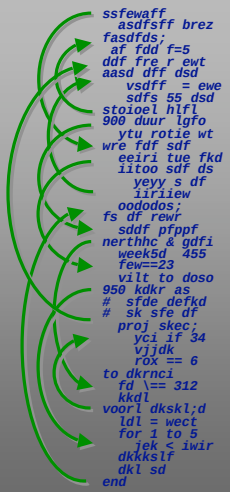
The Problem of Biological Complexity and "Information Overload"

Analogy: Structural Programming

In 1968 computer scientist Edsger Dijkstra wrote a now-classic short note entitled: "*GOTO Considered Harmful*." (Dijkstra (1968) *Comm. ACM* **11**(3):147-148).

In it he criticized programming constructs that allowed undisciplined jumps in flow of control leading to so-called 'spaghetti code,' which made larger programs unwieldy



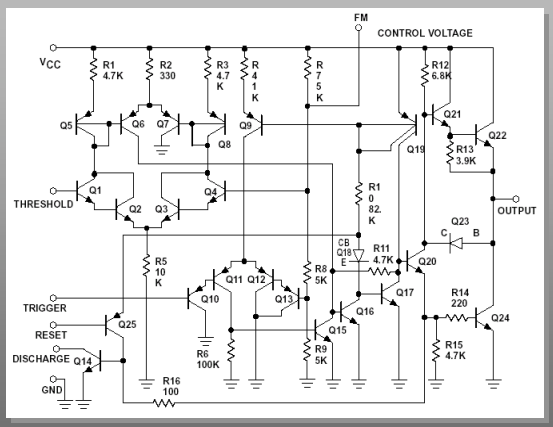
Courtesy: David Searls, Glaxo-Smith-Kline

Analogy: Structural Programming

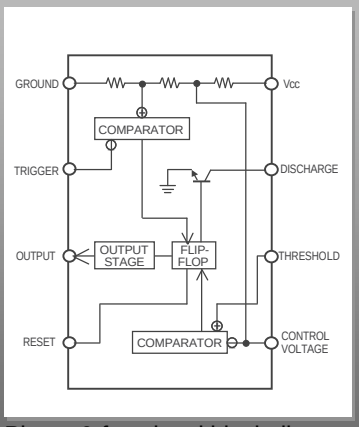
He helped to launch the structured programming movement, which enforced a strictly nested modularity for more manageable growth, debugging, modification, etc.

Courtesy: David Searls, Glaxo-Smith-Kline

Analogy: Modular Design of Integrated Circuits



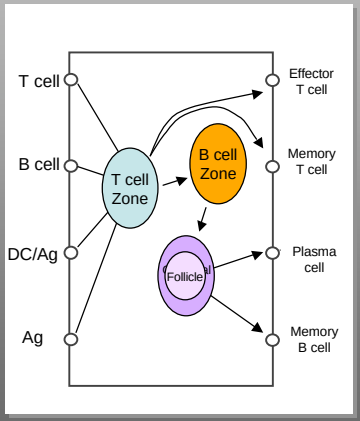
LM555 Timer



Pinout & functional block diagram

Courtesy: David Searls, Glaxo-Smith-Kline

The "Circuitry" of the Primary Immune Response



The "electronic lymph node"

Immunology-- The Whirlwind Tour

Ontogeny of the Acquired Immune System

Step 1. Lymphocytes develop in the bone marrow and thymus

Step 2. Naïve lymphocytes circulate in the blood and lymph

Step 3. The primary immune response occurs in the lymph nodes and spleen

Step 4. Lymphocytes exit the lymph nodes and spleen and become effector lymphocytes--they produce antibody (B cell-derived plasma cells) and become competent to produce cytokines, particularly CD4+ T cells, and kill (CD8+ T cells)

Stages in the Development of a Primary Immune Response

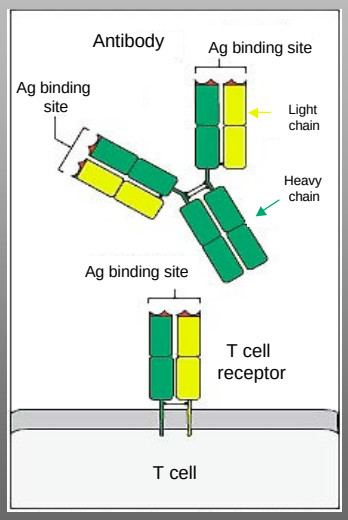
Step 1. Lymphocytes develop in the bone marrow and thymus

The immune repertoire develops

Lymphocytes develop early in life in the 1° lymphoid organs (bone marrow and thymus). They are competent to respond to a broad array of antigens. Diversity in antigen recognition is accomplished by random rearrangements of the **immunoglobulin (Ig) gene** in B cells and the **antigen receptor gene** in T cells (**TCR**).

