Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy

Modulation of the Immune Response

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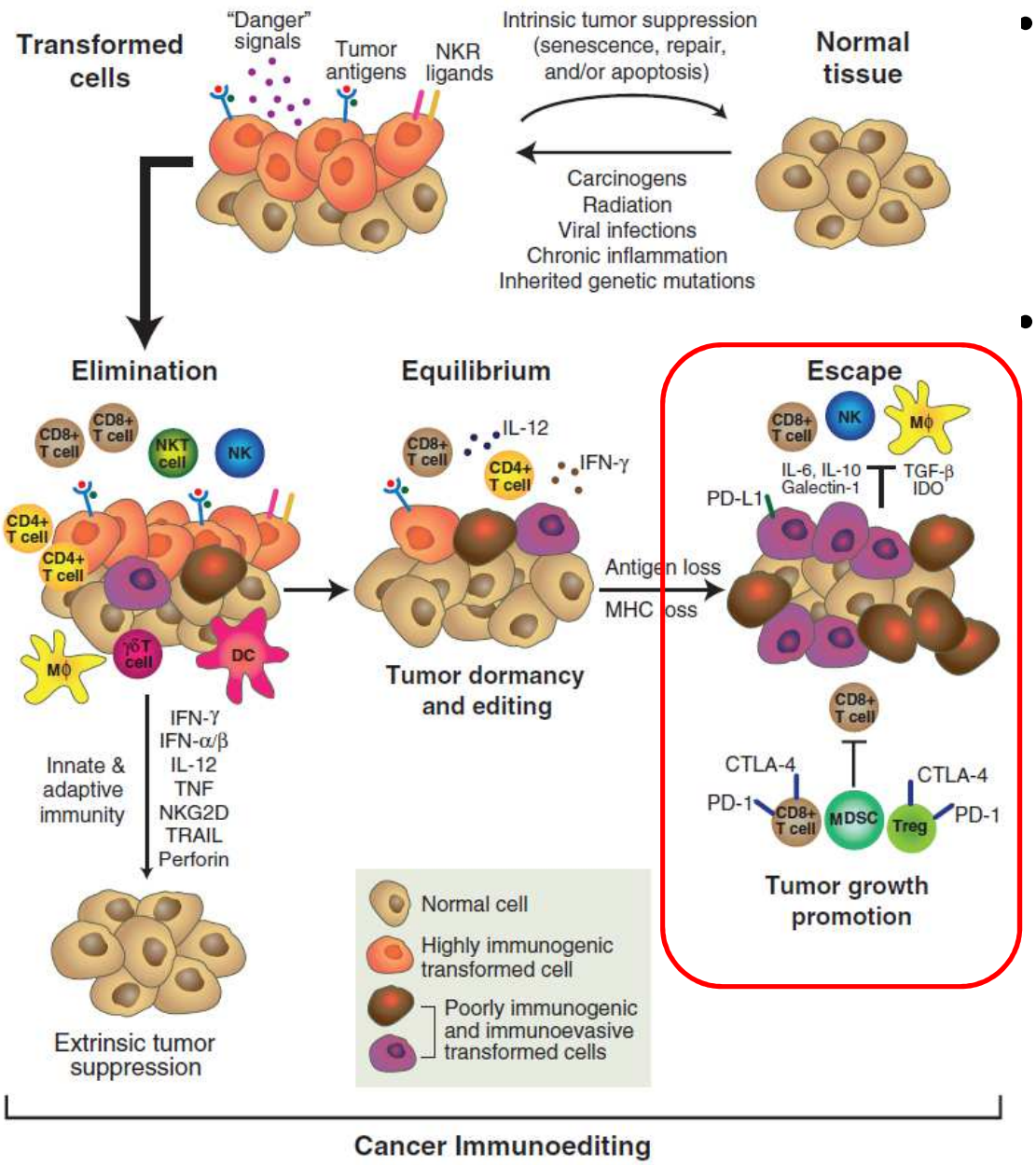
Charlotte, North Carolina

Disclosures

- Shareholder in Bellicum Pharmaceuticals, Inc.
- Collaborative investigator with MedPacto, Inc. and Hoffman-LaRoche

Challenges of Immunotherapy – Tumor Immune Evasion

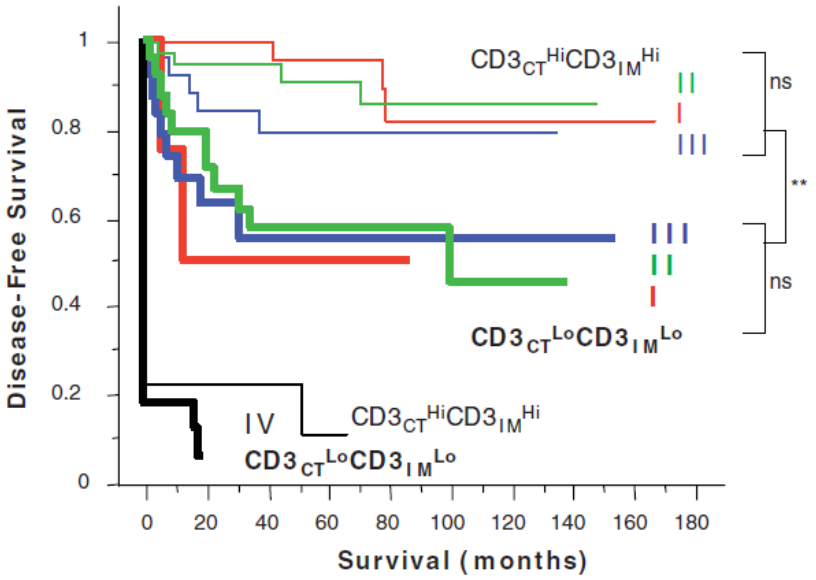


- Cancers evade detection by co-opting the negative regulatory mechanisms which modulate our immune system
- Understanding these complex regulatory networks will allow for the design of more effective strategies to augment the anti-tumor immune response

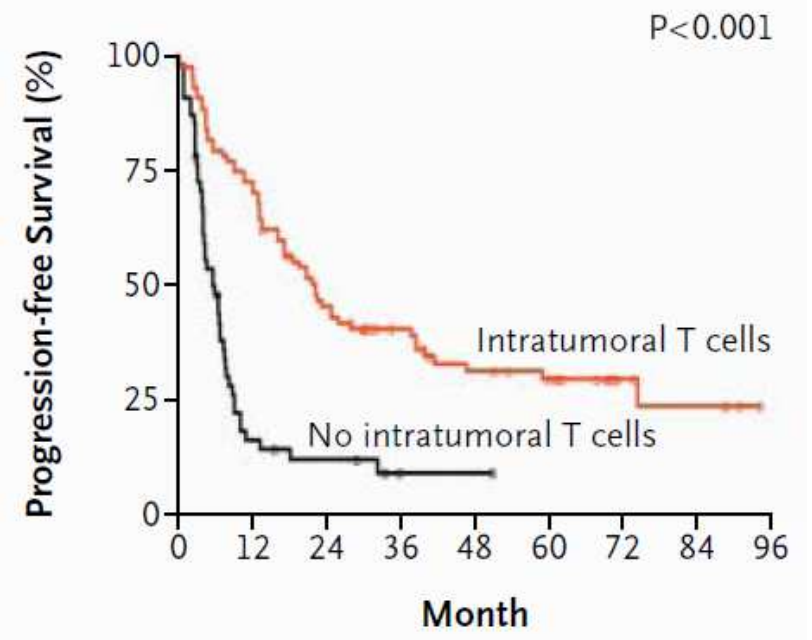
Schrieber, S. et al. *Science*. 2011. 331: 1565.

