SEP Final Exam Review Session

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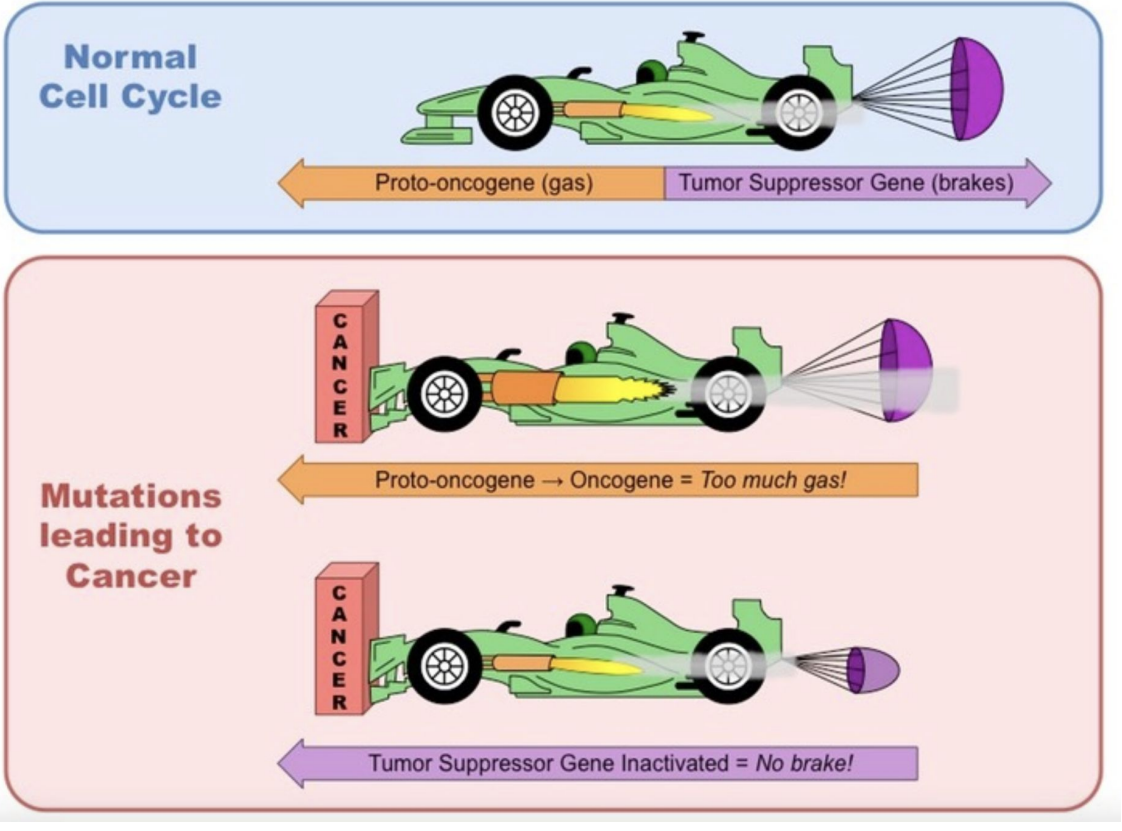
Topics covered in final exam

#	Topic	Instructor
1	Tumor Suppressors	Dr Pablo-Sanchez Vela
2	Oncogenes and Cell Signaling	Dr Sarah Suehnholz
3	Targeted Therapies	Dr Debyani Chakravarty
4	Immune System & Cancer	Dr Lalitha Ramanathapuram
5	Immunotherapy	

