Principles of tumor immunity

Abul K. Abbas MD
UCSF

FOCiS

UCSF
University of California
San Francisco
advancing health worldwide™

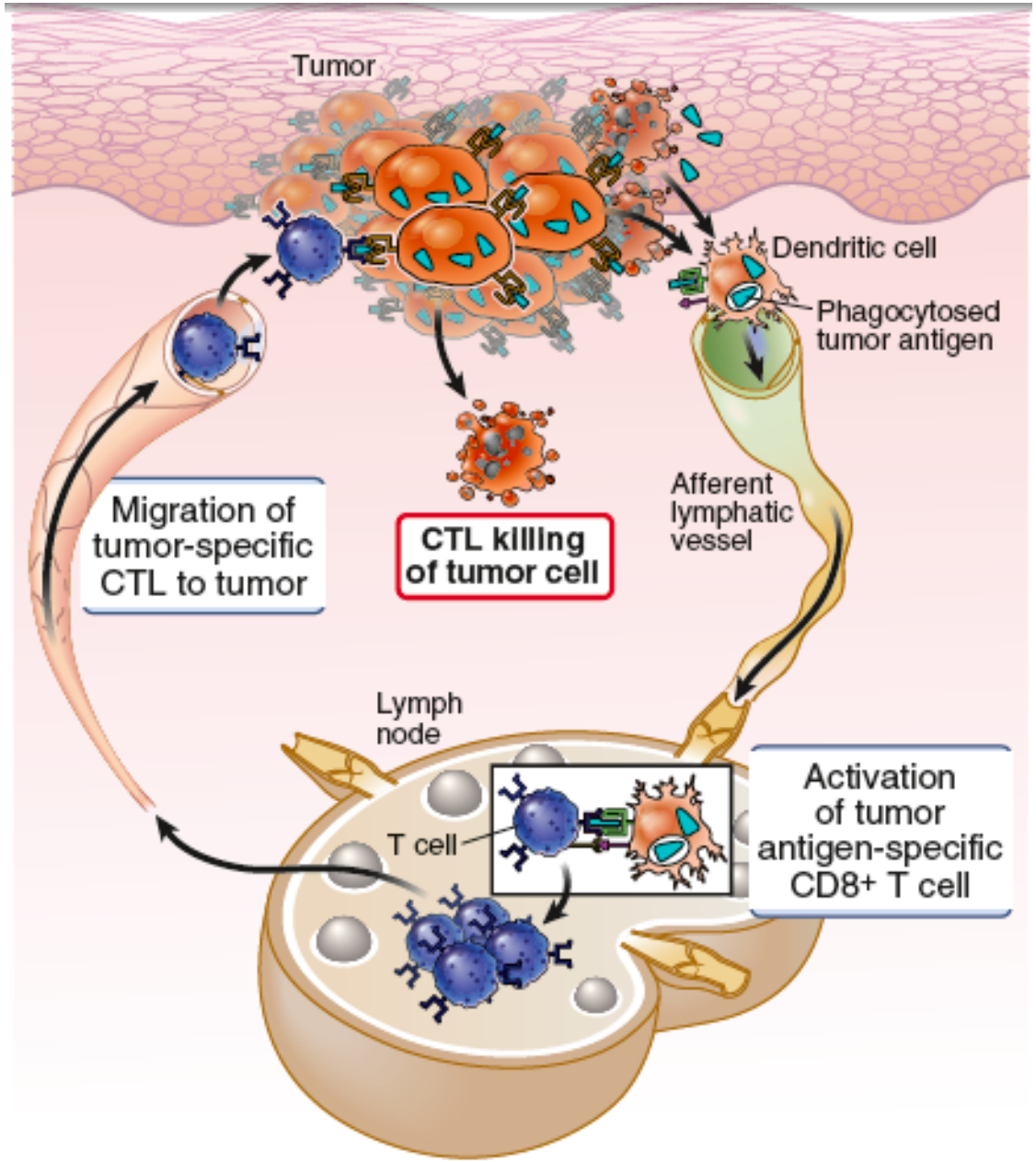
Lecture outline

- Role of the immune system in defending against cancers
  - Initiating anti-tumor immune responses
- Tumor antigens
- Immune evasion by cancers
- Immune cells that promote cancers
- New therapeutic approaches

General principles

- The immune system recognizes and reacts against cancers (immune surveillance)
- The immune response against tumors is often dominated by regulation or tolerance
  - Evasion of host immunity is one of the hallmarks of cancer (Hanahan and Weinberg *Cell* 144:646, 2011)
- Some immune responses promote cancer growth
- Immunotherapies have revolutionized the care of cancer patients

T cell responses to tumors



Initiating CD8+ T-cell responses to tumors

- To initiate T cell responses, dendritic cells capture antigens from site of production and take the antigens to secondary lymphoid organs (e.g., lymph nodes) through which naïve T cells recirculate
  - DCs are located in the correct place (tissues where tumors grow) and migrate to the correct place (co-localize with naïve T cells)
  - Are antitumor responses also initiated in the tumor environment?

