Immune response, dysfunctions and modulation

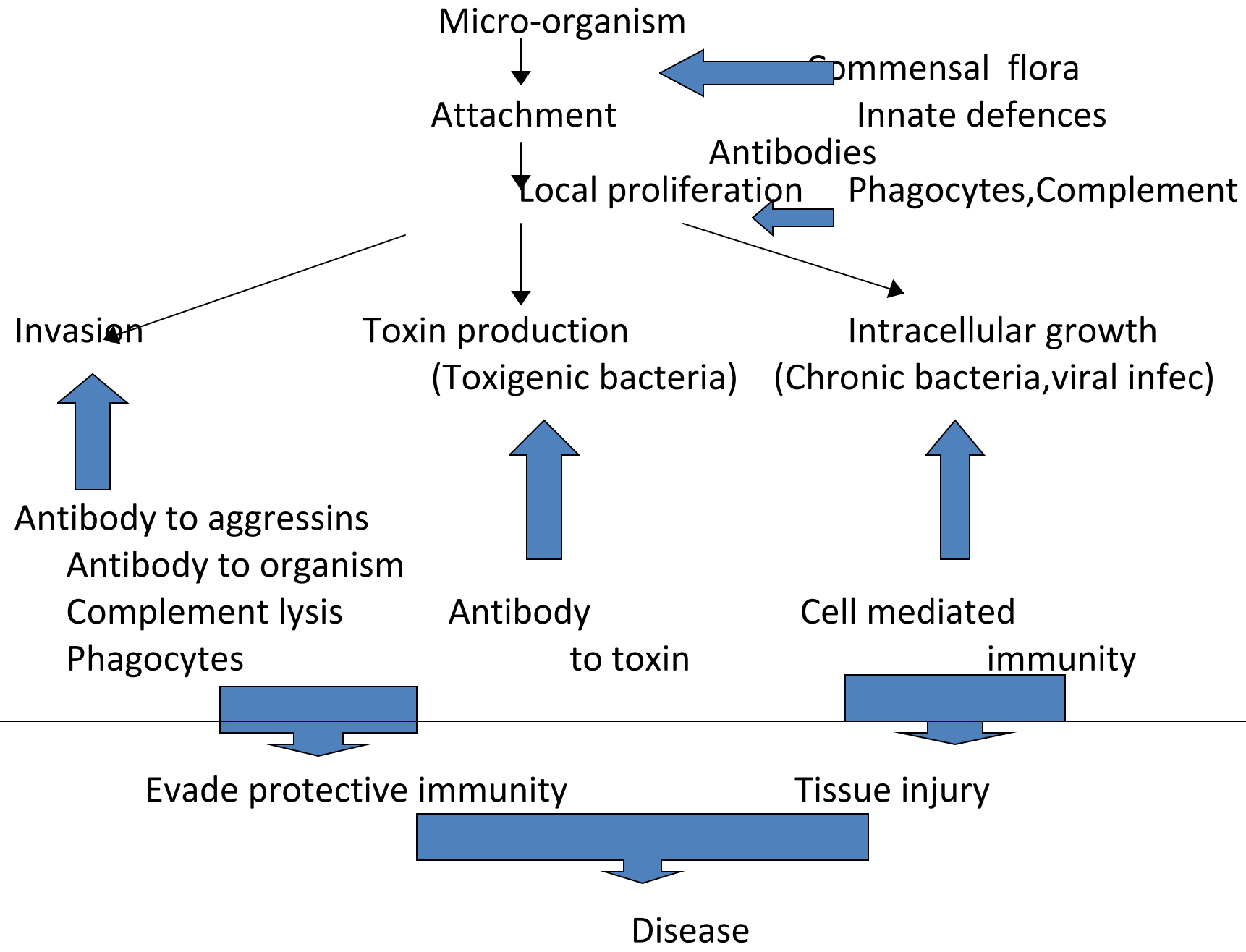
Dr. Nadisha Badanasinghe

Objectives

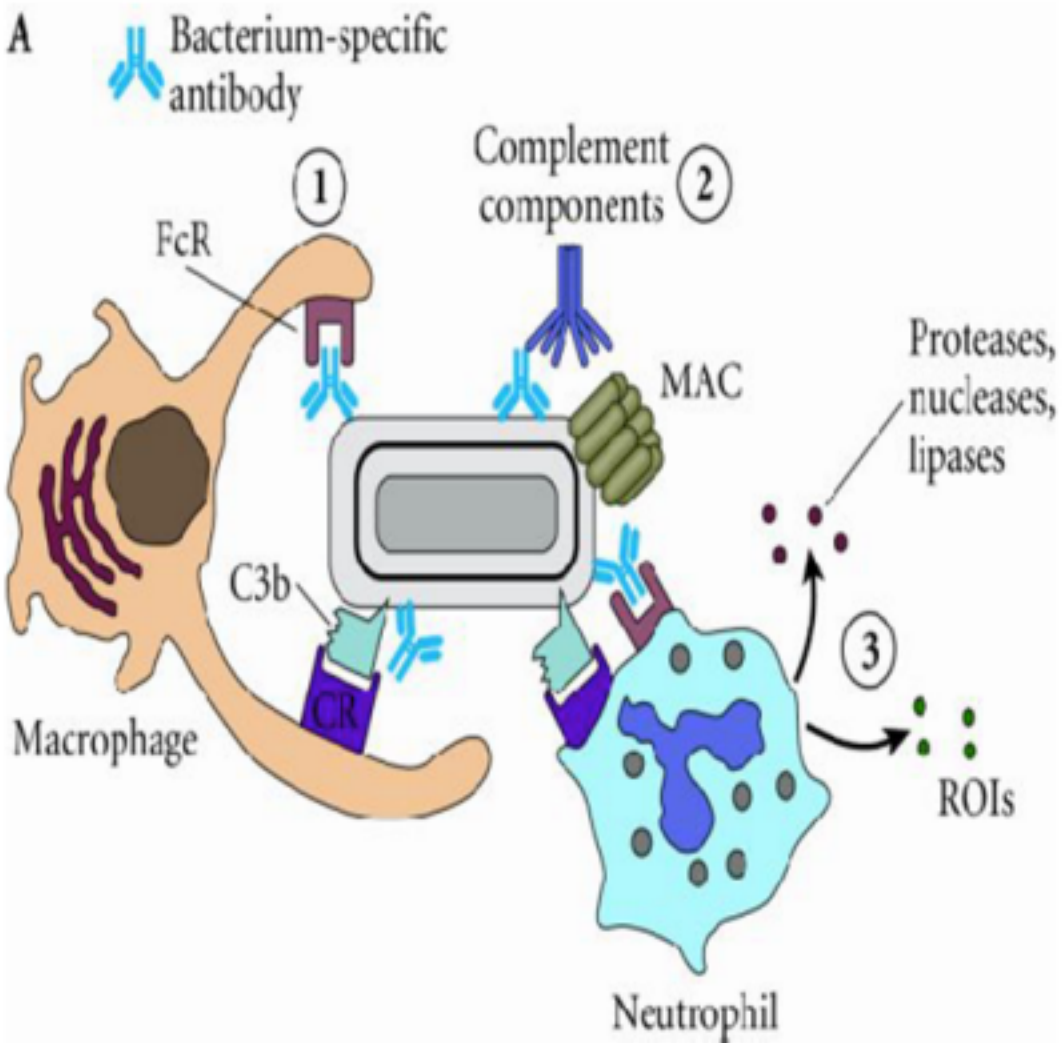
- Immune response to infections and tumors
- Immune dysfunctions and disorders
  - Hypersensitivity
  - Autoimmunity
  - Immune deficiency
- Immune modulation
  - Enhancement
  - Suppression

