NewYork-Presbyterian KIDS
Komansky Children's Hospital

Weill Cornell Medicine

2018 Bloom's Syndrome Conference

Immunology Overview

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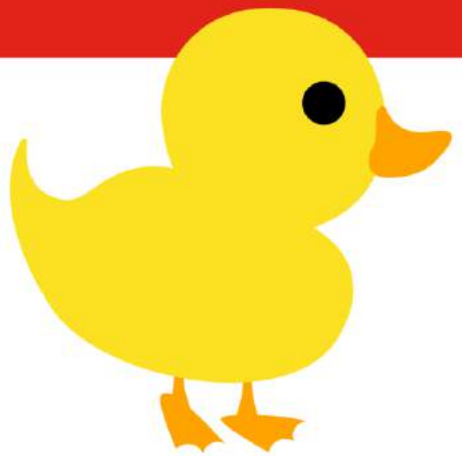


Outline

- What is the immune system?
  - Innate vs Adaptive
  - Cells and functions
  - Immunoglobulin
- How does it all come together?
- What are the immune manifestations of Bloom's syndrome?
  - B cells
  - T cells
  - Immunoglobulin
- When to refer to immunology?
- What sort of testing can be done? What does it mean?
- What treatments are available? When should they be considered?

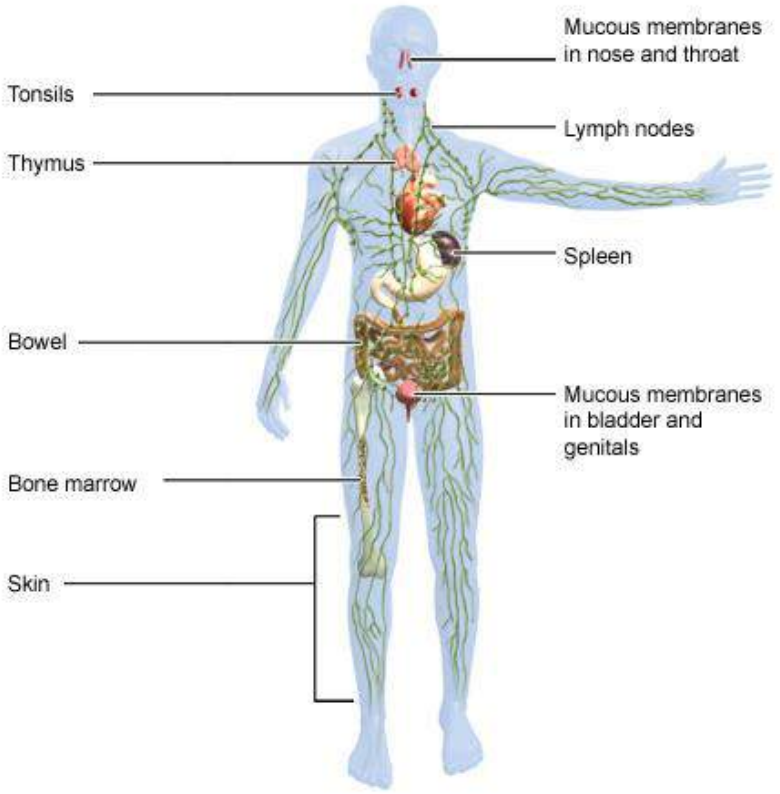
Why do we not get sick every single day?

Functions of the immune system

- Identify threats
- Mount an attack
- Kill the invaders
- Remember that strategy for the next attack

How does it accomplish this?

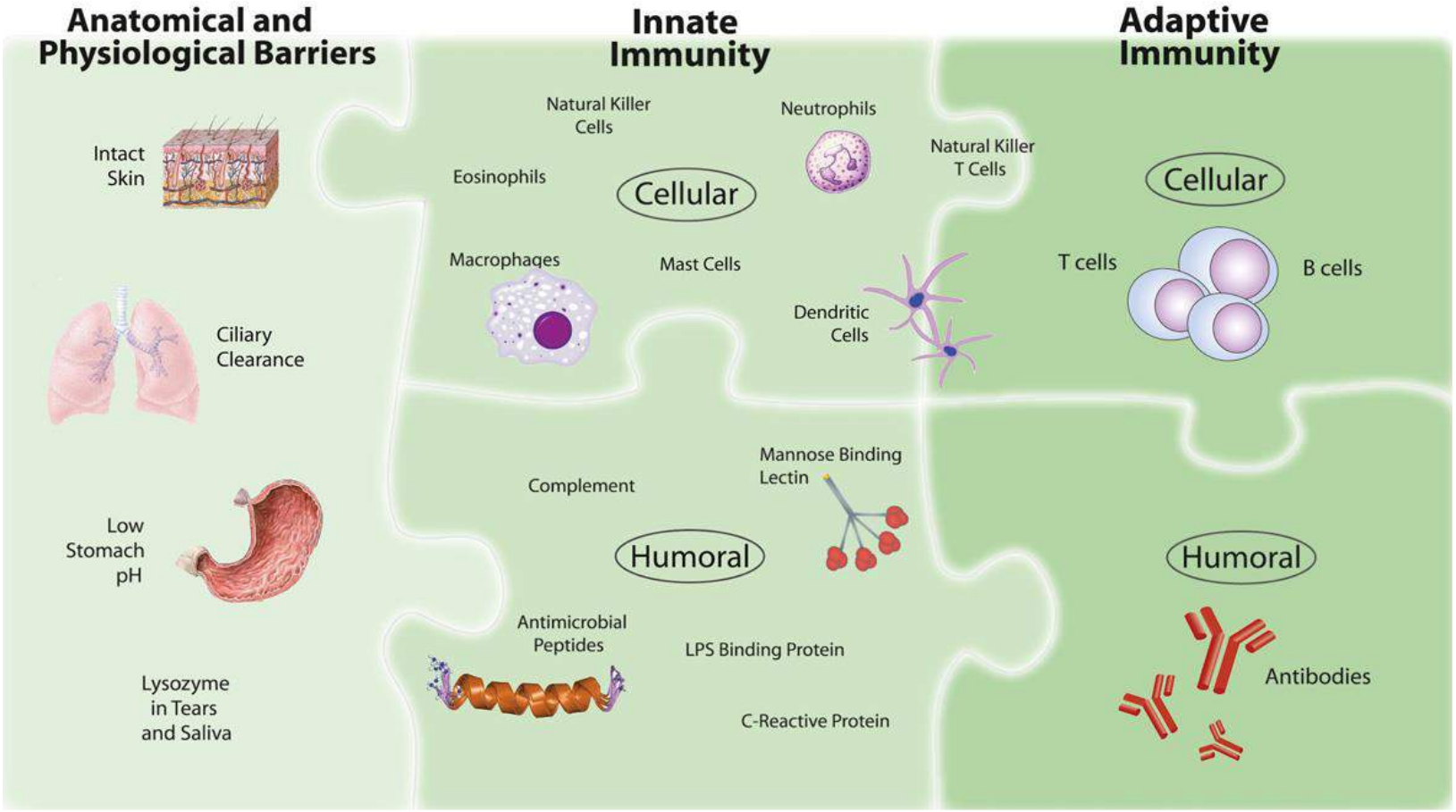
- Physical barriers
  - Mucous membranes in nose, throat, bowel, bladder and genitals
- Mechanical barriers
  - Cilia and mucus
  - Cough and sneeze
  - Vomiting and diarrhea
  - Flushing: tears, urine, saliva, sweat
- Chemical neutralization
  - Enzymes
  - Stomach acid
- Identifies and destroys germs
  - Cells of the immune system



What are the parts of the immune system?

