Immunology

Infection & Vaccines

PD Dr. Jürgen Knobloch

RUB

Microbes and their associated diseases

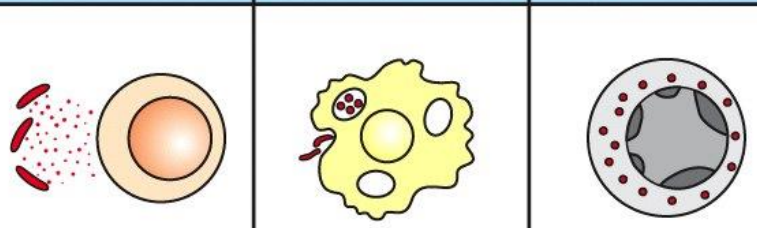
	Direct mechanisms of tissue damage by pathogens		
	Exotoxin production	Endotoxin	Direct cytopathic effect
Pathogenic mechanism			
Infectious agent	*Streptococcus pyogenes* *Staphylococcus aureus* *Corynebacterium diphtheriae* *Clostridiumtetani* *Vibrio cholerae*	*Escherichiacoli* *Haemophilus influenzae* *Salmonella typhi* *Shigella* *Pseudomonas aeruginosa* *Yersinia pestis*	Variola Varicella-zoster Hepatitis B virus Polio virus Measles virus Influenza virus Herpes simplex virus Human herpes virus 8 (HHV8)
Disease	Tonsilitis, scarlet fever Boils, toxic shock syndrome, food poisoning Diphtheria Tetanus Cholera	Gram-negative sepsis Meningitis, pneumonia Typhoid Bacillary dysentery Wound infection Plague	Smallpox Chickenpox, shingles Hepatitis Poliomyelitis Measles, subacute sclerosing panencephalitis Influenza Cold sores Kaposi's sarcoma

Figure 10-5 Immunobiology, 6/e. (© Garland Science 2005)

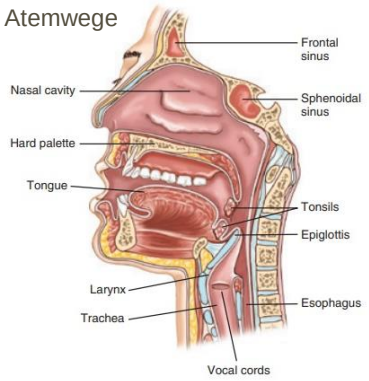
NUCALA
mepolizumab

nexus

GSK

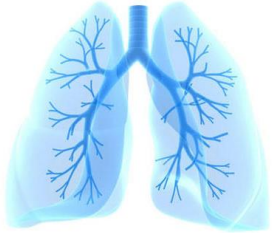
Angeborene/unspezifische Immunantwort

obere Atemwege



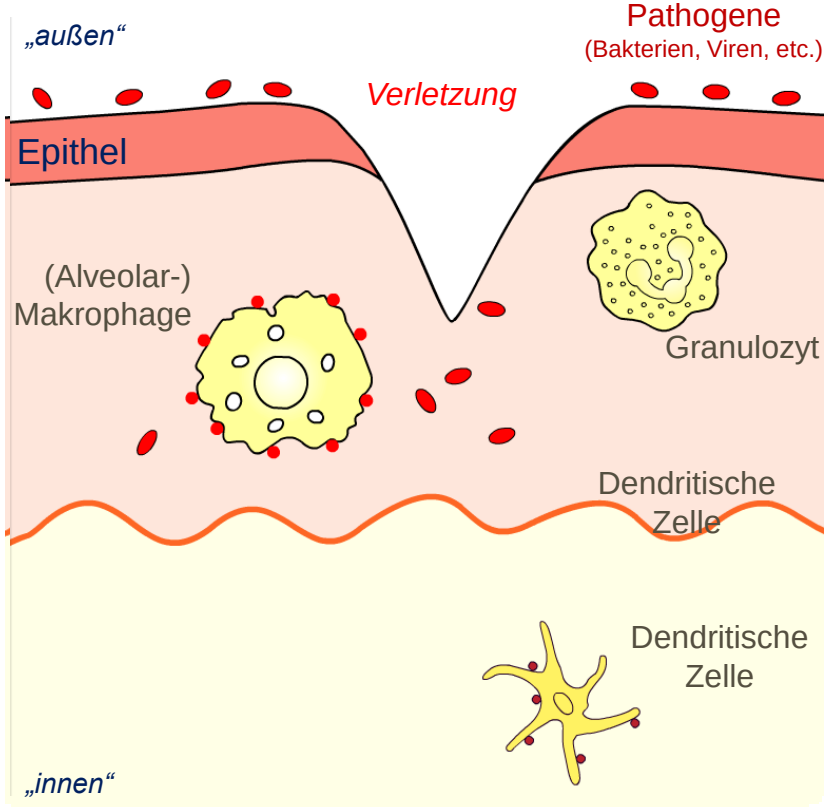
Quelle: www.pharmacy180.com

Lunge



Quelle: istock.com

Bronchus



mod. nach Janeway, 5th ed. 2001, Garland Publishing

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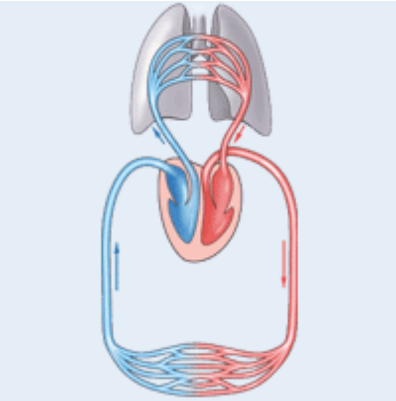
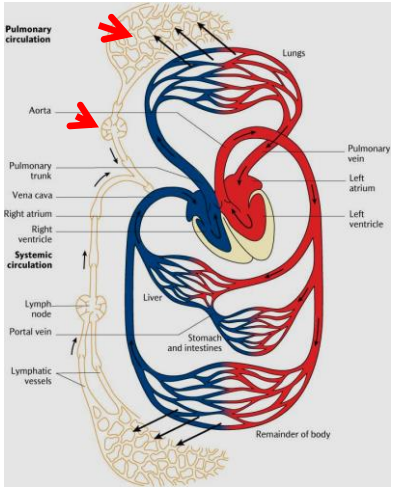
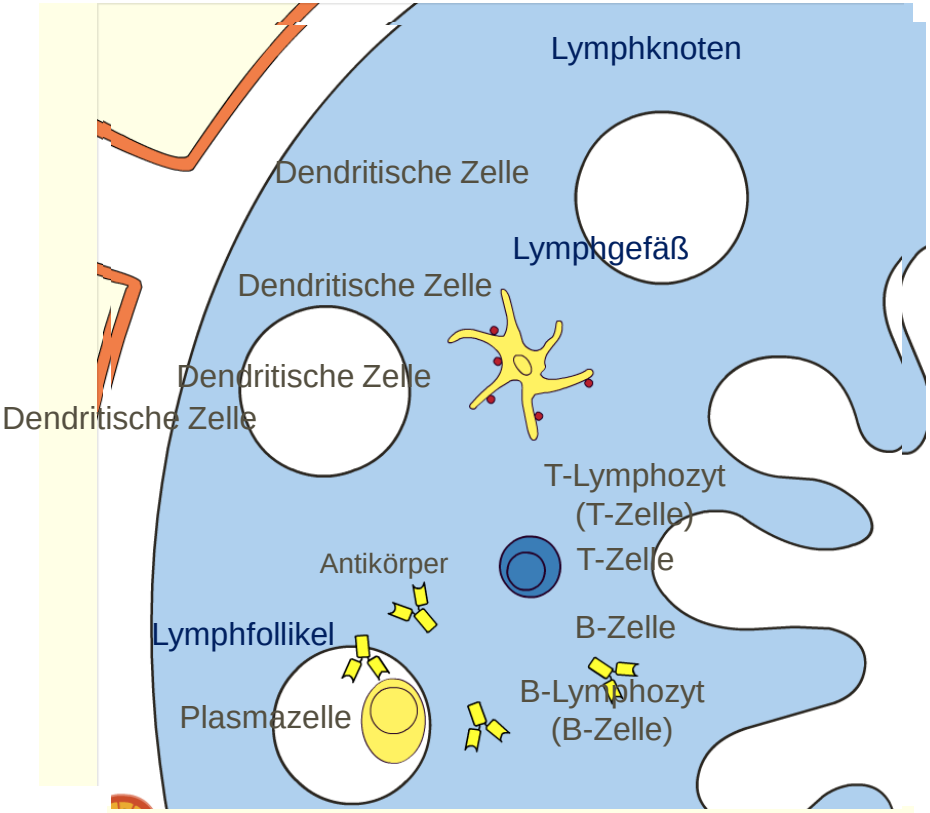
Adaptive/spezifische Immunantwort (I)



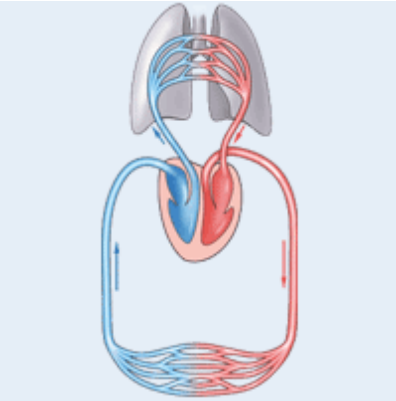


pocketdentistry.com/4-the-circulatory-system/; Elsevier

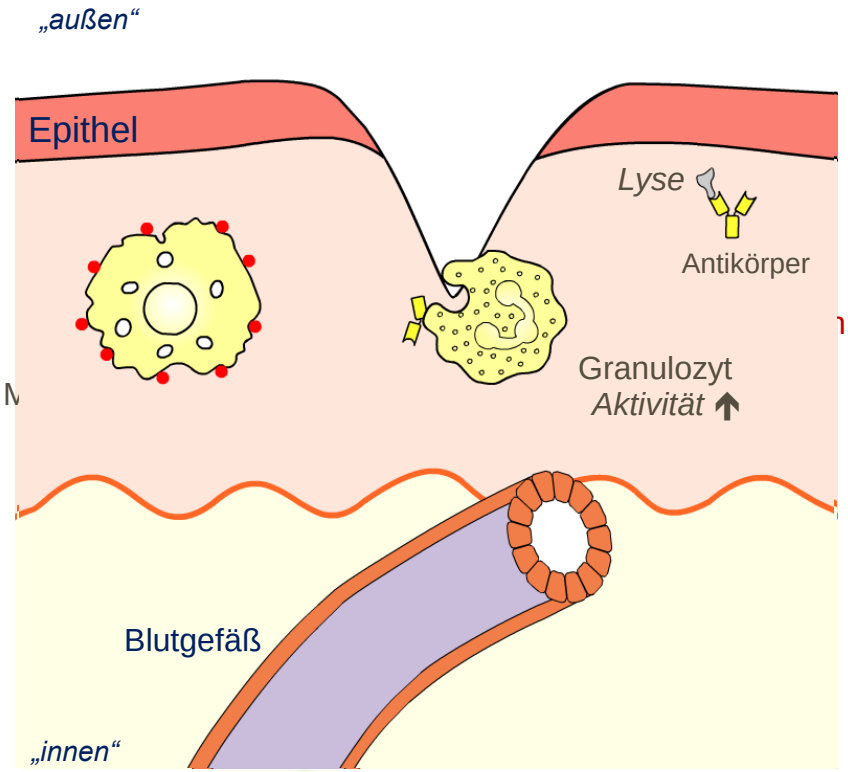


mod. nach Janeway, 5th ed. 2001, Garland Publishing

Adaptive/spezifische Immunantwort (II)



pocketdentistry.com/4-the-circulatory-system/; Elsevier



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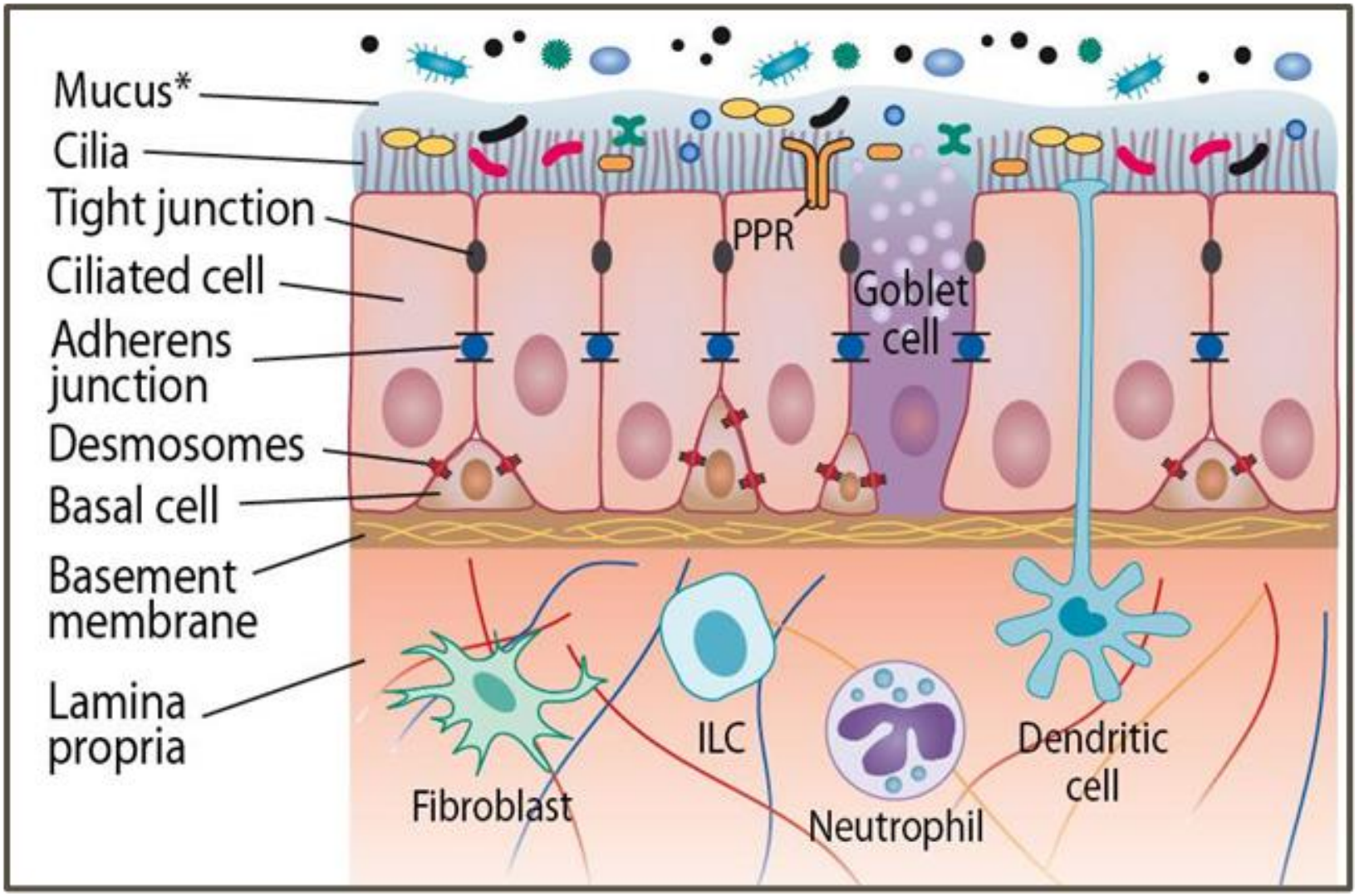
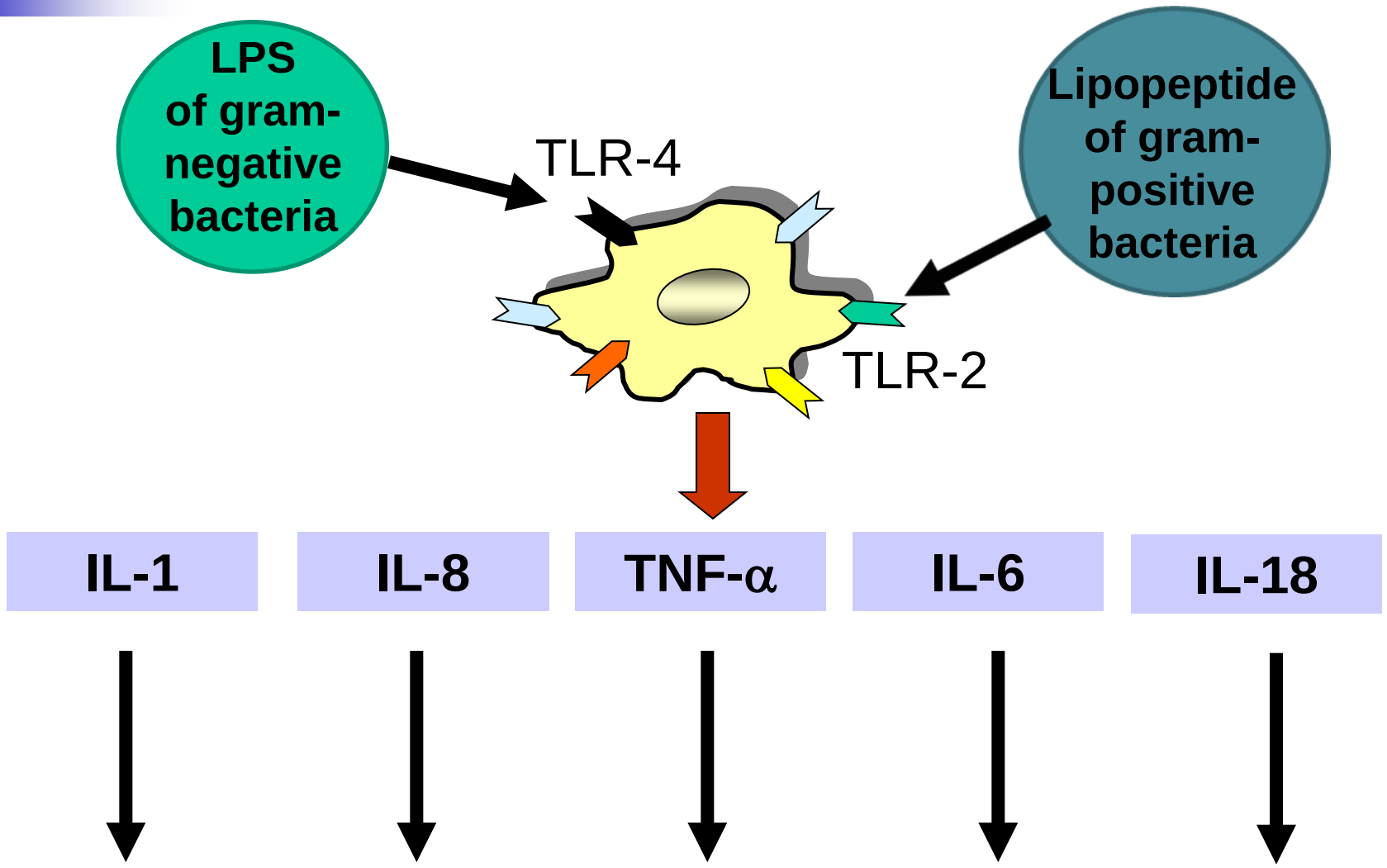
Microbes and their associated diseases



