SLIDE 1 The Humoral Immune Response. During this presentation, we will conclude our discussion of one branch of the adaptive immune response, or antibody-mediated immunity. The humoral immune response generates long-lasting immunity to a pathogen. The processes of clonal selection/expansion & isotype switching lead to the development of memory B cells and high affinity, neutralizing antibodies.

SLIDE 2 Learning objectives for the concepts covered in this part of the presentation.

SLIDE 3 This slide provides a quick review of humoral immunity. The humoral immune response primarily defends against extracellular microbes and toxins. This defense is especially important for “bugs” that have capsules or cellular components that are high in lipids or polysaccharides, as these microbes can avoid T cell-mediated immunity that responds best to protein antigens (not lipids).
Slide 4

**Immune System Fights Back!**

- **Humoral Immune Response:**
  - Outline
  - Clonal Selection & Expansion
  - Primary & secondary responses
  - Changing of the guard: Affinity maturation & Isotype Switching
  - Memory & vaccine intro

Slide 5

**Clonal Selection & Expansion Theory**

- Immune system can distinguish between nearly a billion different antigens
- Every person has a vast pool of clonally derived lymphocytes (T & B) with different Ag receptors
- When an antigen enters, it selects a preexisting clone and activates it

Slide 6

**Clonal Expansion**

- Activated clone expands to make identical effector & memory cell clones
- Plasma cells produce antibodies to clear the antigen & some memory cells remain to prevent future antigen attacks
- Reason why VACCINES work!
  - Vaccinated (given an Ag) as a child so that you will activate the clone & produce antibodies, memory cells
  - If you are re-exposed later in life, your immune system already has clones ready to go!!
  - Some vaccines provide lifetime of immunity

Slide 4 Outline of the components of the humoral immune response.

SLIDE 5 Clonal selection and expansion rapidly creates effector cells that will fight the infection & also memory cells that will live long.

SLIDE 6 This provides the basis of immunologic memory and vaccination.
**Slide 7**
This diagram illustrates the pool of B lymphocytes with different antigen receptors. Once an antigen enters, it “selects” the correct B lymphocyte (with matching receptor). This B cell then expands to create identical clones to quickly fight the infection.

**Slide 8**
Another diagram illustrating clonal selection & expansion. The chosen B cell develops into effector cells (that will produce antibodies) and memory cells (that will remain after the initial infection is cleared).

**Slide 9**
The phases of humoral immune responses are shown here. Note the primary components include: Clonal expansion (after activation of a B lymphocyte), Antibody secretion by effector B cells, Isotype class switching to improve a secondary immune response, Affinity maturation to improve the fit of the antibody, and, the generation of memory B cells. As the B cells mature after expansion, they differentiate into cells that perform a specific function (effector, high affinity cells are preferred, memory).
<table>
<thead>
<tr>
<th>Slide 10</th>
<th>Primary Immune Response</th>
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<tbody>
<tr>
<td>• It takes time to build an effective immune response after Ag recognition</td>
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<tr>
<td>• On first exposure to an antigen, clonal selection will take many days to expand &amp; produce effector cells for antibody production</td>
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<tr>
<td>• Affinity maturation &amp; class switching occur as the immune response progresses (IgM to IgG)</td>
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**SLIDE 10** The primary immune response occurs after first exposure to an antigen. From this point forward, the immune system will be primed and will never completely forget the initial response.

<table>
<thead>
<tr>
<th>Slide 11</th>
<th>The Antibody Response Curve</th>
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**SLIDE 11** This slide illustrates the antibody response curve. Notice that it takes several days to produce an effective immune response.

<table>
<thead>
<tr>
<th>Slide 12</th>
<th>Secondary Immune Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>• On second exposure to the same antigen, memory B cell clones will quickly produce antibodies to fight the infection. Less time is needed as the process of clonal selection has been eliminated, as the memory clones are already present. This slide also illustrates the primary and secondary antibody responses. Notice the size of each response.</td>
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**SLIDE 12** Upon second exposure to the same antigen, memory B cell clones will quickly produce antibodies to fight the infection. Less time is needed as the process of clonal selection has been eliminated, as the memory clones are already present. This slide also illustrates the primary and secondary antibody responses. Notice the size of each response.
SLIDE 13 This diagram indicates the amount of time necessary to create an antibody response. Clonal selection occurs first, followed by a period of expansion, then secretion of antibodies, and finally the development of memory.

