Introduction to the Immune System

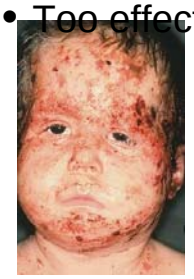
Stephen Canfield, MD, PhD
Division of Pulmonary, Allergy, and Critical Care Medicine

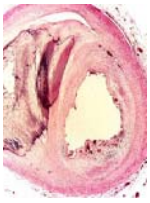
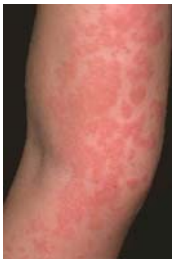
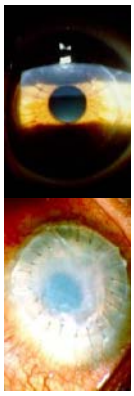
The Immune System in Health

- Defense against invading organisms
- Surveillance against malignancy
- Orchestrator of tissue repair
- Patrol against senescence
- Interface with metabolic processes
  - Body temperature
  - Fe^{3+} balance
  - Body mass

The Immune System in Disease

- Too little - immune deficiency
- Too much - attack on self
- Too long - tissue remodeling
- Too “anxious” - hypersensitivity
- Too effective - graft rejection

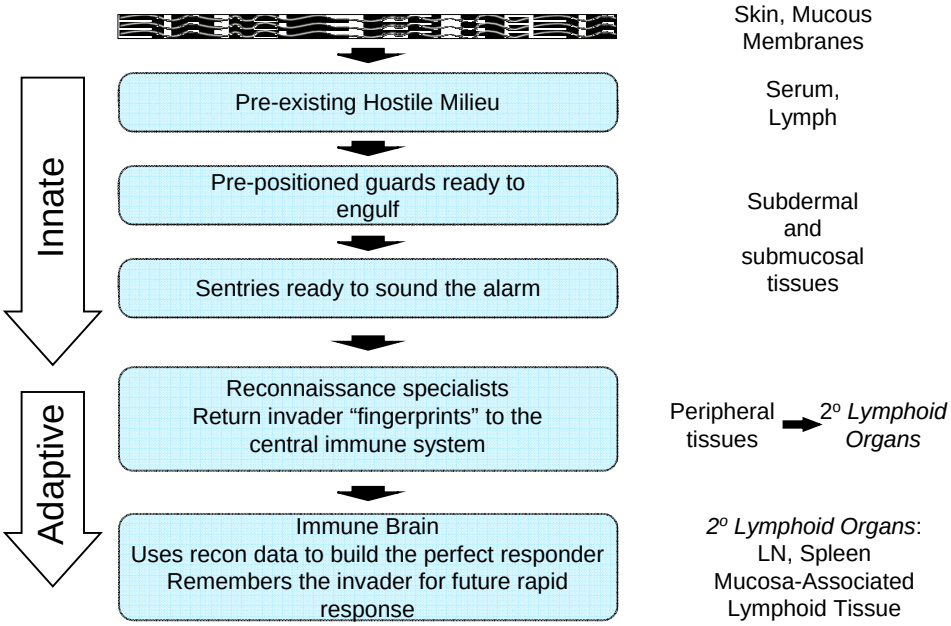


Tips on Challenges You Will Face

- Vast new vocabulary
- “Rules” are built on experimental observation
  - Every rule has an exception
- The “system” is a network of many players
  - Zoom in to study a player, but remember...
  - Zoom back out to see how it fits in big picture
  - The elegance is in the orchestra, not one player
- Understanding is evolving
  - New concepts and new players added every year

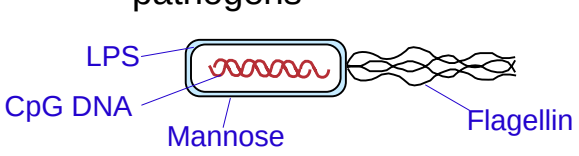
Layers of Defense

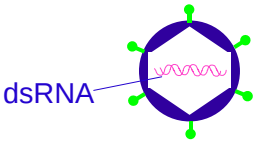


Innate Immune System

Soluble	Cellular
Complement Cascade	*Phagocytes*
	Natural Killers

- Array of sensors for "danger"
  - Recognize pathogen-associated molecular patterns (*PAMP's*) - shared by many pathogens





