IN THE NAME OF GOD

IMMUNOPHARMACOLOGY

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TYPE OF DRUGS

- IMMUNOSUPPRESSORS
- IMMUNOSTIMULANTS
- IMMUNOMODULATORS

DEFINITION & CLINICAL USES

immunosuppressive agents are drugs that inhibit or prevent activity of the immune system.

They are used in immunosuppressive therapy to:
1- Prevent the rejection of transplanted organs and tissues (e.g., bone marrow, heart, kidney, liver).

2- Treat autoimmune diseases or diseases that are most likely of autoimmune origin (e.g., rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus.

3- Treat some other non-autoimmune inflammatory diseases (e.g., long term allergic, asthma control).

GENERAL PRINCIPLES OF IMMUNOSUPPRESSION

- Suppression is more likely achieved if therapy begins before exposure to the immunogen
- Primary immune responses are more easily suppressed than secondary (memory)
- Different immunosuppressants have different effects on different immune reactions

IDEAL IMMUNOSUPPRESSANT

- Strongly Immunosuppressive
- Specific, No Overall Immunosuppression
- Anti-infection ability
- Low Toxicity for Vital Organs
- Low cost
- Long *in vivo* bioactivity
- Easy to use

CLASSIFICATION OF IMMUNOSUPPRESSANT (BASED ON MECHANISM OF ACTION)

- A) Antiprolifirative Agents
  - 1) Drugs Acting on Immunophilins:
    - a) Selective Inhibitors of Cytokine production) (Calcineurin Inhibitors) (e.g: Cyclosporine; Tacrolimus)
    - b) Inhibitor of cytokine function :e.g. Sirolimus; Everolimus). Proliferation Signal Inhibitors (MTOR Inhibitors)
  - 2) Antimetabolites (Azathioprine; Leflunomide ; Methotrexate; Mycophenolate Mofetil)
  - 3) Alkylating Agents (Cyclophosphamide)

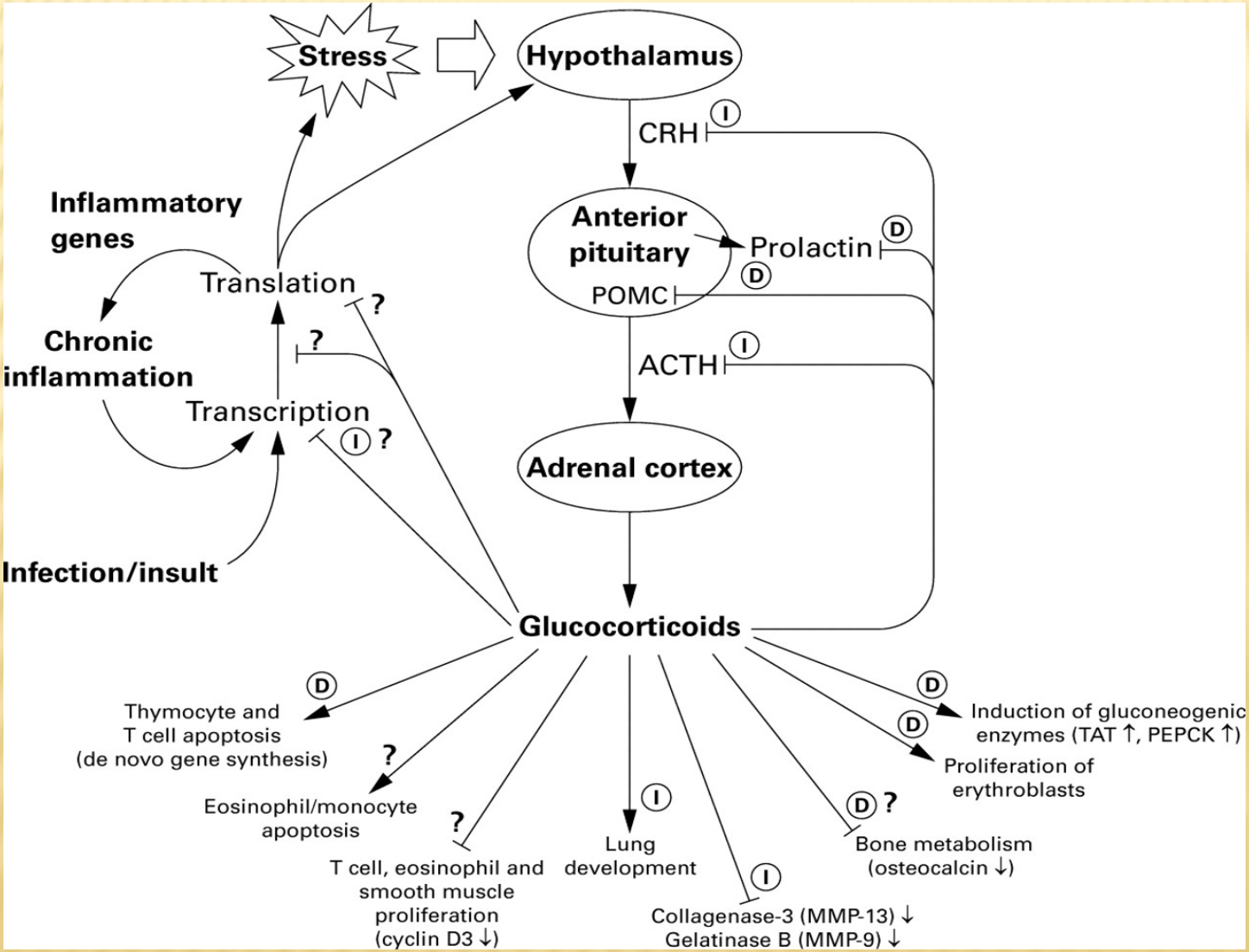
B) Lymphocyte Depletion Agents

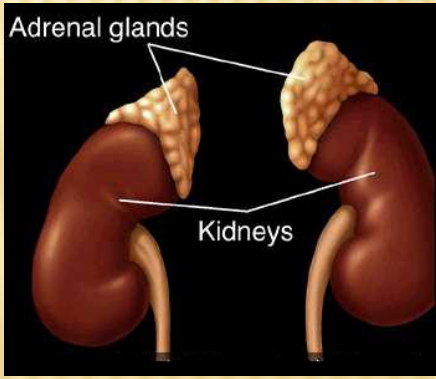
1) Corticosteroids
2) Immunosuppressive Antibodies

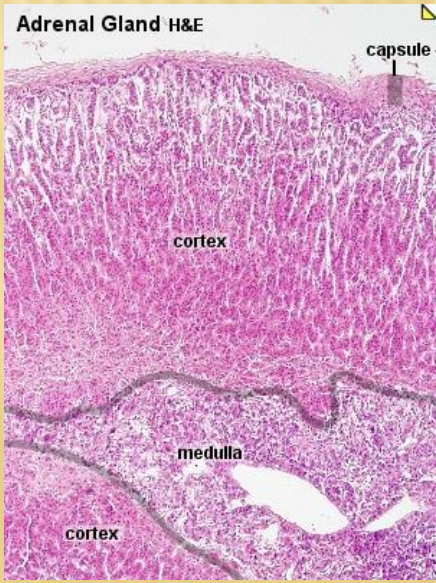
a) Polyclonal Antibodies
b) Monoclonal Antibodies (Selective inhibitors of IL2 :Basiliximab; Daclizumab)

