

Vaccination

Vaccination - the beginning (I)

Edward Jenner (1749 -1823)

Jenner observed that milkmaids were generally immune to smallpox. Based on this he postulated and eventually „experimentally showed“ that the pus in the blisters that milkmaids received from cowpox (a disease similar to smallpox, but much less virulent) protected them from smallpox.



Vaccination - the beginning (II)

Louis Pasteur (1822 -1895)

Pasteur observed that attenuated (=weakened) strains of chicken cholera would allow him to „immunize“ chicken without killing them. He realized that inactivation of otherwise disease causing pathogens (anthrax) could protect animals from subsequent infection with the virulent strain. This was the beginning of the laboratory development of vaccines.



Vaccination - the beginning (II)

Emil von Behring; Shibasaburo Kitasato - 1890

After immunising rabbits with tetanus,
serum collected from these animals
was injected into mice



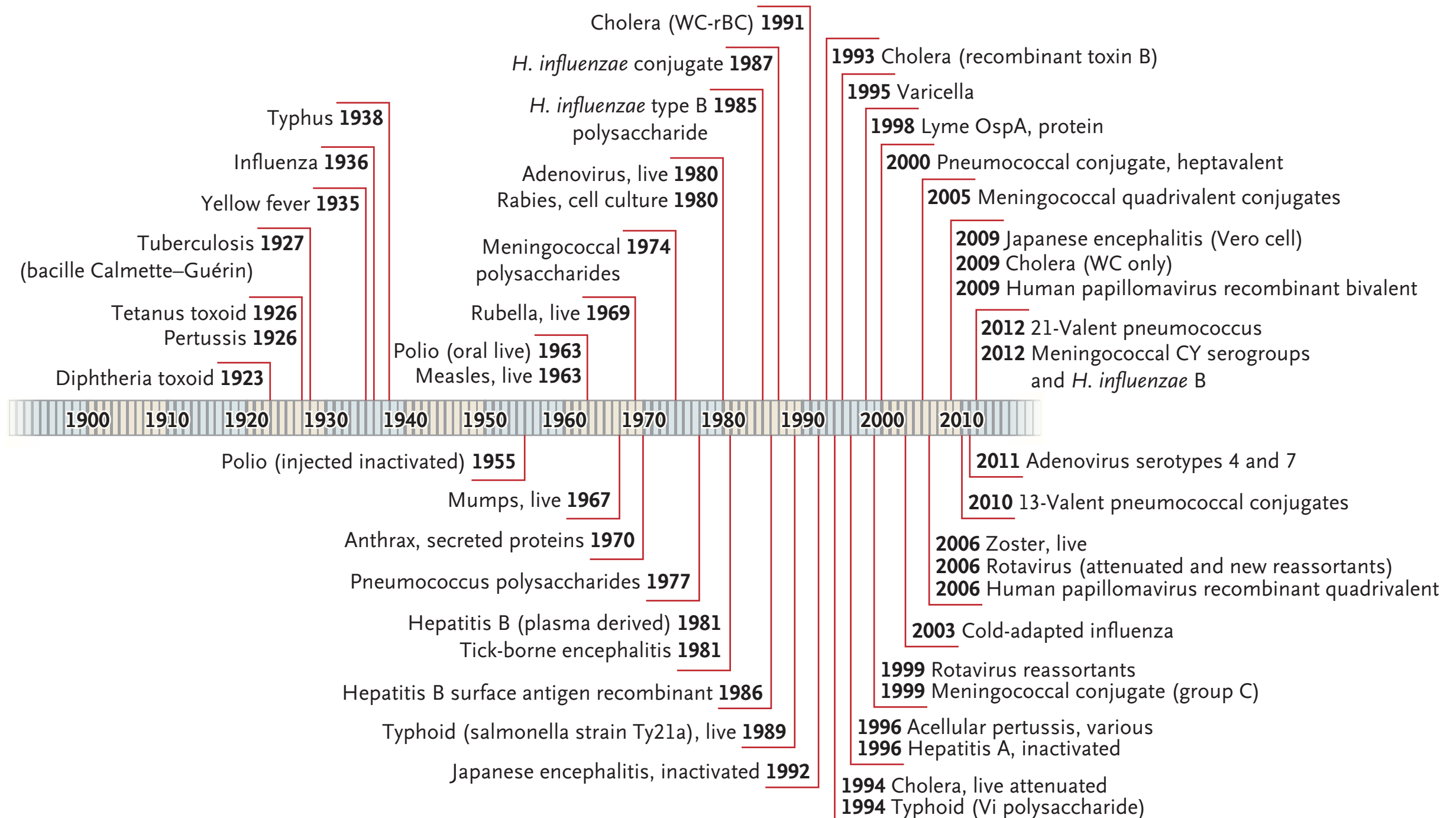
After 24 h mice were challenged with
live, virulent pathogens



Treated mice survived without
showing disease symptoms

Licensure of Commercial Vaccines

B



Immunization - the principles

Immunity to infectious organisms can be achieved by **active** or **passive immunization**.

Passive immunization

Preformed antibodies are transferred to a recipient

- Natural maternal antibodies
- Immune globulin
- Humanized monoclonal antibodies
- Antitoxin

Active immunization

Achieved by inoculation with pathogens that induce immunity but not disease or with pathogenic components

- Natural infection
- Vaccines

Passive immunisation - mechanism of action

Passive immunisation can exert its effects in a number of ways:

- Recruitment of complement for the immediate destruction of the pathogen
- Opsonisation of bacteria to facilitate phagocytosis and killing by macrophages and neutrophils
- Neutralization of toxins and viruses
- Antibody-bound to target cells can recruit NK cells, which kill target cells through ADCC (antibody-dependent cellular cytotoxicity)

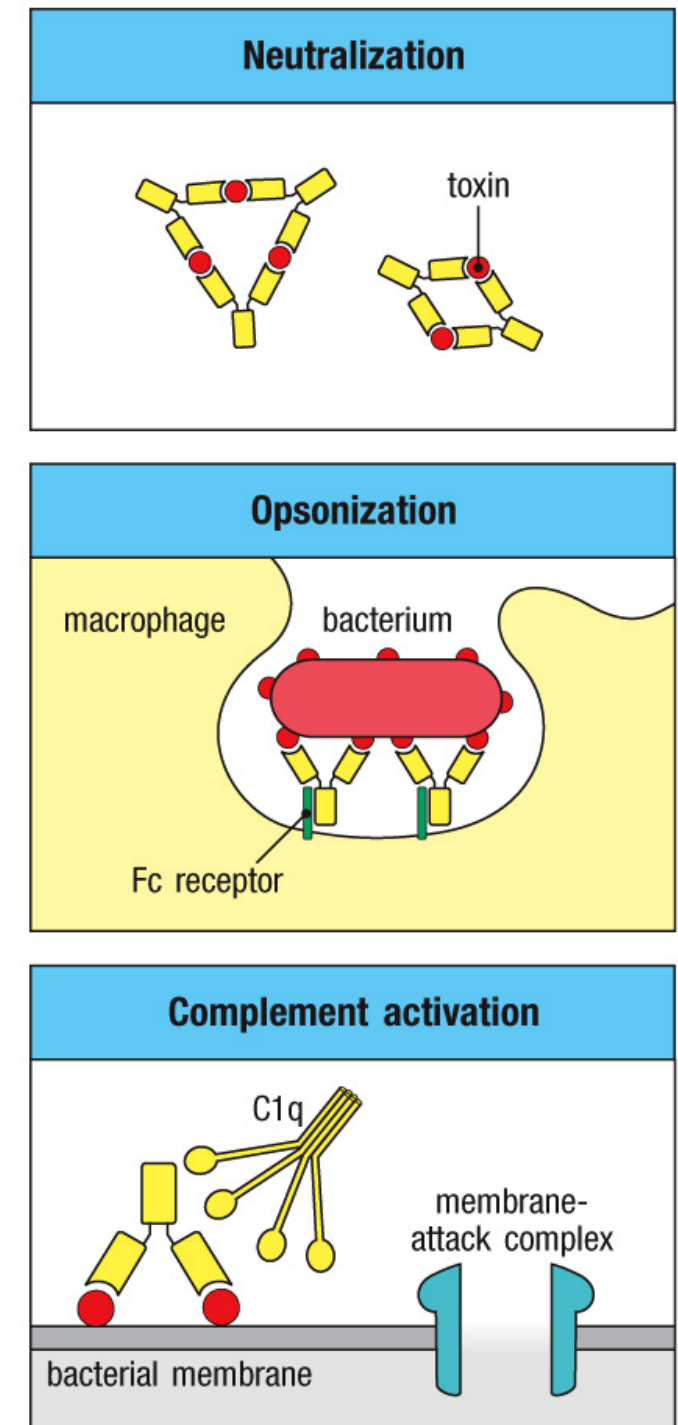


Figure 10.1 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Passive immunization - indications

- Immunodeficiency with inability to produce antibodies (B cell deficiencies)
- Exposure or likely exposure to a disease that will cause complications

Disease	Agent
Botulism	Horse antitoxin
Hepatitis A/B	Pooled human immunoglobulin
Rabies	Human or horse polygonal Ab
Tetanus	Pooled human immunoglobulin or horse antitoxin
Snake bite	Horse antivenin

Passive immunization - caution!

Passive immunisation alleviates and immediate condition, but because passive immunization does not activate the immune system, it generates **no memory response** and the protection provided is only **transient**.

Risks associated with passive immunization:

Anti-isotype response

If an antibody was produced in another species (e.g., horse), the recipient can mount a strong response to the isotypic determinants of the antibody - ultimately leading to anaphylaxis

Anti-allotype response

If human immunoglobulin is used, the recipient can mount a response against the specific allotype - although this response is less pronounced

Active immunization

The goal of active immunisation is to elicit **protective immunity** and **immunological memory**!

Active immunisation can be achieved by natural infection with a microorganism or by delivering a vaccine!

What are vaccines?

- Prevent disease by stimulating immunity without causing disease.
- Are composed of live attenuated microorganisms or non-living components.
- Are used prophylactically in healthy people or (rarely) therapeutically to treat disease!

Vaccine recommendations in Switzerland

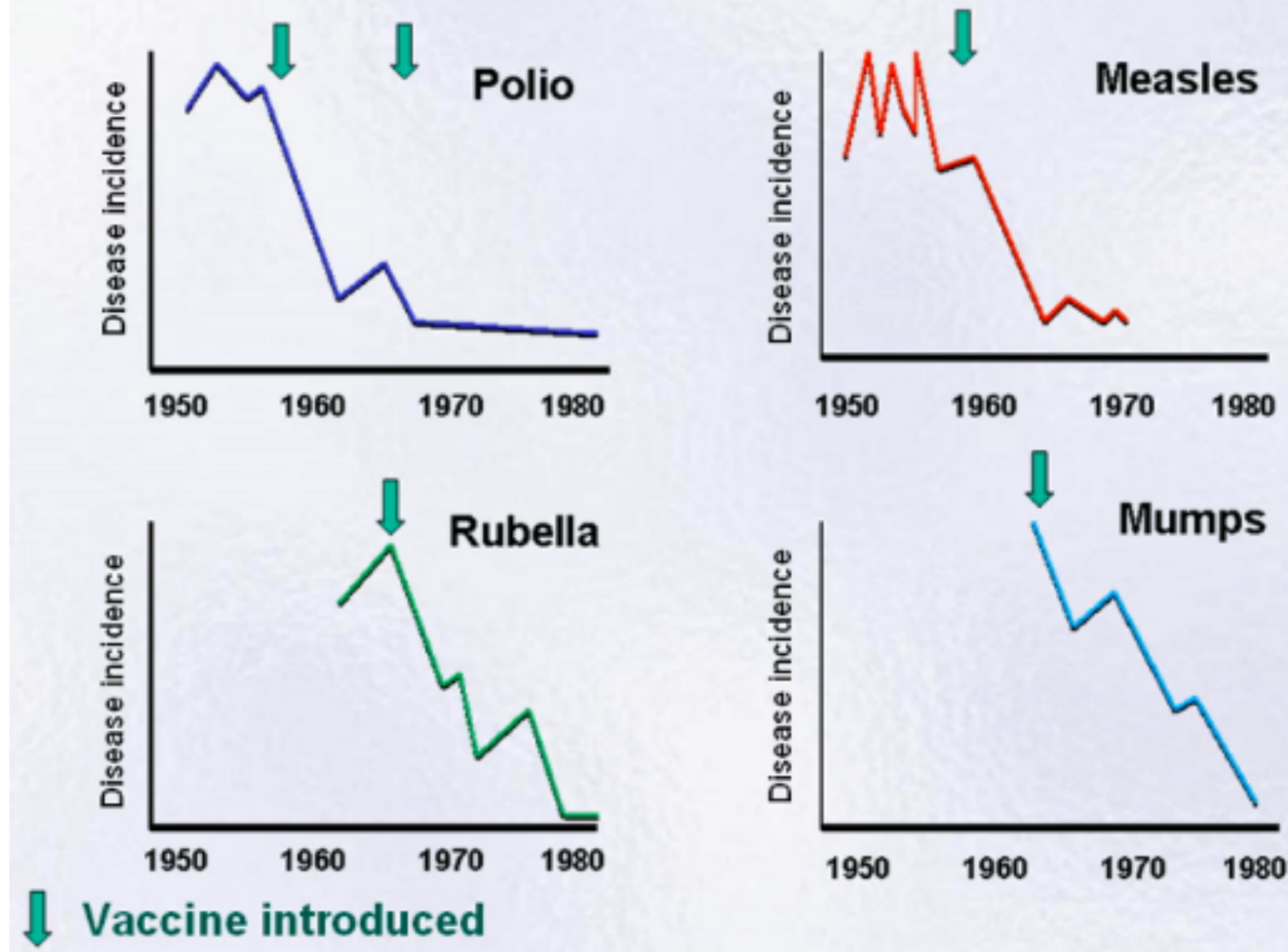
Alter ¹⁾	Diphtherie (D / d) ³⁾ Tetanus (T) ⁴⁾ Pertussis (P _a / p _a) ³⁾	<i>Haemophilus influenzae</i> Typ b (Hib)	Poliomyelitis (IPV)	Masern (M) Mumps (M) Röteln (R)	Hepatitis B (HBV) ¹⁷⁾	Varizellen (VZV)	Humane Papillo- maviren (HPV)	Influenza
Geburt					¹⁸⁾			
2 Monate ²⁾	DTP _a	Hib	IPV		(HBV) ¹⁹⁾			
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⁾

Vaccine recommendations in Switzerland

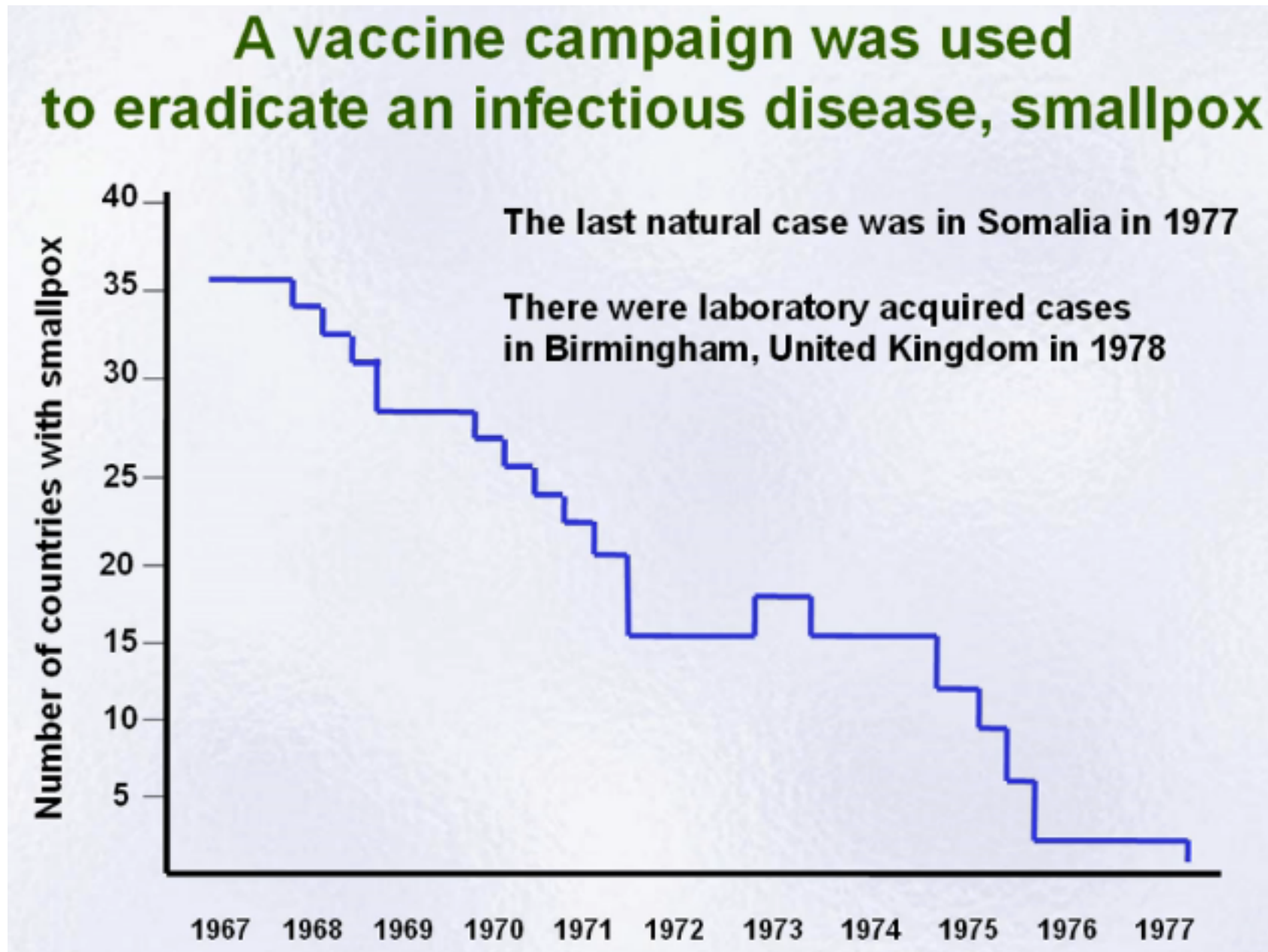
- Young children require boosters (repeated inoculations) to achieve sufficient protection (DTP)
- Live-attenuated vaccines are usually initiated beyond the age of 12 months
- Some vaccines are restricted to a certain sub-population (e.g., elderly)

Active immunization and disease incidence

The introduction of vaccines can have a dramatic impact on disease incidence (examples shown are the USA)



Active immunization and disease incidence



Composition of vaccines

Live attenuated microbes:

E.g., Oral polio, Smallpox, Measles, BCG

Microbes can be attenuated so that they lose their pathogenicity (= ability to cause disease) but they still retain the capability to immunize the host. Some microbes are pathogenic in one species, but not in another species (natural attenuation).

