Cytokines (II)

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Learning Objectives

By the end of this lecture you will be able to:

① Understand the physiological role of IL-1, IL-2, TNF-α, IFN-α/β, and IFN-γ

② Describe three mechanisms to antagonize cytokines

③ Realize the role of cytokines in disease

④ Realize the role of cytokines in therapy

Cytokines function

- Cytokines stimulate the differentiation of stem cells in bone marrow

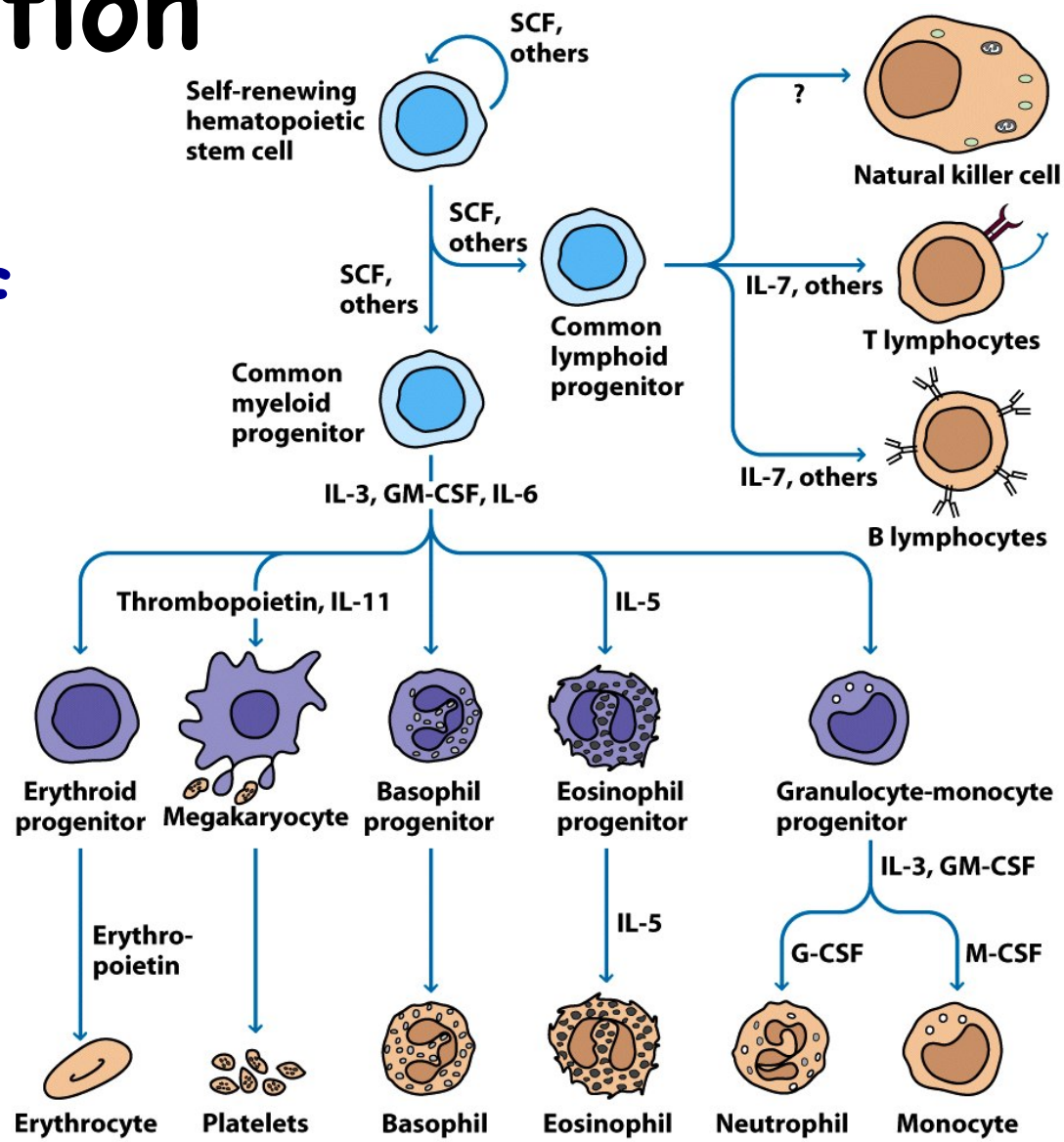
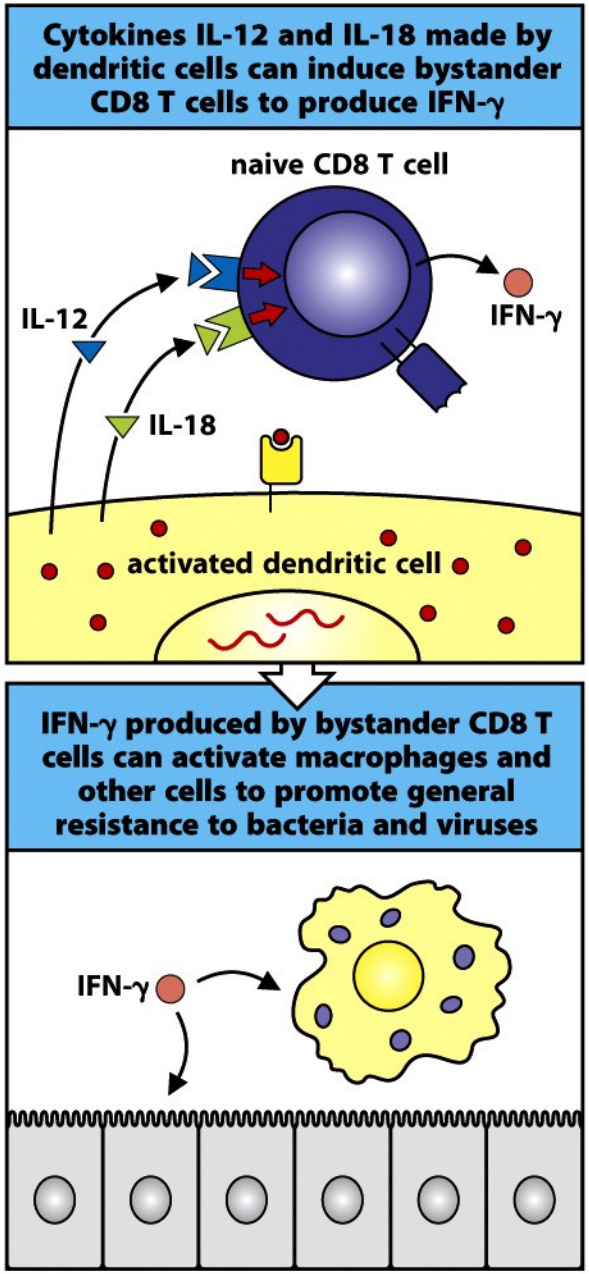