Immunologic Goals of Immunotherapy – T Cells Are Critical

Colon Cancer



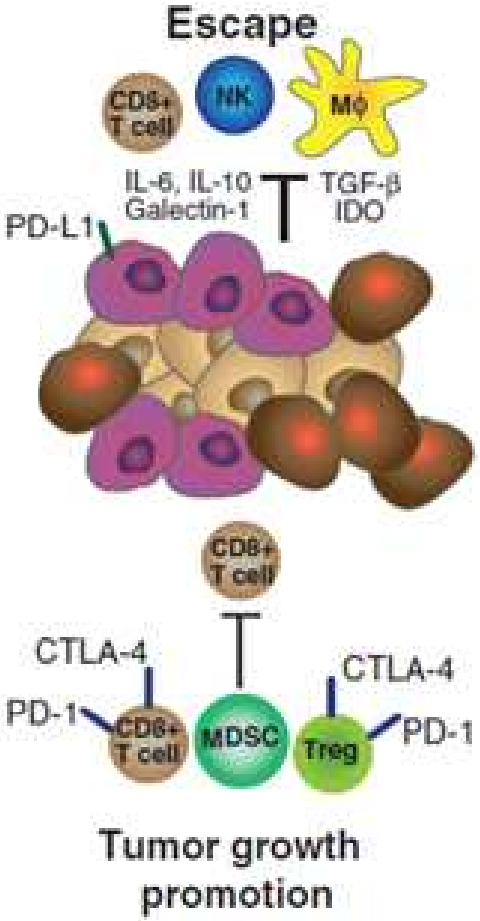
Ovarian Cancer

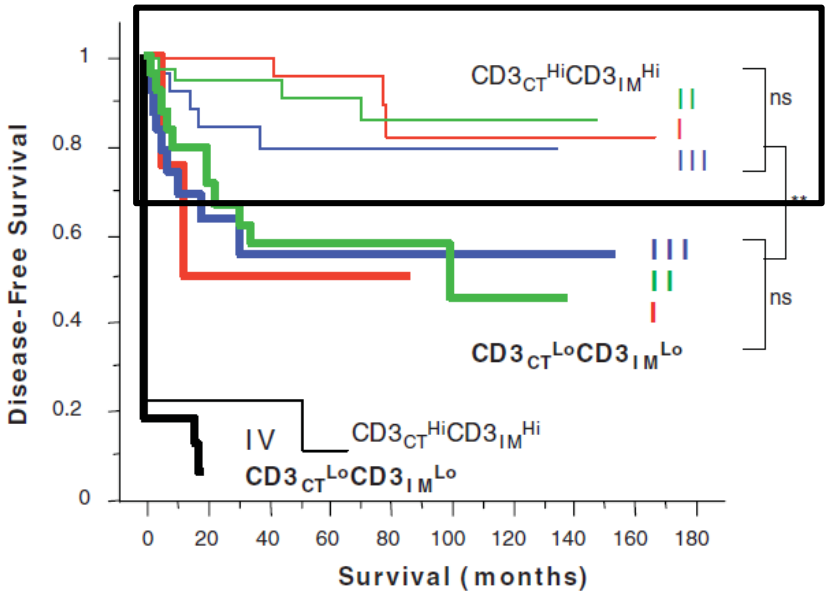


- Tumor-infiltrating lymphocytes correlates with progression-free survival in many solid tumors
- Both clinical and basic scientific data strongly implicate the T cell as playing a critical role in tumor destruction

Galon, J. et al. *Science*. 2006. 313: 1960.
Zhang, L. et al. *NEJM.* 2003. 348: 203.

Overcoming the Hurdles to Clinically Effective Immunotherapy





Modulation of the Immune Response in Cancer

Outline:

I. Dendritic Cell (DC) Maturation/Activation

- A. Antigen Presentation Machinery of DCs
- B. Toll-like receptors (TLRs)

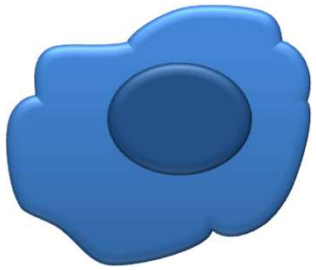
II. DC-dependent T Cell Activation in the Lymph Node

- A. T Cell Co-stimulation
- B. CTLA-4
- C. CD40/CD40L Signaling Axis
- D. IL-2

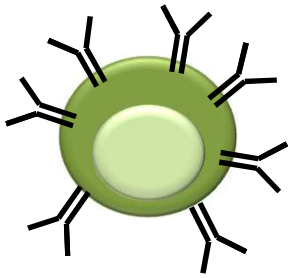
III. T Cell Effector Function in the Peripheral Tissues

- A. Immune Checkpoints in the Tumor Microenvironment
- B. Other Tumor-mediated Immune Evasion Mechanisms

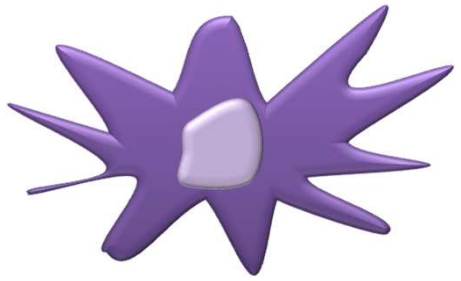
Antigen Presenting Cells (APCs)



Macrophage



B Lymphocyte



Dendritic Cell

- DCs are antigen presenting cells that are capable of stimulating antigen specific naïve T cell activation via the expression of many critical molecules, including the B7 co-stimulatory molecules and the IL-12 cytokine

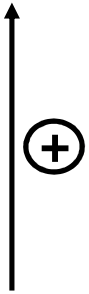
- DCs are the most potent APC in the immune system and the only APC capable of efficient antigen cross-presentation

Dendritic Cell Maturation

Immature Dendritic Cell

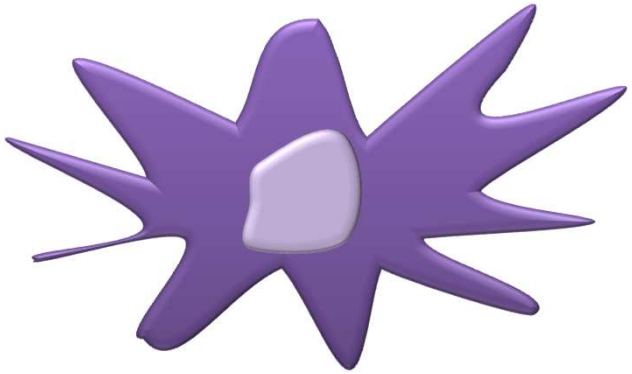
Location: Peripheral Tissues

Function: Antigen Uptake



Danger Signals

- Exogenous Danger Signals (PAMPs, e.g. LPS)
- Endogenous Danger Signals (heat-shock proteins, uric acid, HMGB1)