Immune response

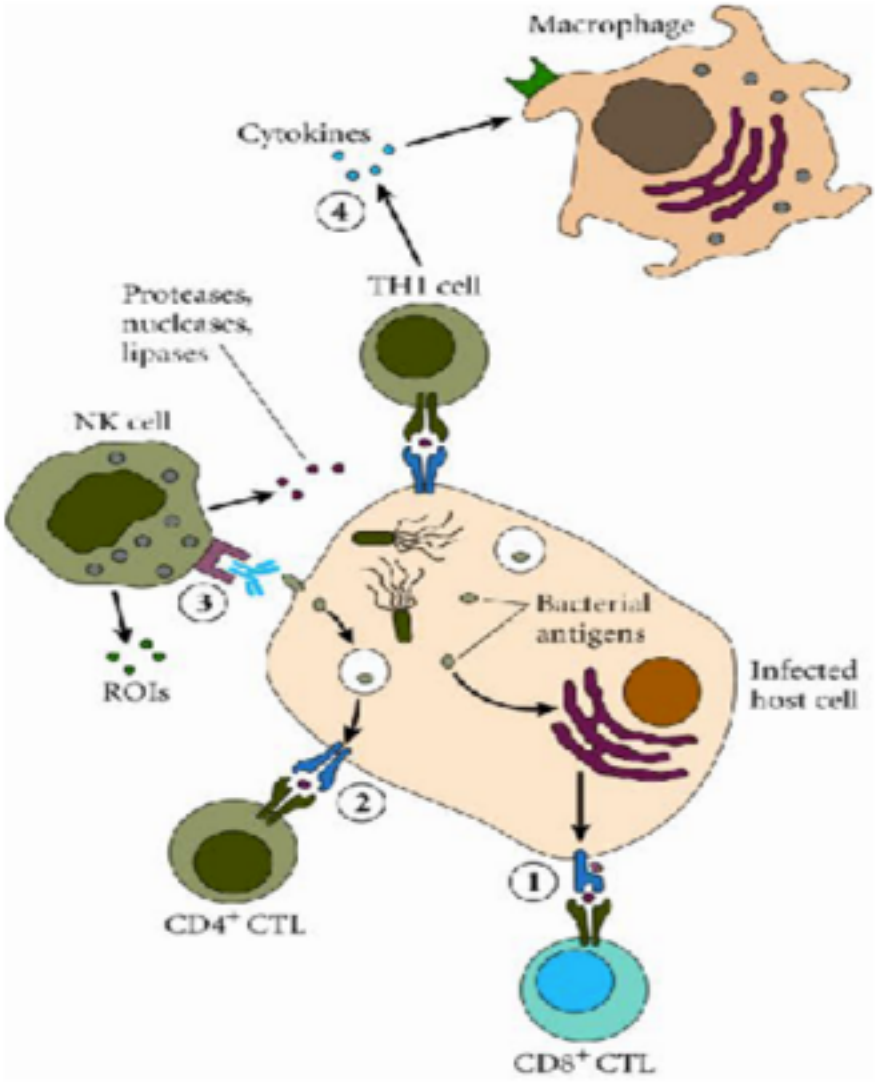
- Immune responses to different types of organisms
  - Extracellular bacteria (Innate and adaptive)
  - Intracellular bacteria (Innate and adaptive)
  - Viruses (Innate and adaptive)
  - Parasites (Innate and adaptive)
  - Tumors
- How theses organisms/ tumors evade immune response


Micro-organism
Commensal flora
Attachment
Innate defences
Antibodies
Local proliferation
Phagocytes,Complement
Invasion
Toxin production
(Toxigenic bacteria)
Intracellular growth
(Chronic bacteria,viral infec)
Antibody to aggressins
Antibody to organism
Complement lysis
Phagocytes
Antibody
to toxin
Cell mediated
immunity
Evade protective immunity
Tissue injury
Disease

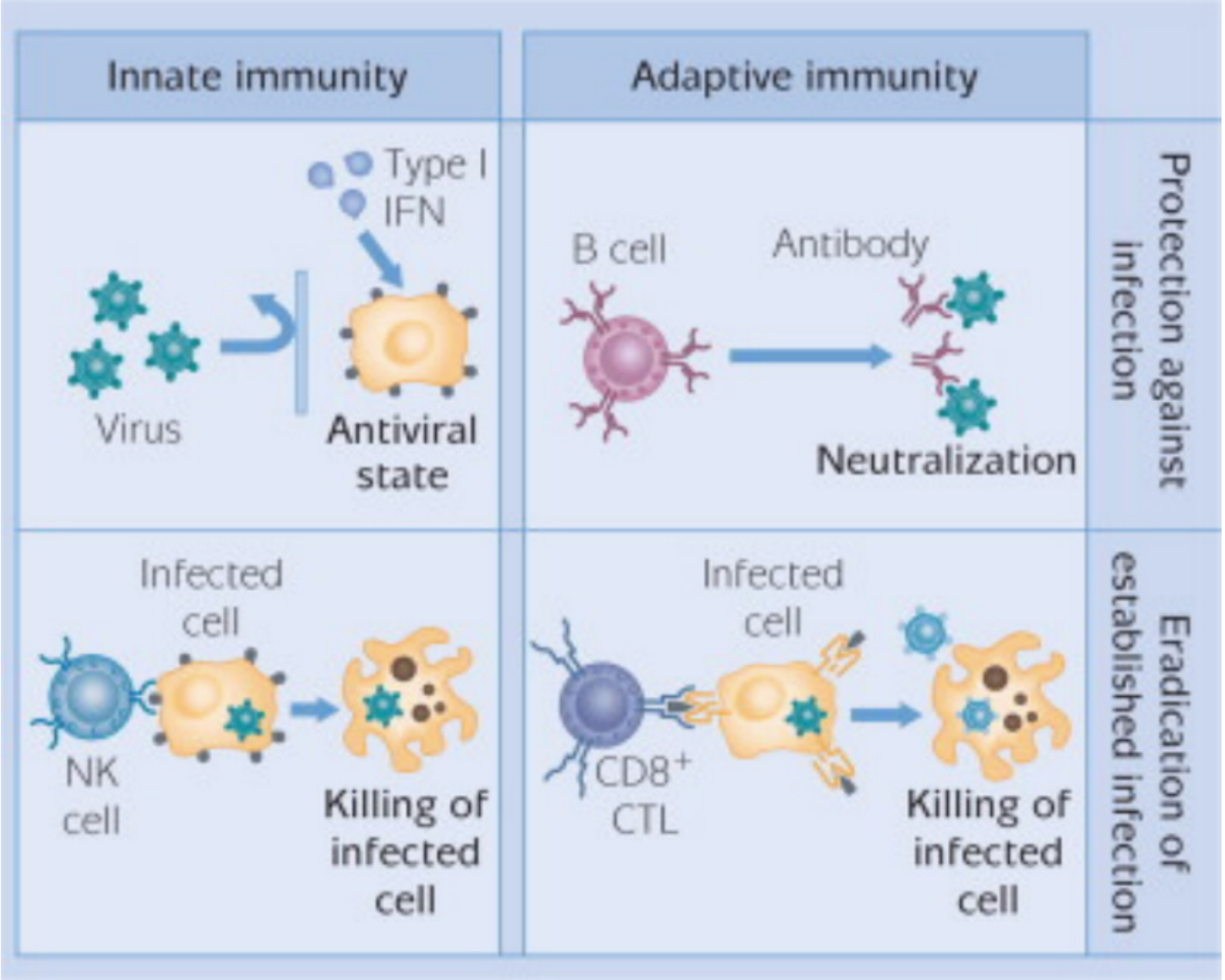
Immune response to extracellular bacterial infections