Figure 12-16
Kuby IMMUNOLOGY, Sixth Edition

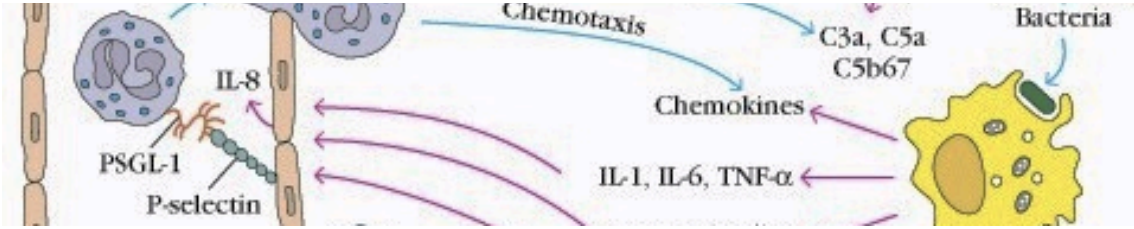
Cytokines function

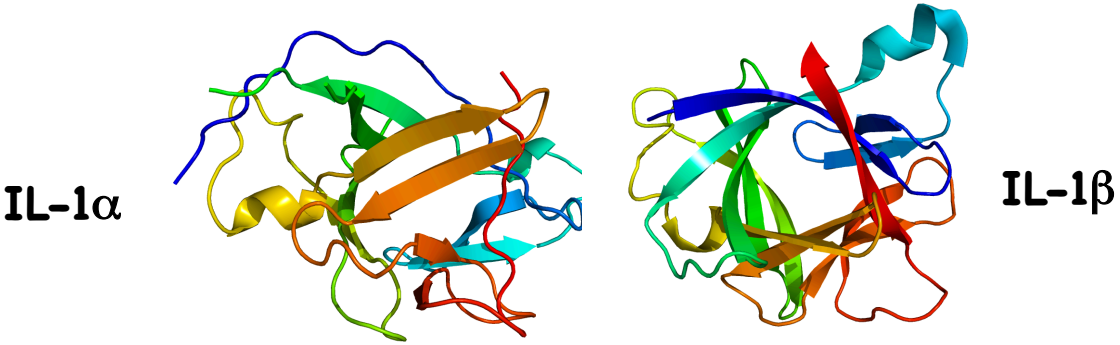
- Facilitate the cross-talk between immunocompetent cells



IL-1

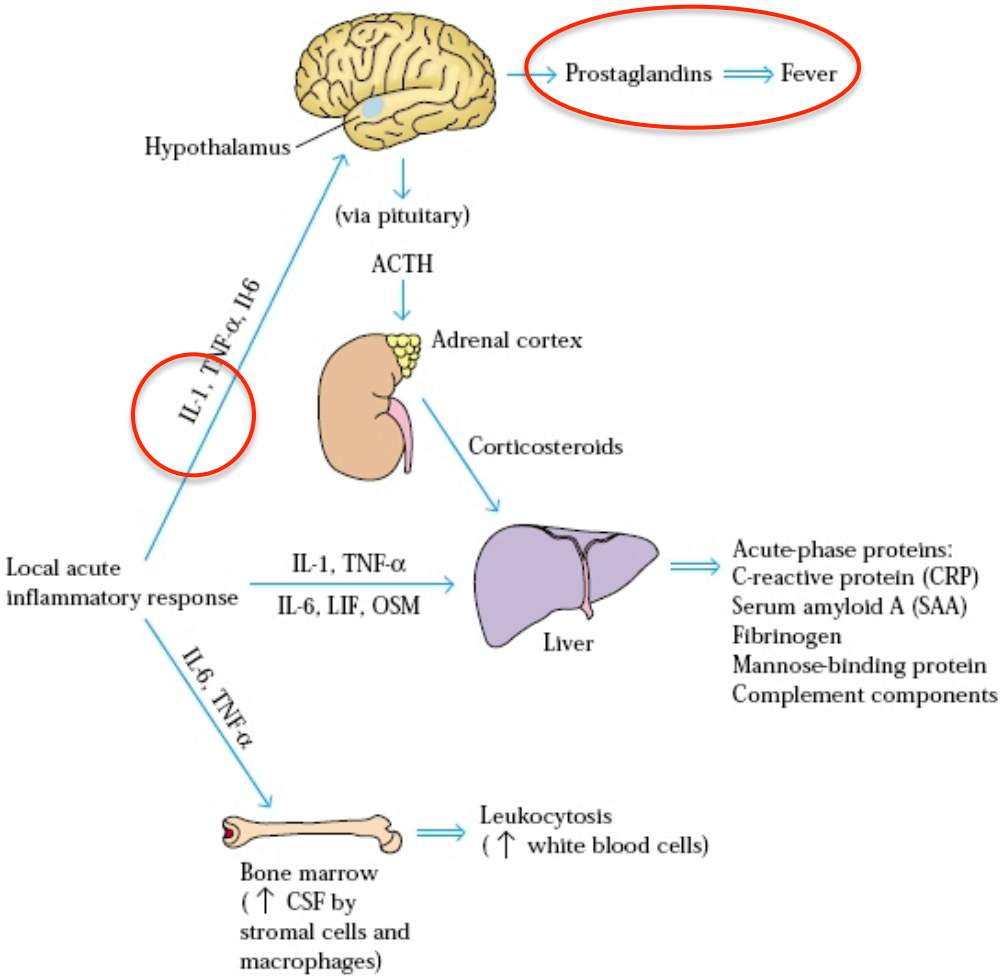
- Synthesized mainly by macrophages, monocytes, DCs, and keratinocytes
- IL-1α is constitutive while IL-1β is inducible
- Proinflammatory cytokine
- Upregulate leukocyte adhesion factors