Conserved structures of pathogens are detected by „Pattern Recognition Receptors“

Receptor characteristic	Innate immunity
Specificity inherited in the genome	Yes
Expressed by all cells of a particular type (eg, macrophages)	Yes
Triggers immediate response	Yes
Recognizes broad classes of pathogen	Yes
Interacts with a range of molecular structures of a given type	Yes
Encoded in multiple gene segments	No
Requires gene rearrangement	No
Clonal distribution	No
Able to discriminate between even closely related molecular structures	No

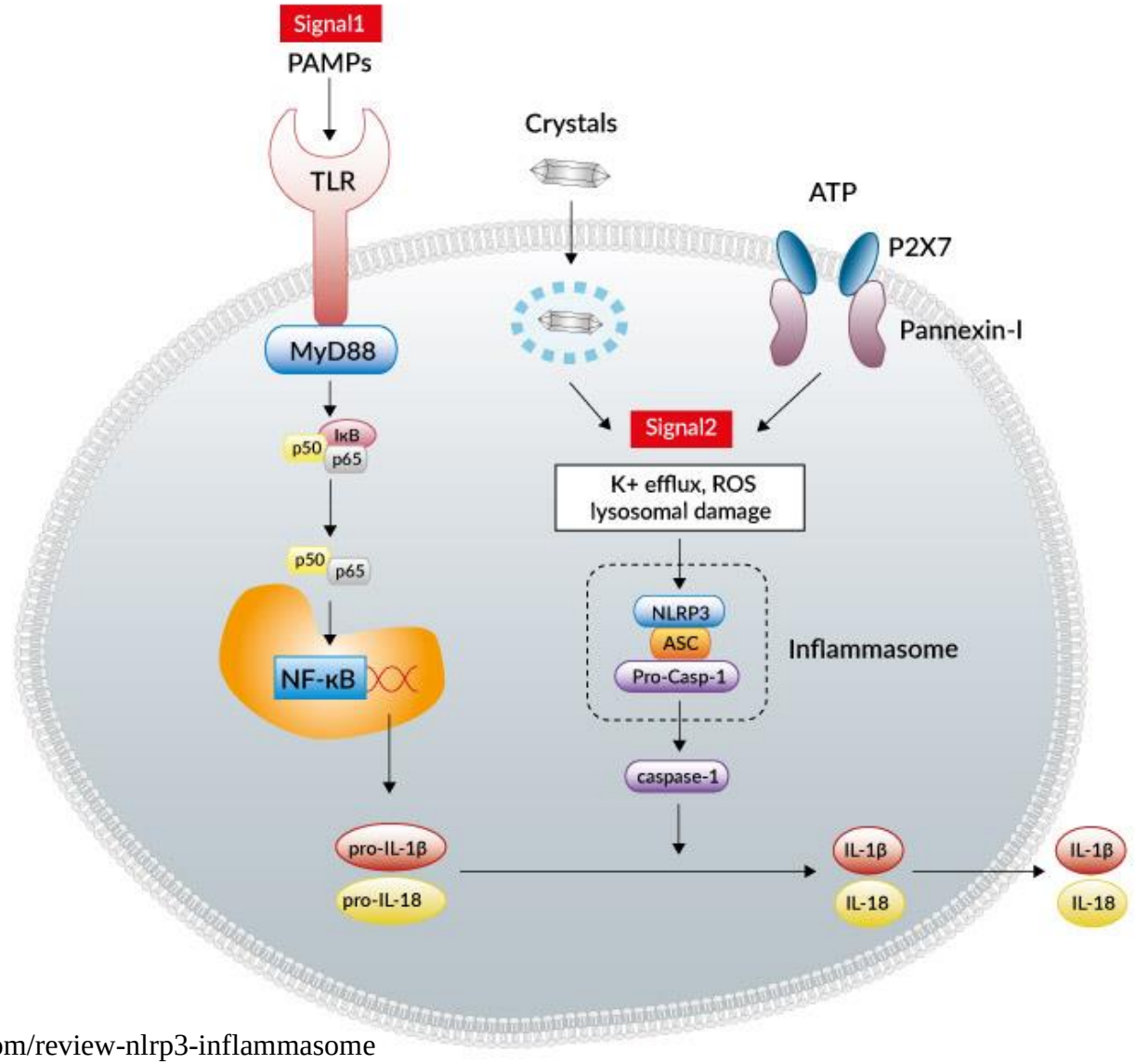
Figure 2-10 Immunobiology, 6/e. (© Garland Science 2005)



Inflammation

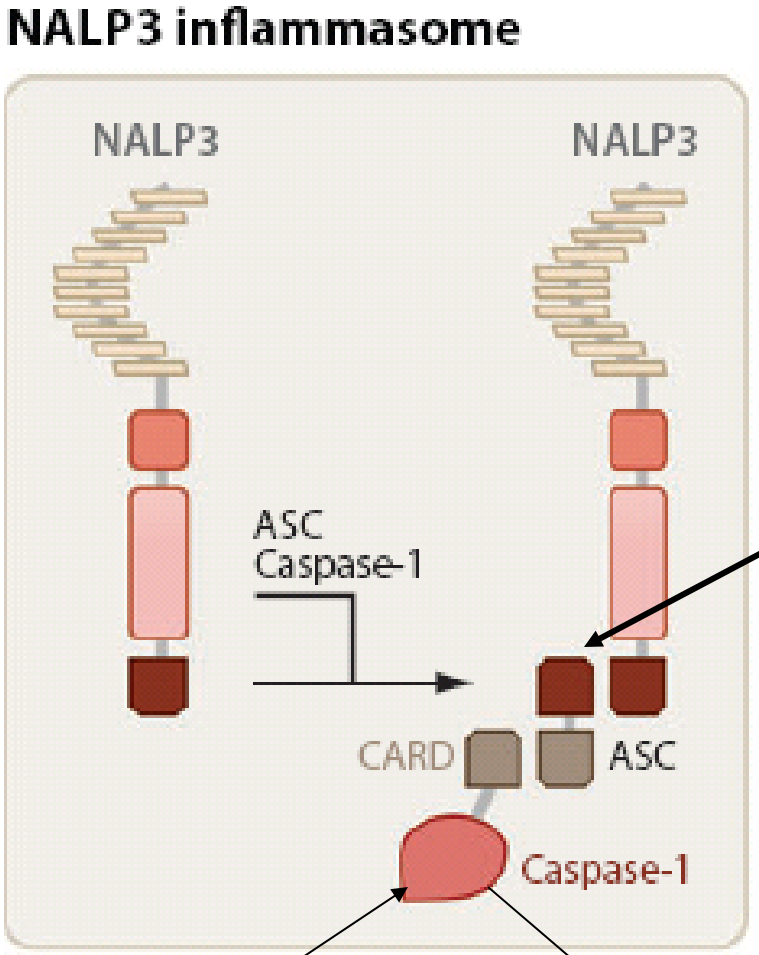
Inflammasome

The inflammasome is activated by damage associated molecular patterns such as ATP or uric acid (“crystals”), ROS and potassium influx (membrane damage)



https://www.invivogen.com/review-nlrp3-inflammasome

Activation of the inflammasom leads to recruitment of Caspase-1



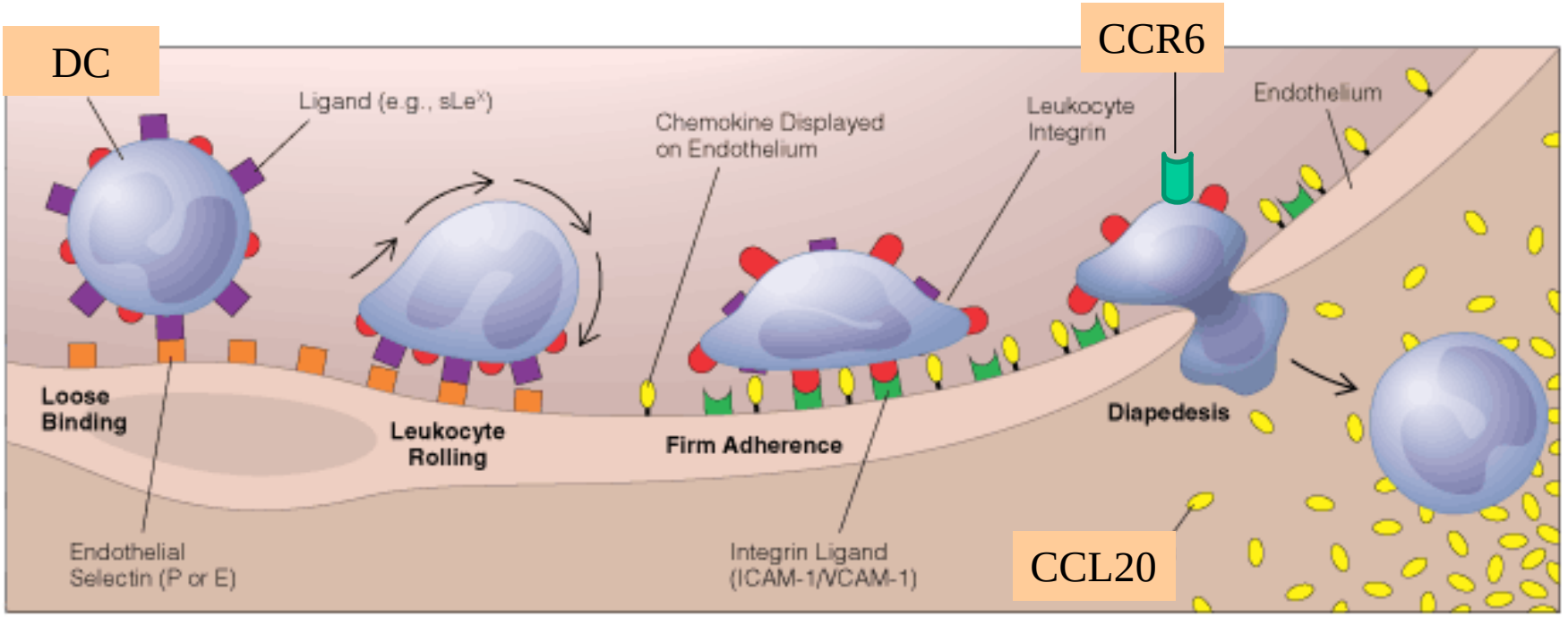
binds to Pyrin Domain after oligomerization!

pro IL-1β
pro IL-18

IL-1β
IL-18

Innate Immunity is the basis for induction of the adaptive immune response.
Chemokines orchestrate the cellular response.