CORTICOSTEROIDS

Biology of Glucocorticoids







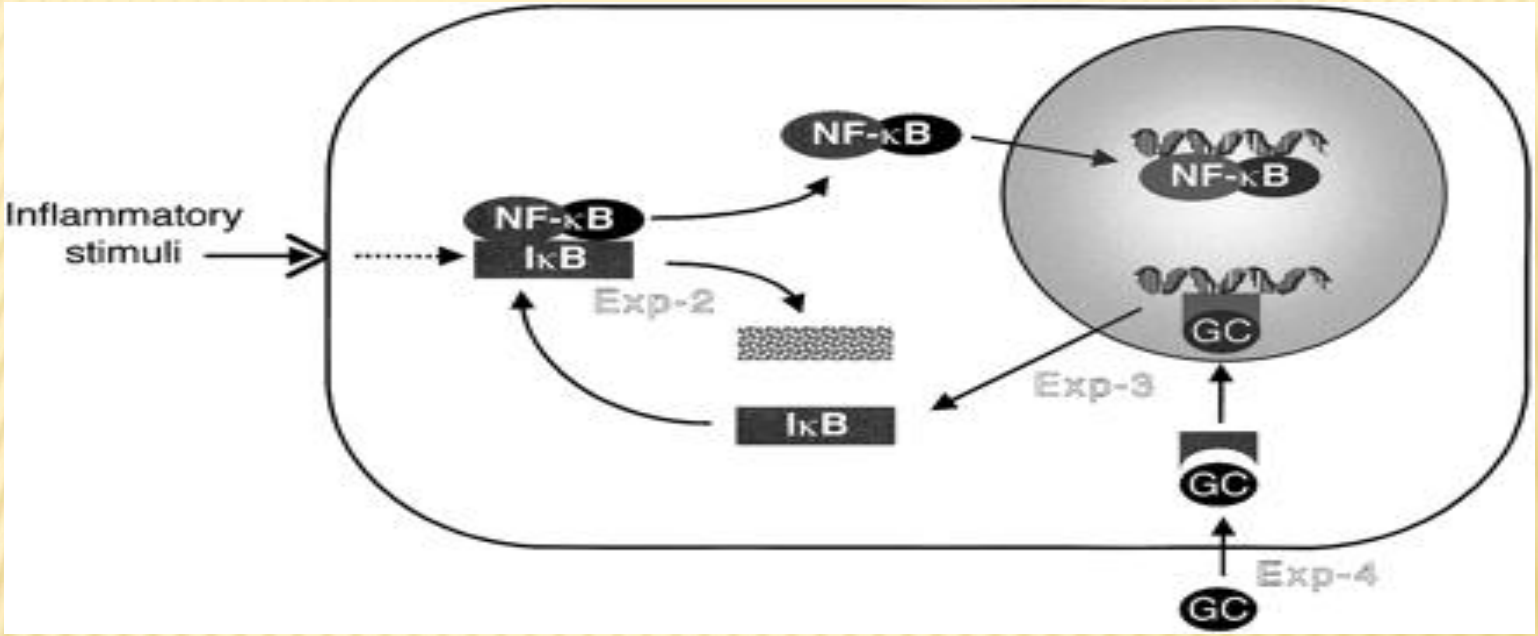
Newton. *Thorax* 2000;**55**:603-613

CORTICOSTEROID ADVERSE REACTIONS

- Indications:
- Prednisone,Methylprednisolone, Beta&Dexamethasone,Hydrocortisone
  - Autoimmune disorders : autoimmune hemolytic anemia, Inflammatory Bowel Dse, Hashimoto's..
  - Modulate allergic reactions, asthma.
  - Organ transplantation

- All commonly occur because high doses used for immunosuppression
- Suppression of Hypothalmic-pituhyitary adrenal axis (HPA) function , Osteoporosis, Hyperglycemia(Diabetes), GI bleeding, poor wound healing , proximal muscle wasting, Cataracts
- HyperlipidemiaWeight gain
- Predisposition to infection(decr. PMN, T cell activity)

MECHANISM OF GC:



Key aspects of intracellular signaling via the NF-κB pathway. Binding of various inflammatory mediators to plasma membrane receptors triggers a cascade of phosphorylation events, ultimately causing dissociation and breakdown of IκB. NF-κB is then free to enter the nucleus and activate transcription of several inflammatory cytokines. Glucocorticoids (GC) enter the cell and bind to cytosolic receptors; the complex moves into the nucleus and increases expression of IκB

CORTICOSTEROIDS

- MOA:
  - Decreased release of kinins and proinflammatory eicosanoids (prostaglandins and leukotrienes)
  - Inhibition of IL-1 and TNF gene expression and synthesis
  - decreased activation of T lymphocytes by inhibition of IL-1 synthesis by macrophages
  - Decreased neutrophil functions esp chemotaxis
  - Inhibit production of inflammatory mediators
  - inhibit T-cell proliferation & T-cell dependent immunity
  - Decreased antibody production (high doses)
- Reduced immune cell content of lymph nodes, spleen and blood (Lympholytic properties), ↑ fractional catabolic rate of IgG

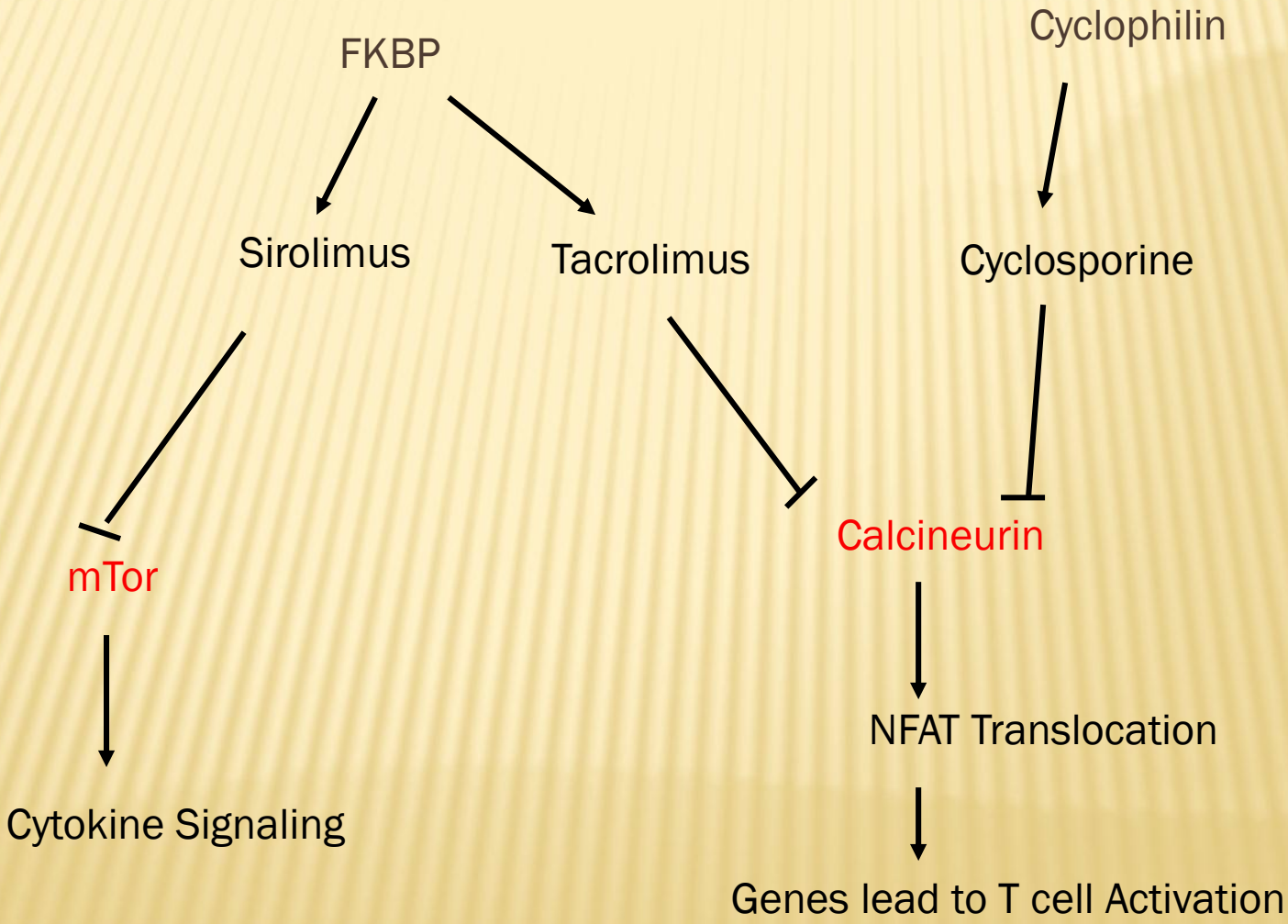
SELECTIVE INHIBITORS OF CYTOKINE PRODUCTION & FUNCTION

DRUGS ACTING ON IMMUNOPHILINS

T-CELL ACTIVATION BLOCKERS:

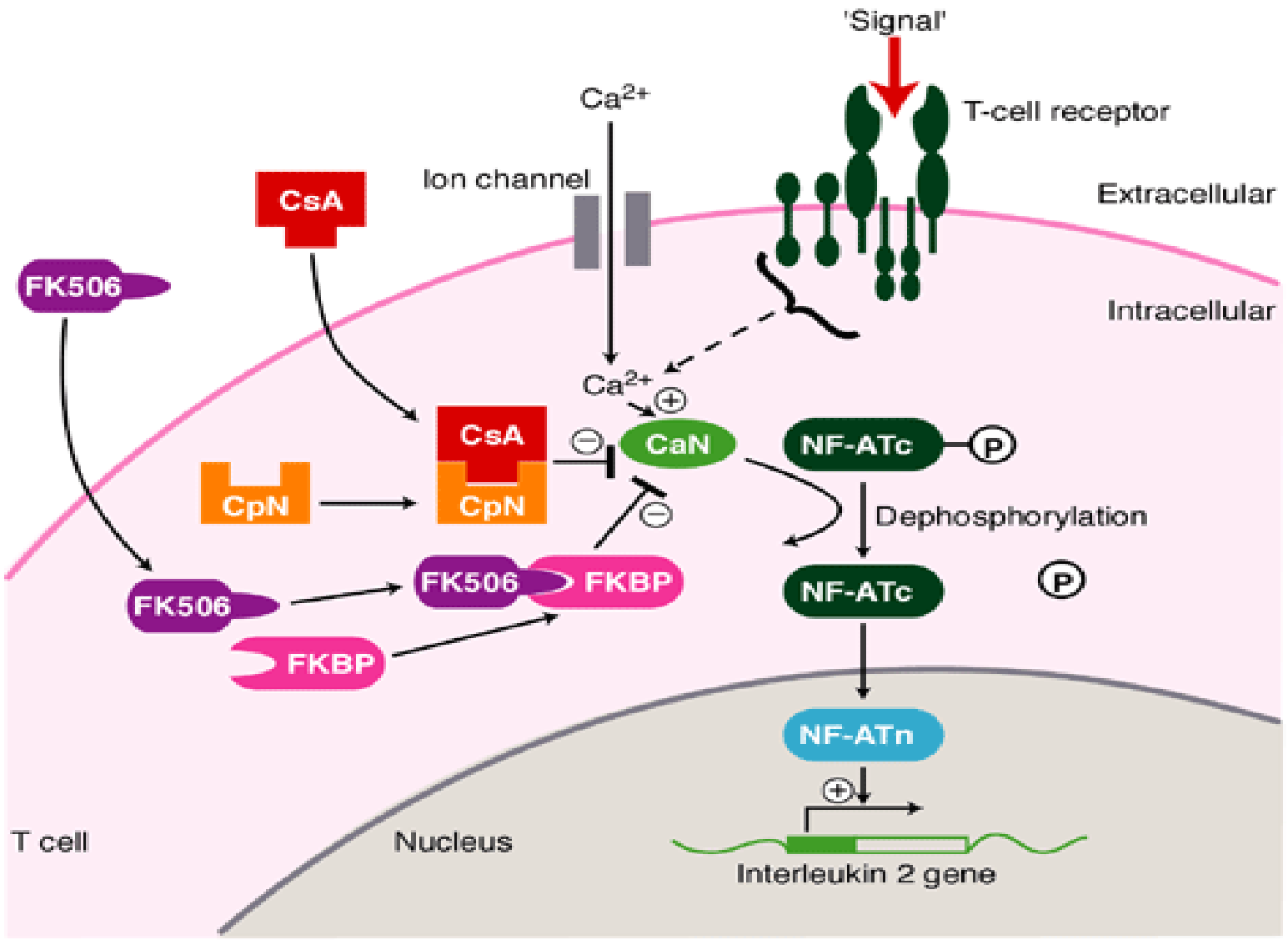
- CYCLOSPORINE (IMINORAL)
- TACROLIMUS (FK506, PROGRAF)
- SIROLIMUS (RAPAMYCIN)

Targets of Immunosuppressants



CYCLOSPORIN

- Structure
  - lipophilic cyclic peptide(Fat-soluble peptide antibiotic).
- Mechanism
  - cyclosporin + cyclophilin → complex → calcineurin↓→ dephosphorylation of nuclear factors of activated T cells↓ → gene transcription↓ → IL-2,3,4↓, TNF-α↓, IFN-γ↓
  - cyclosporin → TGF-β↑ → proliferation of T cells induced by IL-2 ↓, cytotoxic T cells↓



Mechanism of action of cyclosporine or tacrolimus (FK506)

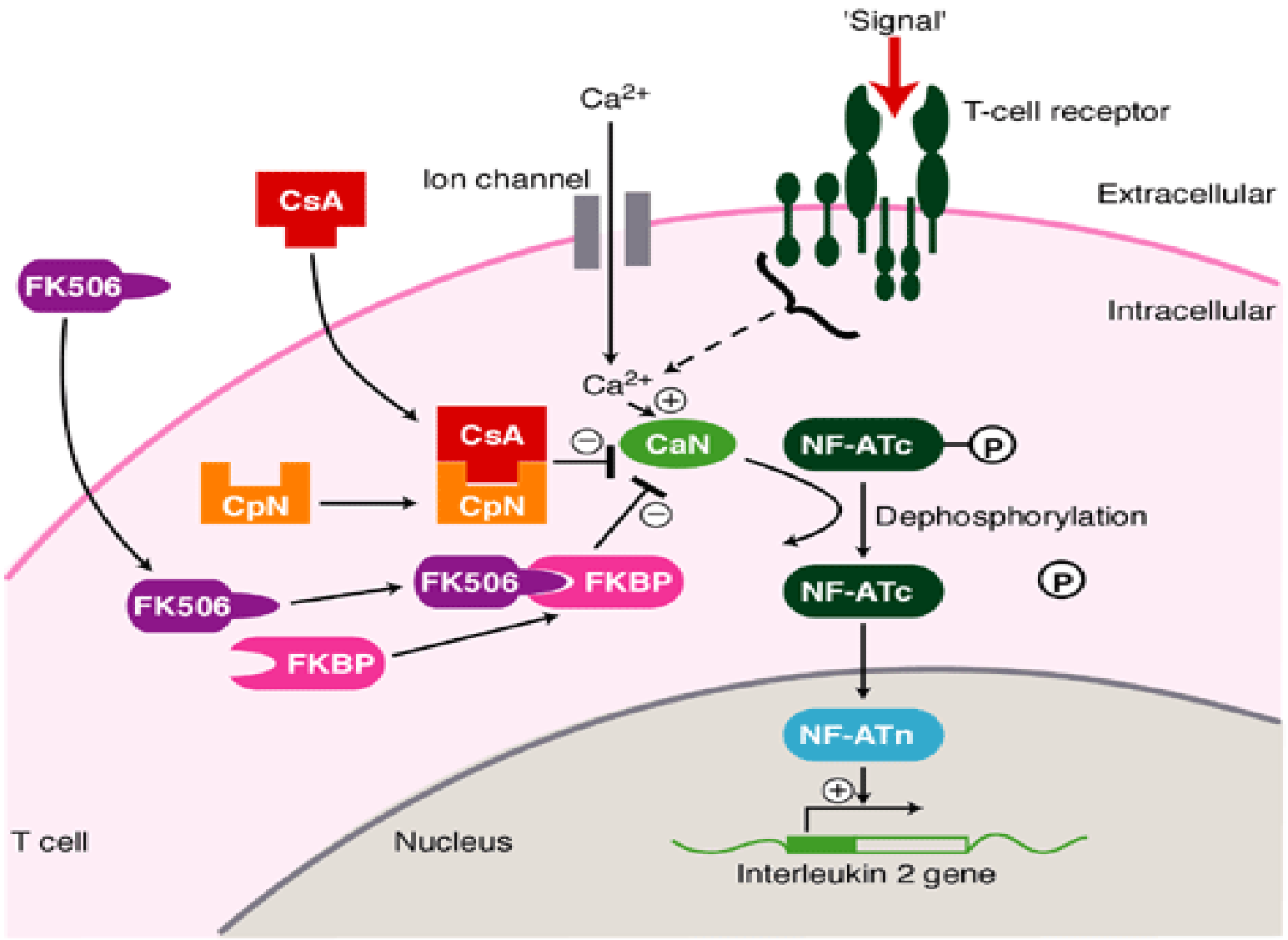
Cyclosporin

- Pharmacokinetics
  - Slowly and incompletely absorbed after oral administration.
  - Almost totally metabolized and excreted in the bile
  - used alone or in combination with prednisone and azathioprine (or other antineoplastic drugs)
- Indications:
  - transplant rejection (kidney, liver, pancreas, cardiac)
  - Autoimmune disorders (uveitis,SLE)
- Adverse Effects
  - nephrotoxicity, hepatotoxicity, hirsutism, neurotoxicity, hyperlipidemia
  - Drug interactions due to induction and inhibition of hepatic cytochrome P450- secondary infection: viral infection- Lymphoma and other cancers (Kaposi's sarcoma, skin cancer), hyperglycemia, osteoporosis,

TACROLIMUS

- Structure
  - macrolide antibiotic produced by *streptomyces tsukubaensis* (structure like erythromycin)
- Mechanism
  - It is not chemically related to cyclosporine, but their machanisms of action are similar, both bind to cytoplasmic peptidyl proly isomerases but tacrolimus binds to different protein (FK-binding protein) that inhibits calcineurin (a phosphatase enzyme involved in gene transcription of IL-2, gamma interferon and other cytokines).

