

# Immune System Basics

## From Friend to Foe: What Happens When Your Immune System Goes Bad?



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ἦξει Δωριακὸς πόλεμος  
καὶ λοιμὸς ἅμ' αὐτῷ.



# Plague of Athens – 430 B.C.

...it was with those who had recovered from the disease that the sick and the dying found most compassion.

These knew what it was from experience, and had now no fear for themselves; for the same man was never attacked twice - never at least fatally.

And such persons not only received the congratulations of others, but themselves also, in the elation of the moment, half entertained the vain hope that they were for the future safe from any disease whatsoever.

Thucydides, History of the Peloponnesian War

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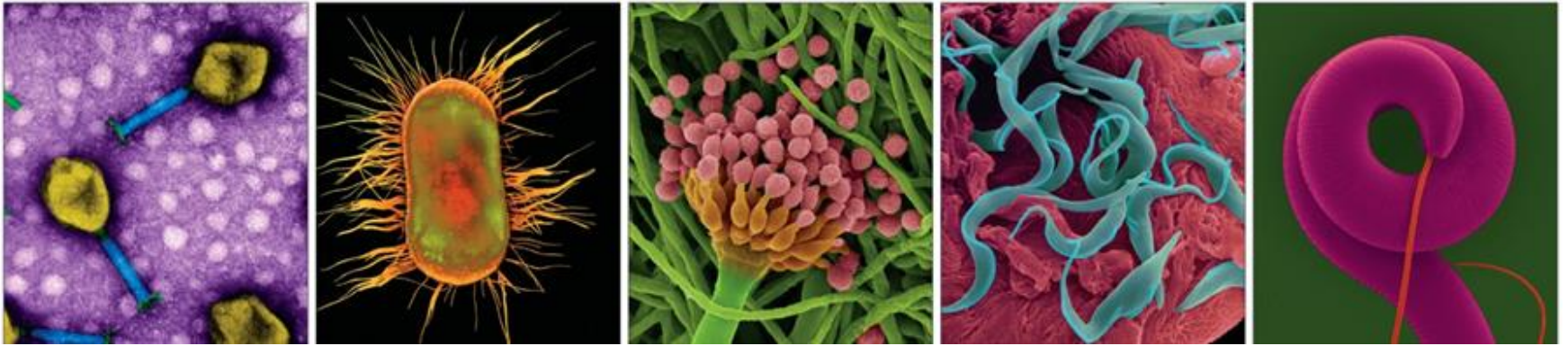
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# The immune system is armed against...

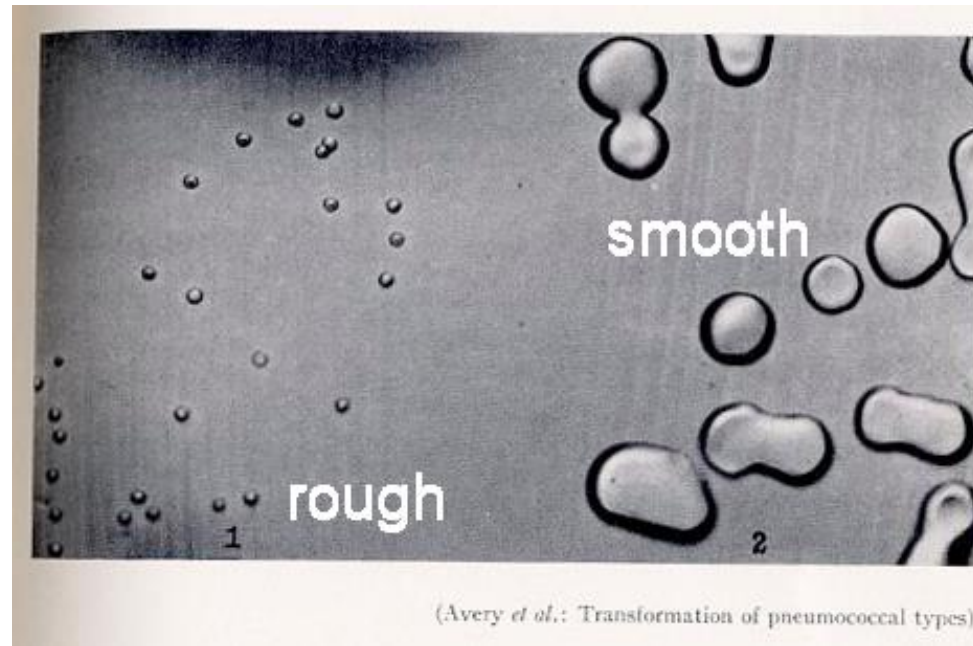
## Pathogens



## Altered self (e.g., cancer)



# Two major types of immunity



(Avery *et al.*: Transformation of pneumococcal types)

