Immunity

Innate
(Neutro, Baso, Eosinophils, Monocytes)

- 1st line of defence mechanism
- Rapid response (3-4 hrs)
- Non-specific
- No memory

Acquired
(T, B lymphocytes)

- 2nd line of defence
- late response (5-7 days)
- Specific
- memory

1° response
- 5-7 days
- memory cells develop

2° response
- 3-4 hrs
(∵ memory cells)

Acquired immunity

Active → better
(∵ memory cells form)

Ag → Abs
- infection
- vaccination

Passive
Give Abs IG
- vertical route
- passive immunisation

Serotherapy / plasmatherapy

Note: ADAPTIVE IMMUNITY
occurs when transfer factor is given
transfer factor - immunologically competent B, T lymphocytes, NK cells
i.e passively transferring cell mediated immunity
used in Rx of lepromatous leprosy.

Innate immunity

1. Ag enters — consists of PAMP - Pathogen associated molecular Pattern
2. recognized by host cell receptors
   - PRR - Pattern recognition receptors (Ex: TLR Toll like receptors)
   - Chemotactic receptors
   - Phagocytic receptors
3. Host cells activated
   - macrophages → monocytes
   - microphages → Neutro, Baso, Eosinophils } phagocytosis → lysozymes, Free radical damage
   - NK cells → [CD 16 | 56]
     - perforins, granzymes
     - cell lysis (Ag lysis)
4. Release cytokines
   - INF, IL, TNF → kill the Ag

If Ag escapes killing by cytokines

IL-1, IL-6, TNF-α

↓

⑤ activates APR (Acute phase reactants)

↓

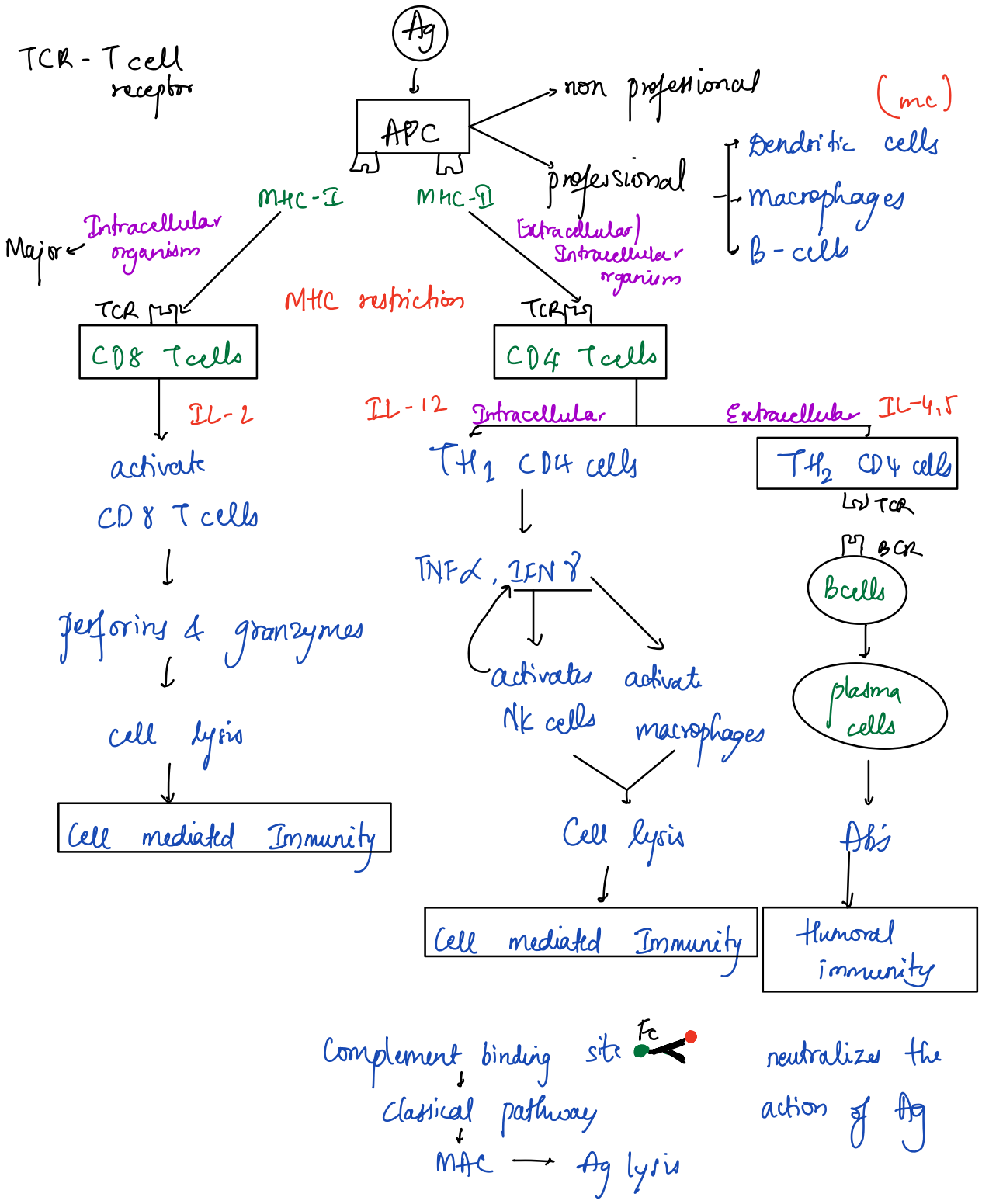
Complement activated (in innate immunity) → Alternate pathway / Lectin pathway → MAC ↓ lysis

