THE UNIVERSITY OF CHICAGO MEDICINE

Immunology 101

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Disclosures

- I served as a consultant on Advisory Boards for Merck and Seattle Genetics.

- I will discuss non-FDA-approved therapies for cancer

Outline

- Innate and adaptive immune systems – brief intro
- How immune responses against cancer are generated
- Cancer antigens in the era of cancer exome sequencing
- Dendritic cells
- T cells
- Cancer immune evasion
- Cancer immunotherapies – brief intro

The immune system

- Evolved to provide protection against invasive pathogens
- Consists of a variety of cells and proteins whose purpose is to generate immune responses against micro-organisms
- The immune system is “educated” to attack foreign invaders, but at the same time, leave healthy, self-tissues unharmed
- The immune system can sometimes recognize and kill cancer cells
- 2 main branches
  - Innate immune system – Initial responders
  - Adaptive immune system – Tailored attack

The immune system – a division of labor

Innate immune system

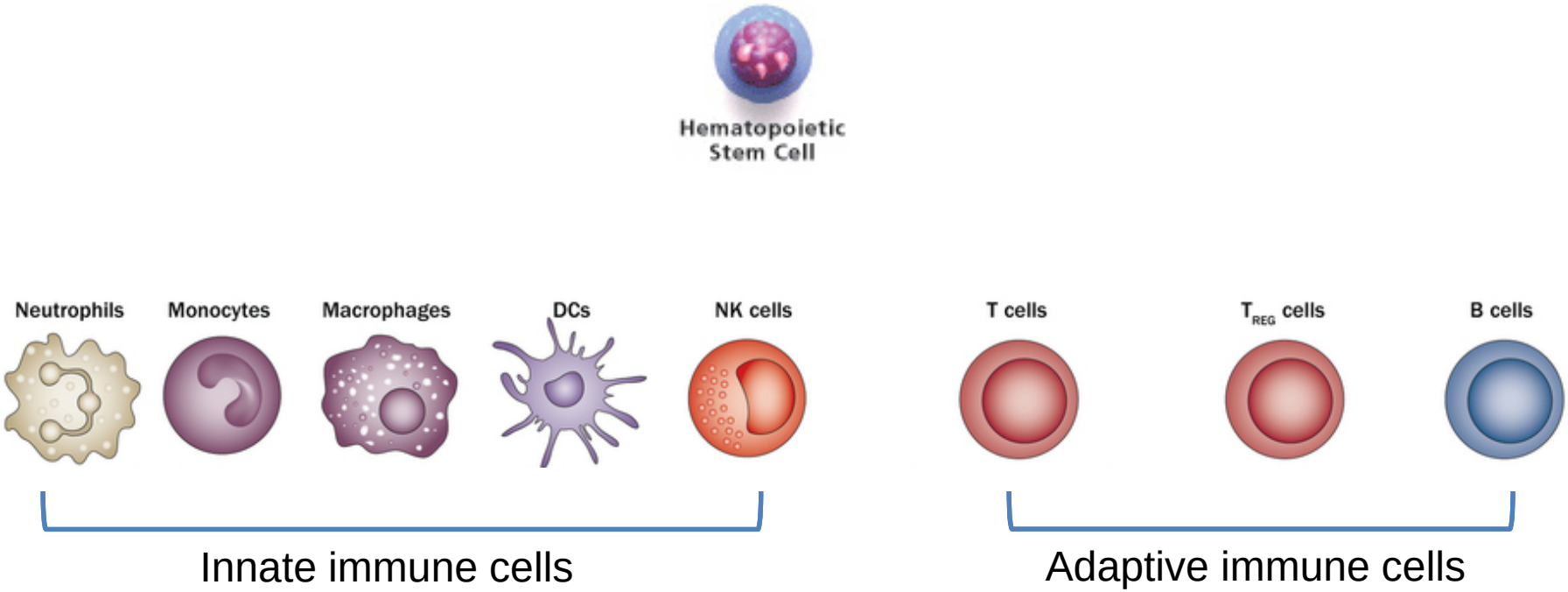
- Initial recognition of non-self (i.e. infection, cancer)
- Comprised of *cells* (granulocytes, monocytes, dendritic cells and NK cells) and *proteins* (complement)
- Recognizes non-self via receptors that “see” microbial structures (cell wall components, DNA, RNA)
  - Pattern recognition receptors (PRRs)
- Necessary for priming adaptive immune responses

The immune system – a division of labor

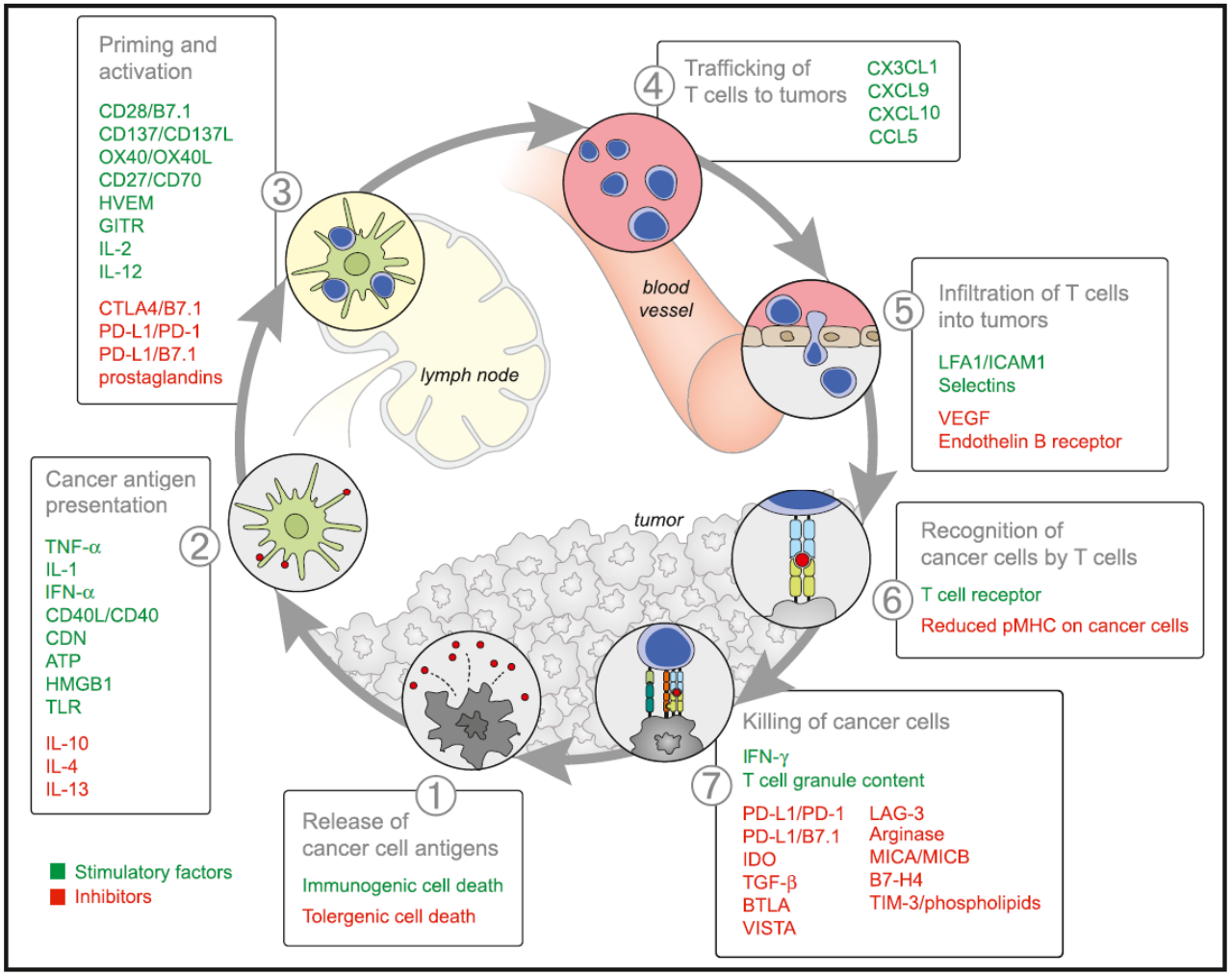
Adaptive immune system

- Provides nearly unlimited diversity of receptors to protect the host from infection
- B cells and T cells
- Have unique receptors generated during development
  - B cells produce antibodies which help fight infection
  - T cells patrol for infected or cancerous cells
    - Recognize “foreign” or abnormal proteins on the cell surface
  - 100,000,000 unique T cells are present in all of us
- Retains “memory” against infections and in some cases, cancer.

Immune cells develop in the bone marrow



Generating an immune response against cancer



Chen and Mellman, Immunity 2013

How are cancer cells seen as “abnormal” by the immune system?