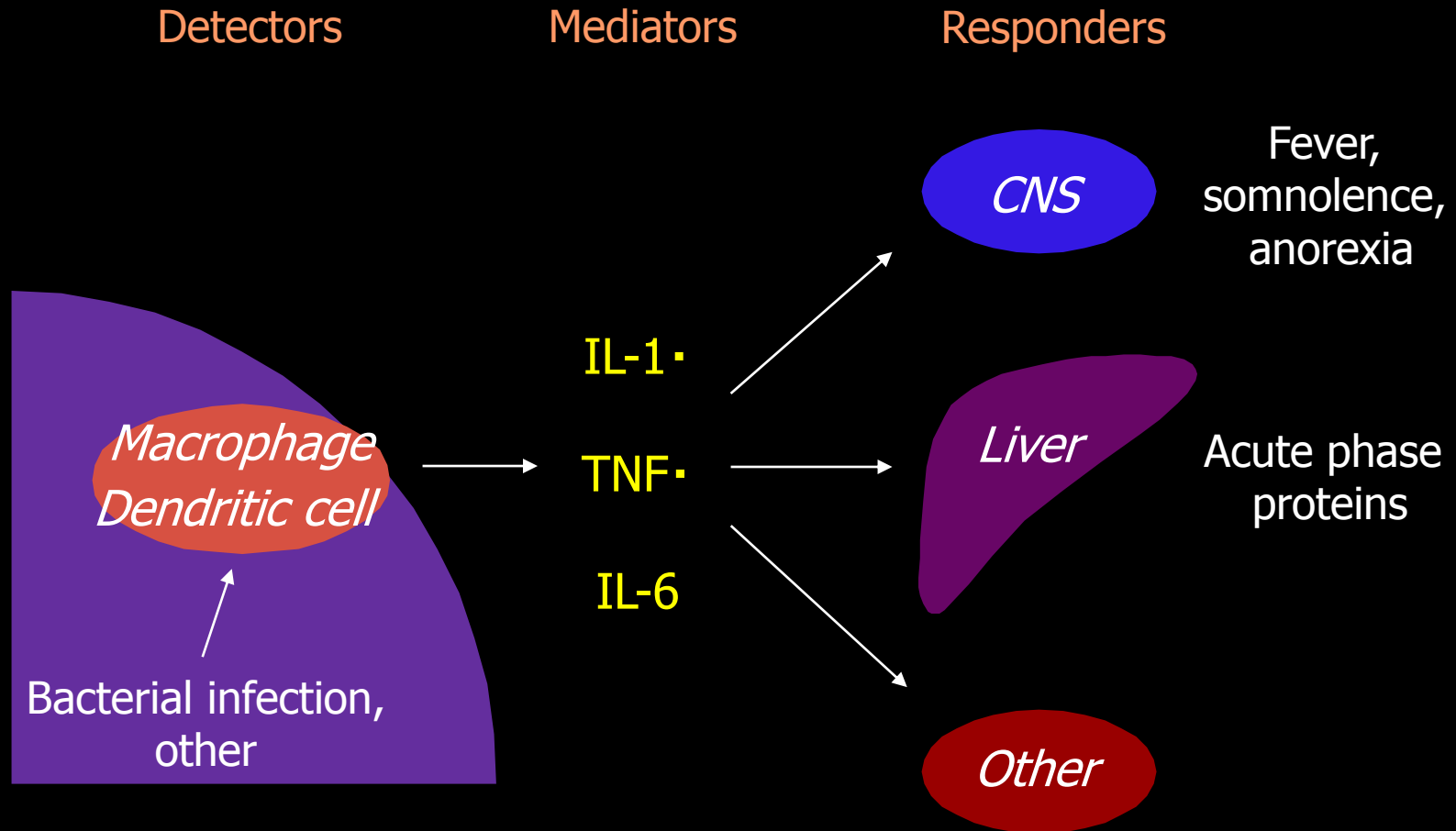
## Innate Immunity

- Genetically hardwired
- Germline evolution
- Stereotypic responses
- First line of defense

