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CLINICAL IMMUNOLOGY 4540-FS2017-0

Immunity to Microbes & Vaccines

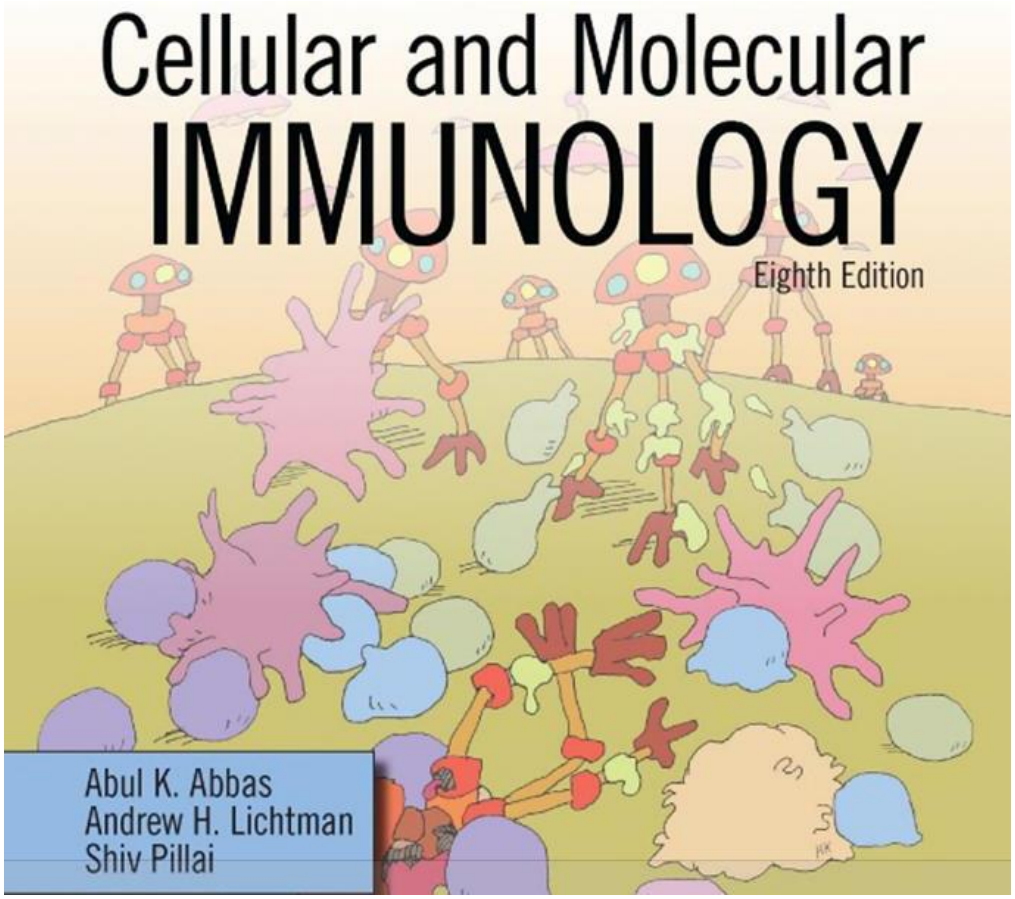
Dr. med. Christoph Hauser
und
Prof. Dr. med. Hansjakob Furrer
Universitätsklinik für Infektiologie
Inselspital

Teaching goals – immunity to microbes

- **Integrate the information about the innate, adaptive, humoral and cellular immune system to understand the responses to the major classes of microbes**
  - **Extracellular bacteria**
  - **Intracellular bacteria**
  - **Fungi**
  - **Viruses**
  - **Parasites**

- **Know examples of immune evasion by microbes**

- **Understand key concepts of microbial pathogenicity from an immunological perspective with some examples**



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

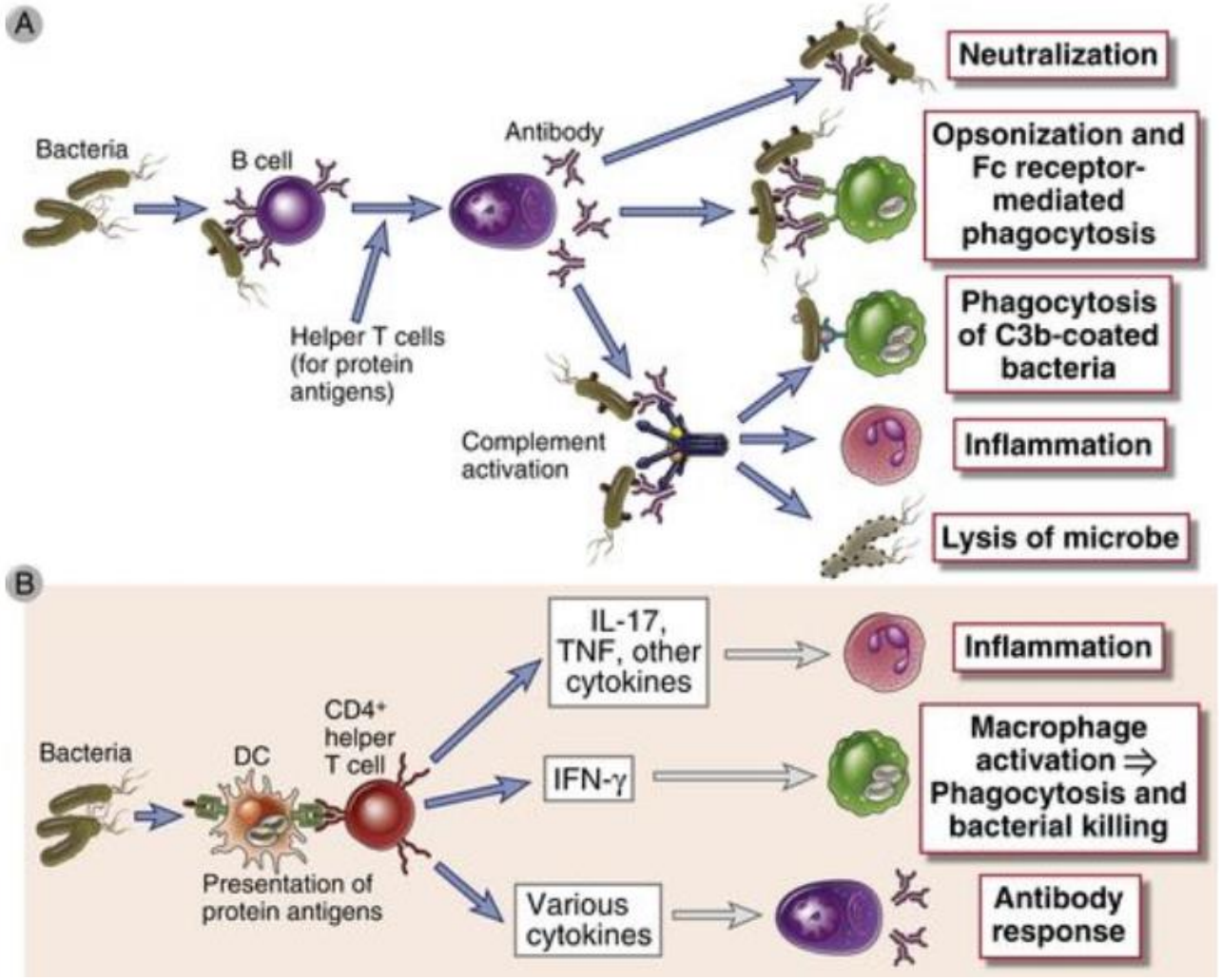
- **Complement activation** through PG and LPS by alternative pathway
- Complement activation by mannose binding lectin pathway

Resulting in

- **Opsonization and enhanced phagocytosis**
- Lysis of susceptible bacteria (e.g. Neisseria) by MAC

- **Activation of phagocytes and inflammation**
  - By mannose-, scavenger receptors
  - Fc- and complement receptors for opsonized bacteria
  - Dendritic cells and activated phagocytes secrete inflammatory and recruiting cytokines

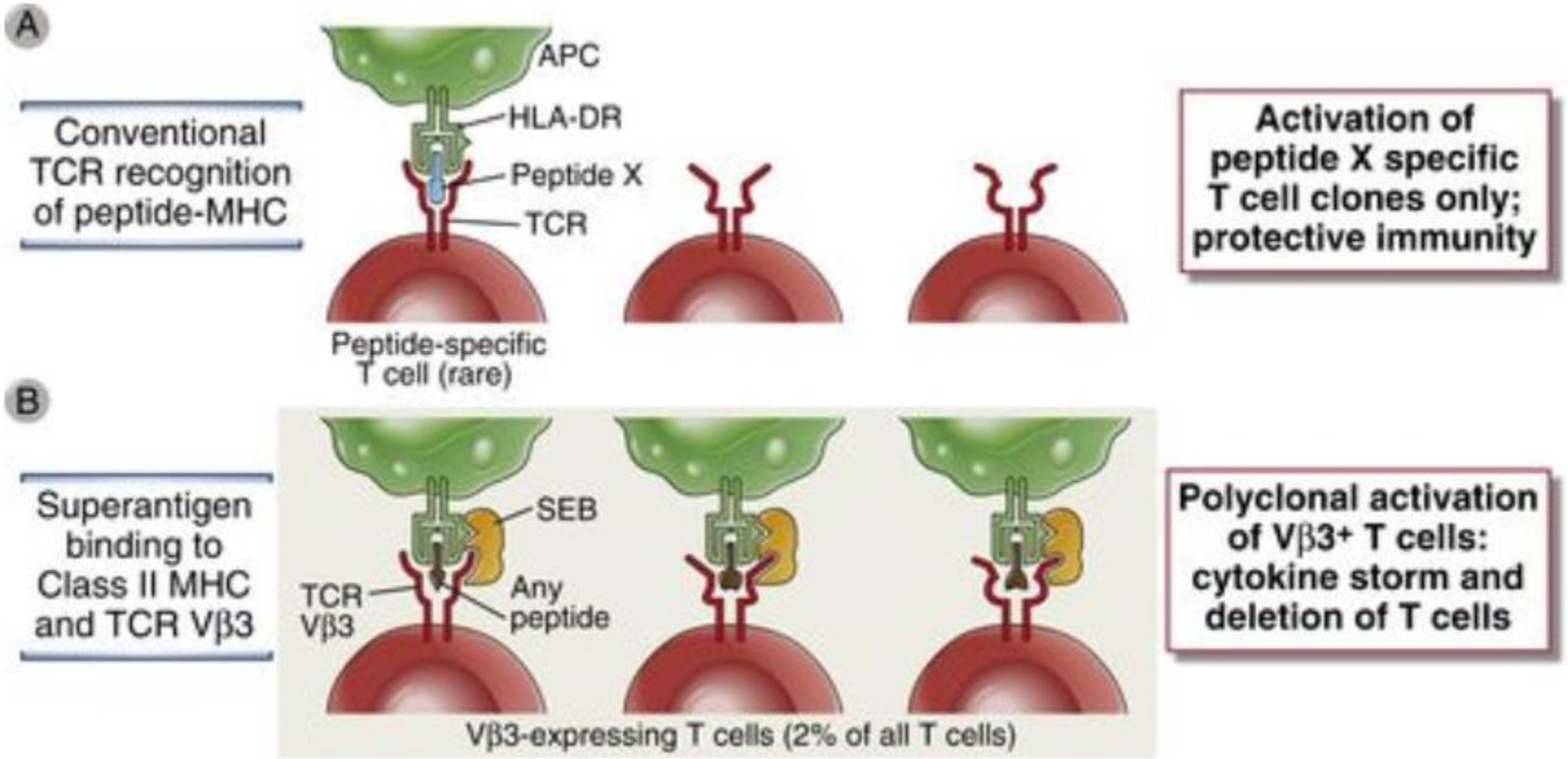
Adaptive immune response to extracellular bacteria