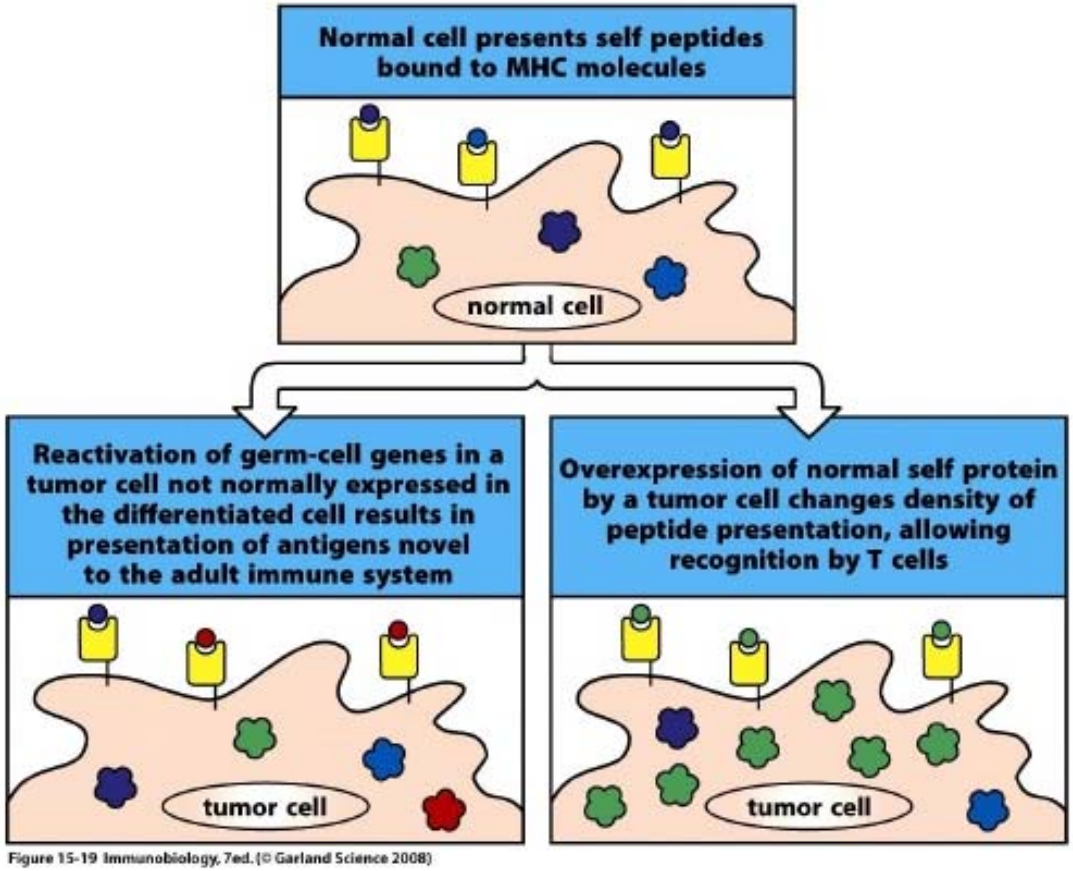


Figure 15-19 Immunobiology, 7ed. (© Garland Science 2008)

Oncofetal antigens (ie. CEA in colon cancer

Over-expressed antigens (ie. WT-1 in AML)

How are cancer cells seen as “abnormal” by the immune system?

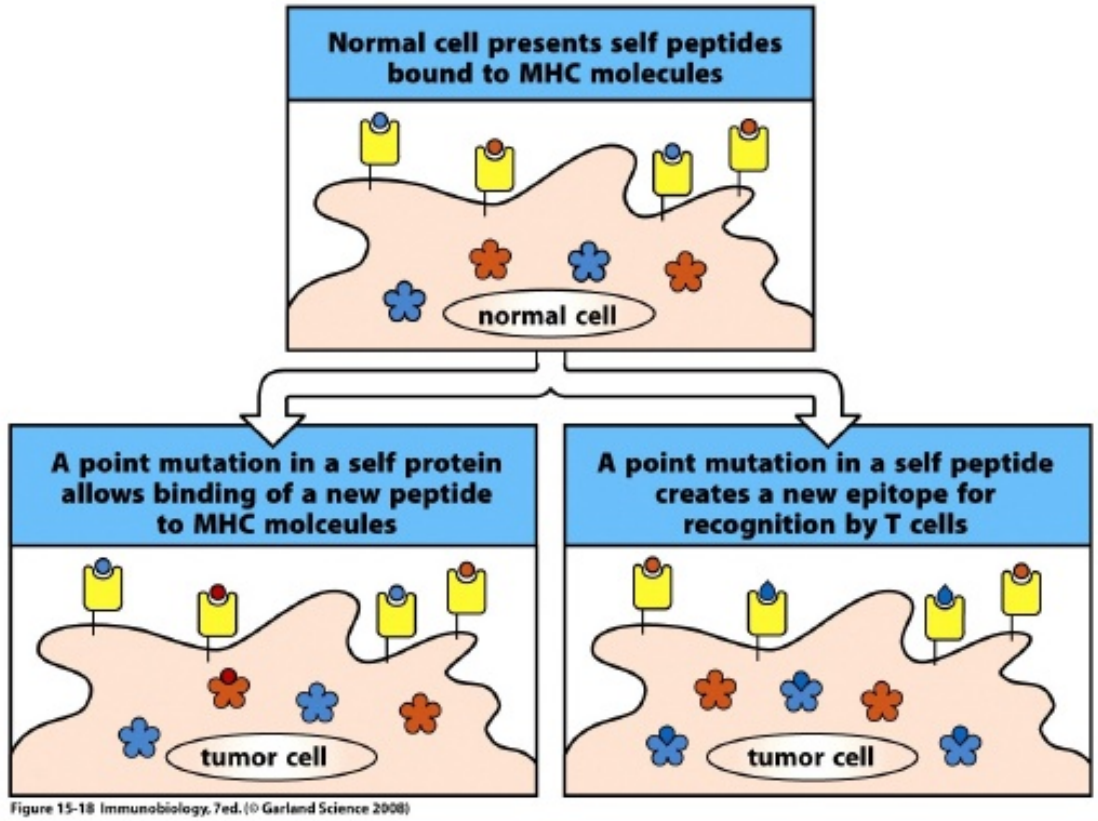
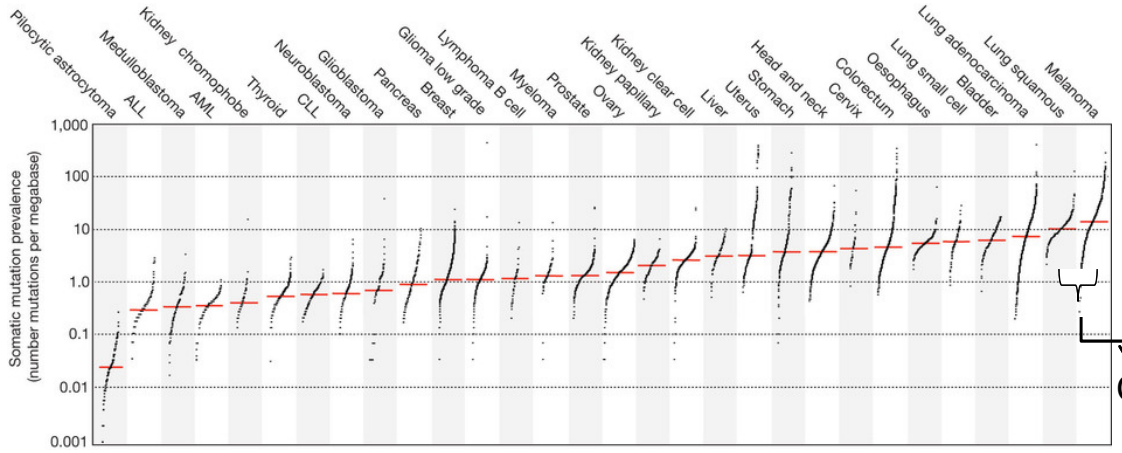


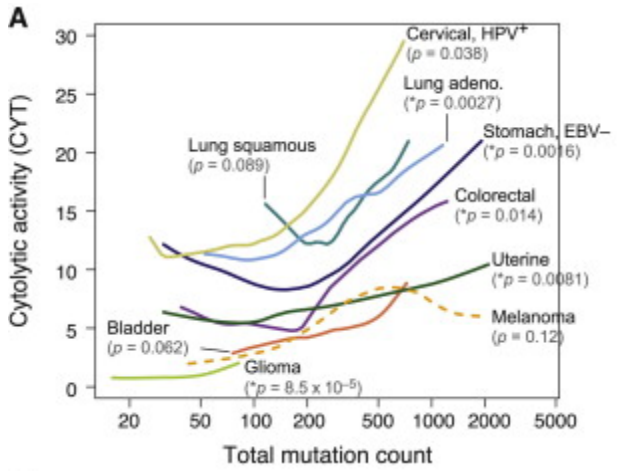
Figure 15-18 Immunobiology, 7ed. (© Garland Science 2008)