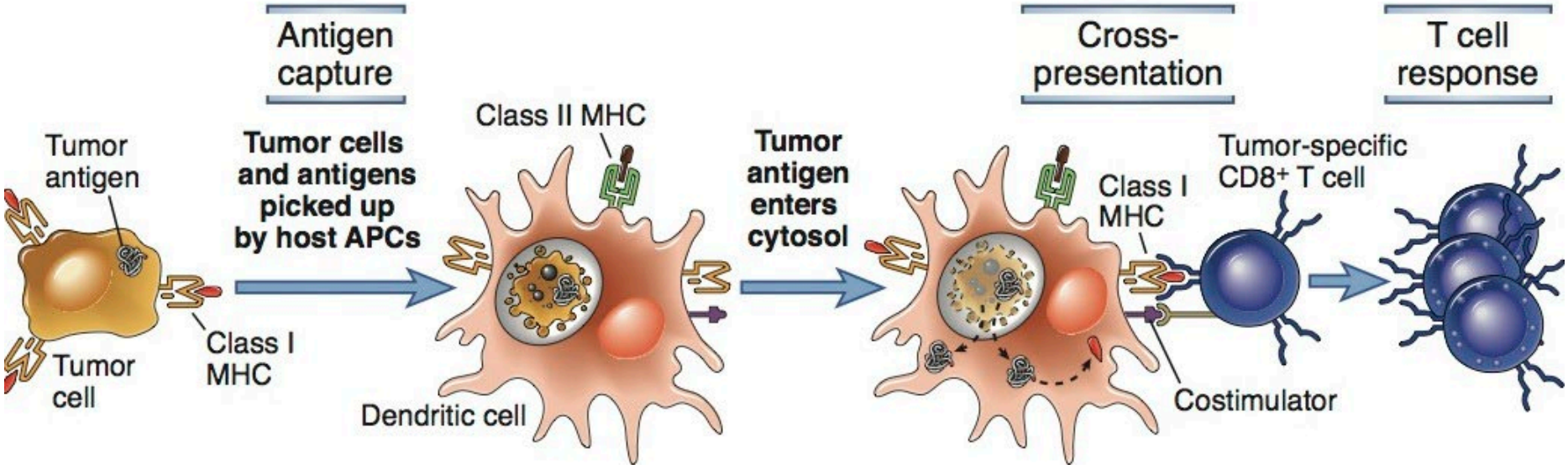
Initiating CD8+ T-cell responses to tumors

- CD8+ T cells recognize antigens present in the cytosol of cells → proteasomal processing and presentation by class I MHC

- But antigens captured by DCs are ingested into vesicles (the common pathway of class II MHC-associated antigen presentation)

- Specialized DCs transfer antigens from vesicles into the cytosol: the pathway of cross-presentation
  - Need to optimize this pathway for promoting anti-tumor immunity

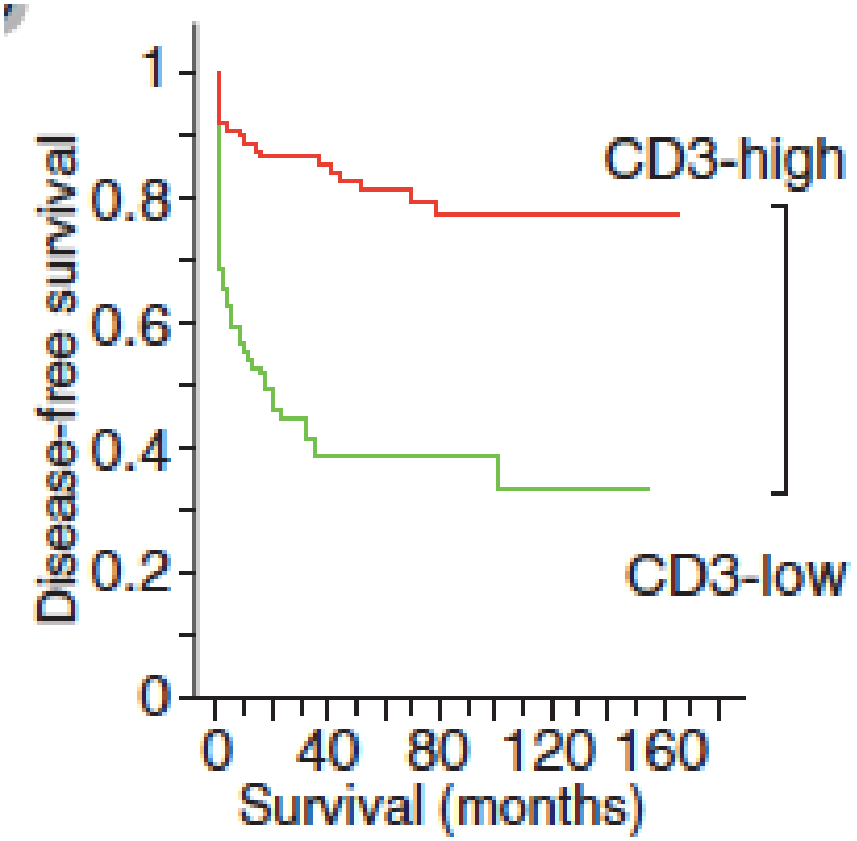
Cross-presentation of tumor antigens



Type 1 conventional DCs (cDC1) are the most potent cross-presenting APCs

Once functional CTLs are generated, they can kill tumor cells producing tumor antigens in the cytosol (peptides presented on class I MHC)