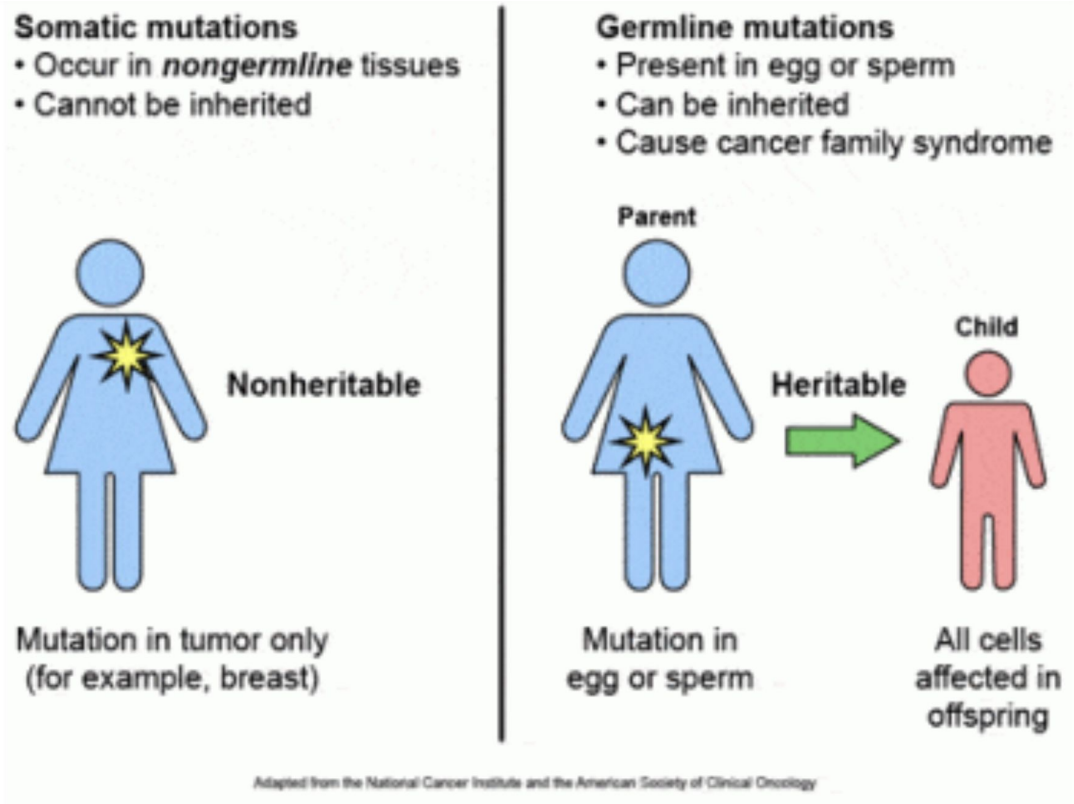
Topic #1: Tumor Suppressors

- Review what you know about the tumor suppressor gene *TP53*
- Define what a **tumor suppressor gene** is. Define an **oncogene**.
- What type of mutations occur in tumor suppressor genes
  - **activating** vs. **inactivating**
  - **somatic** vs. **germline**
  - **driver** vs. **passenger**
- What happens when a tumor suppressor gene such as *TP53* is mutated?
- What type of gene functions do tumor suppressor genes regulate (e.g. cell cycle/proliferation/survival/genome stability)
- What is DNA **methylation**? How is it different from DNA **mutation**? Why is it important in the regulation of tumor suppressor genes?

Oncogenes versus Tumor Suppressor Genes

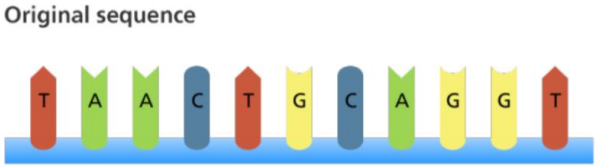


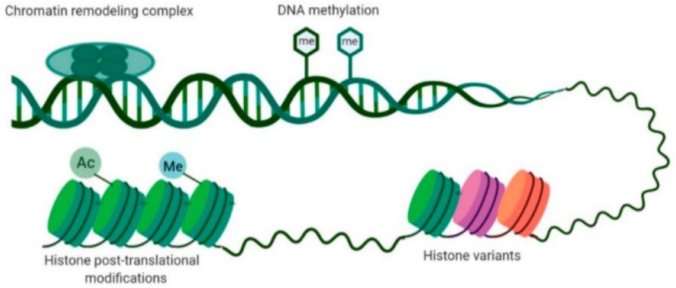
Somatic versus Germline mutations

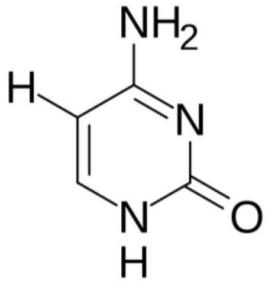


Mutation versus Methylation

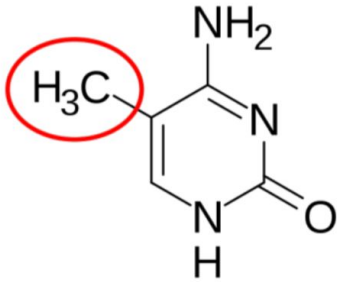
DNA mutation vs DNA methylation:







cytosine



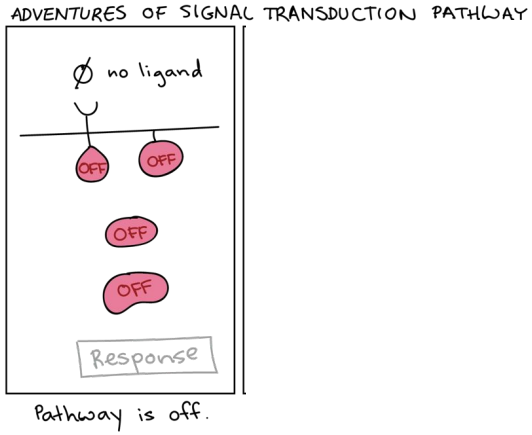
methylated cytosine

Genome Research Limited
MDPI

Topic #2: Oncogenes and Cell Signaling

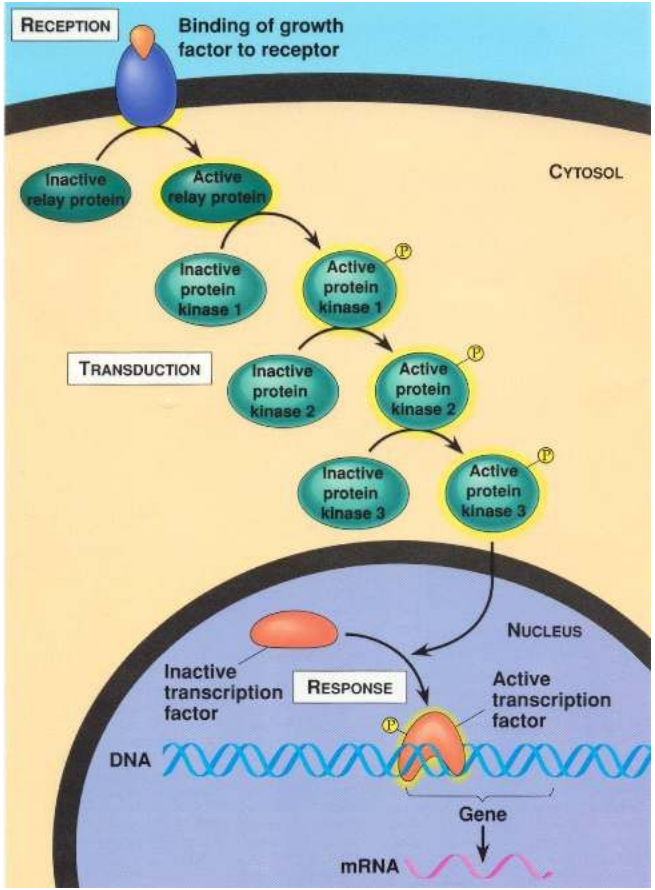
- Define a **signal transduction pathway**:
  A series of chain reactions used by the cell to amplify and send a signal
- Define the following terms: **Protein Kinase**, **Protein Phosphatase**, **Transcription Factor**
- Signaling pathways share a common goal: To produce some kind of **cellular response**
- Cellular responses can happen at 2 levels
  a. **Molecular** e.g. Changes in gene expression
  b. **Macroscopic** e.g Changes in the appearance of the cell – growth, death, movement

