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CLINICAL IMMUNOLOGY 4540-FS2019-0

Immunity to Microbes
Principles of Vaccination

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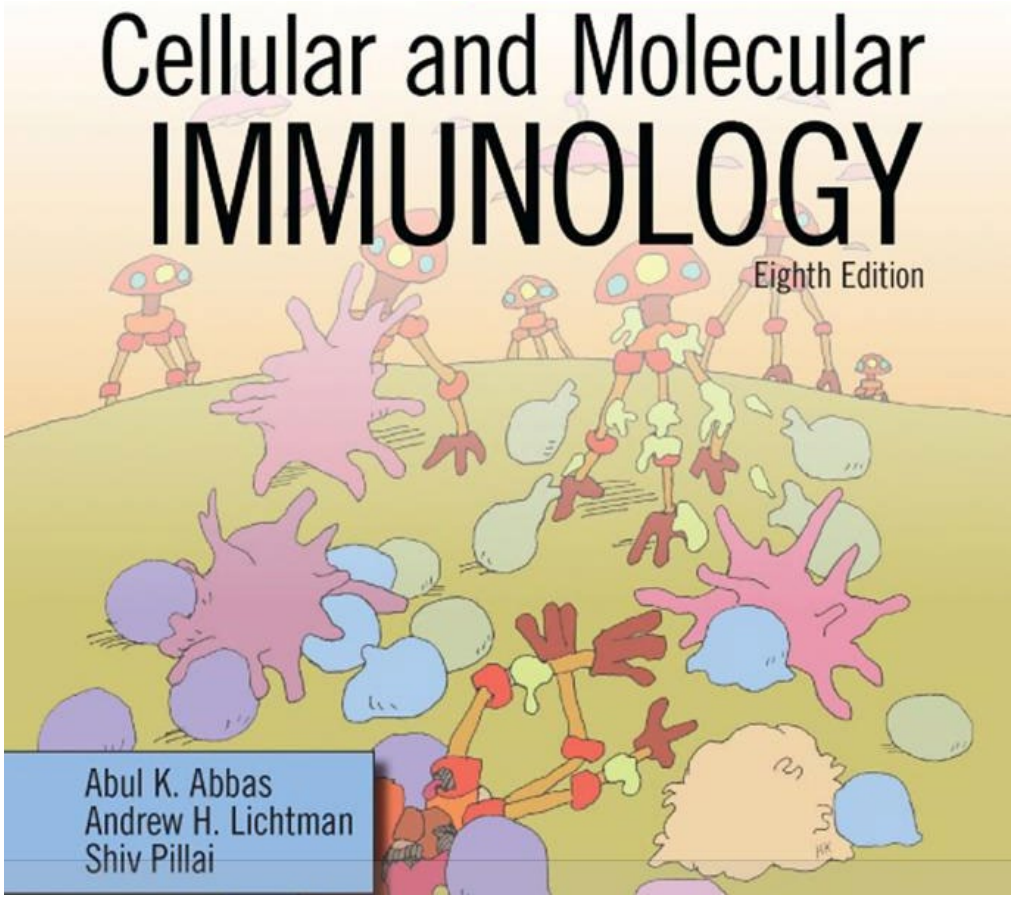
Aims – immunity to microbes

- Understand the responses of the innate, adaptive, humoral and cellular immune system to the major classes of microbes
  - Extracellular bacteria
  - Intracellular bacteria
  - Fungi
  - Viruses
  - Parasites
- Mechanisms of immune evasion by microbes
- Understand key concepts of immunological pathogenicity mediated by microbes



Figures from 6th/8th Ed.

Innate and adaptive immunity

Table 1–2. Features of Innate and Adaptive Immunity

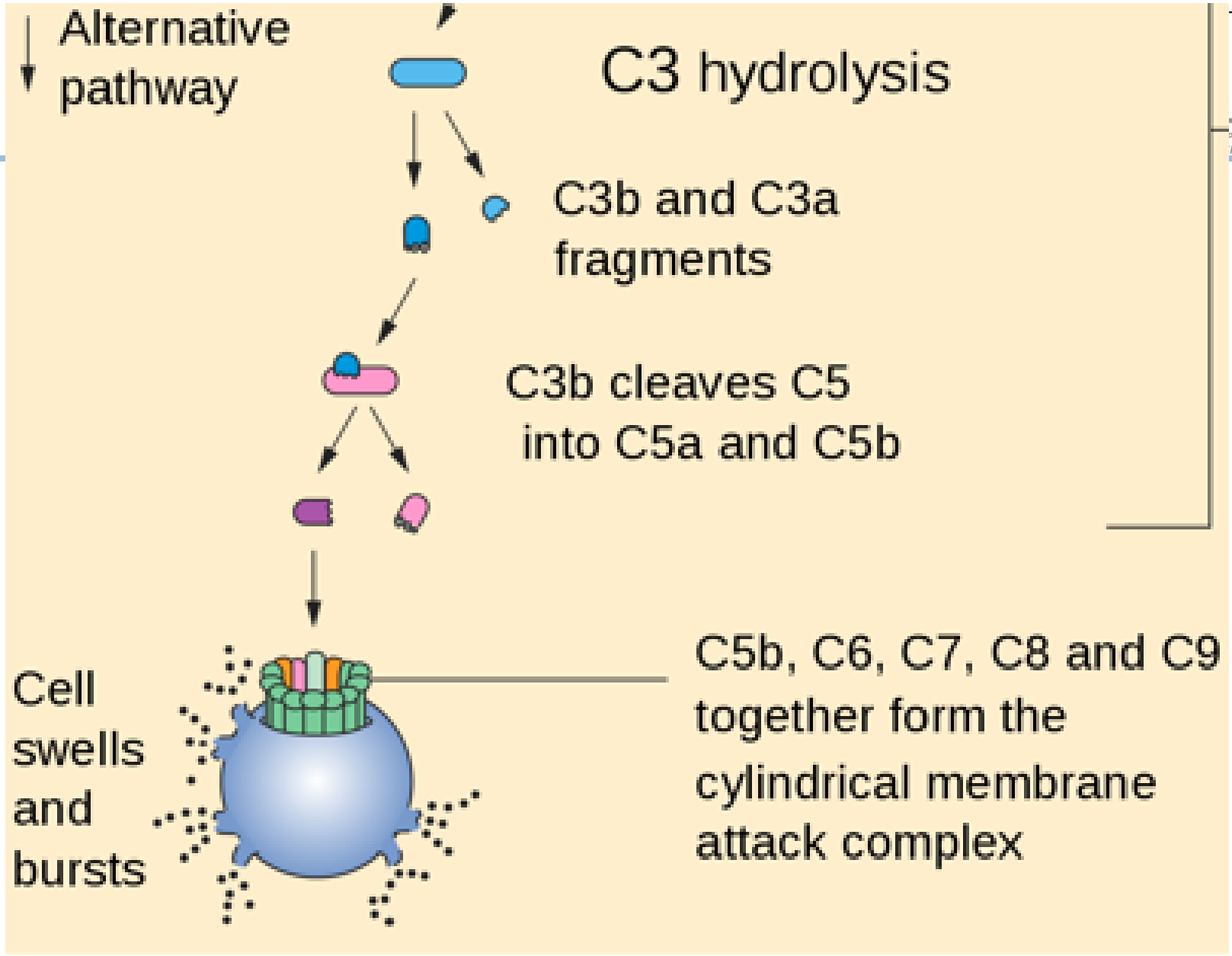
	Innate	Adaptive
Characteristics		
Specificity	For structures shared by groups of related microbes	For antigens of microbes and for nonmicrobial antigens
Diversity	Limited; germline-encoded	Very large; receptors are produced by somatic recombination of gene segments
Memory	None	Yes
Nonreactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial chemicals	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement, others	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells	Lymphocytes

Innate immune response to extracellular bacteria

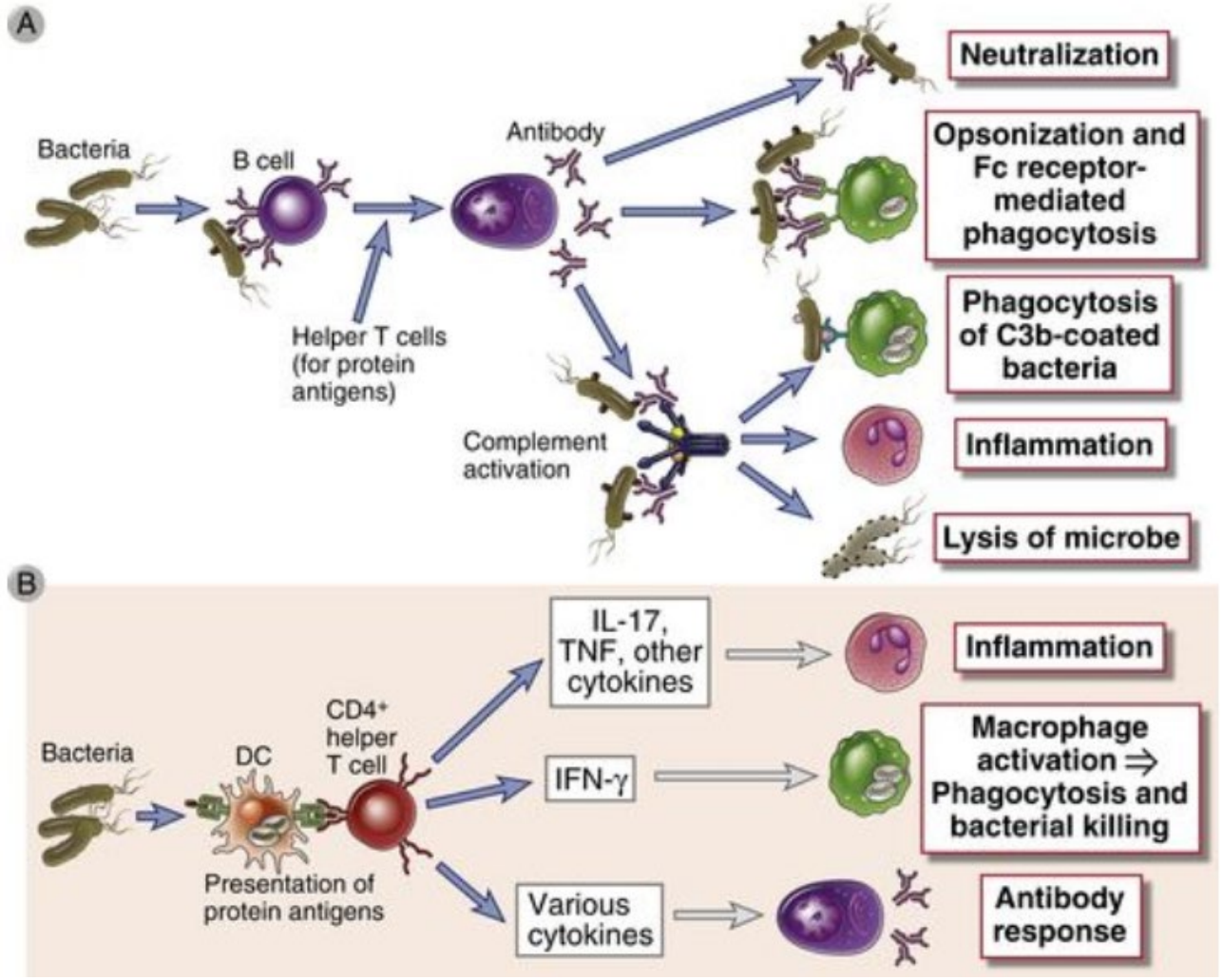
- **Complement activation** (alternative pathway) through
- -Peptidoglycan in the cell wall of Gram-positive bacteria
  -Lipopolysaccharide in Gram-negative bacteria by
  -by mannose on bacterial surface

Leads to

- **Opsonization and enhanced phagocytosis**
- **Lysis of susceptible bacteria** by membran attack complex
- **Activation of phagocytes and inflammation**


Alternative pathway
C3 hydrolysis
C3b and C3a fragments
C3b cleaves C5 into C5a and C5b
Cell swells and bursts
C5b, C6, C7, C8 and C9 together form the cylindrical membrane attack complex

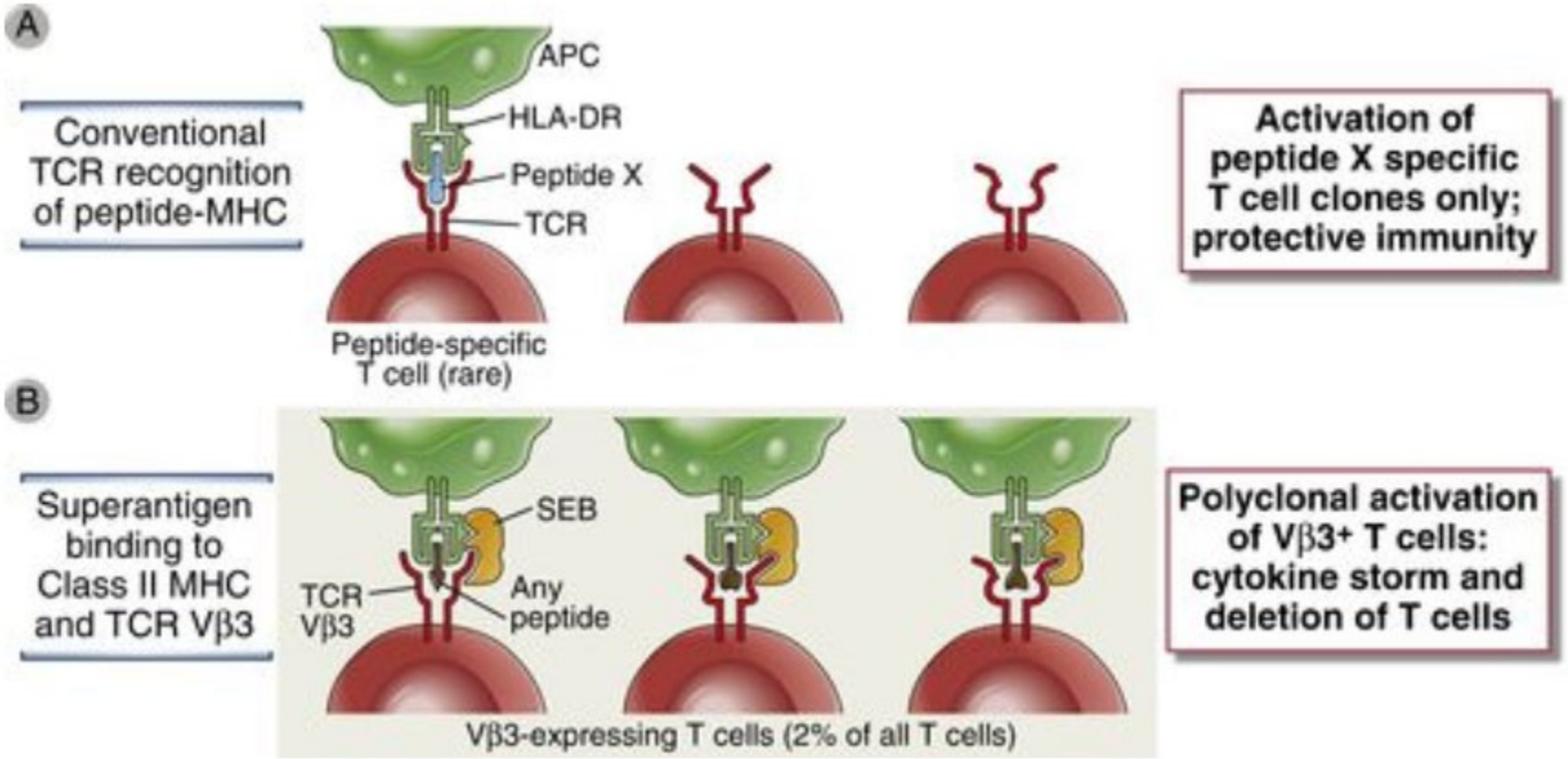
Adaptive immune response to extracellular bacteria



