

IMMUNO-MODULATING DRUGS

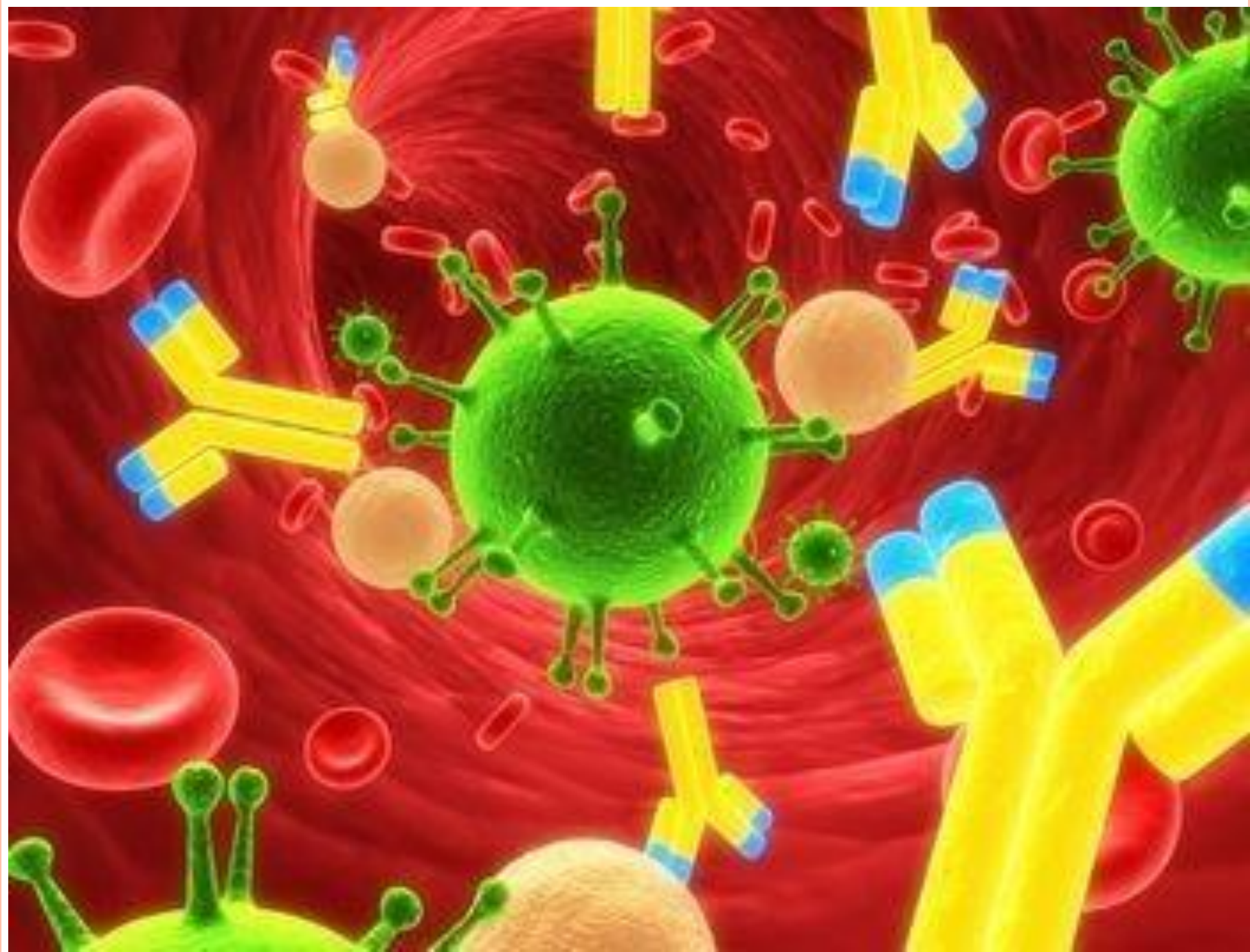
INTRODUCTION/CLASSIFICATION

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

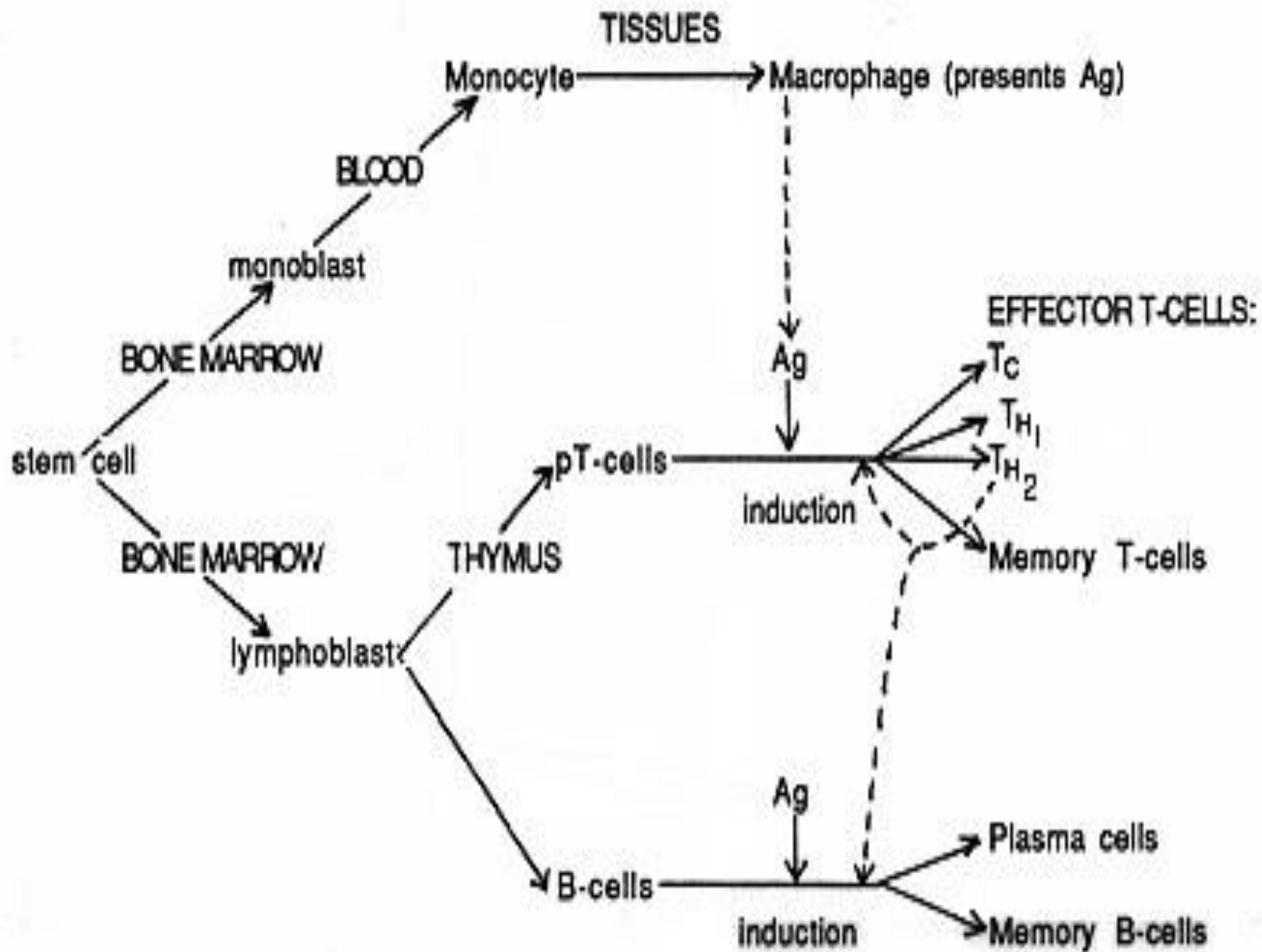


THE IMMUNO SYSTEM

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.





