

# Cancer immunotherapy and its immunologic complications

Abul K. Abbas  
UCSF



University of California  
San Francisco

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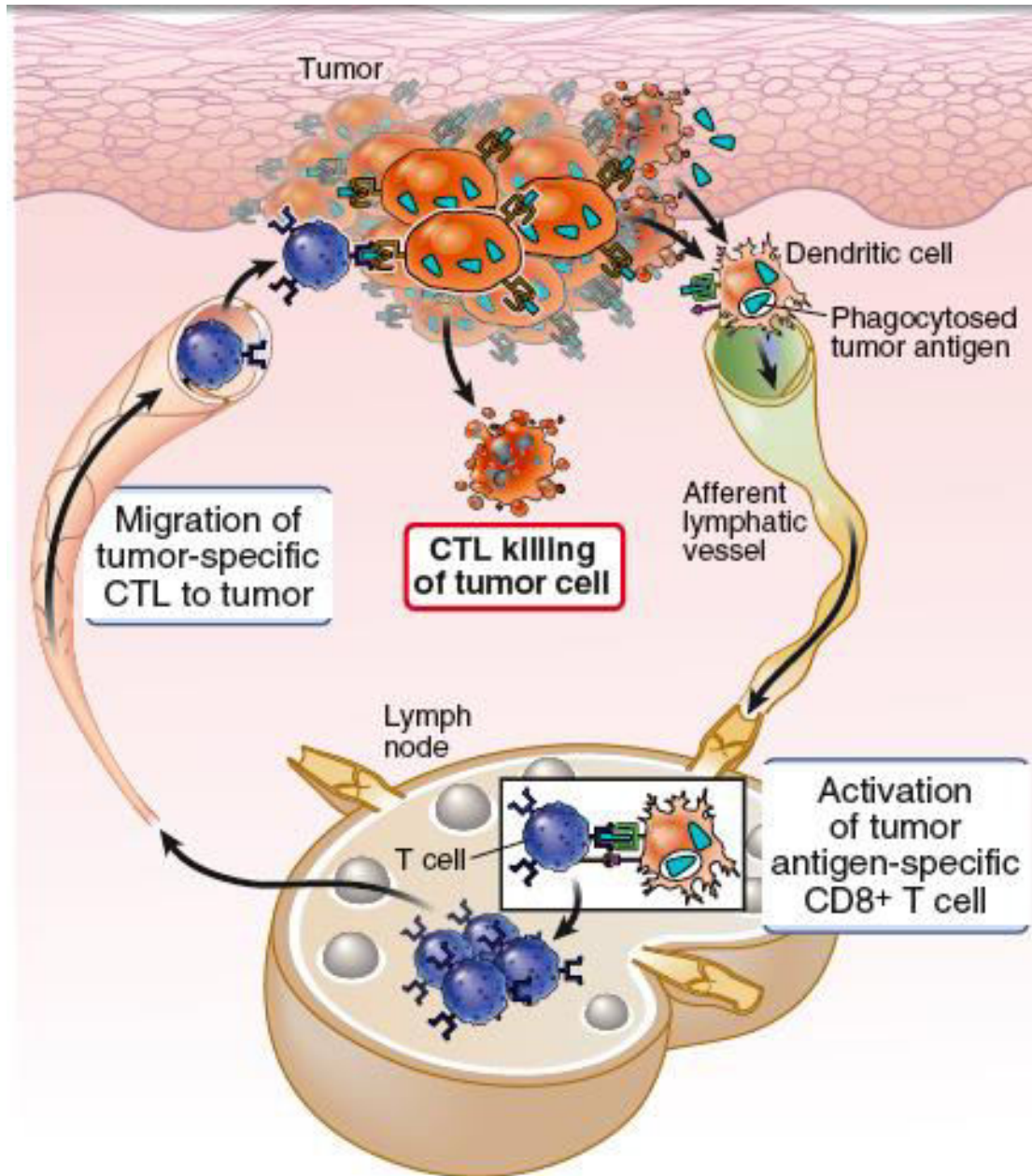
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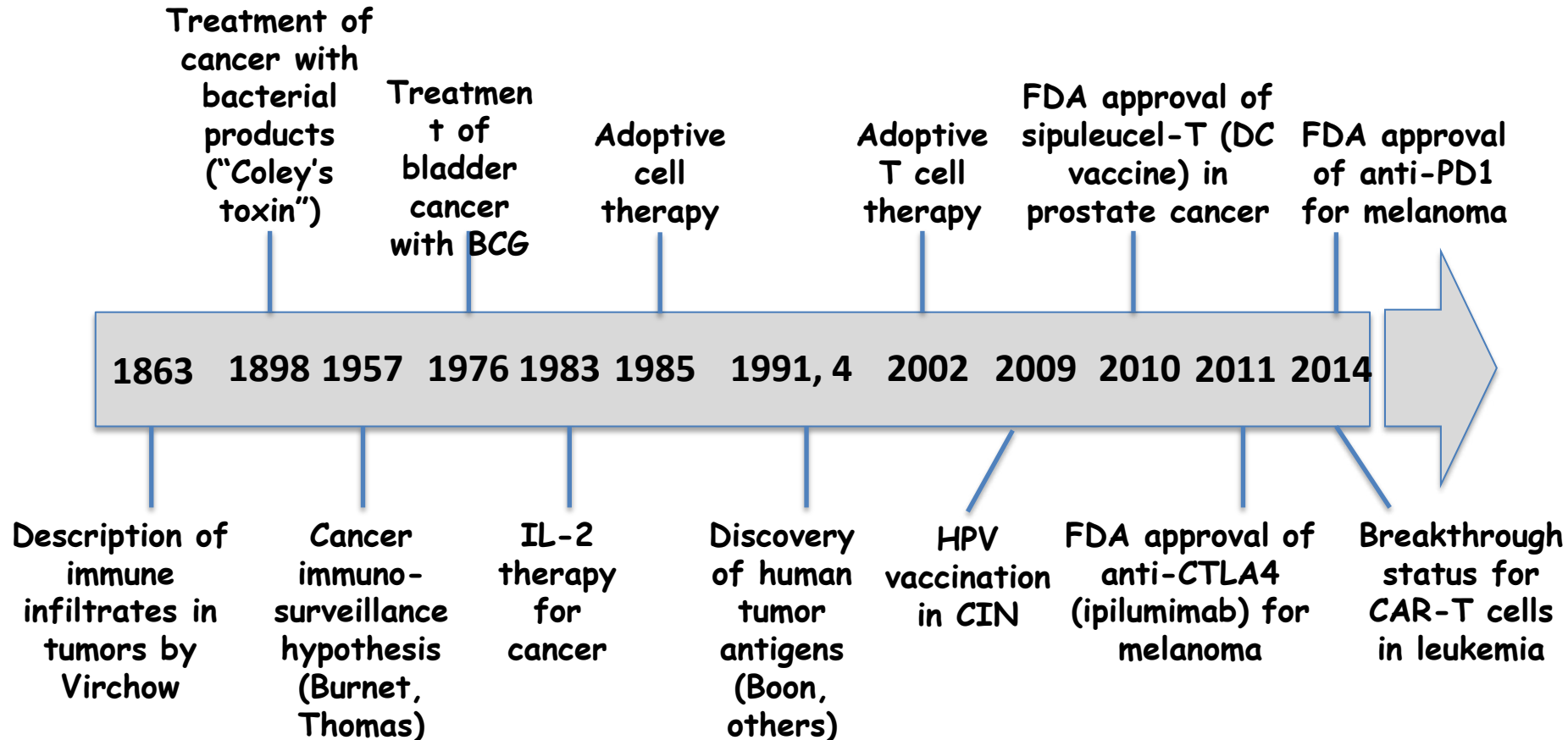
# General principles

