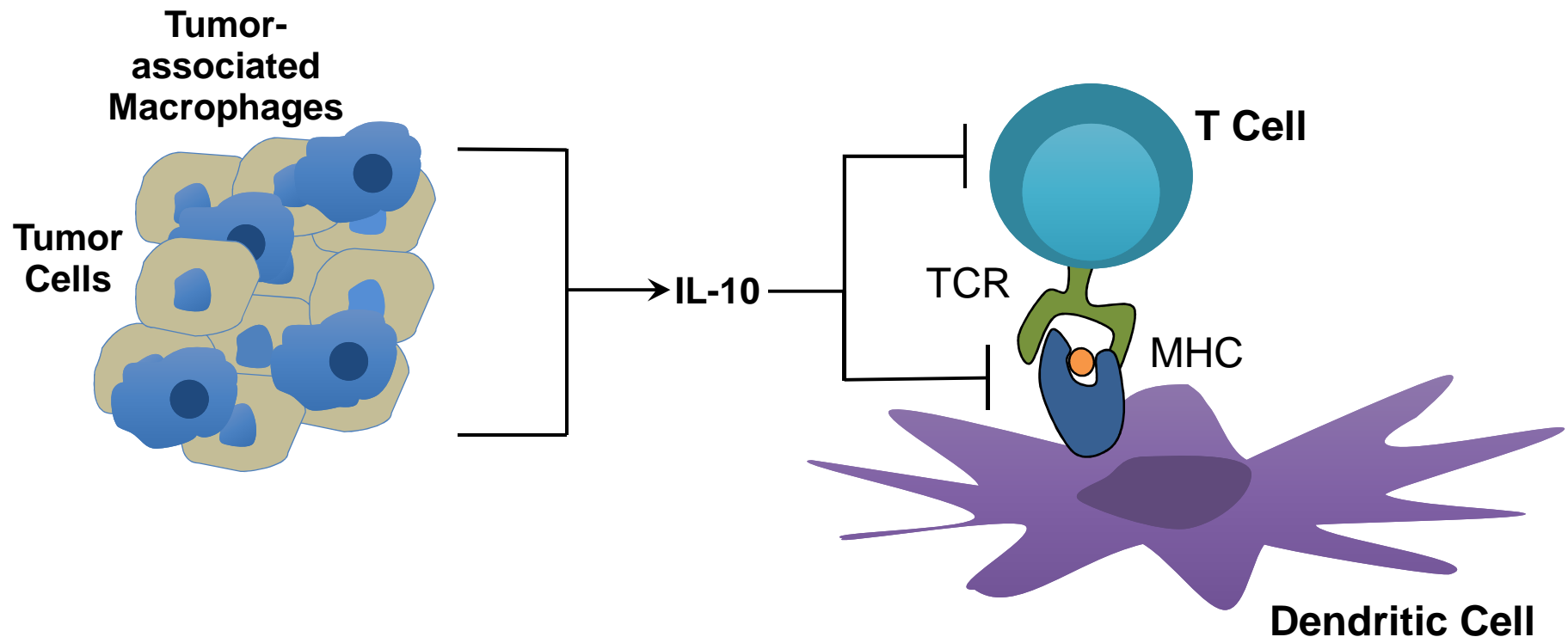
Dendritic Cell

* 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

Tumor Cells

IDO

↓ **Tryptophan**

Inhibition of CD8^{+} T Cell Proliferation

↑ **Kynurenine**

CD8^{+} T cell Apoptosis

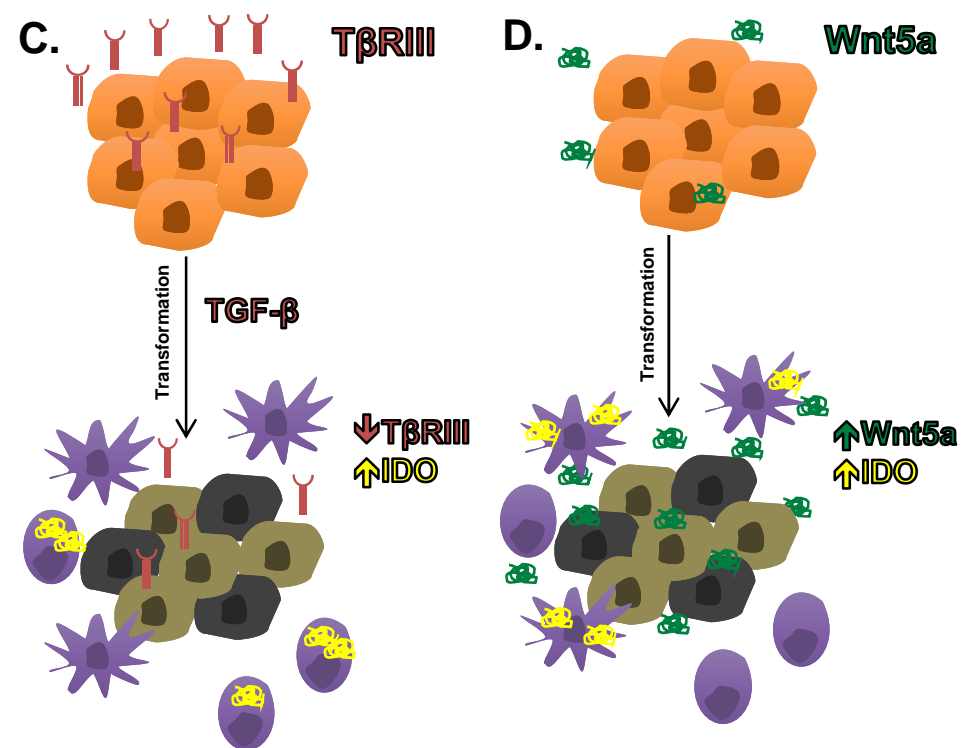Promotion of regulatory T cell development

