Immunity to Infections

Why we have an immune system...

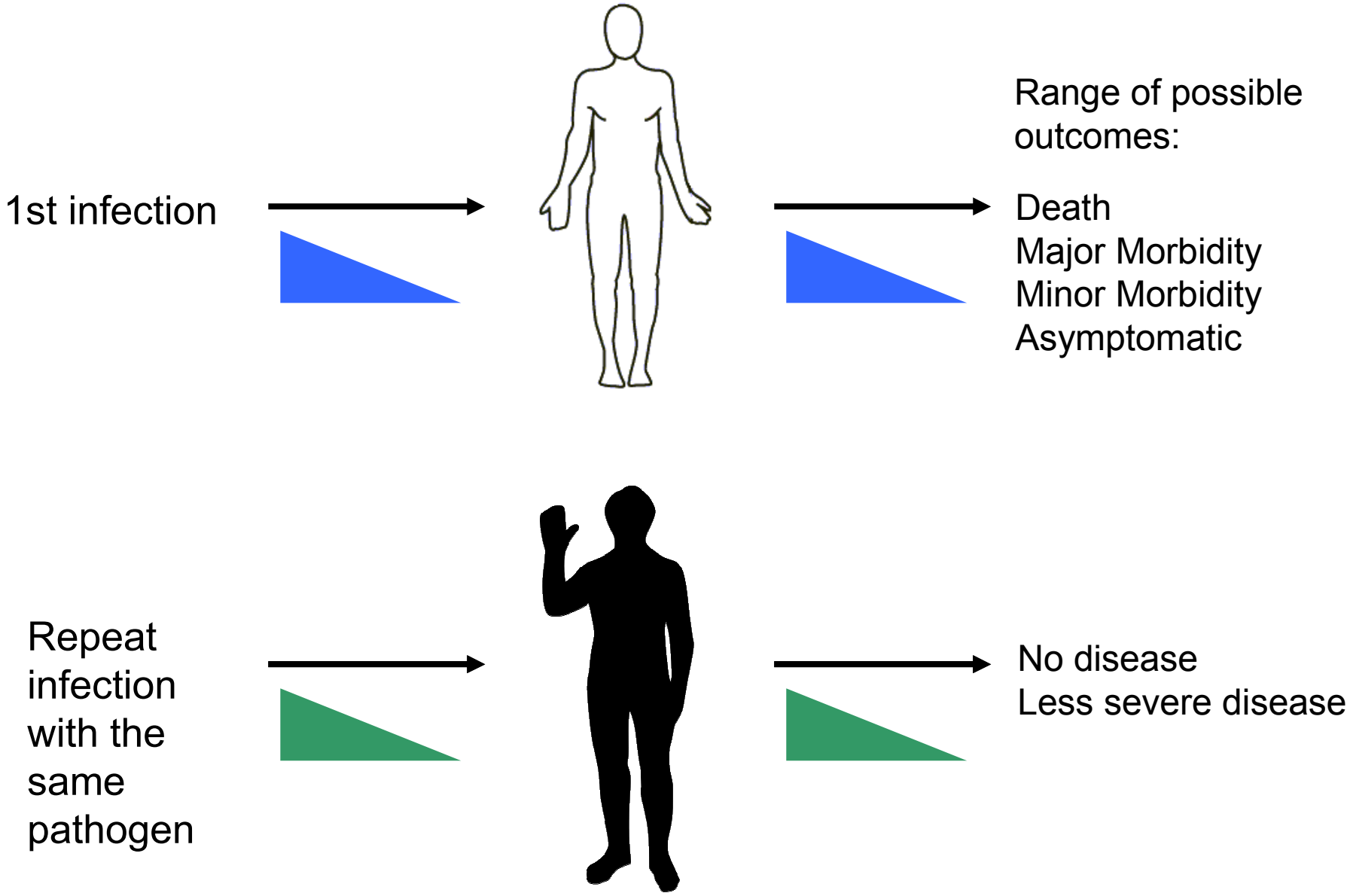
- Host-Parasitic relationship: a form of symbiosis in which one organism benefits (the parasite) while the other is harmed (the host)

- some form of host defense is present in all multicellular organisms
  - some inverts have phagocytes
  - all vertebrates have phagocytes, NK cells, and T and B cells
  - antibodies become more complex (mammals)
  - Toll receptors in drosophila => Toll-like receptors in mammals (an important innate receptor)

