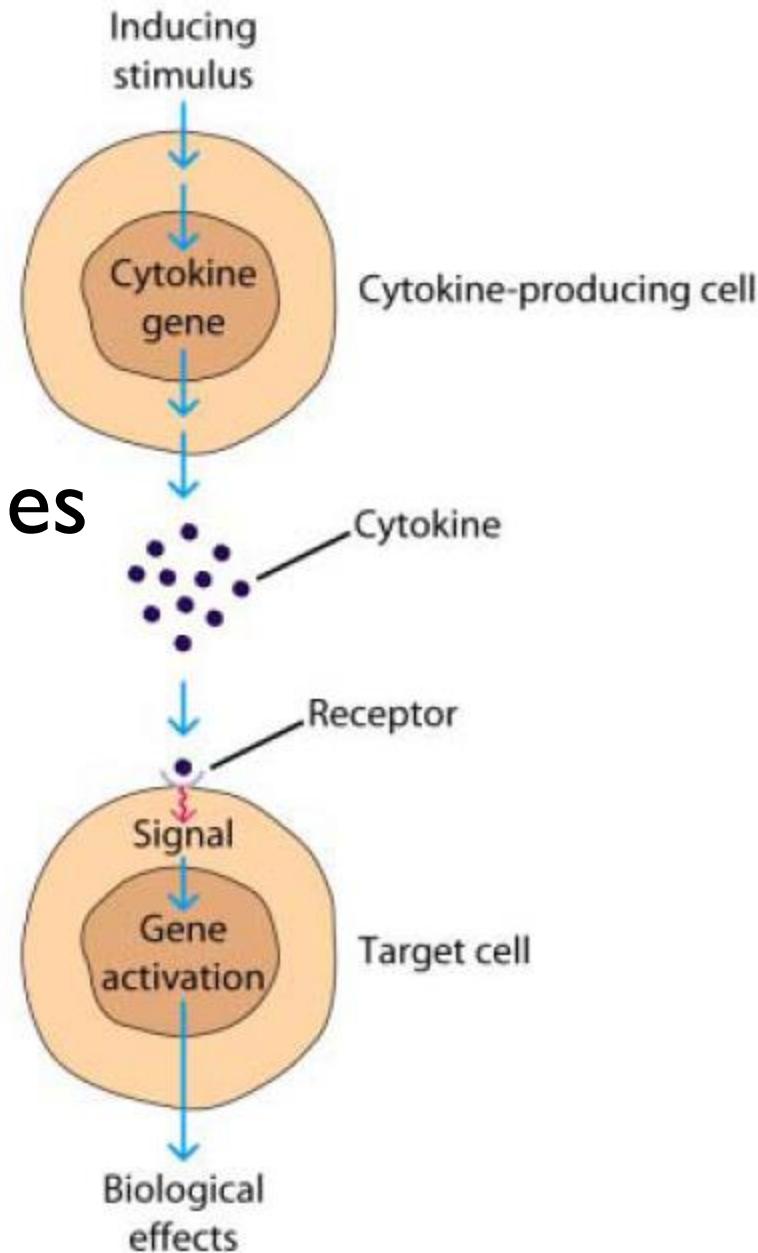




Cytokines

Contents

- Definition of cytokines
- Classification of cytokines
- Structure of cytokines
- Functions of cytokines



History

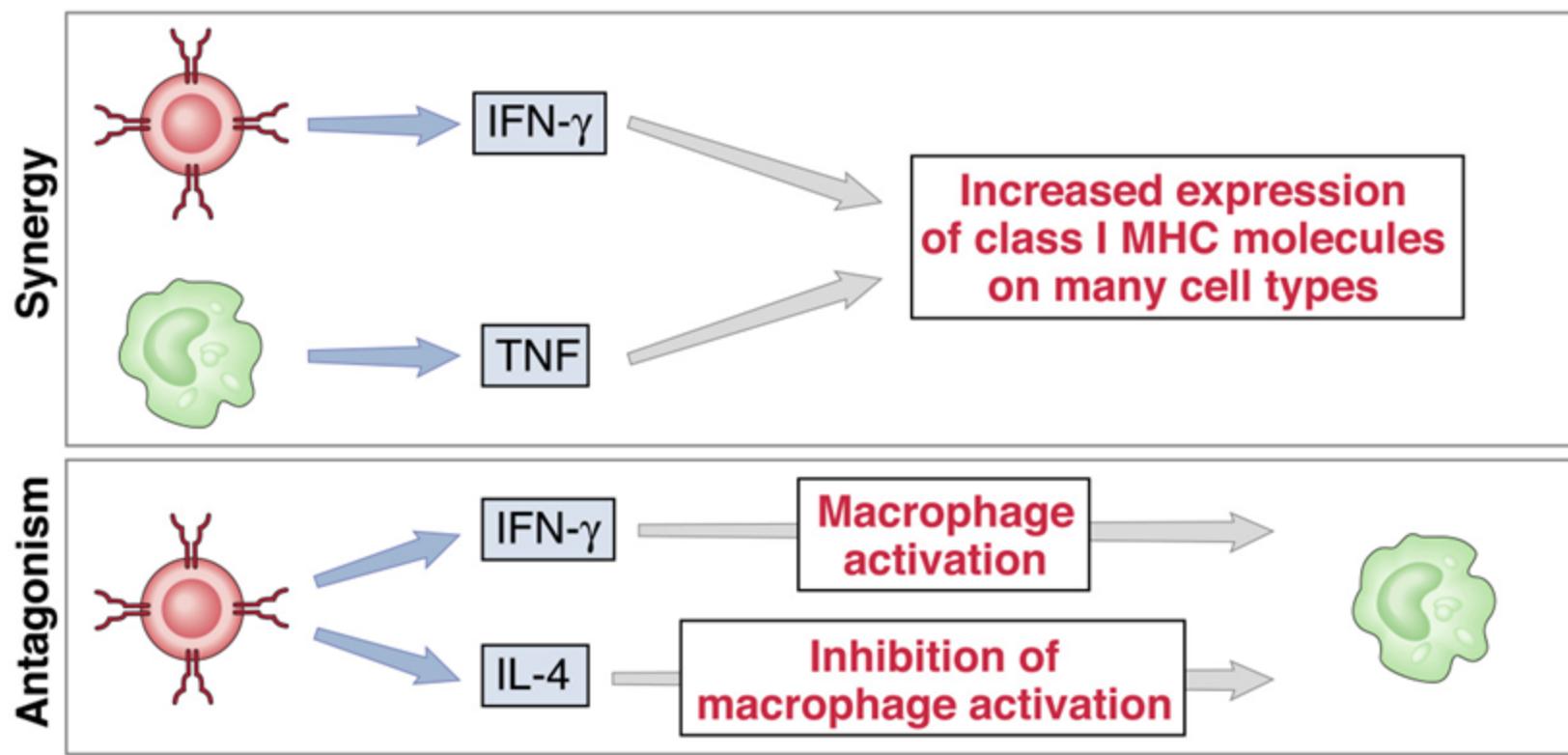
- The term cytokine was proposed by Cohen *et al* in 1974 to replace lymphokine, a term coined in the late 1960's to denote lymphocyte-derived soluble proteins that possess immunological effects.

- Cytokines (Greek *cyto-*, cell; and *-kinos*, movement) are small cell-signaling proteins, peptides, or glycoproteins molecules that are secreted by numerous types of cells especially by monocytes and lymphocytes.
- Low molecular weight (20- 30 KDa)
- Cytokines are chemical messengers; they are extremely potent and act at very low concentrations (10^{-10} - 10^{-12} M).
- They are very specific, and act through specific receptors of the target cell membrane.

