Activation and Regulation of T Lymphocytes

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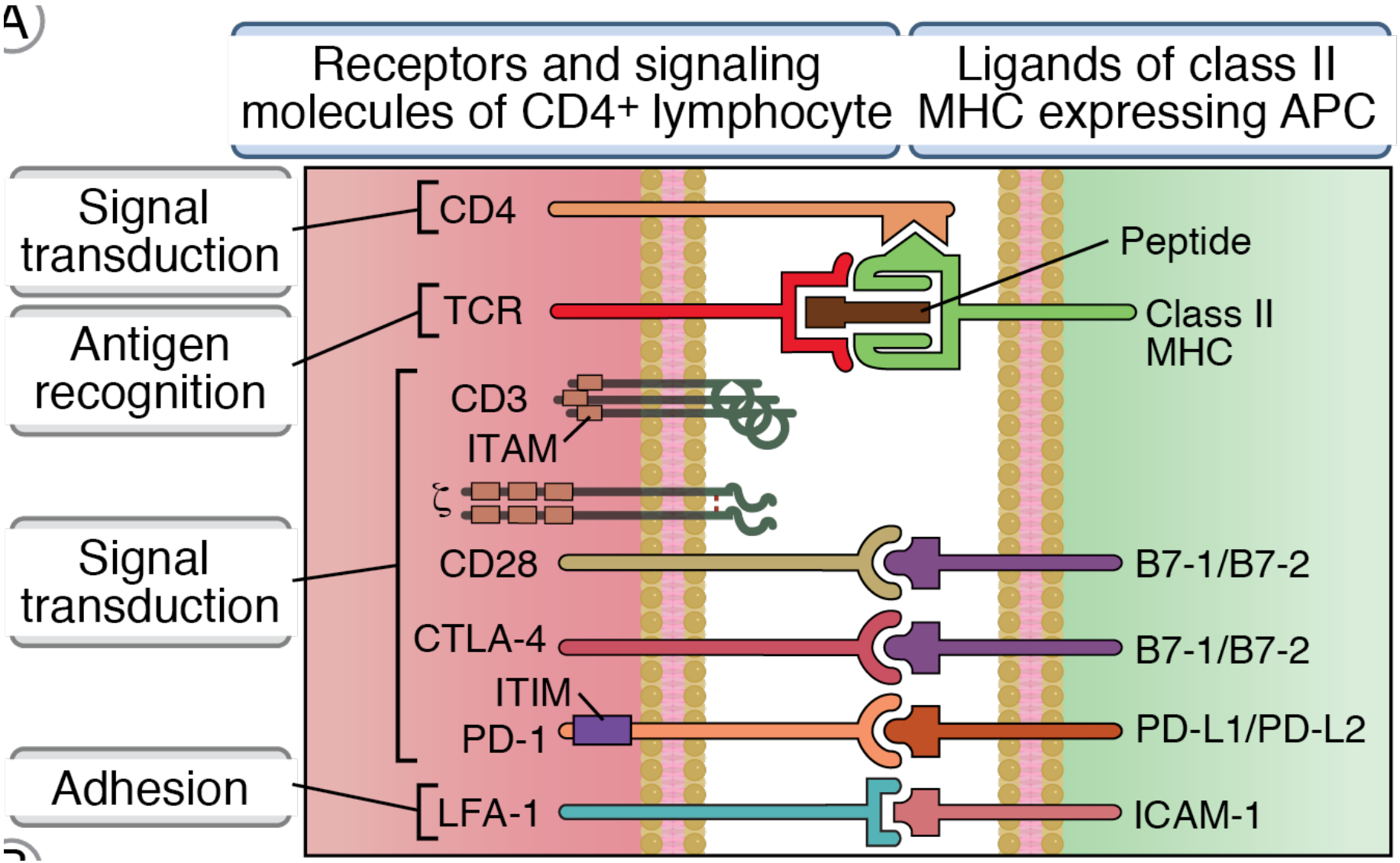
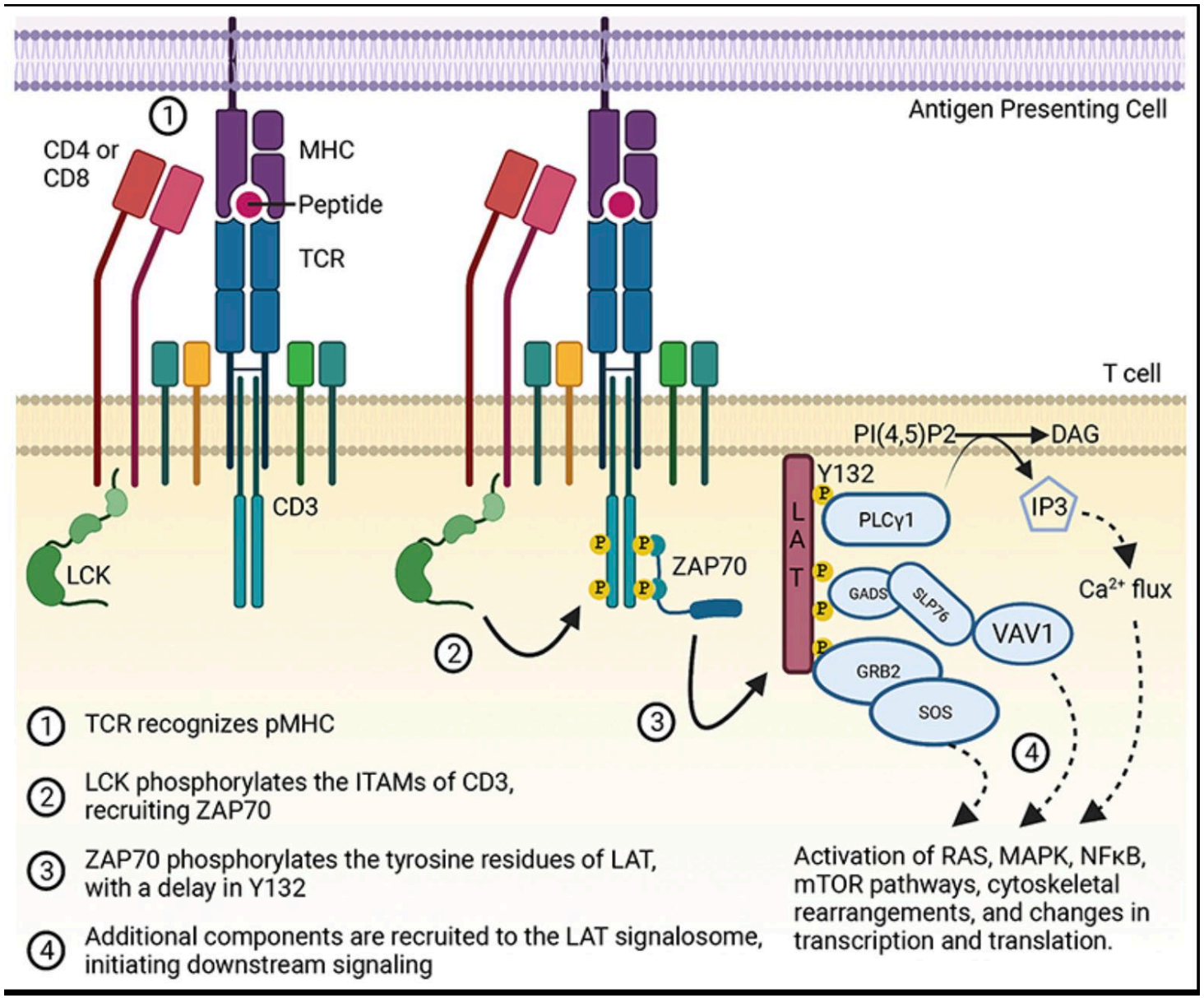
Lecture outline