Entry of DCs into inflamed tissue by diapedesis

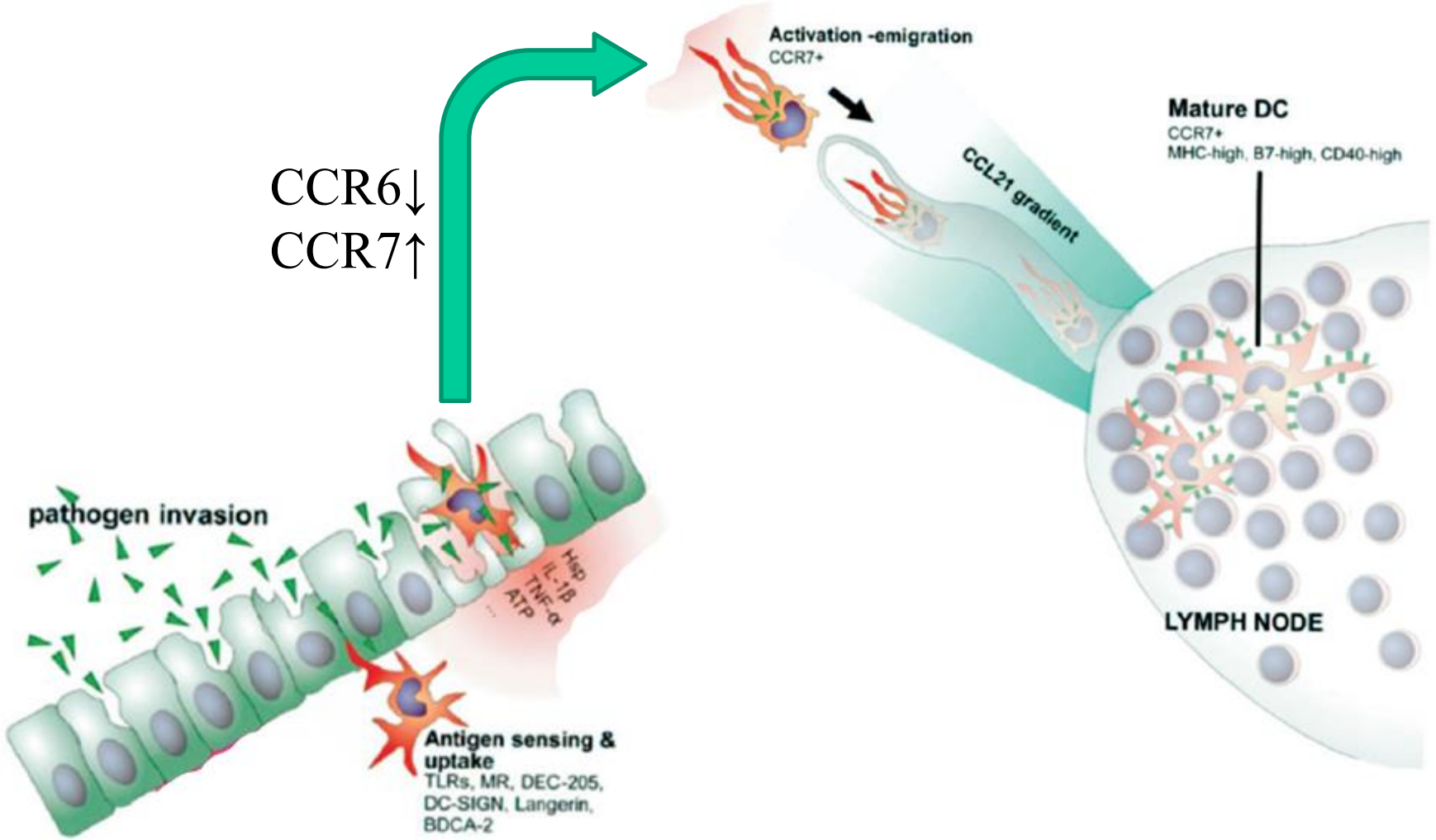


Modified from 2002 Decker Intellectual Properties

Chemokine that is most important for attracting DCs:

⟶ MIP3α (CCL20) binding to CCR6

After activation of DCs at the site of infection cells follow a chemokine gradient to the lymph node



Am J Respir Crit Care Med Vol 172. pp 530–551, 2005

Activated dendritic cells express costimulatory molecules in the lymph nodes

1. DC becomes activated in the tissue leading to down regulation of CCR6 and up-regulation of CCR7

2. DC follows the CCL21 gradient into the lymph node meanwhile upregulating expression of costimulatory molecules

3. DCs interact with T-cells in the paracortical lymph node area

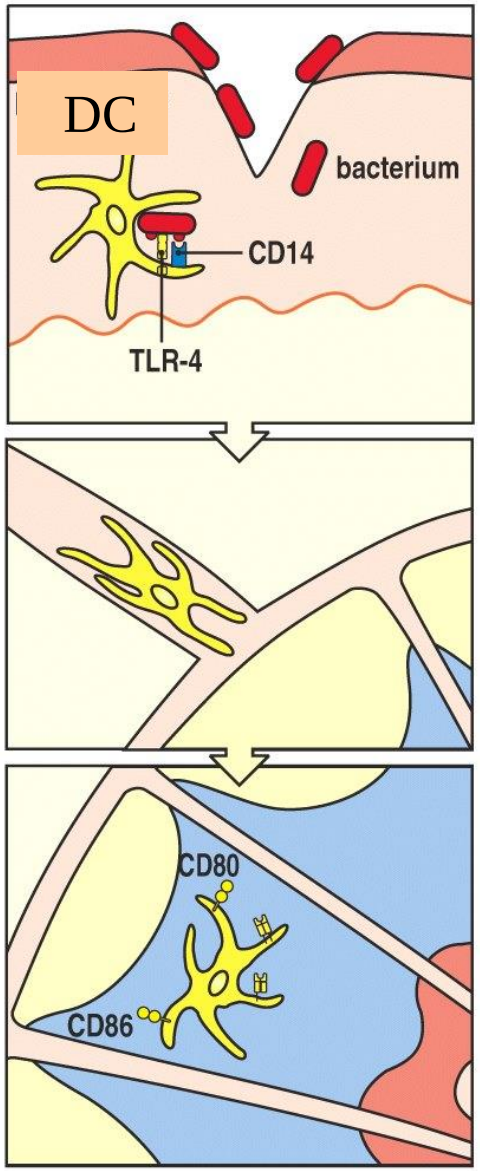
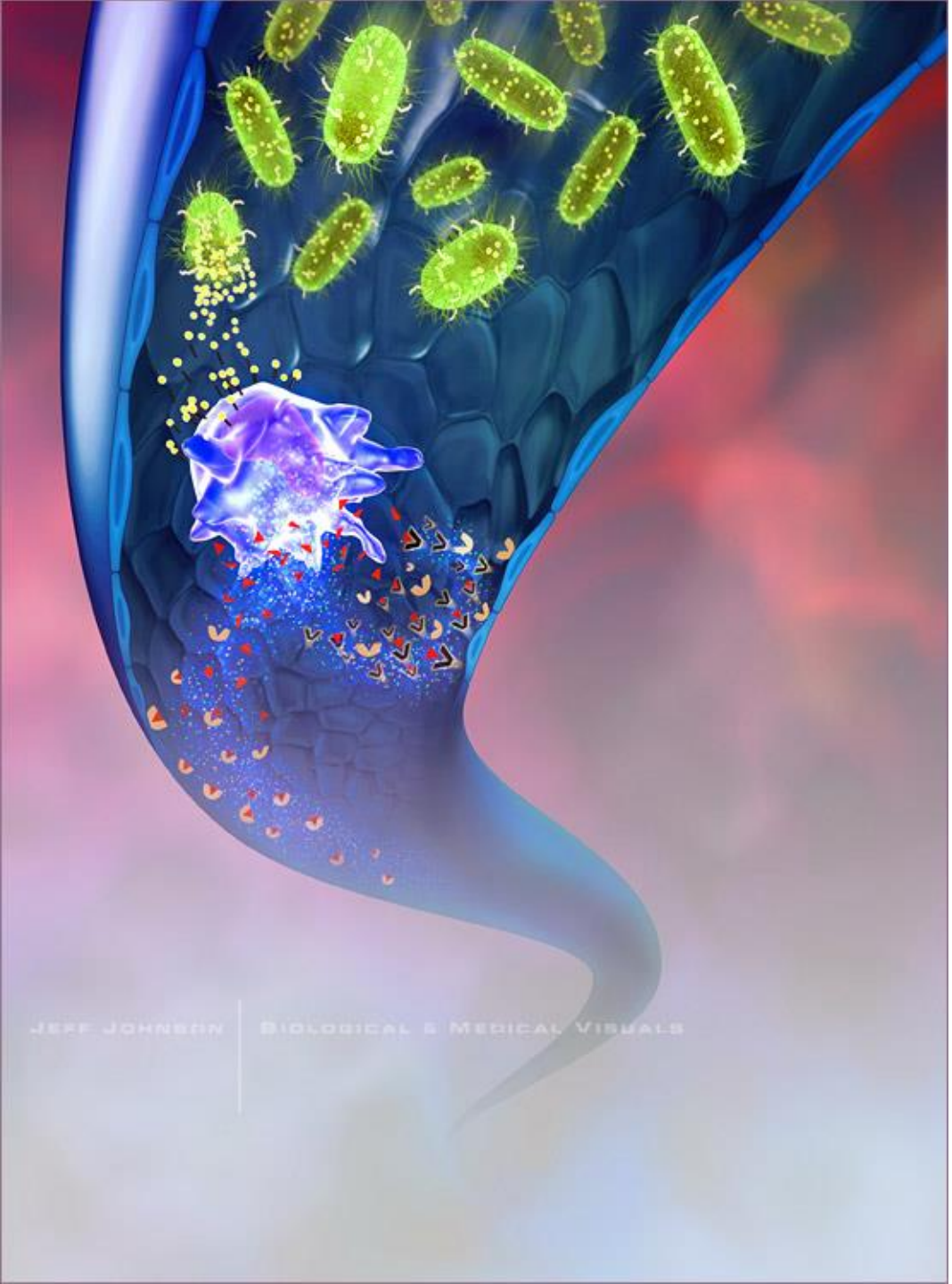


Figure 2-16 Immunobiology, 6/e. (© Garland Science 2005)



But what when things went wrong….

Sepsis

Patient with Sepsis

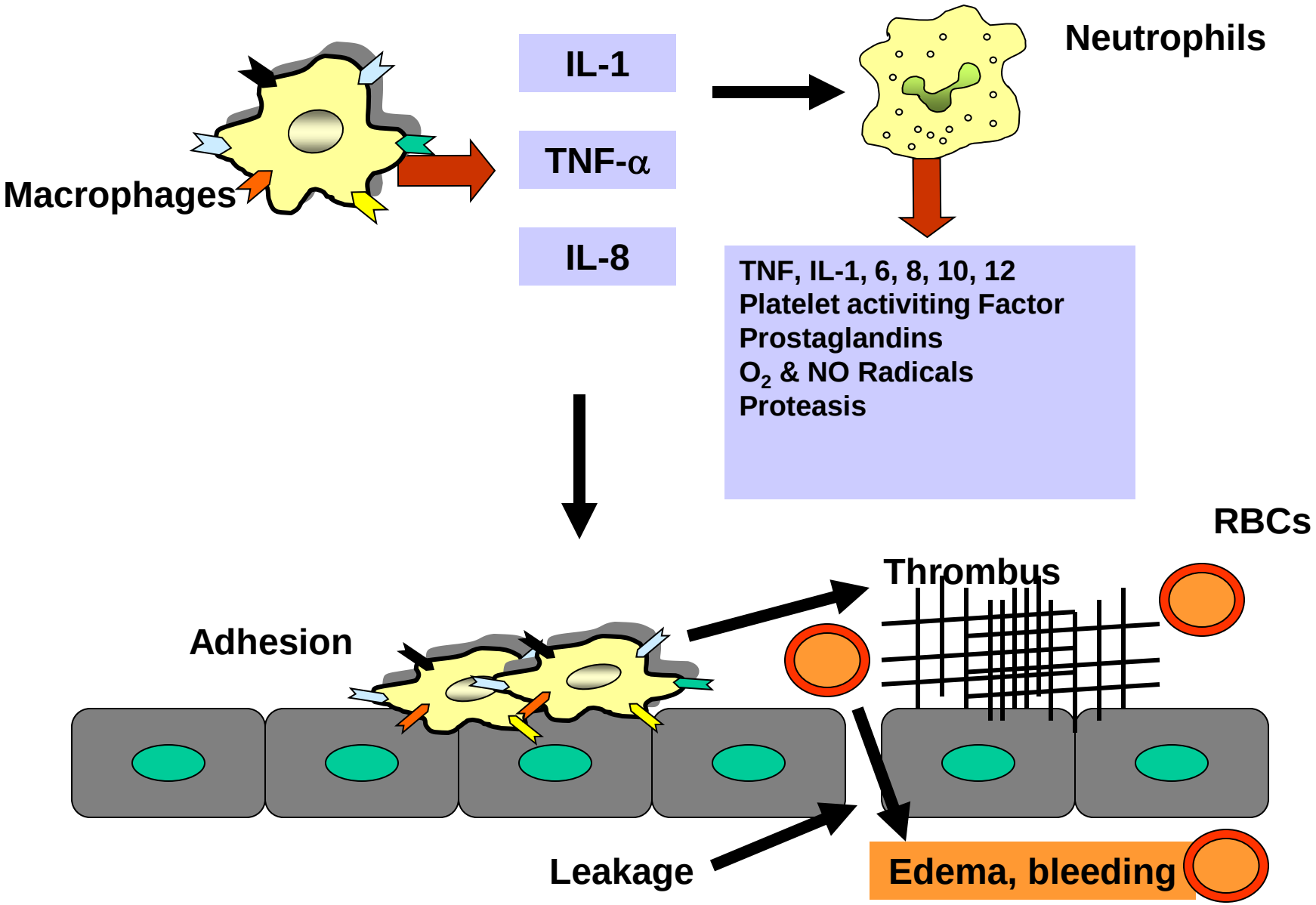
Major causes for Sepsis:

-Trauma; Treatment in an intensive care unit

-Systemic or local infection

-Chronic inflammation of skin and mucosa with endotoxin releasing bacteria or fungi

From local inflammation to systemic disease



TNF-α

Local effects

Activation of the Endothelium inceased Permeability

Local Inflammation

Adhesion of leucocytes to the vessels

Systemic effects

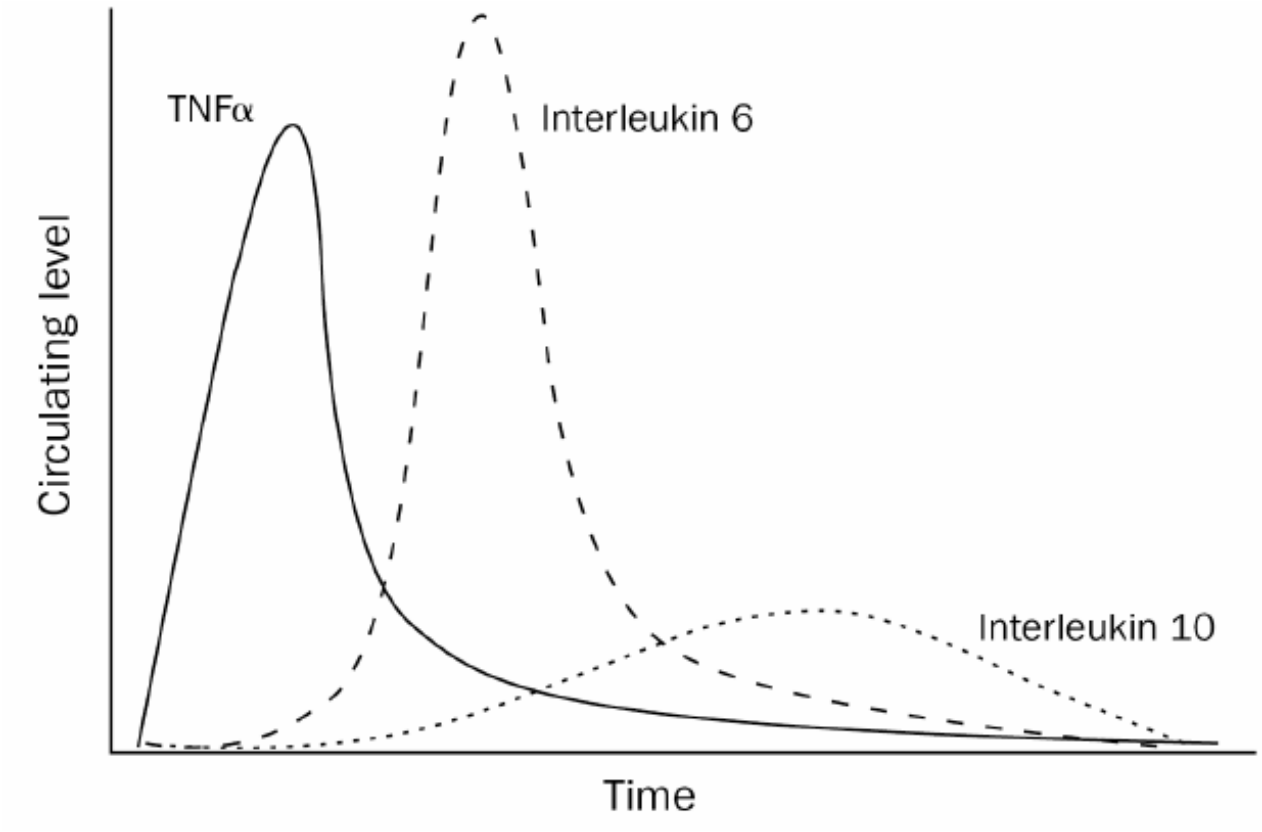
Vasodilation, Hypotonia, Septic Shock

Intravasal blood clotting, Multiorgan failure

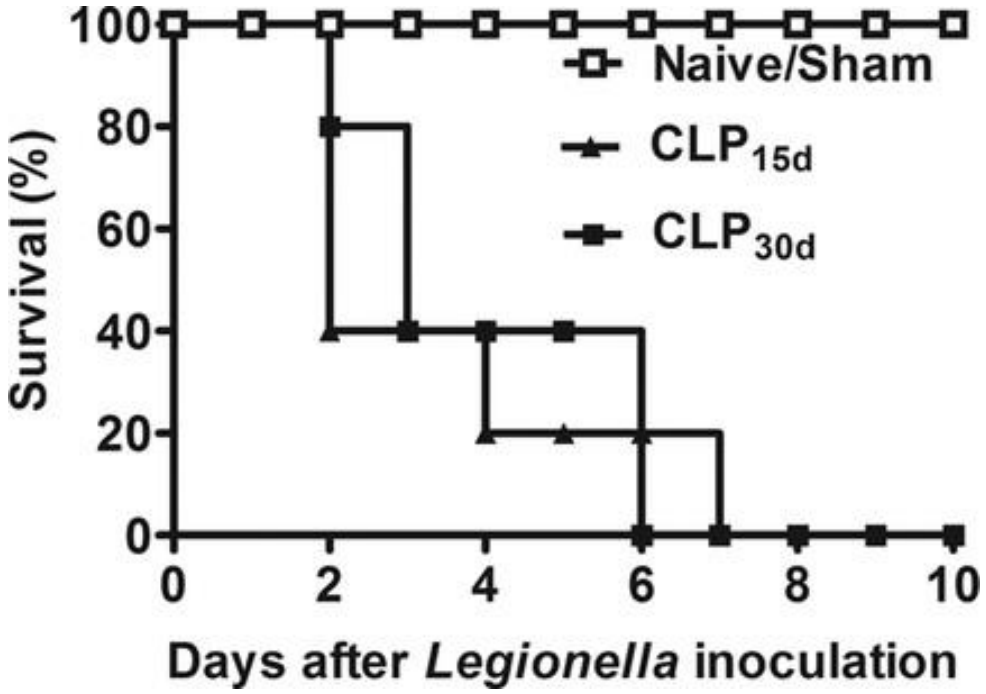
First: systemic inflammation, later: Immune Suppression