Properties of cytokines

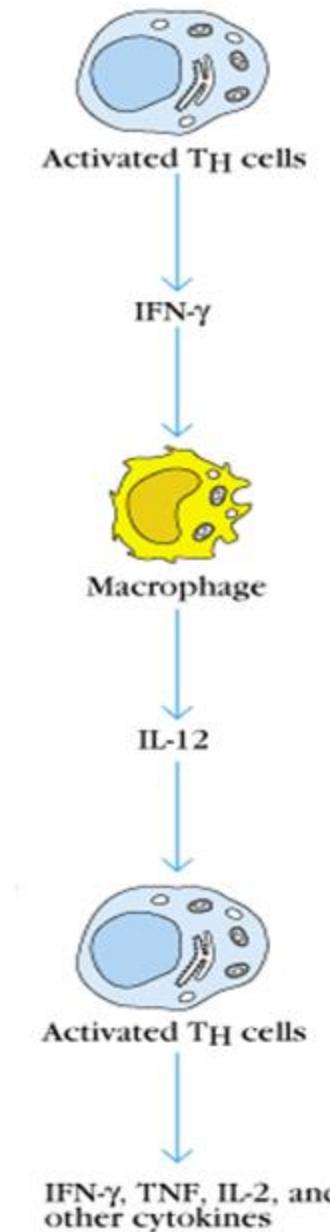
- Synergy
- Antagonism
- Pleiotropy
- Redundancy and
- Cascade Induction

Synergy and Antagonism



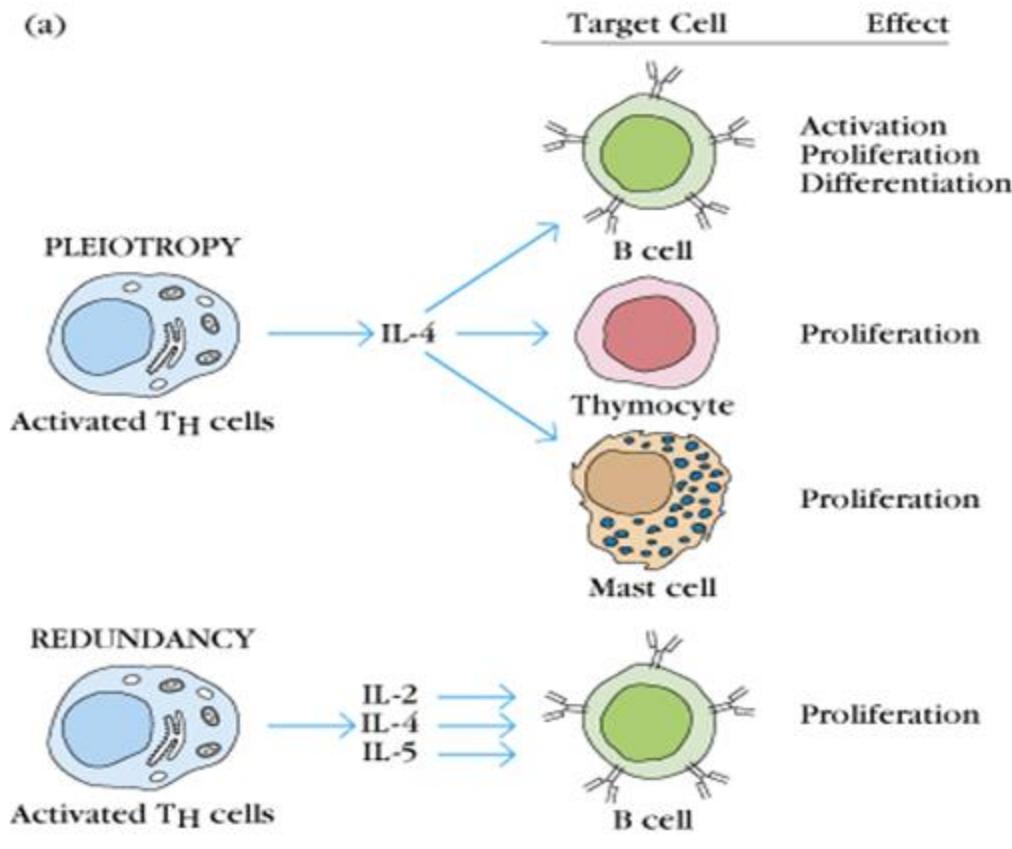
From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 11-2b

(b) CASCADE INDUCTION



- Pleiotropy
- Redundancy and
- Cascade Induction

(a)



Classification of cytokines

- General classification of cytokines
- Cytokines classified into various families
- Classification based on secretory cells
- Classification based on mode of action
- Classification based on cytokine receptors

General classification of cytokines

Table 1: Important classes of Cytokines

1. Growth Factors:

- a. Haemopoietic Growth Factors
 - Granulocyte – Colony Stimulating Factor (G-CSF)
 - Granulocyte Macrophage – Colony Stimulating Factor (GM-CSF)
 - Erythropoietin (EPO)
 - Thrombopoietin
 - Stem Cell Factor or c-kit ligand
- b. Epidermal Growth Factor
- c. Platelet Derived Growth Factor
- d. Transforming Growth Factor β
- e. Fibroblast Growth Factor
- f. Insulin like Growth Factor
- g. Nerve Growth Factor

2. Interleukins

IL – 1 to IL – 18

3. Interferons

IFN – α
IFN – β
IFN – γ

4. Miscellaneous

Tumour Necrosis Factor (TNF), etc.

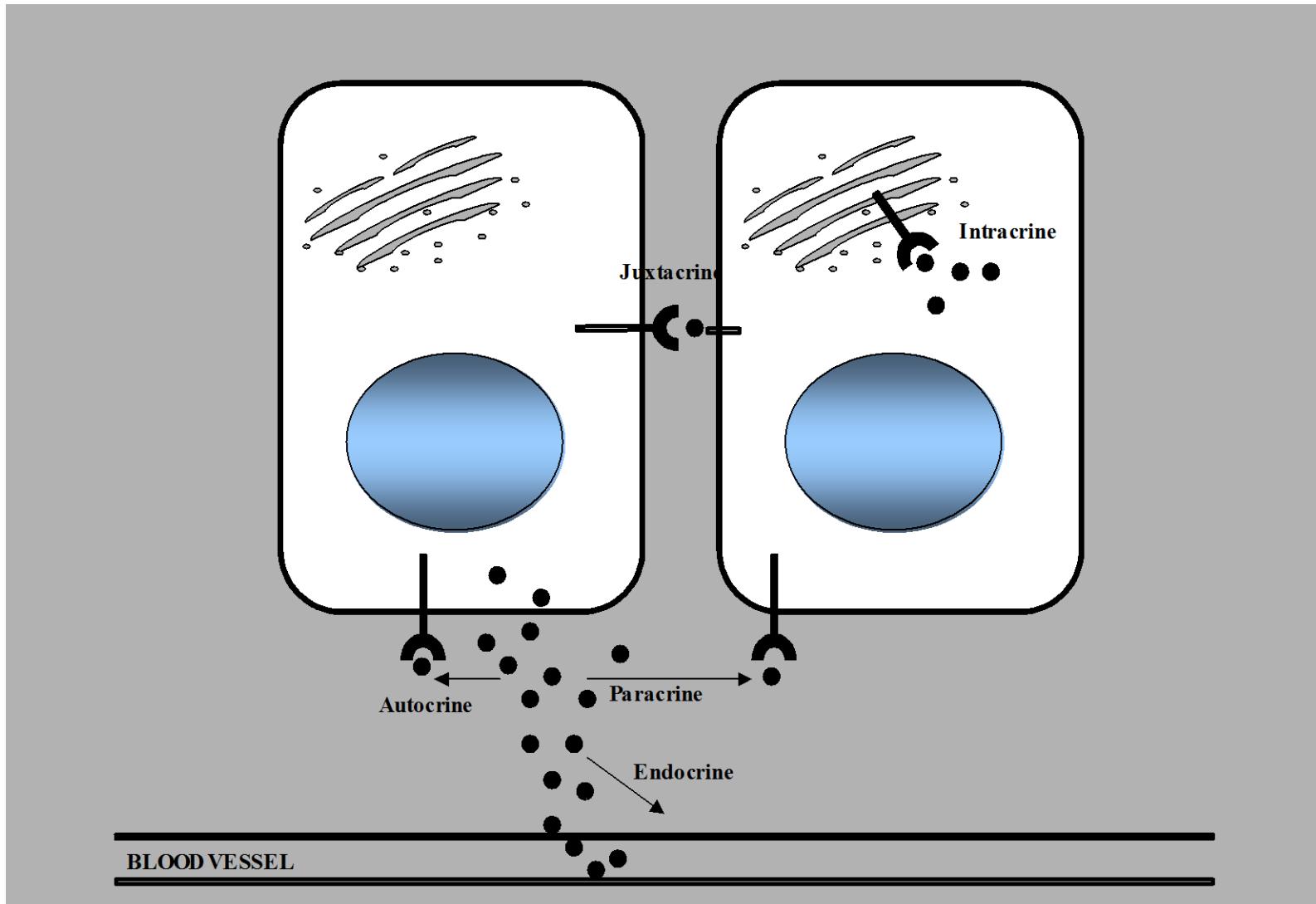
Cytokines classified into various families