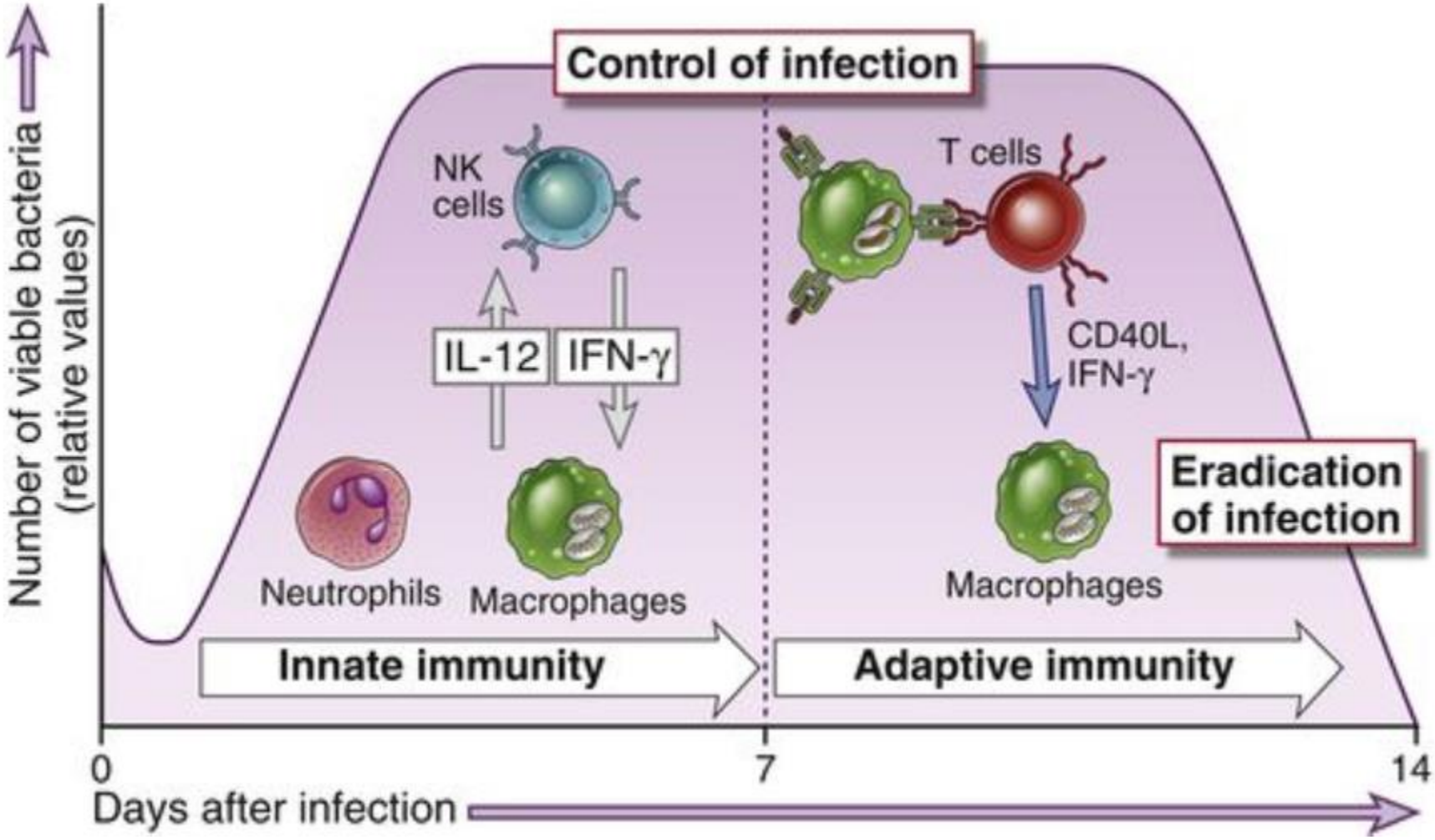
antibody production

CD4 TH17 response

Injurious effects of immune response to extracellular bacteria



Immune response to intracellular bacteria



Immune response to intracellular bacteria

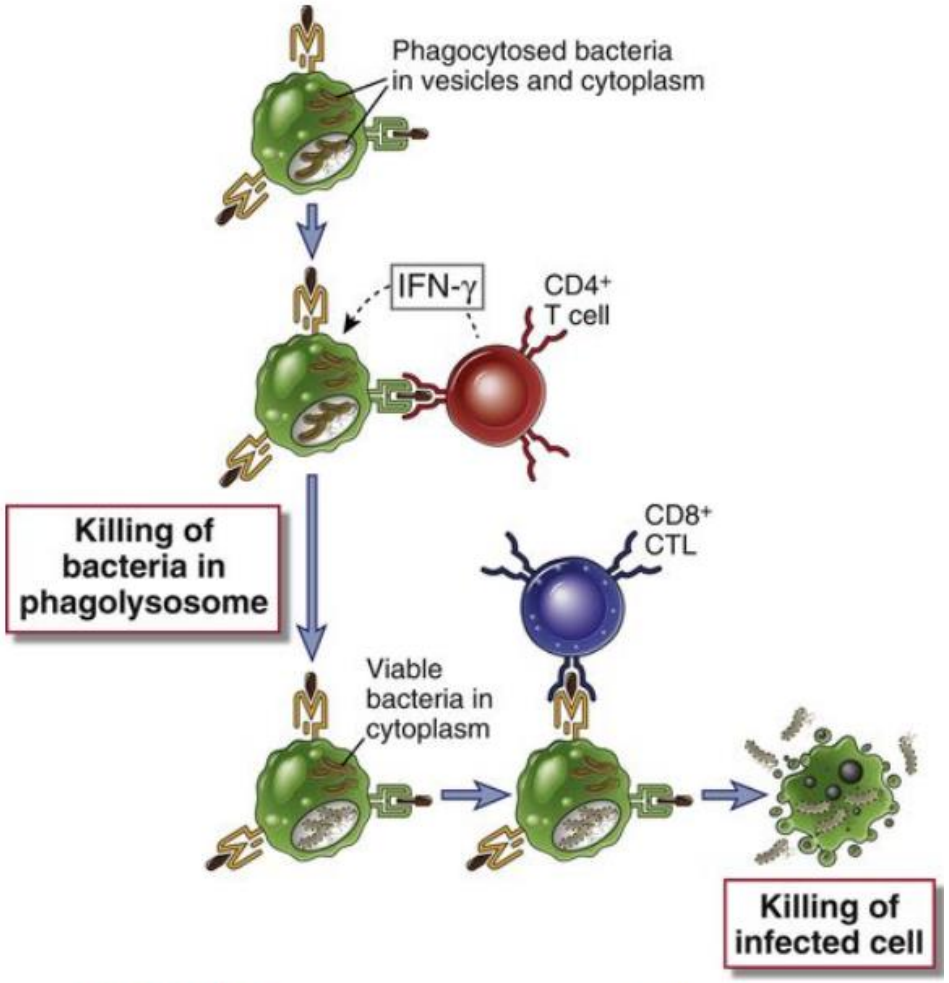


FIGURE 16-5 Cooperation of $CD4^+$ and $CD8^+$ T cells in defense

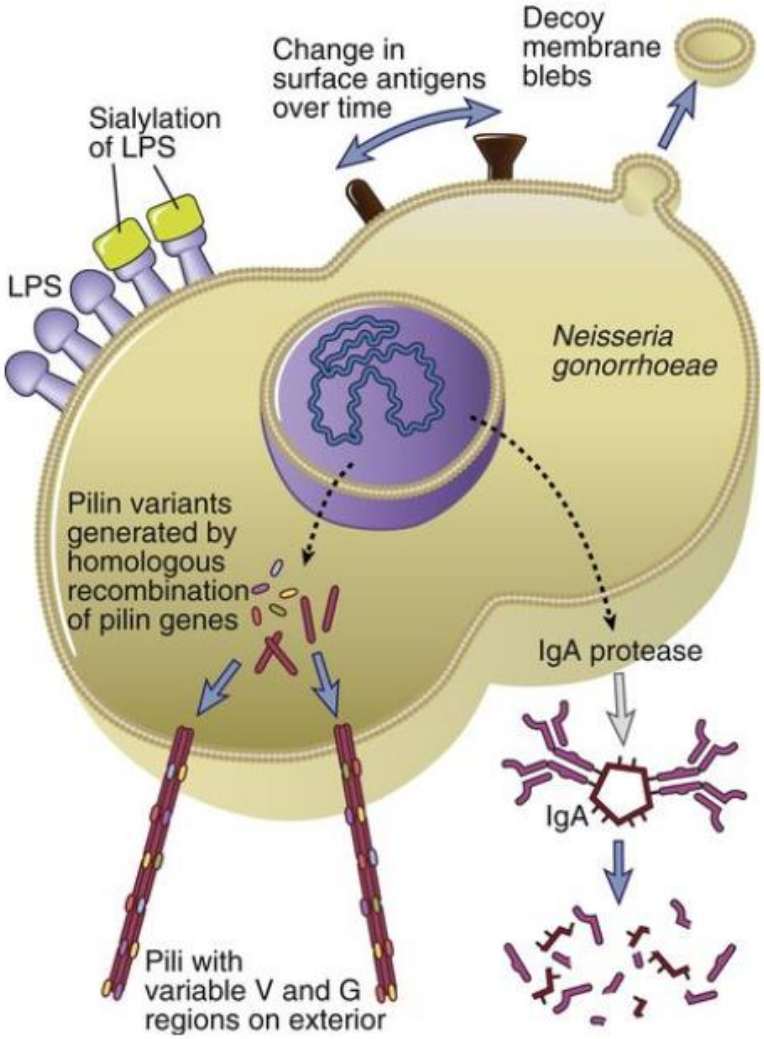
Granulomatous reaction – pathologic response to persistent intracellular bacteria

- Example Mycobacterium Tuberculosis
- With T-cell help (IFN-gamma) macrophages are activated and have enhanced ability to kill intracellular bacteria
- Cell wall components inhibit fusion of phagocytic vacoules 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

Immune evasion by bacteria

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

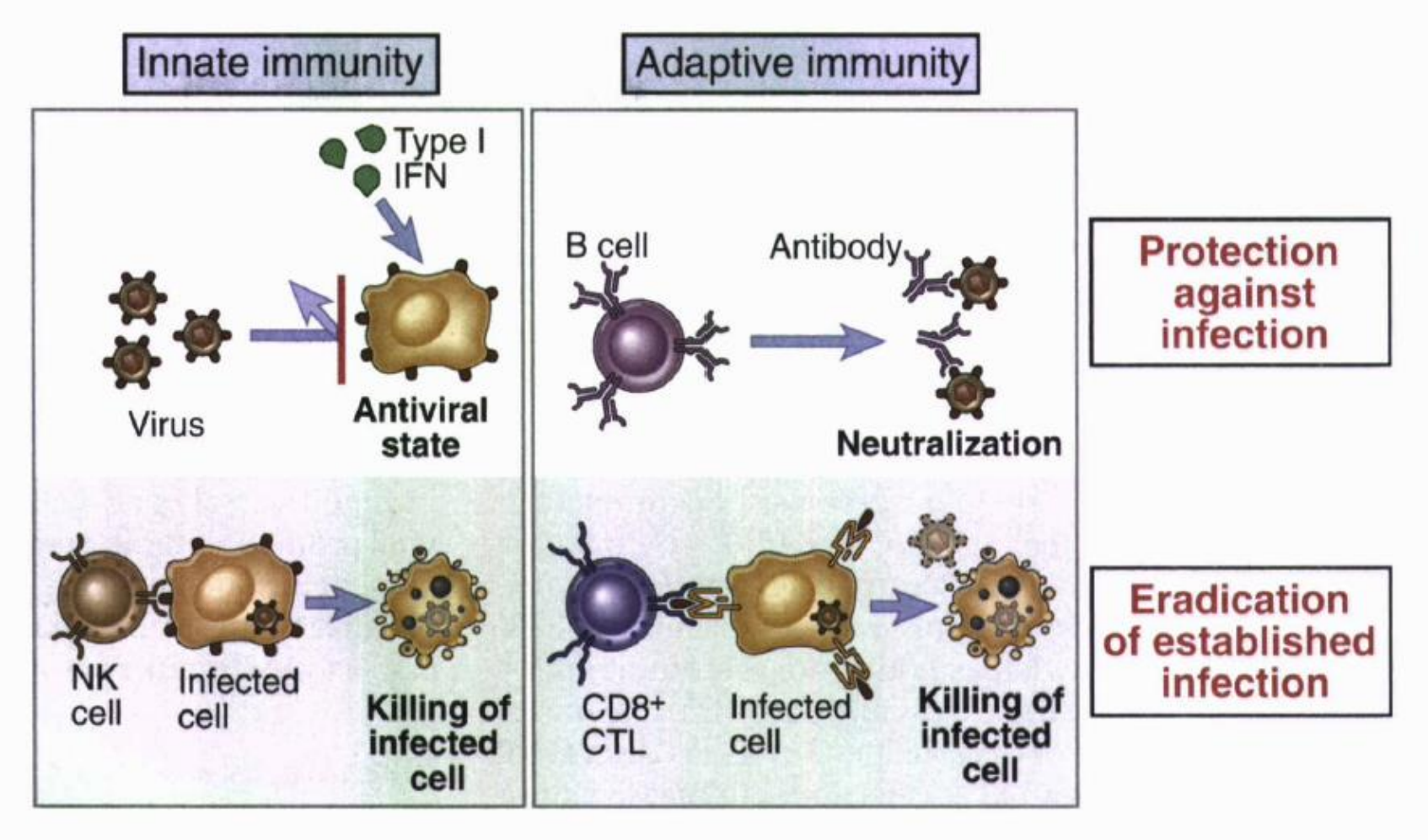


Immunity to fungi

- Innate response mainly by phagocytes (neutrophils and macrophages)
- Liberation of ROS, lysozyme, intracellular digestion
- Detection by dectins

- Adaptive response to fungi
  - Intracellular: mainly CD4/CD8 cooperation as for bacteria, Th1 responses, tendency for chronic granulomatous inflammation
  - Extracellular: dendritic cells activated by glucan sensing lectin **dectin-1**, stimulate TH17 response by IL 6 and 23
  - Antibodies may exert some protection
- Immune evasion (inhibition of cytokine production in phages)

