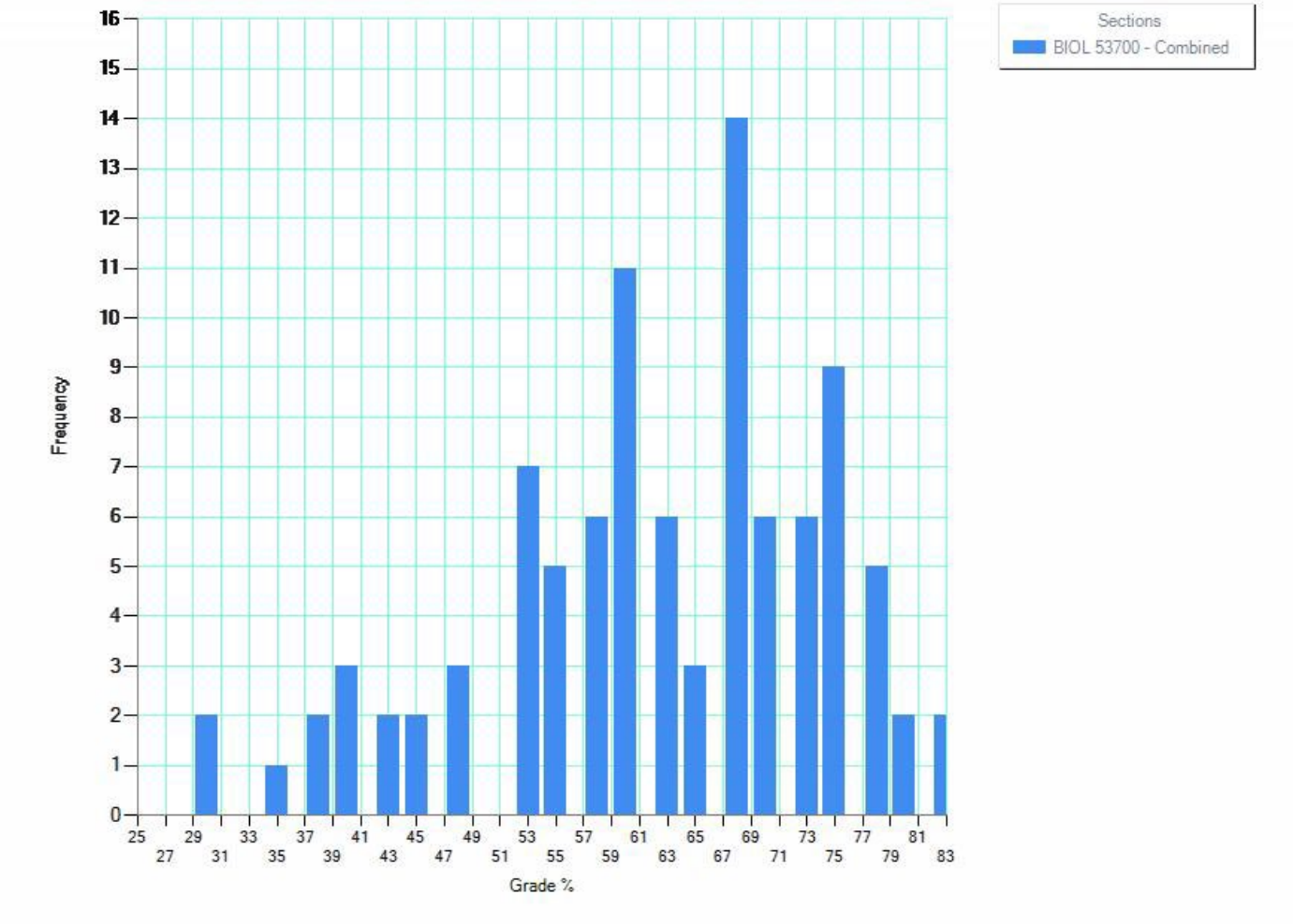
Exam 2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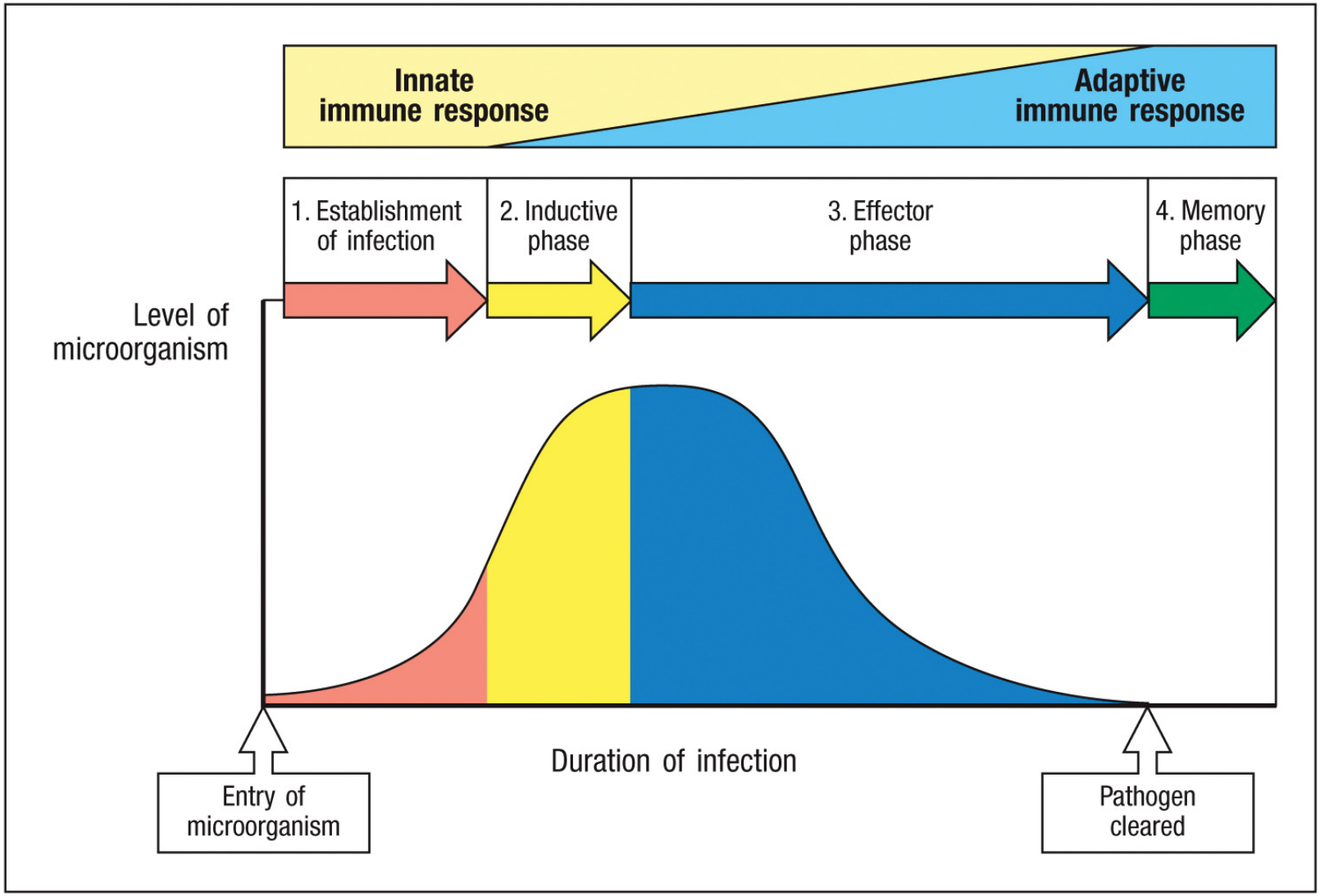
Outline

- Immunological memory

- Vaccines
  - Concepts
  - Methods
  - Challenges

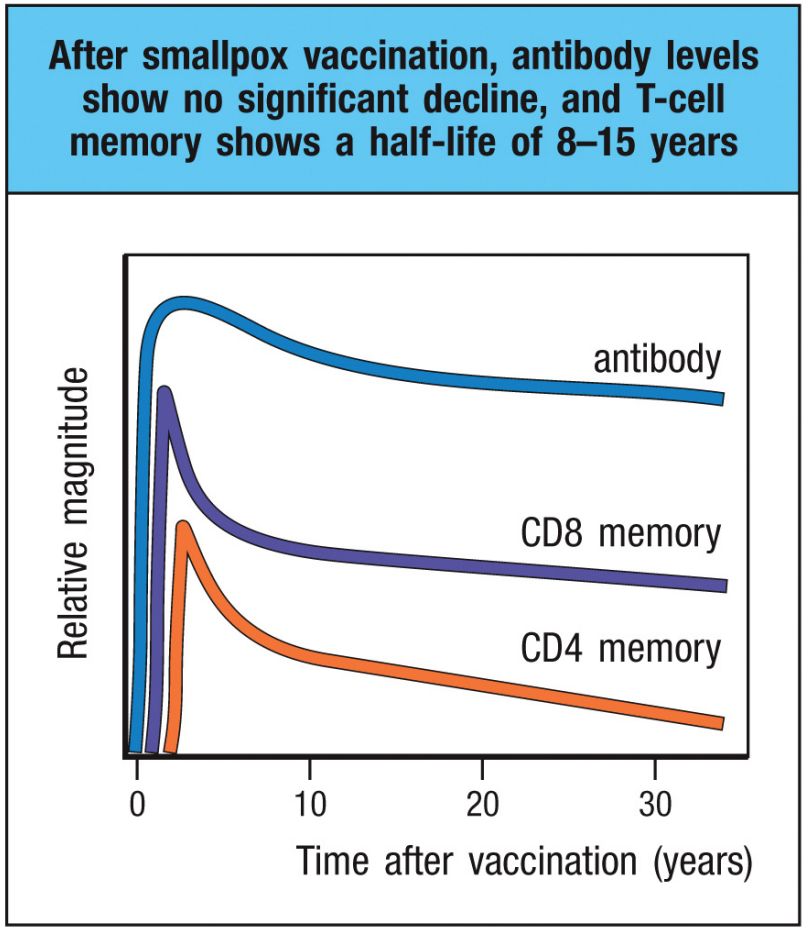
- Immune evasion
  - Antigenic variation (surface protein and receptors)
  - Latency

Immunological Memory

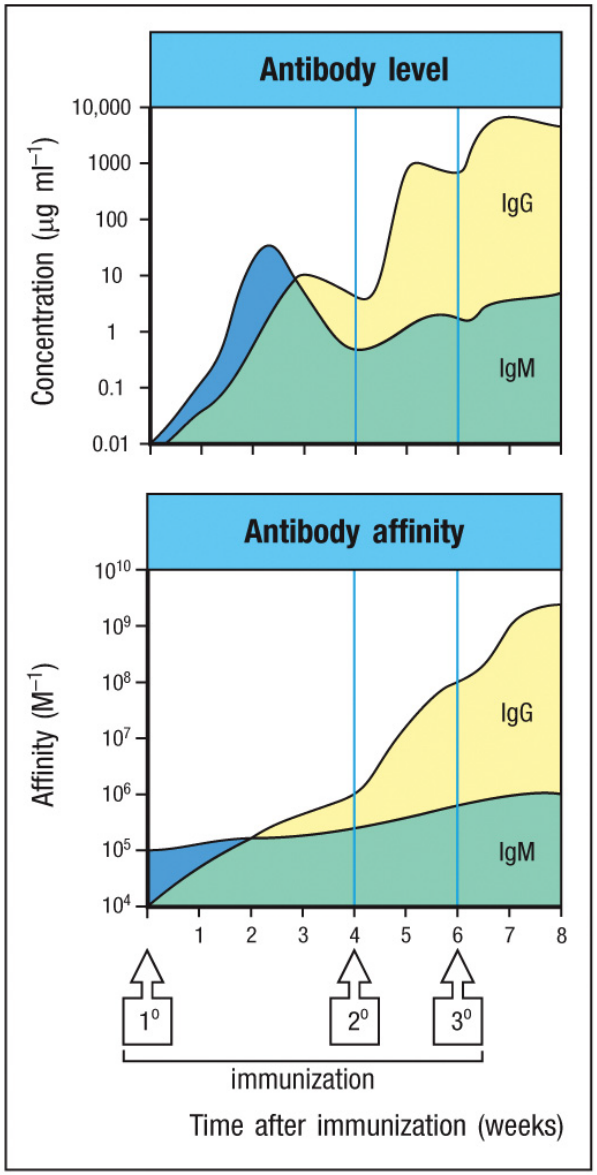


Immunological Memory

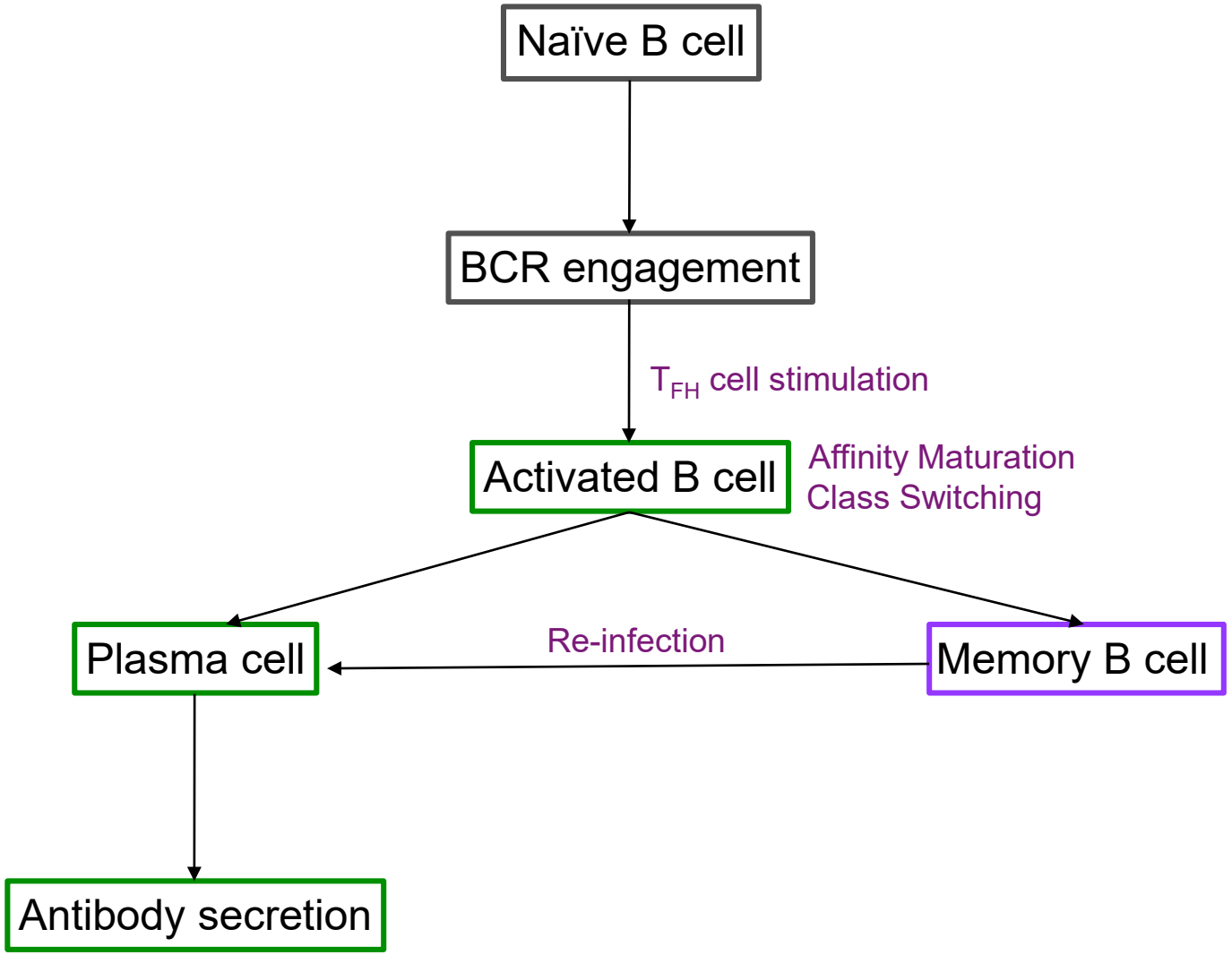
Long-term protection after initial exposure
Specialized memory cells:
Induced during adaptive immune response
Persist in the absence of original antigen