SLIDE 14 This slide compares the immunoglobulin isotypes found in primary and secondary antibody responses. IgM predominates in the primary response. In contrast, IgG predominates in the secondary response.

SLIDE 15 This slide describes the primary and secondary antibody responses. Initial exposure to an antigen (antigen B) always produces a primary antibody response even if the antigen is combined with another antigen (antigen A) that the body has previously produced antibodies to.
Features of Primary and Secondary Antibody Responses

<table>
<thead>
<tr>
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<th>Primary Response</th>
<th>Secondary Response</th>
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<tbody>
<tr>
<td>Lag after immunization</td>
<td>Usually 5-10 days</td>
<td>Usually 1-3 days</td>
</tr>
<tr>
<td>Peak response</td>
<td>Smaller</td>
<td>Larger</td>
</tr>
<tr>
<td>Antibody isotype</td>
<td>Usually IgM &gt; IgG</td>
<td></td>
</tr>
<tr>
<td>Antibody affinity</td>
<td>Lower average</td>
<td>Higher average</td>
</tr>
<tr>
<td>Induced by</td>
<td>All immunogens</td>
<td>Only protein antigens</td>
</tr>
<tr>
<td>Required Immunization</td>
<td>Relatively high doses of antigens, usually with adjuvants</td>
<td>Low doses of antigens, adjuvants not usually necessary</td>
</tr>
</tbody>
</table>

SLIDE 16 This slide provides a chart that indicates the features of both the primary and secondary antibody responses. Notice the differences between the primary and secondary antibody responses.

SLIDE 17 Diagram from the textbook that summarizes the differences between the primary & secondary antibody responses. The secondary immune response occurs after repeat infection with the same organism – notice that the response begins with a memory B cell & not a naïve B cell. This is why the secondary response is much faster, with a higher peak. Again, notice the length of time, peak response, and antibody affinity during each response.

SLIDE 18 This slide illustrates the humoral immune response. Observe the process of B-cell activation through the cognitive phase, the activation phase, and the effector phase.
Isotype Switching
- Progressive change in the relative quantities of Ab isotype with time
- Isotype & subclass depends upon stimulus and location
- For example, IgA & E – MALT
- Usually IgM to IgG
- Requires T cell help (CD4+ cells) & cytokines

SLIDE 19 Isotype switching is the progressive change in the relative quantities of an antibody isotype over time. This usually involves IgM levels decreasing and IgG levels increasing over time; however, the isotypes and subclasses are dependent upon the stimulus and the body location. This effect is dependent on CD4+ Th cells, cytokines, and the CD40 ligand. The mechanism involves cytokine-dependent transcription of DNA in new constant region then recombination. This can occur only with T-dependent antigens.

Affinity Maturation
- Higher average affinity of Abs produced during a secondary response
- Associated with IgM to IgG isotype switch
- T-cell dependent Ags only
- Low Ag dose induces better affinity maturation than high Ag doses; only B cells with high affinity receptors can bind enough Ag, selective clonal expansion
- Somatic hypermutation can increase affinity without changing Ag specificity

SLIDE 21 Affinity maturation is the higher average affinity of antibodies that is produced during a secondary response. It is associated with IgM to IgG isotype switching; and, it can only occur with T-dependent antigens. Low antigen doses induce better affinity maturation than high antigen doses. Only B cells with high affinity receptors can bind enough antigens for this maturation; and there is selective clonal expansion with affinity maturation. Somatic hypermutation can increase affinity without altering the specificity of the antibody.

SLIDE 20 This diagram illustrates the effect cytokines have on the class of antibody produced by the plasma cell. These chemical messengers tailor the immune response. Consequently, T cells (Block Four) are extremely important in helping B cells make antibodies & for isotype switching.
Advantages of High Affinity Antibody

- Hemagglutination
- Hemolysis
- Complement fixation
- Passive cutaneous anaphylaxis
- Bactericidal activity
- Toxin neutralization
- Opsonic activity
- Immune elimination of antigen
- Membrane damage
- Virus neutralization
- Protective capacity against bacteria and viruses
- Enzyme inactivation

SLIDE 22 The development of high affinity antibody is extremely important to protect the body. This slide describes the advantages of high affinity antibodies, which can increase the effectiveness of the antibody response. How are high affinity antibodies produced?