- Hematopoietin family
- Interferon family
- Chemokine family
- Tumor necrosis factor (TNF) family

Classification based on secretory cells

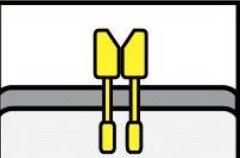
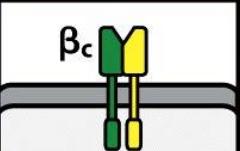
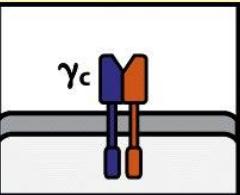
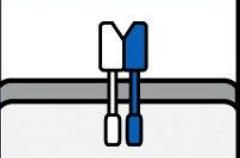
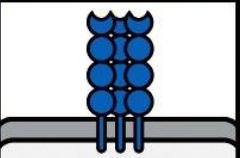
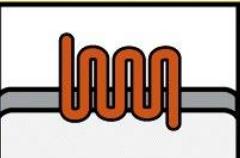
- **Lymphokines:** secreted by lymphocytes
- **Monokines:** secreted by monocytes and macrophages
- **Interleukins:** secreted by some leukocytes and act upon other leukocytes
- **Interferons:** natural killer (NK) and natural killer T (NKT) cells
- **Tumor necrosis factors:** macrophages, CD4+ lymphocytes and NK cells
- **Chemokines:** endothelial cells, myeloblasts, erythroblasts, and megakaryoblasts

Classification based on mode of action



Bafico & Aaronson, Cancer Med, 2002

Classification based on cytokine receptors

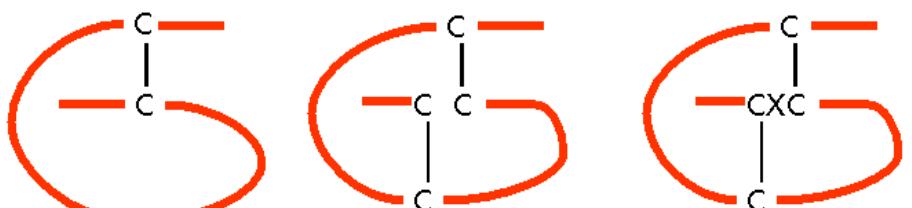
Homodimeric receptors		Receptors for erythropoietin and growth hormone
Heterodimeric receptors with a common chain		Receptors for IL-3, IL-5, GM-CSF, share a common chain, CD131 or β_c (common β chain)
		Receptors for IL-2, IL-4, IL-7, IL-9 and IL-15, share a common chain, CD132 or γ_c (common γ chain). IL-2 receptor also has a third chain, a high-affinity subunit IL-2R α (CD25)
Heterodimeric receptors (no common chain)		Receptors for IL-13, IFN- α , IFN- β , IFN- γ , IL-10
TNF-receptor family		Tumor necrosis factor (TNF) receptors I and II CD40, Fas (Apo1, CD95), CD30, CD27, nerve growth factor receptor
Chemokine - receptor family		CCR1–10, CXCR1–5, XCR1, CX3CR1

Chemokines

Produced by many cell types and binds to glycosaminoglycans (GAGs)

- induce directed chemotaxis of leukocytes
- regulate leukocyte migration in development, homeostasis and activation
- several groups with many members based on location of cystein residues near NH₂-terminus
- C, CC, CXC and CX₃C

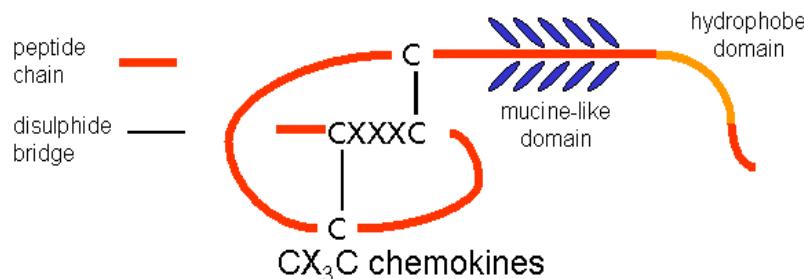
Structure of chemokine classes



C chemokines

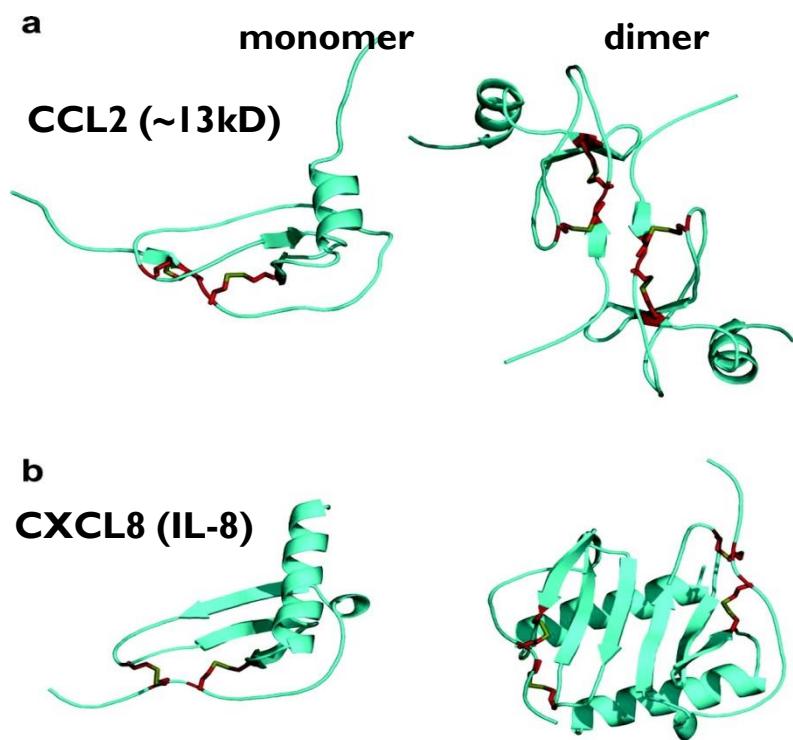
CC chemokines

CXC chemokines



© Kohidai, L.