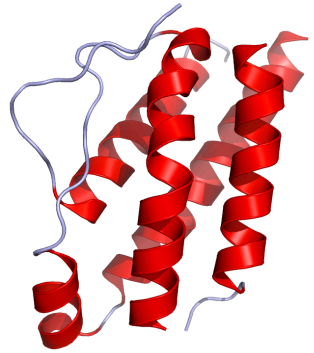
IL-1

- **Endogenous pyrogen**



IL-2

- Synthesized mainly by T cells
- Massively induced after T cell activation



IL-2

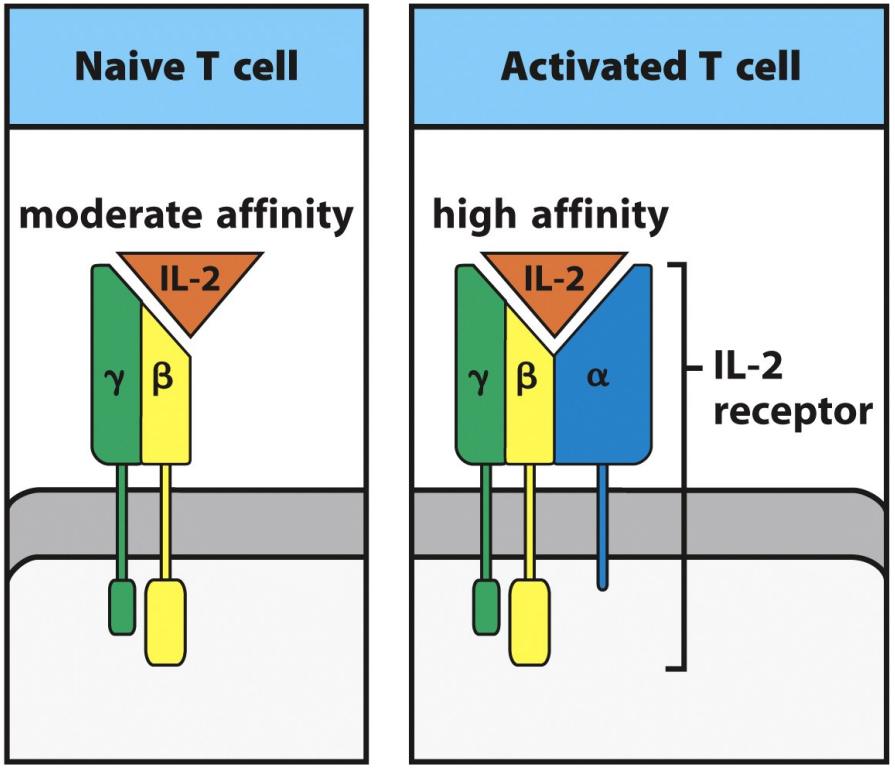
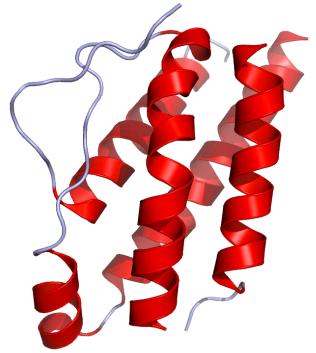


Figure 9.20 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

IL-2



- Autocrine stimulation is necessary for activation and proliferation of both $CD8^+$ and $CD4^+$ cells
- Increases the synthesis of perforin

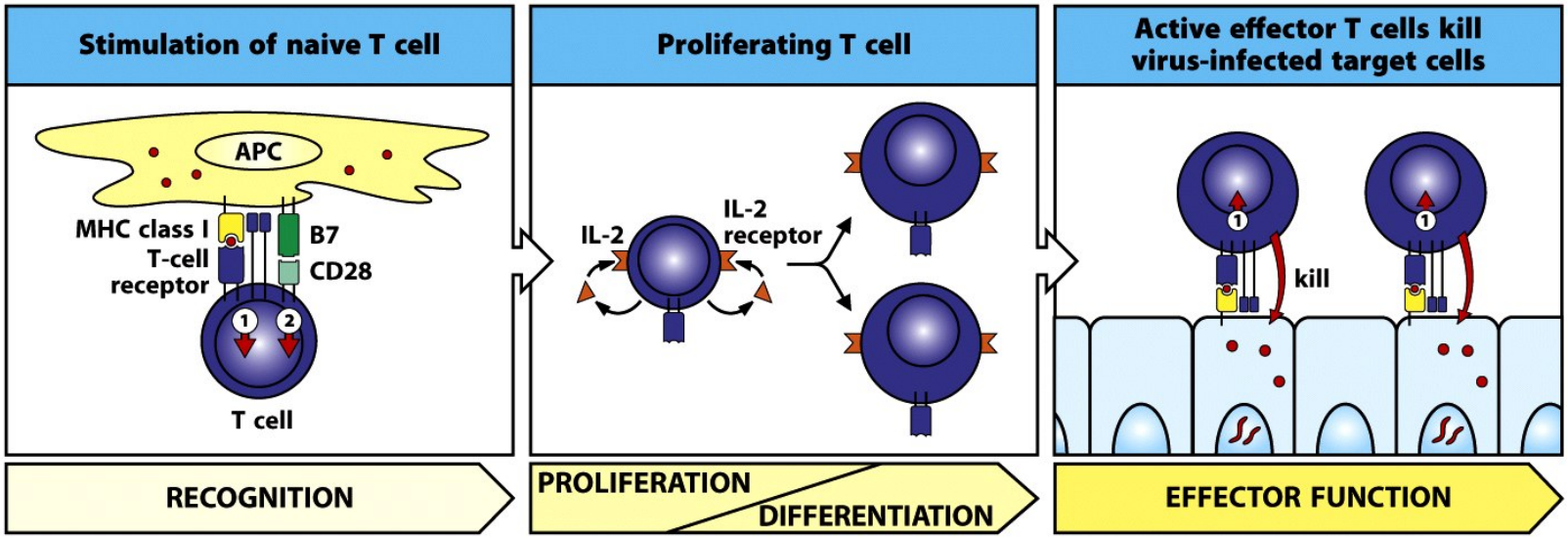
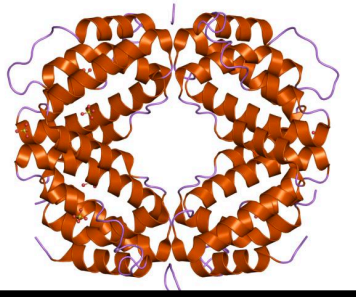


Figure 8-25 Immunobiology, 7ed. (© Garland Science 2008)

Interferons

- **A group of proteins produced by virus-infected cells, or some immune cells, that can induce generalized antiviral state**
  - Type I IFN (IFN-α, and IFN-β) are produced by virus-infected cells as well as monocytes, macrophages, and fibroblasts
  - **Type II IFN (IFN-γ) produced by APCs and activated T cells, recruits T_H1 to the site of inflammation, downregulates the activity of T_H2 cells, upregulates vascular adhesion molecules, upregulates MHC-I/II, and activate macrophages at the site of infection**
  - Type III IFN (IFN-λ) contains 3 molecules called IFN-λ1, IFN-λ2 and IFN-λ3 (also called IL29, IL28A and IL28B respectively) that play a role in stimulating the immune system against viruses