Dead whole microbes:

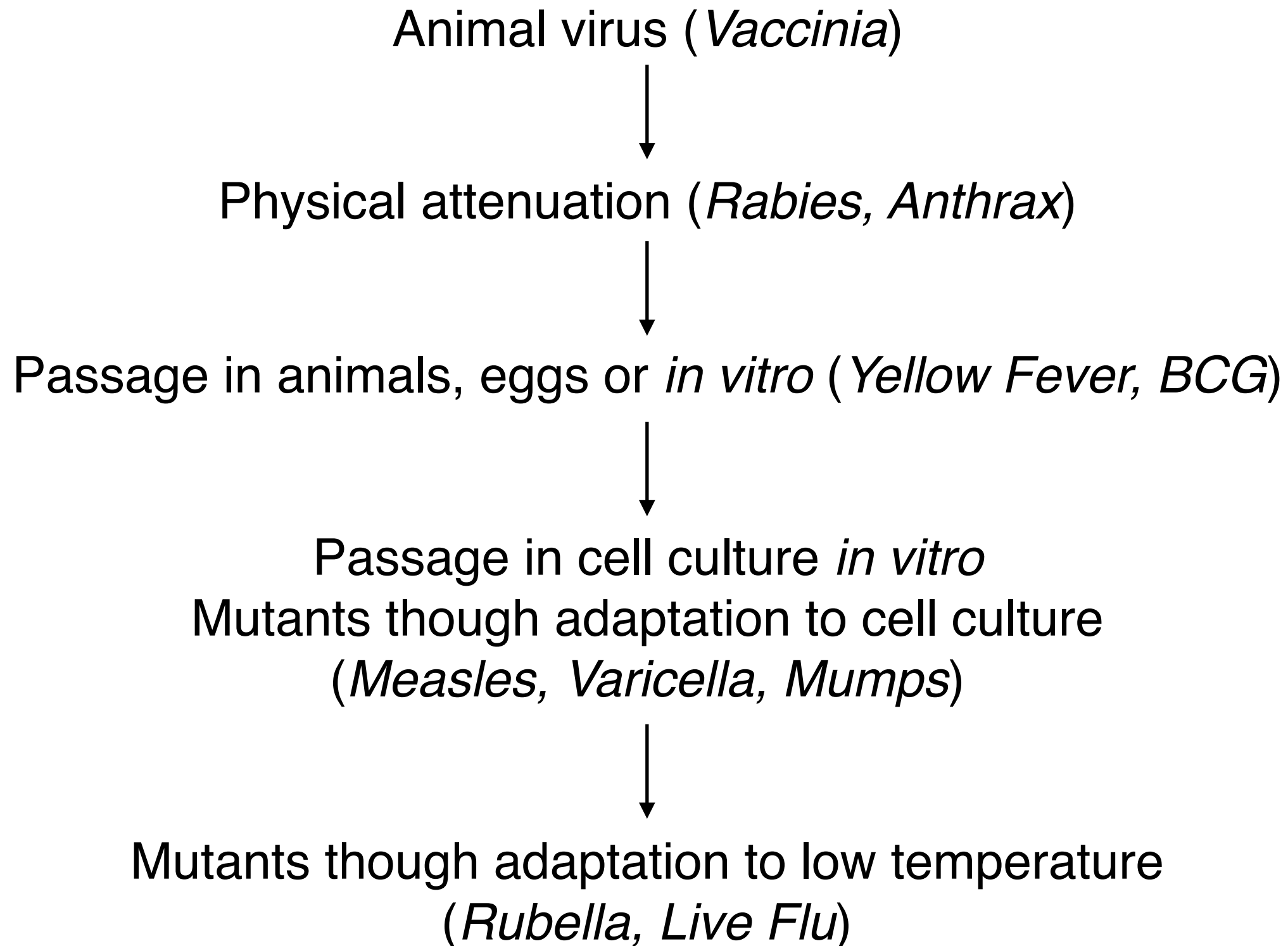
E.g., former whooping cough vaccine

Inactivation by means of heat or chemical substances.

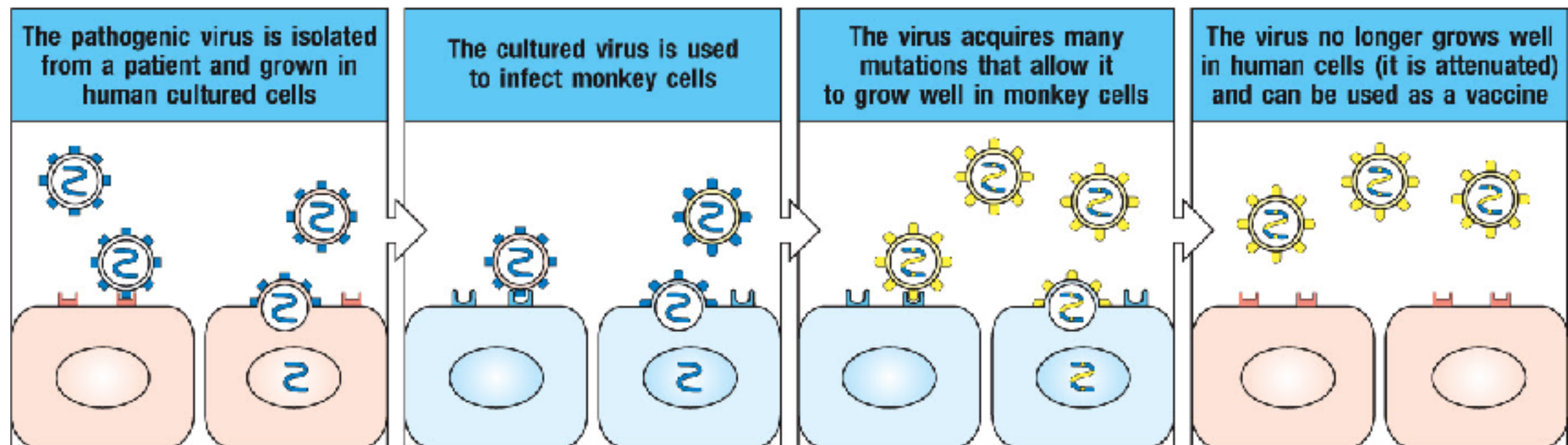
Purified proteins, peptides or non-protein antigens:

E.g., HepB

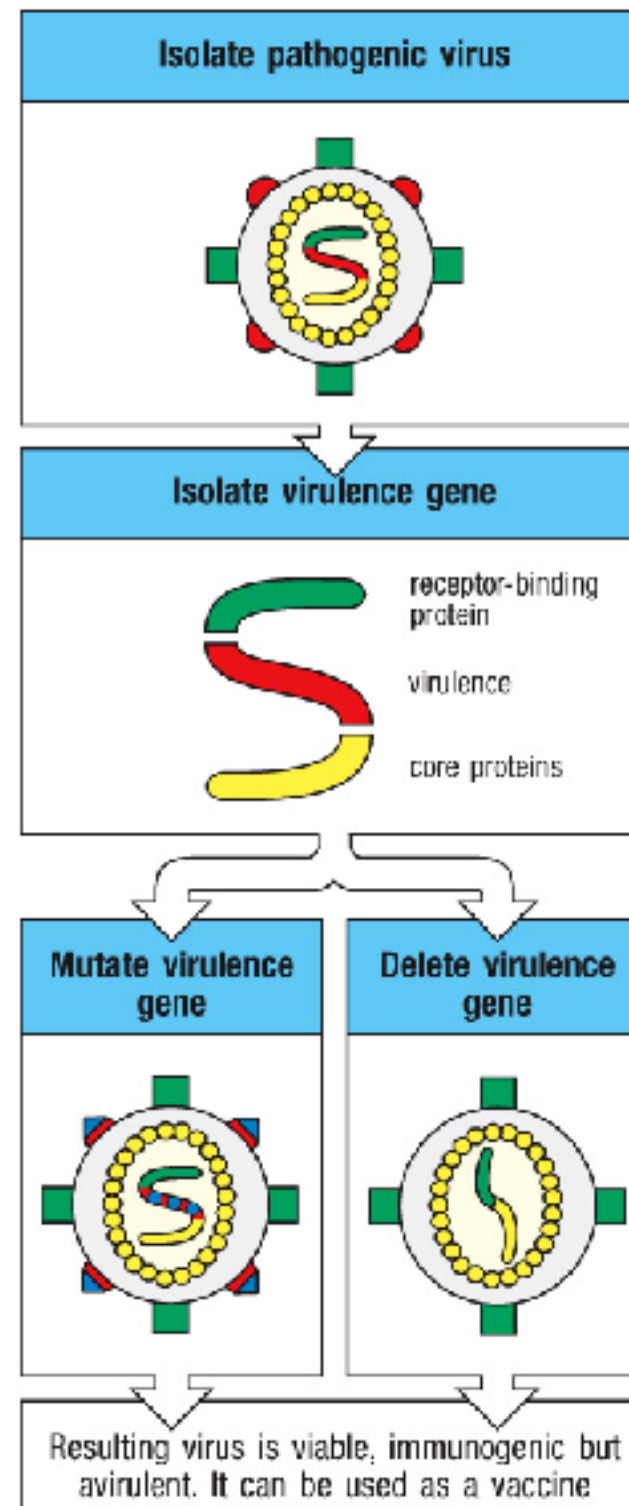
Live attenuated vaccines (I)



Empirical generation of attenuated viruses



Attenuating viruses by gene engineering



Live attenuated vaccines (II)

Capacity of transient growth

- Increased immunogenicity
 - Production of memory responses
 - Induction of cell-mediated responses
- } Often only a single immunization required

Possible risks

- Reversion to virulent form (Polio Vaccine)
- Potential complications similar to those seen in the original disease
- Hyper-virulence in immunosuppressed people

Live attenuated vaccines (III)

TABLE 19-5

Risk of complications from natural measles infection compared with known risks of vaccination with a live attenuated virus in immunocompetent individuals

Complication	Risk after natural disease*	Risk after vaccination†
Otitis media	7%–9%	0
Pneumonia	1%–6%	0
Diarrhea	66%	0
Post-infectious encephalomyelitis	0.5–1 per 1000	1 per 1,000,000
SSPE	1 per 100,000	0
Thrombocytopenia	—‡	1 per 30,000§
Death	0.1–1 per 1000 (up to 5%–15% in developing countries)	0

*Risk after natural measles are calculated in terms of events per number of cases.

†Risks after vaccination are calculated in terms of events per number of doses.

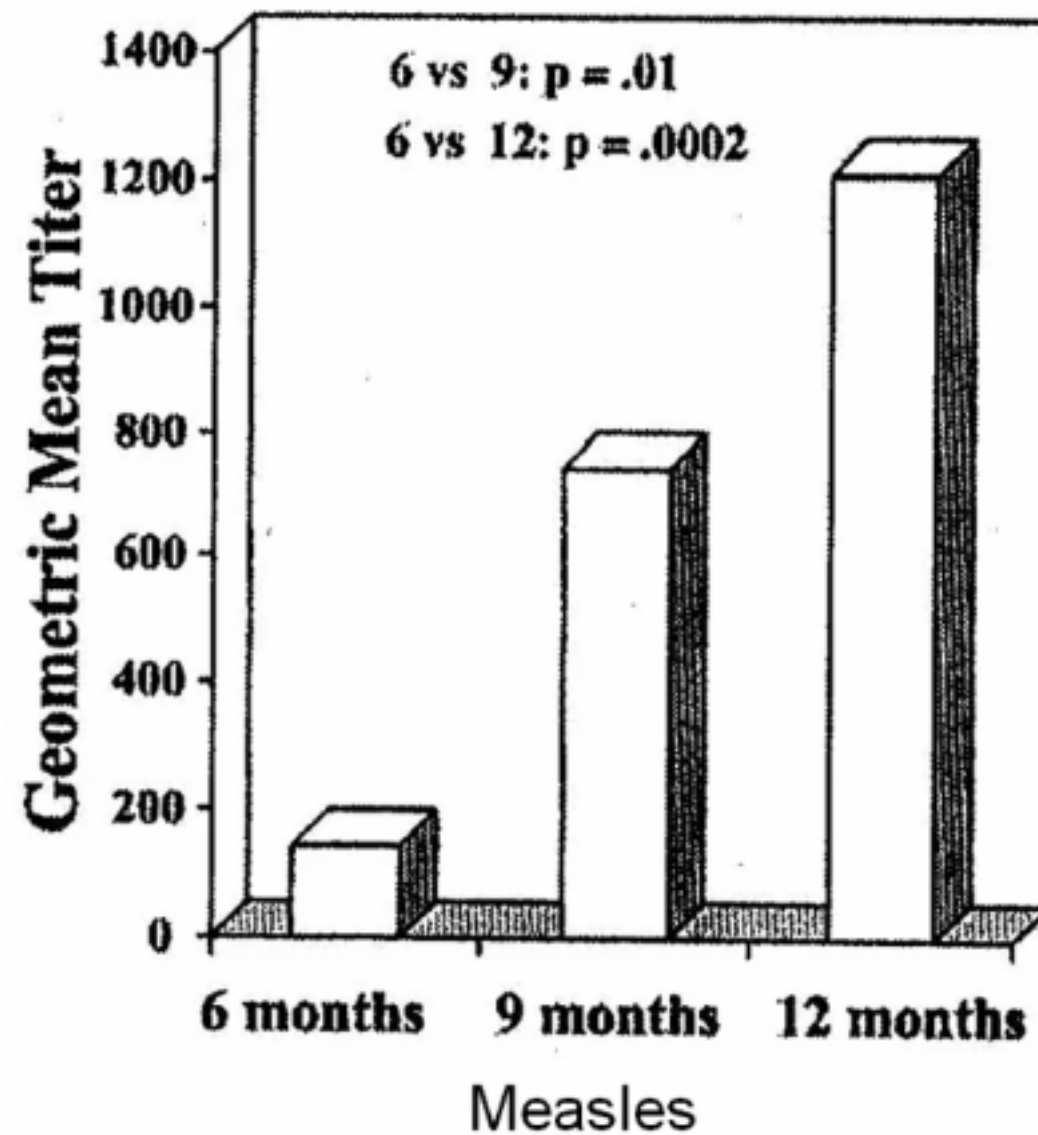
‡Although there have been several reports of thrombocytopenia occurring after measles, including bleeding, the risk has not been properly quantified.

§This risk has been reported after MMR vaccination and cannot be attributed only to the measles component.

MMR=measles, mumps, and rubella.

SSPE=subacute sclerosing panencephalitis.