Regulation of IDO During Tumorigenesis

- Pathways which drive carcinogenesis have also been shown to stimulate IDO expression both intrinsically (by the tumor itself) and extrinsically (within dendritic cells in the tumor microenvironment)
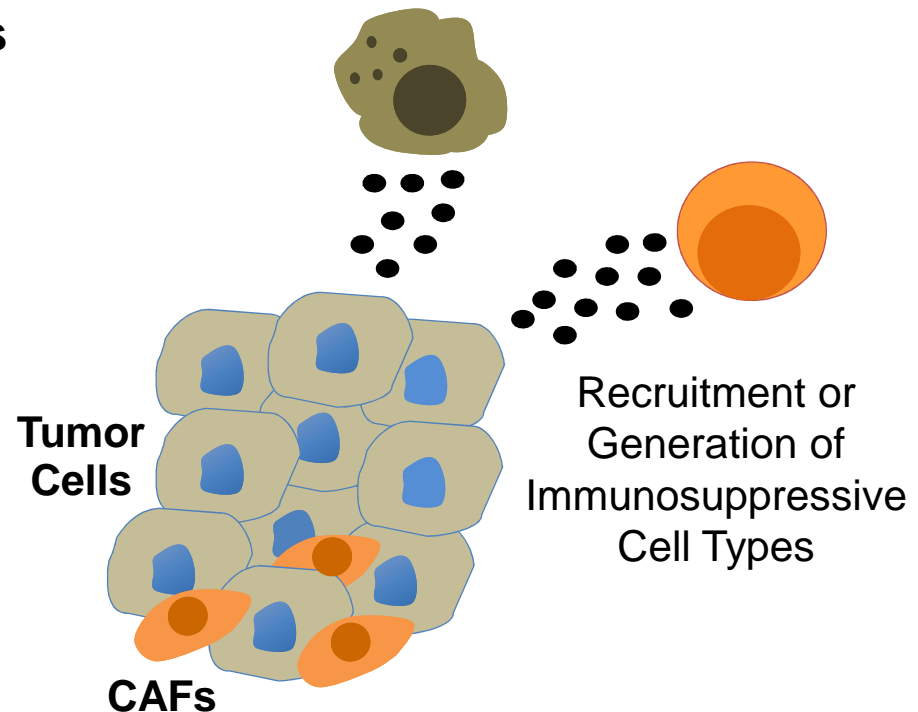
Intrinsic Regulation