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, lysozyme
- **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



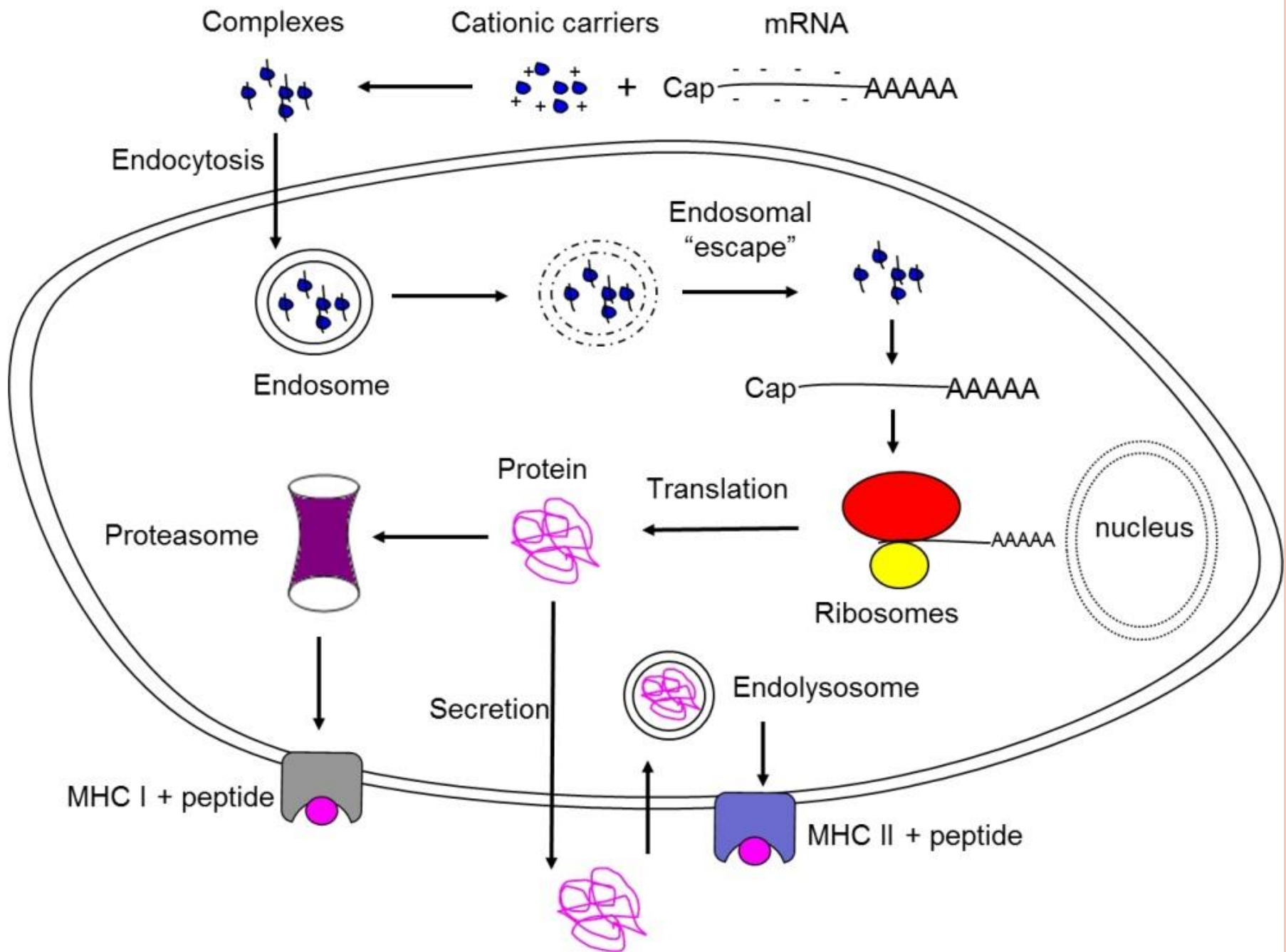
COMPLEMENTS in Innate Immunity:

- 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






INNATE IMMUNITY.....

