# IMMUNO-MODULATING DRUGS

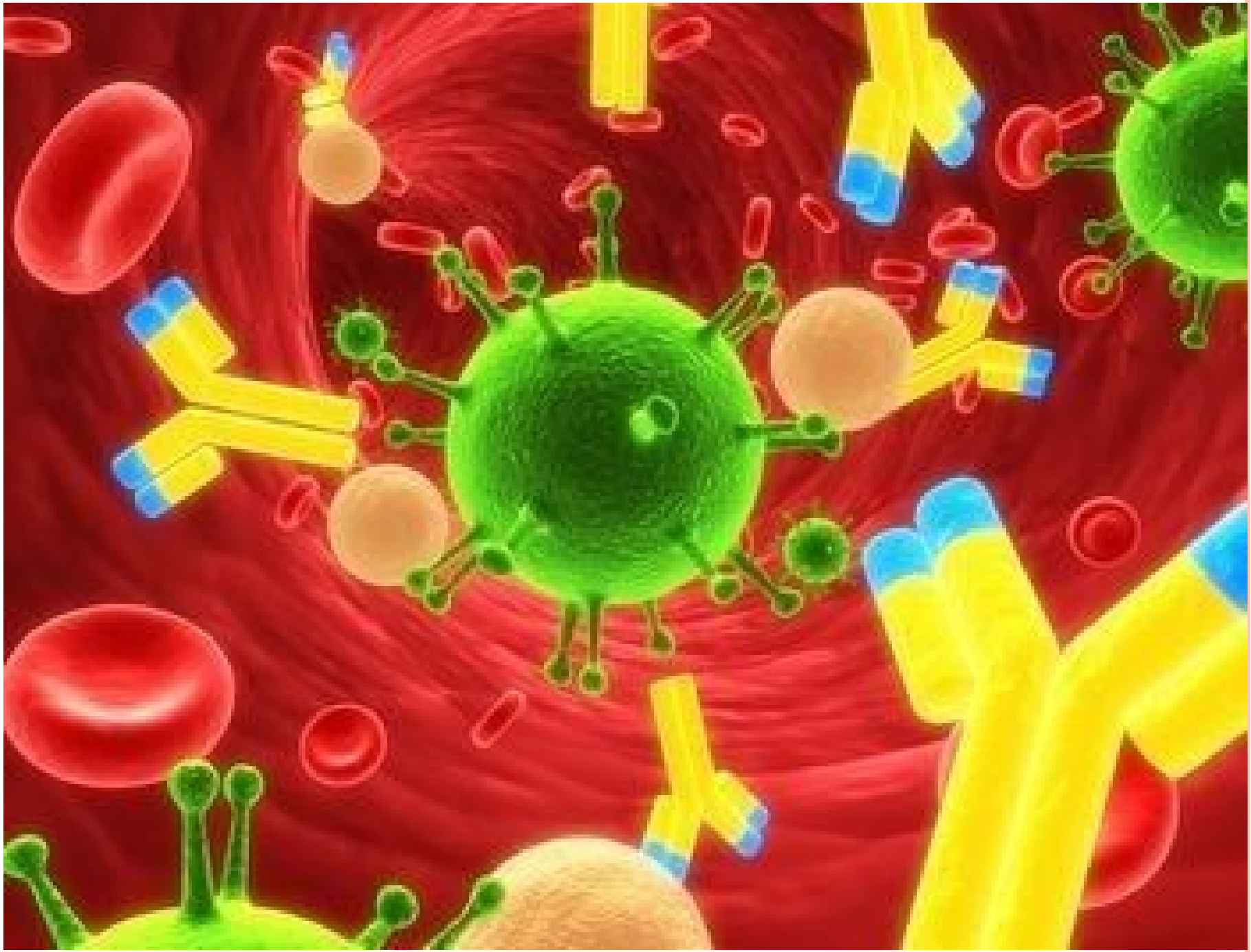
## INTRODUCTION/CLASSIFICATION

DR SHAMS SULEMAN

# LEARNING OBJECTIVES

- Identify the cellular and molecular targets in the immune system for the purpose of pharmacological interventions

- Classify the Immuno-modulating drugs



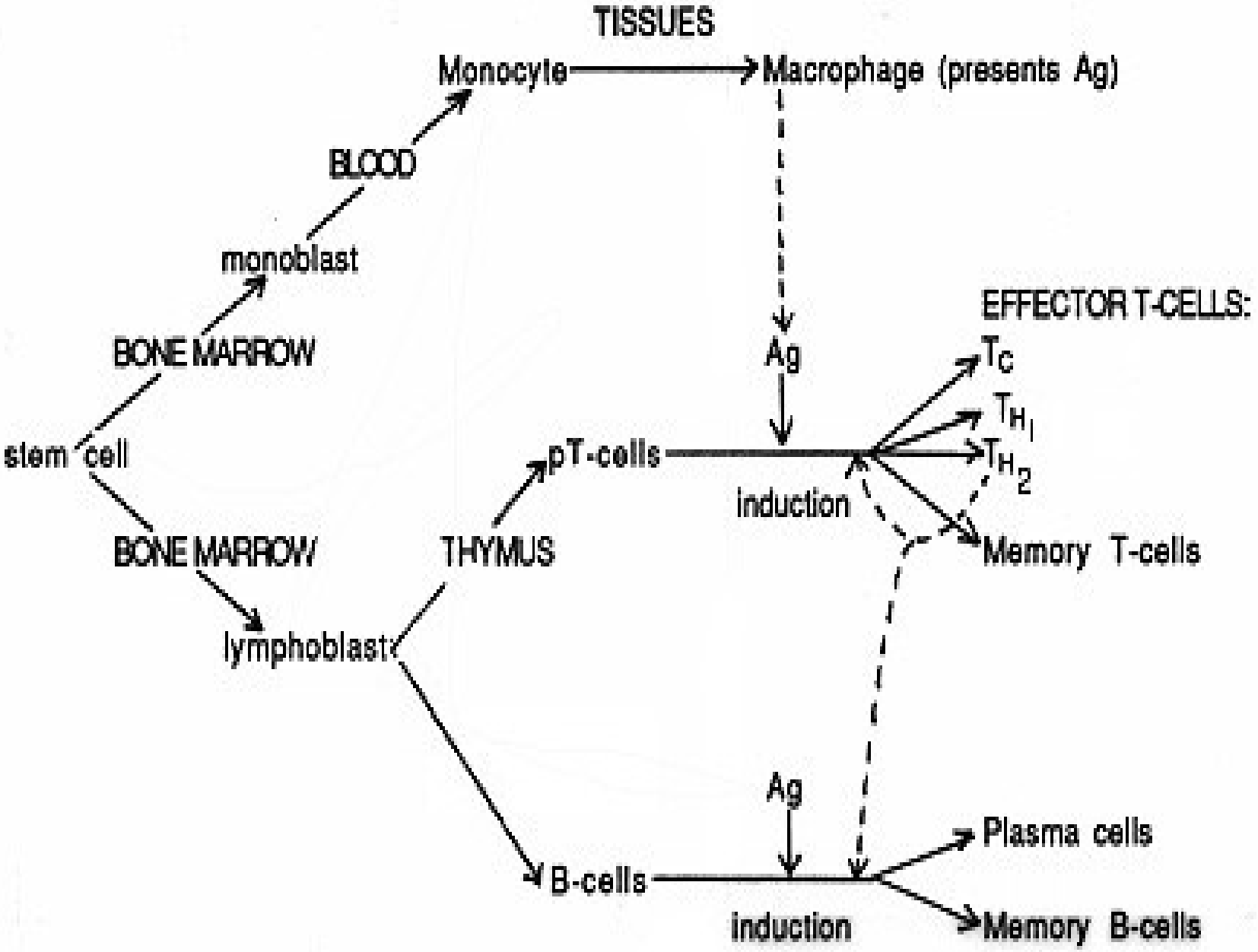
# INTRODUCTION

- Definition
- Types :
  - Natural
  - Acquired
- Natural immunity:
  - Innate
  - Adaptative
- Acquired immunity :
  - Active
  - Passive

# THE IMMUNO SYSTEM

## IMMUNITY :

- It is the ability of the living body or the process to resist various types of organisms or toxins that tend to damage the tissue and organs.

