Cancer immunotherapy

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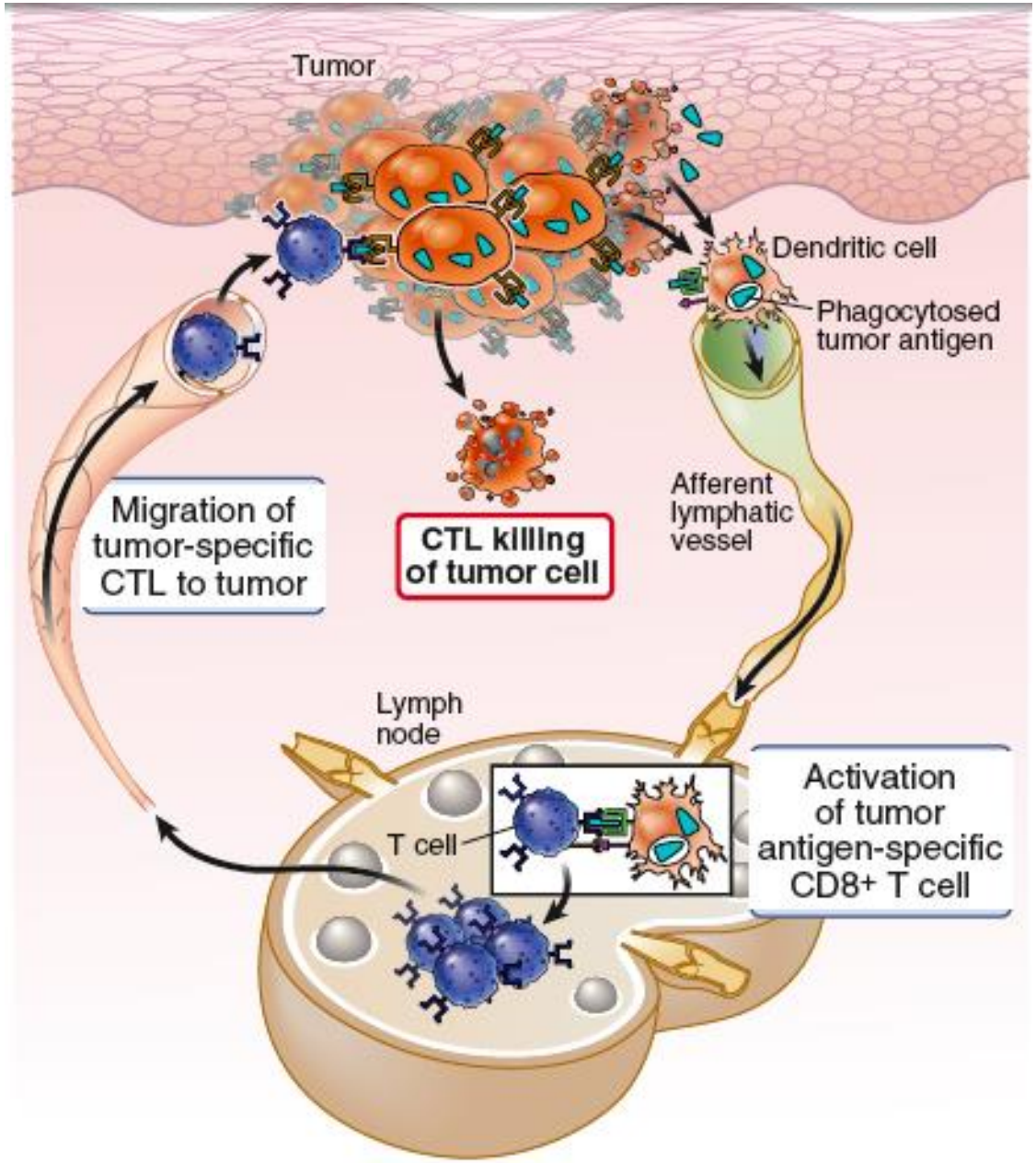
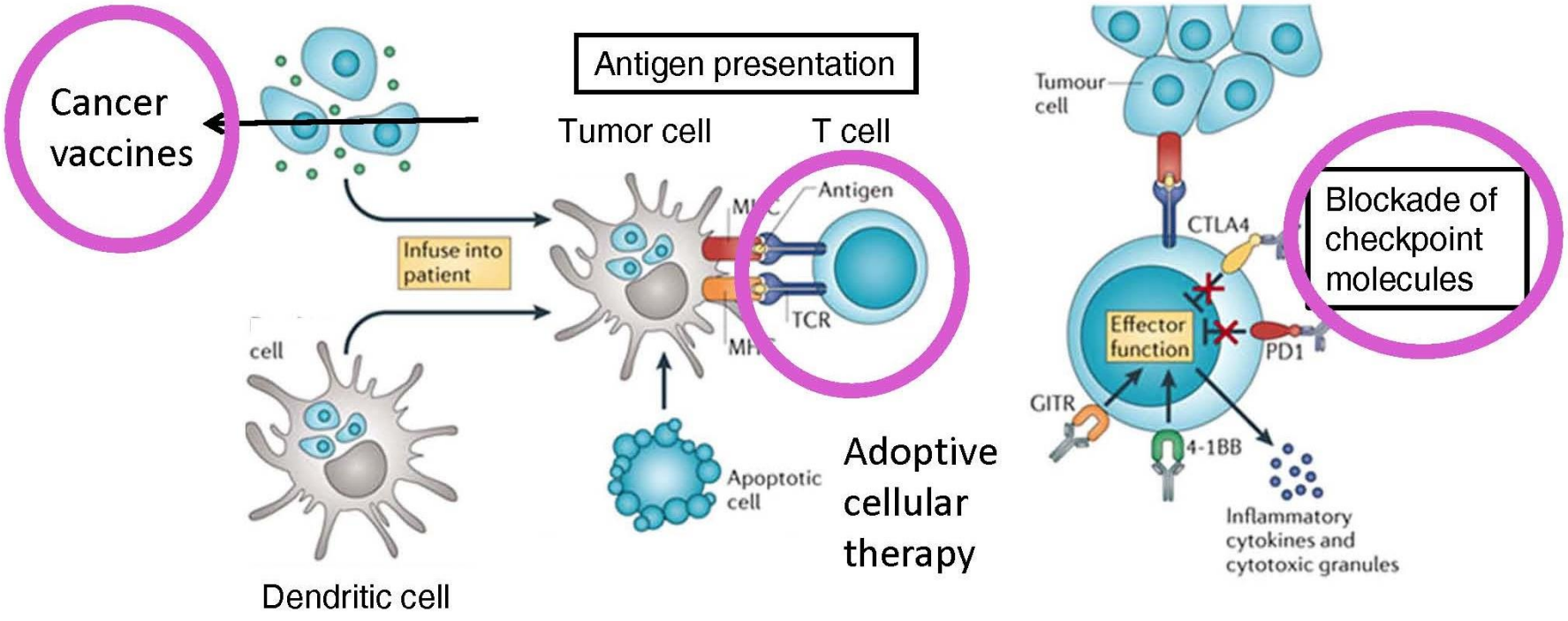
T cell responses to tumors