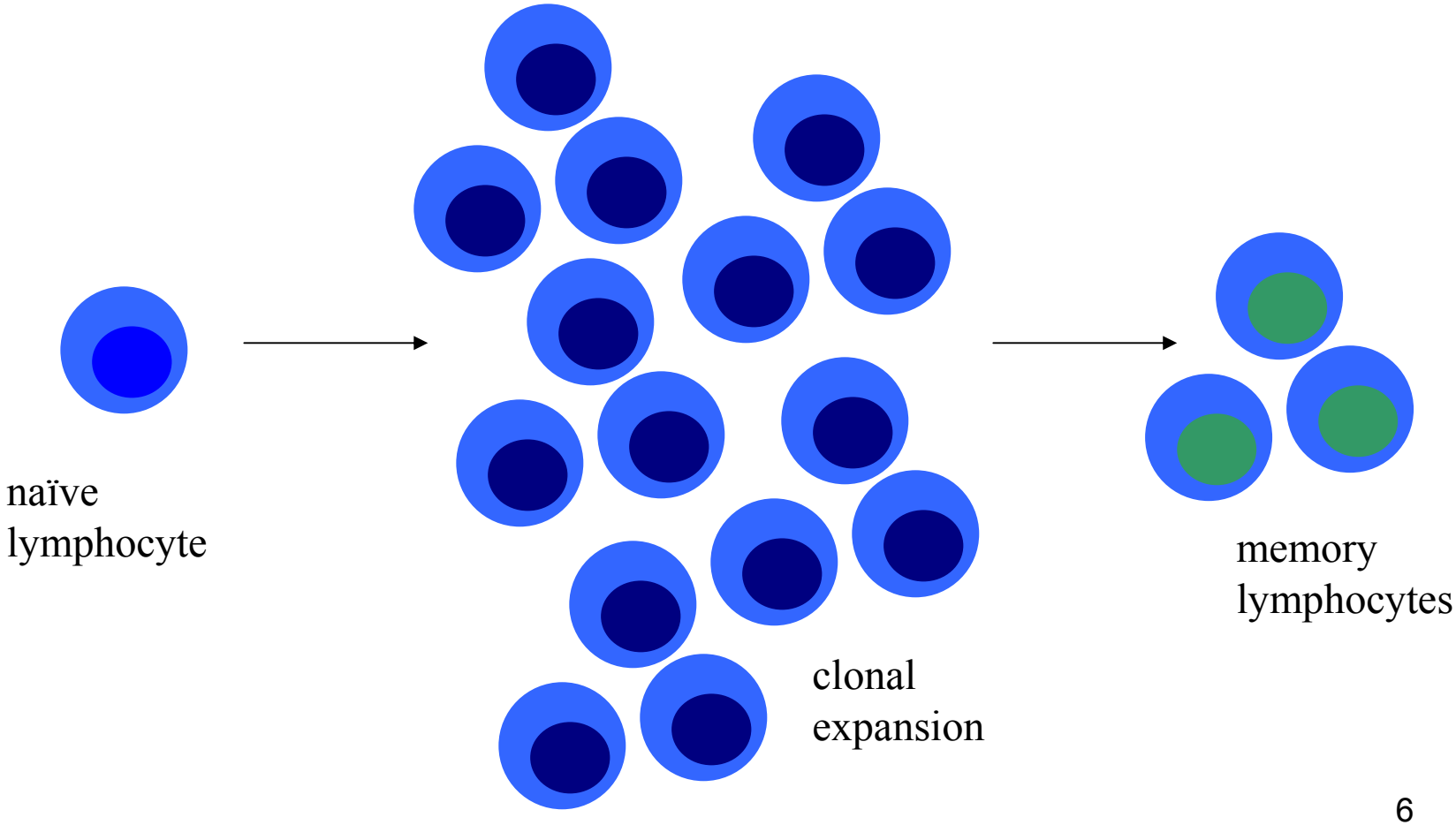
Infectious threats

- viruses, bacteria, fungi, parasites, etc.
- most are friendly or neutral
  - tolerated or controlled
- the minority of microbes cause disease
  - these are termed **virulent** or **pathogenic**
  - microbe entry => invasion and colonization of host tissues => evasion of host immunity => tissue injury/ impairment

- *protection against microbial infection is the main physiological function of the immune system*


1st infection
Range of possible outcomes:
Death
Major Morbidity
Minor Morbidity
Asymptomatic
Repeat infection with the same pathogen
No disease
Less severe disease

Immunological memory



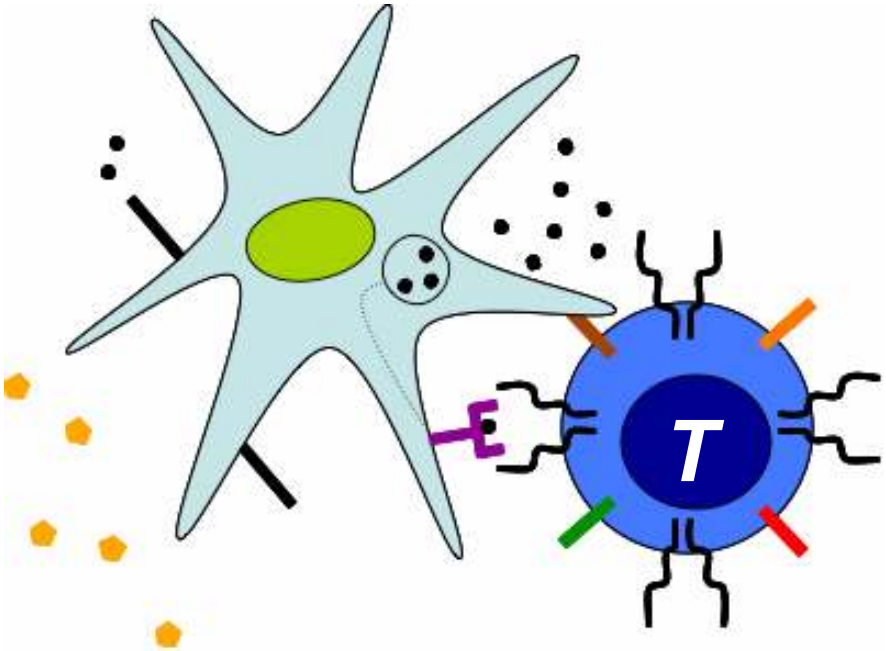
Innate immunity.

