Overview of Lecture: Immune Systems.
see the schedule for reading and watching assignments

Bullet Points:
• Nobel Prize – checkpoint inhibitors
• Selfish Clones
• Cells and systems:
  • Innate immunity
  • Inflammation
  • Fever & Toxic Shock
• Dendritic cells: innate control of adaptive responses
• Adaptive-Acquired immunity
• Antibodies – RAG genes, recombination and diversity
• 'Thymic Education’ - Know thyself!
  • clonal deletion vs suppression
  • (T) Cell-mediated adaptive immunity
  • (B) Humoral adaptive immunity
• immunological memory & vaccines
• Regulatory T cells & the hygiene hypothesis
• Autoimmunity
• Stress, immunity and health

Think Happy Thoughts for better ‘humoral immunity’!
Learning Goals:

1. Be able to describe and explain "the big picture" differences between innate and adaptive (acquired) immunity. What are dendritic cells and how do they integrate (bridge) the innate and adaptive systems?

2. Be able to describe and explain (1) the process that generates the near infinite diversity of antibody structure that results in molecular recognition of near infinite varieties of antigen epitopes, and then either (2a) eliminates the mutant clonal lineages that recognize self-epitopes, or (2b) suppresses them.

3. Be able to describe and explain the roles of B cells, CD4 Helper T cells and CD8 Cytotoxic (killer) T cells in adaptive immunity. What are memory cells and how do they allow vaccination to be effective? What is the primary target of the HIV virus and why does that result in "immune deficiency"?

4. Be able to describe the role of Regulatory T cells in reducing the risk autoimmune diseases and allergies. What is the hygiene hypothesis?
The fundamental property of our immune system is the ability to discriminate “self” from “non-self” so that invading bacteria, viruses and other dangers can be attacked and eliminated.

T cells, a type of white blood cell, are key players in this defense. T cells have receptors that bind to structures recognized as non-self and trigger the immune system to engage in defense. But additional proteins acting as T-cell accelerators are also required to trigger a full-blown immune response.

Other proteins function as brakes on the T cells, [“checkpoints”] inhibiting immune activation. This intricate balance between accelerators and brakes is essential for tight control. It ensures that the immune system is sufficiently engaged in attack against foreign microorganisms while avoiding the excessive activation that can lead to autoimmune destruction of healthy cells and tissues.

James P. Allison [discovered] that T-cell protein CTLA-4 functions as a brake on T cells. He had already developed an antibody that could bind to CTLA-4 and block its function. He now set out to investigate if CTLA-4 blockade could disengage the T-cell brake and unleash the immune system to attack cancer cells. Tasuku Honjo discovered PD-1, another protein expressed on the surface of T-cells, that functions as a T-cell brake, but operates by a different mechanism.

[see figure in the next slide]
James Allison and Tasuku Honjo showed how proteins on immune cells can be used to manipulate the immune system so that it attacks cancer cells. It represents a completely new principle, because unlike previous strategies, it is not based on targeting the cancer cells, but rather the brakes — the checkpoints — of the host immune system.

**IMMUNE BOOST**

Several methods are showing promise in helping immune sentinels called T cells to attack cancer.

**CHECKPOINT INHIBITOR DRUGS**

‘Checkpoint’ proteins block T-cell activity. Inhibitor drugs can release the brakes on T cells at different stages.

The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.
Evolution by Natural Selection is a **Selfish Process**

Things that survive & reproduce relatively more of self become relatively more common over time. An important way to increase survival & reproduction is to **form cooperative coalitions**.

Most cells in a body don’t reproduce across generations; they increase copies of shared genes in their ‘close kin’ - the gametes. It is the job of the **immune system** to stabilize this cooperative coalition of cells by **making sure everyone is on the same team** - the ‘self team.’