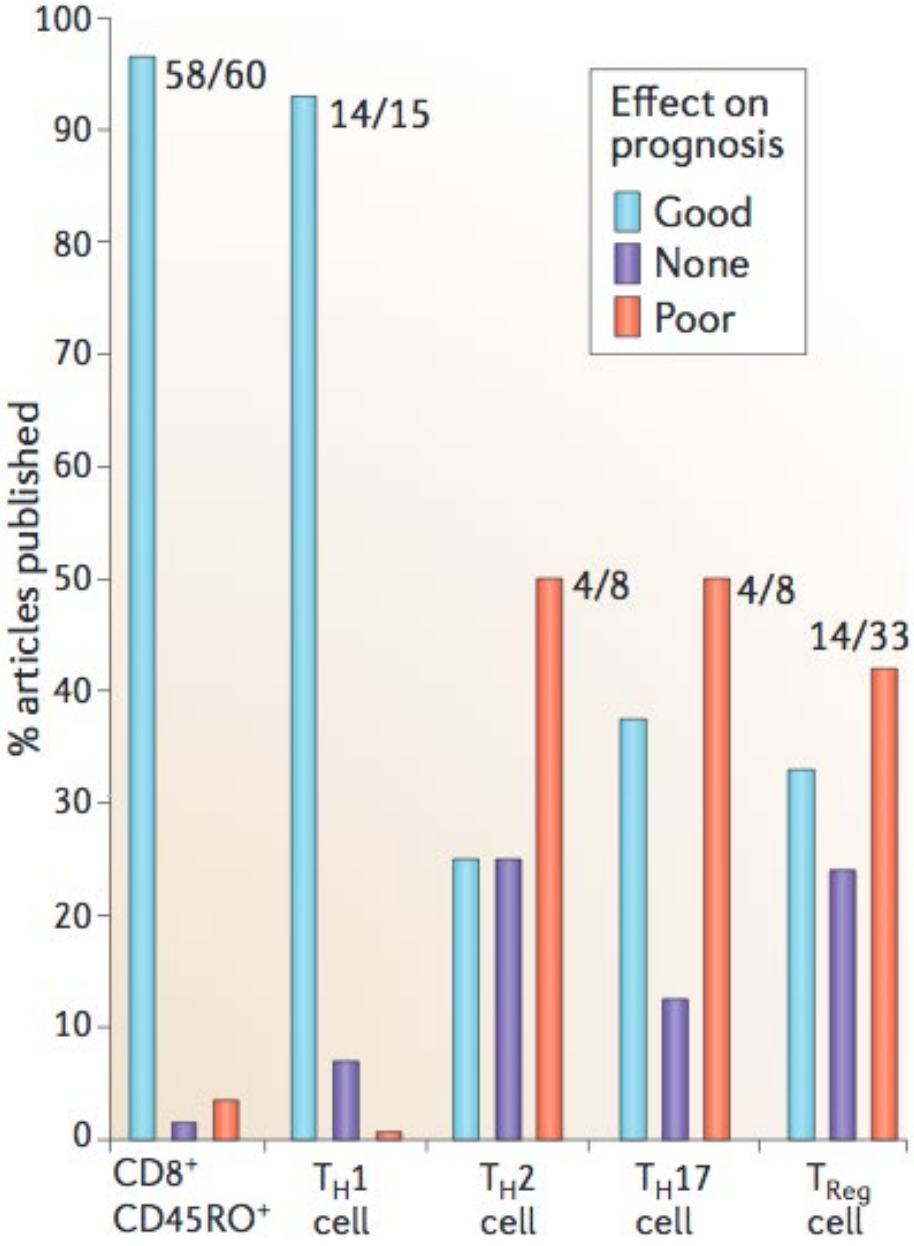
T cell infiltrate in tumor predicts survival



Analysis of T cell infiltrate in colon cancers

In some cancers, "immunoscore" is as good at predicting outcome as histologic grade and clinical stage of tumor