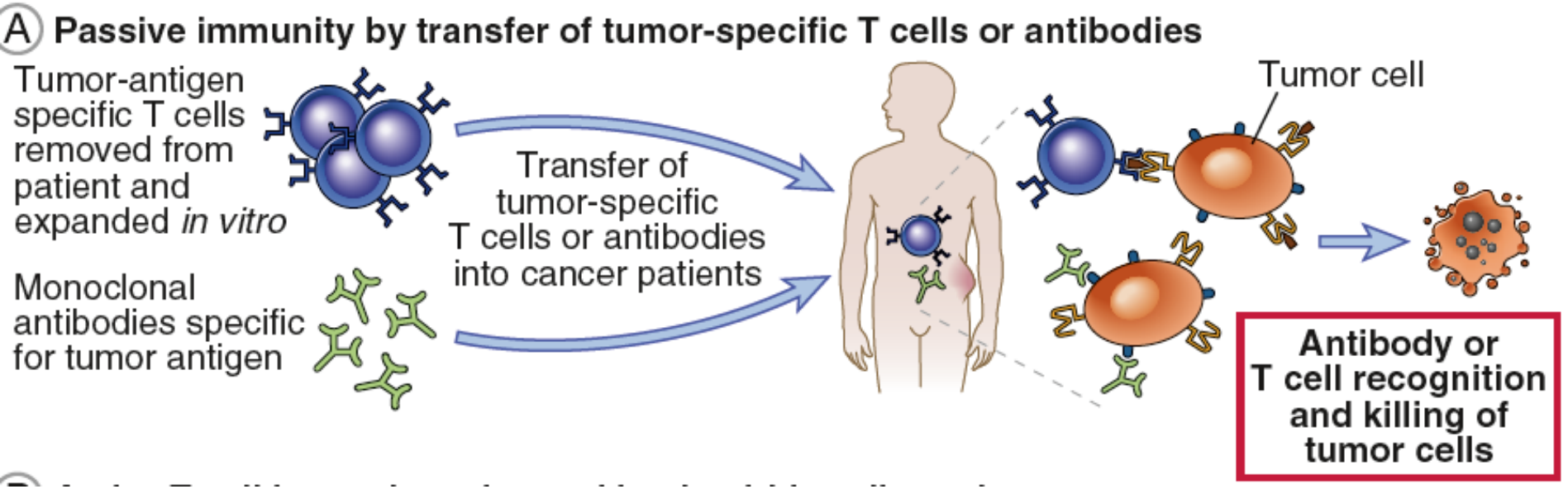


Harnessing the immune system to combat cancer



Vanneman and Dranoff, Nat Rev Can, 2012

Passive immunotherapy



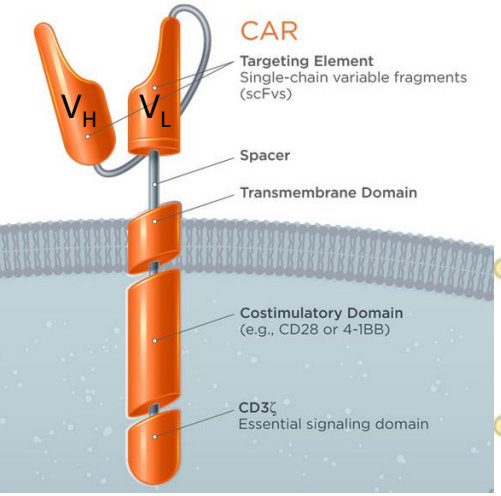
Tumor-specific T cell therapy