  - <u>Rapid</u> activation - no prior contact needed

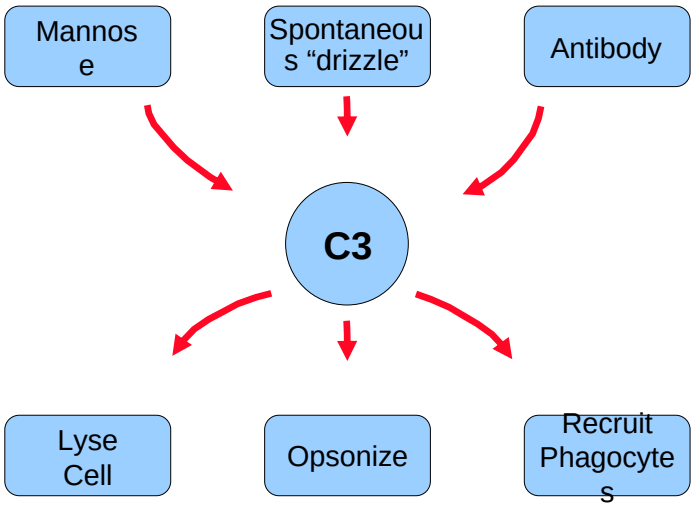
The Complement System

- The pre-existing hostile milieu
  - Set of 25 highly abundant serum proteins
  - Forms a proteolytic cascade at the cell surface

Generation of cell-bound fragments → Lysis of pathogen cell or Tagging of pathogen for phagocytosis: *opsonization*

Release of soluble fragments → Recruit Phagocytes

Complement Cascade Initiation



Complement Cascade Effects

Cells of the Innate System

- Phagocytes
  - Macrophages
  - Neutrophils (aka: polymorphonuclear leukocytes)
  - Dendritic Cells
- Natural Killers (NK) Cells

Macrophages

Tissue-resident sentinels

Arrayed with "sensors":
- PAMP receptors
- Complement R's
- Antibody R's

Reorganize cytoskeleton in response to these inputs:
Seek & Engulf

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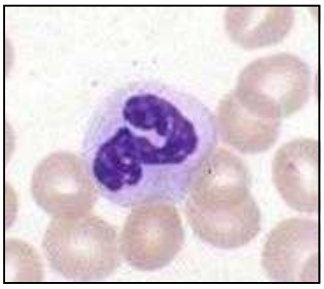
Neutrophils

- Most abundant blood leukocyte
  - 3 million/day exit bone marrow
  - production ↑↑ with infection
- Exit blood → tissue when called
  - Chemotax along gradients:
    - pathogen components
    - complement fragments
    - macrophage signals
  - Engulf and kill
  - Survive hours to days - major component of pus



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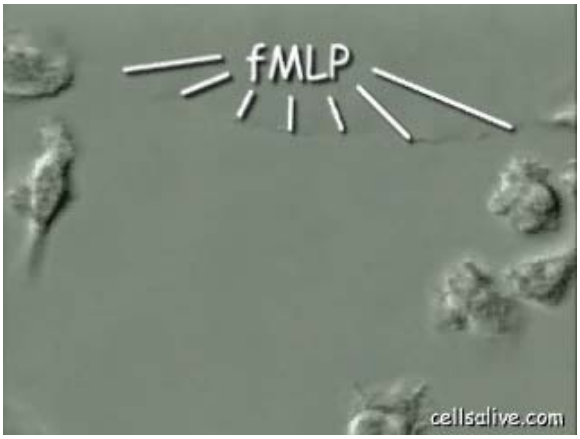
Neutrophil Chemotaxis



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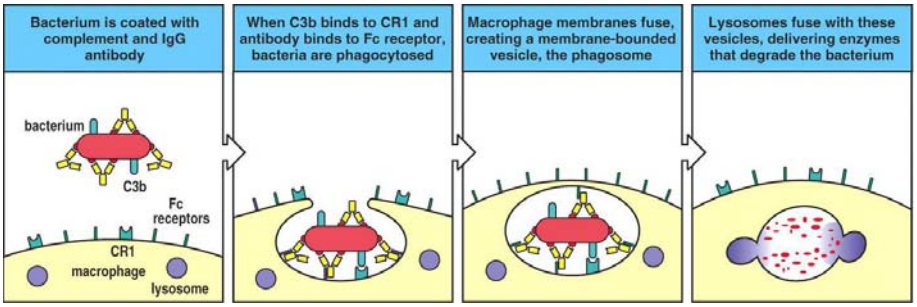
Macrophage/Neutrophil Killing



