Physiology Undergraduate League of Students

McIntyre Medical Building
3655 Promenade Sir William Osler
Montréal, Québec
Canada H3G 1Y6

Phone: 514-398-8253
Email: puls@sus.mcgill.ca
Website: http://puls.sus.mcgill.ca

puls

ntcs

phgy313

set # 12

lecture #:	date:	professor:
30	Monday, April 2nd	Dr. Desbarats

announcements:

- ***The last Immunology lecture*** *(April 11th) will not be a tutorial, but will cover material for final exam.*
- ***The remaining NTCs*** *(last 2 immunology lectures) for NTC Set 13 will be posted on Athena after April 16th, 2007.*
- ***The PULS office is closed*** *for the rest of semester, if you forgot to pick up your NTCs, all the remaining sets available are just outside the office door.*

Good luck on final exams!

L8: IMMUNITY IN TRANSPLANTATION AND PREGNANCY

Solid Organ Transplantation:

- If a recipient received a transplant from a sibling (with same MHC alleles), the recipient will still probably reject the transplant (although, more slowly)
  → rejection due to **minor** histocompatibility antigens
- Thus, unless the patient is receiving an *autologous* transplantation or organ transplant from an *monozygotic* twin, the recipient must receive **immunosuppression** after transplantation procedure

Immunosuppression:

- Immunosuppression is harsh → turns off T cell response to prevent rejection of transplant
  - Immunosuppressed people (ex: AIDS patients, transplant recipients) get **cancers** and **opportunistic infections** (infections that normal healthy people do not get)
  - This tells us that the immune system provides protection against cancers
- Different classes of immunosuppressant drugs for transplant recipients:
  - Inhibition of IL-2 synthesis (ex: cyclosporin)
  - Anti-inflammatory (ex: corticosteroids)
  - Anti-proliferative (also drugs for cancer treatment)
    → Inhibit T cell proliferation
    → Also inhibit native cells (ex: skin cells, bone marrow cells), which accounts for the same side effects seen in chemotherapy-treated cancer patients and immunosuppressed individuals
- These drugs need to be taken for the entire life of a transplant recipient

Bone Marrow Transplantation:

- Used for treatment of cancers (blood cancers and pediatric cancers), bone marrow failure (aplastic anemia), some rare genetic diseases
- Give chemotherapy/radiation to kill cells in child's bone marrow, and give bone marrow from donor (with matched MHC)

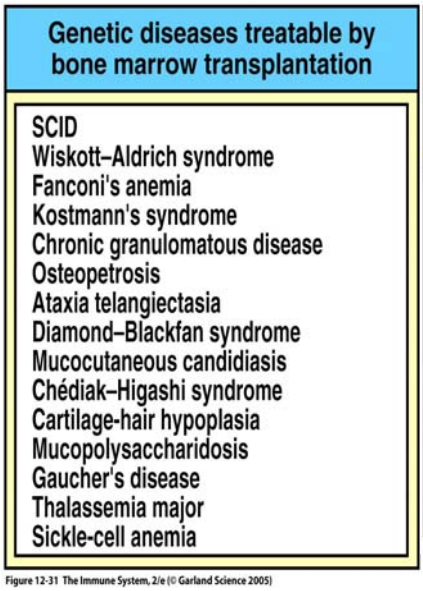


Figure 12-31 The Immune System, 2/e (© Garland Science 2005)

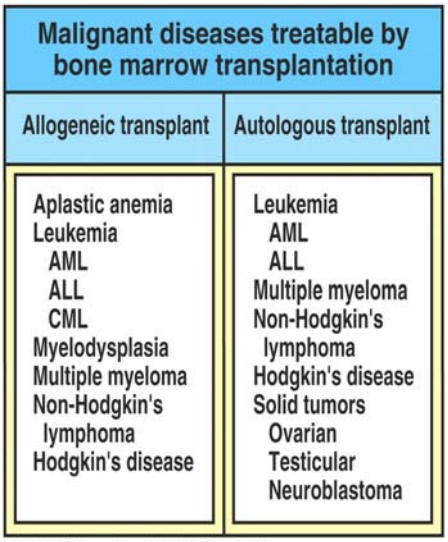


Figure 12-41 The Immune System, 2/e (© Garland Science 2005)