Signal transduction pathway



- When a ligand binds to a receptor, the receptor's intracellular domain changes in some way
- This may be a change in shape, which makes the receptor active as an enzyme or lets it bind other molecules
- The change in the receptor sets off a series of signaling events
- This chain reaction can eventually lead to a cellular response - a change in the cell's behavior or characteristics

Signal transduction pathway



- A series of chain reactions used by the cell to amplify and send a signal
  - It usually involves the activation of proteins and a phosphorylation cascade

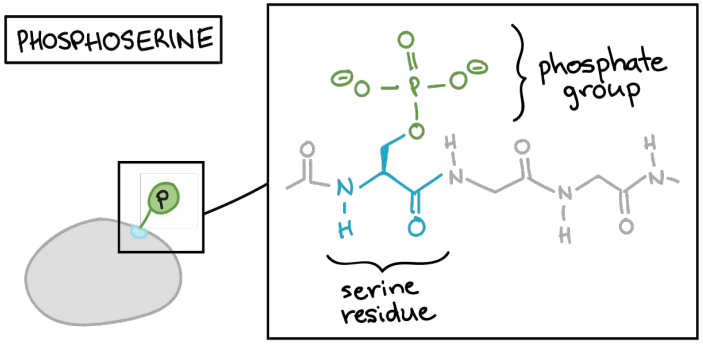
Protein Kinase: enzyme that adds phosphate groups to proteins to *activate* them

Transcription Factor: a protein that can directly bind to DNA to activate or repress genes

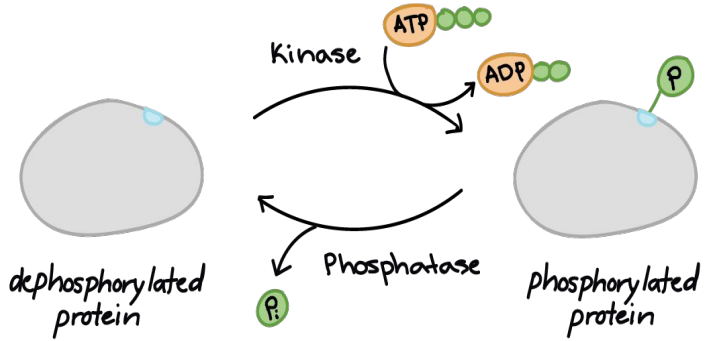
- The terms **upstream** and **downstream** are used to describe molecules or events in the relay chain
  - Name a molecule upstream of protein kinase 2 in the picture
  - Name a molecule downstream of protein kinase 2 in the picture

Phosphorylation

- The addition of a phosphate group to one or more sites on a protein
  - Usually linked to an amino acid with a hydroxyl group (-OH)



- How can adding a phosphate group have such a big effect on the protein?
  - It adds a big negative charge to the protein, which alters the protein's shape and function
  - This can increase or decrease the protein's activity as an enzyme
  - Or providing a docking site for an interacting enzyme
  - Or block another enzyme from binding

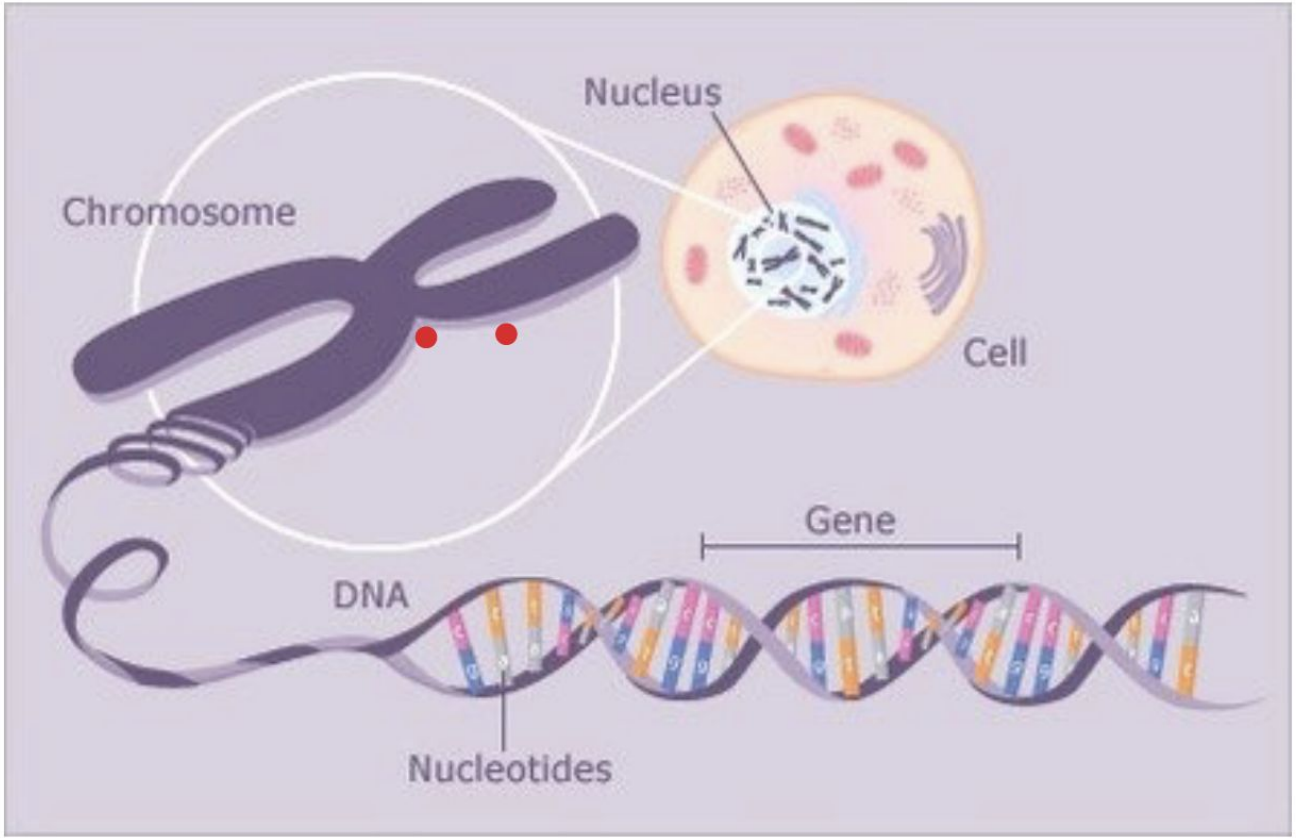


- Phosphorylation is not permanent
  - **Phosphatases** are enzyme that remove phosphate groups from proteins to *deactivate* them