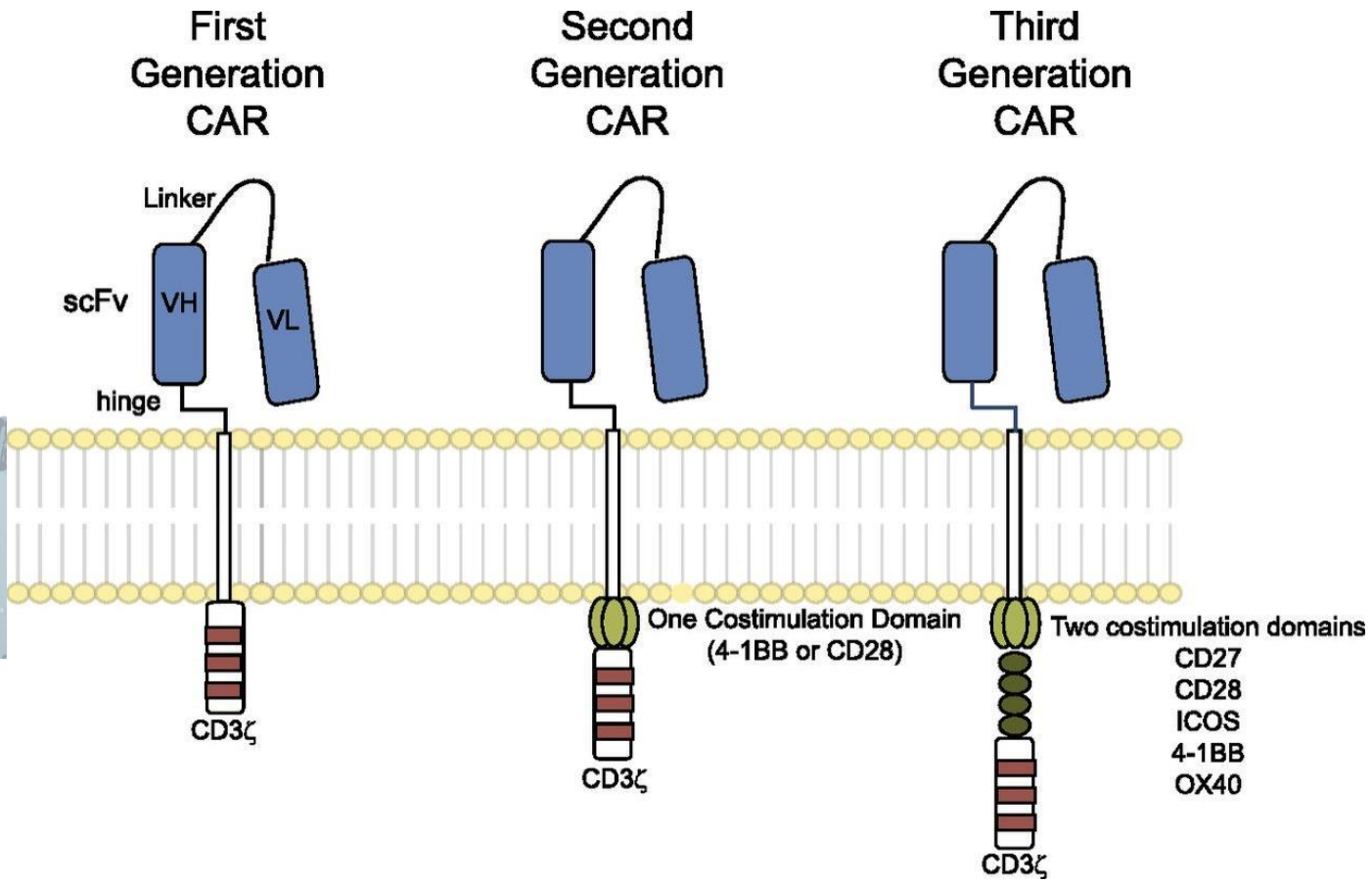
- Problem with initial approaches: not enough tumor-specific T cells

- How to generate large numbers?
  - Transfect tumor-specific antigen receptor into T cells, expand the cells in vitro

