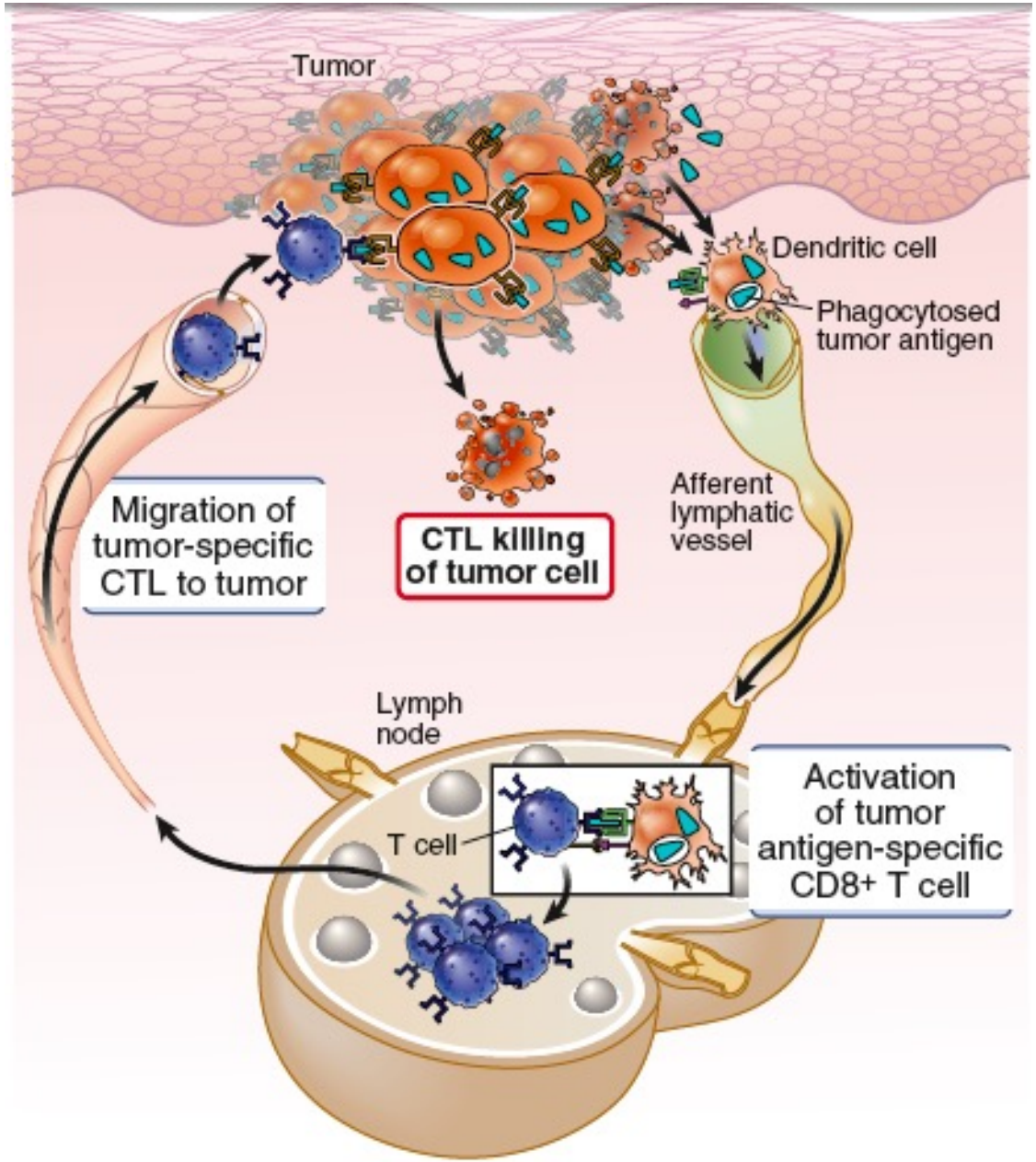
26 Oct 2023,
BT 304
Lecture 34

Tumor/Cancer immunology

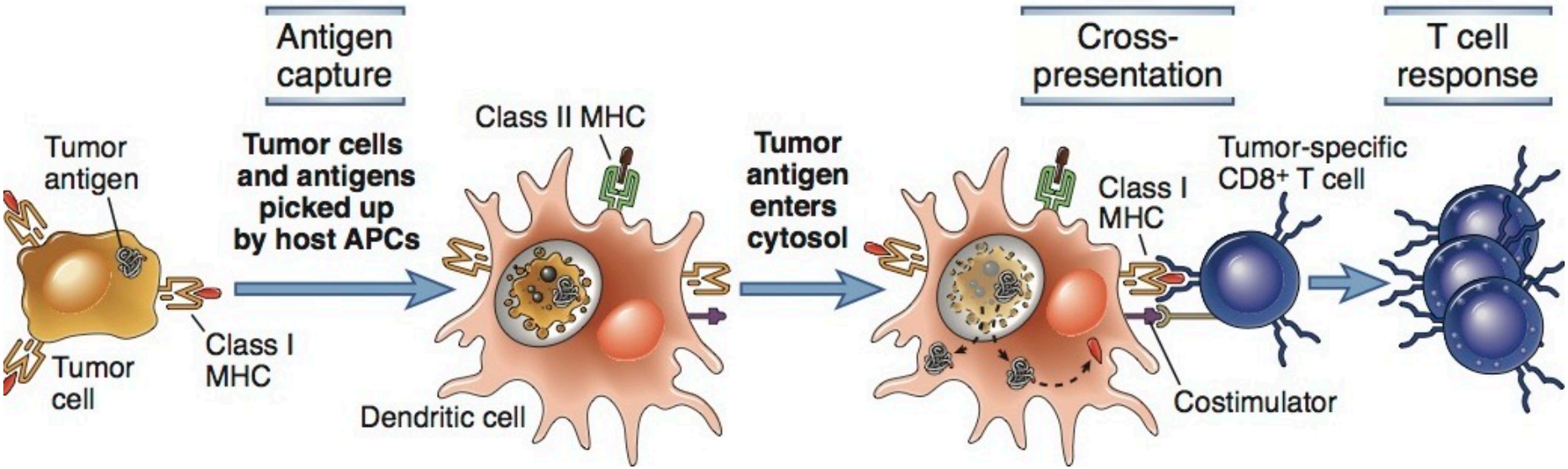
General principles

- 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



Cross-presentation of tumor antigens

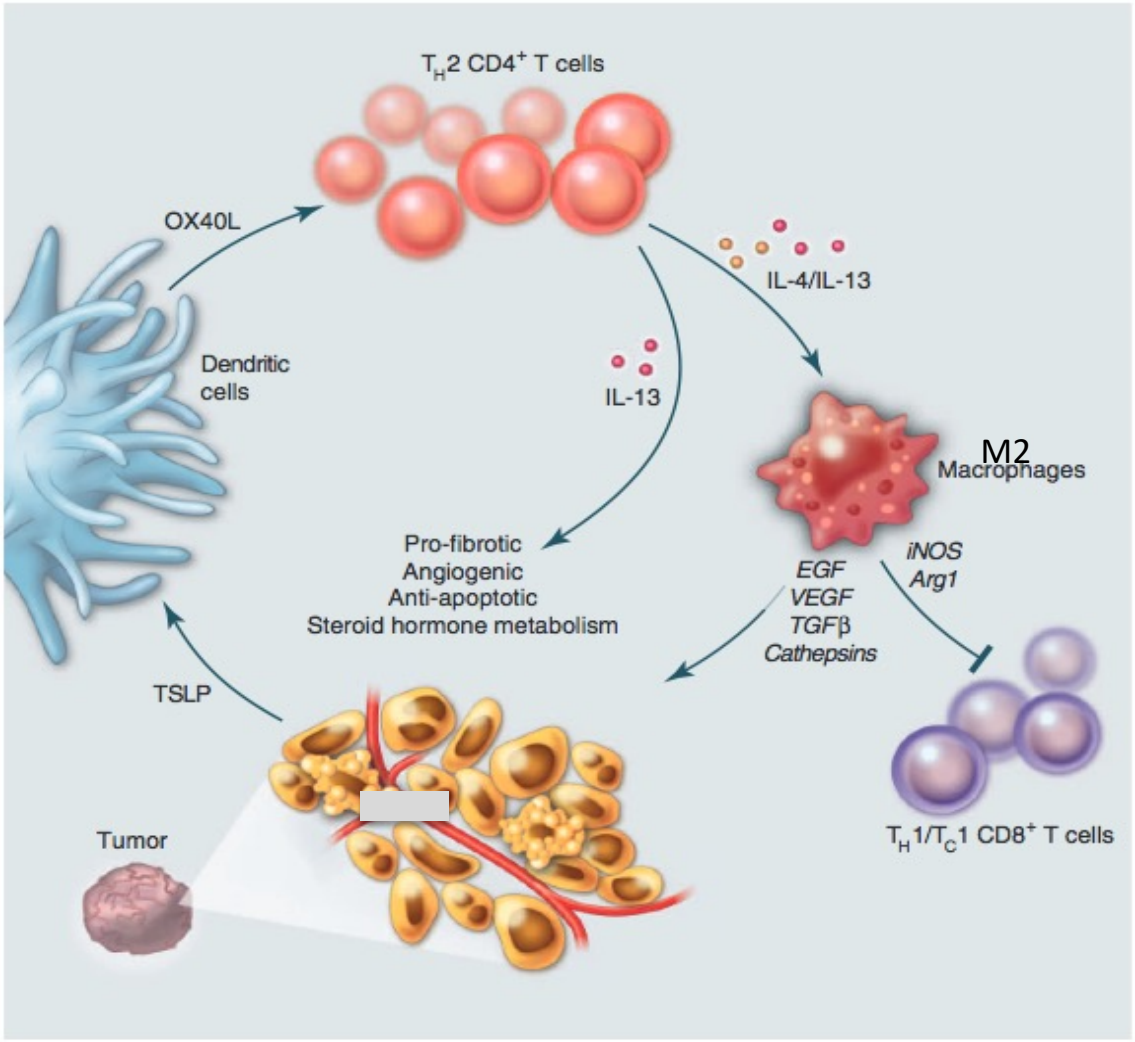


Types of tumor antigens

- **Most tumor antigens that elicit immune responses are neoantigens**
  - Not present normally, so no tolerance
  - Produced by mutated genes that may be involved in oncogenesis or reflect genomic instability
  - In tumors caused by oncogenic viruses (HPV, EBV), neoantigens are encoded by viral DNA

- **Some are unmutated proteins** (tyrosinase, cancer-testis antigens)
  - Derepressed (epigenetic changes), over-expressed