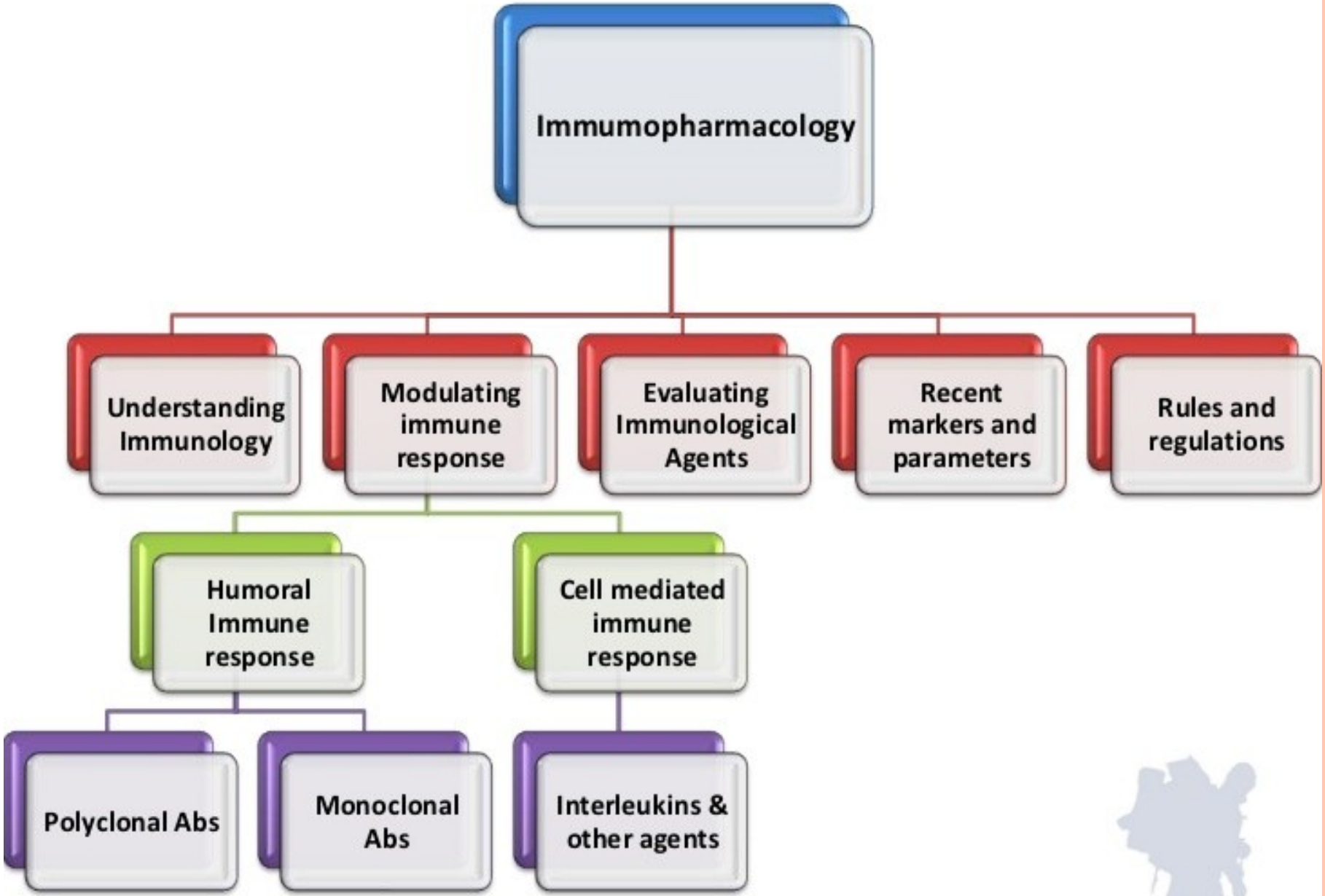

TISSUES
Monocyte
Macrophage (presents Ag)
BLOOD
monoblast
BONE MARROW
stem cell
BONE MARROW
lymphoblast
THYMUS
pT-cells
Ag
induction
EFFECTOR T-CELLS:
Tc
TH1
TH2
Memory T-cells
Ag
B-cells
induction
Plasma cells
Memory B-cells

# Who are involved ?

- Innate
  - Complement
  - Granulocytes
  - Monocytes/macrophages
  - NK cells
  - Mast cells
  - Basophils
- Adaptive:
  - B and T lymphocytes
  - B: antibodies
  - T : helper, cytolytic, suppressor.

## DEFINITION:

- A branch of pharmacology concerned with the application of immunological techniques and theory to the study of the effects of drugs especially on the immune system.
- Immune system : Is an organization of organs, tissues, cells and molecules with specialized roles in defending against microorganisms, viruses and cancer cells.
- The cells of immune system are present throughout the host's body.


Immumopharmacology
Understanding Immunology
Modulating immune response
Evaluating Immunological Agents
Recent markers and parameters
Rules and regulations
Humoral Immune response
Cell mediated immune response
Polyclonal Abs
Monoclonal Abs
Interleukins & other agents

# IMMUNOPHARMACOLOGY

- 2 major components of the immune system:
  - INNATE
    - Physical – skin, mucus membrane
    - Biochemical – complement, lyzosyme
    - Cellular – macrophages, neutrophils
  - ADAPTIVE
    - Antibodies – HUMORAL immunity
    - T-lymphocyte – CELL MEDIATED immunity

## TYPES OF INNATE IMMUNITY:

**Species immunity**

- Resistance to infection varies with species.
- **Eg**: Humans are susceptible to measles infection, whereas dogs are resistant.

**Racial immunity**

- Within a species, different races exhibit differences in their resistance, due to genetic factors.
- **Eg**: Africans are resistant to malarial infections.

**Individual immunity**

- Different individuals in a race exhibit differences in innate immunity.
- Combination of nonspecific and specific resistance. **Eg**: cold attacks in winter.

# INNATE IMMUNITY

- Skin/mucous membranes
- Complement proteins

  Opsonins:  C3a

  Chemoattractants: C3a, C5a

  Membrane Attack Complex: C5….9
- Lysosomes
- Interferons
- Cells:  Neutrophils, Monocytes, Macrophages

# IMMUNOPHARMACOLOGY

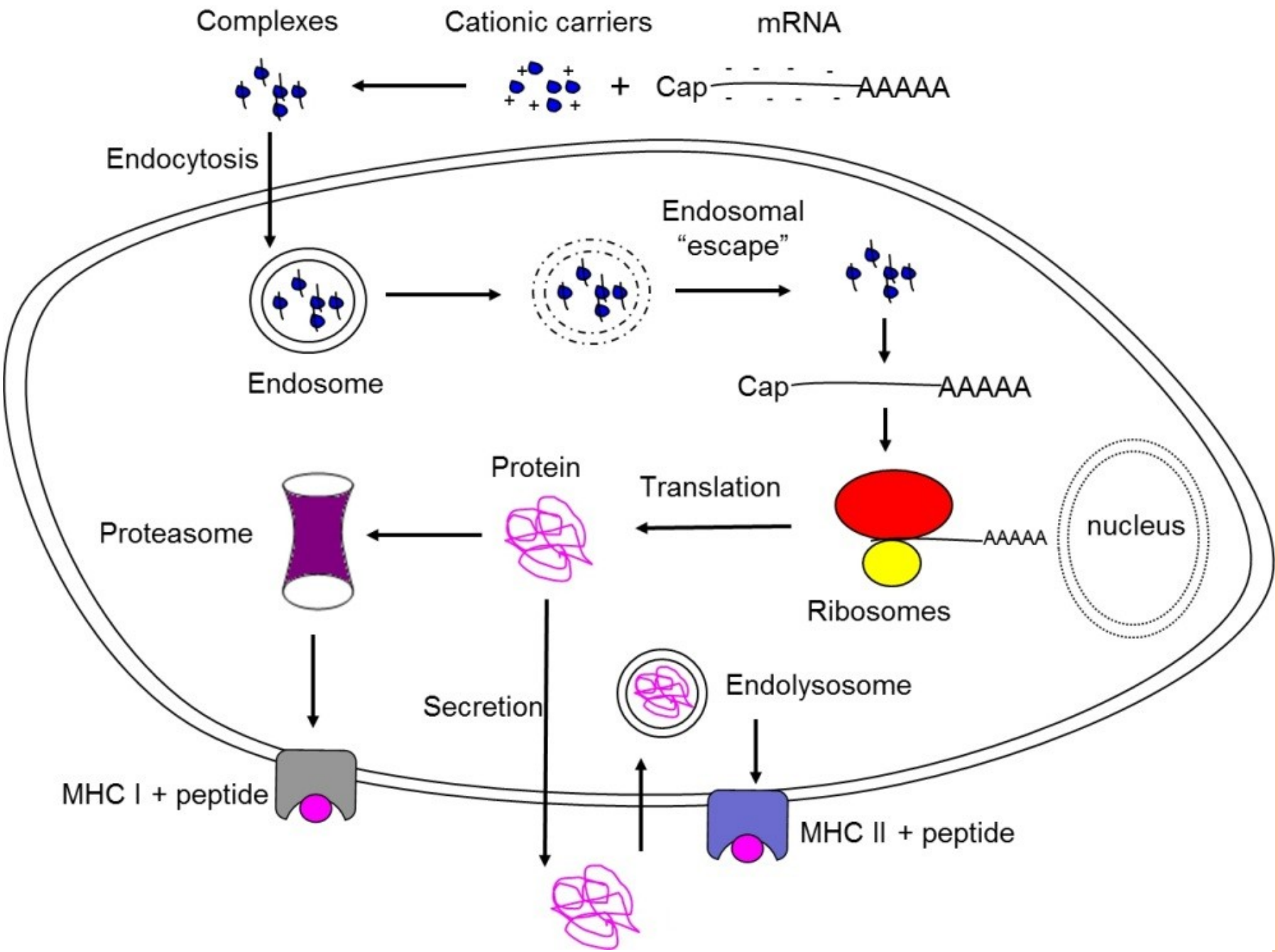
## COMPLEMENTS in Innate Immunity:

1. C3a, C5a → chemotaxis
2. C3b → opsonization
3. C5b, C6, C7, C8, C9 → MAC

# Pattern Recognition Receptors (PRRs)

- **Principle functions of PRRs**
  1.) Opsonization
  2.) Activation of complement
  3.) Phagocytosis
  4.) Activation of proinflammatory signaling pathways
  5.) Induction of apoptosis