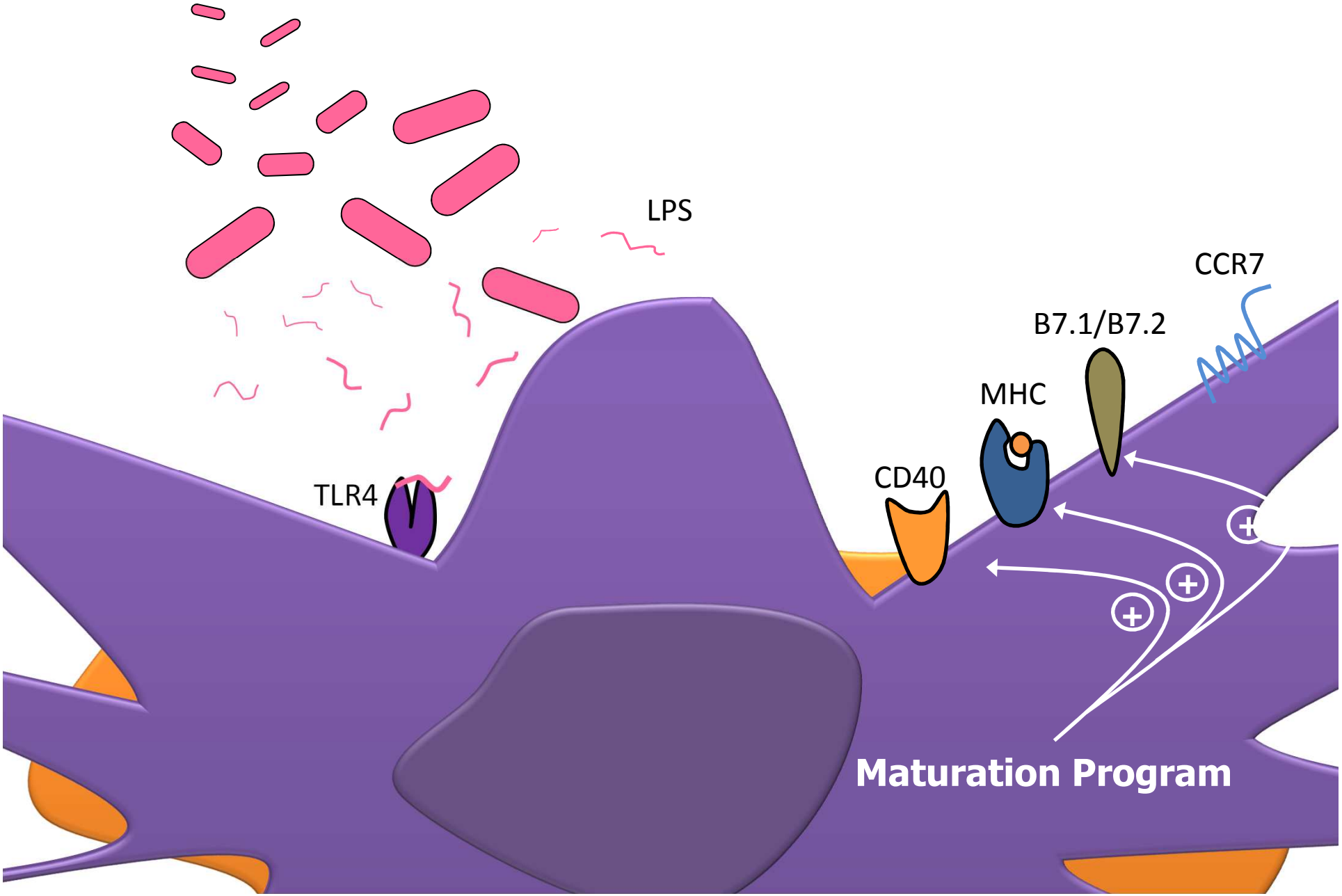


Mature Dendritic Cell

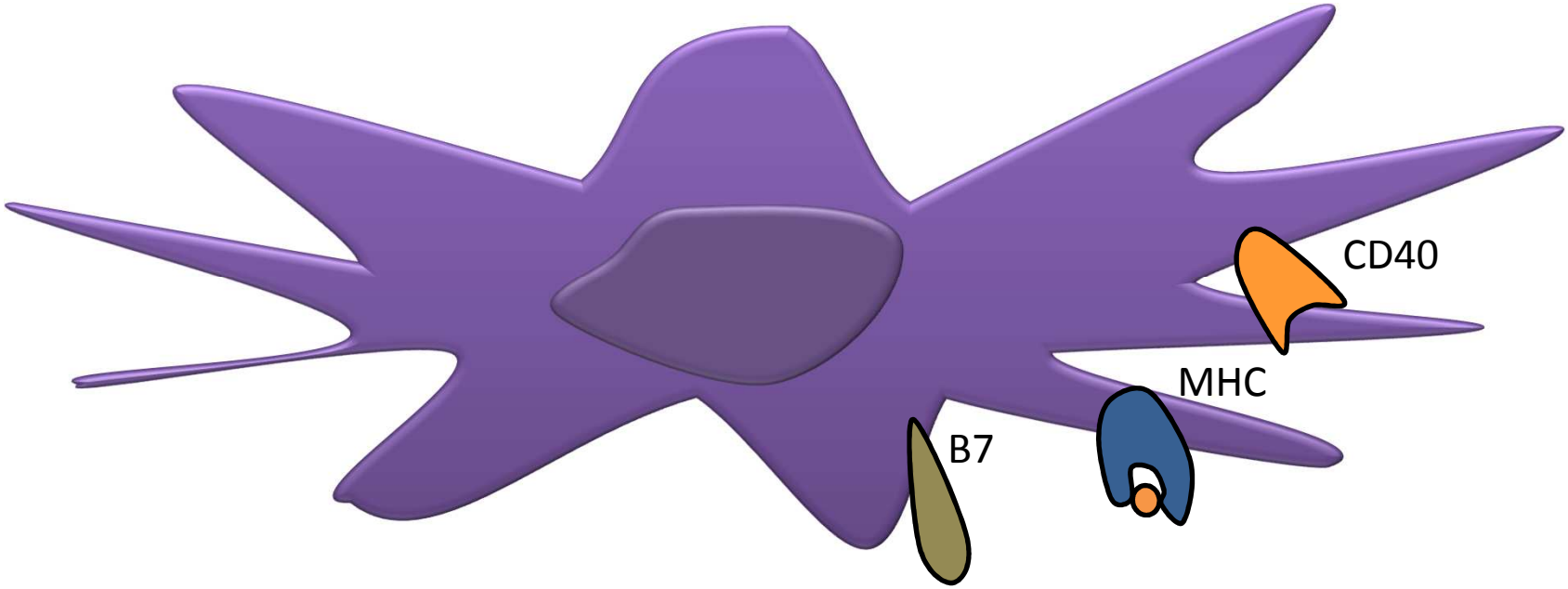
Location: Lymphoid Tissues

Function: T Cell Stimulation

Dendritic Cell Maturation



Molecular Machinery of Antigen Presentation



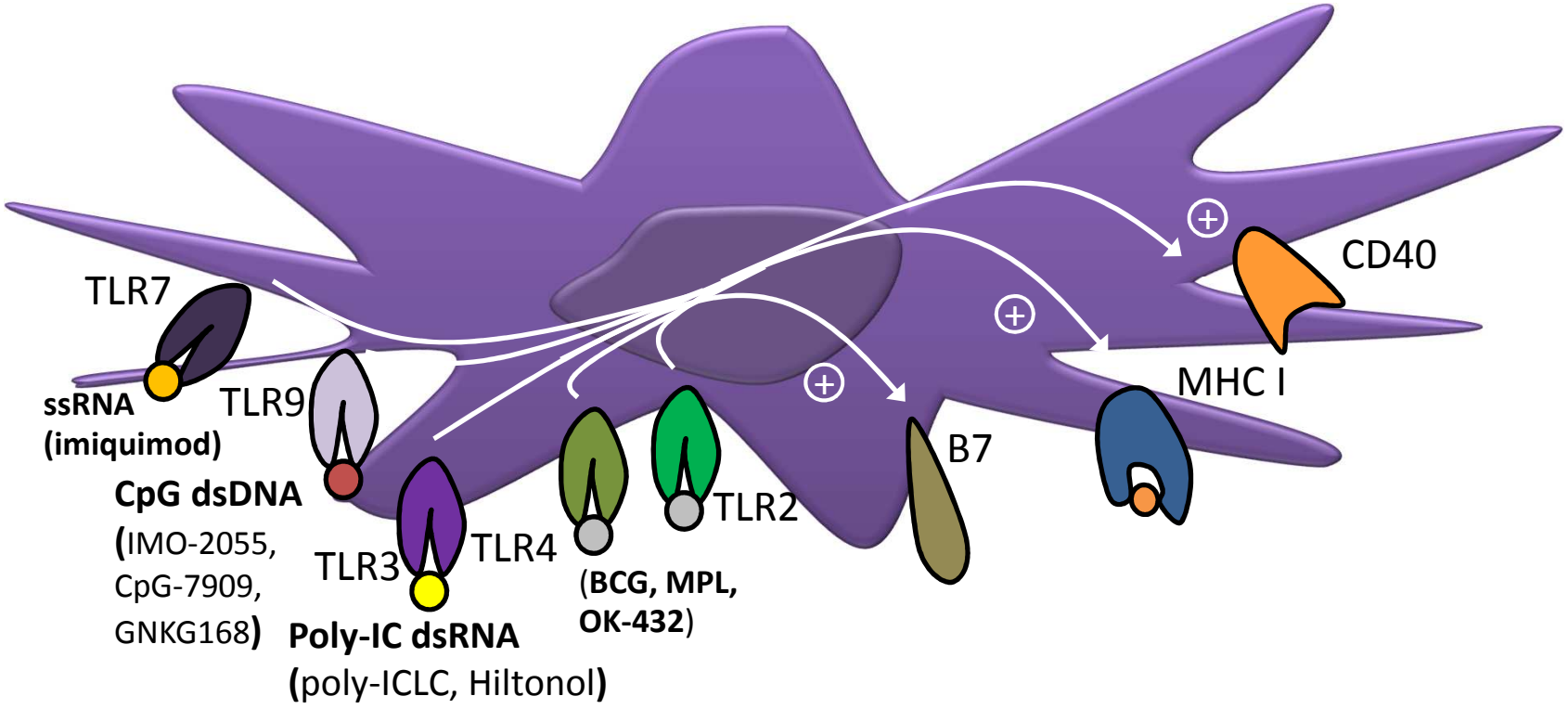
Major Histocompatibility Complex

- Form complexes with digested peptide antigens in the ER
- Class I MHC: presents antigens to $CD8^+$ T cells; Class II MHC: presents antigens to $CD4^+$ T cells

Co-stimulatory Molecules

- B7.1/B7.2 (CD80/CD86) bind to CD28 to promote T cell activation
- CD40 serves to upregulate several other co-stimulatory molecules, antigen-presenting molecules, and cytokines including IL-12

Promoting DC-mediated T Cell Activation : TLRs



- Induction of DC maturation by administration of synthetic TLR agonists
- Therapeutic results have been mixed
  - Induction of IL-10, an immunosuppressive cytokine, as well as PD-L1
- Currently undergoing testing in several early phase clinical trials in combination with immune checkpoint inhibitors and vaccines

