

Advances in Cancer Immunotherapy

Immunology 101 for the Non-Immunologist

Esteban Celis, M.D., Ph.D.
ecelis@gru.edu

Disclosures

Consulting Fees

ViaMunne, Inc.

Contracted Research

Vasculox, Inc.

Hemispherx

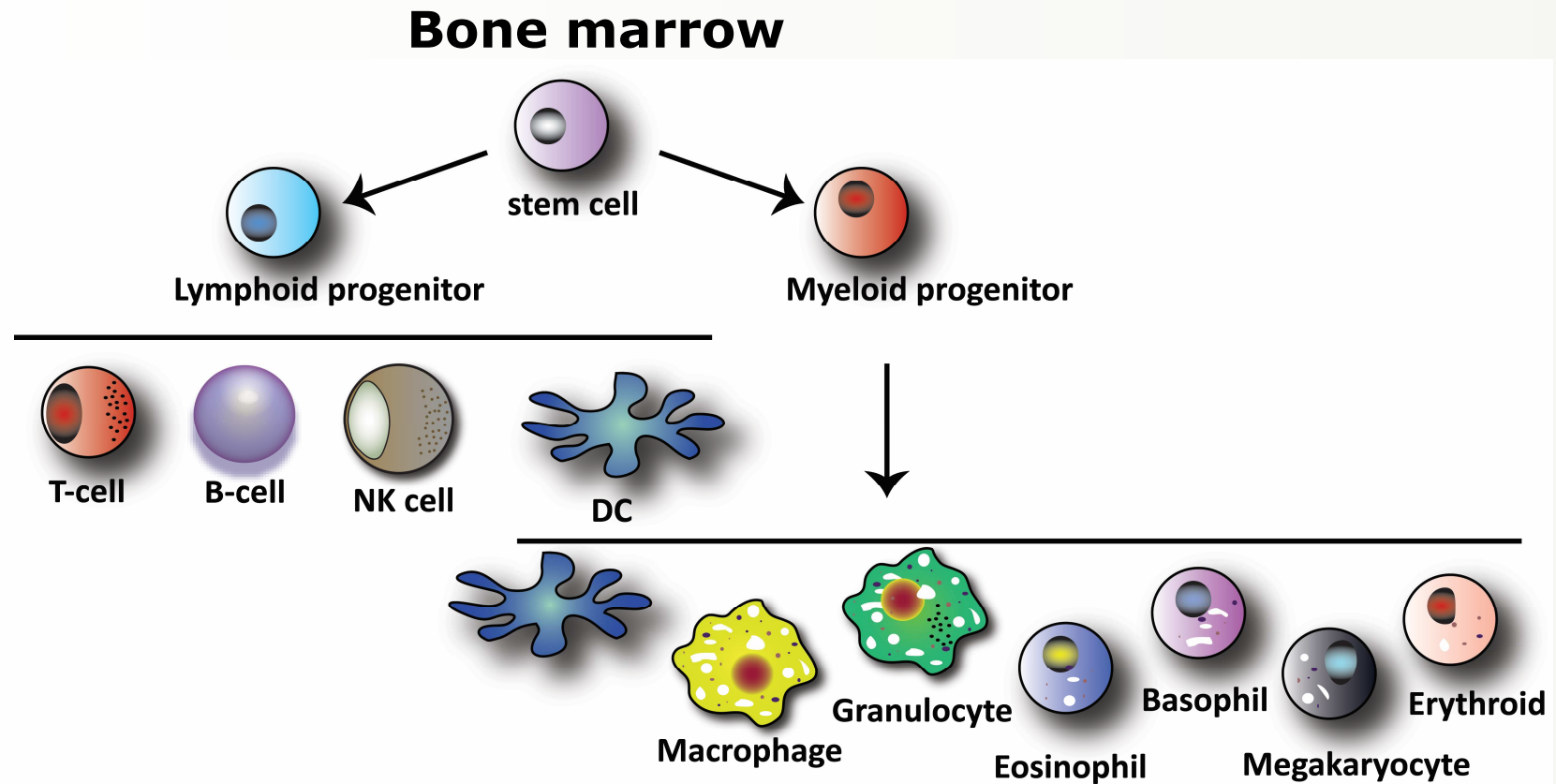
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Cellular Origin of Immune Cells