- Phago-lysosome contents
  - Phagocyte Oxidase → oxygen radicals
  - Inducible NO Synthase → nitric oxide
  - Acid pH
  - Proteases

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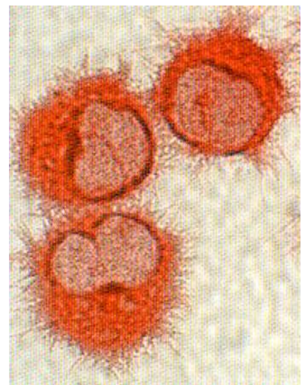
Dendritic Cells

•Phagocyte with a dual career - reconnaissance specialist

- Starts out a tissue-resident sentinel
  - Constant pinocytosis - “small bites” sampling surroundings
- Pathogen contact → career change
  - Picks up stakes - migrates from tissue to local lymph node
  - Literally “presents” pathogen fragments to cells of the adaptive system
  - Bridge between the innate and



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Soluble Intercellular Signals

- *Cytokines* - secretory proteins that mediate immune & inflammatory reactions
  - bind to specific receptors on signal-receiving cells
  - Influence the state of activation, or effector functions of the recipient cell
- *Interleukins* - cytokines that generally function to communicate between leukocytes
- *Chemokines* - small cytokines that function in leukocyte chemotaxis: hence “chemo-” + “-kine”

Innate Call for Help

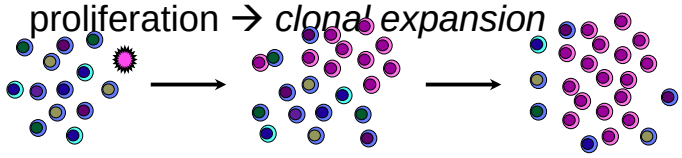
- PAMP recognition → Mϕ activation → ALARM
- → Secrete interleukin-1 (IL-1)
- → Secrete tumor necrosis factor (TNF-α)
- Two critical "innate" immune system cytokines:
  - Activate nearby neutrophils
  - Alter local vascular endothelium to recruit more neutrophils
  - Signal DC's to "mature" - initiate migration
  - Signal hypothalamus to ↑body temperature

Is that all there is?

- Yes, for 99% of the animal kingdom
- But if you're a jawed vertebrate... there's more!
- *Adaptive Immune System: B & T Lymphocytes*
  - Learn from pathogen contact: ↑effectiveness
  - Discern *fine* molecular differences:
    - Single amino acid substitution in a peptide chain
    - Even addition of a phosphate group to an amino acid side chain

How the Immune System Learns

- Each cell is generated with a *unique* Ag receptor
  - Generated randomly
  - Gen. by genomic DNA rearrangement
  - Extremely diverse: ~100 billion possible R's
- *Naive* lymphocytes patrol 2^{o} lymphoid organs
  - Most never find Ag → survive ~3 weeks
  - Lucky few: Ag encounter → activation and proliferation → *clonal expansion*

