B cell receptor

light chains

heavy chains

T-cell receptor

antigen-binding site

variable regions

constant regions

transmembrane region

α chain  β chain
Figure 1-11  The Immune System, 2/e (© Garland Science 2005)
This process creates millions and millions of different B cells every day. Each has a unique Ig receptor. Each B cell expresses 10,000s of copies of this same receptor
Somatic recombination

cut

excised DNA circle

paste

rearranged gene

Figure 1-23  The Immune System, 2/e (© Garland Science 2005)
Figure 2-15 part 2 of 2 The Immune System, 2/e (© Garland Science 2005)
Chromosome in a B cell

Nuclear RNA

mRNA

Membrane receptor on the surface of a B cell
The B cell specific for HIV proliferates

B cell proliferates and some differentiates into plasma cells

Secreted anti-HIV Antibody (Ig)
T cell – B cell interaction that takes place in the germinal center. Promotes proliferation of high affinity B cells, and class switch recombination.

Somatic hypermutation of immunoglobulin V regions in rapidly proliferating germinal center B cells.
Competition for antigen, the high affinity B cells attract signals and survive. The losers die! With time, the amount and affinity of antibodies increase.
This is how the immunoglobulin heavy chain gene locus would appear in a newly formed B cell.

Note: there might still be V-region gene elements upstream, and J-region gene elements downstream. They would not affect the transcription of the rearranged VDJ region. Furthermore, the non-rearranged J-region is in the middle of an intron, and would be spliced out in the final mRNA.
You should know the overall idea of switch recombination, but not the details: it changes the constant region of the Ig gene, so the B cell goes from having an IgM receptor (Cμ) to having (in this case) an IgA receptor (Cα1).
You do not need to know this, it is for your own curiosity only

<table>
<thead>
<tr>
<th>Function</th>
<th>IgM</th>
<th>IgD</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
<th>IgA</th>
<th>IgE</th>
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</thead>
<tbody>
<tr>
<td>Neutralization</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Opsonization</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>*</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Sensitization for killing by NK cells</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sensitization of mast cells</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Activation of complement system</td>
<td>+++</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Property</th>
<th>IgM</th>
<th>IgD</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
<th>IgA</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transport across epithelium</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++(dimer)</td>
</tr>
<tr>
<td>Transport across placenta</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+/–</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diffusion into extravascular sites</td>
<td>+/–</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++(monomer)</td>
<td>+</td>
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<td>Mean serum level (mg ml⁻¹)</td>
<td>1.5</td>
<td>0.03</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>0.5</td>
<td>2.1</td>
<td>5x10⁻⁵</td>
</tr>
</tbody>
</table>

Figure 2-29 The Immune System, 2/e (© Garland Science 2005)
IgM: as a receptor on the surface of B cells is monomeric with two binding sites; as a secreted antibody it is *always* assembled into a pentamer with 10 combining sites.
FYI, IgA in the serum is mainly monomeric, but in secretions it exists as a dimer. It is found in secretions: tears, gut, reproductive tract.
T cell – B cell interaction that takes place in the germinal center. Promotes proliferation of high affinity B cells, and class switch recombination.
The CDRs (complementarity determining regions) are roughly equivalent to the hypervariable regions (HVRs).
What to think about:
How do we get so many different antibodies from a limited number of gene elements?
Are all the receptors on one particular B cell identical?
When would you expect to find that each B cell has a unique receptor?
When might you find two B cells with identical receptors?
What does clonal selection mean?
How does switch recombination affect the antibody response?
When infected with a virus, how is it that the antibody response gets better and better with time (think about the course of an HIV infection)?
What are mechanisms of generating diversity in the populations of B cells?

Let's consider T cells
MHC class I

peptide

MHC class II

cell membrane

Figure 1-25 The Immune System, 2/e (© Garland Science 2005)
The spatial orientation of the TCR is similar to the BCR, but you can see that the 3rd CDR, the most variable portion, is located over the antigen peptide.
Macrophage engulfs and degrades bacterium, producing peptides

Bacterial peptides bound by MHC class II in vesicles

Bacterial peptides transported by MHC class II to the cell surface

T\(\text{H}1\) cell recognizes complex of peptide antigen with MHC class II and activates macrophage

Cell-surface immunoglobulin of B cell binds HIV and engulfs it, producing peptides

HIV peptides bound by MHC class II in vesicles

Bound peptides transported by MHC class II to the cell surface

T\(\text{fh}\) cell recognizes complex of peptide antigen with MHC class II and activates B cell

activates

MHC class II

activates

MHC class II

Figure 1-27 The Immune System, 2/e (© Garland Science 2005)
Neutralizing Antibodies to HIV