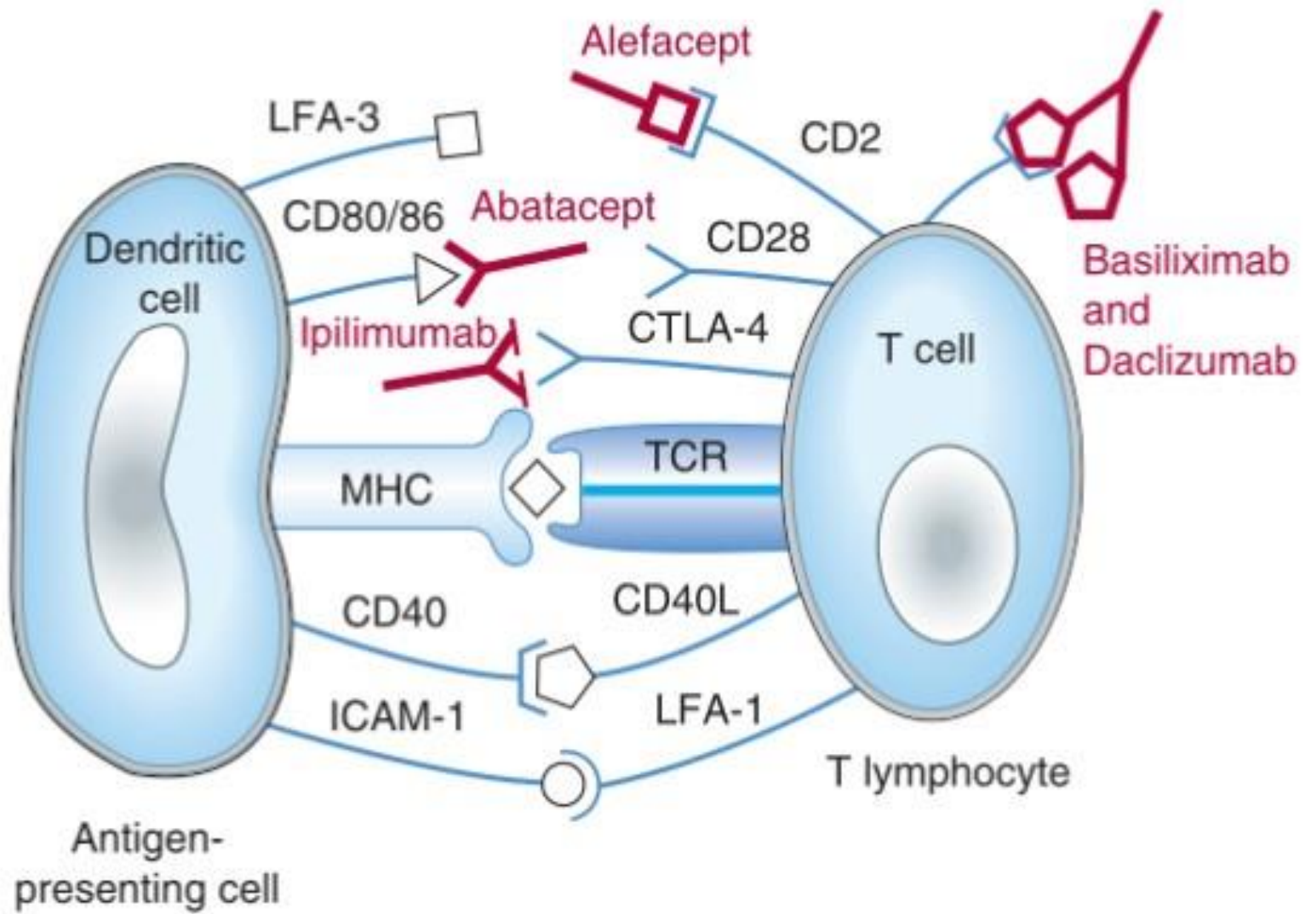
Major Histocompatibility Complex (MHC)

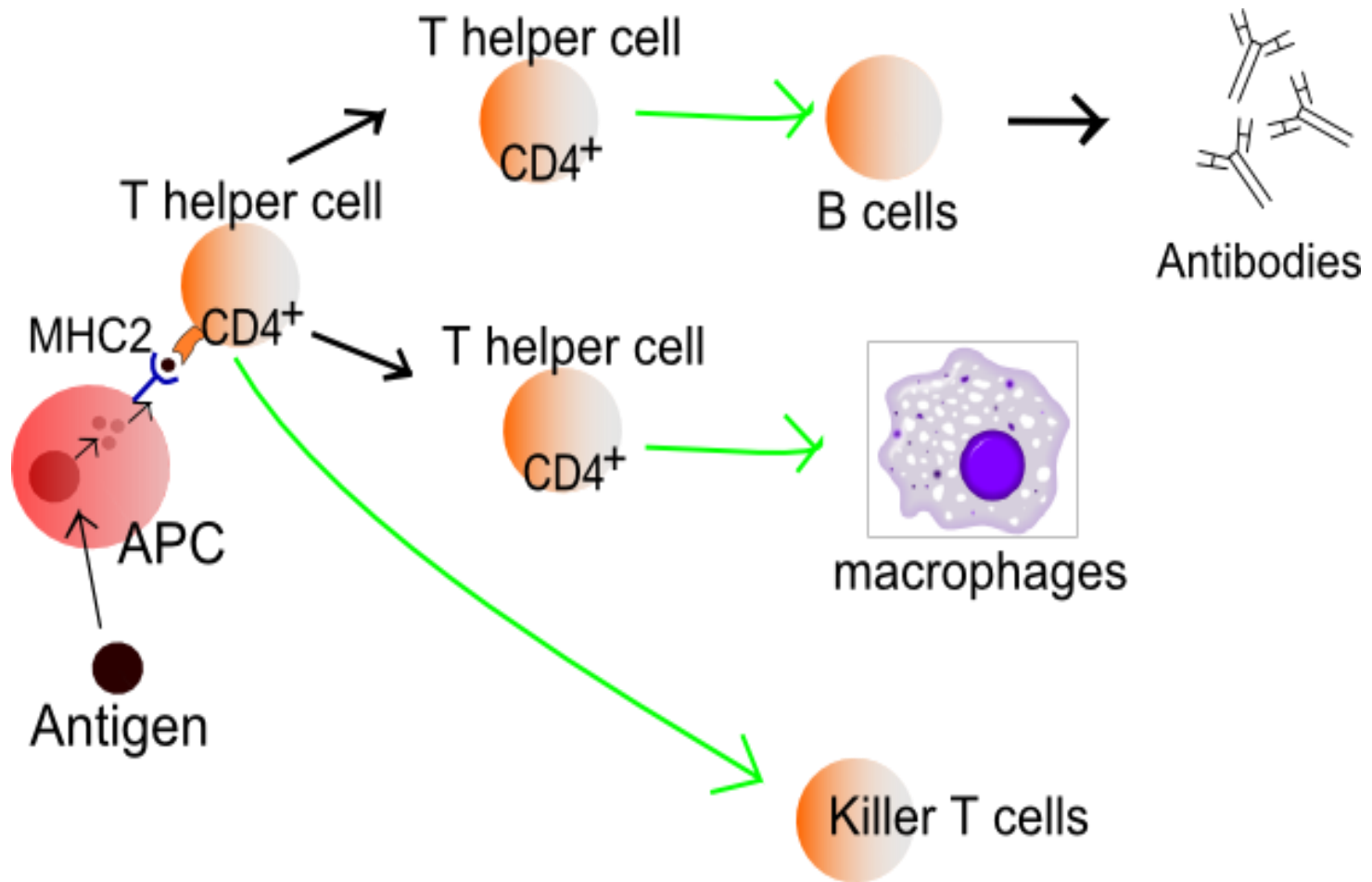
□ MHC 1:

- All cells
- Cytotoxic T cells
- Cell mediated immunity
- Viricidal , tumoricidal.
- Interplays with IL2 , TNF , INF

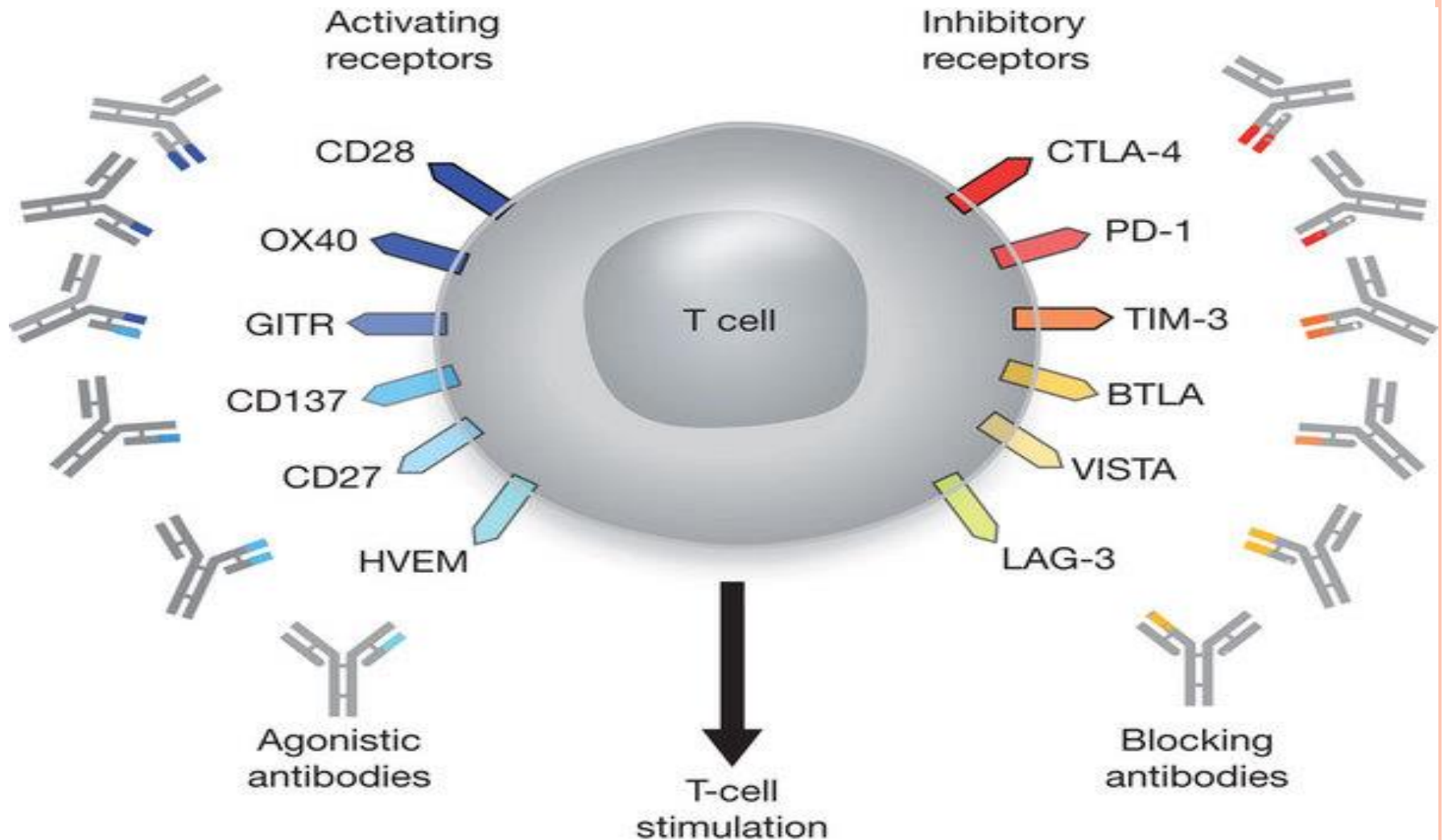
□ MHC II

- 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
- 





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