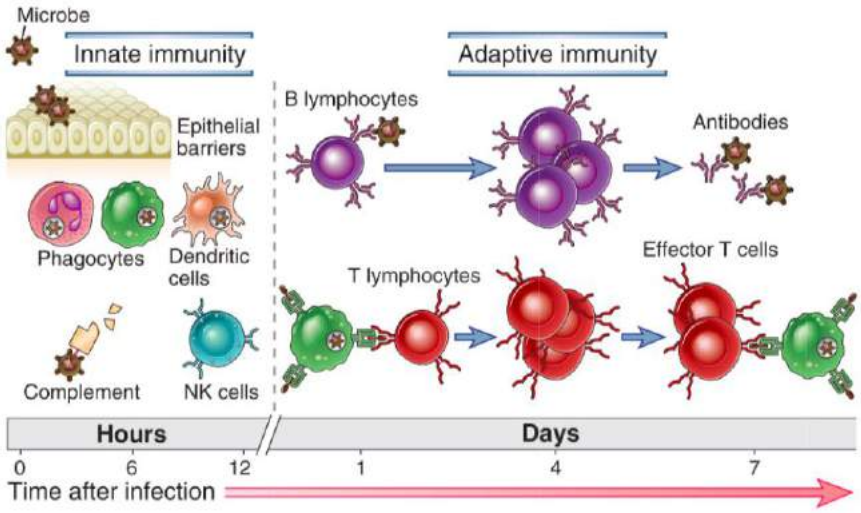
www.ncbi.nlm.nih.gov

Two main branches of the immune system: Innate and Adaptive.



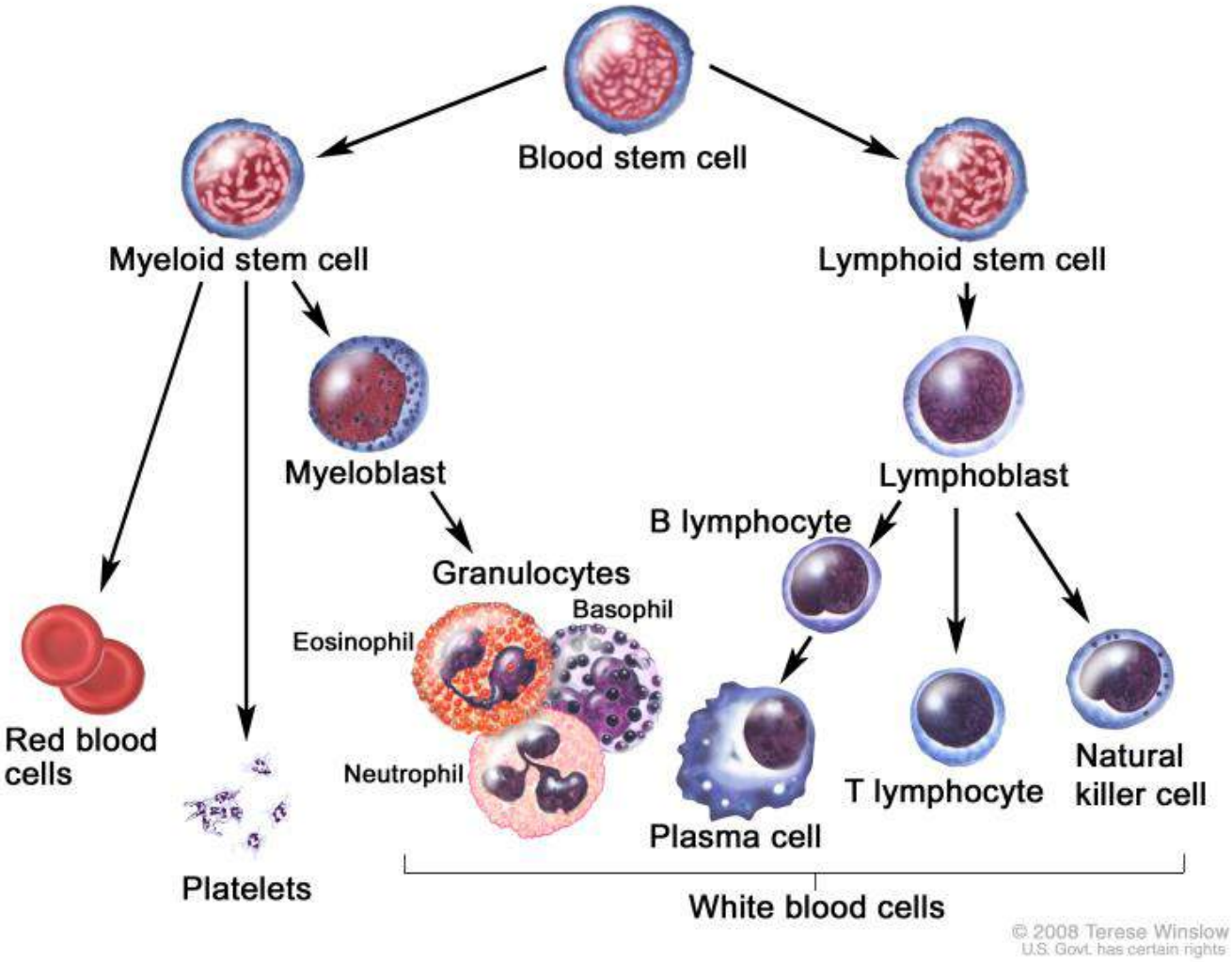
www.semanticscholar.org

What is the difference between innate and adaptive immunity?