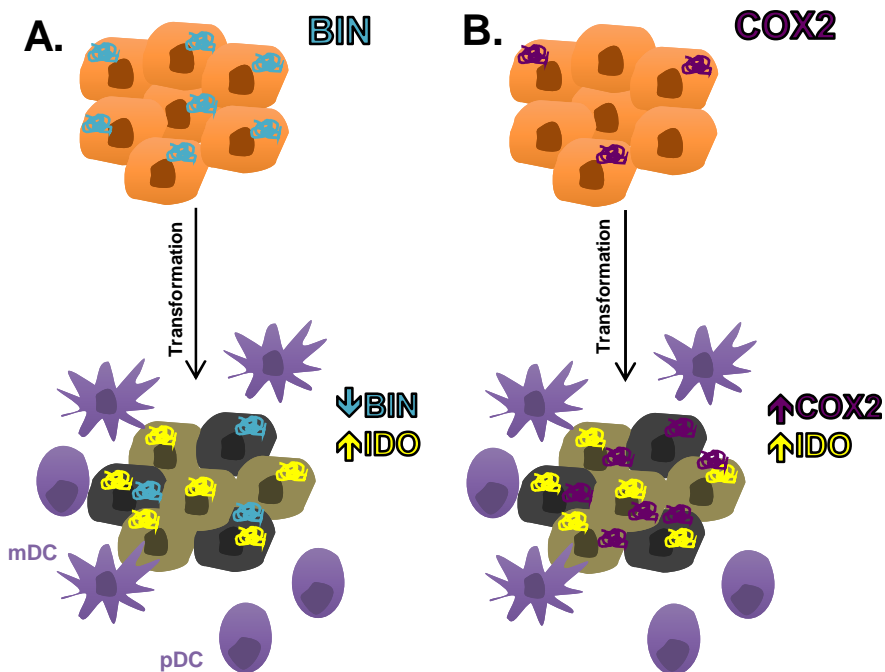
A. BIN

B. COX2

↓BIN
↑IDO

↑COX2
↑IDO

Extrinsic Regulation

C. TβRIII

D. Wnt5a

TGF-β

↓TβRIII
↑IDO

↑Wnt5a
↑IDO

mDC

pDC

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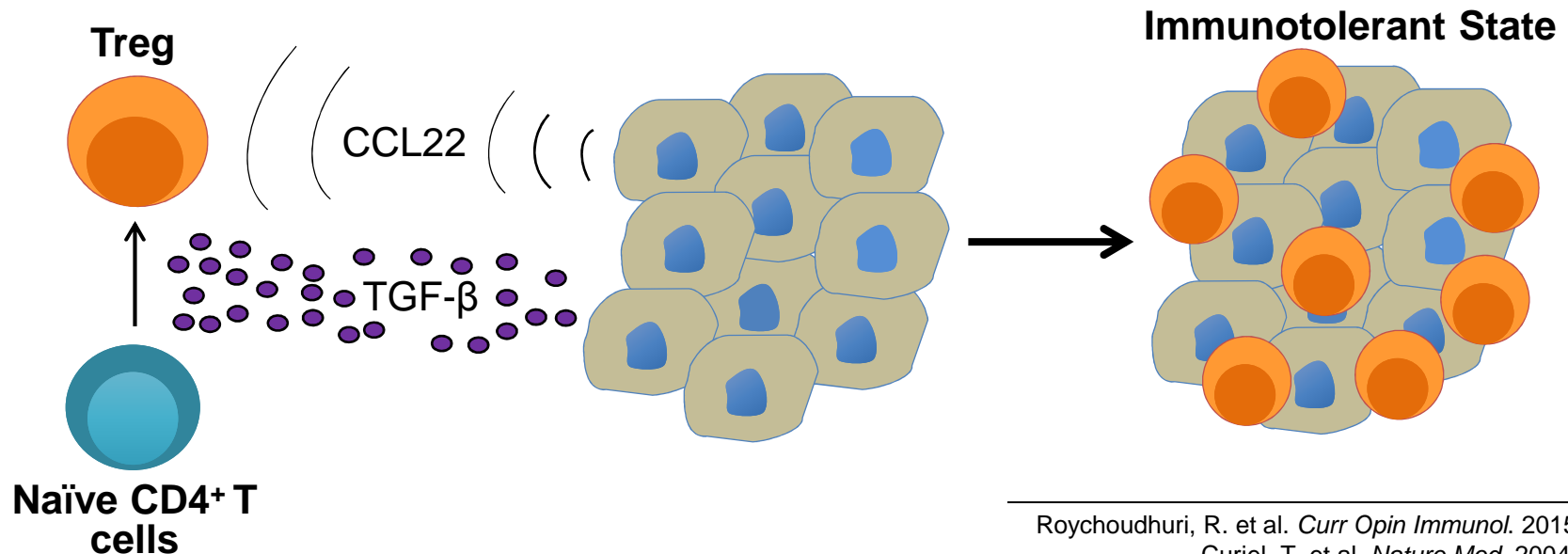
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Tumor Cells