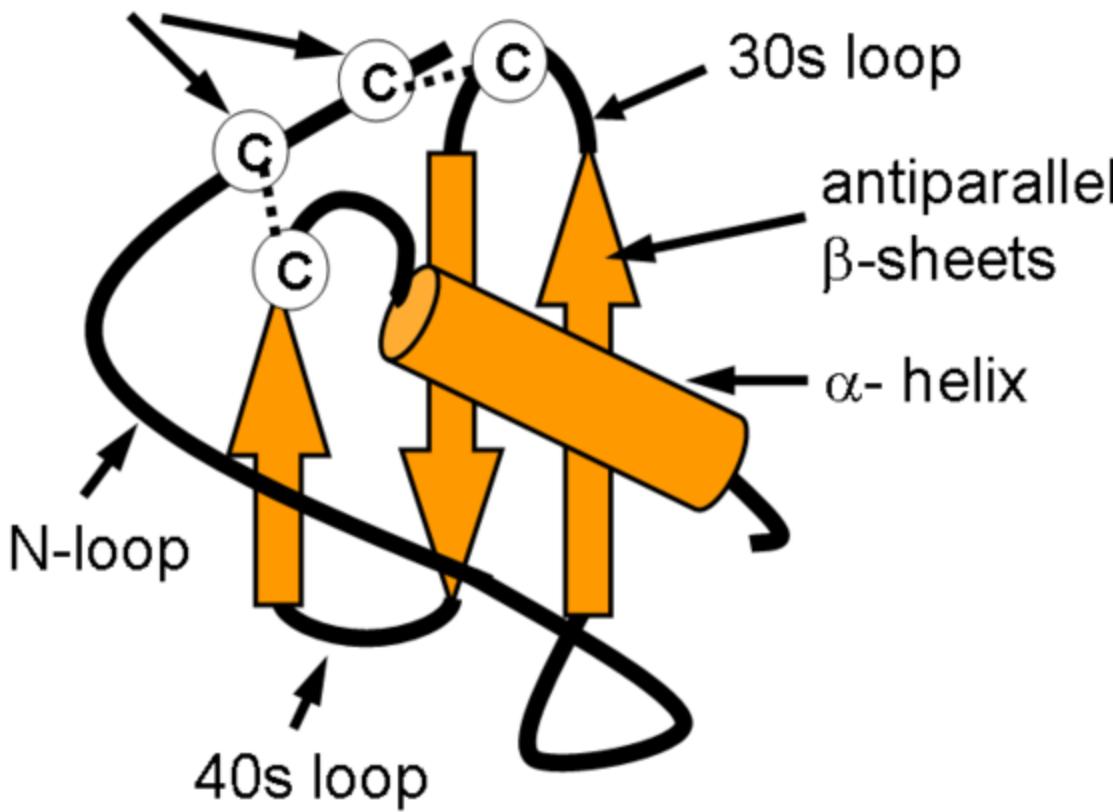
- Form dimers in solution, but interact with receptors as monomers



Allen SJ, et al. 2007.
Annu. Rev. Immunol. 25:787–820

Three dimensional structure of chemokines

disulphide bridges of Cys-Cys



© Kohidai, L.

Typical Greek key structure that is stabilized by disulfide bonds between conserved cysteine amino acid residues.

Interferons

Type-I Interferon (IFN-I)

- produced by many cell types: leukocytes, endothelia, fibroblasts, etc
- Induced by viral double stranded RNA: recognized by TLR3
- Induced by bacterial cell wall components by TLR4
- IFN- α : 14 subtypes
 - drug for hepatitis B and C virus and cancer (melanoma & leukemia)
- IFN- β : single gene product
 - drug for multiple Sclerosis – effective at an early stage
- induces production of IL-15
- plasmacytoid dendritic cells can make large amounts

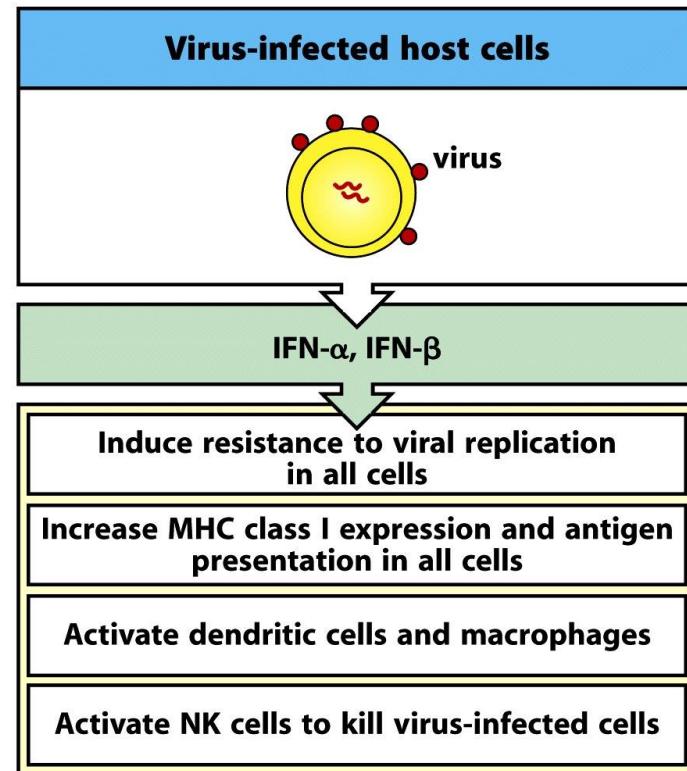
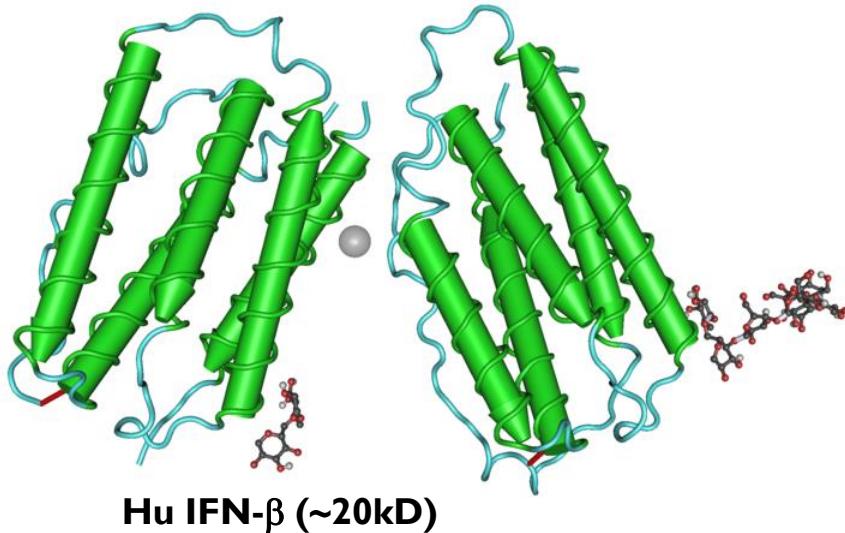
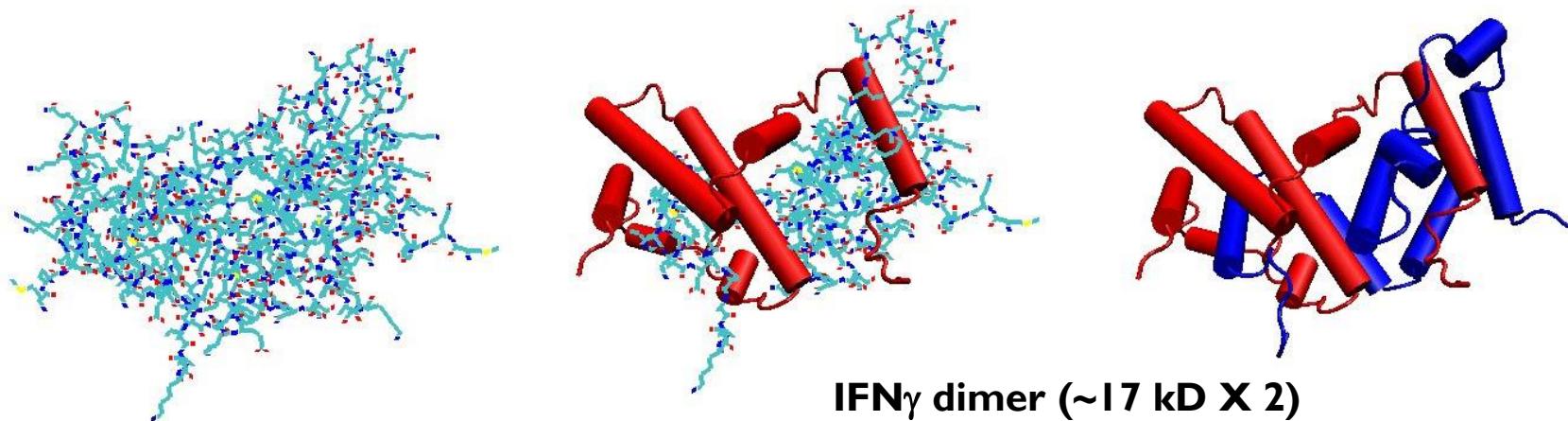


Figure 2-54 Immunobiology, 7ed. (© Garland Science 2008)

Gamma Interferons

Type-II Interferon (IFN-II, IFN- γ):