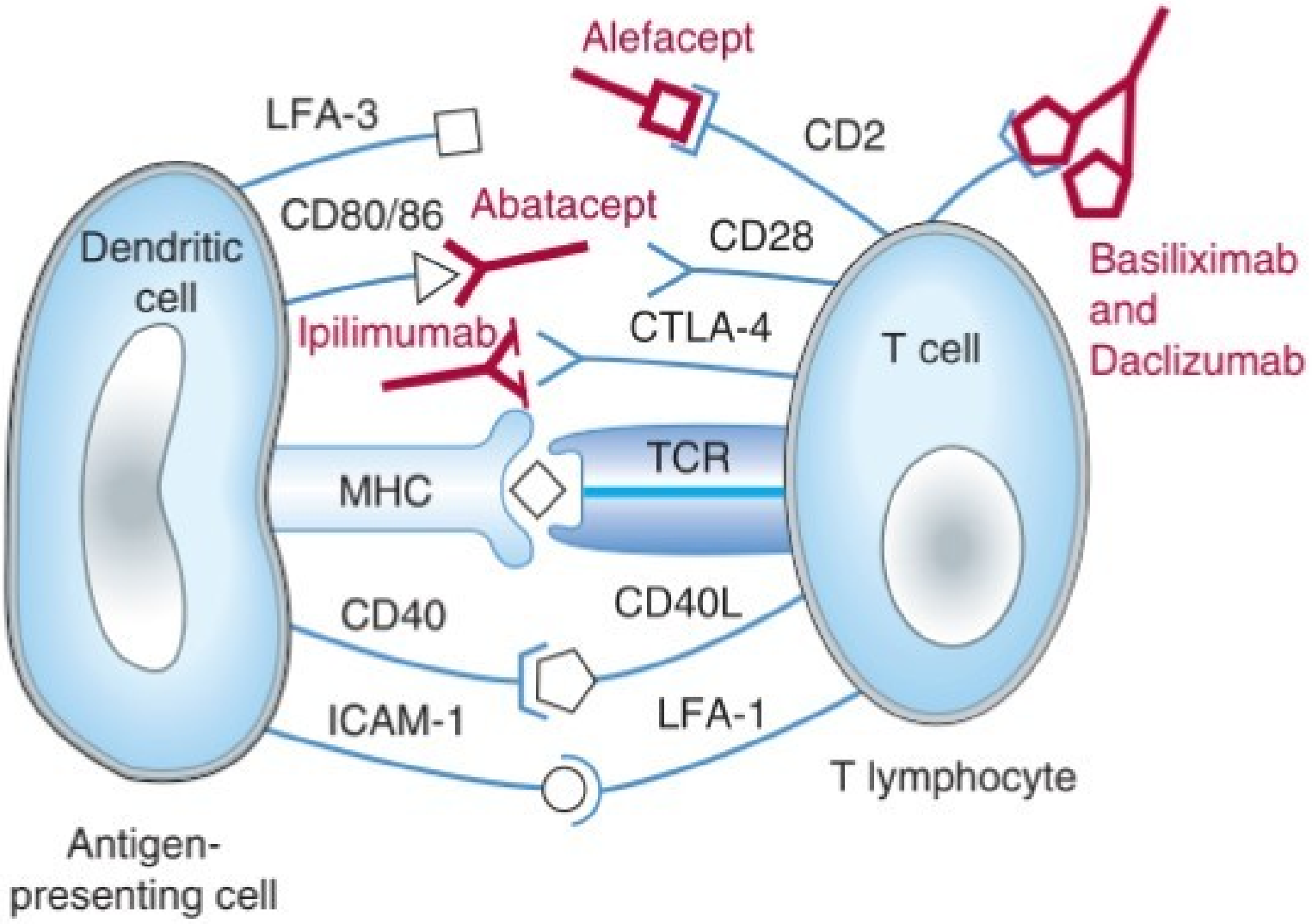
Abbas_Cellular and Molecular Immunology, 9th ed

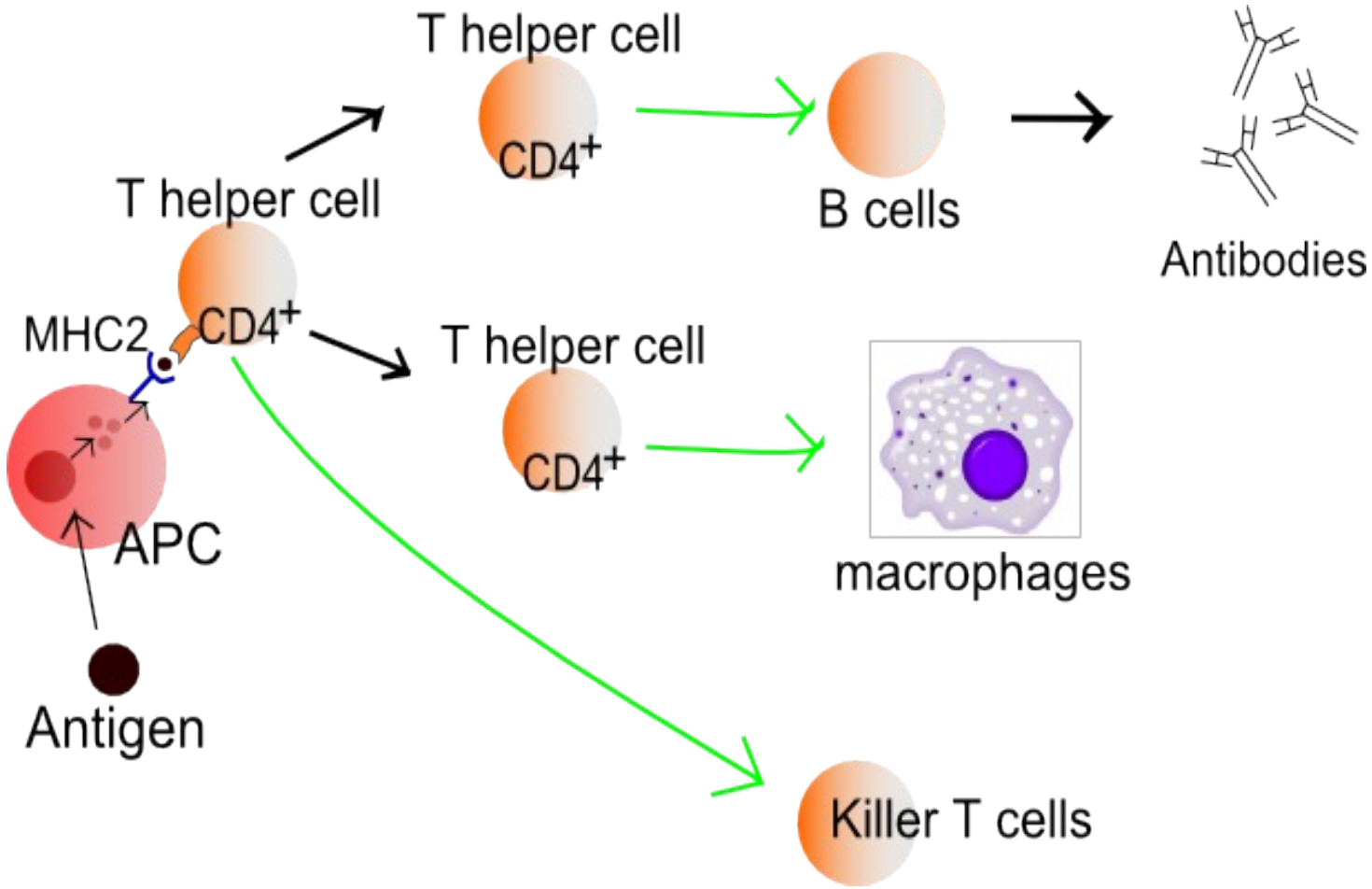

Complexes
Cationic carriers
mRNA
+
Cap
AAAAA
Endocytosis
Endosomal
"escape"
Endosome
Cap
AAAAA
Protein
Translation
Proteasome
AAAAA
nucleus
Ribosomes
Endolysosome
Secretion
MHC I + peptide
MHC II + peptide

# INNATE IMMUNITY…..

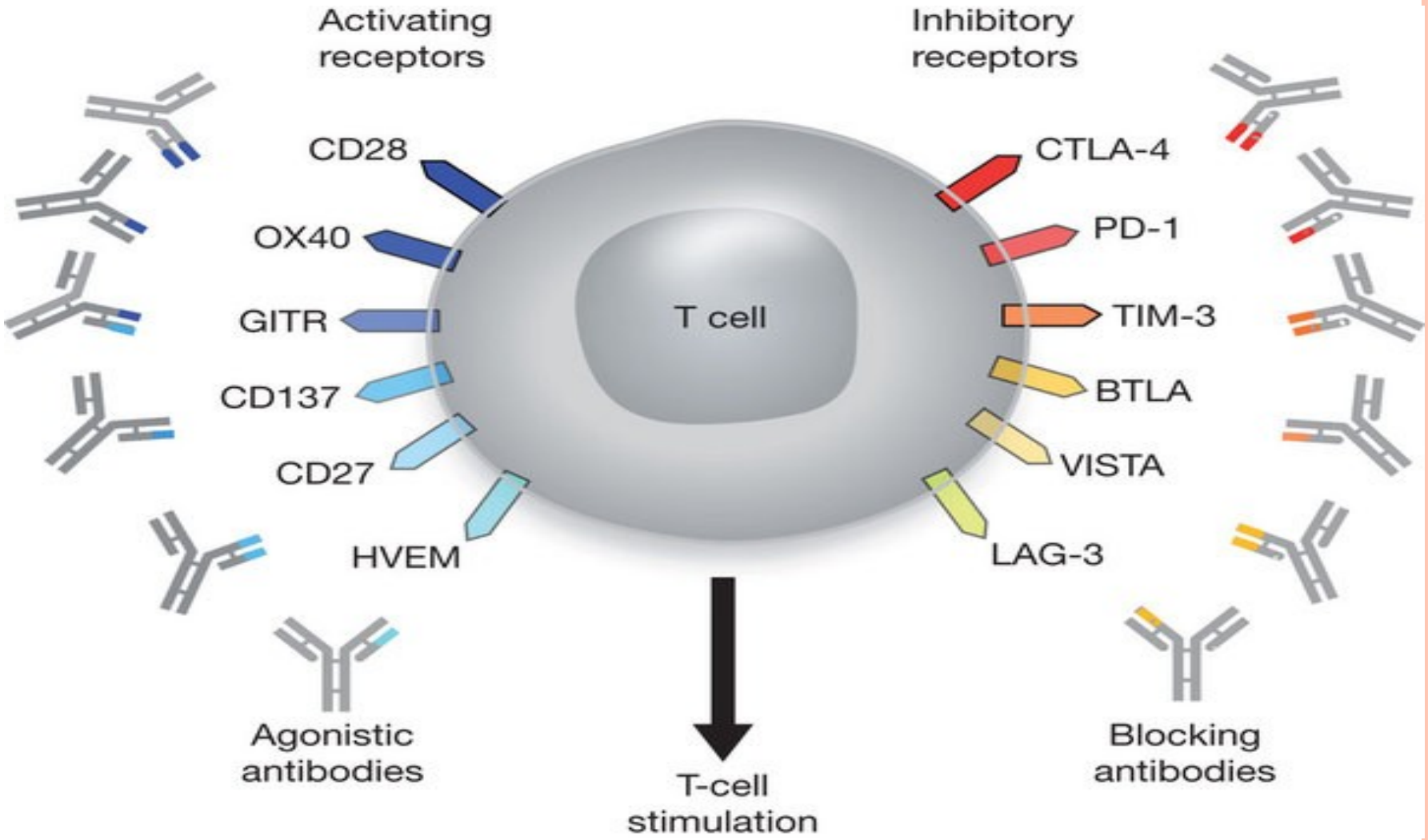
## Major Histocompatibility Complex ( MHC)

- MHC 1:
  - All cells
  - Cytotoxic T cells
  - Cell mediated immunity
  - Viricidal , tumoricidal.
  - Interplays with IL2 , TNF , INF
- MHC II
  - Only present on APCs; involves costimulatory molecules
  - Signal I = Interaction of APC with helper T cells
  - Signal II = CD80/86 interacts with CD28
  - Autoregulation = CTLA4 binds to CD28 setting CD80/86 free again


Alefacept
LFA-3
CD2
CD80/86
Abatacept
CD28
Dendritic cell
Basiliximab and Daclizumab
Ipilimumab
CTLA-4
T cell
TCR
MHC
CD40
CD40L
ICAM-1
LFA-1
T lymphocyte
Antigen-presenting cell


T helper cell
CD4+
B cells
Antibodies
T helper cell
MHC2
CD4+
T helper cell
CD4+
macrophages
APC
Antigen
Killer T cells

# CO-STIMULATORY MOLECULES



## TYPES OF ACQUIRED IMMUNITY:

**Actively acquired immunity**
(adaptive immunity)

- When an individual is exposed to infections or antigens → stimulation of immune response
- Long lasting,.
- Induces immunological memory.