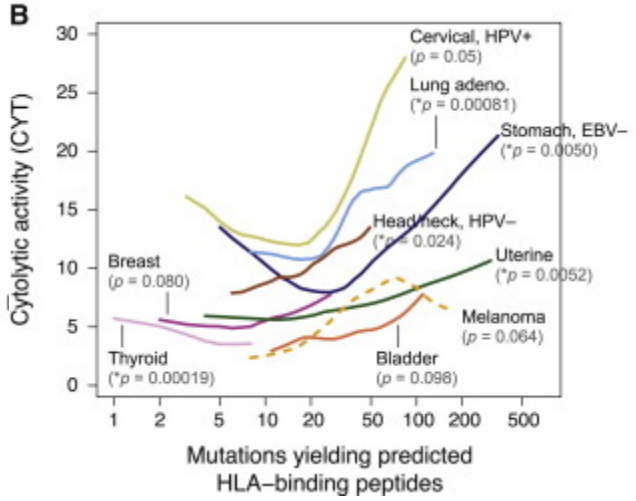
Neo-antigens

Mutational burden in tumors correlates with spontaneous immunity



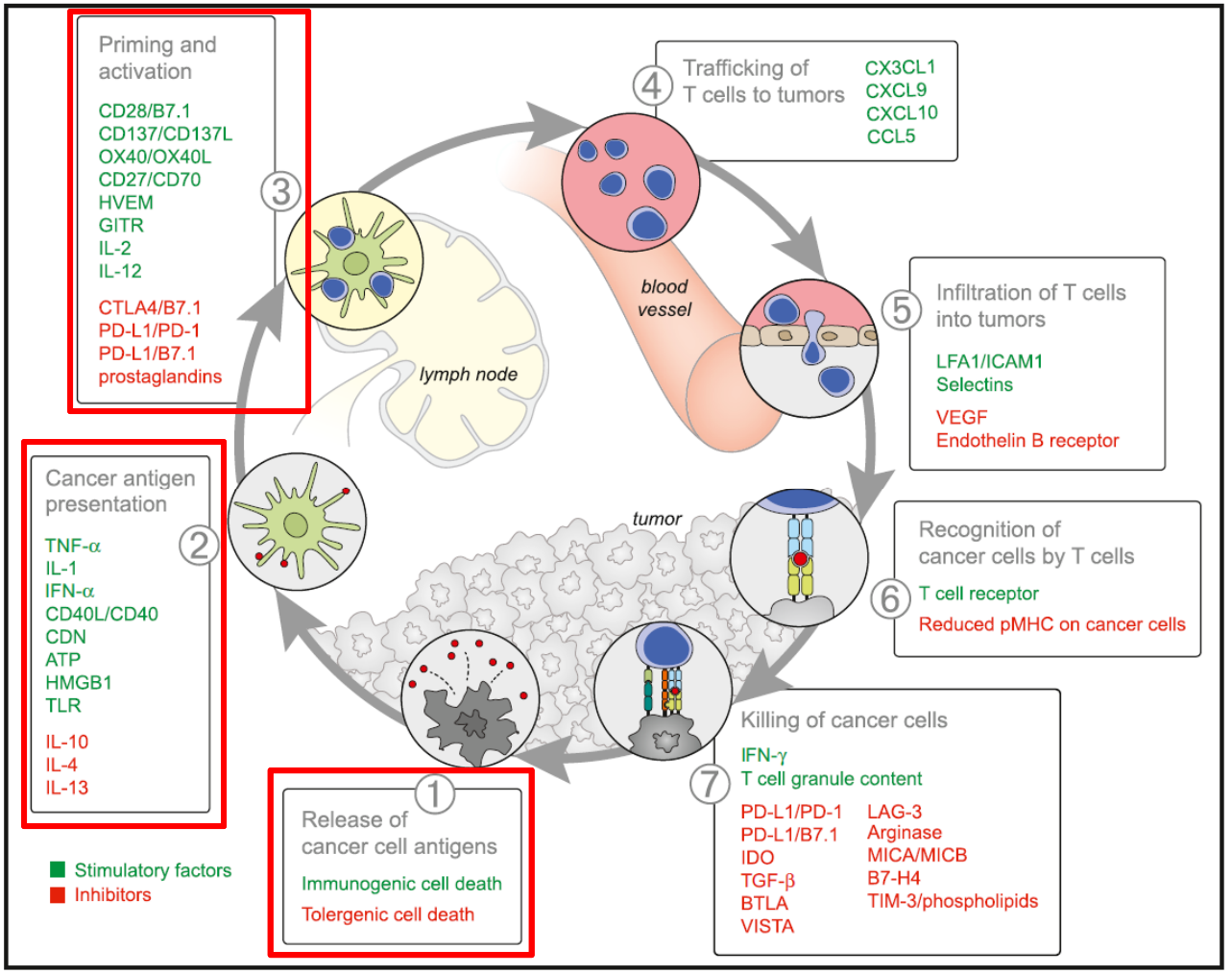
CBT approved





Alexandrov et al, Nature, 2013
Rooney et al, Cell 2015

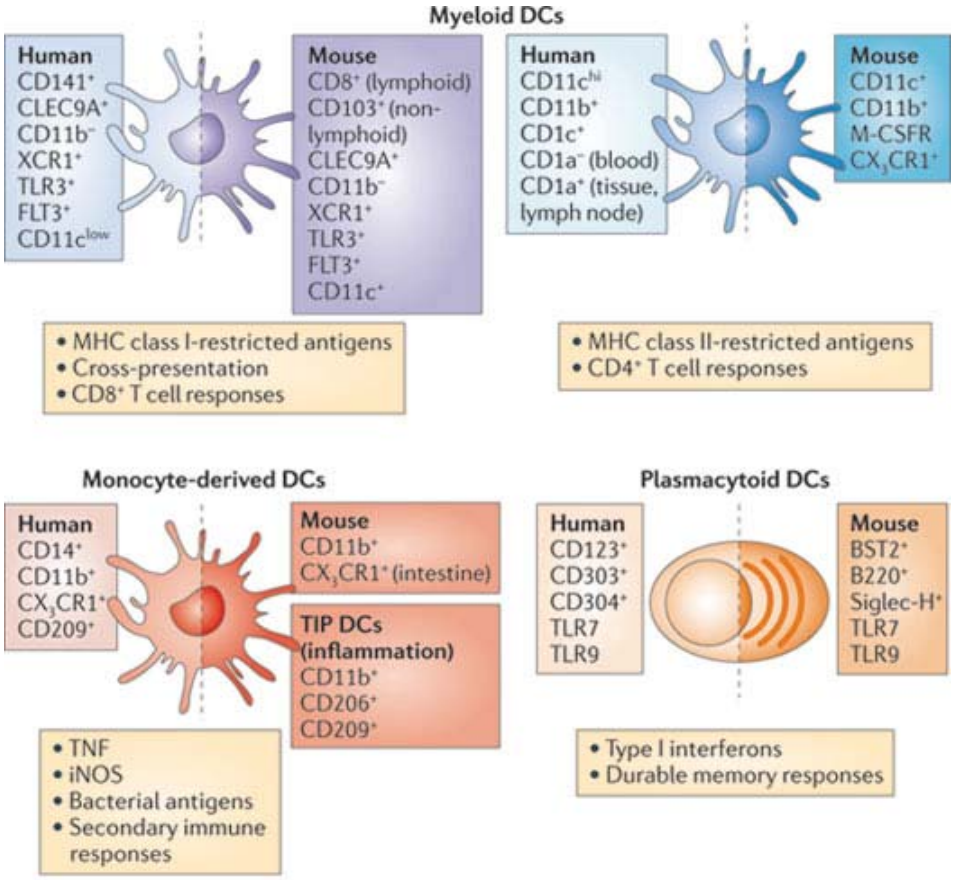
Generating an immune response against cancer – Dendritic cells