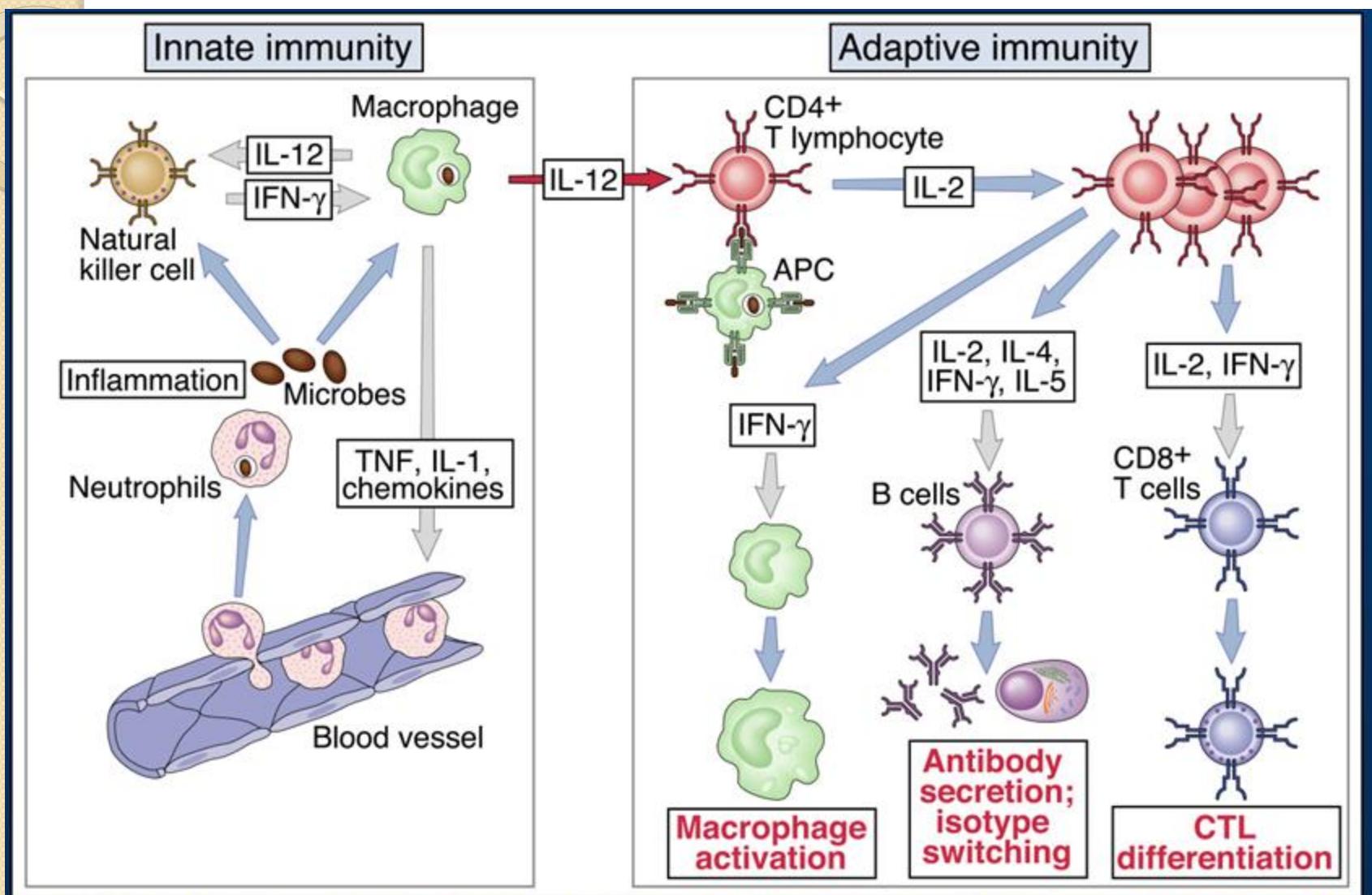
- Produced by NK, NKT, activated T cells and DC
- Increased Ag presentation and expression of MHC by Antigen presenting cells
- Promote leukocyte migration
- Induce NK cell activity
- Induces Th1 cell production and activity
- Suppresses Th2 cell production and activity



Tumor necrosis factor (TNF)

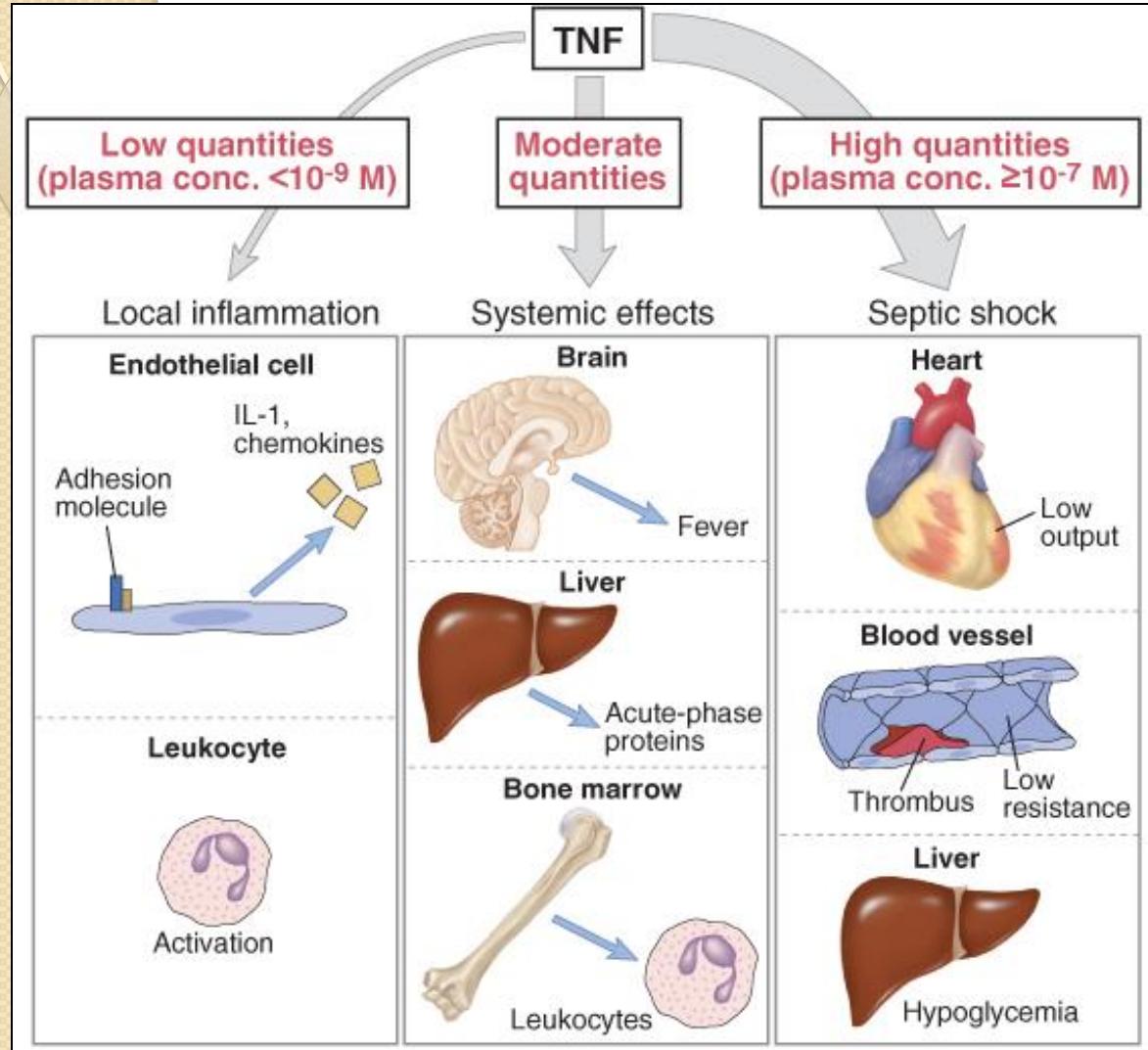
- It is produced by macrophages, lymphocytes, fibroblasts and keratinocytes.
- TNF- α , is the best-known member of this class.
- TNF- α is a monocyte-derived cytokine that has been implicated in tumor regression, septic shock, and cachexia.
- Other one is Lymphotoxin-alpha, formerly known as TNF- β , is a cytokine that is inhibited by interleukin 10.