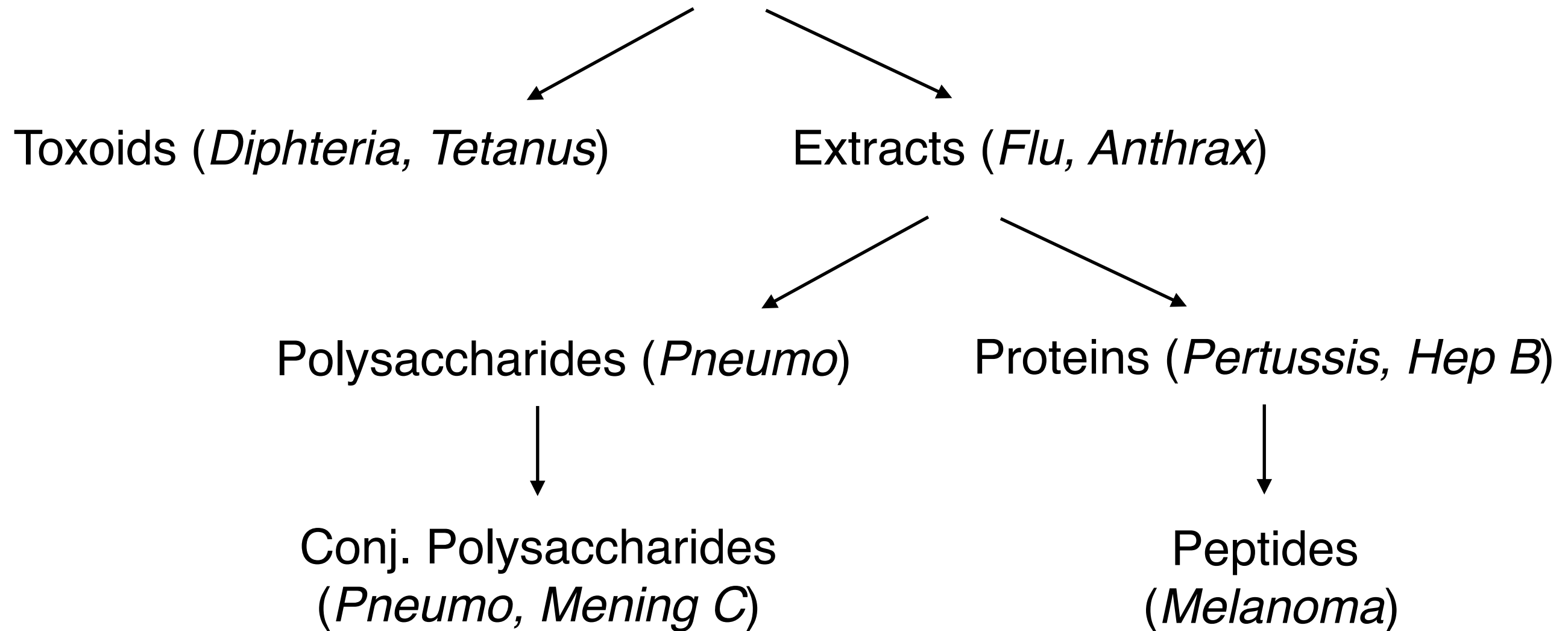
Live attenuated vaccines (IV)



Gans et al., *Vaccine* 21, 2003: 3398-3405

Inactivated Vaccines

Killed whole organisms (*Typhoid, Cholera, Hepatitis A*)



„Killed“ Vaccines

Killing achieved by:

- Heat or chemically (Formaldehyde)

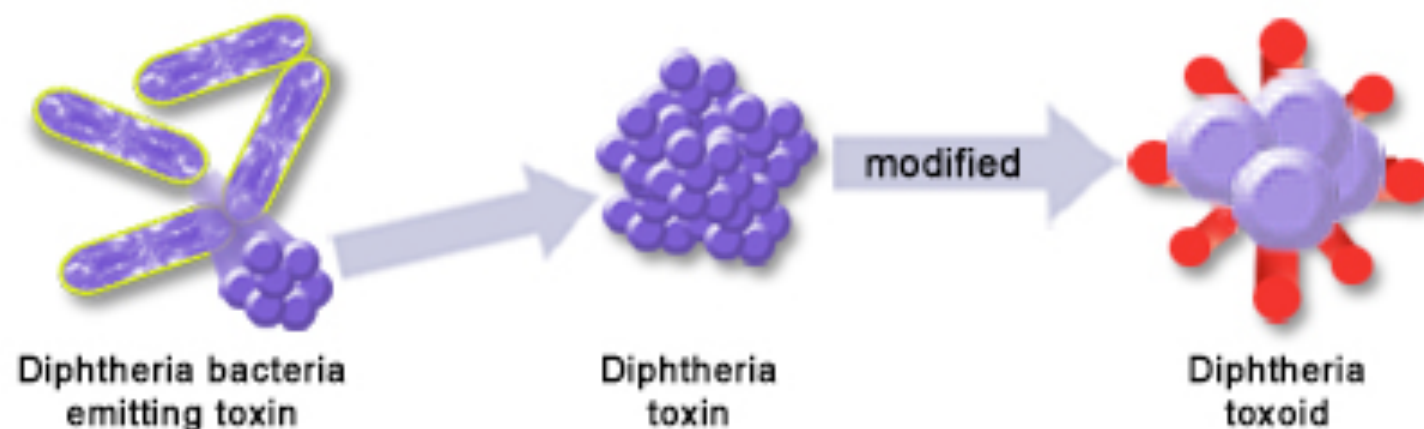
Disadvantages

- Heat may change the structure of the original proteins
- Less effective in immunization ➡ often repeated boosts required
- Less effective in induction of cellular immunity
- Ineffective killing led to serious complications in the past (Salk vaccine)

Toxoids as vaccines

Some bacterial pathogens (those causing Diphtheria or Tetanus) produce **exotoxins** that account for the disease symptoms.

Vaccines had been generated by **inactivation of toxins** (e.g. by formaldehyde). Antibodies generated against these toxins, work by neutralizing the effects of toxins.

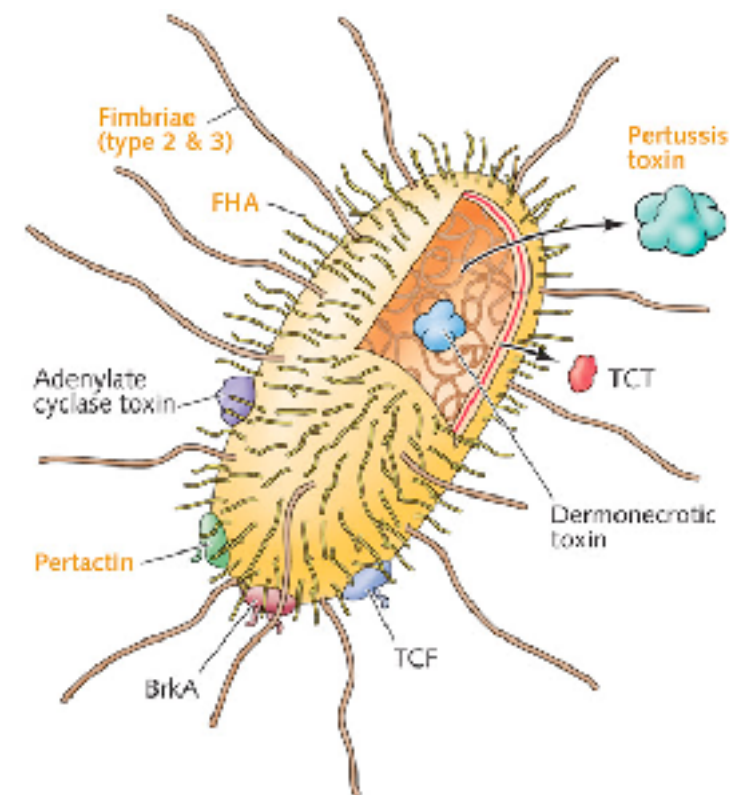
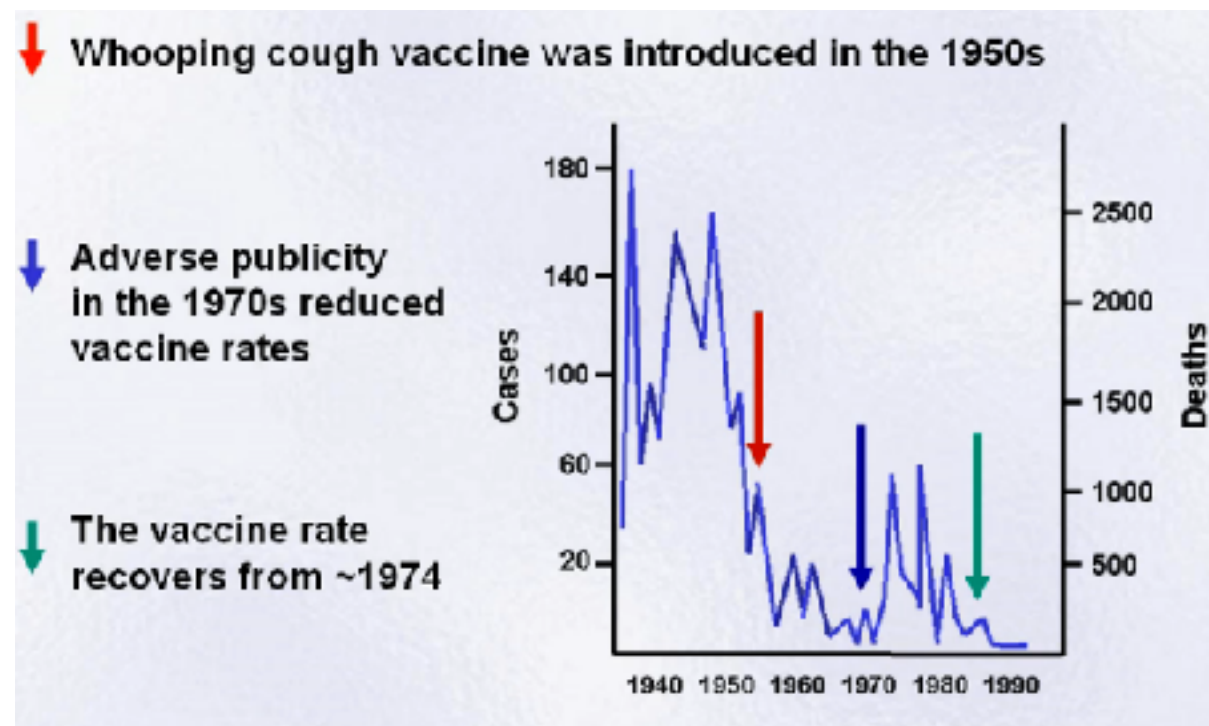


Passive immunity to toxins can be generated by transfer or serum containing anti-toxin antibodies (Diphtheria, Tetanus).

Towards „defined“ vaccines

Example: Whooping cough

- Whooping cough is caused by the bacteria *Bordetella pertussis*



Recombinant vaccine contains:

- Inactivated pertussis toxin*
- Filamentous hemagglutinin*
- Pertactin*

Towards „defined“ vaccines

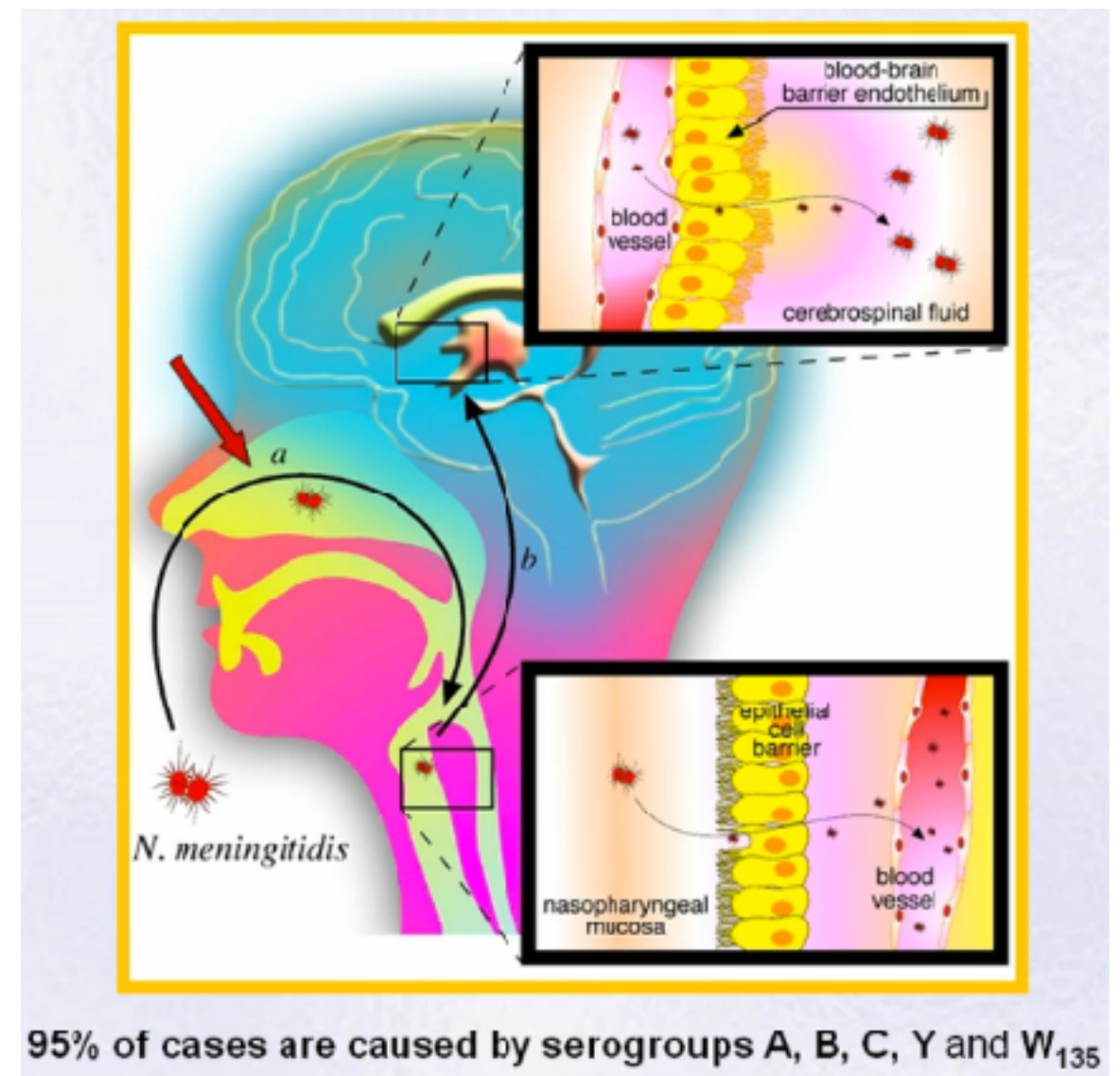
The problem of defined, protein- or peptide-based vaccines is that they are poorly immunogenic!

⇒ Need an adjuvant

Bacterial polysaccharides capsules as vaccines

Example: Meningitis

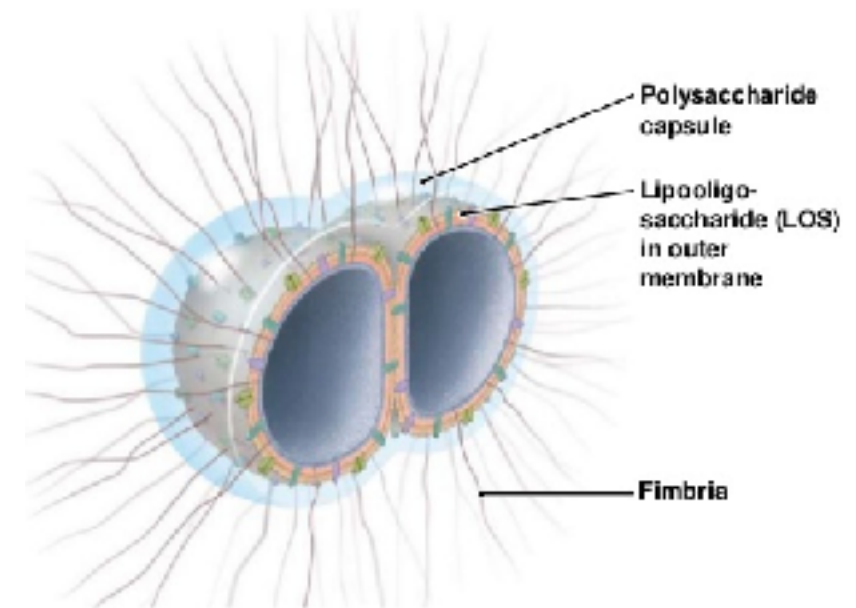
- Meningitis is a disease involving system spread finally affection the meninges of the CNS
- People with meningitis can deteriorate dramatically within hours and die
- Pathogens that are involved:
 - *Haemophilus influenzae*
 - *Neisseria meningitidis*
 - *Streptococcus pneumoniae*



Bacterial polysaccharides capsules as vaccines

Bacterial polysaccharide capsules:

- Major virulence factor, that protects microbes from phagocytosis
- Bacteria may produce a number of different polysaccharide capsules
(e.g. *N.m.* most common A, B, C, Y, W)



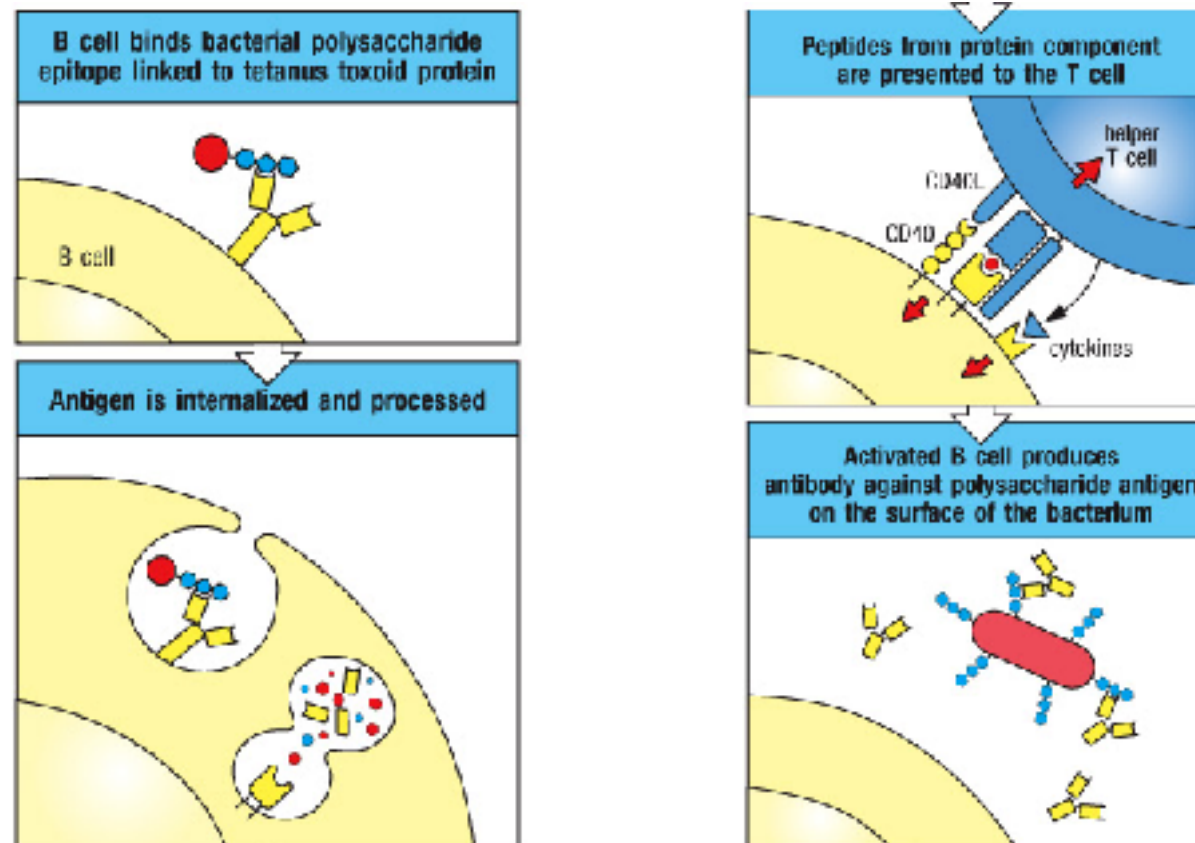
Short-comings of capsular vaccines:

- Induced immunity is weak, because these vaccines fail to induce T cell help (T cell independent antigens)
- They do not effectively induce immune memory or protect infants

Conjugate vaccines

Two components of a conjugate vaccine:

- Polysaccharide antigen
- Protein carrier (e.g. tetanus toxoid)

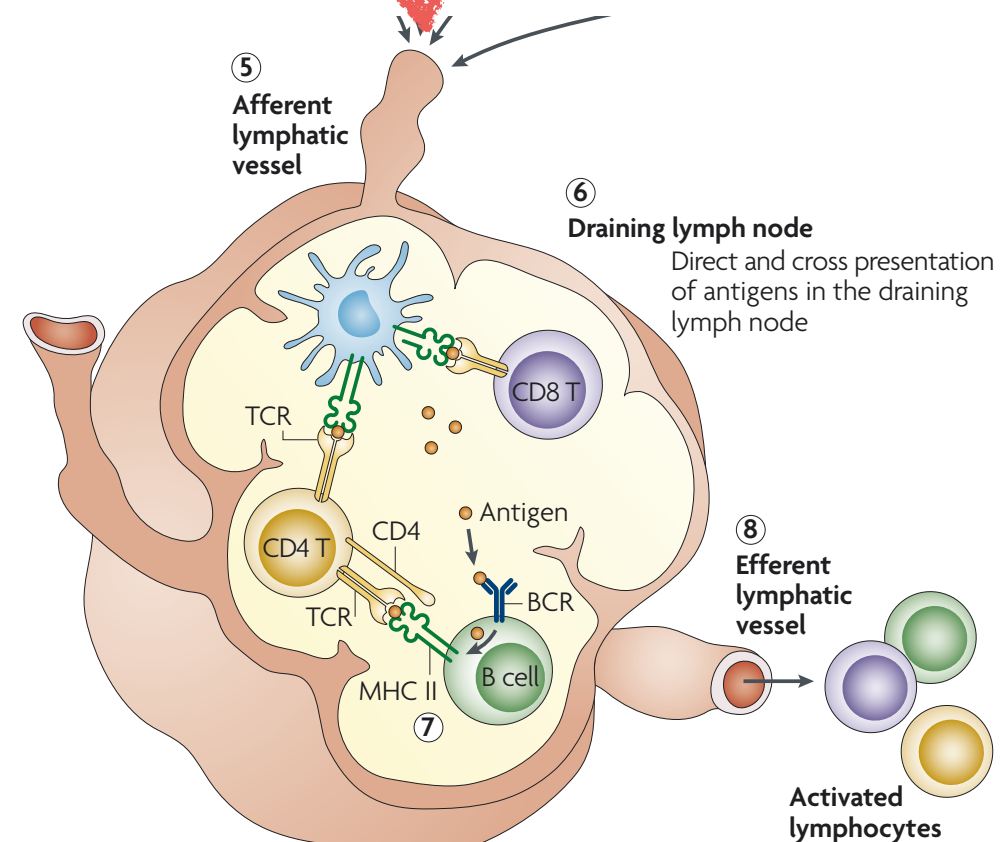
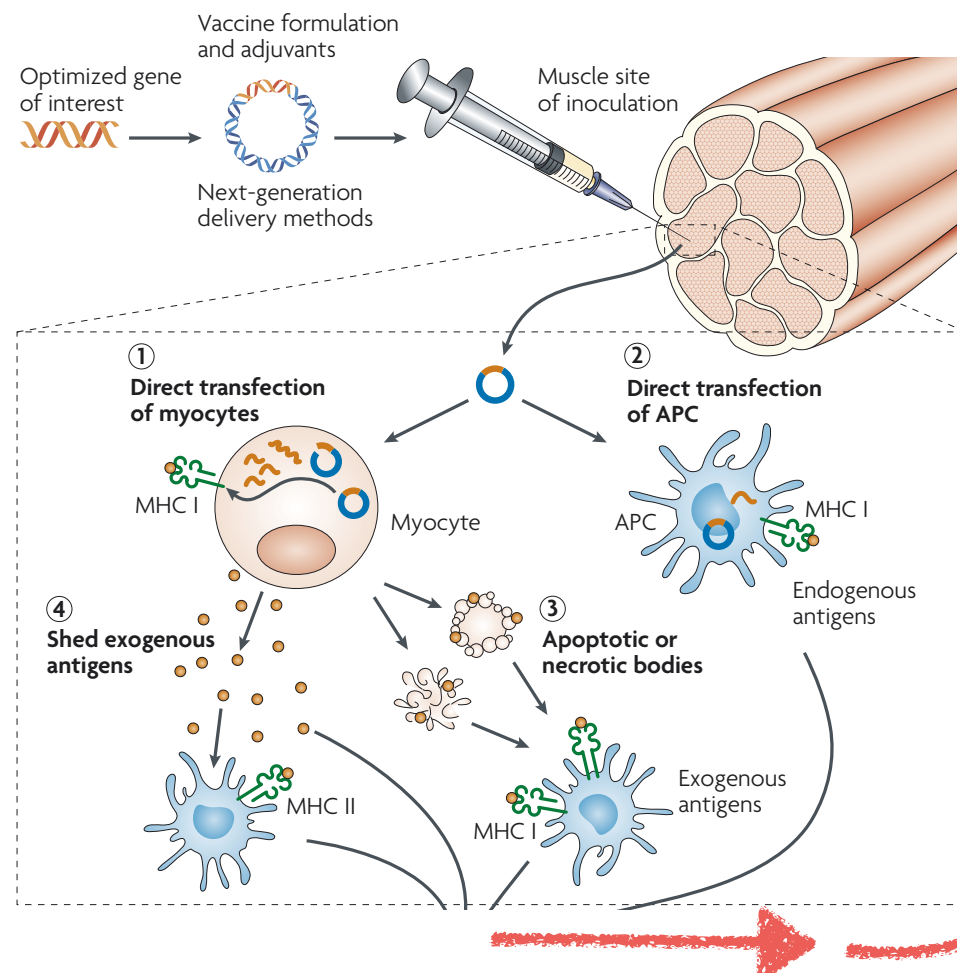


- ➡ Improved immunogenicity
- ➡ Provide longer lasting immunity linked to memory in a T cell dependent manner

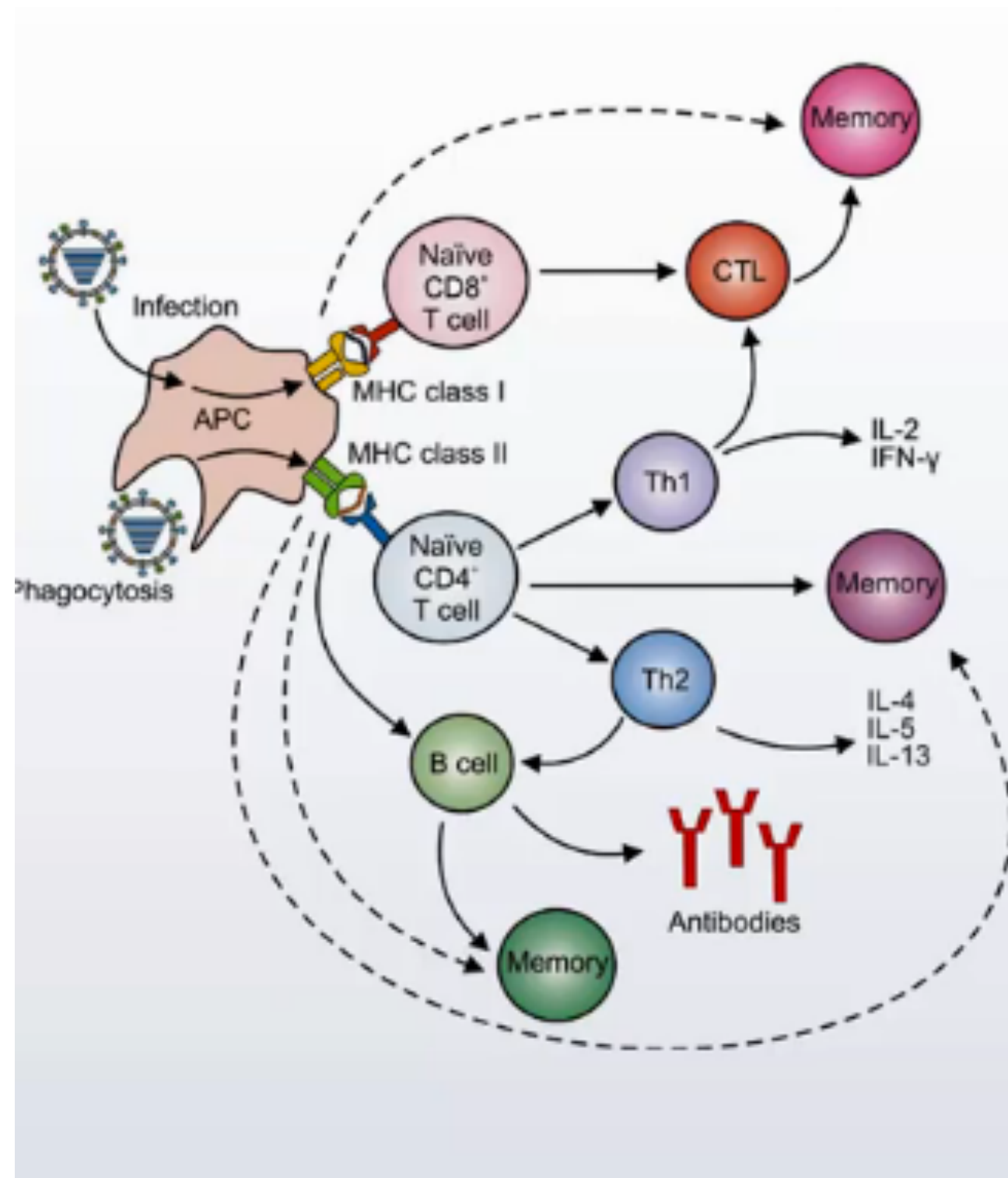
DNA Vaccines

Method: Plasmid DNA encoding for antigenic proteins is directly injected into the muscle of the recipient

- + Encoded protein is expressed in the host in its natural form
- + Induction of both humoral and cellular immune responses
- + Prolonged expression of the antigen generates immunological memory
- + Practical aspects of delivery, manufacturing



Mechanism at play during vaccination



General aspects of vaccination regimens

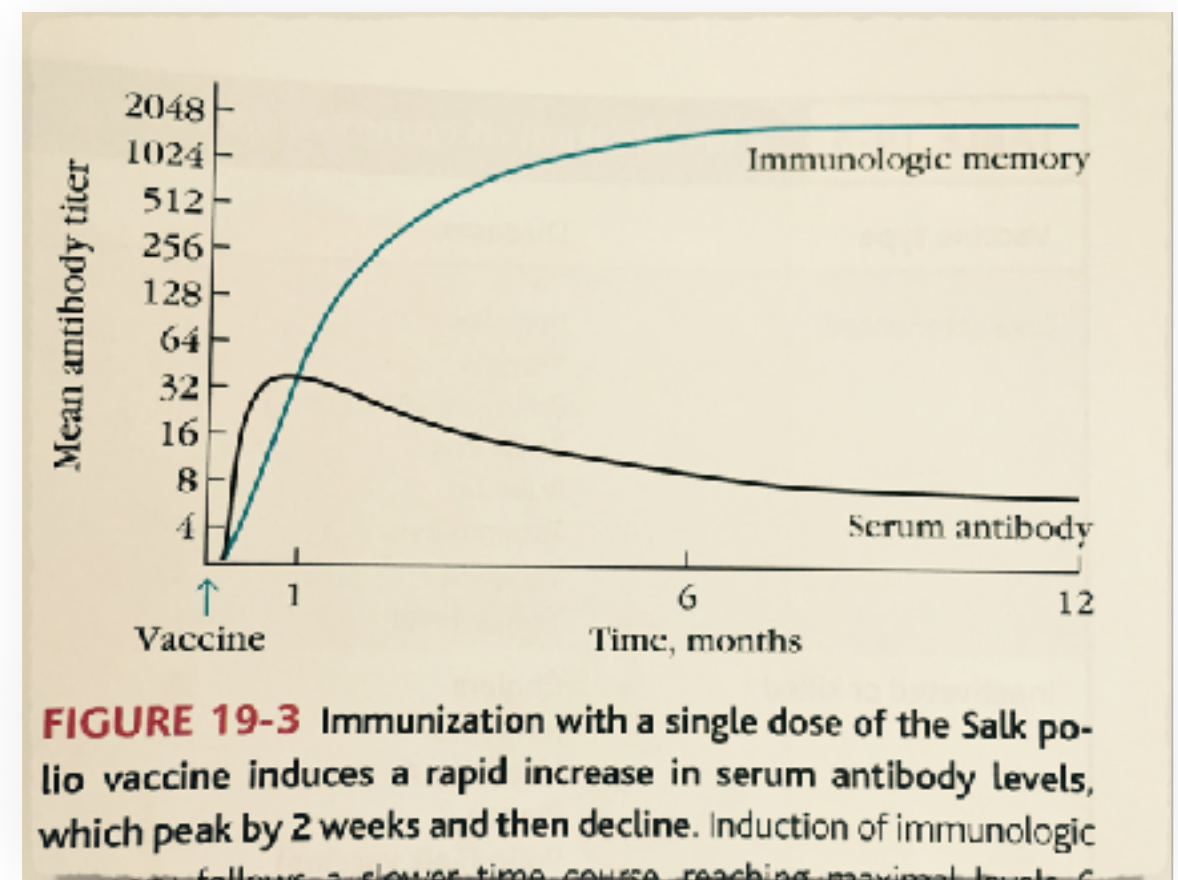
- Most currently available vaccines have been developed **empirically**
- Although the early protective effects are primarily conferred by the induction of AG-specific antibodies, there is more to consider:
 - Quality of the antibody response (e.g., avidity)
 - Persistence of vaccine antibodies
 - Generation of immunological memory

Designing effective vaccines (I)

Almost all current vaccines work through antibodies in serum or mucosa that block infection or bacteremia or viremia. Cellular immunity reduces severity of breakthrough infections.

The role of memory depends on the incubation time of the pathogen:

- Influenza virus (Incubation period 1-2 days)
 - ➡ a vaccine should maintain high levels of neutralizing antibodies
- Poliovirus (Incubation period 3 days before infection neurons)
 - ➡ a vaccine should be designed to induce strong memory responses



Which are the main effectors of vaccine responses?

Vaccine-induced immune effectors are as follows:

- Antibodies prevent or reduce infections by extra- and intracellular agents and clear extracellular pathogens through :
 - binding to the enzymatic active sites of toxins or preventing their diffusion
 - neutralizing viral replication, e.g. preventing viral binding and entry into cells
 - promoting opsonophagocytosis of extracellular bacteria, i.e. enhancing clearance by macrophages and neutrophils
 - activating the complement cascade
- CD8⁺ T cells do not prevent but reduce, control and clear intracellular pathogens by:
 - directly killing infected cells (release of perforin, granzyme, etc.)
 - indirectly killing infected cells through antimicrobial cytokine release
- CD4⁺ T cells do not prevent but participate to the reduction, control and clearance of extra- and intracellular pathogens by :
 - producing IFN- γ , TNF- α / β , IL-2 and IL-3 and supporting activation and differentiation of B cells, CD8⁺T cells and macrophages (Th1 cells)
 - producing IL-4, IL-5, IL-13, IL-6 and IL-10 and supporting B cell activation and differentiation (Th2 cells)

Which are the main effectors of vaccine responses?

