Inflammation
The Inflammatory Response

Inflammatory trigger
- Infection
- Tissue injury
- Tissue stress and malfunction

Physiological purpose
- Host defence against infection
- Tissue-repair response
- Adaption to stress, and restoration of a homeostatic state

Pathological consequences
- Autoimmunity, inflammatory tissue damage and sepsis
- Fibrosis, metaplasia and/or tumour growth
- Shift in homeostatic set points, development of diseases of homeostasis and/or autoinflammatory diseases
Inducers of Inflammation

**Inducers**

- **Sensors**
- **Mediators**
- **Effectors**

**b**

- **Exogenous**
  - Microbial
    - PAMPs
    - Virulence factors
  - Non-microbial
    - Allergens
    - Irritants
    - Foreign bodies
    - Toxic compounds

- **Endogenous**
  - Cell derived
  - Tissue derived
  - Plasma derived
  - ECM derived
    - Signals released from stressed, malfunctioning or dead cells and from damaged tissues
    - Endogenous crystals
    - Products of ECM breakdown

### Examples of inflammatory pathways

<table>
<thead>
<tr>
<th>Inducer</th>
<th>Sensor</th>
<th>Mediator</th>
<th>Effectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipopolysaccharide</td>
<td>TLR4</td>
<td>TNF-α, IL-6 and PGE₂</td>
<td>Endothelial cells, hepatocytes, leukocytes, the hypothalamus, and others</td>
</tr>
<tr>
<td>Allergens</td>
<td>IgE</td>
<td>Vasoactive amines</td>
<td>Endothelial cells and smooth muscle cells</td>
</tr>
<tr>
<td>Monosodium urate crystals and calcium</td>
<td>NALP3</td>
<td>IL-1β</td>
<td>Endothelial cells, hepatocytes, leukocytes, the hypothalamus, and others</td>
</tr>
<tr>
<td>pyrophosphate dihydrate crystals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td>Hageman factor</td>
<td>Bradykinin</td>
<td>Endothelial cells and smooth muscle cells</td>
</tr>
</tbody>
</table>
The Innate Immune Response

• known pathogens trigger the **innate immune response**. The response is **non-specific**, but **fast**. The response is **maximal at the beginning**. It comprises **cellular (cell-mediated)** and **humoral (macromolecule-mediated)** components. There is **no memory effect**.

• involved components are the **complement system**, **leukocytes** (**white blood cells**) including the **phagocytes** (**macrophages, neutrophils, and dendritic cells**), **mast cells**, **eosinophils**, **basophils**, and **natural killer cells**.
The Innate Immune Response (II)

- response to infection by **microbials**
- recognition by tissue **macrophages** of specific **pathogen-associated molecular patterns (PAMPs)** such as the peptidoglycan that is part of all bacterial cell walls or lipopolysaccharides of gram-negative bacteria by toll-like receptors
- interaction with the receptors results in production of pro-inflammatory cytokines, e.g. **tumor necrosis factor TNF-α** and **IL-1**
- IL-1 and TNF-α also lead to activation of **NF-κB**, a transcription factor
- IL-1 and TNF-α cause vascular dilatation and exudation of fluid (containing bradykinin C5a and C3a from the complement system) as well as expression of cell surface adhesion molecules
- C5a and C3a stimulate mast cells to release **histamine**
- cytokines release **eicosanoids** (prostaglandins and leukotrienes)
- cytokines stimulate **NO** synthesis
- leucocytes attach the adhesion molecules and migrate to the pathogen site, where phagocytosis and killing of bacteria takes place
# Leukocytes: Blood cells involved in Anti-Inflammatory Response