Antibody production

CD4 response

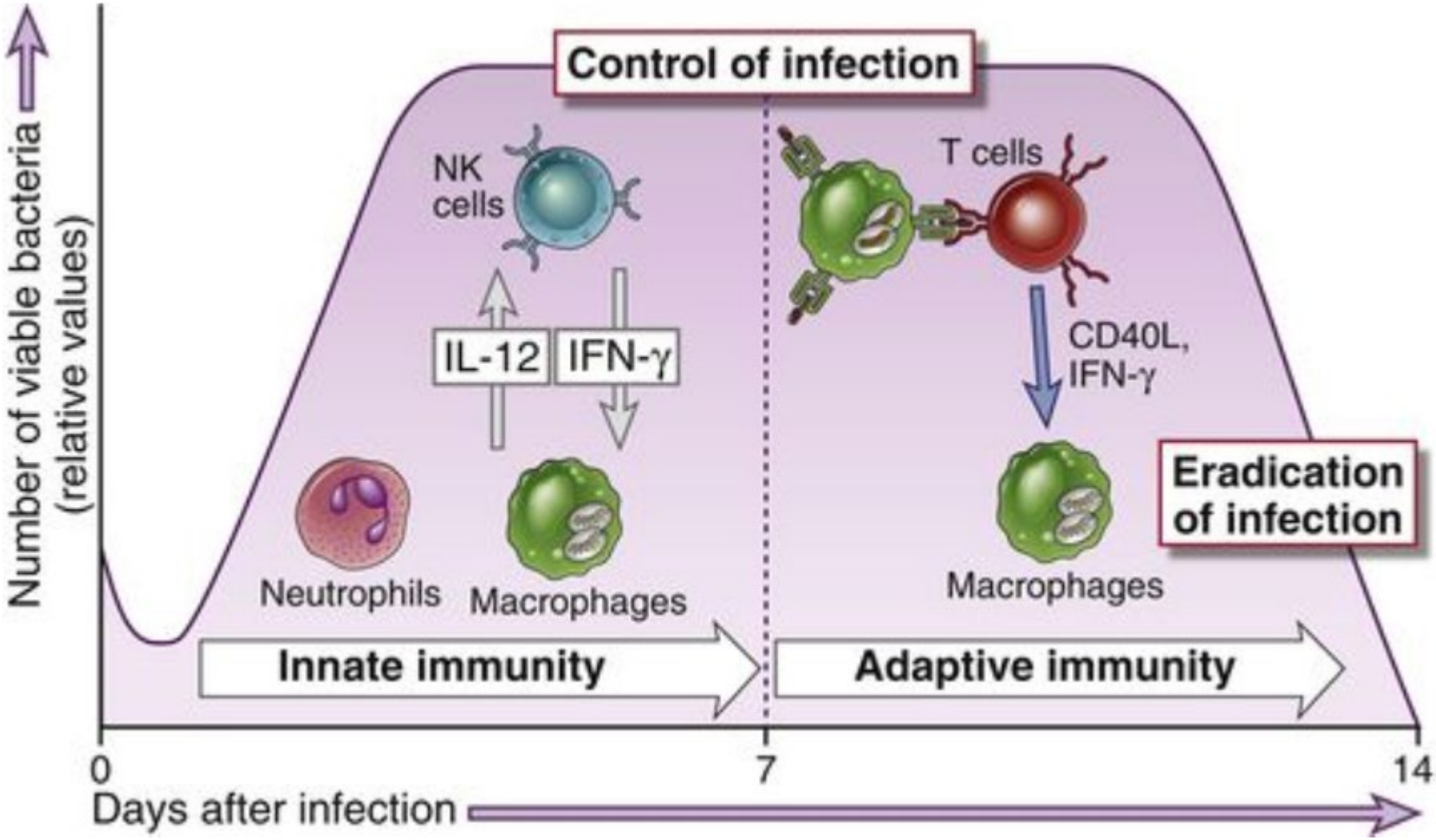
Bacterial superantigen may lead to injurious effects of the immune response



Immune response to intraacellular bacteria

Microbe	Examples of Human Diseases
Intracellular Bacteria	
Mycobacteria	Tuberculosis, leprosy
Listeria monocytogenes	Listeriosis
Legionella pneumophila	Legionnaires' disease

Dynamic of the immune response to intracellular bacteria



Adaptive immune response to intracellular bacteria: CD4+/CD8+ cooperation

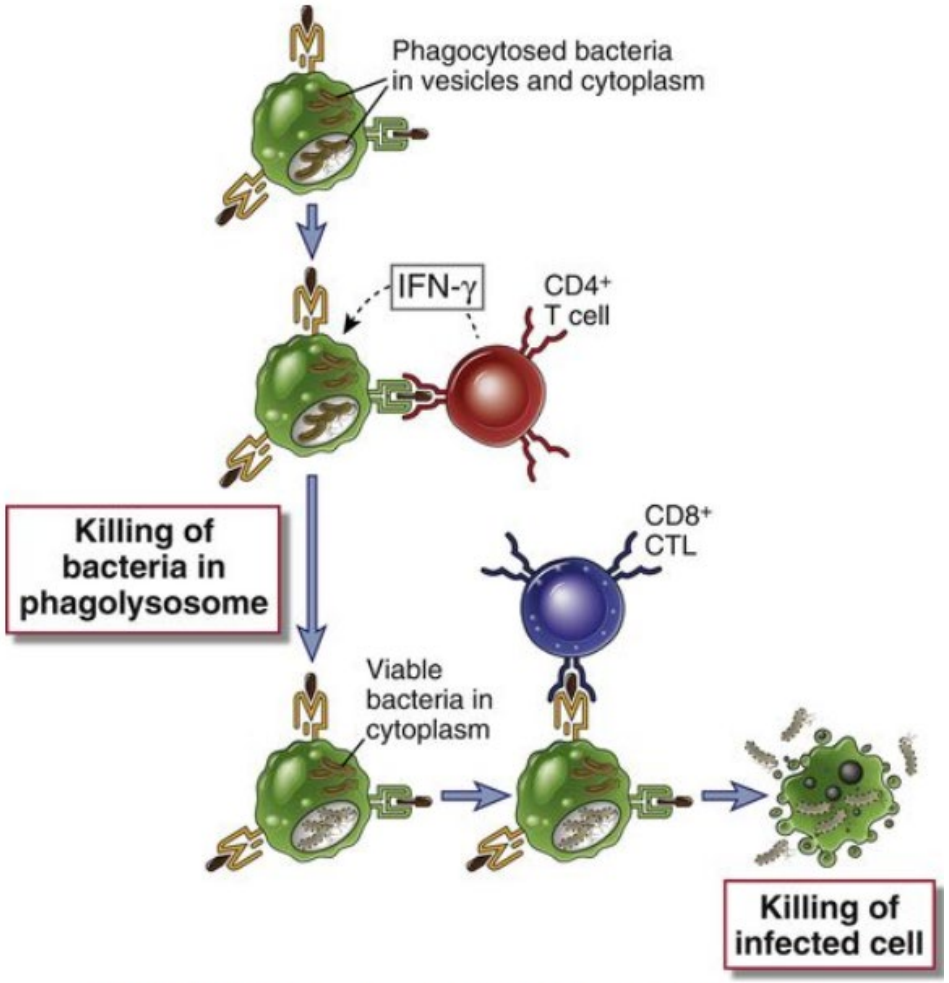
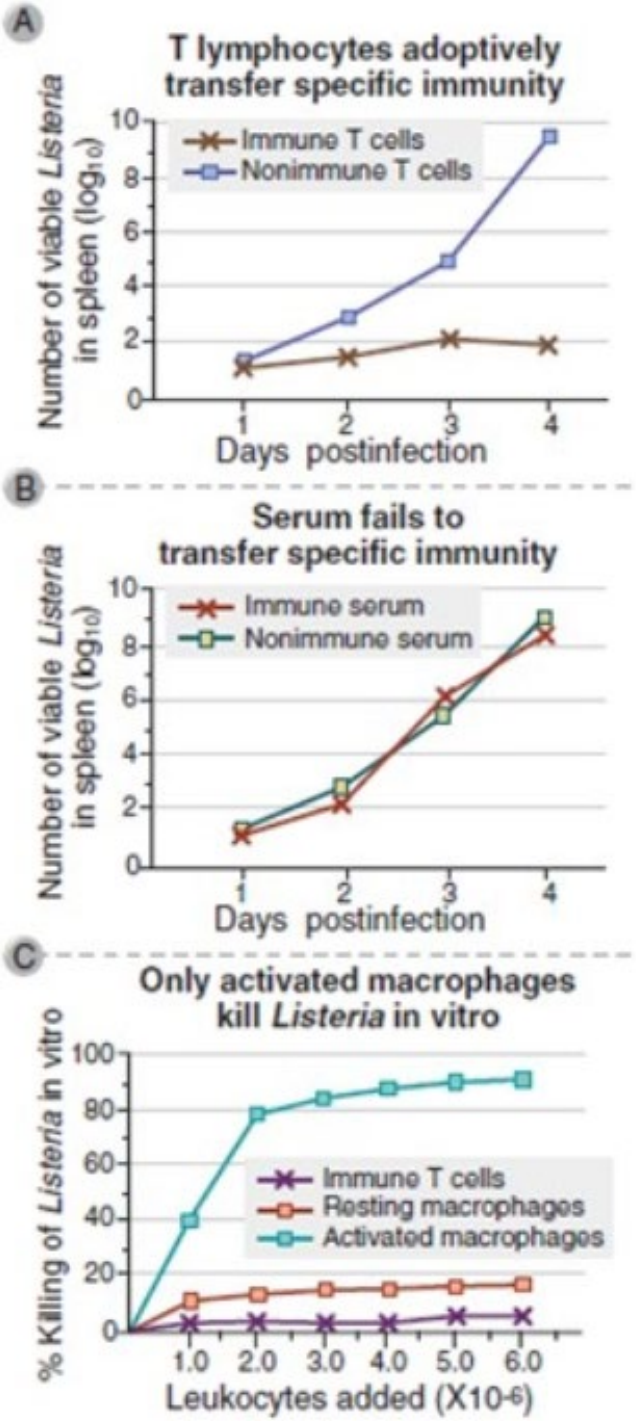


FIGURE 16-5 Cooperation of $CD4^+$ and $CD8^+$ T cells in defense

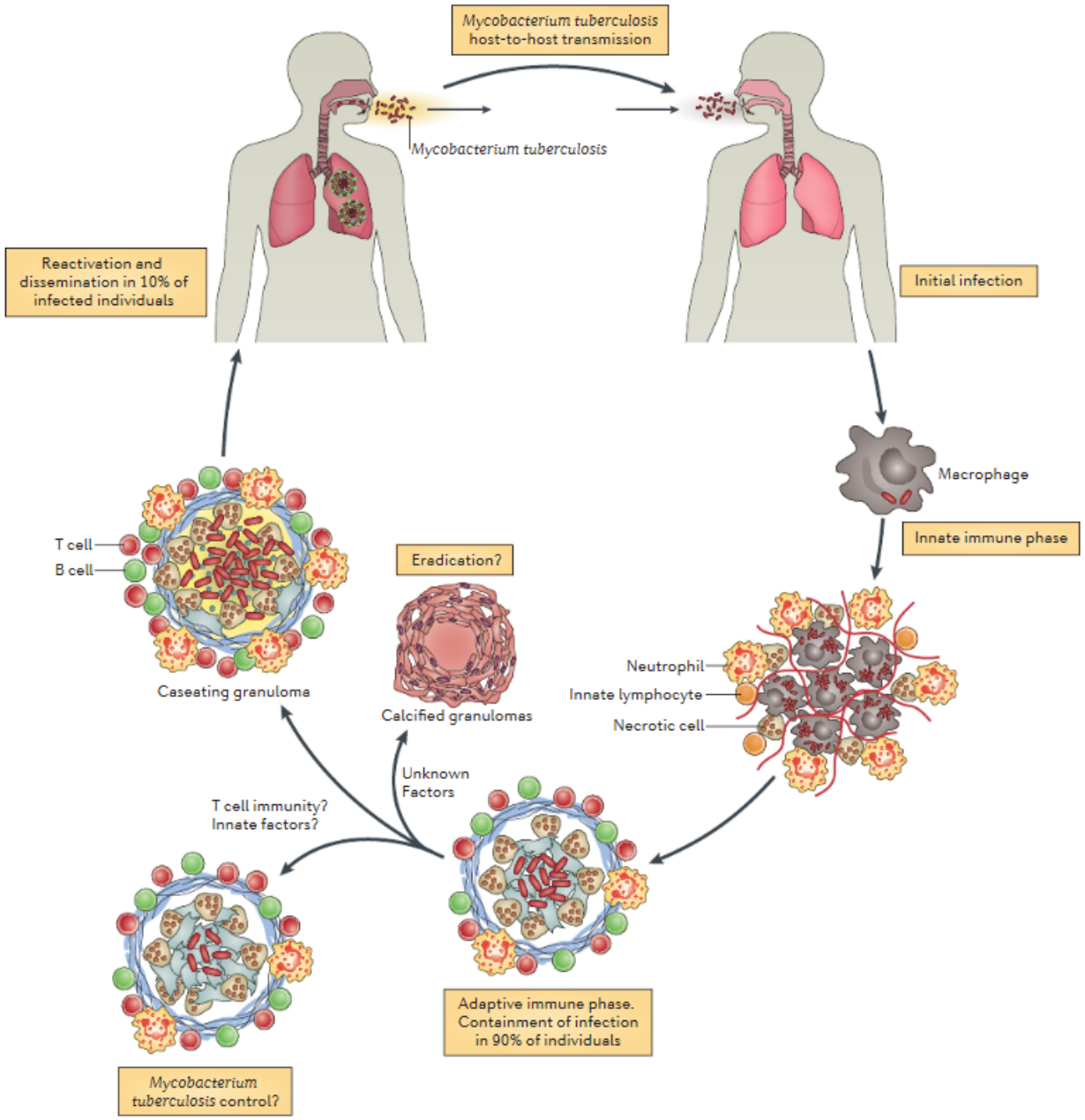
Cell-mediated immunity to *Listeria monocytogenes*



Cellular and Molecular Immunology, 7th ed., 2014 Elservier

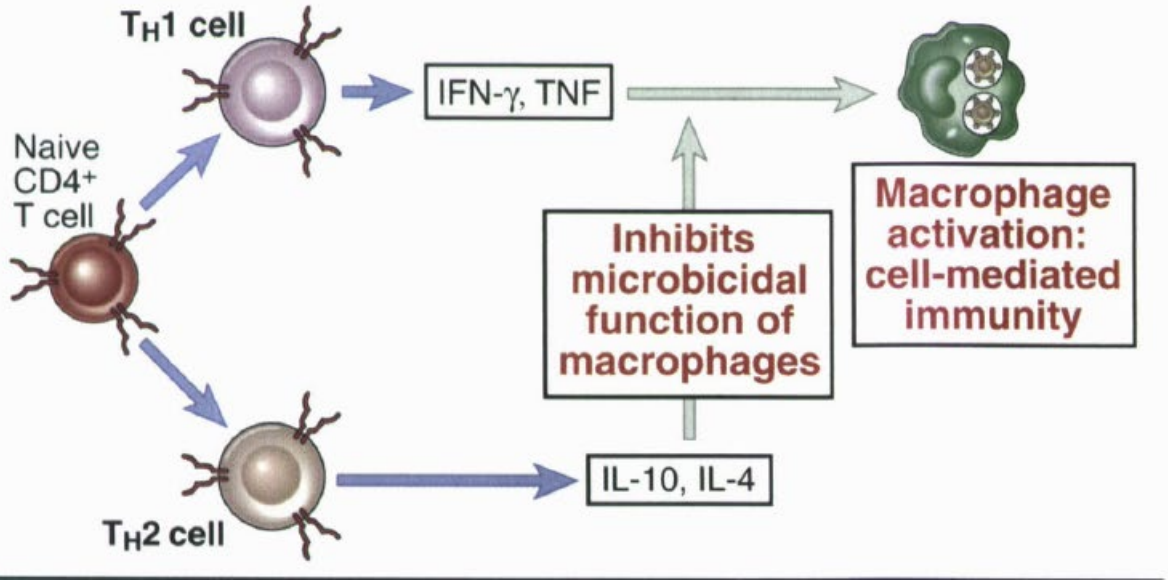
Granulomatous reaction – pathologic response to persistent intracellular bacteria