TNF-α „knock out“ mice are not prone to sepsis

Endotoxin induced inflammation is down regulated by delayed production of IL-10



Mice that survived sepsis show suppression of immune responses



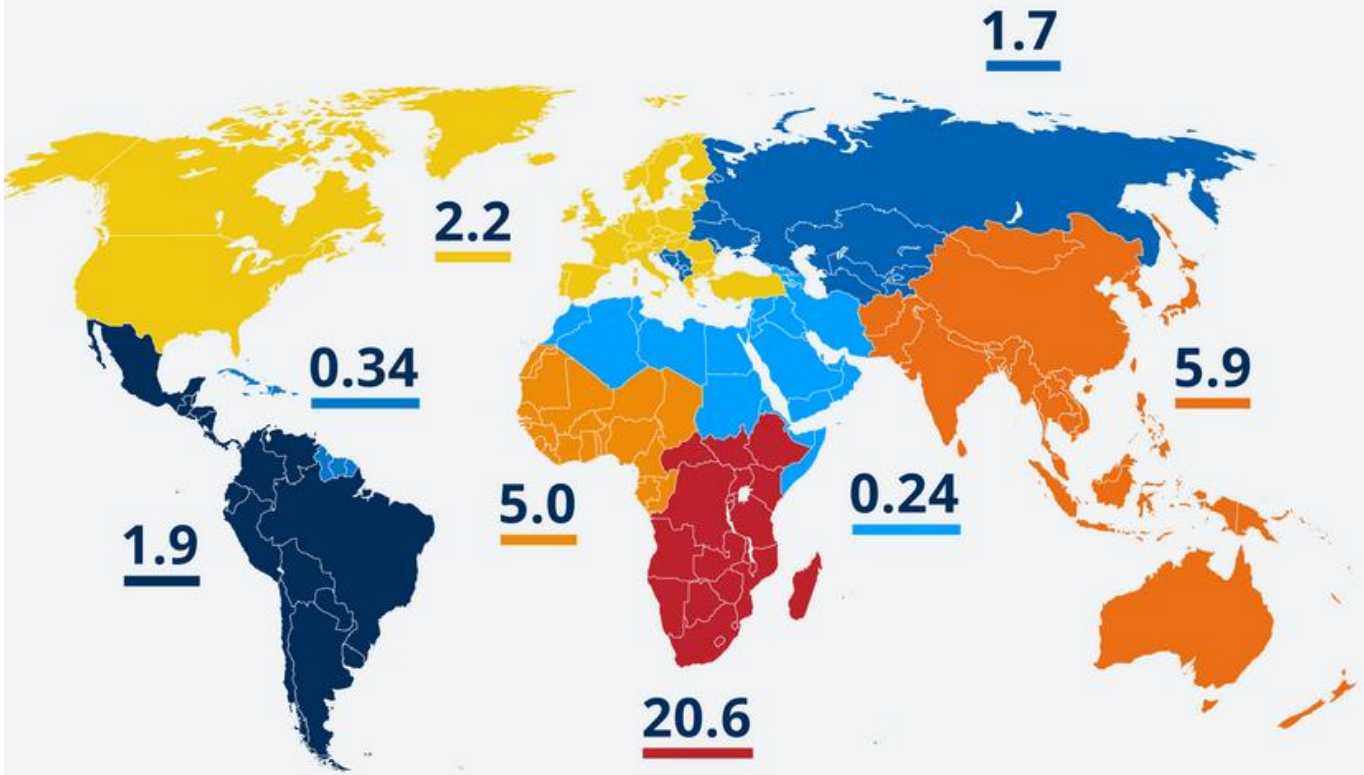
Mice were infected with Legionella 15 or 30 days after surviving sepsis.

Critical Care Medicine 2010;38(8):1718-1725

People estimated to be living with HIV

In millions

Total: **37.9 million**



Source: UNAIDS | 2018

Time course of a HIV Infection

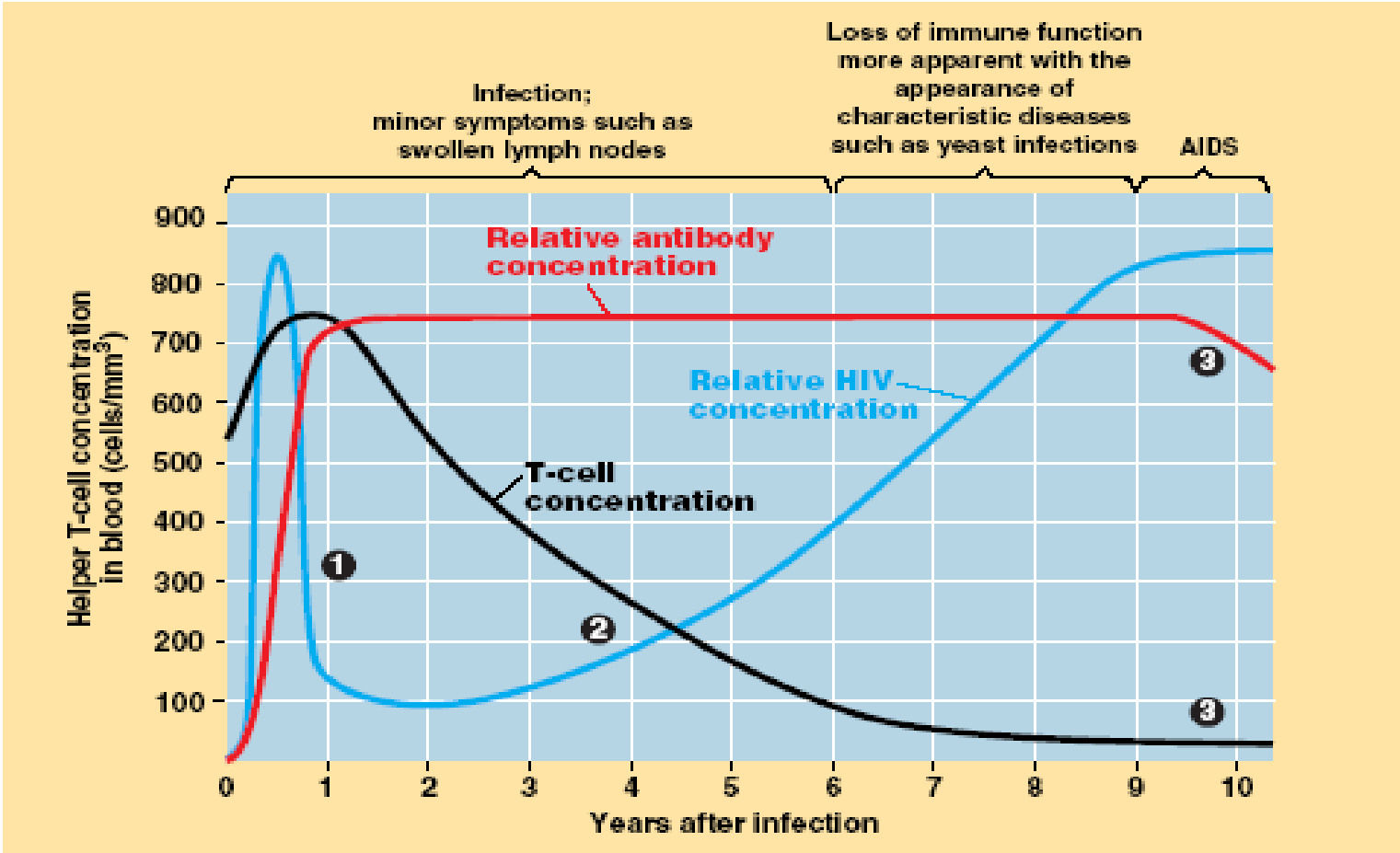
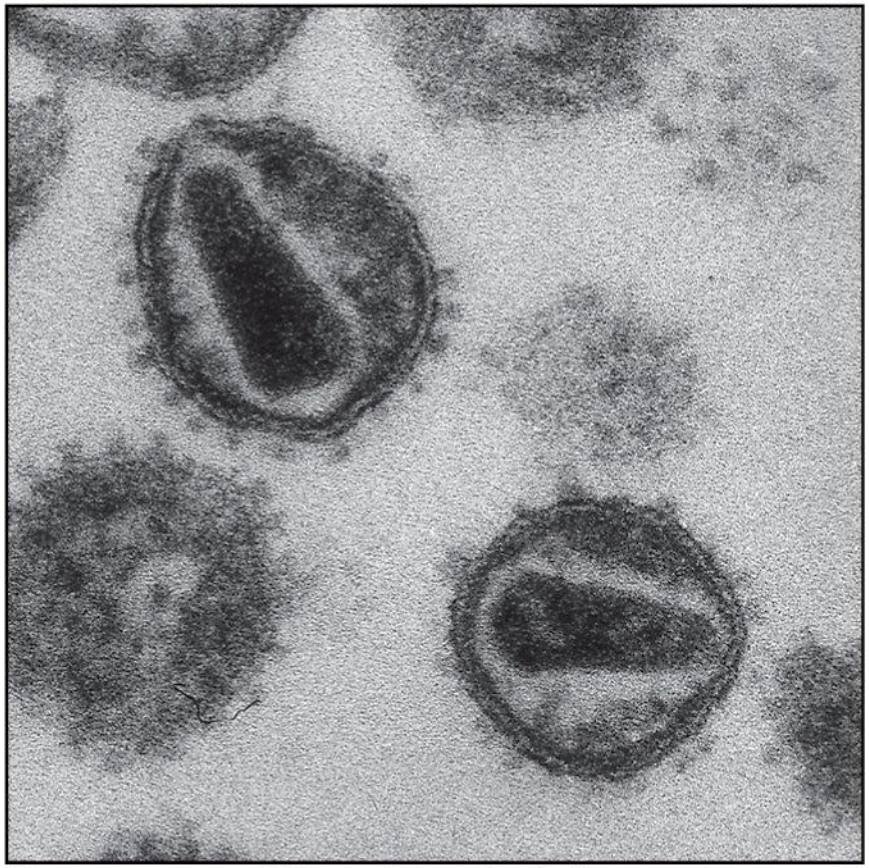


Figure 43.20 in Campbell & Reece (2002).