Repeated Immunization Increase Concentration and Affinity of Antibodies



B Lymphocyte Differentiation



Secondary Immune Response

Memory cells are more efficiently activated than naïve cells:
Higher CXCL13 Receptors
Higher Affinity of BCR
Higher Surface level of MHC II

	Source of B cells	
	Unimmunized donor Primary response	Immunized donor Secondary response
Frequency of antigen-specific B cells	$1:10^4$ to $1:10^5$	$1:10^2$ to $1:10^3$
Isotype of antibody produced	IgM > IgG	IgG, IgA
Affinity of antibody	Low	High
Somatic hypermutation	Low	High

Increased Survival of Memory B Cells

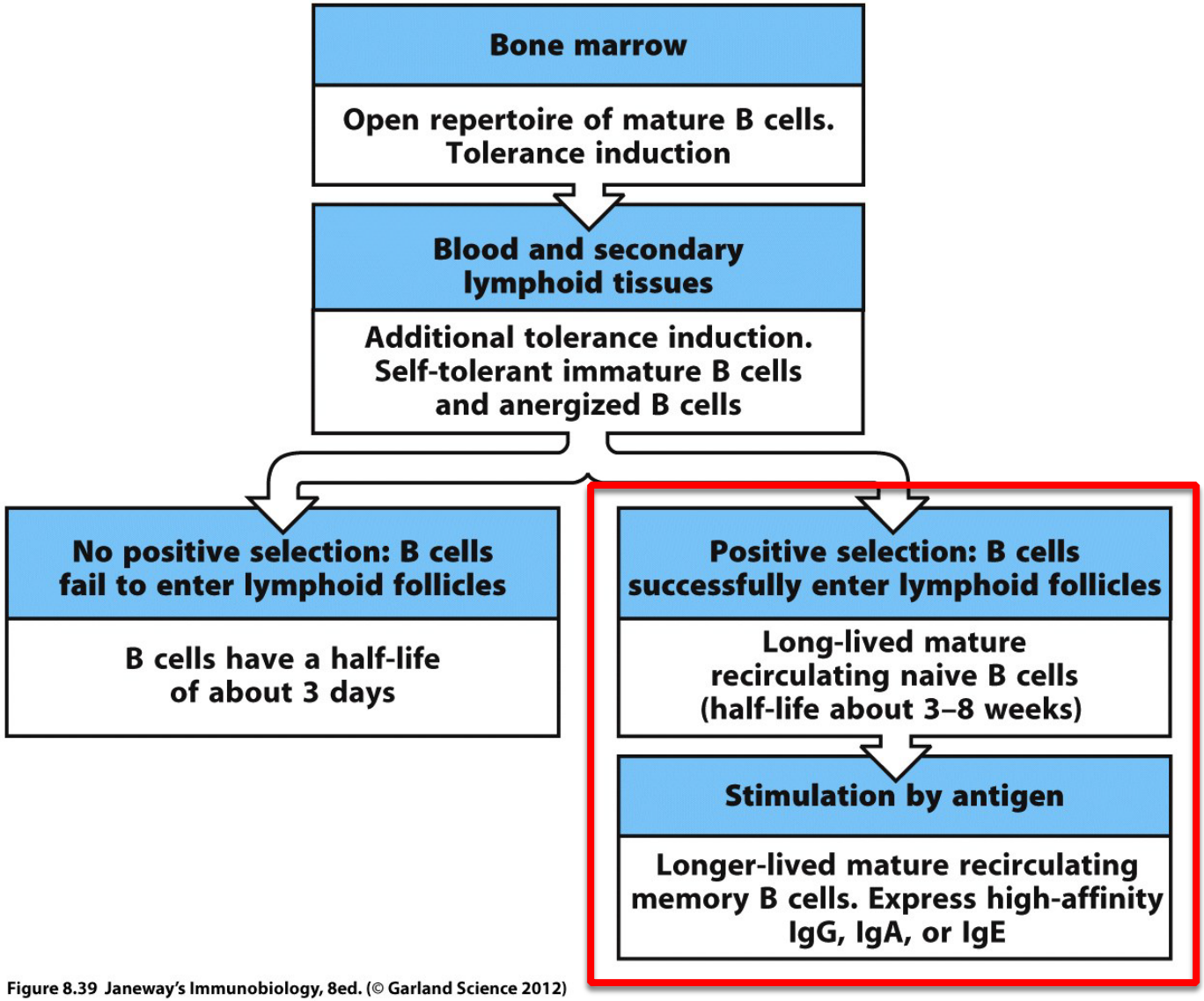
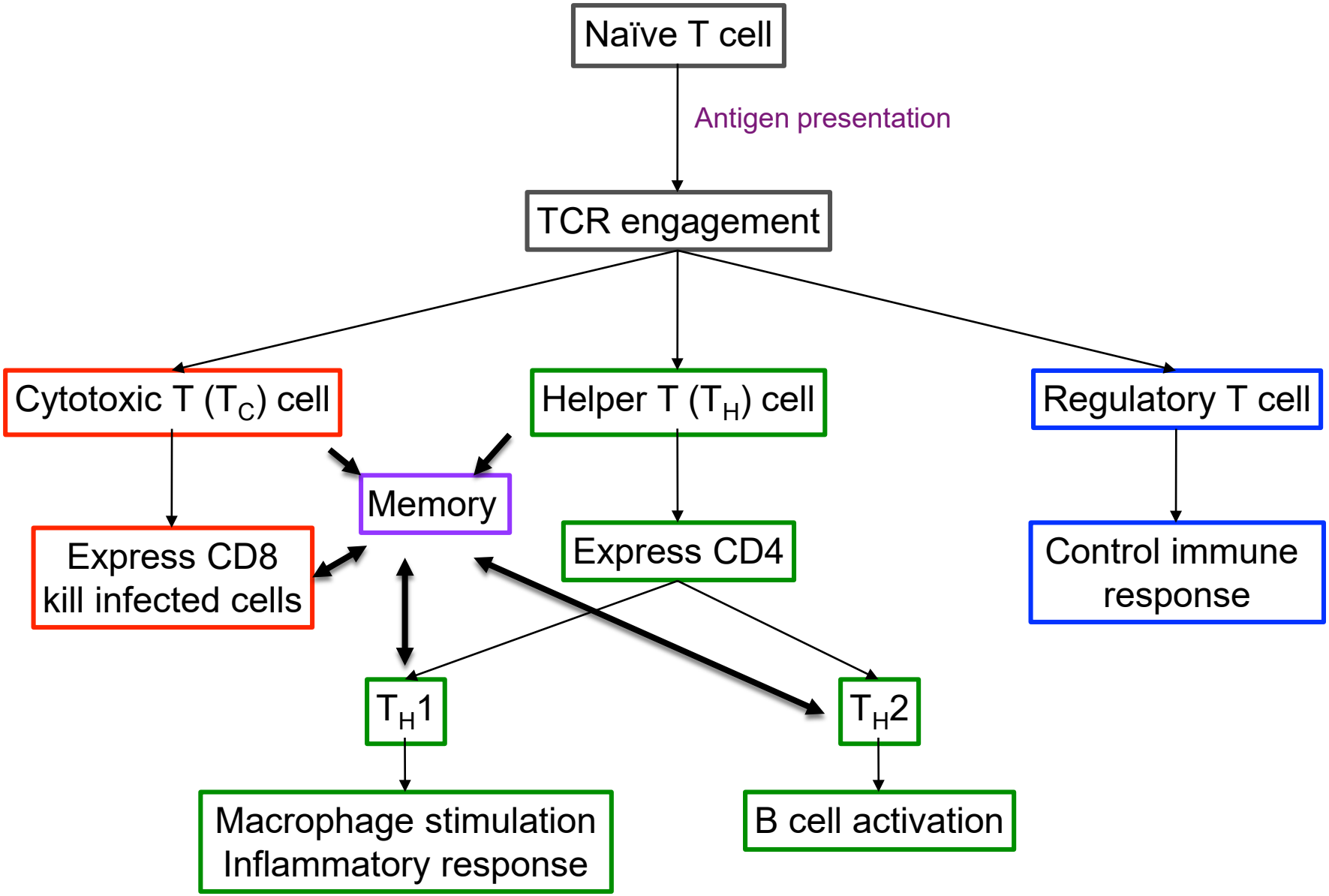


Figure 8.39 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

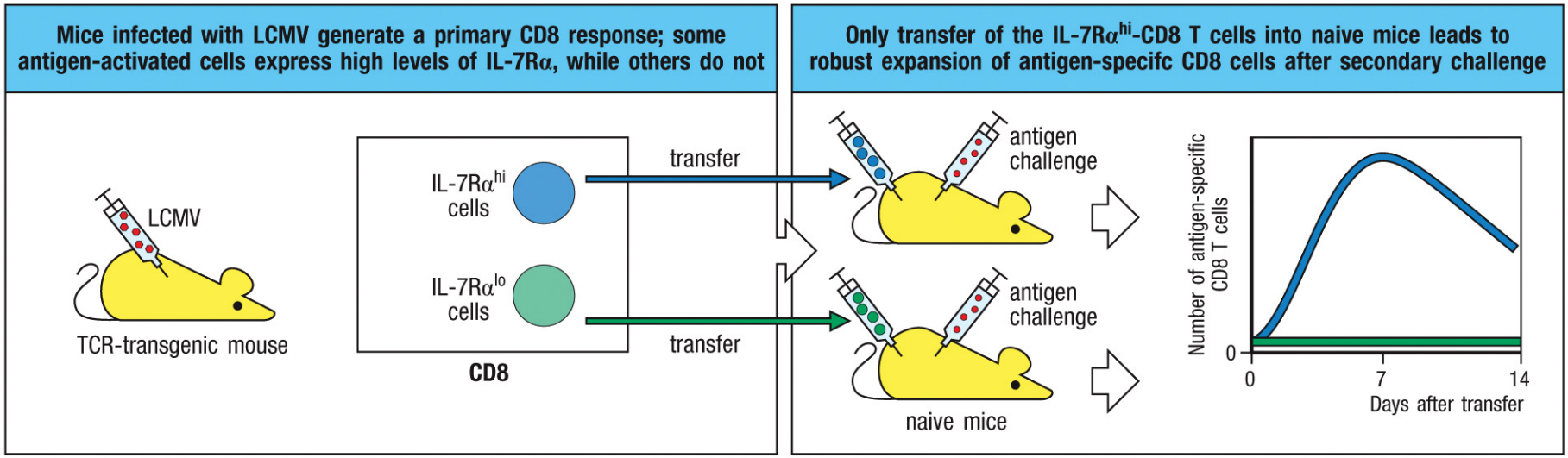
Question

- Why is antibody response in a secondary infection more robust than the initial one?

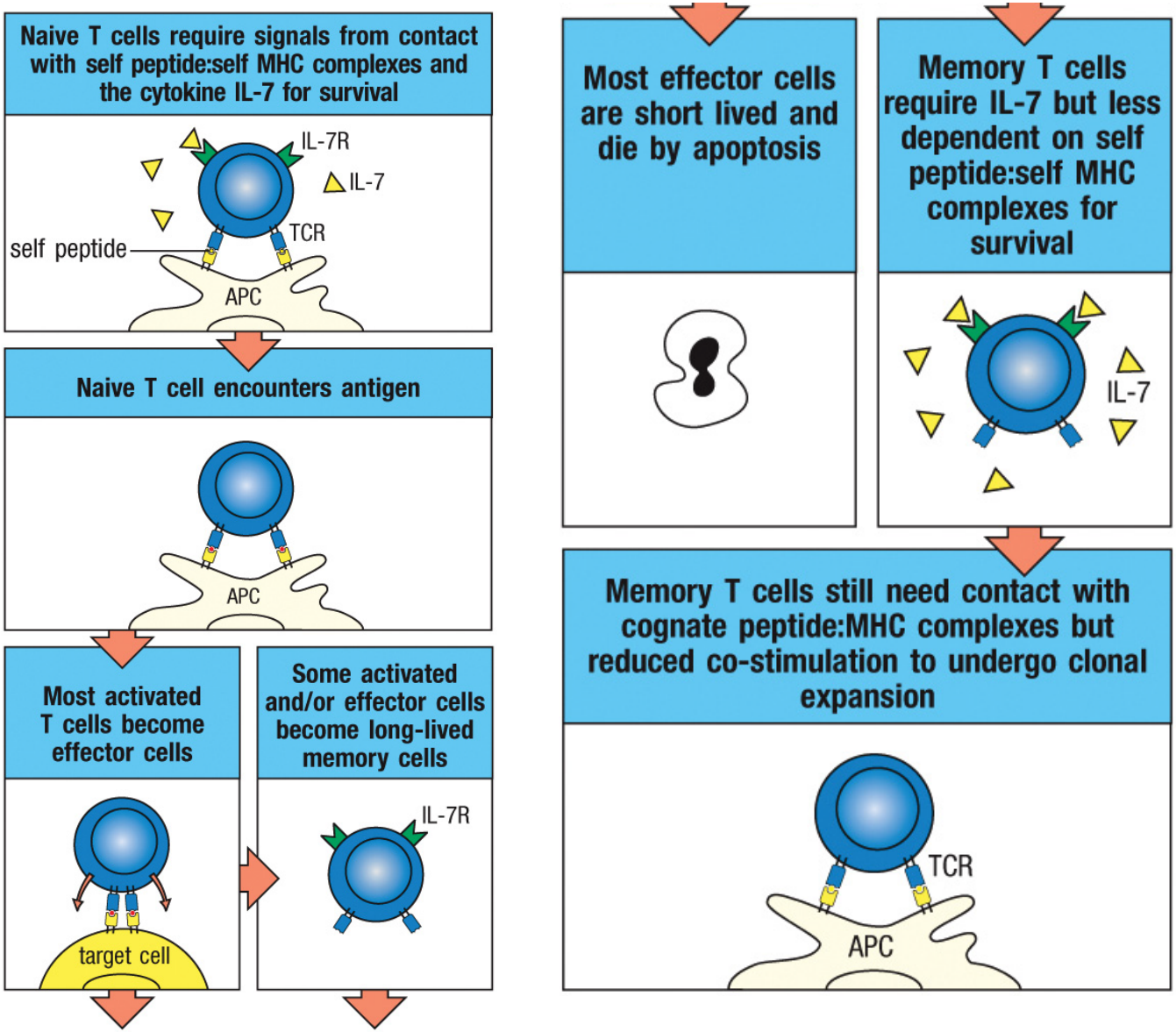
T Lymphocyte Differentiation



Memory T cells arise from effector T cells that maintain sensitivity to IL-7 or IL-15