<table>
<thead>
<tr>
<th>type</th>
<th>percentage</th>
<th>functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>neutrophil</td>
<td>62%</td>
<td>• bacteria • funghi</td>
</tr>
<tr>
<td>eosinophil</td>
<td>2.3%</td>
<td>• larger parasites • modulates allergic response</td>
</tr>
<tr>
<td>basophil</td>
<td>0.4%</td>
<td>• releases histamine</td>
</tr>
<tr>
<td>Leukocytes II</td>
<td>B cells: various pathogens T-cells Thelper: activate and regulate T and B cells cytotoxic T cells: virus-infected and tumor cells natural killer cells: virus-infected and tumor cells</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>lymphocyte</td>
<td>25-33 %</td>
<td></td>
</tr>
<tr>
<td>B cells: various pathogens T-cells Thelper: activate and regulate T and B cells cytotoxic T cells: virus-infected and tumor cells natural killer cells: virus-infected and tumor cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>monocyte</td>
<td>2-8 %</td>
<td></td>
</tr>
<tr>
<td>B cells: various pathogens T-cells Thelper: activate and regulate T and B cells cytotoxic T cells: virus-infected and tumor cells natural killer cells: virus-infected and tumor cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrophage</td>
<td>vacuum cleaner&quot; (phagocytosis) present pieces of pathogens to T cells become tissue macrophages</td>
<td></td>
</tr>
<tr>
<td>antigen-presenting cells process antigens and present them to T-cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dendritic cells</td>
<td>antigen-presenting cells process antigens and present them to T-cells</td>
<td></td>
</tr>
</tbody>
</table>
Cells of the Innate Immune Response

- **dendritic cells**
  - antigen presentation to T-lymphocytes as MHC complexes of processed peptide antigens. Mediate self-tolerance to endogenous sequences.

- **eosinophiles**
  - secrete granule content for extracellular digestion of infectious pathogens that are too large for engulfment (e.g. worms). Contain receptors for antibodies and complement proteins.

- **basophiles and mast cells**
  - Contain high affinity receptors for antibodies (e.g. for IgE). Activation triggers release of inflammatory mediators (histamine, heparin, factors that recruit neutrophils and eosinophils). The result of these is to isolate the inflammatory pathogens and move them from the blood stream into adjacent tissue to fight them.
Cells of the Innate Immune Response (II)

- **macrophages**
  - engulf and thereby destroy pathogens, and present antigens to TH cells. They possess pathogen-specific surface receptors (sugars, LPS). Removal of microbes and apoptotic cells.

- **neutrophiles**

- **natural killer cells**
  - kill infected cells. Kill cells with reduced expression of MHC-1, indicative of an infection. They sense changes on the surface of cell indicating that they are abnormal. Activated by interferon-a, produced by virally infected cells.
Adaptive immune response

• the second line of defines is formed by the adaptive immune system. The response is delayed, but there is a memory effect, such that if the same pathogen invades again the response is fast. It comprises cellular and humoral components.

• the adaptive immune response is comprised of special types of leukocytes called lymphocytes. They mainly comprise B-cells and T-cells. Killer T cells are a sub-group of T cells that kill cells that are infected. Helper T cells help determine which immune responses the body makes to a particular pathogen. These cells control the immune response by directing other cells to perform various tasks.
The Adaptive Immune Response (II)

• key cells are lymphocytes such as
  – B cells that are important for antibody production. They exist in different type: IgM/IgD or IgG/IgA/IgE (differ in their Fc portion)
  – T cells that are important during the induction phase and are responsible for cell-mediated immune reaction
  – (natural killer cells which are specialized lymphoidal cells are part of the innate immune system)

• in the **induction phase** T cells bearing CD4 or CD8 co-receptors are presented with antigen which causes them to proliferate into
  – cytotoxic T cells
  – CD4 bearing Th cells differentiate into Th1 or Th2 cells
  – Th2 cells control antibody-mediated response through interaction with B cells
  – Th1 cells develop into cells that release macrophage-activating cytokines controlling cell-mediated responses
The Adaptive Immune Response (III)

• in the **effector phase** the **antibody-mediated** response takes place leading to
  – activation of the complement cascade
  – ingestion of microorganisms
  – more effective attachment to parasites
  – neutralization of viruses and bacterial toxins

• **cell-mediated response** involve
  – CD8 cytotoxic cells killing virus-infected cells
  – CD4 cells release cytokines that enable macrophages to kill intracellular pathogens
  – memory cells are formed that react rapidly against the antigen is encountered the next time
## Mediators of the acute inflammatory response