- T cell activation
- Costimulation, the B7:CD28 family
- Regulation by coinhibitors: CTLA-4, PD-1

Molecules involved in T cell activation

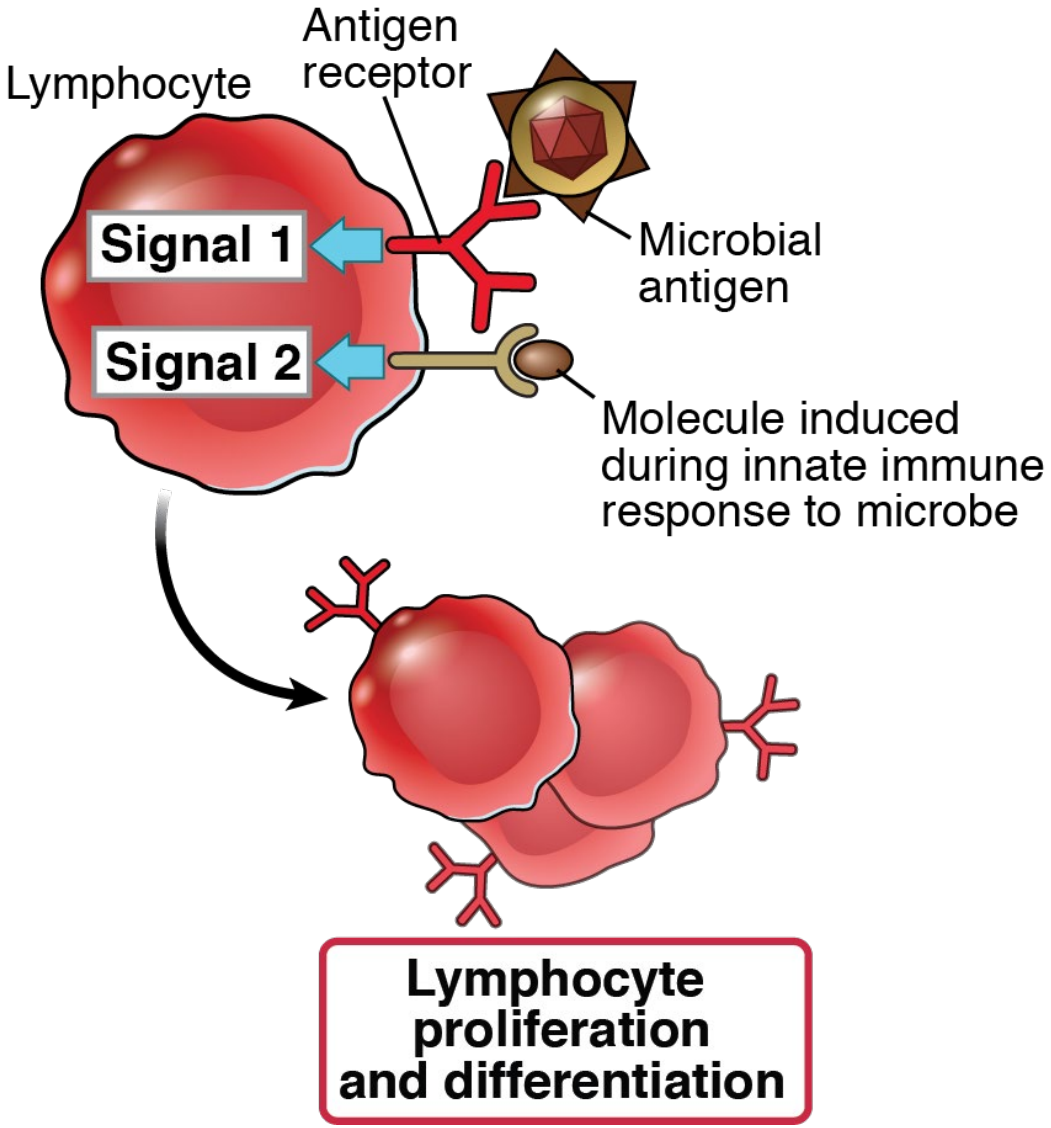


TCR signal transduction

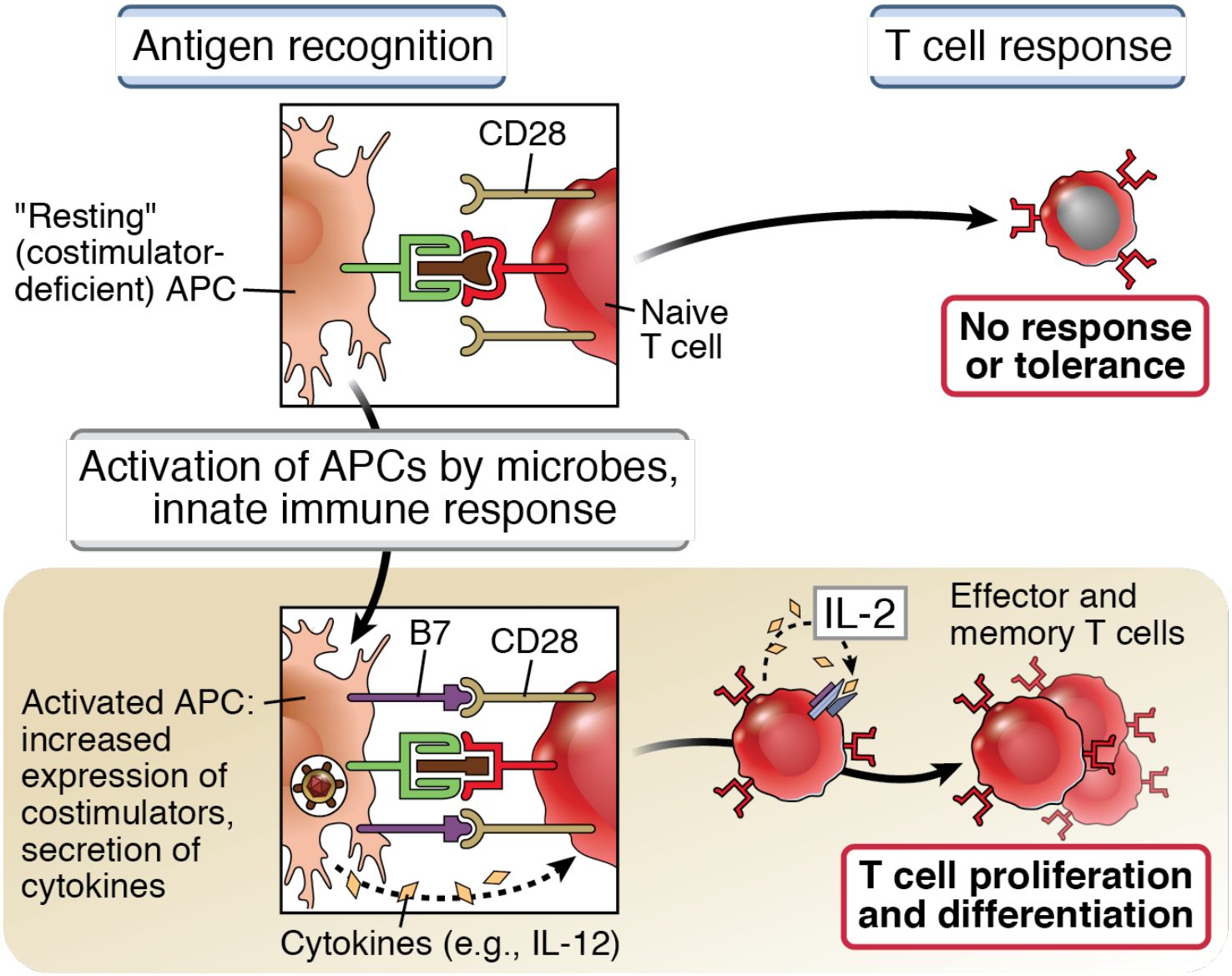