Immune responses that promote tumor growth



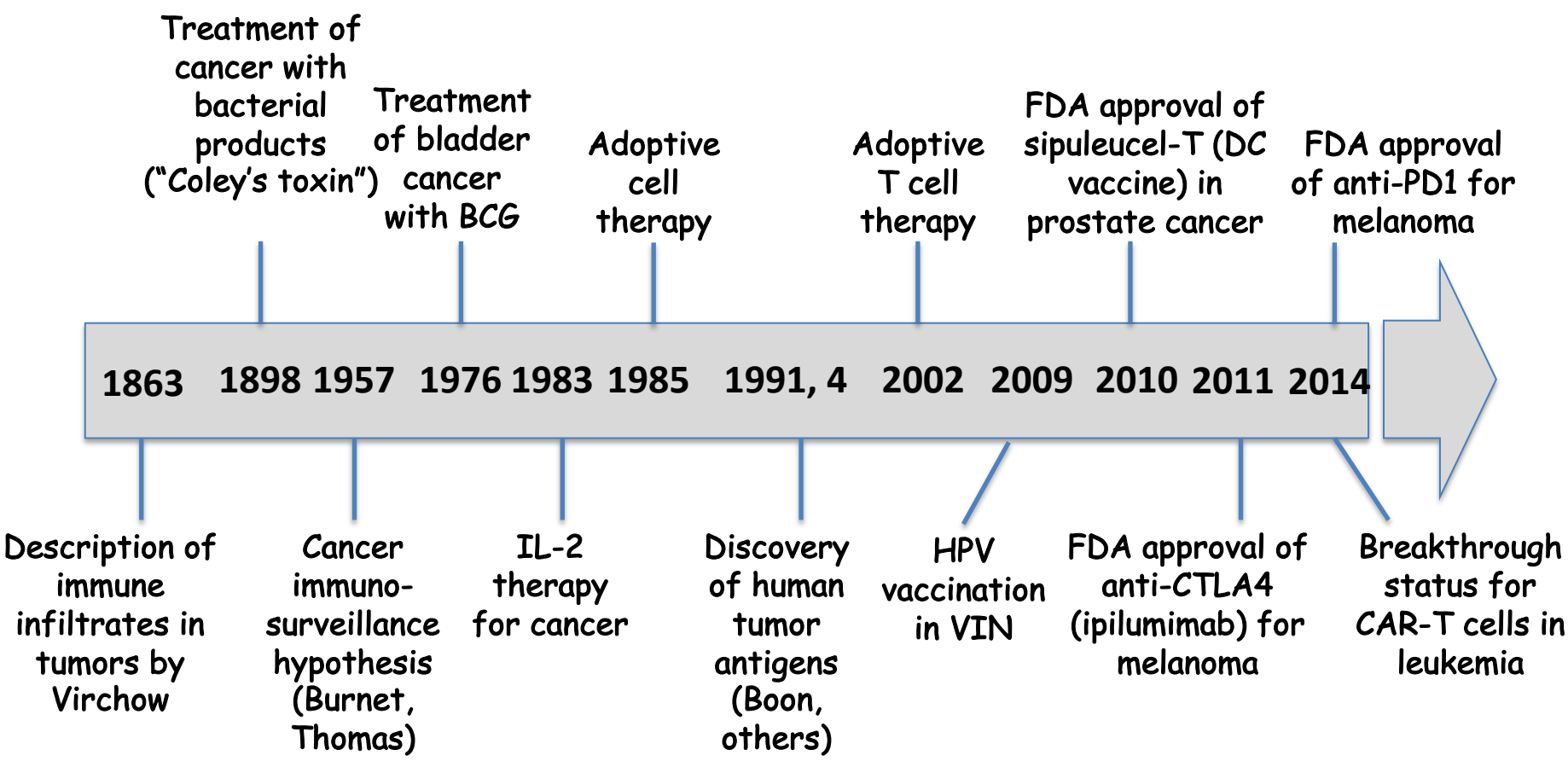
OX40L is the ligand for OX40 (also known as CD134 or TNFRSF4) and is stably expressed on many antigen-presenting cells such as DC2s (a subtype of dendritic cells),macrophages and activated B lymphocytes.
The OX40 molecule, conversely, is present on the surface of activated T lymphocytes (mainly CD4+ T cells), but also on NK cells