Or, you can give yourself a bone marrow transplant:

1. Cord blood banking:

- Take blood (contains *stem cells*) from baby's umbilical cord and freeze
- Later in child's life, if bone marrow transplantation needed, inject thawed cord blood stem cells

2. Marrow depleted of cancer cells:

- Can take the bone marrow from a cancer patient before chemotherapy
- Then, deplete bone marrow of cancer cells with chemotherapy
- After the chemotherapy, reinject bone marrow cells

This procedure does not work if the cancer is too invasive.

Bone marrow transplantation – Procedure:

- Donor's bone marrow is taken from iliac crest, you need to make hundreds of holes because bone marrow is very dense
- Bone fragments are filtered from bone marrow in the operating room
- There are many blood cells as well as stem cells in the marrow
- Filtered marrow is given to recipient and the stem cells will go back to the bone marrow and repopulate it

What are the consequences when the recipient's immune system is not histocompatible to the transplant?

- Solid organ transplantation → Recipient's immune system rejects transplant
- Bone marrow transplantation → Donor's bone marrow (contains active T cells, etc.) rejects the recipient → Called **graft-versus-host-disease (GVHD)**

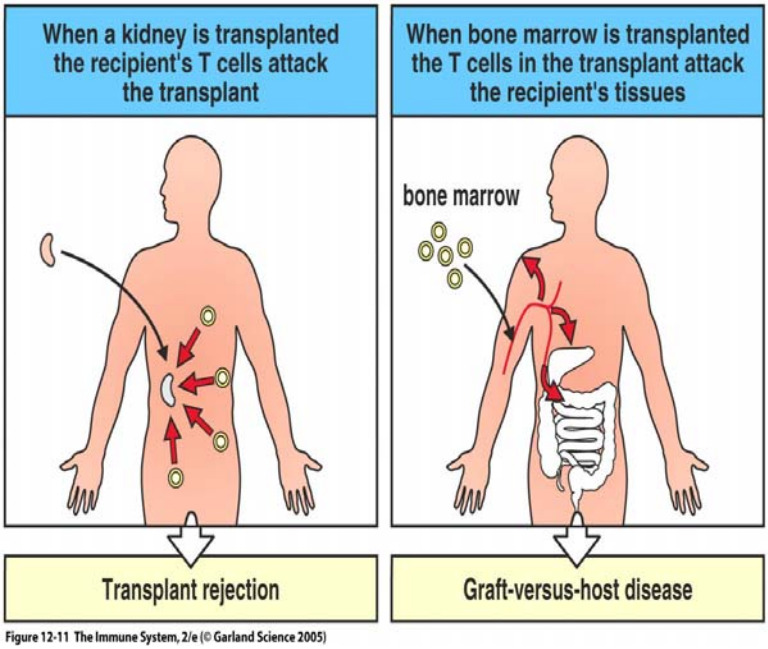


Figure 12-11 The Immune System, 2/e (© Garland Science 2005)

GVHD:

- **Acute GVHD**
  - Occurs in 50% of cases after a bone marrow transplantation
  - Visible skin rashes in recipient indicate the immune attack against the recipient
  - Treated with potent immunosuppressant drugs (usually steroids – see above)
- If MHC alleles are matched between the donor and recipient, the recipient can still get GVHD and potentially die because of **minor histocompatibility antigens**
- Yet still, the better the allele match, the better the survival chances of the recipient
  - Ex: mismatches in *both* MHC I and II alleles increases GVHD risk and decreases survival probability

Who gets GVHD?