Chen and Mellman, Immunity 2013

Dendritic cells are important for priming anti-tumor T cells

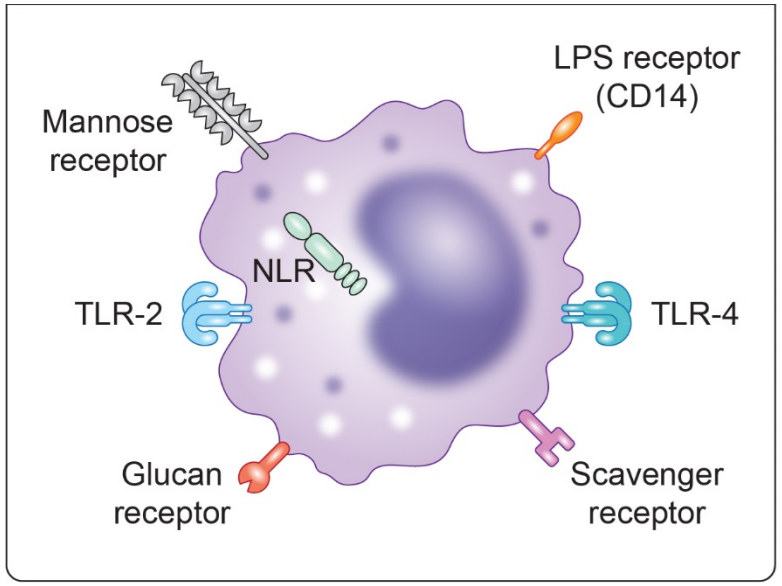
- Ralph Steinman (1970s)
  - DCs - hematopoietic cells specially equipped for antigen presentation and T cell activation
  - Nobel prize in 2011 for discovery of DC
- DC classified functionally in 2 groups
  - Conventional DC
    - Antigen presentation
    - T cell activation
  - Plasmacytoid DC
    - Type I IFN production
    - Important for immune responses against viruses



Colin et al. Nat Rev Immunol 2011

Dendritic cell activation

- DC receive signals through PRRs and other receptors (i.e. CD40) to become activated
  - Activation/licensing of DC results in:
    - HLA upregulation (enhanced antigen presentation to T cells)
    - Upregulation of costimulatory and cell adhesion molecules
    - Production of pro-inflammatory cytokines (IL-12, TNF-α, type I IFNs)
    - Alteration of chemokine receptor expression
    - Migration (to sites of inflammation)
  - Only licensed DC activate naïve T cells
  - Non-licensed DC induce peripheral tolerance (T cell deletion or anergy)

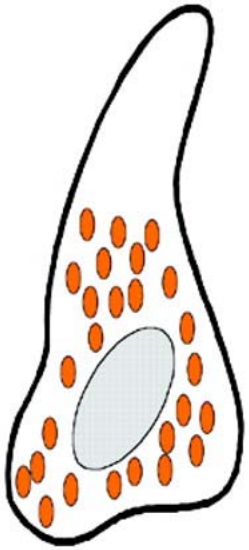


"Danger signals"
- Pathogen-associated molecular patterns (PAMPs)
  - Bacteria proteins
  - viral DNA/RNA
- Damage-associated molecular patterns (DAMPs)
  - Products of dying cells

Types of PRRs
- Toll-like receptors (TLR)
- C-type lectin receptors
- NOD-like receptors (NLRs)
- RIG-I-like receptors

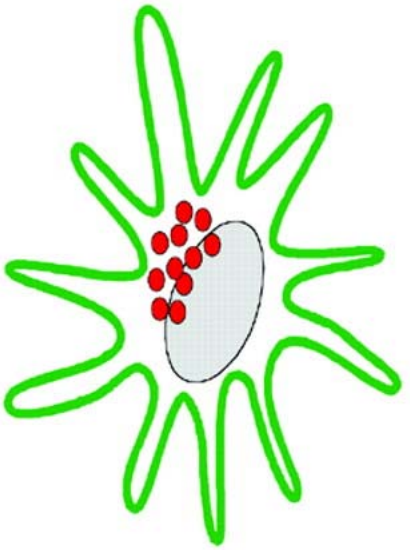
Receptors can be on the cell surface or intracellular (NLRs)

Dendritic cell activation



Microbial products
TNF family

MHC II
lysosome



IMMATURE DC
capture of antigens

- adsorptive uptake, eg, DEC-205, FcR
- macropinocytosis
- phagocytosis: microbes, dying cells

MATURE DC
stimulation of T cell immunity

- CD40, CD86
- CCR7
- IL-12
- High MHC - peptide

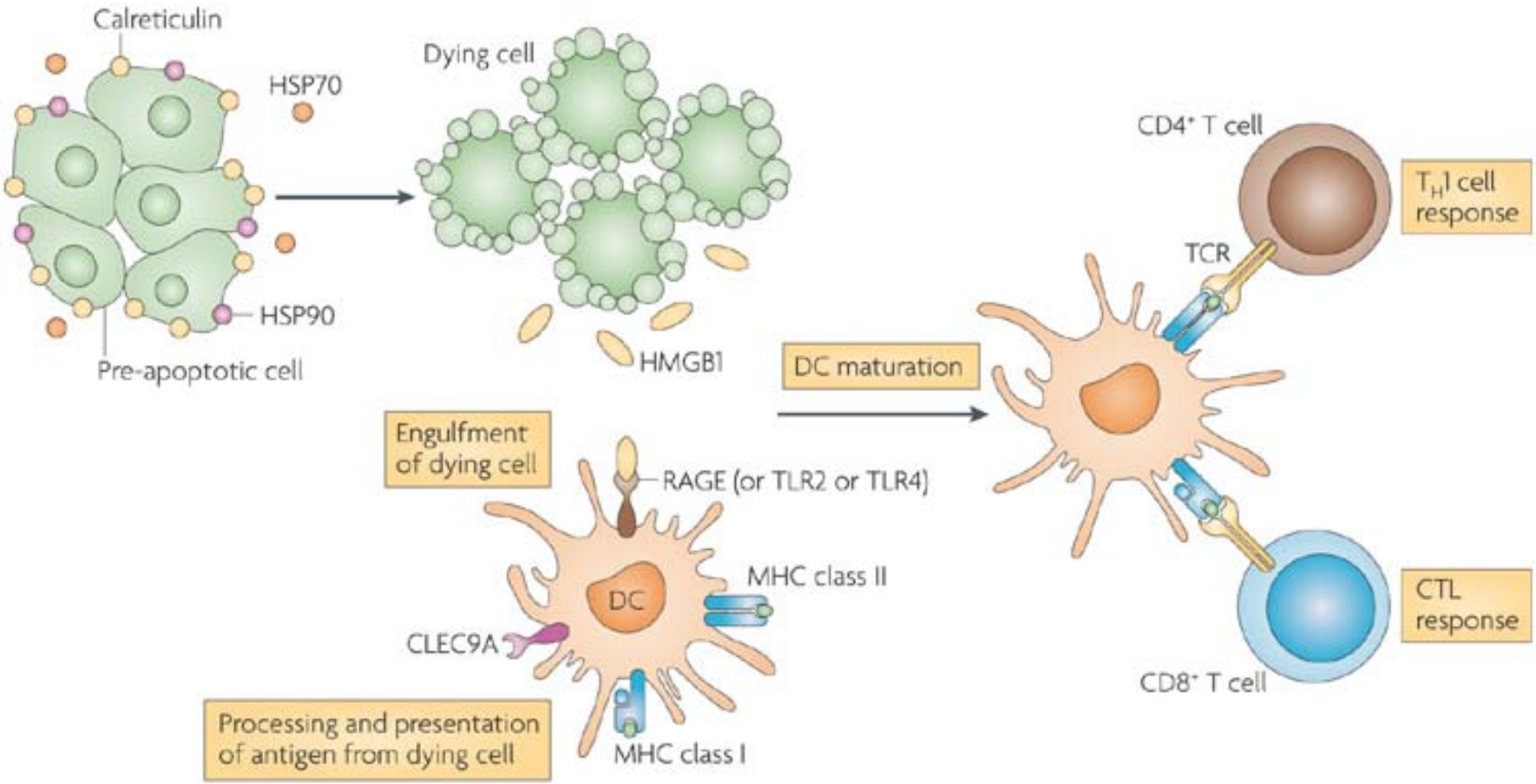
Steinman PNAS 2002

Innate immune sensing of cancer

- Most cancers, which are derived from self-tissues, arise in sterile environments.