- Example *Mycobacterium* spp
- With T-cell help (IFN-gamma) macrophages are activated and have enhanced ability to kill intracellular bacteria
- **Cell wall components inhibit fusion of phagocytic vacuoles with lysosomes**
- Some mycobacteria persist
- Granulomatous reaction: central necrosis, multinucleated giant cells, walled off by lymphocytes contains «latent» infection in 90% of patients
- Genetic polymorphism or any kind of immunosuppression can lead to loss of control either shortly or years after infeciton



Nunez et al Nature Reviews 2014

Importance of T_H1 and T_H2 response



Mycobacterium leprae	Some patients: T_H1	⇒ Tuberculoid leprosy
	Some patients: Defective T_H1 or dominant T_H2	⇒ Lepromatous leprosy (high bacterial count)

Leprosy
Mycobacterium leprae

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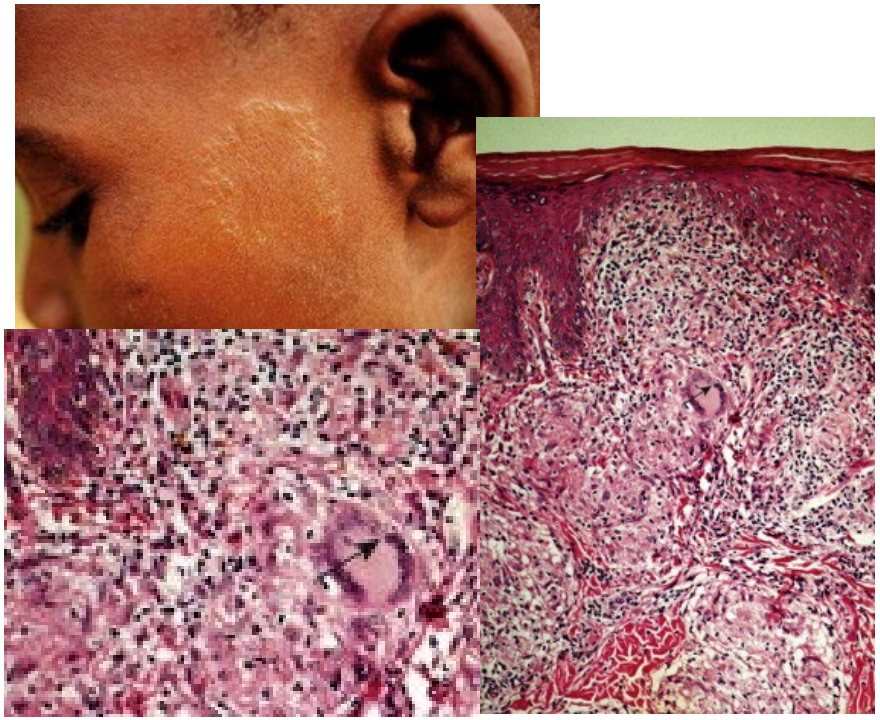
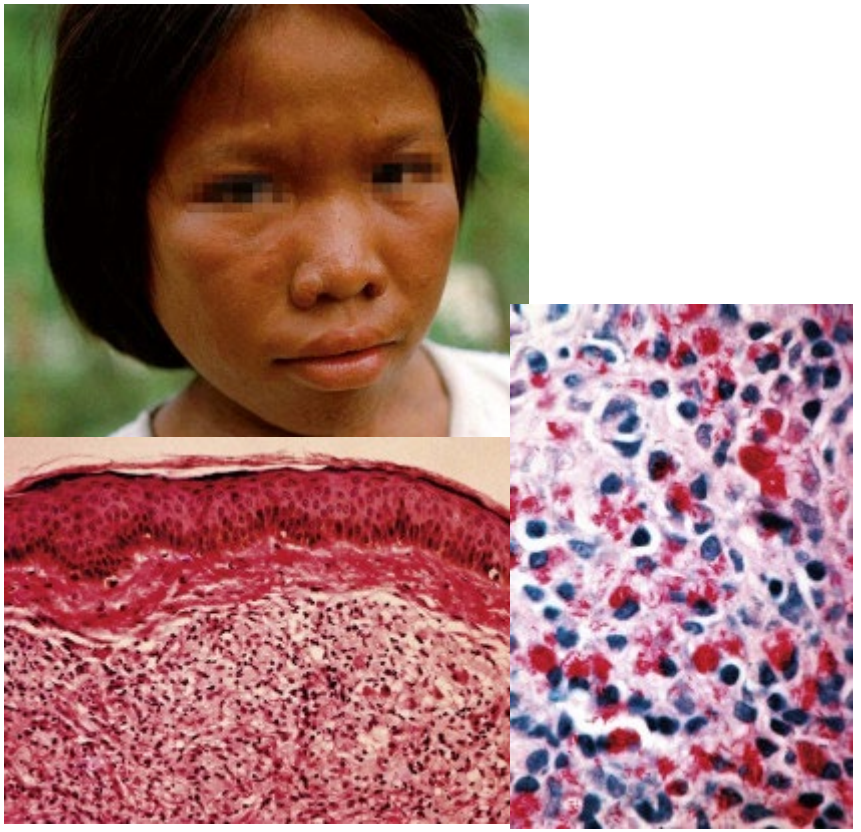
T_H1 Tuberculoid leprosy



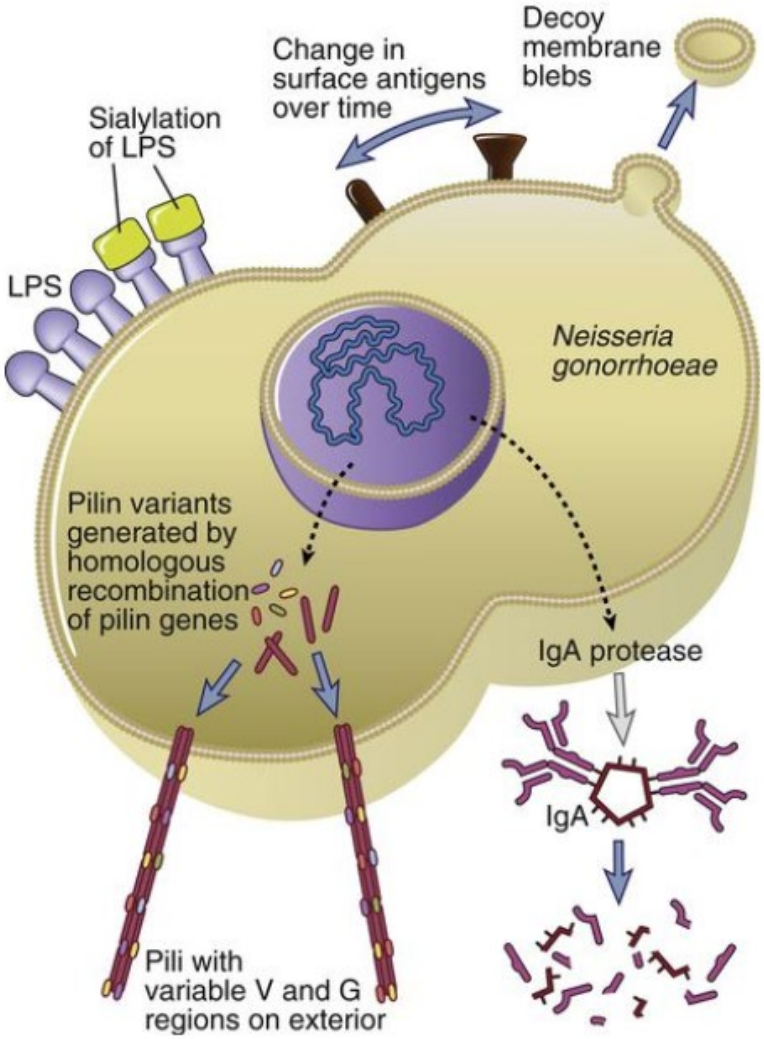
T_H2 Lepromatous leprosy



Immune evasion by bacteria (examples)

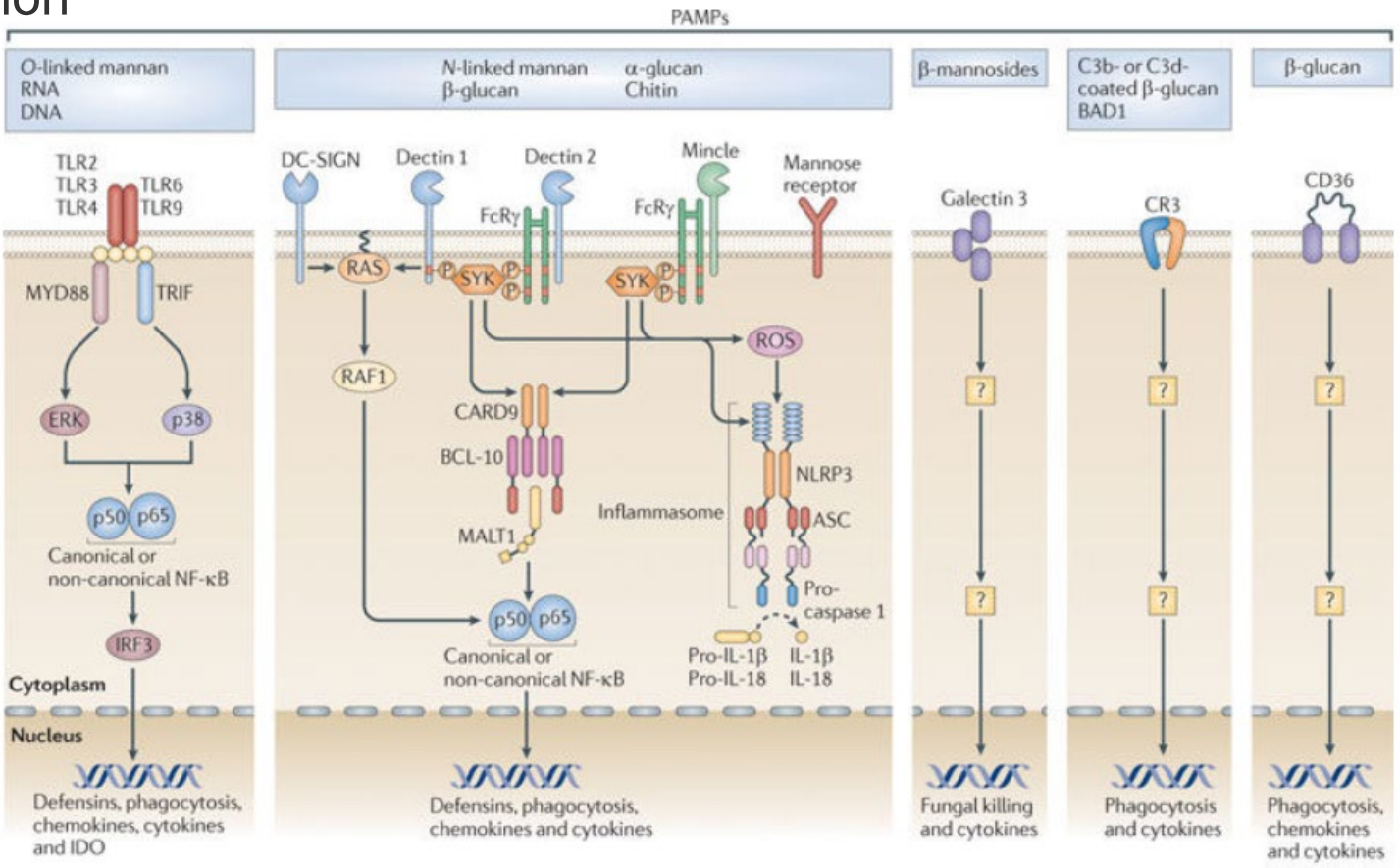
Mechanism of Immune Evasion	Examples
Extracellular Bacteria	
Antigenic variation	*Neisseria gonorrhoeae, Escherichia coli, Salmonella typhimurium*
Inhibition of complement activation	Many bacteria
Resistance to phagocytosis	Pneumococcus, *Neisseria meningitidis*
Scavenging of reactive oxygen species	Catalase-positive staphylococci
Intracellular Bacteria	
Inhibition of phagolysosome formation	*Mycobacterium tuberculosis, Legionella pneumophila*
Inactivation of reactive oxygen and nitrogen species	*Mycobacterium leprae* (phenolic glycolipid)
Disruption of phagosome membrane, escape into cytoplasm	*Listeria monocytogenes* (hemolysin protein)

Immune evasion by bacteria (schematic, example *N. gonorrhoeae*)



Immunity to fungi: innate response

- Innate response mainly by phagocytes (neutrophils and macrophages)
- Liberation of radical oxygen species, lysozyme, intracellular digestion