„Anatomy“ of HIV



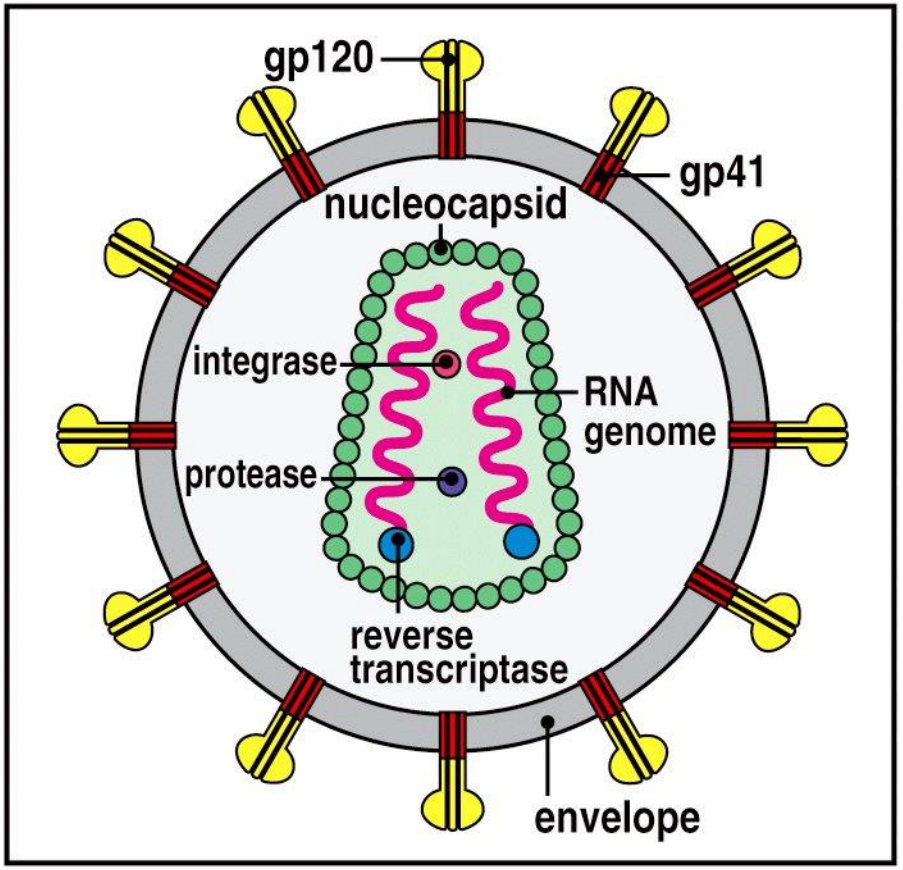


Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

Systemic dissemination of HIV

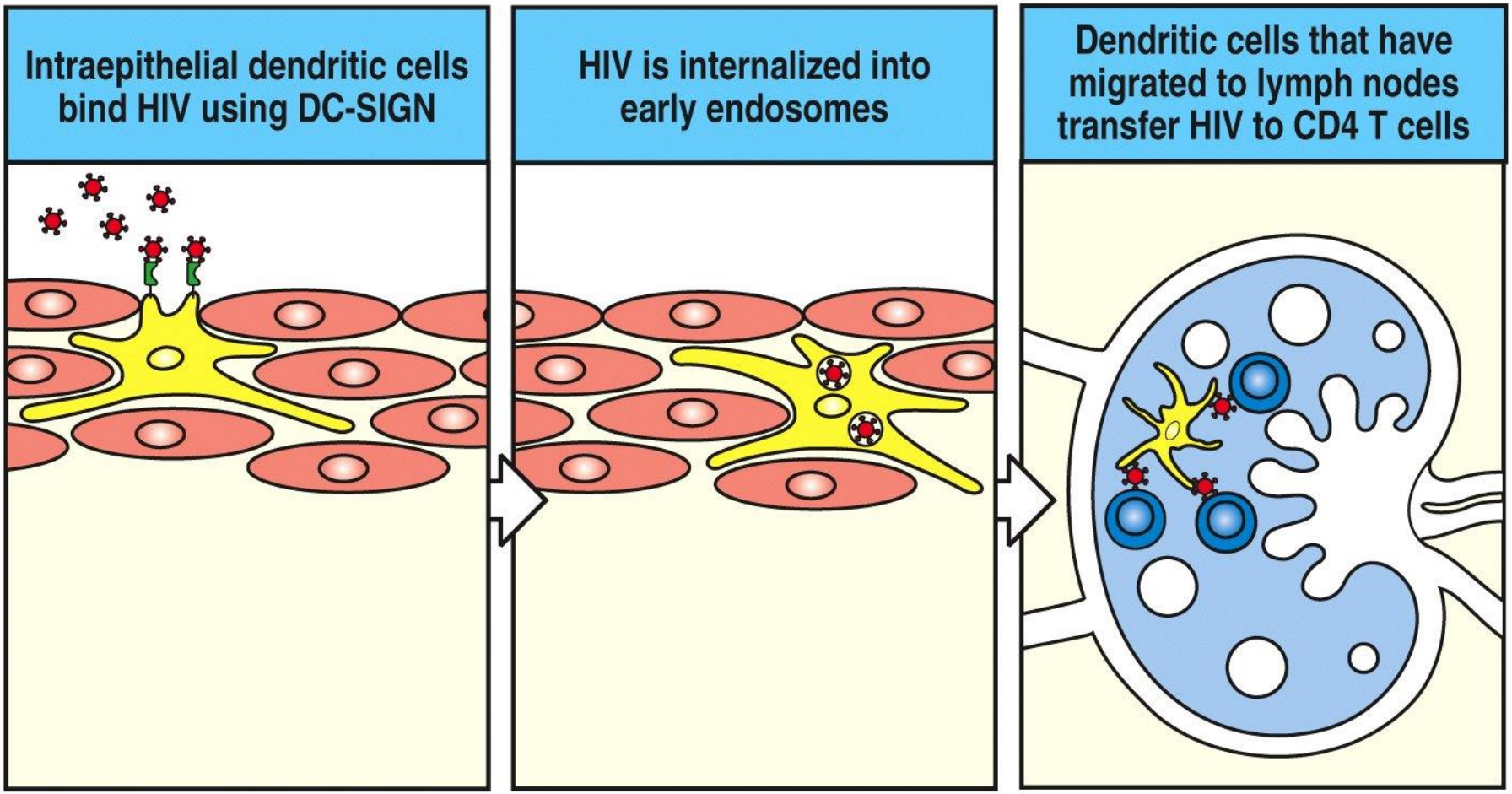
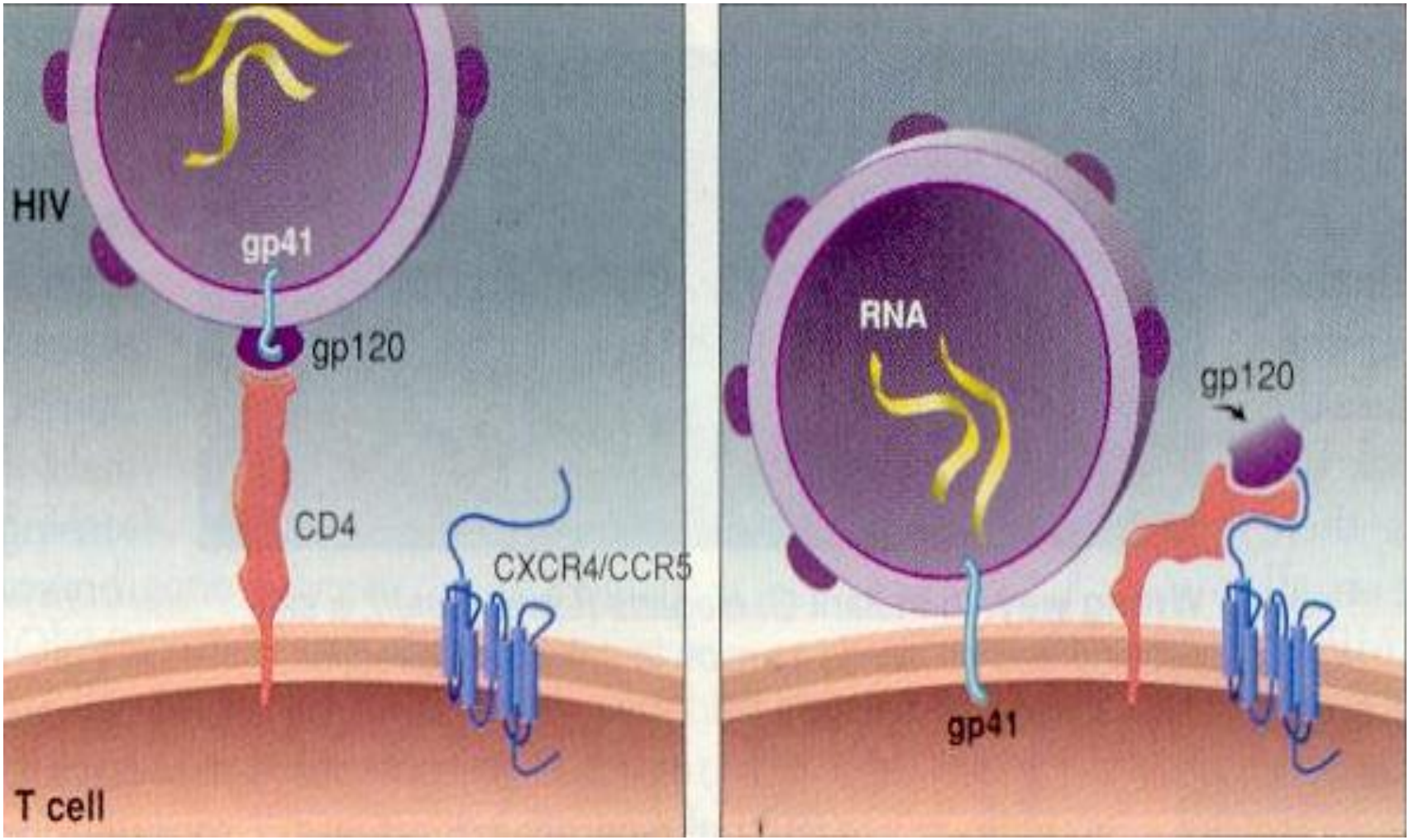


Figure 11-22 Immunobiology, 6/e. (© Garland Science 2005)

Infection of T-helper cells by HIV



Infection of T-Lymphotytes by HIV

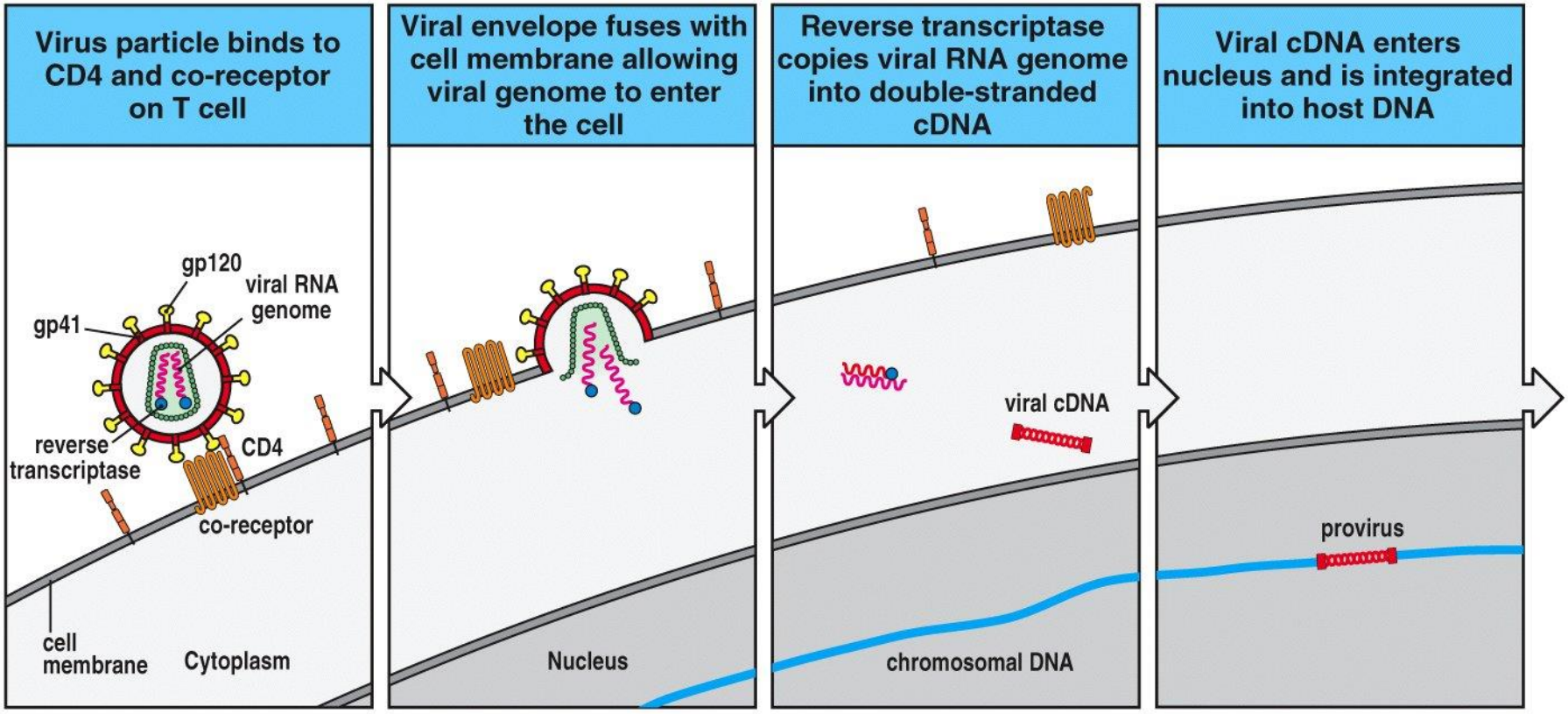


Figure 11-23 Immunobiology, 6/e. (© Garland Science 2005)

Mechanism of replication

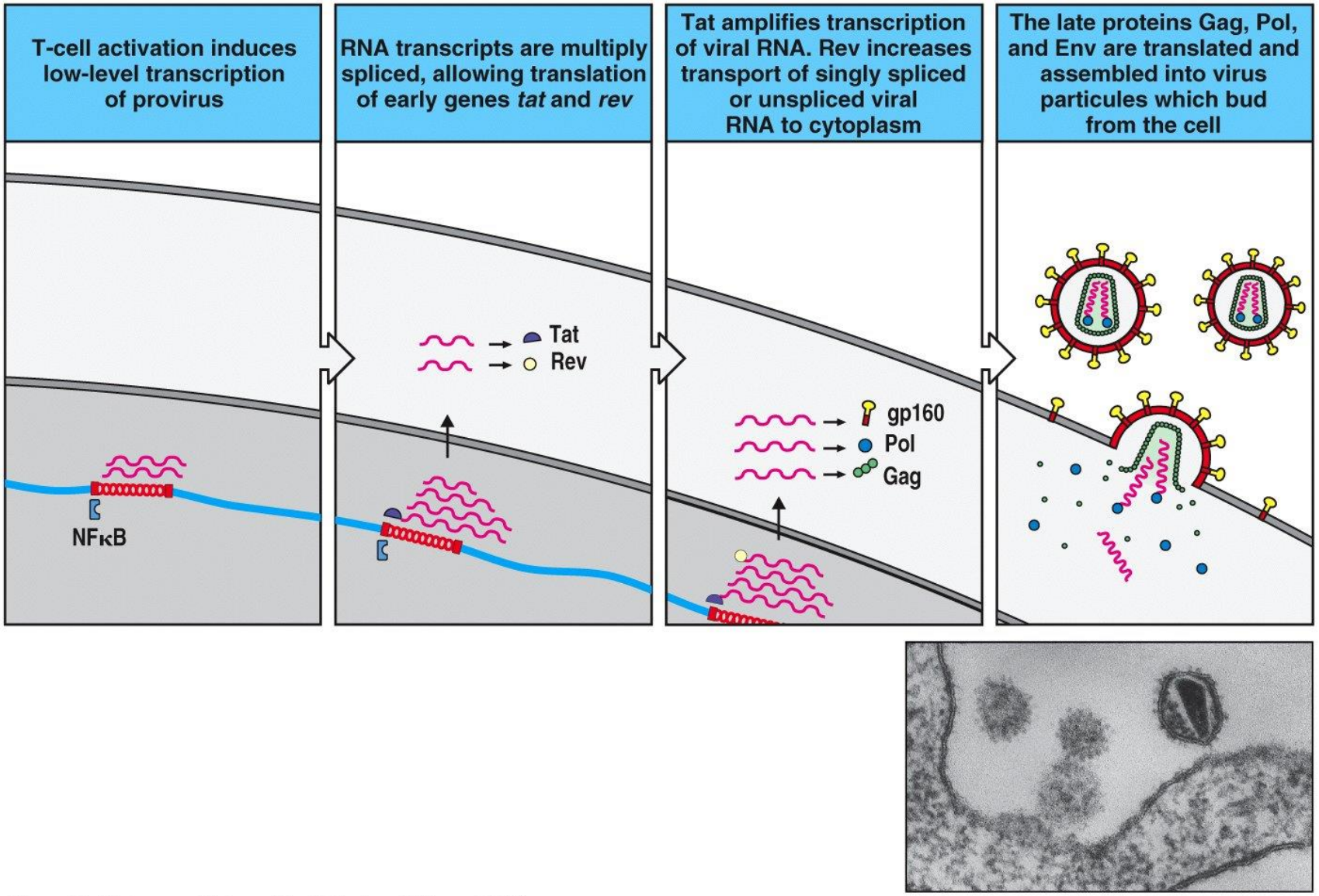
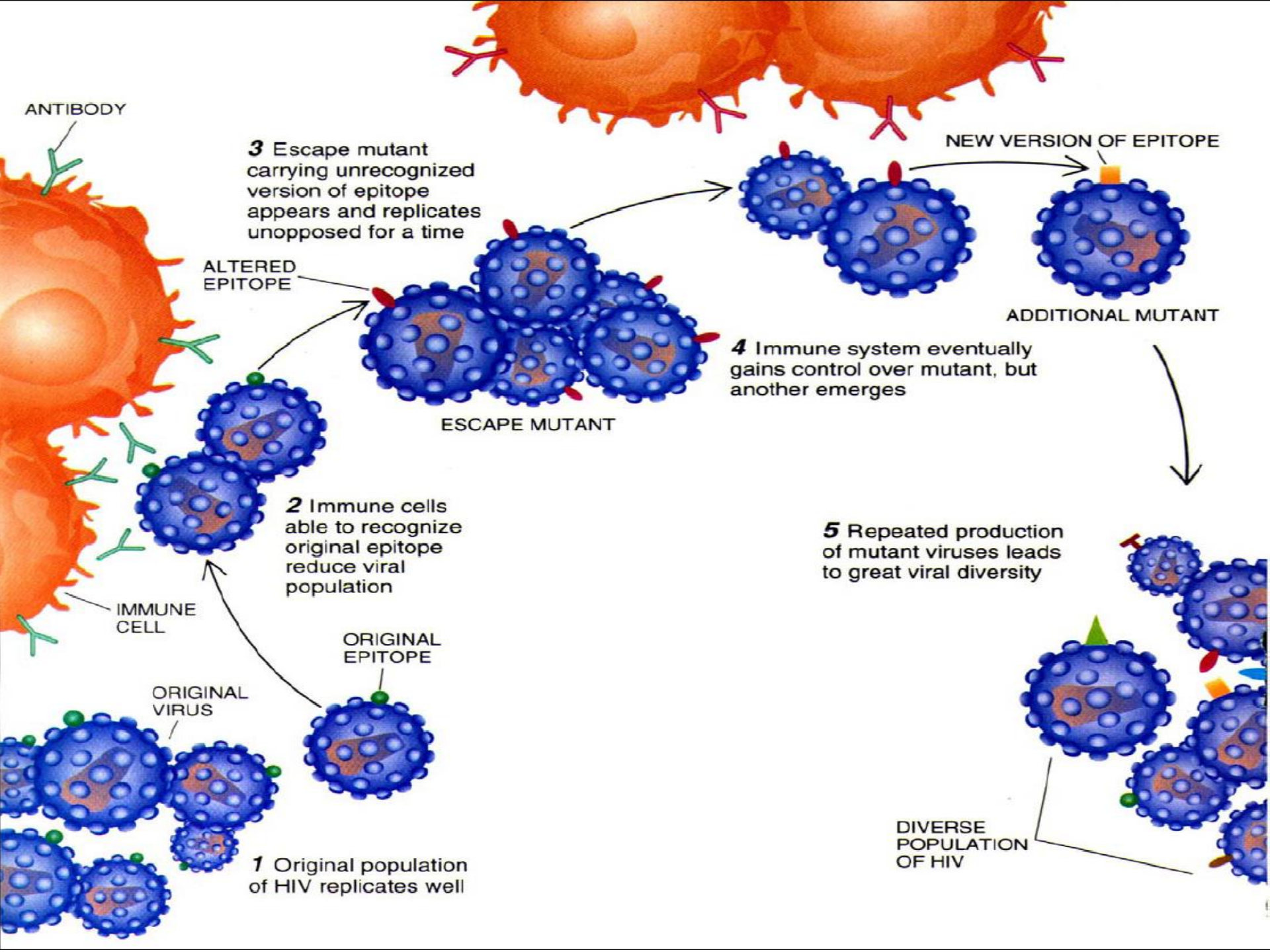