Innate vs Adaptive

- **Innate immunity:**

- Resistance that exists before infection

- First line of defense

- Broad (no) specificity

- Macrophages

- Neutrophils

- Eosinophils

- NK cells

Most potential pathogens are detected before they establish an infection

Innate vs Adaptive

- **Adaptive Immunity**
 - Antigen specific receptors
 - Responds to antigen stimulation with proliferation and differentiation
 - Gives rise to immunologic memory
 - T lymphocyte
 - B lymphocyte – antibody producing cells
 - Professional Antigen Presenting Cells (APC)

Antigen: Molecule (usually a protein) that react with an antibody (**antibody generating**)

General Immune Responses

	Innate	Adaptive
Type of Response	Antigen-Independent	Antigen-Dependent
Time to max response	Immediate	Lag between exposure and response
Specificity	Broad	Antigen-specific
Memory	None	Yes
Evolutionary Origin	Early (vertebrates)	Recent (mammals)
Examples	Inflammation, macrophages	Antibodies, T cell mediated immunity

Adaptive Immunity

- **Cellular immunity:**

- Mediated by T lymphocytes
- Require antigen presentation by a professional antigen presenting cell
- CD4⁺ (helper) T cells: Produce cytokines for activation of other immune cells
- CD8⁺ (cytotoxic) T cells: Recognizes and kills specific target cells: virus-infected cells, tumor cells

- **Humoral immunity:**

- Antibody-mediated immunity
- B cells with help from dendritic cells and T helper cells

Immune Tissues and Organs

Primary lymphoid organs – maturation

- Thymus: The site of T cell maturation.
- Bone marrow: The site of B cell maturation

Secondary lymphoid organs – activation

- Lymph nodes
- Spleen
- Mucosal immune system (mucosal-associated lymphoid tissue, MALT)

Antigen Presenting Cells

Types of antigen presenting cells (APC)

B-cells

Macrophages

Dendritic cells

- Presents peptide derived from antigen to CD8 and CD4 T cells (signal 1)
- Provides co-stimulation signals (signal 2)
- Provides polarization signals

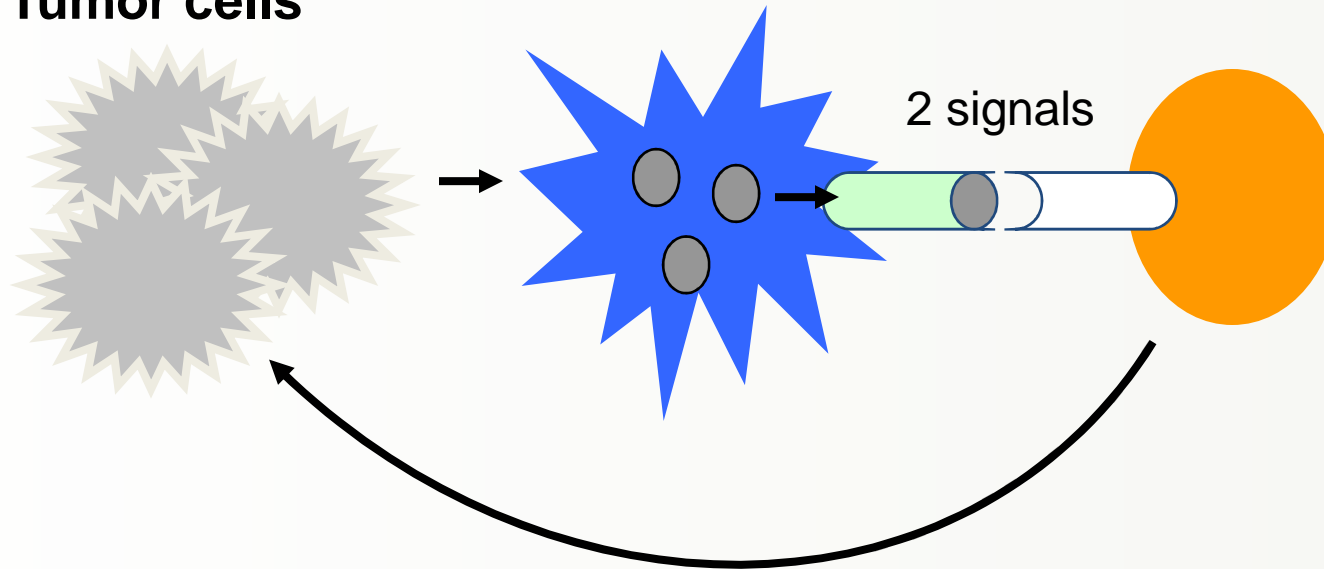
Signal 1 and 2 are required for T cell activation