**Passively acquired immunity**

- There are certain individuals whose immune system does not respond and produce antibodies to foreign antigens.
- So such individuals are immunized.

# ADAPTATIVE IMMUNITY

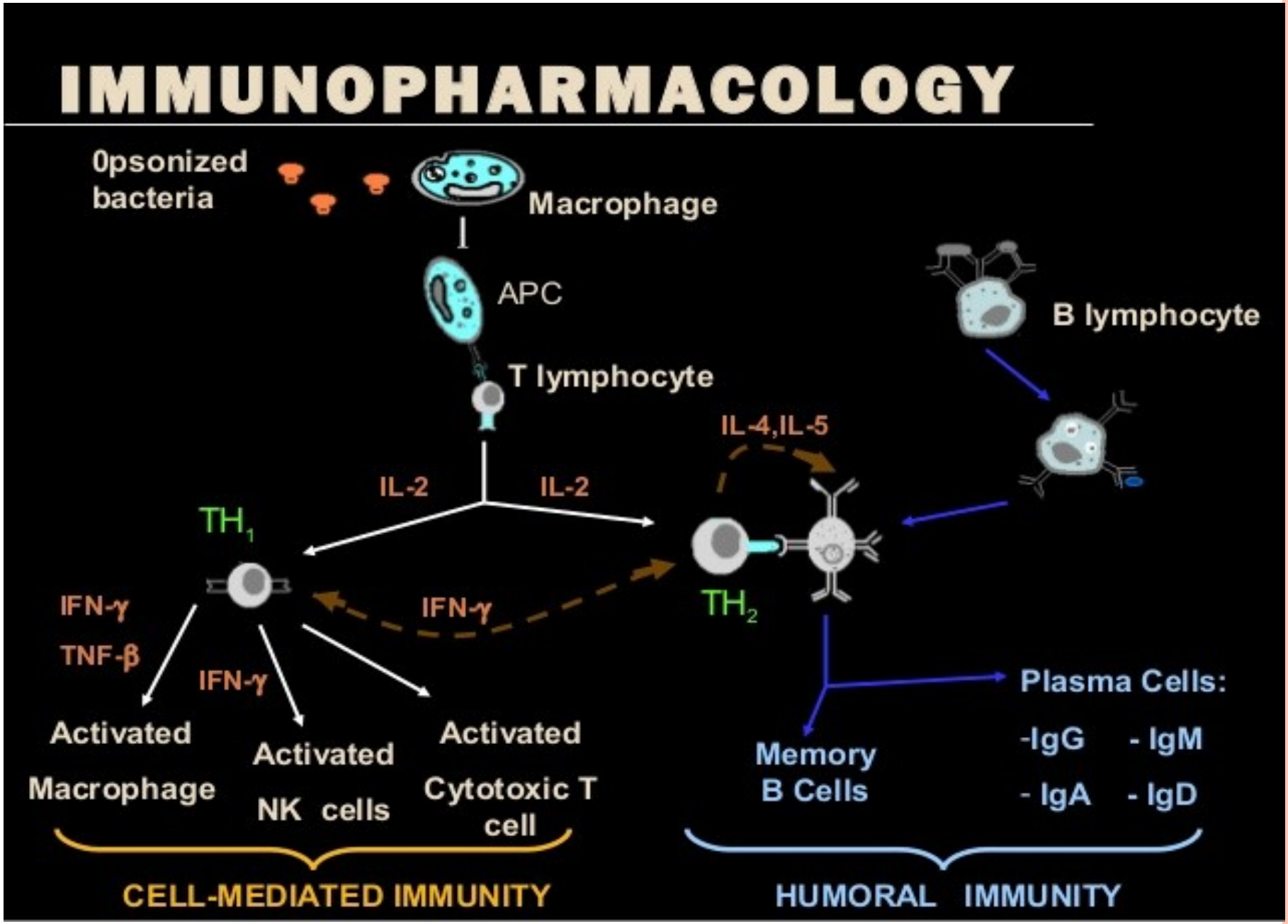
- LAK (Leukocyte Activated Killer) cells
- CD8 Cytotoxic T cells
- APC (Antigen Presenting Cells)
- Helper T cells: TH1, TH2

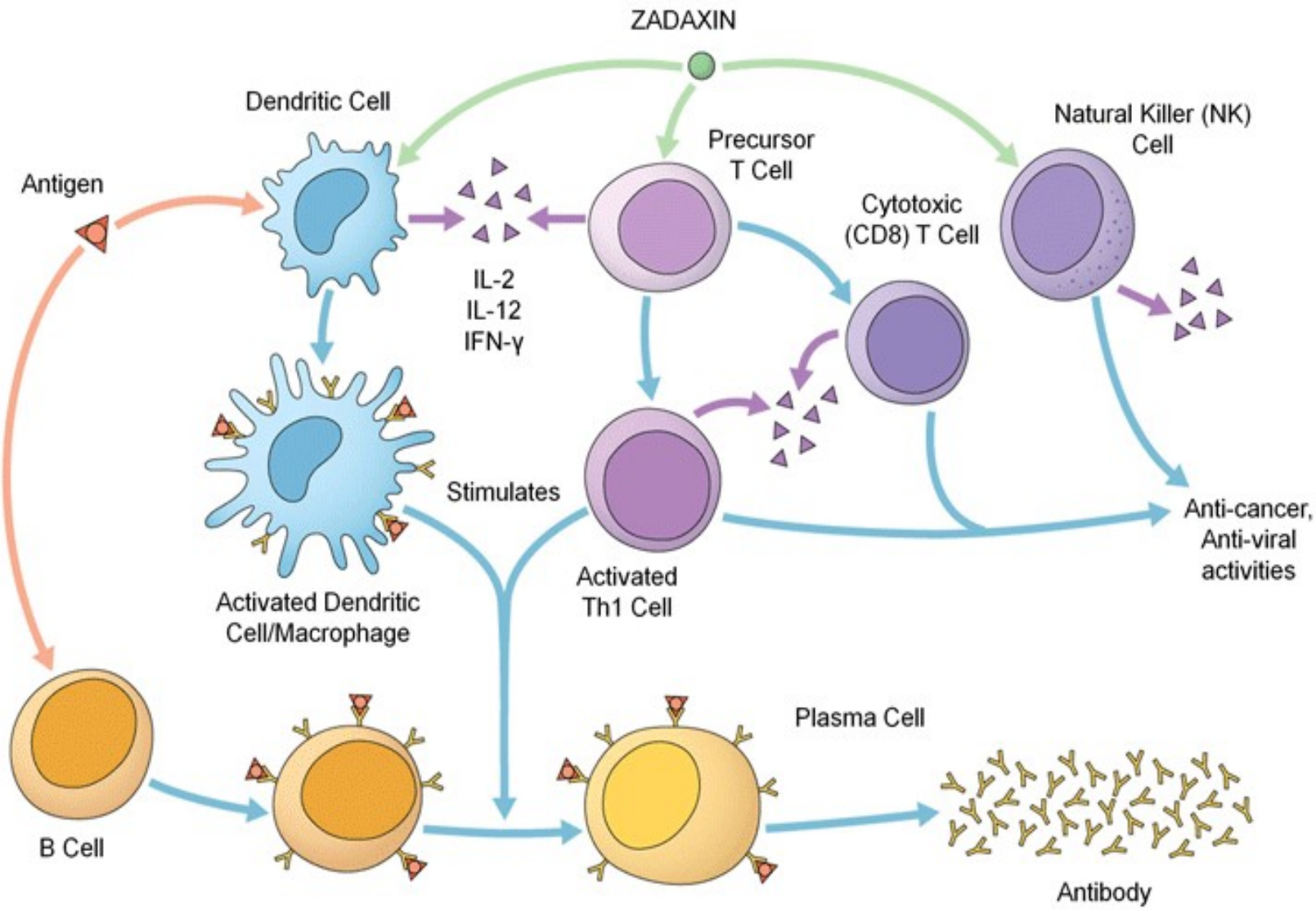
## TH1

- Produce INF$\gamma$, IL2, TNF $\beta$
- Cell mediated immunity
- Interact with intracellular Ag
- Inhibited by IL 10.

## TH2

- B cell proliferation
- Interact with extracellular Ag
- Inhibited by INF $\gamma$.