**Self/non-self Discrimination in Basal Metazoa** ...

**Integrative and Comparative Biology, Sep 2005 by Cadavid, Luis F** ... the basal metazoan phyla Porifera and Cnidaria have the ["innate"] ability to distinguish between their own tissues and those of unrelated members of the same species. ... maintains the genetic integrity of the colony. **{and might be necessary for the evolution of multicellularity}**
Cells of the Immune System

An overview of defenses

**Lymphoid stem cells** develop into lymphocytes: **B cells** and **T cells**.

**Myeloid stem cells** develop into erythrocytes (red blood cells) platelets (clotting) **leucocytes** (white blood cells)
- Basophils (& mast cells) – release histamines, prostaglandins cytokines, pyrogens, etc.
- Eosinophils & Natural Killer cells - ‘bombs’
- Neutrophils & Monocytes → macrophages + Dendritic (antigen presenting) cells (pg 943)

**Mucus** contains **lysozyme**, which digests peptidoglycan is also rich in phagocytes & IgA antibodies

**INNATE IMMUNITY**
- Rapid responses to a broad range of microbes
- Slower response

**ACQUIRED IMMUNITY**
- Slower responses to specific microbes

**Pathogens (microorganisms and viruses)**
- **Barrier defenses:**
  - Skin
  - Mucous membranes
  - Secretions
- **Internal defenses:**
  - Phagocytic cells
  - Antimicrobial proteins
  - Inflammatory response
  - Natural killer cells
- **Humoral response:** Antibodies defend against infection in body fluids.
- **Cell-mediated response:** Cytotoxic lymphocytes defend against infection in body cells.
All organisms have ‘innate’ mechanisms to discriminate self from non-self.

Fujita et al 2004 Immunological Reviews 198: 185-

*In jawed vertebrates* Immunity to infection is mediated by two general systems: **acquired** (or adaptive) and **innate** (or natural).

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**The CRISPR-Cas immune system:** Biology, mechanisms and applications
D Rath et al. BiochimieVolume 117, October 2015, Pages 119–128

*A recent discovery is the adaptive immune system in prokaryotes,*

a type of system previously thought to be present only in vertebrates.
The system, called CRISPR-Cas, provide sequence-specific adaptive immunity and fundamentally affect our understanding of virus–host interaction.

CRISPR-based immunity acts by integrating short virus sequences in the cell's CRISPR locus, allowing the cell to remember, recognize and clear infections.
When injured, **mast cells** \{specialized leucocytes in connective tissue & mucosa\} release **histamine**, triggering dilation of nearby capillaries. \{**anti-histamines fill receptor cell ‘locks’ w/o turning the key - block histamine keys**\}

Small proteins called **chemokines** \{or **cytokines**\} are secreted by many cell types: **attract** [leucocytes – “white blood cells”, including various T-cells] and signal them to increase production of microbe–killing compounds.
Certain bacterial infections can induce an overwhelming systemic inflammatory response known as septic shock. Characterized by high fever and low blood pressure, septic shock is the most common cause of death in U.S. critical care units. (especially bad after quorum sensing & ‘surprise attack’)
The text reads:

**REVIEW**

**Regulation of Adaptive Immunity by the Innate Immune System**


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**Bacteria** detected by **Dendritic Cells (DC)** … are internalized into the phagosome where **bacterial antigens** are processed for presentation on **MHC class II**.

**Bacterial antigens (red)** and **PAMPs** (Pathogen-Associated Molecular Patterns, blue) in the same phagosome indicates to the **DC** their common origin.

… recognition of bacterial PAMPs promotes the selection of bacterial antigens for optimal presentation [to the adaptive immune system] on **MHC class II**.

**TLR** {Toll-Like Receptor} signaling also leads to the induction of **costimulatory molecules and cytokines** necessary for activation and differentiation of **T lymphocytes**. - adaptive
Acquired {Adaptive} immunity: [bits of] Foreign invaders [in vertebrates] inevitably come into contact with B cell or T cell lymphocytes

Each B cell or T cell (lymphocyte) has on its surface many antigen receptor proteins (attached antibodies) that can bind a particular piece (epitope) of a foreign antigen.
**Antibodies** are large protein molecules known as **immunoglobulins**.