<table>
<thead>
<tr>
<th>Mediators known to drive the acute inflammatory response</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The clotting system products (plasmin, fibrinopeptides)</td>
</tr>
<tr>
<td>- Fibrinolytic system products (fibrin)</td>
</tr>
<tr>
<td>- Kinins (bradykinin)</td>
</tr>
<tr>
<td>- Vasoactive amines (histamine and 5-hydroxytryptamine)</td>
</tr>
<tr>
<td>- Substance P</td>
</tr>
<tr>
<td>- Complement system by-products</td>
</tr>
<tr>
<td>- Eicosanoids (prostaglandins, leukotrienes and platelet activation factor)</td>
</tr>
<tr>
<td>- Cell-adhesion molecules</td>
</tr>
<tr>
<td>- Cytokines</td>
</tr>
<tr>
<td>- Chemokines</td>
</tr>
<tr>
<td>- Oxygen-derived free radicals</td>
</tr>
<tr>
<td>- Nitric oxide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mediators recently found to be involved in pro-resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cyclopentenone prostaglandins</td>
</tr>
<tr>
<td>- Lipoxins/resolvens</td>
</tr>
<tr>
<td>- NFκB (p50/p50)</td>
</tr>
<tr>
<td>- Mediators of apoptosis (caspases, CD44, etc.)</td>
</tr>
<tr>
<td>- Annexin-1</td>
</tr>
</tbody>
</table>
# Anti-Inflammatory Targets

## Major anti-inflammatory targets (by class)

<table>
<thead>
<tr>
<th>Target class</th>
<th>Specific targets</th>
<th>Examples of approved drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzymes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX-2</td>
<td>Celebrex®, Arcoxia®</td>
<td></td>
</tr>
<tr>
<td>COX-1 and COX-2</td>
<td>Voltaren®, NSAIDs</td>
<td></td>
</tr>
<tr>
<td>IMPDH</td>
<td>Cellcept®</td>
<td></td>
</tr>
<tr>
<td><strong>G-protein-coupled receptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CysLT1</td>
<td>Singulair®, Accolate®</td>
<td></td>
</tr>
<tr>
<td>H1</td>
<td>Zyrtec®, Clarinex®</td>
<td></td>
</tr>
<tr>
<td><strong>Nuclear hormone receptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Flonase®, Flixonase®, Nasonex®</td>
<td></td>
</tr>
<tr>
<td><strong>Cytokines and cytokine receptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α and TNF-RII</td>
<td>Remicade®, Enbrel®, Humira®</td>
<td></td>
</tr>
<tr>
<td>IL-1β and IL-1RA</td>
<td>Kinneret®</td>
<td></td>
</tr>
<tr>
<td>IL-2 and IL-2R</td>
<td>Zanapex®, Simulect®</td>
<td></td>
</tr>
<tr>
<td>Interferon α2</td>
<td>Peginteron®, Pegasys®</td>
<td></td>
</tr>
<tr>
<td>Interferon β1</td>
<td>Avonex®, Rebif®, Betaseron®</td>
<td></td>
</tr>
<tr>
<td>Interferon γ</td>
<td>Actimmune®</td>
<td></td>
</tr>
<tr>
<td><strong>Cell interaction molecules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cell adhesion molecules and co-stimulatory molecules)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFA-1 and CD11a</td>
<td>Raptiva®</td>
<td></td>
</tr>
<tr>
<td>CD2 and LFA-3</td>
<td>Amevive®</td>
<td></td>
</tr>
<tr>
<td>VLA-4 and CD49d</td>
<td>Tysabri®</td>
<td></td>
</tr>
<tr>
<td>CTLA-4-Ig</td>
<td>Orencia™</td>
<td></td>
</tr>
</tbody>
</table>
Nitric oxide (NO)

- Nitric oxide is also **generated by phagocytes** (monocytes, macrophages, and neutrophils) as part of the human immune response.

- Phagocytes are armed with **inducible nitric oxide synthase** (iNOS) which is activated by interferon-gamma (IFN-γ) as a single signal or by tumor necrosis factor (TNF) along with a second signal.

- Conversely, transforming growth factor-beta (TGF-β) provides a strong inhibitory signal to iNOS whereas interleukin-4 (IL-4) and IL-10 provide weak inhibitory signals.