Memory and Naive T cells



Memory T Cells are Distinct from Effector T Cells

Homing

Homing

Survival

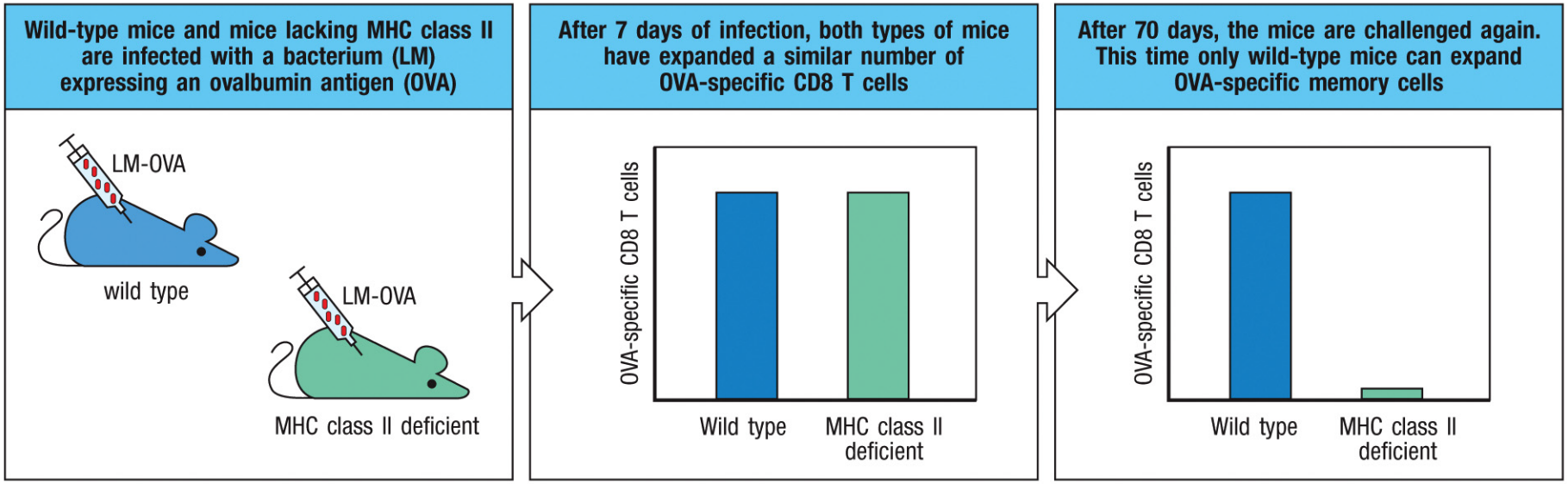
Immune response

Survival

Protein	Naive	Effector	Memory	Comments
CD44	+	+++	+++	Cell-adhesion molecule
CD45RO	+	+++	+++	Modulates T-cell receptor signaling
CD45RA	+++	+	+++	Modulates T-cell receptor signaling
CD62L	+++	–	Some +++	Receptor for homing to lymph node
CCR7	+++	+/–	Some +++	Chemokine receptor for homing to lymph node
CD69	–	+++	–	Early activation antigen
Bcl-2	++	+/–	+++	Promotes cell survival
Interferon-γ	–	+++	+++	Effector cytokine; mRNA present and protein made on activation
Granzyme B	–	+++	+/–	Effector molecule in cell killing
FasL	–	+++	+	Effector molecule in cell killing
CD122	+/–	++	++	Part of receptor for IL-15 and IL-2
CD25	–	++	–	Part of receptor for IL-2
CD127	++	–	+++	Part of receptor for IL-7
Ly6C	+	+++	+++	GPI-linked protein
CXCR4	+	+	++	Receptor for chemokine CXCL12; controls tissue migration
CCR5	+/–	++	Some +++	Receptor for chemokines CCL3 and CCL4; tissue migration
KLRG1	–	+++	Some +++	Cell surface receptor

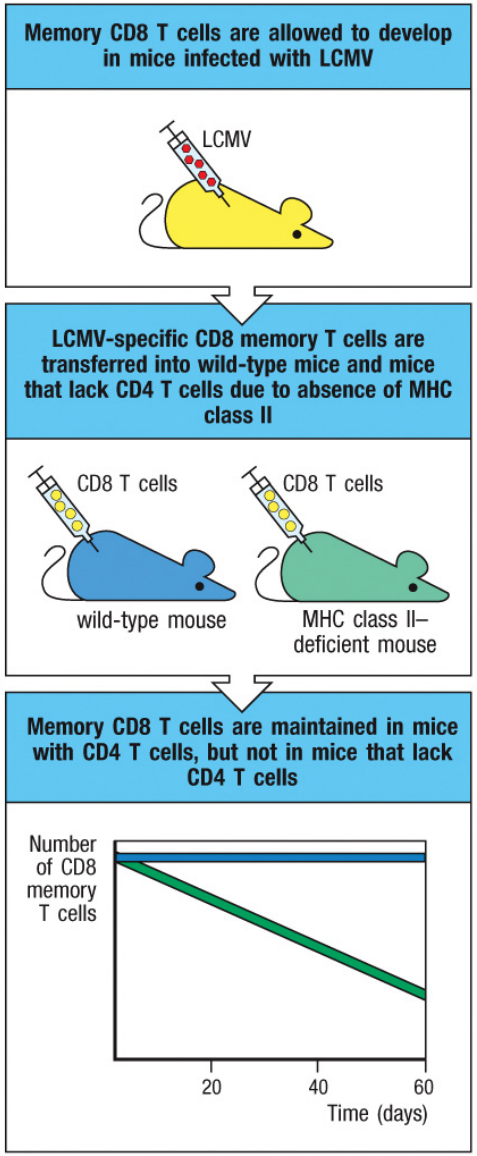
Figure 11.27 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

CD4 T-Cell Help Is Required for the Development of CD8 Memory

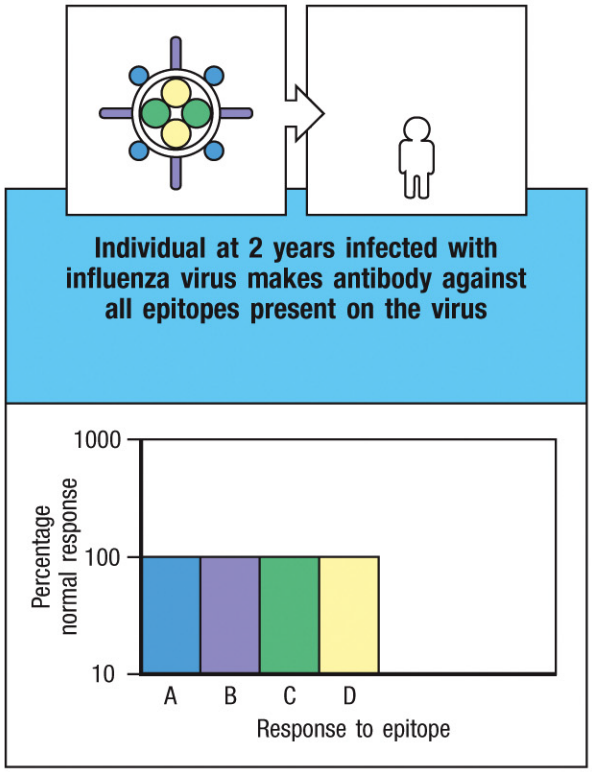


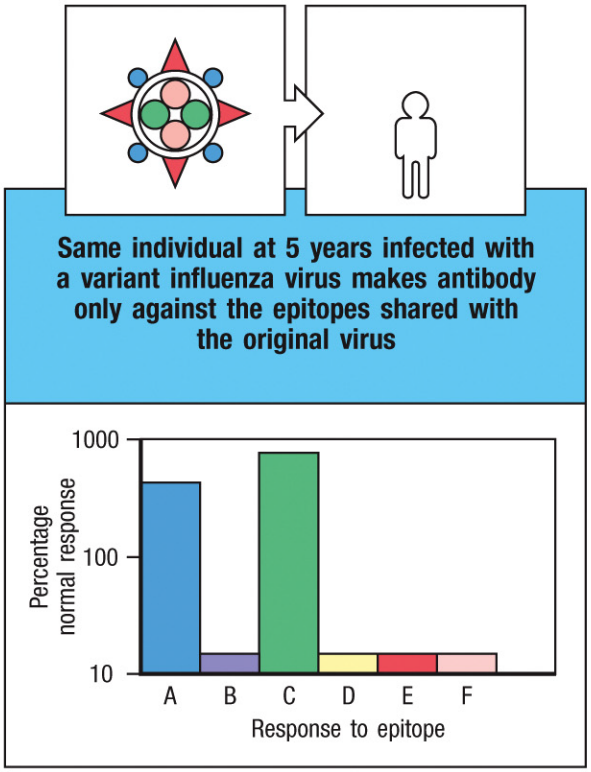
Primes effector T cells to generate CD8 memory cells
Promote reactivation of CD8 memory cells
Maintain CD8 memory cell numbers

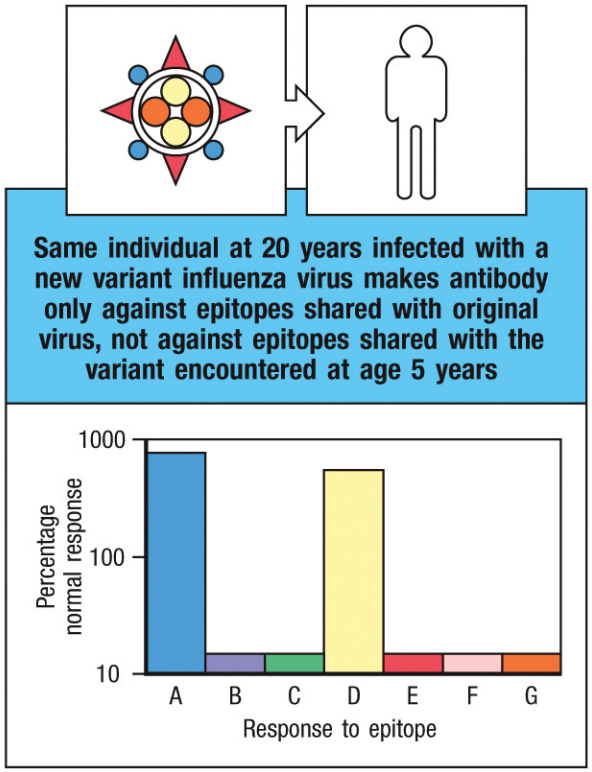
CD4 T cells maintain CD8 Memory Cells



Original Antigenic Sin







Outline

- Immunological memory

- Vaccines
  - Concepts
  - Methods
  - Challenges

- Immune evasion
  - Antigenic variation
  - Latency

Concepts

Features of effective vaccines	
Safe	Vaccine must not itself cause illness or death
Protective	Vaccine must protect against illness resulting from exposure to live pathogen
Gives sustained protection	Protection against illness must last for several years
Induces neutralizing antibody	Some pathogens (such as polio virus) infect cells that cannot be replaced (e.g., neurons). Neutralizing antibody is essential to prevent infection of such cells
Induces protective T cells	Some pathogens, particularly intracellular, are more effectively dealt with by cell-mediated responses
Practical considerations	Low cost per dose Biological stability Ease of administration Few side-effects
Perceived as safe	The perception of whether a vaccine is safe will influence the adoption by the public

Immune compromised population

In a large percentage of vaccinated population

Effective memory cells: B and T cell activation

Very successful in controlling certain infections
Toxins, extracellular pathogens, viral reinfection

Problem: elicit an effective T response

Large vaccinated population will decrease the circulation of the pathogens

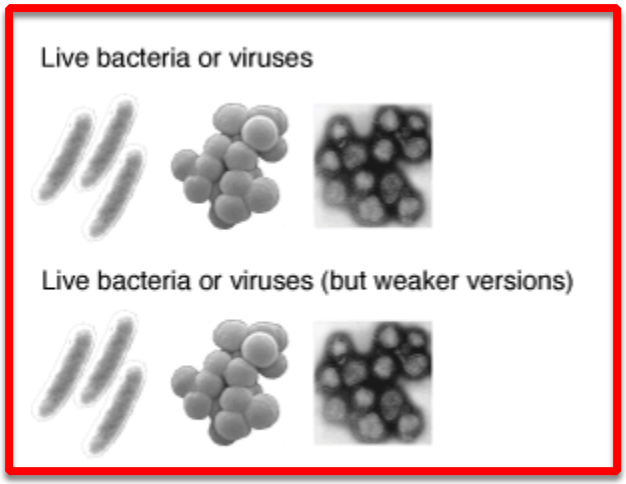
Public concerns

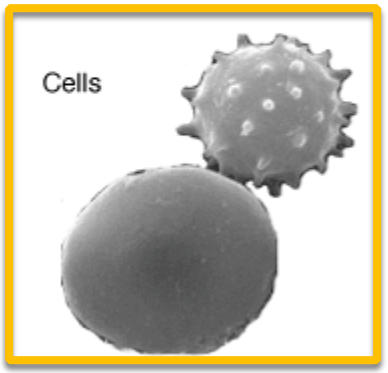
Public Concerns

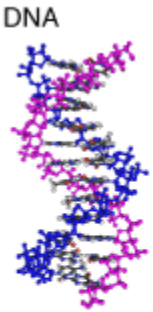
Measles Resurgent

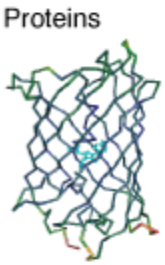
Methods

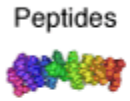
Top choice: Elicit Proper Immune response
Safety issue