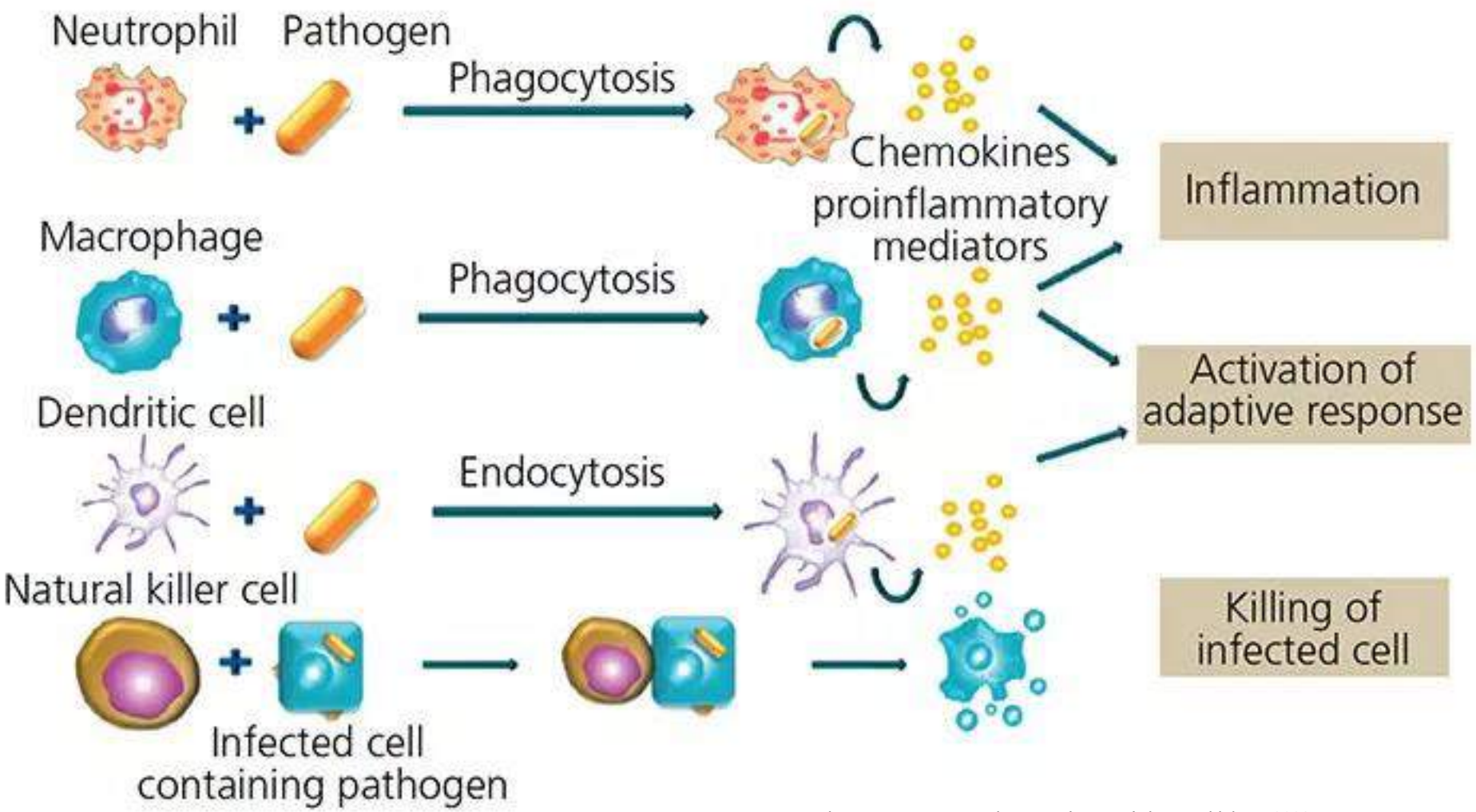


- **<u>Innate immune response</u>**
  - Cells are non-specific
  - Distinguish invader from human but not one invader from another
  - Very fast (minutes to hours)
  - No memory, responds the exact same way every time.
- **<u>Adaptive immune response</u>**
  - Highly specific for each invader
  - The adaptive response can tell one germ from another
  - Can take weeks
  - Has memory: the adaptive system responds faster and stronger each time

What are the cells of the innate immune system?

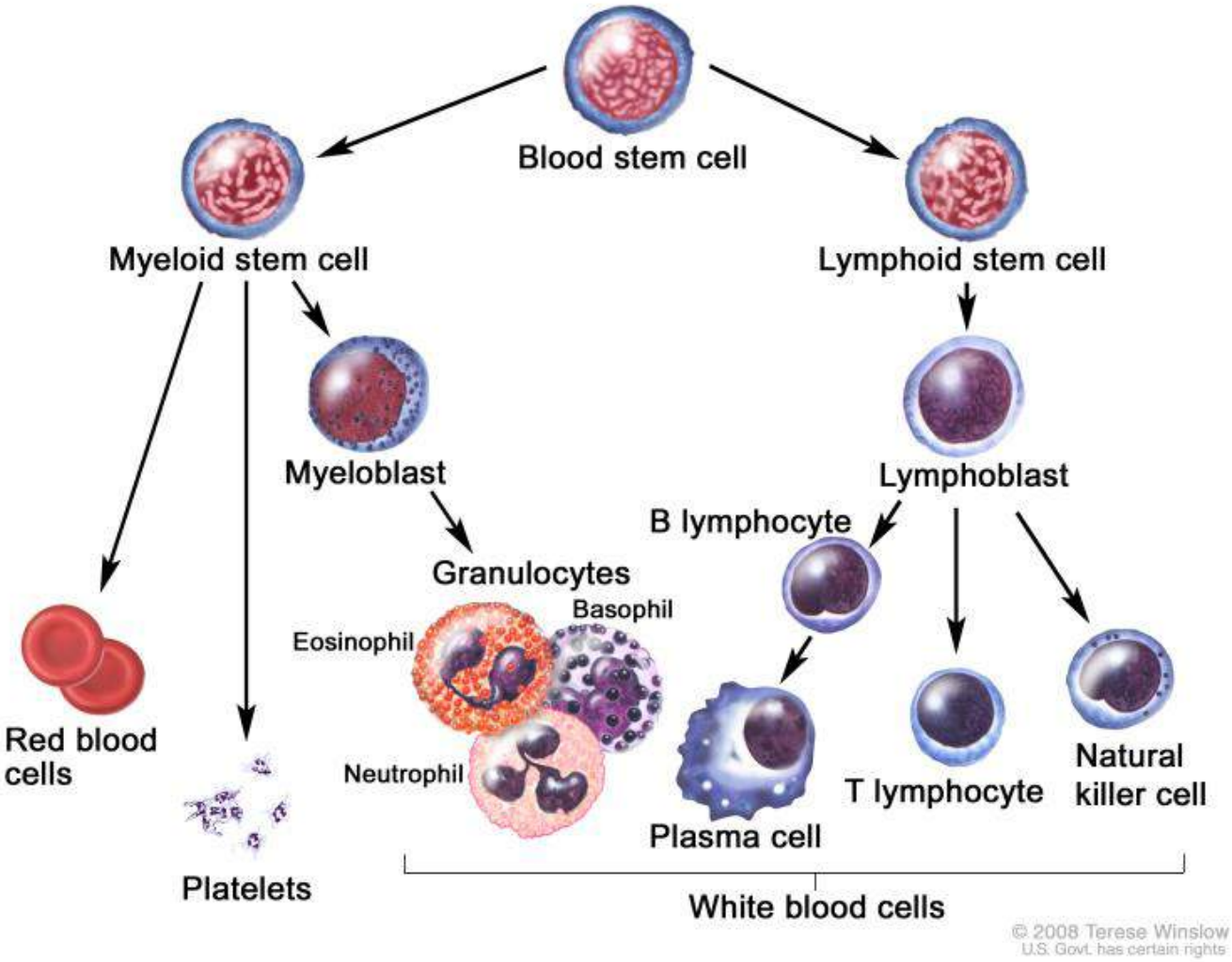


How do the innate cells do their job?