IMMUNOPHARMACOLOGY
0psonized bacteria
Macrophage
APC
T lymphocyte
B lymphocyte
IL-4,IL-5
IL-2
IL-2
TH1
TH2
IFN-γ
IFN-γ
TNF-β
IFN-γ
Activated Macrophage
Activated NK cells
Activated Cytotoxic T cell
Memory B Cells
Plasma Cells:
-IgG
- IgM
- IgA
- IgD
CELL-MEDIATED IMMUNITY
HUMORAL IMMUNITY


ZADAXIN
Dendritic Cell
Antigen
Precursor
T Cell
Natural Killer (NK)
Cell
Cytotoxic
(CD8) T Cell
IL-2
IL-12
IFN-γ
Stimulates
Activated Dendritic
Cell/Macrophage
Activated
Th1 Cell
Anti-cancer,
Anti-viral
activities
B Cell
Plasma Cell
Antibody

# ADAPTATIVE IMMUNITY…

- **Cytokines**
  - IL1 …..24
  - IL27…..32
  - INF α, β, γ
  - TNF α, β
  - G.CSF
  - GM.CSF
  - Erythropoietin
  - TNF

# Comparative features of innate and adaptive immunity

| Attribute | Innate immunity | Adaptive immunity |
|---|---|---|
| Response time | Immediate responses and do not require prior exposure to microbe. | Several days as clones of antigen-specific lymphocytes |
| Diversity | No appreciable change in quality or magnitude of **repeated exposure** (exception NK cell) | Repeated exposure to a microbe enhances rapidity, magnitude, and **effectiveness** |
| Number & Type of receptor | Recognizes only about **1000 products of microbes** and damaged cells. | Recognize **millions** of different microbial antigens, and can also recognize non microbial environmental Ag |
| Memory response | No memory cell or Trained immunity | Memory cell |

Abbas_Cellular and Molecular Immunology, 9th ed

# APPLIED IMMUNOLOGY

## ***Therapeutic uses***

- Transplant rejection , acute and chronic cases:

***(NOT IN HYPERACUTE AND ACCELERATED)***

  - Autograft
  - Isograft
  - Allograft
  - Xenograft

- Autoimmune disorders.
- Malignancies .
- Proliferative disorders.

# APPLIED IMMUNOLOGY

## SOURCES

- Monoclonal/polyclonal antibodies ; obtained by
  Inoculation
  Hybridoma
  DNA recombinant
  (Chimeric, Humanized)

- Monoclonal = specific, homogenous, expensive

- Polyclonal = nonspecific, variable, inexpensive

# HYBRIDOMA

- Hybridoma = Milstein & Kohler in 1975.

- Hybridomas

  Antibody-forming cells == fused to immortal Plasmacytoma cells.

# APPLIED IMMUNOLOGY

## NOMENCLATURE

- **Muro** = Murine/Mouce source
- **XI or IZ** = Human source
- **UMAB/ZUMAB** = Humanized
- **IMAB/XIMAB** = Chimeric

# BASIC PHARMACOLOGY

## IMMUNOMODULATORS

- Immunosuppressants
- Immunostimulants

# IMMUNOSTIMULANTS

- Aldesleukin: Recombinant IL 2
- Interferon: α, β, γ
- BCG (Bacille Calmette Guerrian):
  TB, In-situ Carcinoma Urinary bladder
- Recombinant TNF α
- Thalidomide: Erythema Nodosum Leprosum, M Myeloma
- Levamisole: Colorectal carcinoma, R . A,
  Hodgkin lymphoma
- Lipopolysaccharides; Gram negative endotoxins

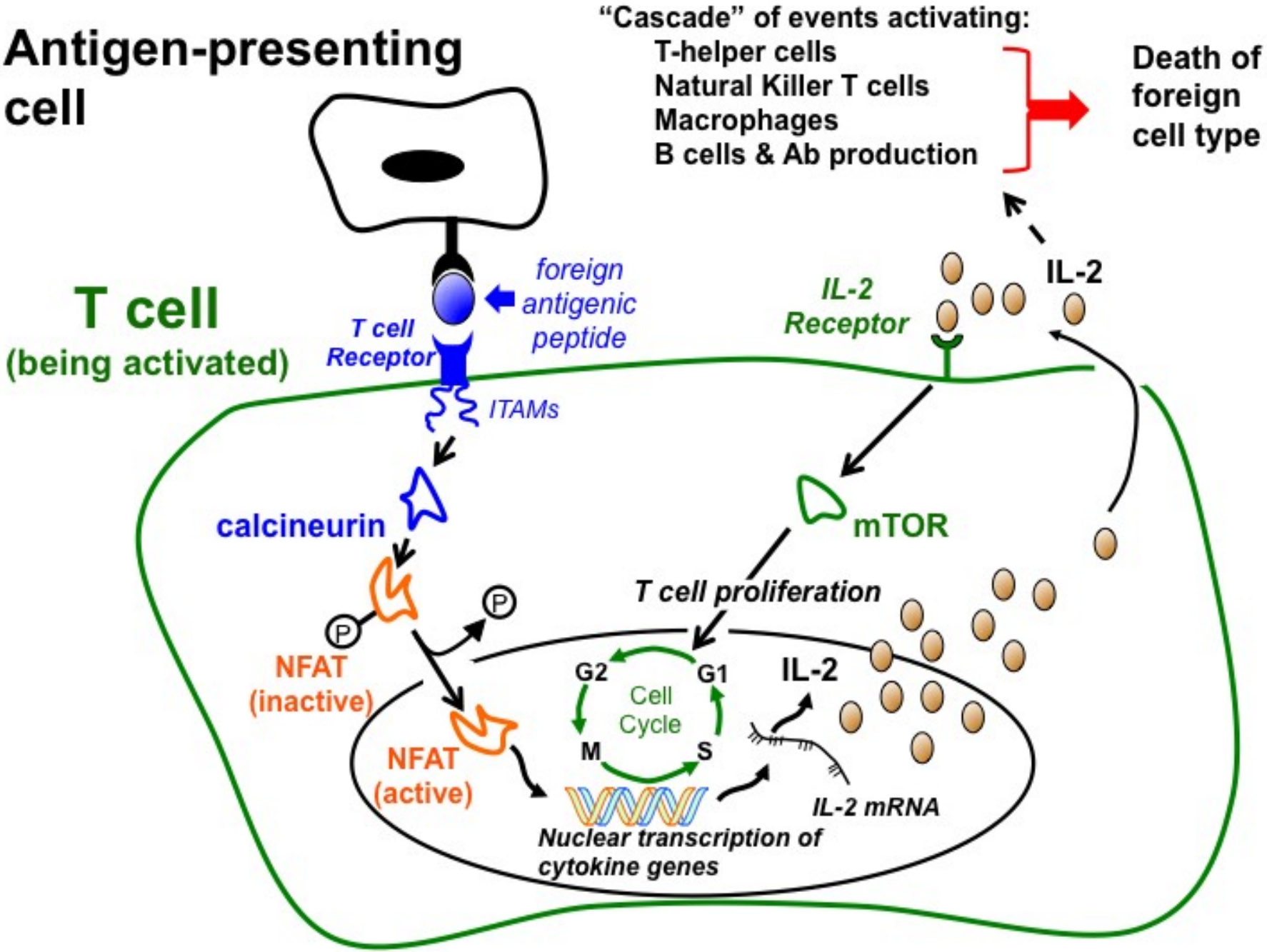
# IMMUNOSUPPRESSANTS

## CLASSIFICATION

- **A:-Corticosteroids**
  - Methylprednisolone
  - Prednisolone
  - Prednisone

# IMMUNOSUPPRESSANTS

- **B:-Immunophilin ligands: Antibiotics**
  - Cyclosporine A (CsA)
  - Tacrolimus (TAC)
  - Pimecrolimus
  - Mammalian target of rapamycin (MTOR) inhibitors
    - Sirolimus (SIR)
    - *(Rapalogs) of SIR*
      - Evorilimus
      - Temsirolimus
  - Fingolimod


Antigen-presenting cell
"Cascade" of events activating:
T-helper cells
Natural Killer T cells
Macrophages
B cells & Ab production
Death of foreign cell type
T cell
(being activated)
foreign antigenic peptide
T cell Receptor
ITAMs
IL-2 Receptor
IL-2
calcineurin
mTOR
T cell proliferation
NFAT (inactive)
NFAT (active)
G2
G1
Cell Cycle
M
S
IL-2
IL-2 mRNA
Nuclear transcription of cytokine genes

# IMMUNOSUPPRESSANTS

- **C:-Enzyme inhibitors**
  - Mycophenolate Mofetil (MMF)
  - Mycophenolate sodium(MMS)
  - Mizoribine
  - Leflunamide
  - Pentostatin (ADA inhibitor)

# IMMUNOSUPPRESSANTS

- **D:- Cytotoxic agents**
  - Azathioprine (AZT)
  - 6 Mercaptopurine (6 MP)
  - Cyclophosphamide
  - Hydroxychloroquine
  - Methotrexate
  - Thalidomide
  - *(Immunomodulatory derivatives of thalidomide* ***(IMIDS)***
    - Lenalidomide
    - Pomalidomide )

# IMMUNOSUPPRESSANTS

- **D:- …….Cytotoxic agents**

  - Sulphasalazine
  - Cytosine Arabinoside (Cytarabine)
  - Dactinomycin
  - Leflunomide/ FK778
  - Vincristine
  - Vinblastine
  - Pentostatin
  - Fingolimod
  - D Penicillamine (cysteine analogue)

# IMMUNOSUPPRESSANTS

- **E:- Immunosuppressive antibodies**

  - Anti thymocyte globulin (ATG / ALG)
  - Muromonab CD3 (OK3)
  - Polyclonal Intra Venous Immuno Globulins (IVIG)
  - Hyper immune Globulin
    - HBV,
    - Rabies
    - Tetanus,
    - Digoxin
  - Rho (D) immune Globulins.