Innate and adaptive immune responses against viruses



Innate and adaptive immune responses against viruses

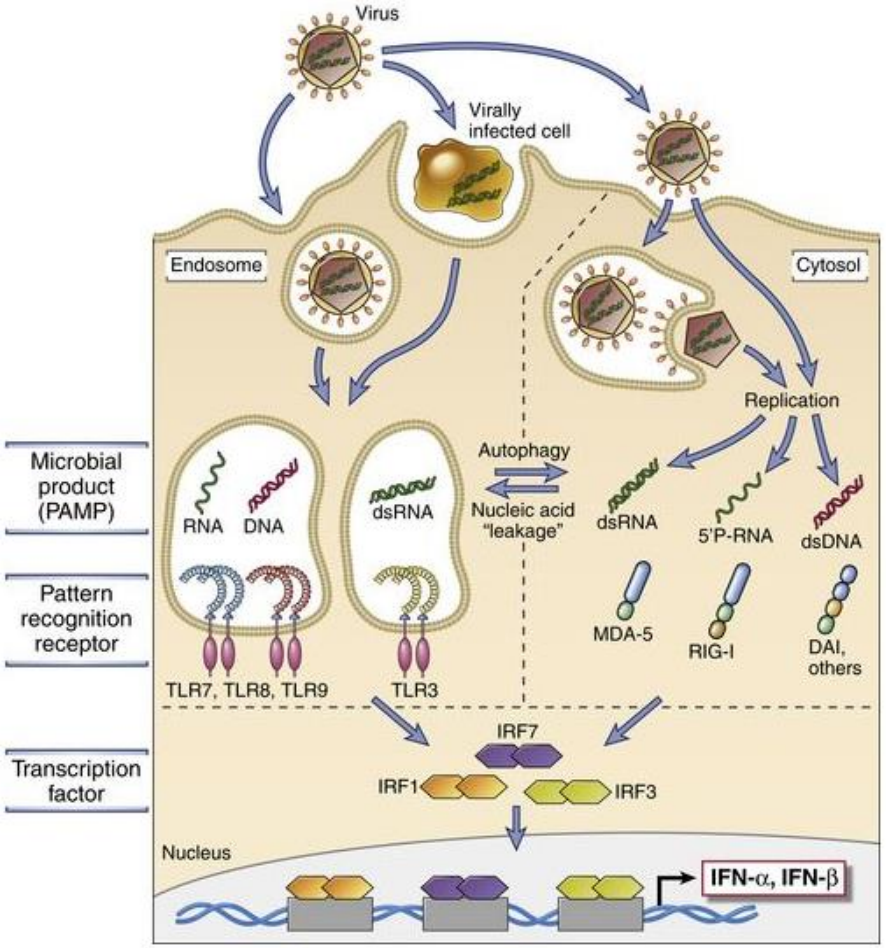


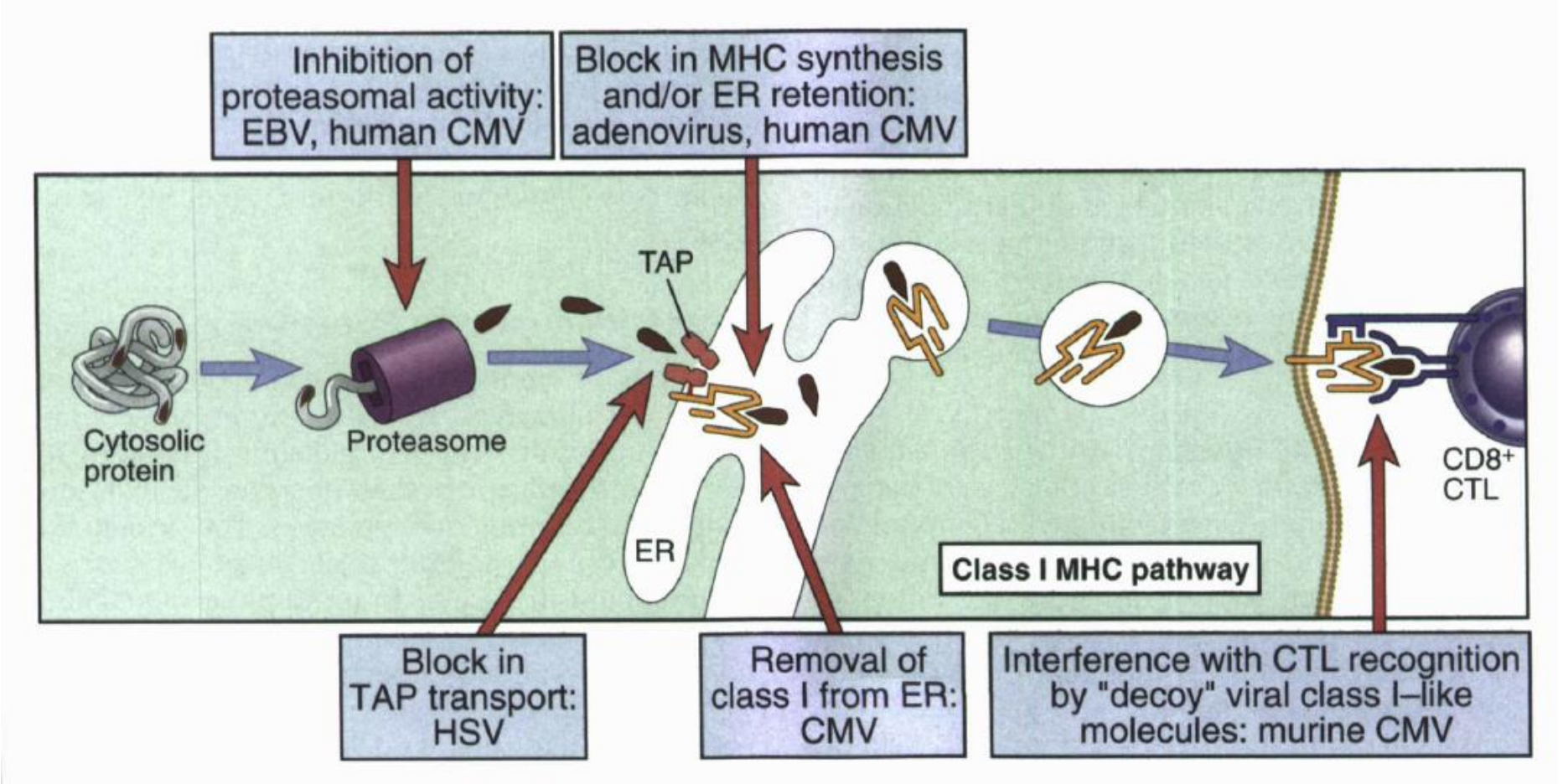
FIGURE 4-16 Mechanisms of induction of type I interferons by viruses. Viral nucleic acids and proteins are recognized by several cellular receptor families (TLRs, the family of cytosolic RIG-like receptors, or RLRs, which include MDA-5, RIG-I, DAI and others, and cytosolic DNA sensors), which activate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

Evasion from immune response

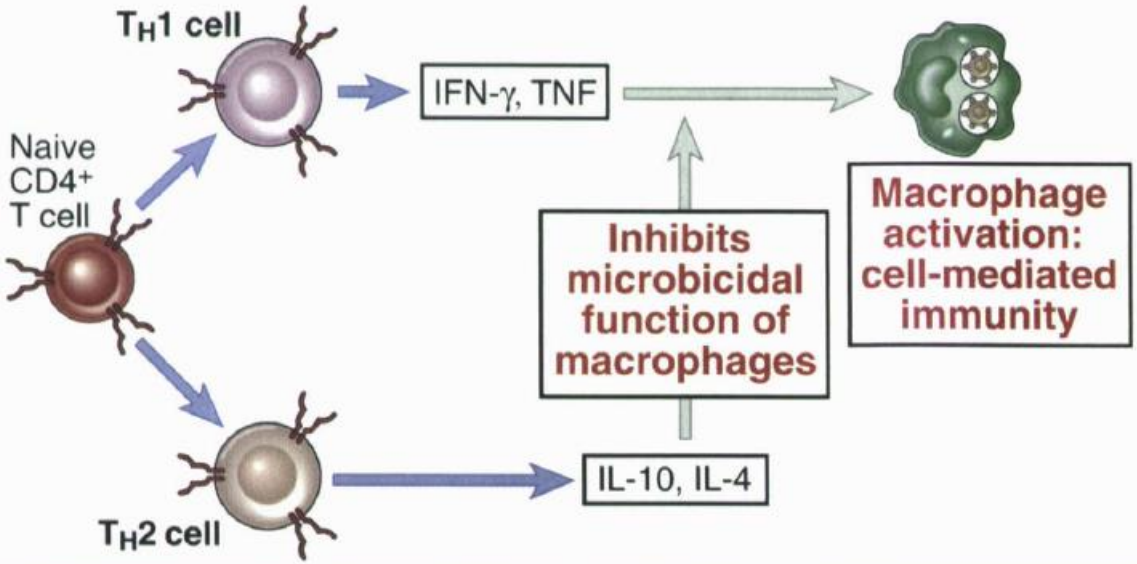
Mechanism of immune evasion	Examples
Antigenic variation	Influenza, rhinovirus, HIV
Inhibition of antigen processing	
Blockade of TAP transporter	Herpes simplex
Removal of class I molecules from the ER	Cytomegalovirus
Production of cytokine receptor homologs	Vaccinia, poxviruses (IL-1, IFN-γ) Cytomegalovirus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



T_H1 and T_H2 response



Infection	Response	Outcome
Leishmania major	Most mouse strains: T_H1	⇒ Recovery
	BALB/c mice: T_H2	⇒ Disseminated infection
Mycobacterium leprae	Some patients: T_H1	⇒ Tuberculoid leprosy
	Some patients: Defective T_H1 or dominant T_H2	⇒ Lepromatous leprosy (high bacterial count)

FIGURE 15–5 Role of T cells and cytokines in determining outcome of infections. Naive $CD4^+$ T lymphocytes may differentiate into T_H1 cells, which activate phagocytes to kill ingested microbes, and T_H2 cells, which inhibit macrophage activation. The balance between these two subsets may influence the outcome of infections, as illustrated by *Leishmania* infection in mice and leprosy in humans.

Leprosy
Mycobacterium leprae

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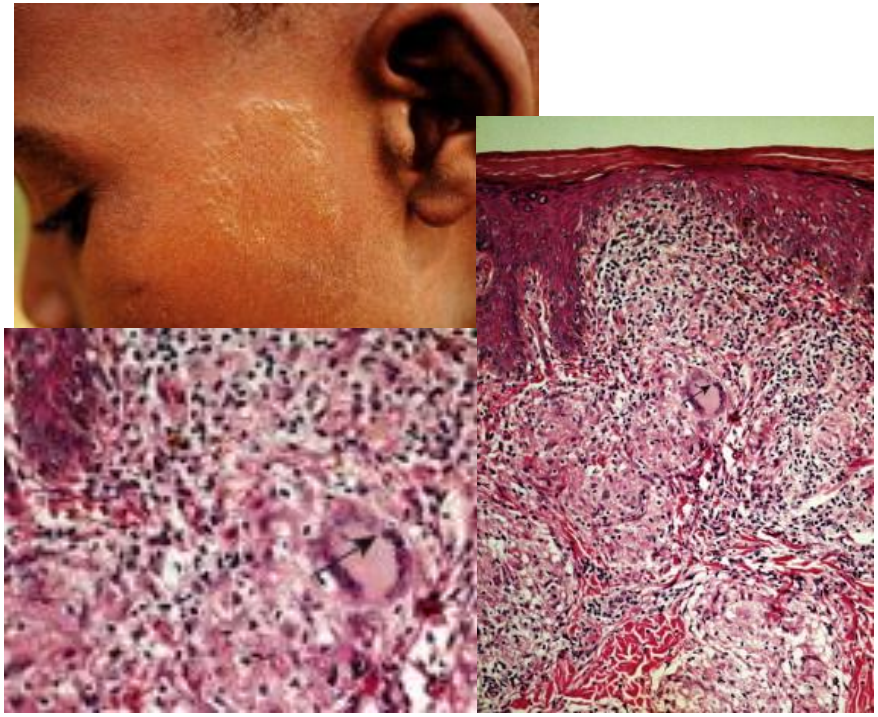
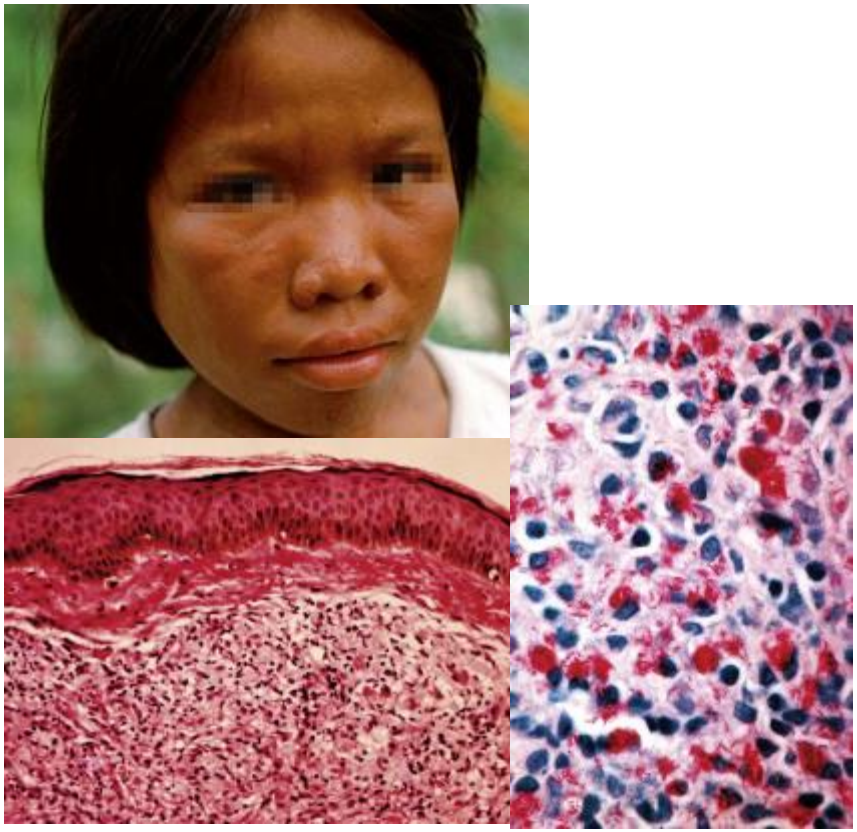
T_H1 Tuberculoid leprosy



T_H2 Lepromatous leprosy



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.