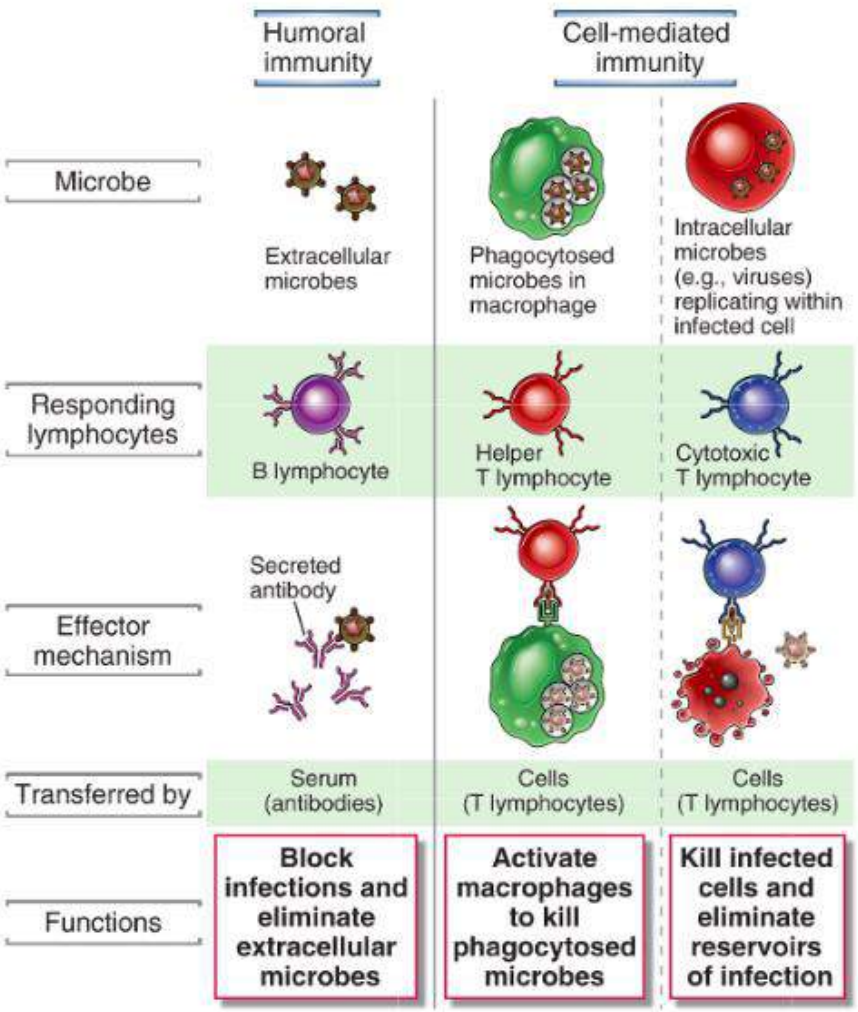


Murphy KM, Travers P, Walport M.: *Janeway's Immunobiology. 2008*

What are the cells of the adaptive immune system?