The type of the vaccine effector response that is generated depends on the type of vaccine:

- Capsular polysaccharide elicit B cell responses in a T cell-independent manner
- Conjugation of bacterial PS to a protein carrier involved CD4 T cells
>> generation of higher-affinity antibodies and immune memory
- Live, attenuated vaccines generate also CD8 cytotoxic T cell responses

Vaccines induce distinct type of immunity

Major licensed viral and bacterial vaccines for humans according to the mechanism of disease prevented by the vaccine

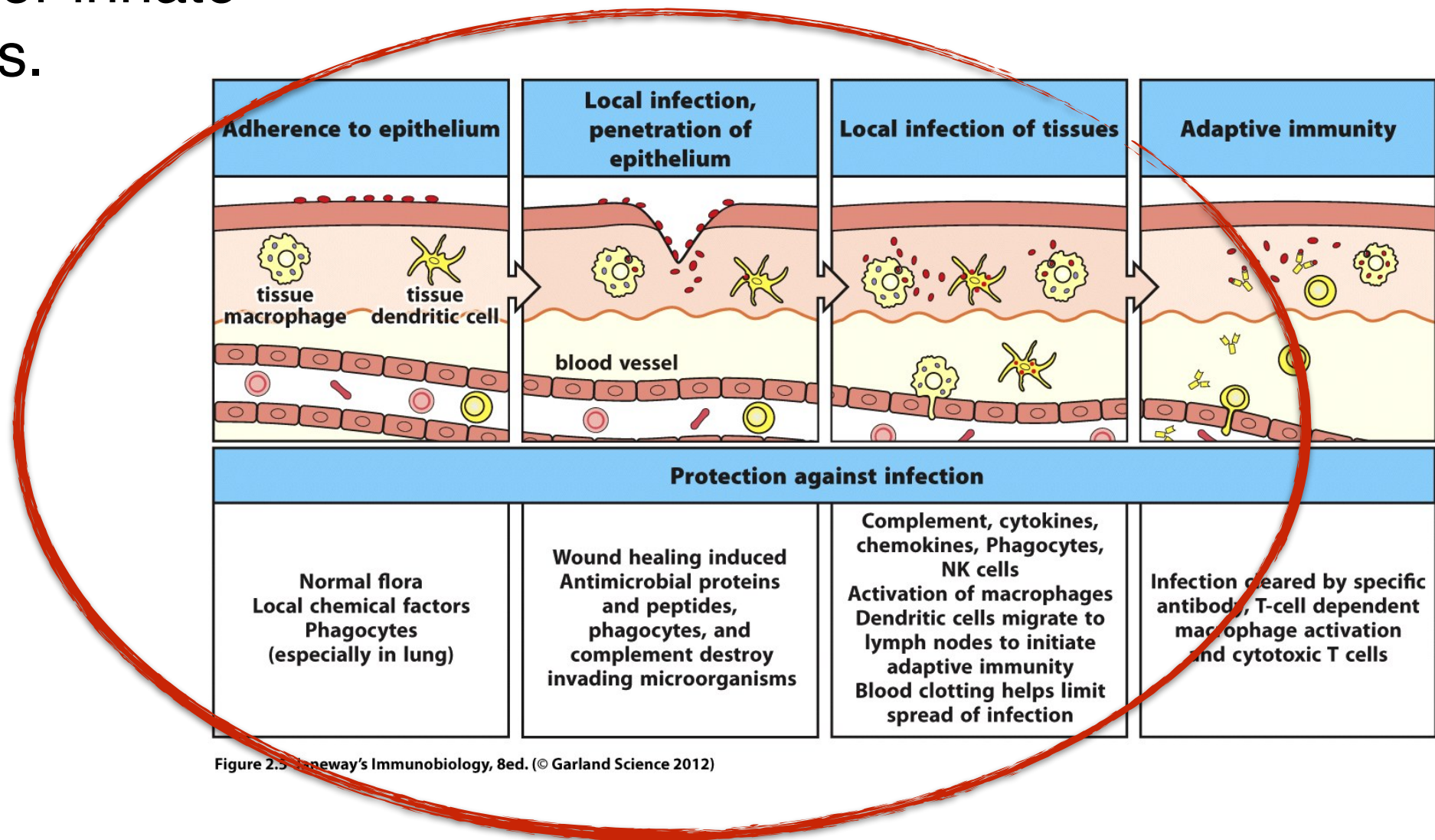
<u>Viral</u>	Viremia:	Smallpox, Yellow Fever, Measles Mumps, Rubella, Polio, Varicella, Hepatitis A, Hepatitis B Japanese Encephalitis, Tick-Borne Encephalitis
	Mucosal replication:	Influenza, Rotavirus, HIV
	Neuronal invasion:	Rabies
	Neuronal latency	Zoster
<u>Bacterial</u>	Bacteremia:	Hemophilus Influenzae, Type b Meningococcal, Pneumococcal, Typhoid (Vi)
	Mucosal replication:	Pertussis, Typhoid (Ty 21a)
	Toxin production:	Diphtheria, Tetanus, (Pertussis) Cholera, Anthrax
	Macrophage replication:	Tuberculosis

Plotkin S. C.R. Acad. Sci. 1999, 322: 943-951

Under normal circumstances, immunisation **DOES NOT** elicit sufficiently high and sustained antibody titers on mucosal surfaces to **PREVENT local infection.** Instead, most vaccines limit **PROPAGATION** and **SPREAD** and thereby **CLINICAL DISEASE!**

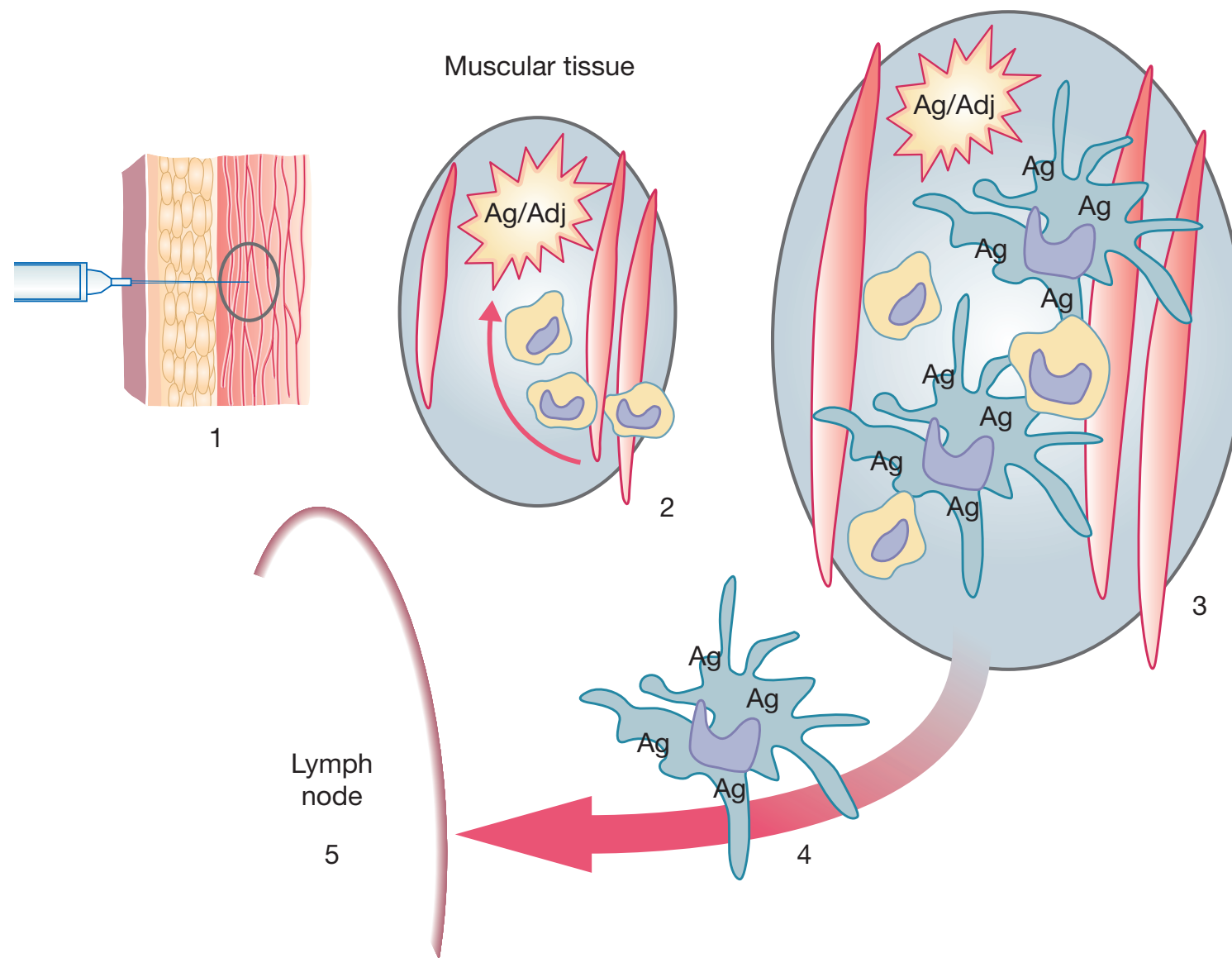
Designing vaccines for active immunization

The majority of infections are dealt with by non-specific or innate immune mechanisms.



Vaccination „educates“ the adaptive immune system to deal rapidly with pathogens not readily eliminated by innate immunity.

From innate to adaptive immunity - the first steps after immunization

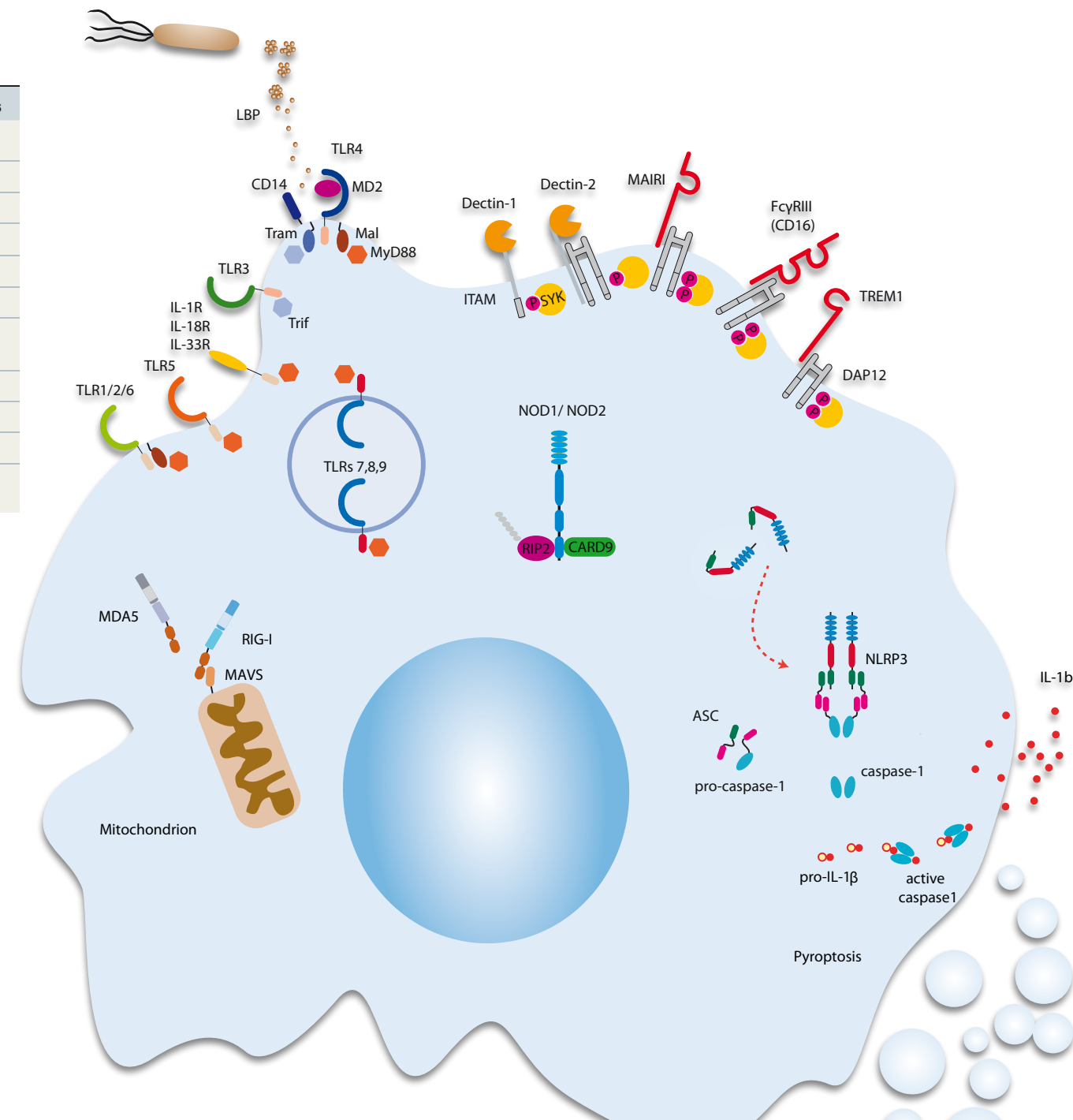


The first step towards efficient vaccines is to trigger efficient innate immune responses in AG-presenting cells (DCs)

Activation of Pattern recognition receptors

Activation is triggered through engaging different types of Pattern recognition receptors

Receptors	Ligands	Demonstrated ligands in vaccine antigens
TLR1	Certain bacterial lipoproteins	
TLR2	Peptidoglycan, lipoproteins, glycolipids, lipopolysaccharide	BCG, Hib-OMP, pneumococcal PS
TLR3	Viral double-stranded RNA	BCG, pneumococcal PS, HPV-VLPs
TLR4	Bacterial lipopolysaccharides	
TLR5		
TLR6	Bacterial flagellins	
TLR7	Lipotechoic acid, lipopeptides	Yellow-fever, live attenuated influenza, whole cell influenza
TLR8	Single-stranded RNA	
TLR9	Single-stranded RNA	Yellow-fever
TLR10	Single-stranded RNA	Yellow-fever
NOD1, NOD2	CpG oligonucleotides Peptidoglycans	Pneumococcal PS



Dissemination of the vaccine

An important feature of live vaccines is their **dissemination** pattern and the site of injection:

Live vaccines (e.g., BCG) disseminate systemically >> launch multiple foci >> high immunogenicity and the site of injection is not important

Non-live vaccines by definition cannot replicate, thus are more limited in time and space >> the site of injection is important (usually skin or muscle because of the presence of DCs in high density)

Adjuvants enhance the efficacy of non-live vaccines

- A vaccine „adjuvant is a component added to a vaccine to enhance the immune response“.
- No clear definition - defined by what they do
- Many diverse substances have been described
- A small percentage have advanced to clinical trials
- A very small percentage are included in licensed products

Benefits of Vaccine Adjuvants

- Increased antibody titers
- Induced response more rapidly
- Allow antigen dose reduction or fewer doses
- Increased breadth of response to overcome pathogen diversity
- Induce long-lasting immune memory responses
- Overcome poor immune response in elderly and young children

Mechanism of action of adjuvants

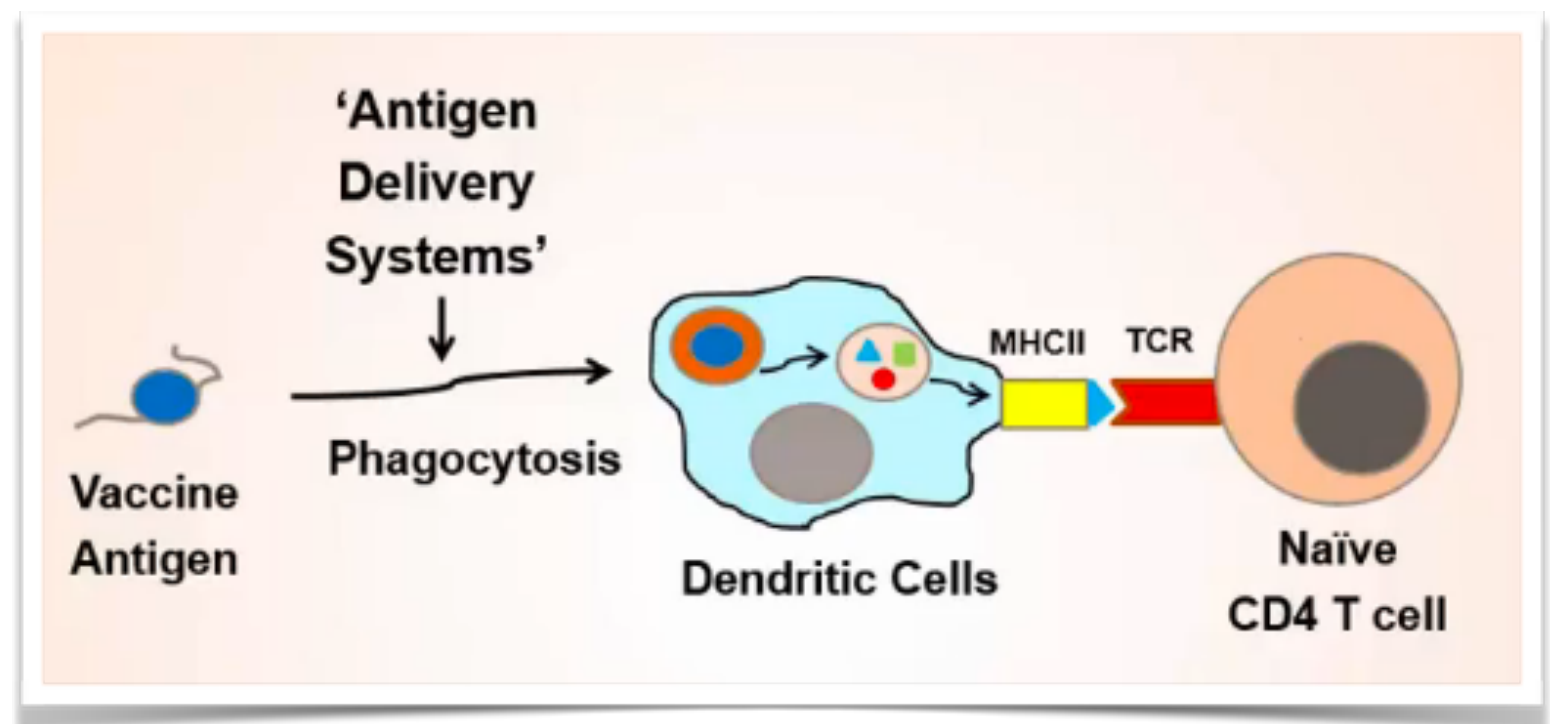
1) Improve up-take by APCs

Most widely used adjuvant: ALUM

Emulsification in mineral oil

Incorporation into nanoparticles, which helps to retain antigens in the body

2) Activation of PRRs



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 <i>Bordetella pertussis</i>	Aluminum hydroxide gel with killed <i>B. pertussis</i>	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

Designing effective vaccines (II)

Some immune responses **correlate** with protective activity but for many vaccines we do not know what the correlates are.

Adjuvants can enhance immunity.