- The immune system recognizes and reacts against cancers
- The immune response against tumors is often dominated by regulation or tolerance
  - Evasion of host immunity is one of the hallmarks of cancer
- Some immune responses promote cancer growth
- Defining the immune response against cancers will help in developing new immunotherapies

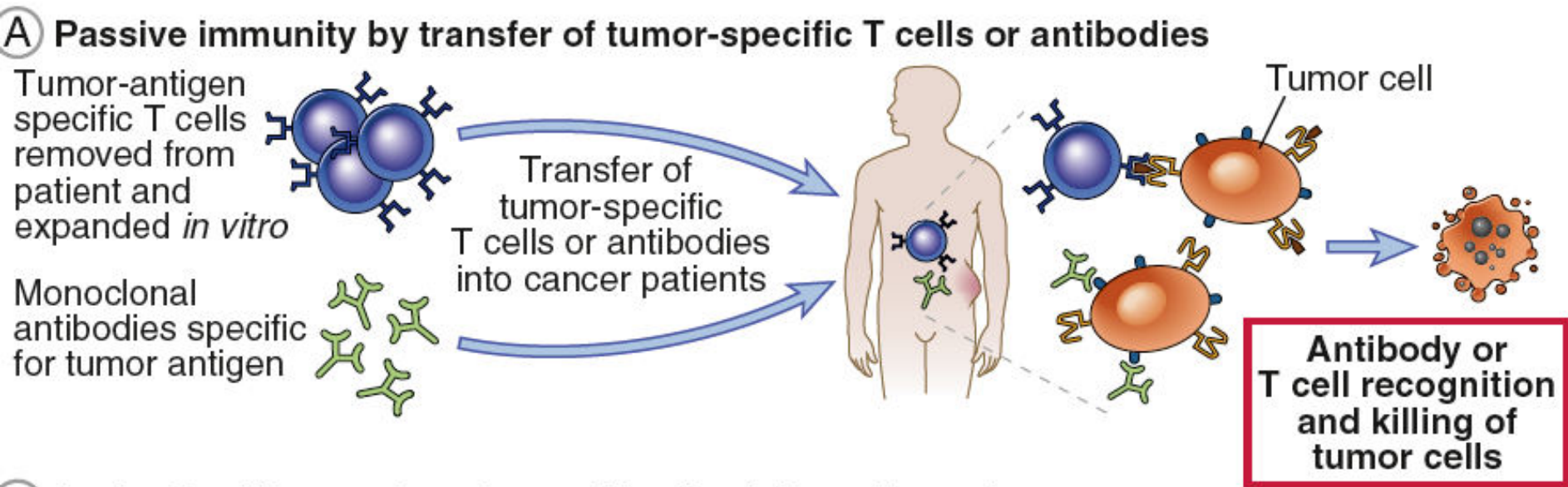