- adaptive response typically takes 1-2 weeks to develop
- in the meantime, innate immunity:
  - contains the infection transiently
  - induces adaptive T and B cell responses
- in many cases innate immunity is also involved in pathogen clearance during the peak of the adaptive response

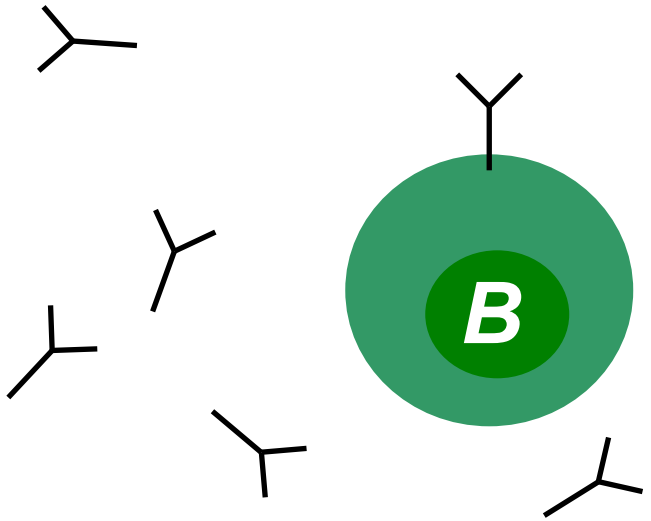
Basic principles of immunity

- defense is mediated by effector mechanisms aimed at containment and clearance
- pathogens receive specialized responses
- pathogen survival hinges around evasion of effector responses.

Cellular versus Humoral immunity



T helper type 1 (Th1)