Specific considerations for the immunization of **specific groups**:

- *Infants*: Shortly after birth the presence of maternal antibodies may counteract the efficacy of vaccination (multiple boosters necessary)
- *Elderly*: In the elderly immunization is more difficult achieve
- *Travels*
- Workers in the health sectors

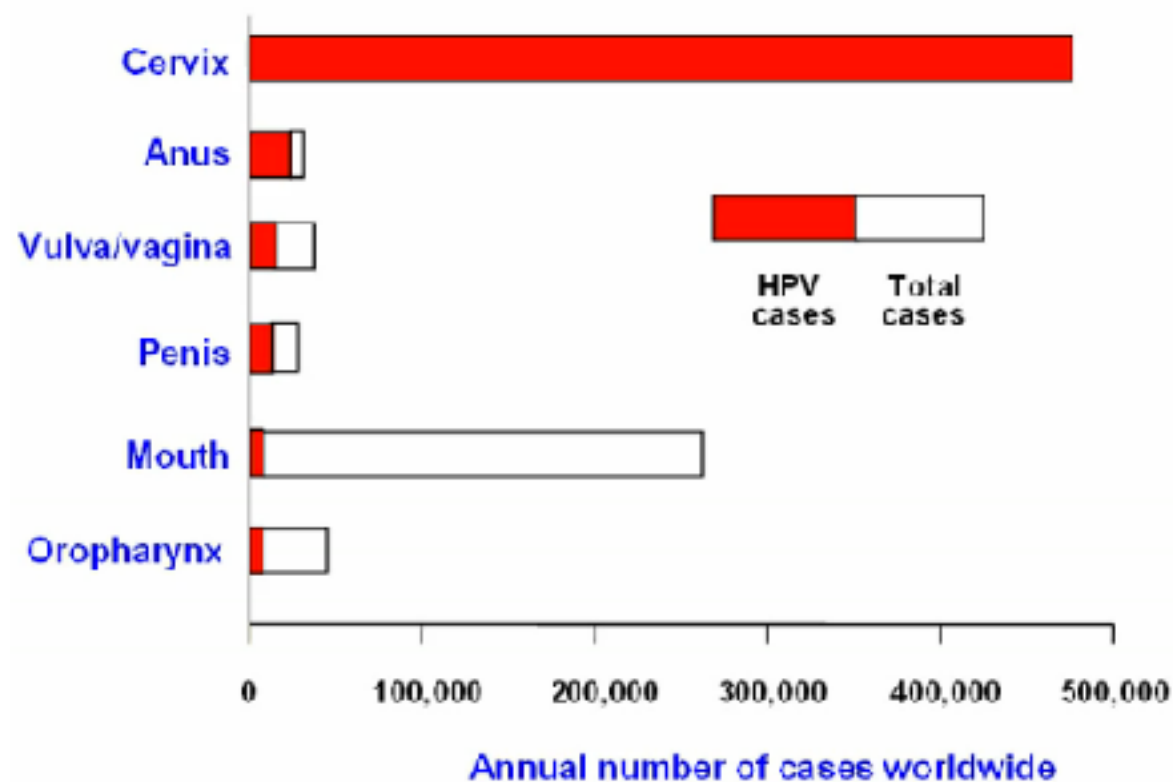
Herd immunity:

Vaccines are nor 100% efficient (e.g. some individuals may not respond to vaccination), yet vaccination of the major populations will decrease the odds of infections of those individuals.

Vaccination against tumors

Human Papillomavirus vaccine

Papillomaviruses (>80) identified, but only a few can cause cancer (HPV-16, HPV-18)



Based on data from Parkin, *Int J Cancer* 118: 3030, 2006

Gardasil: phase 3 prophylactic efficacy results

	Vaccine		Placebo		Efficacy	C.I.
	n	Cases	n	Cases		
*HPV16 or 18 CIN 2/3 or AIS	8487	0	8460	53	100%	93 - 100
**HPV16 or 18 VIN2/3 or VaIN2/3	8641	0	8667	24	100%	83 - 100
*HPV6, 11, 16, 18 CIN1 or greater	7858	4	7861	83	95%	87 - 99
*HPV6, 11, 16, 18 genital warts	7897	1	7899	91	99%	94 - 100

Results in HPV DNA and seronegatives at baseline after three doses (*) or after at least one dose (**), as reported in Gardasil package insert; Average duration of follow-up: 1.5 years after the last vaccination

Exercise I

LETTER

doi:10.1038/nature18300

Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy

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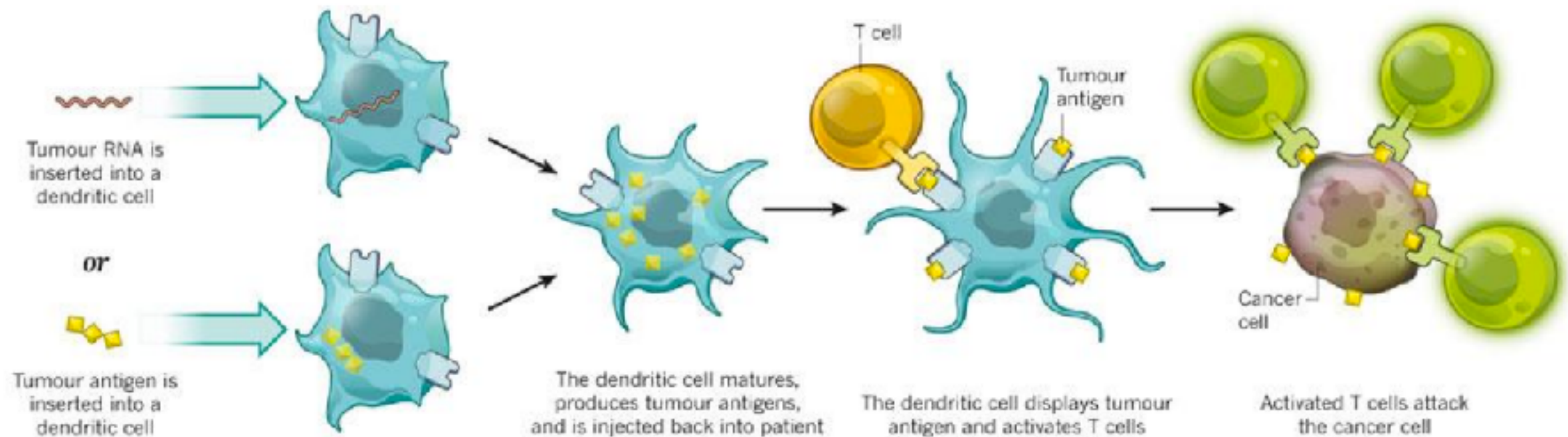
Goal:

A vaccination strategy against cancer that targets existing tumours by recruiting immune mechanisms normally used against viral infection

Exercise I

HOW THE CANCER VACCINES WORK

In the immune system, dendritic cells can be used to trigger a response against cancer cells in various ways. In these two examples, antigens are introduced directly into the dendritic cells or generated *in situ* using tumour RNA. The cells then produce tumour antigens and direct T cells to seek out and destroy the cancer cells.

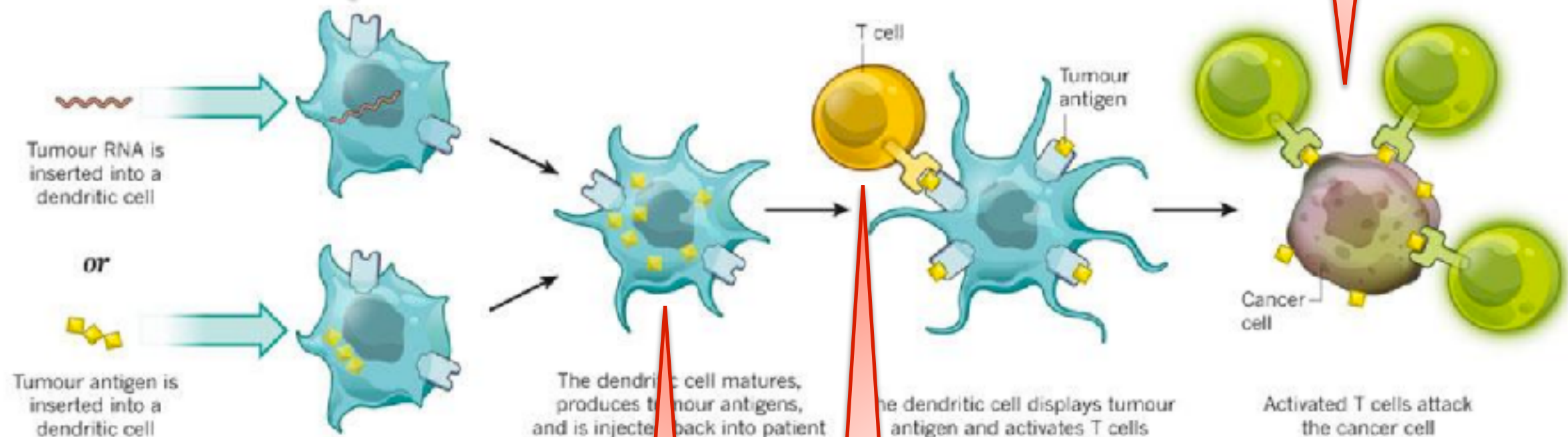


Exercise I

Delivery to DCs

In the immune system, dendritic cells can be used to trigger a response against cancer cells in various ways. In these two examples, antigens are introduced directly into the dendritic cells or generated *in situ* using tumour RNA. The cells then produce tumour antigens and direct T cells to seek out and destroy the cancer cells.

Tumor-specific



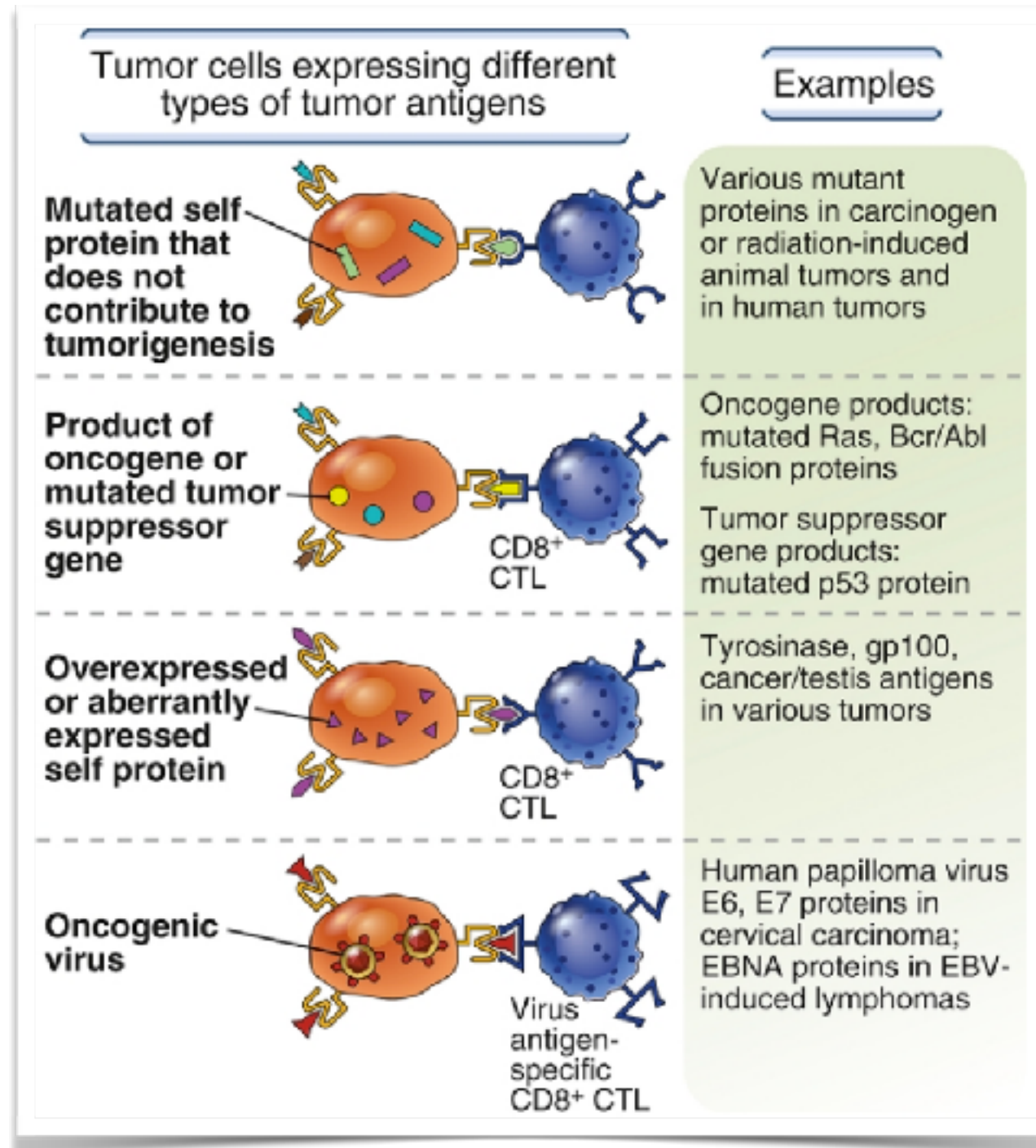
Activation of DCs

Activation of CTLs

Tumor antigens

Malignant tumors express various types of molecules that may be presented to T cells and recognized as „foreign“:

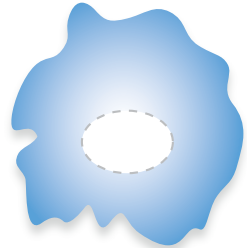
- Products of diverse mutated genes: mutations in genes that are not involved in the process of tumorigenesis (passenger mutations)
- Products of oncogenes or tumor suppressor genes
- Aberrantly expressed proteins: antigens are unmated by expression is dysregulated (Cancer-testis antigens (NY-ESO1, MAGE-1,3))
- Virus-derived oncogenes



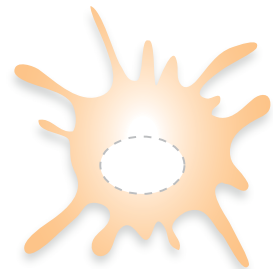
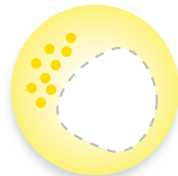
Flow cytometry

To identify and distinguish different cell populations (e.g., B cells and T cells) but also to measure the activation status of one given cell populations the expression levels of cell-surface proteins (and also intracellular markers) can be determined using a **flow cytometer**.

Macrophages

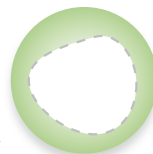


NK cells

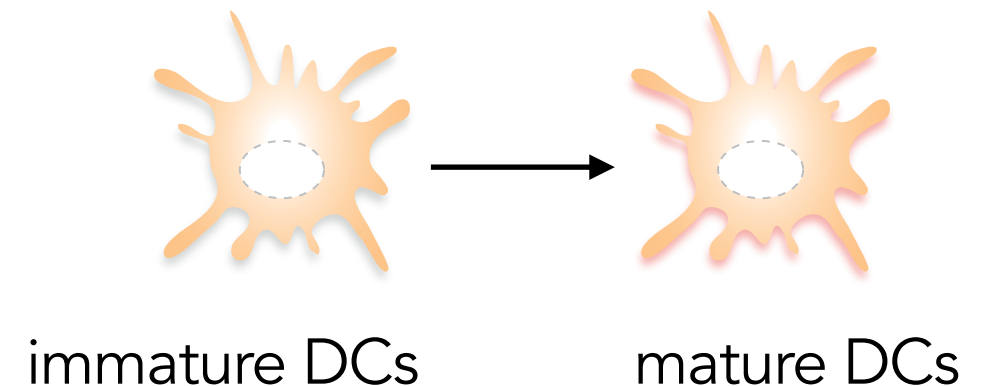
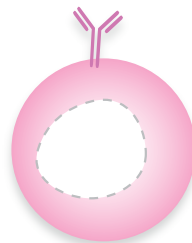


