Immune System

- An **immune system** is a collection of mechanisms within an organism that protects against disease by identifying and killing pathogens and tumor cells.
- It detects a wide variety of agents, from viruses to parasitic worms, and needs to distinguish them from the organism's own healthy cells and tissues in order to function properly.

Immune System

Disorders in the immune system can result in disease.

- Immunodeficiency diseases occur when the immune system is less active than normal, resulting in recurring and life-threatening infections.
- Immunodeficiency can either be the result of a genetic disease, such as severe combined immunodeficiency, or be produced by pharmaceuticals or an infection, such as the acquired immune deficiency syndrome (AIDS) that is caused by the retrovirus HIV.

Immune System

- In contrast, autoimmune diseases result from a hyperactive immune system attacking normal tissues as if they were foreign organisms.
- Common autoimmune diseases include
  - Rheumatoid arthritis,
  - Diabetes mellitus type 1
  - Lupus erythematosus.
- Immunology covers the study of all aspects of the immune system which has significant relevance to human health and diseases.

Immune System

Layered defense

- The immune system protects organisms from infection with layered defenses of increasing specificity.
- Most simply, physical barriers prevent pathogens such as bacteria and viruses from entering the organism.
- If a pathogen breaches these barriers, the **innate immune system** provides an immediate, but non-specific response.
- However, if pathogens successfully evade the innate response, vertebrates possess a third layer of protection, the **adaptive immune system**, which is activated by the innate response.

Immune System

- Both innate and adaptive immunity depend on the ability of the immune system to distinguish between self and non-self molecules.
- In immunology, ***self* molecules** are those components of an organism's body that can be distinguished from foreign substances by the immune system.
- Conversely, ***non-self* molecules** are those recognized as foreign molecules.
- One class of non-self molecules are called **antigens** (short for *anti*body *gene*rators) and are defined as substances that bind to specific immune receptors and elicit an immune response.

Innate Immune System

- Microorganisms or toxins that successfully enter an organism will encounter the cells and mechanisms of the innate immune system.
- The innate response is usually triggered when microbes are identified by pattern recognition receptors, which recognize components that are conserved among broad groups of microorganisms, or when damaged, injured or stressed cells send out alarm signals, many of which (but not all) are recognized by the same receptors as those that recognize pathogens.
- Innate immune defenses are non-specific, meaning these systems respond to pathogens in a generic way.
- This system does not confer long-lasting immunity against a pathogen. The innate immune system is the dominant system of host defense in most organisms.

Innate Immune System

- Inflammation
  - Inflammation is one of the first responses of the immune system to infection
- Complement system
  - The complement system is a biochemical cascade that attacks the surfaces of foreign cells. It contains over 20 different proteins and is named for its ability to “complement” the killing of pathogens by antibodies.

Innate Immune System

- Cellular barriers
  - Leukocytes (white blood cells) act like independent, single-celled organisms and are the second arm of the innate immune system. The innate leukocytes include the phagocytes (macrophages, neutrophils, and dendritic cells), mast cells, eosinophils, basophils, and natural killer cells. These cells identify and eliminate pathogens, either by attacking larger pathogens through contact or by engulfing and then killing microorganisms.

Adaptive Immune System

- The adaptive immune system evolved in early vertebrates and allows for a stronger immune response as well as immunological memory, where each pathogen is "remembered" by a signature antigen.
- The adaptive immune response is antigen-specific and requires the recognition of specific “non-self” antigens during a process called antigen presentation.
- Antigen specificity allows for the generation of responses that are tailored to specific pathogens or pathogen-infected cells.
- The ability to mount these tailored responses is maintained in the body by "memory cells". Should a pathogen infect the body more than once, these specific memory cells are used to quickly eliminate it.

Adaptive Immune System

- Lymphocytes
  - The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow. B cells are involved in the humoral immune response, whereas T cells are involved in cell-mediated immune response.
- Killer T cells
  - Killer T cell are a sub-group of T cells that kill cells infected with viruses (and other pathogens), or are otherwise damaged or dysfunctional.
- Helper T cells
  - Helper T cells regulate both the innate and adaptive immune responses and help determine which types of immune responses the body will make to a particular pathogen. These cells have no cytotoxic activity and do not kill infected cells or clear pathogens directly. They instead control the immune response by directing other cells to perform these tasks.

Components of the immune system

Innate immune system	**Adaptive immune system**
Response is non-specific	Pathogen and antigen specific response
Exposure leads to immediate maximal response	Lag time between exposure and maximal response
Cell-mediated and humoral components	Cell-mediated and humoral components
No immunological memory	Exposure leads to immunological memory
Found in nearly all forms of life	Found only in jawed vertebrates

Immune System Modulation

- **Immunomodulation**
  - Change in the body's immune system, caused by agents that activate or suppress its function.
- **Immunostimulant**
  - A substance that increases the ability of the immune system to fight infection and disease.
- **Immunosuppression**
  - Suppression of the body's immune system and its ability to fight infections and other diseases.
- **Immunotherapy**
  - Treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases.