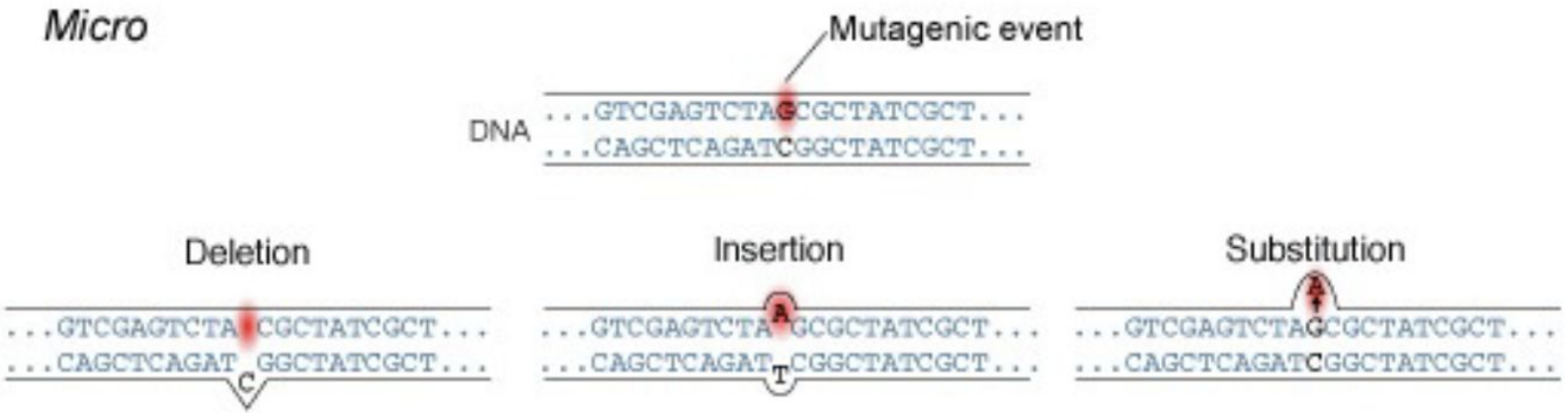
Topic #3: Targeted Therapies

- Describe the organization of DNA in a cell
- Know the types of mutations in cancer
- Understand the concept of targeted therapies

Organization of DNA in a cell



Types of Mutations in Cancer



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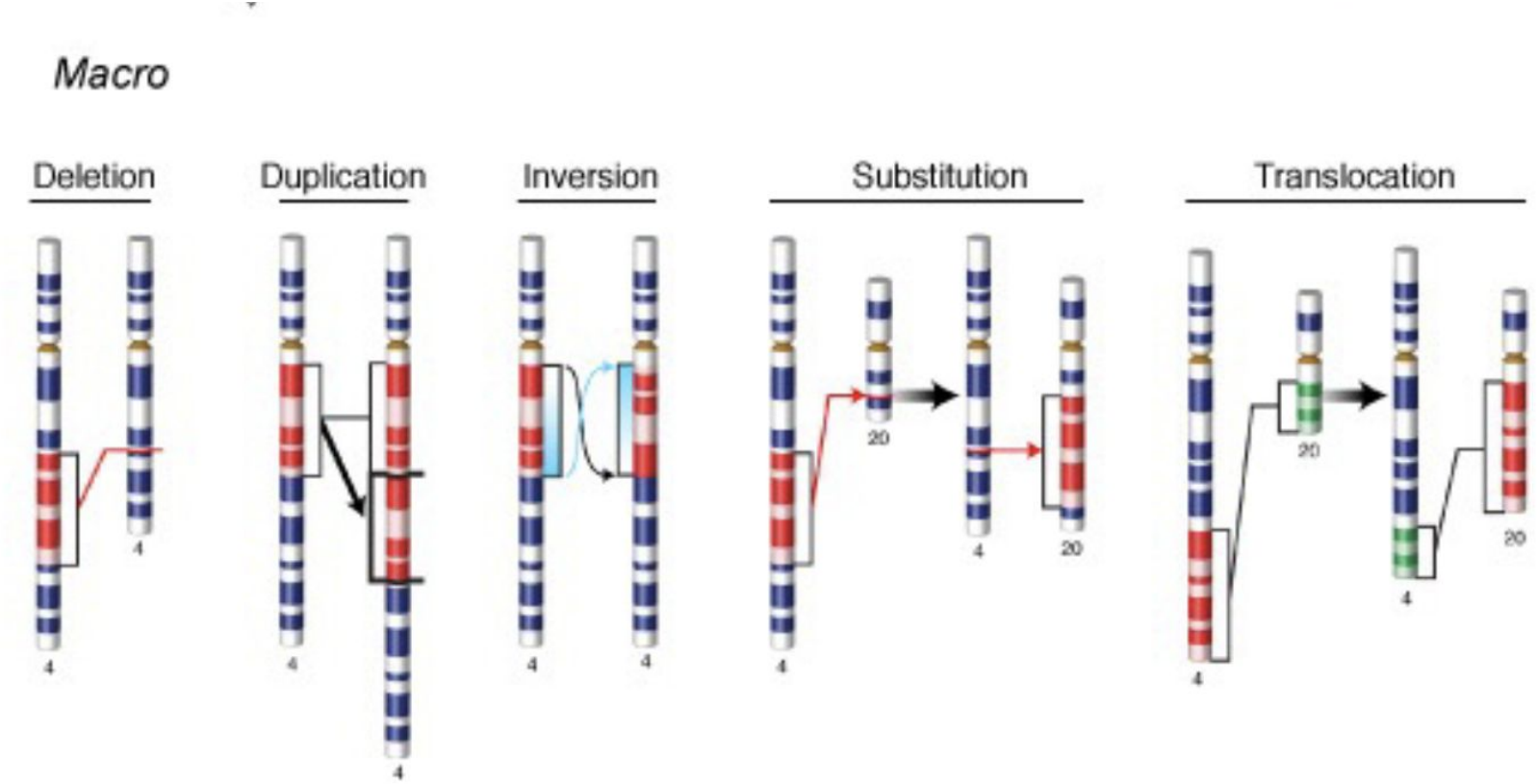
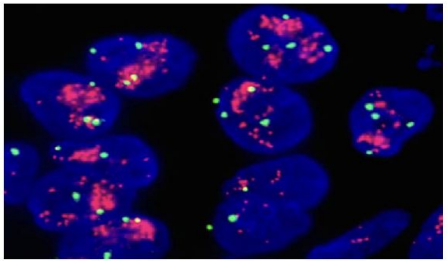