CAFs

Recruitment or Generation of Immunosuppressive Cell Types

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

Treg

CCL22

TGF-β

Naïve CD4$^+$ T cells

Immunotolerant State

Roychoudhuri, R. et al. *Curr Opin Immunol.* 2015. 33: 101

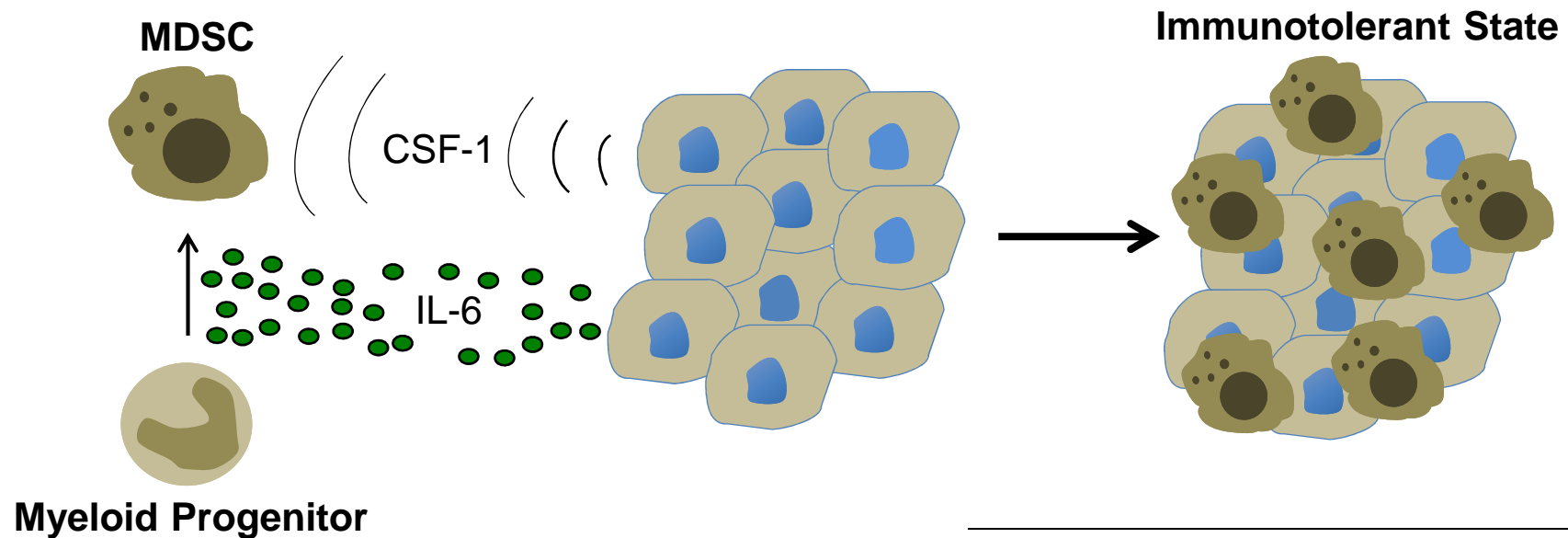Curiel, T. et al. *Nature Med.* 2004. 10: 942.