- The endothelium (inner lining) of blood vessels uses **nitric oxide to signal the surrounding smooth muscle to relax, thus resulting in vasodilation and increasing blood flow**

- In this way the immune system may regulate the armamentarium of phagocytes that play a role in inflammation and immune responses.
Substance P

- is a neuropeptide belonging to the class of **Tachykinins**
- sequence: Arg Pro Lys Pro Gln Gln Phe Phe Gly Leu Met
- associated with some inflammatory processes in the joints
- its function is to cause pain, particularly in arthritis, low back pain as well as in migraine headaches
- the endogenous receptor for Substance P is neurokinin 1 receptor, a GPCR
- substance P is one of the important complex mechanisms involved in pain perception
- substance P-induced vasodilatation is dependent on nitric oxide release
- neuropeptides such as substance P, neurokinin A and calcitonin gene-related peptide (CGRP) act on mast cells, resulting in the release of histamine

### Substance P-mediated actions on immunoinflammatory cells

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>T and B lymphocytes</td>
<td>Proliferation, phosphatidylinositol hydrolysis</td>
</tr>
<tr>
<td>B lymphocytes</td>
<td>Enhanced immunoglobulin synthesis</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Chemotaxis, IL-1 and TNF-α production</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Phagocytosis, oxidative burst, eicosanoid production, lysosomal enzyme release, IL-1 and TNF-α release, enhanced cytotoxicity, 5’-nucleotidase downregulation</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Chemotaxis, augmented phagocytosis, lysosomal enzyme release</td>
</tr>
<tr>
<td>Mast cells</td>
<td>Histamine release, leucotriene generation</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Increased Fc receptor (IgG, IgE) expression, cytotoxicity</td>
</tr>
<tr>
<td>Astrocytes</td>
<td>Prostanoid synthesis</td>
</tr>
</tbody>
</table>
Cytokines

- interleukins (expressed by white blood cells)
- chemokines
- interferons
- colony-stimulating factors
- growth factors and tumor necrosis factors

- act on (GPCRs) and kinase-linked receptors
- can be pro-inflammatory (TNF-α, IL-1) that start a secondary cascade of chemokines
- can be anti-inflammatory (TGF-β, IL-4, IL-10 and IL-13). Inhibit chemokine production
Cytokines (II): Chemokines

- **chemotactic cytokines. Chemotaxis** is the directed movements of cells according to chemical signals
- chemoattractant cytokines that control migration of leucocytes
- subdivided into C-X-C and C-C group
- C-X-C chemokines (e.g. IL-8) act on neutrophils
- C-C chemokines (e.g. RANTES and MCP-1) act on monocytes, eosinophils involved in chronic inflammatory responses
- chemokines act through GPCRs
- alteration or inappropriate expression of chemokine receptors can lead to multiple sclerosis, some cancers, rheumatoid arthritis and cardiovascular diseases
- the host chemokine system is exploited by the HIV virus. The virus binds to a chemokine (CXCR5) receptor
Cytokines (III): Interferons

- natural cell-signaling proteins produced by the cells of the immune system in response to challenges such as viruses, parasites and tumor cells.
- Interferons belong to the large class of glycoproteins known as cytokines.
- Interferons are produced by a wide variety of cells in response to the presence of double-stranded RNA, a key indicator of viral infection.
- Interferons assist the immune response by **inhibiting viral replication** within host cells, **activating natural killer cells** and **macrophages**, increasing antigen presentation to lymphocytes, and inducing the resistance of host cells to viral infection.

<table>
<thead>
<tr>
<th>Table 1 Major characteristics of interferons</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNα</td>
</tr>
<tr>
<td>Type</td>
</tr>
<tr>
<td>Receptor</td>
</tr>
<tr>
<td>Structure</td>
</tr>
<tr>
<td>Cell source</td>
</tr>
<tr>
<td>Inducers</td>
</tr>
<tr>
<td>Activation</td>
</tr>
<tr>
<td>Commercially available recombinant products</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Histamine $H_1$ and $H_4$ receptors in allergic inflammation