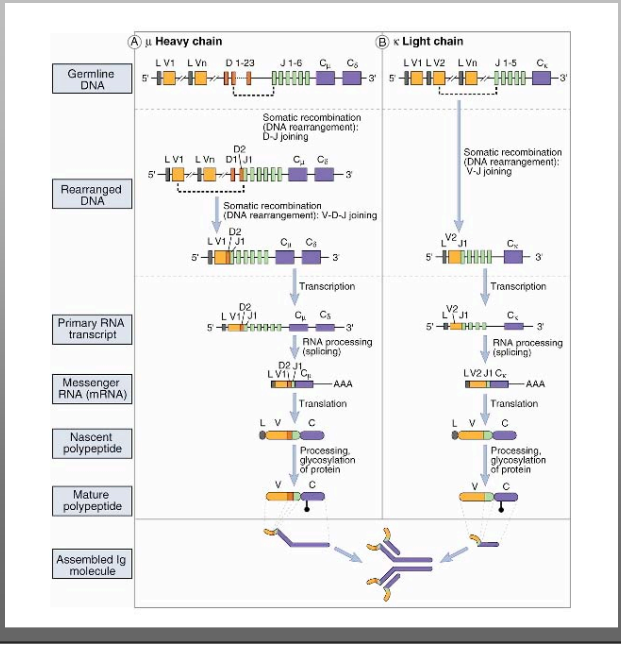
Those lymphocytes that survive do so through **positive** selection. Unproductive or inefficient interactions between lymphocyte and antigen results in death by **negative selection**.

Antibody (Ig) and TCR are the Only Genes that Undergo Somatic Cell Recombination



How is Diversity in Antigen Recognition Achieved?

Ig Maturation



What Happens in the Thymus?

Ordered TCR gene rearrangement and TCR expression

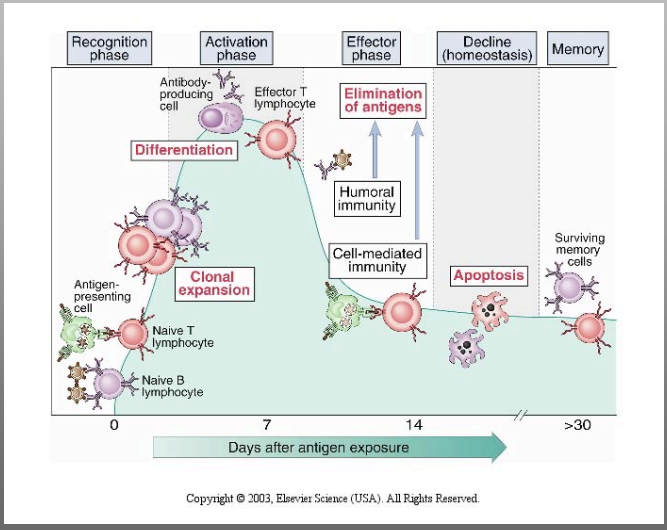
Ordered expression of surface molecules, including the TCR, CD4 and CD8

Selection of the T cell repertoire through positive and negative selection

The Primary Immune Response

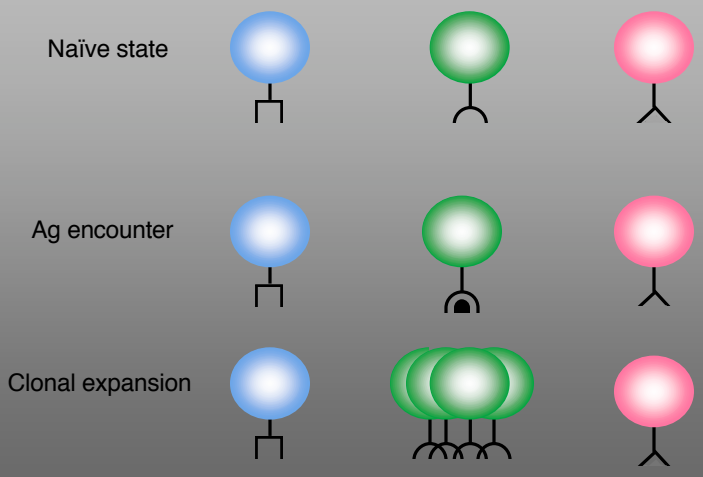
Input: Ag-loaded APCs and naïve lymphocytes
Output: Effector and memory lymphocytes

Phases of the Primary Immune Response



Question: How do specific antigen-recognizing lymphocytes “know” to be activated?