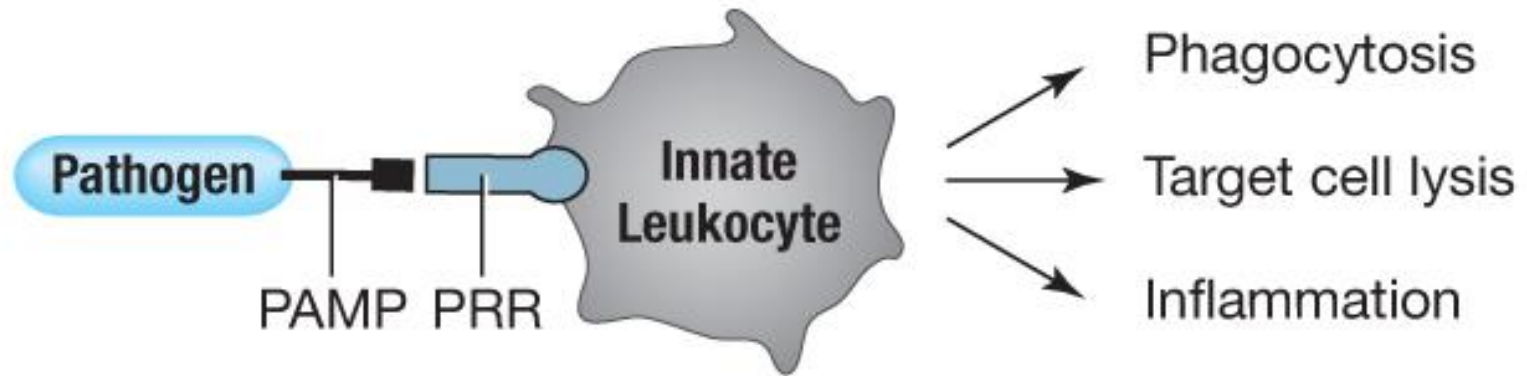
## Adaptive Immunity

- Plastic
- Somatic evolution
- Idiosyncratic responses
- Delayed, efficient

# Innate Immunity: Immediate, Hardwired Responses



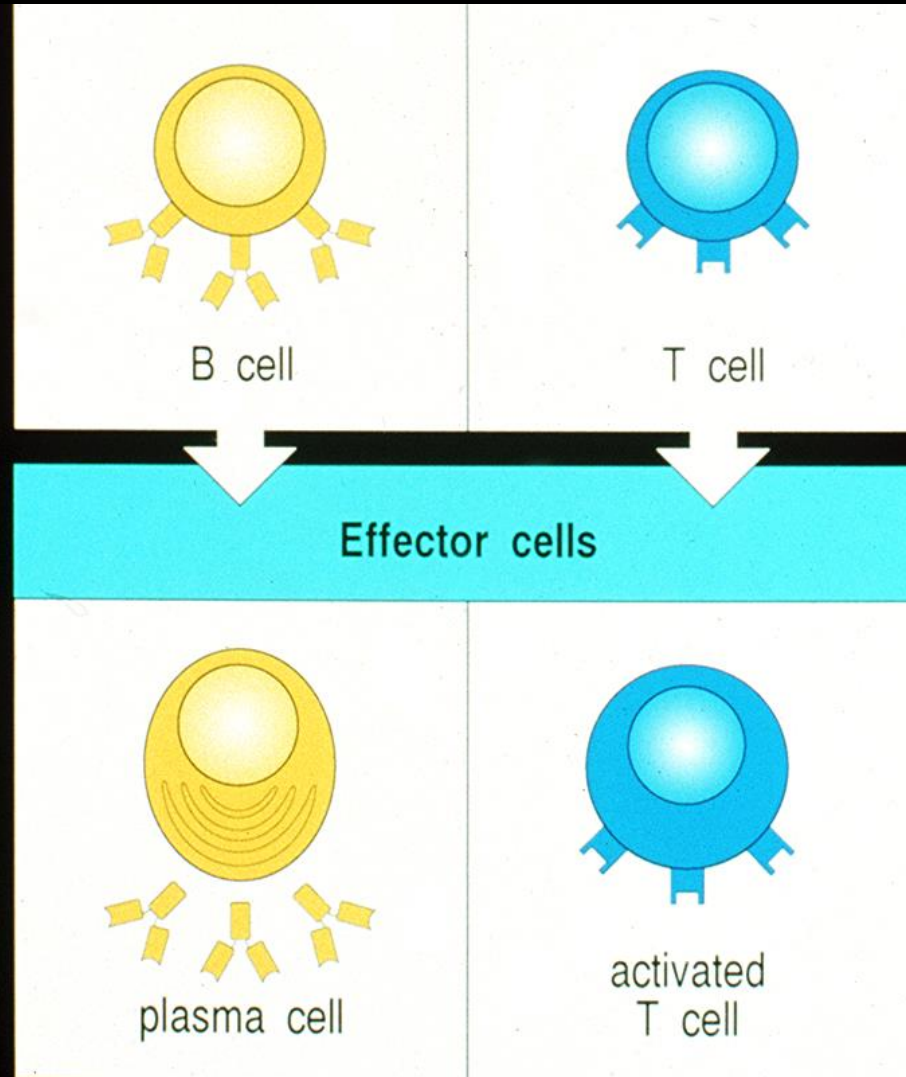
# Innate Immune Cells Detect Shared Properties of Pathogens



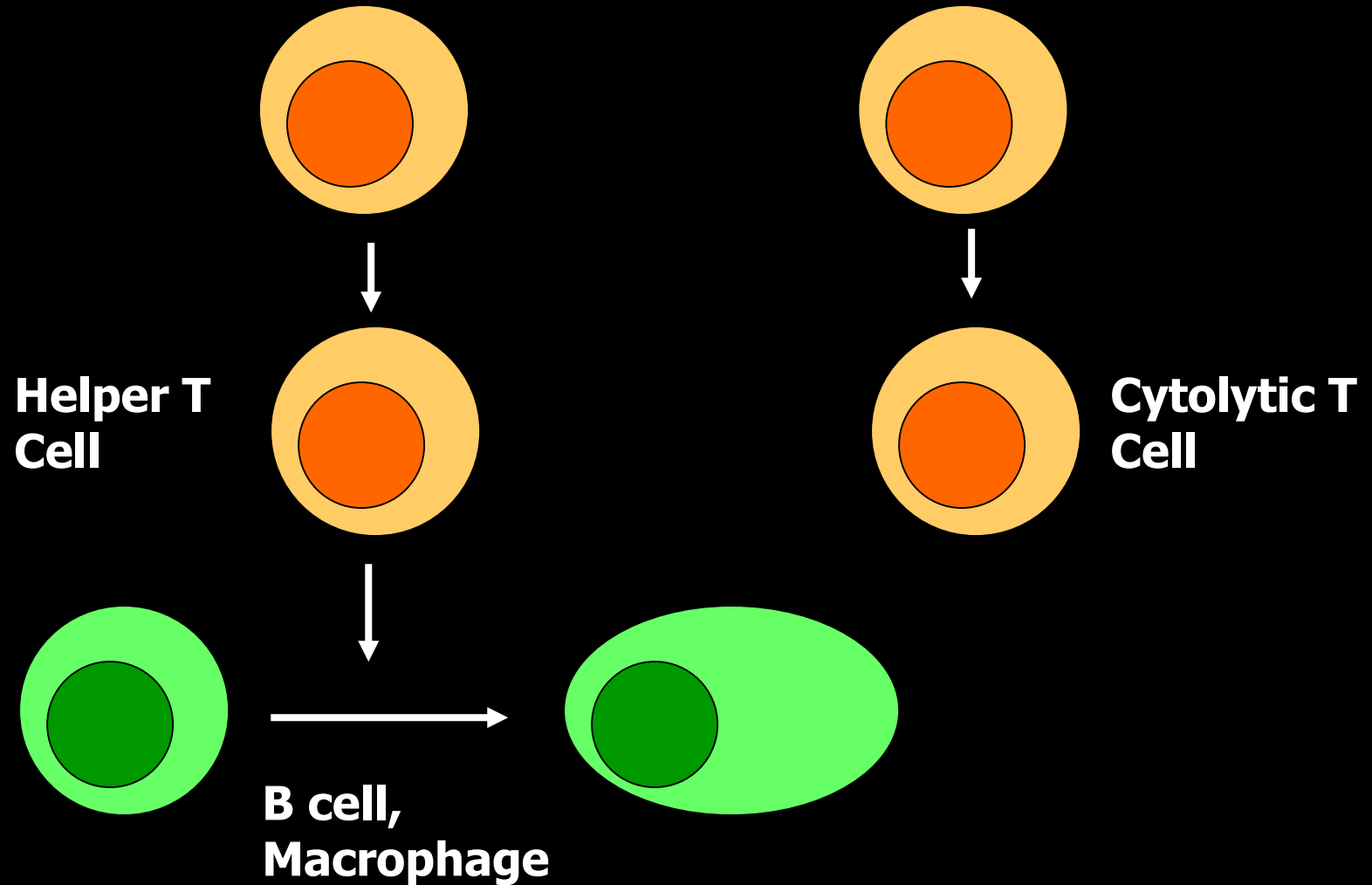
**Bacterial cell wall components**  
**Components of flagella**  
**Modified DNA**  
**Double-stranded RNA**