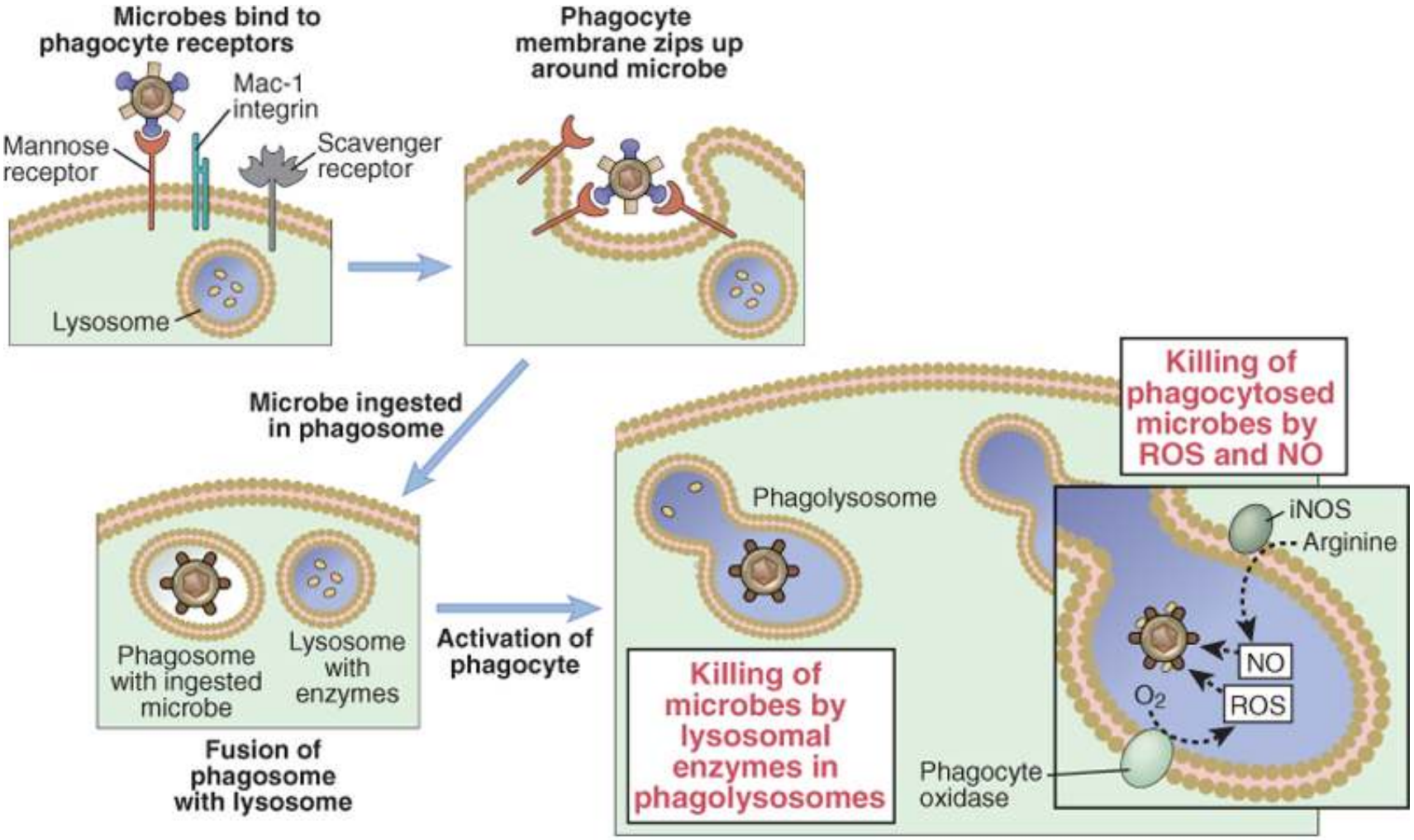


T helper type 2 (Th2)

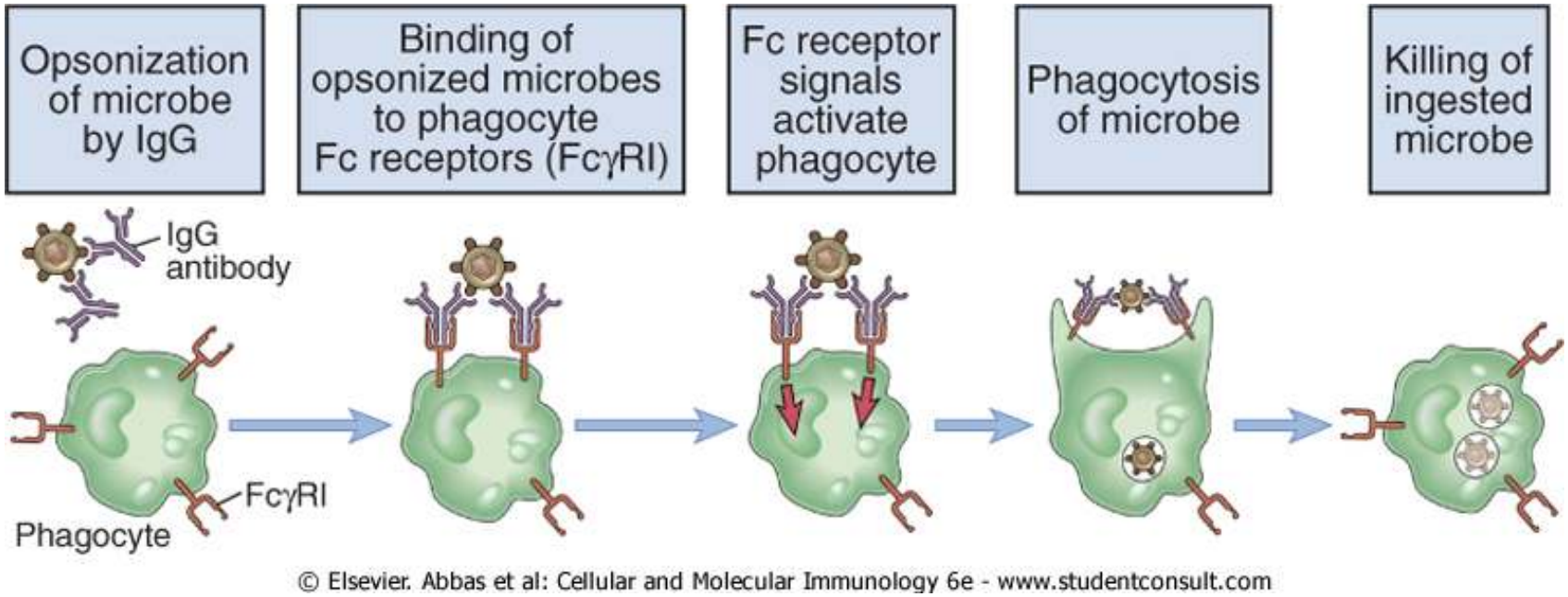
Where the microbe lives plays a role in determining what type of immune response will be effective...

- extracellular bacteria => antibody response
- intracellular bacteria => cell-mediated response
- viruses => both
- parasites => varies depending on the life cycle, structure, etc (often both)

Mechanisms of clearance: Phagocytosis



Mechanisms of clearance: Opsonization



General features of immunity to different classes of microbes...