Immunotherapies

Therapeutic manipulation with the immune system

- Immunopotentiation:
- Enhancement (optimalisation) of the immune response
  - Immunisation:
    - passive
    - active
    - to prevent infection
- Therapeutic administration of immunomodulators

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Immunotherapies

- **Vaccines**
  - toxoid, attenuated live, killed cell vaccines, subcellular, DNA, peptide
- **Adjuvants**
  - nonspecific immune stimulant
- **Passive Antibody**
  - IVIG, humanized monoclonal antibodies or immunotoxins
- **Cytokines** (IFN, IL-10, IL-12) **or cytokine antagonists**
  - anti-TNF, soluble cytokine receptors

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Immunotherapies

- Immunopotentiation
  - local
  - systemic
  - mucosal
- Immunosubstitution:
  - administration of intravenous immunoglobulins (IVIGs)
- Immunorestauration:
  - bone marrow transplantation

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Immunopotentiating Agents

- Nutrition elements
- Immunomodulators of microbial origin:
  - whole bacterial cells (BCG)
  - immunotherapy of adenoca of urine vesicle
- Bacterial lysates:
  - mixture of undefined (or semidefined) bacterial compounds
  - treatment of chronic respiratory and urinary infections (bronchovaxom, etc.)
- Mechanisms of action:
  - activation of macrophages
  - active immunisation

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Immunopotentiating Agents

- Chemical immunomodulators:
  - stimulation of T cell immunity
  - antiviral and anticancer activity
  - levamisol, isoprinosine
- Thymic hormons:
  - stimulation of T cell immunity
  - thymosin
- Recombinant cytokines:
  - produced by biotechnology in recombinant form
  - rCSF: stimulation of myeloid cells differentiation *(leukopenic patients)*
  - recombinant interferons: antiviral and antitumor effects
  - recombinant interleukins: rIL-2 (antitumor effect)

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Immunosuppression

- Immunosuppression involves an act that reduces the activation or efficacy of the immune system.
- It is the suppression of the body's immune system and its ability to fight infections and other diseases.
- Some portions of the immune system itself have immuno-suppressive effects on other parts of the immune system, and immunosuppression may occur as an adverse reaction to treatment of other conditions.
- Deliberately induced immunosuppression is generally done
  - to prevent the body from rejecting an organ transplant, treating graft-versus-host disease after a bone marrow transplant,
  - for the treatment of auto-immune diseases such as rheumatoid arthritis or Crohn's disease.

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Immunosuppressives

- Non-steroidal antiinflammatory drugs
  - inhibition of cyclooxigenase (COX) catalysing metabolism of arachidonic acid
  - decreased production of prostaglandins and leukotriens
  - acetylosalicylic acid, numerous other drugs
  - COX_2:
    - inducible enzyme
    - inflammatory response
    - new inhibitors without side effect

Immunosuppressives

- glucocorticoids
  - the most useful antiinflammatory and immunosuppressive drugs
  - lipophilic compounds difusion into the cell
  - cytoplasmic receptor
  - translocation into nucleus
  - serves as transcription factors (GRE: glucocorticoid response elements)
  - inhibition of transcription of proinflammatory cytokines genes (IL-1, TNFα, IL-6)
  - induction of lipocortins which inhibit phospholipase A2
  - induction of apoptosis of lymphocytes
  - inhibition of T cell functions
  - downmodulation of proinflammatory cytokines
  - inhibition of granulocyte functions

Immunosuppressives

- **Chemotherapeutics**
  - action on the level of DNA
  - antiproliferative effect
  - cytotoxic effect
    - antimetabolites:
      - metothrexate, azathioprine
    - mitotic drugs:
      - colchicine
    - alkylating drugs:
      - cyclophosphamide:
        - inhibition of autoantibodies production

Immunosuppressive Agents

- **Corticosteroids**
  - block cellular infiltration, cytokine release, T cell maturation, etc.
- **Azathioprine**
  - inhibit lymphocyte proliferation
- **Cyclosporine**
  - inhibit IL-2 gene expression
- **Anti-lymphocyte serum**
  - causes lymphocyte destruction and removal

Cytotoxic Agents as Immunosuppressants

- Antineoplastic drugs will also prevent clonal expansion of T- and B-cells
  - **azathioprine**
    - prodrug of nucleotide anti-metabolite
  - **mycophenolate mofetil**
    - becomes MPA; inhibits IMP dehydrogenase
  - **cyclophosphamide**
    - DNA alkylating agent
  - **methotrexate**
    - inhibits dihydrofolate reductase

Currently Used Immunosuppressants

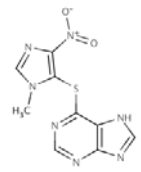
Category	Drugs
Alkyl Agent	Cyclophosphamide
Antimetabolic Agent	Azathioprin (Aza)
Steroids	Predenisone,Prednisolone, Dexamethasone, etc
Biological Agents	ALG (anti-lymphocyte globulins), ATG (anti-thymocyte globulins), OKT3
Fungus Products	CsA FK506 Rapamicin Cellcept (mycophenolate mofetil)
Chinese Medicine	

Azathioprine

- An immunosuppressive agent used in combination with cyclophosphamide and hydroxychloroquine in the treatment of rheumatoid arthritis.