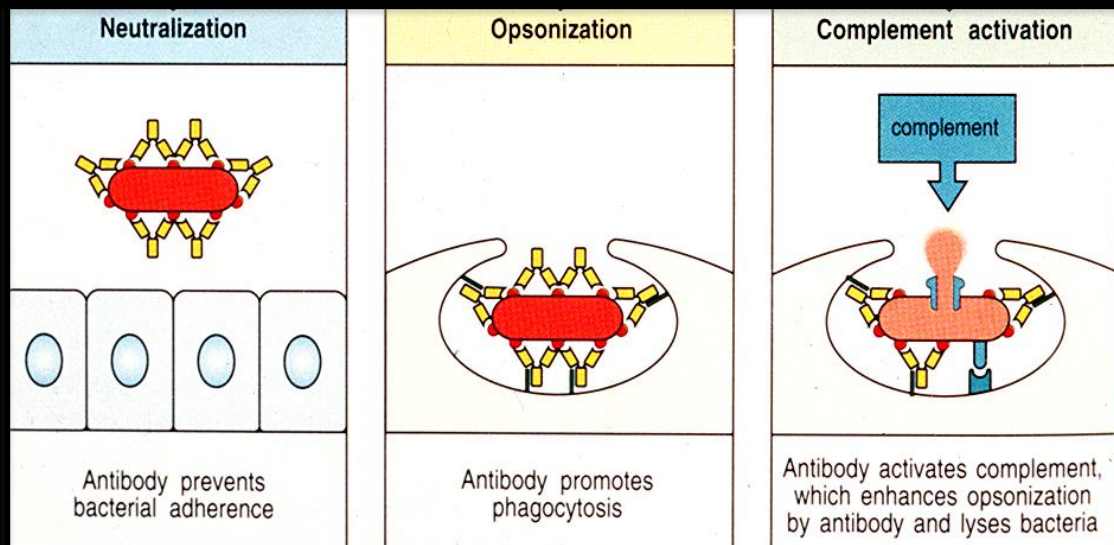
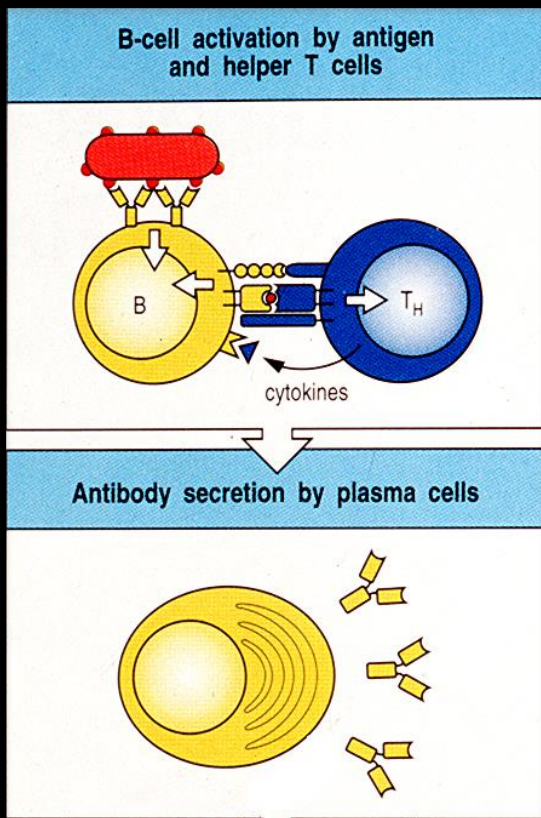
# Adaptive Immune Cells Express Receptors of Exquisitely High Specificity and Diversity