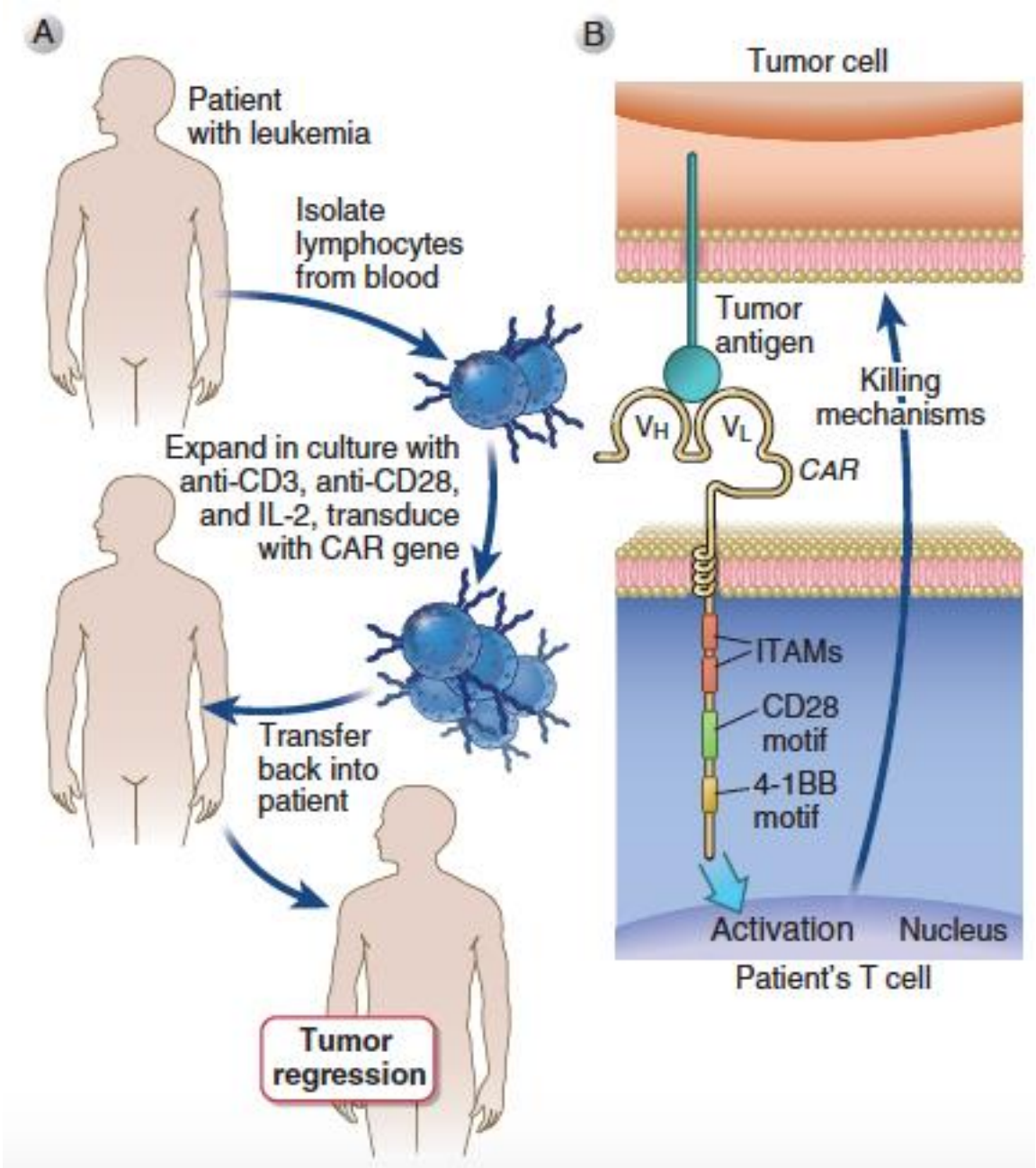
- Which tumor-specific antigen receptor to express in T cells?
  - Problems with expressing TCR
  - Alternative: chimeric antigen receptors

Development of chimeric antigen receptors





Chimeric antigen receptor-T cell (CAR-T) therapy



- *Remarkable success in B cell acute leukemia (targeting CD19); up to 90% complete remission*
- *Risk of cytokine storm*
- *Outgrowth of antigen-loss variants of tumors?*