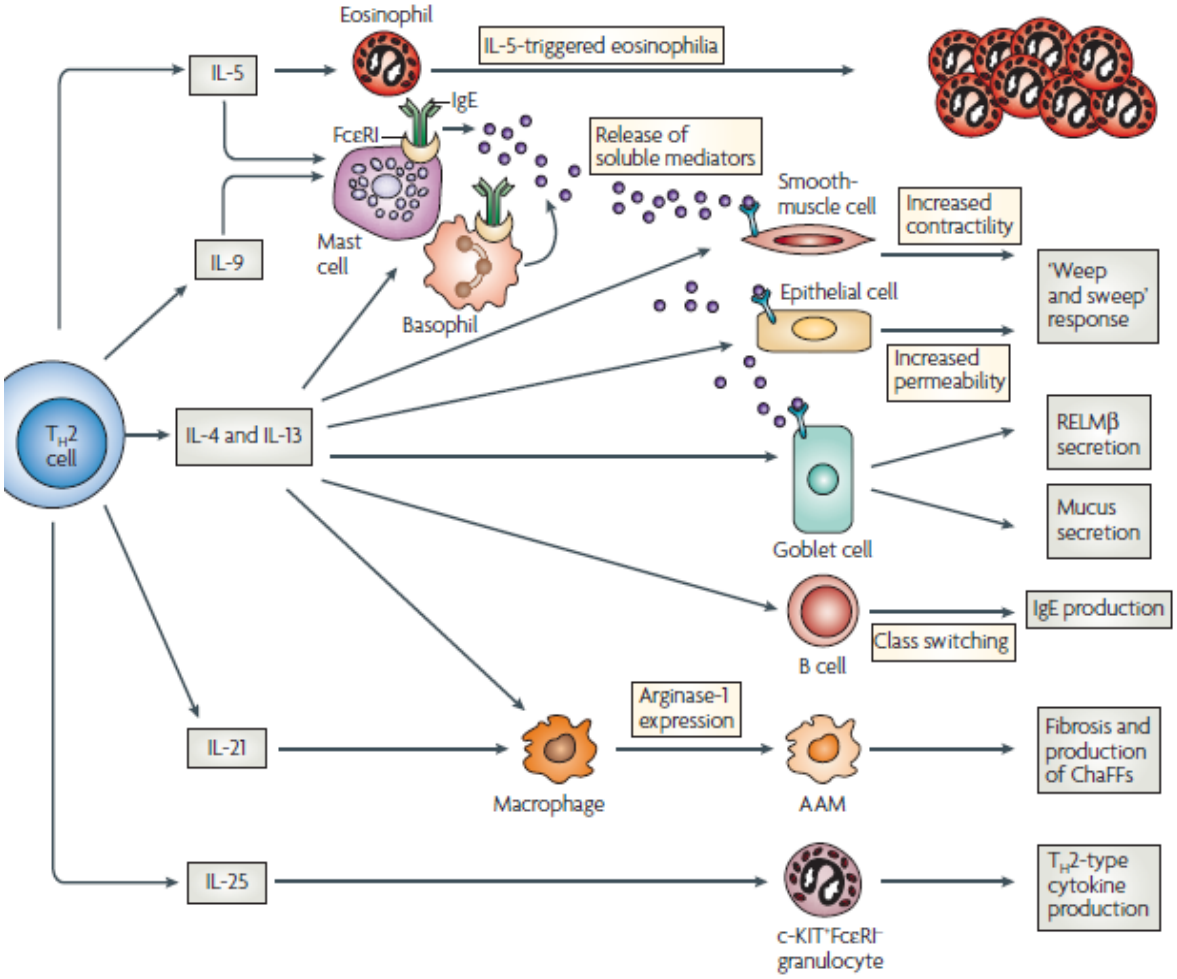
T_H1

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

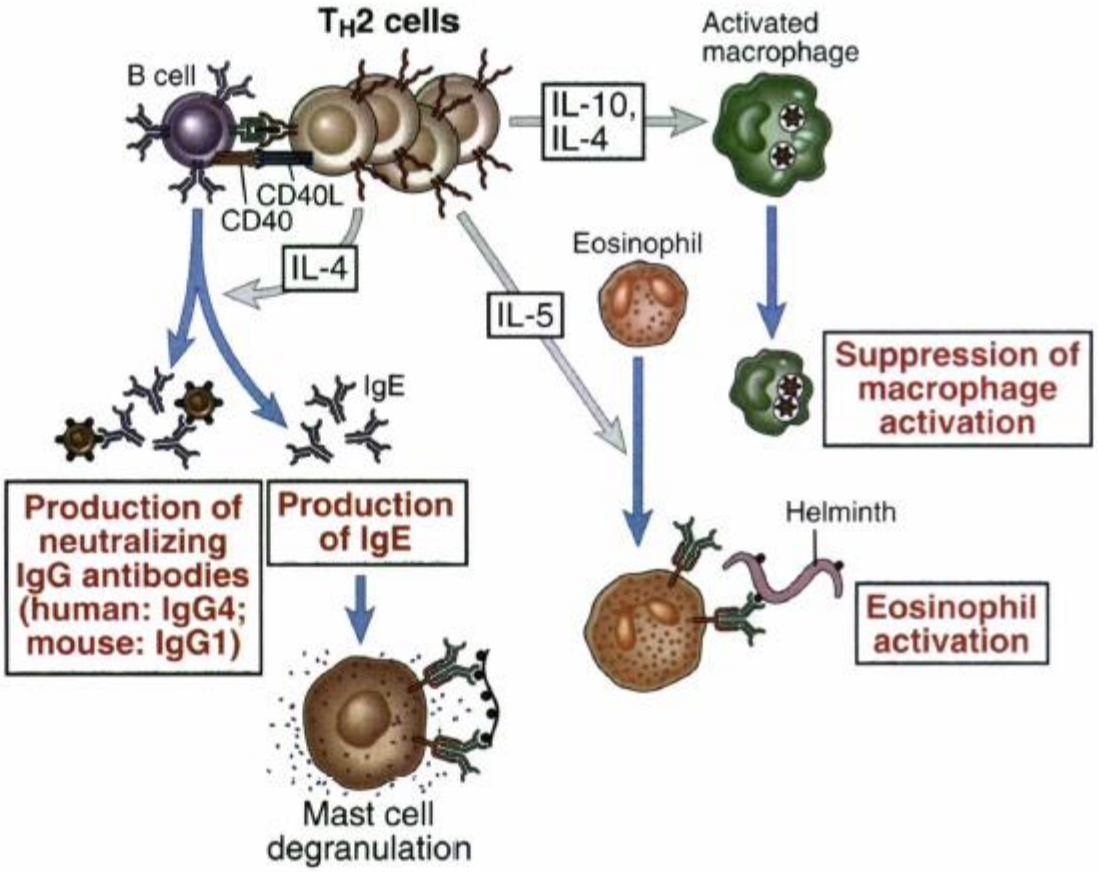


FIGURE 13–13 Effector functions of T_H2 cells. $CD4^{++}$ T cells that differentiate into T_H2 cells secrete IL-4 and IL-5. IL-4 acts on B cells to stimulate production of antibodies that bind to mast cells, such as IgE. IL-4 is also an autocrine growth and differentiation cytokine for T_H2 cells. IL-5 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.

Key concepts of microbial pathogenicity

- 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 *Listeria monocytogenes*	Tuberculosis, leprosy Listeriosis	Macrophage activation resulting in granulomatous inflammation and tissue destruction 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 CD_4^+ T cells, functional impairment of immune cells (see Chapter 20)

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Opportunistic Infections under immunosuppressive «Biologicals» illustrate specificity of protection of various effectors

TABLE 88-1 Main Immunobiologics Used to Treat Inflammatory and Autoimmune Diseases and Associated Risk of Infections

Name	Type	Target	Effects	Primary Indication Within the Field of Inflammatory Diseases	Secondary Indications	Associated Infections
Infliximab	Chimeric IgG1	TNF	Neutralization of soluble and transmembrane TNF and inhibition of binding to TNFRs Induces apoptosis of activated T cell and macrophages	Crohn's disease; colitis ulcerosa; RA; ankylosing spondylitis; psoriatic arthritis	Behçet's disease; refractory uveitis; sarcoidosis	Invasive skin and soft tissue infections; septic arthritis (predominantly staphylococcal infections); legionellosis; TB and NTBM diseases; fungal infections (histoplasmosis, coccidioidomycosis, aspergillosis, pneumocystosis); nocardiosis; leishmaniasis; HBV reactivation
Adalimumab	Human IgG1	TNF				
Golimumab	Human IgG1	TNF				
Etanercept	TNF-R2 extracellular domain–Fc (IgG1) fusion protein	TNF	Neutralization of soluble TNF-α	RA; ankylosing spondylitis; psoriatic arthritis	Psoriasis; JIA	
Certolizumab pegol	Humanized Fab; PEG conjugate	TNF	Neutralization of soluble and transmembrane TNF and inhibition of binding to TNFRs	RA; Crohn's disease; ankylosing spondylitis; psoriatic arthritis		
Rituximab	Chimeric IgG1	CD20	Induces apoptosis, ADCC and CDC	RA; ANCA-associated vasculitis; autoimmune cytopenias	SLE; autoimmune skin disease; other connective tissue diseases	HBV reactivation; rare cases of opportunistic infections (PML, pneumocystosis, toxoplasmosis); may induce neutropenia or hypogammaglobulinemia
Belimumab	Human IgG1	Soluble BlyS	Ligand binding and neutralization	SLE	Sjögren's syndrome	Rare cases of opportunistic infections (coccidioidomycosis, CMV pneumonia, PML)
Atacicept	Fusion protein composed of extracellular domains of TACI receptor and Fc segment of human IgG	B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL)	Binds both cytokines involved in B cell function and survival	Trials (SLE, MS, RA)		May induce hypogammaglobulinemia
Abatacept	Fusion protein composed of the extracellular domain of CTLA-4 and a modified Fc portion of IgG1	Competes for binding to CD80/CD86: interaction with T cells	Inhibits T-cell activation by disrupting CD28 co-stimulation	RA, JIA	SLE	Respiratory infections; HBV reactivation
Tocilizumab	Humanized IgG1	IL-6 receptor	Receptor binding and ligand blockade Inhibits proliferation and differentiation of T cells and terminal differentiation of B cells; inhibits production of acute phase reactants	RA; JIA	Autoinflammatory disorders; large-vessel vasculitides	Respiratory infections; may induce neutropenia
Anakinra	rhIL-1Ra	IL-1R (competes with IL-1 for binding to IL-1R)		RA	Autoinflammatory disorders	Respiratory infections
Canakinumab	Human IgG1	IL-1β	Ligand binding and receptor antagonism	CAPS; NOMID	JIA; autoinflammatory disorders; acute gout	Insufficient data

Furrer & Hauser

Cohen et al Infectious Diseases 4th Ed. 2016

Opportunistic Infections under immunosuppressive «Biologicals» illustrate specificity of protection of various effectors

TABLE 88-1 Main Immunobiologics Used to Treat Inflammatory and Autoimmune Diseases and Associated Risk of Infections (Continued)

Name	Type	Target	Effects	Primary Indication Within the Field of Inflammatory Diseases	Secondary Indications	Associated Infections
Ustekinumab	Human IgG1	p40 subunit of IL-12 and IL-23	Ligand binding and receptor antagonism; inhibition of T lymphocytes (Th1, Th17)	Psoriasis; Psoriatic arthritis		*C. difficile* and viral enteritis; urinary tract infection; genital abscesses; HBV reactivation
Secukinumab	Human IgG1κ	IL-17A		Psoriasis		Bacterial infections; non-invasive *Candida* infections; may induce neutropenia
Natalizumab	Humanized IgG4	α4 subunit of α4β1 and α4β7 integrins	Inhibits leukocyte adhesion	MS	Crohn's disease	Rare cases of PML
Vedolizumab	Humanized IgG1 (Fc-engineered to silence effector functions)	α4β7 integrin	Inhibits migration of memory T lymphocytes into inflamed gastrointestinal parenchymal tissue	Ulcerative colitis, Crohn's disease		Insufficient data
Omalizumab	Humanized IgG1	IgE → mast cells, basophils	Ligand binding and receptor antagonism; downregulation of high-affinity IgE receptor	Asthma; chronic idiopathic urticaria	Mastocytosis	None, although theoretical risk of parasitic infections
Eculizumab	Humanized IgG2 and IgG4	Complement C5	Inhibits cleavage to C5a and C5b and prevents generation of membrane attack complex (C5b–C9)	Paroxysmal nocturnal hemoglobinuria	Thrombocytic thrombopenic purpura	Susceptibility to meningococcal infection

ADCC, antibody-dependent cellular cytotoxicity; CAPS, cryopyrin-associated periodic syndromes; CDC, complement-dependent cytotoxicity; JIA, juvenile idiopathic arthritis; MS, multiple sclerosis; NK, natural killer cells; NOMID, neonatal onset multisystem inflammatory disease; NTBM, nontuberculous mycobacteria; RA, rheumatoid arthritis; TB, tuberculosis; TNF, tumor necrosis factor.

Furrer & Hauser

Cohen et al Infectious Diseases 4th Ed. 2016

Food for thought – (Immuno)pathogenesis

- Obligate, facultative and opportunistic pathogens
- Why does this happen to me? (Why immune responses fail to protect in some individuals but not in others)
  - Epidemiology
  - Ecology
  - Genetics
  - Demographics
  - Co-Morbidities including various states of congenital or acquired immunodeficiencies
- Jarisch-Herxheimer and paradoxical reaction under Therapy
- IRIS, immunoreconstitution (lecture 7.4. Prof. Seitz)

Introduction to vaccines

- Continuous arm race between host and pathogen
- For exclusive human pathogens co-evolution most marked
- Different pathogens – different strategies
- Co-existence in some better than in others
- Vaccine efforts as the most recent evolutionary step from us

- 1796: Jenner's vaccination
- Basic principle of vaccination:
  - Active: expose individual with attenuated, killed or partial organisms that allow for development of immune response without the risk of (severe) disease
  - Passive: adoptive transfer of specific effector mechanisms from other, previously actively immunized individuals

Swiss routine vaccine program 2016

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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]

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 ,…

- Sepcial exposures: FSME, Rabies, …

- High risks: 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

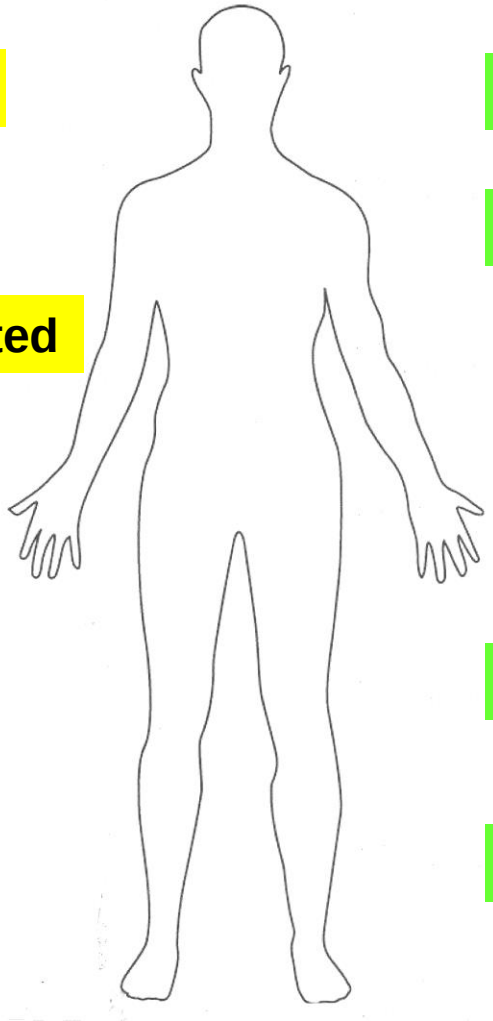
Types of vaccines

Passive: antibodies

Active: live, attenuated

Active: inactivated

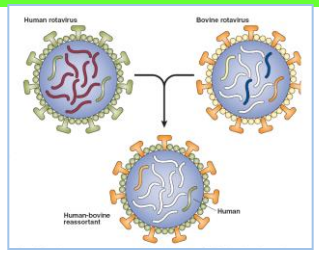
Active: component



Newer technologies

- Recombinant (e.g. Rotavirus)