T Cell Activation

Virally Infected cells;
Tumor cells

Dendritic Cell

T Cell



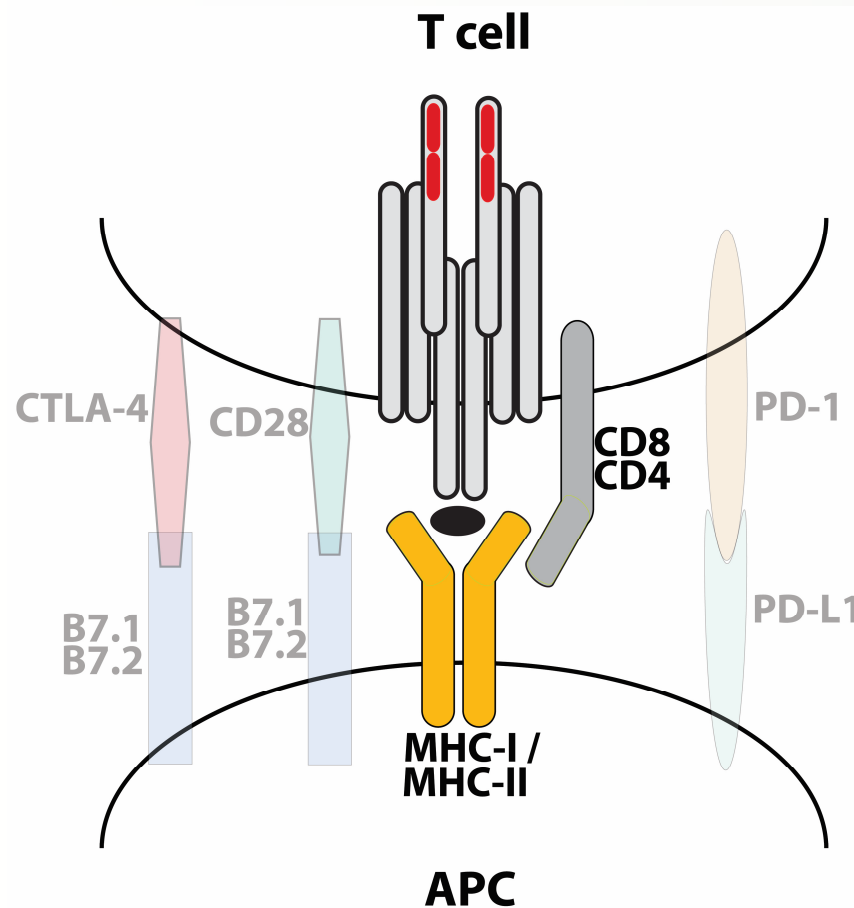
T cells respond to
infection / tumor

Signal 1: Major Histocompatibility Complex

Presents peptide antigens to the T cell receptor (TCR)