Richard et al., Trends Imm 2021

The two-signal requirement for lymphocyte activation



Role of costimulation in T cell activation

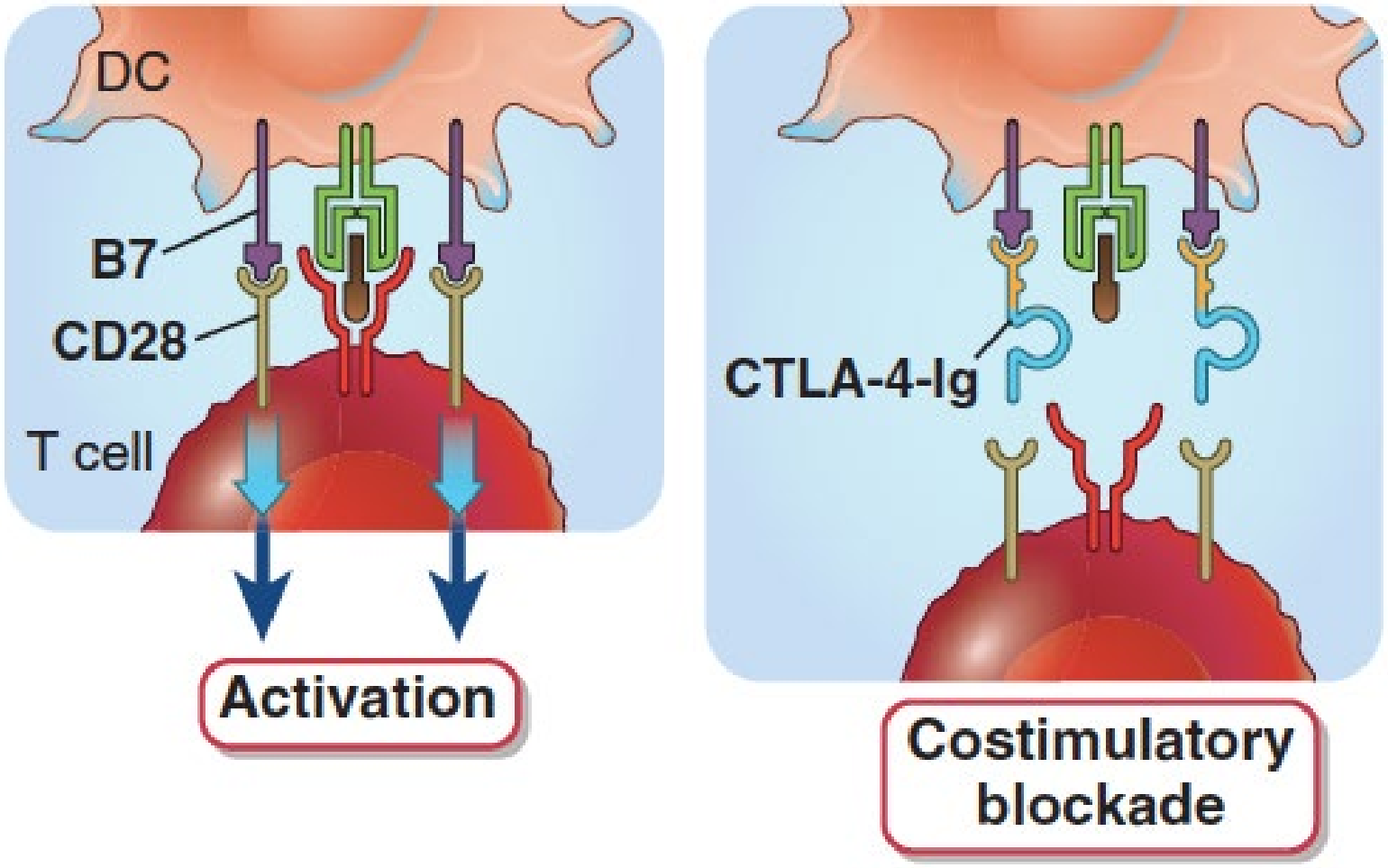


Costimulation

- Required for initiating T cell responses (activation of naïve T cells)