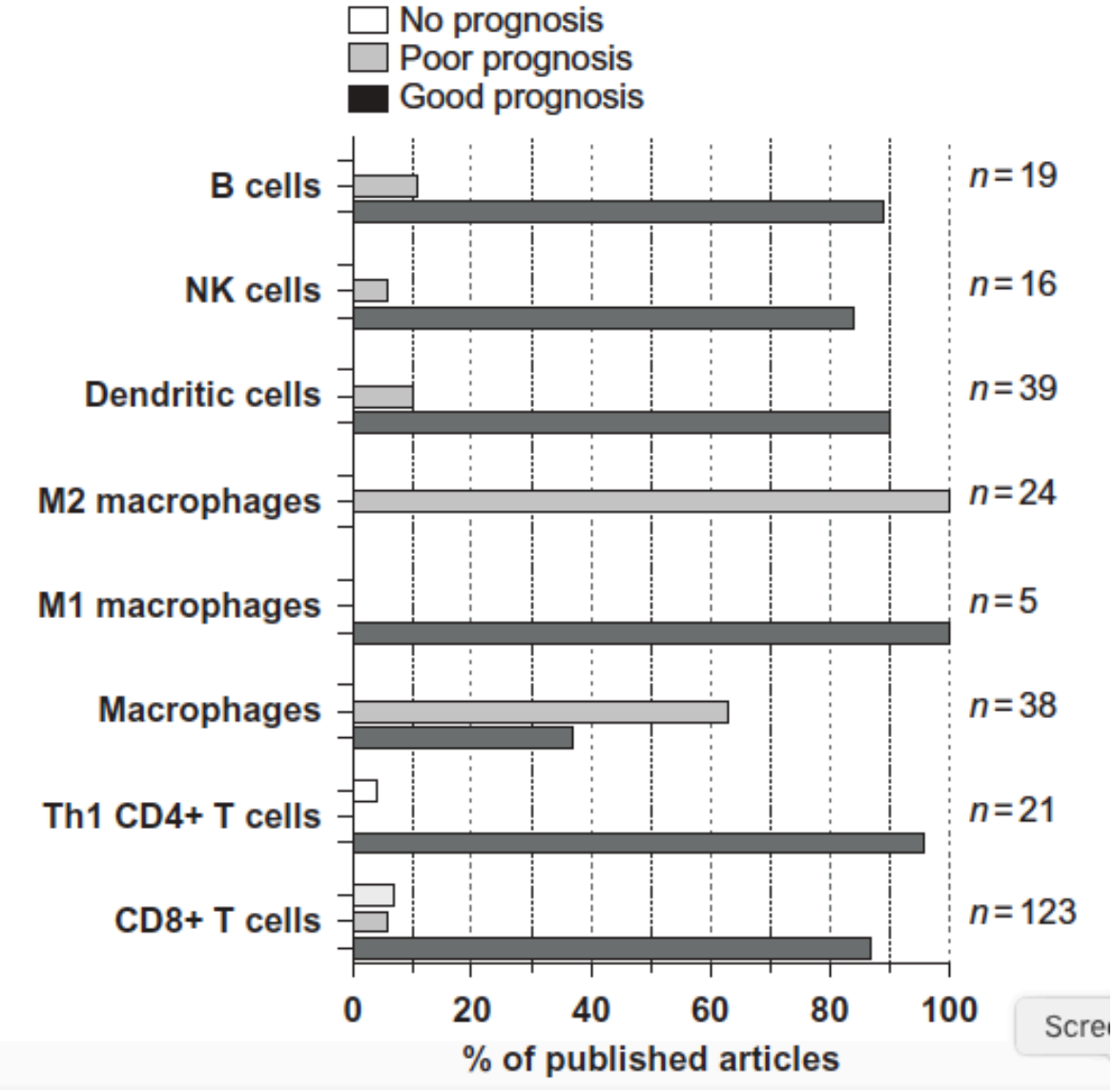
T cell phenotypes that predict better survival



Analysis of 124 published articles on correlation of T cell subsets and prognosis of 20 cancer types