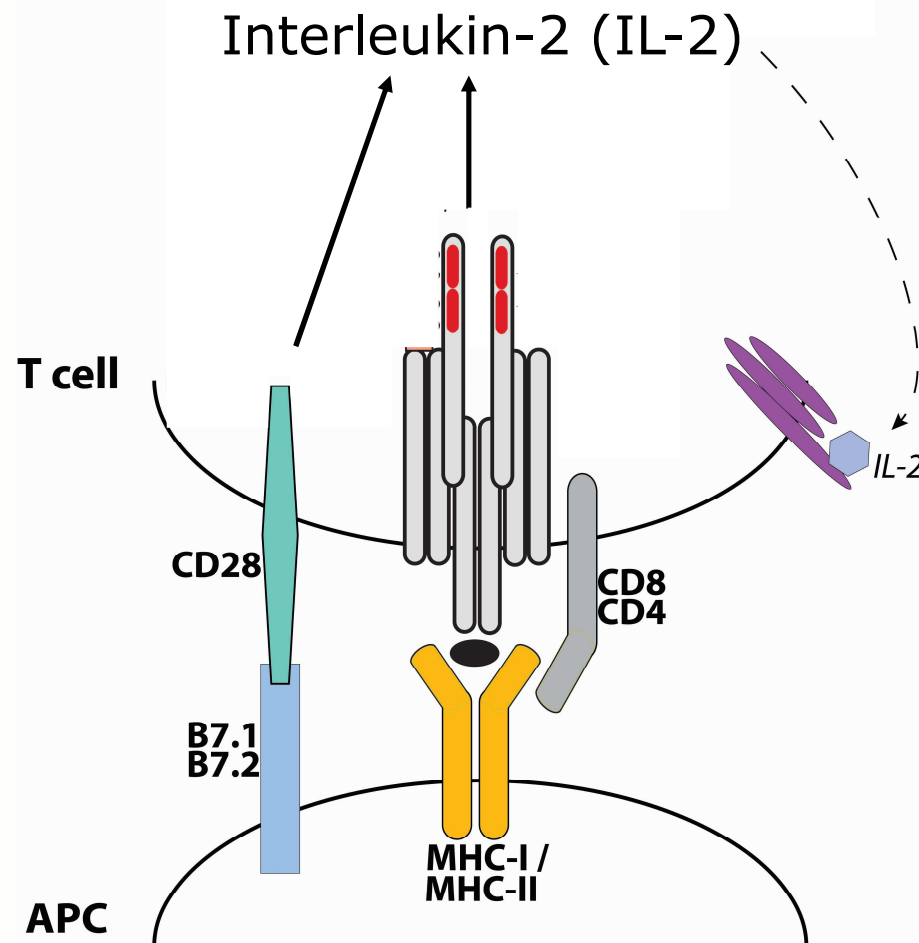
- **MHC class I (HLA-A/B/C)**
 - Presents peptide to CD8 T cells
 - Typically peptides derived from endogenous proteins
 - Restricted peptide size (8-11 aa)
 - Expressed on most cells
- **MHC class II (HLA-DR)**
 - Presents peptides to CD4 T cells
 - Typically peptides derived from exogenous proteins
 - Broader peptide size (18-20 aa)
 - Only expressed by APCs