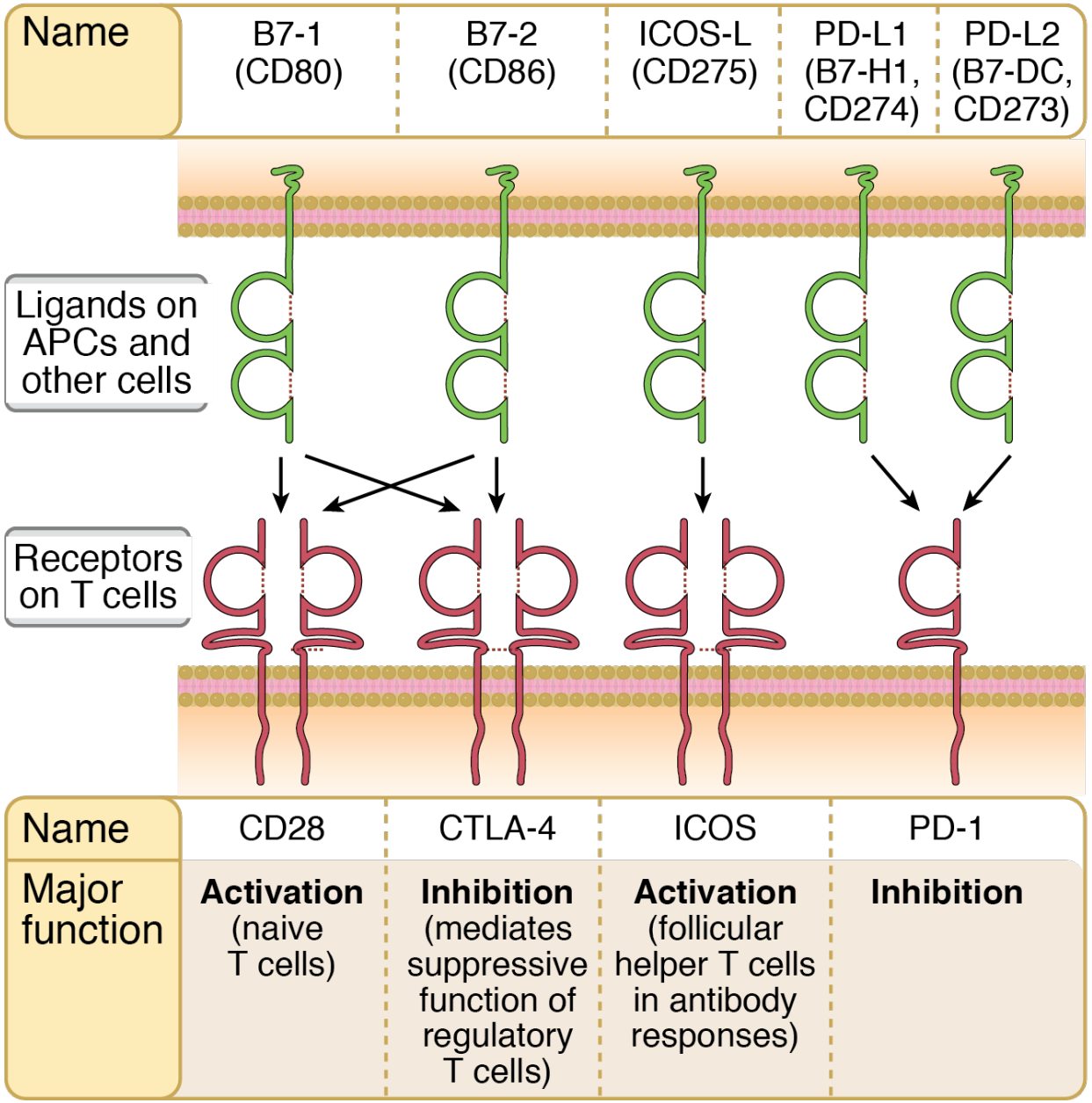
- Ensures that T cells respond to microbes (the best inducers of costimulators) and not to harmless antigens
  - Source of costimulation during responses to tumors, transplants?

Costimulatory blockade



CTLA4-Ig (abatacept/belatacept) is approved for rheumatoid arthritis, graft rejection

The B7:CD28 families



Inhibitory receptors of T cells

- Prevent reactions against self antigens
- Limit immune responses in situations of persistent stimulation: some tumors, chronic infections
  - Therapeutic application: checkpoint blockade for cancer immunotherapy

Opposing functions of CD28 and CTLA-4

- CD28 on T cells recognizes B7 on APCs → T cell activation

- CTLA-4 recognizes B7 → inhibition of T cells
  - Knockout of CTLA-4 in mice or mutations in humans results in systemic inflammatory disease