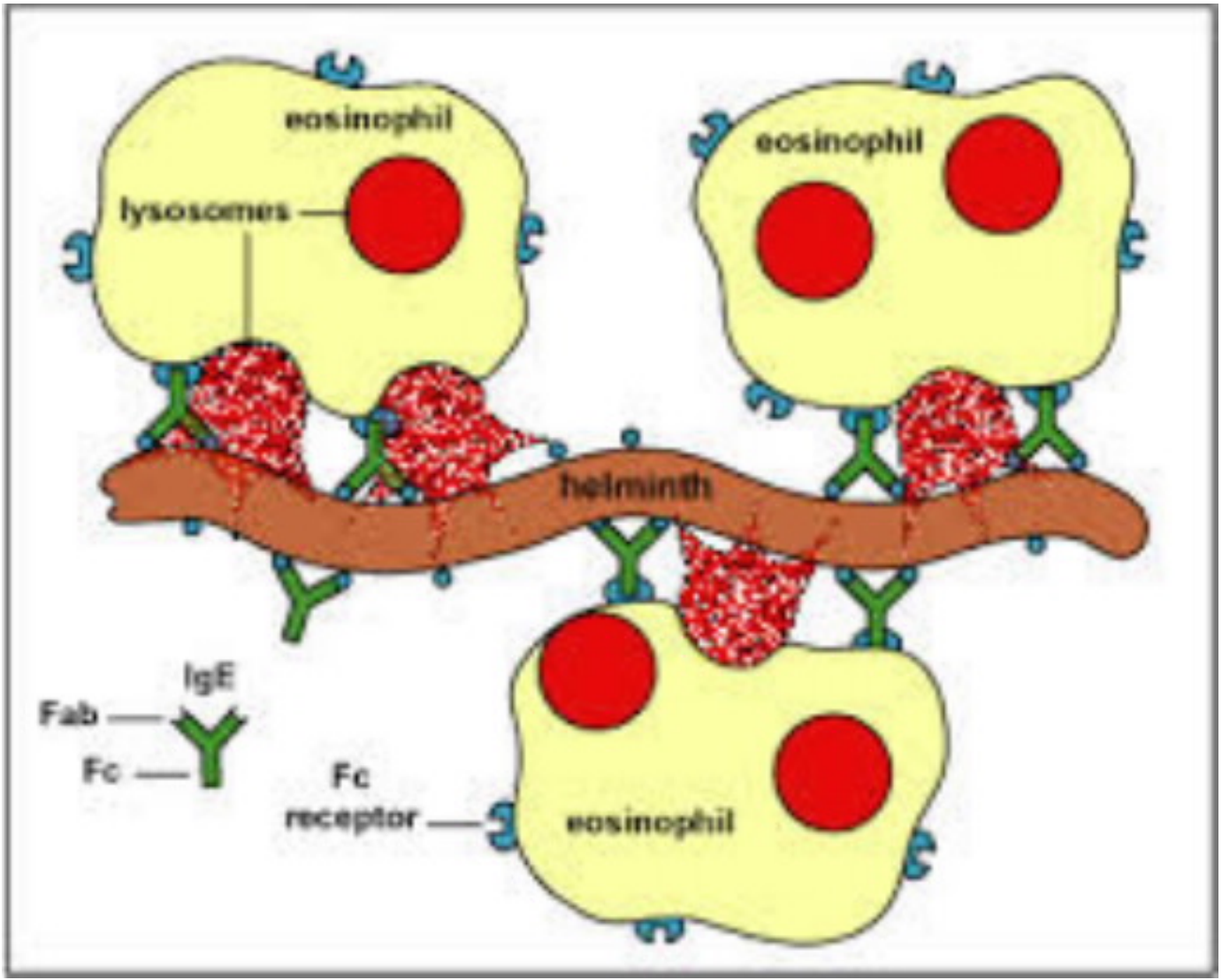
Immune response to intracellular bacterial infections