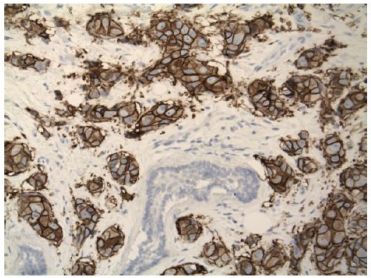
The Concept of Targeted Therapies: Herceptin

20-25% of invasive breast cancers overexpress HER2
HER2 overexpression promotes cell proliferation and survival

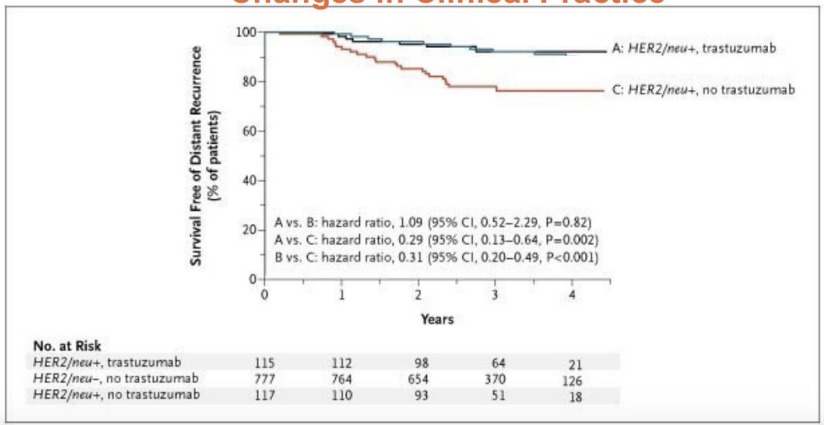
DNA Sequencing → Discovery of a driver mutation
ERBB2 amplification



Protein → Overexpression of the HER2 protein

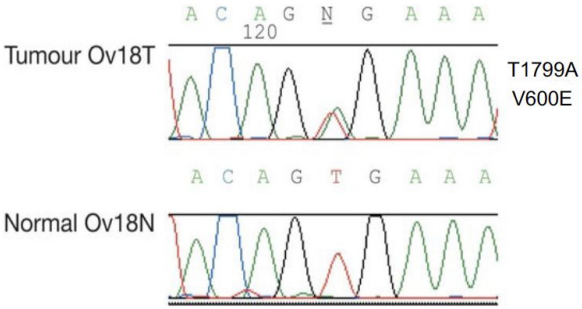


Changes in Clinical Practice

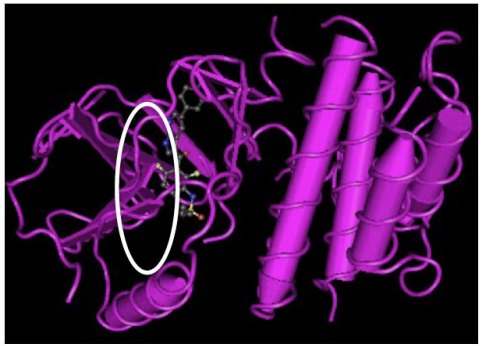


The Concept of Targeted Therapies: Vemurafenib

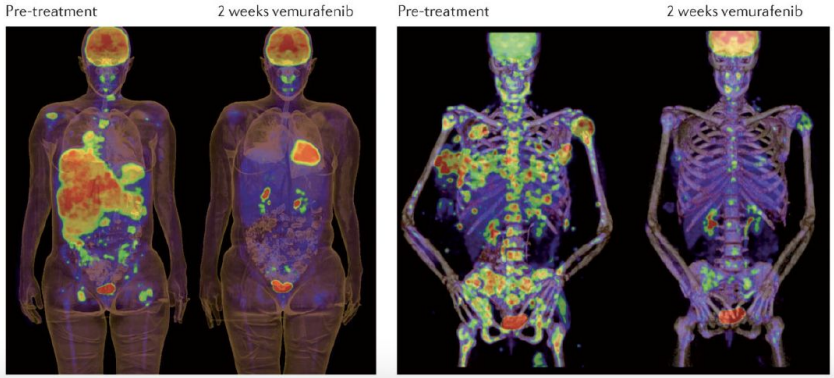
DNA Sequencing →
Discovery of a driver mutation
BRAF V600E