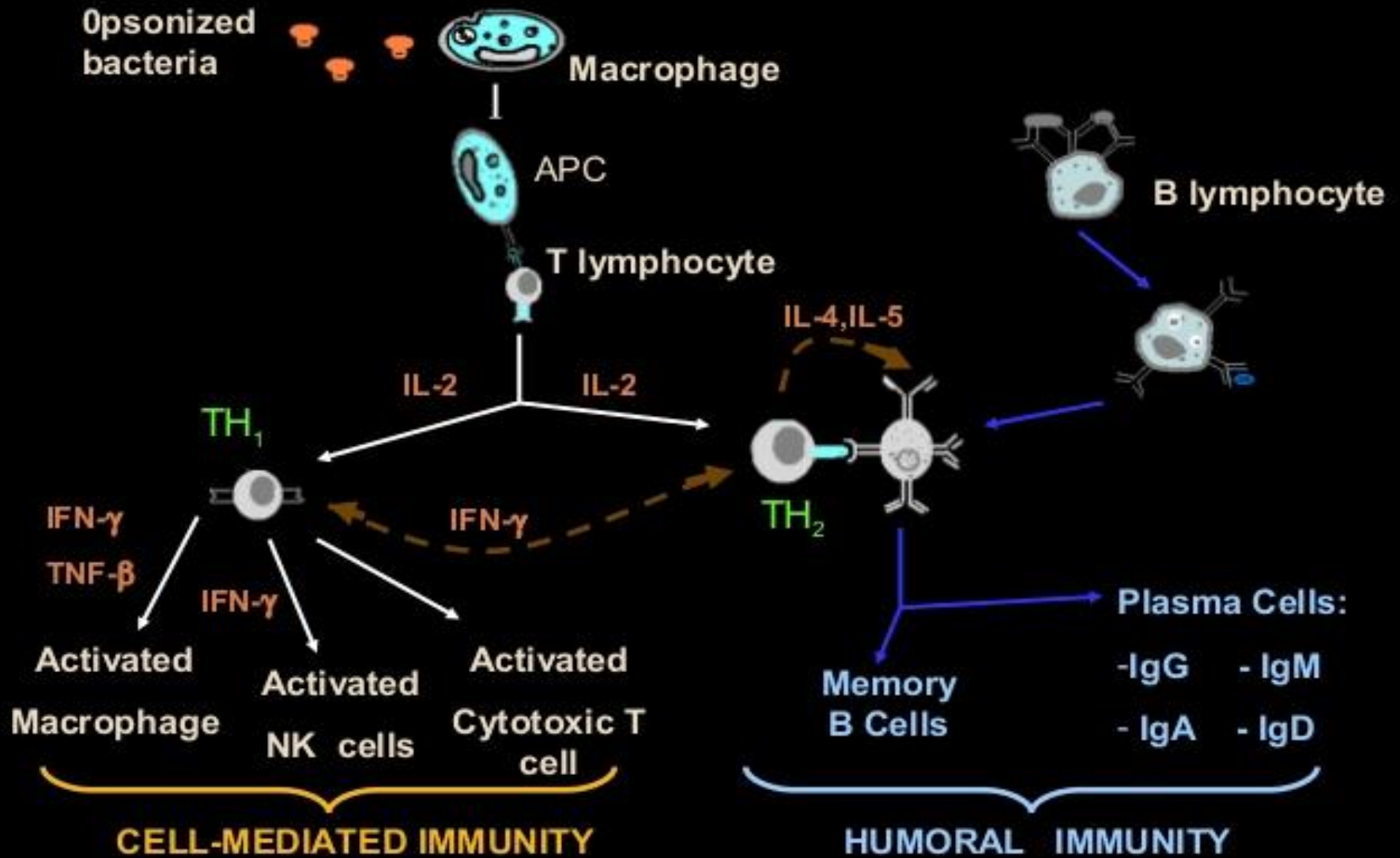
- Produce $\text{INF}\gamma$, IL2, $\text{TNF}\beta$
- Cell mediated immunity
- Interact with intracellular Ag
- Inhibited by IL 10.

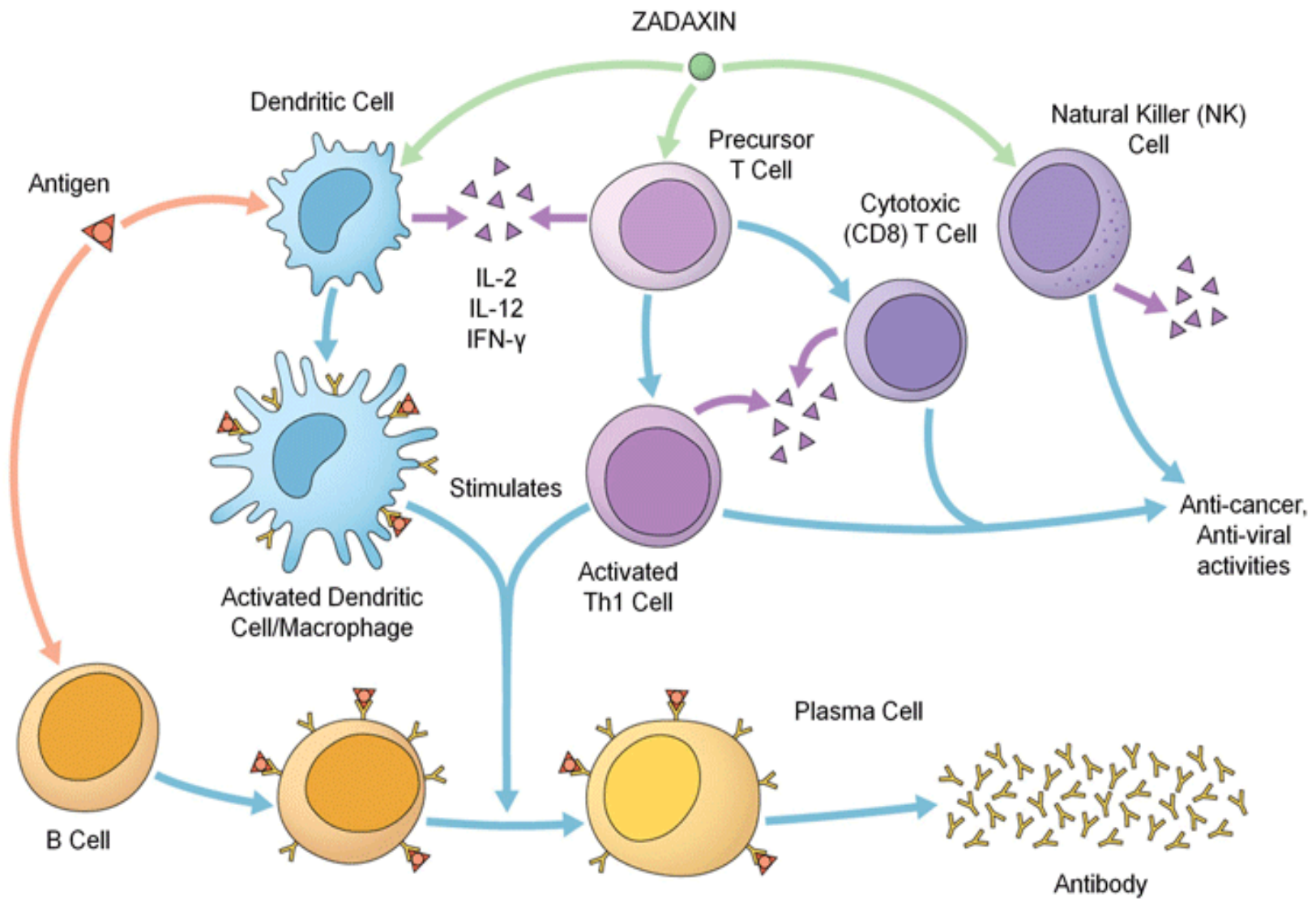
TH2

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



IMMUNOPHARMACOLOGY





ADAPTATIVE IMMUNITY...