Figure 11-25 Immunobiology, 6/e. (© Garland Science 2005)


ANTIBODY
3 Escape mutant carrying unrecognized version of epitope appears and replicates unopposed for a time
NEW VERSION OF EPITOPE
ALTERED EPITOPE
ADDITIONAL MUTANT
4 Immune system eventually gains control over mutant, but another emerges
ESCAPE MUTANT
2 Immune cells able to recognize original epitope reduce viral population
5 Repeated production of mutant viruses leads to great viral diversity
IMMUNE CELL
ORIGINAL EPITOPE
ORIGINAL VIRUS
DIVERSE POPULATION OF HIV
1 Original population of HIV replicates well

- HIV hides in the genome of immune cells. Therefore the virus can not be easily recognized by the immune system
- Activation of T-lymphocytes by Interleukin-2 produces new virus
- HIV shows a high mutation rate.
- Immune response of CD8+ cytotoxic T-cells towards HIV infected cells is weak.

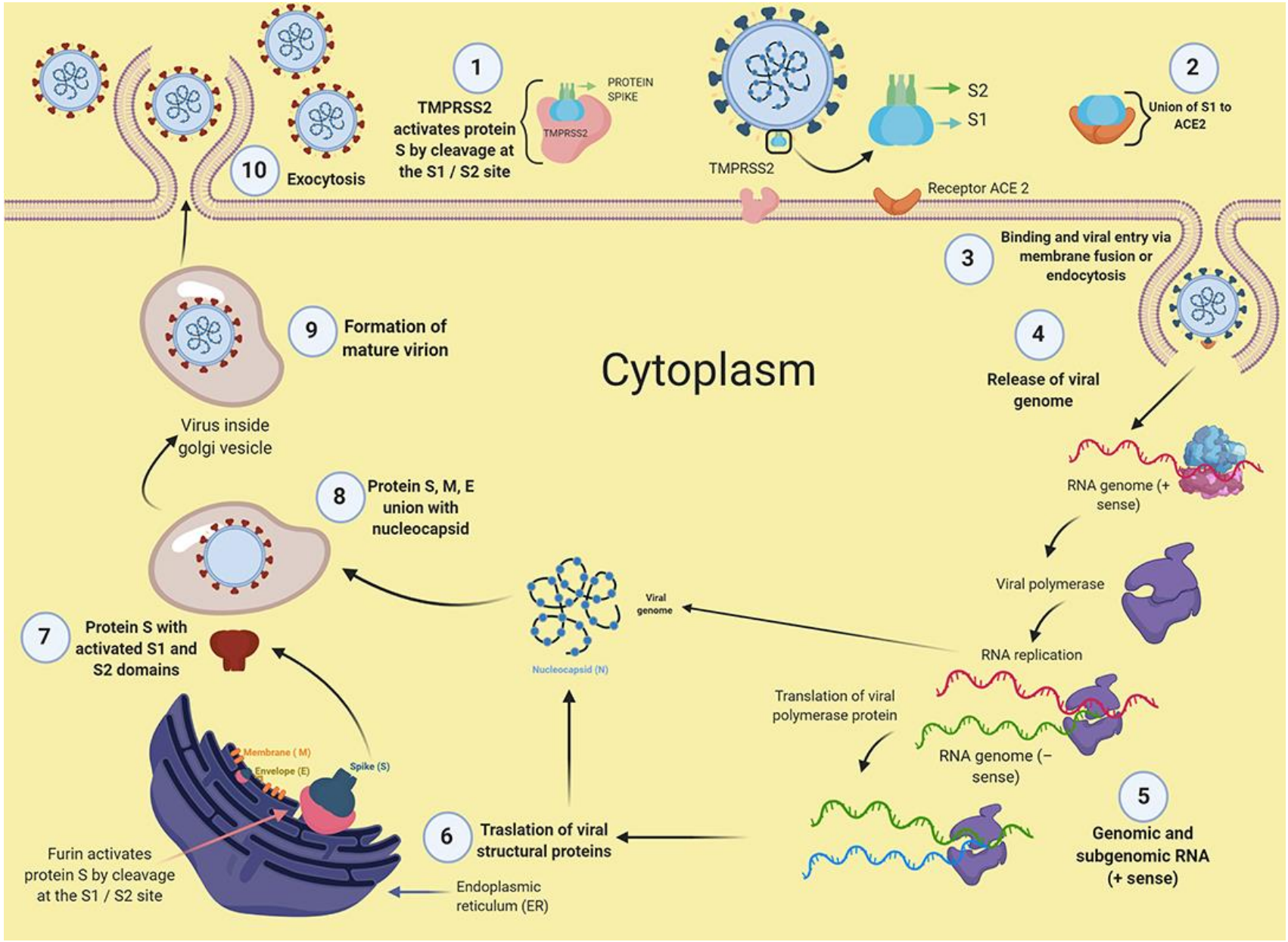
Opportunistic infections leading to the disease pattern of AIDS

Infections	
Parasites	*Toxoplasma* spp. *Cryptosporidium* spp. *Leishmania* spp. *Microsporidium* spp.
Intracellular bacteria	*Mycobacterium tuberculosis* *Mycobacterium avium intracellulare* *Salmonella* spp.
Fungi	*Pneumocystis carinii* *Cryptococcus neoformans* *Candida* spp. *Histoplasma capsulatum* *Coccidioides immitis*
Viruses	Herpes simplex Cytomegalovirus Varicella zoster

Malignancies
Kaposi's sarcoma - HHV8 Non-Hodgkin's lymphoma, including EBV-positive Burkitt's lymphoma Primary lymphoma of the brain

Figure 11-30 Immunobiology, 6/e. (© Garland Science 2005)

Sars-CoV2 Infection: Mechanism



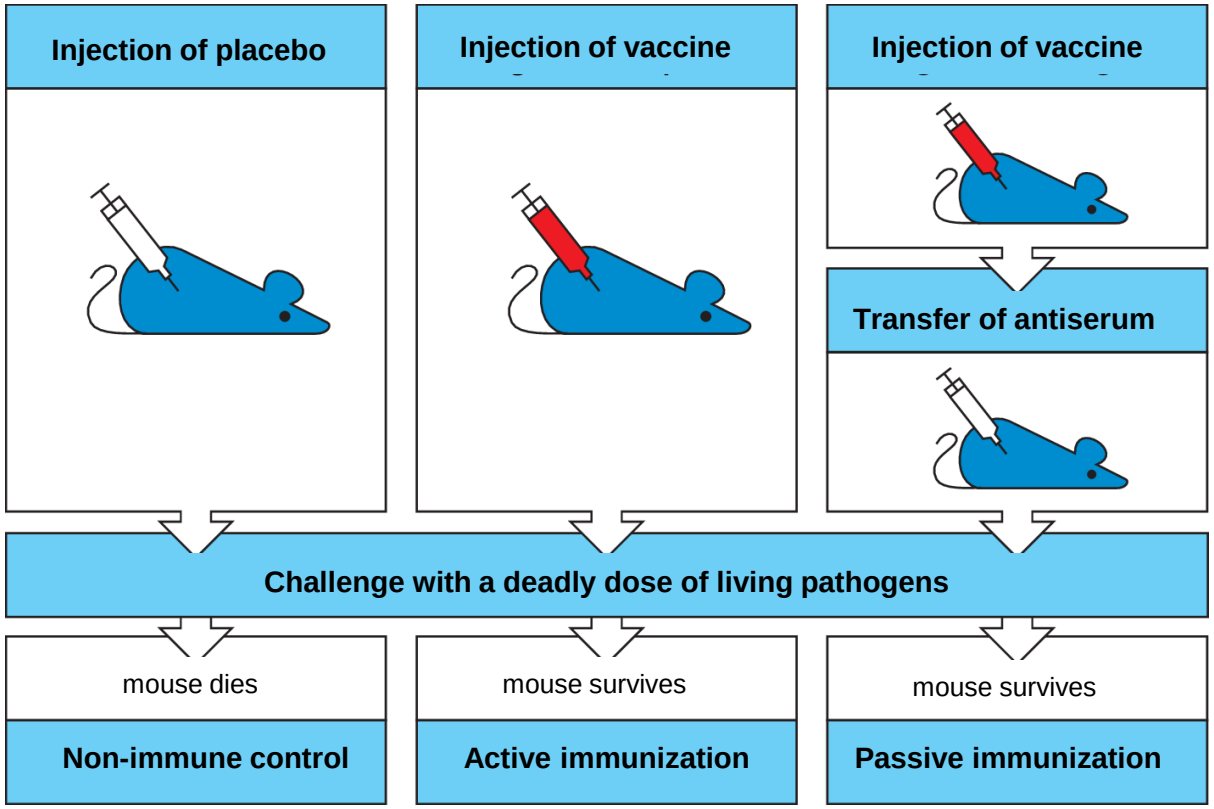
doi.org/10.3389/fneur.2020.01039

Classification of vaccines

Vaccines
(active Immunization)

Antisera und immunglobulines
(passive Immunization)

Passive vs. Active Immunization



Janeway Immunologie (2018) Springer Spektrum, 9. Auflage

Passive Immunization

Development of serum therapy against diphtheria by Emil von Behring in the 1890s

Darstellung der Serumproduktion – Intoxikation der Pferde (links) und Aderlass zur Blutabnahme (rechts) und ›Serumherstellung‹ in den Behringwerken, Fritz Gehrke 1906

Immunologie in Deutschland, Deutsche Gesellschaft für Immunologie (Hg.), 2017

Passive Immunization

e.g.: Snake Venoms – Antivenin / Antivenom

The puff adder in Africa is extremely poisonous: between five and ten million people on the continent struggle with the consequences of a poisonous snake bite every year. (Imago / McPhoto)
www.deutschlandfunk.de

Active immunization - a success story in immunology

Abb. 3: Bildliche Darstellung der vermeintlich ersten Kuhpocken-Vakzination an James Phipps durch Edward Jenner 1796, Gemälde von Ernest Board (Abdruck mit freundlicher Genehmigung der Wellcome Collection London).

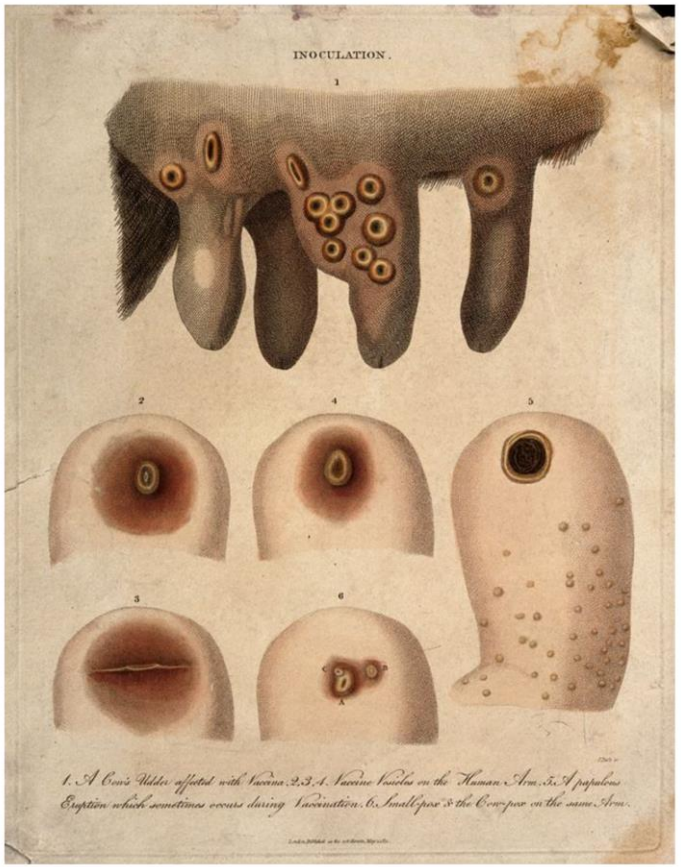
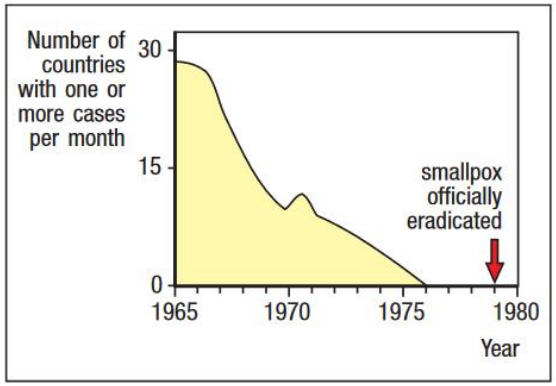
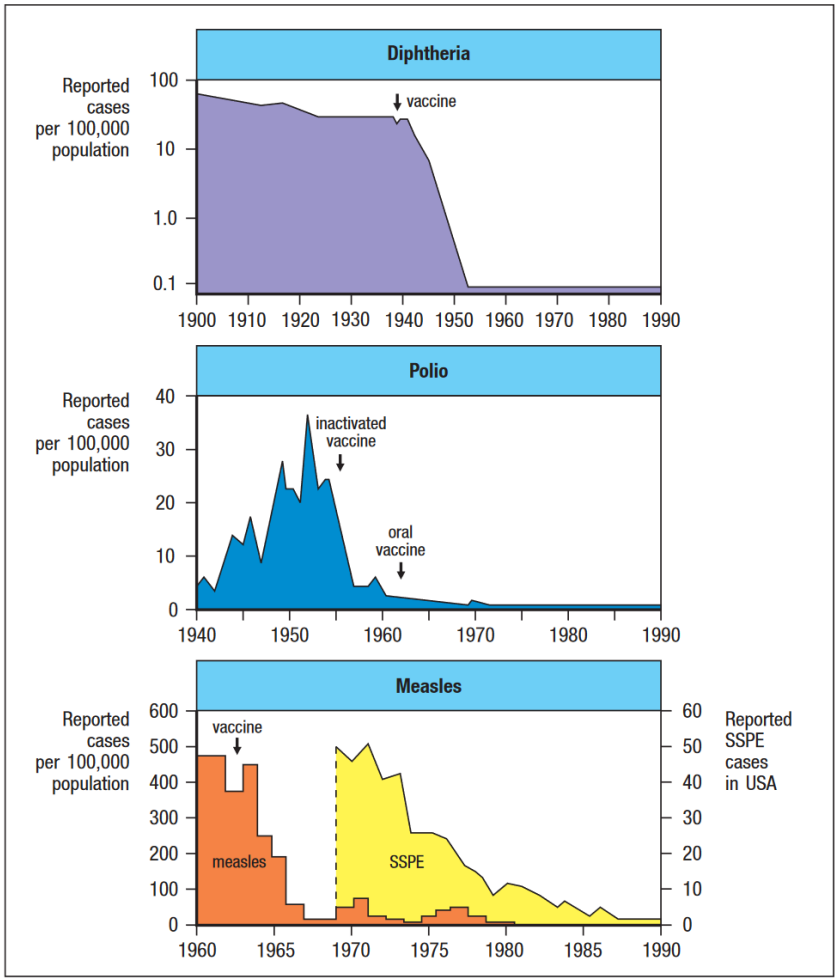


Abb. 2: Bildliche Darstellung der Kuhpocken am Euter einer Kuh (1), Kuhpocken-Pusteln auf einem menschlichen Arm (2–5) sowie Kuh- und Menschenpocken auf einem Arm (6), Darstellung von J. Pass 1811 (Abdruck mit freundlicher Genehmigung der Wellcome Collection London).