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.
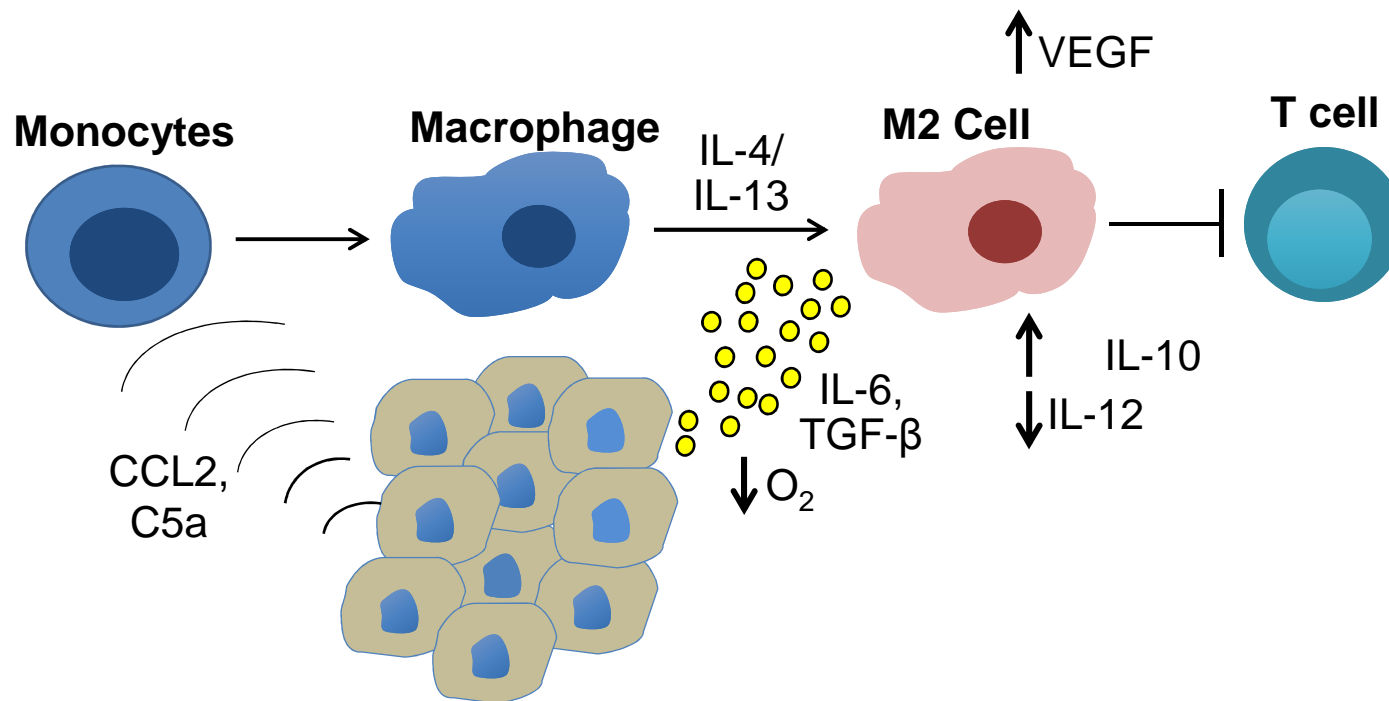
MDSCs: Myeloid-derived Suppressor Cells