and neutrophils. The ligation of OX40-OX40L is a source of survival signal for T cells and enables the development of memory T cells. Signaling through these two molecules also leads to polarization towards Th2 immune response even in an environment with low levels of IL-4 cytokine.

- Thymic stromal lymphopoietin (TSLP)

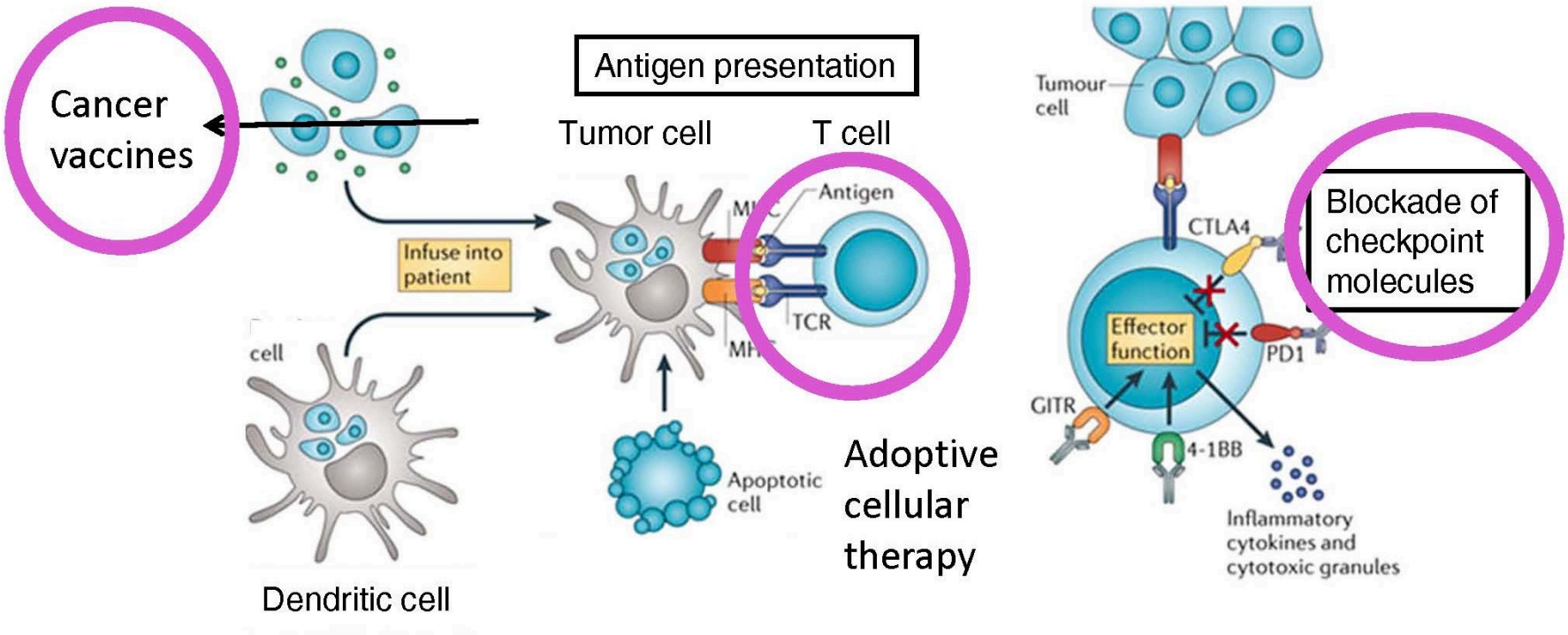
A cytokine shown to activate the maturation of a specific subset of dendritic cells