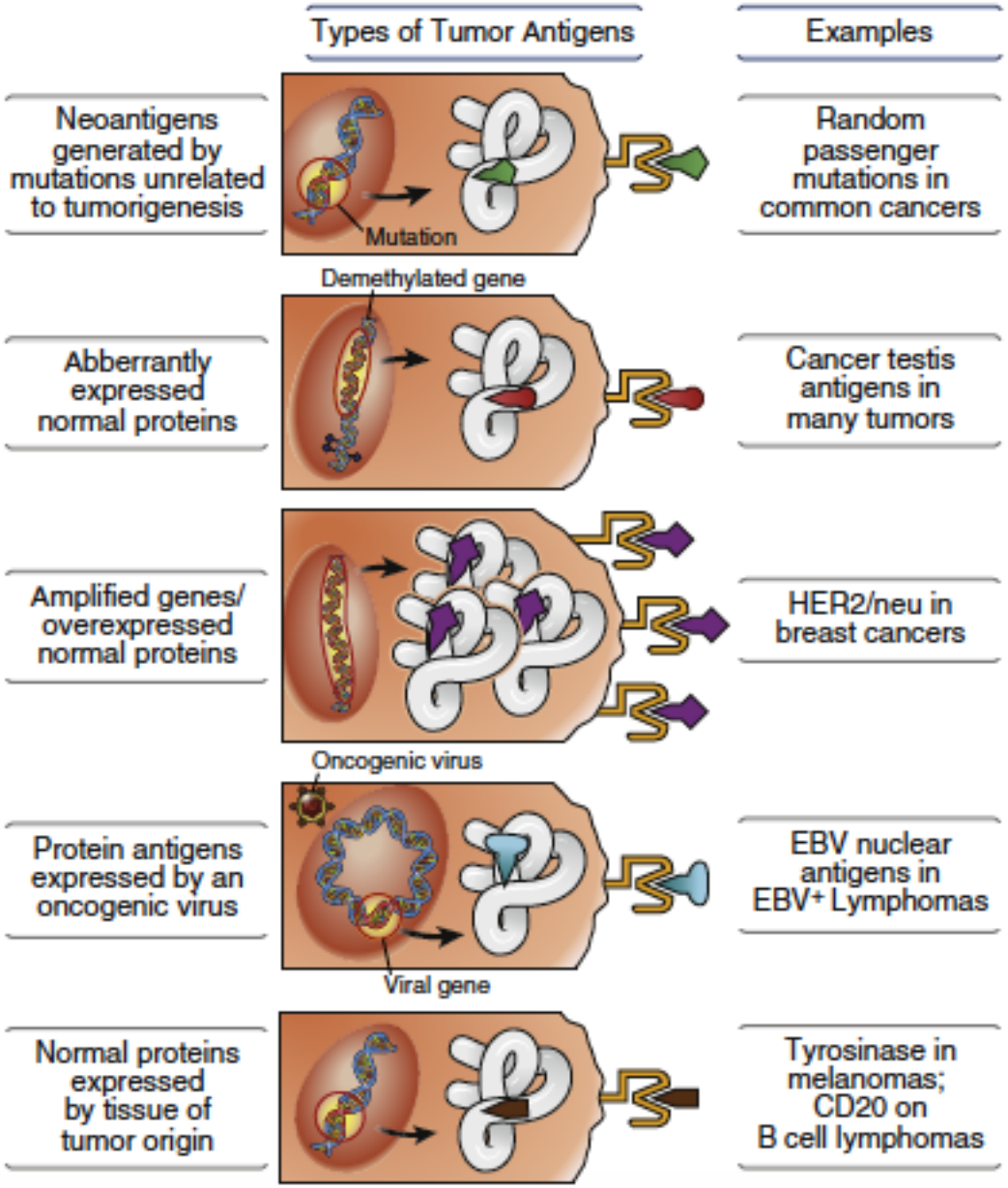
Fridman et al. Nat Rev Cancer 12:298, 2012

Prognostic significance of other immune cell types



Becht et al. Adv Immunol 130:95, 2016

Types of tumor antigens



Types of tumor antigens

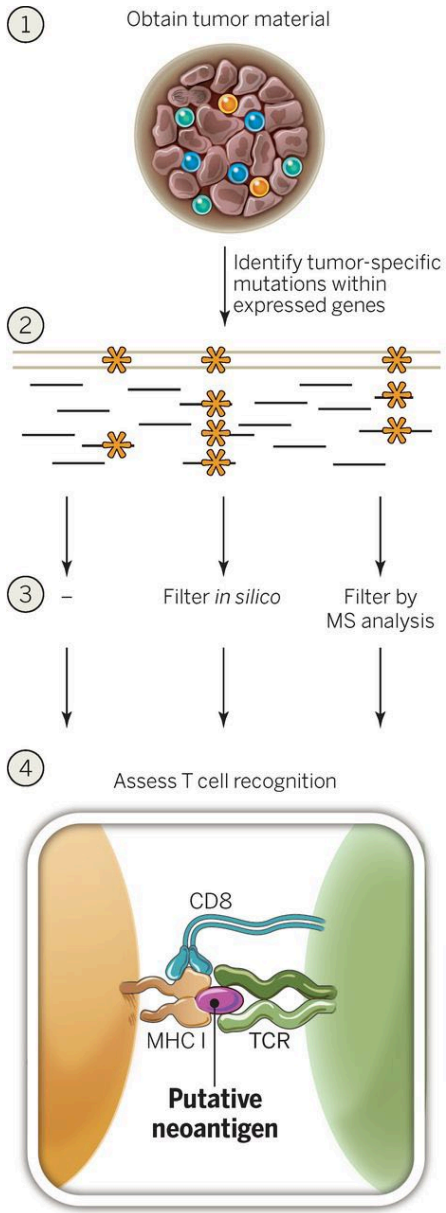
- Tumor antigens:
  - Must be tumor-specific (not in normal cells)
  - Must be capable of stimulating CD8 T cell responses in patients