The Clonal Selection Theory



Three Types of APCs

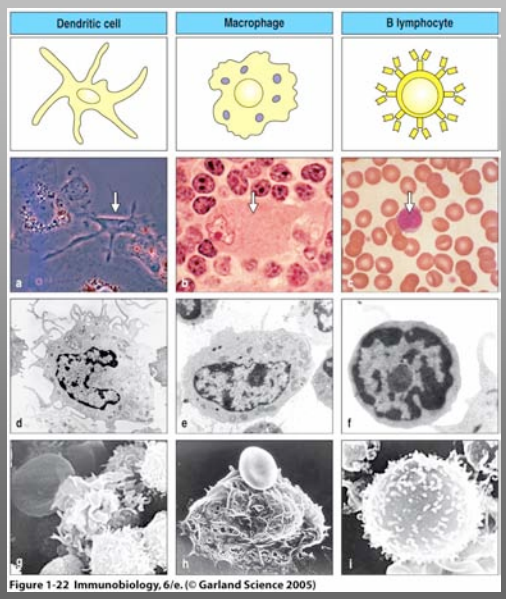


Figure 1-22 Immunobiology, 6/e. (© Garland Science 2005)

The Itinerant Dendritic Cell

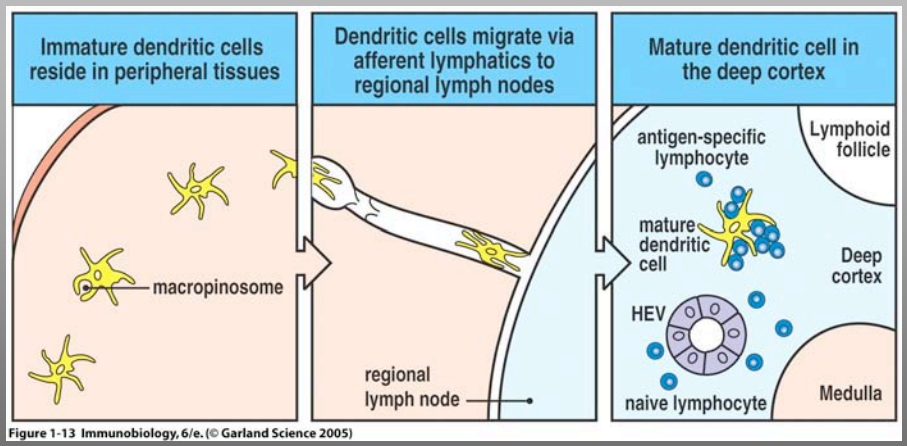
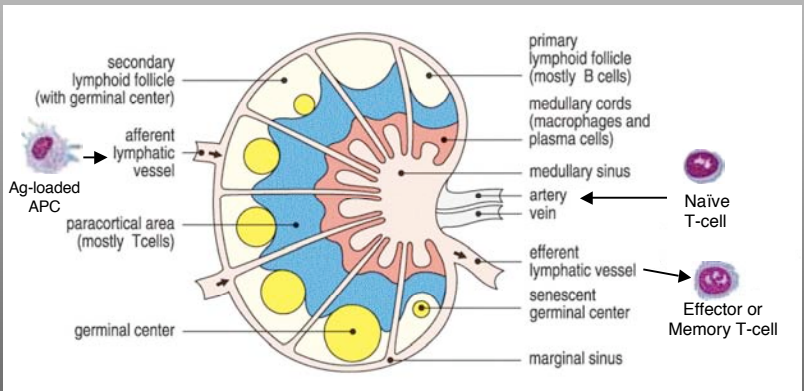