Note: Interferons

- Alpha IFN (Leukocyte interferon) → by leucocytes — antiviral activity
- Beta IFN (Fibroblast interferon) → by fibroblasts & epithelial cell — antiviral activity
- Gamma IFN (Immune interferon) → by T-lymphocytes — immunomodulatory & anti proliferative action

Properties:
- non toxic, non antigenic
- non dialysable, non sedimentable
- Species specific
- inactivated by proteases
- belongs to class of cytokine
- Stable @ pH over (2-10) except IFN β (labile @ pH 2)

Acquired immunity



Antigen presenting cells

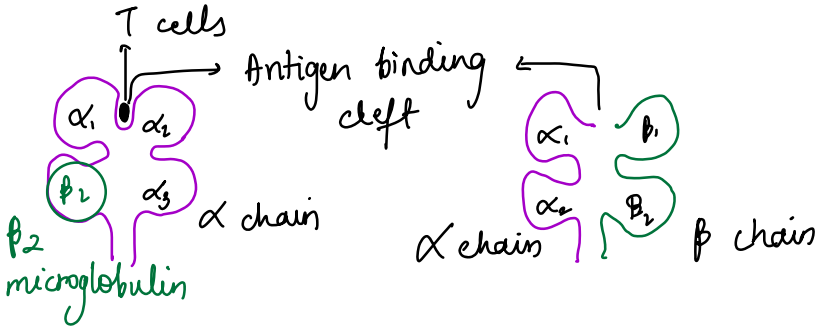
professional
- Dendritic cells (m c)
- Macrophages
- B cells

MHC receptors proteins coded by HLA gene → chr 6p

MHC - I ← codes	MHC - II ← codes	MHC - III ← codes
HLA A, B, C genes	HLA DP, DQ, DR genes	HLA genes
- all nucleated cells & platelets	- only on APC	- release complement factor, TNF, HSP
- mainly responsible for cell mediated immunity	- mainly responsible for humoral immunity	- involved in immunity