- During inflammation, histamine is released from stores in mast cells and basophils.
- Histamine acts on vascular smooth muscle cells (causing contraction of bronchi and broncholi) and endothelial cells, leading to increased vascular permeability.
- Histamine is also a neurotransmitter in the CNS.
- Histamine receptors are GPCRs that share conserved motifs with monamine receptors.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$H_1$</th>
<th>$H_2$</th>
<th>$H_3$</th>
<th>$H_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best characterized</td>
<td>Acute allergic</td>
<td>Gastric acid</td>
<td>Neurotransmitter</td>
<td>Immunomodulator</td>
</tr>
<tr>
<td>function</td>
<td>reactions</td>
<td>secretion</td>
<td>modulation</td>
<td></td>
</tr>
<tr>
<td>G-protein coupling</td>
<td>$G\alpha_q$</td>
<td>$G\alpha_s$</td>
<td>$G\alpha_{so}$</td>
<td>$G\alpha_{so}$</td>
</tr>
<tr>
<td>Major signalling</td>
<td>Increases in Ca$^{2+}$</td>
<td>Increases in cAMP</td>
<td>Inhibition of cAMP</td>
<td>Increases in Ca$^{2+}$</td>
</tr>
<tr>
<td>pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine $pK_a$</td>
<td>4.2</td>
<td>4.3</td>
<td>7.8</td>
<td>8.1</td>
</tr>
</tbody>
</table>
Histamine receptors and receptor ligands

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>H₁</th>
<th>H₂</th>
<th>H₃</th>
<th>H₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine pKᵢ</td>
<td>7.9</td>
<td>&gt;10,000&lt;sup&gt;+&lt;/sup&gt;</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Loratadine pKᵢ</td>
<td>6.8</td>
<td>ND</td>
<td>ND</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Cetirizine pKᵢ</td>
<td>8.0</td>
<td>ND</td>
<td>ND</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Fexofenadine pKᵢ</td>
<td>8.3</td>
<td>ND</td>
<td>ND</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Ranitidine pKᵢ</td>
<td>&lt;4</td>
<td>7.1</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Cimetidine pKᵢ</td>
<td>&lt;5</td>
<td>6.2</td>
<td>&lt;5&lt;sup&gt;+&lt;/sup&gt;</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Thioperamide pKᵢ</td>
<td>&lt;5</td>
<td>&lt;4</td>
<td>7.3</td>
<td>7.2</td>
</tr>
<tr>
<td>JNJ 7777120 pKᵢ</td>
<td>&lt;5</td>
<td>&gt;4.5</td>
<td>5.3</td>
<td>8.4</td>
</tr>
</tbody>
</table>
NF-κB

- NF-κB is a major transcription factor that regulates genes responsible for both the innate and adaptive immune response

- NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens

- plays a key role in the anti-inflammatory immune response

- upon activation of either the T- or B-cell receptor, NF-kB becomes activated through distinct signaling components

- Activation of the NF-κB is initiated by the signal-induced degradation of IκB proteins. This occurs primarily via activation of a kinase called the IκB kinase
Mediators of Inflammation: Eicosanoids

**Prostaglandins** and related compounds are collectively known as eicosanoids. They are not preformed but generated in-situ from phospholipids.

Most are produced from **arachidonic acid**, a 20-carbon polyunsaturated fatty acid (5,8,11,14-eicosatetraenoic acid).

Examples of eicosanoids: prostaglandins, prostacyclins, thromboxanes, leukotrienes

**Prostaglandins** all have a cyclopentane ring.

- A letter code is based on ring modifications (e.g., hydroxyl or keto groups).
- A subscript refers to the number of double bonds in the two sidechains.

![Prostaglandin structure: PGE2](image)

**Thromboxanes** are similar but have instead a 6-member ring.
Biosynthesis of Arachidonic Acid
Arachadonic Acid Cascade

Cell Membrane Phospholipids

Arachadonic Acid

Cyclooxygenases

Prostaglandins
Thromboxanes
Prostacyclins

Lipoxygenases

Leukotrienes
Prostaglandins

Peroxidase

Prostaglandins
Pain
Inflammation

Thromboxanes
Blood Clotting

Prostacyclins
Blood Clotting
Prostaglandin Receptors

- Prostaglandins & related compounds are transported out of the cells that synthesize them.

- Most affect other cells by interacting with plasma membrane **G-protein coupled receptors.**

- Another prostaglandin receptor, designated **PPARγ**, is related to a family of nuclear receptors with transcription factor activity.