- **Cytokines**
 - IL124
 - IL2732
 - 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

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

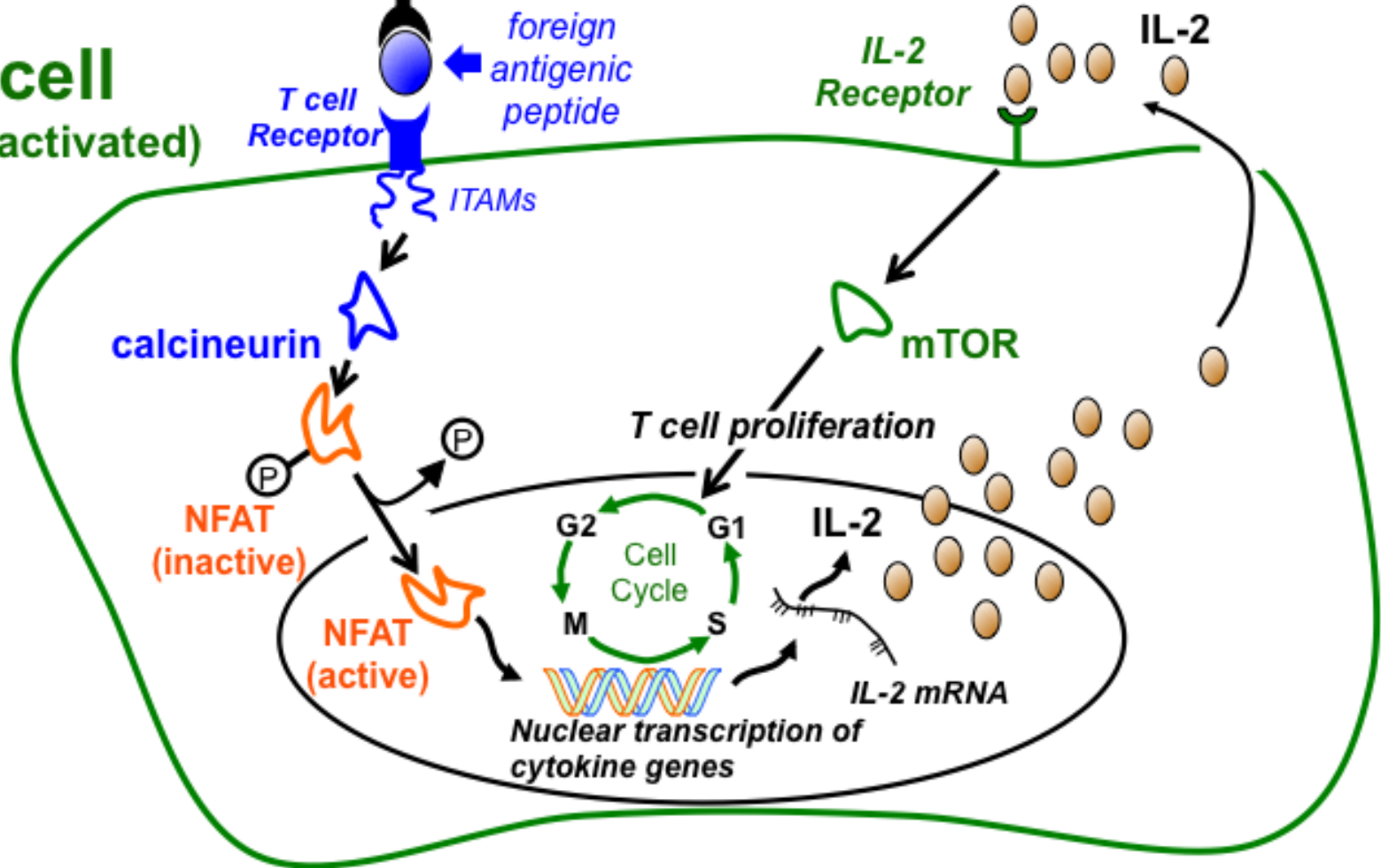


“Cascade” of events activating:

- T-helper cells
- Natural Killer T cells
- Macrophages
- B cells & Ab production

Death of foreign cell type

T cell
(being activated)



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.
- Gefitinib (iressa) ; Tyrosine kinase.
- Erlotinib ; Tyrosine kinase.