Graft rejection

GVHD

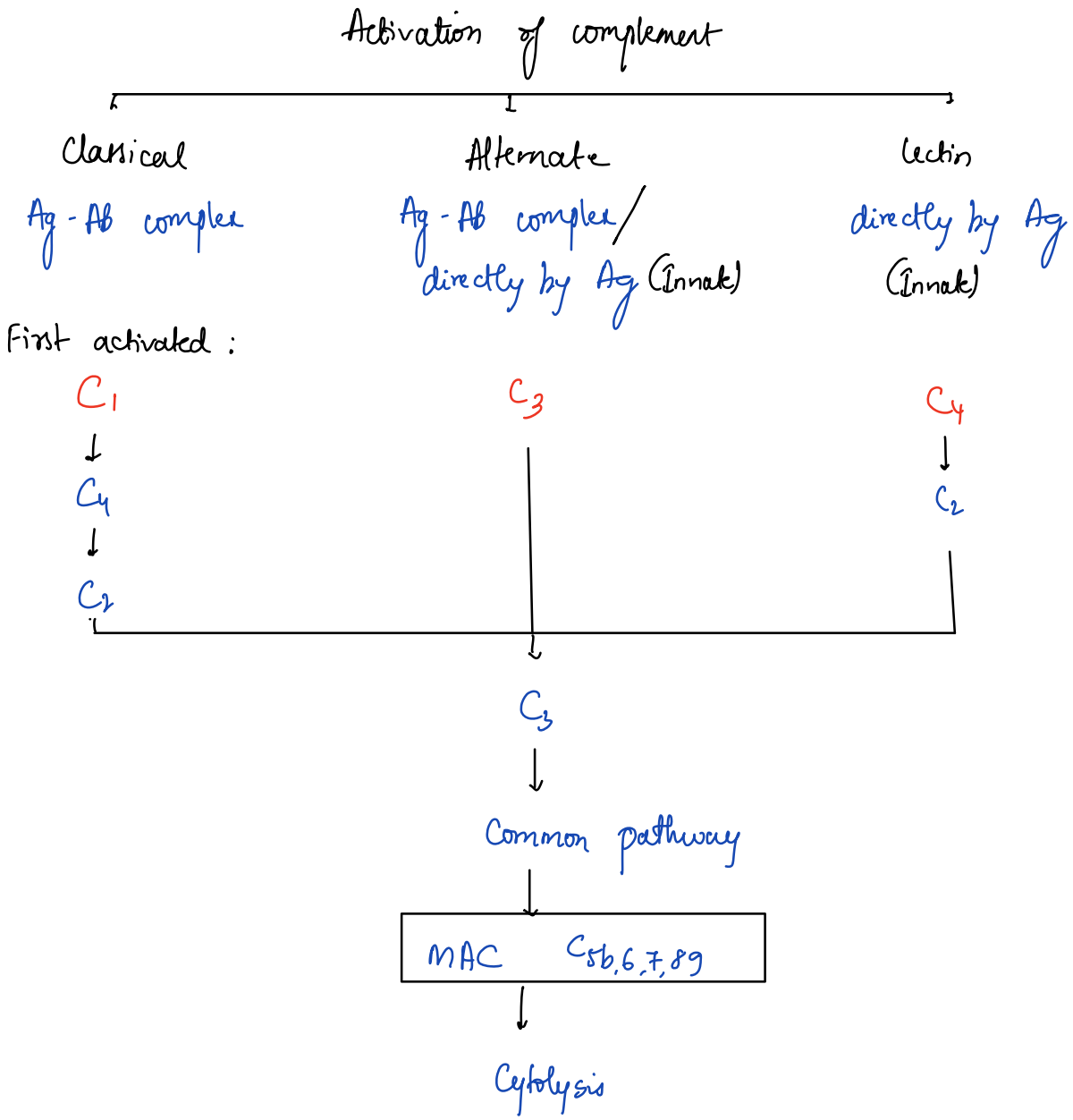


HLA associated diseases

- HLA B
  - → B5
    - Behcet's disease
    - Polycystic kidney disease
  - → B27
    - Psoriasis
    - Ankylosing spondylitis
    - Inflammatory bowel disease
    - Reiter's disease

- HLA DR
  - → DR 2 — Multiple sclerosis
  - → DR 3 — Myasthenia gravis, SLE, Type I DM
  - → DR 4 — Rheumatoid arthritis, Type I DM
  - → DR 5 — Hashimoto's thyroiditis
  - → DR 6 — Congenital Adrenal Hyperplasia

Complement — Group of proteins (inactive)



Complement Deficiency Disorders

1) C_1 deficiency - Heredetary Angioneurotic Edema (HAE)

2) C_1, C_4, C_2 deficiency - SLE

3) MAC deficiency ($C_{5b,6,7,8,9}$) - Neisseria infection (Disseminated gram -ve infection)

4) DAF (CD55) (Decay accelerating factor) - PNH Paroxysmal Nocturnal Hemoglobinuria

5) Factor H, I, D - Pyogenic infections, Immune complex disorders

Antigen

Self

Tolerance: No immune response by our immune system against self Ag.