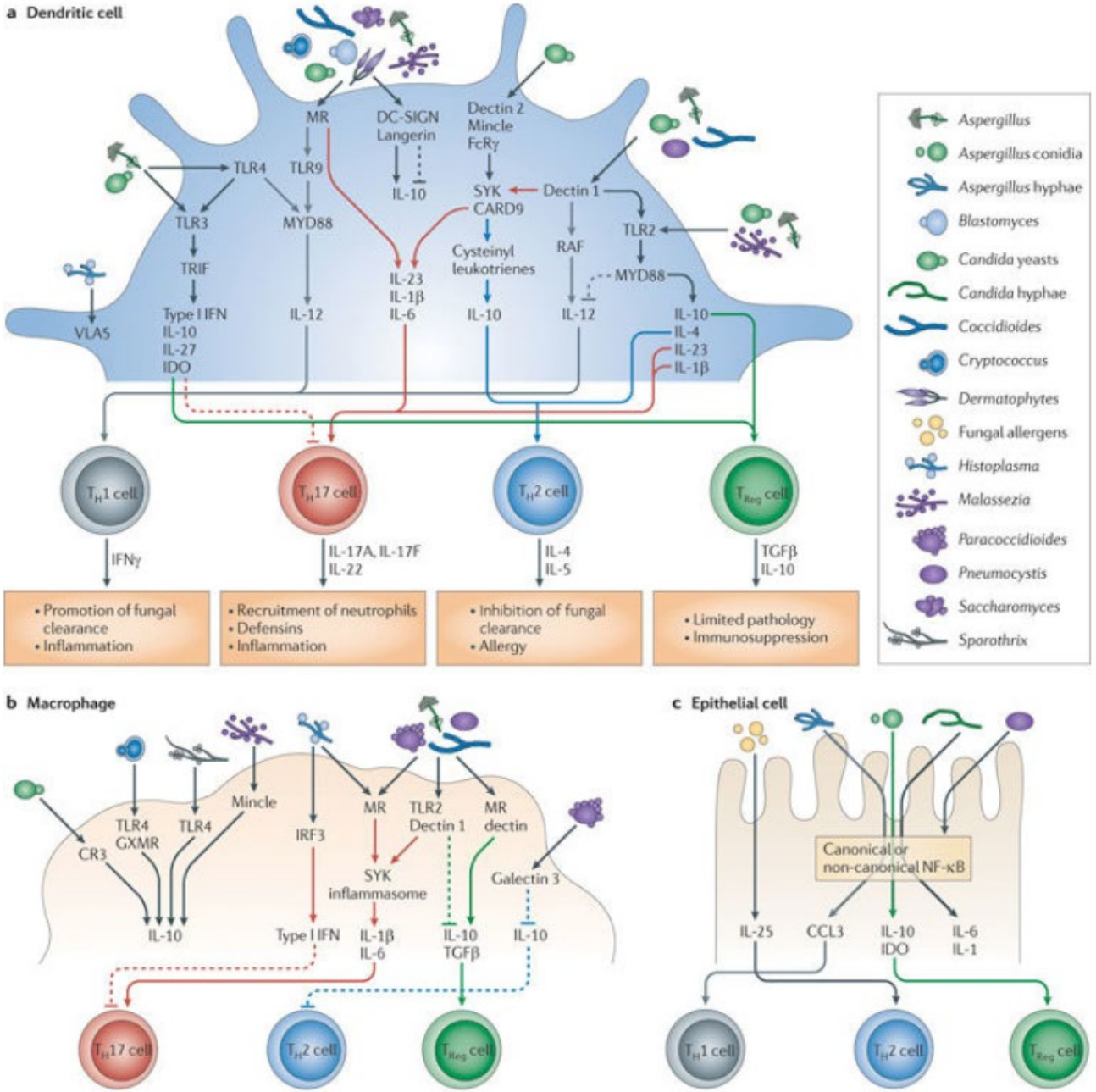


Romani 2011

nature REVIEWS IMMUNOLOGY

Adaptive Immunity to fungi

- Adaptive response to fungi
  - Intracellular: mainly CD4/CD8 cooperation (similar as for bacteria); Th1 responses; tendency to chronic granulomatous inflammation
  - Antibodies may exert some protection
- Immune evasion (inhibition of cytokine production in phagocytes)



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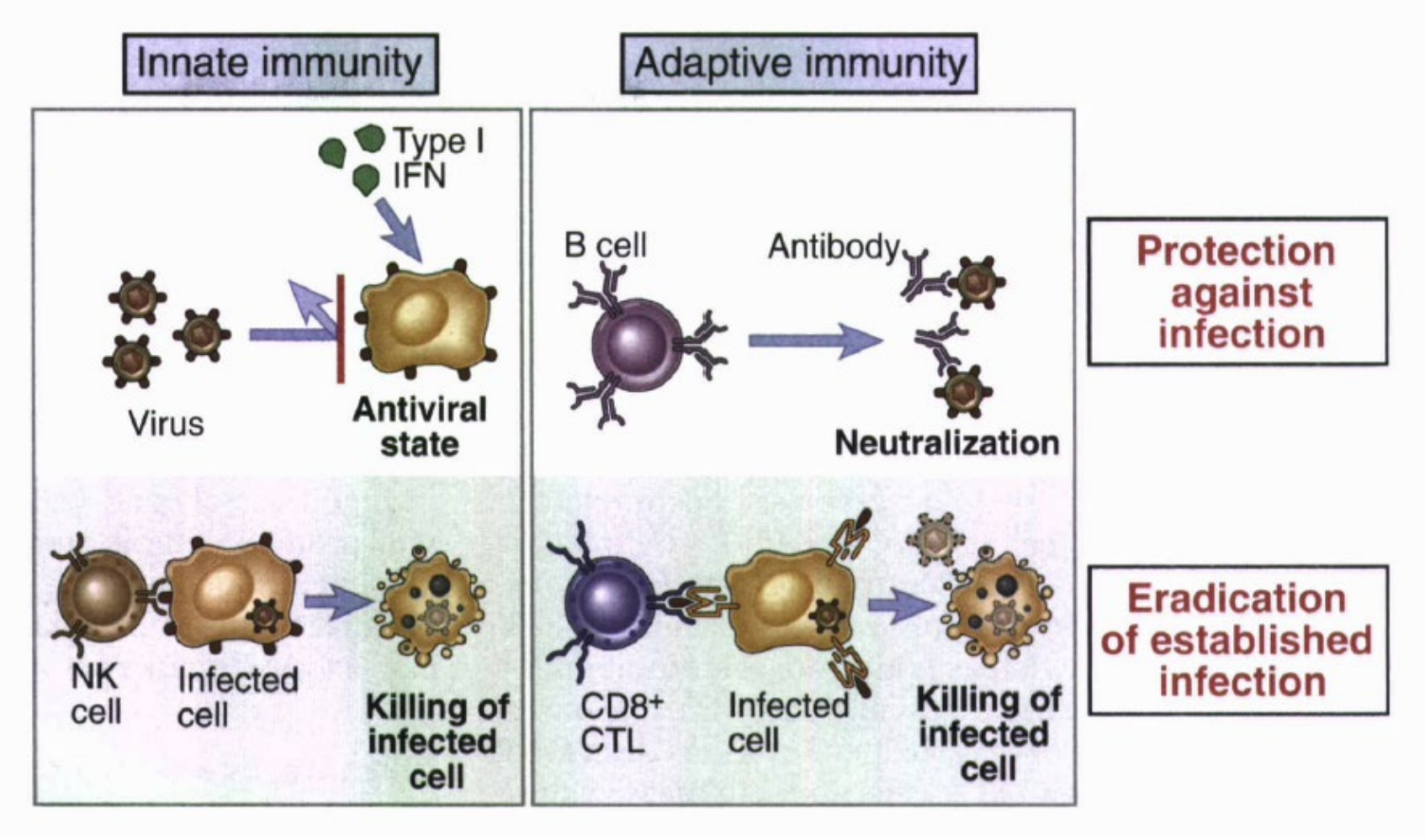
Romani 2011

Innate and adaptive immune responses against viruses



Innate immune responses against viruses

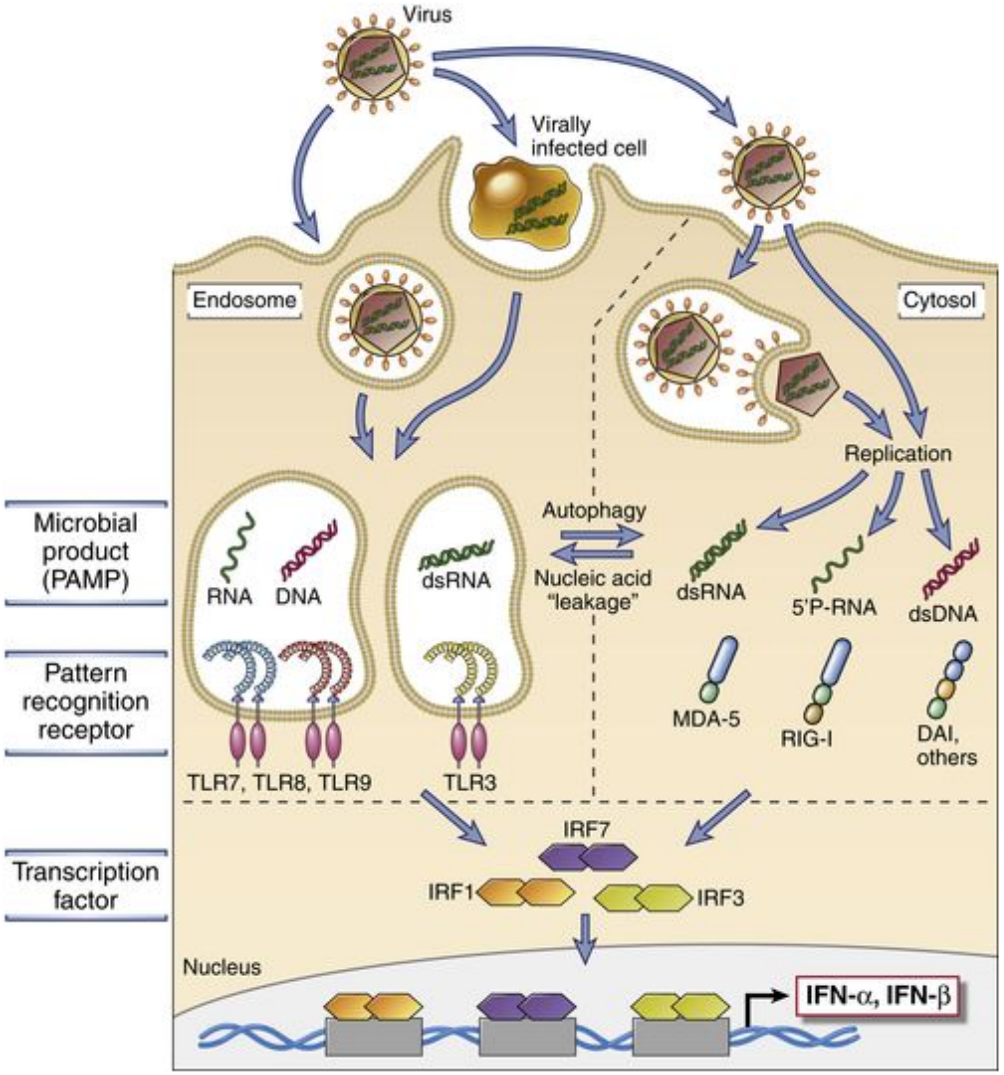


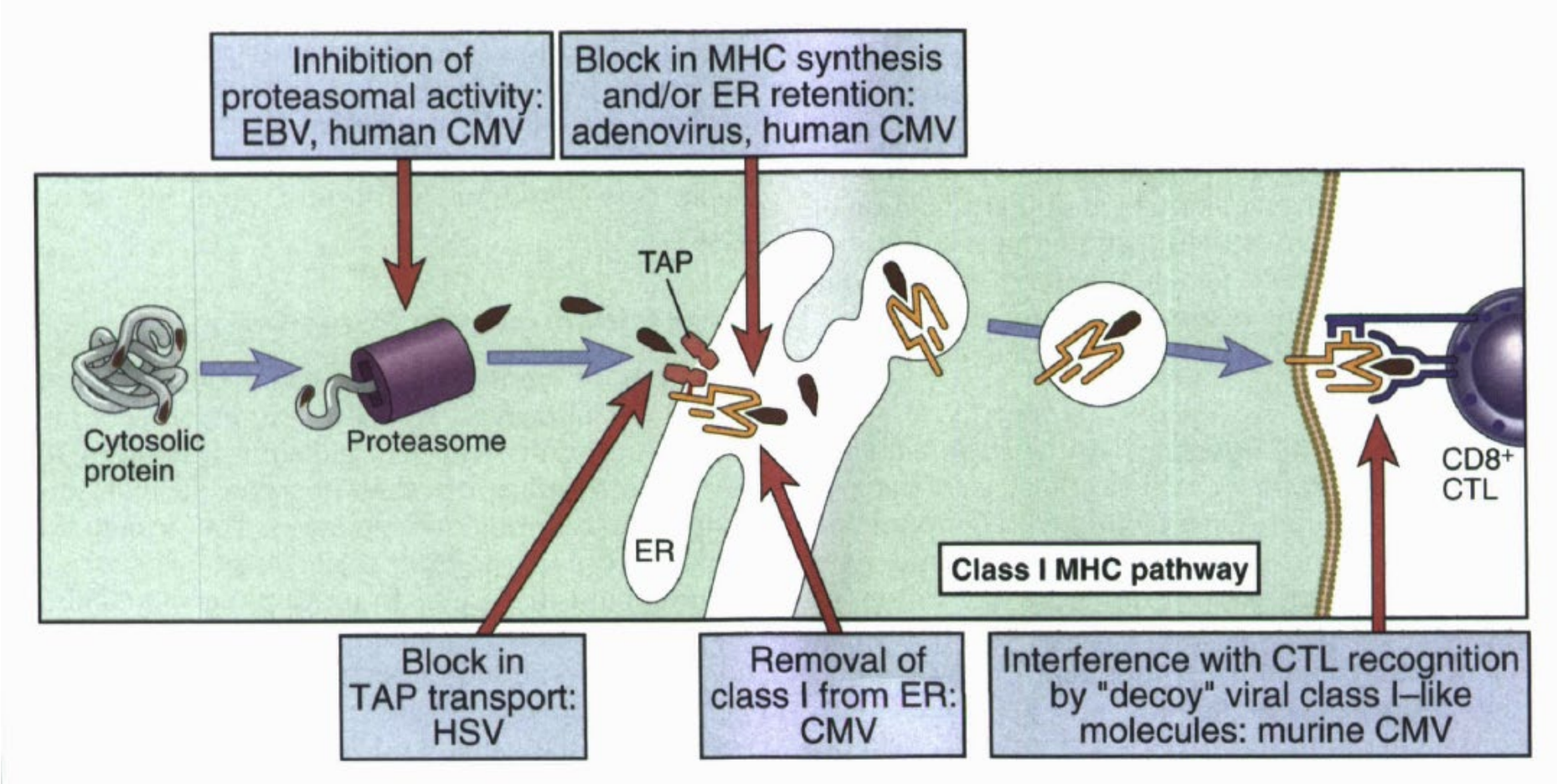
FIGURE 4-16 Mechanisms of induction of type I interferons by viruses. Viral nucleic acids and proteins are recognized by several cellular receptor families (TLRs, the family of cytosolic RIG-like receptors, or RLRs, which include MDA-5, RIG-I, DAI and others, and cytosolic DNA sensors), which activate transcription factors (the IRF proteins) that stimulate the production of type I interferons IFN-α and IFN-β.

Viral immune evasion: overview

Mechanism of immune evasion	Examples
Antigenic variation	Influenza, rhinovirus, HIV
Inhibition of antigen processing	
Blockade of TAP transporter	Herpes simplex
Removal of class I molecules from the ER	Cytomegalovirus
Production of cytokine receptor homologs	Vaccinia, poxviruses (IL-1, IFN-γ) Cytomegalovirus (chemokine)
Production of immunosuppressive cytokine	Epstein-Barr virus (IL-10)
Infection of immunocompetent cells	HIV

Abbreviations: ER, endoplasmic reticulum; HIV, human immunodeficiency virus; TAP, transporter associated with antigen processing.

Evasion from immune response: Inhibition of antigen processing by viruses



Immune response to protozan parasites

Parasite	Diseases	Principal mechanisms of protective immunity
Protozoa		
Plasmodium species	Malaria	Antibodies and $CD8^+$ CTLs
Leishmania donovani	Leishmaniasis (mucocutaneous, disseminated)	$CD4^+$ T_H1 cells activate macrophages to kill phagocytosed parasites
Trypanosoma brucei	African trypanosomiasis	Antibodies
Entamoeba histolytica	Amebiasis	Antibodies, phagocytosis
Metazoa		
Schistosoma species	Schistosomiasis	ADCC mediated by eosinophils, macrophages
Filaria, e.g., *Wuchereria bancrofti*	Filariasis	Cell-mediated immunity; role of antibodies?

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CTLs, cytotoxic T lymphocytes.