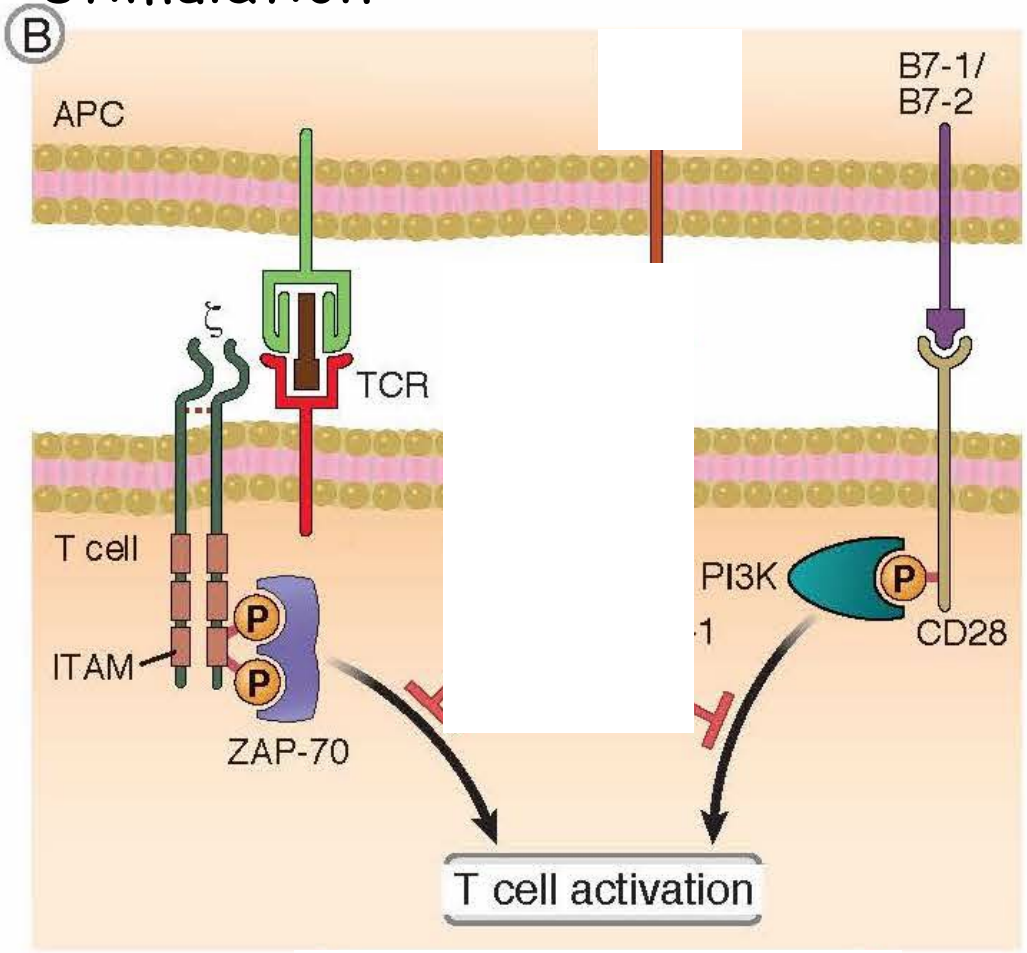
The PD-1 inhibitory pathway

- PD-1 recognizes two widely expressed ligands (PD-L1, PD-L2)
- Knockout of PD-1 leads to autoimmune disease (less severe than CTLA-4-KO)
- Role of PD-1 in T cell suppression in chronic infections, tumors?