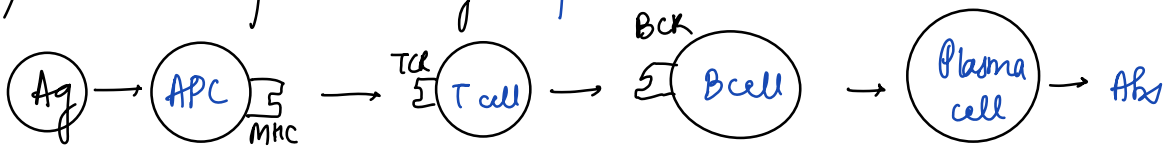
- Sequesterated (Hidden): Cornea, lens, Sperms
- Non sequesterated

Foreign

- T cell dependent Ag
- T cell independent Ag
- Superantigen
- Heterophile Ag

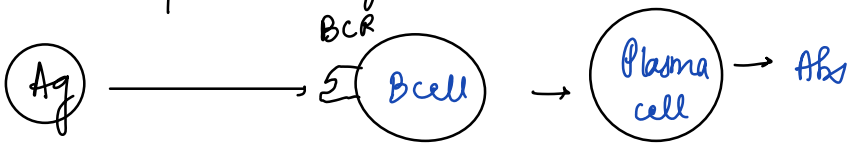
	Origin	Maturation
T, B	Bone marrow	Thymus Bone marrow

1) T cell dependent Ag (protein Ag)



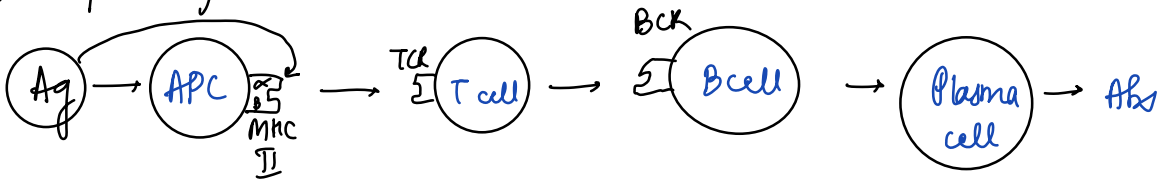
Processing of Ag → (N) activation of T cells → (N) activation of B cells → (N) Immune response

2) T cell independent Ag (lipid & carbohydrate Ag)



Polyclonal activation of B cells → Exaggerated immune response

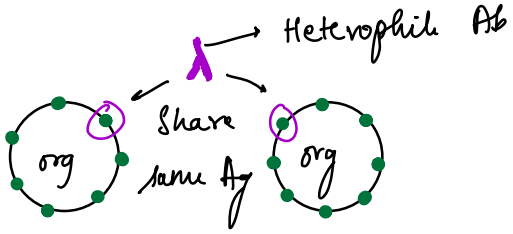
3) Superantigen



Ag directly binds to side of β chain of MHC II receptor → polyclonal activation of T cells f/b B cells → Exaggerated immune response

No processing of Ag

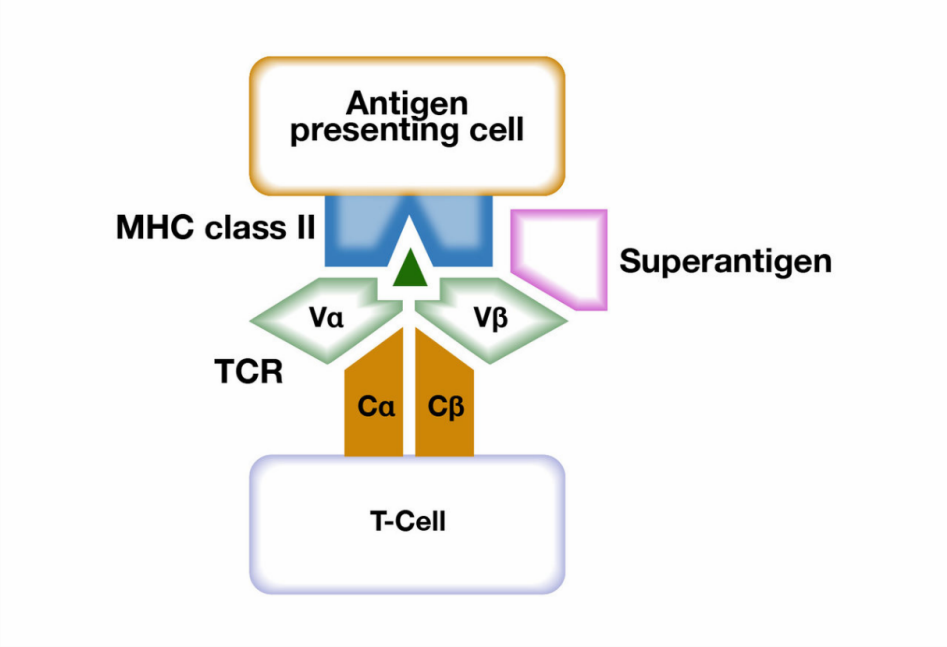
4) Heterophile Ag



The given image depicts a **Superantigen**. *Enterococcus faecalis* does not produce superantigens.