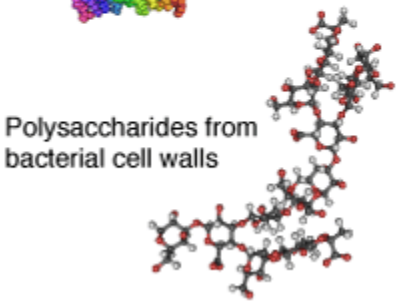












Others: Safer but harder

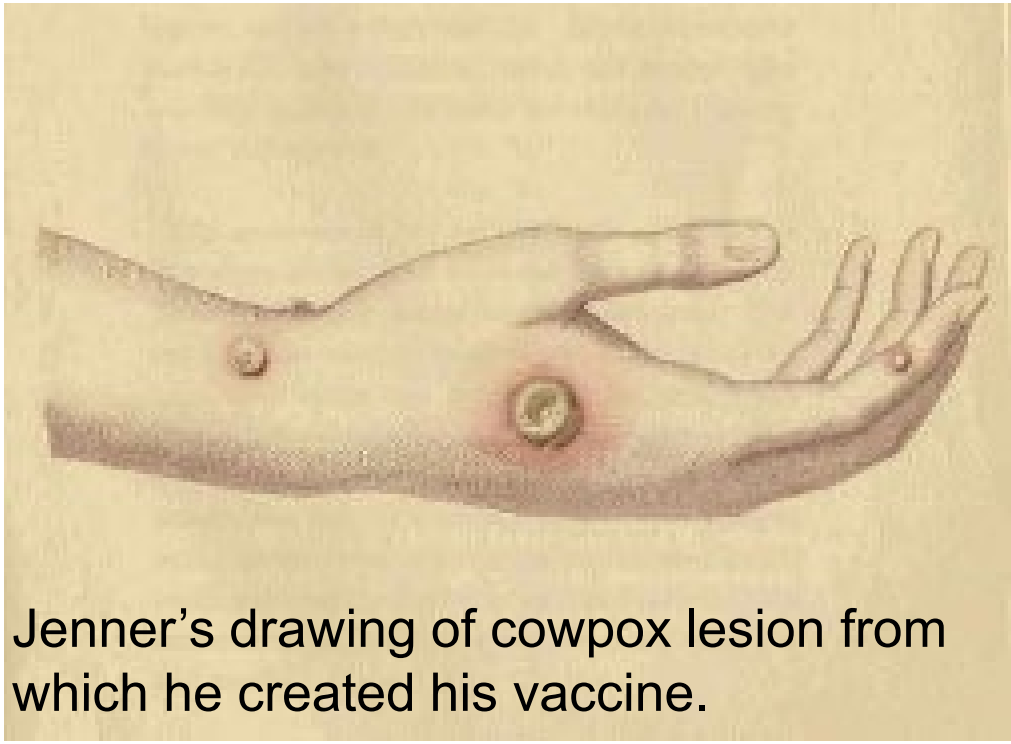
- **Prime Dendritic cells (Inflammation)**
  Avoid Tolerance
- **Induce proper response (Antigen Presentation)**
  CD8 or CD4 activation
  Most vaccines induce CD4 and antibody response
- **Mucosal or Systemic**

Direct loading of Dendritic Cells

Immunology Began with Immunization

1796 Edward Jenner **cowpox vaccine against smallpox**

Figure 1-1 Immunobiology, 7ed. (© Garland Science 2008)



Jenner's drawing of cowpox lesion from which he created his vaccine.

Shared Antigenic Elements In Vaccination

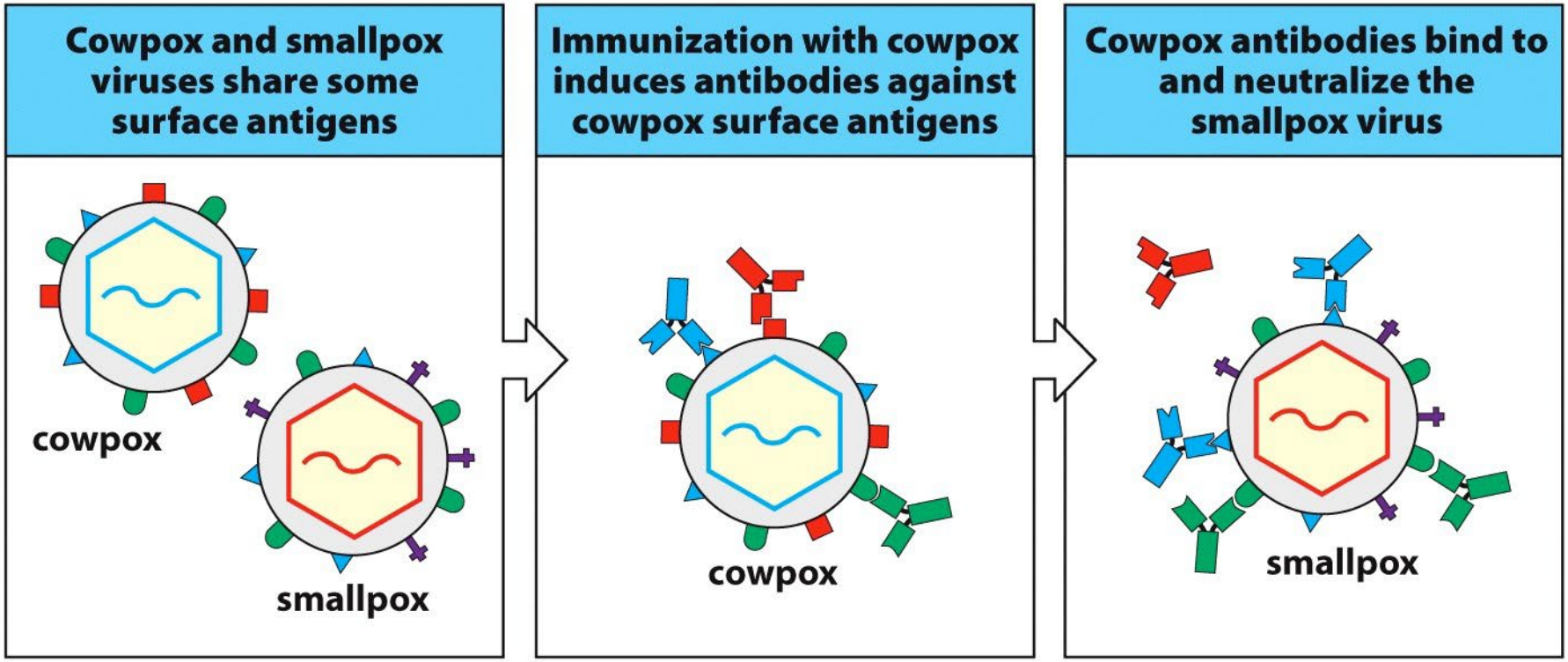
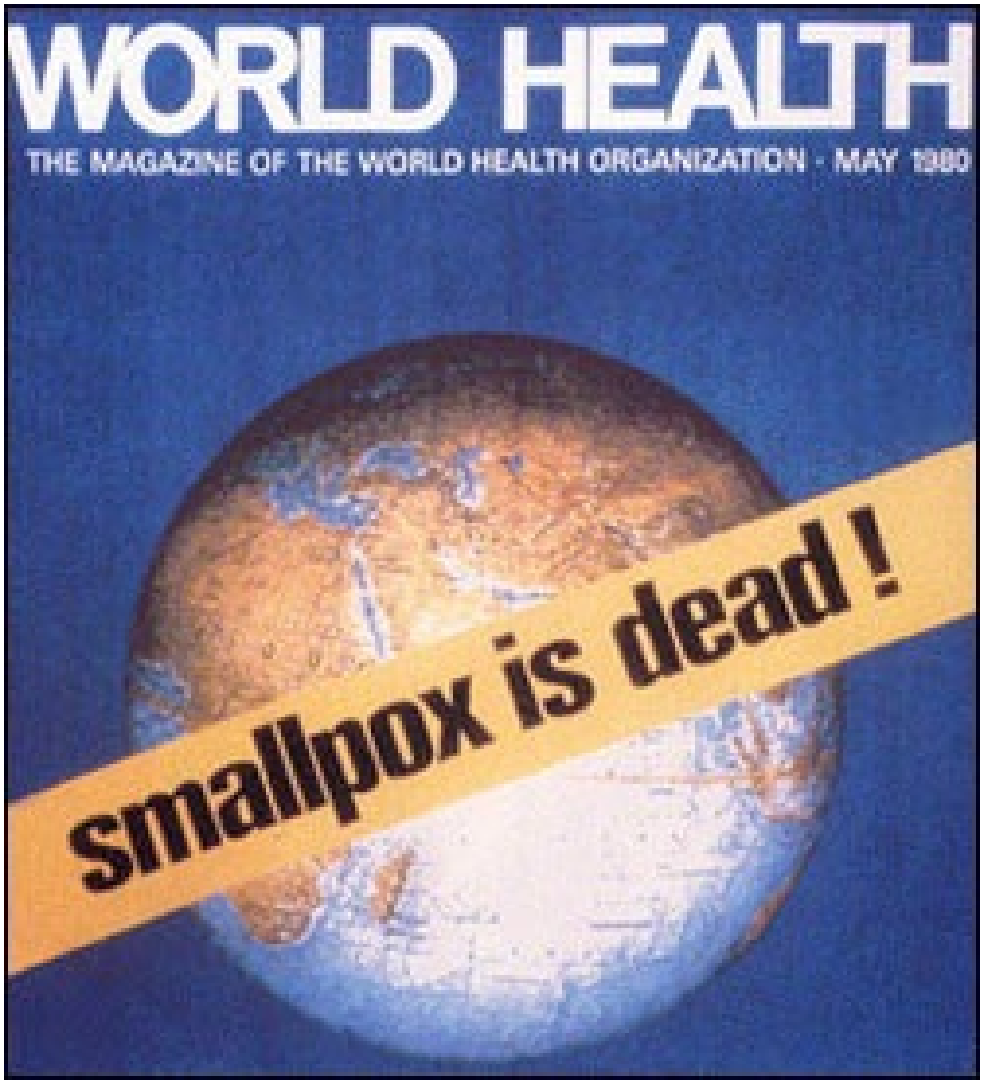


Figure 14.1 The Immune System, 3ed. (© Garland Science 2009)

Complete Eradication of Smallpox Was Announced in 1980



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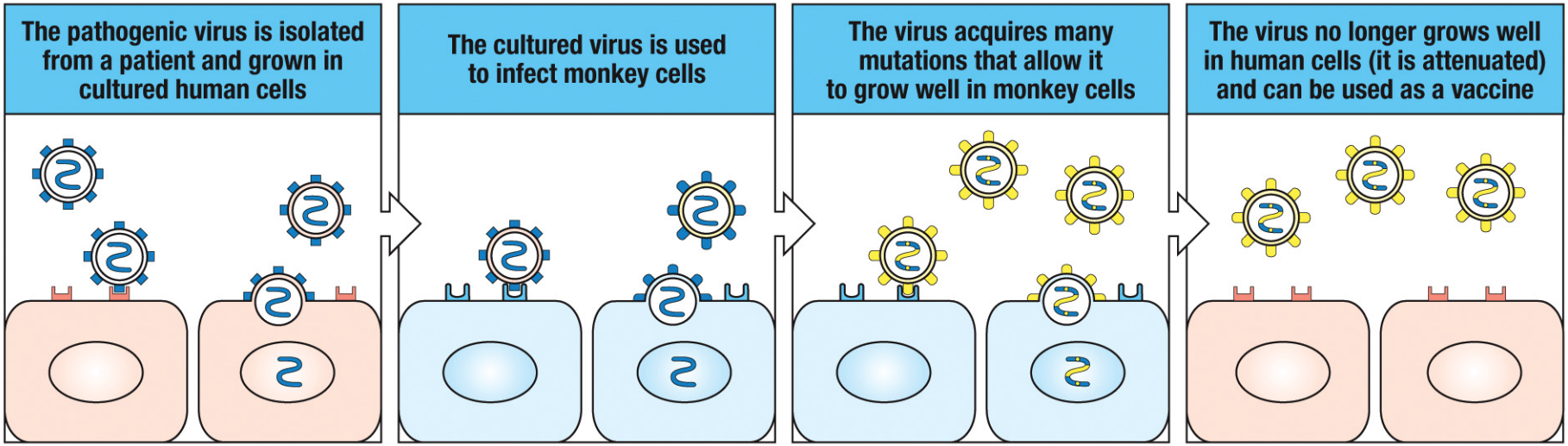
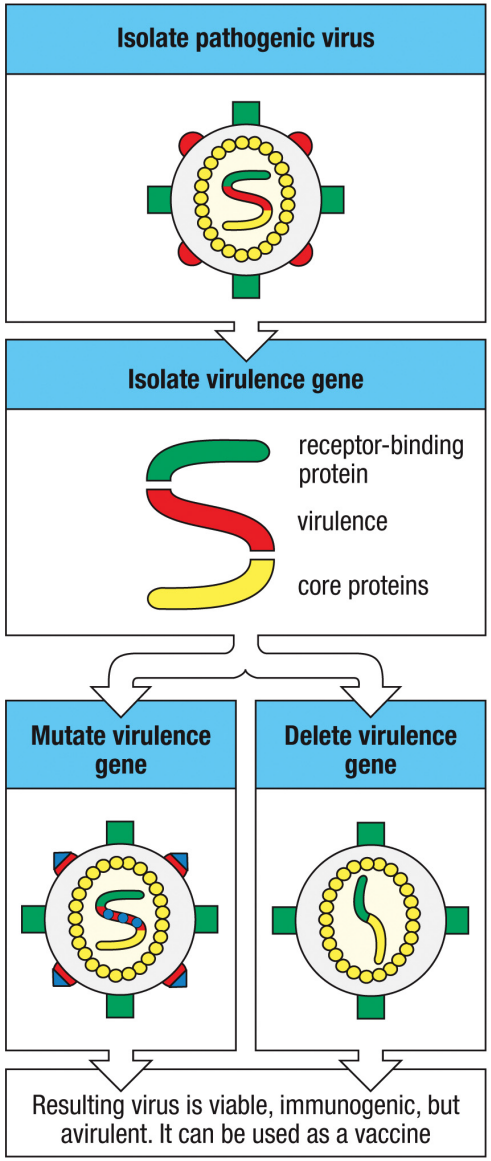
Attenuated Vaccine