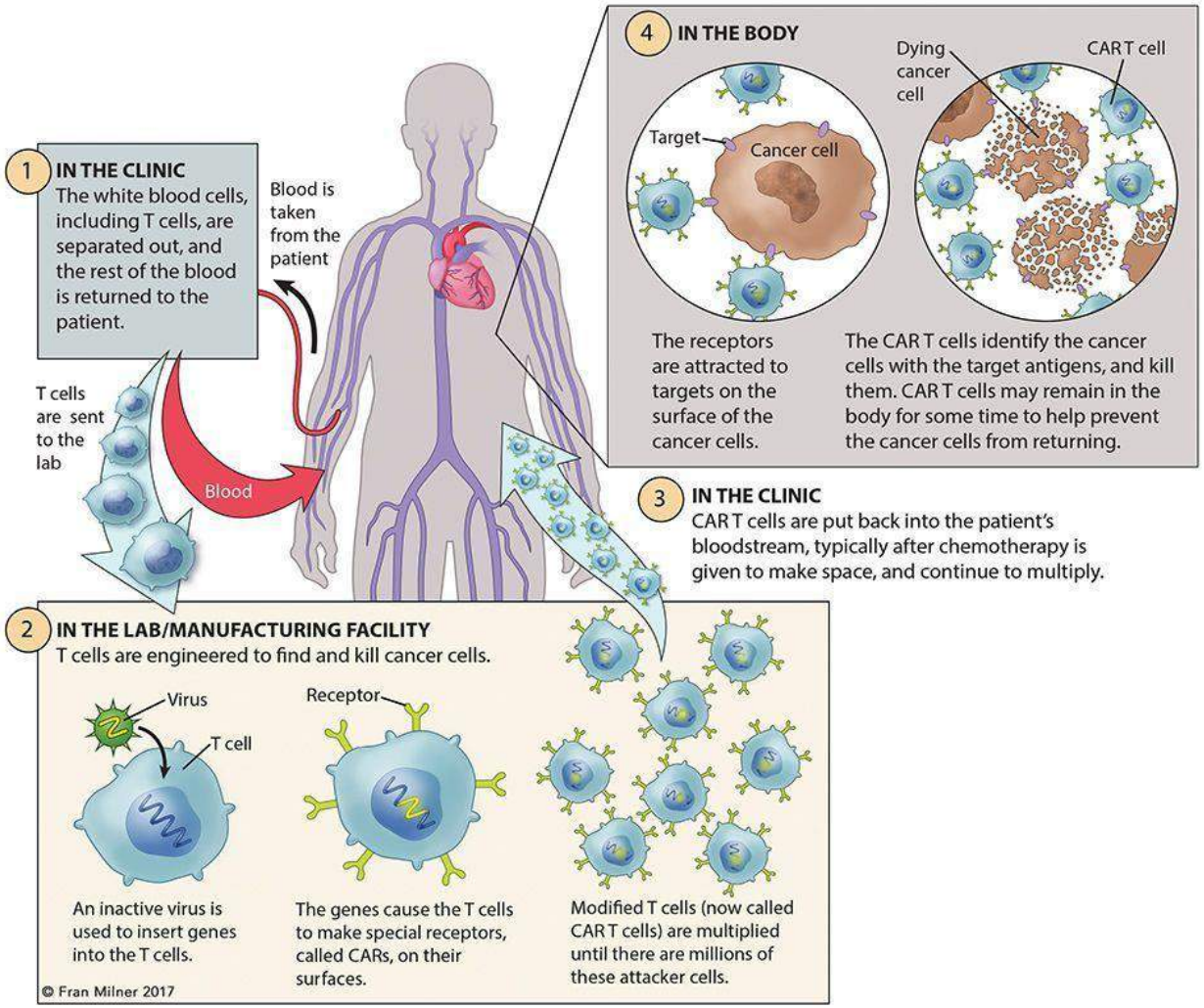


The adaptive immune system : Humoral vs Cell Mediated

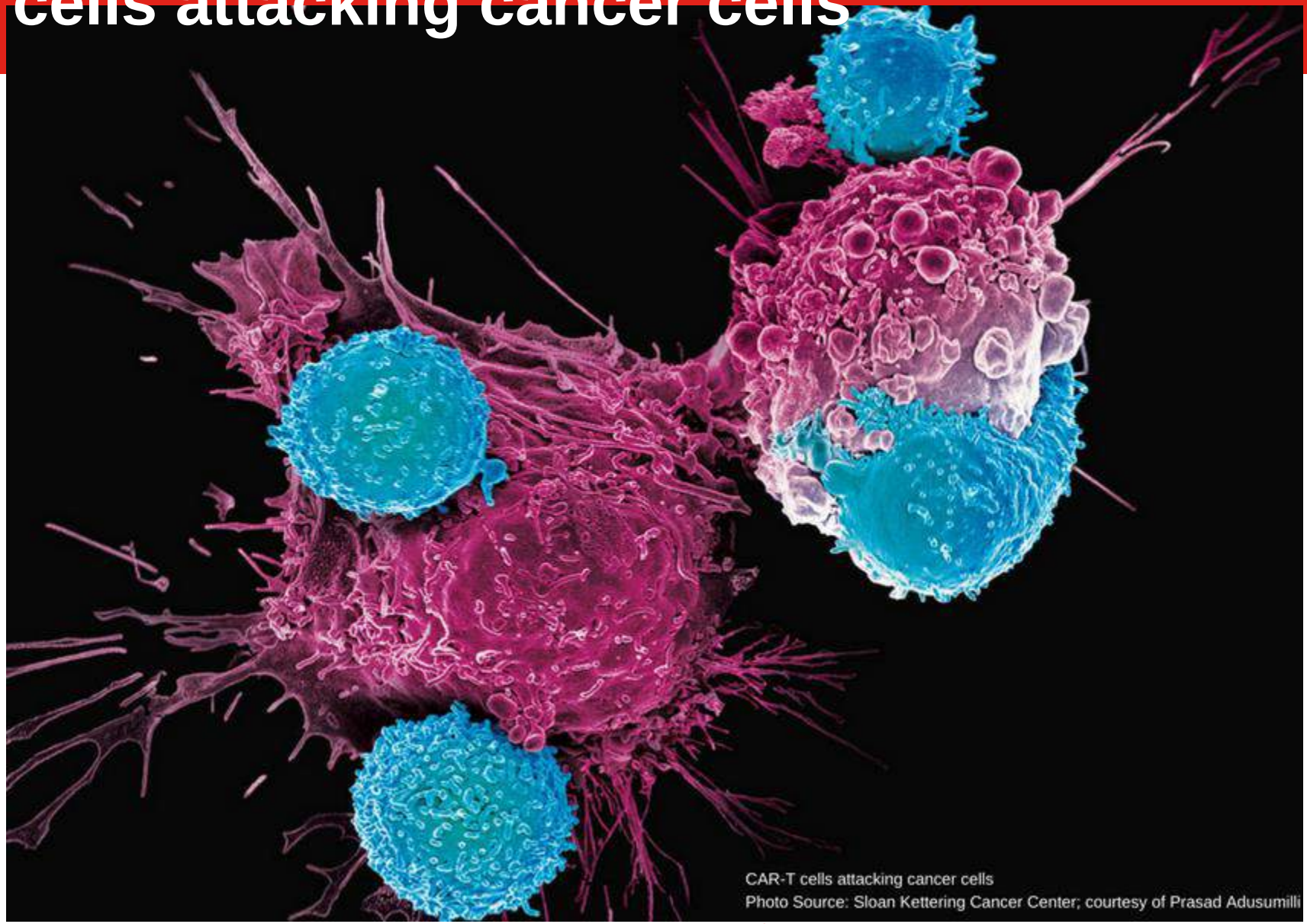


Abbas, Cellular and Molecular Immunology 2014

T cells and cancer - CAR T cells

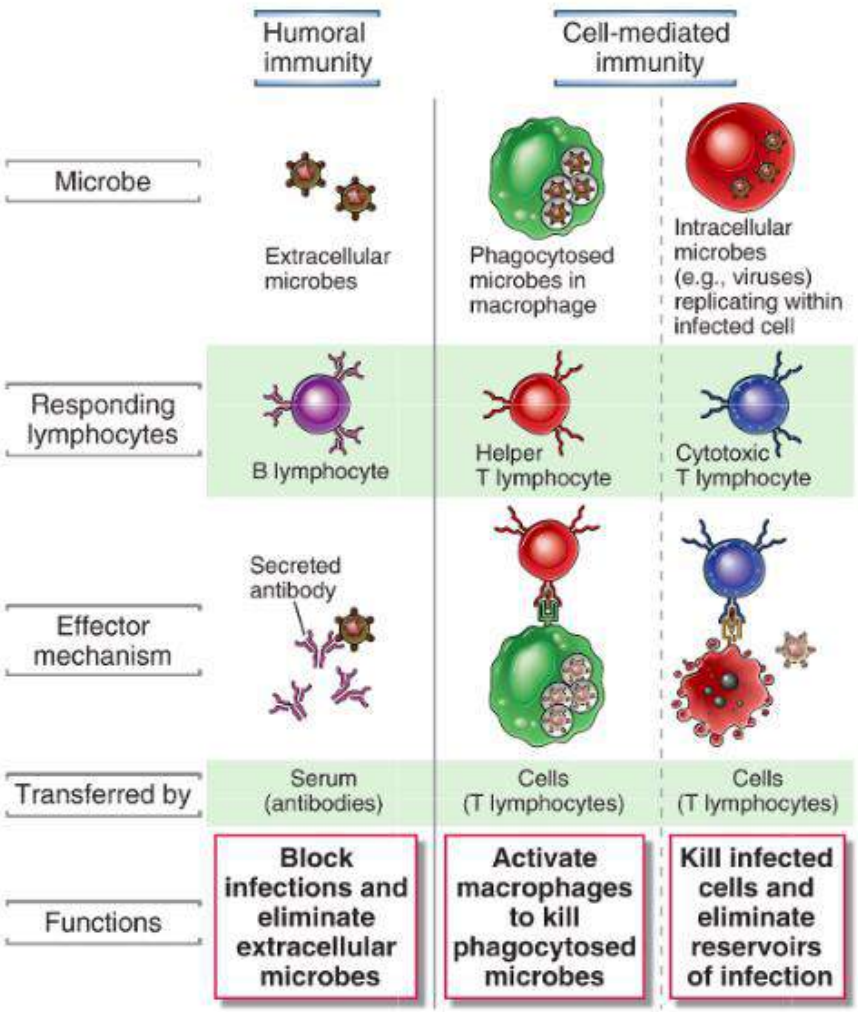


T cells attacking cancer cells



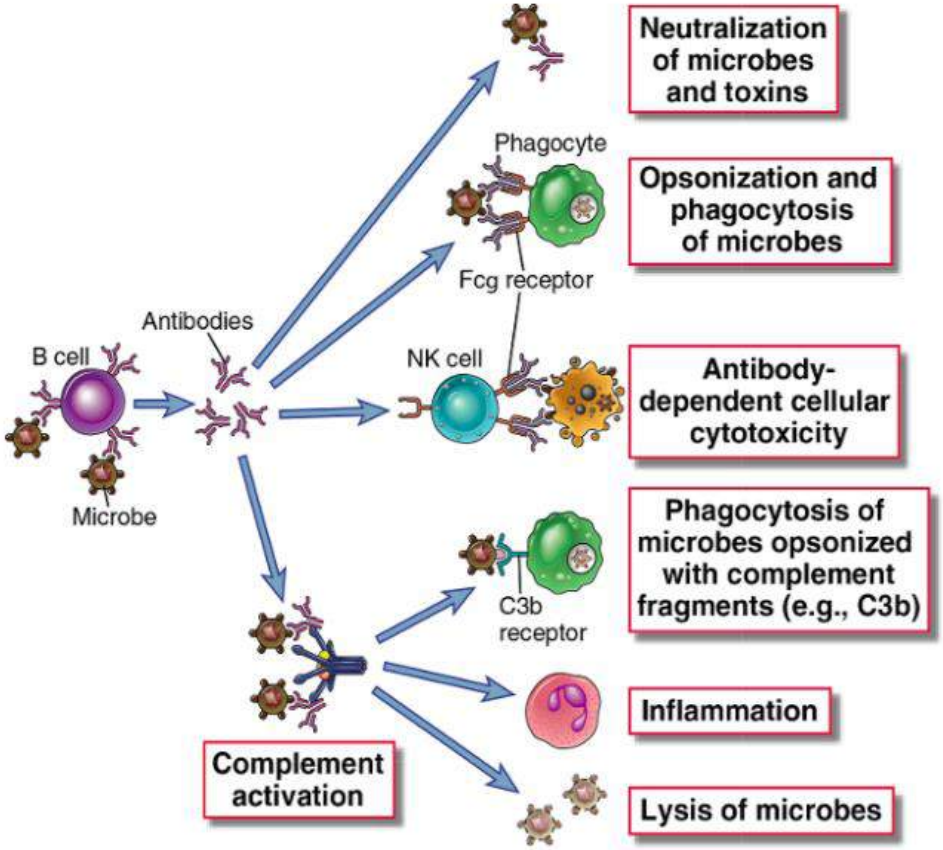
CAR-T cells attacking cancer cells
Photo Source: Sloan Kettering Cancer Center; courtesy of Prasad Adusumilli