# T cells Play a Central Role in Adaptive Immune Responses



# T cells and B cells Collaborate to Make Antibodies



# Mutual Activation: T cell and B cell

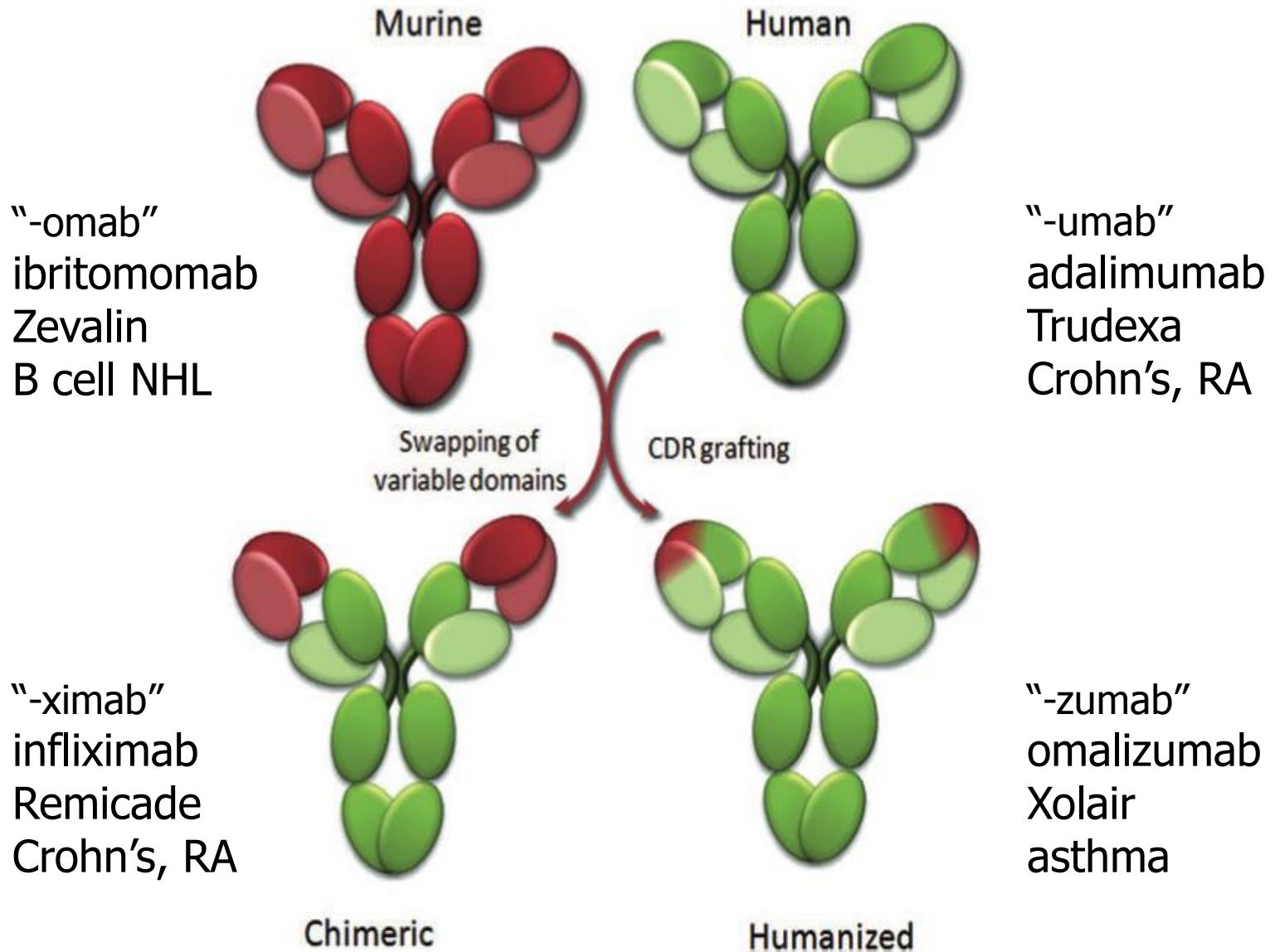


# Emil von Behring - Antitoxins



Transfer of immunity to tetanus and diphtheria toxins by serum  
Christmas Eve, 1890

# Mouse, human and hybrid antibodies are widely used as therapeutic agents

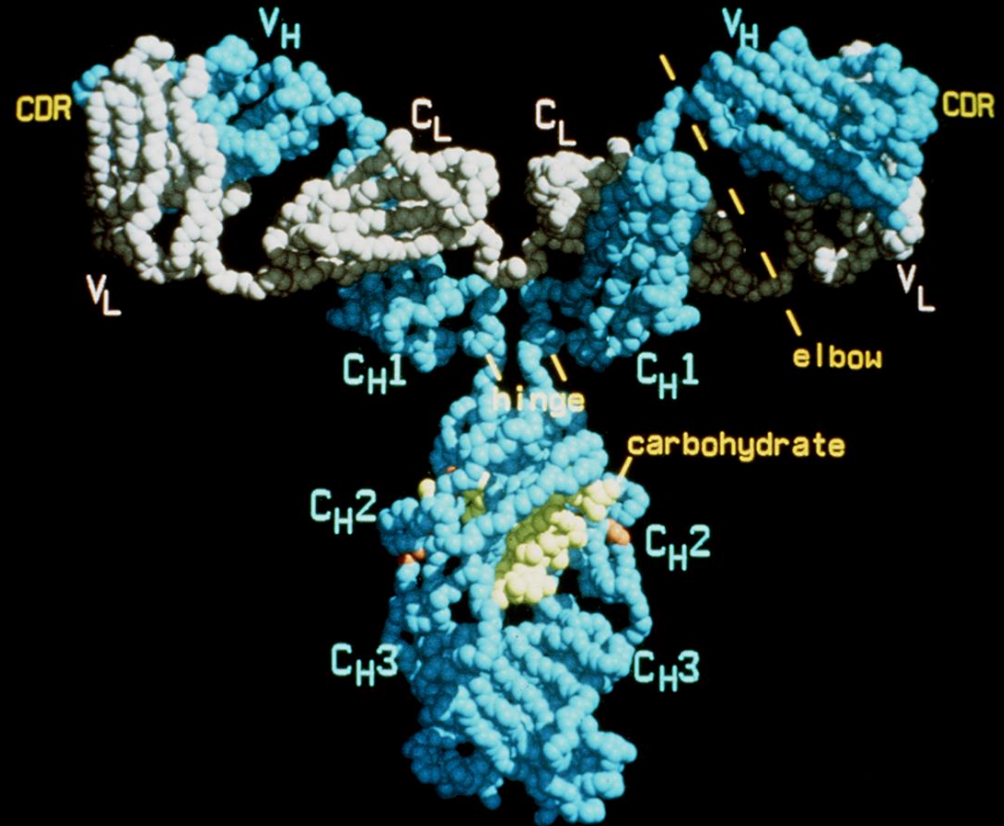


# Antibody Diversity and the Coding Paradox

Number of different antibodies in a typical mammal:  **$> 10^9$**

Coding sequence required if each the product of distinct genes:  **$2 \times 10^{12}$  bp**