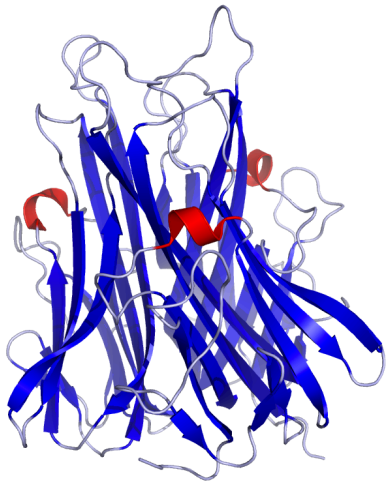
Targets of IFN-γ



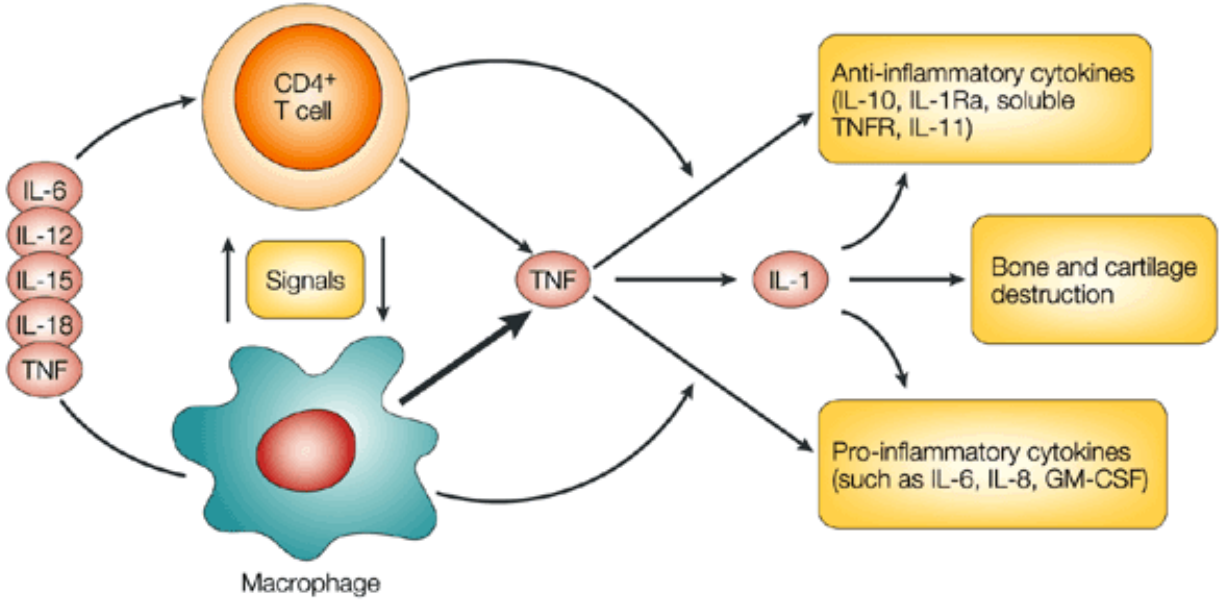
Target cell	Action
Epithelium & Endothelium	Activation and upregulation of adhesion molecules
NK cell	Increase NK cell cytotoxic activity
T_H cell	T_H activation, orientation toward T_H1, inhibition of T_H2 activity
Neutrophils and macrophages	Activation of intracellular killing machinery
Other cells	Upregulation of MHC-I and MHC-II

Tumor Necrosis Factor alpha

- Secreted mainly by macrophages, monocytes, neutrophils, and activated T cells and NK cells. It causes inflammation, acute phase response, neutrophil activation, and death of many cell types



TNF-α



Nature Reviews | Immunology

TABLE 12-1 Functional groups of selected cytokines*

Cytokine†	Secreted by‡	Targets and effects
	SOME CYTOKINES OF INNATE IMMUNITY	
Interleukin 1 (IL-1)	Monocytes, macrophages, endothelial cells, epithelial cells	Vasculature (inflammation); hypothalamus (fever); liver (induction of acute phase proteins)
Tumor necrosis factor-α (TNF-α)	Macrophages	Vasculature (inflammation); liver (induction of acute phase proteins); loss of muscle, body fat (cachexia); induction of death in many cell types; neutrophil activation
Interleukin 12 (IL-12)	Macrophages, dendritic cells	NK cells; influences adaptive immunity (promotes T_H1 subset)
Interleukin 6 (IL-6)	Macrophages, endothelial cells	Liver (induces acute phase proteins); influences adaptive immunity (proliferation and antibody secretion of B cell lineage)
Interferon α (IFN-α) (this is a family of molecules)	Macrophages	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
Interferon β (IFN-β)	Fibroblasts	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
	SOME CYTOKINES OF ADAPTIVE IMMUNITY	
Interleukin 2 (IL-2)	T cells	T-cell proliferation; can promote AICD. NK cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	T_H2 cells, mast cells	Promotes T_H2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T_H2 cells	Eosinophil activation and generation
Transforming growth factor β (TGF-β)	T cells, macrophages, other cell types	Inhibits T-cell proliferation and effector functions; inhibits B-cell proliferation; promotes isotype switch to IgA; inhibits macrophages
Interferon γ (IFN-γ)	T_H1 cells, $CD8^+$ cells, NK cells	Activates macrophages; increases expression MHC class I and class II molecules; increases antigen presentation

*Many cytokines play roles in more than one functional category.
†Only the major cell types providing cytokines for the indicated activity are listed; other cell types may also have the capacity to synthesize the given cytokine.
‡Also note that activated cells generally secrete greater amounts of cytokine than unactivated cells.

Cytokine Antagonists

- Cytokine antagonists be one of the following:
  ① Regulatory soluble proteins in blood stream
  ② Viral proteins
  ③ Pharmaceuticals

Cytokine Antagonists

- Cytokine antagonists be one of the following:

① Regulatory soluble proteins in blood stream:

Some can block cytokines receptors e.g. IL-1R antagonist (IL-Ra)

Soluble cytokine receptors obtained by enzymatic cleavage of the extracellular part of the receptor e.g. sIL-2R

Cytokine Antagonists

- Cytokine antagonists be one of the following:

② Viral proteins:

Cytokine homologs

Cytokine binding proteins

Homologs of cytokine receptors

Interference with intracellular signaling

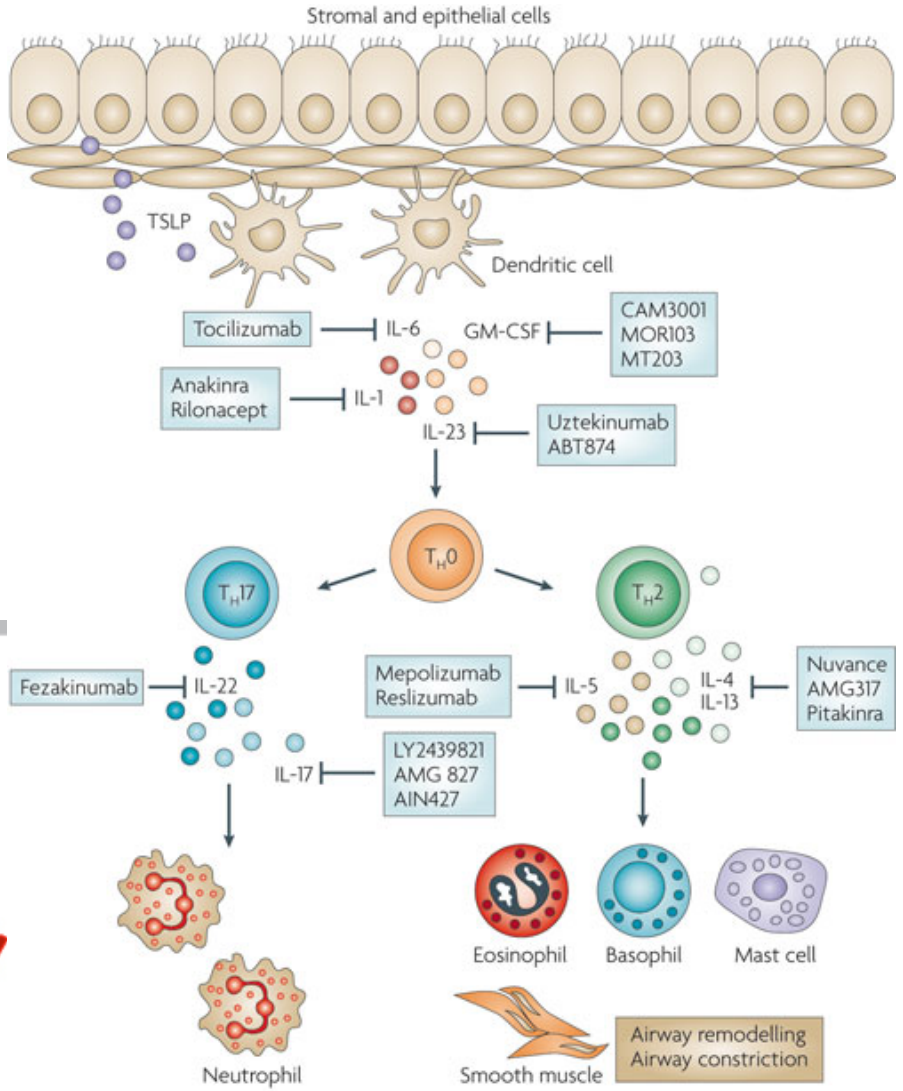
Interference with cytokine secretion

Cytokine Antagonists

- Cytokine antagonists be one of the following:

③ Pharmaceuticals:

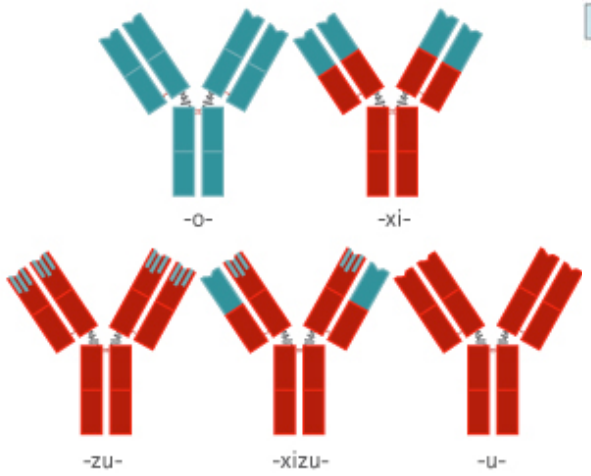
Mostly biological (e.g. mAb)



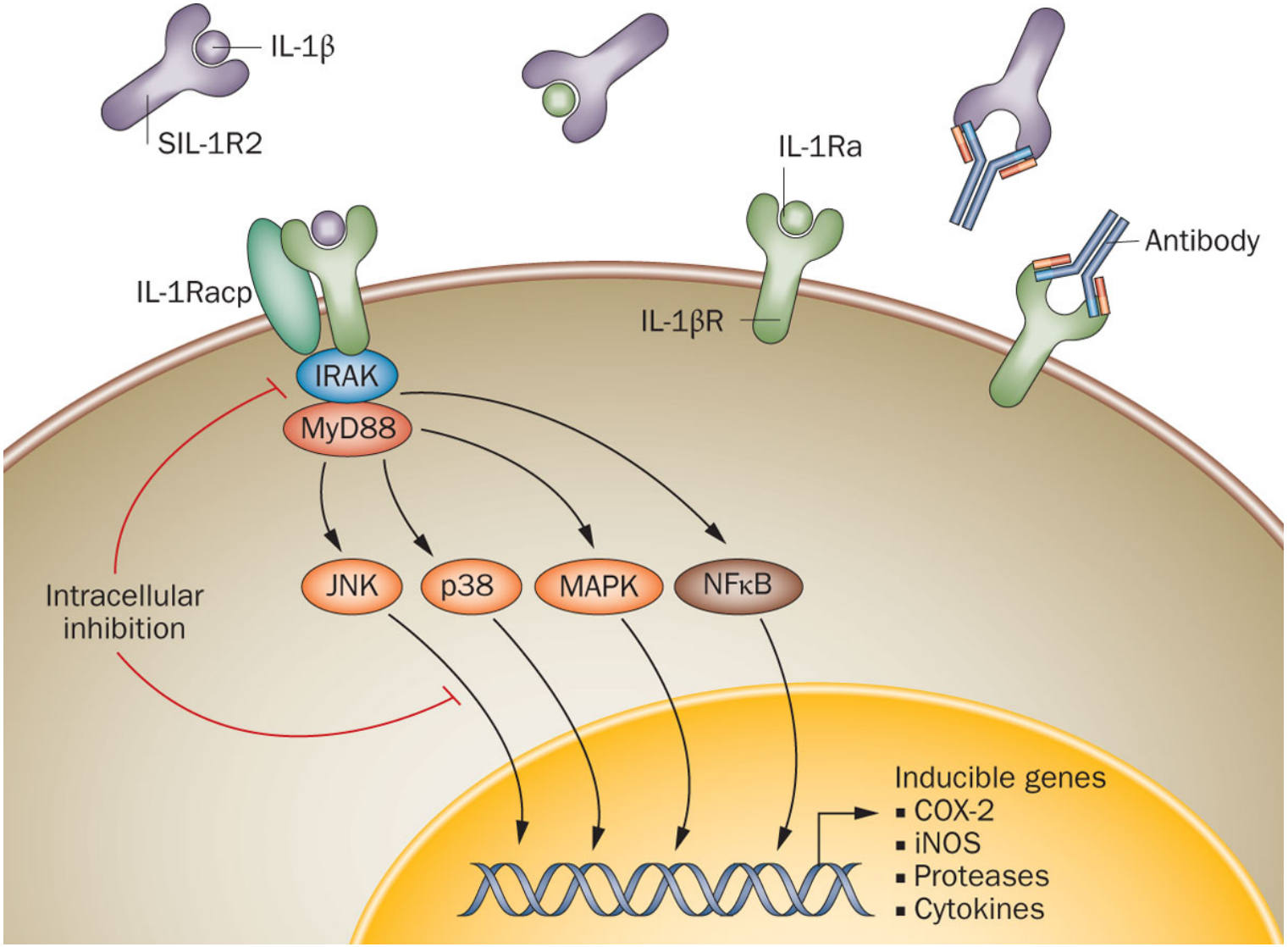
Components

Substem for origin / source

Source substems: mouse (top left), chimeric (top right), humanized (bottom left), chimeric/humanized (bottom middle), and human (bottom right) monoclonal antibodies. Human parts are shown in red, non-human parts in blue.