Buckland BC
Nat Med2005



- 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

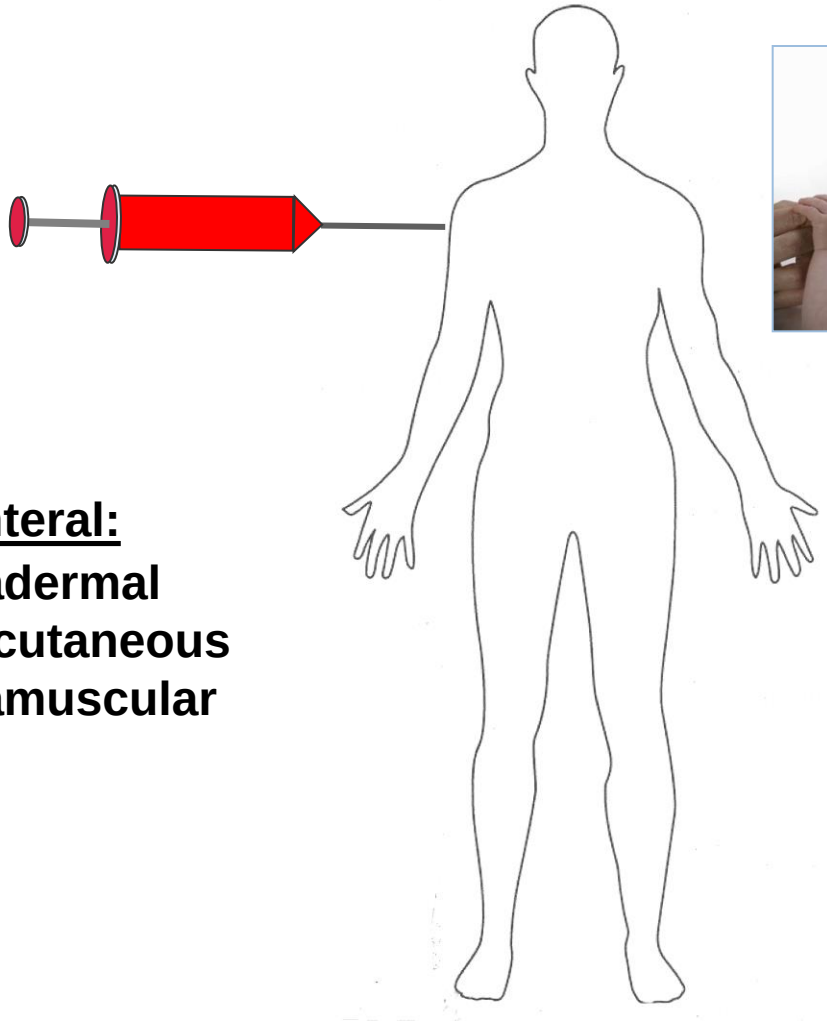
Use of vaccine induced antibodies for passive immunisation

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**

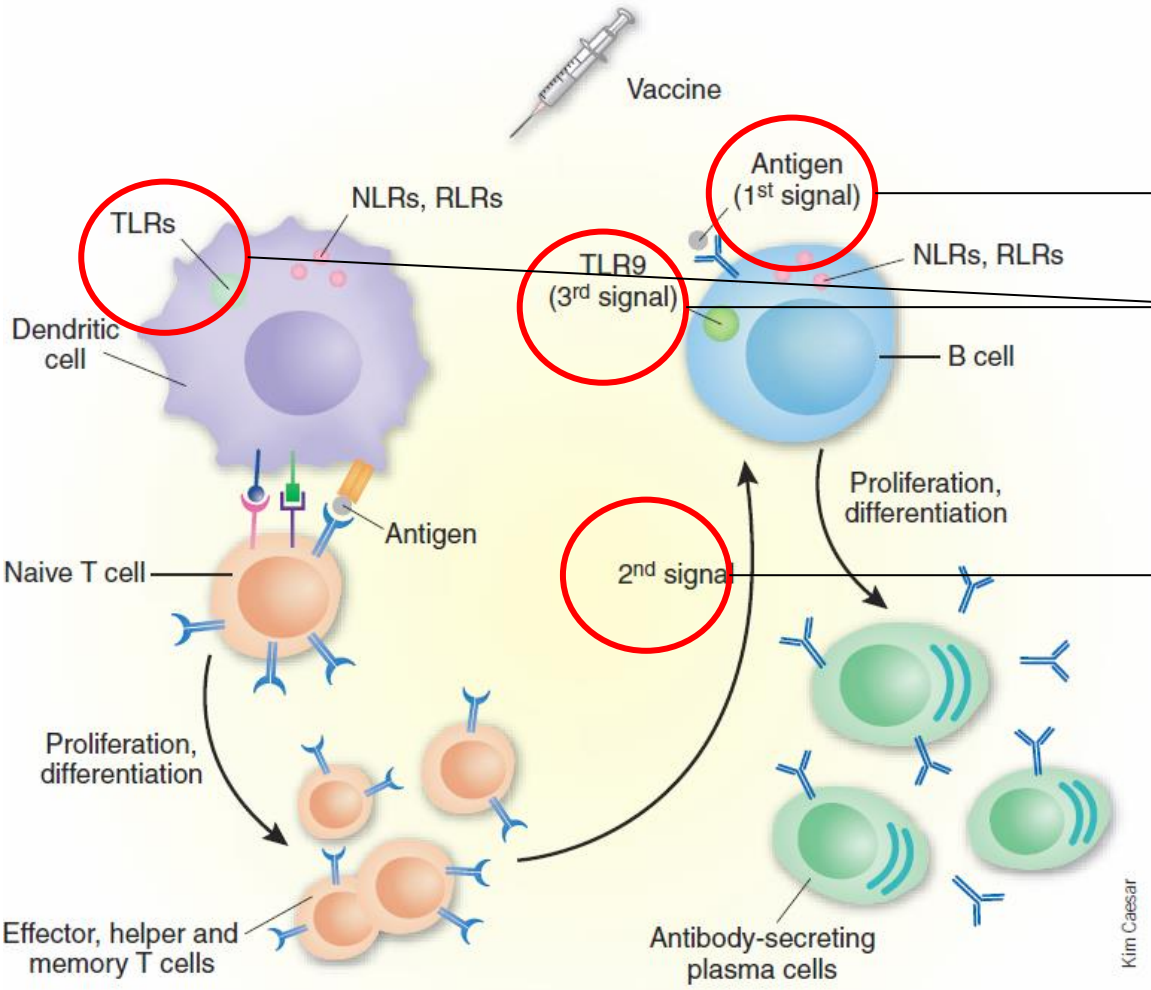
Poliomyelitis vaccines: oral-live vs. parenteral inactivated

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

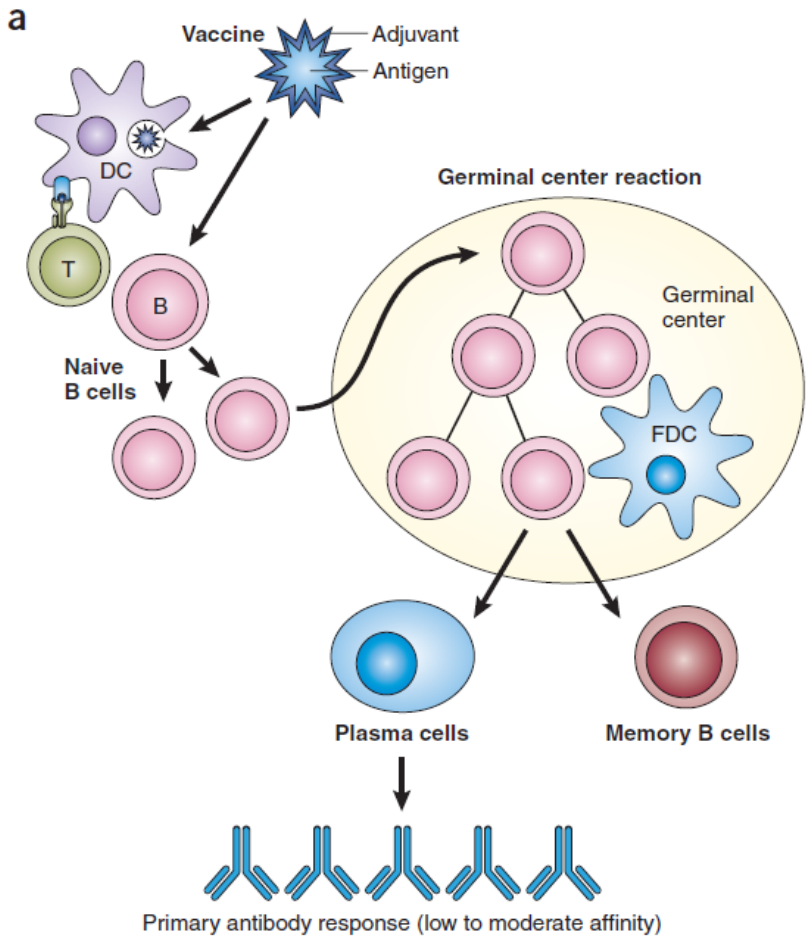


Adaptive B cell

Innate

Adaptive T Help

Primary immune response to vaccines

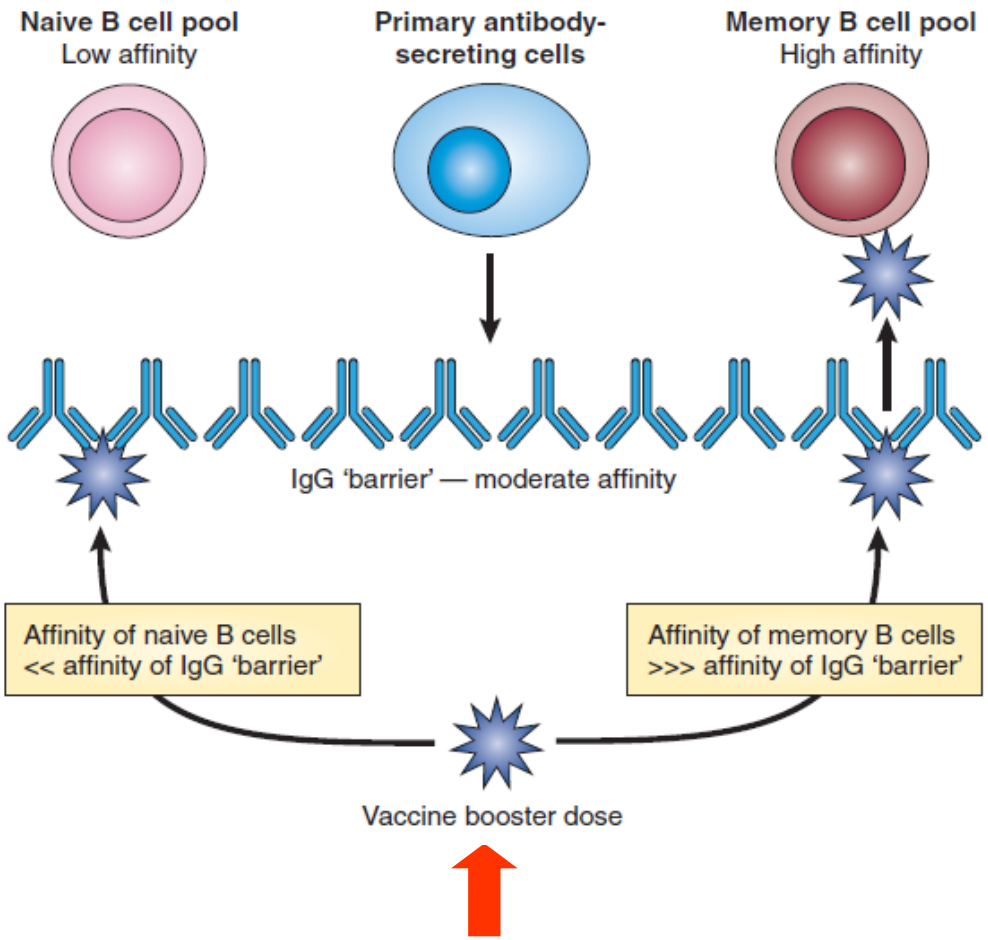


What have we learned (in retrospect)

- **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**
  little analyzed
- **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

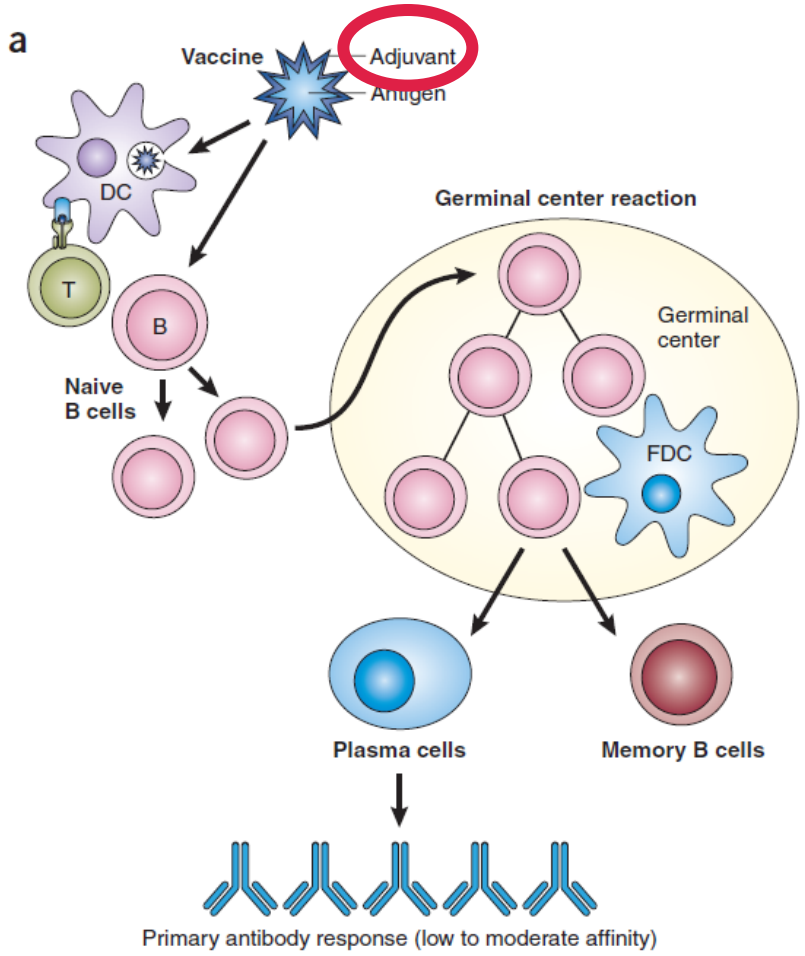
Antigen persistence? (animal models)

"Nature of antigen"

Booster dose

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

Adjuvant



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

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

Importance of early response: depends on infectious agent etc.