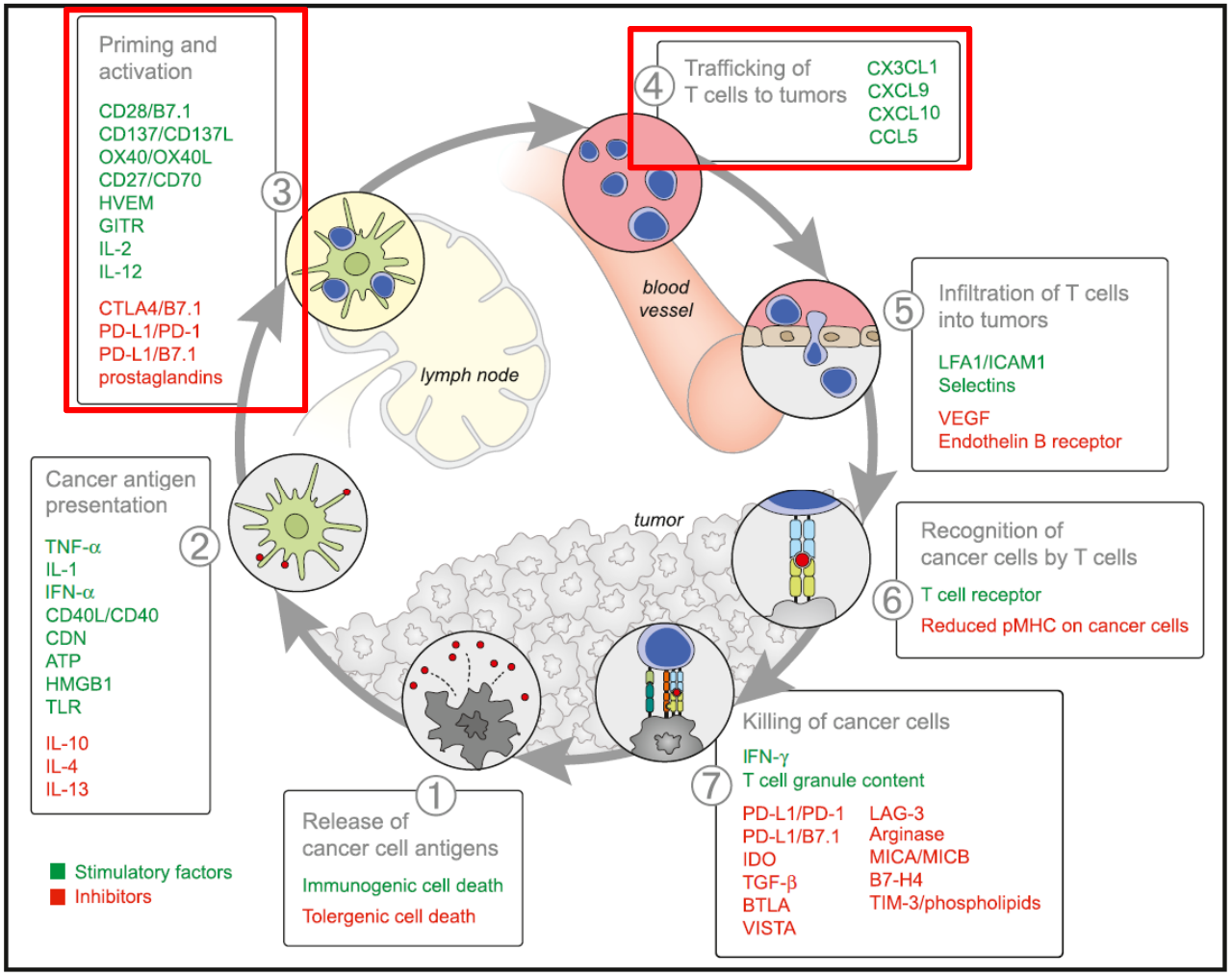
- How then, are cancer cells “sensed” by the host innate immune system?

Dendritic cells sense “danger” signals released by dying cancer cells



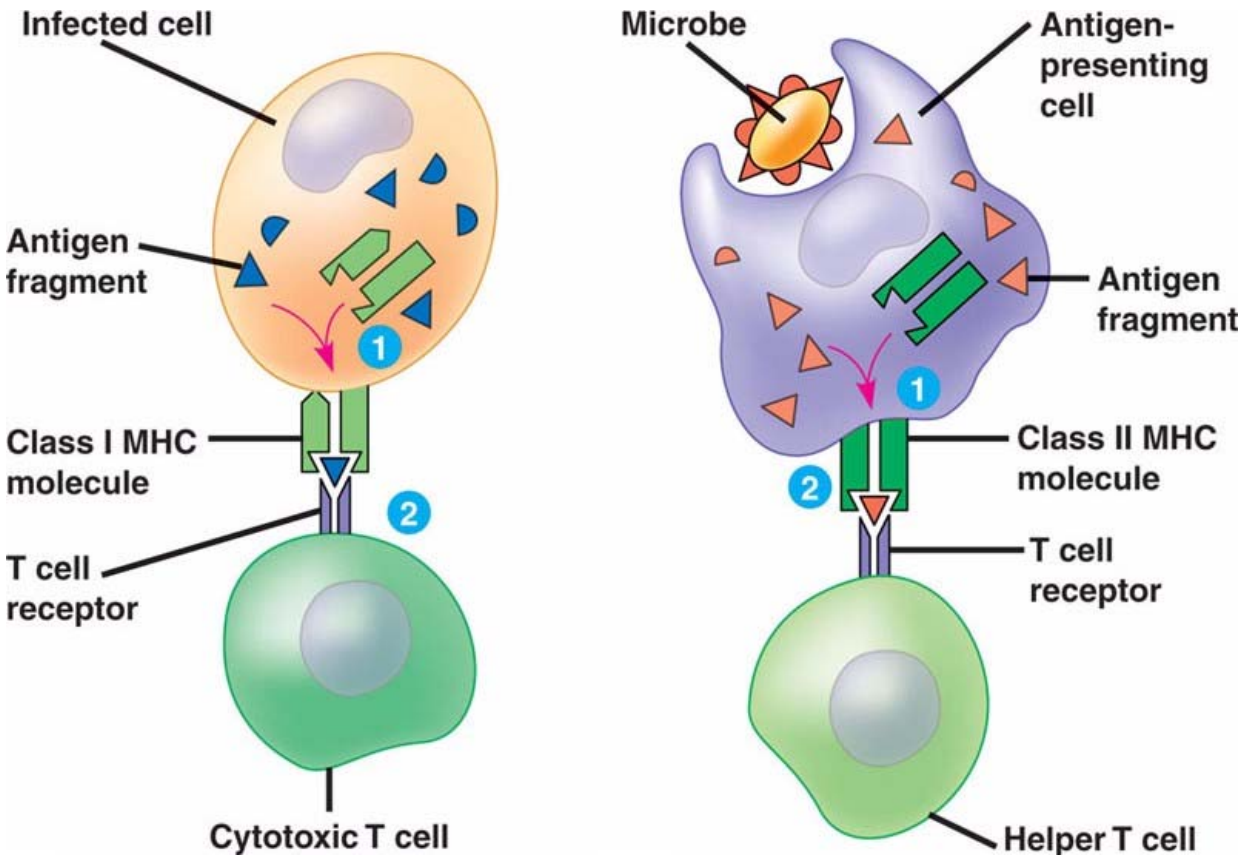
Green D. et al. Nat Rev Immunol 2009

Generating an immune response against cancer – T cell activation



Chen and Mellman, Immunity 2013

T cells are activated by APCs



Antigen – a substance recognized by receptors on immune cells

T cell activation 101

- Naïve T cell - a T cell that has not encountered its cognate antigen
- 2 signals (at least) are required to optimally activate a naïve T cell
  1. MHC-peptide : TCR (***signal 1***)
  2. B7 : CD28 (***signal 2***)

  Cytokines (***signal 3***)
- Activated T cells proliferate, differentiate into effectors and traffic to sites of inflammation (i.e. the tumor)
- In reality, things are more complicated…..

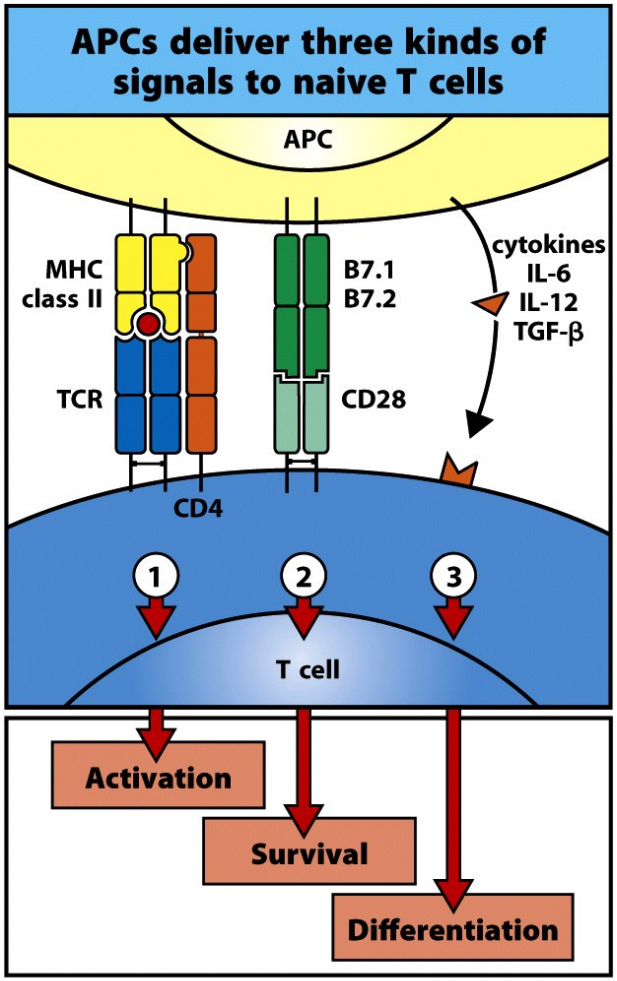


Figure 8-19 Immunobiology, 7ed. (© Garland Science 2008)