- Effects of a particular prostaglandin may vary in different tissues, depending on which receptors are expressed.
Action of Cyclooxygenases (COX)

\[
\text{Cyclooxygenase} \quad \text{O}_2 \quad \text{PGH}_2
\]
Cyclooxygenases

- two highly homologous proteins: COX-1 and COX-2
- COX-1 is essential for thromboxane formation in blood platelets, and for maintaining integrity of the gastrointestinal epithelium.
- COX-2 levels increase in inflammatory diseases such as arthritis. Inflammation is associated with up-regulation of COX-2 & increased amounts of particular prostaglandins.
- COX-2 expression is increased in some cancer cells.
  
  **Angiogenesis** (blood vessel development), which is essential to tumor growth, requires COX-2.

  Overexpression of COX-2 leads to increased expression of VEGF (vascular endothelial growth factor).
# Selective COX-2 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemistry</th>
<th>COX-1: COX-2 ratio</th>
<th>Pharmacokinetics</th>
<th>Metabolism</th>
<th>Urinary excretion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Sulphonamide</td>
<td>30</td>
<td>22–40</td>
<td>11</td>
<td>97</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>Sulphonyl</td>
<td>276</td>
<td>92–93</td>
<td>10–17</td>
<td>87</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>Sulphonamide</td>
<td>261</td>
<td>83</td>
<td>8–11</td>
<td>98</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>Sulphonyl</td>
<td>344</td>
<td>100</td>
<td>22</td>
<td>92</td>
</tr>
<tr>
<td>Luminacoxib</td>
<td>Phenyl acetic</td>
<td>433</td>
<td>74</td>
<td>3–6</td>
<td>98</td>
</tr>
</tbody>
</table>
• most NSAIDs inhibit both COX I & COX II.

• selective COX-2 inhibitors have been developed, e.g., Celebrex and Vioxx.

• COX-2 inhibitors are anti-inflammatory & block pain, but are less likely to cause gastric toxicity associated with chronic use of NSAIDs that block COX-1.

• A tendency to develop blood clots when taking some of these drugs has been attributed to:
  • decreased production of an anti-thrombotic (clot blocking) prostaglandin (PGI₂) by endothelial cells lining small blood vessels
  • lack of inhibition of COX-1-mediated formation of pro-thrombotic thromboxanes in platelets.
Aspirin

• irreversibly acetylates Ser-259 in human platelet close to the catalytic site, thereby preventing access to the catalytic site.
• Aspirin irreversibly inhibits COX-1 and modifies the enzymatic activity of COX-2.
• Normally COX-2 produces prostanoids, most of which are pro-inflammatory. Aspirin-modified COX-2 produces lipoxins, most of which are anti-inflammatory.
• consumption about 40’000 tons/year

![Diagram of COX-1/COX-2](image)
Lipoxins/Resolvins

- metabolism of arachidonic acid gives rise to the lipoxin (LX) family of eicosanoid metabolites
- they constitute **anti-inflammatory** mediators
- Lipoxin signaling through the lipoxin receptor inhibits chemotaxis, transmigration, superoxide generation and NF-κB activation
- During inflammation, cells die by apoptosis. As part of resolution, lipoxins signal macrophages to the remains of these cells (phagocytosis)

![Lipoxin A4](lipoxin_a4.png)

![Lipoxin B4](lipoxin_b4.png)
Leukotrienes in inflammation

• produced in areas of inflammation in blood vessel walls as part of the pathology of atherosclerosis.

• implicated in asthmatic constriction of the bronchioles.

• some leukotrienes act via specific G-protein coupled receptors (GPCRs) in the plasma membrane.

Anti-asthma medications include:

• inhibitors of 5-Lipoxygenase, e.g., Zyflo (zileuton)

• drugs that block leukotriene-receptor interactions: Singulair (montelukast) & Accolate (zafirlukast) block binding of leukotrienes to their receptors on the plasma membranes of airway smooth muscle cells.
Asthma

• disease characterized by shortness of breath, chest tightness and cough
• reversible bronchoconstriction
• inflammation in airway mucosa
• infiltration of eosinophils, increased numbers of T_{H2} cells relative to T_{H1} cells, and increased numbers of activated mast cells
• systemic evidence of allergic sensitization (elevated titers of immunoglobulin E)
• possibly life-threatening
• 4 billion $ market
## Asthma Therapies