DCs

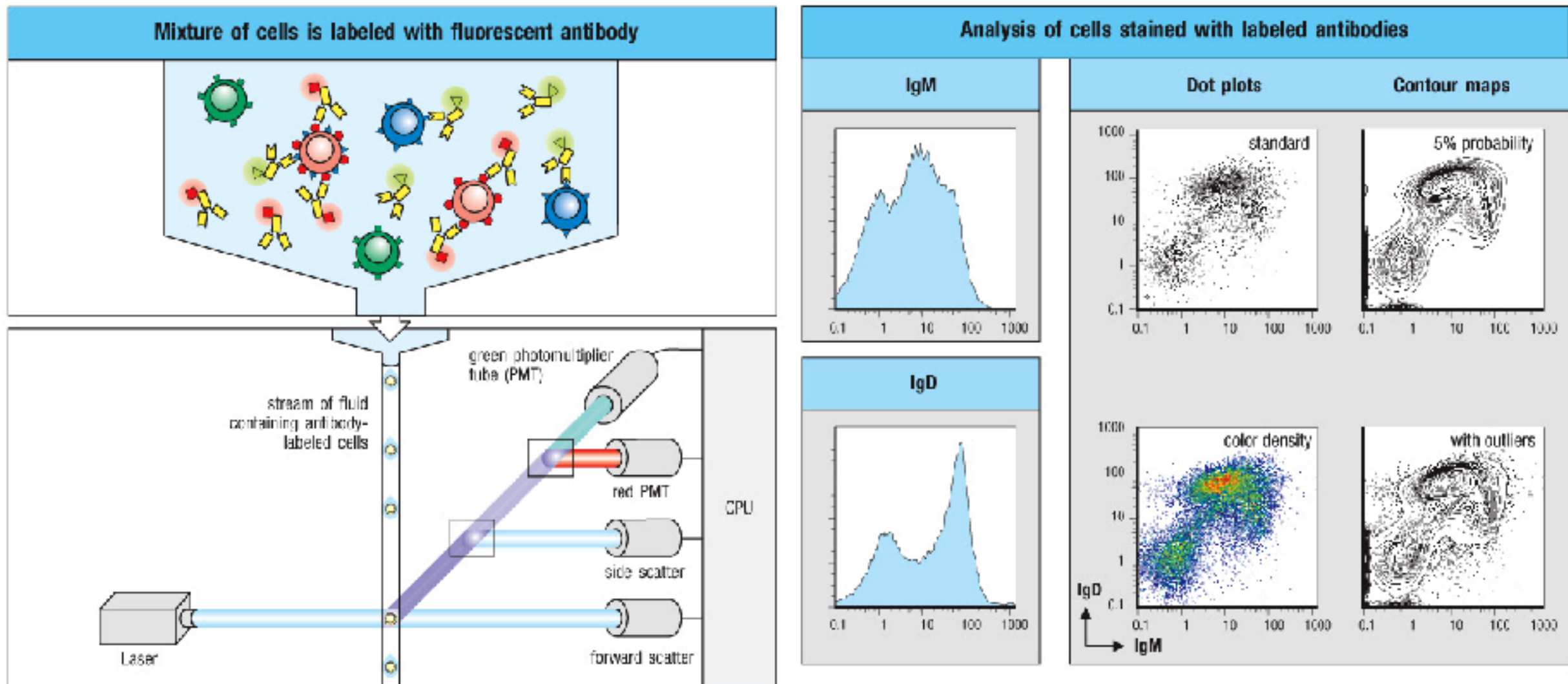
T cells



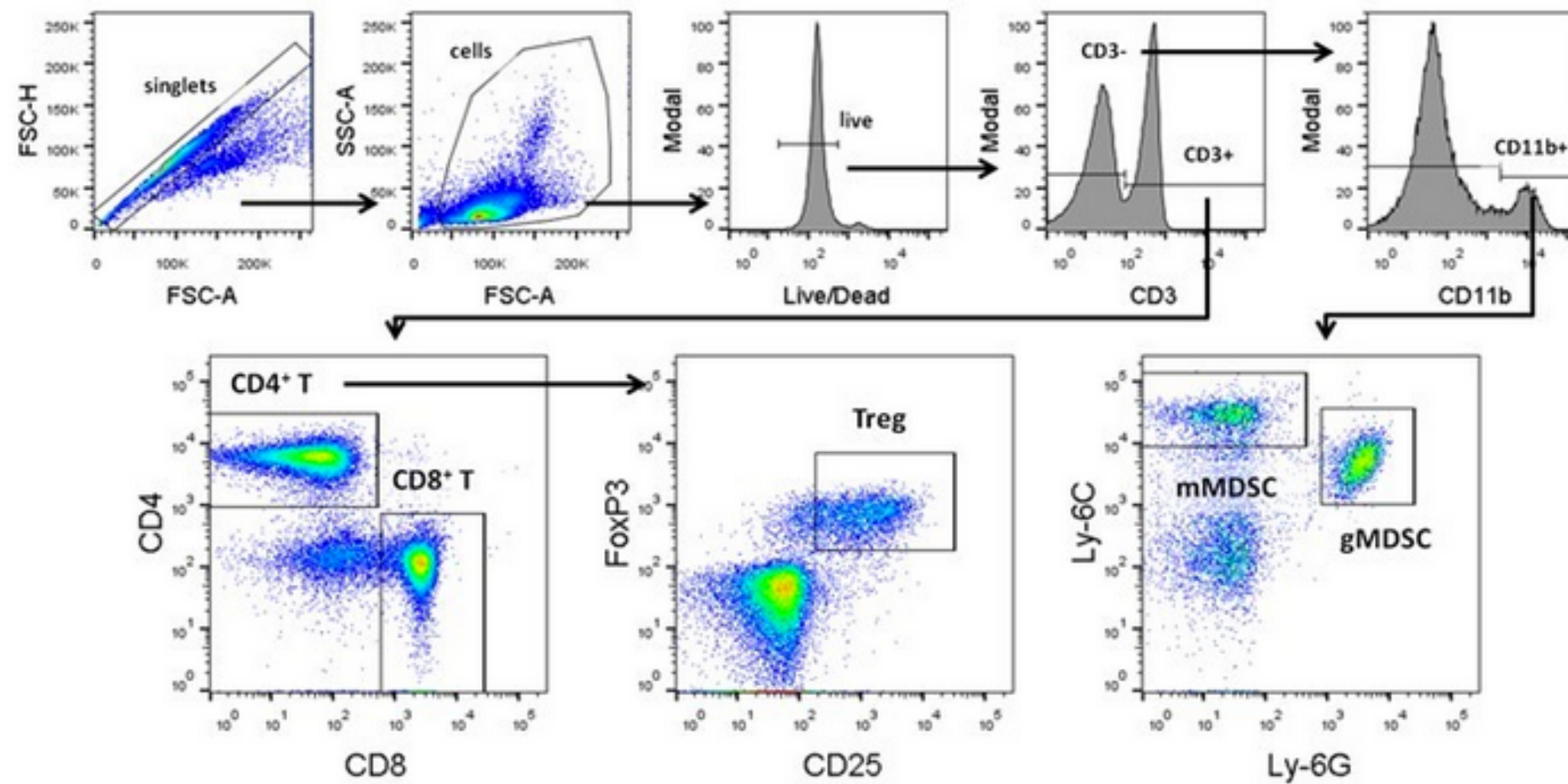
B cells



Working principle of flow cytometry



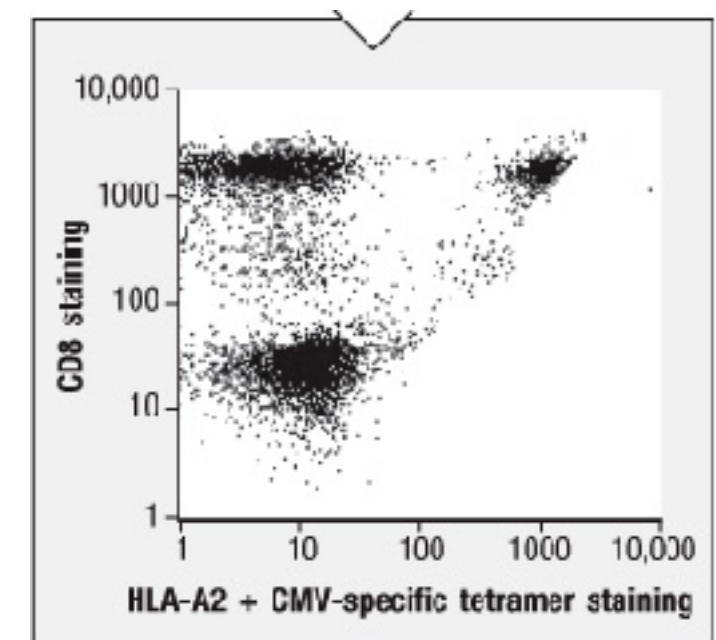
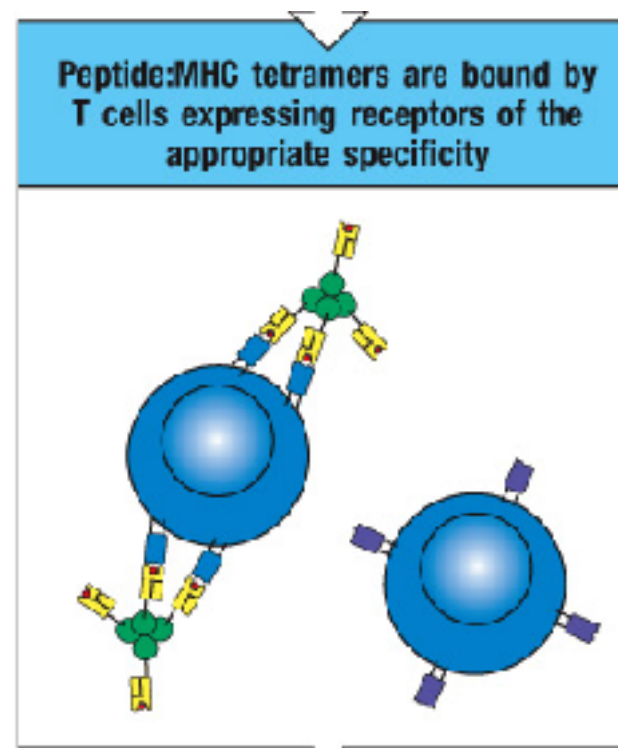
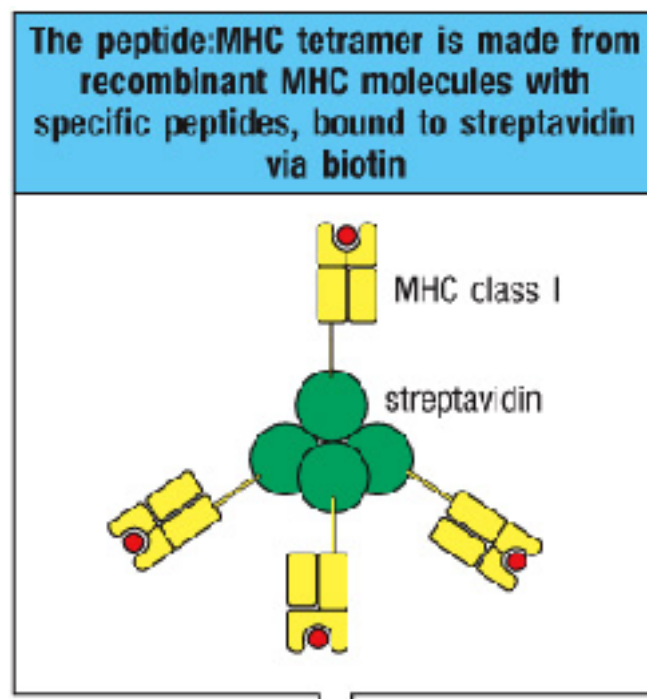
Example: Profiling immune cells by FACS



Quantification of antigen-specific T cells

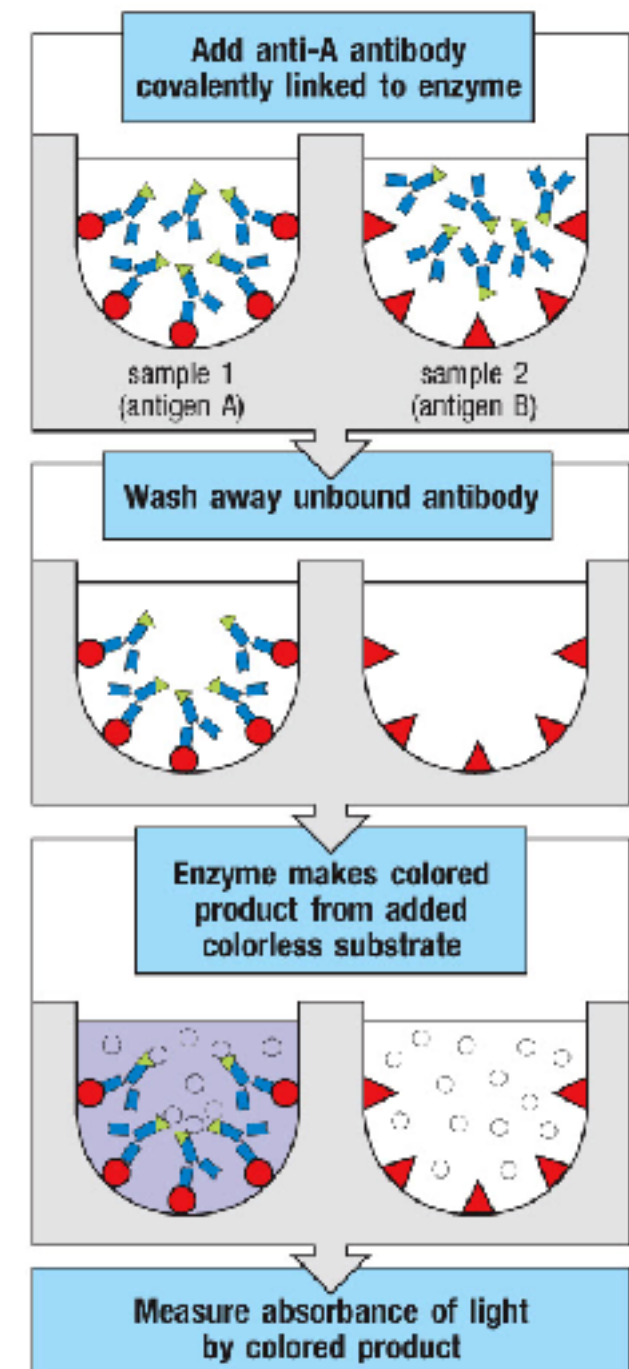
Identification of AG-specific T cells requires a multimeric peptide:MHC complex:

Peptide:MHC tetramers are formed from recombinant refolded peptide:MHC complexes containing one single epitope. The MHC molecule contains a Biotin-tag. Addition of streptavidin, which binds biotin, creates a tetramer. The tetramer binds to its corresponding TCR with high avidity allowing to label AG-specific T cells. The streptavidin is linked to a fluorochrome allowing for the detection of T cells via FACS.

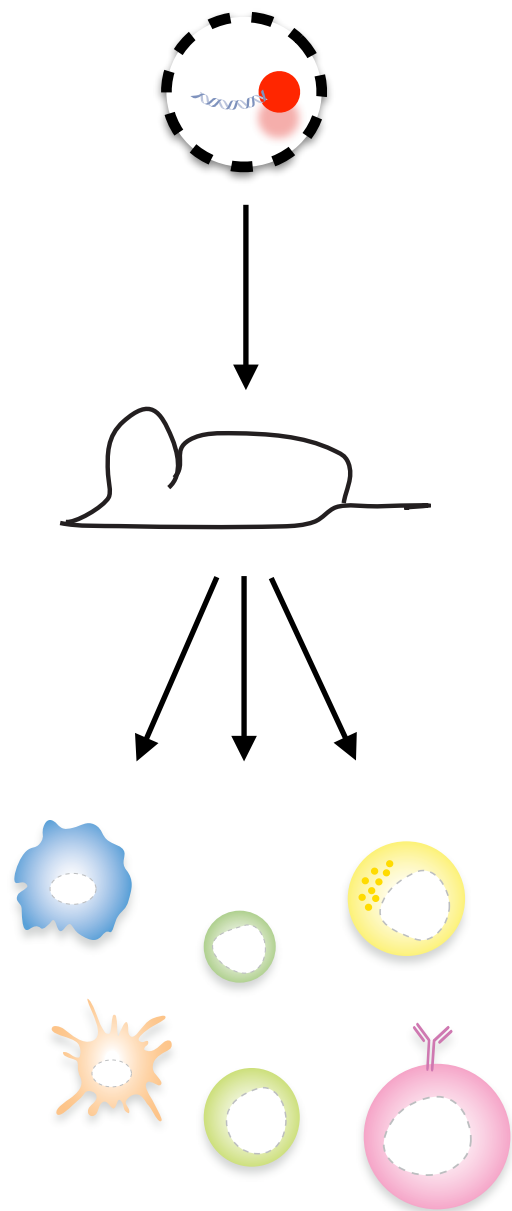


Enzyme-linked immunosorbent assay

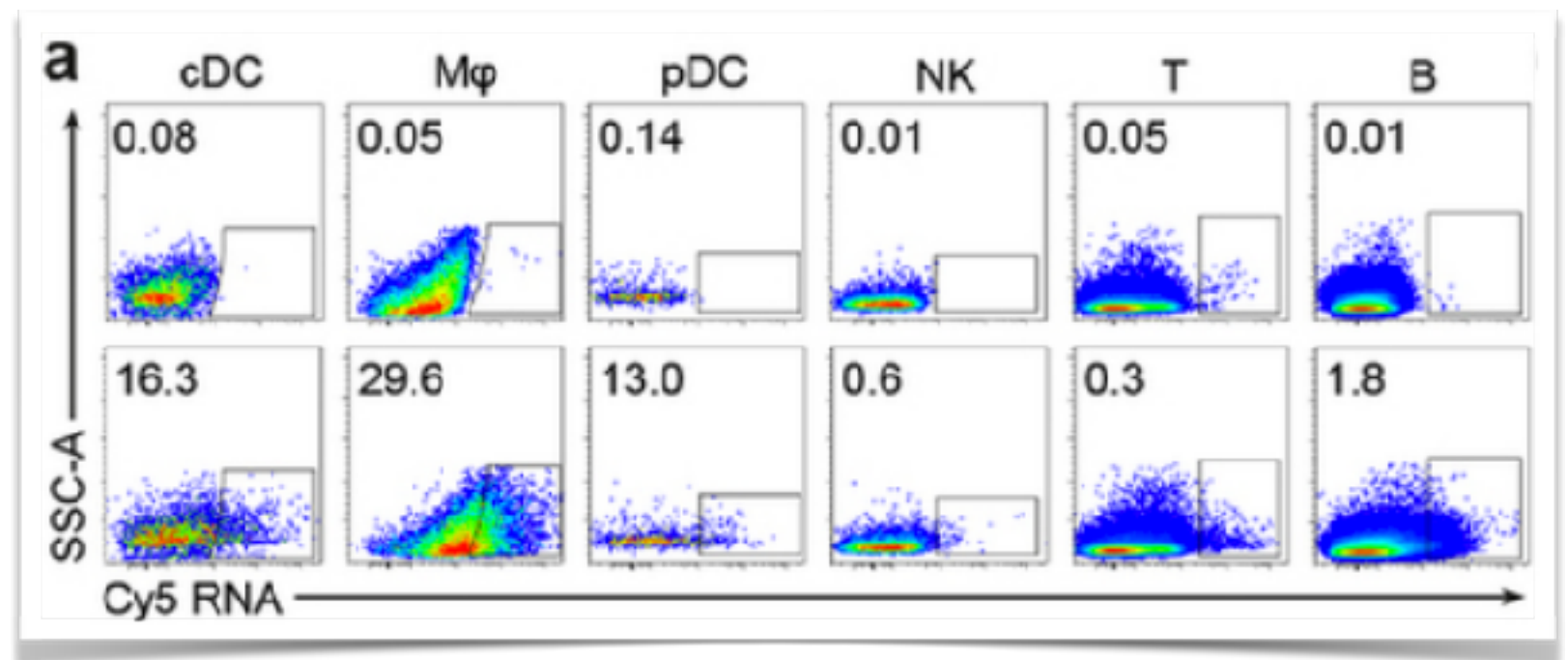
To detect an antigen (e.g., cytokine), purified antibody specific for antigen A is linked chemically to an enzyme. The samples are loaded into microtiter plates. The labeled antibody is added and after incubation the non-bound antibody is washed away. Finally bound antibody is detected by an enzyme-dependent color-change reaction.