Positive and negative costimulatory receptors

Modulate magnitude of T cell activation and effector function

Positive costimulatory receptors:

- CD28 (classical)
- ICOS (inducible costimulator)
- CD27 (TNF family receptor)

Negative costimulatory receptors:

- CTLA-4 (cytotoxic lymphocyte antigen – 4)
- PD-1 (programmed death -1)
- TIM-3 (T cell immunoglobulin mucin -3)

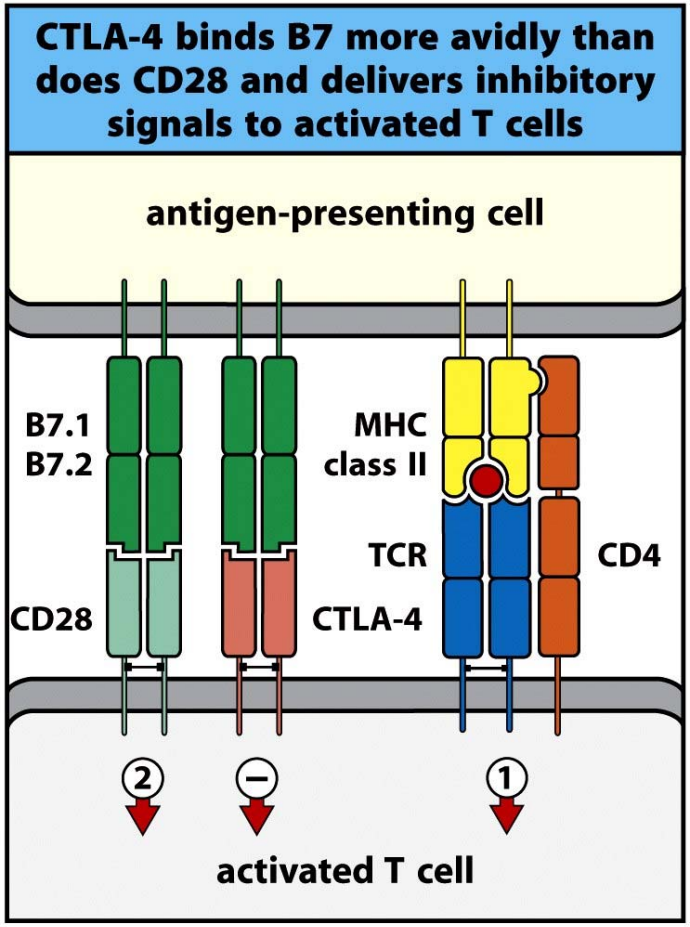
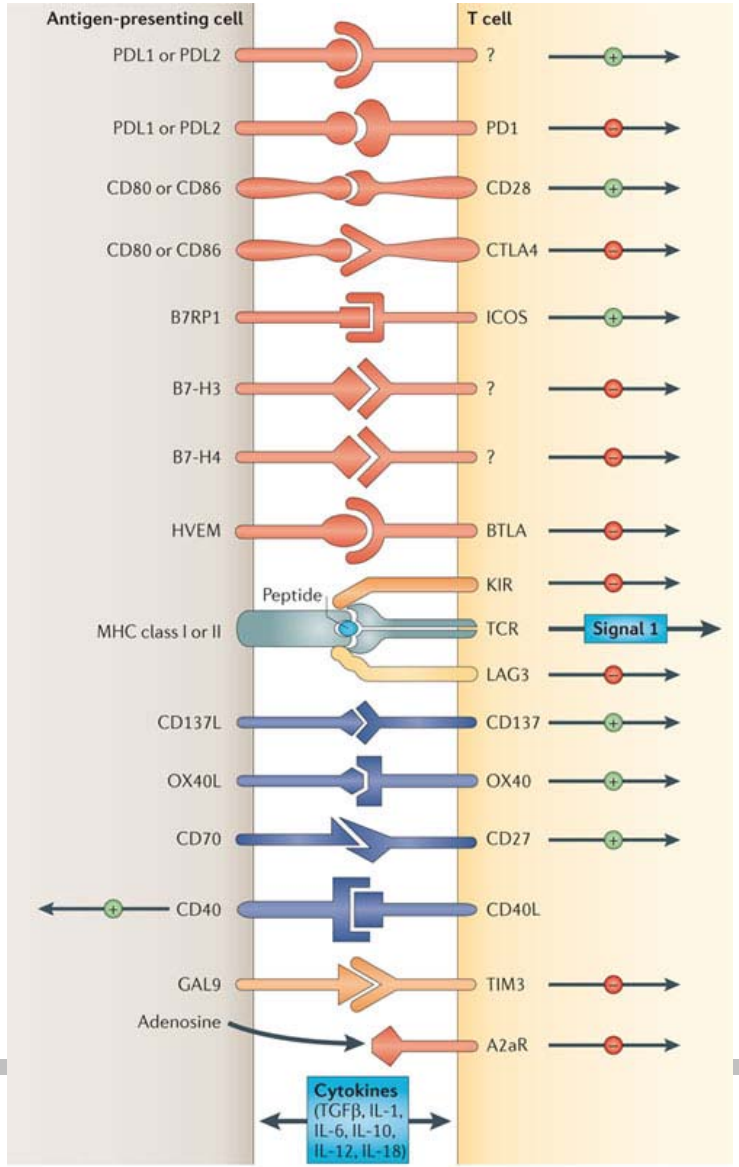


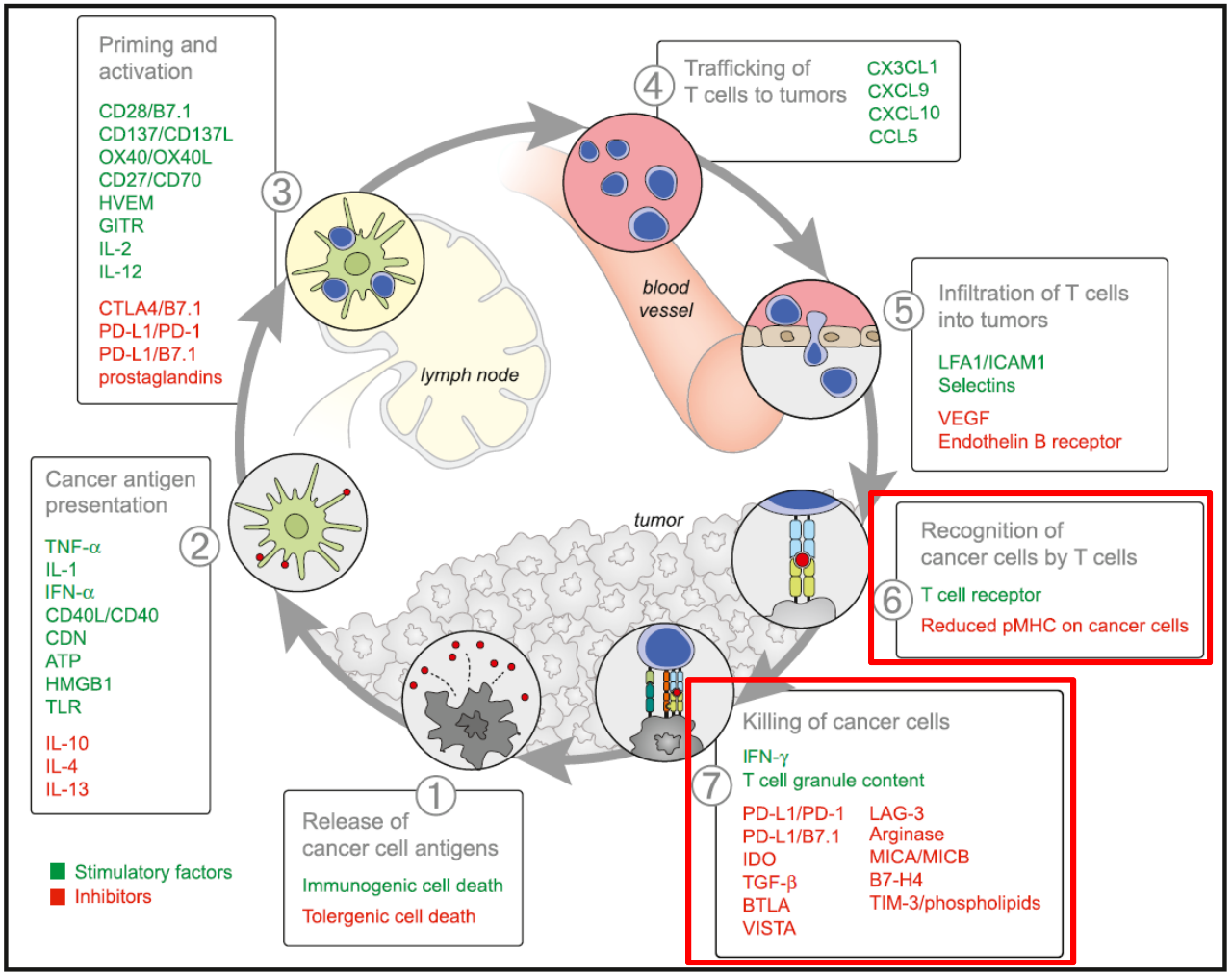
Figure 8-22 Immunobiology, 7ed. (© Garland Science 2008)