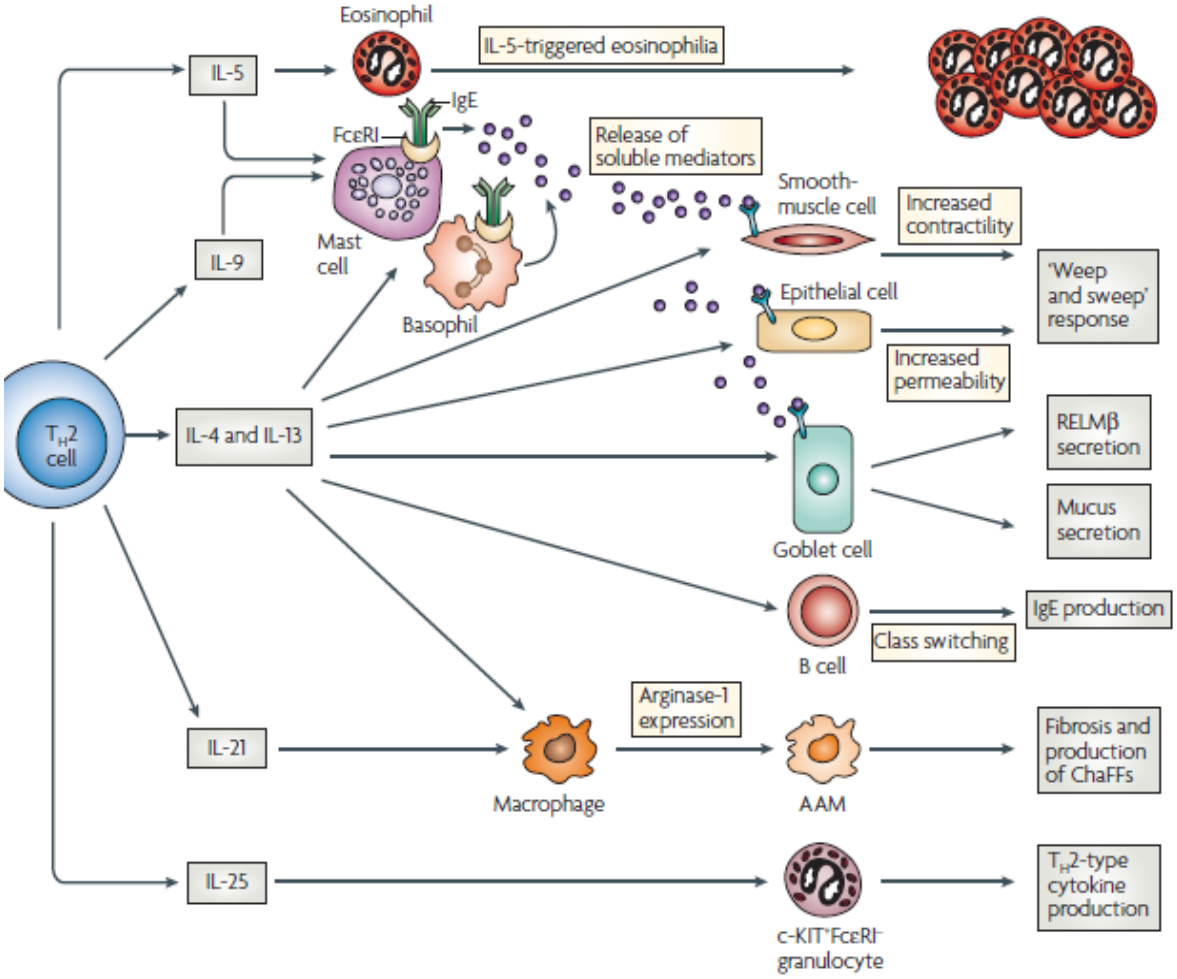
T_H1

T_H2

Helminth infection induces T_H2 response

Helminths to big for «normal» immune response (phagocytosis, CTL)

But basic protein of eosinophils can destroy helminths and mast cell mediarors lead to expulsion of helminths



T_H2 effector functions

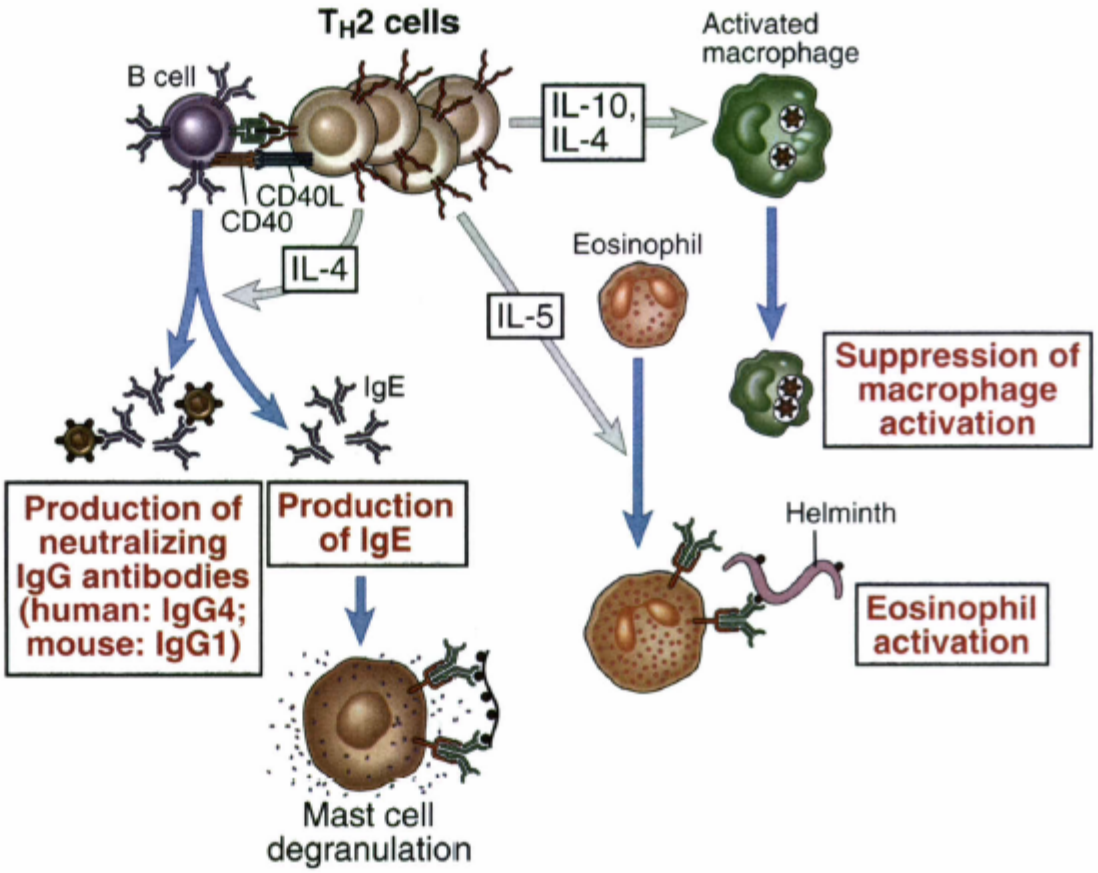


FIGURE 13–13 Effector functions of T_H2 cells. $CD4^{++}$ T cells that differentiate into T_H2 cells secrete IL-4 and IL-5. IL-4 acts on B cells to stimulate production of antibodies that bind to mast cells, such as IgE. IL-4 is also an autocrine growth and differentiation cytokine for T_H2 cells. IL-5 activates eosinophils, a response that is important for defense against helminthic infections. Cytokines from T_H2 cells also inhibit macrophage activation and T_H1-mediated reactions. APC, antigen-presenting cell.

Immune evasion by parasites

Mechanism of Immune Evasion	Examples
Antigenic variation	Trypanosomes, *Plasmodium*
Acquired resistance to complement, CTLs	Schistosomes
Inhibition of host immune responses	Filaria (secondary to lymphatic obstruction), trypanosomes
Antigen shedding	Entamoeba

CTL, cytotoxic T lymphocyte.

Immunological pathogenicity mediated by microbes

- Direct killing of host cells infected
- Killing or functional impairment of host cells by toxins
  - Endotoxins: liberated by lysis of the microbe, component of cell envelope or cytoplasm
  - Exotoxins: secreted
- By stimulating immune responses damaging infected and uninfected (innocent bystander) host cells
- Immunological sequelae: molecular mimicry, immune complexes…

Microbe	Examples of Human Diseases	Mechanisms of Pathogenicity
Extracellular Bacteria		
Staphylococcus aureus	Skin and soft-tissue infections, lung abscess Systemic: toxic shock syndrome, food poisoning	Skin infections: acute inflammation induced by toxins; cell death caused by pore-forming toxins Systemic: enterotoxin ("superantigen")-induced cytokine production by T cells causing skin necrosis, shock, diarrhea
Streptococcus pyogenes (group A)	Pharyngitis Skin infections: impetigo, erysipelas; cellulitis Systemic: scarlet fever	Acute inflammation induced by various toxins (e.g., streptolysin O damages cell membranes)
Streptococcus pyogenes (pneumococcus)	Pneumonia, meningitis	Acute inflammation induced by cell wall constituents; pneumolysin is similar to streptolysin O
Escherichia coli	Urinary tract infections, gastroenteritis, septic shock	Toxins act on intestinal epithelium chloride and water secretion; endotoxin (LPS) stimulates cytokine secretion by macrophages
Vibrio cholerae	Diarrhea (cholera)	Cholera toxin ADP ribosylates G protein subunit, which leads to increased cyclic AMP in intestinal epithelial cells and results in chloride secretion and water loss
Clostridium tetani	Tetanus	Tetanus toxin binds to the motor end plate at neuromuscular junctions and causes irreversible muscle contraction
Neisseria meningitidis (meningococcus)	Meningitis	Acute inflammation and systemic disease caused by potent endotoxin
Corynebacterium diphtheriae	Diphtheria	Diphtheria toxin ADP-ribosylates elongation factor 2 and inhibits protein synthesis

Intracellular Bacteria		
Mycobacteria	Tuberculosis, leprosy	Macrophage activation resulting in granulomatous inflammation and tissue destruction
Listeria monocytogenes	Listeriosis	Listeriolysin damages cell membranes
Legionella pneumophila	Legionnaires' disease	Cytotoxin lyses cells and causes lung injury and inflammation
Fungi		
Candida albicans	Candidiasis	Acute inflammation; binds complement proteins
Aspergillus fumigatus	Aspergillosis	Invasion and thrombosis of blood vessels causing ischemic necrosis and cell injury
Histoplasma capsulatum	Histoplasmosis	Lung infection caused by granulomatous inflammation

Viruses		
Polio	Poliomyelitis	Inhibits host cell protein synthesis (tropism for motor neurons in the anterior horn of the spinal cord)
Influenza	Influenza pneumonia	Inhibits host cell protein synthesis (tropism for ciliated epithelium)
Rabies	Rabies encephalitis	Inhibits host cell protein synthesis (tropism for peripheral nerves)
Herpes simplex	Various herpes infections (skin, systemic)	Inhibits host cell protein synthesis; functional impairment of immune cells
Hepatitis B	Viral hepatitis	Host CTL response to infected hepatocytes
Epstein-Barr virus	Infectious mononucleosis; B cell proliferation, lymphomas	Acute infection: cell lysis (tropism for B lymphocytes) Latent infection: stimulates B cell proliferation
Human immunodeficiency virus (HIV)	Acquired immunodeficiency syndrome (AIDS)	Multiple: killing of $CD4^+$ T cells, functional impairment of immune cells (see Chapter 20)

Aims – Principles of Vaccination

Introduction

The federal vaccine program

Types of vaccines currently in use, including their advantages and disadvantages

The impact of the route of administration of a vaccine

Important effectors of vaccine response

Importance of adjuvant / examples

Introduction to the term „herd immunity“

„New“ vaccines

Introduction to vaccines

- Continuous race between host and pathogen
- For exclusive human pathogens: important co-evolution
- Different pathogens – different strategies
- Co-existence may be desired or not
- Vaccine efforts exert evolutionary pressure

Introduction to vaccines

- 1796: First vaccination by Jenner

Basic principle of vaccination

- Active: expose individual with attenuated, killed or split organisms that leads to the development of an immune response without the risk of (severe) disease

vs.

- Passive: adoptive transfer of specific effector mechanisms from other, previously actively immunized individuals

Federal vaccine program

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Tabelle 1
Empfohlene Basisimpfungen 2016
Stand 2016
Empfehlungen der Eidgenössischen Kommission für Impffragen und des Bundesamtes für Gesundheit

Alter [1]	Diphtherie (D / d) [3] Tetanus (T) [4] Pertussis (P_a / p_a) [3]	*Haemophilus influenzae* Typ b (Hib)	Poliomyelitis (IPV)	Masern (M) Mumps (M) Röteln (R)	Hepatitis B (HBV) [17]	Varizellen (VZV)	Humane Papillo-maviren (HPV)	Influenza
Geburt					18)			
2 Monate [2]	DTP_a	Hib	IPV		(HBV) [19]			
4 Monate [2]	DTP_a	Hib	IPV		(HBV) [19]			
6 Monate	DTP_a	Hib	IPV		(HBV) [19]			
12 Monate		10)		MMR [14]				
15–24 Monate	DTP_a	Hib [10] [11]	IPV	MMR [14]	(HBV) [19]			
4–7 Jahre	DTP_a [5] [6]		IPV	15)				
11–14 / 15 Jahre	dTp_a [3] [5] [7] [8]		12)	15)	HBV [19]	VZV [21]	HPV [23]	
25–29 Jahre	dTp_a [9]		13)	16)	20)	22)		
45 Jahre	dT [9]		13)	16)	20)	22)		
≥ 65 Jahre	dT [9]		13)		20)			24)

www.ekif.ch, www.infovac.ch

Swiss routine vaccine program 2016

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Tabelle 5
Empfohlene ergänzende Impfungen
Stand 2016

Alter [1]	Pneumokokken	Meningokokken der Gruppe C	Humane Papillomaviren
2 Monate	PCV 13 [2] [3]		
4 Monate	PCV 13		
6 Monate	[4]		
12 Monate	PCV 13 [5]		
12–15 Monate		MCV-C [6]	
11–14/15 Jahre		MCV-C [7]	HPV bei Jungen [8]
Junge Frauen (20–26 Jahre) Jungen und junge Männer (15–26 Jahre)			HPV [8]

Additional vaccines for special indications:

- Travel: Yellow fever, Japanese encephalitis, etc..

- Special exposures: FSME, Rabies, etc ..