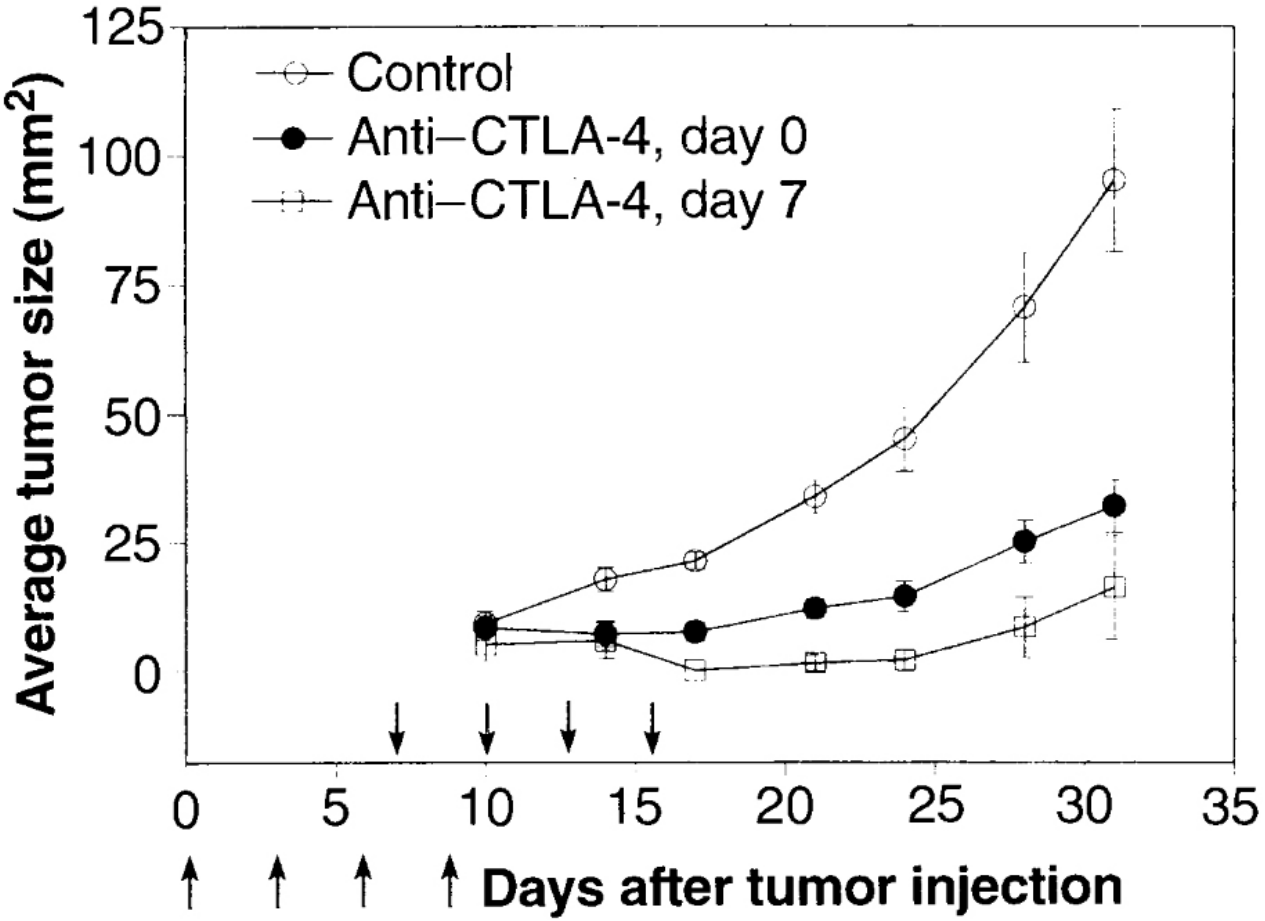
Limitations and challenges of CAR-T cell therapy

- Cytokine release syndrome – many T cells respond to target antigen
- Not yet effective against solid tumors
- Resistance due to loss of target antigen
- Technically challenging and expensive