T cell activation

TCR stimulation

CD28 costimulation

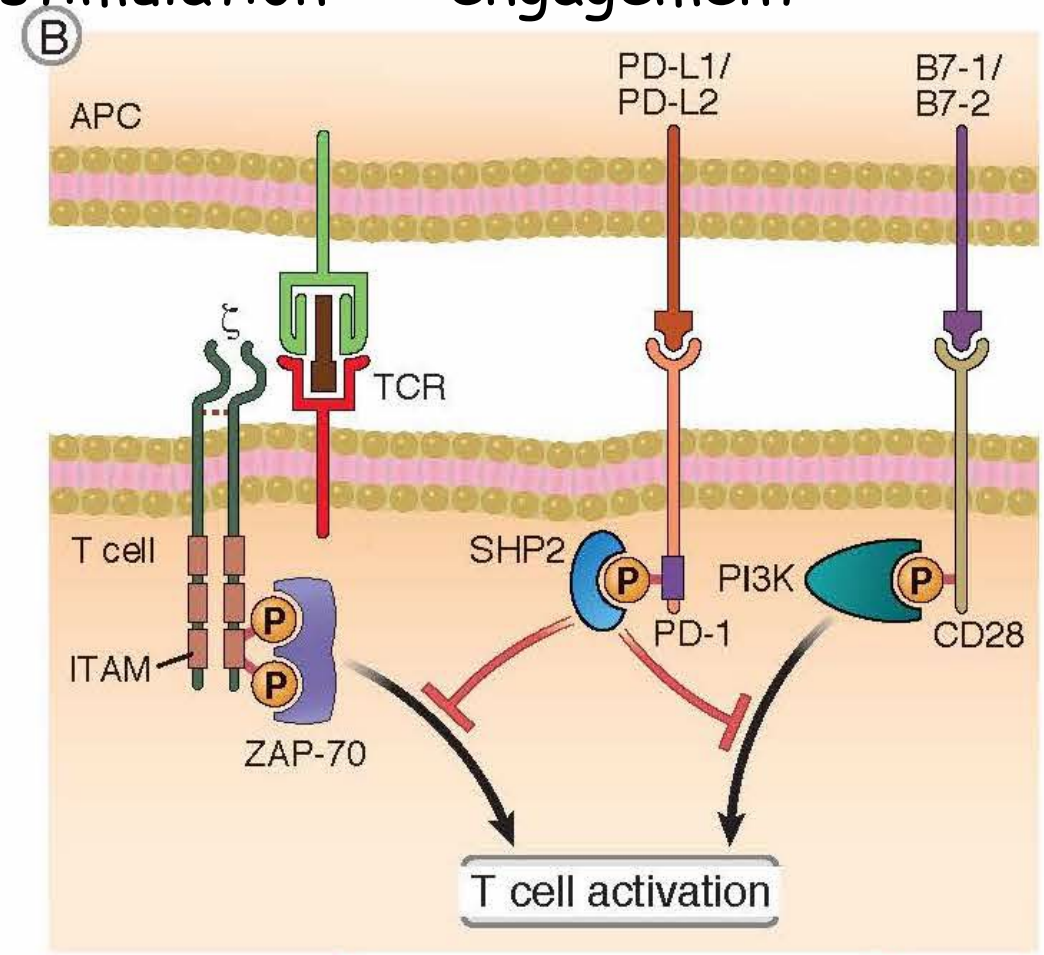


Action of PD-1

TCR stimulation

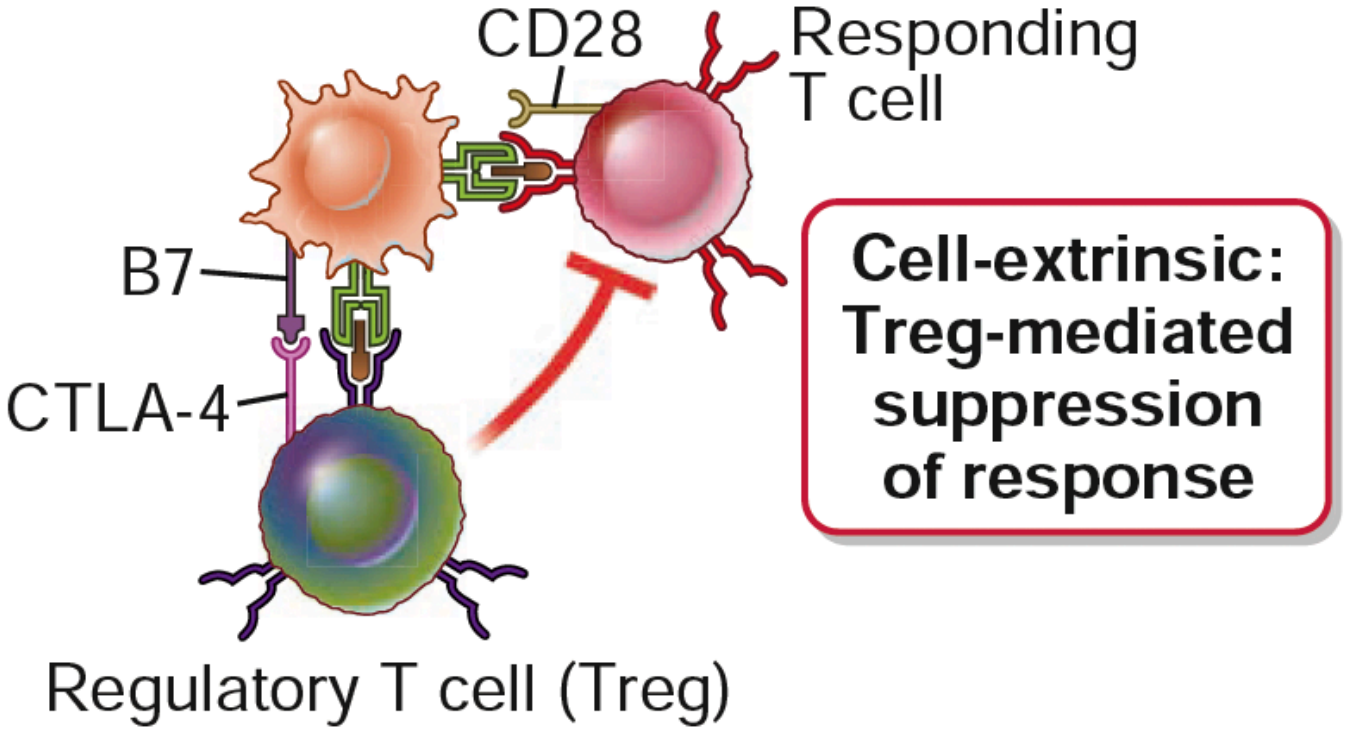
PD-1 engagement

CD28 costimulation



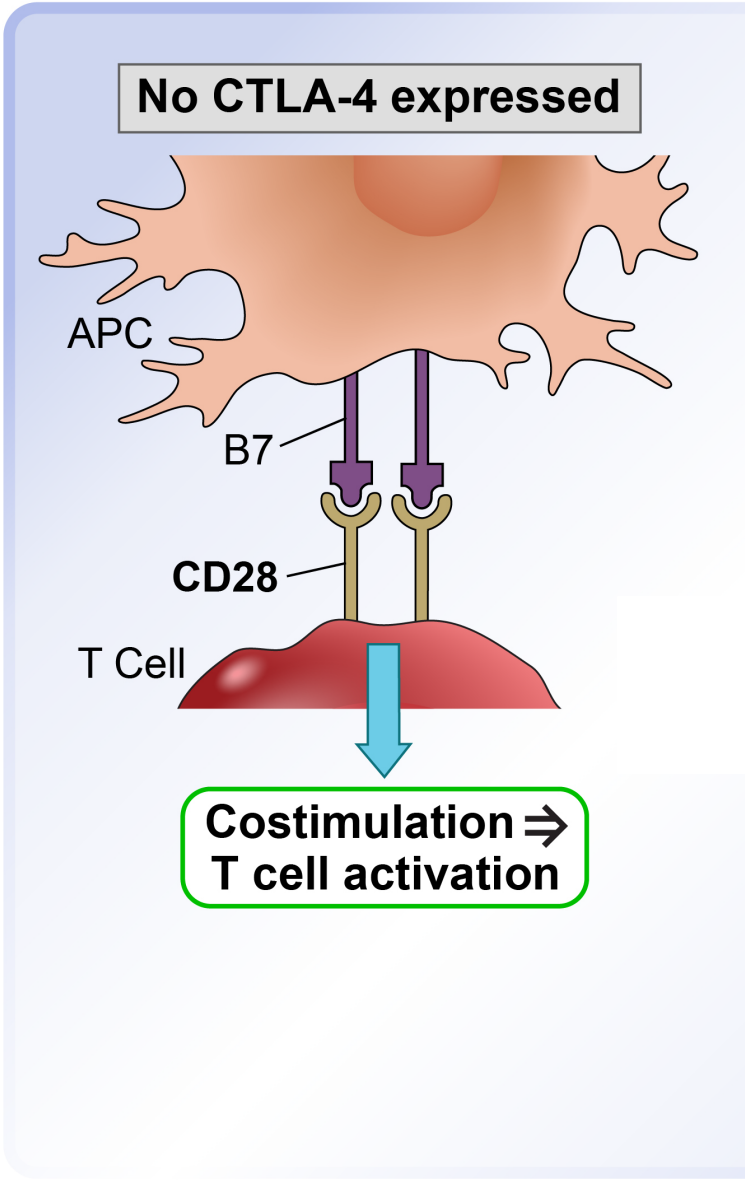
PD-1 inhibits signals from the TCR complex and CD28