Example:
Tetanus-Toxin (TeNT)

Neutralization before up-take into neuron !!

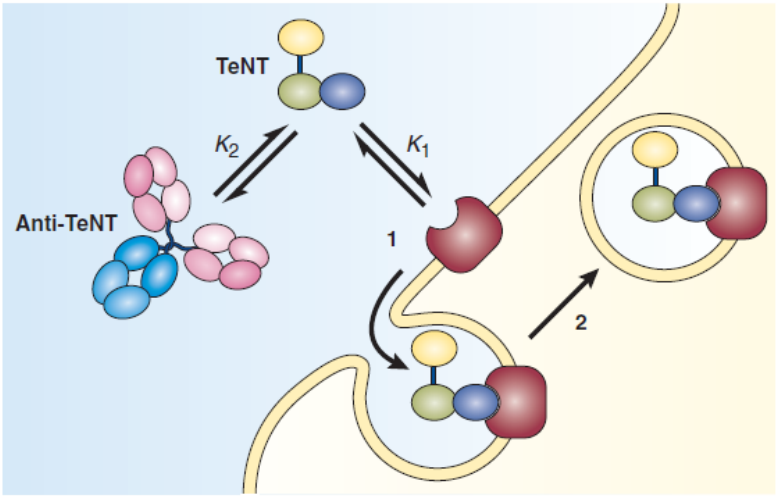


Figure 2 Vaccine-induced anti-tetanus toxin (TeNT) antibodies compete with TeNT receptors at cell surface. Their relative affinities for TeNT (K_1, K_2) determine the outcome. Once TeNT is internalized, it can no longer be captured by antibodies and the intoxication sequence cannot be stopped.

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

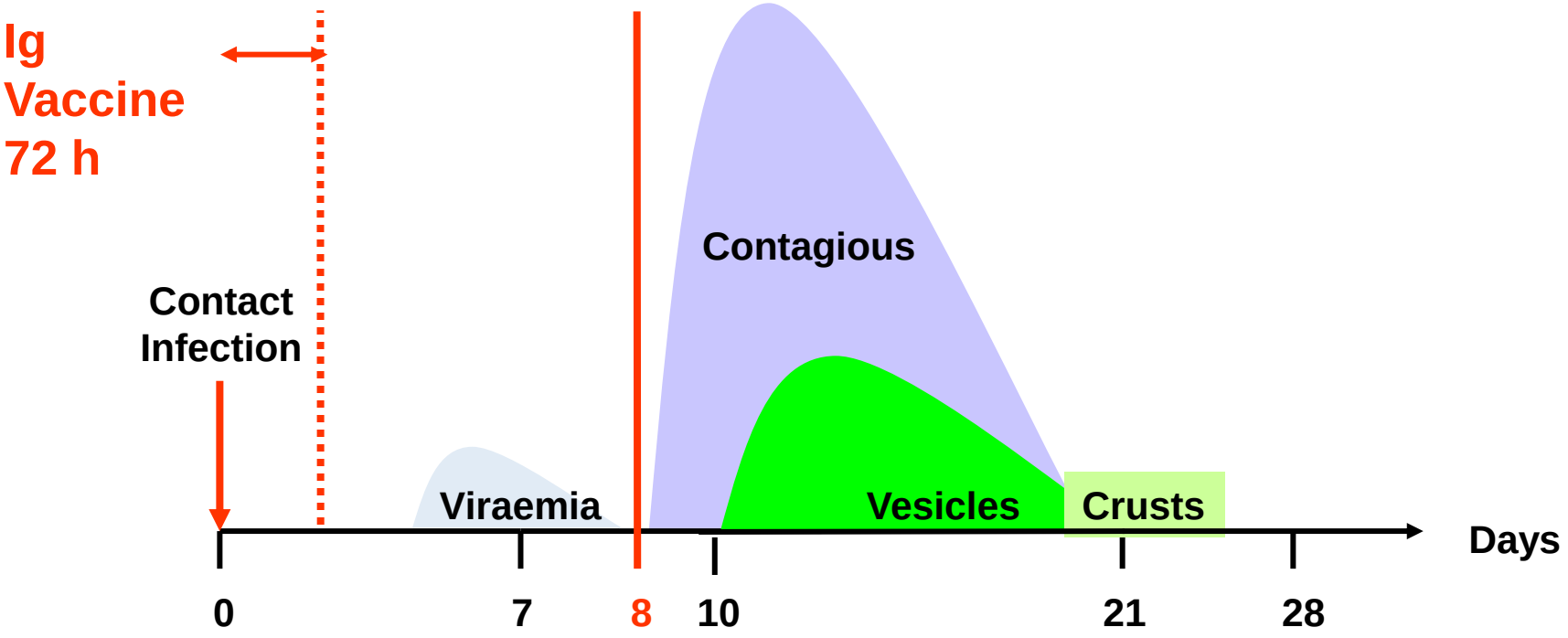
Incubation period 4-12 wks
Time to recruit memory cells

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)**

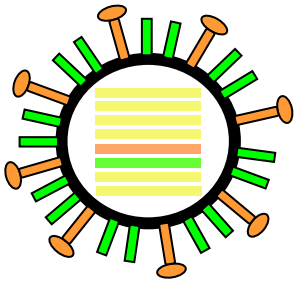
Surrogate: Vaccine record!! (= empiric), e.g. 2 doses MMR vaccine

Antigen variation / strain diversity

Example: influenza virus / vaccine

Hämagglutinin (H, n=15)

Neuraminidase (N, n=9)



RNA, segmented
→AG drift / shift

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

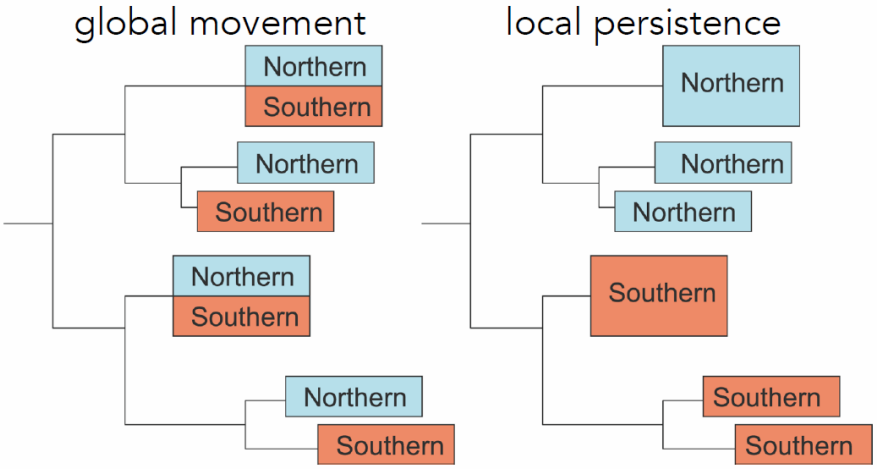
“Pandemic vaccine”

H5N1 vaccine: conserved epitope
crossreactive?

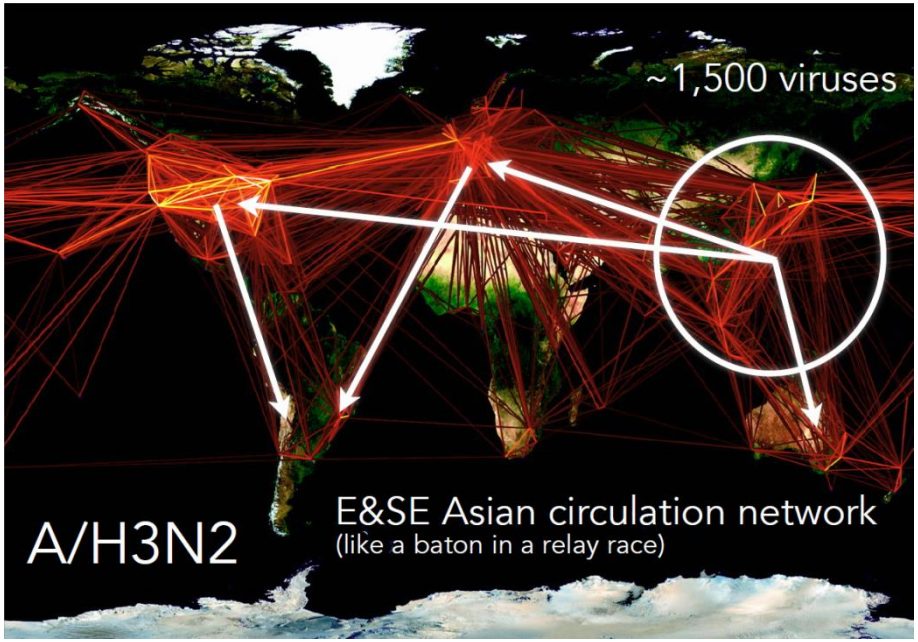
Reverse genetics for new strains??

Influenza Spreading

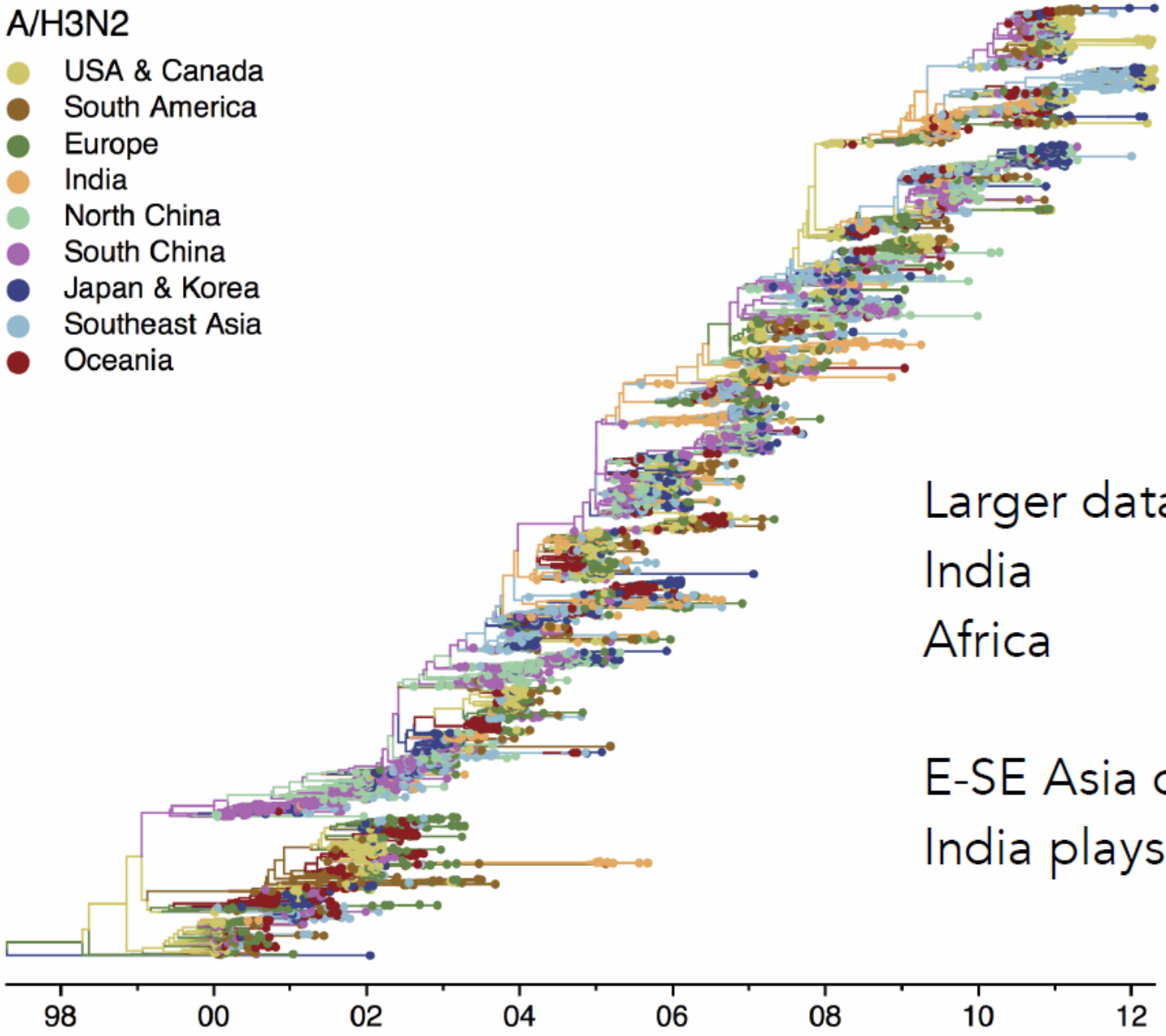
Hypothesis testing - persistence



A/H3N2, New York State and New Zealand



The global dynamics of influenza viruses - Swiss Virology Meeting 2017 - Colin Russell