Extracellular bacteria

Intracellular bacteria

Viruses

Parasites

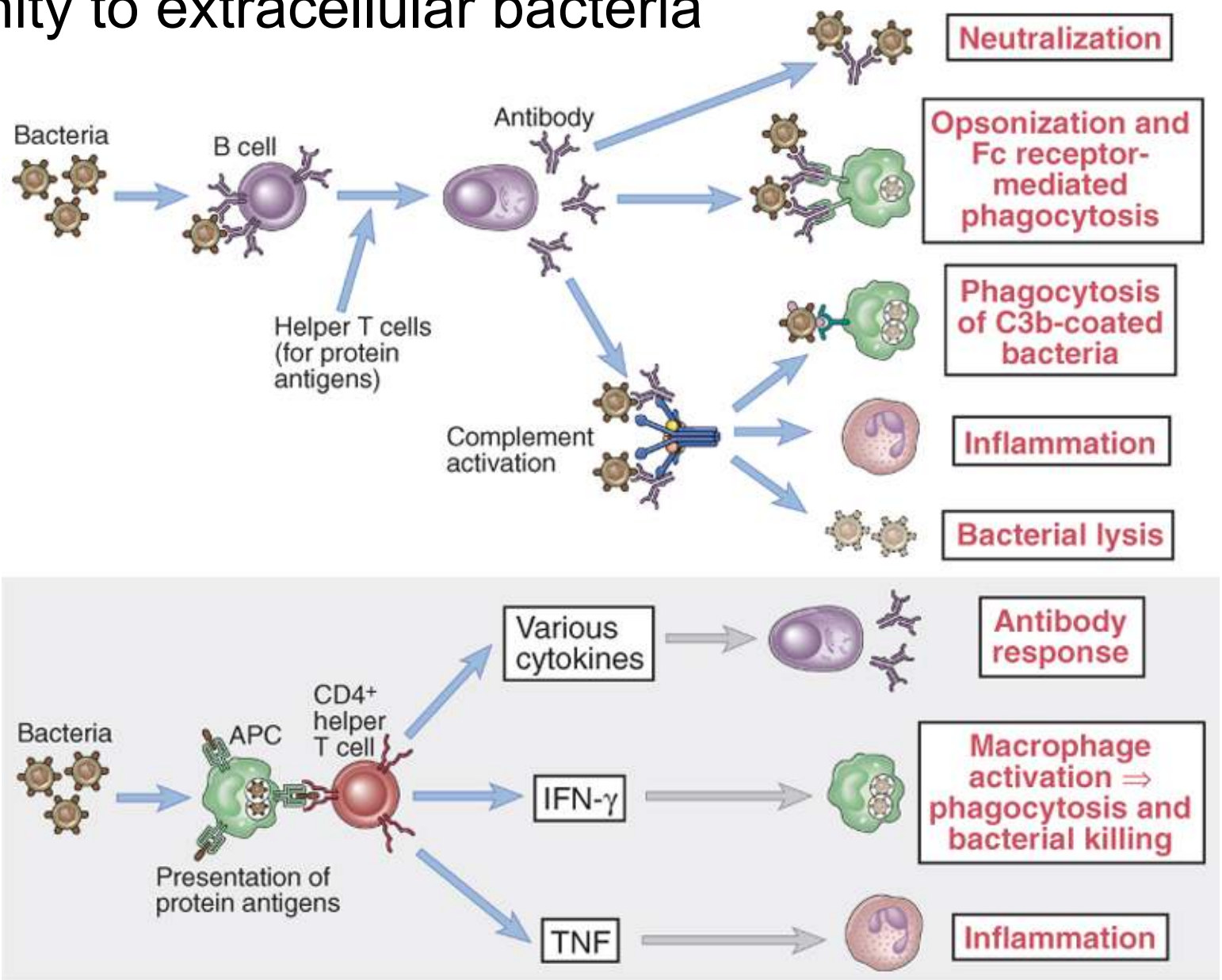
Extracellular bacteria

- Innate response involves activation of:
  - complement (alternate) => LPS, PG, mannose
  - TLR pathways, later activating adaptive response
  - inflammatory response and influx of WBC
    - can also cause fever, injury
  - phagocytes => enhanced activity, opsonization, pathogen receptors
    - neutrophils, macrophages, dendritic cells (DCs)

Extracellular bacteria (2)

- Adaptive response, which relies mostly on antibody (humoral) responses
  - block infection, eliminate microbes, neutralize toxins
  - usually directed towards cell wall and secreted products
  - opsonization, activation of classical complement
  - CD4 response => cytokines and co-stimulation that help the mAb response
  - Th1 cells => critical for neutrophil recruitment