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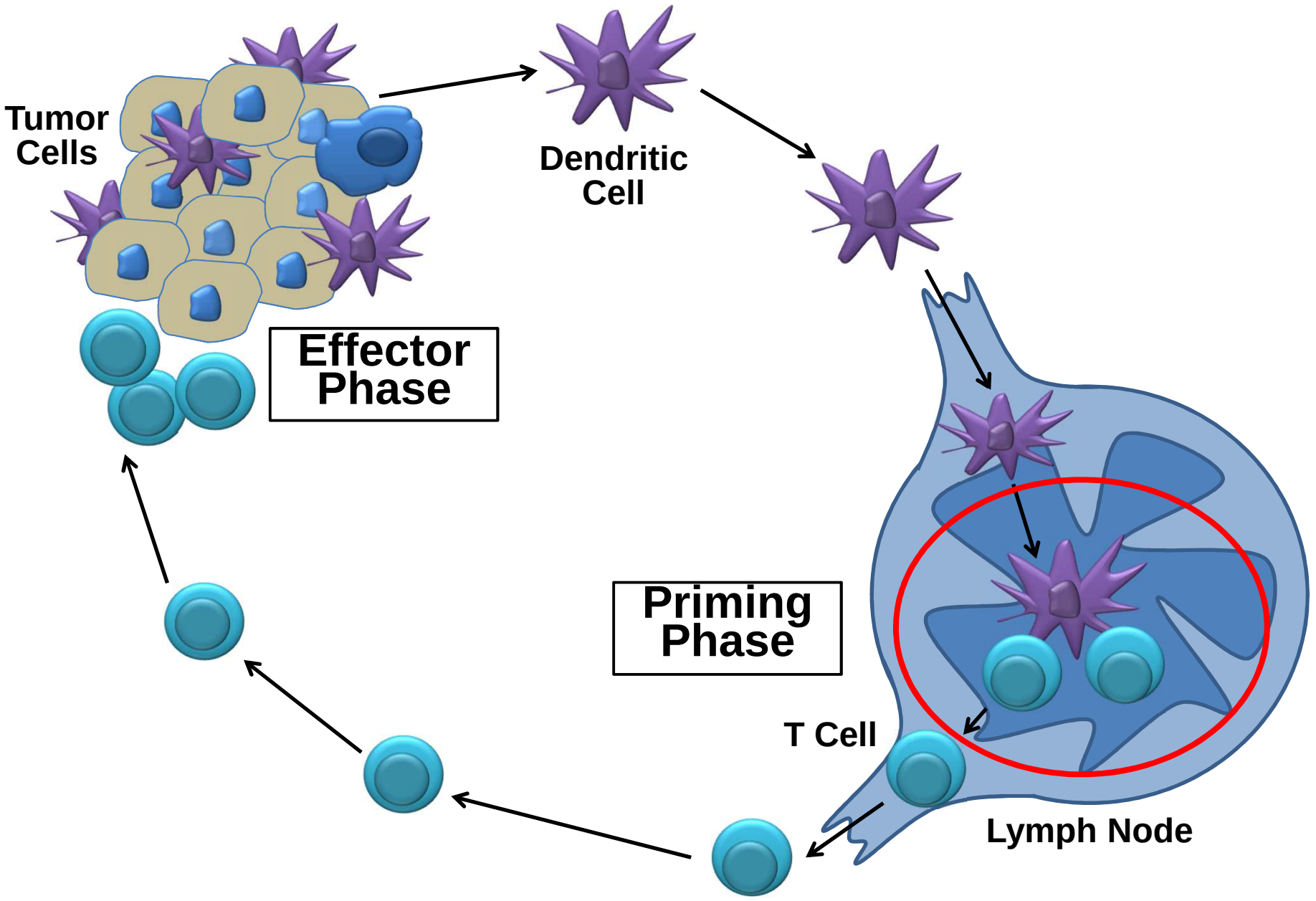
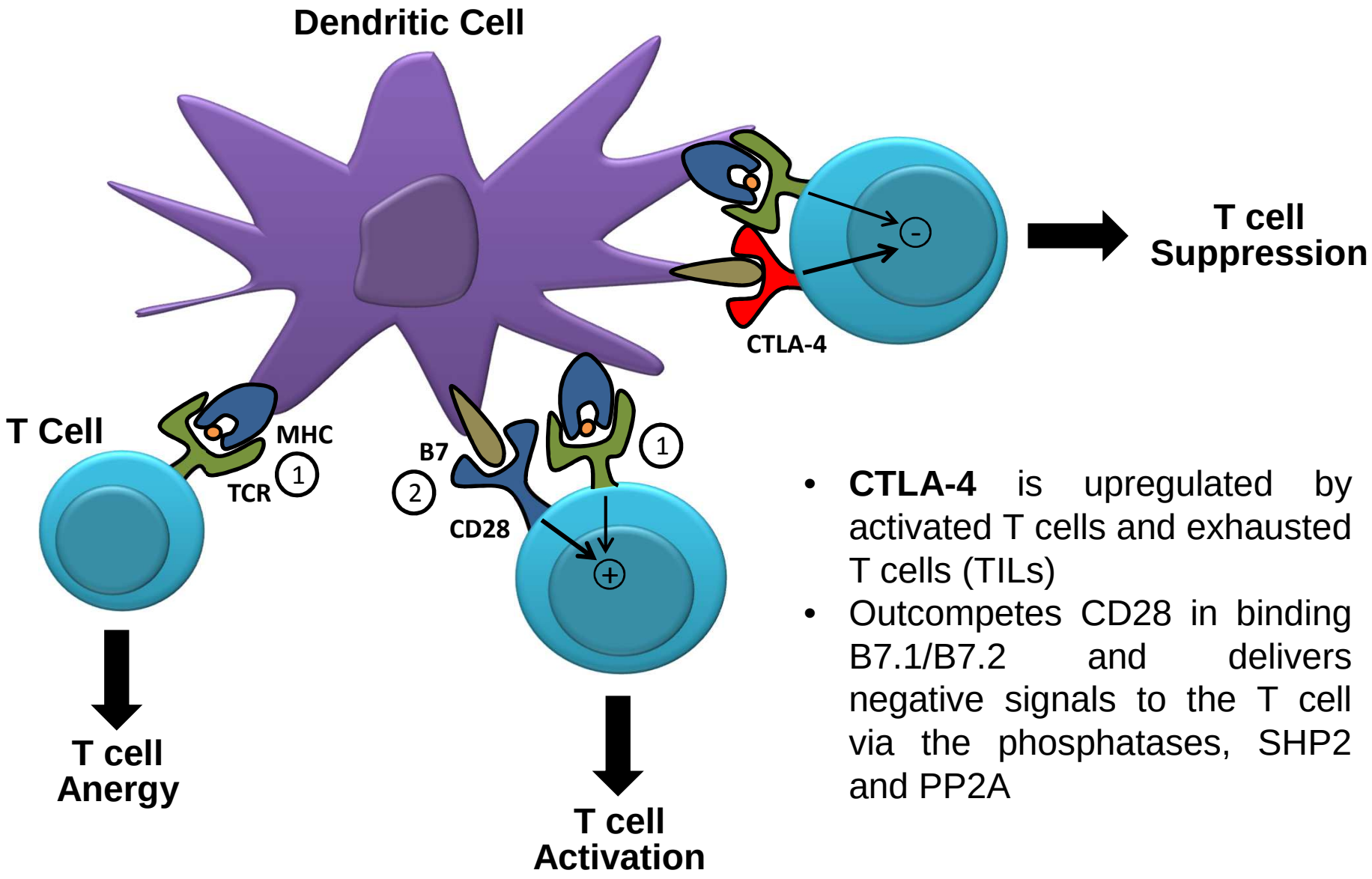
T Cell Priming in the Lymph Node Microenvironment