Azathioprine

- 6-(3-methyl-5-nitroimidazol-4-yl)sulfanyl-7H-purine
- Formula: $C_9H_7N_7O_2S$



Azathioprine

Pharmacology

- Azathioprine is a chemotherapy drug, now rarely used for chemotherapy but more for immunosuppression in organ transplantation and autoimmune disease such as rheumatoid arthritis or inflammatory bowel disease or Crohn's disease.
- It is a pro-drug, converted in the body to the active metabolite 6-mercaptopurine.
- Azathioprine acts to inhibit purine synthesis necessary for the proliferation of cells, especially leukocytes and lymphocytes. It is a safe and effective drug used alone in certain autoimmune diseases, or in combination with other immunosuppressants in organ transplantation.

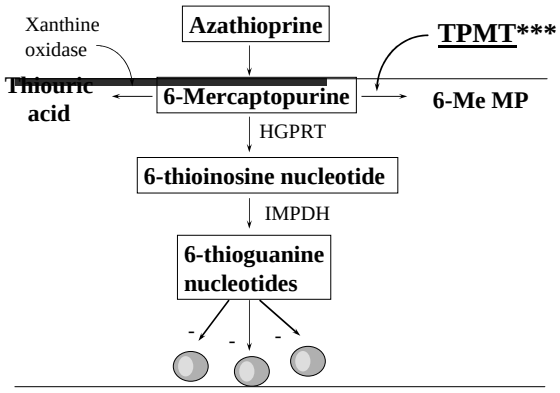
Azathioprine

- Its most severe side effect is bone marrow suppression, and it should not be given in conjunction with purine analogues such as allopurinol.
- The enzyme thiopurine S-methyltransferase (TPMT) deactivates 6-mercaptopurine. Genetic polymorphisms of TPMT can lead to excessive drug toxicity, thus assay of serum TPMT may be useful to prevent this complication.

Azathioprine

Mechanism of Action

- Azathioprine antagonizes purine metabolism and may inhibit synthesis of DNA, RNA, and proteins.
- It may also interfere with cellular metabolism and inhibit mitosis. The mechanism of action of azathioprine in rheumatoid arthritis is not known but is most likely related to its immunosuppressive action.



Cyclosporine

- **Cyclosporin**
  - **cyclosporine**
  - **cyclosporin**
- Is an immunosuppressant drug widely used in post-allogeneic organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection.
- Apart from in transplant medicine, cyclosporin is also used in psoriasis, severe atopic dermatitis and infrequently in rheumatoid arthritis and related diseases, although it is only used in severe cases

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Cyclosporine

- Cyclosporin, tacrolimus
  - Inhibit T cell activation, suppresses humoral
  - immunity, DTH, GVHD
- ID implications
  - Vaccinations less effective
  - Difficult to interpret skin tests
  - Infections: Fungal, CMV/other viral, bacterial
  - Drug interactions

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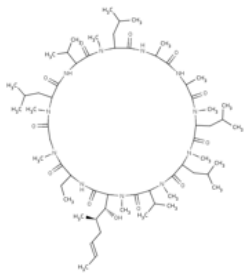
Cyclosporine

- **30-ethyl-33-[(E,1R,2R)-1-hydroxy-2-methylhex-4-enyl]-1,4,7,10,12,15,19,25,28-nonamethyl-6,9,18,24-tetrakis(2-methylpropyl)-3,21-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecazacyclotritriacontane-2,5,8,11,14,17,20,23,26,29,32-undecone**



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Cyclosporine

Pharmacology

- Used in immunosuppression for prophylactic treatment of organ transplants,
- Cyclosporine exerts specific and reversible inhibition of immunocompetent lymphocytes in the G0-or G1-phase of the cell cycle.
- T-lymphocytes are preferentially inhibited.
- The T1-helper cell is the main target, although the T1-suppressor cell may also be suppressed.
- Sandimmune (cyclosporine) also inhibits lymphokine production and release including interleukin-2.

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Cyclosporine

Mechanism of Action

- Cyclosporine binds to cyclophillin.
- The complex then inhibits calcineurin which is normally responsible for activating transcription of interleukin 2.
- Cyclosporine also inhibits lymphokine production and interleukin release.
- In ophthalmic applications, the precise mechanism of action is not known. Cyclosporine emulsion is thought to act as a partial immunomodulator in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

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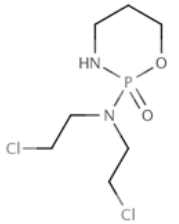
Cyclophosphamide



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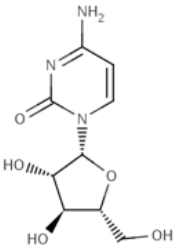
Cytarabine



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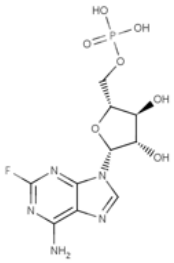
Fludarabine



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