Total size of human genome:  **$3 \times 10^9$  bp**

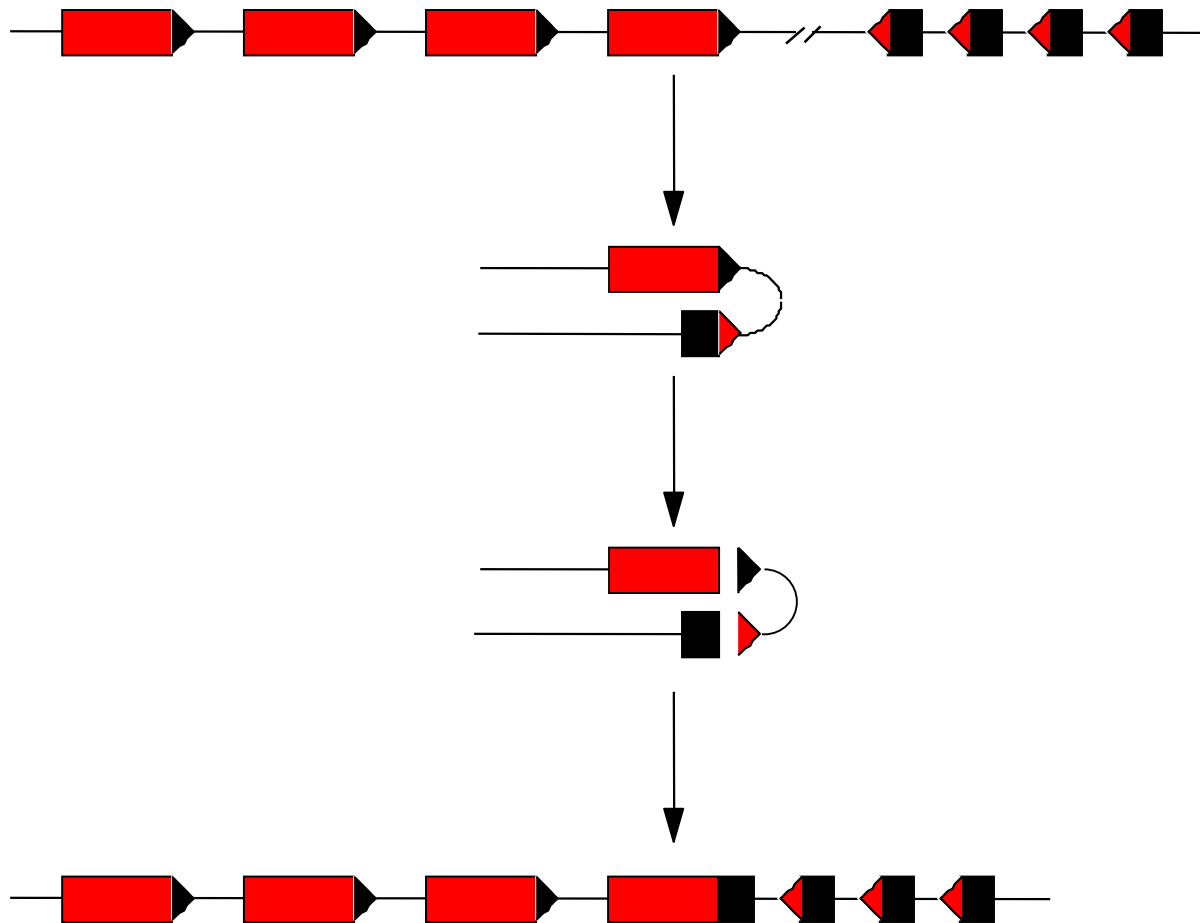


# The Solution: Let's Hit the Slots!

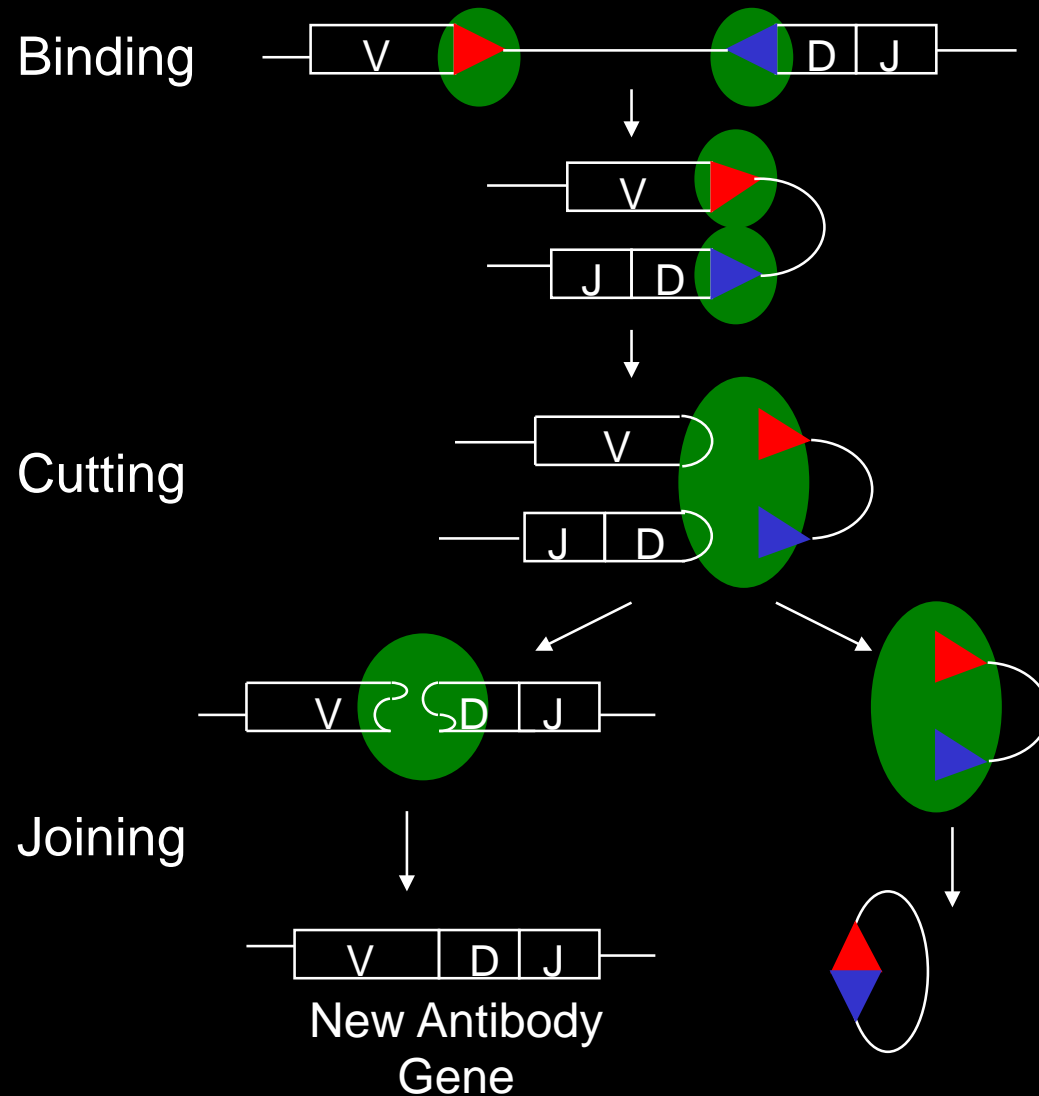




# Antigen Receptor Genes are Assembled from Discrete Gene Segments to Make Many Combinations



# Recombination is Initiated by a Molecular Scissors Called RAG



# Shuffling of antigen receptor genes: frequent and dangerous

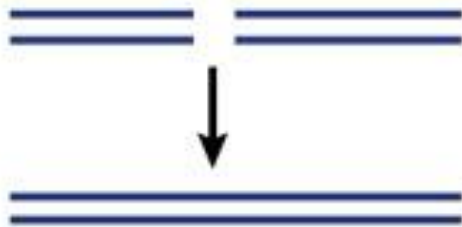
- A major cause of leukemia and lymphoma
- Two protective mechanisms:
  - No recombination at “dangerous” times
  - No recombination without the ignition key