Memory

- The capacity to mount a secondary response to the same Ag
- Larger numbers of antigen-specific T & B lymphocytes produced as a result of clonal expansion during the primary response
- Memory T cells have higher affinity TcR antigen receptors & IgG is made earlier by B cells
- Memory T cells respond to lower doses of Ag
- Memory CD4+ T cells produces cytokines more rapidly

SLIDE 23 Memory is the capacity to mount a secondary response to the same antigen. With memory, there is a larger number of antigen-specific T-cells and B-lymphocytes produced as a result of clonal expansion during the primary response. Memory T cells have higher affinity TcR antigen receptors; and, IgG is made earlier by B cells during the secondary response. In addition, memory T cells respond to lower doses of antigen; and, memory CD4+ T-helper cells can produce cytokines more rapidly. The secondary response is more productive that the primary response.

Anatomy & Humoral Immunity

SLIDE 24 Lymph nodes are central to the development of the humoral immune response. B cells are located in close proximity to antigen presenting & T cells in the lymph node. This close location allows for rapid selection & activation the specific B cell that matches the antigen once the antigen enters the lymph node. Remember, lymph drains from the tissues and extremities into the nodes & allows for all the immune cells to come together to generate an adaptive response. Affinity maturation occurs in the germinal centers, as well as class switching in both the follicles and germinal centers. Plasma cells can migrate to the bone marrow and continue to produce antibodies, sometimes after the antigen is eliminated! Memory B cells develop in the germinal centers and then enter the circulation. Memory B cells do no produce antibody, but circulate in the blood and can survive for months or years until the next antigen exposure (to produce a rapid secondary immune response)
| Slide 25 | Memory & Vaccination
- The capacity of the immune system to remember a pathogen has practical applications – Memory is the key!!
- Vaccines are the most important application of the humoral immune response |
| Slide 25 | SLIDE 25 The humoral immune response has been applied to vaccine development. The process of clonal selection & expansion to generate effector and memory cells allow for immunization to provide long-lasting protective immunity to a person. |
| Slide 26 | Extremely Brief Intro to Vaccines
- Principle of vaccination: introduce harmless antigen(s) with epitopes also found on the pathogen
- The immune system develops its own immunity against the pathogen
- 5 types: live, killed/inactivated, subunit, toxoid, & recombinant vaccines |
| Slide 26 | SLIDE 26 A live, virulent organism cannot be used as a vaccine because it would cause the very disease it would prevent. Consequently, the first step in making a vaccine is to separate the two effects of disease causing organisms. In practice, this means isolating or creating an organism, or part of one, that is unable to cause full blown disease, but that still retains the antigens that will induce the host’s immune response. |
| Slide 27 | Vaccine Intro
- Most vaccines generate antibody response, not cell-mediated
- Vaccination stimulates clonal expansion of B cells to antigen(s) like those found on real pathogen
- Generates memory
  - If a person is re-exposed to the real agent, the immune system can quickly neutralize the agent (protective immunity) via humoral immunity |
| Slide 27 | SLIDE 27 Vaccines usually generate antibody mediated immunity and the production of antibodies & memory cells. Consequently, if a person is later exposed to the real pathogen, the secondary immune response will prevent disease based on the original clonal selection & expansion form the vaccine antigens. Cell-mediated immunity is only generated with a live vaccine. |
In Summary
• Clonal selection & expansion theory
• Differences between the primary & secondary immune response
• Understand processes of isotype switching and affinity maturation to improve immune response
• Describe how memory is generated, where memory cells reside

Self-Test Questions
• What is clonal selection? Are the B cells created after the antigen enters?
• What isotype is produced during the primary immune response? Secondary?
• What is needed to stimulate isotype switching?
• What is affinity maturation? How does this improve the immune response? Where does it occur in the lymph node?
• Why do vaccines generate protective immunity (in terms of the humoral immune response)?

SLIDE 28 What you need to know . . .

SLIDE 29 Self-test questions to review your understanding of this presentation.