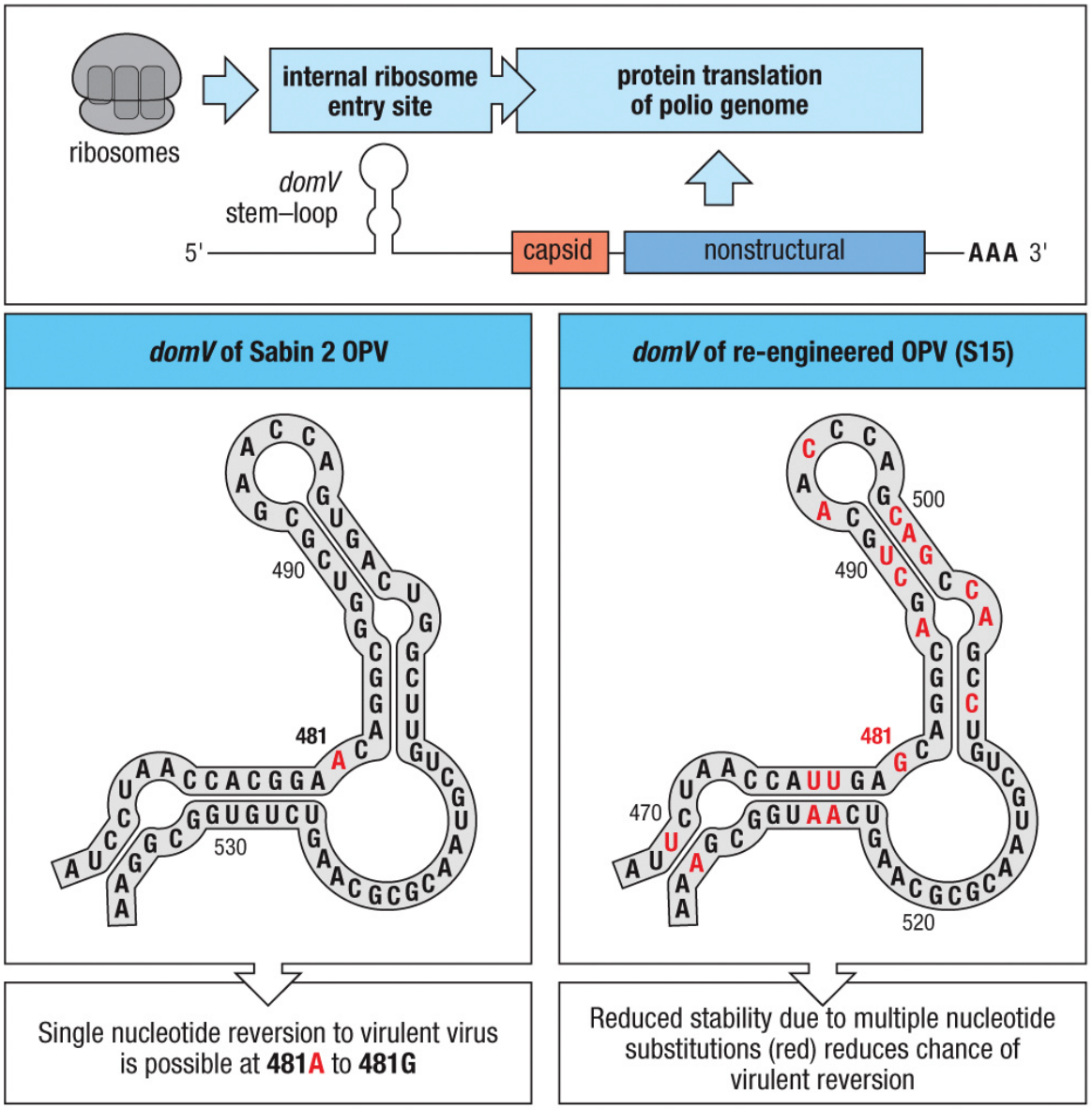


Risks:
loose the mutations causing attenuation
Cause very strong inflammation

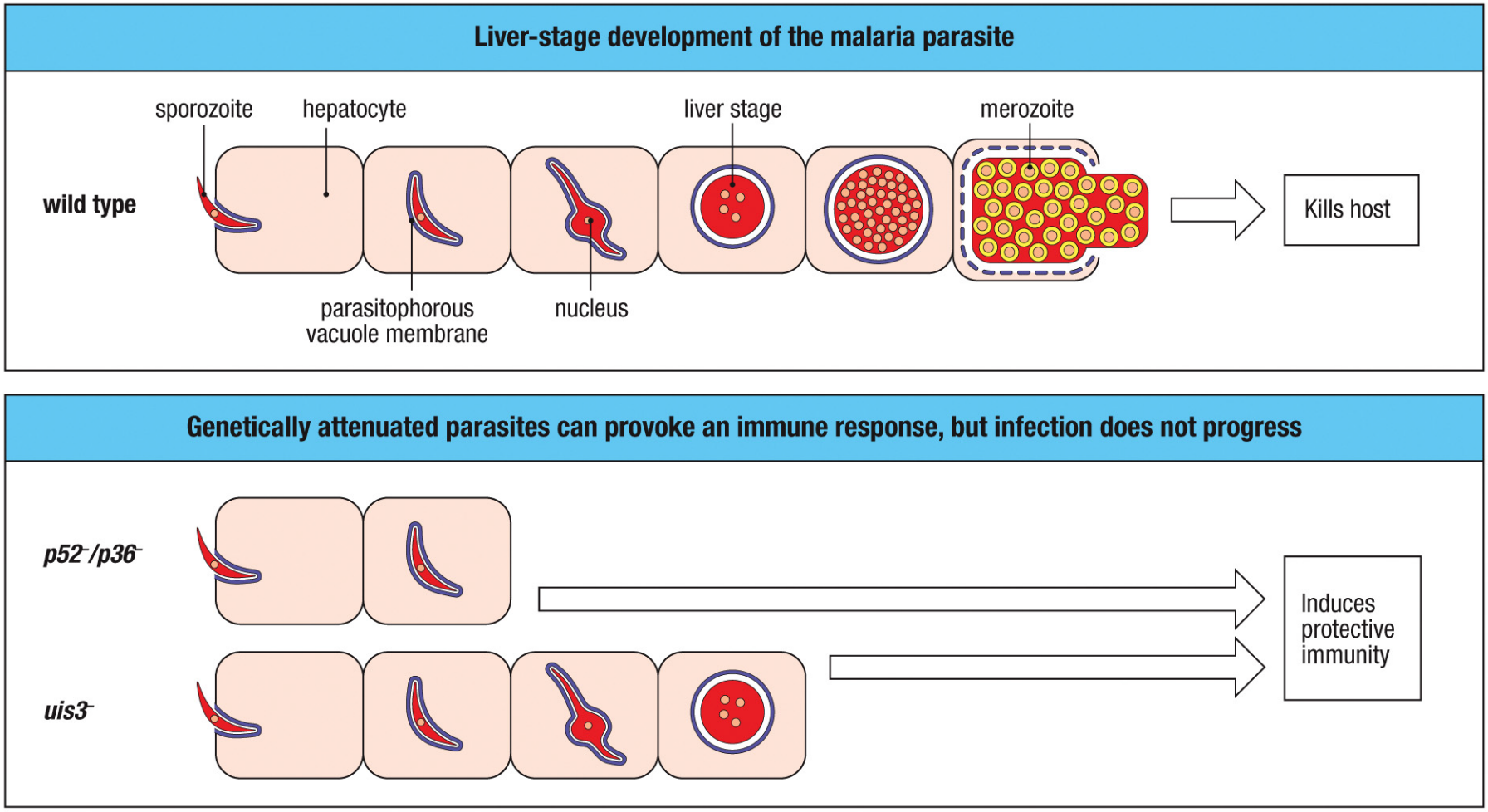
Attenuation Through Recombinant DNA Techniques Create Avirulent, Non-Pathogenic Virus



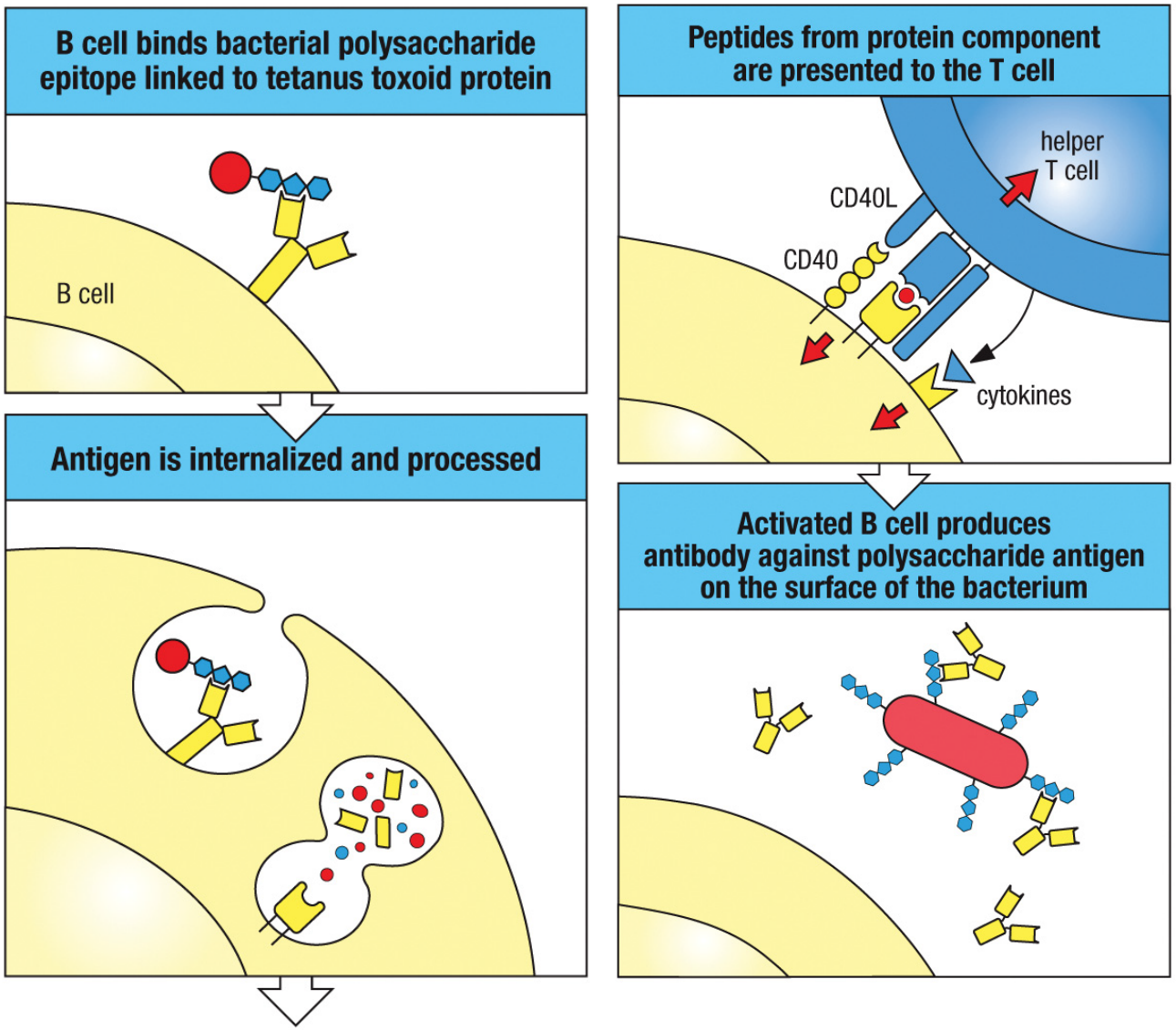
Attenuation Through Recombinant DNA Techniques