Larger dataset (>7x)

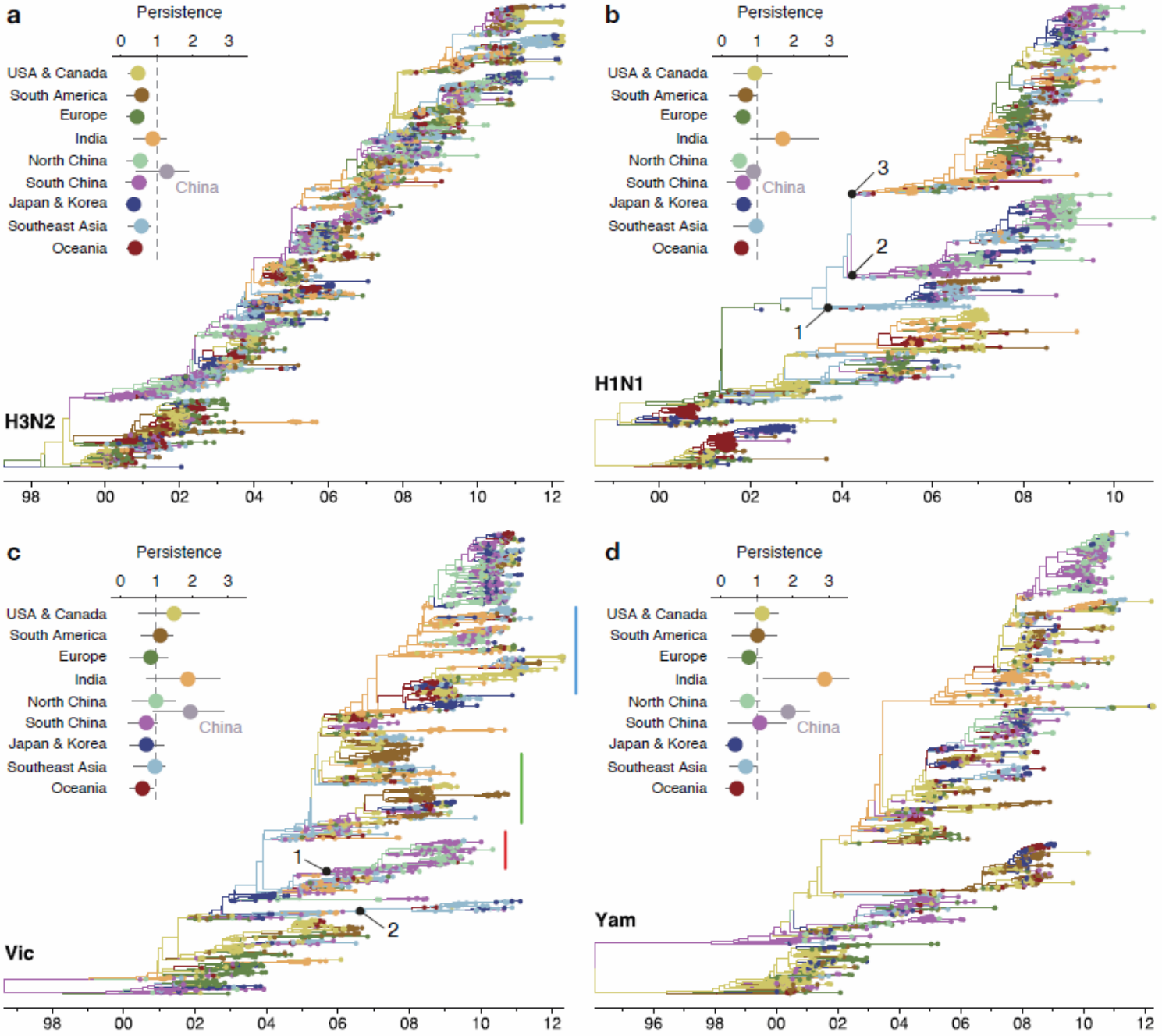
India

Africa

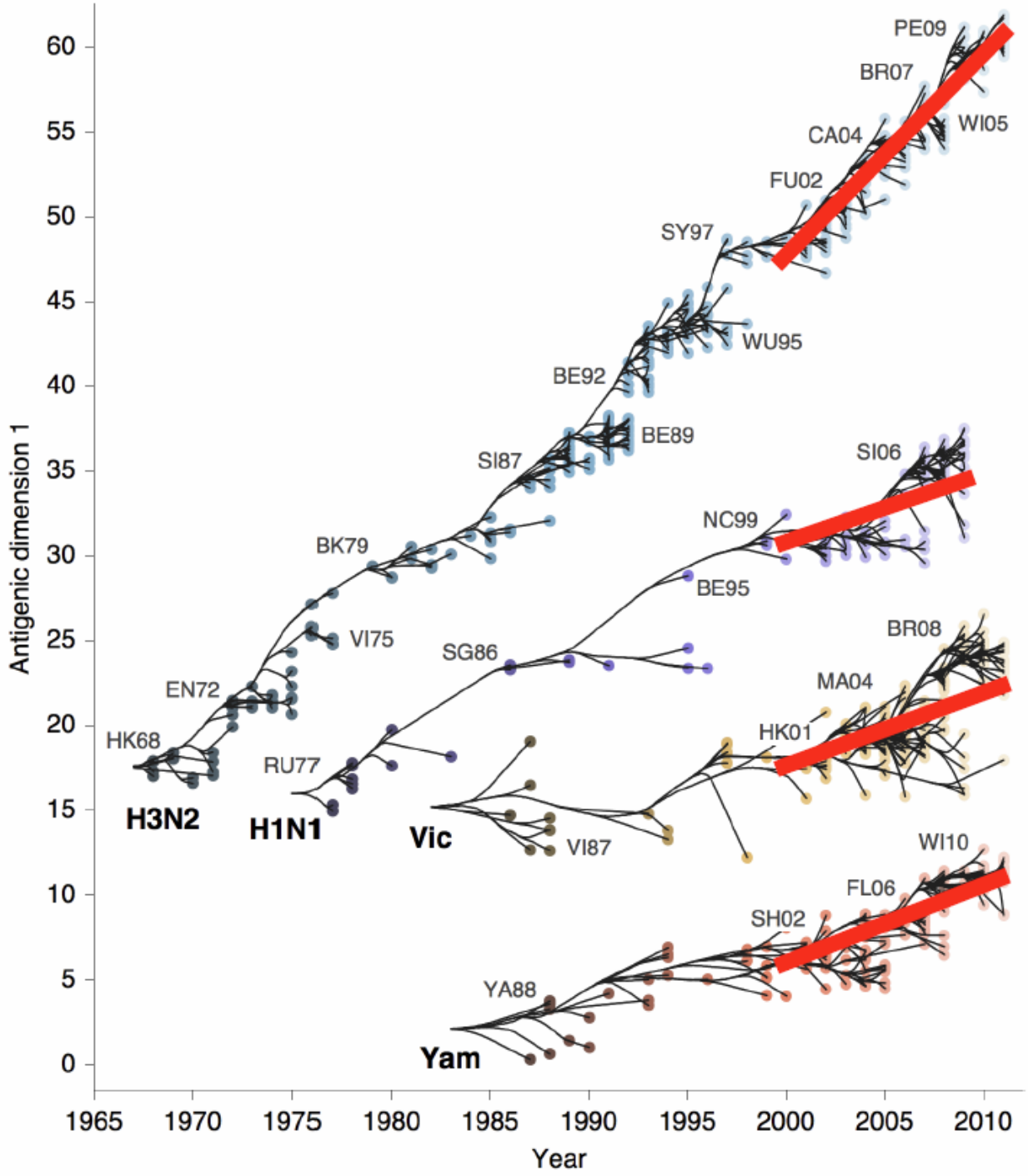
E-SE Asia dominant

India plays key role

Bedford,…, Russell. *Nature* 2015

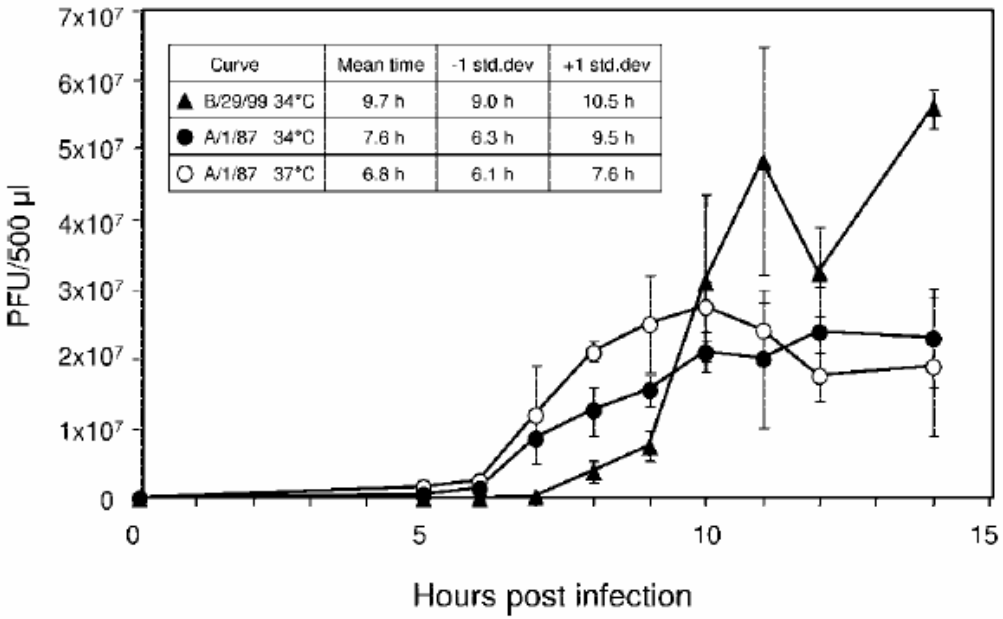


Bedford,…, Russell. *Nature* 2015


Antigenic dimension 1
Year
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
0
5
10
15
20
25
30
35
40
45
50
55
60
H3N2
H1N1
Vic
Yam
HK68
EN72
VI75
BK79
SI87
BE89
BE92
WU95
SY97
FU02
CA04
WI05
BR07
PE09
RU77
SG86
BE95
NC99
SI06
HK01
MA04
BR08
VI87
YA88
SH02
FL06
WI10

Direct quantitation of replication and polymerase error rate

Replication



Error Rate

H3N2: 2.0×10^{-6}

B: 0.6×10^{-6}

Nobusawa & Sato, *J Virol*, 2006

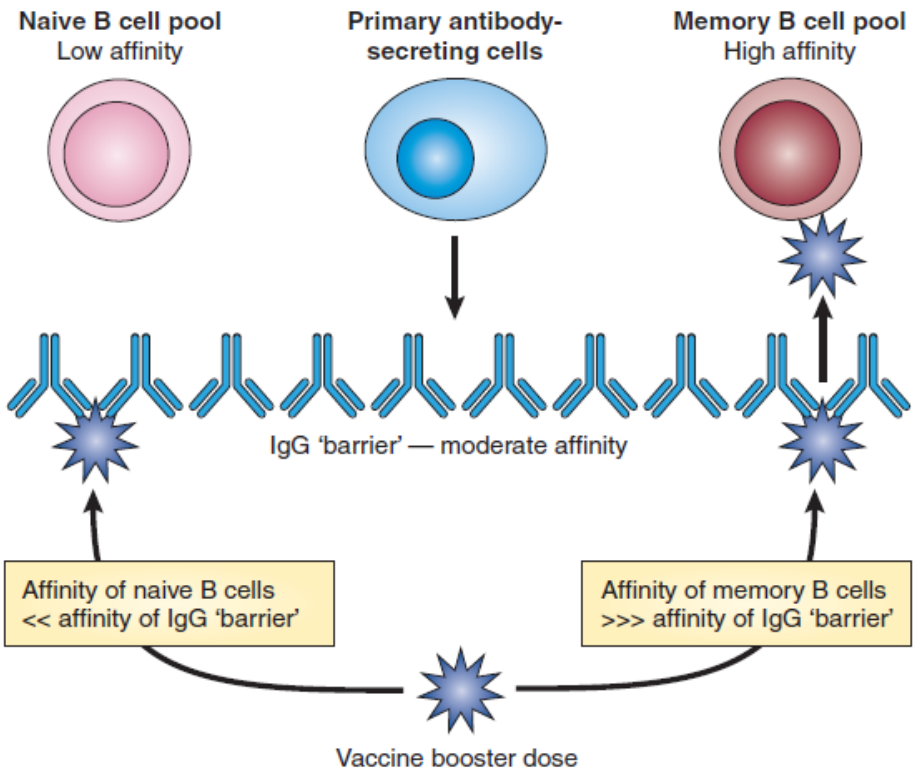
The global circulation patterns of seasonal influenza viruses vary with rates of virus evolution

India plays a critical role in the global circulation and evolution of seasonal influenza viruses

Strategies for selecting vaccine strains should vary by region for subtypes other than H3N2

The global circulation patterns of other pathogens could be driven by similar factors

Antigenic sin



Vaccine efficacy might be modulated by prior vaccination

"Original antigenic sin"

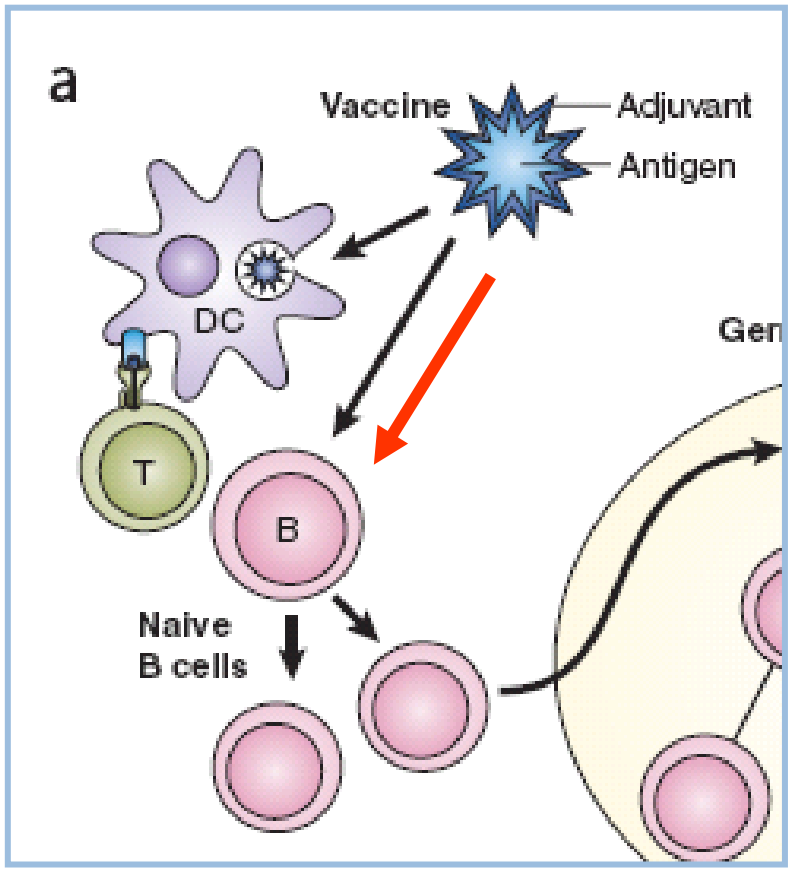
Cross-reactive epitopes preferentially reactivate high-affinity memory B-cells rather than lower affinity naive B-cells.