**IgM** combines in star-shaped clusters. It tends to remain in the **bloodstream**, where it is very effective in killing bacteria. *IgM is the most ancient antibody class and has the same function in all gnathostomes.*

**IgG**, the major immunoglobulin in the blood, is also able to enter **tissue spaces**; it works efficiently to coat microorganisms, {interfere with function & flag for destruction}

**IgA** - a doublet - concentrates in body fluids such as tears, saliva, milk, mucous; ... in a position to guard the entrances to the body.

**IgE** is normally present in only trace amounts, but it is responsible for the symptoms of allergy {it triggers mast cells in mucous membranes to release histamines}.

**IgD** is inserted into the membrane of B cells, where it regulates the cell's activation.

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**ACQUIRED IMMUNITY**
- Slower responses to specific microbes
  - Humoral response (antibodies)
  - Cell-mediated response (cytotoxic lymphocytes)
Vertebrate chromosomes have only hundreds of receptor-encoding genes, but ~$10^8$ different kinds of B cells making ~$10^8$ different antibodies.  

**Antibody Genes**  
Scientists long wondered how all the genetic information needed to make millions of different antibodies could fit in a limited number of genes.

The origins of the RAG genes – from transposition to V(D)J recombination  
The Recombination Activating Genes (Rag1 and Rag2) …evolved from a selfish DNA transposon [of viral origin] into a sophisticated DNA recombinase essential for immunity.
The established textbook story:

Immature thymocytes (B and T cells) … migrate into the thymus.

{~∞ random thymocyte antibody genotypes created by mutation and splicing processes.)

Immature T cells are screened against self-antigens.

Self-tolerance results from clonal deletion in thymus of any immature T cells that react strongly to self}

Nature 420, 468 - 469 (05 December 2002);

Immunology: Education and promiscuity. WILLIAM R. HEATH AND HAMISH S. SCOTT

To fight off microbial infections, our bodies call into action a type of immune cell known as a T cell. Sometimes, however, these cells mistake part of our body (self) for a microbe (non-self), ... lead to autoimmune diseases such as multiple sclerosis and juvenile diabetes.

To prevent this, T cells must undergo a strict education in the thymus, where they are tested for reactivity to as many self-proteins as possible; if reactive, they are eliminated.

Writing in Science, Anderson and colleagues report that organ-specific self-proteins (such as insulin, from the pancreas) can be 'promiscuously' expressed in the thymus ... allows developing T cells to become familiar with many of the body's molecules, including those normally not expressed in the thymus ...
To create a diverse repertoire of antigen receptors, maturing B and T lymphocytes [use a] semi-random process of recombination that not only generates antigen receptors with the ability to recognize foreign epitopes but also endogenously expressed self epitopes as well.

The potential to mount an immune response against self must therefore be controlled in order to avoid autoimmune disease.

The clonal selection theory … provides a model for immunologic tolerance to self: lymphocytes only express antigen receptors of one specificity, and those lymphocytes specific for self are clonally deleted.

As a result of studies in mice, it became generally accepted that the deletion of self-specific ab T cells is a very efficient mechanism for reducing the threat of autoimmunity.

Assessing the effect of clonal deletion in humans has been more difficult.
Instead, it might be that

self-specific CD8+ T cells are imprinted with a less harmful genetic program, either in the thymus or in the periphery, and that this, together with other peripheral tolerance mechanisms such as CD4+ regulatory T cells, is the principal bulwark against autoimmunity.

The presence of an abundant pool of self-specific peripheral T cells—as opposed to their elimination by clonal deletion—is important because it further shifts burden of maintaining tolerance to other mechanisms that must function for the life of the individual.

So why aren’t these self-specific cells removed in the thymus? We suggest that the reason is that they might still be needed to defend against pathogens, which are under selection to mimic “self” epitopes and evade immune recognition which historically are a much greater threat than autoimmunity to children and young adults, the main drivers of a population’s survival.