- Most tumor antigens that elicit immune responses are neoantigens
  - Produced by mutated genes that are usually not involved in oncogenesis and reflect and reflect environmental carcinogen exposure and genomic instability (passenger mutations)
  - Cytosolic proteins so presented by class I MHC
  - Mutations have to be in MHC-binding epitopes
  - Not present normally, so no tolerance

Other tumor antigens

- Viral proteins
  - Only in tumors caused by oncogenic viruses (HPV, EBV)
- Unmutated proteins (tyrosinase, cancer-testis antigens)
  - Derepressed (because of epigenetic changes) or over-expressed (gene amplification)
- Cell surface antigens are often differentiation antigens that are also present in normal cells
  - Major challenge for CAR-T therapy for solid tumors

Identification of tumor neoantigens

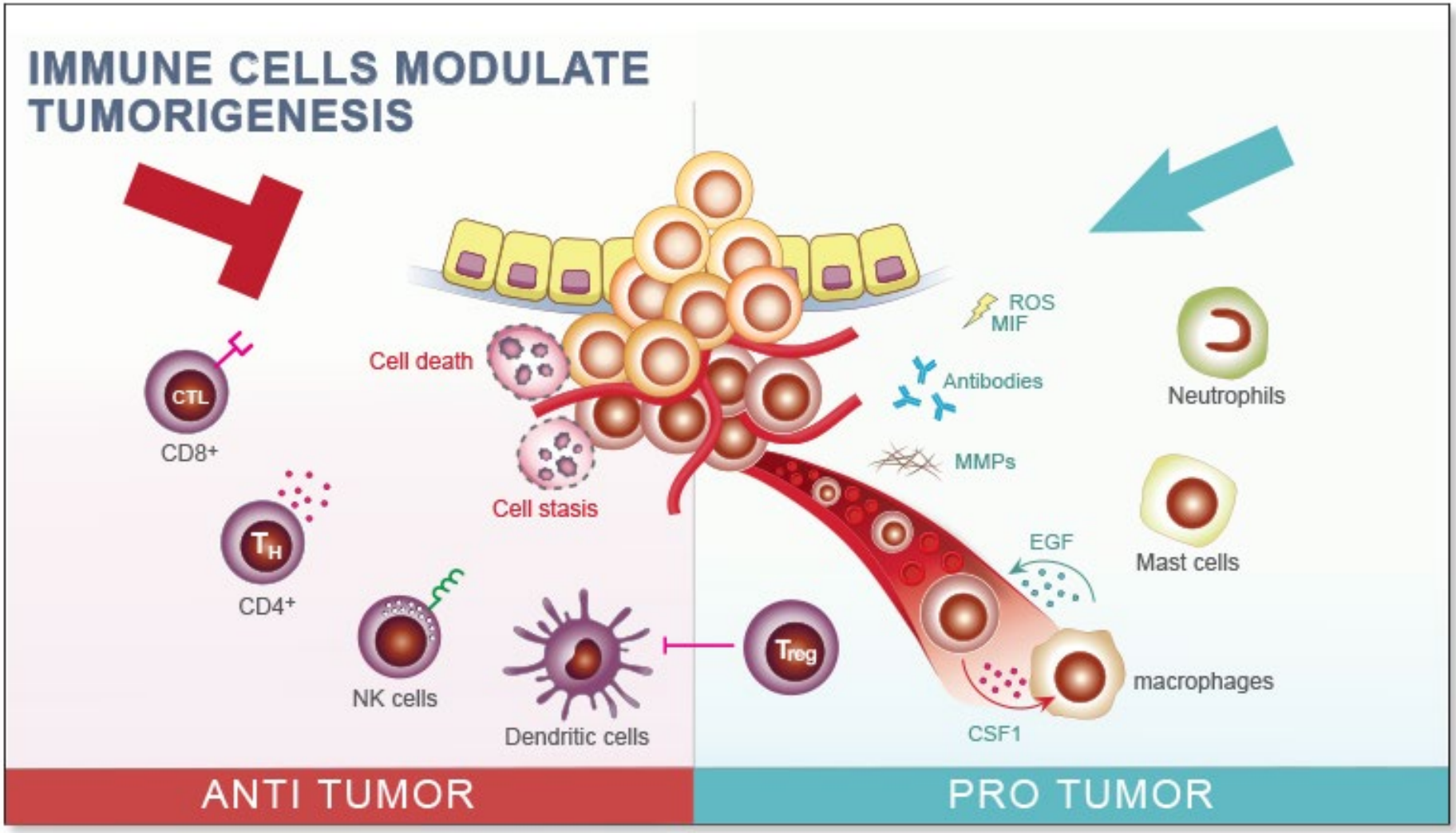


Next gen sequencing and/or RNA-seq

Identification of HLA-binding peptides

MHC-peptide multimer and/or functional assays

Ton N. Schumacher, and Robert D. Schreiber Science 2015;348:69-74



From M. DuPage, UC-Berkeley

Cell types that may promote cancers

- Foxp3+ regulatory T cells (Tregs)
  - Variable results in humans
- Alternatively activated (M2) macrophages
  - Mechanism of action?
- Myeloid-derived suppressor cells (MDSC)
  - Poorly defined markers
- B cells
  - In experimental models only