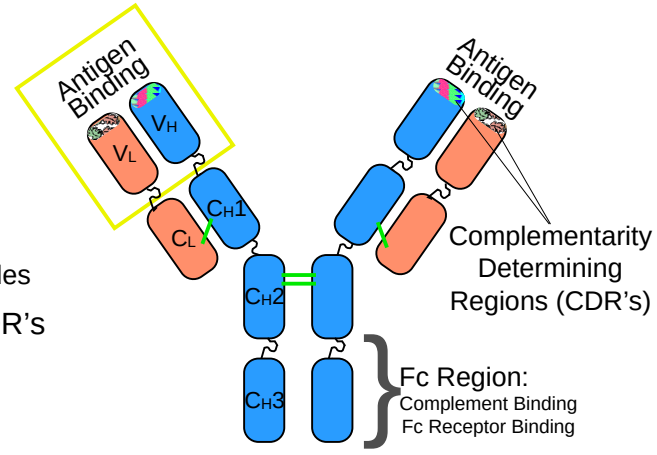


B Lymphocytes

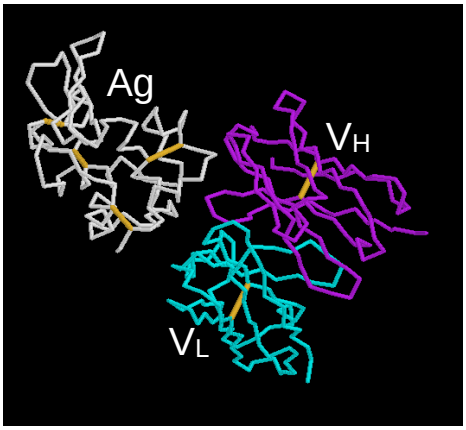
- Develop in the bone marrow
- Each new B cell makes a <u>unique</u> antigen receptor (BCR)
  - This BCR is an *immunoglobulin* (Ig), aka, antibody
    - Ag binding by BCR → *clonal expansion*
      - Some daughter cells become *plasma cells*: immunoglobulin secreting factories
      - Others become *memory B cells*: long-lived, capable of rapid response on re-encounter of antigen

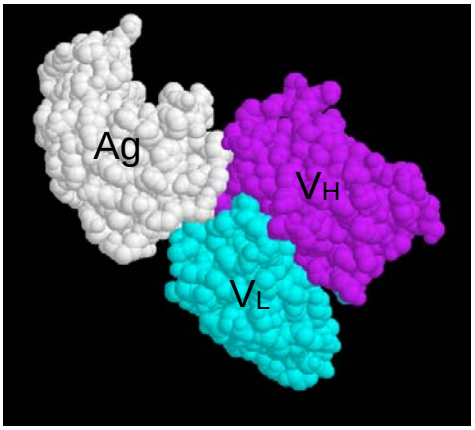
Immunoglobulins

- Tetramer
  - 2 H chains + 2 L chains
  - Interchain disulfides
- Variable End - CDR's
  - Huge diversity
- Constant End
  - Determines Ig Class:
  - IgM, IgD, IgG, IgA, IgE
- and effector functions



Immunoglobulin-Antigen Binding



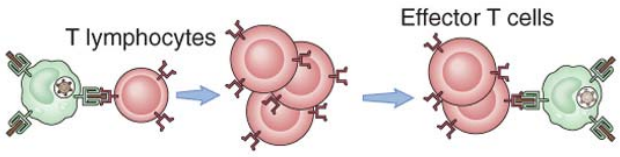


T Lymphocytes

- Hematopoietic origin (marrow) but most of their development occurs in the *thymus*
- Like B cells, T cells:
  - Utilize a surface Ag receptor (TCR)
  - Extreme diversity of Ag binding
  - Ag receptor triggering is required to initiate clonal expansion
  - Ag "experienced" cells produce a long-lived memory population

T Lymphocytes

- Unlike B cells, T cells:
  - Never secrete their Ag receptor
  - Cannot bind free antigen molecules - only peptides of 8-25 amino acids
  - Require that Ag be *presented* to them on a special "billboard"*:*
    - *Major Histocompatibility Molecule*



Major Histocompatibility Molecules

- Two Classes: I and II
- Highly *polymorphic*
  - Vary greatly from one individual to the next
- Identified as the basis for organ rejection between genetically non-identical individuals
- Also termed “Human Leukocyte Antigens” (HLA)

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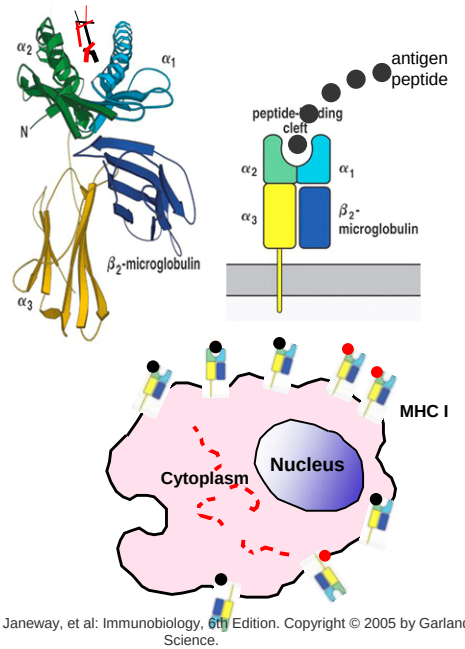
•MHC Class I

- Expression:
  - •All nucleated cells
- Structure:
  - •α-chain + β_2 microglobulin
- Antigenic peptides:
  - •Derived from cell’s cytoplasm (generally from proteins made within the cell)