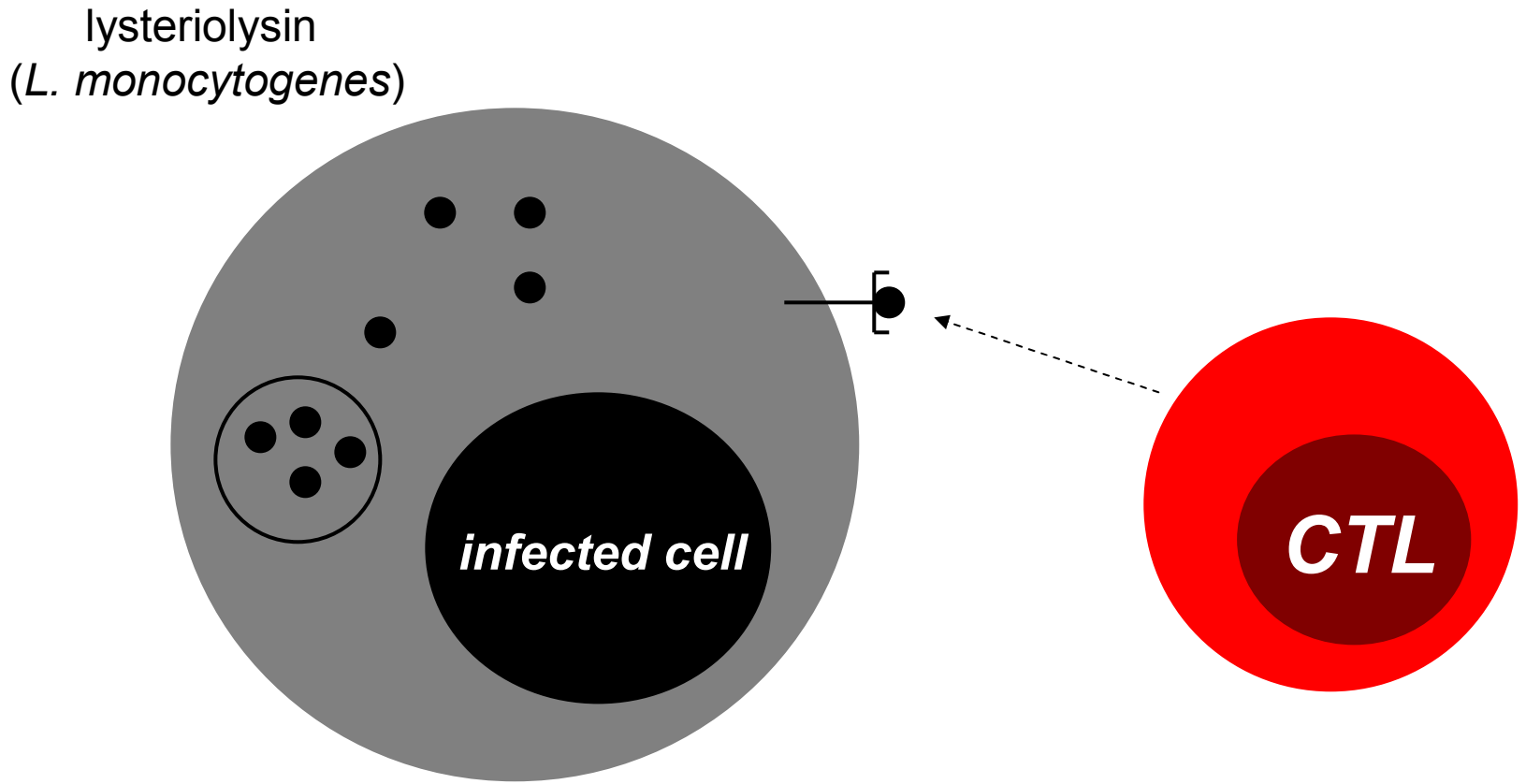
Immunity to extracellular bacteria



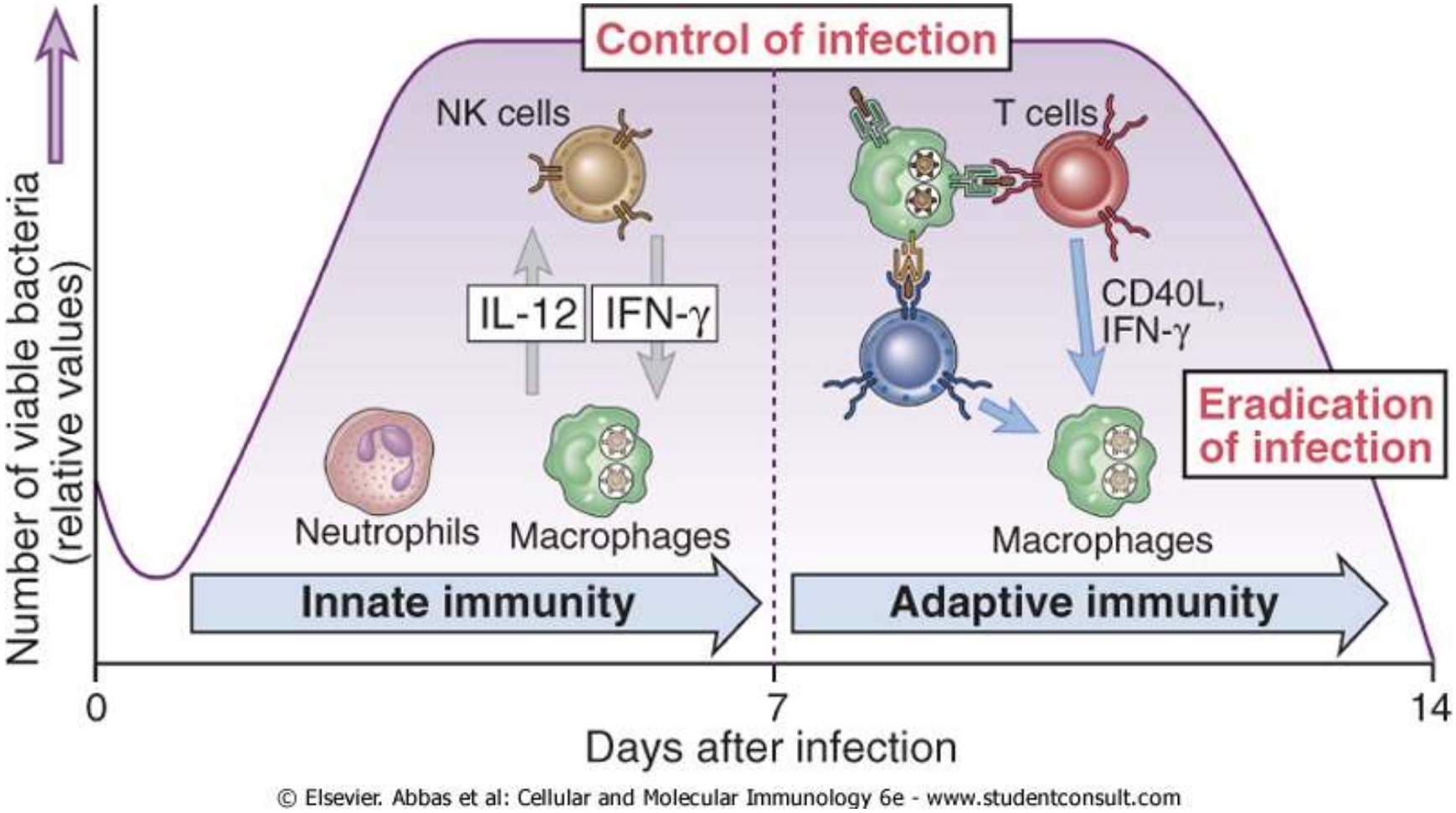
Intracellular bacteria

- adapted to replicate inside cells, often phagocytes
- no antibody accessibility => CMI is critical
- activation of NK cells => kill infected cells, secrete Th1 cytokines
- IL-12 => key to inducing a Th1 response
- macrophage activation via CD40L and IFN-γ => increases killing of ingested microbes
  - induction of ROS, NO, lysosomal enzymes (anti-microbial)
- if bacteria escapes phagosomes -> cytosol, they can be recognized by CD8+ T cells

Intracellular bacteria



Immunity to intracellular bacteria



Examples of Microbial Evasion of Immune Defenses.