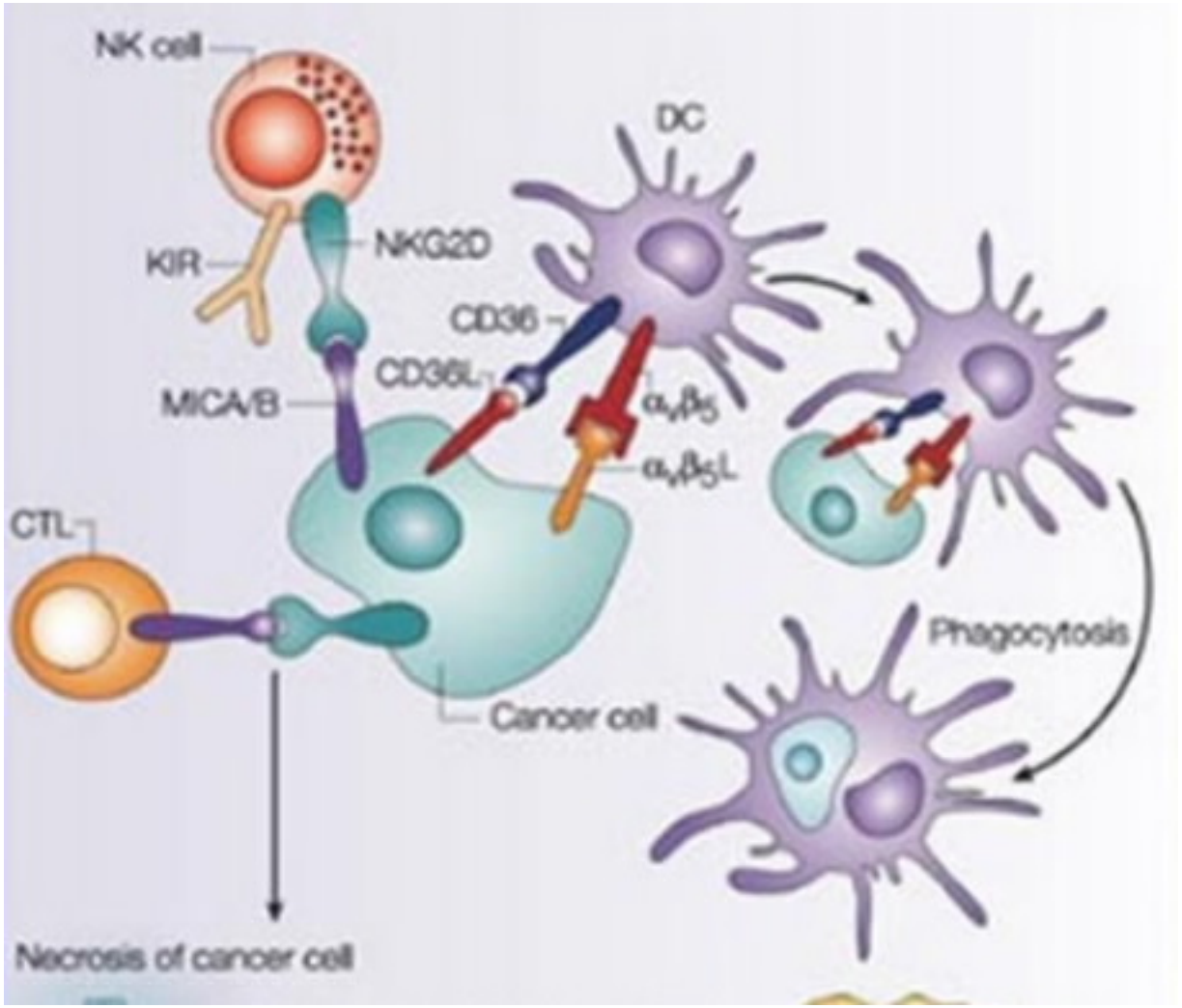
Immune response to viral infections

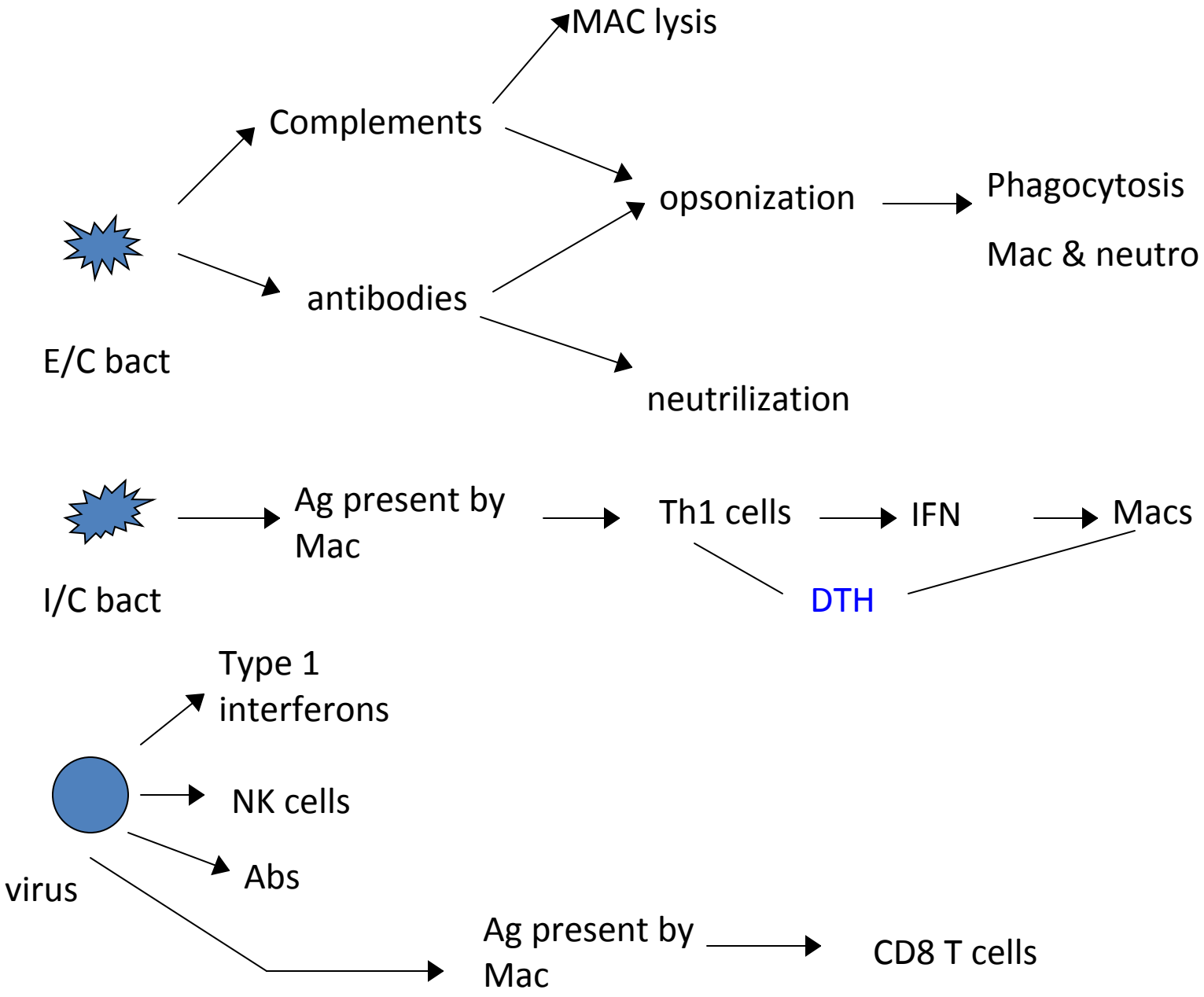


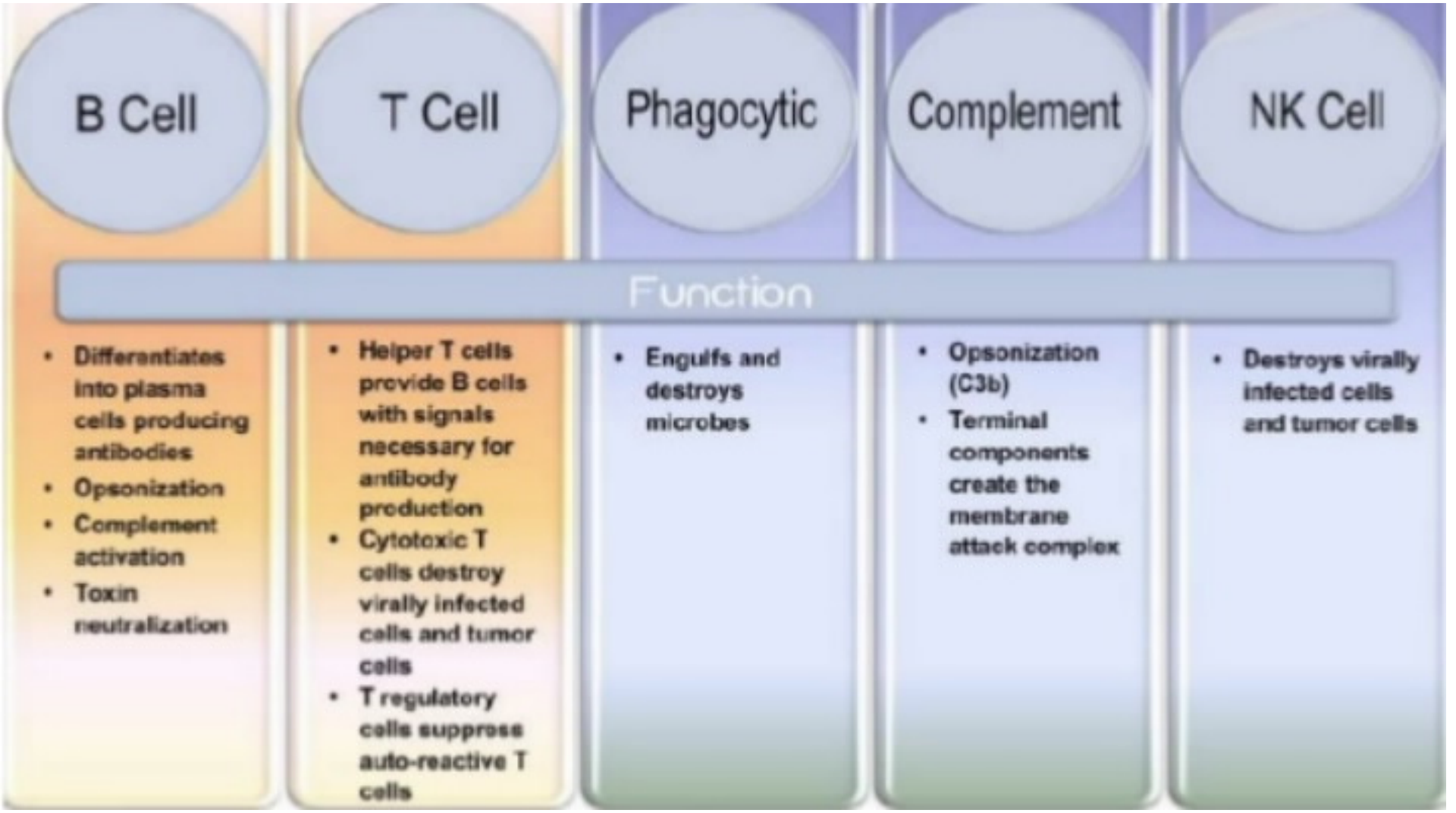
Immune response to parasites

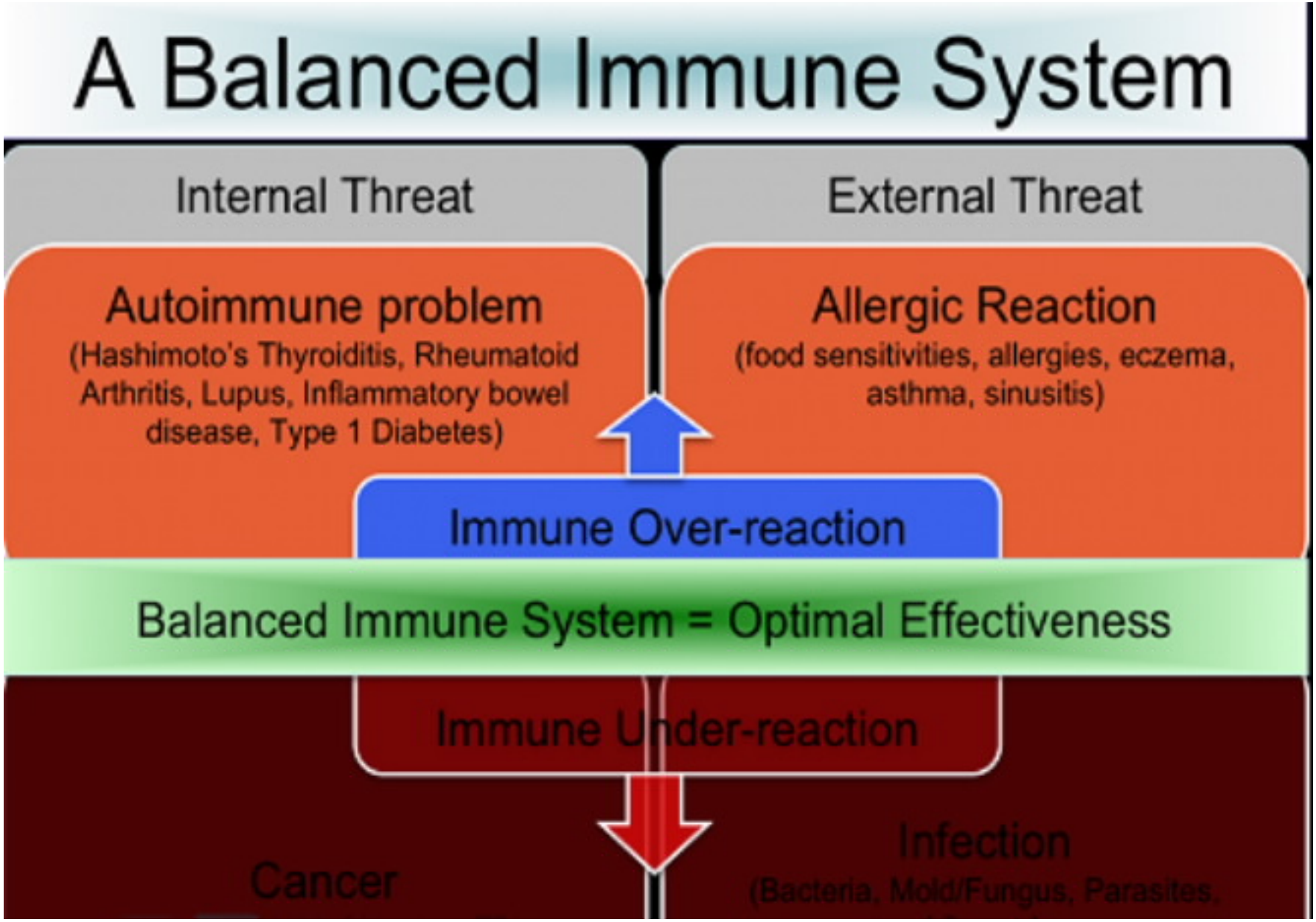


Immune response to tumor cells




MAC lysis
Complements
opsonization
Phagocytosis
Mac & neutro
antibodies
E/C bact
neutrilization
Ag present by Mac
Th1 cells
IFN
Macs
I/C bact
DTH
Type 1 interferons
NK cells
Abs
virus
Ag present by Mac
CD8 T cells


B Cell
T Cell
Phagocytic
Complement
NK Cell
Function
• Differentiates into plasma cells producing antibodies
• Opsonization
• Complement activation
• Toxin neutralization
• Helper T cells provide B cells with signals necessary for antibody production
• Cytotoxic T cells destroy virally infected cells and tumor cells
• T regulatory cells suppress auto-reactive T cells
• Engulfs and destroys microbes
• Opsonization (C3b)
• Terminal components create the membrane attack complex
• Destroys virally infected cells and tumor cells

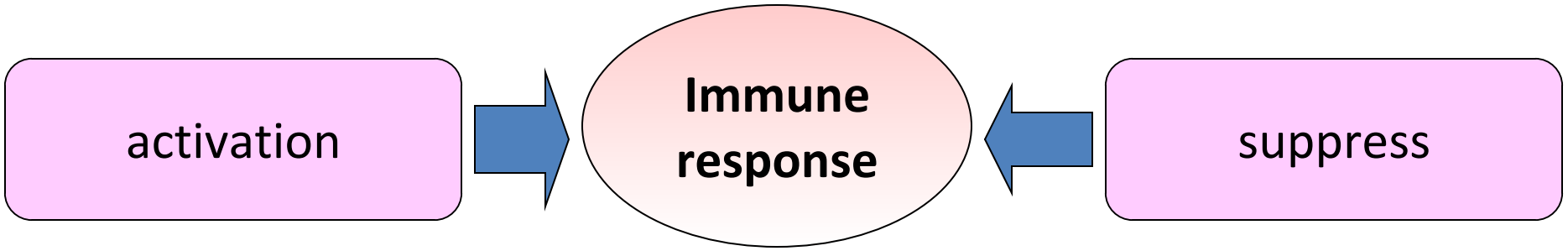

A Balanced Immune System
Internal Threat
External Threat
Autoimmune problem
(Hashimoto's Thyroiditis, Rheumatoid Arthritis, Lupus, Inflammatory bowel disease, Type 1 Diabetes)