The adaptive immune system : Humoral vs Cell Mediated



Abbas, Cellular and Molecular Immunology 2014

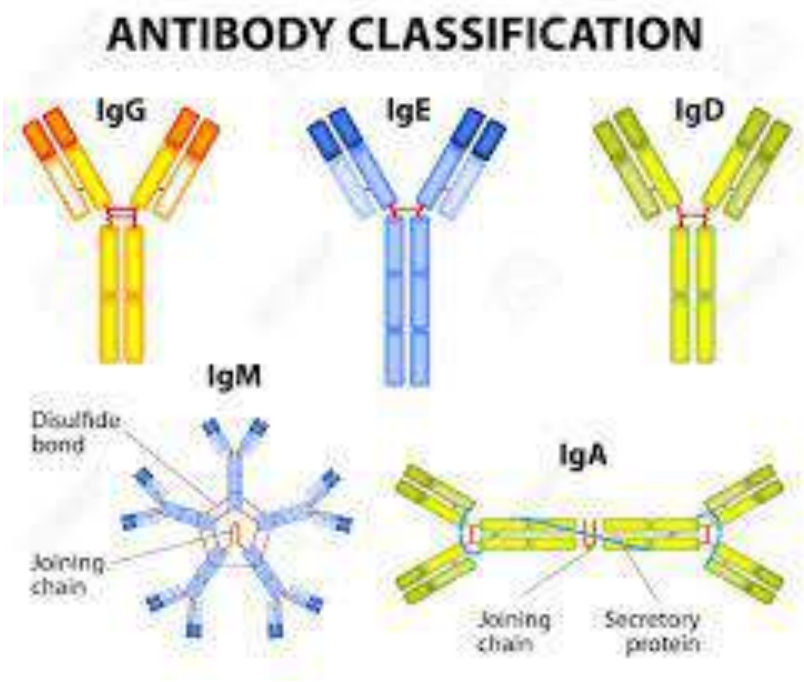
What are immunoglobulins?



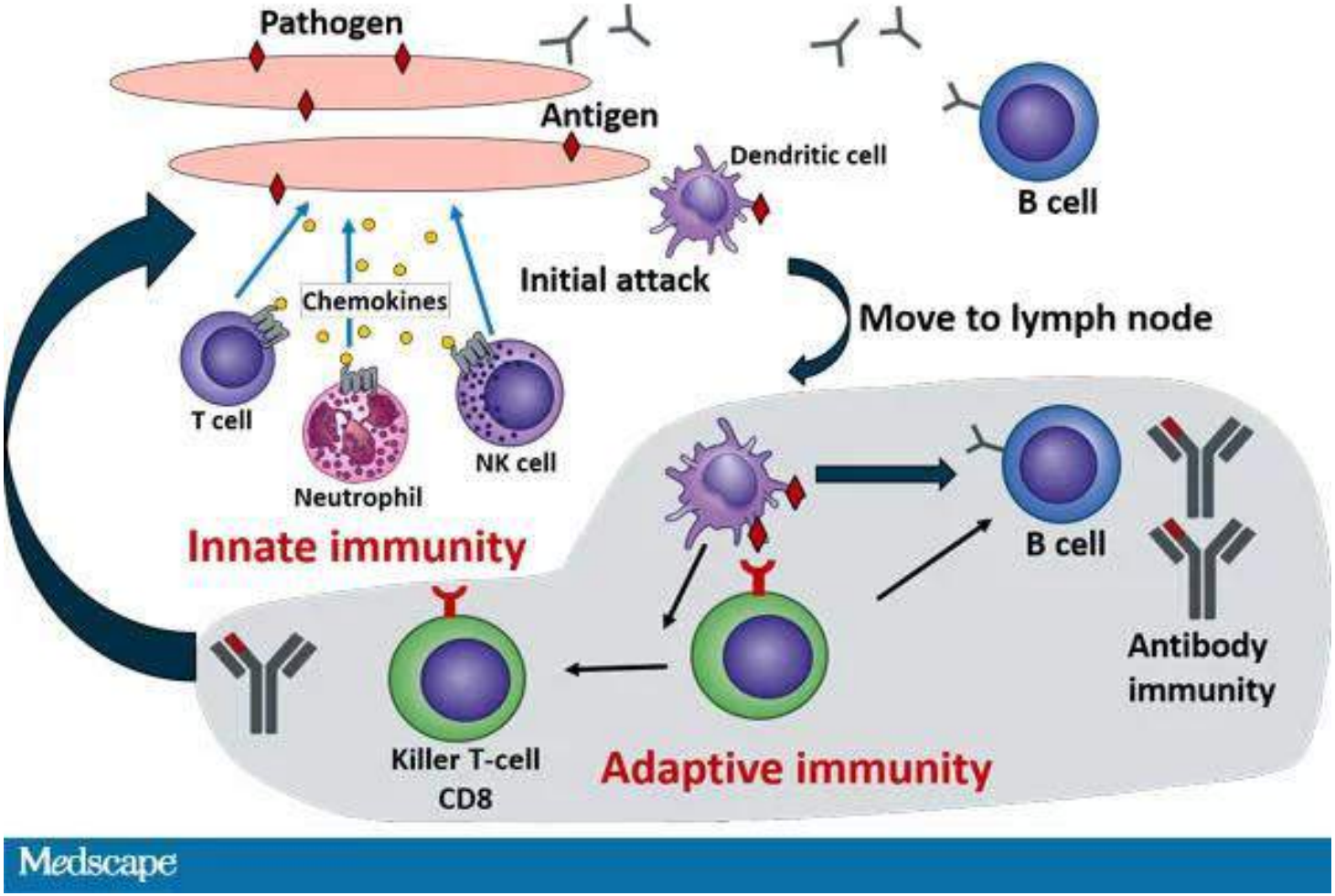
- Immunoglobulin are antibodies
  - They help identify pathogens to other cells and complement
  - flag for destruction

What are immunoglobulins?