- **Anybody who is immunosuppressed** and receives active donor T cells in an **allograft** (transplant from another human individual)
- **Healthy** recipients *cannot* get GVHD because their levels of active T cells outnumber the donor T cell levels → The allograft does not succeed in reacting against the recipient
- **Newborn** babies *can* get GVHD from a transfusion of whole blood → The newborn does not have a good T cell response
  - Thus, irradiate the blood before giving the transfusion to the baby

Could GVHD ever be *useful*?

- Yes – this is an aggressive immune attack, and can be used to kill cancer cells in Graft-versus-leukemia-effect

Graft-versus-leukemia-effect:
- Give chemotherapy to a sick individual, and this will kill most, but not all, cancer cells
- The remaining cancer cells can be killed by a bone marrow transplantation → The bone marrow allograft prevents the reoccurence of the leukemia

Pregnancy – Nature's Allotransplants:

The fetus carries both the mother and father's genes, and thus, there are genes that are foreign to the mother. So, why doesn't the mother reject her baby?

- **Allorecognition** (recognition of MHC molecules other than self) by mother's immune system of foreign fetus occurs
    - This is important for a healthy pregnancy
    - Results in production of factors (IL's, cytokines) that support the pregnancy
- **MHC I is reduced** at the maternal-fetal interface
    - Thus, **maternal NK activity is reduced** at pregnancy (high NK activity increases miscarriage rate) → NK cells would destroy fetal tissue
- Placenta produces hormones (**progesterone**) that **shifts immunity from Th1 to Th2 response**
    - Th1 response destroy tissues
- The fetal tissue does not express anything that could trigger innate immune response (ex: PAMPs)
- Essentially the mom's immune system supports a healthy baby
    - An infection of the fetus triggers an immune response, causing a miscarriage

L9: IMMUNITY IN ATYPICAL VIRAL INFECTIONS AND CANCERS

We already know about the Th1-mediated immune response against viruses. First exposure generates memory cells, whereas second exposure results in a more rapid immune response.
This, however, does not occur in atypical viruses.

Atypical Viruses:

The "common cold":
- Due to hundreds of different viruses with unrelated antigens, but related symptoms
- People get 2-5 colds on average every year, unless they are young or have kids, then they get more
- Half of 'colds' are caused by **rhinoviruses** (RNA virus); the other half by **adenoviruses** (DNA virus) and **coronaviruses** (RNA virus)
- Over one hundred different rhinoviruses cause 'colds'
- A rhinovirus is made up of a protein capsid with a genome of single-strand RNA
- Viruses with this simple structure are called *picornaviridae*

Influenza: (The flu is not a 'cold')
- 2 surface molecules: **Hemagglutinin** → helps the virus get into the host cell
  Neuraminidase → helps the virus get out of the host cell
- **segmented RNA genome**

These viruses proliferate using host cell machinery. Transcription of DNA to RNA is not 'proofread'. Thus, RNA viruses mutate faster than DNA viruses. Mutations can therefore accumulate (even in the same infection), making it harder for the immune system to recognize the virus. This can give rise to an **epidemic**.