# IMMUNOSUPPRESSANTS

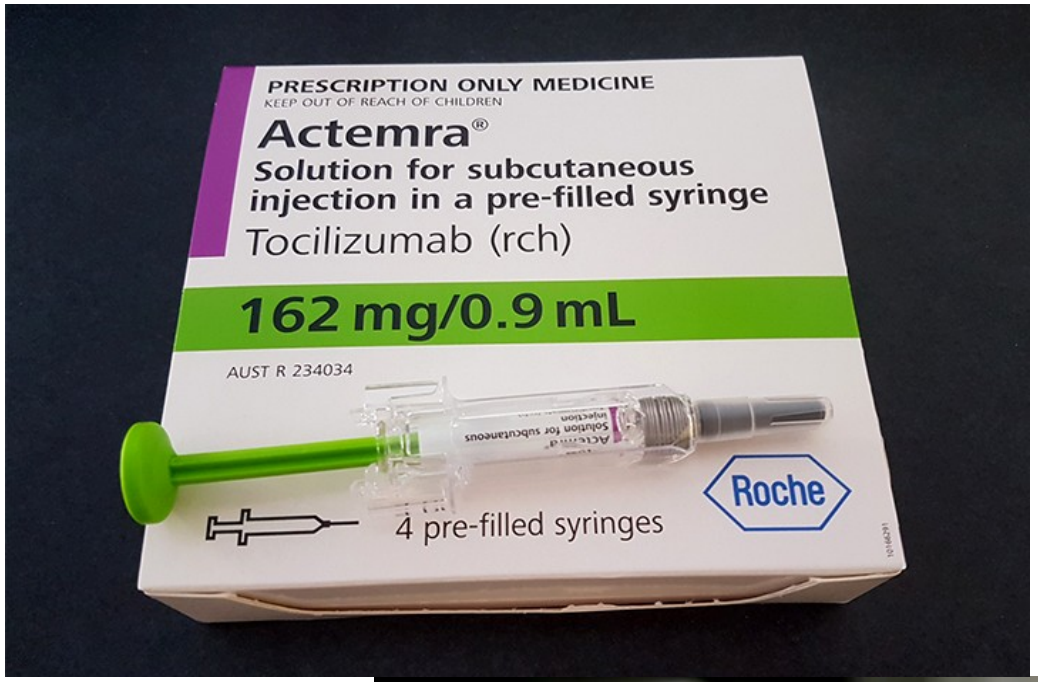
## F:- MONOCLONAL ANTIBODIES (MAB)

- **1:-** ***Antitumor MAB***
  - Alemtuzumab ; anti CD 52 .
  - Bevacizumab ; VEGF.
  - Cetuximab ; VEGF.
  - Gemtuzumab ; CD3
  - Rituximab ; CD20
  - Trastuzumab ; HER-2/ neu
  - Imatinib ; Tyrosine kinase.
  - Geftinib (iressa) ; Tyrosine kinase.
  - Erlotinib ; Tyrosine kinase.

# IMMUNOSUPPRESSANTS.. MAB

- **2:- Isotopes for tumors (scan/ destroy)**

  - Acritumomab ; C E A.
  - Capromab penditide ; P S A.
  - Ibritumomab ; CD20.
  - Nofetumomab ; oat cell carcinoma
  - Tositumomab ; CD20.


PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Actemra®
Solution for subcutaneous injection in a pre-filled syringe
Tocilizumab (rch)
162 mg/0.9 mL
AUST R 234034
4 pre-filled syringes
Roche


Actemra®
(tocilizumab)
200 mg/10 mL
Sterile Solution
For Intravenous use only
Ronly
For single use only.
Preservative-free. Discard unused portion
Vial Contains:
200 mg in 10 mL
Single Use Vial
Roche


RoActemra®
20 mg/mL
solution à diluer
pour perfusion
Tocilizumab
400 mg/20 mL
Voie intraveineuse pour perfusion après dilution
1 flacon de 20 mL
Roche

# IMMUNOSUPPRESSANTS.. MAB

- **3:- <u>Anti inflammatory/immune MAB</u>**

- ***Anti IL 6***
  - Tocilizumab (IL 6 Receptor antibody)
  - Sarilumab (IL 6 Receptor antibody)
  - Siltuximab (IL 6 neutralizing antibody)
- ***Anti TNFα***
  - Adalimumab
  - Etanercept
  - Infliximab
- ***Anti CTLA-4***
  - Iplimumab

# IMMUNOSUPPRESSANTS.. MAB

- ***Anti CD28***
  - **Ab**atacept ;CD80/86
- ***Anti LFA 3***
  - Alefacept ; CD2
- ***IL2 antagonist***
  - Basiliximab
  - Daclizumab

# IMMUNOSUPPRESSANTS.. MAB

- ***IL 1 antagonists*** Anakinra

- ***Anti LFA-1***

  Efalizumab ;ICAM 1

- ***Anti IgE antibodies***

  Omalizumab

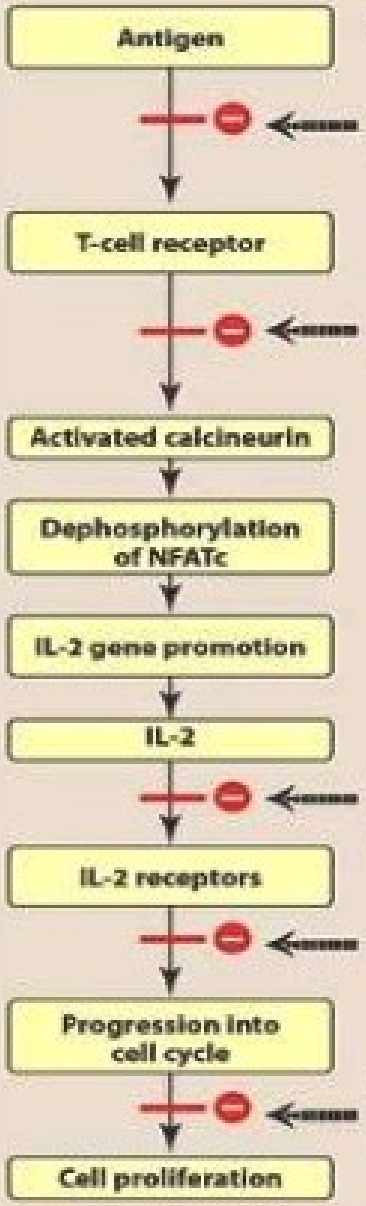
# IMMUNOSUPPRESSANTS.. MAB

- ***Miscellaneous anti inflammatory MABs***
  - Abciximab
  - Palivizumab
  - Immunomodulators for HIV:
    Inosiplex
    DTC (Diethyl Carbamate)
  - Immunomodulators for DiGeorge Syndrome
    Thymosin