Allergic Reaction
(food sensitivities, allergies, eczema, asthma, sinusitis)
Immune Over-reaction
Balanced Immune System = Optimal Effectiveness
Immune Under-reaction
Cancer
Infection
(Bacteria, Mold/Fungus, Parasites,

Immune Regulation

- A balance between
  - activation and
  - suppression

  } of effector cells

- to achieve an efficient immune response without damaging the host.



Immune Regulation

- The immune system should react against foreign antigens, But not self antigens

- The activated immune system should be turned off when the foreign antigen is killed

- The immune system should be unresponsive to self antigens

“ immunological tolerance”

Central Tolerance

Peripheral tolerance

Autoimmunity

- The response of the adaptive immune system to self antigens that occurs when mechanisms of self tolerance fails.

  "acquired immune reactivity to self antigens"

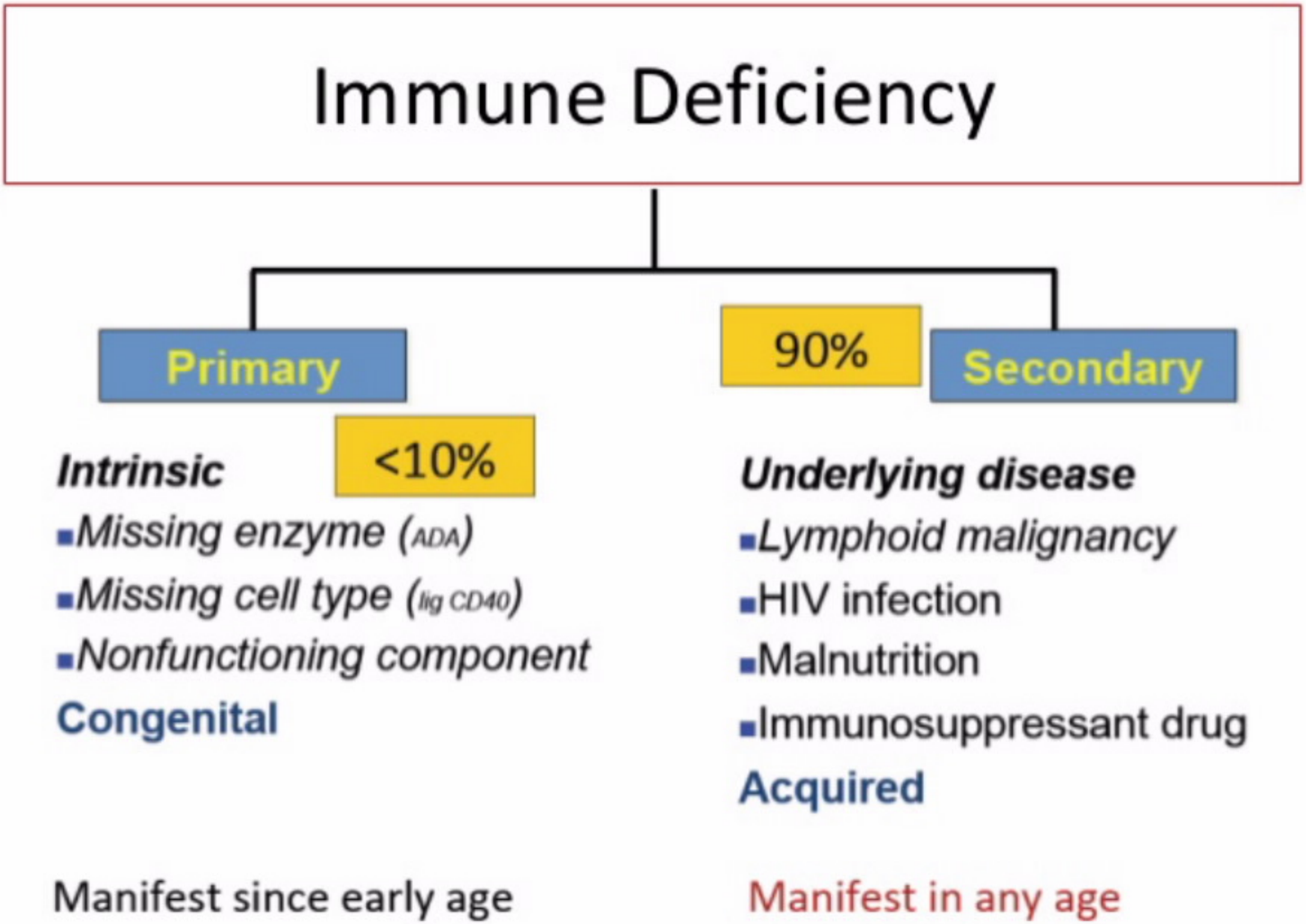
Autoimmunity

- Mechanisms of tolerance
- Mechanisms of breaking of tolerance

Immune deficiency

- Know the major primary immunodeficiencies and their features
- Understand the relationship between site of lesion and resulting immunodeficiency
- When to suspect
- How to investigate