Superantigens are a third variety of the biological class of antigens that activate a very large number of T cells, irrespective of antigen specificity. This means they can activate T-cells directly **without being processed by antigen-presenting cells** (APCs).

- The variable β region of T-cell receptor (vβ of TCR) appears to be the receptor for superantigens.
- They directly bridge non-specifically between MHC–II of APCs and T-cells.



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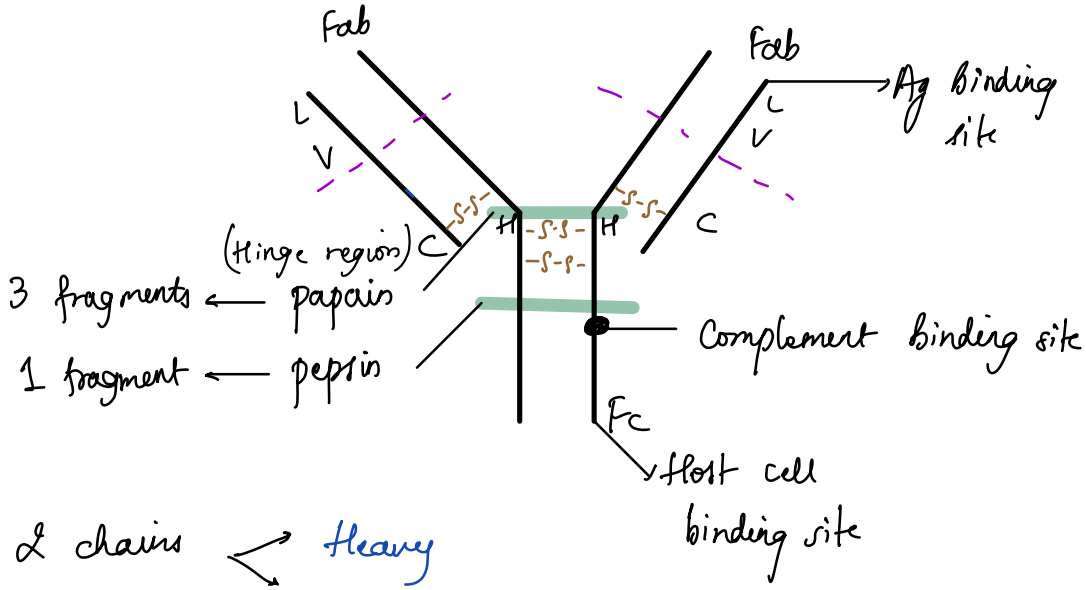
Examples of superantigens:

- Bacterial
  - Staphylococcal toxin
  - Streptococcal toxin
  - *Mycoplasma arthritidis* mitogen 1
  - *Yersinia enterocolitica*
  - *Yersinia pseudotuberculosis*
- Viral
  - Epstein–Barr virus (EBV)
  - Cytomegalovirus (CMV))
  - Rabies nucleocaspid
  - HIV-encoded negative regulatory factor.
- Fungal
  - *Malassezia furfur.*

Antibody



- 2 chains → Heavy, Light
- 2 regions → Constant, Variable
- 2 fragments → Fab, Fc
- 3 binding sites → Antigen binding site, Host cell binding site, Complement binding site
- 2 enzymes
  - papain (act at hinge region) → 3 fragments – Fc + 2 Fab
  - pepsin (act below hinge region) → 1 fragment – 1 $F(ab)_2$

Fab:
- Fragment, antigen binding
- Determines idiotype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell

Fc (5 C's):
- Constant
- Carboxy terminal
- Complement binding
- Carbohydrate side chains
- Confers (determines) isotype (IgM, IgD, etc)

Fab ⟶ Idiotypes

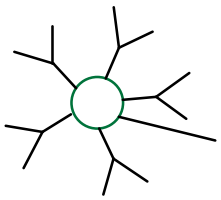
Fc ⟶ Isotypes

Epitope - smallest unit of antigenecity

Ig G A M D E

Ab Isotypes	Serum conc	t1/2	Heat stability	Carbohydrate concentration	Molecular weight
** Ig G	max	max	heat stable	minimum	
Ig M Pentamer					maximum
Ig A					
Ig D					
Ig E	min	min	heat labile	maximum	