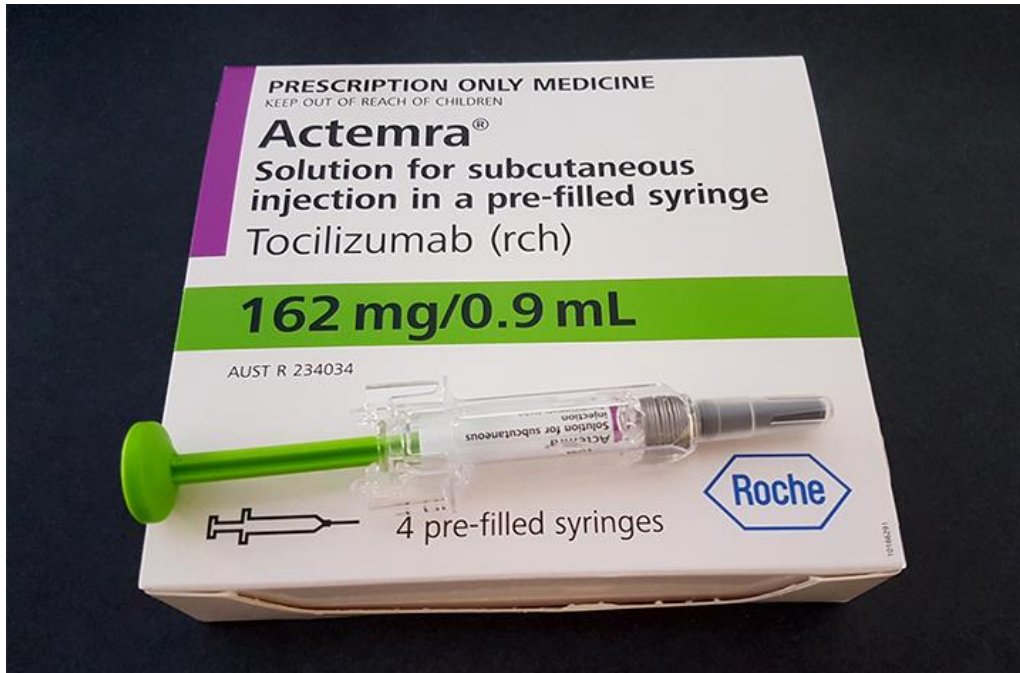


IMMUNOSUPPRESSANTS.. MAB

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

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





IMMUNOSUPPRESSANTS.. MAB

❖ 3:- Anti inflammatory/immune MAB

❑ *Anti IL 6*

- Tocilizumab (IL 6 Receptor antibody)
- Sarilumab (IL 6 Receptor antibody)
- Siltuximab (IL 6 neutralizing antibody)