# T cell responses to tumors



# The history of cancer immunotherapy: from empirical approaches to rational, science-based therapies



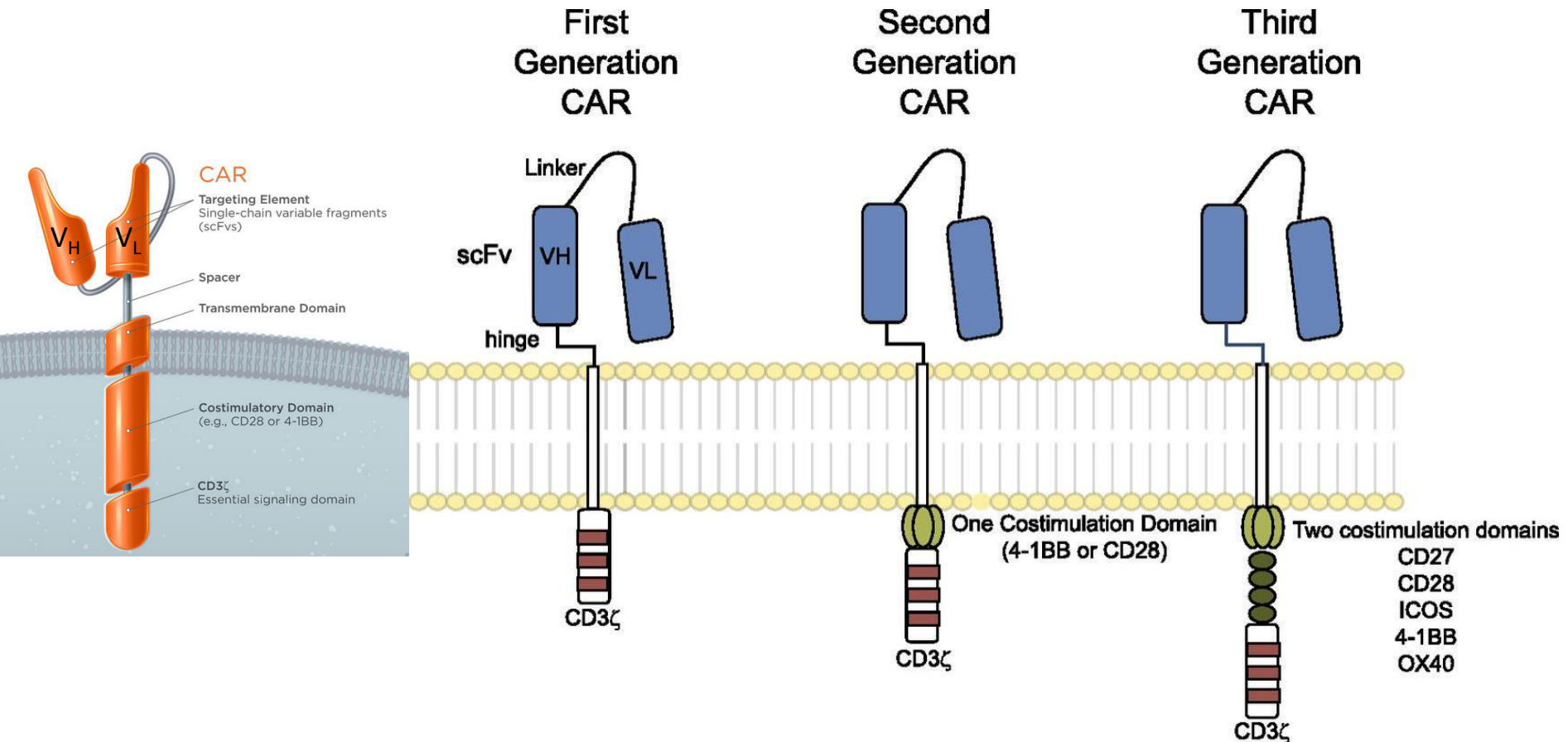
# Passive immunotherapy



# Tumor-specific T cell therapy

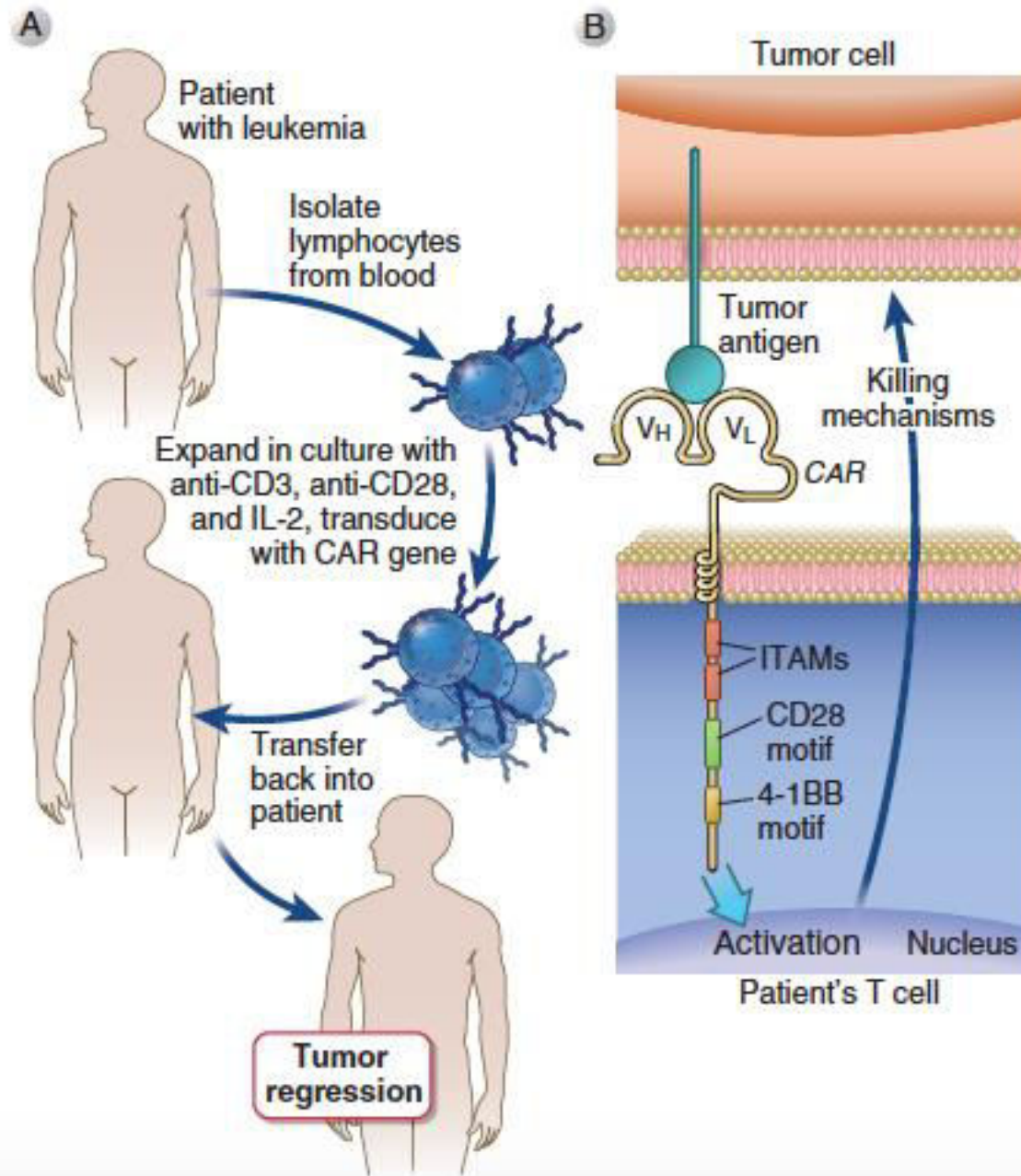
- Problem with initial approaches: not enough tumor-specific T cells
- How to generate large numbers?
  - Transfect tumor-specific antigen receptor into T cells, expand the cells in vitro
- Which tumor-specific antigen receptor to express in T cells?
  - Problems with expressing TCR
  - Alternative: 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
- Exhaustion of transferred T cells
- Technically challenging and expensive