Immune Deficiency

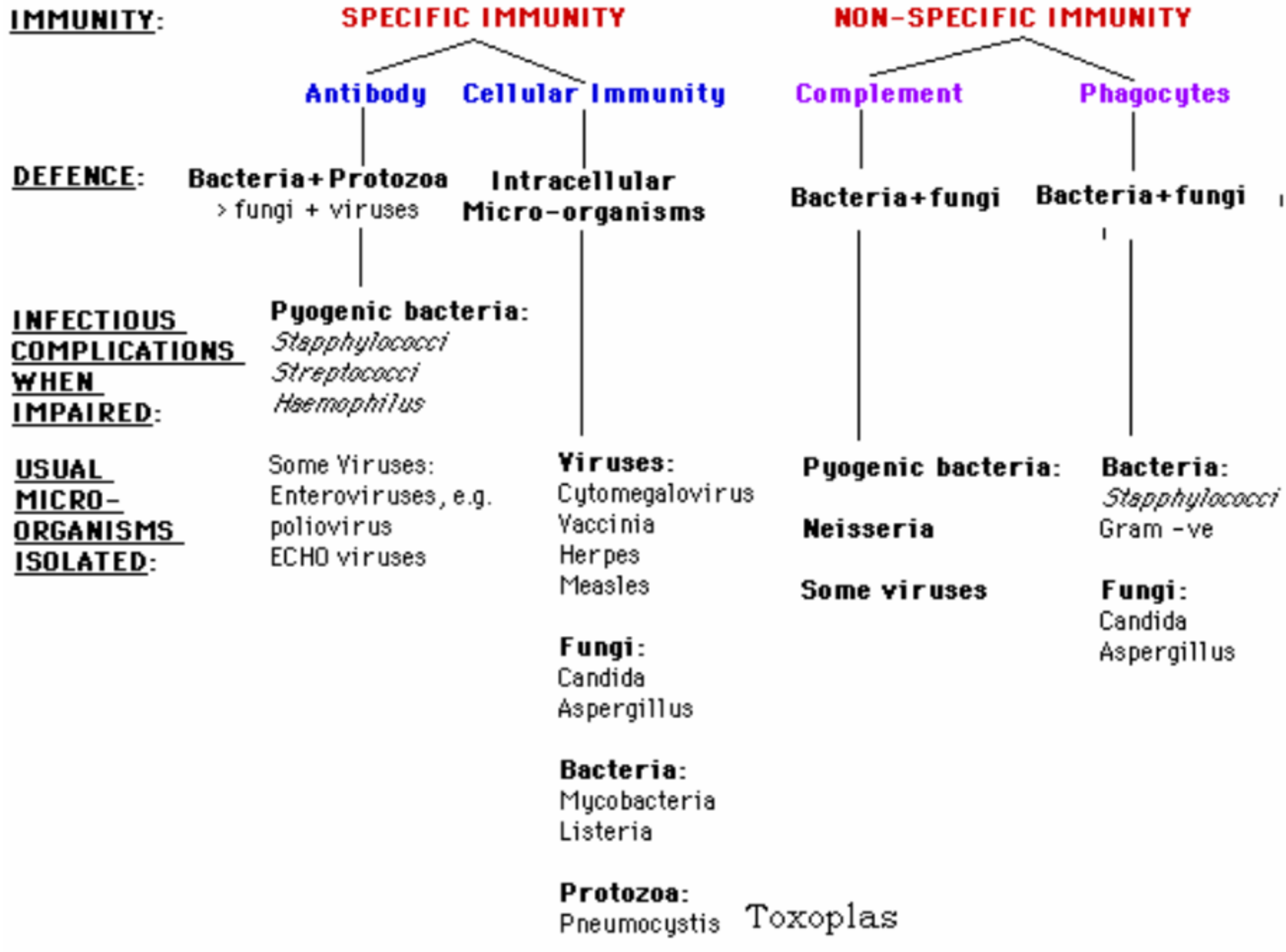


When to suspect

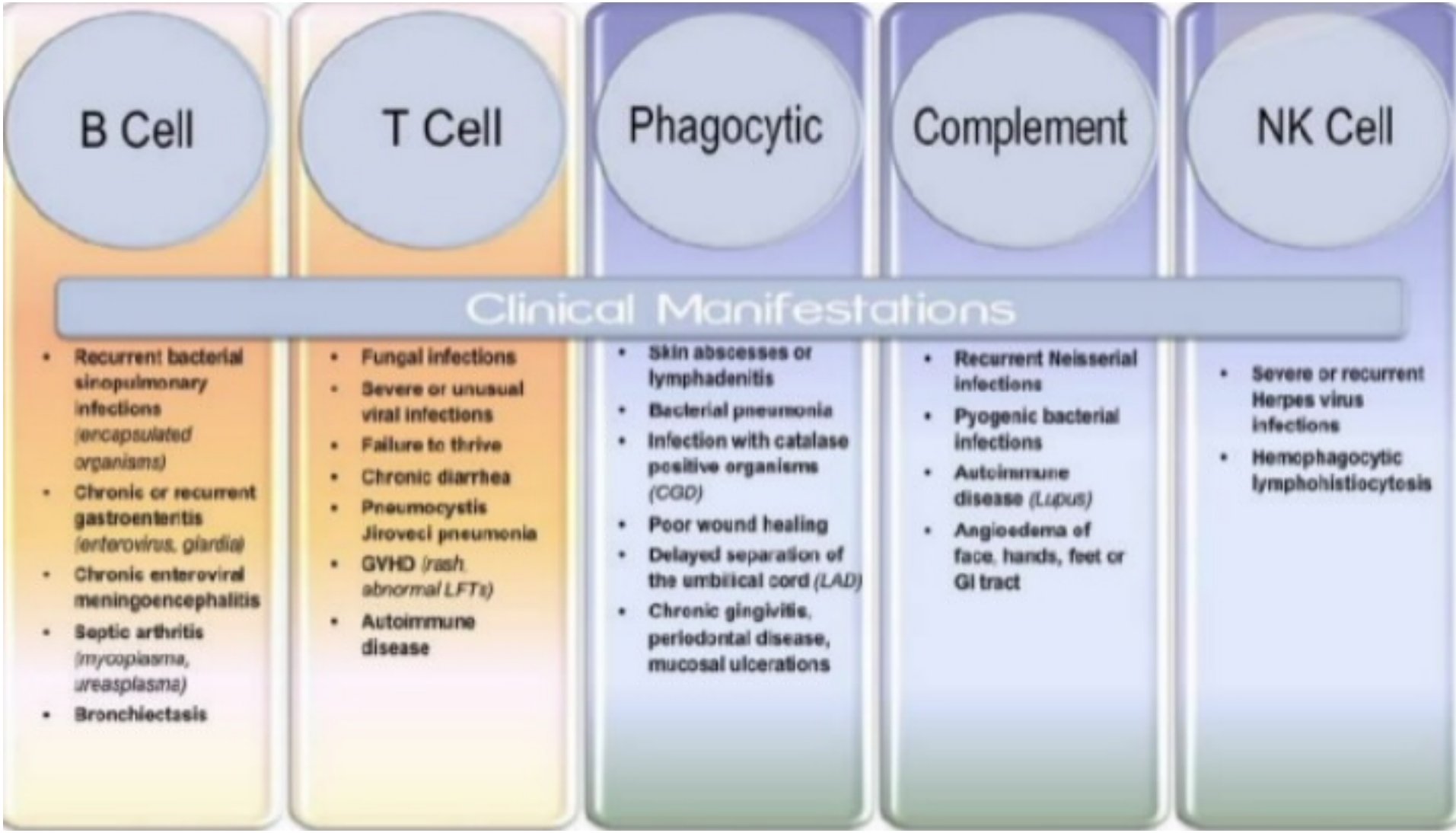
- Severe, Persistent, Unresponsive or Recurrent Infections.