- Patients at risk: Influenza

„THE GOOD OLD DAYS….“ some examples

	Morbidity/Mortality per year in CH	
Disease	**without vaccine**	**with vaccine**
Diphtheria	**4‘000 cases**	**Last case 1983**
Poliomyelitis	**800 cases**	**Last case 1982**
Invasive *H. influenzae* type b	**180 cases**	**17** (<17 yrs old)
Tetanus	**50 cases**	**16** (none <20 yrs old)
Congenital Rubella	**30-50 cases**	**1?** (not complete)
Pertussis	**140 deaths**	**?**

Zimmermann HP et al. Rev Med Suisse Romande 1998; www.bag.admin.ch

GOALS OF A VACCINE

Protect individual: infection
(disease)
(clear disease)

By mimicking infection in terms of long lasting immune response without doing harm

"Optional": Give indirect protection (herd immunity)
Support global eradication of pathogen

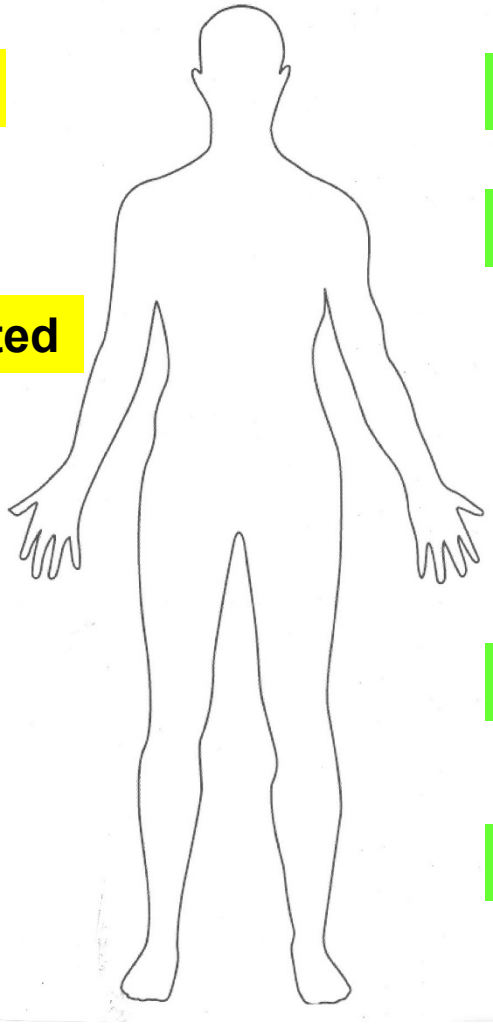
Types of vaccines

Passive: antibodies

Active: live, attenuated

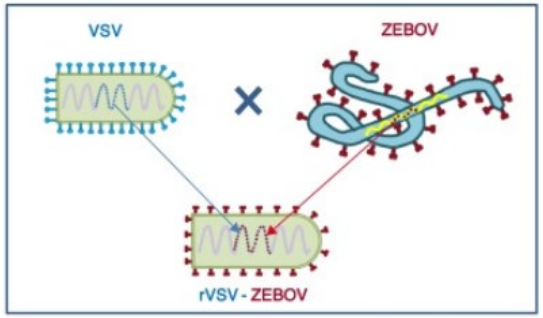
Active: inactivated

Active: component



Newer technologies

- Recombinant (e.g. VSV-ZEBOV)



- Vector based (e.g. lactobacilli)

DNA vaccines

Types of vaccines

Vaccine	Advantage	Disadvantage
Passive (antibodies)	Rapid protection Minimal side effects	Short duration No memory
Active		
Whole cell/virus	Variety of antigens	Side effects
Live, attenuated	Replicates: antigen↑	May cause disease
Inactivated	Does not replicate	pot. less immunogenic
Component	Target antigen known Less side effects	Restricted immune response to target antigen

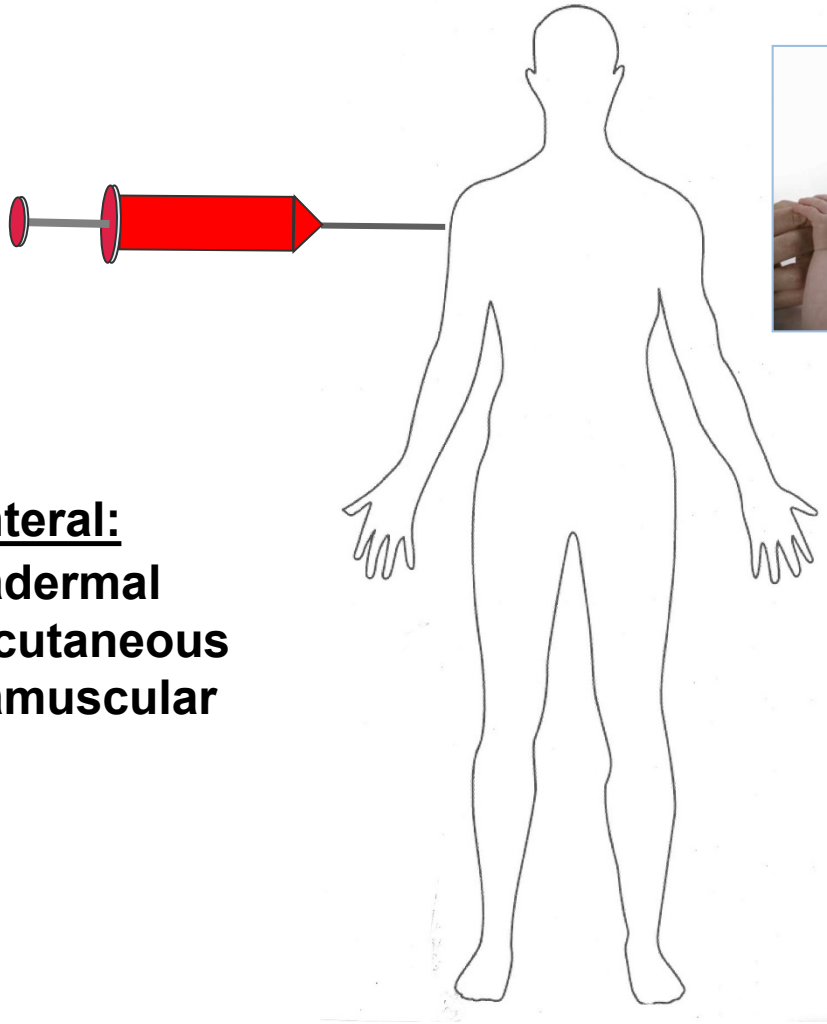
Passive immunisation

Table 1 Protection achieved in humans by passive administration of vaccine-induced antibodies

	Infection or disease	Evidence of effects of passive antibodies
Bacterial toxins	Tetanus	Passive antibodies and maternal immunization are highly effective; can also provide post-exposure prophylaxis in nonimmune individuals
	Diphtheria	Passive antibodies prevent intoxication; effects on infection are unknown
	Pertussis	Maternal antibodies are effective if present in high titer; passive antibodies have been used as therapy, resulting in decreased pathology
Encapsulated bacteria	*H. influenzae*	In high-risk infants, BPIG given at 2, 6 and 10 months of age provides significant protection from invasive infection during infancy
Viruses	Measles	Passive immunoglobulin can prevent disease and transmission to susceptible contacts
	Rabies	Human rabies immunoglobulin is used in conjunction with vaccine to neutralize virus at site of entry and prevent its spread to CNS
	Smallpox	Passive immunoglobulin prevents spread of smallpox to contacts; treatment of vaccine complications
	Hepatitis A	Vaccine shows 85–90% efficacy in high-risk individuals; also used as post-exposure prophylaxis
	Hepatitis B	HBIG shows 80–90% efficacy in high-risk liver transplant to prevent recurrence of infection
	RSV	Humanized monoclonal antibody (palivizumab) shows 55% efficacy in preventing hospitalization in high-risk infants
	Varicella zoster	VZIG is efficacious even soon after exposure

BPIG, bacterial polysaccharide immunoglobulin; CNS, central nervous system; HBIG, hepatitis B immunoglobulin; RSV, respiratory syncytial virus; VZIG, varicella zoster immunoglobulin.

Route of administration



Parenteral:
- Intradermal
- Subcutaneous
- Intramuscular

Mucosal:
- Ingestion
- Aerosol

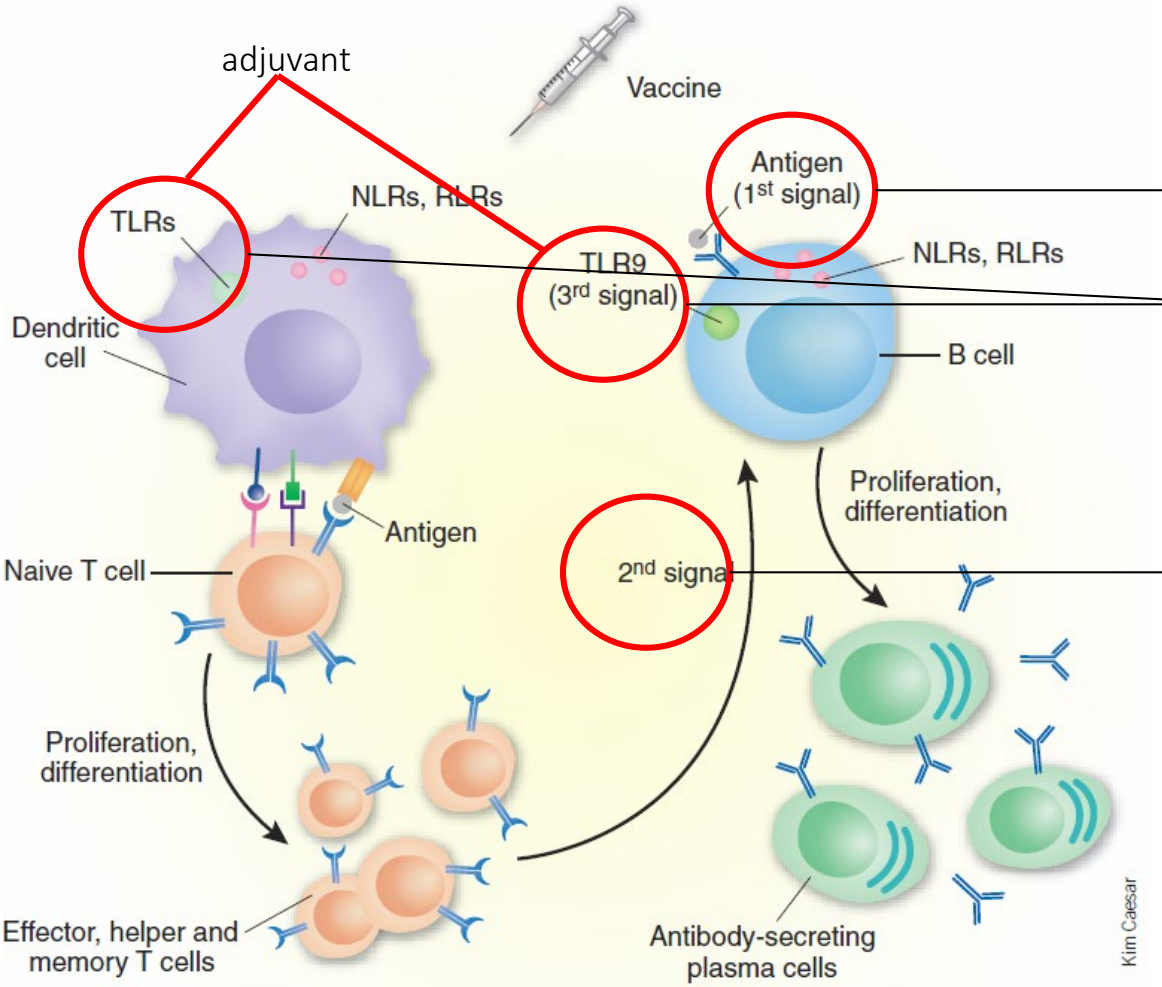
Poliomyelitis vaccines: oral-live vs. parenteral inactivated

Whole virus Inactivated Parenteral

++	Serum antibody titres	+
	Duration of protection	↑
(+)	Pharyngeal viral excretion	+
(+)	Prevent intestinal infection	+
-	Spread of vaccine virus	+
-	Vaccine disease	+
-	Interference with other enteroviral infection in the intestine	+

Whole virus Live Oral

Immunologic interactions in successful Vaccines NATURE BIOTECHNOLOGY 2007; 25 :303