T cell activation is regulated through checks and balances



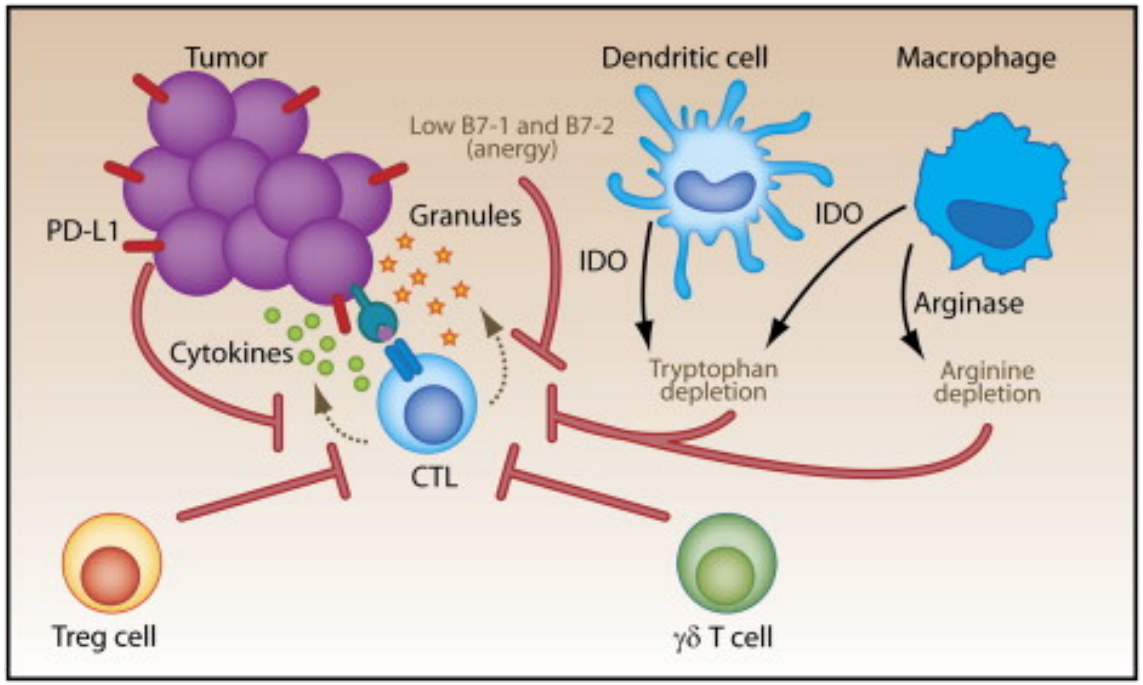
Pardoll D. Nat Rev Cancer 2012

Generating an immune response against cancer – Tumor micro-environment



Chen and Mellman, Immunity 2013

Cancers can effectively evade the immune system



Immune evasion mechanisms

- Tumor-induced T cell anergy
- Expression of negative costimulatory receptors on T cells (CTLA-4, PD-1, TIM-3)
- Regulatory T cells
- Suppressive myeloid cells (MDSC, TAM)
- Secretion of inhibitory cytokines (IL-10, TGF-β)
- Antigen-loss variants (loss of MHC)
- Production of enzymes which deplete essential amino acids (IDO, arginase)

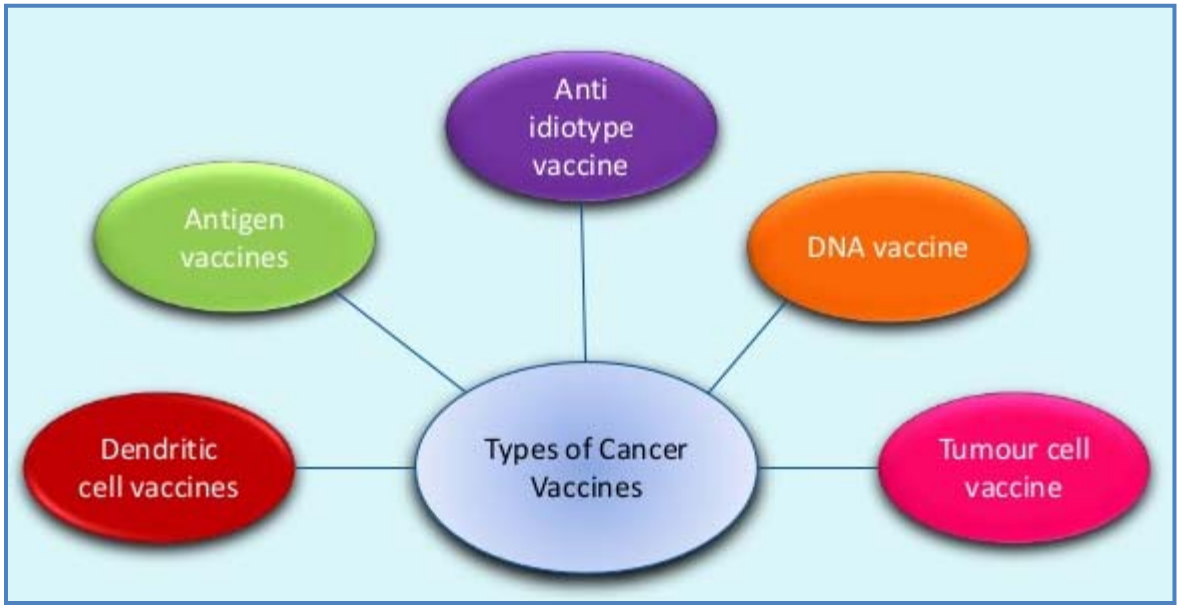
Cancer immunotherapy makes its mark

Cancer immunotherapies

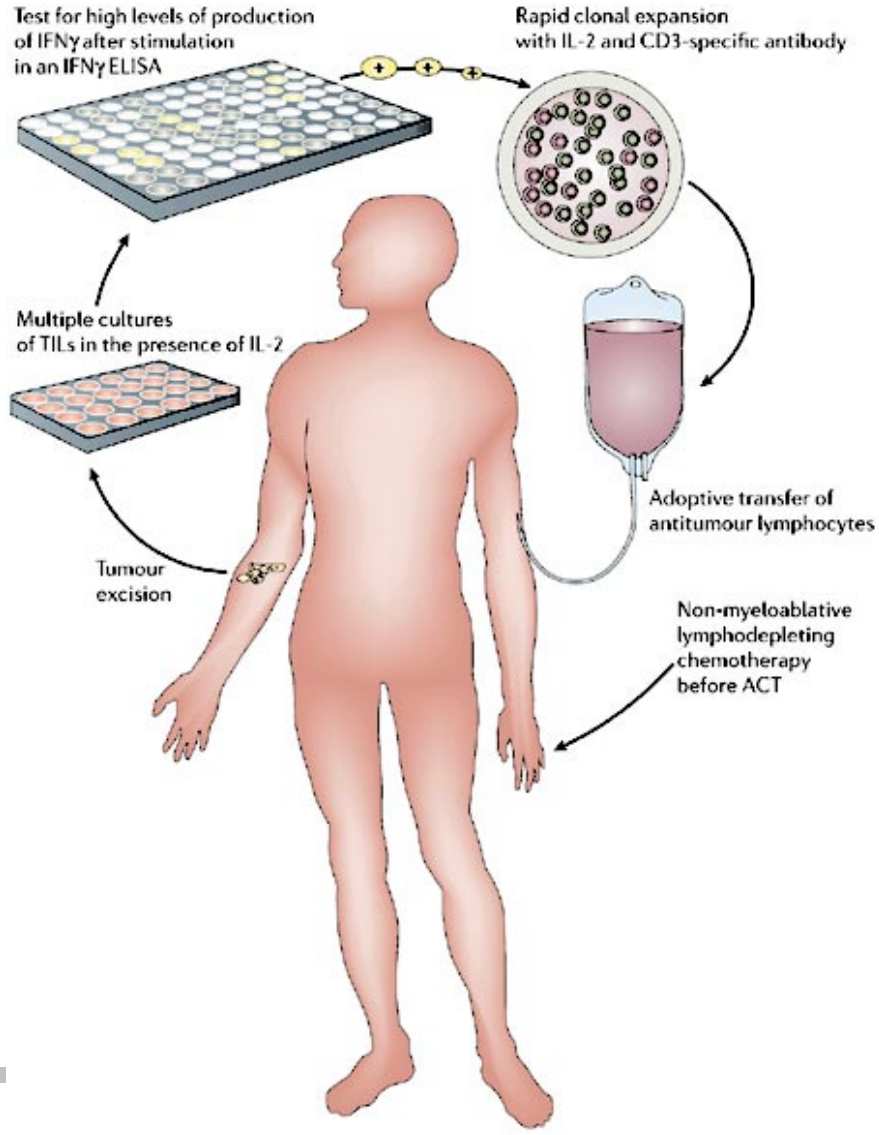
- Cancer vaccines
  - Peptide-based
  - Cellular-based (i.e. DC vaccines)
- Adoptive T cell therapy
  - Ex vivo expansion of tumor-infiltrating T cells and infusion into cancer-bearing hosts
  - Tumor Ag-specific TCR transduced T cell therapy
  - Chimeric antigen receptor (CAR) adoptive therapy (CD19)
- Immune checkpoint blockade
  - CTLA-4 blockade
  - PD-1 blockade
- Reversal of immune evasion
  - Treg depletion
  - IDO inhibition (1-MT and derivatives)
  - Prevention of tumor-induced T cell anergy (lymphodepleted host and adoptive T cell therapy)