[recall “antagonistic pleiotropy” – selection for benefits to young as costs to old]

[which are under selection to mimic “self” epitopes and evade immune recognition]
at the heart of the immune system

HIV infects & kills CD4+ Helper T cells

Plus Regulatory T\textsubscript{reg} cells that subdue the helpers and killers
The next time that an individual encounters that same antigen, the immune system is primed to destroy it quickly.

Immunity: Short- and Long-Term Cell Memory
Whenever T cells and B cells are activated, some become **memory cells**.

Short-term immunity can be transferred passively via antibody-containing serum; similarly, **infants are protected by antibodies they receive from their mothers** (IgG antibodies cross the placenta, IgA antibodies are passed in breast milk).

Note the use of passive immunity w/ IgG at 1st birth of Rh+ baby by Rh- mom: pre-empts development of active Rh+ memory & strong attack on 2nd Rh+ child.
Early exposure to germs has lasting benefits.

Findings help to explain how microbes programme a developing immune system. Exposure to germs in childhood is thought to alter the immune system and protect children from developing allergies and asthma, but the pathways by which this occurs have been unclear. Now, researchers have identified a mechanism in mice …

In a study published online today in Science, researchers show that in mice, exposure to [specific strains of commensal gut bacteria] in early life can reduce the body’s inventory of natural killer T (NKT) cells, which help to fight infection but can also turn on the body, causing disorders such as asthma or inflammatory bowel disease. The study supports the 'hygiene hypothesis', which contends that such autoimmune diseases are more common in the developed world where the prevalence of antibiotics and antibacterials reduce children’s exposure to microbes. [Regulatory T cells (T_{reg}) fail to “tame” the killer T_{K} cells - allergies]

http://weom/2013/05/06/why-dirty-pacifiers-may-be-your-childs-friend/

MAY 6, 2013 … In a study published Monday in the journal Pediatrics, scientists report that infants whose parents sucked on their pacifiers to clean them developed fewer allergies than children whose parents typically rinsed or boiled them.
Feeding Babies Foods With Peanuts Appears To Prevent Allergies


Regulatory T cells in allergic diseases
M N Rivas T A Chatila  2016 American Academy of Allergy, Asthma & Immunology
http://dx.doi.org/10.1016/j.jaci.2016.06.003

Regulatory T (Treg) cells play a key role in sustaining immune tolerance to allergens, yet mechanisms by which Treg cells fail to maintain tolerance in patients with allergic diseases are not well understood.
On 24 July 2017, pharmaceutical firm Eli Lilly announced that it would pay up to US$400 million to support the development of a drug that stimulates regulatory T cells. T cells are often thought of as soldiers in the immune system’s battle against foreign invaders. But there are many kinds of T cell, each armed with a different set of skills. Regulatory T cells serve to dampen immune responses - rather than attack invaders – and are important for preventing autoimmunity. People with autoimmune disorders [and severe allergy problems] often also have reduced levels of regulatory T-cell activity, … bolstering such cells could reduce the immune system’s attack on the body.
Researchers have long known that social class affects health. In the Nov. 25 issue of the journal Science, a team of researchers reports that for 45 female rhesus monkeys, their relative position in the dominance hierarchy altered the functioning of their immune systems, with lower ranked monkeys showing lower levels of some types of disease-fighting cells.

Social stress in laboratory rats - Behavior, immune function, and tumor metastasis.
Stefanski V. PHYSIOLOGY & BEHAVIOR 73 (3): 385-391 JUN 2001
… in subdominant males after 2 days of continuous social confrontation elevated plasma concentrations of adrenal hormones …
{adrenal-cortical cortisol is an immune suppressant}
lower numbers of blood CD4 and CD8 T cells as well as reduced activity levels of natural killer (NK) cells …
A 10-fold lower tumor clearance in subdominant males …

Excess mortality among the bereaved was evident …