Signal 1: Antigen Presentation



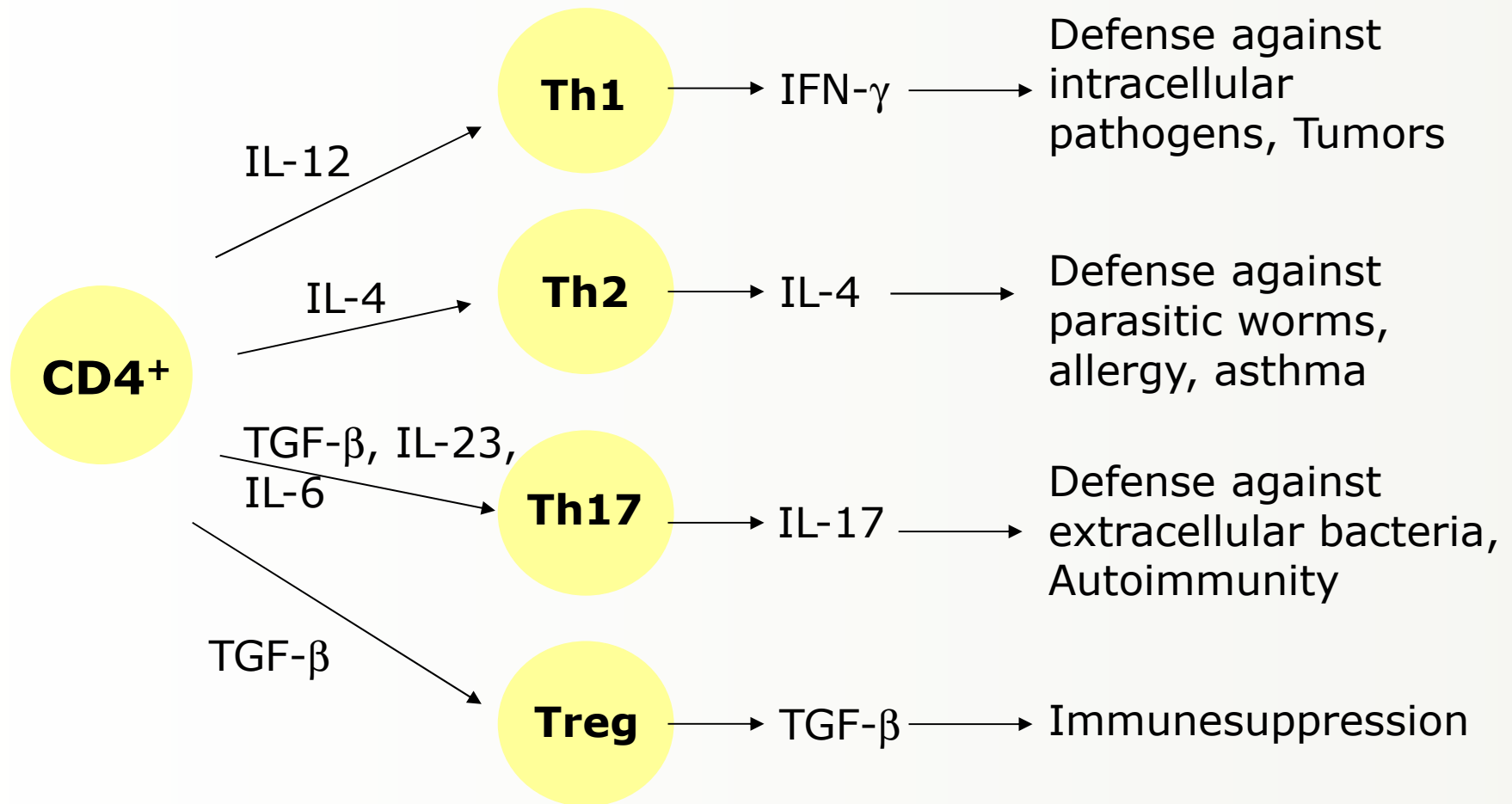
- Initial signal for T cell activation
- In the absence of signal 2, T cells will not be activated, may undergo apoptosis

Signal 2: Co-Stimulation



- Signaling between CD28 on T cells and B7.1/B7.2 on APC
- Leads to production of IL-2 required for T cell survival and proliferation