Adaptive B cell

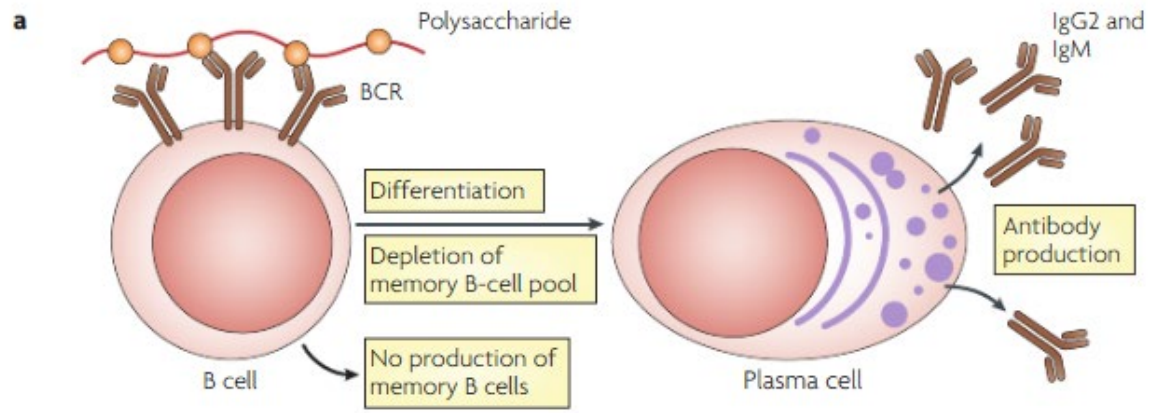
Innate

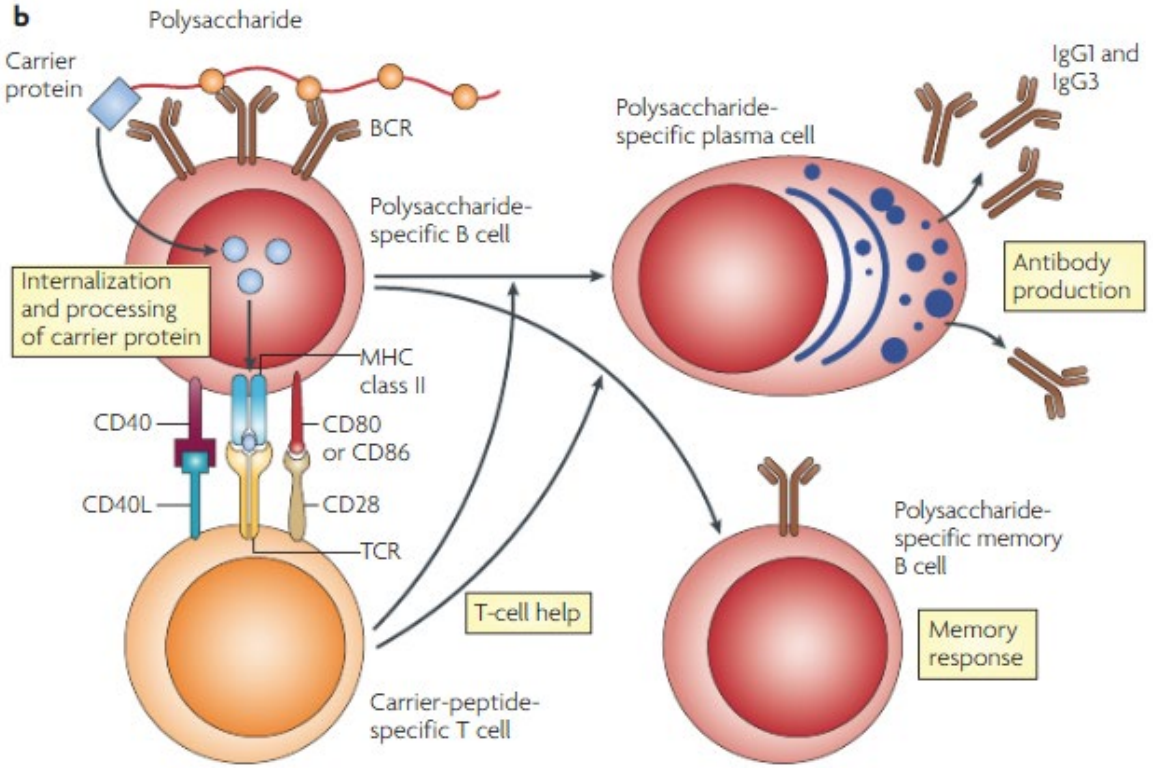
Adaptive T Help

Pollard et al 2009

Vaccines against bacterial polysaccharides

e.g. *Streptococcus, pneumoniae, Haemophilus influenzae, Neisseria meningitidis*





UN-conjugated

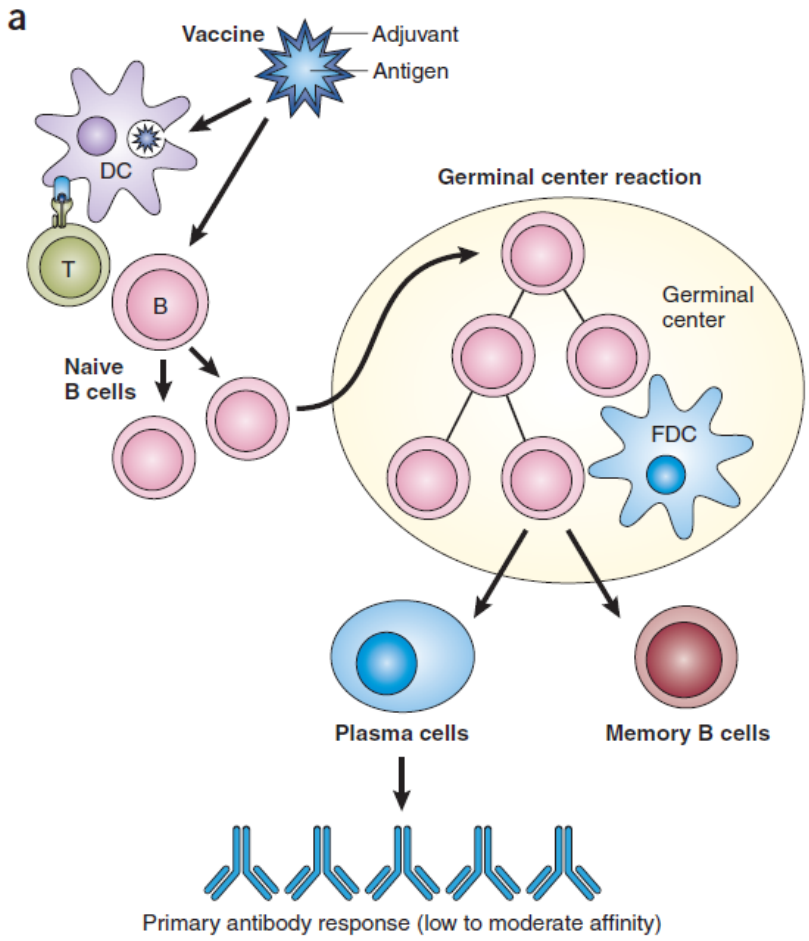
Vs

conjugated

Pollard et al 2009

NATURE REVIEWS | IMMUNOLOGY

Primary immune response to vaccines

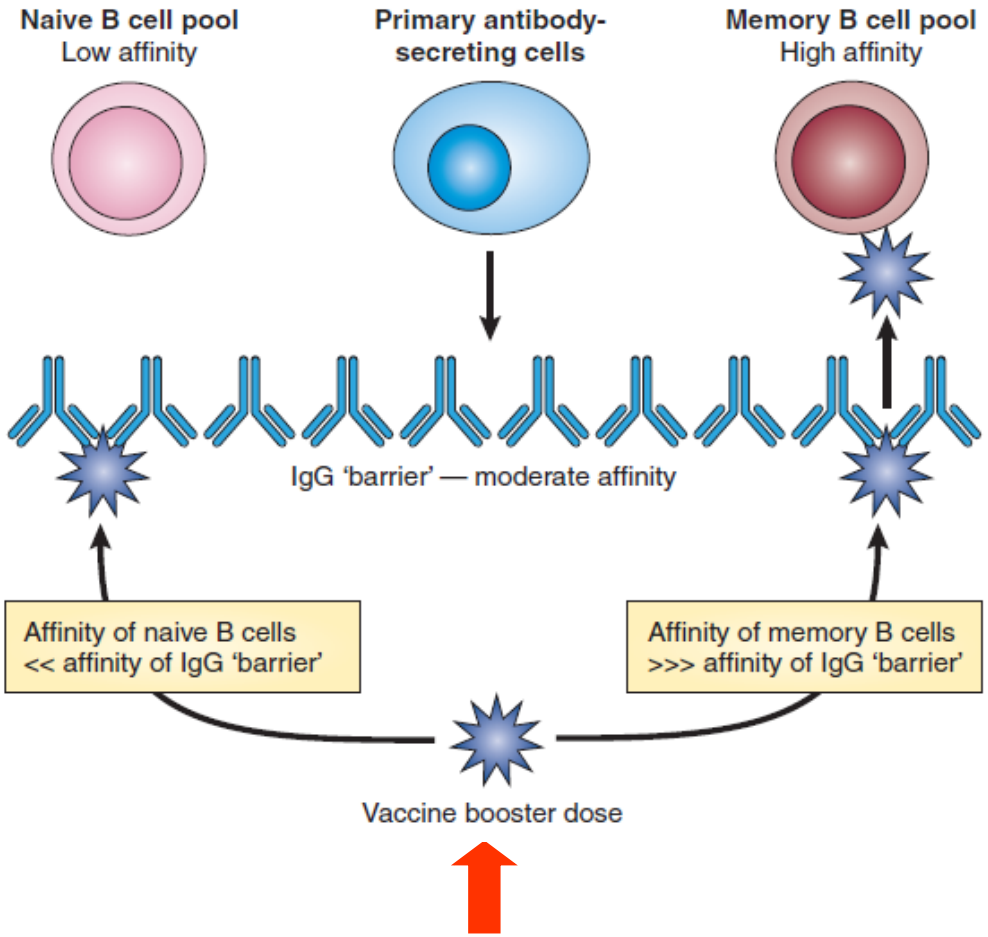


What have we learned (in retrospect)

- Early protection: antibody-dependent
- Quality (e.g. avidity) → efficacy
- Mucosal vaccines: IgA response
- Duration: B-cell memory
  persis. Ab prod. (early response)
- T-cell response: important
  less well described
- Complicating: antigenic variation
  strain diversity
  influence of age

Lambert PH, Siegrist CA. Nature Medicine. 2005;11:S54.

Boosting, affinity maturation



→ **favors short term response**

Rapid vaccine schedules
(several, closely spaced doses)

→ **support immune memory**

Lower antigen dose

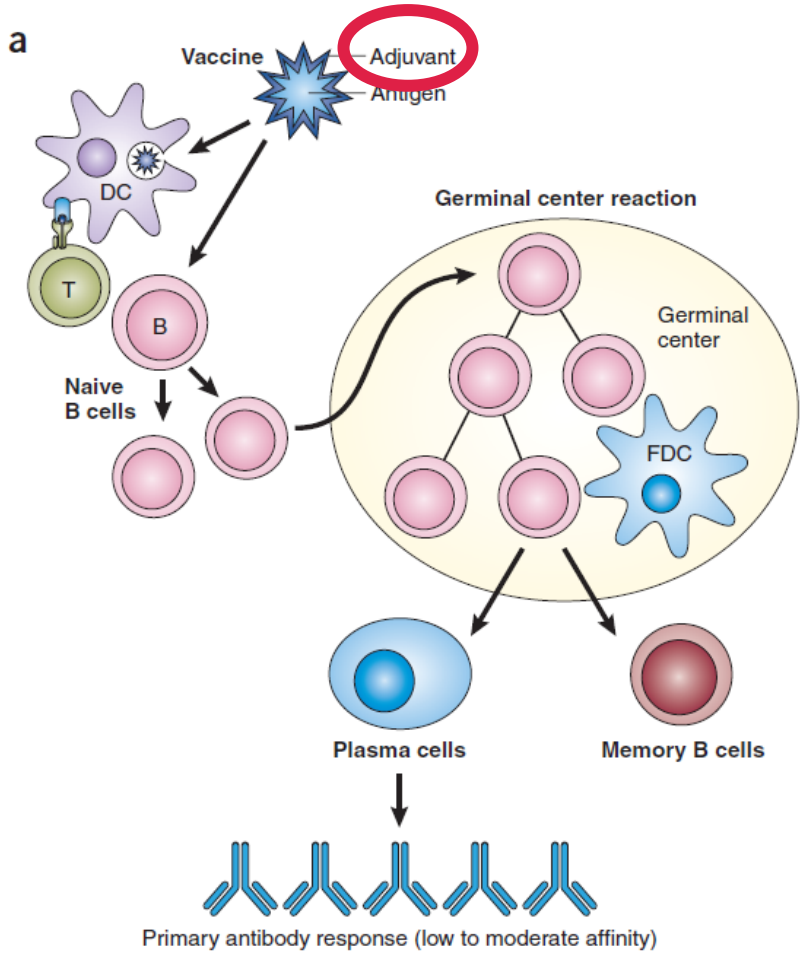
Antigen persistence? (animal models)

"Nature of antigen"

Booster dose

Lambert PH, Siegrist CA. Nature Medicine. 2005;11:S54.

Adjuvant



Lambert PH, Siegrist CA. Nature Medicine. 2005;11:S54.

Goal: **enhance Ab affinity maturation process**

mostly by enhancing innate response

specially important for inactivated and component vaccines

Adjuvant:
Aluminium salt

Experimental
- CpG oligos
- (mod.) *E. coli* heat labile toxin

Importance of early response: depends on infectious agent etc.

Example:
Tetanus-Toxin (TeNT)

Neutralization before up-take into neuron !!

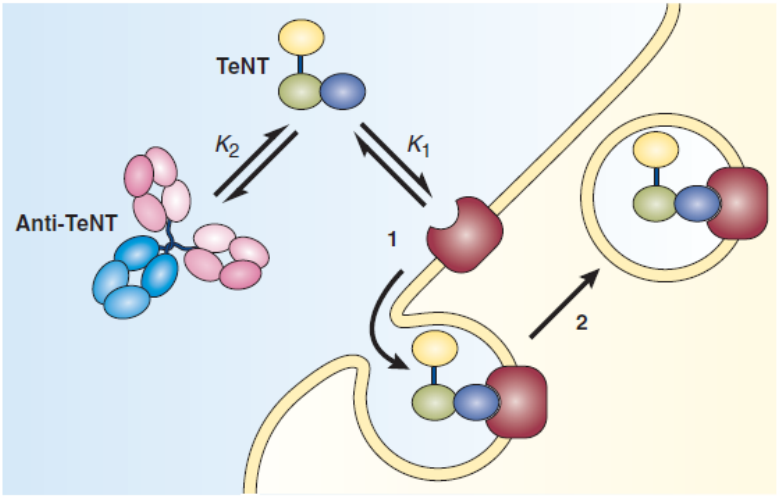


Figure 2 Vaccine-induced anti-tetanus toxin (TeNT) antibodies compete with TeNT receptors at cell surface. Their relative affinities for TeNT (K_1, K_2) determine the outcome. Once TeNT is internalized, it can no longer be captured by antibodies and the intoxication sequence cannot be stopped.

Lambert PH, Siegrist CA. Nature Medicine. 2005;11:S54.

Example:
Hepatitis B virus

Memory → long lived protection
= anti-HBs Ag titer ever >100 U/L

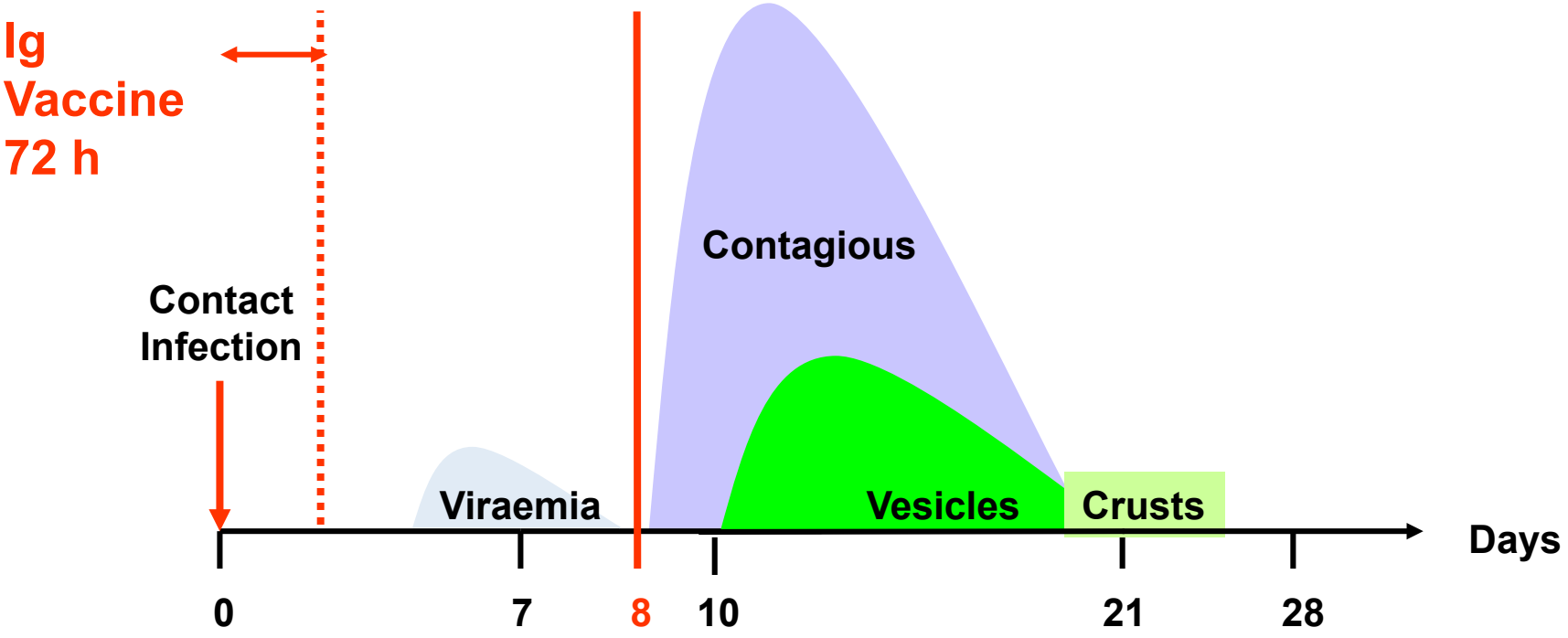
Incubation period 4-12 wks
Time to recruit memory cells

Role of T-cell response??

Passive/active immunisation after exposure?

Need to know natural history of infection
Often narrow time window (48-72-96h after first exposure)

Example: Varizella-Zoster virus:



Can vaccine protection be measured in the individuum?