# FLOW CHART:

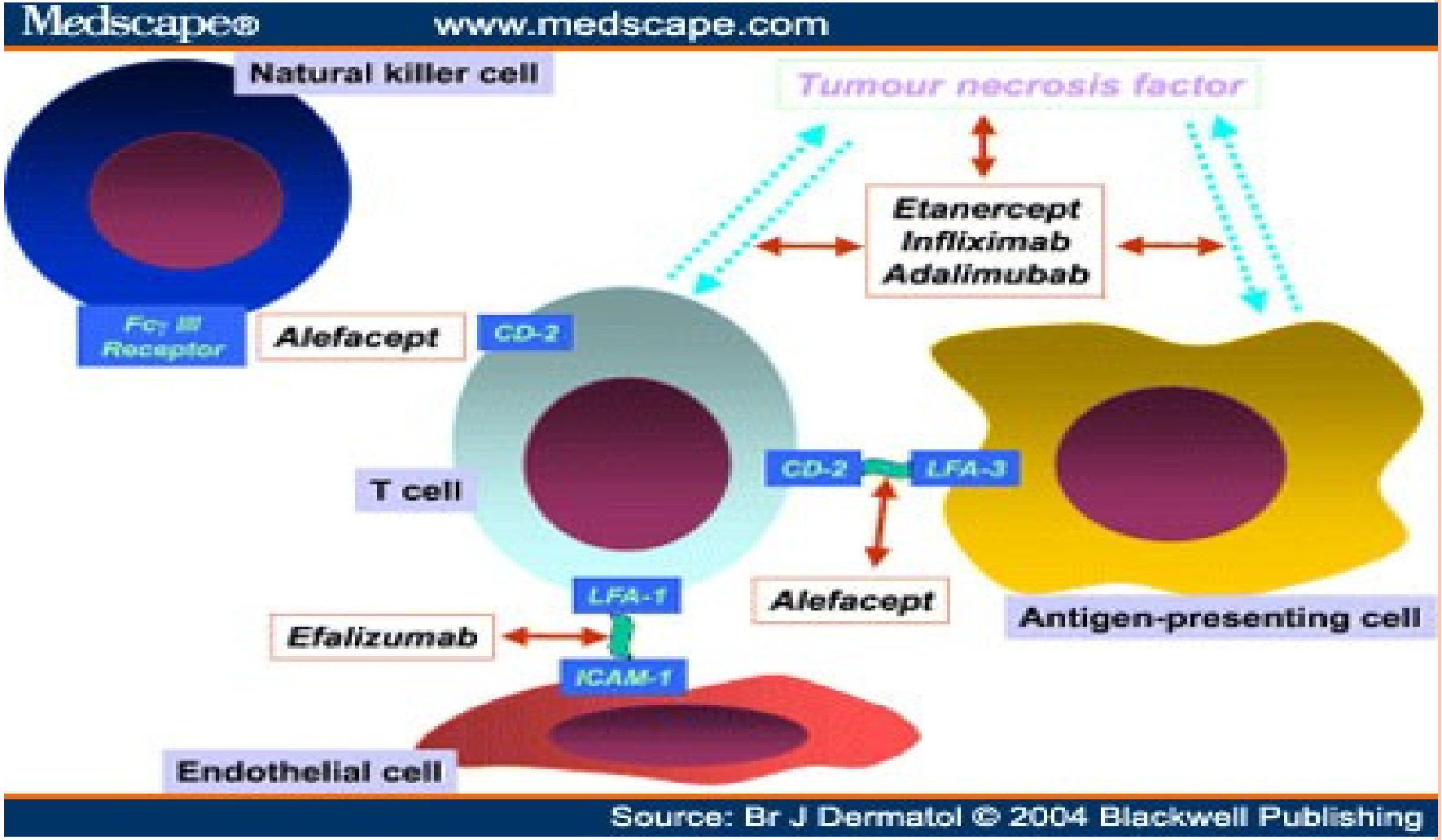
# *INTERACTIONS*

# ACTION OF IMMUNOSUPPRESSANTS

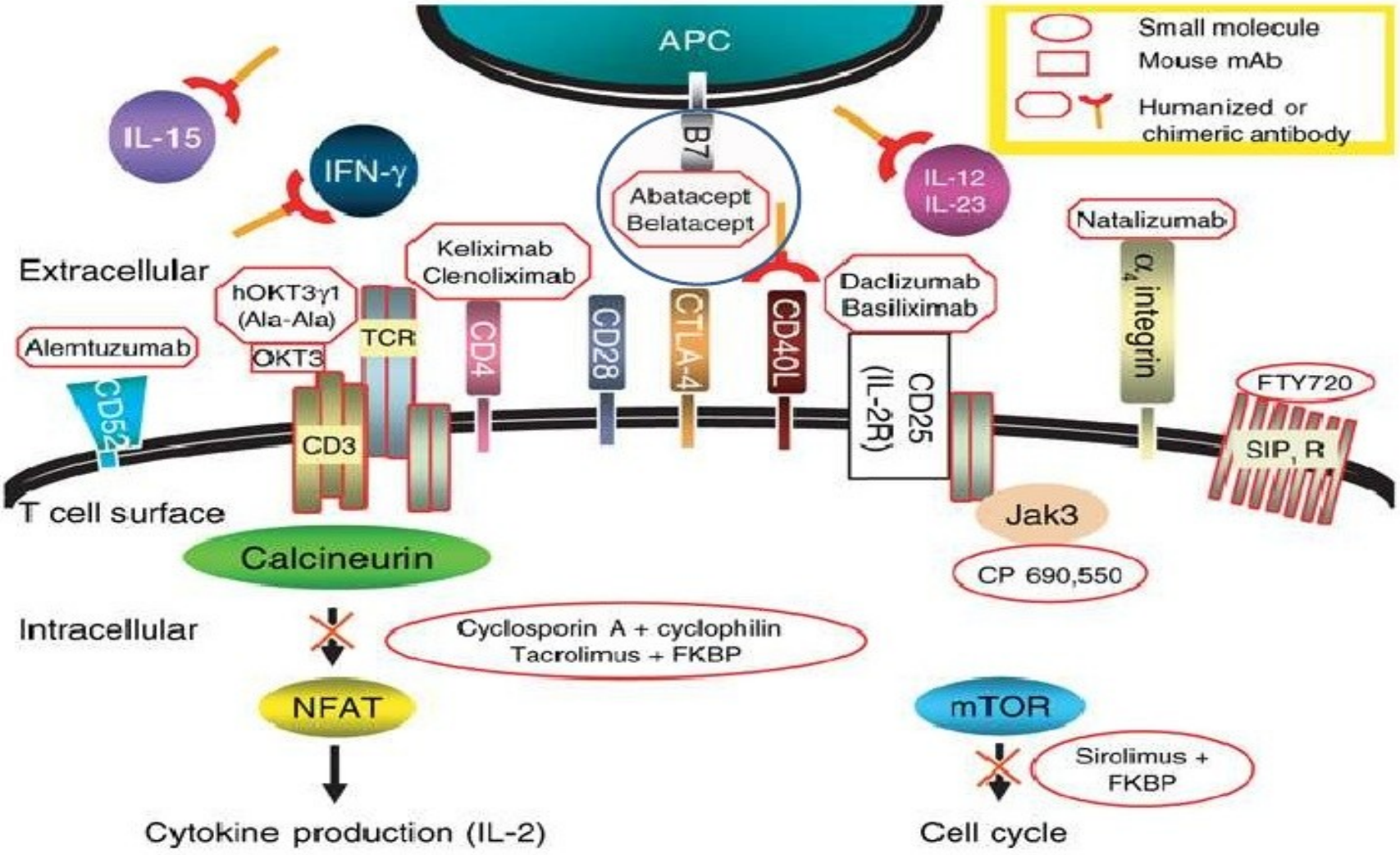



| DRUG | ACTION | ADVERSE EFFECTS |
|---|---|---|
| *Alemtuzumab* | Depletion of T lymphocytes | Cytokine release syndrome; neutropenic, pancytopenia |
| *Antithymocyte globulins* | Destruction of T lymphocytes | Profound immunosuppression |
| *Muromonab-CD3* | Destruction of T lymphocytes | Cytokine release syndrome |
| *Cyclosporine* | Blocks calcineurin and inhibits IL-2 synthesis | Nephrotoxicity, neurotoxicity, hepatotoxicity |
| *Tacrolimus (FK506)* | Blocks calcineurin and inhibits IL-2 synthesis | Nephrotoxicity, neurotoxicity, diabetes |
| *Basiliximab* | Blocks the IL-2 receptor | Gastrointestinal disorders |
| *Daclizumab* | Blocks the IL-2 receptor | Gastrointestinal disorders |
| *Sirolimus* | Blocks cytokine-stimulated cell proliferation | Hyperlipidemia, thrombocytopenia, leukopenia, headache, nausea |
| *Azathioprine* | Inhibits purine synthesis | Bone marrow suppression, hepatotoxicity, thrombocytopenia, anemia, neoplasia |
| *Mycophenolate mofetil* | Inhibits purine synthesis | GI upset, nausea, diarrhea, leukopenia, tumors, increases susceptibility to infection |

# FLOW CHART


Medscape®
www.medscape.com
Natural killer cell
Tumour necrosis factor
Etanercept
Infliximab
Adalimubab
Fcγ III Receptor
Alefacept
CD-2
T cell
CD-2
LFA-3
Alefacept
Antigen-presenting cell
LFA-1
Efalizumab
ICAM-1
Endothelial cell
Source: Br J Dermatol © 2004 Blackwell Publishing

# FLOW CHART


APC
Small molecule
Mouse mAb
Humanized or chimeric antibody
IL-15
IFN-γ
B7
Abatacept
Belatacept
IL-12
IL-23
Natalizumab
Extracellular
Keliximab
Clenoliximab
hOKT3γ1 (Ala-Ala)
OKT3
TCR
CD4
CD28
CTLA-4
CD40L
Daclizumab
Basiliximab
CD25 (IL-2R)
α4 integrin
Alemtuzumab
CD52
CD3
FTY720
S1P, R
T cell surface
Jak3
CP 690,550
Calcineurin
Intracellular
Cyclosporin A + cyclophilin
Tacrolimus + FKBP
NFAT
mTOR
Sirolimus + FKBP
Cytokine production (IL-2)
Cell cycle

# FLOW CHART: *INTERACTIONS*

## ***ANTIGEN ++++ RECEPTOR***

- Alemtuzumab
- ATG
- Muromonab CD3

## ***RECEPTOR++++++ IL 1***

- Anakinra

# FLOW CHART: *INTERACTIONS*

## ***RECEPTOR+++++++ TNFα***

- Adalimumab
- Etanercept
- Infliximab
- Thalidomide

## ***RECEPTOR+++++++ Ig E***

- Omalizumab

# FLOW CHART: *INTERACTIONS*

## ***RECEPTOR +++ ACTIVATED CALCINEURIN***

- Cyclosporin
- Tacrolimus

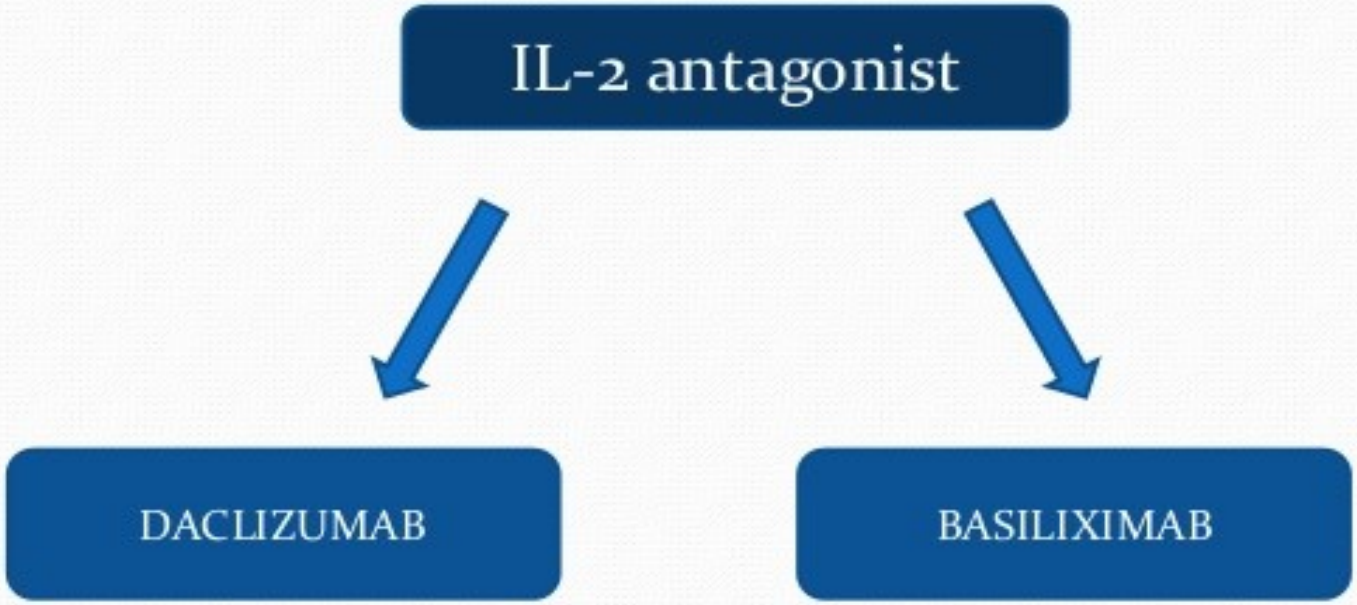
*CALCINEURIN / N.F.A.T c*_____

_____*N.F.A.T / IL 2 gene*

_____*IL 2 gene / RIBOSOMES*

- **Anti CD25 (IL-2 R alpha) on T lymphocytes**
  - Basiliximab
  - Daclizumab

# *INTERLEUKIN-2 RECEPTOR antagonist:-*




- Both agents have been approved for prophylaxis of acute rejection in renal transplantation.