Coussens et al. Science 339:286, 2013

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

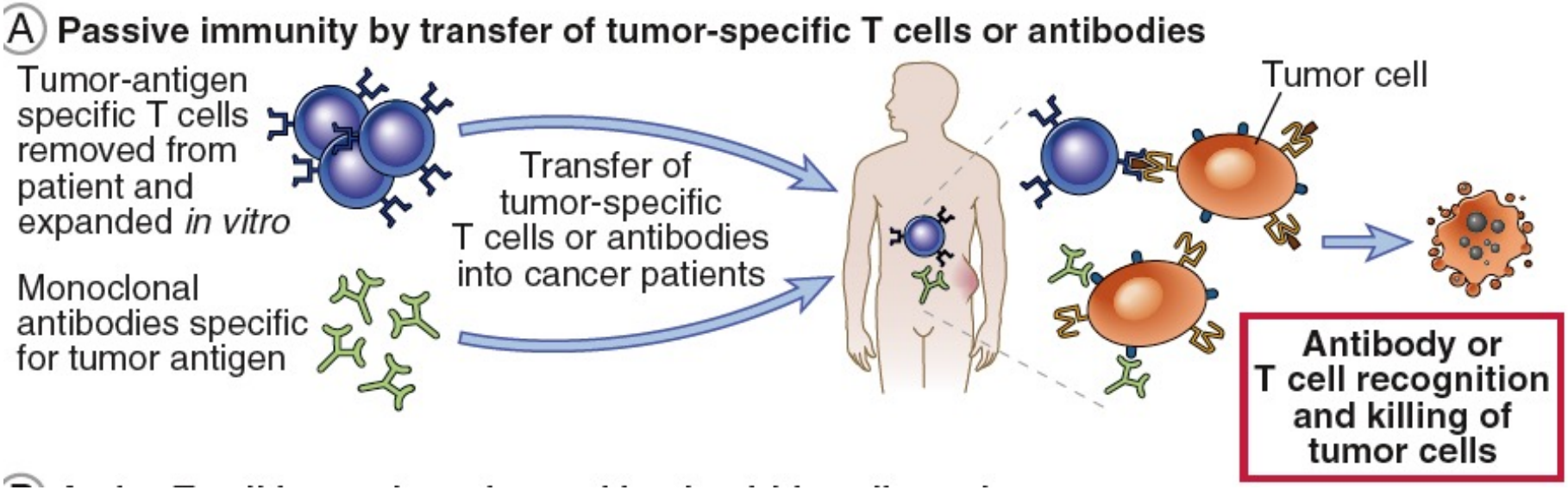


Harnessing immune system to combat cancer

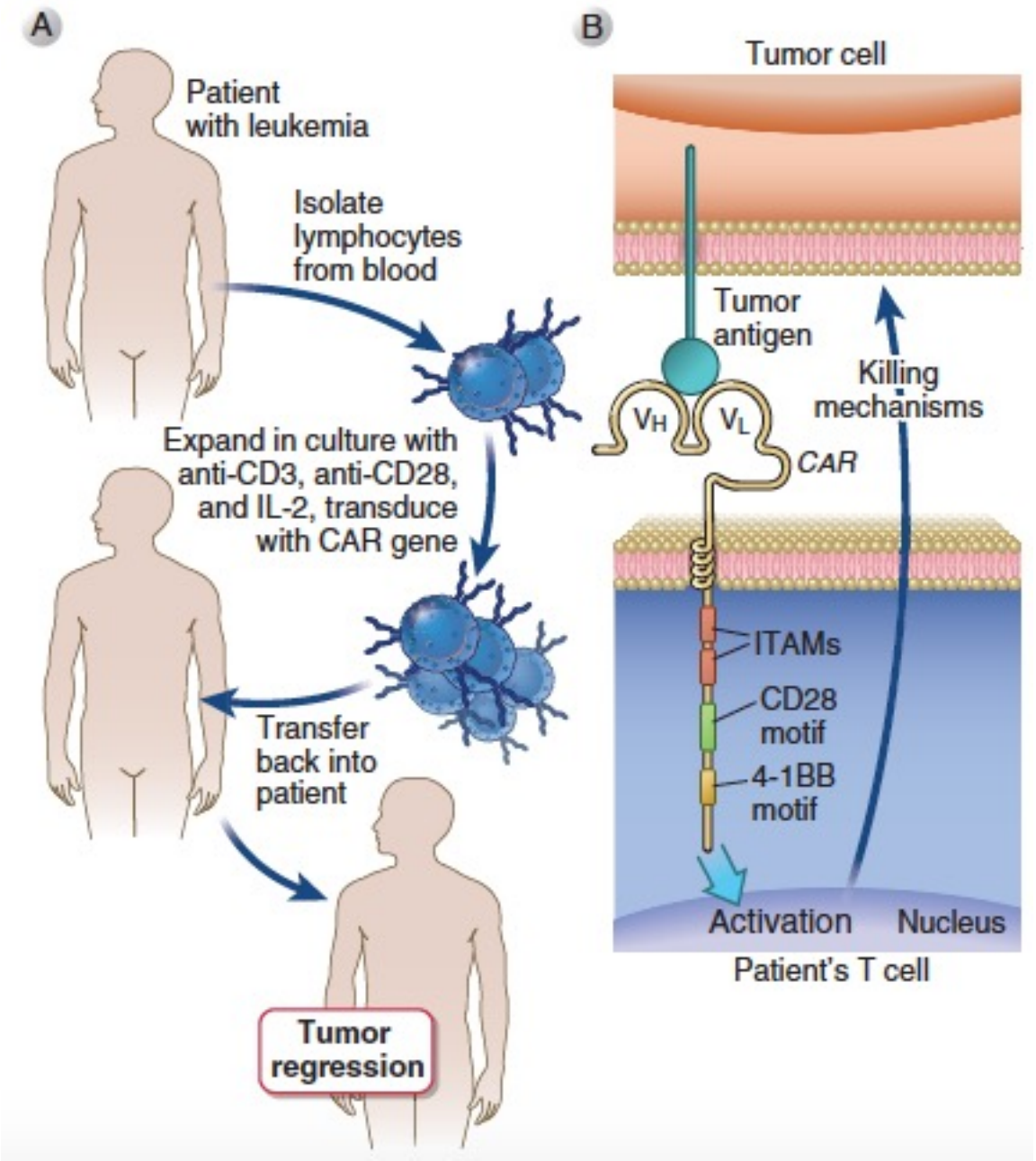


CTLA-4 or **CTLA4** (**cytotoxic T-lymphocyte-associated protein 4**), is a protein receptor that functions as an immune checkpoint and downregulates immune responses. CTLA-4 is constitutively expressed in regulatory T cells but only upregulated in conventional T cells after activation – a phenomenon which is particularly notable in cancers. It acts as an "off" switch when bound to CD80 or CD86 on the surface of antigen-presenting cells.

Passive immunotherapy



Chimeric antigen receptors (CAR)



- ***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 storm – many T cells respond to target antigen
  - Requires anti-inflammatory therapy (anti-IL-6R)
  - Risk of long-term damage (especially brain)
- Unclear how well it will work against solid tumors
  - Problem of T cells entering tumor site
- Will tumors lose target antigen and develop resistance?
- Technical and regulatory challenges of producing genetically modified CAR-T cells for each patient
  - Prospect of gene-edited "universal" CAR-T cells?