CTLA-4 on Tregs inhibits responding T cells

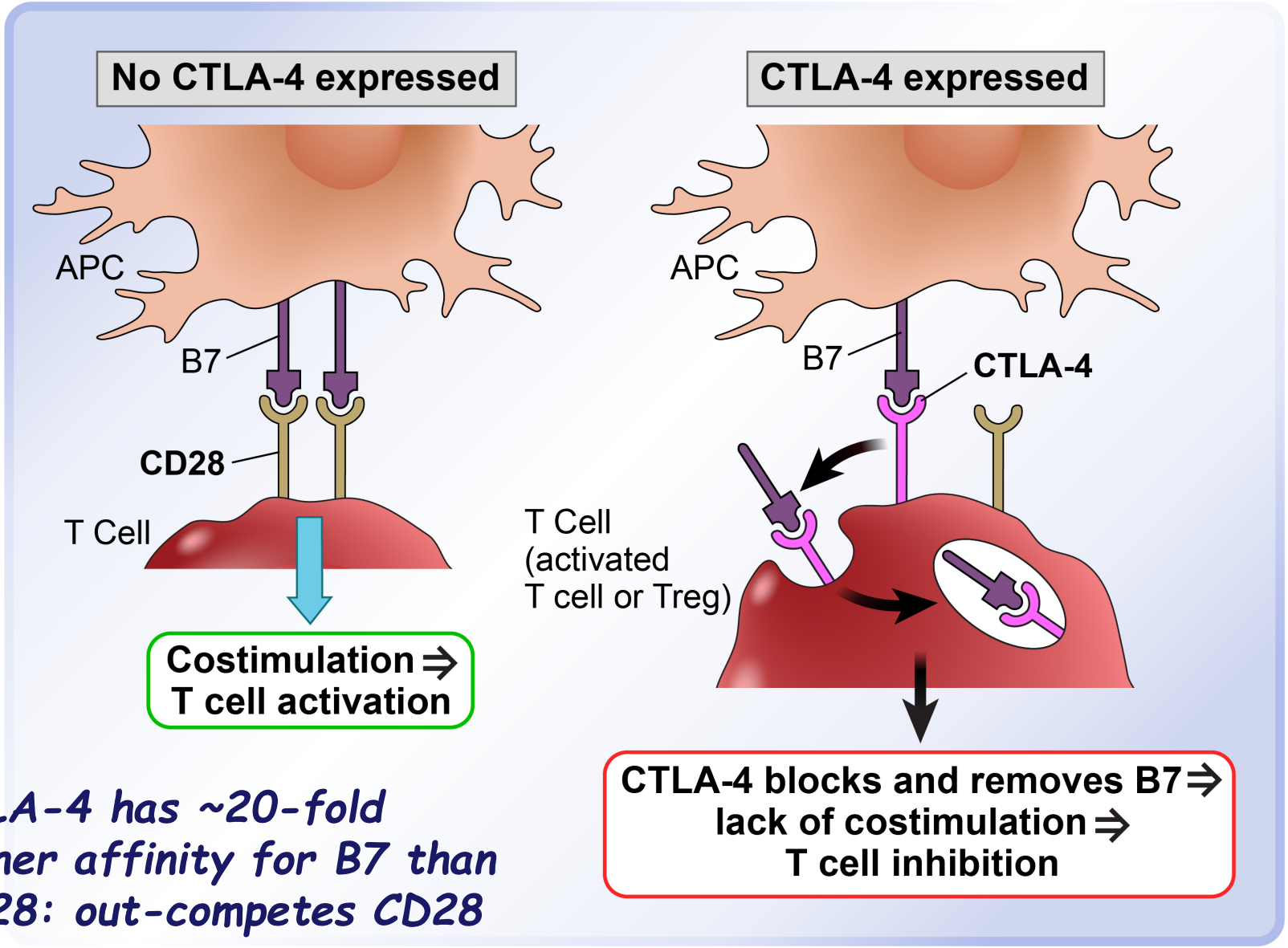


Tregs are the only cells that constitutively express high levels of CTLA-4 (transient expression on recently activated conventional T cells)
Deletion of CTLA-4 in Tregs recapitulates germline deletion

B7 engages CD28 in the absence of CTLA-4



CTLA-4 blocks and removes B7

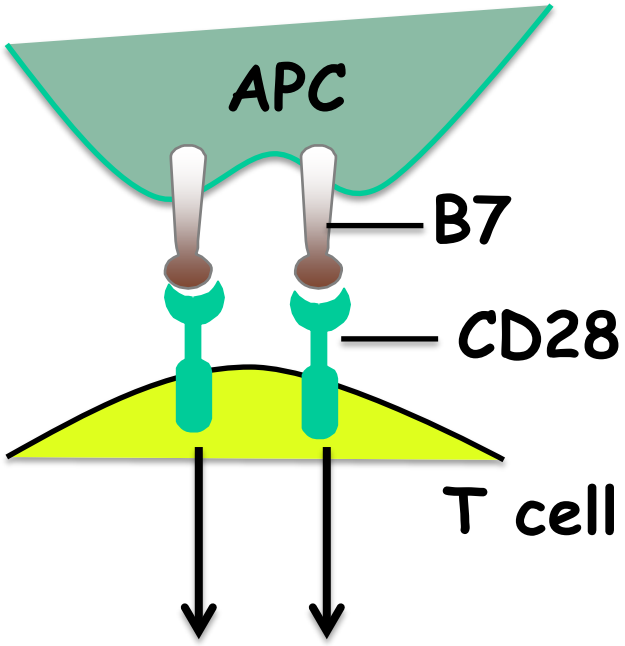


CTLA-4 has ~20-fold higher affinity for B7 than CD28: out-competes CD28

Functions of CTLA-4

- Limits activation of responding T cells
- How does the T cell choose to use CD28 to be activated (e.g., with microbes) or CTLA-4 to shut down (e.g., with self Ag)?
  - Level of B7 expression and affinity of receptors: Low B7 (e.g., when DC is displaying self or tumor antigen) --> engagement of high-affinity CTLA-4
  - High B7 (e.g., after microbe encounter) --> engagement of lower affinity CD28