    - 10-100 times more potent than cyclosporine



Mechanism of action of cyclosporine or tacrolimus (FK506)

TACROLIMUS

- Bioavailability
  - given by IV infusion or orally.
  - used concomitantly with corticosteroids.

- FK506 (Tacrolimus) is approved for prevention of solid-organ allograft rejection(For liver, kidney, heart, pancreas, and bone marrow transplant applications) and eczema (topical)
  - Treatment begins prior to surgery, and is maintained well afterwards
- Adverse Effects
  - nephrotoxicity, increased risk of lymphomas, hypersensitivity, hyperglycemia, hypertension, neurotoxicity (tremor, headache, motor disturbances, seizures)- gastrointestinal dysfunction.

SIROLIMUS

- Structure
  - Macrolide derived from fungus *Streptomyces hygroscopicus*
  - Structurally similar with FK binding (like tacrolimus)

Indications:

used for prophylaxis of organ transplant rejection(Kidney & heart) in combination with a calcineurin inhibitor and glucocorticoids

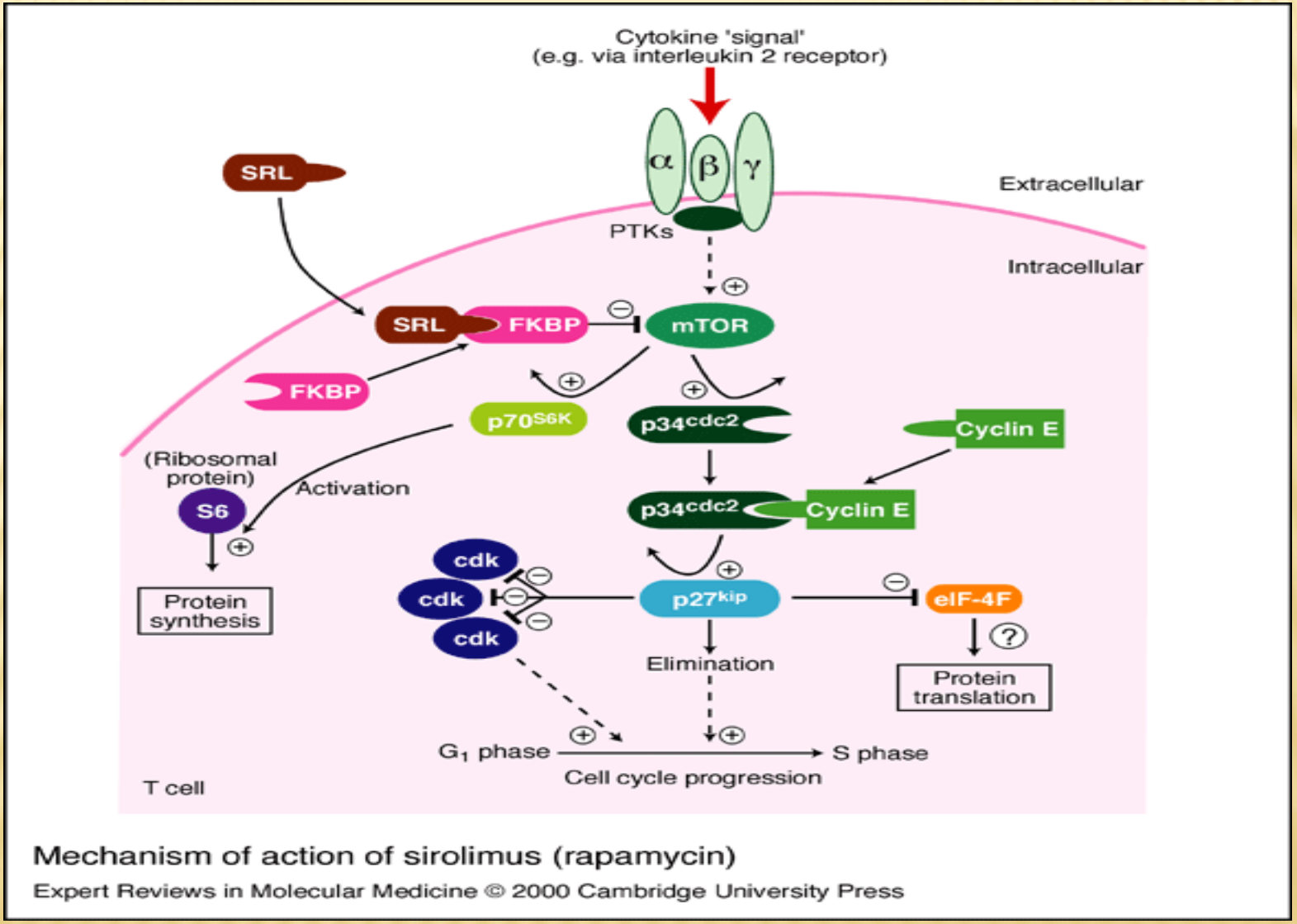
Bioavailability

- hepatic metabolism by CYP4503A4 (drug interactions may occur)
- long half-life (60 hours).
- impaired renal function when combined with cyclosporine.

SIROLIMUS

- mTOR initiates cascade of events (including cyclin dependent kinases) that promote T lymphocyte proliferation and differentiation
- **other theoretical actions include:**
  - Potent inhibitor of B-cell proliferation & Ig production (humoral immunity)
  - inhibition of antibody-dependent cellular toxicity
  - inhibition of lymphocyte activated killer cells(LAK)
  - inhibition of natural killer cells(NK)
  - inhibition of immune and nonimmune cell proliferation (via inhibition of growth factor signaling) (may explain antitumor actions)
  - Mesenchymal cell proliferation(Vascular smooth muscle cells, Endothelial cells & Fibroblasts).

Target of Rapamycin



Mechanism of action of sirolimus (rapamycin)

Everolimus (Zortress®)

- Analog of Sirolimus
- Recent approval for renal transplant
- Being investigated for heart transplant

MYCOPHENOLATE MOFETIL (CELLCEPT)

- **Structure**
  - A semisynthetic Prodrug hydrolyzed into mycophenolic acid (active form), isolated from the mold *Penicillium glaucum*

- **Mechanism**
  - inhibits inosine monophosphate dehydrogenase involved in de novo synthesis of purines
  - selectively suppressess T- and B-cell proliferation
  - Also suppresses some macrophage functions (may explain anti-inflammatory actions).
- Pharmacokinetics
  - oral absorption and hepatic metabolism

MYCOPHENOLATE MOFETIL

- Indications:
- Renal, liver & heart transplantation
- More recent agent that is now preferred to azathioprine
  - **Note:** in renal or liver transplant, patients may take the followings:
  - Corticosteriods as prednisolone (Low dose) + cyclosporine or Tac + **Mycophenolate Mofetil**
- Adverse Effects
  - GI (nausea, gastritis, diarrhea)
    - Enteric coated mycophenolate Na may be better tolerated
  - increased incidence of lymphomas and other malignancies-

Leukopenia and thrombocytopenia (dose-related)- CMV infections

NEW IMMUNOSUPPRESSANTS

- Fingolimod(FTY720)(prodrug: requires phosphorylation):

  Sphingosine 1-phosphate receptor (S1P-R) agonist

  Reduces recirculation of lymphocytes from lymphatic system to the blood.

  Useful in combination therapy but not alone(MS).

  Toxicity: lymphopenia, decreased heart rate.