# FLOW CHART: *INTERACTIONS*

***MEMBRANE IL 2 RECEPTOR+++ CELL CYCLE***

- Sirolimus

***CYTOPLASMIC RECEPTORS+++ GENES***

- Glucocorticoids
- [

***PROGRESSION OF CELL CYCLE***

- Azathioprine
- Mycophenolate
- Methotrexate

# TRANSPLANT: APPLIED PHARMACOLOGY

## SUMMARY

- Graft rejection is an immunologic response displaying the attributes of specificity , memory , and self / nonself recognition . There major types of rejection reactions :-
- Hyperacute rejection mediated by preexisting host antibodies to graft antigens.
- Acute graft rejection in which T helper cells mediate tissue damage
- Chronic rejection involve both cellular and humoral immune components.

# TRANSPLANT: APPLIED PHARMACOLOGY

## CONT.....

- The immune response to tissue antigens encoded within MHC is the strongest force in rejection.
- The match between a recipient and potential graft donor is assessed by typing MHC class I and class II antigens.
- The process of graft rejection occurs in two stages –sensitization and effector stage.
- Certain sites in the body including cornea of eye , brain , testes ,and uterus do not reject transplants despite genetic mismatch between donor and recipient.
- Specific tolerance to alloantigens is induced by exposure to them in utero or by injection of neonates.

# CLINICAL PHARMACOLOGY IMMUNOSUPPRESSANT IN ORGAN TRANSPLANT

**Immunosuppressive drugs used to treat transplant rejection**

**Calcineurin inhibitors**
- Ciclosporin
- Tacrolimus

**mTOR inhibitors**
- Sirolimus
- Everolimus

**Anti-proliferatives**
- Azathioprine
- Mycophenolic acid

**Corticosteroids**
- Prednisolone
- Hydrocortisone

**Antibodies**
- Monoclonal anti-IL-2Rα receptor antibodies
  - Basiliximab
  - Daclizumab
- Polyclonal anti-T-cell antibodies
  - Anti-thymocyte globulin (ATG)

# CLINICAL PHARMACOLOGY IMMUNOSUPPRESSANT IN ORGAN TRANSPLANT

## Classification of Immunosuppressive Therapies Used in Organ Transplantation

- Glucocorticoids
- Small-molecule drugs
  - Immunophilin-binding drugs
    - Calcineurin inhibitors
      - Cyclophilin-binding drugs: cyclosporine,ISA(TX)247
      - FKBP12-binding drugs: tacrolimus,modified release tacrolimus
    - Target-of-rapamycin inhibitors: sirolimus,everolimus
  - Inhibitors of nucleotide synthesis
    - Purine synthesis (IMPDH) inhibitors
      - Mycophenolate mofetil
      - Enteric-coated mycophenolic acid
      - Mizoribine
    - Pyrimidine synthesis (DHODH) inhibitors
      - Leflunomide
      - FK778
  - Antimetabolites: azathioprine
  - Sphingosine-1-phosphate–receptor antagonists:Fingolimod

# CLINICAL PHARMACOLOGY IMMUNOSUPPRESSANT IN ORGAN TRANSPLANT

- Protein drugs
  - Depleting antibodies (against T cells, B cells, or both)
    - Polyclonal antibody: horse or rabbit antithymocyte globulin
    - Mouse monoclonal anti-CD3 antibody (muromonab-CD3)
    - Humanized monoclonal anti-CD52 antibody (alemtuzumab)
    - B-cell–depleting monoclonal anti-CD20 antibody (rituximab)
  - Nondepleting antibodies and fusion proteins
    - Humanized or chimeric monoclonal anti-CD25 antibody (daclizumab, basiliximab)
    - Fusion protein with natural binding properties:CTLA-4–Ig Belatacept
  - Intravenous immune globulin

# IMMUNOSUPPRESSION IN ORAGN TRANSPLANTATION

| INDUCTION REGIMEN | MAINTENANC-E REGIMEN | ANTI-REJECTION REGIMEN |
| --- | --- | --- |
| Given in perioperative period. | Given for prolonged period. | Given to suppress an episode of acute rejection. |
| Cyclosporine+ Predisolone+ Azathioprine | Cyclosporine+ Predisolone+ Azathioprine | Methylprednisolone 0.5-1g i.v. daily for 3-5 days. |

# CLINICAL PHARMACOLOGY

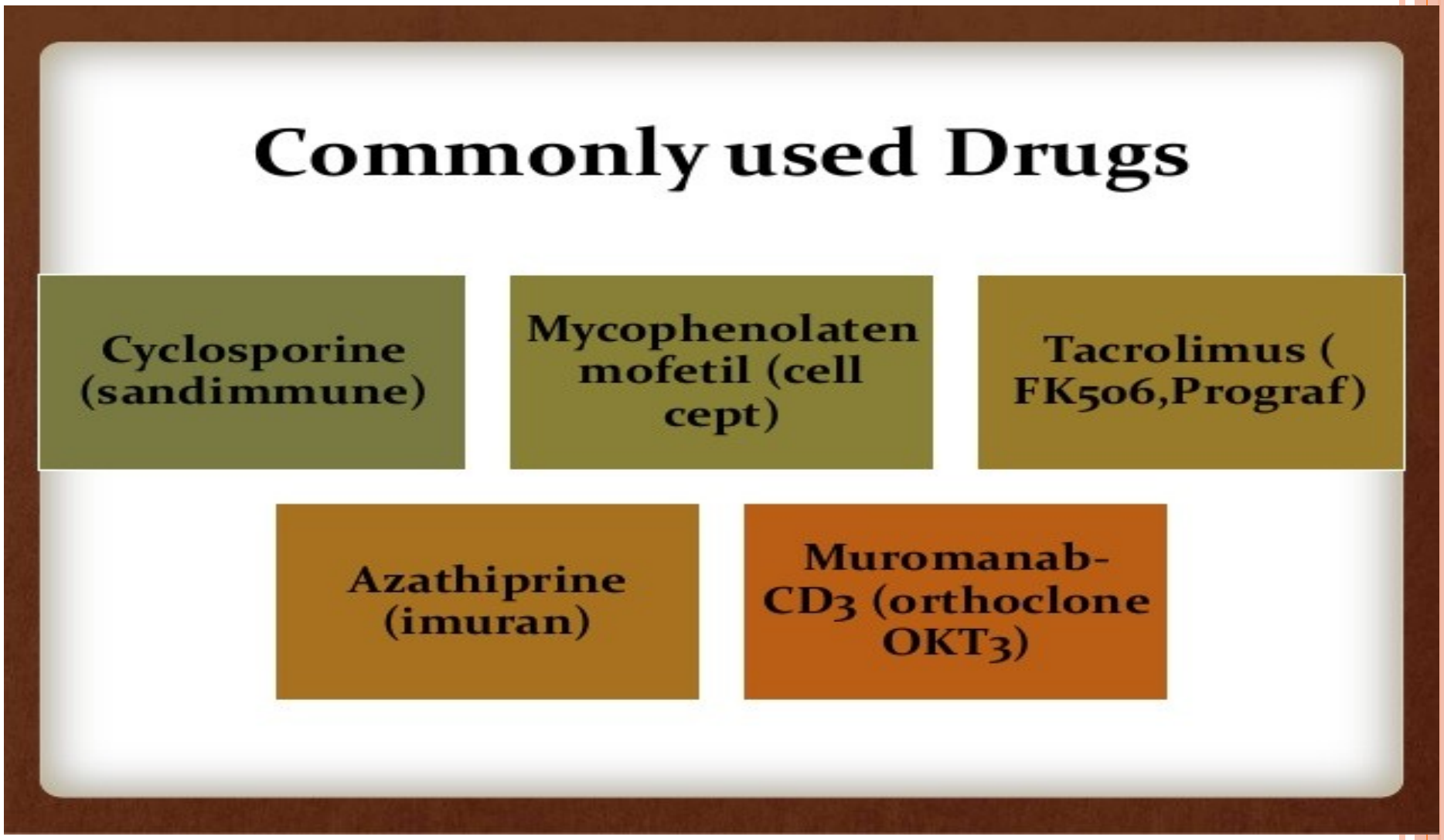
**Table 1**

**Oral Immunosuppressants Commonly Used in Maintenance Therapy**

| Drug | Type of Transplant | Metabolism | Adult Dosing Guide |
|---|---|---|---|
| Cyclosporine (Neoral) | Kidney, liver, heart | Liver (CYP3A4) | Kidney: 9 ± 3 mg/kg/day*<br>Liver: 8 ± 4 mg/kg/day*<br>Heart: 7 ± 3 mg/kg/day* |
| Cyclosporine (Sandimmune) | Kidney, liver, heart | Liver (CYP3A4) | 10 to 15 mg/kg/day, then tapered by 5%/week to 5 to 10 mg/kg/day* |
| Tacrolimus | Kidney, liver (heart—not FDA approved) | Liver (CYP3A4) | Kidney: 0.2 mg/kg/day in two divided doses every 12 hours*<br>Liver: 0.1 to 0.15 mg/kg/day in two divided doses every 12 hours* |
| Sirolimus | Kidney (heart, lung, islet cell—not FDA approved) | Liver (CYP3A4) | Loading dose: 6 mg; maintenance dose in combination with cyclosporine is 2 mg/day*<br>In absence of cyclosporine, dose is about four times higher* |
| Azathioprine | Kidney | Erythrocytes, liver | 3 to 5 mg/kg/day; then 1 to 3 mg/kg/day |
| Mycophenolate mofetil | Kidney, liver, heart | Liver (glucunoryl transferase) | 1,000 mg twice daily |
| Mycophenolate sodium | Kidney | Liver (glucunoryl transferase) | 720 mg twice daily |

** Further dosing needs to be adjusted based on recommended trough concentration guidelines of the institution.*

# GROUP: IMMUNOSUPPRESSANT



# REFERENCES


- **Basic and Clinical Pharmacology: Katzung BG, Masters SB, Trevor AJ. 14th Edition.**
- **Katzung & Trevor's Pharmacology: Examination & Board Review. 12th Edition**
- **Lippincott's Illustrated Reviews: Pharmacology, Clark MA, Finkel R, Rey JA, Whalen K. 7th Edition**
- **Goodman & Gilman's The Pharmacological Basis of Therapeutics: Brunton LL. 12th Edition**

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