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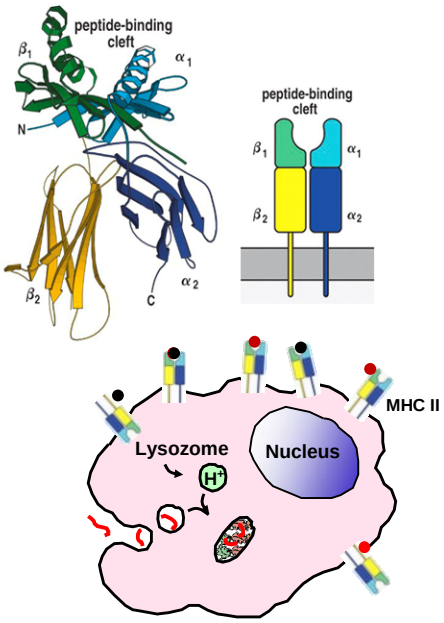
•MHC Class II

- Expression:
  - •A*ntigen presenting cells* (APC's)
  - •Examples - macrophages, dendritic cells, B cells
- Structure
  - •α and β chains
- Antigenic peptides
  - •Derived from the cell's endocytic compartment (generally from proteins external to the cell)



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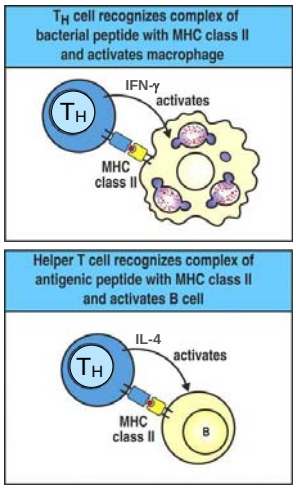
T Cell Career Paths

- CD4$^+$ T cells
  - Most commonly termed "helper T cells" (T_H's)
  - Recognize Ag peptide presented by MHC Class II
  - Provide <u>essential</u> activation signals to B Cells, CD8$^+$ T cells, and phagocytes
    - soluble - cytokines
    - surface molecules - *CD40L*



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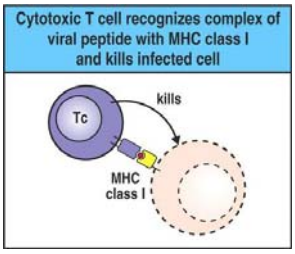
T Cell Career Paths

- $CD8^+$ T cells
  - Most commonly termed "cytotoxic T cells" (CTL's)
  - Recognize Ag peptide presented by MHC Class I
  - Kill target cells expressing abnormal cytoplasmic proteins
    - Infected by intracellular pathogen - eg, virus



- Killing
- puncture cell membrane
- Induce programmed cell death
  - or *apoptosis*

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Natural Killer (NK) Cells

- Lymphocyte without BCR or TCR - "innate" like
- Don't require prior contact or clonal expansion
- Receptors recognize distressed cells:
  - Virally infected
  - DNA damaged
  - Transformed (malignant)
- Also recognize cells opsonized by Ig
- Kill, using a mechanism similar to CTL's

Innate vs. Adaptive Immunity

	Innate	Adaptive
On first contact	Immediate response	5-10 days for clonal expansion
Receptor Specificity	Broad classes of molecules	Highly specific for a single structure
Ligands	Microbial origin	Potentially any protein, lipid, or carbo
Memory	None	Long-lived
Recurrent contact	Same response as previously	Rapid response tailored to pathogen

Autoimmunity:

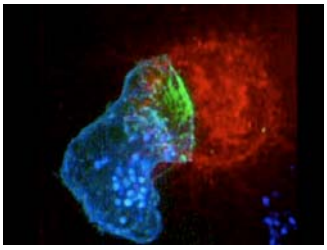
Distinguishing native tissue from foreign pathogen

- Innate System - inherent in the receptors
  - Directed at microbial molecules (PAMP's)
- Adaptive System - <u>not</u> inherent in the receptors
  - Able to bind anything - protein, carbohydrate, lipid
  - Need safeguards to ensure non-reactivity with native (self) molecules - that is, to maintain *tolerance*