Manipulating the tumor microenvironment

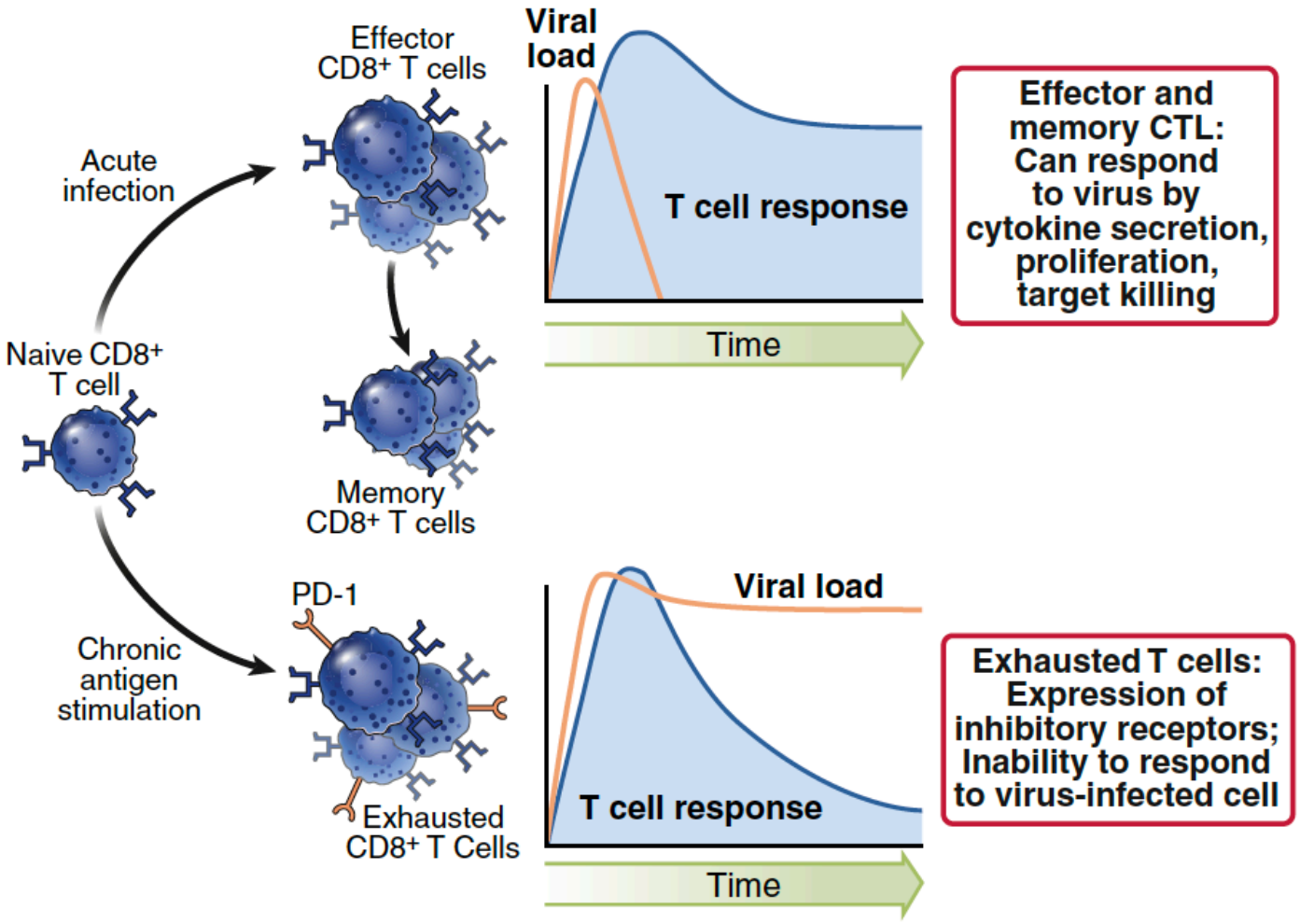
- Goal: stimulate protective (anti-tumor) cells and disable or eliminate pro-tumor cells

- Challenges:
  - Heterogeneity (TME varies in the same tumor type in different individuals and sometimes at different sites in the same patient)
  - Lack of markers for cell type-specific deletion (e.g., MDSCs)
  - Systemic depletion can cause serious adverse effects (e.g., Tregs)