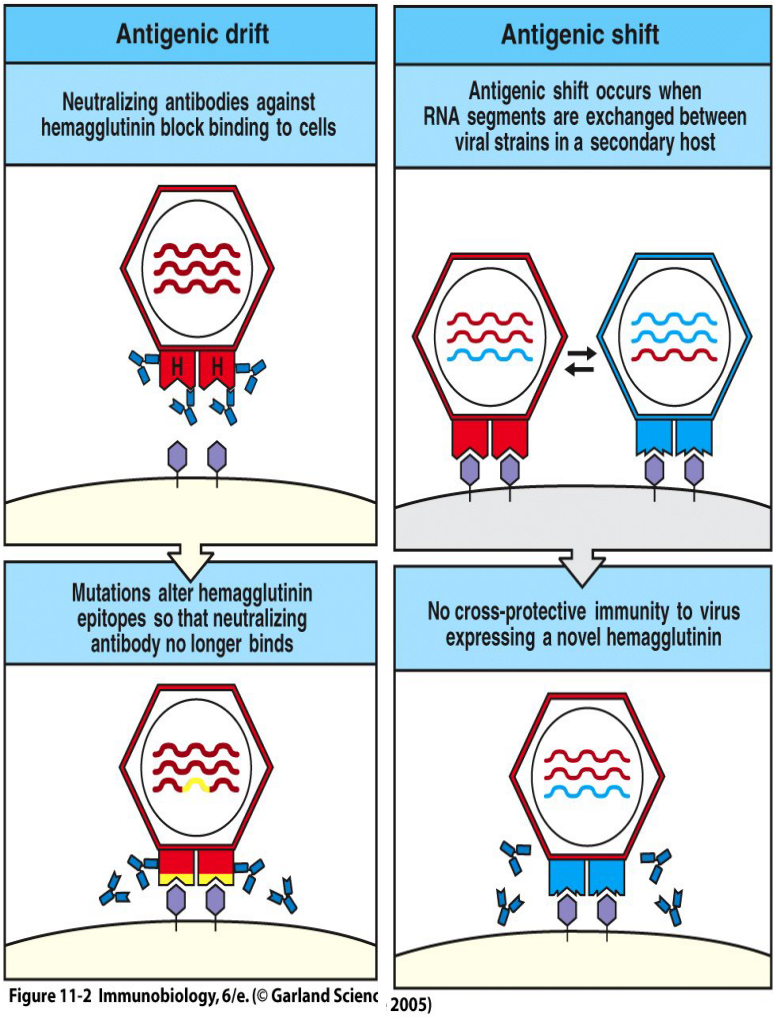
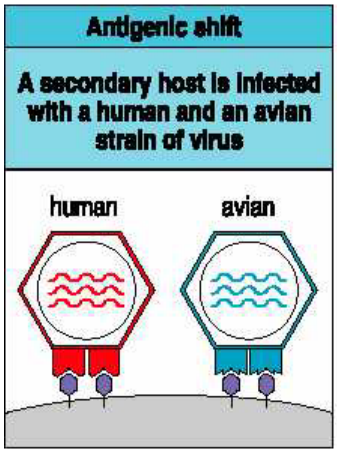


Figure 11-2 Immunobiology, 6/e. (© Garland Scienc 2005)

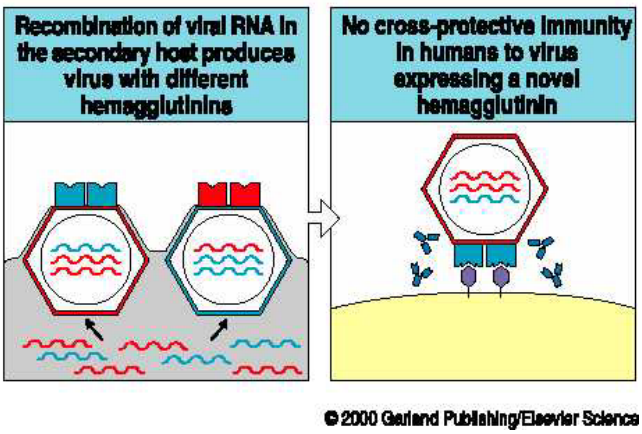
Why flu epidemics?

Antigenic Drift:
- Point mutations cause small differences in structure of viral surface antigens (due to lack of proofreading)

Antigenic Shift:
- Occurs when two different virus strains infect same cell simultaneously → the two segmented viral genomes are reassorted when the virus is packaged → new viral strain → epidemic arises (if nobody in human population has immunity to this new strain)



Ex – Avian Influenza (H5N1):
- In antigenic **shift**, if one of the two combined strains are from animals (ex: bird), it is *less* likely that some human individuals have immunity to the new viral strain (ex: avian flu)
- In the avian flu, the mortality rate is high (>80%)



How are viruses contagious?