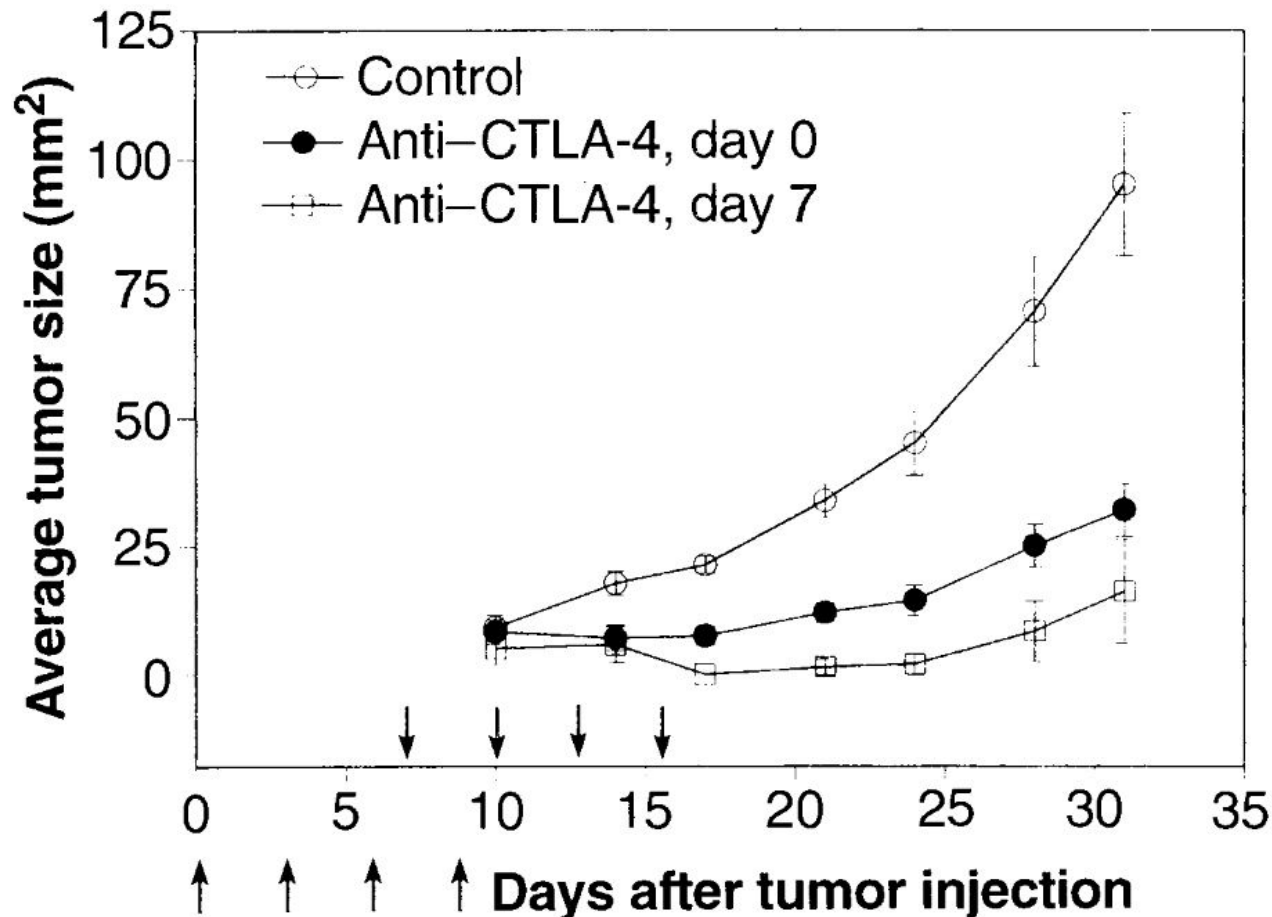
# Cytokine release syndrome

- Caused by large number of T cells responding to target antigen
- Similar to septic shock
- Good clinical response with anti-IL6R (tocilizumab)
- Some complications (e.g. encephalopathy) may not be as responsive as systemic complications