Attenuation Through Recombinant DNA Techniques

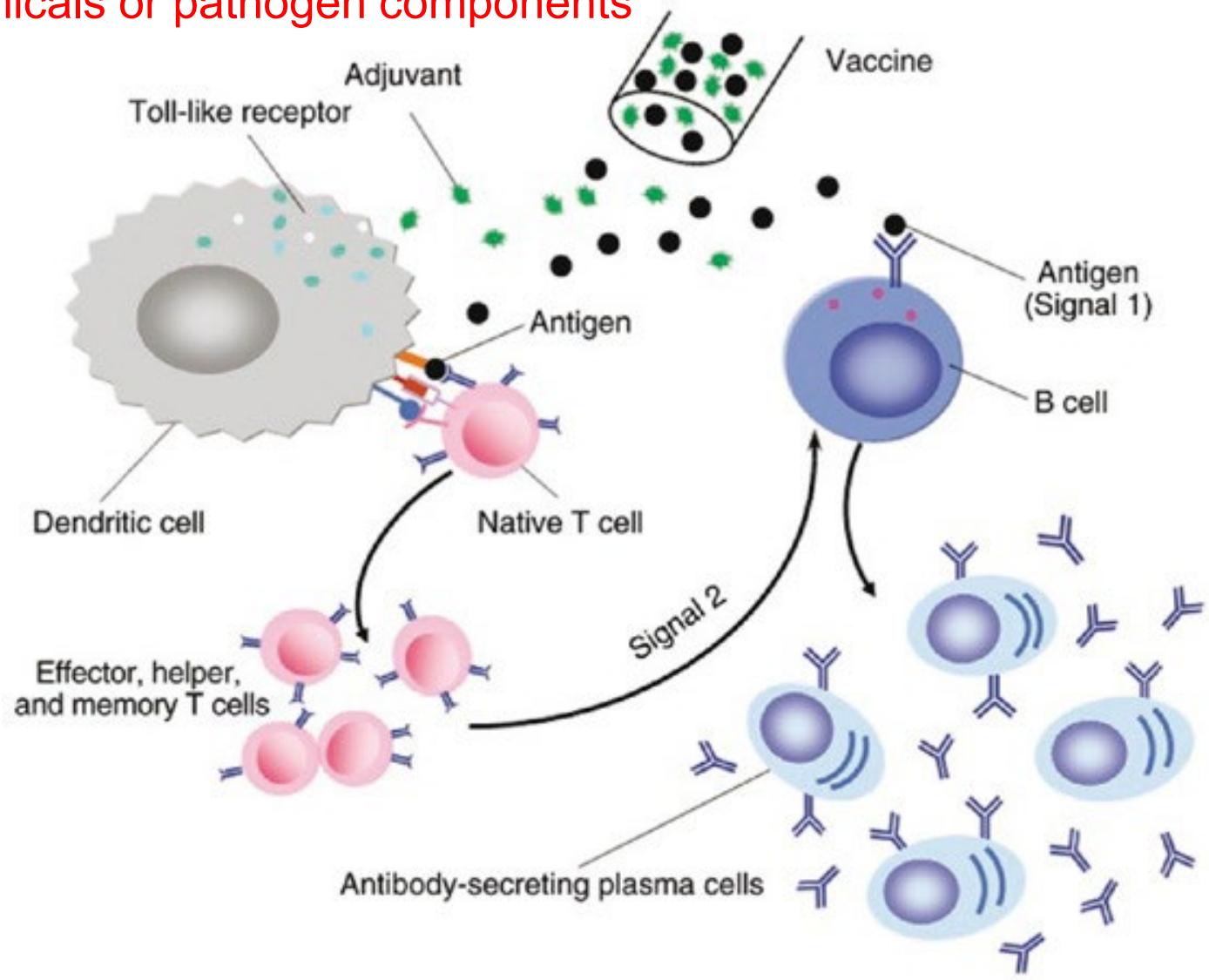


Conjugate Vaccines



Adjuvants are Required for Conjugate Vaccines

Chemicals or pathogen components

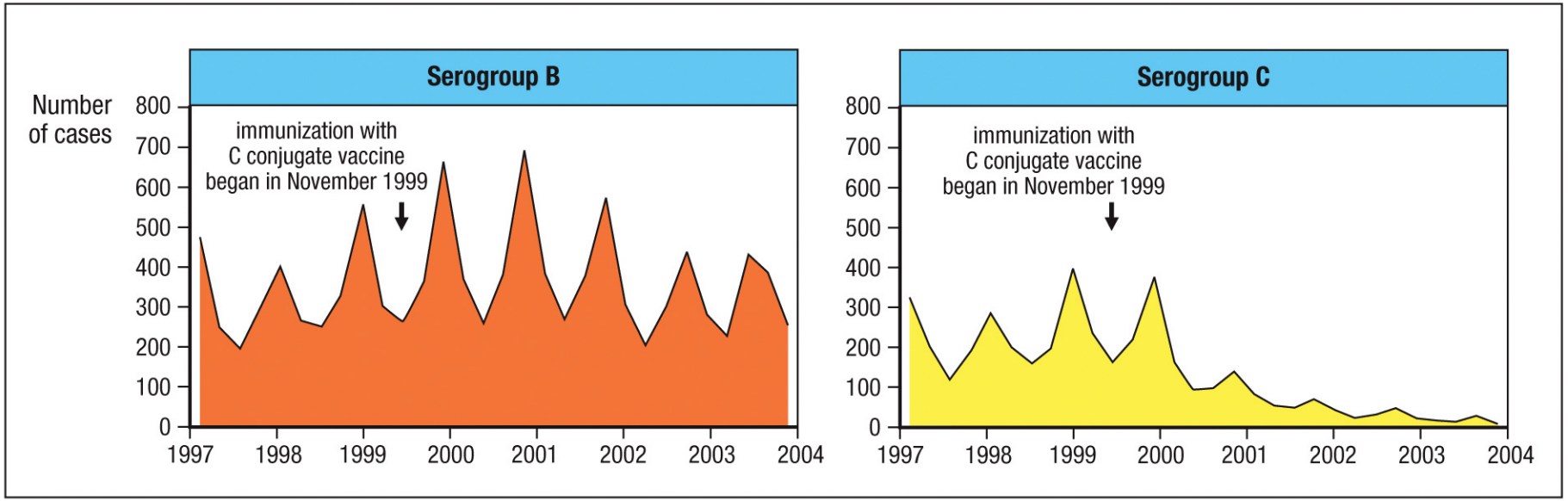


http://www.nature.com/ki/journal/v73/n7/images/ki200857f1.jpg

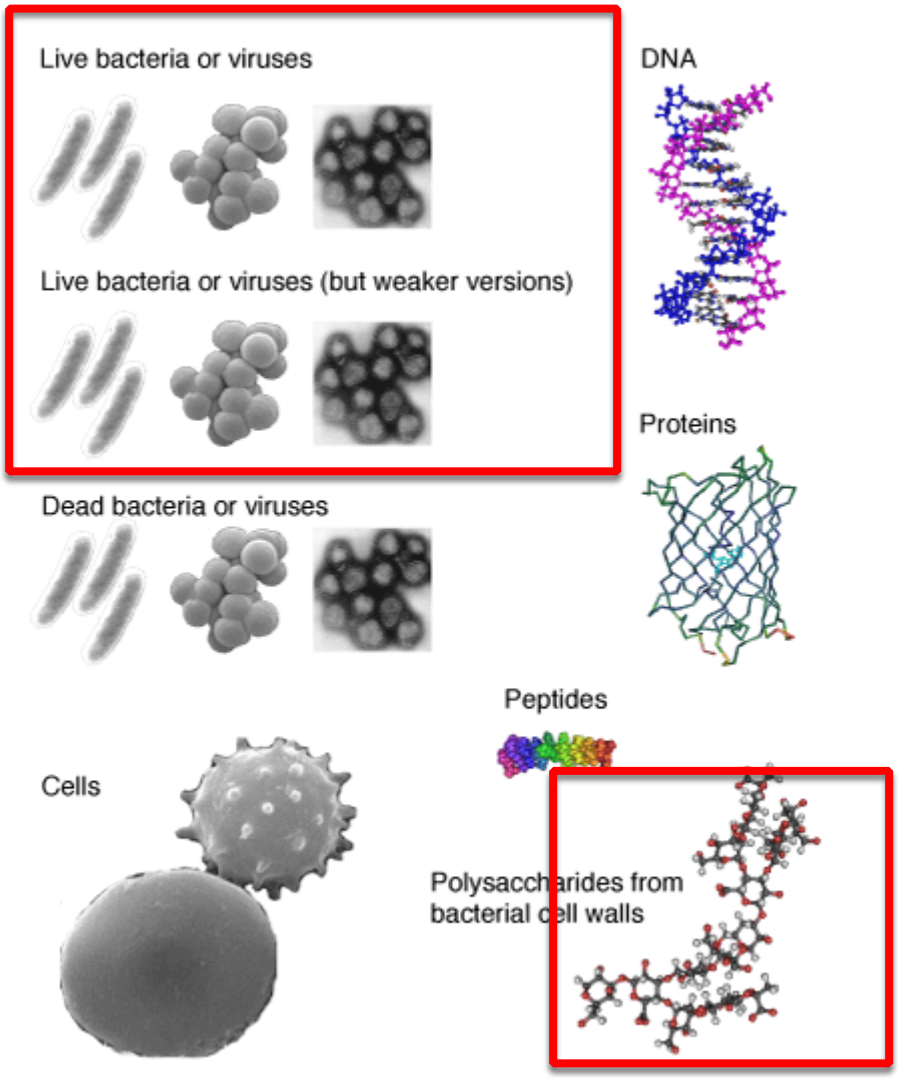
Adjuvants

Adjuvants used in FDA-approved vaccines	
Adjuvant	**Vaccine**
Alum (various aluminum salts)	Diphtheria/tetanus/ whooping cough Pneumococcal conjugate vaccine
Aluminum hydroxide	Cervarix
D,L-alpha-tocopherol (vitamin E) and squalene	H5N1 influenza vaccine
Squalene and water emulsion	Fluad (seasonal influenza vaccine)
CpG 1018 (synthetic DNA)	Hepatitis vaccine (Heplisav-B)
Quillaja saponaria (lipid from evergreen tree)	Shingrix (shingles vaccine for elderly)

Success of *Neisseria Meningitidis* C Vaccine



Newer Methods



Recombinant Peptide Vaccines

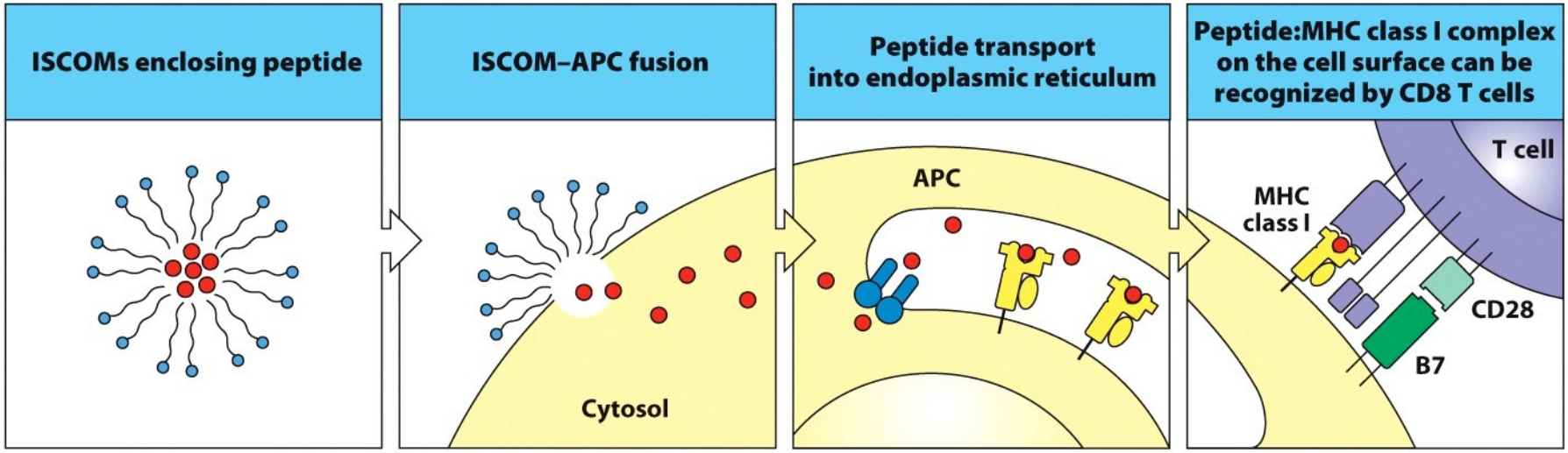


Figure 14.5 The Immune System, 3ed. (© Garland Science 2009)

ISCOM: Immune stimulatory complex (lipid micelles carrying immunogenic peptides)

Limitations:

High polymorphism of human HLA gens

Loading of HLA-ABC genes

-Longer peptides

Not great for infectious disease: antibodies against a single epitope on a pathogen are rarely protective. Failed in clinic

Use a whole protein--Novavax

Recombinant DNA Vaccines

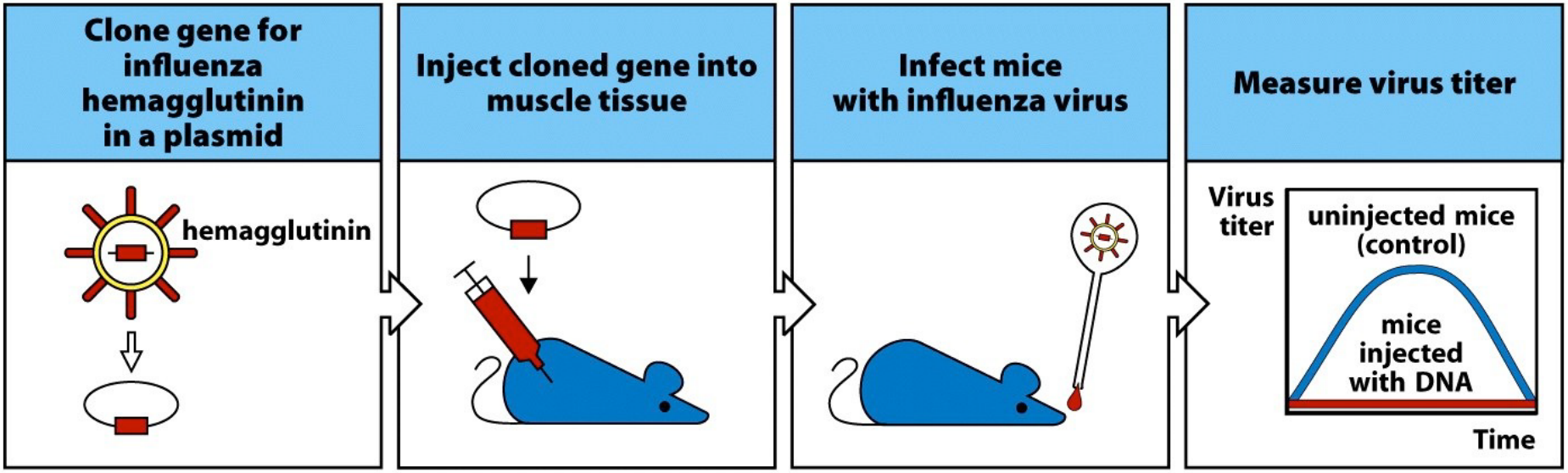
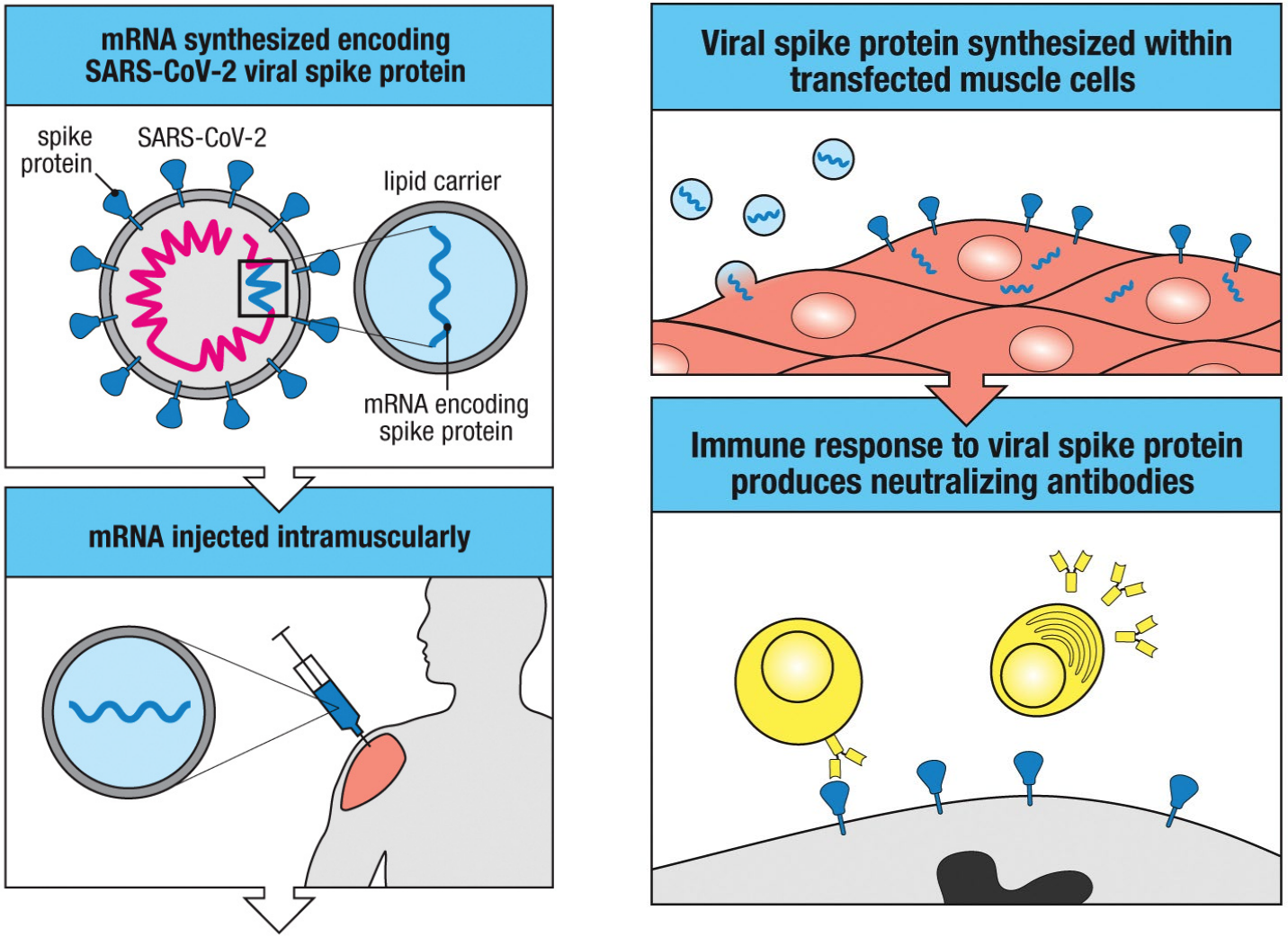


Figure 15-32 Immunobiology, 7ed. (© Garland Science 2008)

Enhancement by adjuvants expressed by the DNA

Newer generation: RNA vaccine
RNA can act as an adjuvant

RNA-based Vaccines



mRNA acts as an adjuvant

Challenges

- Generation of long lasting antibody response
  - IgA type
  - Effective protection require preexisting antibodies (Neutralization)
    - Toxin damage
    - Reinfection
- Generation of robust CD8 response
  - Chronic intracellular infections
  - MHC I and dendritic cells
  - CD4 Cells have to be activated too
  - Higher dose of antigen
  - Strong inflammation

Question

What is NOT required for the generation of CD8 Memory T cells?