Note: All are monomers except Ig M ⟶ pentamer



5 units held together by J chain

Ig G

- max serum conc
- max t½
- heat stable
- min carbohydrate concentration

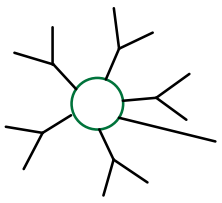
Serotypes		Deficiencies
G_1 (mc)	- all functions	Bacterial infection
G_2	- does not cross placenta	encapsulated organisms
G_3	- all functions	Viral inf
G_4	- does not fix complement	parasitic inf

Functions:
- fix the complement – MAC → Ag lysis (classical)
- crosses placenta → immunity to baby
- precipitation & neutralization → Ag-Ab reactions

Ig M

only pentamer

- max molecular wt



Functions:
- fix the complement – MAC → Ag lysis (classical)
- does not cross placenta
- Agglutination → Ag-Ab reaction

IgA

Functions: - fix the complement → MAC → Ag lysis (alternate)
- via breastmilk → immunity to baby (local immunity)

IgA
- Dimer - secretory / mucosal IgA → (never enter blood)
- monomer - Blood

IgD

IgD & IgM → surface receptors on B cells

IgE

- ↑ed in allergic manifestations
- ↑sed in parasitic infection

cannot fix complement
- IgG4
- IgA
- IgD
- IgE

Note: - Monoclonal Ab - can bind to one specific Ag
- polyclonal Ab - can bind to any Ag on specific organism

Ag-Ab reaction

Precipitation | Agglutination | Neutralization

1) Precipitation

Soluble Ag + Ab IgG ⟶ precipitation

Ex:

→ Streptococcal grouping → Lancefield classification

→ Syphilis ⟶ flocculation test
- Tube – Kahn
- Slide – VDRL, RPR

→ Special tests
- B. anthracii – Ascoli thermo ppt test
- C. diptheria – Elek's gel ppt test
- E. coli – Eiken's ppt test

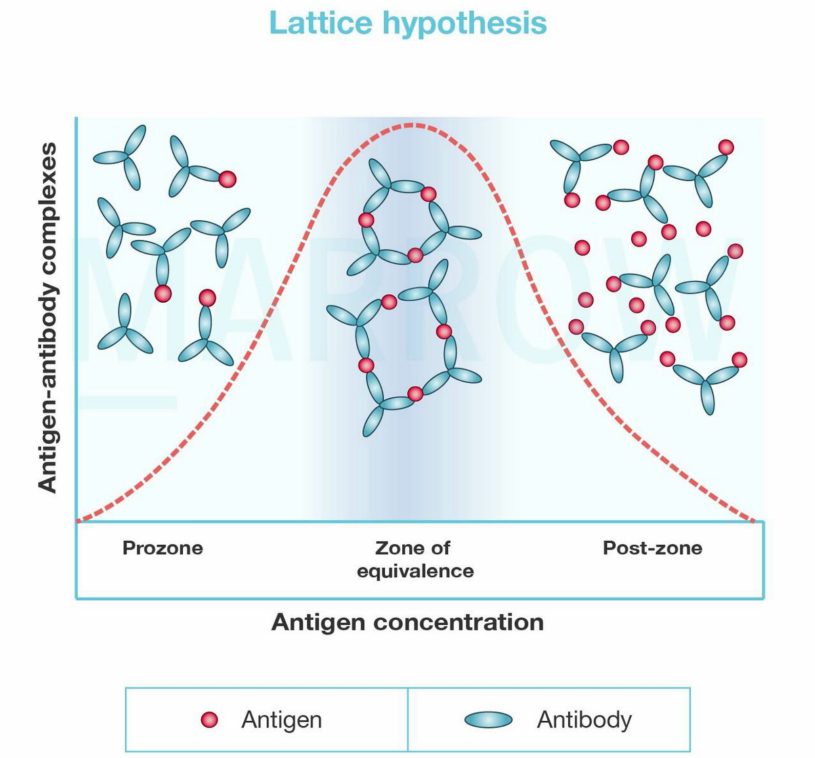
→ Immunodiffusion tests

		Diffusion	Dimension
a)	Oudin	1	1
b)	Okley Fulthrope	2	1
c)	Radial	1	2
d)	Ouchterlony	2	2