# Immune checkpoints

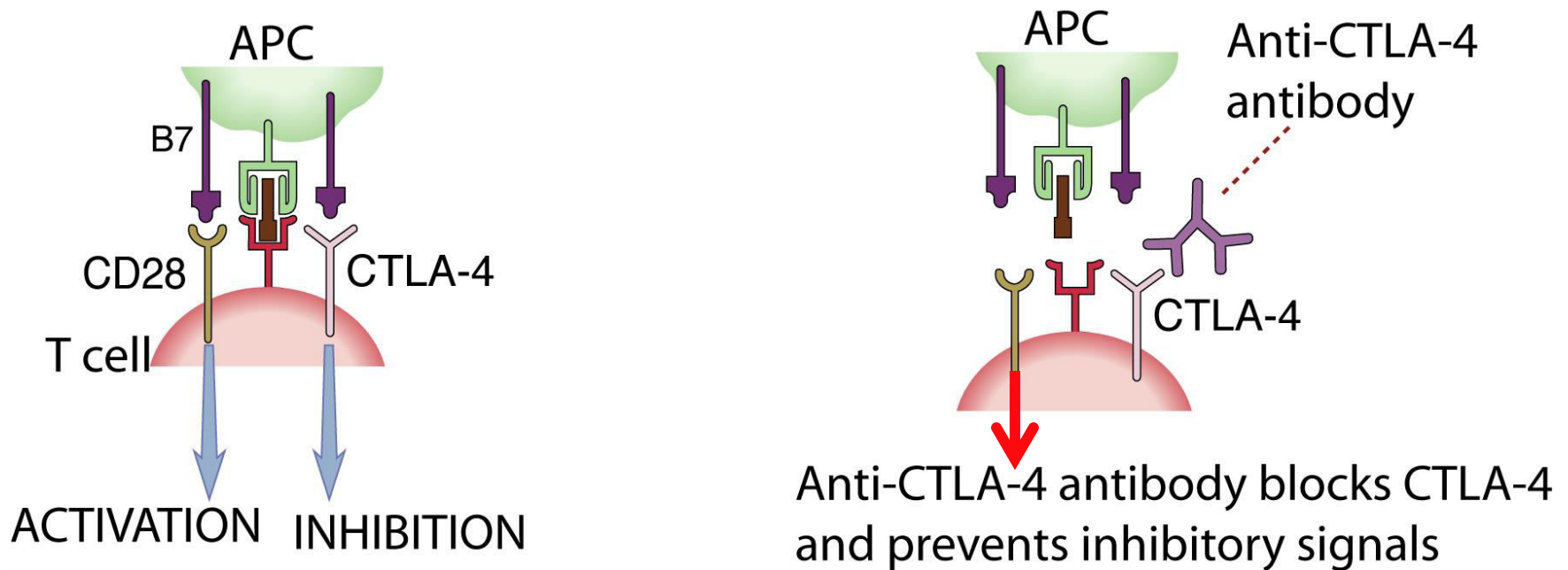
- Inhibitory receptors on T cells block activation
- CTLA-4: competes with CD28, reduces costimulation
- PD-1: activates phosphatase, blocks kinase-dependent signals from CD28 and TCR
- Many others described