Importance: Surrogate for clinical efficacy studies
Document individual protection for high risk situations

<u>Measurement of antibody titres in serum</u>:

- **Threshold defined for relatively few vaccines, examples:**
  - **Hepatitis B**
  - **Tetanus toxin**
  - **FSME**
  - **Rabies**
  - **etc.**

- **Cannot extrapolate to wild-type infection (e.g. measles)**
- **Quantity ≠ quality (e.g. avidity of antibodies, route of administration)**

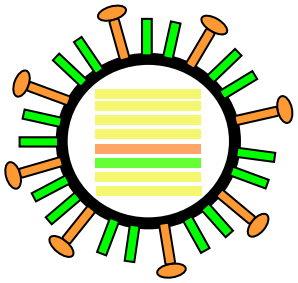
Surrogate: Vaccine record!! (= empiric), e.g. 2 doses MMR vaccine

Antigen variation / strain diversity

Example: influenza virus / vaccine

Hemagglutinin (H, n=15)

Neuraminidase (N, n=9)



RNA, segmented
→AG drift / shift

Seasonal vaccines
- Four strains
- Yearly up-date (WHO)

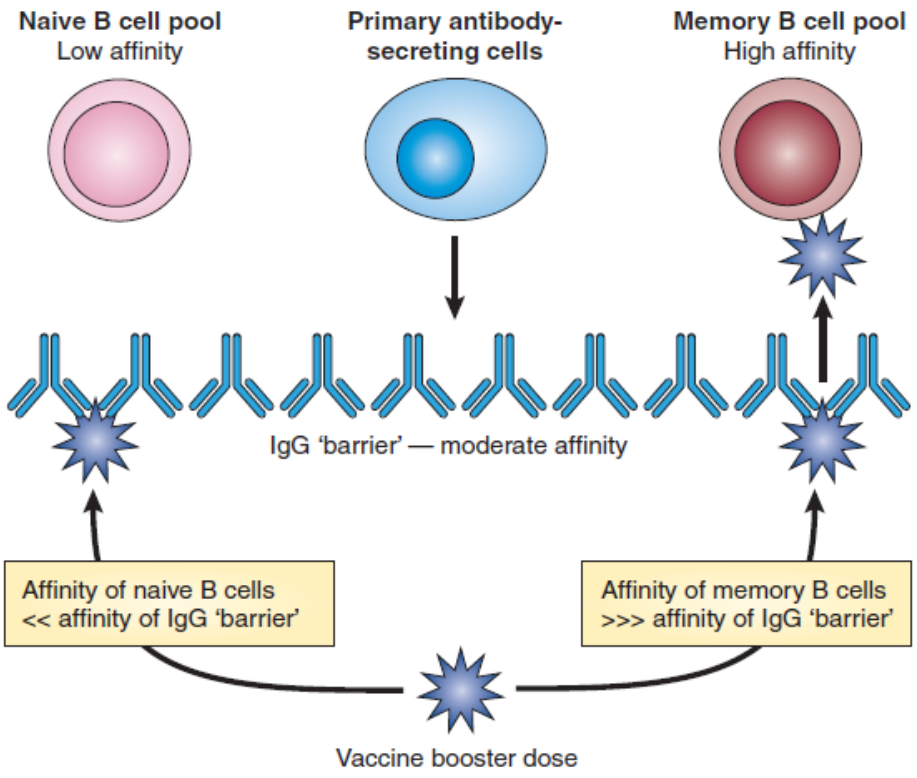
"Pandemic vaccine"

H5N1 vaccine: conserved epitope
crossreactive?

Reverse genetics for new strains??

Get away from egg embryos?

Antigenic sin



Vaccine efficacy might be modulated by prior vaccination

"Original antigenic sin"

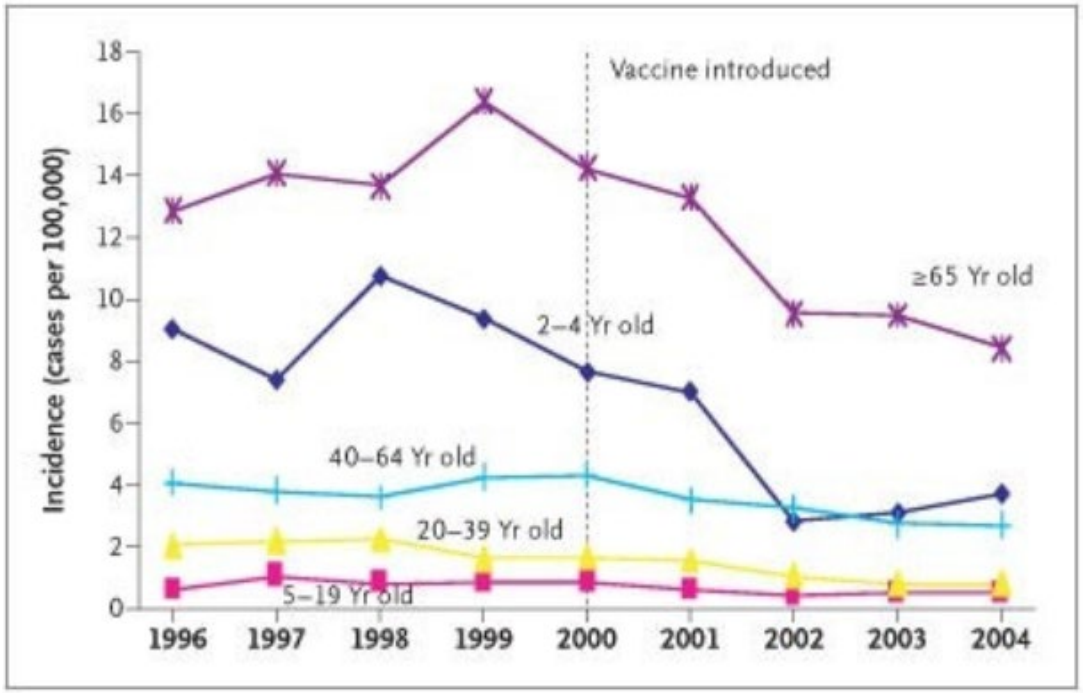
Cross-reactive epitopes preferentially reactivate high-affinity memory B-cells rather than lower affinity naive B-cells.

Individuals exposed 50 yrs earlier to H1N1 Influenza virus strain respond differently to a new H1N1 vaccine strain than adults that had never been exposed to H1N1

Lambert PH, Siegrist CA. Nature Medicine. 2005;11:S54.

Herd immunity

= indirect protection of susceptibles by reduced circulation of pathogen

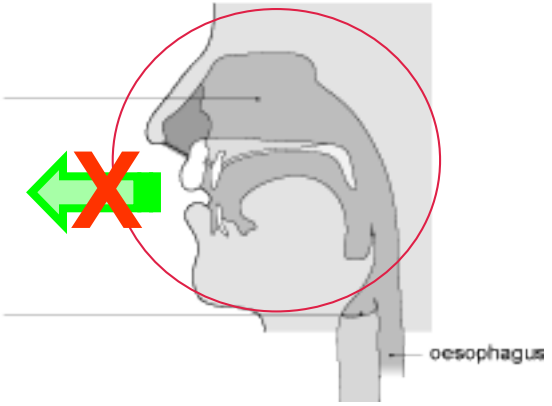


Vaccine was given to <2 yrs old!!

Conjugated pneumococcal polysaccharide vaccines

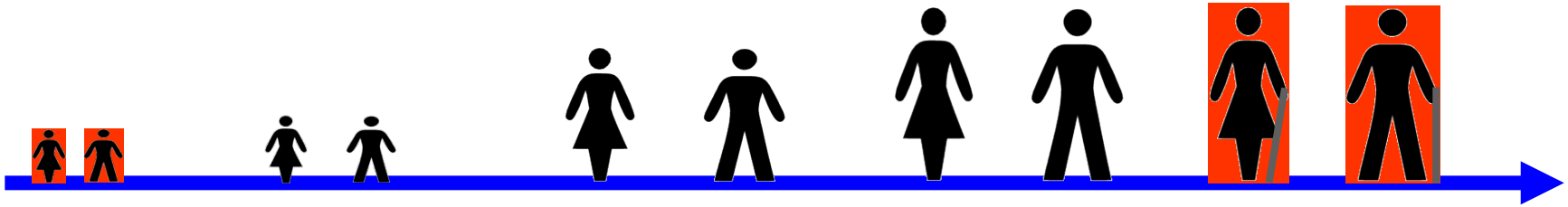
⟶ Reduce colonisation

⟶ Reduce transmission



Kyaw MH et al. NEJM 2006;354:1455.

Vaccination at the extremes of age



Newborns to 1 year of life

Immature immune system

Poor response to T-cell indep. ag

- IgM to IgG2 switch ↓

- Complement-mediated reaction ↓

- Splenic marginal zone organ ↓

Response to T-cell dep. ag ↓

- IFN-γ by CD4⁺T_H1 cells ↓

Inhibiting maternal antibodies

Affects B-cell response - mechanisms?

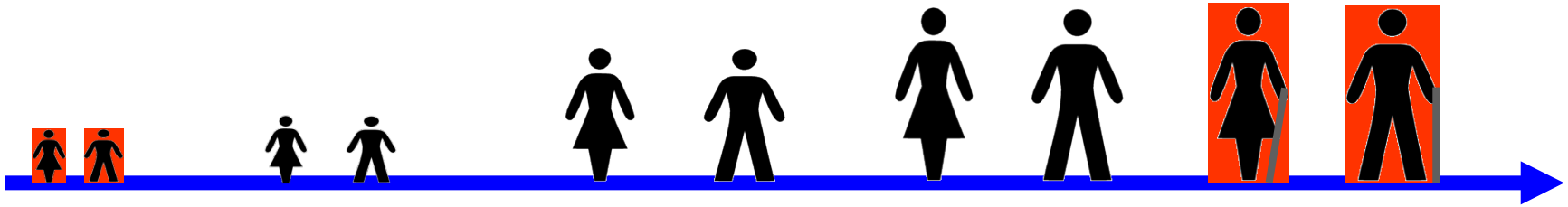
- Inhibition of live virus vaccines

- FcR mediated inhibition of B-cell activation

- Specific epitope neutralization/ competition with antigen specific B-cell receptors→ ratio maternal ab : vaccine antigen (impact of adolescent immunization?)

Siegrist CA. Vaccine 2003;21:3406

Vaccination at the extremes of age



<u>Elderly: impaired immune response – very late in life</u>
Not well investigated

Not all vaccines are equally affected by immune senescence:
- Pneumococcal poylsaccharid vaccine: +++
- Tetanus-Toxoid booster: (+)

Immunology:
- Rapid waning of antibody response
- Relativ restriction of T-cell repertoire

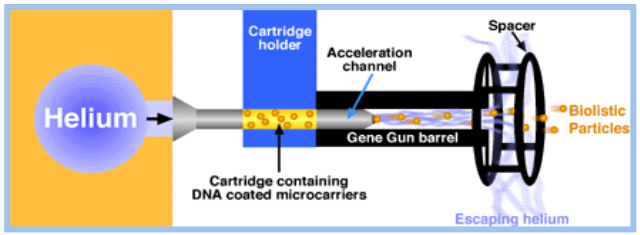
Evidence for the importance of T-cell response for vaccine immunity

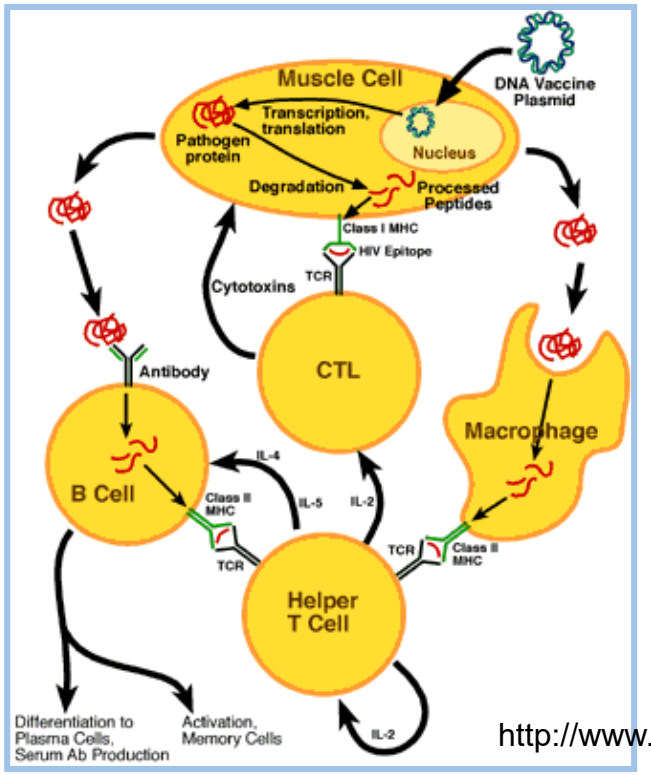
Table 2 Evidence for roles of vaccine-induced T-cell effectors against disease

Vaccine	Evidence
	Major role
BCG	Negligible antibody response; protection is lost if CD4 T-cell deficiency; *in vitro* *M. tuberculosis* 'clearing' from infected cells
	Some contribution
Pertussis	Persistence of protective efficacy after antibody decline
Measles	Reduced disease severity in absence of detectable antibody response
Influenza	Some protection against cross-reactive A strains in absence of protective levels of antibody

Lambert PH, Siegrist CA. Nature Medicine. 2005;11:S54.

DNA vaccines





http://www.brookscole.com/

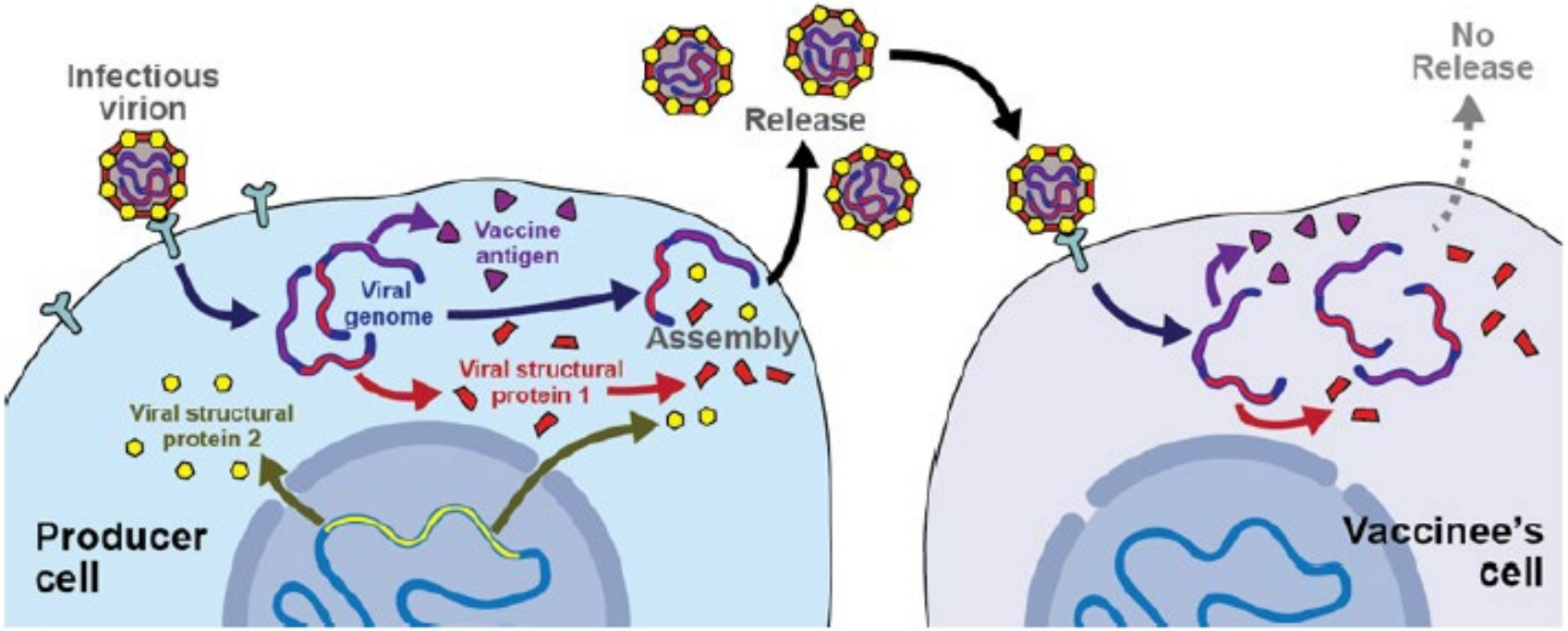
Vaccine =
- **naked DNA on plasmid with strong promoter**
- **Enters cell nucleus → antigen production**

Current problems
- **Limited immunogenicity**
- **Various strategies for enhancement proposed**

Hung C-F et al. Exp. Mol Med 2007; 39:679

The future: Viral vector vaccines ?
-> Example rLCMV

Principle:
- commensal / «attenuated» pathogen*
- biological property of interest:
e.g. compartmentalization to intestinal mucosa)
- genetic engeneering: vaccine antigen(s)



Pinschewer et al, SMW 2017

The future: Viral vector vaccines ?
-> Example rLCMV