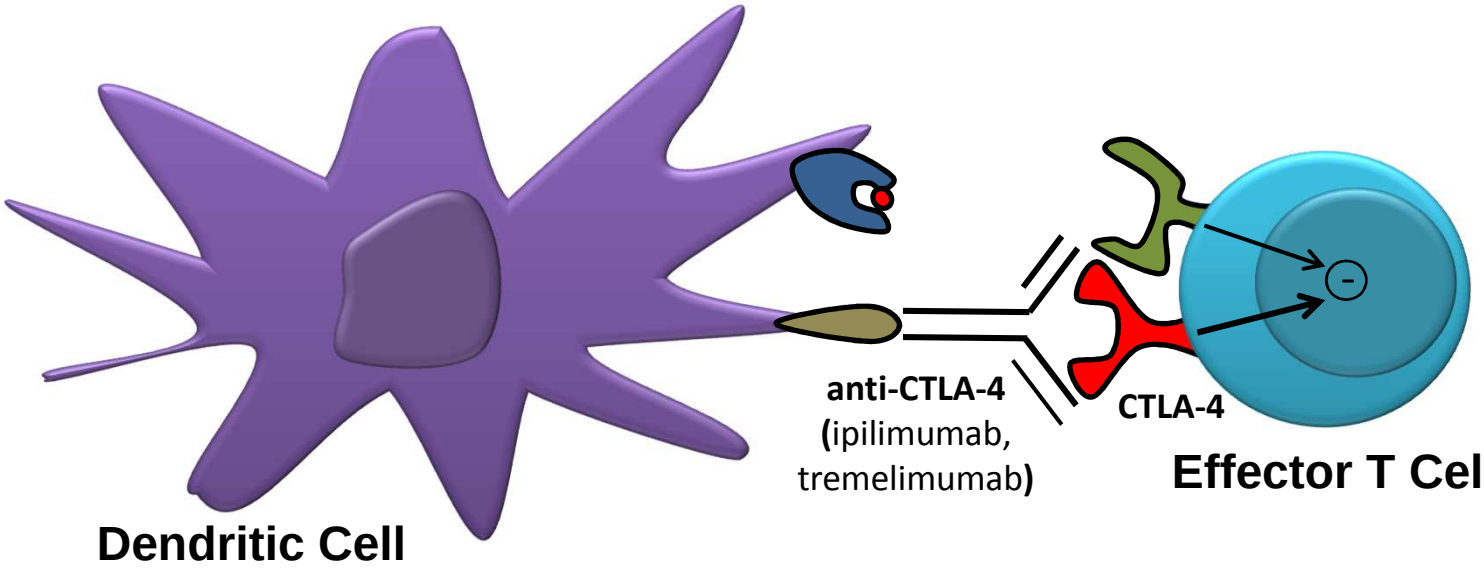


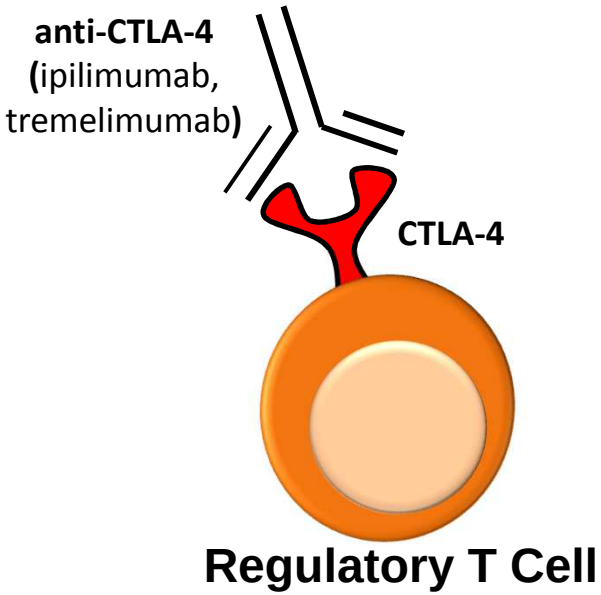
Dendritic Cell-mediated T cell Activation in the Lymph Node



- **CTLA-4** is upregulated by activated T cells and exhausted T cells (TILs)
- Outcompetes CD28 in binding B7.1/B7.2 and delivers negative signals to the T cell via the phosphatases, SHP2 and PP2A

Promoting T Cell Activation : CTLA-4

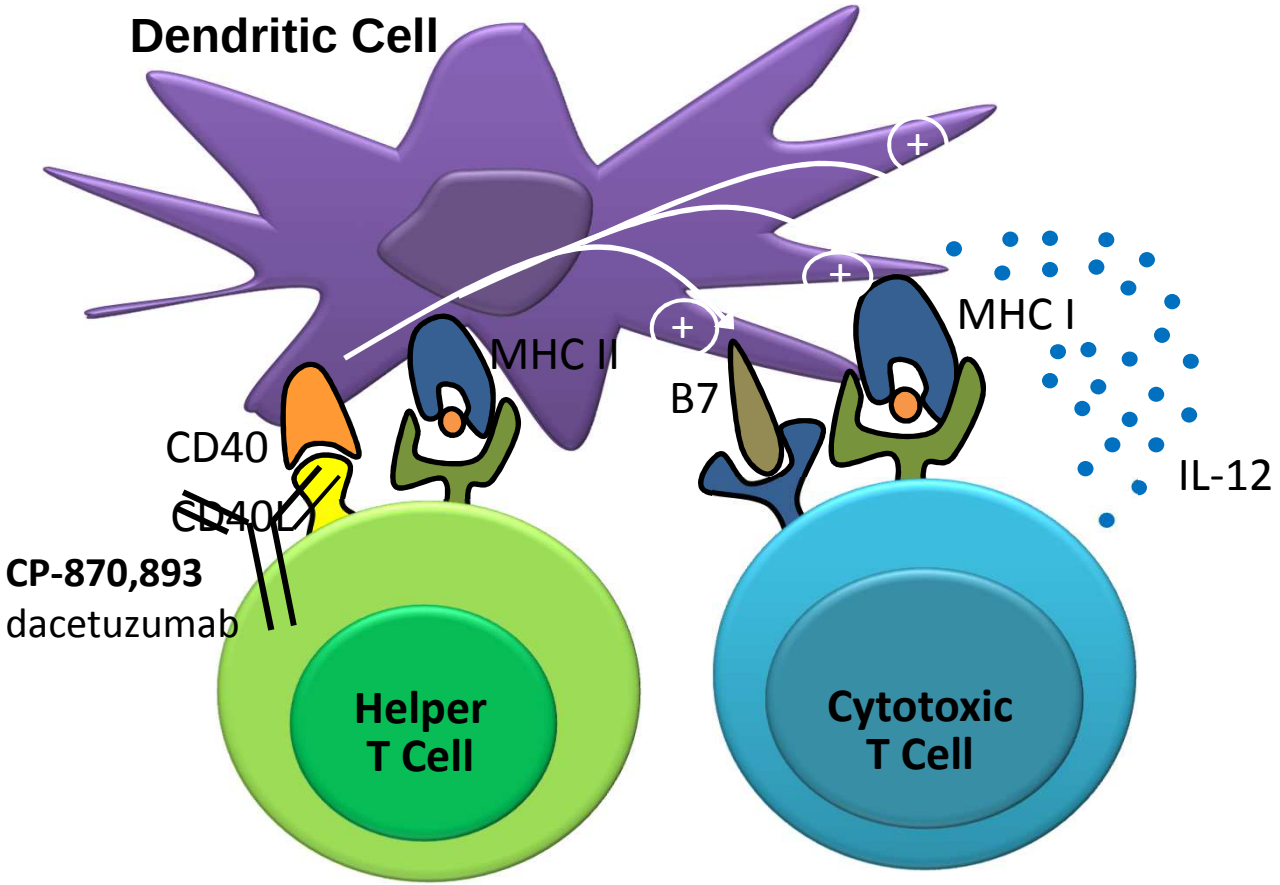




Mechanisms of anti-CTLA-4 mAb Therapy

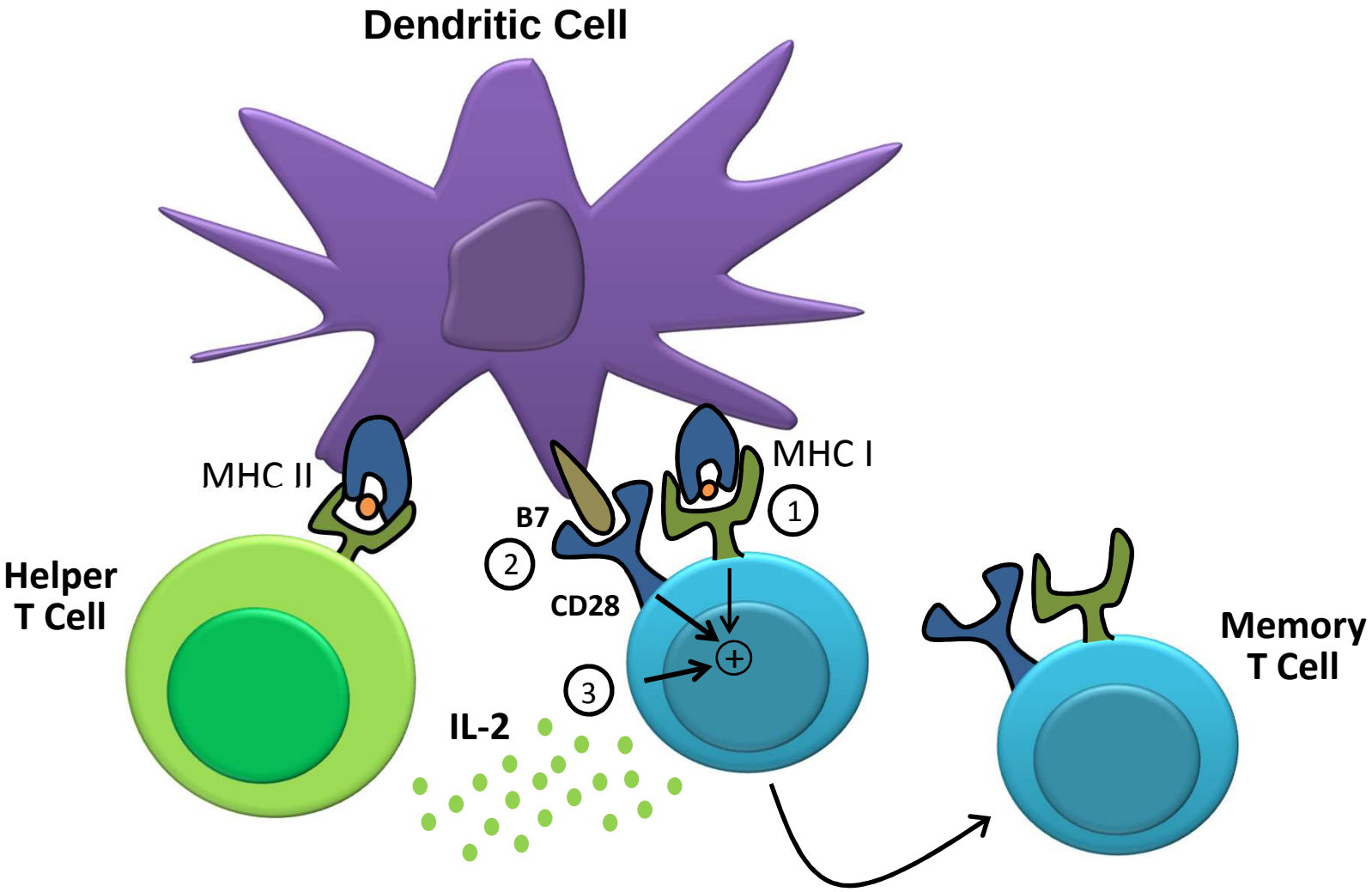
- Enhancement of effector T cell activation (primarily $CD4^+$ T_{Helper} cells)
- Depletion of regulatory T cell populations
- Further discussion covering CTLA-4 blockade will be led by Dr. Asim Amin