Drug Development →
Inhibits the mutant protein
Vemurafenib



Changes in Clinical Practice

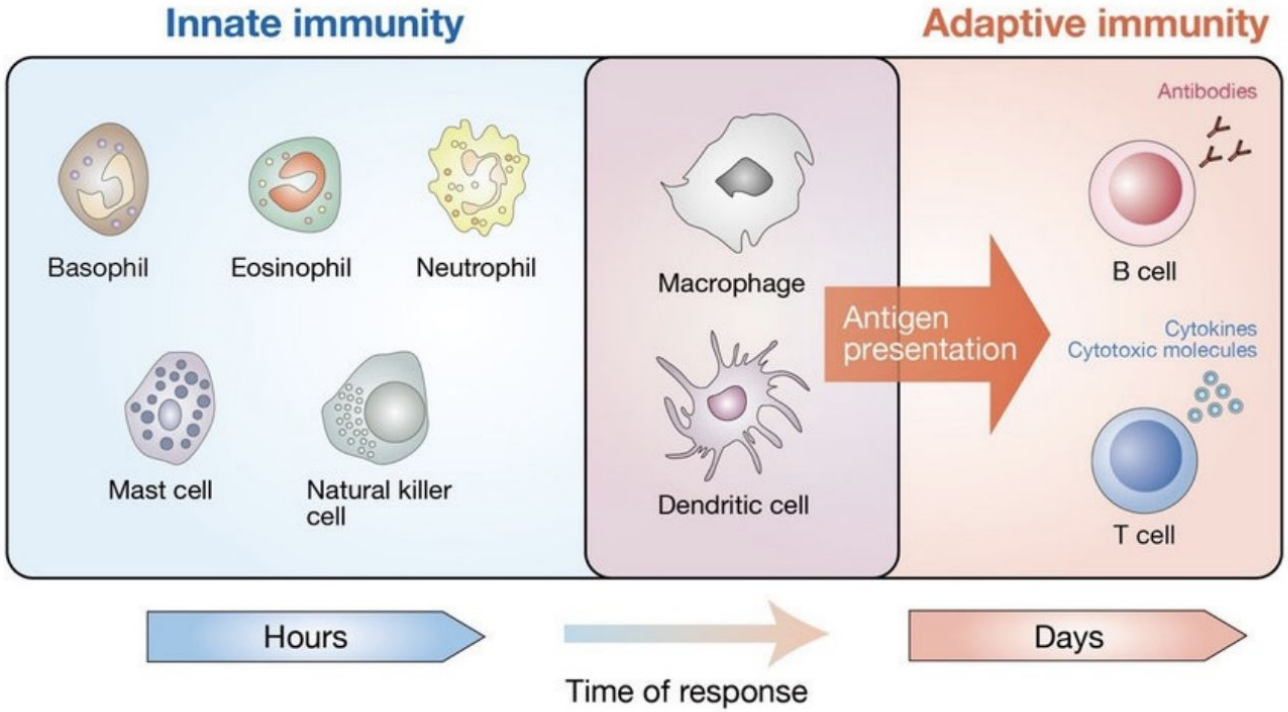


Topics #4: Immunology

- The **Immune System** is designed to recognize what is non-self / foreign
- The **Immune System** complex network that helps the body fight infections and other diseases
- **Immunology** is the study of components/structure/function of the Immune System
- **Immunity** is the body's ability to resist or eliminate potentially harmful materials or cells
- **Immune Response**: Collective and coordinated response to substances the body sees as harmful or foreign
- **Antigen**: Any substance that causes the body to make an immune response against it; includes toxins, chemicals, bacteria, viruses, parasites etc.
- **Antibody:** Protein(s) produced in response to and counteracting a specific antigen.