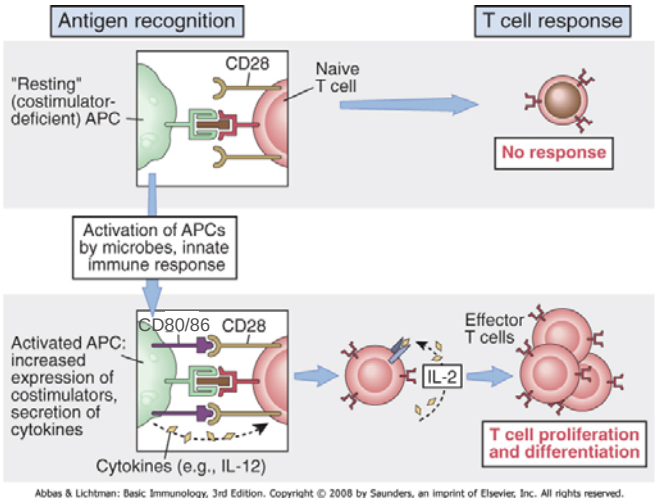
One Layer of Safeguard:

T Cell Activation requires Innate/Adaptive Cooperation

- Naive T cells require two discreet activation signals
  - *Signal I*: TCR binding to peptide/MHC
  - *Signal II*: *Co-stimulation* provided by the APC
    - Involves binding of T cell CD28 to APC CD80 & 86
    - Occurs at contact site between T cell and APC



T Cell Activation: Under Innate Cell Control



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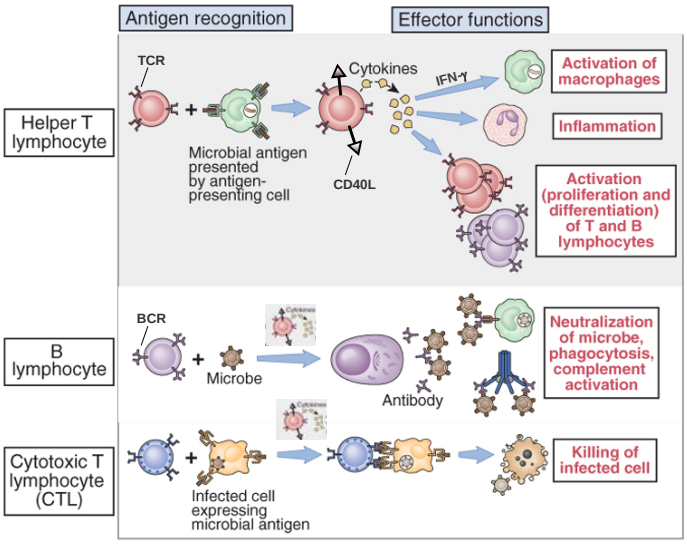
Lymphocyte Effector Functions



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Summary

1. We are protected from dissolution at the hands of microbes by an army of specialists each of which provides an essential piece of a complex defense.
2. The innate arm, the most ancient, is the first to respond. It's cells utilize evolutionarily conserved pathogen characteristics to recognize "danger" and act rapidly to tag, engulf, lyse, or wall off the invader.
3. The innate system simultaneously provides pathogen-specific information (in the form of MHC/peptides) and essential activation signals (in the form of CD80 and CD86) to the adaptive system resulting in helper T cell activation and differentiation.
4. a) $CD4^+$ T cells provide cytokine and contact-dependent help to B cells, resulting in a highly specific, high affinity antibody response.

- b) $CD4^+$ T cell help and immunoglobulins provide reciprocal signals to the innate system, greatly facilitating phagocytosis and killing.

5. The adaptive system utilizes a unique gene rearrangement technique to generate awesome diversity and subtlety in antigen recognition: the lymphocyte repertoire.
6. T cell direction, required for the optimal immune response, is completely dependent on the peptides presented. Highly polymorphic MHC genes, and co-dominant expression of multiple MHC molecules helps ensure that every individual can make a response to some part of every pathogen. However, not all MHC's are alike - some are better than others at engendering a particular response. This may be anti-bacterial, antiviral, or anti-self.

Helpful Hints

- Read Sompayrac in full early
- Easy read, great for framework
- Good glossary at the back of Abbas
- List of surface molecules, Abbas Appendix II
- Searchable Janeway on line
- (http://www.ncbi.nlm.nih.gov/books/
- bv.fcgi?call=bv.View..ShowTOC&rid=imm.TOC&depth=2)
- Recent journal reviews listed on Courseworks for a different perspective