Cytokine Antagonists



Cytokine-Related Disease

- SCID
- Defective IFN-γ receptors
- Septic shock
- Bacterial toxic shock
- Chagas's disease
- CAPS
- Rheumatoid arthritis (RA)

Severe Combined Immunodeficiency

- SCID is an immunodeficiency disease caused by several genetic reasons
- Low number of circulating lymphocytes
- Defective thymus
- Non-proliferating T cells
- Usually fatal in early years of life
- Patient susceptible of all kinds of infections

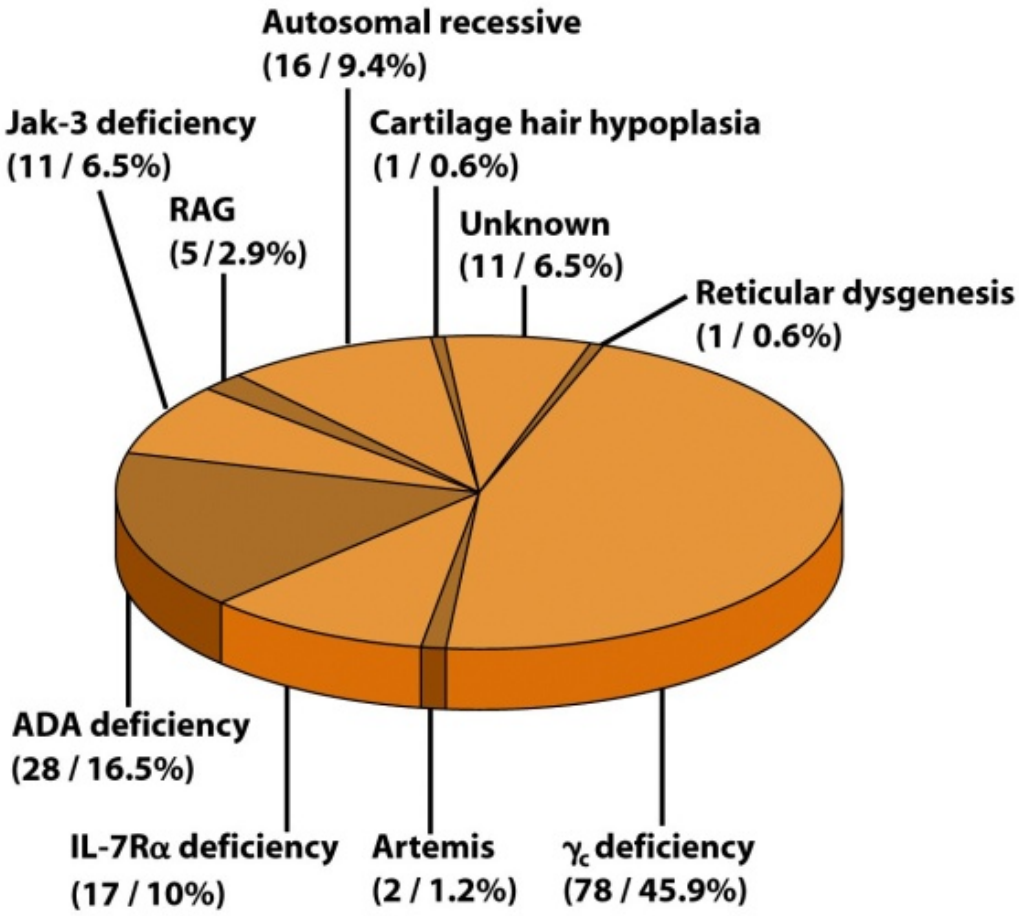
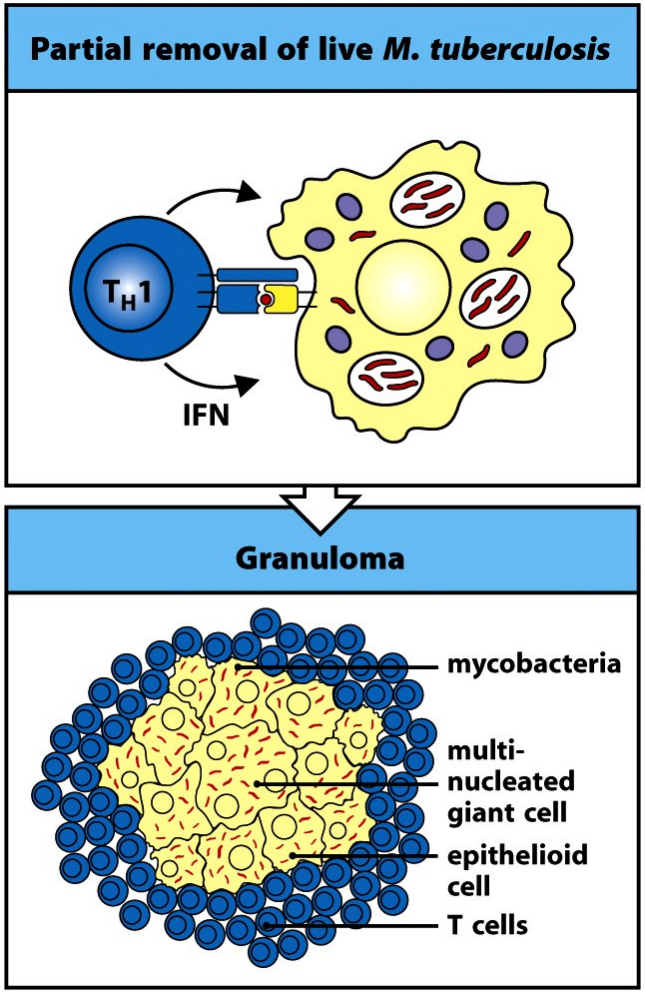


Figure 20-3a
Kuby IMMUNOLOGY, Sixth Edition

Defective IFN-γ receptors

- Patients suffer from mycobacterial infection



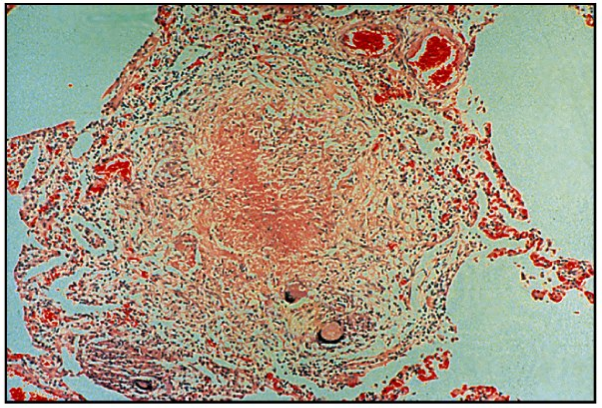


Figure 8-44 Immunobiology, 7ed. (© Garland Science 2008)