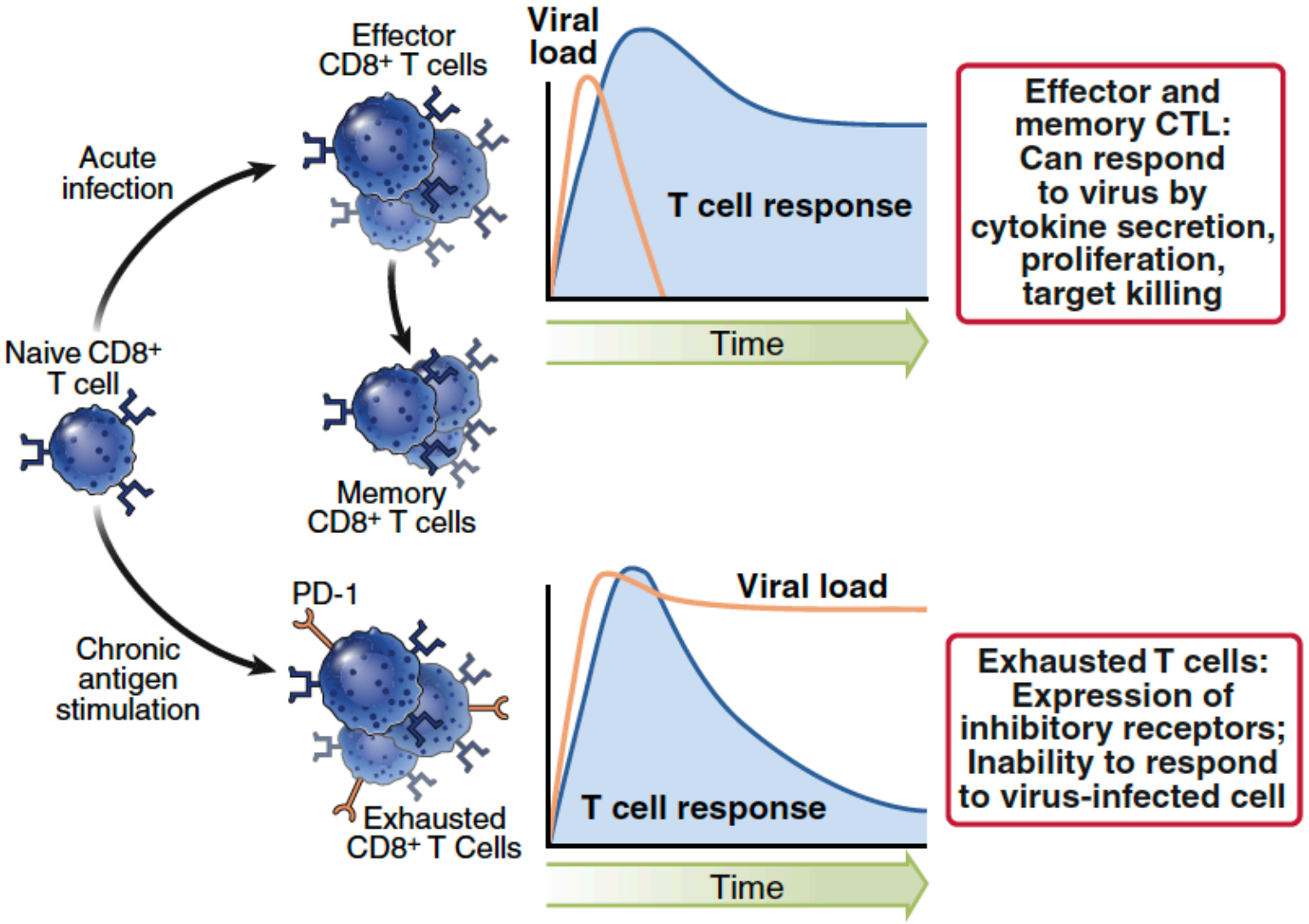
Consequence of mutations in the CTLA-4 pathway



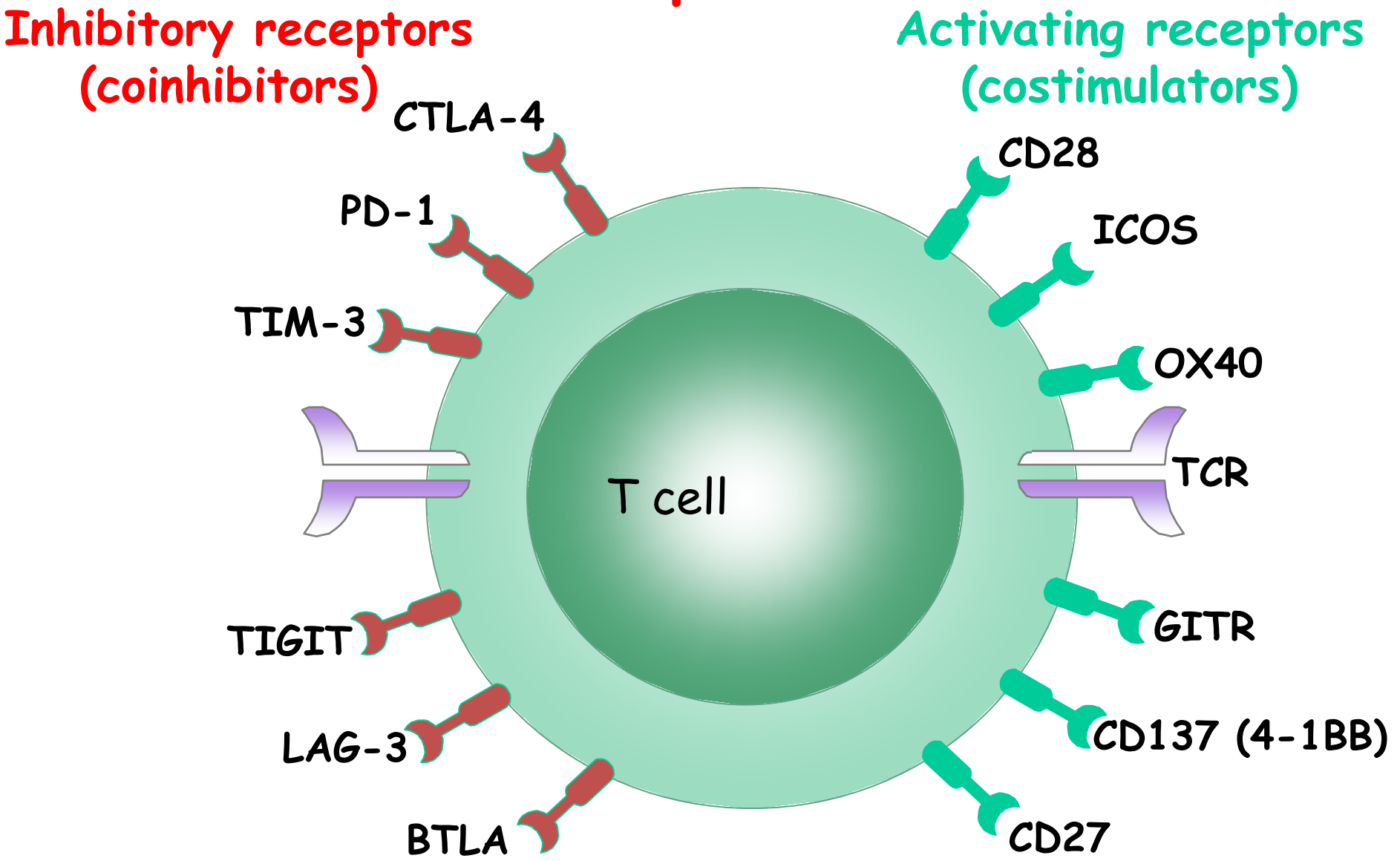
Unopposed costimulation →
Excessive T cell activation

Therapy?

Chronic infections induce T cell exhaustion



T cell activating and inhibitory receptors



Costimulators and inhibitors other than the B7:CD28 family

- Many proteins of the TNF-receptor and Ig families are expressed on T cells and implicated in T-cell activation and control
  - Functions often demonstrated in complex experimental systems or in vitro
  - Often expressed on both effector and regulatory T cells, so functions unclear
  - Roles in disease (human or animal models) not definitely established

- Possible therapeutic targets?