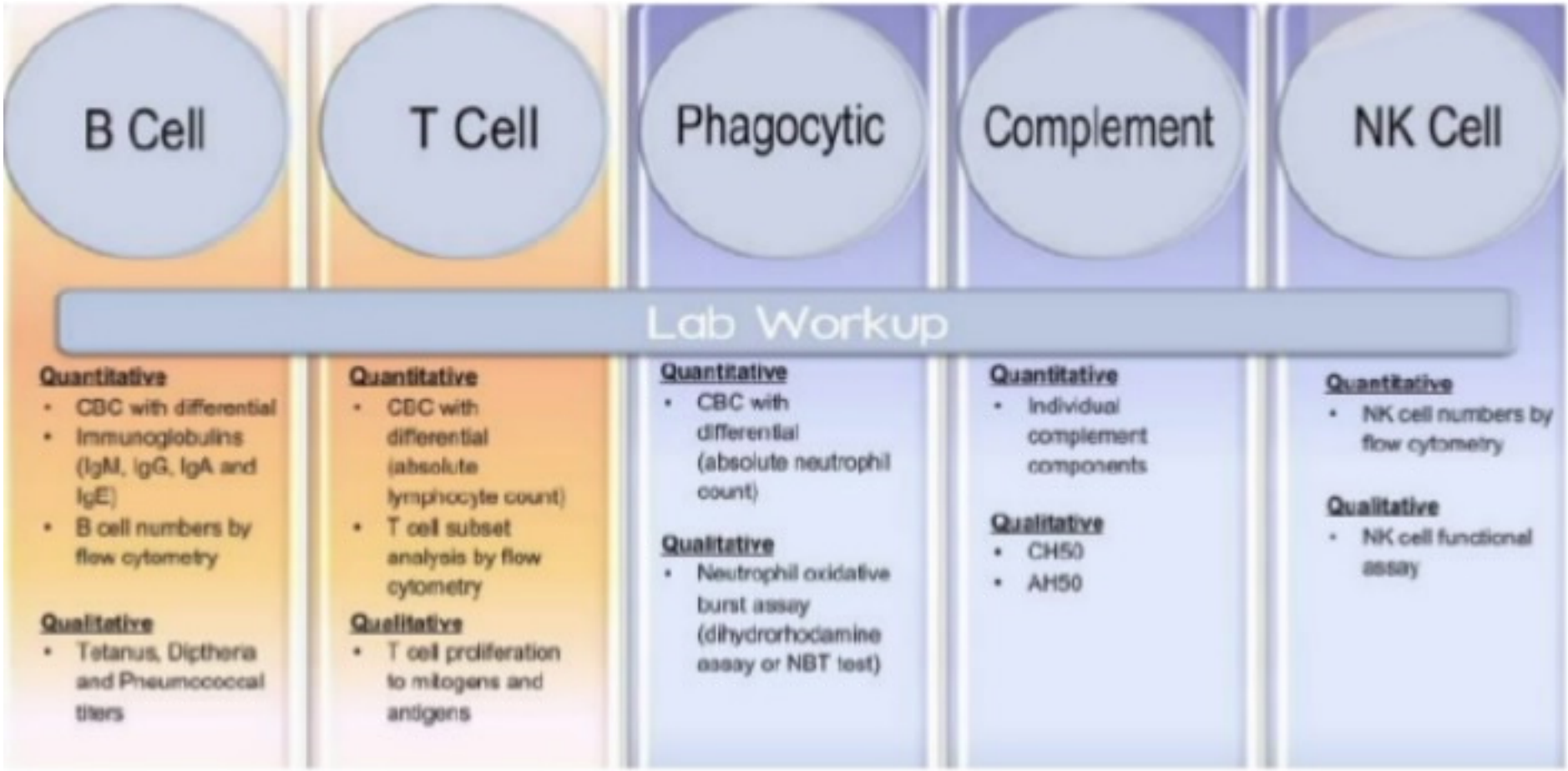
  (SPUR)
- Unusual or opportunistic infections
- Infants with
  - Family history of ID
  - Syndromes known to be associated with ID
  - Failure to thrive
  - Lymphopaenia
- Patients with persistent infection with low virulent org., persistent diarrhoea, poor response to antibiotics
- Opportunistic cancers

Common Infections Associated with Immunodeficiency

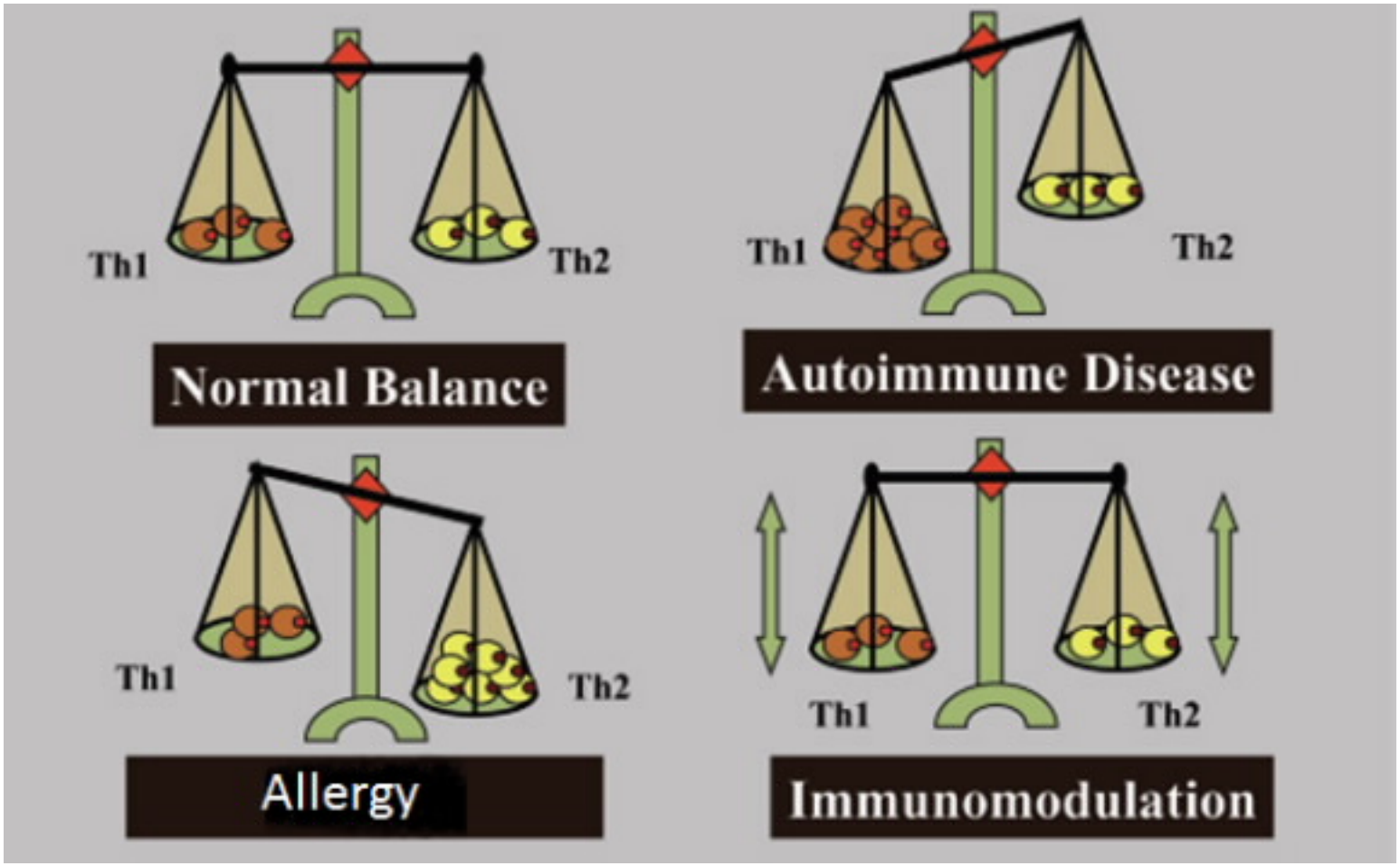


Clinical manifestations




B Cell
T Cell
Phagocytic
Complement
NK Cell
Lab Workup
Quantitative
CBC with differential
Immunoglobulins (IgM, IgG, IgA and IgE)
B cell numbers by flow cytometry
Qualitative
Tetanus, Diptheria and Pneumococcal titers
Quantitative
CBC with differential (absolute lymphocyte count)
T cell subset analysis by flow cytometry
Qualitative
T cell proliferation to mitogens and antigens
Quantitative
CBC with differential (absolute neutrophil count)
Qualitative
Neutrophil oxidative burst assay (dihydrorhodamine assay or NBT test)
Quantitative
Individual complement components
Qualitative
CH50
AH50
Quantitative
NK cell numbers by flow cytometry
Qualitative
NK cell functional assay

Th1 Th2


Th1
Th2
Normal Balance
Th1
Th2
Autoimmune Disease
Th1
Th2
Allergy
Th1
Th2
Immunomodulation