# Cutting of Antibody Genes is Strictly Timed in Developing Immune Cells

## RAG On

Repair by non-homologous end-joining



G1 phase

## RAG Off

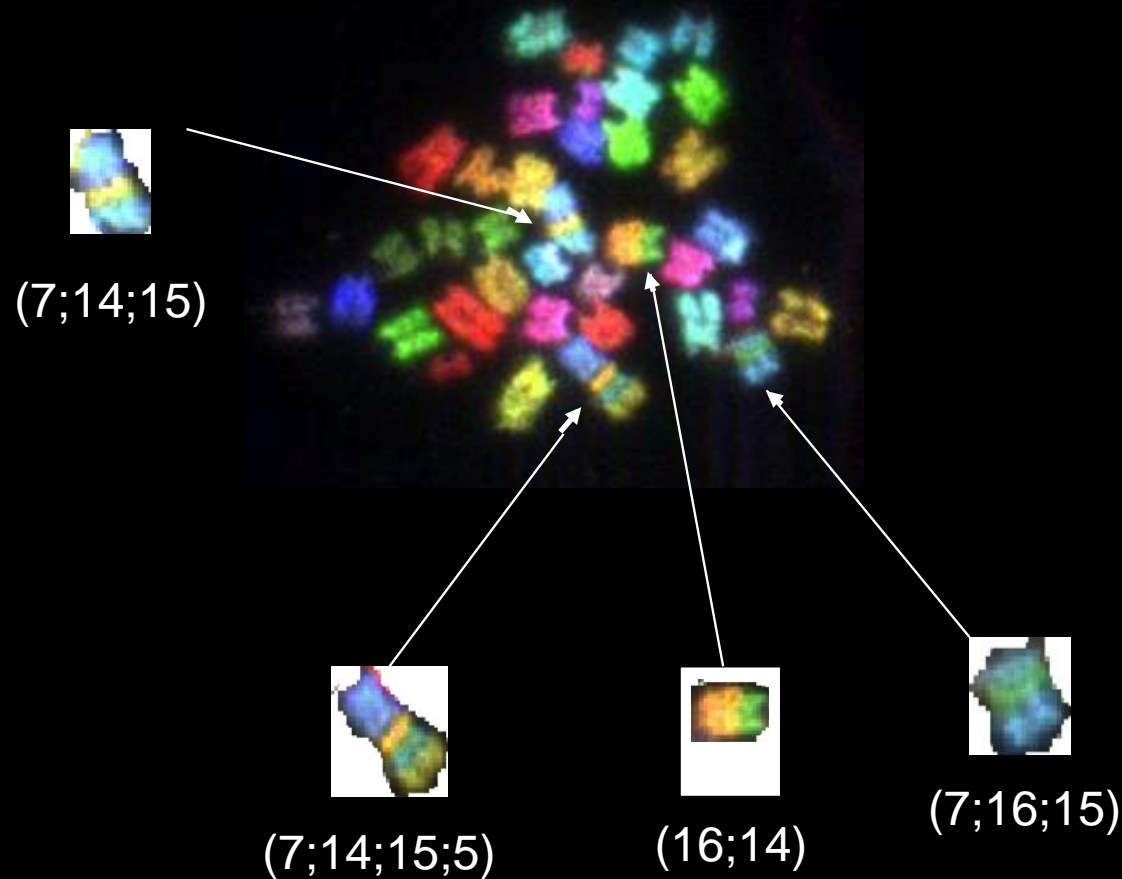
Repair by homologous recombination with sister chromatid