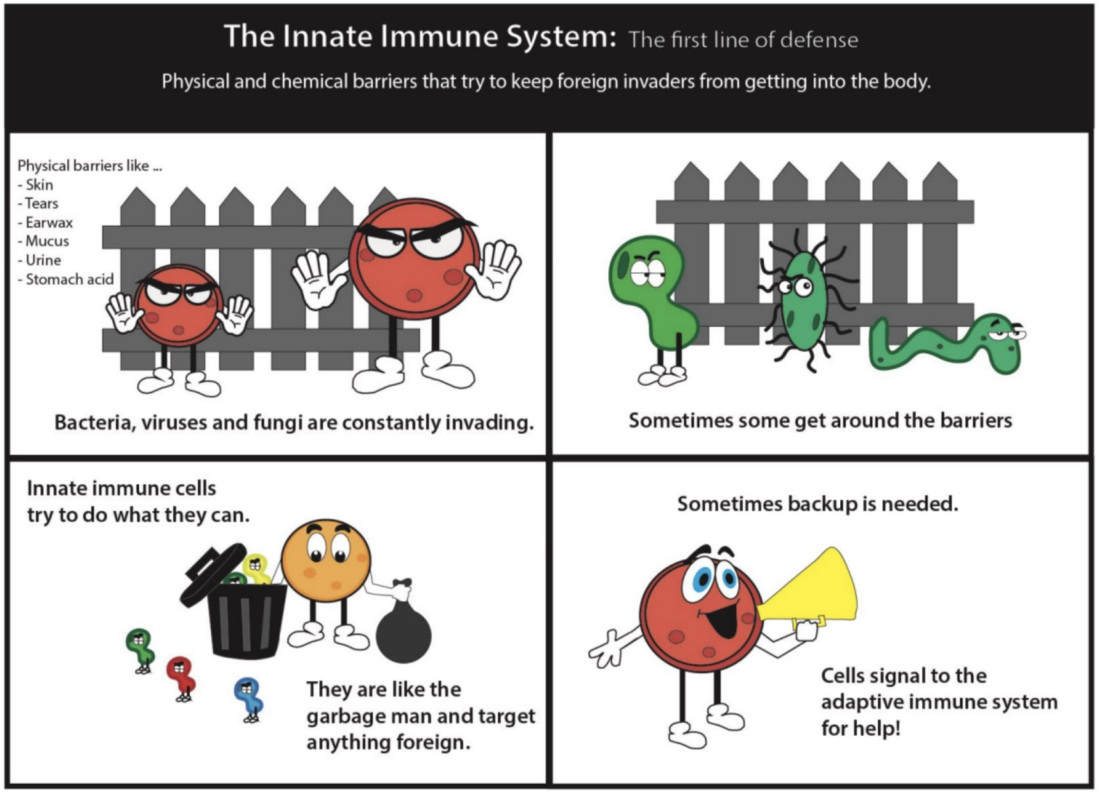
2 mechanisms of Immune Responses

To coordinate an immune response, we rely on two distinct mechanisms



Innate Immune System

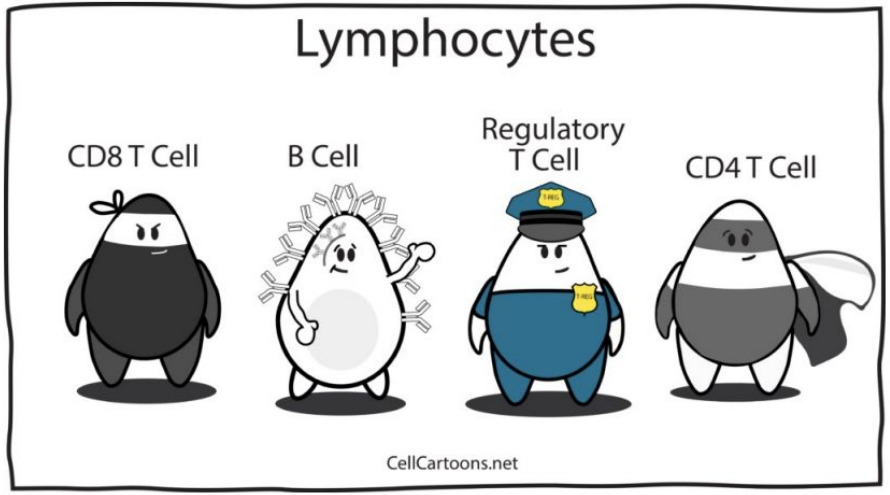
- Present at birth
- First line of Defense
- Rapid Response (hours)
- Non-specific- not directed against any one pathogen
- No long-term memory- same response after repeated exposure
- Composed of
  - 1) physical and chemical barriers,
  - 2) cellular components and molecules secreted by the cells (Inflammation, Phagocytosis, Complement System)



Adaptive Immunity

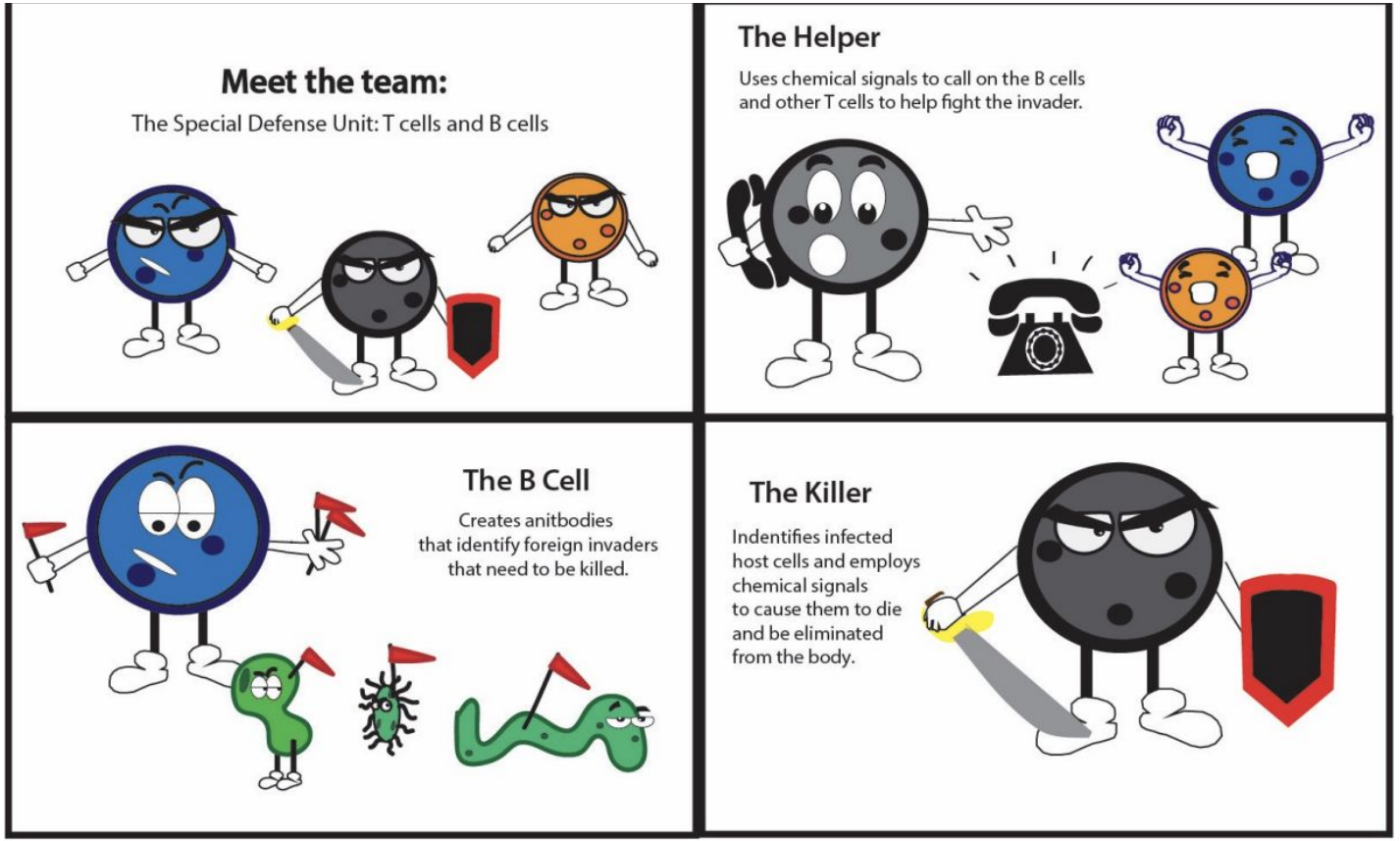
- When pathogens are able to bypass innate immune defenses, the adaptive immune system is activated.
- Second line of Defense-acquired after exposure to a pathogen
- Slow response (days-weeks)
- Specific
- Gives rise to long term memory
- Second exposure to same pathogen leads to a faster, stronger/robust response