- **Pimecrolimus** (Elidel)
  - Calcineurin inhibitor like cyclosporine
  - Approved for topical treatment of eczema

CYTOTOXIC AGENTS
ANTI-METABOLITES

Azathioprine (prodrug of nucleotide anti-metabolite)

Leflunomide (prodrug of an inhibitor of pyrimidine synthesis)

Cyclophosphamide (DNA alkylating agent)

methotrexate (inhibits dihydrofolate reductase)

Azathioprine(Imuran^{R})

- Well absorbed from GI tract
- Inhibit purine synthesis→ interferes with nucleic acid metabolism → inhibits cellular & humoral responses
- **Indications:**

  Renal allograft,

  Treatment of autoimmune disorders: rheumatoid arthritis, systemic lupus erythematosus(SLE), Autoimmune hemolytic anemia, Crohn's disease.
- **Toxicities:**
  - Bone marrow suppression
  - GI disturbances
  - Skin rashes, drug fever, hepatic dysfunction
  - Highly teratogenic

LEFLUNOMIDE

A prodrug of an inhibitor of pyrimidine synthesis rather than purine synthesis. Inhibits lymphoid cells.

Indications: Mainly for rheumatoid arthritis.

- It is orally active, and the active metabolite has a long half-life of several weeks.
- **Toxicities:**

  liver damage, renal impairment, Headache, nausea & diarrhea

  teratogenic effects.

ALKYLATING AGENT(CYCLOPHOSPHAMIDE)

- Most potent immunosuppressive drug.

- Cyclophosphamide (CTX) destroys proliferating lymphoid cells but also appears to alkylate some resting cells.
- B cells is more sensitive than T cells.

- **Indications:**

  Organ transplants, autoimmune disorders: SLE, Bleeding syndromes,
- **Adverse reactions:**

  bone marrow suppression, gastrointestinal symptoms, hemorrhagic cystitis, Pancytopenia,

ANTIBODIES AS IMMUNOSUPPRESSIVE AGENTS

- **Polyclonal Antibodies**: Antilymphocytic antibody(ALG)

  Immune Globulin IV, Hyperimmune Immunoglobulins

- **Monoclonal Antibodies:** Muromonab-CD3, Basiliximab , Daclizumab , Palivizumab, Rituximab, Trastuzumab,....

- **Rh_o(D) Immune Globulin Micro-Dose:**

Polyclonal Antibodies

- Antilymphocyte Globulin
  polyclonal antibody

- Antithymocyte Globulin-Rabbit (Thymoglobulin)
  used to treat acute renal transplant rejection
  Composed of antibodies to variety of T cell markers

- Mechanisms:
  Antibodies bind to the surface of circulating T lymphocytes forming a complex. This complex will be phagocytosed in liver or spleen and leading to destruction or inactivation of T cells.

PK: Administered by IM or slow IV infusion with long half-life of 3-9 days

Side Effects:

1) Mainly result from the introduction of foreign proteins obtained from heterogeneous serum (Anaphylactic and serum sickness reactions; Local pain and erythema at site of injection).

2) Chills & fever and Leukopenia & thrombocytopenia

3) Viral infections and skin rashes

4) Lymphoma and cancer

Clinical Uses of ALG :

1) hyperacute phase of allograft rejection

2) To prepare the bone marrow transplanted patient (Large doses of ALG for 7 days)

2) IMMUNE GLOBULIN INTRAVENOUS (IGIV):

Prepared from a pool of thousands of healthy donors.

Uses

patients with antibody deficiencies, thrombocytopenic purpura (ITP) in children(↑ catabolic of AutoAb) وGuillain–Barre syndrome, myasthenia gravis, SLE.

3) Hyperimmune Immunoglobulins :

antidotes

Monoclonal Antibodies

1) Muromonab-CD3 (IL-2-antagonist):

- monoclonal antibody to CD3 on T cell
- inhibits cytotoxic T killer cell function
- opsonizes circulating T lymphocytes and enhances their removal

mainly for cases of acute allograft rejections of kidney, heart and liver. it is also used to deplete T cells from donor bone marrow before transplantation.

Advantage over ALG: More specific and T lymphocytes return to normal within 24 hr.

SIDE EFFECT OF MUROMONAB

- Its use has been declined much because of multiple side effects and the emergence of newer and more selective antibodies therapy
  - Anaphylaxis may occur
  - Cytokine release syndrome, flu-like to dangerous shock-like reactions can occur, & high fever
  - CNS: Seizures, encephalopathy, cerebral edema & headache
  - Infection like CMV
  - Contraindicated with pregnancy, history of seizures, uncompensated heart failure

- 2) Modified Types of monoclonal antibodies (e.g: Selective Inhibitors of IL2):

- Note: Monoclonal Antibodies are not limited for immunosuppression but could be utilized for other purposes.
- By using the genetic engineering, most murine amino acids of Muromonab have been replaced by human ones; producing monoclonal antibody designated humanized (e.g. Daclizumab; Transtuzumab). While the chimeric (Mixed) antibodies contain XI in their name (e.g. Abciximab; Infliximab; Rutuximab).
- Advantages over polyclonal antibodies

Table 56–3. Characteristics of monoclonal antibodies (MAbs).

MAb	Characteristics and Clinical Uses
Abciximab	Antagonist of glycoprotein IIb/IIIa receptor, preventing cross-linking reaction in platelet aggregation. Used post-angioplasty and in acute coronary syndromes
Daclizumab	Binds to the alpha subunit of the IL-2 receptor, preventing lymphocyte activation. Used in renal transplants
Infliximab	Antibody targeted against TNF-α. Used in Crohn's disease and rheumatoid arthritis
Muromonab	Antibody to the T3 (CD3) antigen on thymocytes. Used in acute renal allograft rejection
Palivizumab	Antibody to surface protein of RSV. Used for prophylaxis and treatment of respiratory syncytial viral infection
Rituximab	Binds to the CD20 antigen on B-lymphocytes and recruits immune effector functions to mediate lysis. Used in B cell non-Hodgkin's lymphoma
Trastuzumab	Binds to the HER2 protein on the surface of tumor cells. Cytotoxic for breast tumors that overexpress HER2 protein

B- SELECTIVE IL-2 RECEPTOR ANTAGONISTS

BASILIXIMAB & DACLIZUMAB

- They bind to the α-chain of the IL-2R (CD25 subunit) on the activated T-cells
- Pharmacokinetics: Given by IV route. Baciliximab has higher affinity for IL-2 receptor than Daclizumab. days.Administered in two doses; the first at 2-hours before transplantation & the second at 4 days after surgery. has serum half-life of 20 days & receptor blockade for 120 days has serum half-life of 7. Administered in 5 doses; the first 24 hours before transplantation and next 4 doses at 14-days intervals
- Prophylaxis against acute rejection of kidney ransplantation
- Gastrointestinal toxicity ,Used in combination with steroids or CsA

ALEMTUZUMAB (CAMPATH)

- New humanized monoclonal antibody Immunosuppressant
- Binds to CD52 (antigen present on surface of all T and B cells).
- Used for refractory B- cell chronic lymphocytic leukemia and lymphomas.

- Some bone marrow cells express CD52 including some CD34+ cells. Also for stem cell transplant.

3- RH0(D) IMMUNOGLOBULIN

- Rho(D) Immune Globulin (Rhogam)
- Rhogam is an immunoglobulin that recognizes the Rho(D) antigen
- Prepared from pooled sera from Rho-negative volunteers immunized with D^+ erythrocytes
- When a Rho(D)-negative mother carries a Rho(D)-positive fetus, mother becomes sensitized
- Subsequent pregnancies can strengthen response increasing chance of Ab transfer to fetus

IMMUNOSTIMULANTS

Immunostimulants

Increase the immune responsiveness of patients who have either selective or generalized immunodeficiency.

USES:

- immunodeficiency disorders
- Chronic infections
- cancer

- In contrast to adjuvants, immunostimulants need not be administered together with an antigen to enhance an immune response.
- Immunostimulants vary according to their origin, their mode of action, and the way in which they are used.

Bacteria and Bacterial Products

- A wide variety of bacteria have been employed as immunostimulants.
- These usually act as sources of pathogen-associated
- molecular patterns and stimulate one or more TLRs.

- MOA:
- they activate macrophages and dendritic cells and stimulate cytokine synthesis.
- The most potent of these cytokine synthesis enhancers is **bacille Calmette-Guérin (BCG)**
- the live attenuated vaccine strain of *Mycobacterium bovis.*
- *BCG generally* enhances B and T cell–mediated responses, phagocytosis, allograft rejection, and resistance to infection.
- Unfortunately, whole BCG induces tuberculin hypersensitivity in treated patients.