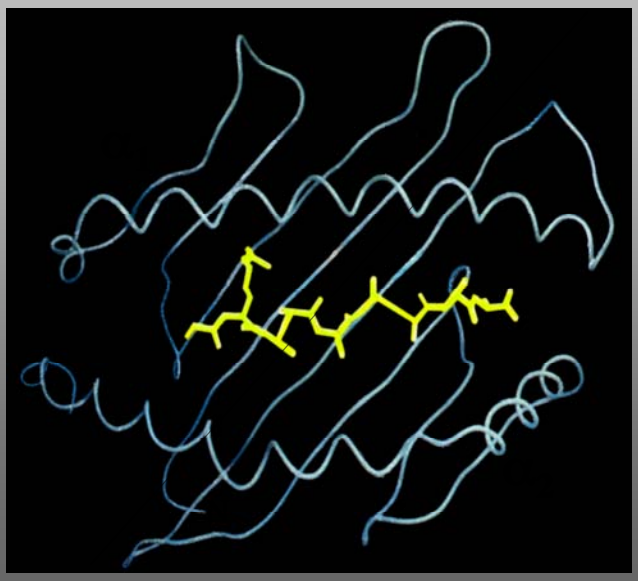
Figure 1-13 Immunobiology, 6/e. (© Garland Science 2005)

Functional Anatomy of a Lymph Node

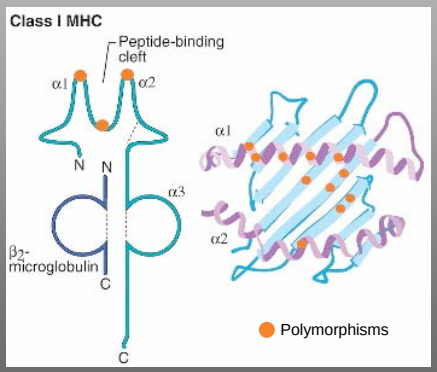


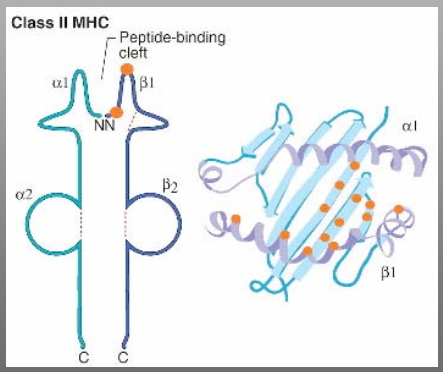
The Antigen "Vetting" Process: Who Decides Which Antigens are Presented?

Structure of Peptide-binding Class I MHC Domains



Contact Between the TCR and MHC/peptide: Not All MHC Molecules are Created Equal

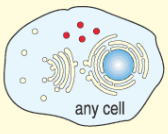
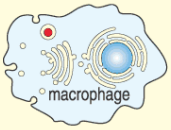
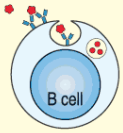




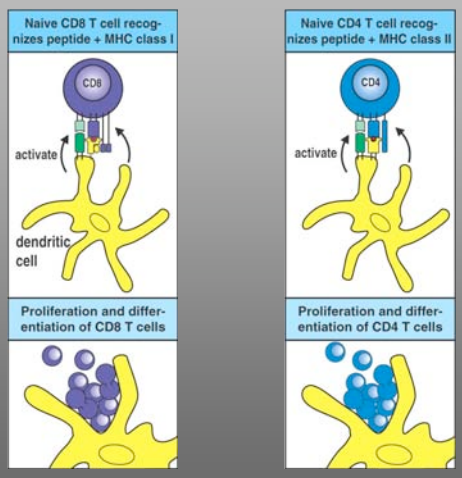
The "Fit" Between MHC Molecules and Peptide Defines MHC Restriction

Polymorphisms (allelic differences within a population) of the MHC loci account for the variability of the immune response between individuals