- Viruses recognize cells with correct receptors for the viral antigens
- If the virus mutates to bind receptors located at the *top* (vs. bottom) of the lung → highly contagious (person-to-person transmission)
- The virus is poorly contagious if it binds receptors at the *bottom* of the lung
- It is calculated that there needs to be 5 point mutations for the virus to be able to bind receptos at the top of our lungs

Influenza viruses are named according to (ex: A/Puerto Rico/8/34):
- Strain: A, B or C (strains B and C don't really cause disease)
- Town/country where first discovered

- Number of isolates
- Year the virus first appeared

Immunological naming by antigenic subtype of viruses (Ex: Avian Flu = H5N1):
- By antigenic subtype: **H**emagglutinin and **N**euraminidase strains

Therefore, an influenza **pandemic** is most likely triggered by:
- An antigenic shift in a current flu virus that can pass between humans

HIV/AIDS Epidemic:
Two strains: HIV-1 (affects most of developed world) and HIV-2 (affects Africa, SE Asia)

- HIV targets CD4+ cells (central cells of the *adaptive* immune response)
    - CD4+ cells helps CTL to kill virally infected cells and help with antibody production
- Thus, one becomes extremely immunosuppressed without C4+ cells → die of opportunistic infections or cancers (*not* because of the virus itself)

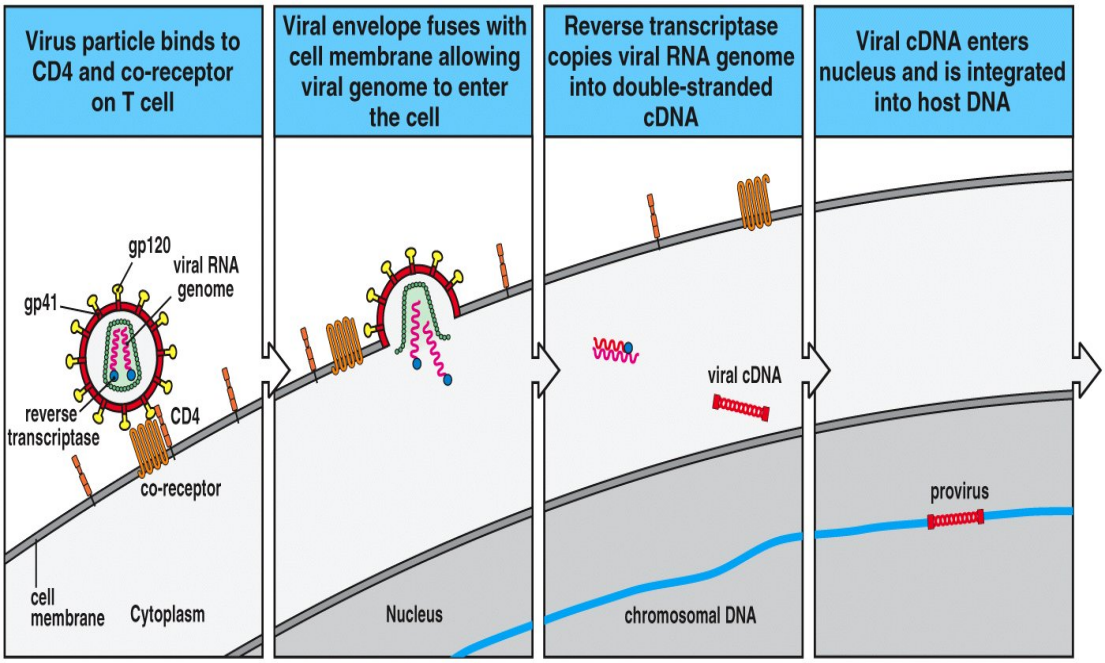


Figure 11-23 Immunobiology, 6/e. (© Garland Science 2005)

- Viral receptor (**gp120**) *specifically* attaches to **CD4** molecule as a receptor → infects helper T cells (Th1, Th2)
- Virus also has a co-receptor (a chemokine R) expressed on most T cells
- Viral envelope fuses with cell membrane
- Reverse transcription of HIV genome by reverse transcriptase in CD4 cell
- RNA genome is reverse transcribed to DNA → DNA provirus copy hides/integrates into host genome (Ex: same with herpes virus → cold sores or chickenpox/varicella)