- To prevent sensitization, purified cell wall fractions of BCG have therefore been developed
- Several active constituents have been identified.

- One of these is **trehalose dimycolate**, which promotes nonspecific immunity against several bacterial infections and may provoke regression of some experimental tumors.
- Another is **muramyl dipeptide (MDP)**, a simple mycobacterial glycopeptide that enhances antibody production, stimulates polyclonal activation of lymphocytes, and activates macrophages

Complex Carbohydrates

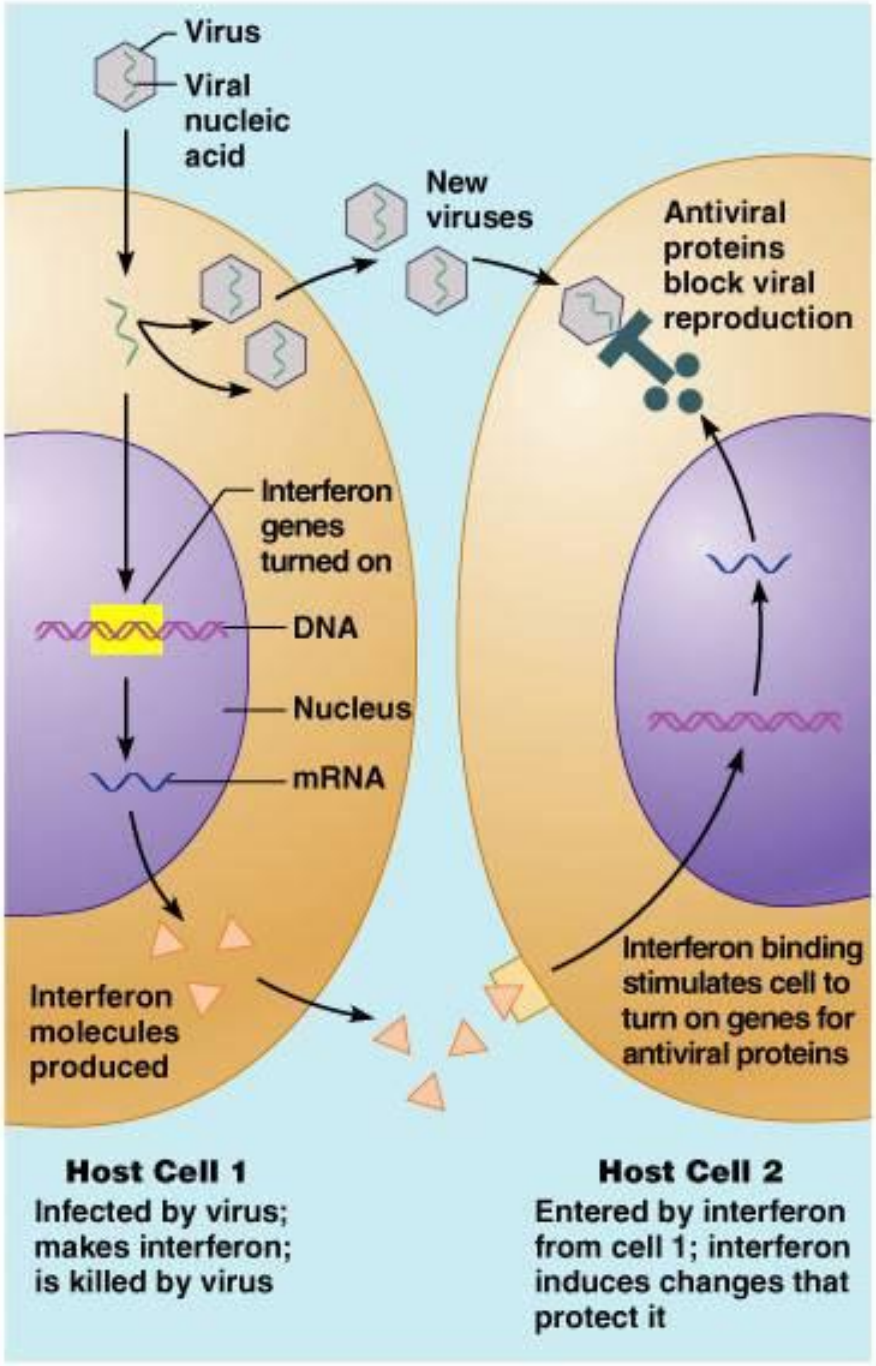
- Certain complex carbohydrates derived from yeasts, namely,zymosan, glucans, aminated polyglucose, and lentinans can also activate macrophages.
- These may function as adjuvants and potentiate resistance to infectious agents

LEVAMISOLE (LSM):

- functions in a manner similar to the thymic hormone thymopoietin .
  that is, it stimulates T cell differentiation and T cell response to antigens.
- Enhances interferon production, and increases FcR activity.

- It probably also enhances cell-mediated cytotoxicity, lymphokine production, and suppressor cell function.
- Levamisole stimulates the phagocytic activities of macrophages and neutrophils.
- It promotes the activation and maturation of dendritic cells. Its effects are greatest in animals and humans with depressed T cell function; it has little or no effect on the immune system of healthy animals and humans.
- Levamisole may therefore be of assistance in the treatment of chronic parasitic worm infections and neoplastic diseases but may exacerbate disease caused by excessive T cell function.

IMMUNOSTIMOLATORY CYTOKINES



General Action of Interferons

- Interferons are small proteins released by macrophages, lymphocytes, and tissue cells infected with a virus.

When a tissue cell is infected by a virus, it releases interferon. Interferon will diffuse to the surrounding cells. When it binds to receptors on the surface of those adjacent cells, they begin the production of a protein that prevents the synthesis of viral proteins. This prevents the spread of the virus throughout the body.

- Three types of interferons: alpha, beta and gamma.

INTERFERONS

- Interferon (INF): INF-α,β,γ
  - Antiviral, anticancer, immunomodulating effects.
  - Antiviral effects : INF-α,β > INF-γ
  - immunomodulating effects: INF-γ
  - Adverse Effects: flu-like symptoms, fatiguemalaise
- Type I IFNs (IFN-α, β):
- acid-stable proteins; act on same target cell receptor
- induced by viral infections
- leukocyte produces IFN-α
- Fibroblasts & endothelial cells produce IFN-β
- Type II IFN (IFN-γ):
- acid-labile; acts on separate target cell receptors
- Produced by Activated T lymphocytes.

Interferon Effects:

IFN- γ : Immune Enhancing

- increased antigen presentations with macrophage, natural killer cell, cytotoxic T lymphocyte activation

IFN- α, β :

- effective in inhibiting cellular proliferation

  (more effective than IFN- γ in this regard)

USES:

- Interferon Alpha : malignant melanoma, renal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma
- Interferon Beta : relapsing type MS
- Interferon Gamma: (stimulates NK cells and macrophages)

Different Interferon Drugs

• Interferons are broken down into recombinant versions of a specific interferon subtype and purified blends of natural human interferon.

• Many of these are in clinical use and are given IM or SC.

• **Recombinant forms of alpha interferon include:**

- Alpha-2a drug name Roferon
- Alpha-2b drug name Intron A
- Alpha-n1 drug name Wellferon
- Alpha-n3 drug name AlferonN
- Alpha-con1 drug name Infergen

•**Recombinant forms of beta interferon include:**

- Beta-1a drug name Avonex
- Beta-1b drug name Betaseron

•**Recombinant forms of gamma interferon include:**

- Gamma-1b drug name Acimmune

Interferon Beta-2a (Avonex)

• Clinical trials showed that it slowed MS progression and had an extra benefit of slowing or preventing the development of MS-related brain atropy.

•The exact mechanism of IFN beta activity in treating MS is unknown, but studies have shown that interlukin 10 levels in the cerebrospinal fluid were increased in patients

• Some side effects include:

- •Flu-like symptoms
- •Muscle aches
- •Chills

Combination Therapy with Ribavirin

- Many times interferons are used in combination with Ribavirin
- It is a purine nucleoside analogue with a modified base and a D-ribose sugar moiety.

- It inhibits the replication of a variety of RNA and DNA viruses and is serves as an immunomodulator to enhance type 1 cytokine production. This increases the end of treatment response and reduces post-treatment relapse.