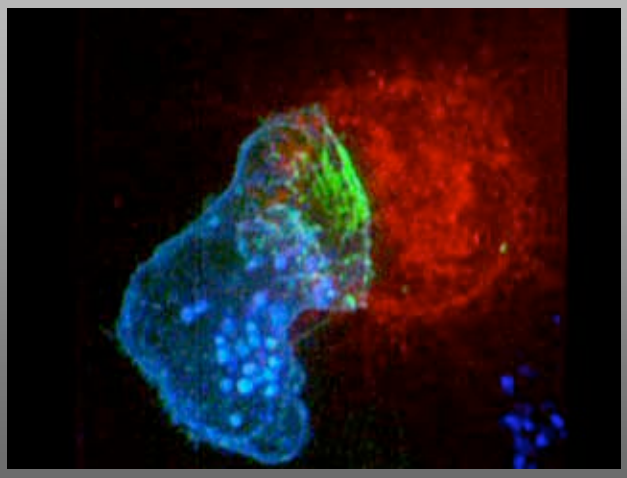
Functions of MHC I and II

	Cytosolic pathogens	Intravesicular pathogens	Extracellular pathogens and toxins
			
Degraded in	Cytosol	Endocytic vesicles (low pH)	Endocytic vesicles (low pH)
Peptides bind to	MHC class I	MHC class II	MHC class II
Presented to	CD8 T cells	CD4 T cells	CD4 T cells
Effect on presenting cell	Cell death	Activation to kill intravesicular bacteria and parasites	Activation of B cells to secrete Ig to eliminate extracellular bacteria/toxins

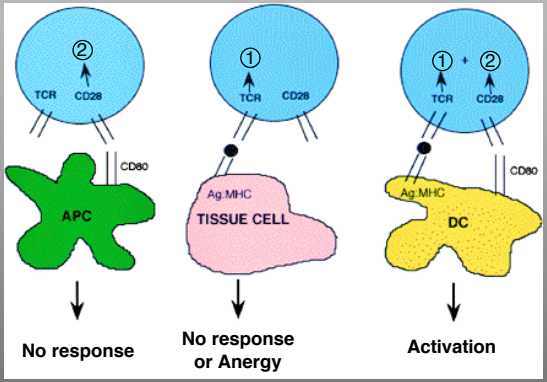
Antigen Presentation at the Cellular Level



The "Immunologic Synapse"



The Two-Signal Theory of T-cell Activation



APC = Antigen-presenting cells
TCR = T cell receptor for antigen
DC = Dendritic cell
CD80 = Co-stimulatory receptor

CD4+ T Cells Activate Macrophages and B cells

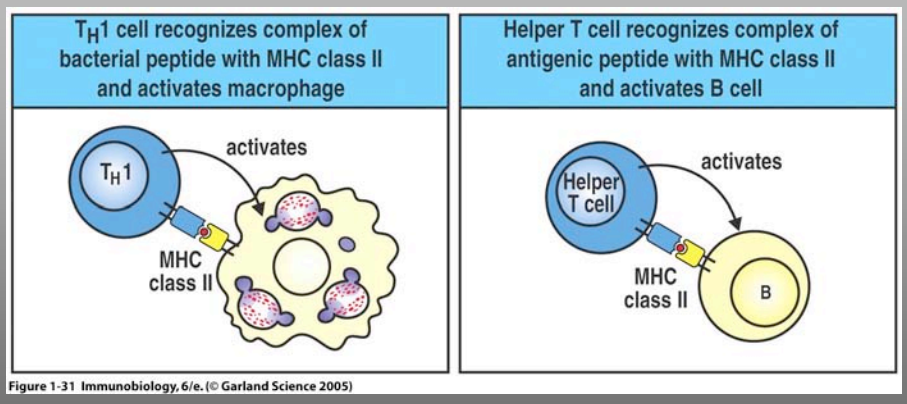
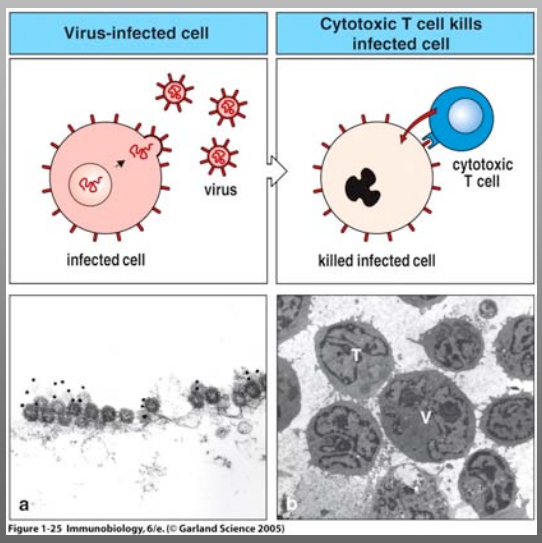


Figure 1-31 Immunobiology, 6/e. (© Garland Science 2005)