Septic shock

- Bacterial Septic Shock
- Certain Gram -ve bacteria e.g. *E. coli*
- Symptoms: severe drop in blood pressure, fever, diarrhea, blood clotting
- Endotoxin (LPS) bind TLRs (TLR4) on dendritic cells and macrophages
- Over production IL-1 and TNF-α
- Cytokine imbalance causes abnormal temp, abnormal respiration, capillary leakage, tissue injury, organ failure
- Treatment: TNF-α mAb and rIL-1Rα

Bacterial toxic shock

- Many bacteria produce toxins that act as superantigens
- Bind simultaneously to Class II MHC and T cell receptor, activating T cell despite antigenic specificity
- Toxic Shock Syndrome Toxin-1 causes massive increase in IL-1 and TNF-α

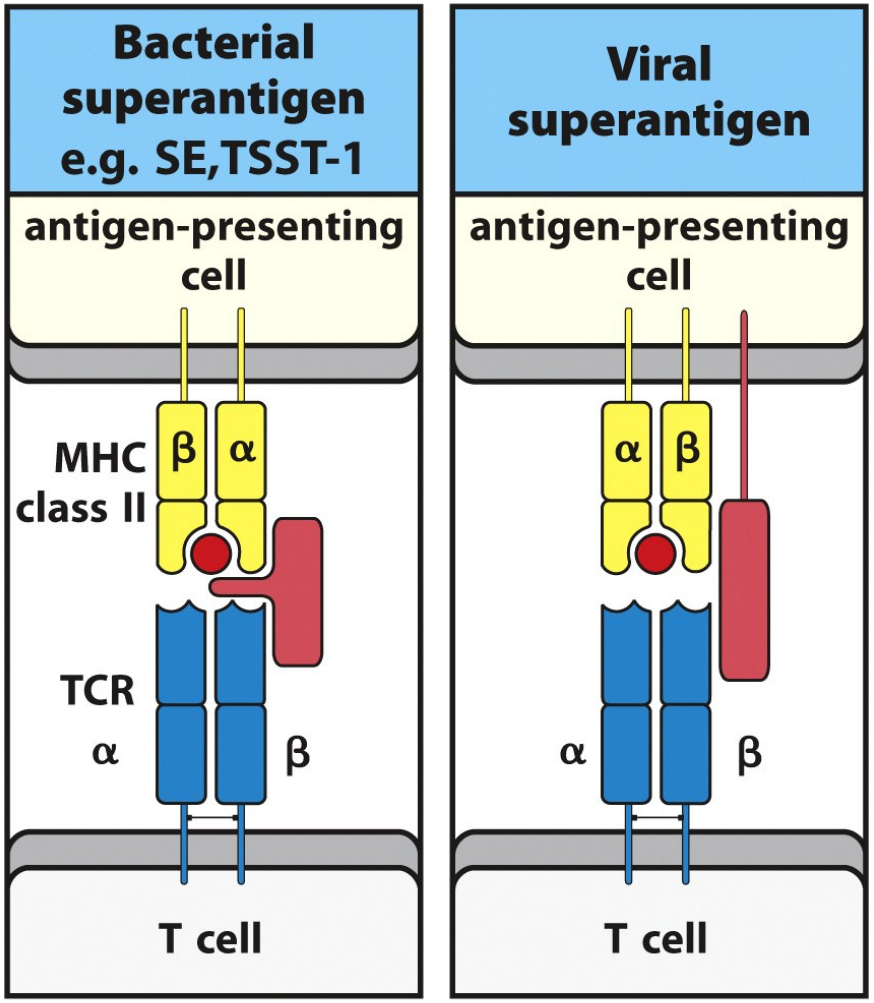
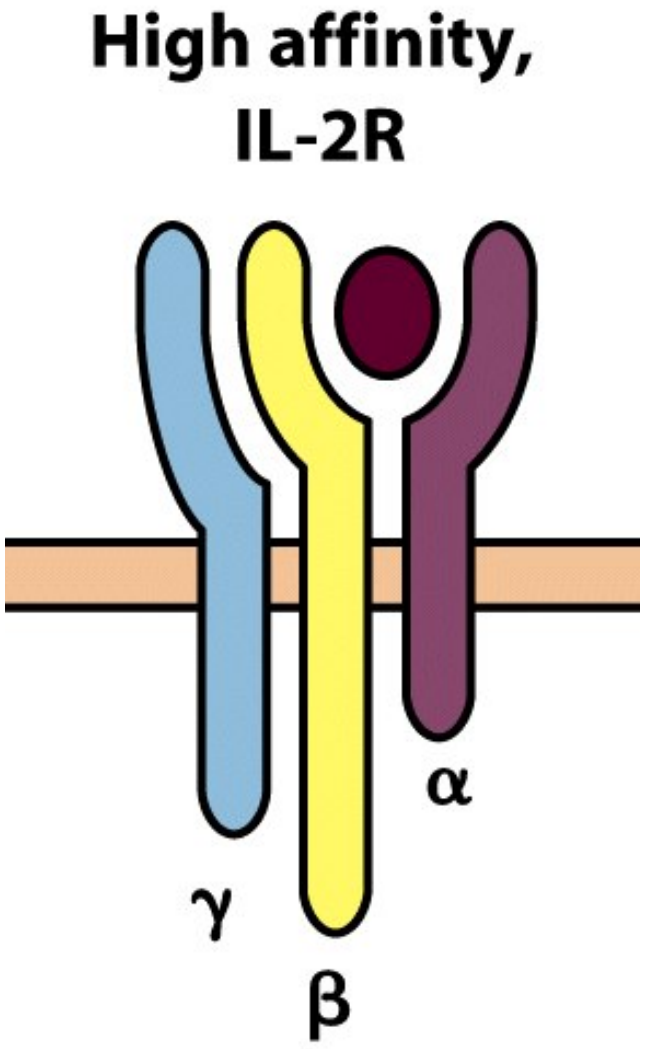


Figure 6.23 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Chagas's disease

- Caused by *Trypanosoma cruzi* and eventually leads in the chronic form to several types of cardiomyopathy

- Accompanied by severe immunosuppression due to reduction in CD25



CAPS

- Cryopyrin-associated periodic syndrome
- Combined inherited diseases causes over-production of IL-1β
- Shot intense inflammation, rashes, fever, eye redness, joint pain, deafness

Rheumatoid arthritis (RA)

- Synovial macrophages produces high levels of TNF-a and IL-2
- Stimulation of polymorphonuclear leukocytes
- Release of other cytokines and factors
- Bone degradation

Cytokine-based therapies

- Problems with cytokine-based therapy include:
- Effective dose levels
- Short half-life
- Potent biological response modifiers
- Can cause unpredictable side effects