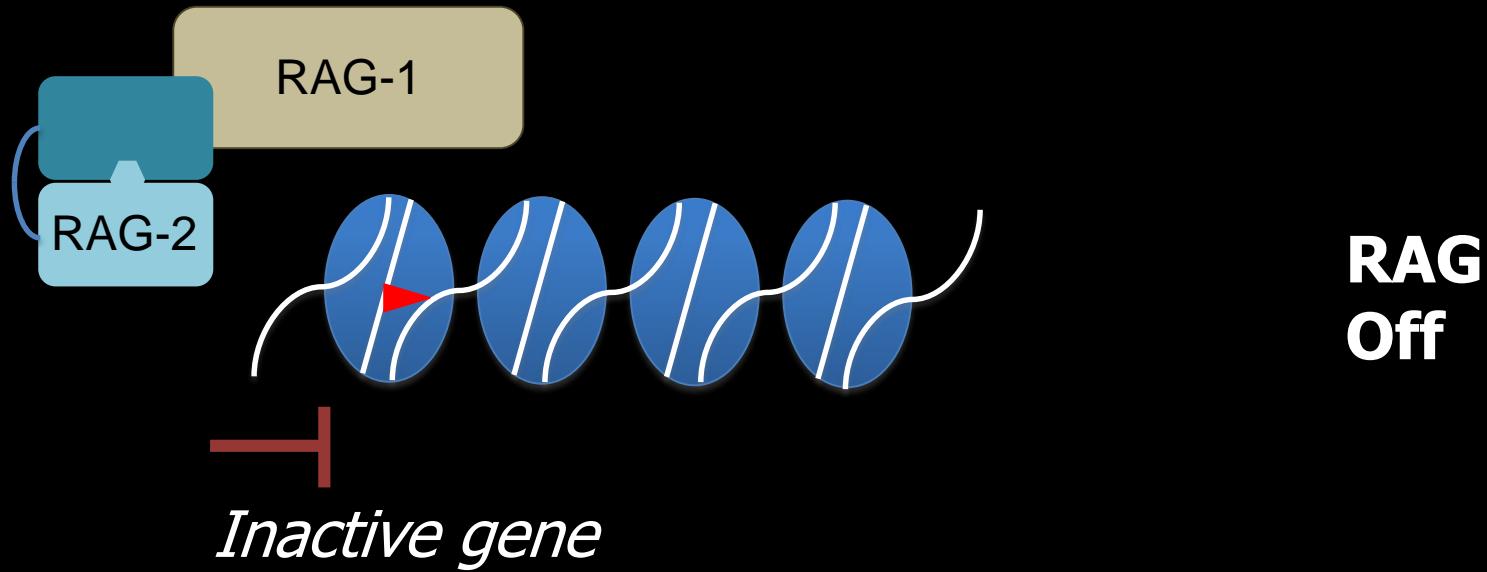
S-G2 phase



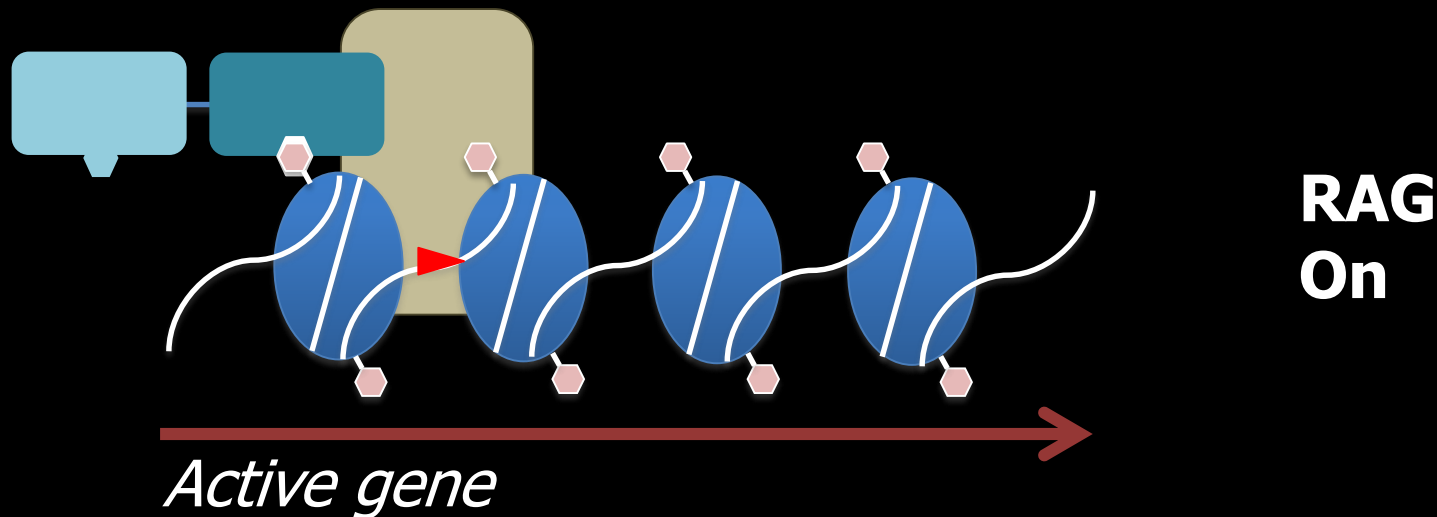
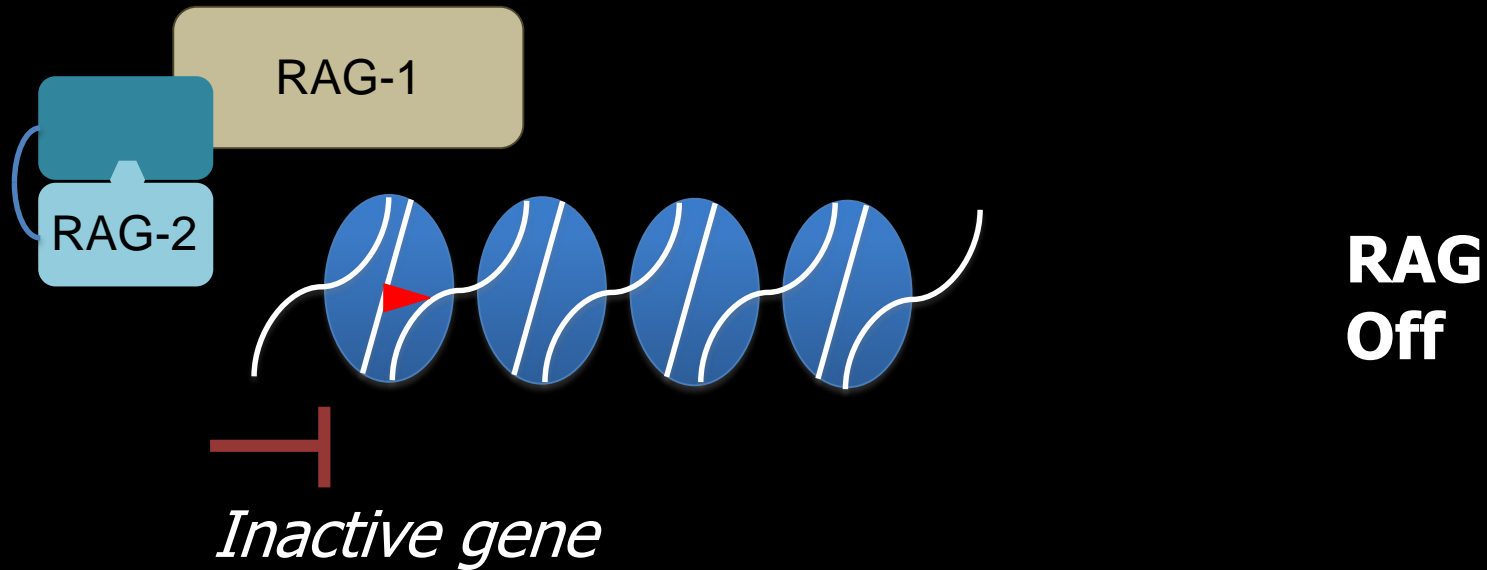
# Mistimed Recombination Disrupts the Genome and Causes Lymphoma



# Only Active Genes Carry the Ignition Key



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# Mistakes in DNA Rearrangement are a Major Cause of Leukemia and Lymphoma

- More than 10 million DNA rearrangements per hour in each of us
- 40 – 70 percent of all B cell progenitor cancers are caused by mistakes in recombination
- Regulatory mechanisms restrict recombination to protect against genomic damage.
- When these mechanisms fail the cancer-causing potential of V(D)J recombination is unmasked.



# Going Rogue

- Cancer
- Allergy and Asthma
- Autoimmune Diseases
- Immune Deficiency Diseases