Promoting DC-mediated T cell Activation: CD40



- $CD4^+$ T_{Helper} cells license DCs to activate $CD8^+$ cytotoxic T cells via CD40L-CD40 stimulation
- Expression induced during DC maturation; potently stimulates co-stimulatory molecule and pro-inflammatory cytokine expression
- Anti-CD40 agonistic antibody is in clinical trial testing in combination with chemotherapy and anti-CTLA-4 blockade

Promoting T Cell Activation : IL-2



- Induces T cell and NK cell proliferation and cytolytic activity
- Promotes T cell survival and memory T cell development

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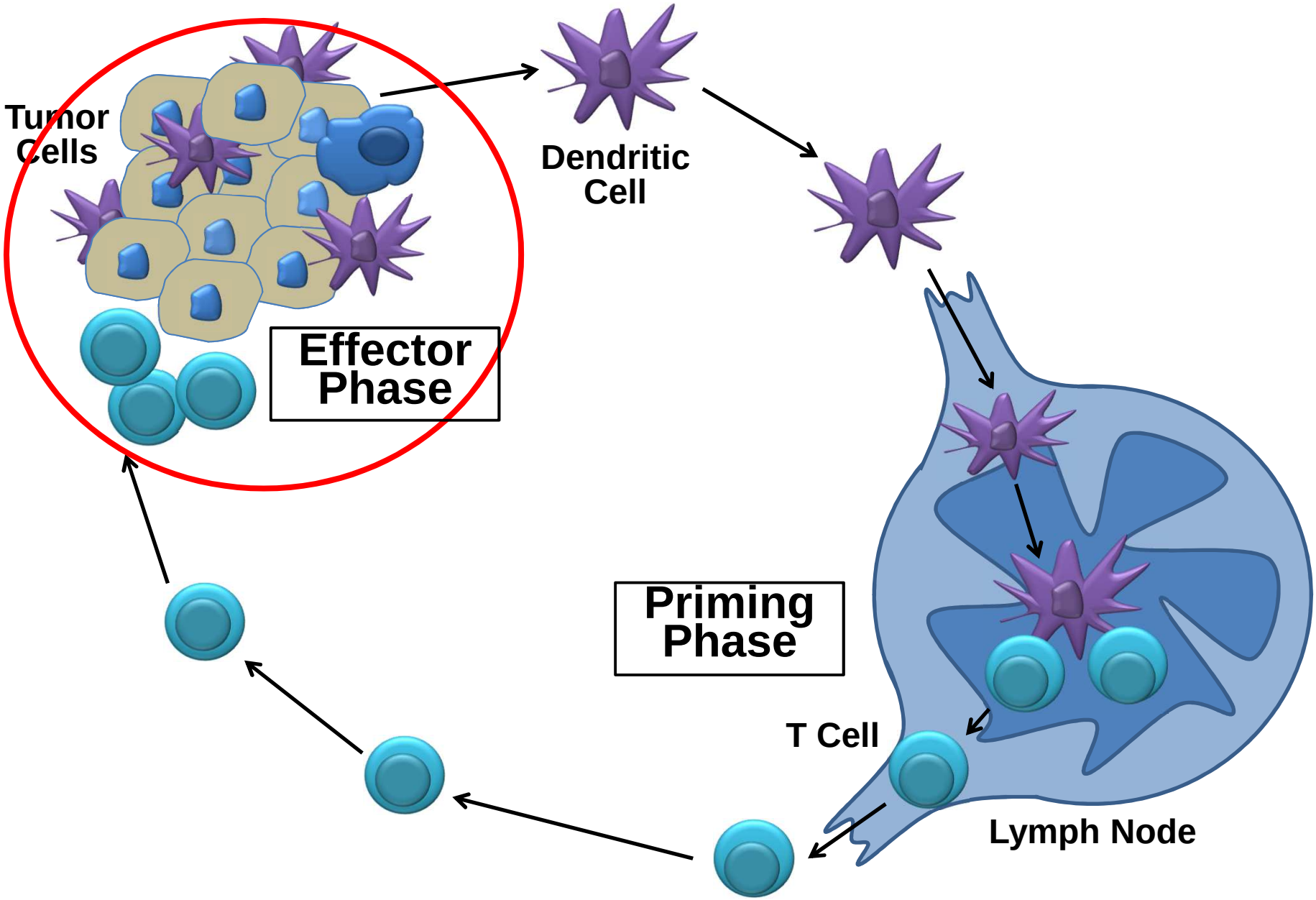
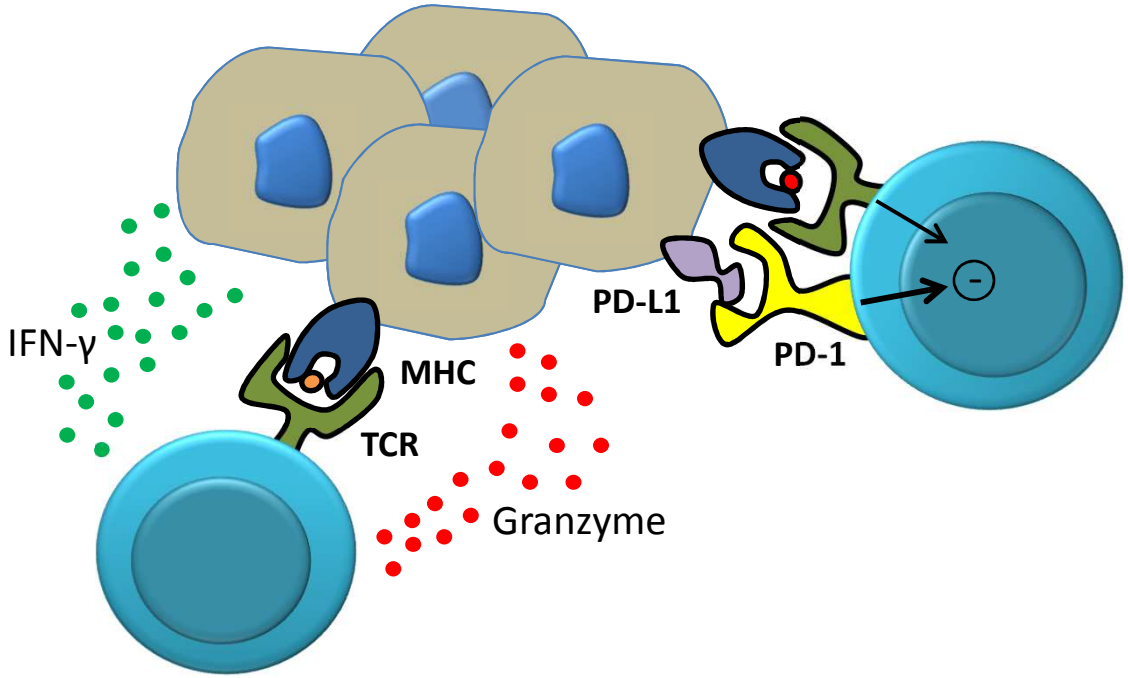
T Cell Effector Function in the Tumor Microenvironment