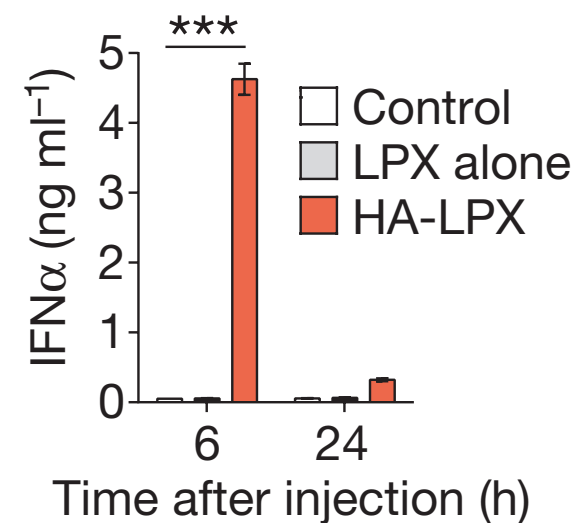
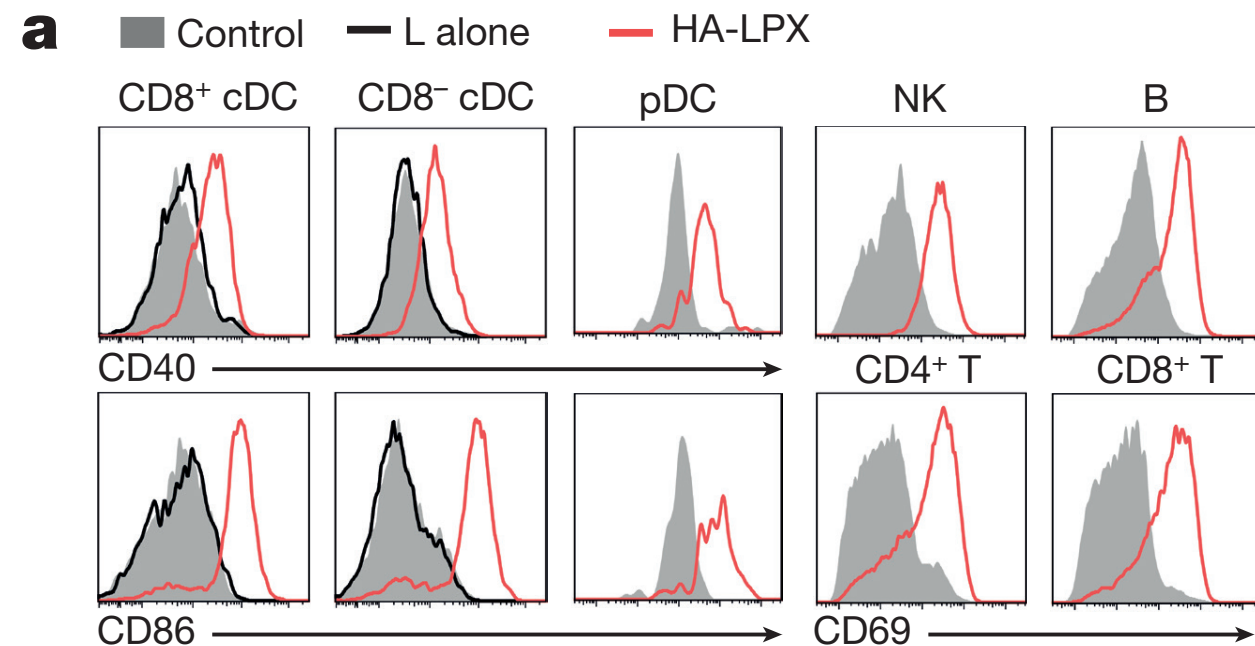
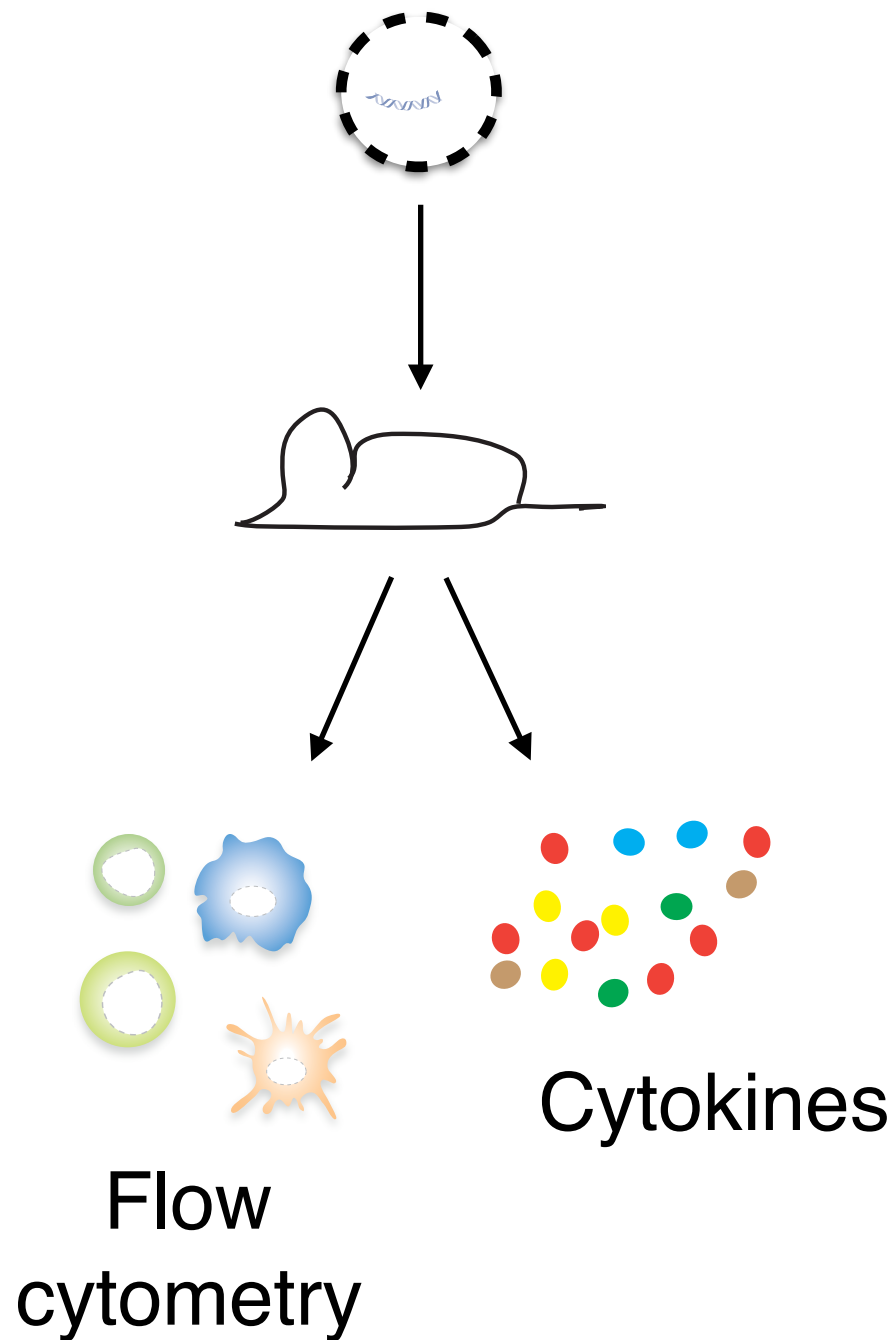
Q1: Are RNA-LPX taken up by DCs?



Flow cytometry

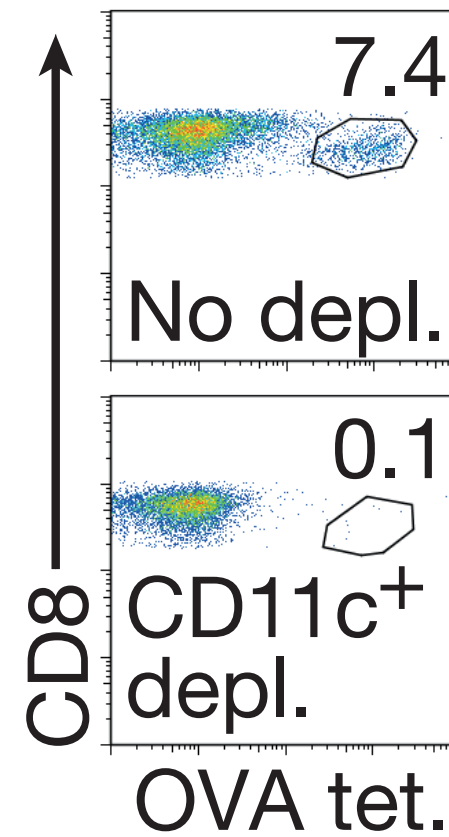
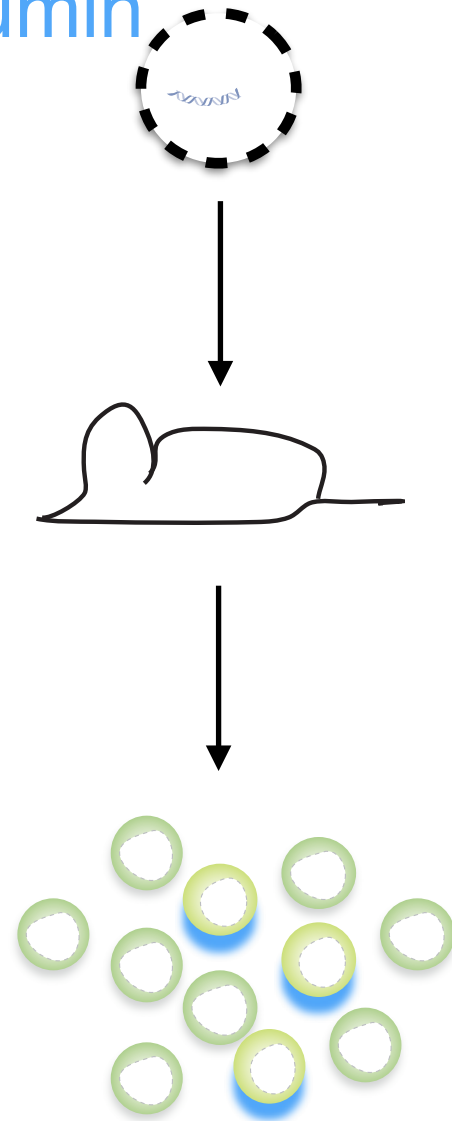


Q2: Do RNA-LPX activate an innate immune response?



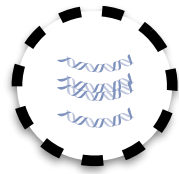
Q3: Are AG-specific T cells generated?

Ovalbumin

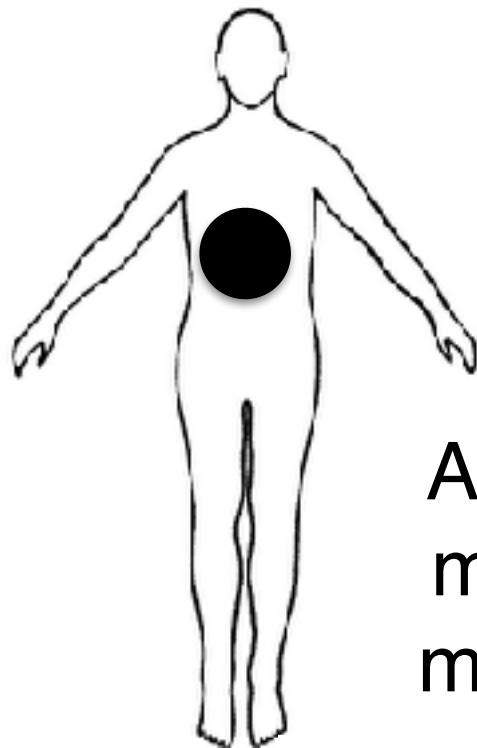


Q4: Can RNA-LPX be harnessed as cancer vaccine in humans?

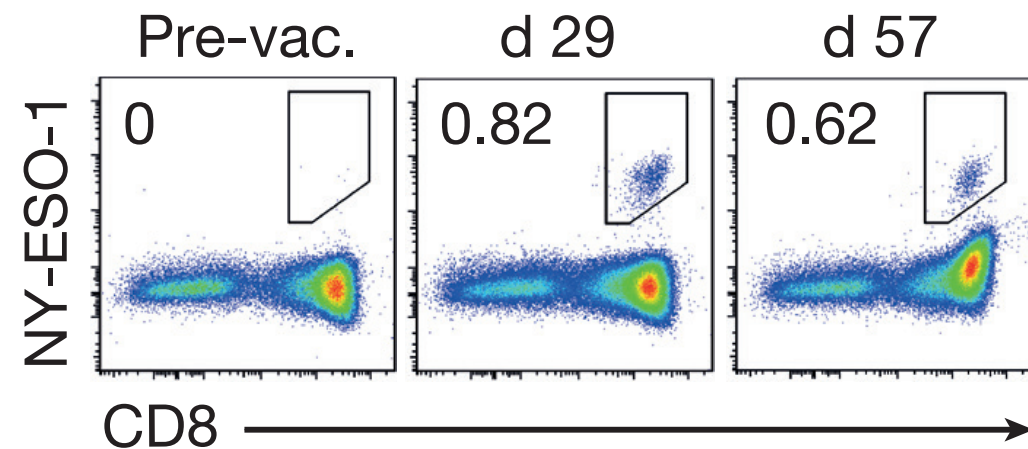
NY-ESO-1,
MAGE-A3,
tyrosinase,
TPTE



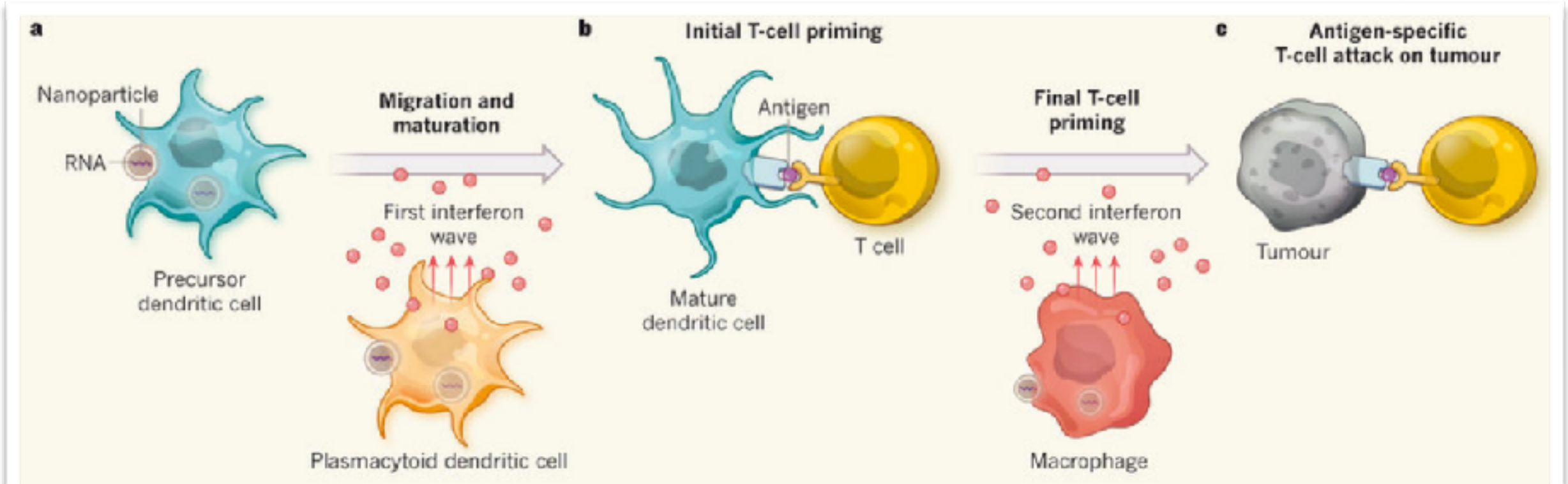
5 doses i.v.



Advanced
malignant
melanoma



Conclusion



Exercises

What are the advantages and disadvantages of using live attenuated organisms as vaccines?

Exercises

What are the advantages and disadvantages of using live attenuated organisms as vaccines?

Advantages:

- Induction of strong immune responses
- Often lifelong protection with few doses
- Generates humoral and cellular responses

Disadvantages:

- Reversion to virulent form
- Requires refrigerated storage
- Potential complications in immunosuppressed people

Exercises

Indicate whether each of the following statements is true or false!

- Transplacental transfer of maternal IgG antibodies against measles confers short-term immunity on the fetus.
- Attenuated vaccines are more likely to induce cell-mediated immunity than killed vaccines are.
- Adjuvant are generally included in attenuated vaccines.

Exercises

Indicate whether each of the following statements is true or false!

- Transplacental transfer of maternal IgG antibodies against measles confers short-term immunity on the fetus. ✓
- Attenuated vaccines are more likely to induce cell-mediated immunity than killed vaccines are. ✓
- Adjuvant are generally included in attenuated vaccines. ✗

Exercises

A young girl who had never been immunized to tetanus stepped on a rusty nail and got a deep puncture wound. The doctor cleaned the wound and gave the child an injection of tetanus antitoxin.

- Why was antitoxin given instead of tetanus vaccine?
- If the girl receives no further treatment and steps again on a nail in three years will she be immune to tetanus?

Exercises

Explain the phenomenon of herd immunity. How does it relate to the appearance of certain epidemics?

Exercises

List conditions that require passive instead of active immunization?

Exercises

Explain the relationship between incubation period of a pathogen and the approach needed to achieve effective active immunization!

Exercises

Some parents choose not to vaccinate their infants! What could be the consequences if a significant proportion was not vaccinated against childhood diseases such as measles or pertussis?

Exercises

For each of the following conditions indicate what type of vaccine is used?

- Polio
- Tetanus
- Hepatitis B
- Measles
- *Neisseria meningitidis*
- Live attenuated
- Killed microbe
- Inactivated toxin
- Purified proteins