Immunostimulatory Cytokines

- **Interleukin-2 (aldesleukin)**
  - T cell proliferation, Th, NK, LAK cell activation
  - release of multiple cytokines :TNF, IL-1, IFN-γ
  - Treatment of malignant melanoma, renal cell carcinoma, Hodgkin disease
  - Adverse Effects: fever, anorexia

- **Colony Stimulating Factors**
- **G-CSF (Filgrastim)(Neupogen®)**
  - **treat neutropenia**
- **GM-CSF (Sargramostim)(Leukine®)**
  - **myeloid recovery after bone marrow transplant**

Other Hematopoetic Growth Factors

- **Erythropoietin alpha (Epoetin alpha) (Procrit®)**
  - Produced by recombinant DNA technology
  - Stimulates division and differention of erythroid progenitor cells
  - Used for anemia due to renal failure or cancer chemotherapy
  - Adverse effects include hypertension, headache, hypersensitivity reactions are rare
- **Darbopoetin alpha (Aranesp®)**
  - Recombinant long-acting erythropoetin (3X epoetin)

IMMUNOSTIMOLATORY MONOCLONAL ANTIBODYS

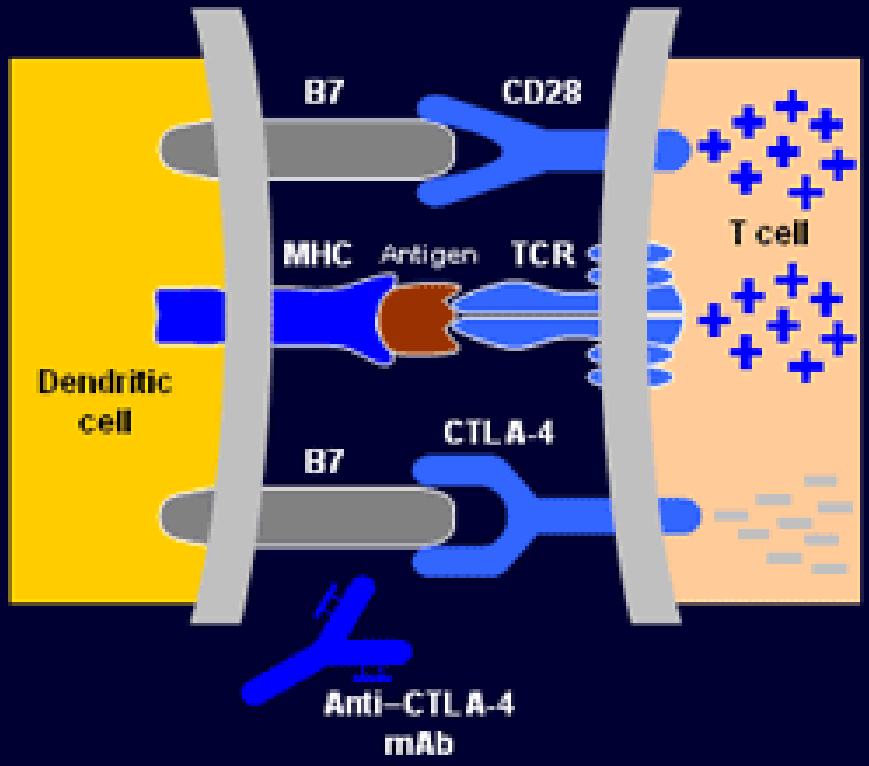
- Using mAbs to stimulate the immune response against cancer cells is a new indirect mode of action, achieved by either blocking inhibitory ‘immune checkpoint’ receptors such as cytotoxic T-lymphocyte-associated protein 4 (**CTLA-4**, **Ipilimumab**
- or triggering activating receptors such as **4-1BB** or **CD40**.

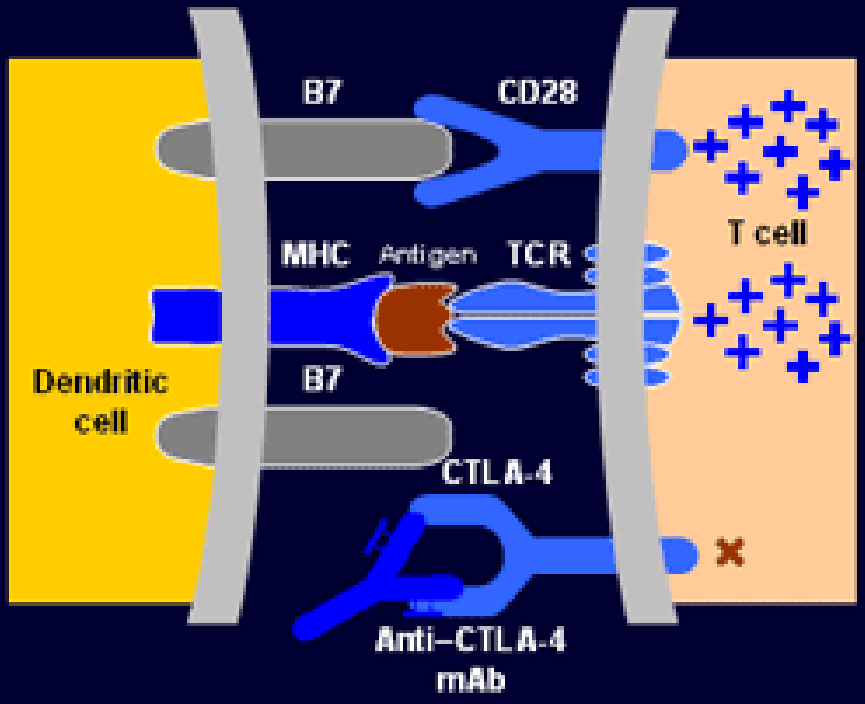
- mAbs that function as agonist or super-agonist ligands for costimulatory receptors;
- mAbs that enhance the activation and/or maturation of antigen-presenting cells (APCs);
- mAbs that delete or inhibit immunosuppressive mechanisms such as regulatory T cells.

- First immunostimulatory mAbs :
- **Anti-CTLA-4 (Ipilimumab)**
- **anti-4-1BB(CD137)**
- **anti-CD40**

- Antibodies to costimulator receptors (on T cell) or ligands (on antigen presenting cell)
  - **Anti-CTLA4 (blocks B7 binding to T cell CD28)**
  - **Anti-CD40 (inhibits macrophage and endothelial activation by blocking T cell CD40 ligand binding to macrophage CD40)**