Immune checkpoints

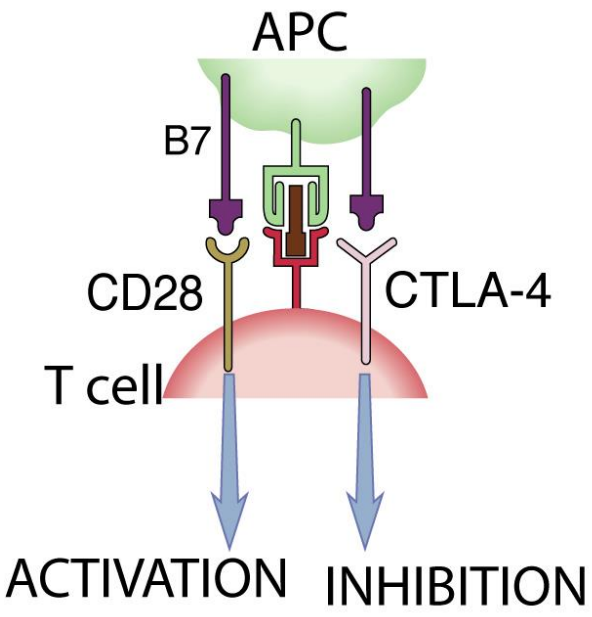
- Inhibitory receptors on T cells ("coinhibitors") block activation
- CTLA-4: competes with CD28, reduces costimulation
- PD-1: activates phosphatase, blocks kinase-dependent signals from CD28 and TCR
- Many others described

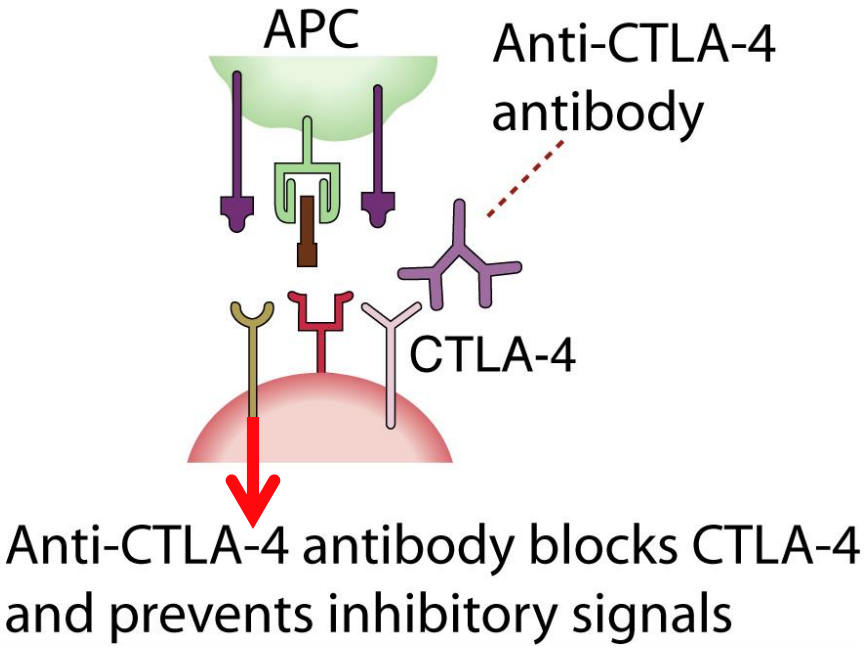
Blocking CTLA-4 promotes tumor rejection: CTLA-4 limits immune responses to tumors



Administration of antibody that blocks CTLA-4 in tumor-bearing mouse leads to tumor regression

Checkpoint blockade: Removing the brakes on the immune response





Anti-CTLA-4 antibody is approved for tumor immunotherapy (enhancing immune responses against tumors)

Even more impressive results with anti-PD-1 in cancer patients

Risks of blocking CTLA-4 or PD-1

- Blocking a mechanism of self-tolerance leads to:

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- Blocking a mechanism of self-tolerance leads to:

- Autoimmune reactions
  - Immune related adverse events
  - Severity of adverse events has to be balanced against potential for treating serious cancers
  - More severe with anti-CTLA4 than with anti-PD1 antibody

What types of tumors respond best to checkpoint blockade therapy

- Many mutations in tumor (mutations produce neoantigens that are recognized by T cells)
- Tumor infiltrate contains many T cells with high expression of PD-1, CTLA-4