Functions of cytokines



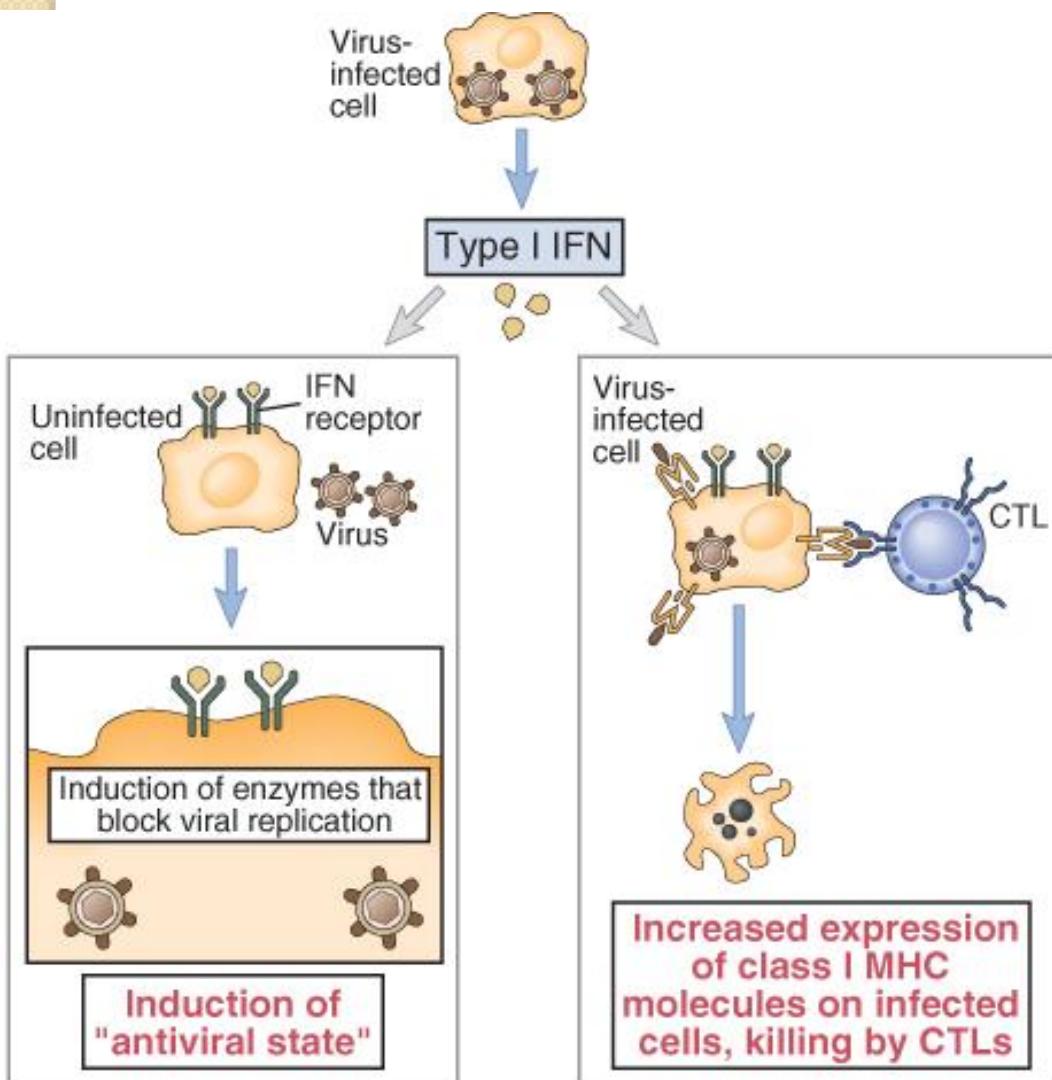
From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 11-1

Functions of Tumor Necrosis Factor (TNF)



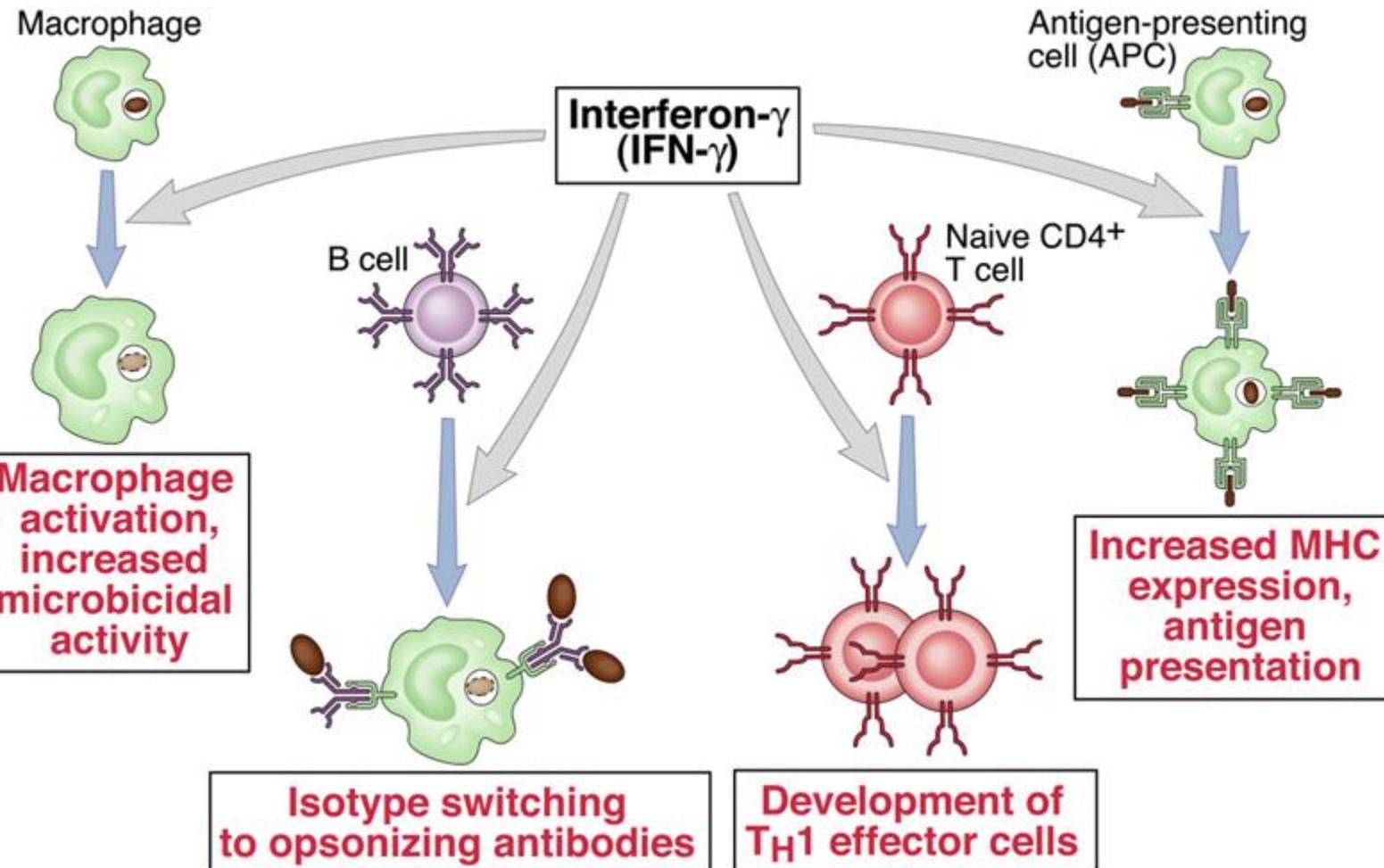
- The release of TNF- α by macrophages induces local protective effects, but TNF- α can have damaging effects when released systemically (septic shock).