CTLA-4 Blockade Prevents Downregulation of T Cells





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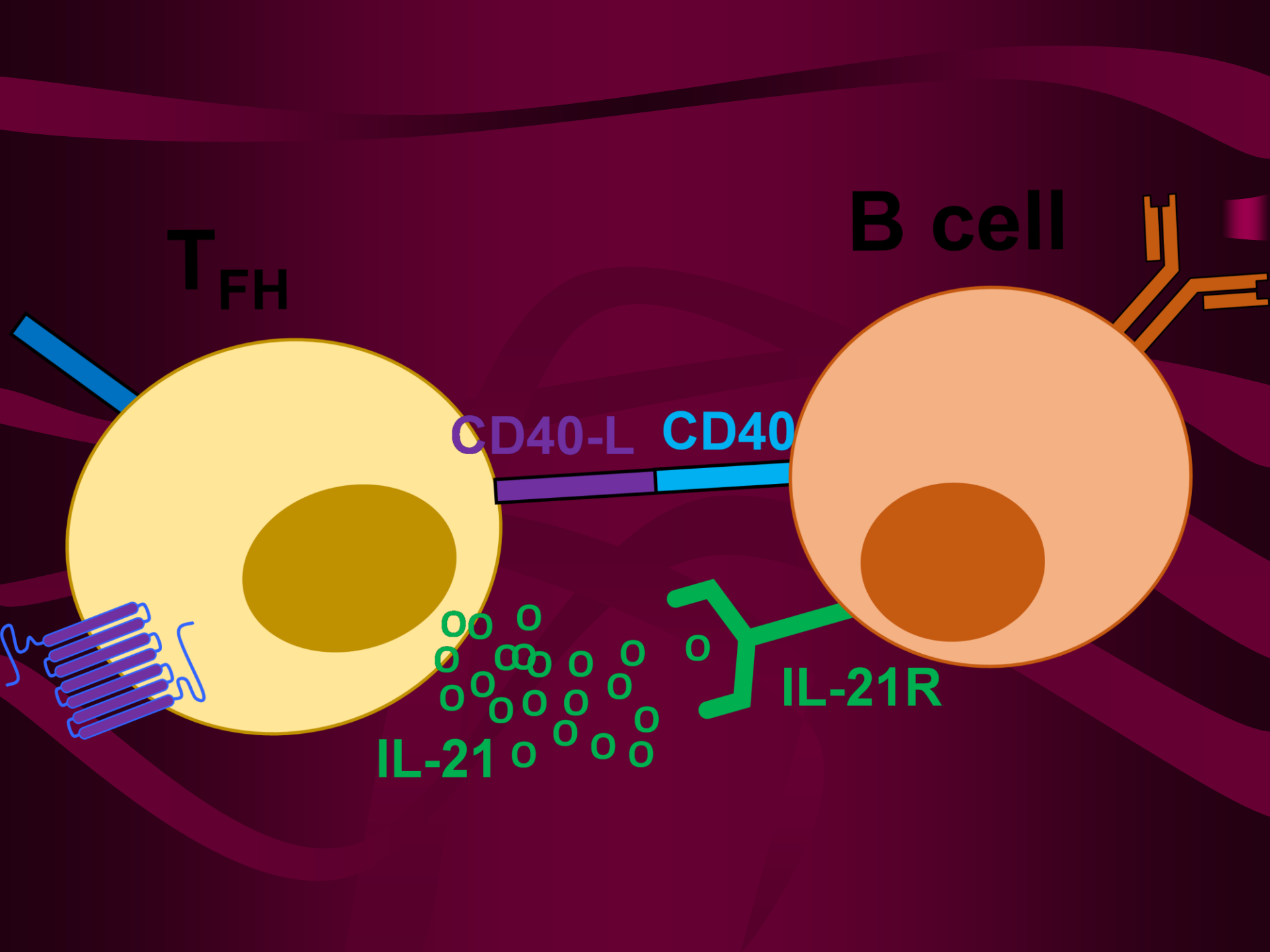
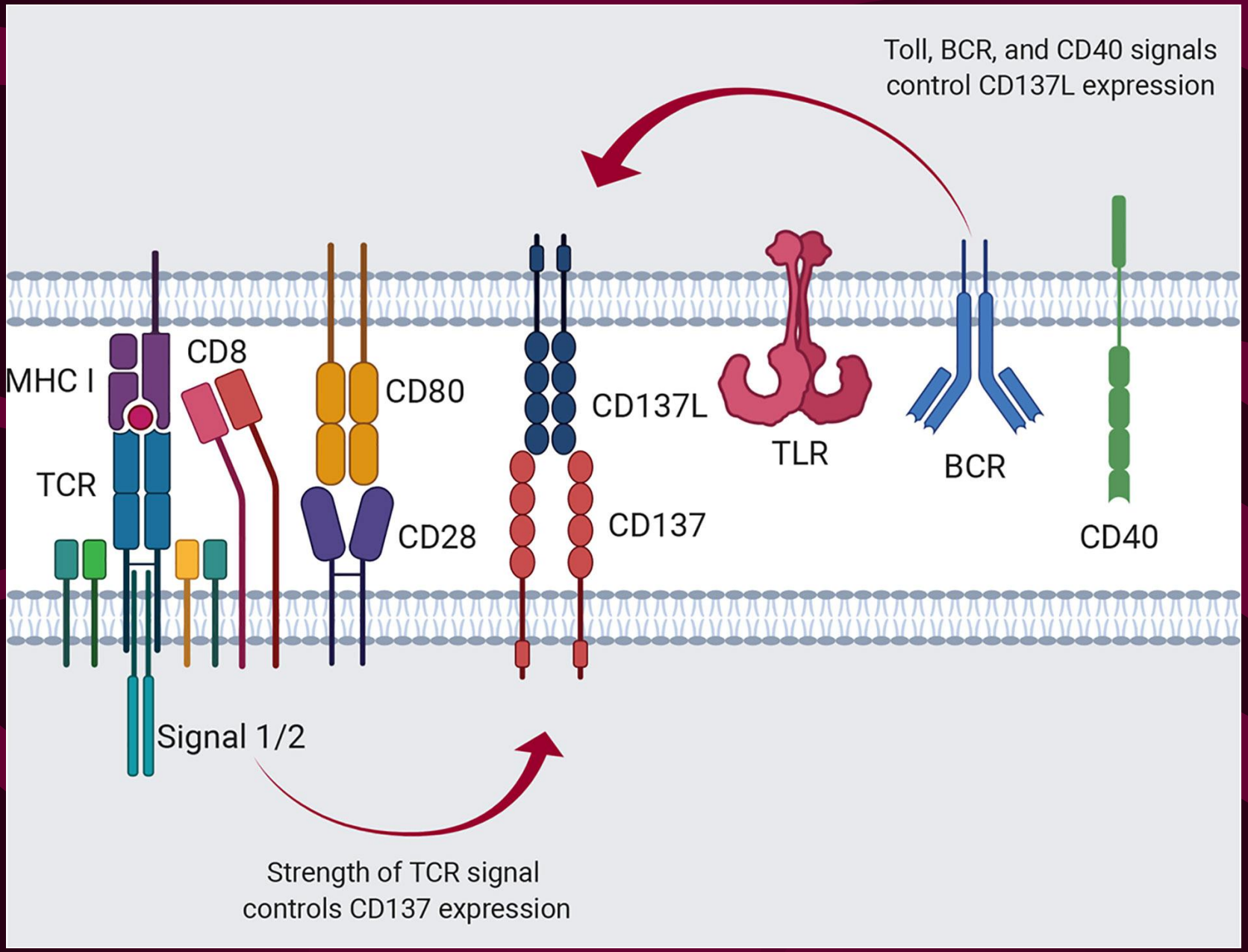

T FH
B cell
CD40-L
CD40
IL-21
IL-21R


Toll, BCR, and CD40 signals
control CD137L expression
MHC I
CD8
TCR
CD80
CD28
CD137L
CD137
TLR
BCR
CD40
Signal 1/2
Strength of TCR signal
controls CD137 expression

Other Immunostimulants

- **Thymic Hormones (THYMOSIN)**
  - **Improve primary immune deficiency in children**
  - Uses:
  - DiGeorge Syndrome of T cell deficiency

Immunomodulators

Vitamins

- Some vitamins, most notably A, D, and E, play a key role in regulating immunity.

- **Vitamin A** metabolites, especially retinoic acid, enhance cytotoxicity and T cell proliferation by stimulating IL-2 production
- Retinoic acid can inhibit B cell proliferation and inhibit B cell apoptosis.
- Retinoic acid also enhances dendritic cell antigen presentation and maturation. Vitamin A metabolites can modulate the Th1-Th2 balance as well as the differentiation of Treg and Th17 cells

• Vitamin D

- **Vitamin D**, also plays a key role in immunity.
- The most important form, vitamin D3, is synthesized within the skin or the liver, kidneys, and lymphoid tissues.
- Macrophages and dendritic cells require vitamin D for the production of the antimicrobial peptide cathelicidin.
- The vitamin D receptor is upregulated by IL-15 triggered by T cell receptor (TCR) activation.

Vitamin E

- **Vitamin E** promotes B cell proliferation; the effect is most marked in the primary immune response. *In some cases* this increased antibody production may lead to increased disease resistance.
- It can act as an adjuvant when administered with *Brucella ovis vaccine,* clostridial toxoid, and *Escherichia coli J5 vaccine.*
- Vitamin E can reduce the age-related decline in immune function by a direct action on T cells

Thalidomide

- A Sedative drug
- Has immunomodulatory actions

- Favors Th2 over Th1
- Suppress TNF-α production
- Reduces phagocytosis by neutrophils
- Increases IL-10 production
- Enhanced T-cell production of cytokines – IL-2, IFN-γ
- NK cell-mediated cytotoxicity against tumor cells
- Antiangiogenesis action: teratogenicity & anticancer **(Lenalidomide, Actimid)**
- Indications
  - Erythema nodosum leprosum (skin manifestations of SLE)
  - Lung transplantation
  - Multiple myeloma

Immunization

- Active – Stimulation with an Antigen
- Passive – Preformed antibody
- **Active immunization: Vaccines.**
- Administration of antigen as a whole, killed organism, or a specific protein or peptide constituent of an organism
- Anticancer vaccines – immunizing patients with APCs expressing tumor antigen.

Immune Globulin

- Nonspecific immunoglobulins
  - Antibody-deficiency disorders
- Specific immune globulins:
- inadequate time for active immunization(Antidotes)
  - High titers of desired antibody
  - Hepatitis B, Rabies, Tetanus


THANK YOU