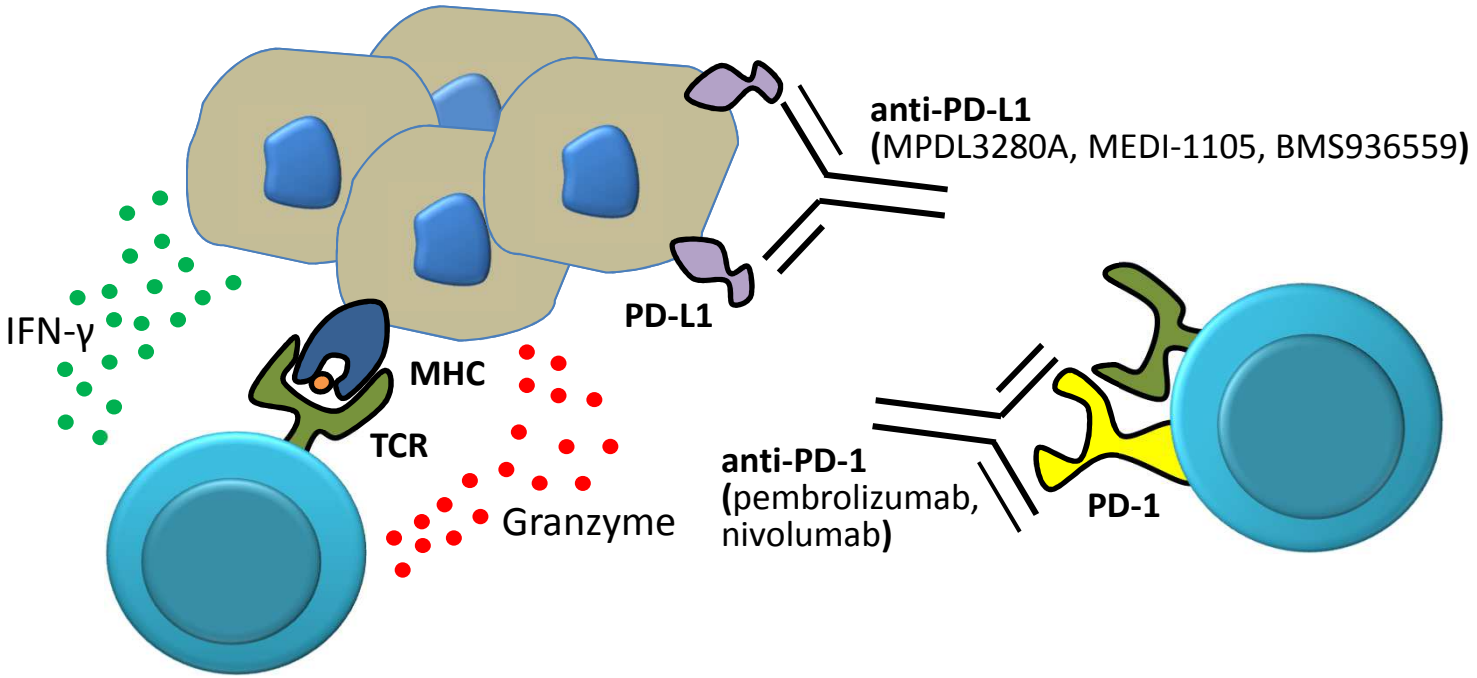


T Cell-mediated Tumor Cell Killing in Peripheral Tissues



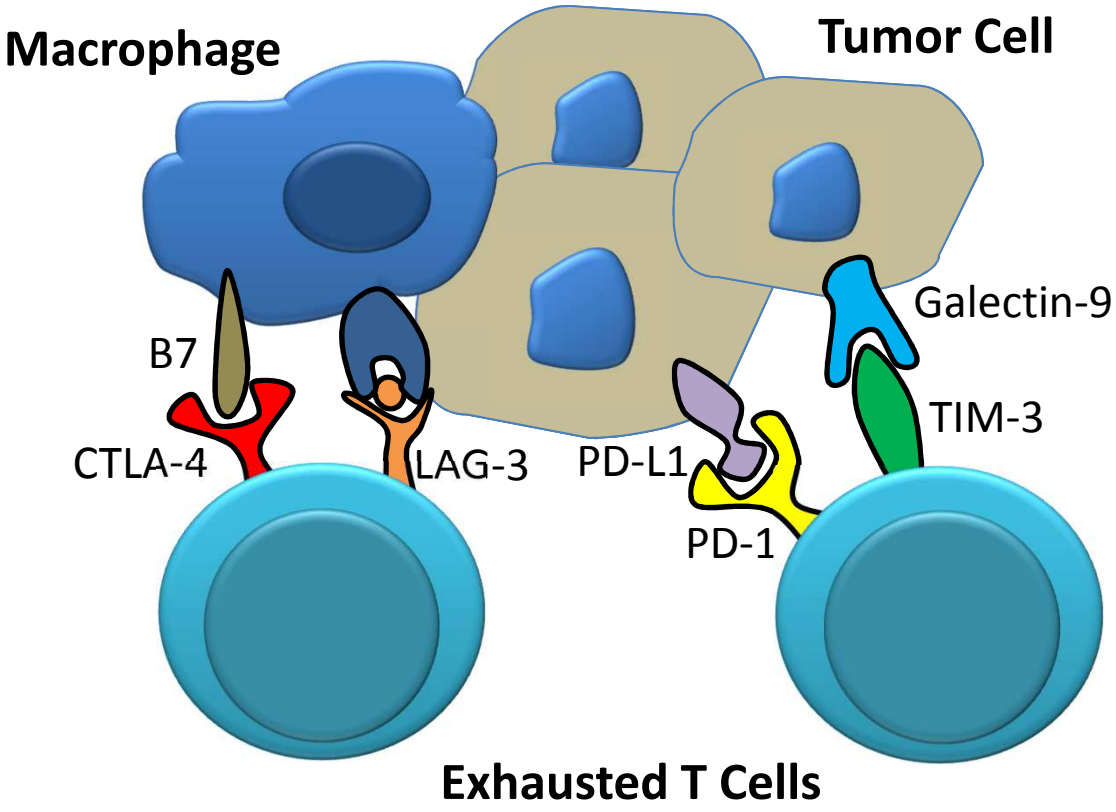
- PD-L1 expression regulated via two general mechanisms
  1. Innate immune resistance: oncogenic signaling pathways
  2. Adaptive immune resistance: upregulated by IFN-γ in peripheral tissues
- PD-1 expression is upregulated by activated T cells and anergic or exhausted T cells
- PD-1 functions via the SHP2 phosphatase to inhibit downstream activation signals elicited by the TCR