Functions of interferons



- Antiviral effects of Type I Interferons (IFN-a/b)

Functions of interferon- γ



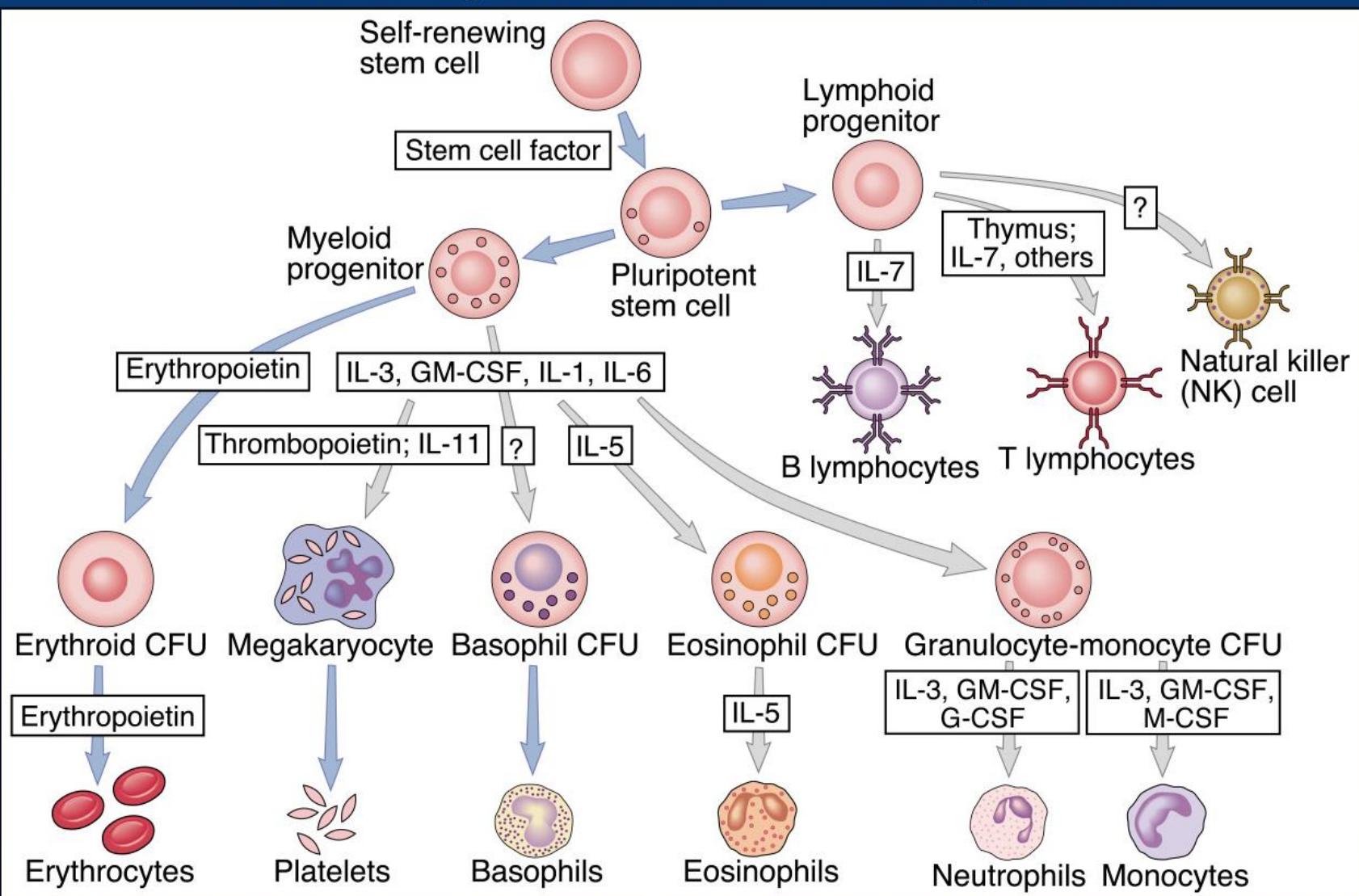
From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 11-14

Role of cytokines in regulating Ig isotype expression

Cytokines	IgM	IgG3	IgG1	IgG2b	IgG2a	IgE	IgA
IL-4	Inhibits	Inhibits	Induces		Inhibits	Induces	
IL-5							Augments production
IFN- γ	Inhibits	Induces	Inhibits		Induces	Inhibits	
TGF- β	Inhibits	Inhibits		Induces			Induces

Fig 9.7 © 2001 Garland Science

Roles of cytokines in hematopoiesis



Cytokines required for organization of lymphoid tissues

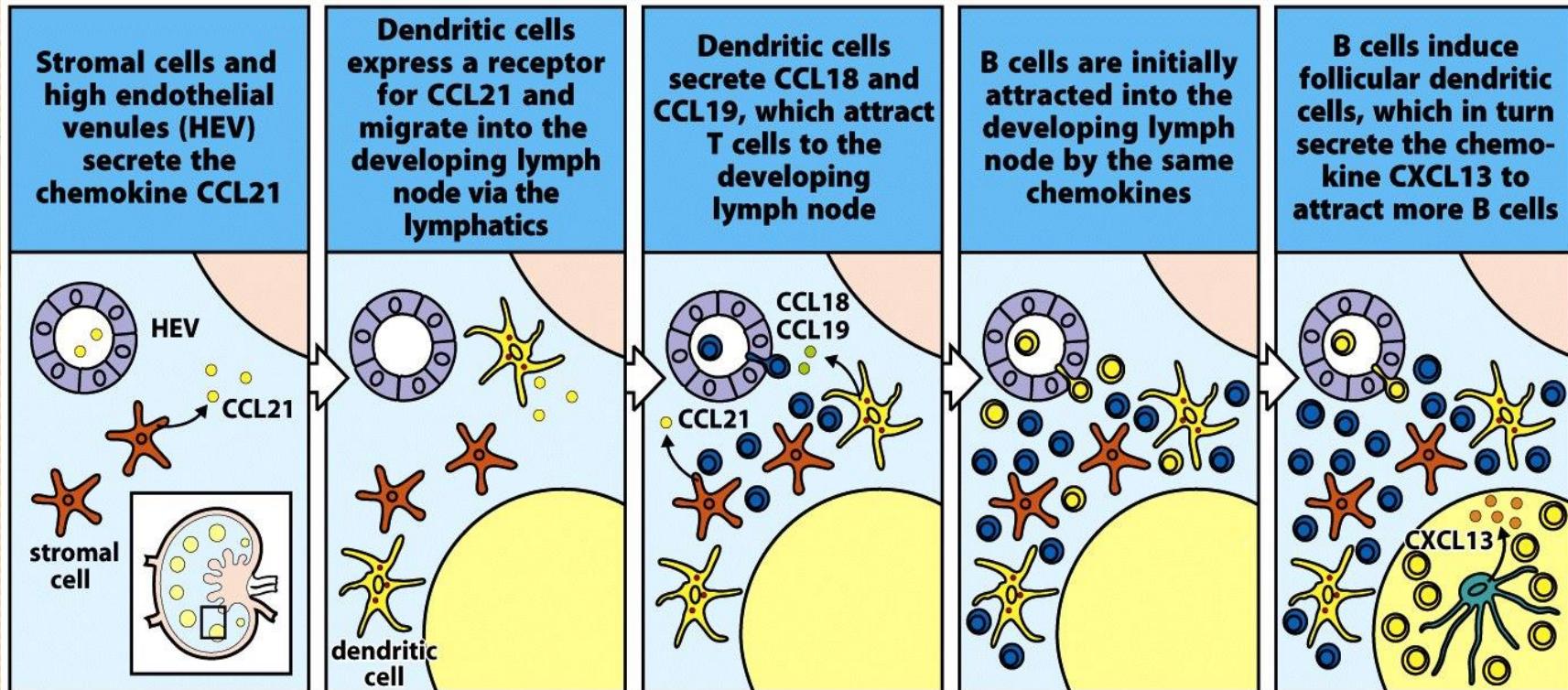


Figure 7-38 Immunobiology, 7ed. (© Garland Science 2008)

CCL21, CCL19

- produced by stromal cells, HEV and interdigitating DC
- recruits T cells and DC into LN and T cell areas (mutual reinforcement)
- recruits B cells into LN (B cells pass through T cell area to follicle)