# 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

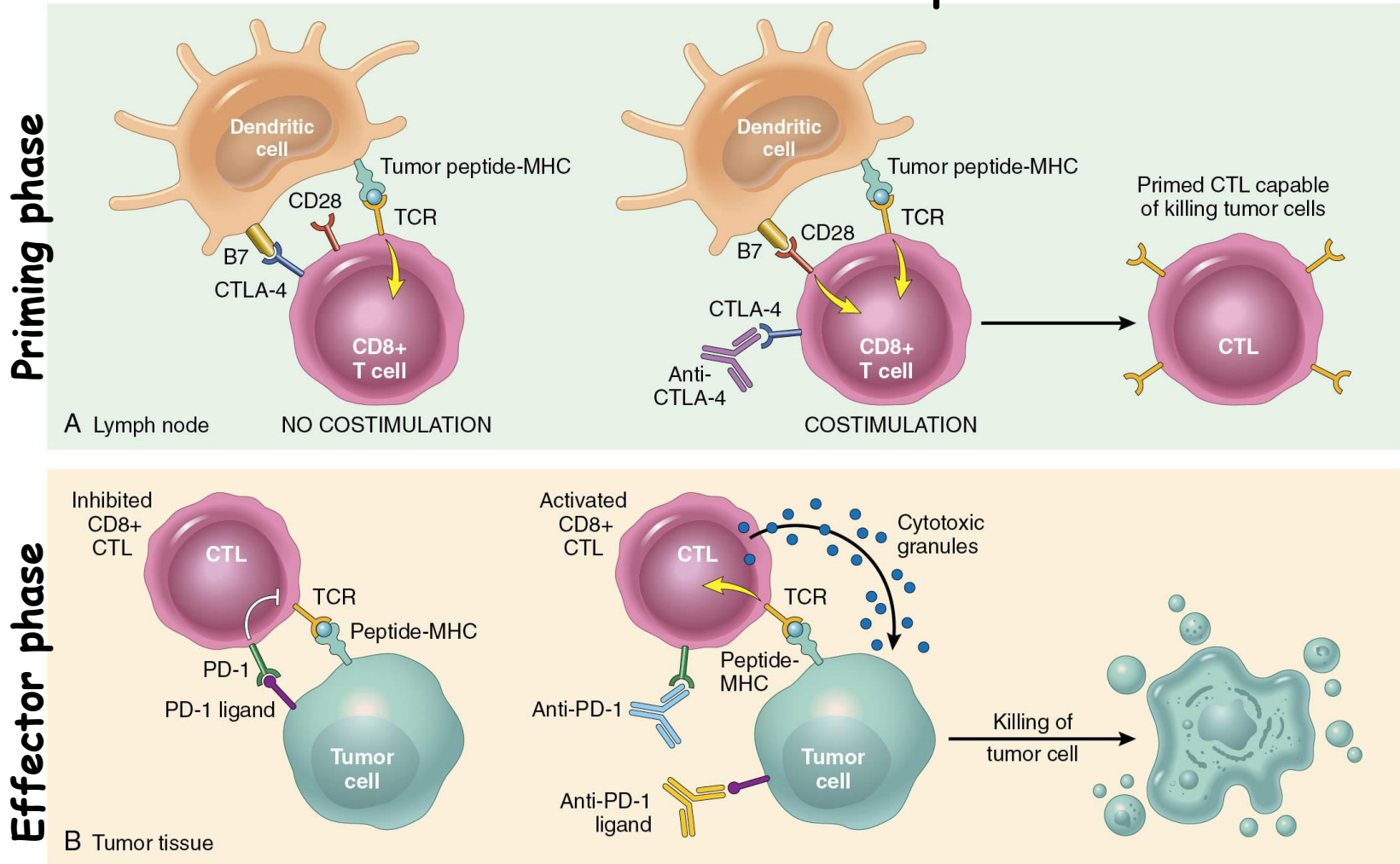


**Anti-CTLA-4 antibody is approved for tumor immunotherapy (enhancing immune responses against tumors)**

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

# Checkpoint blockade for cancer immunotherapy

## Checkpoint blockade





# Is checkpoint blockade more effective than vaccination for tumor therapy?

- Tumor vaccines have been tried for many years with limited success
- Immune evasion is a hallmark of cancer
  - Multiple regulatory mechanisms
- **Vaccines have to overcome regulation**
  - Tumor vaccines are the only examples of therapeutic (not prophylactic) vaccines
  - Vaccination after tumor detection means regulatory mechanisms are already active

## Risks of blocking CTLA-4 or PD-1

- **Blocking a mechanism of self-tolerance leads to:**

## Risks of blocking CTLA-4 or PD-1

- 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

# Autoimmune complications of checkpoint blockade

- **Most often grade 1 or 2**
  - Manageable with conservative therapy and withdrawal of immunotherapy
  - More severe with combinations of checkpoint blockers
- **Unusual features**
  - Anti-PD1/PDL1: brittle diabetes
  - Anti-CTLA4: anterior pituitary inflammation
  - Combination: myocarditis
  - All: colitis, arthritis

# Response to checkpoint blockade