Promoting T Cell Killing in the Peripheral Tissues: PD-1

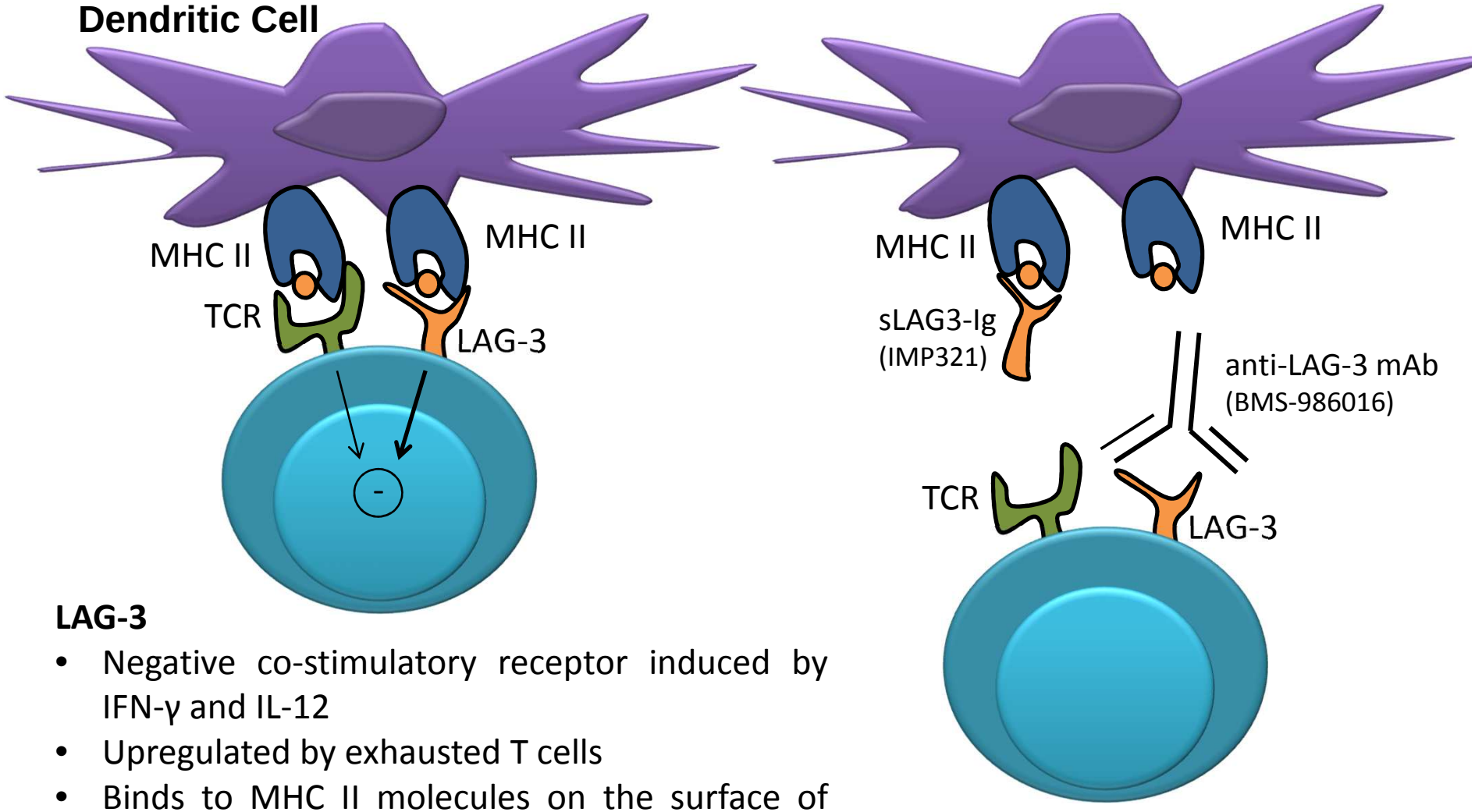


- Further discussion covering PD-1 blockade will be led by Dr. John Powderly

Multiple Immune Checkpoints Exist in the Tumor Microenvironment



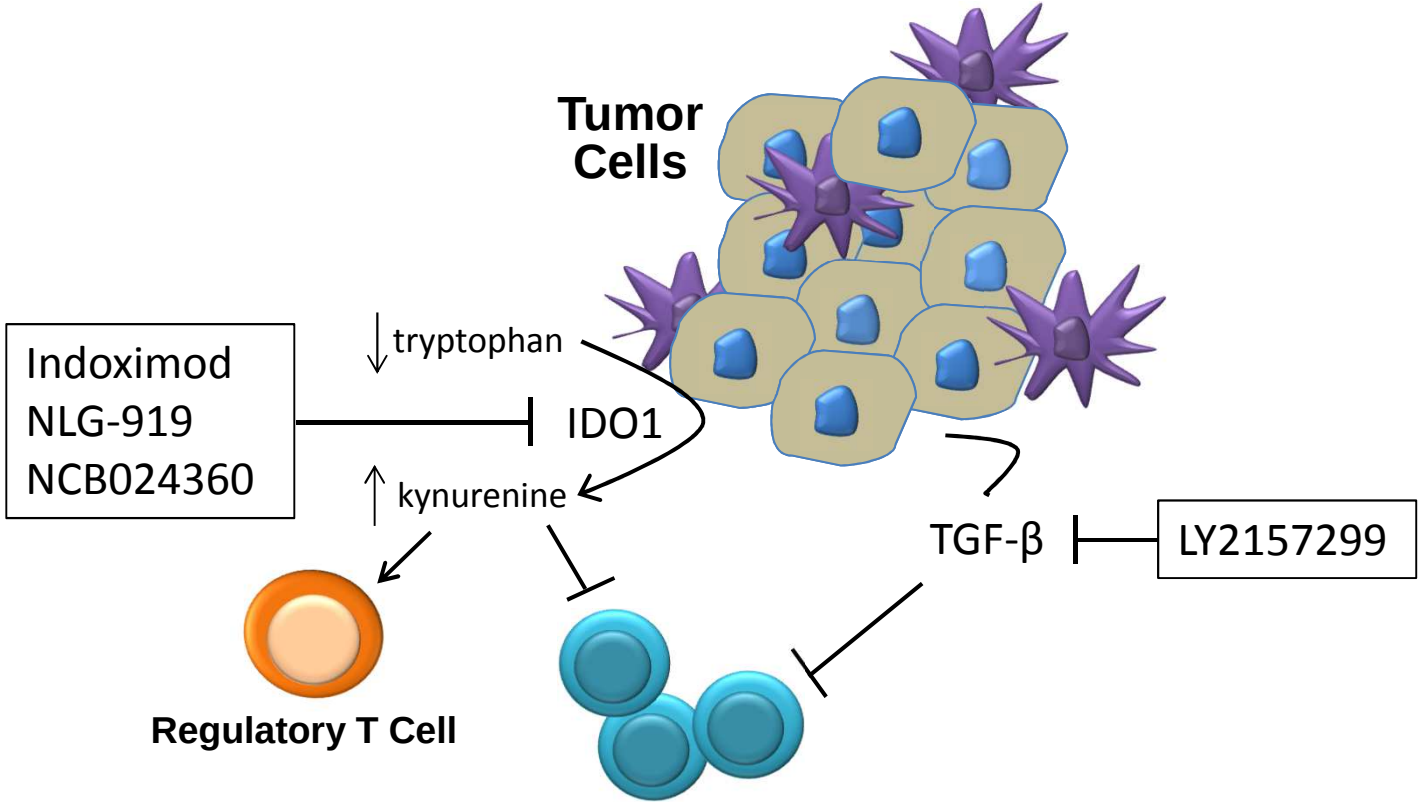
Promoting T Cell Killing in the Peripheral Tissues: LAG-3



LAG-3

- Negative co-stimulatory receptor induced by IFN-γ and IL-12
- Upregulated by exhausted T cells
- Binds to MHC II molecules on the surface of tumor-infiltrating DCs and macrophages
- Dual blockade with anti-PD-1 mAb shown to be synergistic in pre-clinical studies; Phase I studies are ongoing

Other Tumor-mediated Immune Evasion Mechanisms



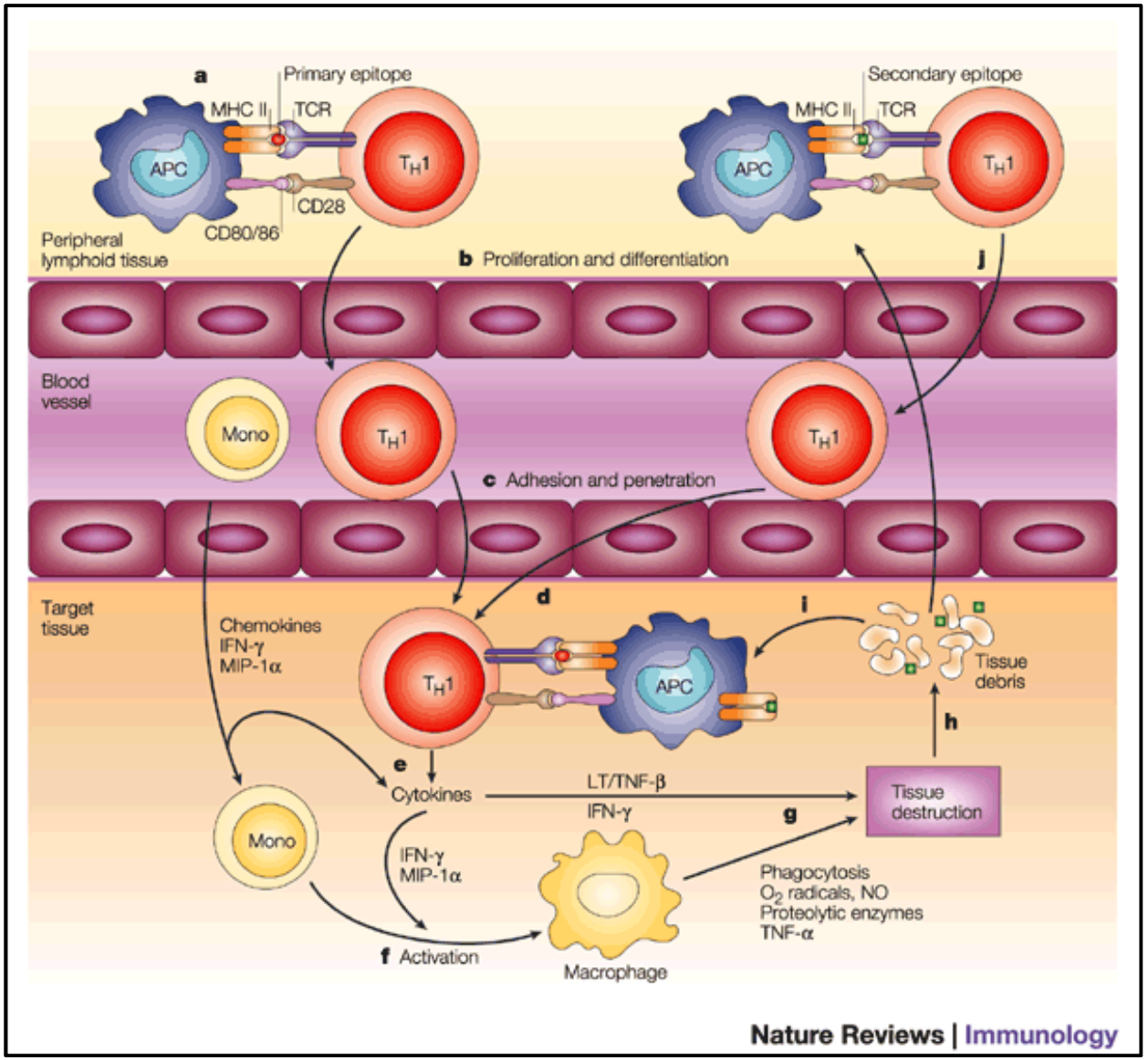
Indoleamine 2,3-dioxygenase (IDO)

- Catalyzes the conversion of tryptophan to the kynurenines
- Suppresses T cell proliferation/activation
- Promotes regulatory T cell differentiation and activation
- Upregulated by tumor cells and DCs within the tumor microenvironment

Transforming Growth Factor-β (TGF-β)

- Pleiotropic immunosuppressive cytokine
- Upregulated by many cancer types

Epitope Spreading is Necessary for the Generation of Clinically Meaningful Responses to Cancer Immunotherapy



Vanderlugt, C. and Miller, S. *Nature Rev Immunol.* 2002. 2: 85.

Next Steps

- Defining functionally synergistic therapeutic combinations involving both immunotherapeutic and chemotherapeutic agents

- Establishment of predictive biomarkers for individual immunotherapeutic agents in different cancer types

- Understanding mechanisms of primary and acquired resistance to individual immunotherapeutic agents

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