Hypersensitivity

- Classification
- Immuno-pathological basis
- Examples
- Investigation
- Management

Hypersensitivity/ allergy

Type	Immune mechanism	Time of onset
I	IgE mediated	2-30 mins (immediately)
II	Ab & complement	5-8 hrs (intermediate)
III	Ag/ab complexes	2-8hrs (intermediate)
IV	T cell mediated	24-72 hrs (delayed)

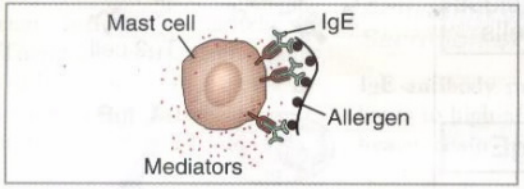
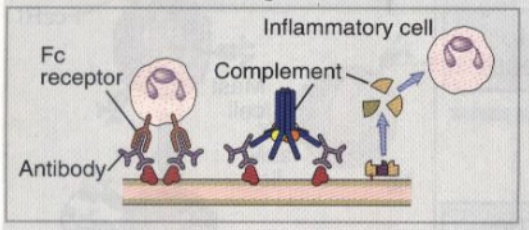
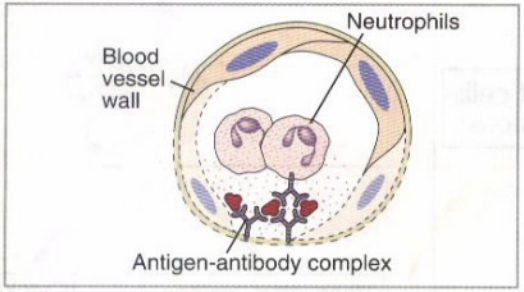
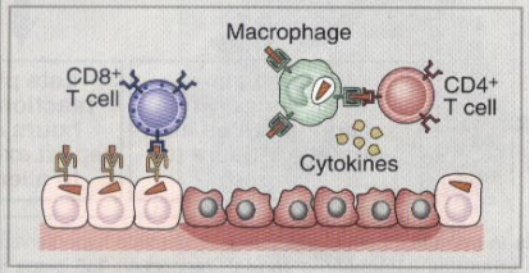
Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	T_H2 cells, IgE antibody, mast cells, eosinophils 	Mast cell–derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils)
Antibody-mediated diseases (Type II)	IgM, IgG antibodies against cell surface or extracellular matrix antigens 	Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Opsonization and phagocytosis of cells Abnormalities in cellular function, e.g., hormone receptor signaling
Immune complex–mediated diseases (Type III)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane 	Complement and Fc receptor-mediated recruitment and activation of leukocytes
T cell–mediated diseases (Type IV)	1. $CD4^+$ T cells (delayed-type hypersensitivity) 2. $CD8^+$ CTLs (T cell–mediated cytolysis) 	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell lysis, cytokine-mediated inflammation

Figure 11–1 Types of hypersensitivity diseases. In the four major types of hypersensitivity reactions, different immune effector mechanisms cause tissue injury and disease.

Table 1 - Laboratory tests used to determine the immune mechanisms of ARs according to the classification proposed by Gell and Coombs

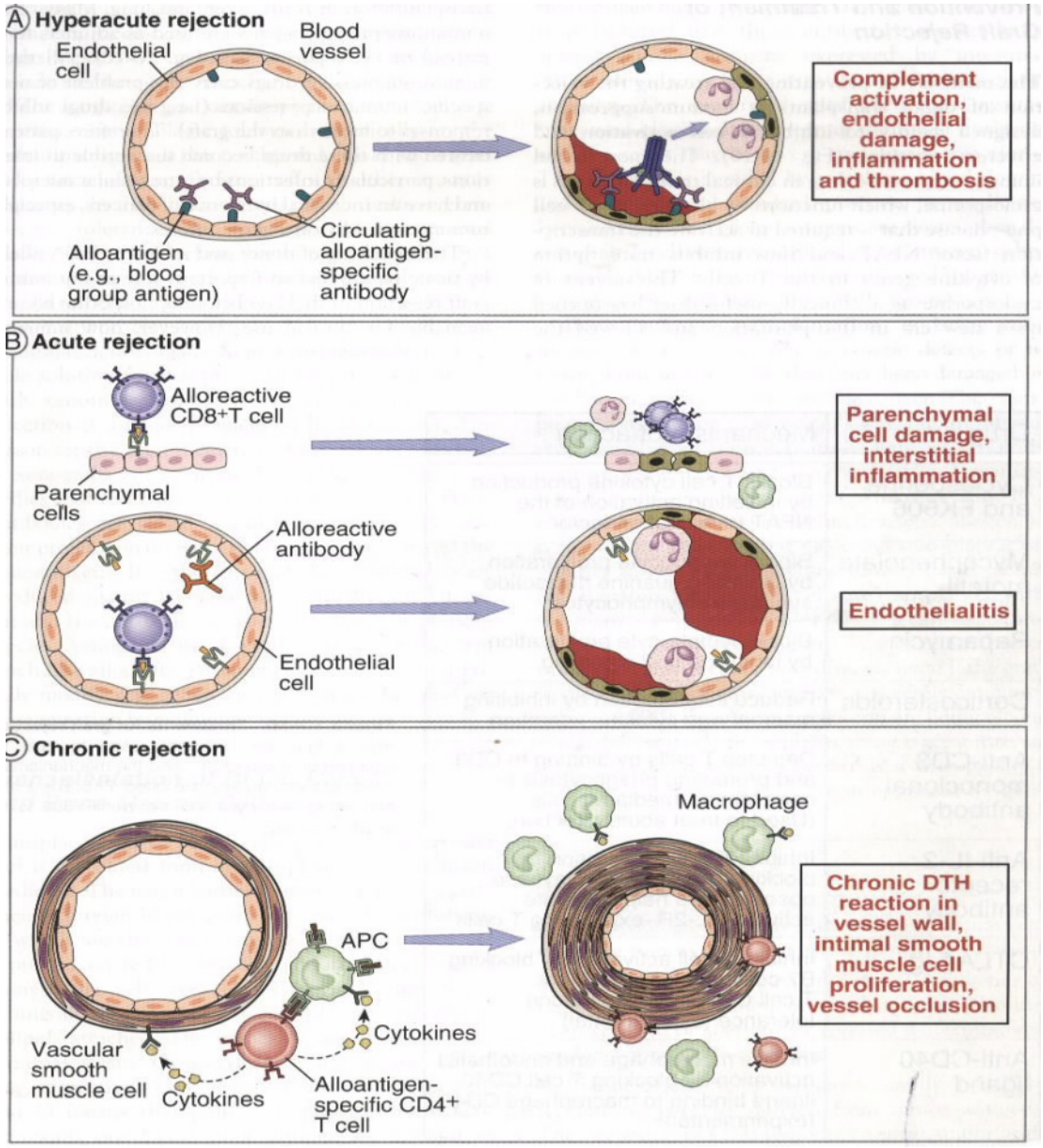
Reaction type	Immune mechanisms	Laboratory tests
I (immediate)	IgE - basophils and/or mast cells	Skin and intradermic tests, RAST, basophil histamine release
II (cytotoxic)	IgG and/or IgM - antigens in the cells membrane	Coombs' test (IAT, DAT)
III (immune complexes)	IgM an/or IgG complexes - soluble antigens	Complement (C3, C4), Immunehystochemical test (IIF, DIF)
IV (late)	T Cells	Epidermal (patch) and intradermic test, *in vitro* lymphocyte transformation, cytokines measures

RAST = radioallergosorbent assay (serum specific IgE); IAT/DAT = indirect antiglobulin test/direct antiglobulin test; IIF/DIF = indirect immunofluorescence/direct immunofluorescence test.

Graft rejection

- Types of rejection
- Underlying mechanisms
- How to prevent

Graft rejection



Immune modulation

- Vaccination
  - Types of vaccines
  - Underlying basis
  - EPI vaccines
  - Non EPI vaccines
  - New modifications in vaccines

Immune stimulants

- Vaccines
- Immunoglobulins
- Transfer of effector T cells
- Transfer of cytokines

Immune suppressors

- Corticosteroids
- Cytotoxic drugs
  - Azathioprine
  - Cyclophosphomide
  - Methotrexate
- Other Immunomodulatory drugs
  - hydroxychloroquine

Other immune modulators

- Biologicals (monoclonal antibodies)
- Desensitization
- Genetherapy