Immunotherapy – vaccines

Cancer vaccine – a combination of cancer cells or antigens and an adjuvant injected into a person to stimulate an immune response against live cancer cells in the body

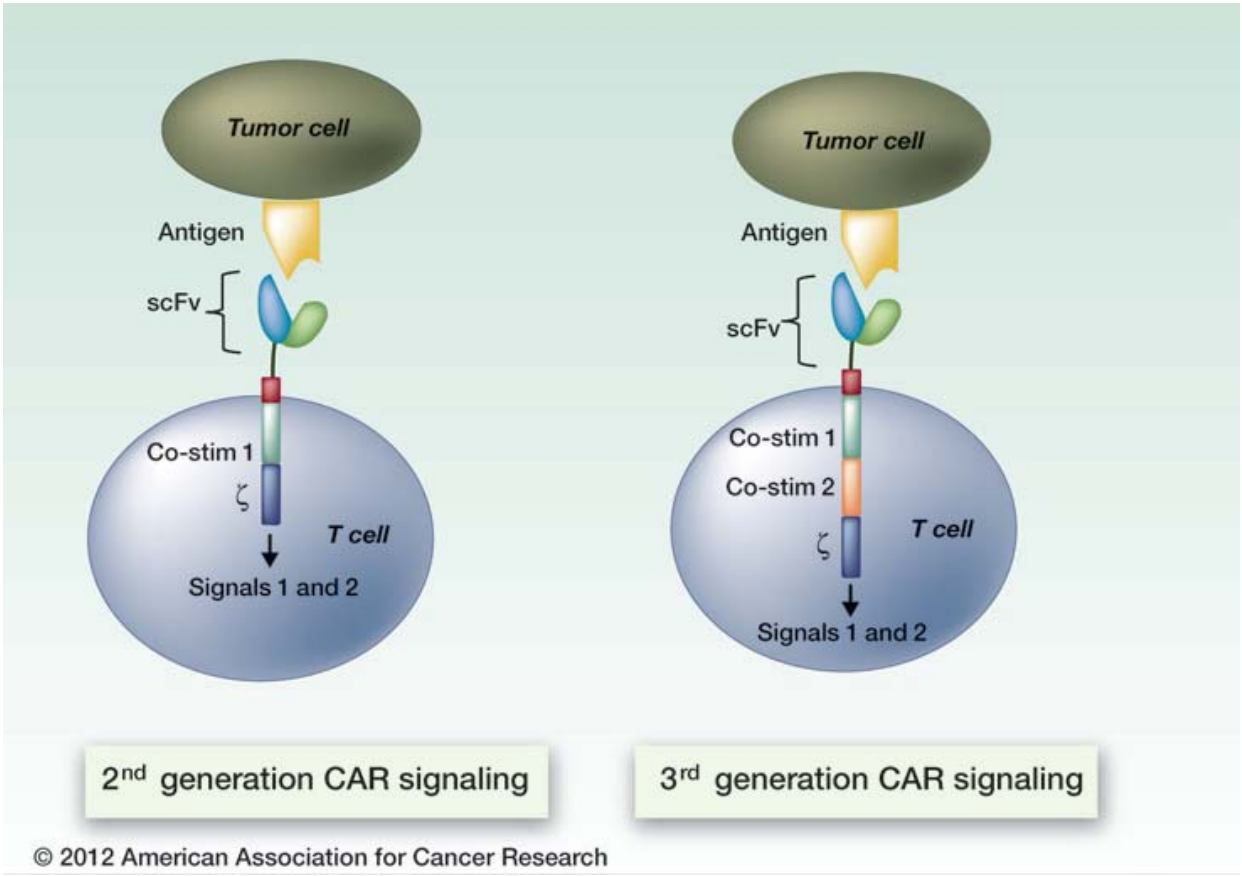


Immunotherapy – Adoptive T cell therapy



Gattinoni et al, Nat Rev Immunol 2006

Immunotherapy - CAR T cell therapy



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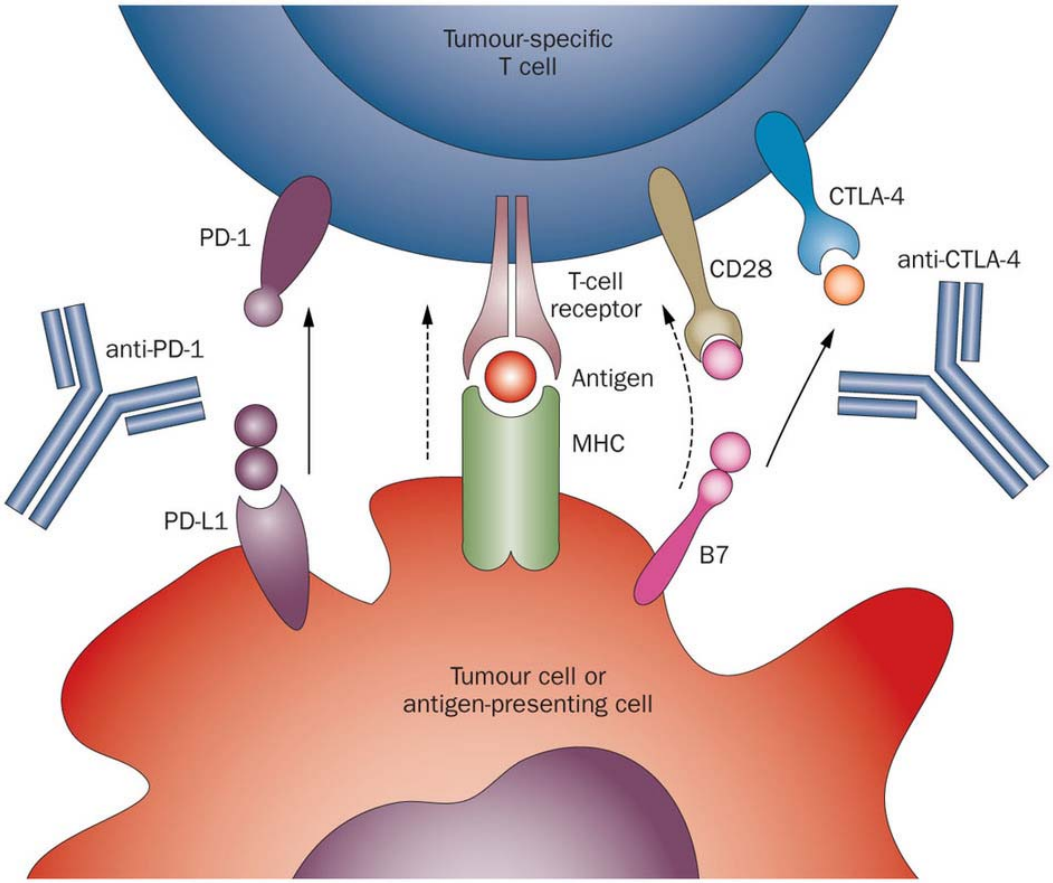
Immunotherapy - Checkpoint blockade



Drake et al, Nat Rev Clin Oncol 2014

Conclusions

- The immune system, which developed to fight infections, can also recognize and kill cancer cells
- Cancers express antigens in the form of mutated or over-expressed proteins that can be seen as “foreign” to T cells of the immune system
- Although immune responses are generated against cancer in some patients, they are often suppressed and ineffective
- The 3 main types of immunotherapy for cancer are: cancer vaccines, adoptive T cell therapy and checkpoint blockade

Questions?

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