Tumor immune evasion mechanisms

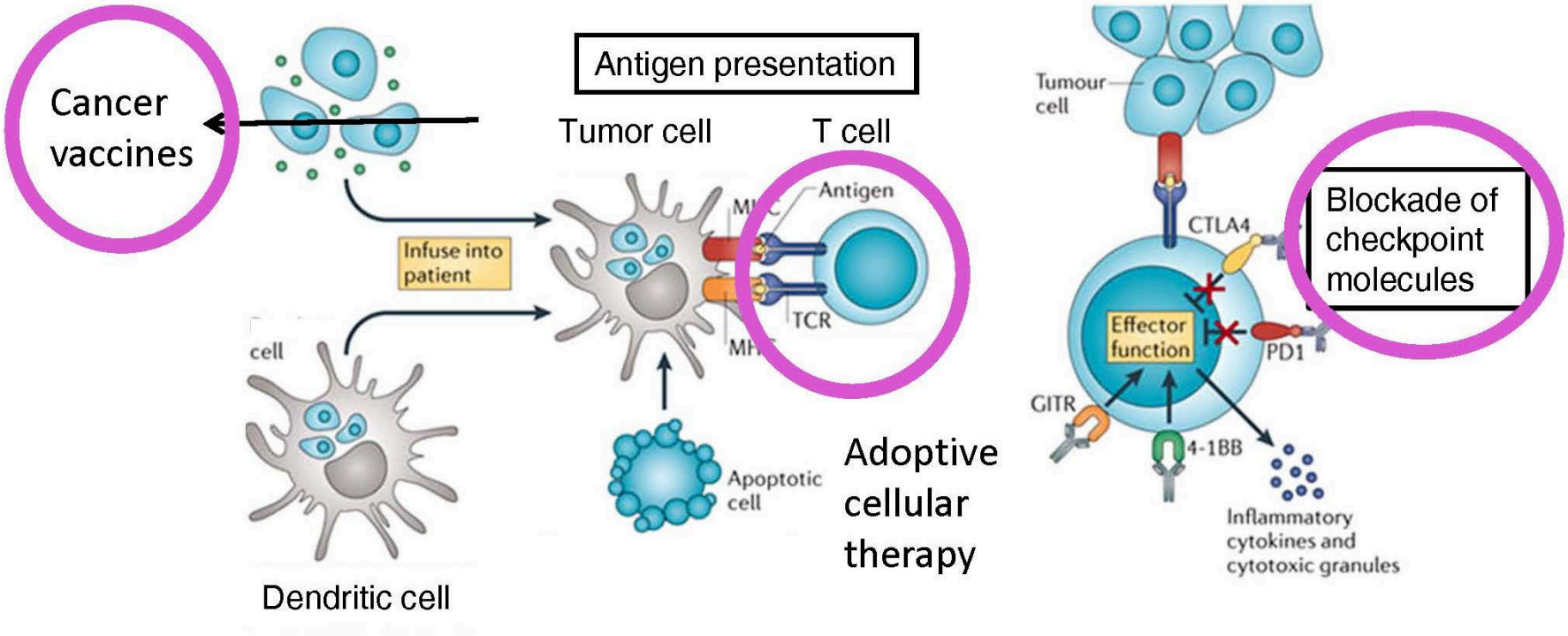
- Loss of MHC and proteins involved in antigen processing
  - Mutations in β2-microglobulin
- T cell exhaustion
  - Repeated stimulation of T cells
- Expression of PD-L1
  - PD-L1 is also induced on myeloid cells in the tumor microenvironment
- Secretion of immunosuppressive molecules
  - TGF-β, others

T cell exhaustion



The same principle applies to stimulation by tumors

Harnessing the immune system to combat cancer



Vanneman and Dranoff, Nat Rev Can, 2012

Cancer vaccines

- Which antigens?
- How to induce potent CTL responses?
- Avoiding immune evasion by tumors
- Overcoming tumor-induced immune regulation (e.g., checkpoints)
- Changes in tumor antigens with clonal evolution

Adoptive cellular therapy

- Limiting factor is frequency of tumor-specific T cells
  - Initial attempts with cells from patients had mixed success (too few tumor-specific T cells?)
  - Rationale of CAR-T
- Challenges with CAR-T therapy
  - Toxicity (strong T cell activation)
  - Immune evasion mechanisms of tumors
  - T cell exhaustion
  - Unable to target tumor-specific antigen for solid tumors

Checkpoint blockade therapy

- Based on defining checkpoints (brakes) in immune responses
  - CTLA-4: removes B7, competitive inhibitor of CD28
  - PD-1: signaling inhibitor
  - Others: not well defined

Functions of CTLA-4 and PD-1

	CTLA-4	PD-1
Major site of action	Lymphoid organs	Peripheral tissues
Stage of immune response suppressed	Induction	Effector phase
Mechanism of action	Removes B7, out-competes CD28	Signaling inhibitor of CD28 and TCR
Cell type suppressed	CD4+ > CD8+	CD8+ > CD4+

Challenges in checkpoint blockade

- Effective in only a minority of patients
  - Combination strategies to increase the frequency of responders; so far, only successful combination is blocking CTLA-4 and PD-1
- Toxicity: autoimmune reactions
  - Cannot separate anti-tumor effect from autoimmunity
- Lack of predictive biomarkers
  - Which patients will respond?