Polarization

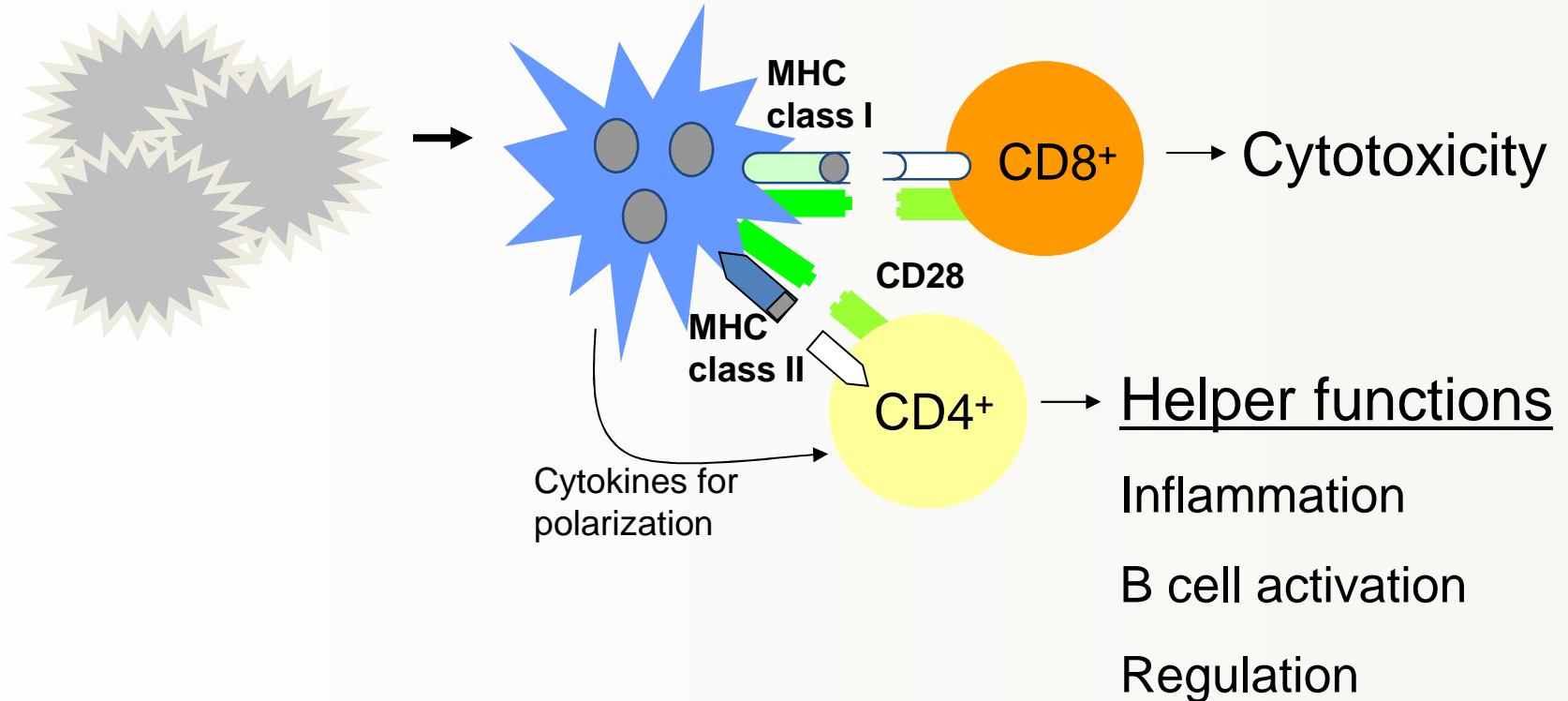


T Cell Activation

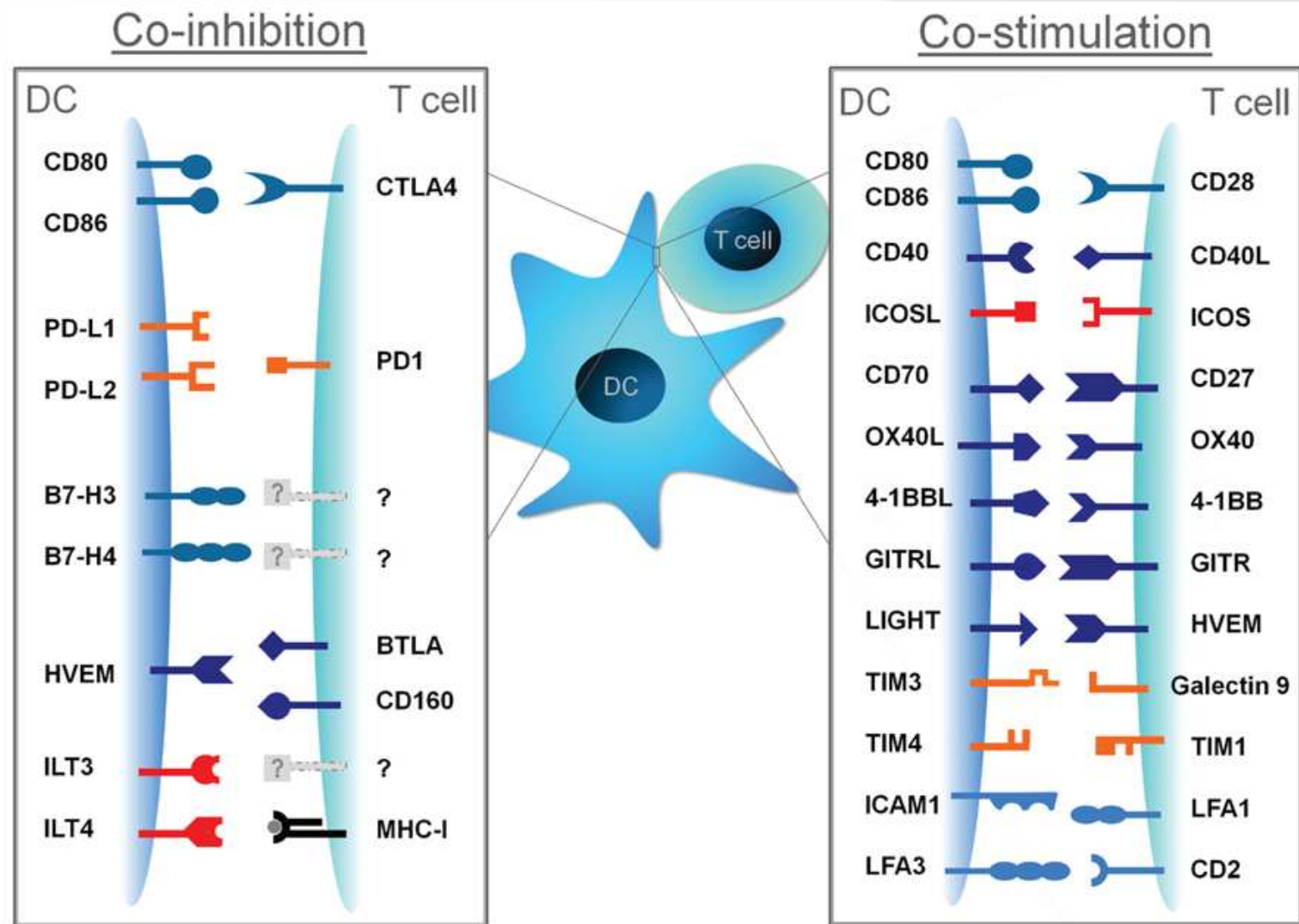
Virally Infected cells
Tumor cells

Dendritic Cell

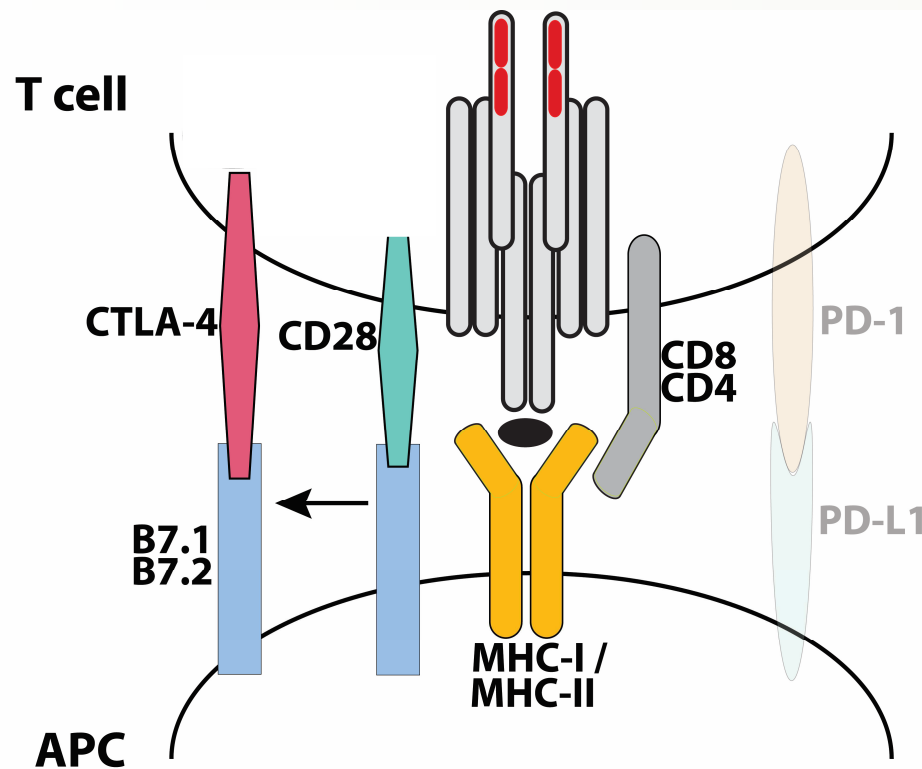
T cells



Regulation of T cell Activity



Regulation of T Cell Activity

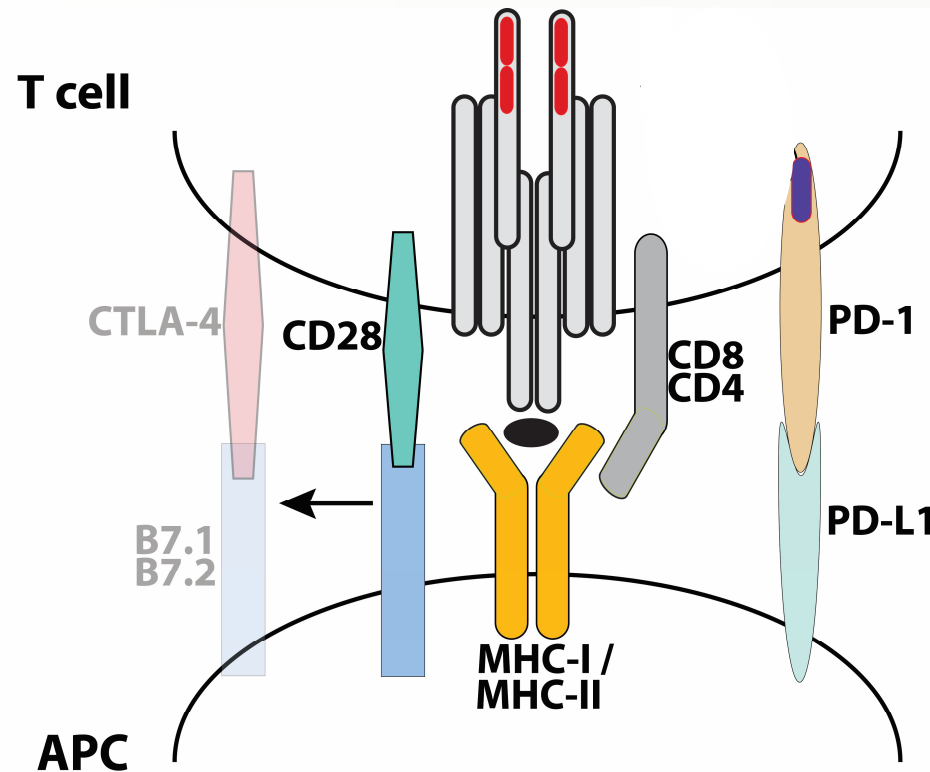


CTLA-4

- Induced in activated T cells
- Also binds to B7.1 and B7.2
- Higher affinity than CD28
- Squelches the CD28 signal

Net effect of CTLA-4 signaling is to shut off T cell activity

Regulation of T Cell Activity



PD-1

- Expressed on chronically activated T cells; marker of T cell exhaustion
- Binds to PD-L1/PD-L2
- Constitutively expressed on many cells (APCs, tumor cells)

Blocking the PD-1/PD-L1 pathway can reverse T cell unresponsiveness in chronic viral infections

Tolerance:

Ignorance to Self Antigens

Mechanisms:

- **Clonal deletion of T cells that recognize “self”**

Occurs in the thymus

- **Clonal inactivation of T cells in the periphery**

Regulatory T cells (Tregs)

Myeloid Derived Suppressor Cells (MDSC)

These mechanisms also participate in the induction of tolerance to gut flora, fetus, and tumors.

Summary

Normal immune state is in balance

- Allows recognition of pathogens while avoiding reactivity to self
- Has built in mechanisms to limit the immune response
- Tumors tip the balance to a non-responsive state
- Approaches to enhance activation while blocking the suppression mechanisms can allow immune recognition of the tumor