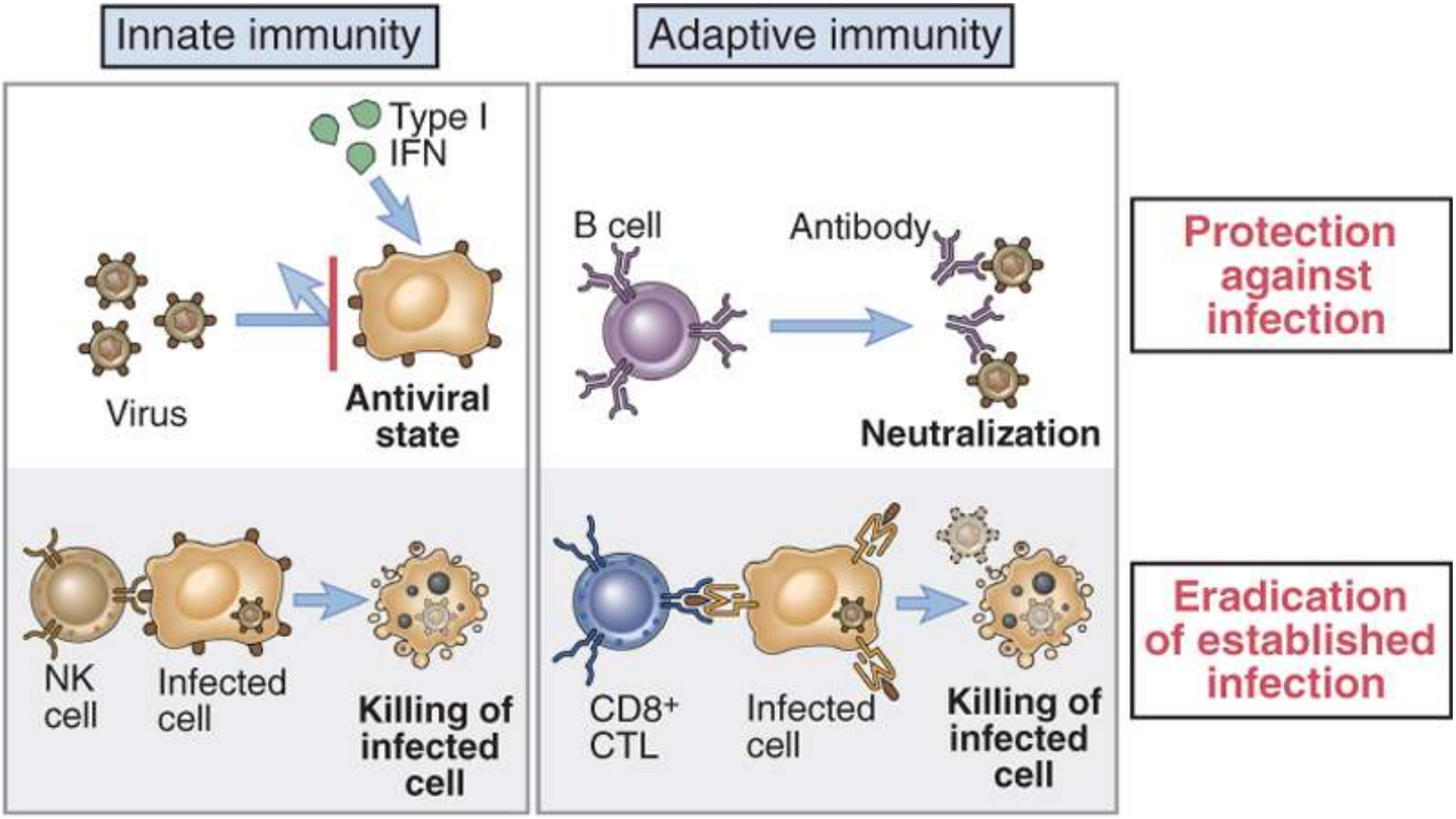
Pathogen	Mechanism	Result
Streptococcus pneumoniae	Capsule	Avoids phagocytosis
Gram positive bacteria, some gram negative bacteria	Resist insertion of complement MAC	Avoid complement-mediated lysis
Mycobacterium tuberculosis	Blocks lysosome fusion with phagosome	Avoids antibody and complement opsonization, macrophage killing
Listeria monocytogenes	Escapes phagosome into cytoplasm	Avoids macrophage killing, presentation on Class II MHC
Toxoplasma gondii	Escapes phagosome into own cytoplasmic vesicle	Avoids macrophage killing, presentation on both Class I and Class II MHC
Treponema pallidum	Covers membrane with host proteins	Avoids immune system recognition
Neisseria meningitidis *Neisseria gonorrhoeae* *Haemophilus influenzae*	Expresses IgA protease	Avoids IgA neutralization
Pseudomonas aeruginosa	Secretes elastase that inactivates C3a and C5a	Blocks inflammation
Staphylococcus aureus	Secretes superantigens	Suppresses immune response
Mycobacterium leprae	Stimulates Th2 response	Suppresses Th1 response

Viruses

- take over cellular machinery => injury + death
- use cell-surface receptors to enter various cell types
- immunity => blocking infection and clearing infected cells
- Innate response involves:
  - NK killing, cytokine secretion
  - infected cells, plasmacytoid DCs => secrete Type 1 interferons

Adaptive immunity to viruses

- antibody response:
  - early in infection, or when virus is between cells
  - neutralization => prevents attachment, entry to cell
  - opsonization, complement activation
  - IgA important mucosally
- CD8+ T cell response:
  - detects virus inside cytoplasm (infected cells, ingested)
  - usually require CD4 help (same as abs)
  - secrete cytokines, kill infected cells (Perforin-granzyme pathway)
  - can target more conserved regions of viral genomes



Anti-viral immunity

Viral evasion

- evolution (antigen variation)
- HLA down-regulation
- homologs to human proteins (EBV -> IL-10)
- CTL exhaustion

Parasites

- infect 30% of the world's population
- protozoa, helminths, ectoparasites
- complex life cycles with intermediate hosts
- most cause chronic infections => weak innate immunity and evade adaptive responses

Parasites (2)

- Innate:
  - many parasites can resist phagocytosis
  - some bind TLRs and activate APCs
- Adaptive:
  - differs widely depending on life cycle, structure of the pathogen
  - if intracellular => similar to intracellular bacteria
  - extracellular => special types of antibody responses (IgE)

Depending on the parasite...

Parasite/Disease	**Immunity**
Protozoa	
Plasmodium spp. (malaria)	antibody and CD8+ CTL
Leishmania	CD4+ Th1, macrophage act.
Trypanosoma	antibodies
Entamoeba (Amebiasis)	antibodies, phagocytosis
Metazoa	
Schistosoma spp.	ADCC via eosinophils, macrophages, Th2
Filaria	cell-mediated immunity, ?antibodies

Evasion

- change antigenicity
  - stage specific, programmed (Trypanosomes), shedding
- resist effector mechanisms aimed at clearance
  - ie. tegument is difficult to phagocytose
- sequester away from immune responses
  - insides cells, in cysts, intestinal lumen
- induce T cell tolerance
  - Tregs