- There are 4 major types of immunoglobulin
  - IgM, IgA, IgG, IgE
    - IgM is the initial antibody found on B cells
    - Once activated by T cells B cells can switch to IgA, IgG and IgE
    - IgA is mostly on GI and Respiratory Tract
    - **IgG is the primary circulating antibody**
    - IgE circulates and sits on mast cells

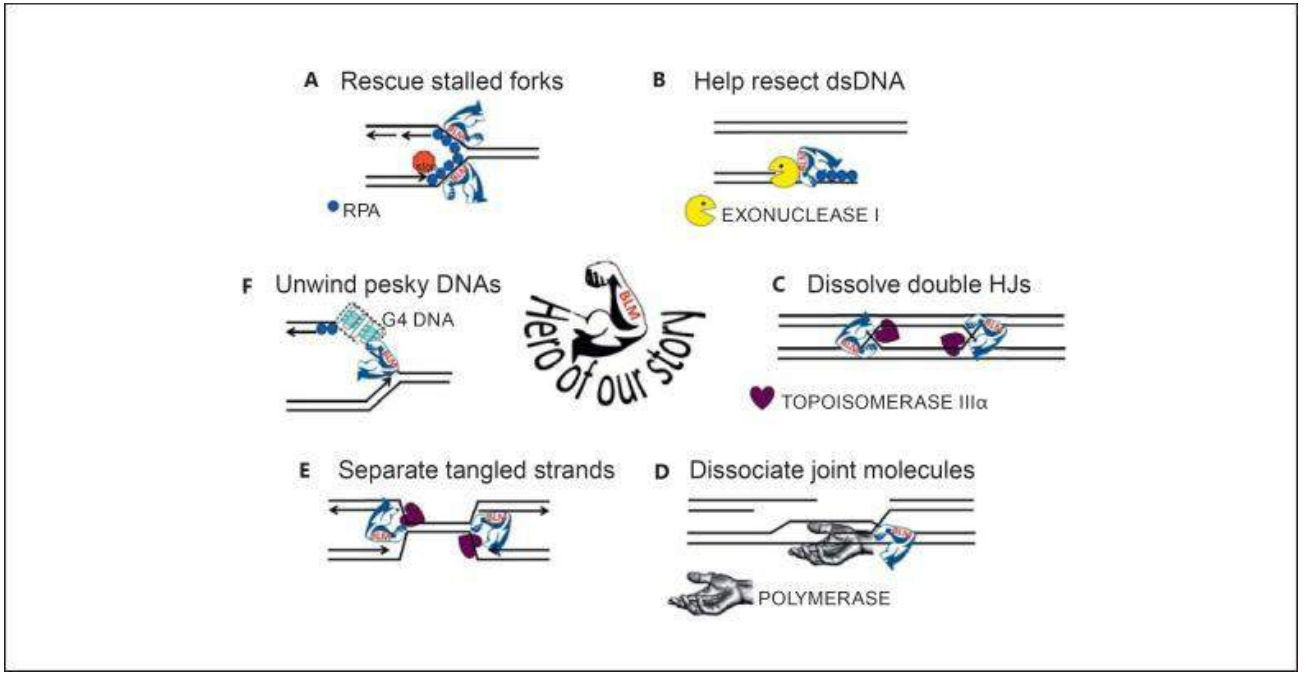


How does it all come together?



What is the immune defect in Bloom's Syndrome?

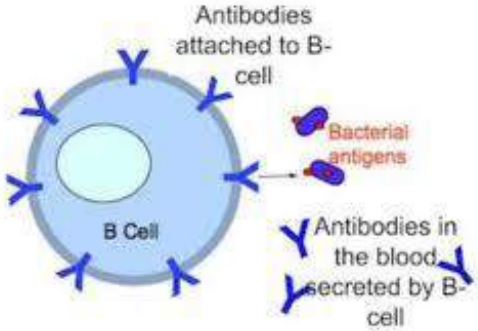
- The BLM gene is important in maintaining genomic stability



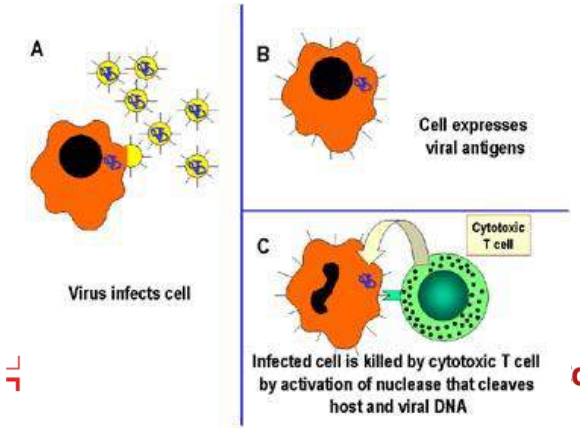
- B and T cells undergo a higher rate of gene rearrangement and replication than most cells of the body
  - DNA repair is essential for the development of the antigen receptors on B and T cells
  - also needed for cell proliferation
  - B cell class switching

How does Bloom syndrome affect the cells?

- **B cells – antibody producing cells**
- Typically total number of B cells is normal
- Decreased mature B cells with normal or increased naïve mature and transitional B cells decreased (suggests impaired maturation)
- Immunoglobulins may be low
  - Possibly due to impaired maturation
  - Or due to defective stimulation by T helper cells
- Class switch may be impaired



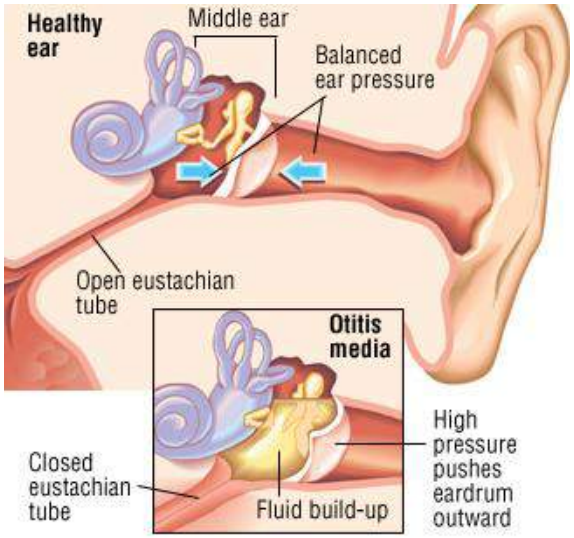
- **T cells – two types killer cells and helper cells**
  - Total T cell number is significantly lower in children and low in adults
  - CD4+ helper T cells are decreased in all patients
  - CD8+ killer T cells low normal
  - Absolute CD4 CD8 naïve, effector and memory T cell populations are reduced but have a normal distribution



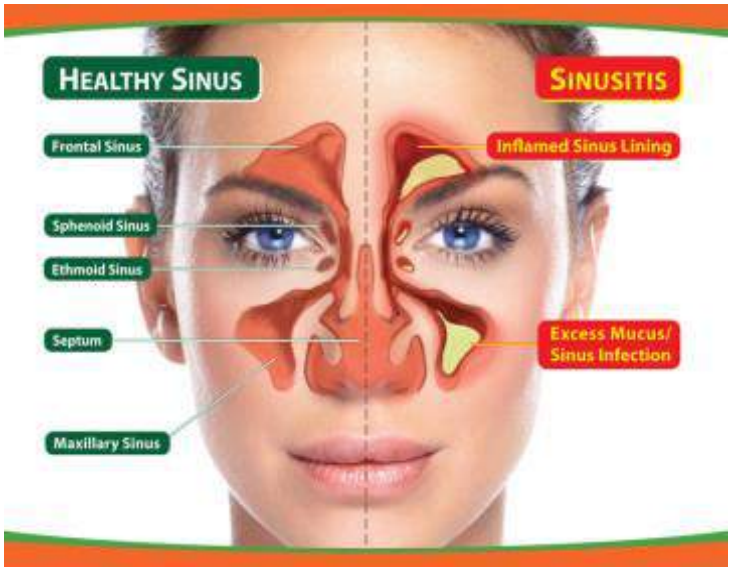
How does this manifest itself?