High amounts and High affinity IgG

Antibody (μg ml⁻¹ serum)

Primary response

Secondary response

lag phase

response to vaccine A
Or early response to HIV infection

response to vaccine B

vaccine A

vaccines A+B

Days

Figure 1-30 The Immune System, 2/e (© Garland Science 2005)
Kinetics of a CD8 cytotoxic T Cell Response

- **Expansion**
- **Effector**
- **contraction via apoptosis**
- **Memory**

**Cell Number**
- 100
- 1,000
- 10,000
- 100,000
- 1,000,000
- 10,000,000

**time post-infection**
- LCMV
- week
- month
Collision and nonspecific adhesion

cytotoxic T cell

MTOC
LG

Specific recognition redistributes cytoskeleton and cytoplasmic components of T cell

Release of lytic granules at site of cell contact

Figure 6-28 The Immune System, 2/e (© Garland Science 2005)
<table>
<thead>
<tr>
<th></th>
<th>Dendritic cells</th>
<th>Macrophages</th>
<th>B cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antigen uptake</strong></td>
<td>+++ Macropinocytosis and phagocytosis by tissue dendritic cells. Viral infection</td>
<td>Phagocytosis +++</td>
<td>Antigen-specific receptor (Ig) +++</td>
</tr>
<tr>
<td><strong>MHC expression</strong></td>
<td>Low on tissue dendritic cells. High on dendritic cells in lymphoid tissues</td>
<td>Inducible by bacteria and cytokines – to +++</td>
<td>Constitutive. Increases on activation +++ to +++</td>
</tr>
<tr>
<td><strong>Co-stimulator delivery</strong></td>
<td>Constitutive by mature, nonphagocytic lymphoid dendritic cells +++</td>
<td>Inducible – to +++</td>
<td>Inducible – to +++</td>
</tr>
<tr>
<td><strong>Antigen presented</strong></td>
<td>Peptides Viral antigens Allergens</td>
<td>Particulate antigens. Intracellular and extracellular pathogens</td>
<td>Soluble antigens Toxins Viruses</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Lymphoid tissue Connective tissue Epithelia</td>
<td>Lymphoid tissue Connective tissue Body cavities</td>
<td>Lymphoid tissue Peripheral blood</td>
</tr>
</tbody>
</table>

Figure 6-38 The Immune System, 2/e (© Garland Science 2005)
How can we create a vaccine to effectively control HIV?

1. The problem is that HIV mutates so quickly
2. There is a strong antibody response that inactivates the virus at first, but eventually escape variants grow out
3. There are some parts of the virus that must stay constant, if we could make an antibody response against these parts, we might be able to formulate a successful vaccine (Broadly neutralizing antibodies--Dr. William Schief, TSRI)
4. Alternatively, or in concert, we might be able to make vaccine that activates a population of CD8 effector T cells to control virus-infected CD4 T cells
The acquired immunodeficiency syndrome (AIDS)-causing lentiviruses, HIV and SIV normally evade host immunity (otherwise they would not be viruses). Picker and colleagues report a form of persistent SIV vaccine that establishes indefinitely, high-frequency, SIV-specific effector memory T-cell ($T_{EM}$) responses at potential sites of SIV replication in rhesus macaques. This immunity stringently controls highly pathogenic SIV$_{MAC239}$ infection early after mucosal challenge.

No SIV-mediated pathogenesis (loss of effector site CD4 T cells) was noted in Group A and B controllers (Supplementary Fig. 7), and the vast majority of blood and lymph node mononuclear cell specimens from these macaques were negative for cell-associated SIV RNA and DNA.

Importantly, the stringent control of SIV infection in protected Group A and B rhesus macaques was not associated with CD8 T-cell responses restricted by protective MHC alleles (Supplementary Fig. 3b) or with TRIM5 polymorphisms associated with target cell susceptibility to SIV infection (Supplementary Fig. 9).
**Comparative analysis of SIV pathogenesis (CCR5+, CD4+ T cell depletion) in Group A-D RM.**

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Annu. Rev. Med. 63:95–111
Stages of primary infection

**Step 1**
Mucosal translocation and initial infection

**Step 2**
Local replication at portal of entry

**Step 3**
Early spread (amplification and broadcast of infection)

**Step 4**
Generalized systemic replication

Vaccine intervention

Abs

$T_{EM}$ responses
(CMV vectors)

$T_{CM}$ responses
(nonpersistent vectors)

Annu. Rev. Med. 63:95–111