AC Hüntelmann, *Immunologie,* Band 3, Heft 3 (2019)

Active immunisation - a success story in immunology





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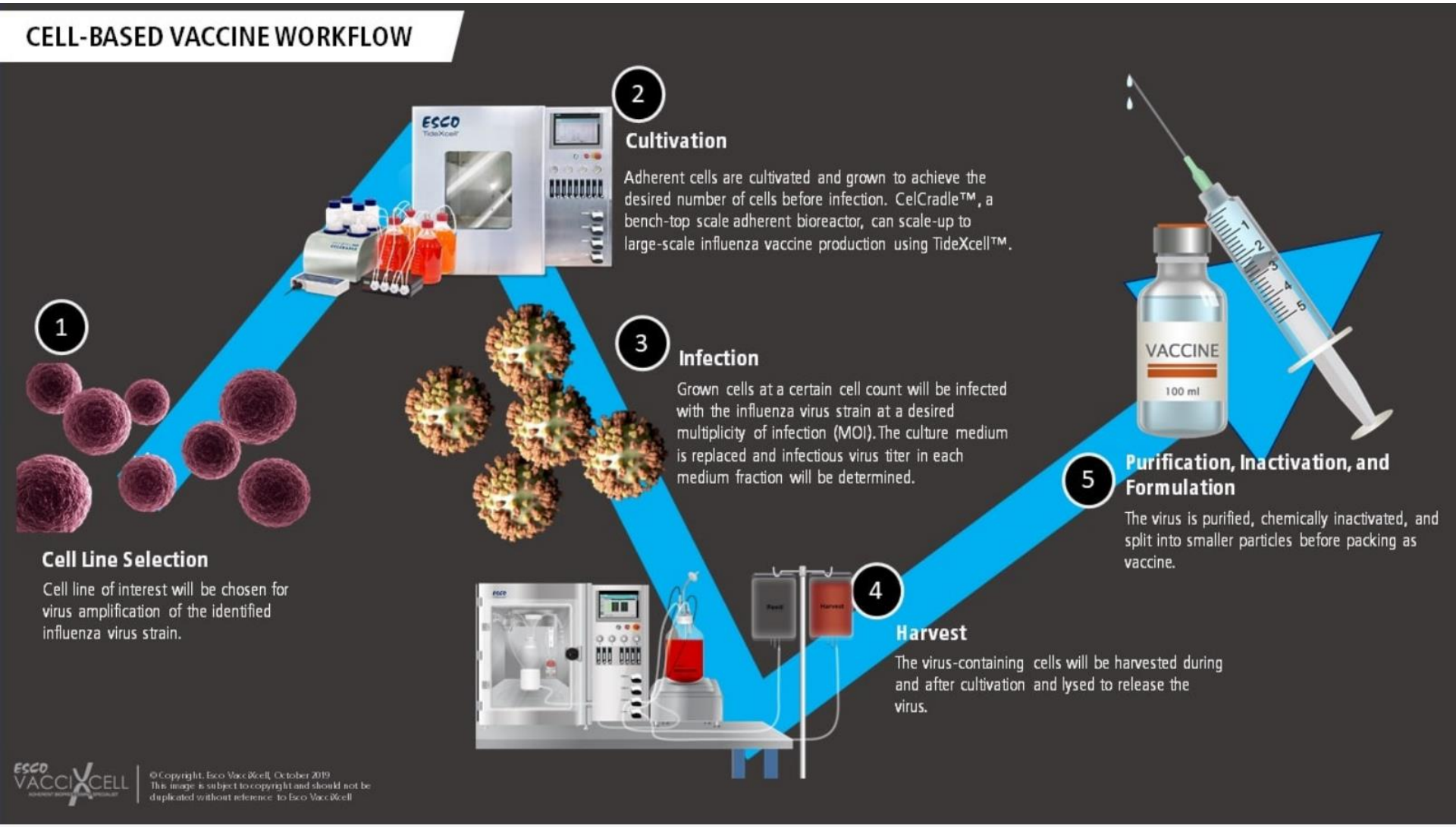
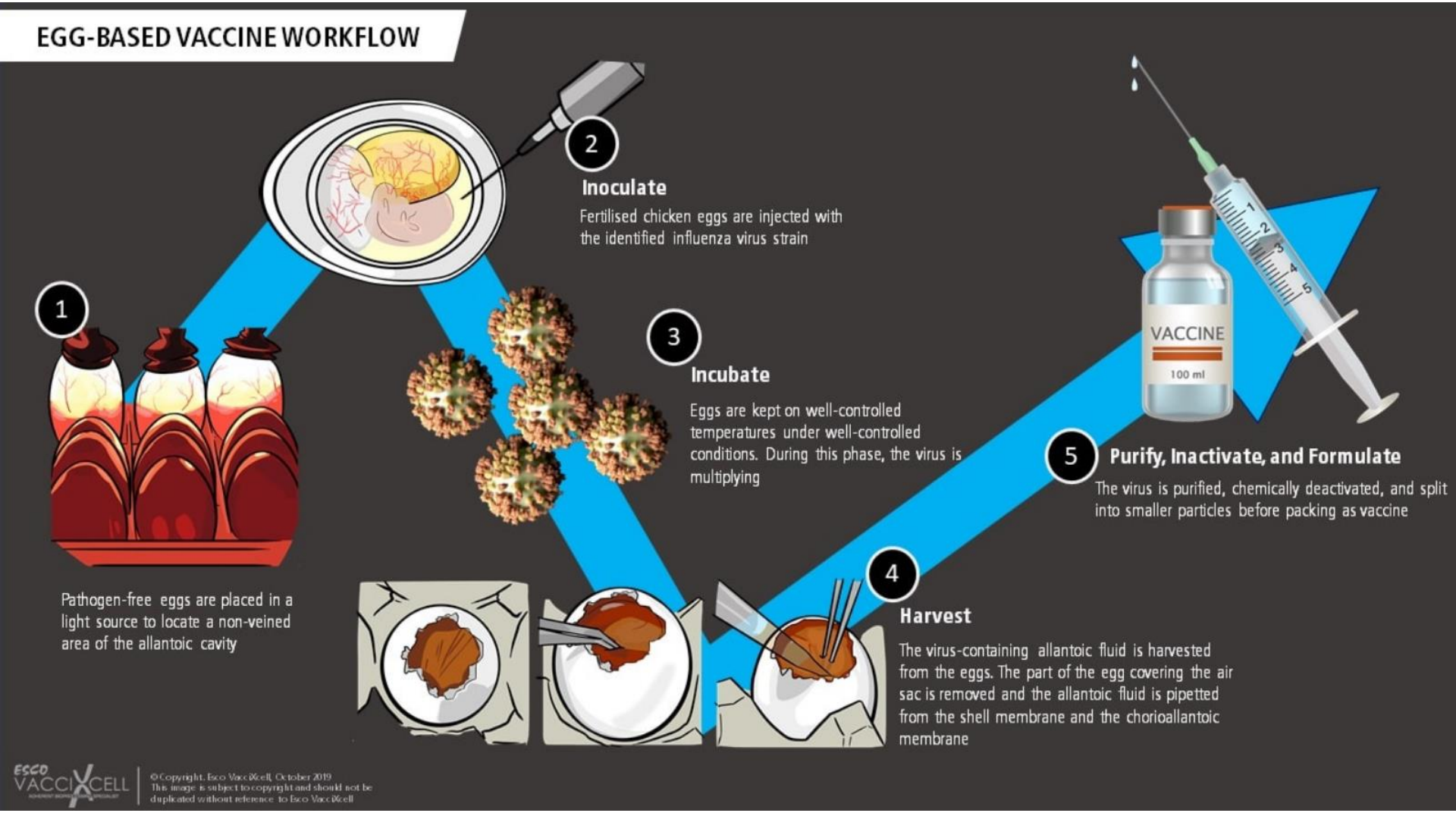
Production of Influenza vaccines in cell culture



Production of Influenza vaccine in hen eggs



Production of an attenuated virus vaccine in cell culture

Production of an attenuated viral vaccine nowadays

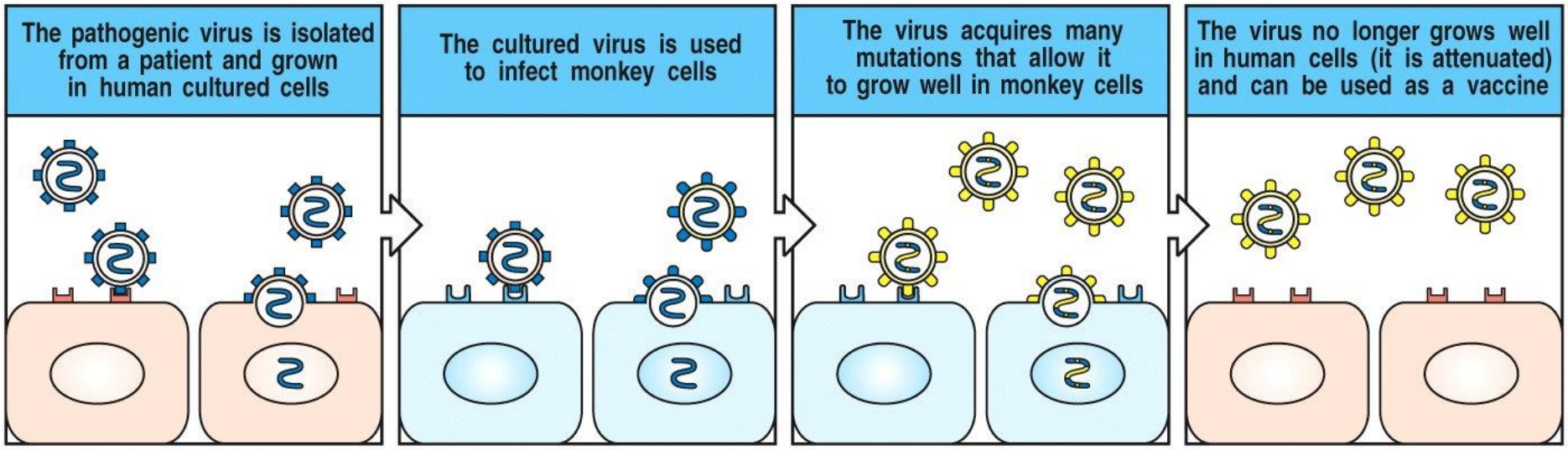


Figure 14-24 Immunobiology, 6/e. (© Garland Science 2005)

Janeway Immunology, Springer Spektrum

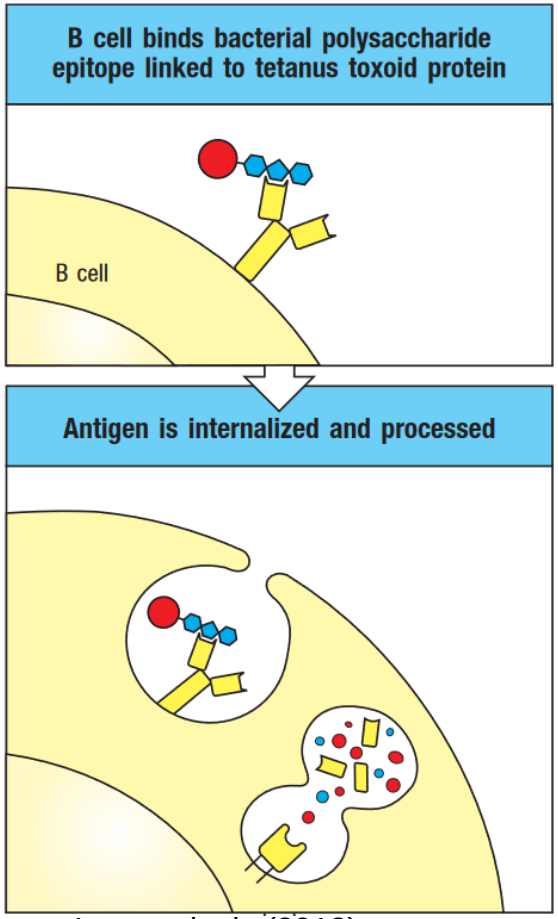
Role of adjuvants in increasing the immunogenicity of vaccine antigens

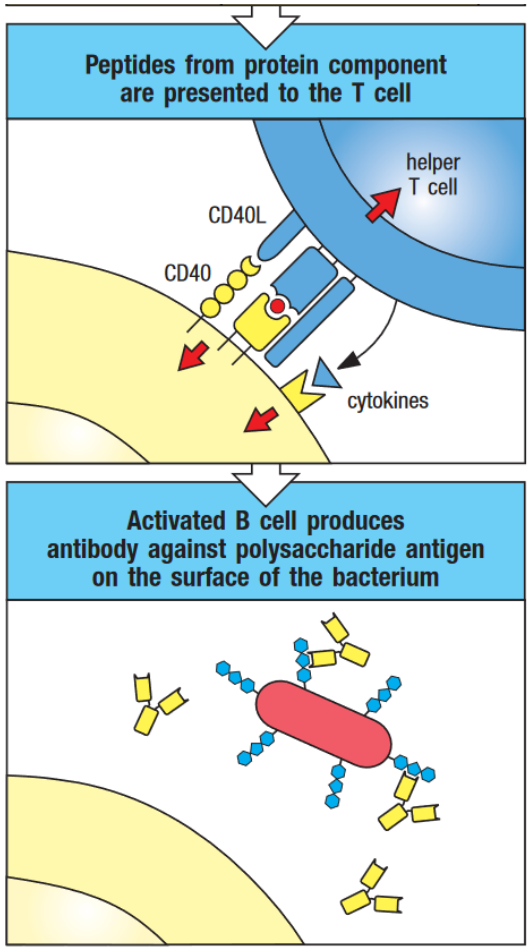
Adjuvants that enhance immune responses		
Adjuvant name	**Composition**	**Mechanism of action**
Incomplete Freund's adjuvant	Oil-in-water emulsion	Delayed release of antigen; enhanced uptake by macrophages
Complete Freund's adjuvant	Oil-in-water emulsion with dead mycobacteria that stimulate C-type lectin receptors	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators in macrophages
Freund's adjuvant with MDP	Oil-in-water emulsion with muramyl dipeptide (MDP), a constituent of mycobacteria that stimulates NOD-like receptors	Similar to complete Freund's adjuvant
Alum (aluminum hydroxide)	Aluminum hydroxide gel	Delayed release of antigen; enhanced macrophage uptake
Alum plus *Bordetella pertussis*	Aluminum hydroxide gel with killed *B. pertussis*	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators
Immune stimulatory complexes (ISCOMs)	Matrix of Quil A containing viral proteins	Delivers antigen to cytosol; allows induction of cytotoxic T cells
TLR agonists	Lipopolysaccharide, flagellin, lipopeptides, ds-RNA, unmethylated DNA	Inflammatory cytokine production, induction of co-stimulators, enhanced antigen presentation to T cells
NOD-like receptor (NLR) agonists	Muramyl dipeptide (bacterial cell wall constituent)	Inflammatory cytokine production, induction of co-stimulators, enhanced antigen presentation to T cells
C-type lectin receptor agonists	Mycobacterial cell wall component trehalose-6,6′-dimycolate	Inflammatory cytokine production