- A) protein antigen
- B) Dendritic cells
- C) CD4 helper cells
- D) B cells
- E) Cytokines

Outline

- Immunological memory

- Vaccines
  - Concepts
  - Methods
  - Challenges

- Immune evasion
  - Antigenic variation (surface protein and receptors)
  - Latency

Bacteria Subvert the Host Immune System

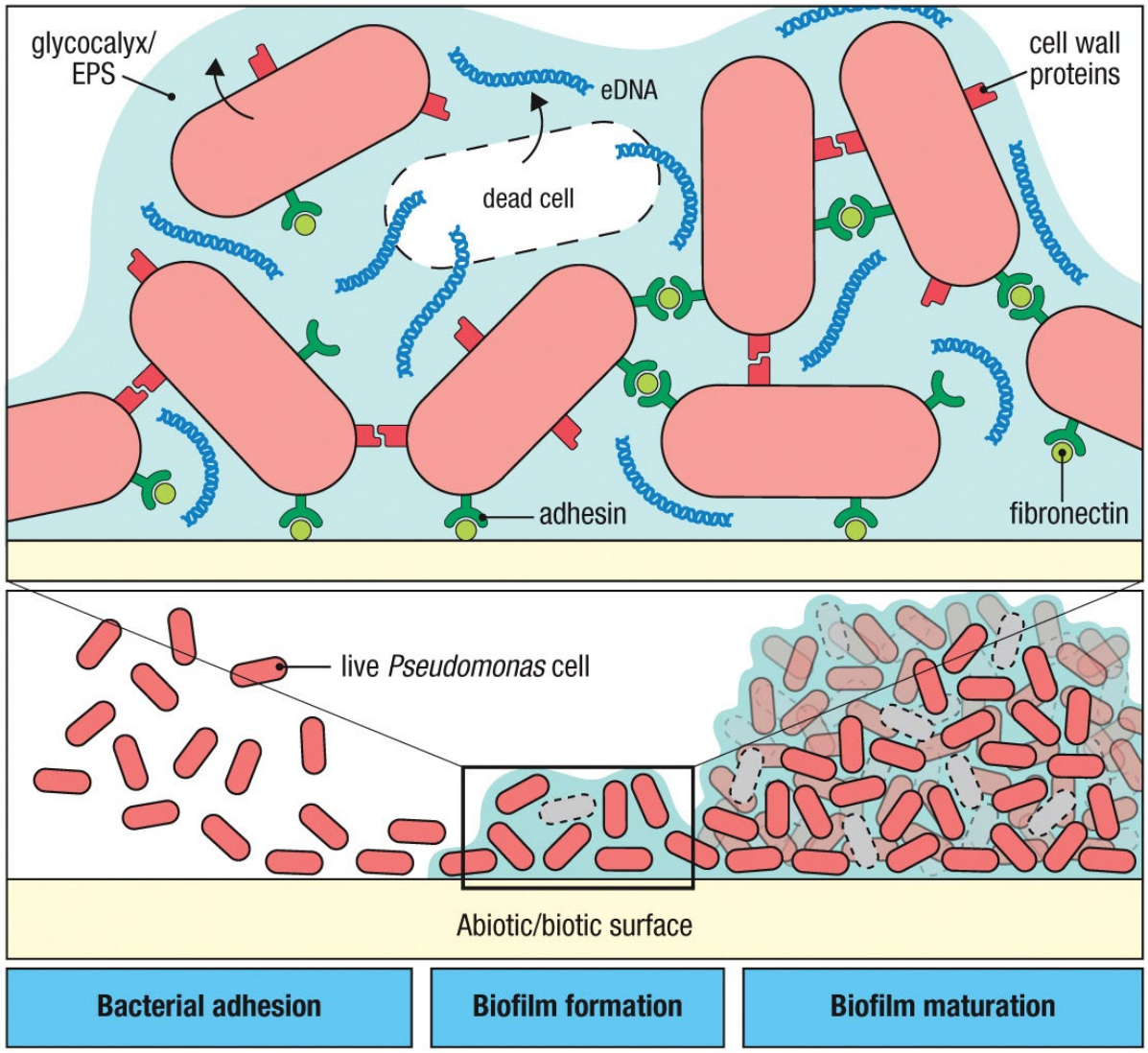
Extracellular Bacteria

Bacterial strategy	Mechanism	Result	Examples
Extracellular bacteria			
Shielding or inhibition of MAMPs	Capsular polysaccharide	Block detection of lipopolysaccharide (LPS)	*K. pneumoniae*
	Hypoacylation of lipid A	Antagonism of TLR-4	*P. gingivalis*
	Coating of bacterium by host proteins (e.g., fibrin)	Block detection of peptidoglycan	*S. aureus*
Antigenic variation	Modulation of expressed pili, fimbriae	Antibodies that block bacterial attachment become ineffective	*N. gonorrhoeae, E. coli*
Inhibition of opsonization	Secretion of complement-degrading factors	Cleavage of complement components	*N. meningitidis, P. aeruginosa, S. aureus*
	Capsular polysaccharide	Block fixation of complement	*S. pneumoniae, H. influenzae, K. pneumoniae*
	Expression of Fc-binding surface molecules (e.g., Protein A)	Prevents binding of antibody to Fc receptors of phagocytes	*S. aureus*
	Production of biofilms	Shielding of bacteria from phagocytosis	*S. epidermidis, S. aureus, P. aeruginosa*
Inhibition/scavenging of reactive oxygen species (ROS)	Secretion of catalase and superoxide dismutase	Neutralize ROS produced by NADPH and myeloperoxidase (MPO)	*S. aureus, B. abortus*
Resistance to antimicrobial peptides (AMPs)	Secretion of AMP-degrading peptidases	Cleavage of AMPs	*E. coli*
	Modulation of cell membrane phospholipids	Prevents binding, functional insertion of AMPs in cell membrane	*S. aureus*

Intracellular Bacteria

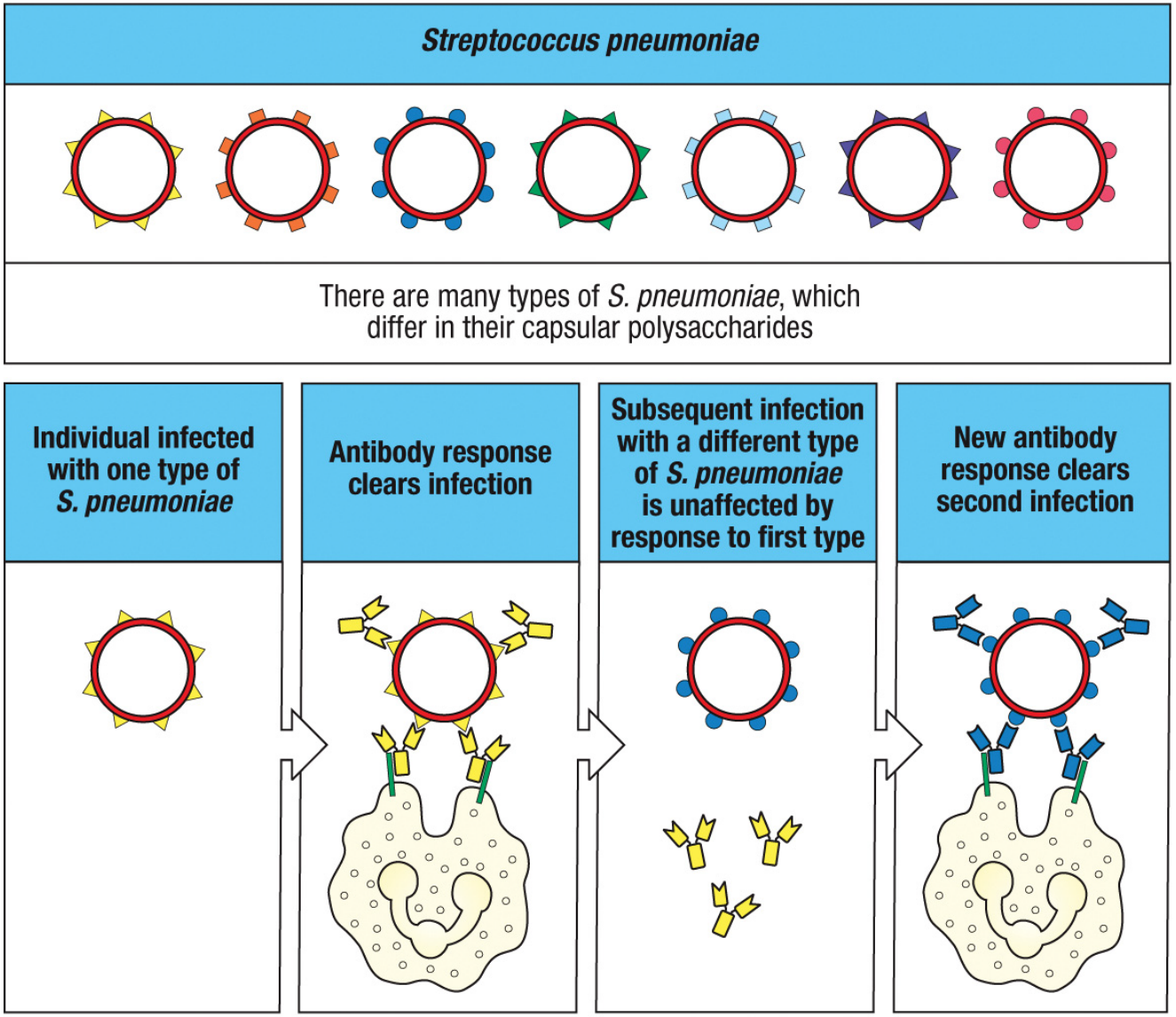
Bacterial strategy	Mechanism	Result	Examples
Intracellular bacteria			
Antigenic variation	Modulation of expressed pili, fimbriae	Antibodies that block bacterial attachment become ineffective	*Salmonella* spp.
Inhibition of MAMP recognition/ signaling	Production of peptidoglycan hydrolase	Block detection of peptidoglycan by NODs	*L. monocytogenes*
	Secretion of intracellular toxins	Block NFκB and MAP kinase signaling pathways	*Y. pestis*
Resistance to anti-microbial peptides	Secretion of AMP-degrading peptidases	Cleavage of AMPs	*Y. pestis*
	Modulation of cell membrane phospholipids	Prevents binding, functional insertion of AMPs in cell membrane	*Salmonella* spp.
Inhibition of fusion of phagosome with lysosome	Release of bacterial cell wall components	Inhibits phago-lysosomal fusion	*M. tuberculosis, M. leprae, L. pneumophila*
Survival within phagolysosome	Waxy, hydrophobic cell wall containing mycolic acids and other lipids	Resistance against lysosomal enzymes	*M. tuberculosis, M. leprae*
Escape from phagosome	Production of hemolysins (e.g., listeriolysin O)	Lysis of phagosome; escape into cytosol	*L. monocytogenes, Shigella* spp.