- 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

  o 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)

  o Express high levels of TGF-β

MDSC

CSF-1

IL-6

Immunotolerant State

Myeloid Progenitor

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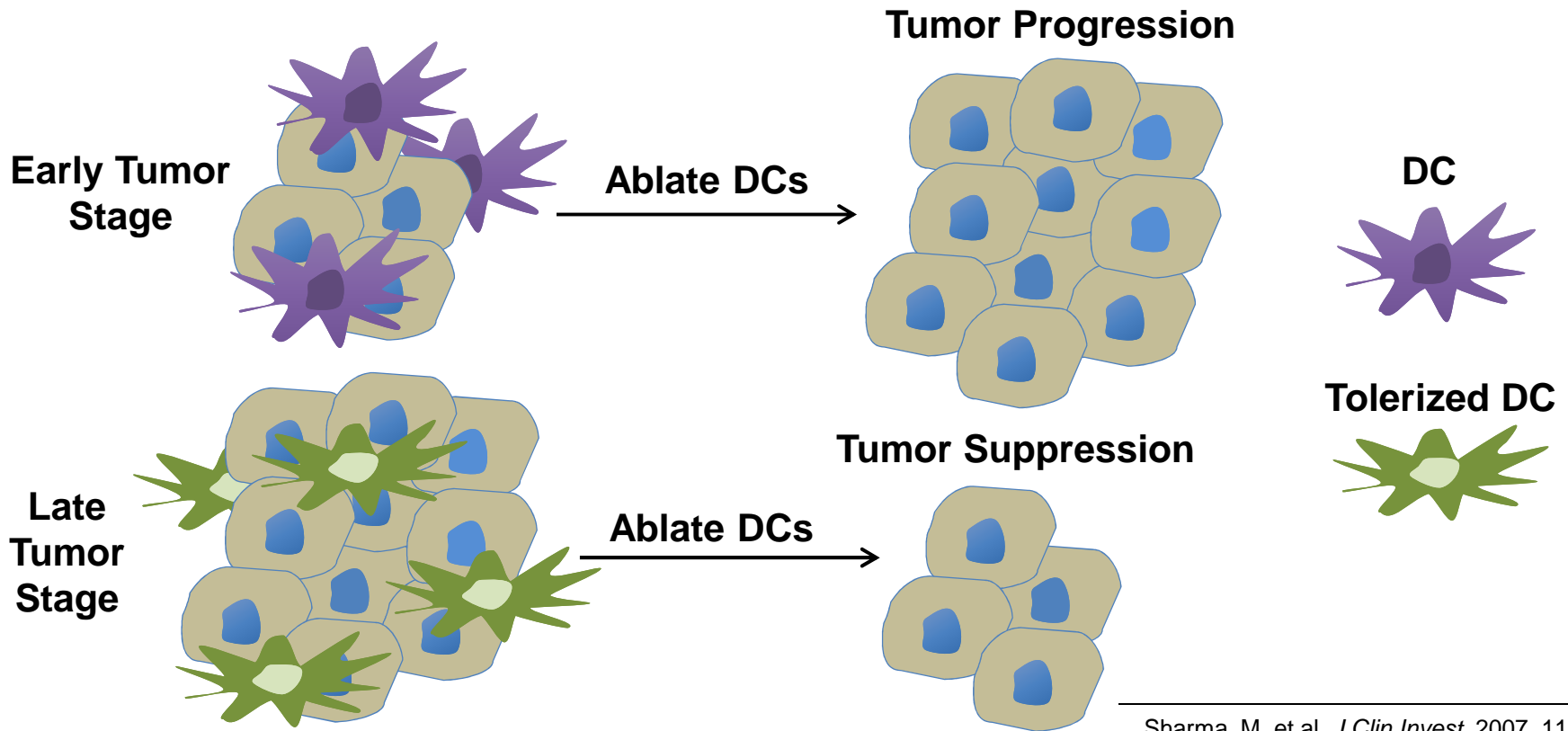
Sharma, M. et al. *J Clin Invest*. 2007. 117: 2570.
Scarlett, U. et al. *J Exp Med*. 2012. 209: 495.
Hurwitz, A. and Watkins, S. *Cancer Immunol Immunother*. 2012. 61: 289.

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)

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!

Learn more at www.sitcancer.org/2015

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.*

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