Only in animal vaccine due to strong side-effects

Janeway Immunologie (2018)
Springer Spektrum, 9. Auflage

Conjugate vaccines have been developed as a result of linked recognition between T and B cells





Janeway Immunologie (2018)
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e.g. Neisseria meningitidis (meningococcus), Strepto coccus pneumoniae (pneumococcus), and H. influenzae

List of Antiviral vaccines

Color code:
Inactivated
Protein
Attenuated

Virus	Diseases or conditions	Vaccine(s)
Hepatitis A virus	Hepatitis A	Hepatitis A vaccine
Hepatitis B virus	Hepatitis B	Hepatitis B vaccine
Human papillomavirus	Cervical cancer, Genital warts, anogenital cancers	HPV vaccine
Influenza virus	Influenza	Influenza vaccine
Measles virus	Measles	MMR vaccine
Mumps virus	Mumps	MMR vaccine
Polio virus	Poliomyelitis	Polio vaccine
Rabies virus	Rabies	Rabies vaccine
Rotavirus	Rotaviral gastroenteritis	Rotavirus vaccine
Rubella virus	Rubella	MMR vaccine
Variola virus	Smallpox	Smallpox vaccine
Yellow fever virus	Yellow fever	Yellow Fever vaccine

Source:Wikipedia

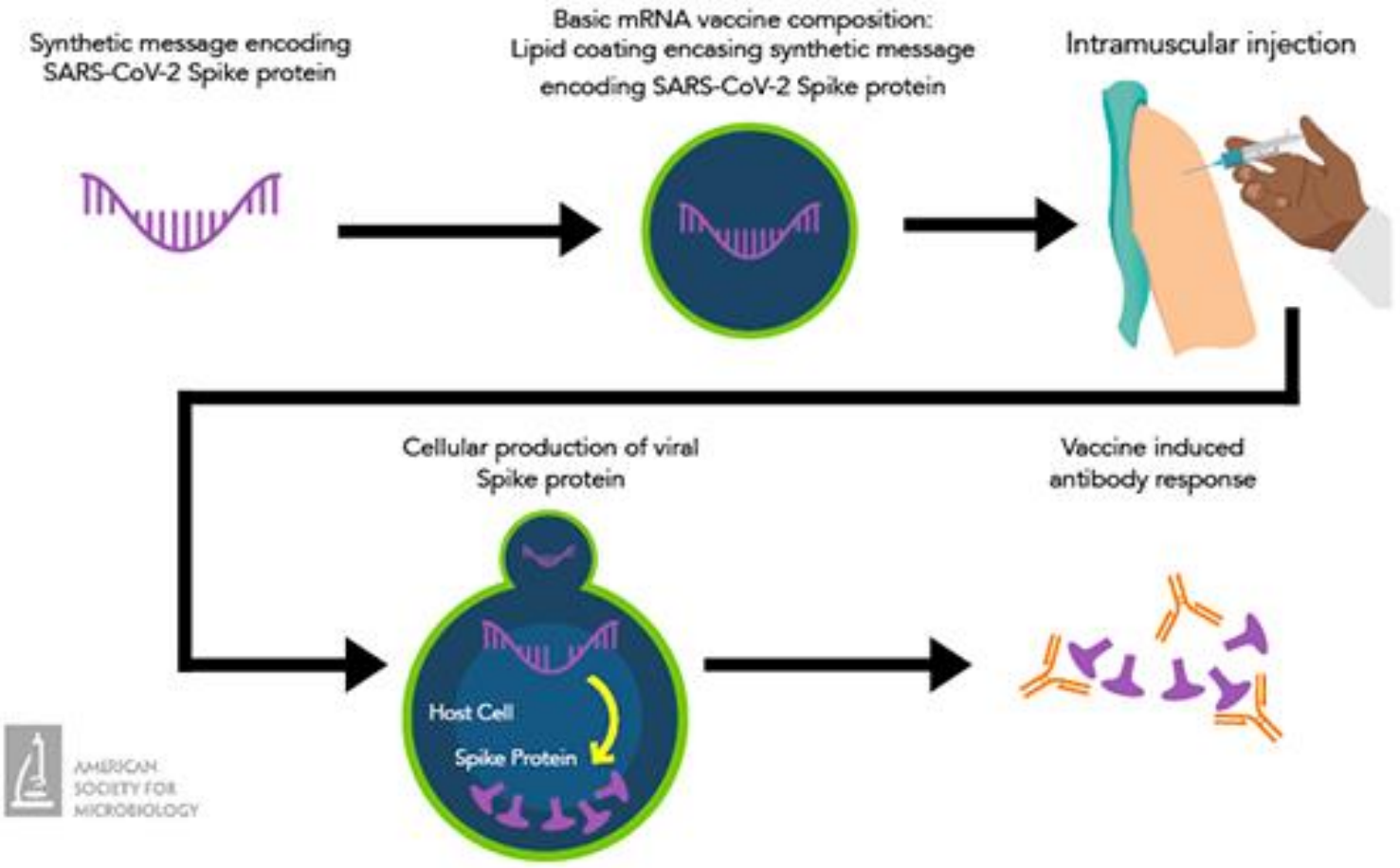
List of Antibacterial vaccines

Color code:
Inactivated
(Glyco)Protein
Attenuated

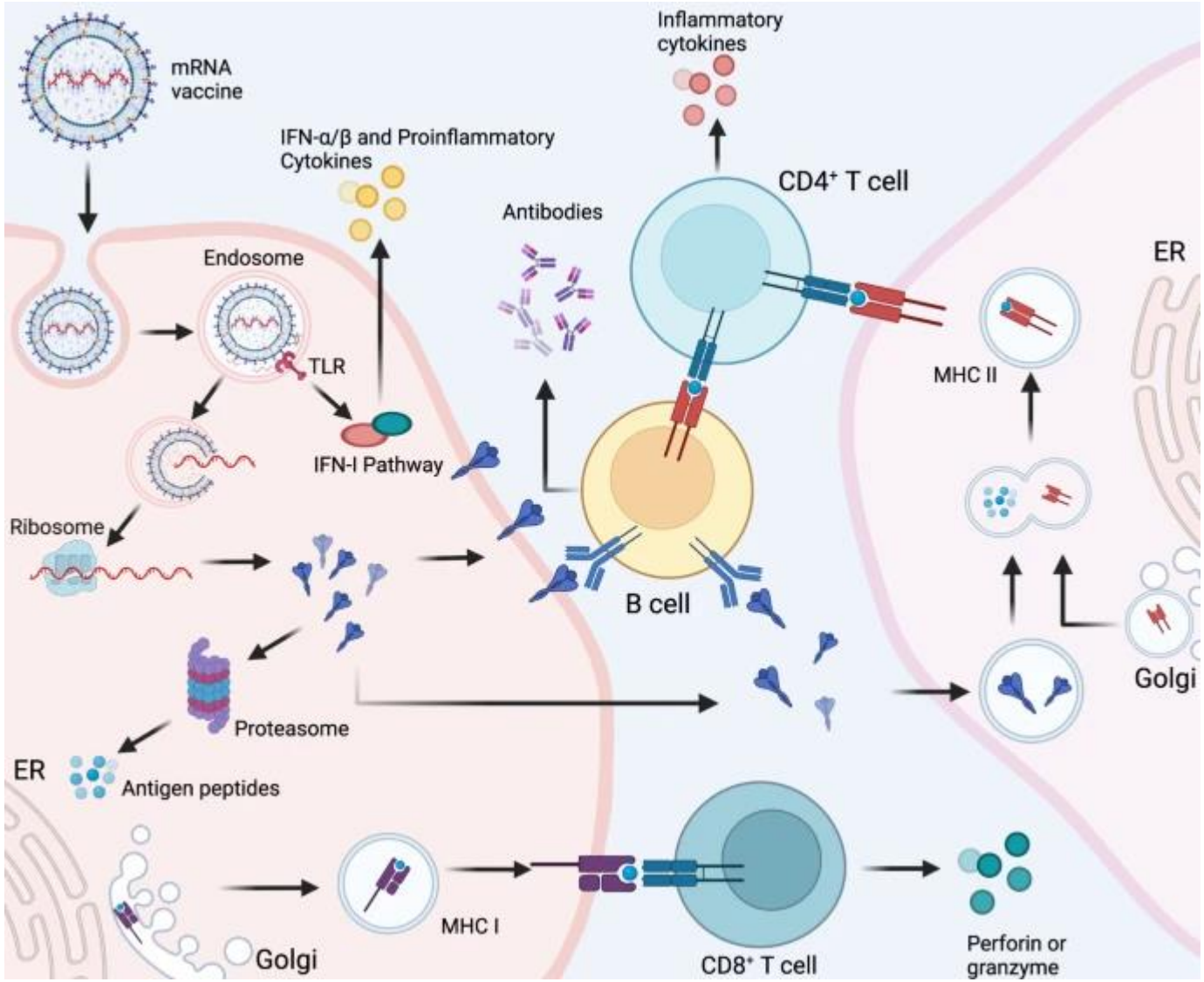
Bacterium	Diseases or conditions	Vaccine(s)
Bacillus anthracis	Anthrax	Anthrax vaccines
Bordetella pertussis	Whooping cough	DPT vaccine
Clostridium tetani	Tetanus	DPT vaccine
Corynebacterium diphtheriae	Diphtheria	DPT vaccine
Haemophilus influenzae type B (Hib)	Epiglottitis, meningitis, pneumonia	Hib vaccine
Mycobacterium tuberculosis	Tuberculosis	(Tuberculosis (BCG) vaccine)
Neisseria meningitidis	Meningococcal meningitis	Meningococcal vaccine
Salmonella typhi	Typhoid fever	Typhoid vaccine
Streptococcus pneumoniae	Pneumococcal pneumonia	Pneumococcal conjugate vaccine
Vibrio cholerae	Cholera	Cholera vaccine

Source:Wikipedia

Covid 19 mRNA vaccine

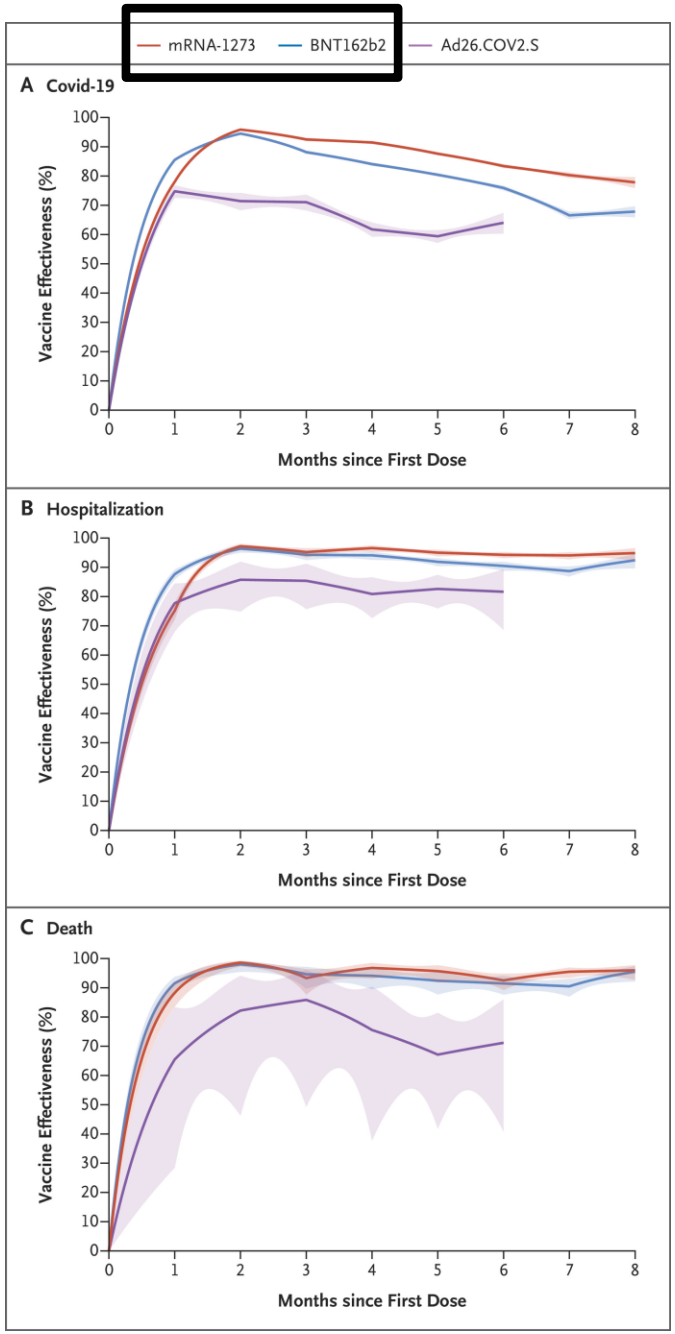


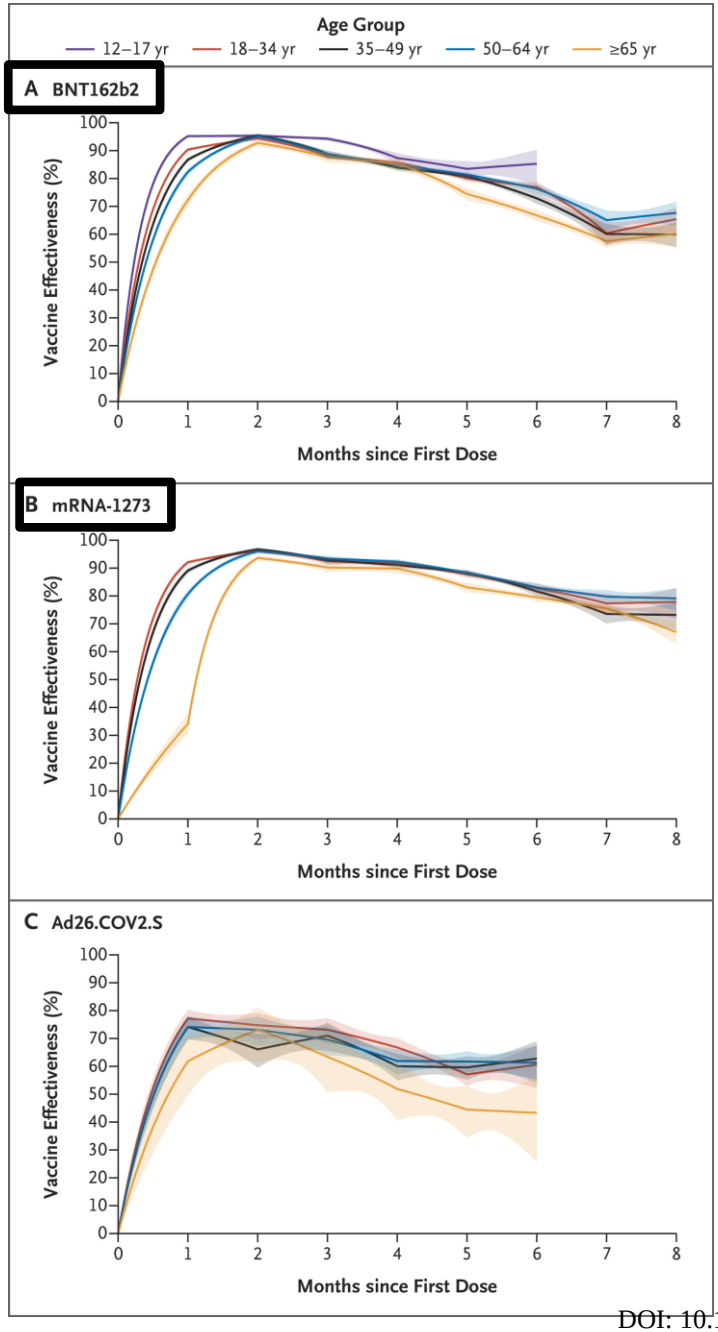
Cellular and humoral immune responses induced by messenger RNA (mRNA) vaccine



doi.org/10.1038/s41392-022-00950-y

Effectiveness of Covid 19 mRNA vaccines





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