Biofilms Restrain Immune Clearance

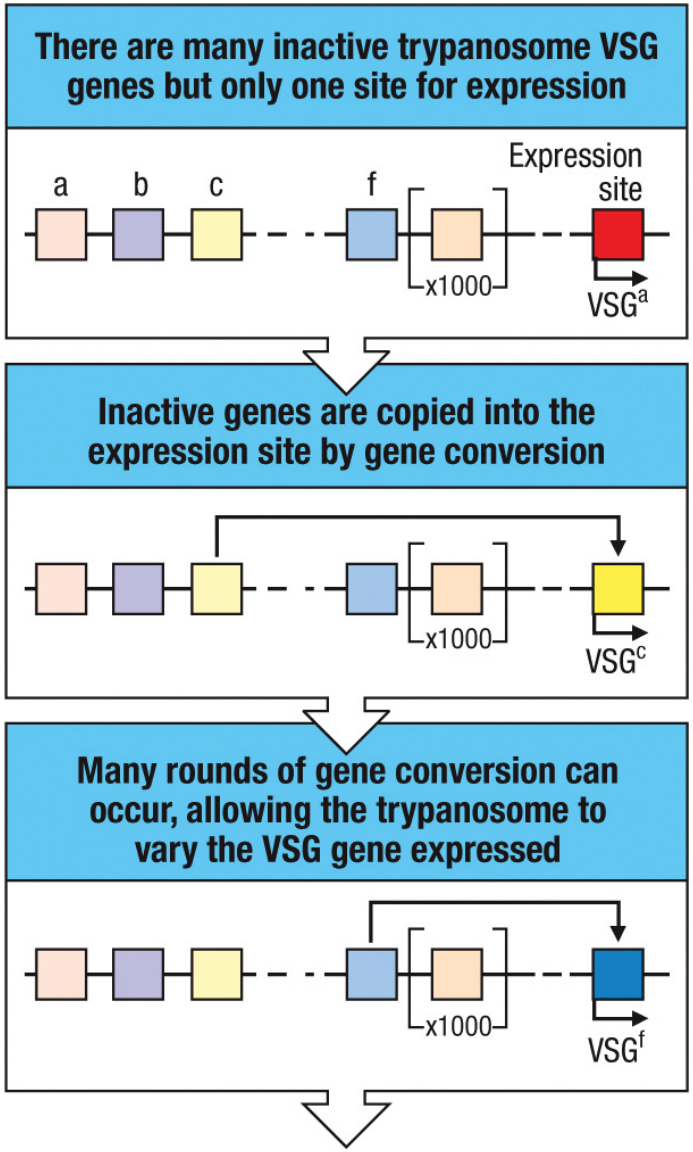


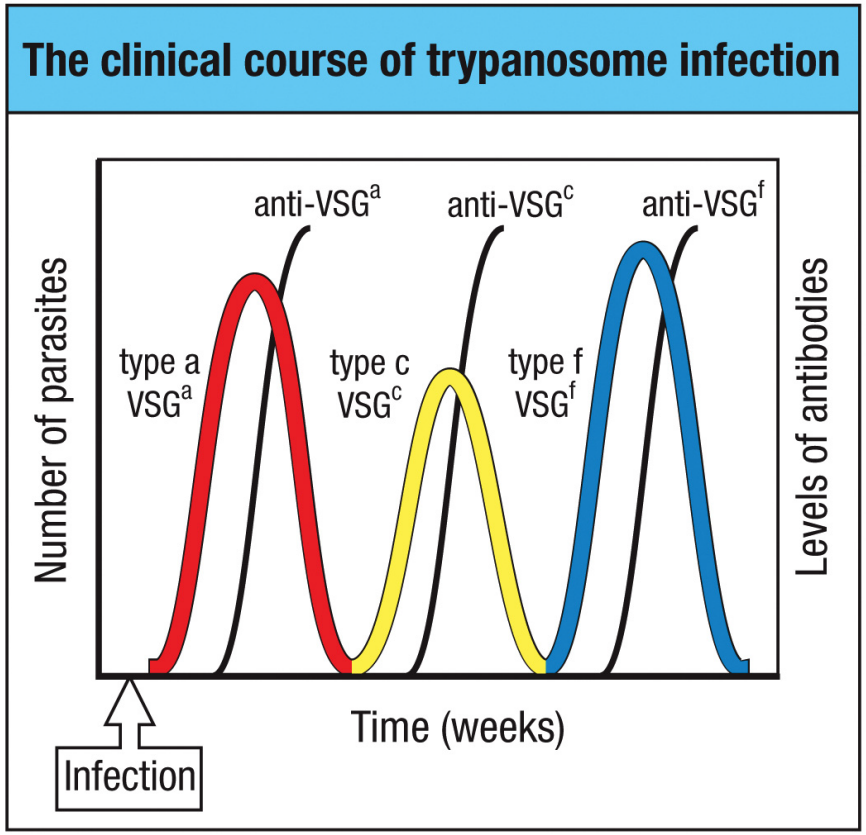
EPS: extracellular polymeric substance

Antigenic Variation Allows Repeated Infection with the Same Pathogen



Gene Conversion Prolongs the Infection





Viruses Subvert the Host Immune System

Viral strategy	Specific mechanism	Result	Virus examples
Inhibition of inflammatory response	Viral interference in interferon induction and signaling	Impedes interferon response	HCV, HBV, herpesviruses, adenovirus
	Virally encoded chemokine receptor homolog, e.g., β-chemokine receptor	Sensitizes infected cells to effects of β-chemokine; advantage to virus unknown	Cytomegalovirus
	Virally encoded soluble cytokine receptor, e.g., IL-1 receptor homolog, TNF receptor homolog, interferon-γ receptor homolog	Blocks effects of cytokines by inhibiting their interaction with host receptors	Vaccinia Rabbit myxoma virus
	Viral inhibition of adhesion molecule expression, e.g., LFA-3, ICAM-1	Blocks adhesion of lymphocytes to infected cells	Epstein–Barr virus
	Protection from NFκB activation by short sequences that mimic TLRs	Blocks inflammatory responses elicited by IL-1 or bacterial pathogens	Vaccinia
Blocking of antigen processing and presentation	Inhibition of MHC class I expression	Impairs recognition of infected cells by cytotoxic T cells	Herpes simplex Cytomegalovirus
	Inhibition of peptide transport by TAP	Blocks peptide association with MHC class I	Herpes simplex
Inhibition of humoral immunity	Virally encoded Fc receptor	Blocks effector functions of antibodies bound to infected cells	Herpes simplex Cytomegalovirus
	Virally encoded complement receptor	Blocks complement-mediated effector pathways	Herpes simplex
	Virally encoded complement control protein	Inhibits complement activation by infected cell	Vaccinia
Immunosuppression of host	Virally encoded cytokine homolog of IL-10	Inhibits T_H1 lymphocytes Reduces interferon-γ production	Epstein–Barr virus

Antigenic Drift and Shift

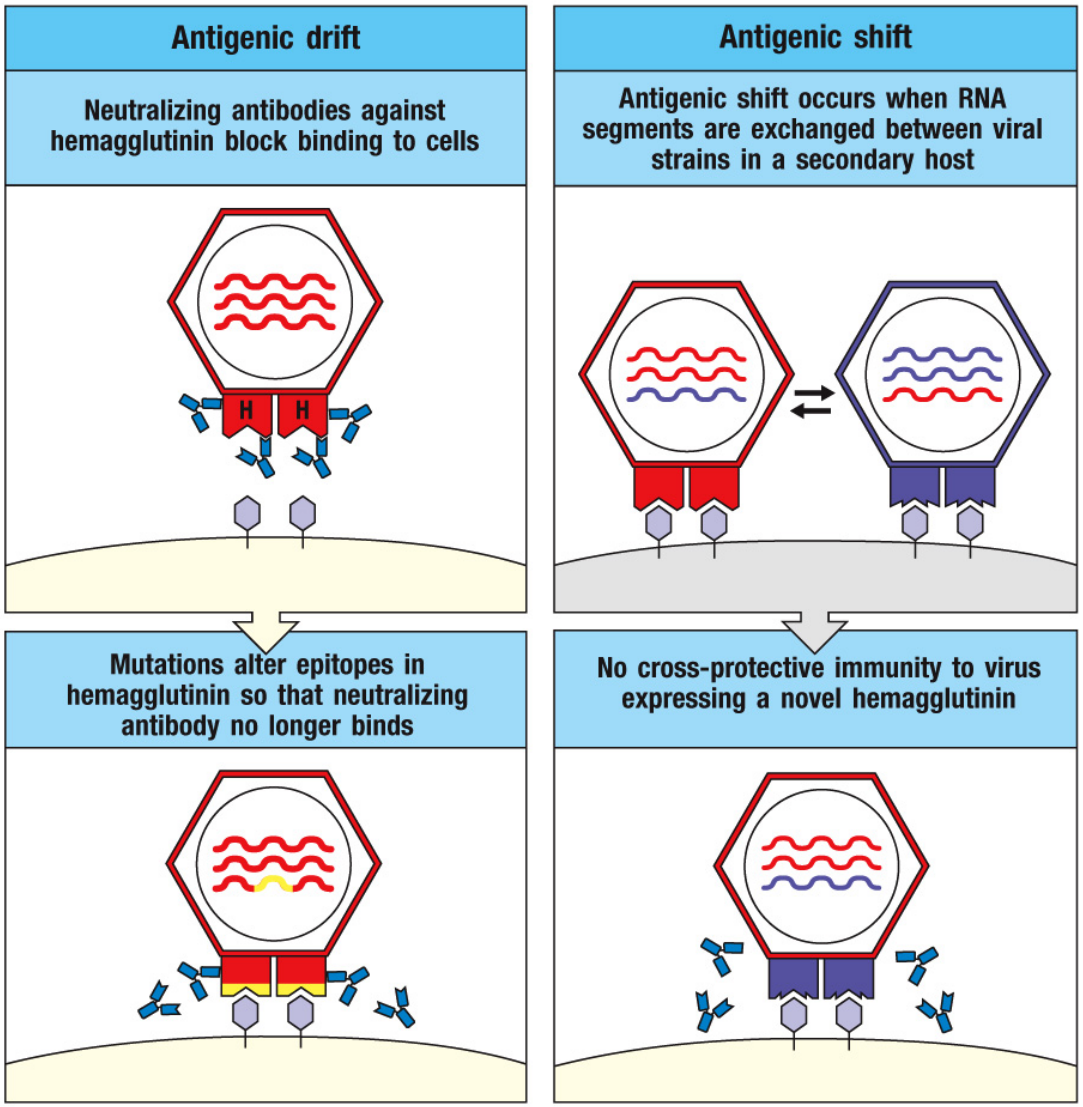
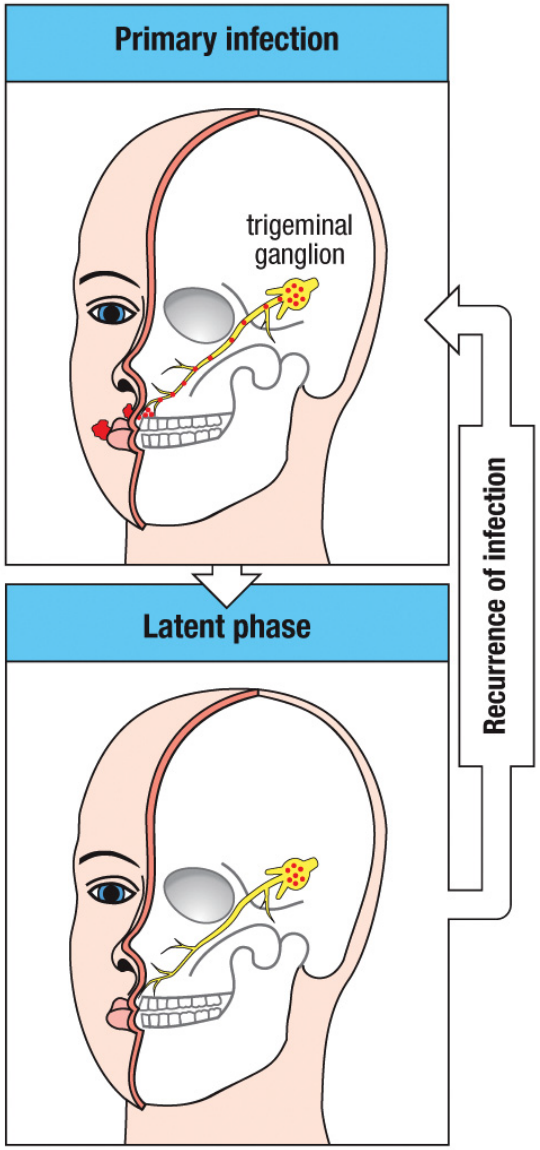


Figure 13.22 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Latent Viruses “Hide” from the Immune System

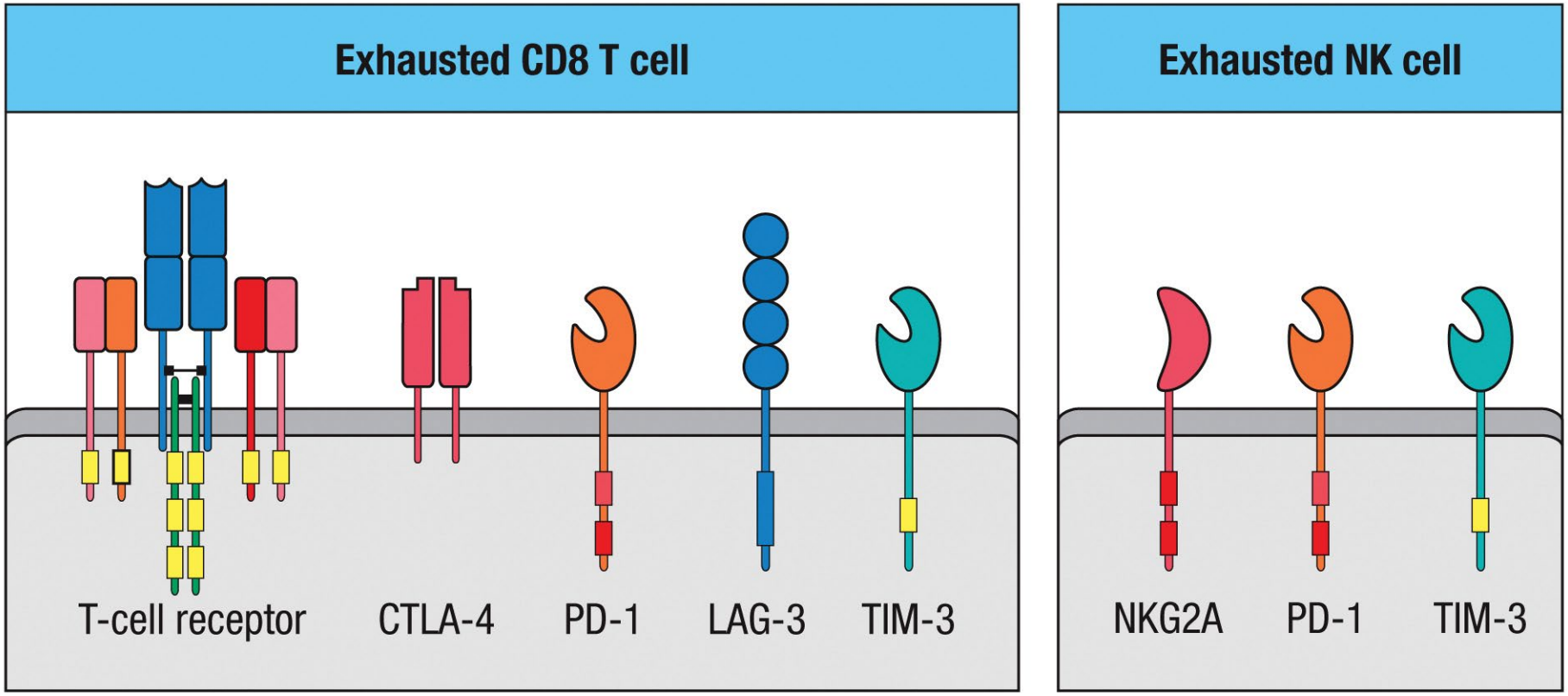


Herpesvirus
Lifelong infections

Neurons: immunoprivilliged site; neurons carry very low levels of MHC I

Virus doesn’t proliferate, thus limited presentation on MHC I for CD8 cells

Chronic Infections Induce Exhaustion



Three challenges

- Long last antibody response
- Robust CD8 T cells
- Immune evasion

- What can you do?