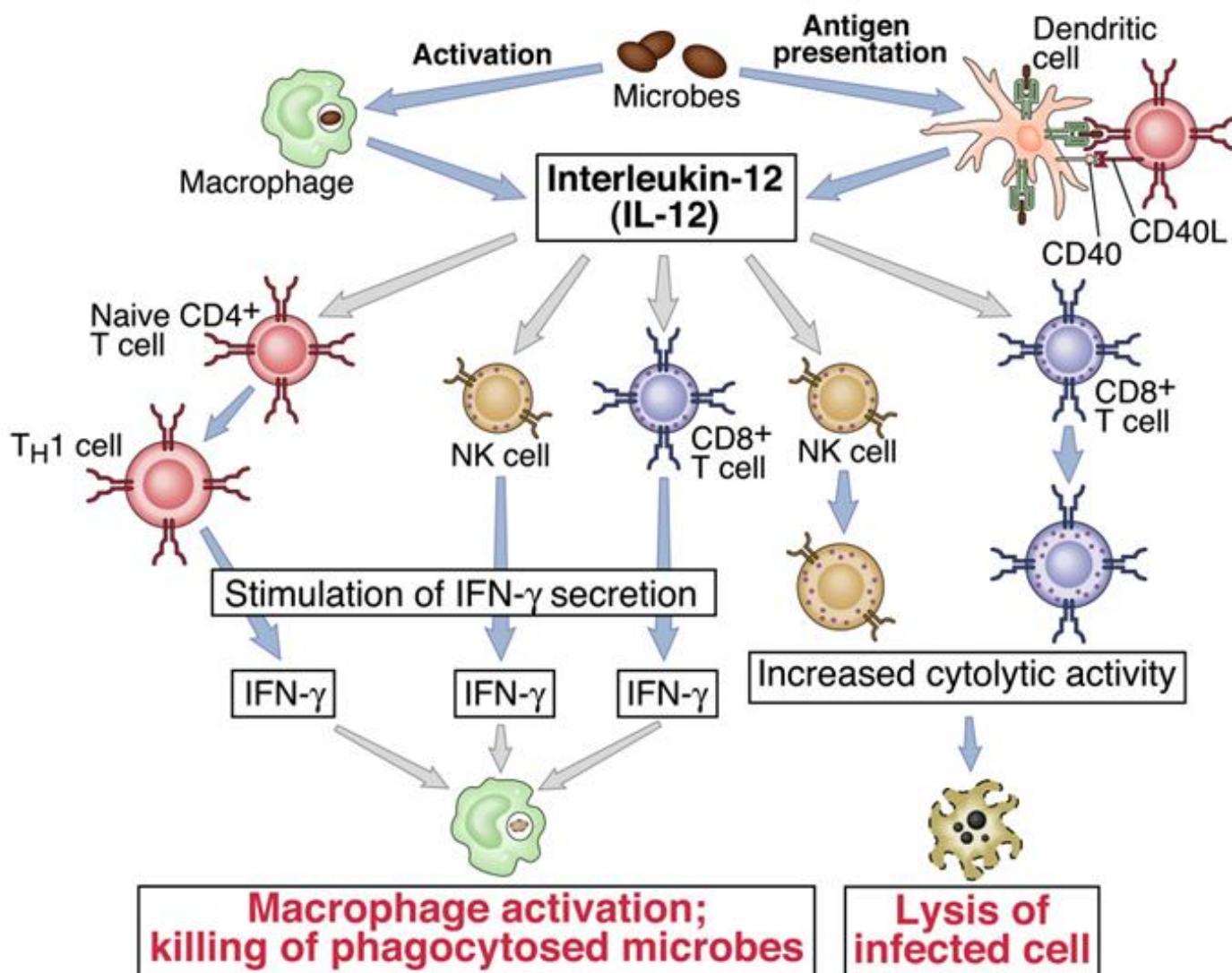
CXCL13

- produced by follicular dendritic cells
- recruits B and activated T cells (T_{FH}) into B cell follicles
- B cells in turn produce Lymphotoxin
- promotes development of follicular DC

CCL18

- produced by APC, including DC
- recruits B and T cells into LN

Functions of interleukin - 12



Cytokines have many other biological functions

TABLE 12-1 Functional groups of selected cytokines¹

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 _H 1 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 AIID; NK cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	T _H 2 cells; mast cells	Promotes T _H 2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T _H 2 cells	Eosinophil activation and generation
Interleukin 25 (IL-25)	Unknown	Induces secretion of T _H 2 cytokine profile
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 IgE; inhibits macrophages
Interferon γ (IFN- γ)	T _H 1 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.

Commercially available cytokines

Factor	Clinical uses	Dose	Side effects
(i) Recombinant -human Erythropoietin (Epoget; Procrit)	<ul style="list-style-type: none"> Anaemia of chronic renal disease (in predialysis, dialysis dependent and chronic anaemia patients) Treatment of anaemia in cancer patients on chemotherapy. Anaemia in adult cancer patients with platinum chemotherapy Autologous predonation blood collection Anaemia in HIV infection to permit use of AZT MDS Post autologous peripheral blood stem cell transplantation 	(i) 50 – 100 u/kg thrice weekly (ii) In MDS 150 – 300 ug per kilogram per day	Hypertension; Seizures; Iron Deficiency; Thrombosis
(ii) Recombinant human Dysuria; granulocyte colony- stimulating factor (G- CSF) (Filgastrim; grade children; Neupogen)	<ul style="list-style-type: none"> Chemo induced Neutropenia Optimization of chemotherapy Escalation of chemotherapy Peripheral progenitor cell mobilization Mobilization of donor's stem cells Congenital Neutropenia 	(i) 5 ug/kg.s.c/d until ANC \geq 1.0 X10 ⁹ /l (ii) For mobilization of peripheral blood stem cells: 4.0 ug/kg, S.C/day with apheresis collection after 5 th and 6 th daily dose	Musculoskeletal pains; Liver enzymes elevation; Transient Hypotension; Allergic type reactions; Splenomegaly; Sweet's Syndrome; Low fever; Osteopenia in Capillary leak syndrome
(iii) Recombinant – human macrophage colony- pain;Chills; stimulating factor (GM- CSF) (Sargramostim;Leucomex) leak;Thrombotic Hypotension;Conjuctivitis;	<ul style="list-style-type: none"> Acceleration of myeloid recovery in patients with Lymphoma who are undergoing autologous bone marrow transplantation 	250ug/s.c/day Or 5 ug/kg/d/s.c	Fever; Nausea; Fatigue; Headache; Bone Myalgias; Diarrhoea; Anorexia; Arthralgias; Skin rashes; Facial flushing; Capillary events;

v) Interferon - α	<ul style="list-style-type: none"> • Chronic Myeloid Leukaemia • Chronic Hepatitis C • Hairy Cell Leukaemia 	3 millions U thrice weekly S.C	Fever; Shivering; Myalgias; Flu – like features; Lethargy; Malaise; Anorexia; Alopacia;
Weight loss; Depression; Leucopenia;	<ul style="list-style-type: none"> • Kaposi Sarcoma • Cutaneous T cell Lymphoma • Low grade NHL • Multiple Myeloma 		Thrombocytopenia; Hyperthyroidism.
Pegylated IFN (Peg- Intron)		0.5 – 2.0 ug/kg body weight Once weekly; S.C	
(v) Thrombopoietin	<ul style="list-style-type: none"> • To treat thrombocytopenia due to myelosuppressive therapy • To increase platelet yield in plateletpheresis donors 	1 – 3 ug/kg body weight	
(vi) Interleukin 2 (Proleukin)	<ul style="list-style-type: none"> • Advanced renal cell carcinoma 		
(vii) Recombinant Interleukin -11 (Neumega)	<ul style="list-style-type: none"> • Treatment of severe thrombocytopenia due to myelosuppressive therapy in patients with non-myeloid malignancies 		
(viii) IL- 3 reaction;fever;	<ul style="list-style-type: none"> • Chemotherapy induced myelosuppression 	,5,10 or 15ug/kg s.c or continuous i.v infusion	Injection site headache;rash;flu- like symptoms; facial flushing.

In conclusion cytokines works for