  Mediated by Lymphocytes
  - B-cells- Humoral Immune Response
  - T cells- Cell-mediated Immune Response



The Adaptive Immune Response

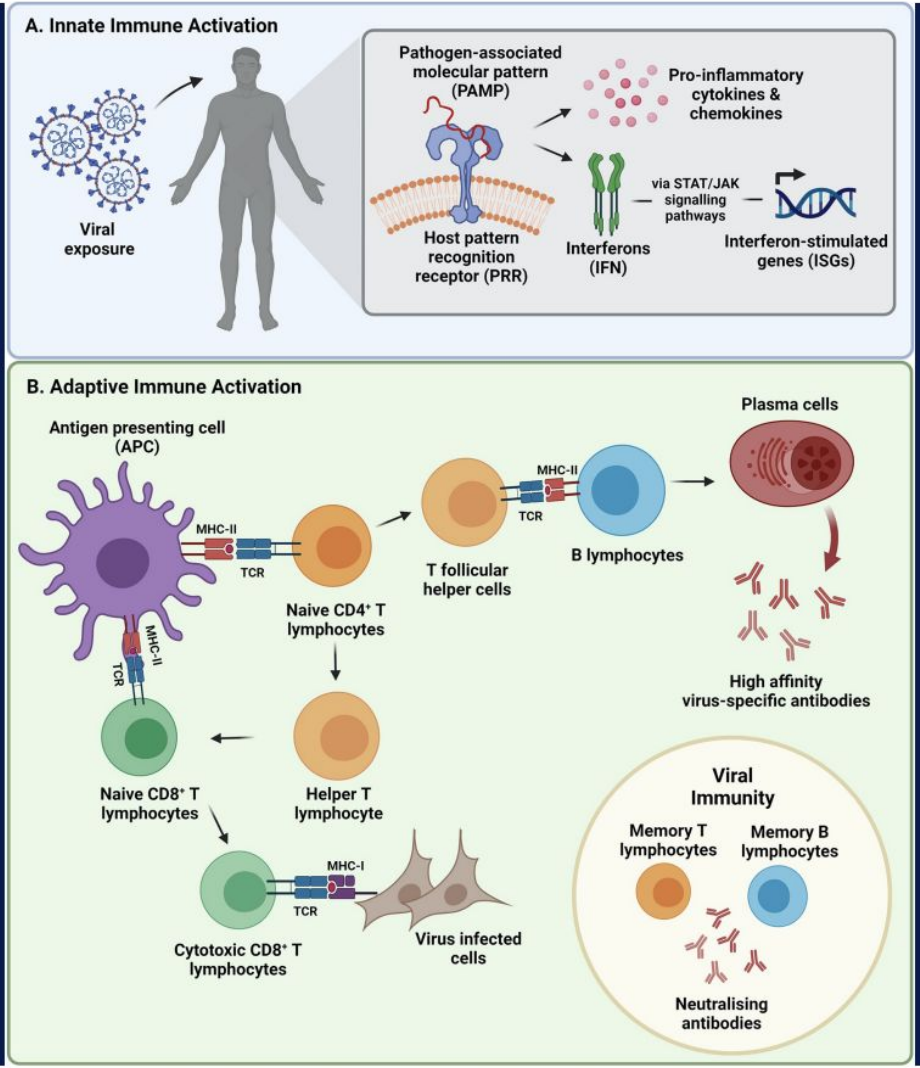
Cells that are called in to fight the infection. This response is specific to the type of invader



Tying it all together…

Immune system in action when a Virus attacks

How does our Immune System work?
https://www.youtube.com/watch?v=PSRJfaAYkW4



Topic #5: Immunotherapy

- Cancer immunosurveillance is an important host protection process that decreases cancer rates through inhibition of carcinogenesis and maintaining cellular homeostasis
- Cancer immunotherapy (also called immuno-oncology) is the artificial stimulation of the immune system to treat cancer, improving on the immune system's natural ability to fight the disease
- Cellular immune mechanisms can recognize unique antigens expressed by cancer cells and eliminate them before they present clinically as tumors.
- Tumor antigens can be viral proteins found in tumors caused by viruses, neo-antigens from mutated proteins or overexpressed self antigens.
- Similar to when the body encounters a pathogen, T cells act as sentinels in recognizing and eliminating continuously arising, nascent transformed cells.

Types of Immunotherapy

- Non-Specific Immunotherapies i.e. Cytokines
  - Immunotherapies • Cytokines- molecules that immune cells secrete to communicate with each other - are often used as a form of non-specific immunotherapy
- Antibody therapies: Heat-seeking missiles, selectively targeting one specific antigen
  - Antibodies are proteins made by B-cells that circulate in the blood and protect us from free-floating pathogens and cancer cells
  - physically interfere with important signaling molecules on cancer cells and halt their growth
  - promote destruction by macrophages or NK cells
  - activate complement that causes tumor cells to burst
- Cancer Vaccines: Goal of Cancer Vaccines is to present cancer antigens to the immune system in order to trigger an immune response against cancer.
  - Two broad classes of cancer vaccines:
    - Preventive vaccines- like vaccines against infectious diseases in that the aim is to prevent cancer from forming in the first place
    - Therapeutic vaccines- are designed to stimulate an immune response against an existing cancer, in the hope of destroying it.
- Checkpoint Blockade
- Cell Therapies
  - Adoptive cell therapy is a way to enrich and expand cancer- specific T cells from a person’s own body and then give them back to the patient in vastly increased numbers

Checkpoint Blockade

- Immune checkpoints are a normal part of the immune system, they prevent an immune response from being so strong that it destroys healthy cells in the body
- T cells have checkpoint proteins that act like brakes. Checkpoint inhibitors bind to these proteins and “take the brakes off” the immune response, enabling a stronger attack against cancer