Lattice hypothesis

explains precipitation reactions

amount of precipitate formed is greatly influenced by relative proportions of antigens & antibodies



Prozone phenomenon - excessive antibodies

Zone of equivalence optimum proportion
∴ max precipitation

Post zone phenomenon excessive antigen

2) Agglutination

Insoluble Ag + Ab (IgM) ⟶ Agglutination

Ex:

→ Heterophile Agglutination Test — Ag:

- Paul Bunnel test - EBV — Sheep RBC
- Weil Felix test - Rickettsia — proteus OXK, OX2, OX19
- Cold Agglutinin test } Mycoplasma — Human RBC
- Strepto coccal MG test } — Streptococcal Mg

→ Agglutination tests

- WAT - Widal — Salmonella
- MAT - Microscopic — leptospira
- SAT - Standard — Brucella
- HAT - Hemagglutination — fimbria (pili), Influenza

→ Other

- Rose Waller test - detect RA factor (Haemagglutination)
- Coombs test - detect Rh incompatibility

3) Neutralization

Ag + Ab → Neutralization of action

Ex:

- Tuberculin test (skin)
- Lepromin test (skin)
- Shick test (skin) - susceptibility test for C. diptheria
- Dick test (skin) - susceptibility test for Streptococcus
- ASO test - Streptococcus
- Naegler's reaction - Cl. perfringens
- Viral Neutralization tests - viruses (Gold std)

If Shick test ⊕ → need immunization

Immunodeficiency disorders

1) B cell defect (Humoral deficiency disorders)

- X linked agammaglobulinemia / Bruton's disease
  failure of differentiation of pre B cells → B cells
  Tyrosine kinase enzyme deficiency
  live vaccines C/I
  (tonsils & LN are atrophic)

- Combined variable deficiency
  failure of differentiation of B cells → plasma cells
  intrinsic B cell defect
  (Giardia infection is common)

- Selective IgA deficiency
  failure of differentiation of B cells → plasma cells
  IgA specific cytokines deficiency
  ↑susceptibility to Giardia
  asymptomatic

2) T cell defect (cellular deficiency disorders)

- **Digeorge syndrome / Thymic hypoplasia**
  congenital development defect
  3rd & 4th pharyngeal pouch
  Chr 22q11

- **PNP deficiency syndrome** (Purine nucleoside phosphorylase) — Chr 14
  purine —PNP ✗→ hypoxanthine ----- uric acid
  ∴ purine is accumulated
  → toxic to T cells

- **Chronic mucocutaneous candidiasis** (IL-17 defect)
  - T cell defect (CMI deficient)
  idiopathic

- **Hyper IgE (Job syndrome)** autosomal dominant
  deficiency of Th17 due to STAT3 mutation

Cold (noninflamed) staphylococcal Abscesses, retained Baby teeth, Coarse facies, Dermatologic problems (eczema), ↑ IgE, bone Fractures from minor trauma

↑ IgE
↑ eosinophils

Learn the ABCDEF's to get a Job!

- **IL-12 receptor deficiency** ↓Th1 response
  mc cause of mendelian susceptibility of Mycobacterial diseases

3) Combined (B & T cell) defects

- SCID (Severe combined immunodeficiency)
  Stem cells are defect
  - IL-7 defective (mc) - XLR
  - ADA deficiency - AR
  - JAK-3 mutation
  - RAG mutation

- Wiskott Aldrich Syndrome
  WASP gene mutation
  ↳ wasp protein
  precursor lymphoid cells → lymphoid cells (T & B cell)

- Ataxia telangiectasia
  - kinase enzyme deficiency
  - exact mechanism not known

- Hyper IgM syndrome

4) Phagocytic deficiency disorders

- Chediak Higashi disease
  defect in phagosome lysosome fusion
  LYST gene mutation

- Lazy leukocyte syndrome
  defect in chemotaxis
  idiopathic

- Chronic granulomatous diseases
  NADP oxidase deficiency → oxidative burst absent
  ↓
  NADP oxidase gene mutation

- leukocyte adhesion defect

- Cyclic neutropenia

Note: Nude mice (lack of body hair)

lack thymus ∴ cannot generate mature T cells

∴ Absence of T lymphocyte prevents it from rejecting allografts & xenograft