❑ *Anti TNF α*

- Adalimumab
- Etanercept
- Infliximab

❑ *Anti CTLA-4*

- Iplimumab



IMMUNOSUPPRESSANTS.. MAB

□ ***Anti CD28***

- **Abatacept ;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



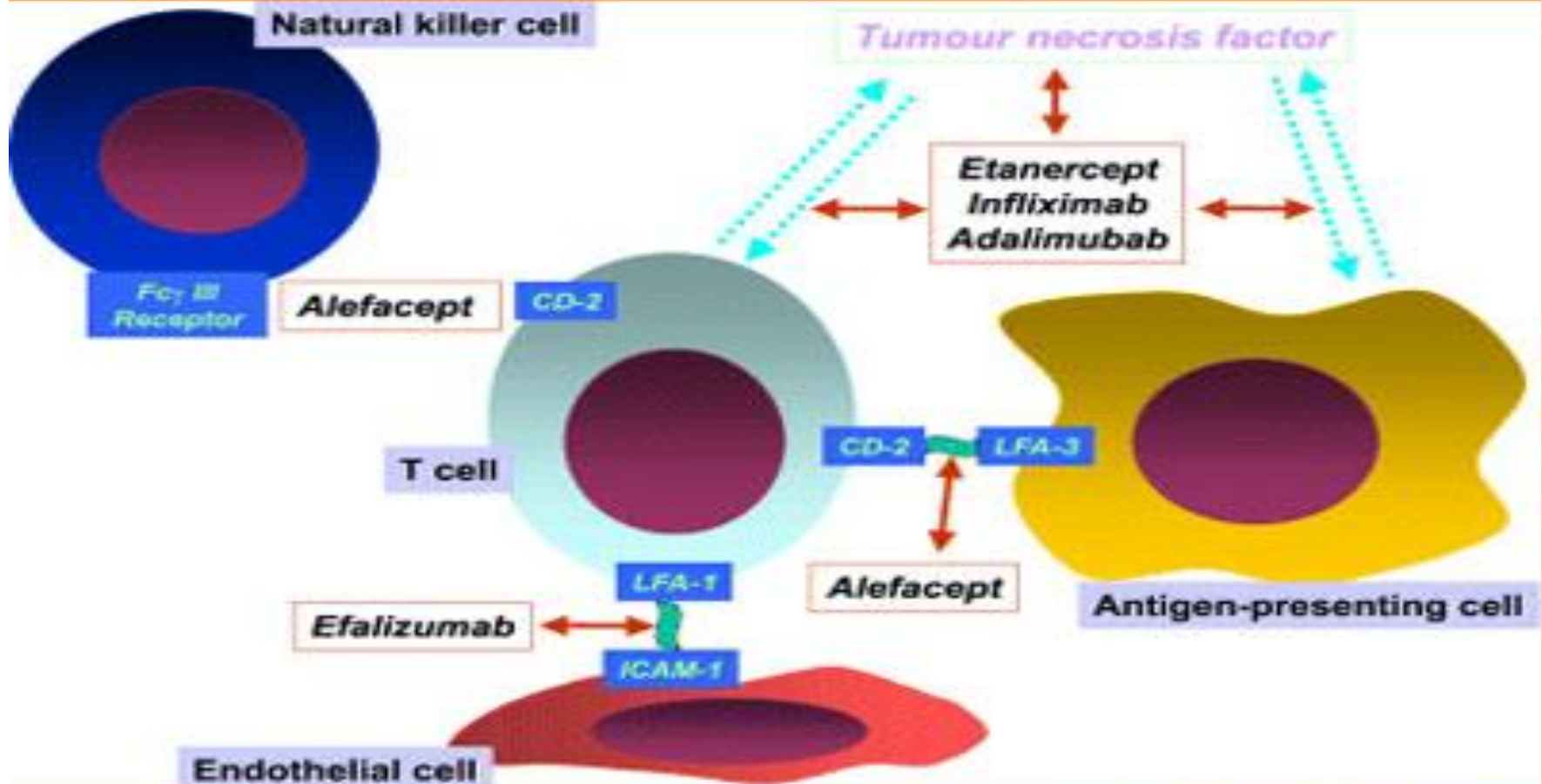
ACTION OF IMMUNOSUPPRESSANTS

	DRUG	ACTION	ADVERSE EFFECTS
<pre> graph TD A[Antigen] --> B[T-cell receptor] B --> C[Activated calcineurin] C --> D[Dephosphorylation of NFATc] D --> E[IL-2 gene promotion] E --> F[IL-2] F --> G[IL-2 receptors] G --> H[Progression into cell cycle] H --> I[Cell proliferation] </pre>	<p><i>Alemtuzumab</i></p> <p><i>Antithymocyte globulins</i></p> <p><i>Muromonab-CD3</i></p>	<p>Depletion of T lymphocytes</p> <p>Destruction of T lymphocytes</p> <p>Destruction of T lymphocytes</p>	<p>Cytokine release syndrome; neutropenic, pancytopenia</p> <p>Profound immunosuppression</p> <p>Cytokine release syndrome</p>
	<p><i>Cyclosporine</i></p> <p><i>Tacrolimus (FK506)</i></p>	<p>Blocks calcineurin and inhibits IL-2 synthesis</p> <p>Blocks calcineurin and inhibits IL-2 synthesis</p>	<p>Nephrotoxicity, neurotoxicity, hepatotoxicity</p> <p>Nephrotoxicity, neurotoxicity, diabetes</p>
	<p><i>Basiliximab</i></p> <p><i>Daclizumab</i></p>	<p>Blocks the IL-2 receptor</p> <p>Blocks the IL-2 receptor</p>	<p>Gastrointestinal disorders</p> <p>Gastrointestinal disorders</p>
	<p><i>Sirolimus</i></p>	<p>Blocks cytokine-stimulated cell proliferation</p>	<p>Hyperlipidemia, thrombocytopenia, leukopenia, headache, nausea</p>
	<p><i>Azathioprine</i></p> <p><i>Mycophenolate mofetil</i></p>	<p>Inhibits purine synthesis</p> <p>Inhibits purine synthesis</p>	<p>Bone marrow suppression, hepatotoxicity, thrombocytopenia, anemia, neoplasia</p> <p>GI upset, nausea, diarrhea, leukopenia, tumors, increases susceptibility to infection</p>

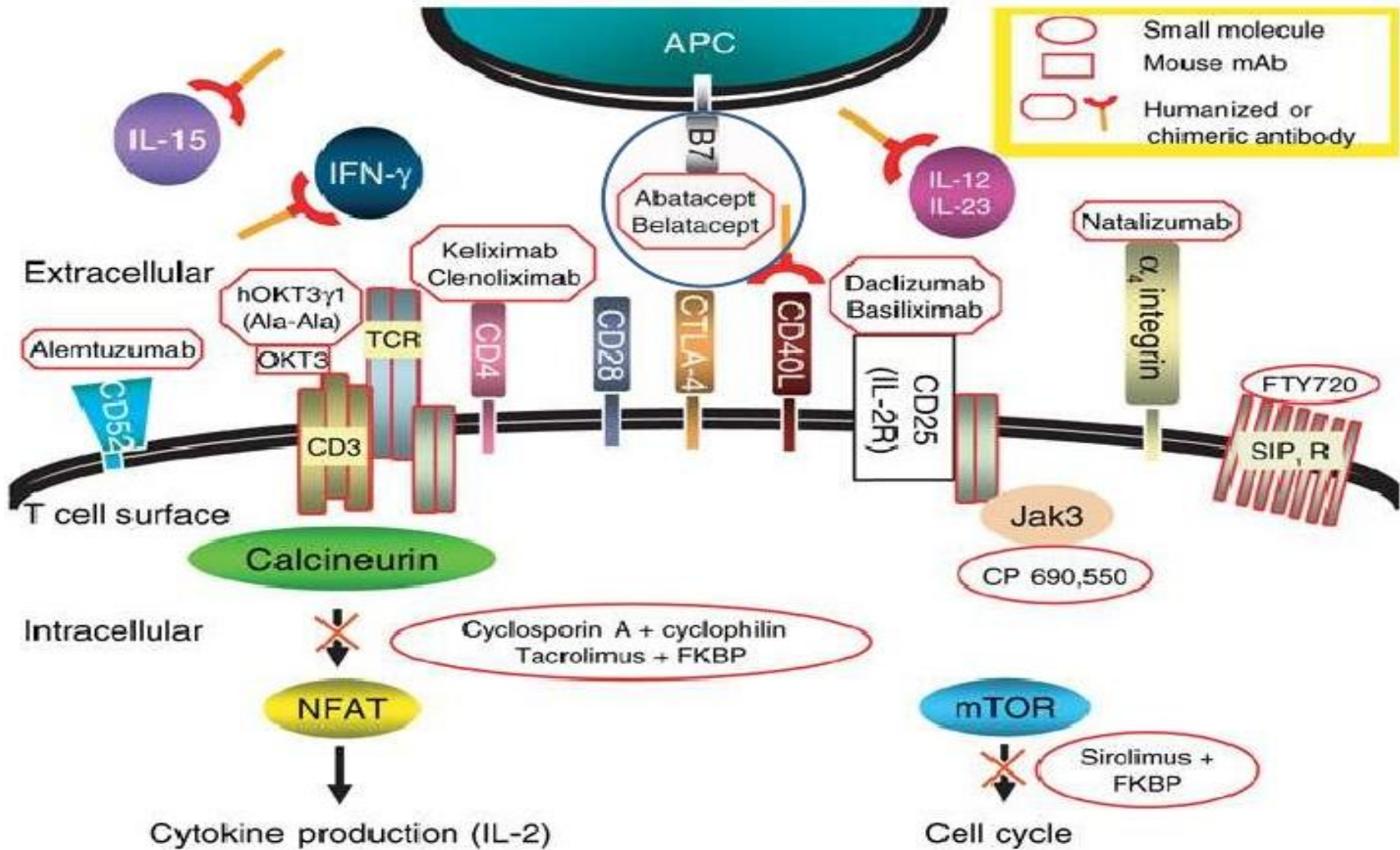
FLOW CHART

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FLOW CHART



FLOW CHART: *INTERACTIONS*

ANTIGEN +++++ RECEPTOR

- Alemtuzumab
- ATG
- Muromonab CD3

RECEPTOR+++++++ IL 1

- Anakinra



FLOW CHART: *INTERACTIONS*

RECEPTOR+++++++ TNF α

- 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:-

IL-2 antagonist

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graph TD; A[IL-2 antagonist] --> B[DACLIZUMAB]; A --> C[BASILIXIMAB];
```

DACLIZUMAB

BASILIXIMAB

- 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-2R α 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

Given in
perioperative
period.

Cyclosporine+
Predisolone+
Azathioprine

MAINTENANC -E REGIMEN

Given for
prolonged
period.

Cyclosporine+
Predisolone+
Azathioprine

ANTI- REJECTION REGIMEN

Given to
suppress an
episode of
acute rejection.

Methylprednis
olone 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* Liver: 8 ± 4 mg/kg/day* 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* 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* 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

Commonly used Drugs

**Cyclosporine
(sandimmune)**

**Mycophenolaten
mofetil (cell
cept)**

**Tacrolimus (
FK506,Prograf)**

**Azathioprine
(imuran)**

**Muromanab-
CD₃ (orthoclone
OKT₃)**

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