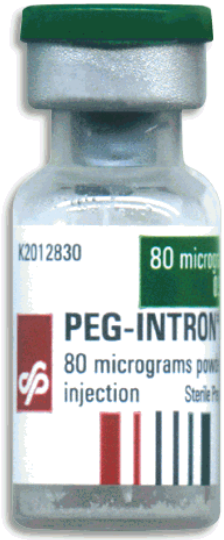
IL-11

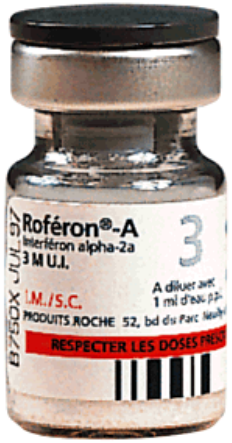
- IL-11 has many actions including proliferation and differentiation of platelet progenitors

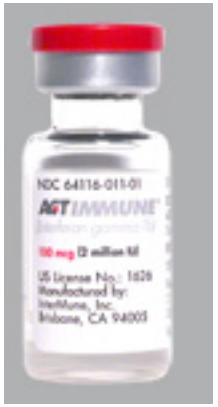
- Recombinant IL-11 (oprelvekin) is indicated to prevent severe thrombocytopenia following immunosuppressive therapy in patients with non-myeloid malignancies

IFN-α IFN-β and IFN-γ

- Used for treatment of several diseases ranging from viral infections such as hepatitis C to malignancies such as leukemias and lymphomas

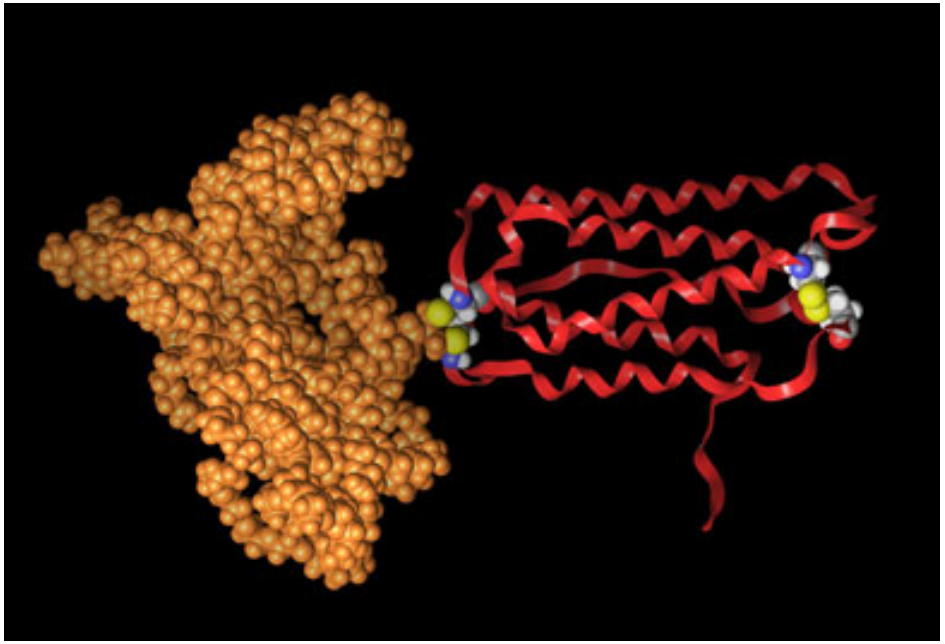




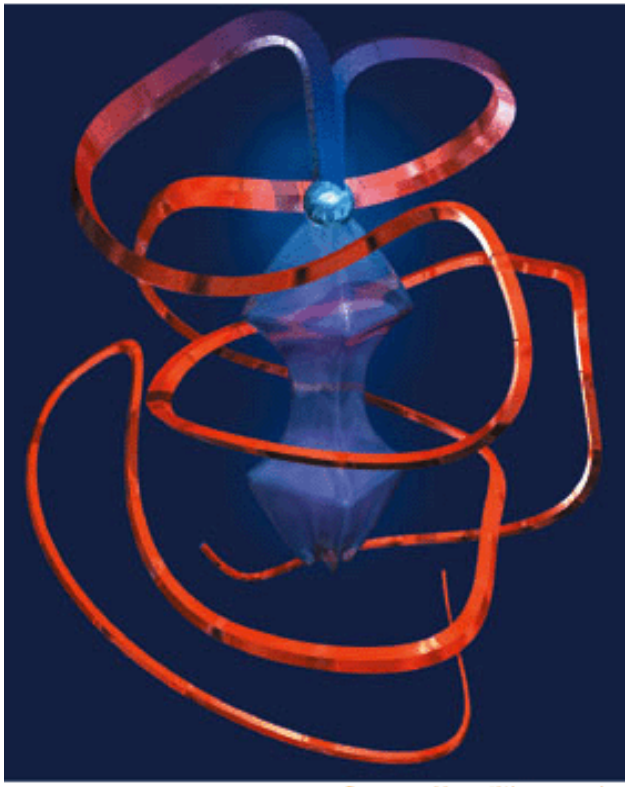


Peg-Intron

- Chemical attachment of polyethylene glycol (PEG) to IFN-α



Interferon alfa is surrounded by a PEG chain.



Source: Hepatitis-care.de

Cytokine-based therapies in clinical use

Agent	Nature of agent	Clinical application
Enbrel	Chimeric TNF-receptor/IgG constant region	Rheumatoid arthritis
Remicade or Humira	Monoclonal antibody against TNF-α receptor	Rheumatoid arthritis Crohn's disease
Roferon	Interferon α-2a*	Hepatitis B Hairy-cell leukemia Kaposi's sarcoma
Intron A	Interferon α-2b	Hepatitis C† Melanoma
Betaseron	Interferon β–1b	Multiple sclerosis
Avonex	Interferon β–1a	Multiple sclerosis
Actimmune	Interferon γ–1β	Chronic granulomatous disease (CGD) Osteopetrosis
Neupogen	G-CSF (hematopoietic cytokine)	Stimulates production of neutrophils Reduction of infection in cancer patients treated with chemotherapy, AIDS patients
Leukine	GM-CSF (hematopoietic cytokine)	Stimulates production of myeloid cells after bone marrow transplantation
Neumega or Neulasta	Interleukin-11 (IL-11), a hematopoietic cytokine	Stimulates production of platelets
Epogen	Erythopoietin (hematopoietic cytokine)	Stimulates red-blood-cell production

*Interferon α-2a is also licensed for veterinary use to combat feline leukemia.

†Normally used in combination with an antiviral drug (ribavirin) for hepatitis C treatment.

Unnumbered table pg 323

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- ✓ Understand the physiological role of IL-1, IL-2, TNF-α, IFN-α/β, and IFN-γ
- ✓ Describe three mechanisms to antagonize cytokines
- ✓ Realize the role of cytokines in disease
- ✓ Realize the role of cytokines in therapy