→ thus, can hide in the host chromosal DNA and lie latent for years, only to become reactivated later, and spread more

NB: HIV is reactivated when the T cell it is lying latent in becomes activated in an immune response
- T cell activation stimulates transcription of provirus
- Viral proteins transcribed/translated
- New virions are packaged and bud from the infected T cell

HIV is unique because it subverts the immune system by infecting CD4 cells. When HIV makes copies of itself and exits cell, the virus kills/cripples the CD4 cell. Thus, everytime the virus is activated, CD4 levels drop.

Three phases:

1. Infection → Flu-like disease
    - CD4 levels normal
    - The immune system responds, and symptoms appear as if in any acute viral infection (ex: 'cold')
2. Throughout the years, CD4 count drops
    - When your CD4 count drops below 500 μl^{-1} of blood → immune system begins to fail → opportunistic infections
3. At <200 cells μl^{-1} of blood → AIDS
    - Once this threshold is crossed, and if left untreated → death quickly follows

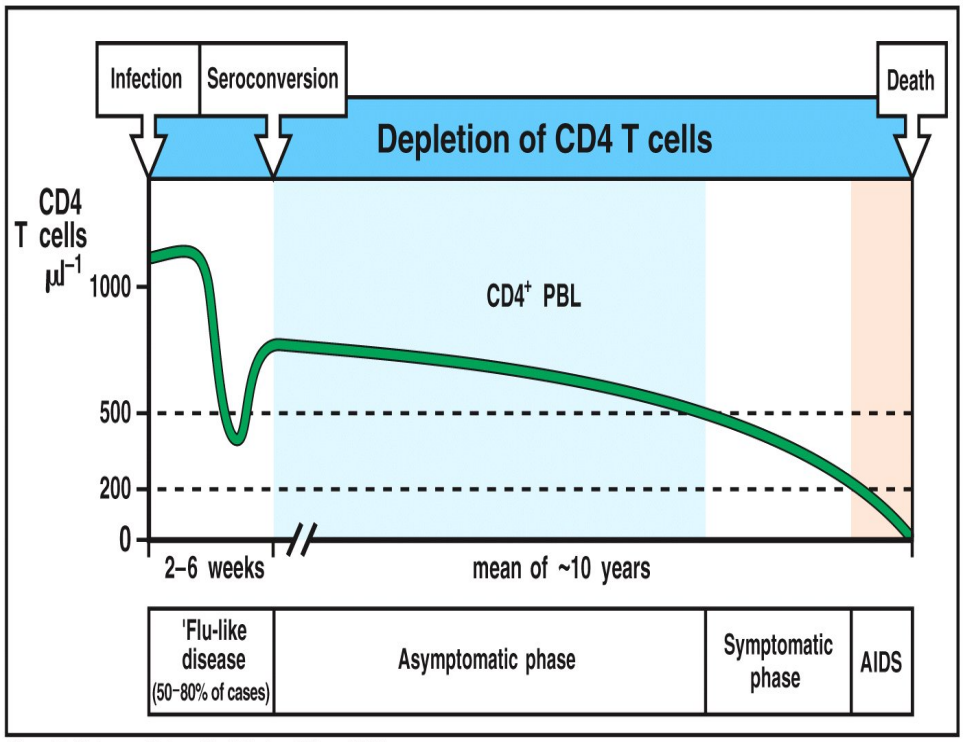


Figure 11-20 Immunobiology, 6/e. (© Garland Science 2005)

Opportunistic infections of AIDS patients are: intracellular pathogens, viruses, fungal infections, cancers, parasitic pathogens (all mediated by helper T cells)

PCP = Pneumocystis carinii pneumonia

- A particular fungal infection that AIDS patients (immunosuppressed) receive