CD8+ CTLs Kill Viral-infected Cells



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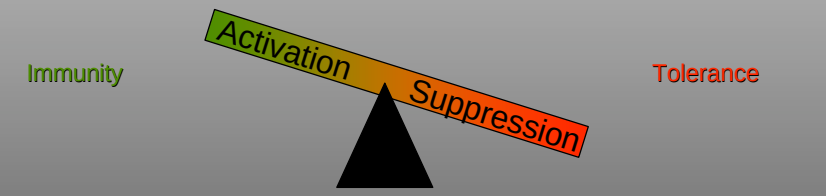
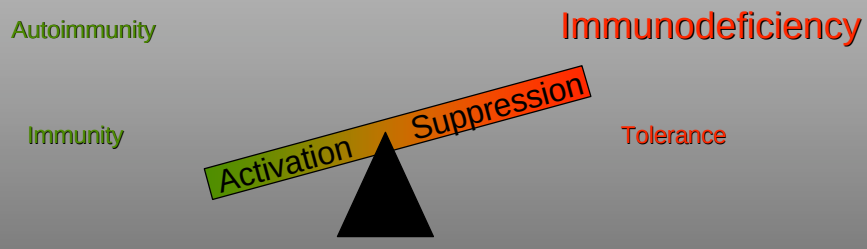
Regulation of the Immune Response: a Conceptual View

Immunity — Activation / Suppression — Tolerance

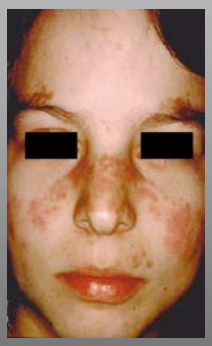
Regulation of the Immune Response: a Conceptual View

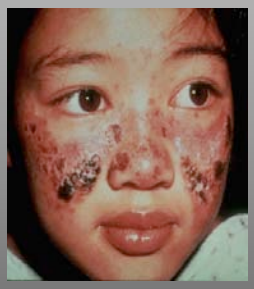


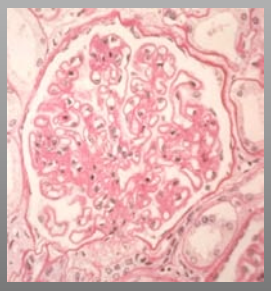
Regulation of the Immune Response: a Conceptual View



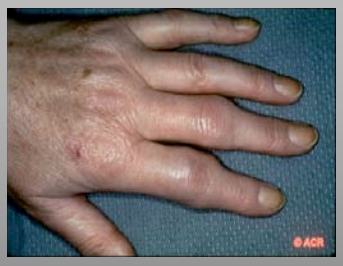
Systemic Lupus Erythematosis (SLE): An Autoimmune Disease

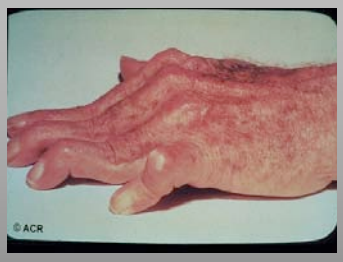


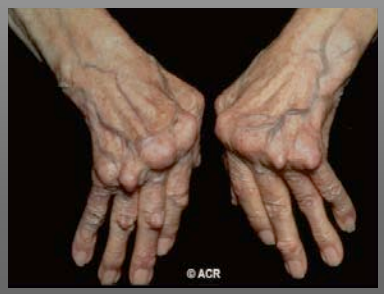




Clinical Manifestations of Rheumatoid Arthritis







Summary

1. The immune system is complex. Try to understand it in terms of specific functional modules.

2. Diversity in antigen recognition is accomplished, in part, by rearrangements in the Ig and TCR loci. This occurs in the bone marrow and thymus, respectively.

3. The T and B cell repertoire determines the spectrum of antigens that can be recognized in an individual's lifetime. The nature of this repertoire is determined by the Major Histocompatibility Complex (MHC), which binds peptide antigen.

4. In a primary immune response, antigen presenting cells (APCs) present antigen bound to MHC molecules to T cells in the lymph nodes and spleen. T cells "help" B cells to develop further and clonally expand in germinal centers of these organs.

5. Lymphocytes exit these organs to become effector or memory cells. Effector cells secrete Ab (plasma cells) or cytokines (CD4+ T cells) and kill virally-infected cells (CD8+ T cells). Memory cells re-circulate until they encounter Ag again.

6. The immune system is tightly regulated. It exists in a delicate balance of immunity and tolerance. A lack of tolerance to self antigen coupled to excessive immune activation (or inadequate immune suppression) can lead to autoimmunity.