Infections in Bloom's Disease

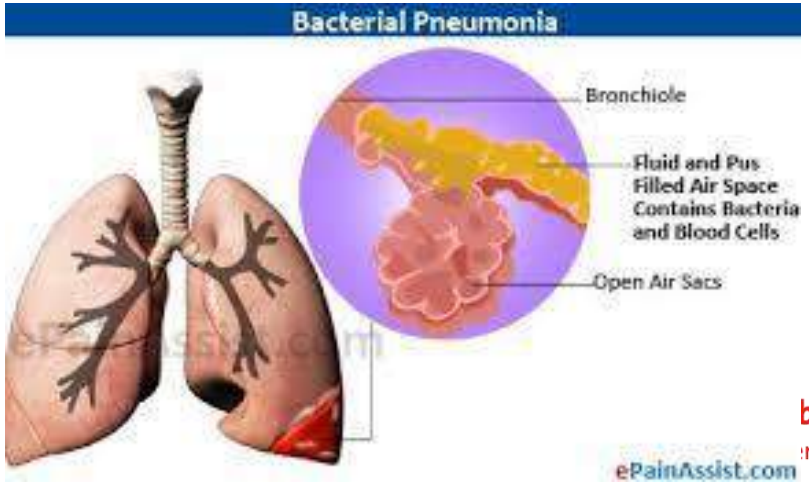
Children -Ear Infections



Adults- Sinusitis



Pneumonia



When to refer to immunology?

- Frequent or recurrent infections
  - chronic or recurrent sinusitis despite anatomically corrective surgery,
  - more than one pneumonia in a 10-year period
  - multiple episodes of bronchitis per year
  - bronchiectasis, severe pneumonia with empyema or blood-borne infection
- Infections that are hard to treat
  - Require a longer course of antibiotics or IV antibiotics
- Particularly severe infections
  - infection requiring ICU stay
- Opportunistic infections
  - infections not commonly seen in healthy people and commonly seen in people with immune abnormalities

What lab tests should be done?

- Immunoglobulin levels (LOW)
- Immunoglobulin function (NO OR POOR RESPONSE TO VACCINES)
  - Vaccine titers
- Lymphocyte screen
  - Total lymphocytes – MAY BE NORMAL
  - Total T and B cells – MAY BE NORMAL
  - Total subsets of T helper, T killer and mature memory B cells

    DECREASES MAY INDICATE DEFICIENCY

What are the available treatments?

- Prophylactic antibiotics
  - Targeted to recurrent infection

What are the available treatments?

- Sinus infections
  - Daily nasal lavage
  - Prophylactic antibiotics

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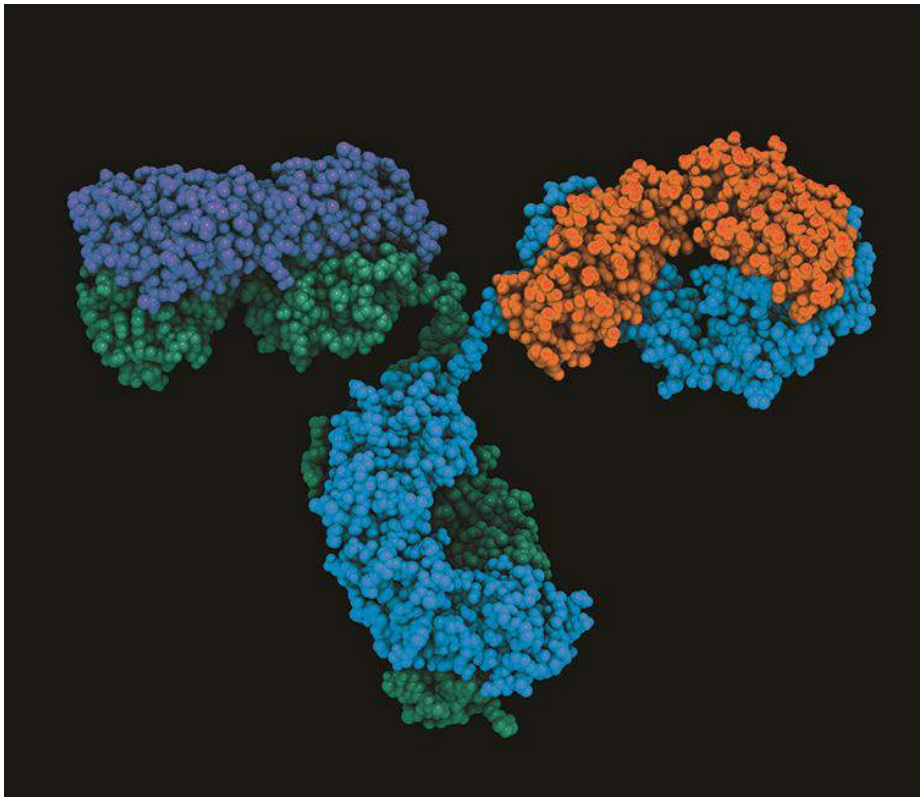
Treatments

- Bronchiectasis (permanent enlargement of lung airways)
  - Cough assist devices
  - Vibration vests

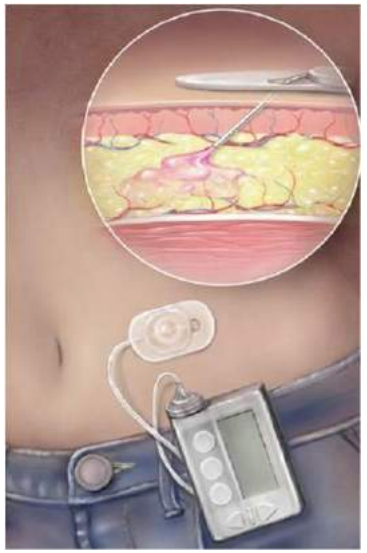
Treatments?

- Replacement immunoglobulin
  - If levels and vaccine titers low



What is IVIG or SCIG?

- What is immunoglobulin replacement and how does it work?
  - Immunoglobin replacement is a blood product.
  - It contains the IgG antibodies of the community or group from which the blood was sourced.
  - It is a pooled product, reflects the antibody of the population as a whole
  - It is not IgA or IgM - it only replaces IgG
  - High doses are used to suppress the antibody response in people with autoimmune disease – is not for everyone.



Summary:

- No issues? – watchful surveillance
- Recurrent infection?
  - Immune workup
    - Immunoglobulin + vaccine titers normal but recurrent infection
    - Consider prophylactic antibiotics
- Immunoglobulin levels (LOW)
  - Immunoglobulin function (NO OR POOR RESPONSE TO VACCINES)

    - consider immunoglobulin replacement

Questions?

Thank You