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.

Vaccines against bacterial polysaccharides

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



T-cell independent antigens
e.g. repetitive carbohydrates
crosslinking of B-cell receptors

⟶ Directly stimulate B-cells

⟶ IgM and IgG2 ab secreting cells

⟶ Inefficient ag-specific memory B cells

⟶ Inefficient in children <2 yrs

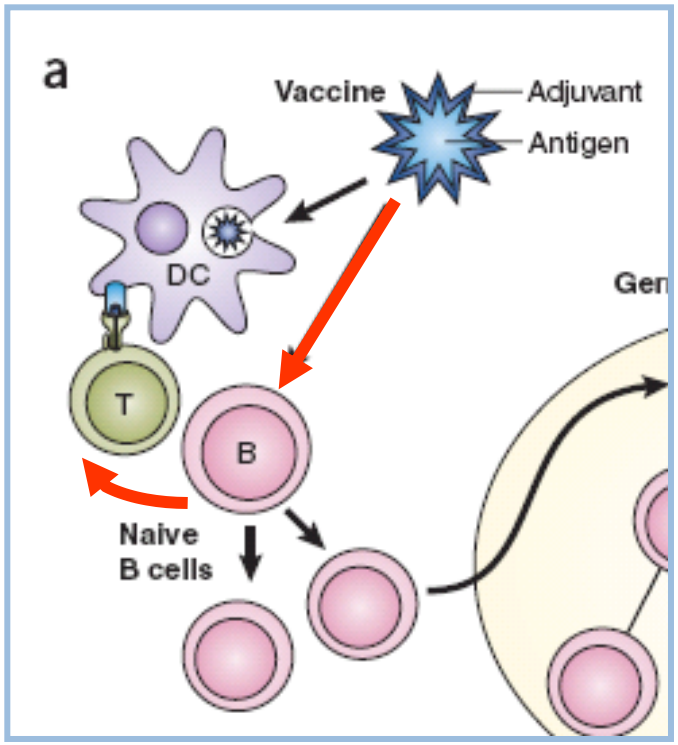
⟶ Inefficient in immunosuppressed

⟶ tolerance upon repeated doses?

⟶ PPV: Marginal zone depletion, mostly IgM and low affinity IgG2, extinction upon rechallenge (Birjandi SZ et al. 2011, Bradeur J, J. Immunol 1980)

Vaccines against bacterial polysaccharides

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



Conjugated vaccines

Polysaccharide – carrier protein

e.g. CMR_{197} mutated toxin C. diphtheria

⟶ T-cell dependent immune response

⟶ IgM and IgG2 ab secreting cells

⟶ Ag-specific memory B cells

⟶ Efficient in children <2 yrs

Specific B cell to recognize the polysaccharide antigen and endocytose the coupled antigen complex. Some of the resultant helper peptides are loaded onto MHC class II on the surface of the B cells and provide for a cognate interaction between the antigen-specific CD4+ helper T cell and B cell.

Herd immunity

= indirect protection of susceptibles by reduced circulation of pathogen

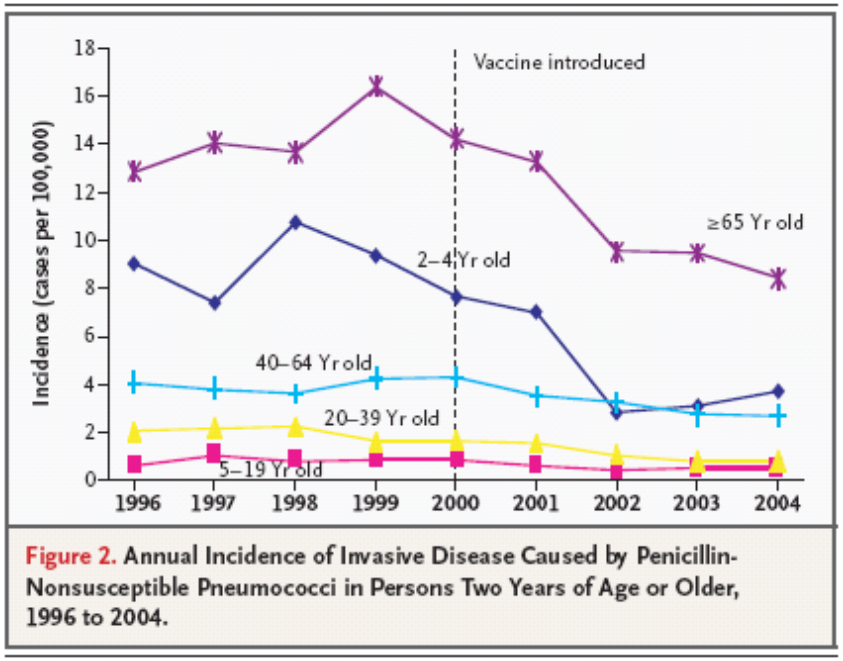
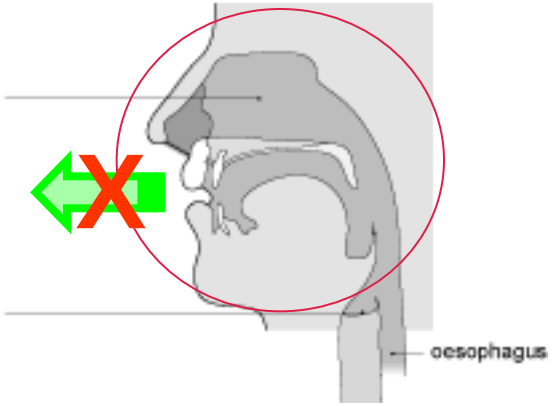


Figure 2. Annual Incidence of Invasive Disease Caused by Penicillin-Nonsusceptible Pneumococci in Persons Two Years of Age or Older, 1996 to 2004.

Conjugated pneumococcal polysaccharide vaccines

⟶ Reduce colonisation

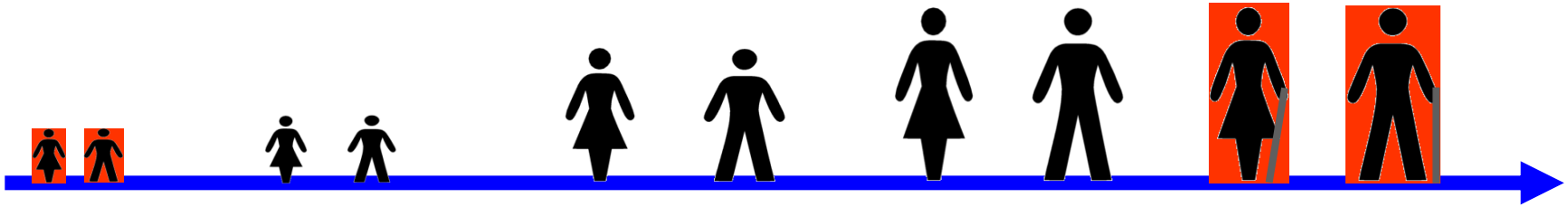
⟶ Reduce transmission



Vaccine was given to <2 yrs old!!

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?

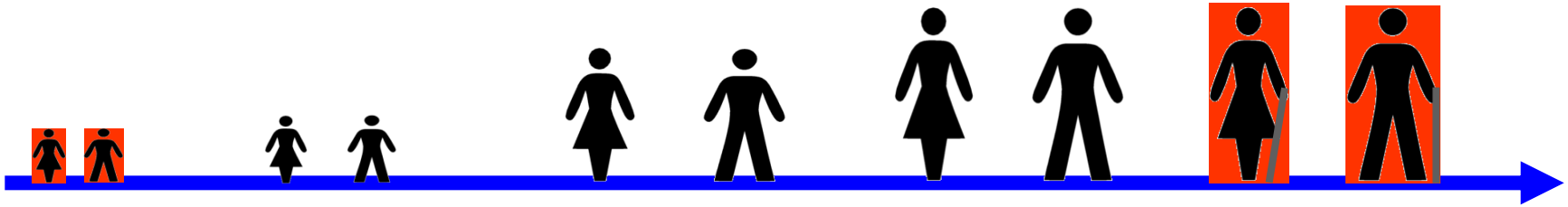
- Inhibition of live virus vaccines

- 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

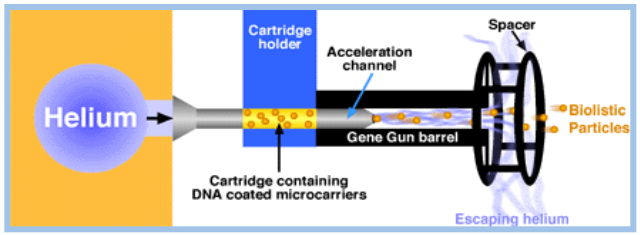
Evidence for the importance of T-cell response for vaccine immunity

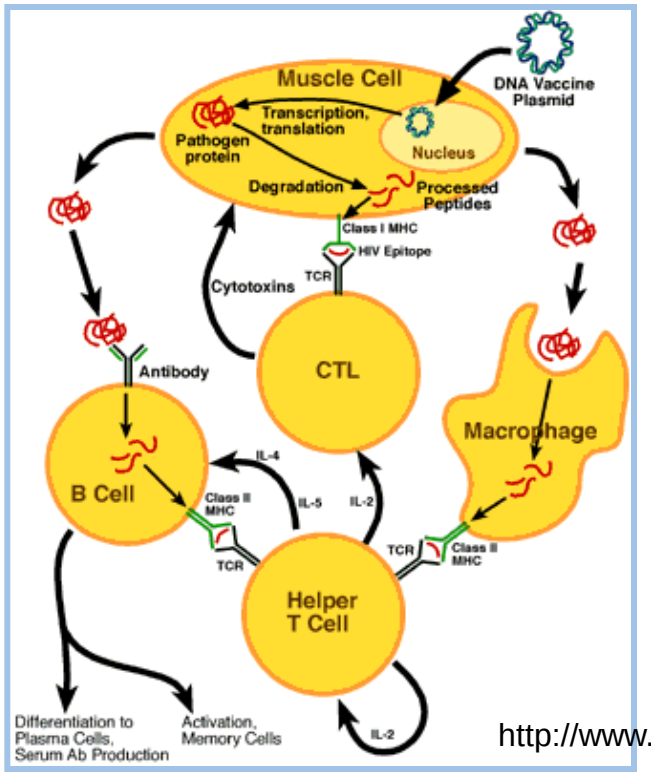
Table 2 Evidence for roles of vaccine-induced T-cell effectors against disease

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**

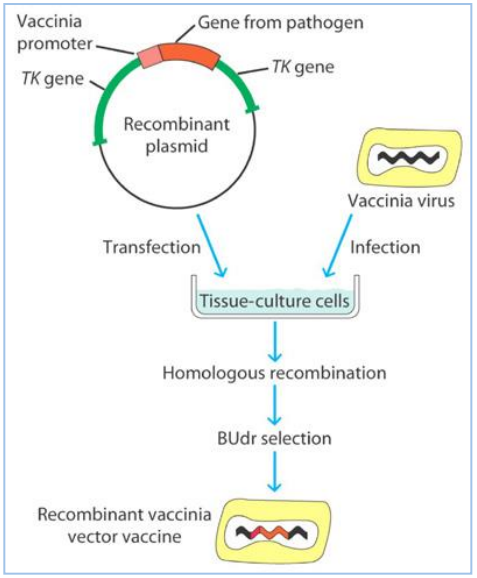
Current problems
- **Limited immunogenicity**
- **Various strategies for enhancement proposed**

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

Vector vaccines:
e.g. lactic acid bacilli, vaccinia virus

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

Example: vaccinia virus http://www.brown.edu/



Example: lactic acid bacilli

Product	Model	Application
DNA		Vaccines
Peptide		HIV-1, fusion inhibitors; colitis, trefoil peptides
ScFvs		Anti-infectives
Antigens		Vaccines
Cytokines		Inflammatory bowel disease and colitis, vaccine adjuvants
Enzymes		Therapy for colitis and enzyme deficiencies
Allergen		Therapy and prevention of allergy

Wells JM, Mercenier A. Nat Rev Microbiol 2008;6:349

Teaching goals – Vaccines

Apply the knowledge of immune response to microbes to vaccine

Appreciate the public health impact of vaccines

Know characteristics of a vaccine

Know different types of vaccines currently in use
their advantages and disadvantages

Know the impact of administration route of a vaccine

Know the important effectors of vaccine response

Know the importance of adjuvant / examples

Know the term herd immunity