### Table 1 | Pharmacological agents commonly used in adult asthma therapy

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Drug class</th>
<th>Relief of bronchoconstriction</th>
<th>Anti-inflammatory action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol, salmeterol, formoterol and others</td>
<td>$\beta_2$-adrenoceptor agonists</td>
<td>Highly effective</td>
<td>Not effective</td>
</tr>
<tr>
<td>Zileuton, montelukast, zafirlukast</td>
<td>Leukotriene modifiers</td>
<td>Not effective</td>
<td>Minimally effective</td>
</tr>
<tr>
<td>Budesonide, triamcinolone acetonide, flunisolide and others</td>
<td>Inhaled corticosteroids</td>
<td>Not effective</td>
<td>Moderately effective</td>
</tr>
<tr>
<td>Prednisone, methylprednisolone</td>
<td>Oral or intravenous corticosteroids</td>
<td>Not effective</td>
<td>Highly effective</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Methylxanthine</td>
<td>Minimally effective or moderately effective</td>
<td>Minimally effective</td>
</tr>
</tbody>
</table>
Action of Bronchodilators

- **β<sub>2</sub>-Agonist**
  - VIP
  - PGE<sub>2</sub>

- **β<sub>2</sub>-Adrenoceptor**
  - VIP receptor or PGE<sub>2</sub> receptor

- **G<sub>S</sub>**
- **AC**

- **PDE**
- AMP → Cyclic AMP → ATP

- **Theophylline**
- PDE3 inhibitors

- **PKA**

- **K<sup>+</sup> channel openers**

- **Ca<sup>2+</sup>-activated K<sup>+</sup> channel**

- **↓PI/Ca<sup>2+</sup>**
- **↓MLCK**
- **↑Na<sup>+</sup>/K<sup>+</sup>ATPase**

- **Bronchodilatation**
A **bronchodilator** is a substance that dilates the bronchi and bronchioles, decreasing airway resistance and thereby facilitating airflow.

**β2 agonists**

- **Salbutamol**
- **Salmeterol**
- **Efedryna**
- **Levalbuterol**
- **Clenbuterol**

**adrenalin**
Anti-Inflammatory Drugs: Corticosteroids

- Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex.
- Corticosteroids are involved in immune response and regulation of inflammation.
- The corticosteroids are synthesized from cholesterol within the adrenal cortex.
Leukotrienes are fatty molecules of the immune system that contribute to inflammation in asthma and bronchitis.

The name is derived from the words leukocyte and triene (indicating the compound's three conjugated double bonds).

Leukotrienes are produced in the body from arachidonic acid by the enzyme 5-lipoxygenase.

Leukotrienes act principally on a subfamily of G protein coupled receptors. They are involved in asthmatic and allergic reactions and act to **sustain inflammatory reactions**.

**Leukotriene receptor antagonists** are used as anti-asthma drugs.
• Explain terms pharmacodynamics, pharmacokinetics, bioavailability
• Uptake routes for drugs
• Body fluid compartments, volume of distribution
• Drug absorption in the intestinal tract, transport through epithelial cells
• Blood-brain barrier
• Efflux pumps
• Binding to plasma proteins
• Metabolic phase 1 and 2
• Elimination of drugs
• Dosing
• Drug toxicity
• Phases of drug development
• Target identification
• Biophysics of drug-receptor interactions
• Polar surface area
• Binding affinities
• Properties of fragments, leads and drugs
• Lipinski rules
• Screening techniques
• Virtual screening
• Isosters/bioisosters
• QSAR relationships
• Hansch equation (which terms are included?)
• 3D QSAR
• Explain terms pharmacodynamics, pharmacokinetics, bioavailability pharmacophores
• changing solubility
• prodrugs
• drug delivery systems
• fragments-based drug design, SAR-by-NMR
• properties of fragments vs drugs
• rational drug design
• methods (roughly): X-ray, NMR, SPR, Ultracentrifugation, ITC, DSC, Thermafluor
• most important receptors, mode of action, structures (roughly)
• dose-response curves, binding curves, definition of Kd, agonist, antagonist (full and partial, inverse ag.)
• determination of Kd
• antibacterials: strategies, membranes of mammalian, gram +/- cells, action and targets of antibiotics
• antiviral drugs: strategies, HIV/influenza treatments
• anticancer drugs: hallmarks of cancer, mode of action of anti-cancer drugs, antibodies
• anti-inflammatory drugs: immune response, innate and adaptive immune system, pain mediators