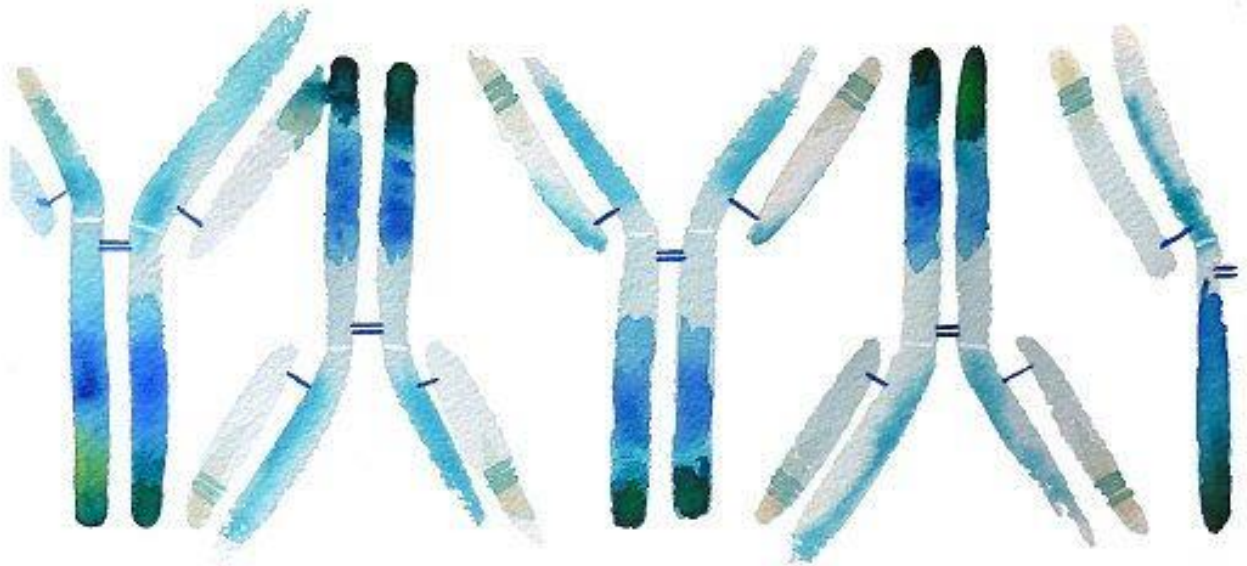
Medical Immunology



Anas Abu-Humaidan
M.D. Ph.D.

Lecture 15

B cell response

In this lecture we will discuss:

- B-cell response / T-dependent B-cell response
- Vaccine types

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

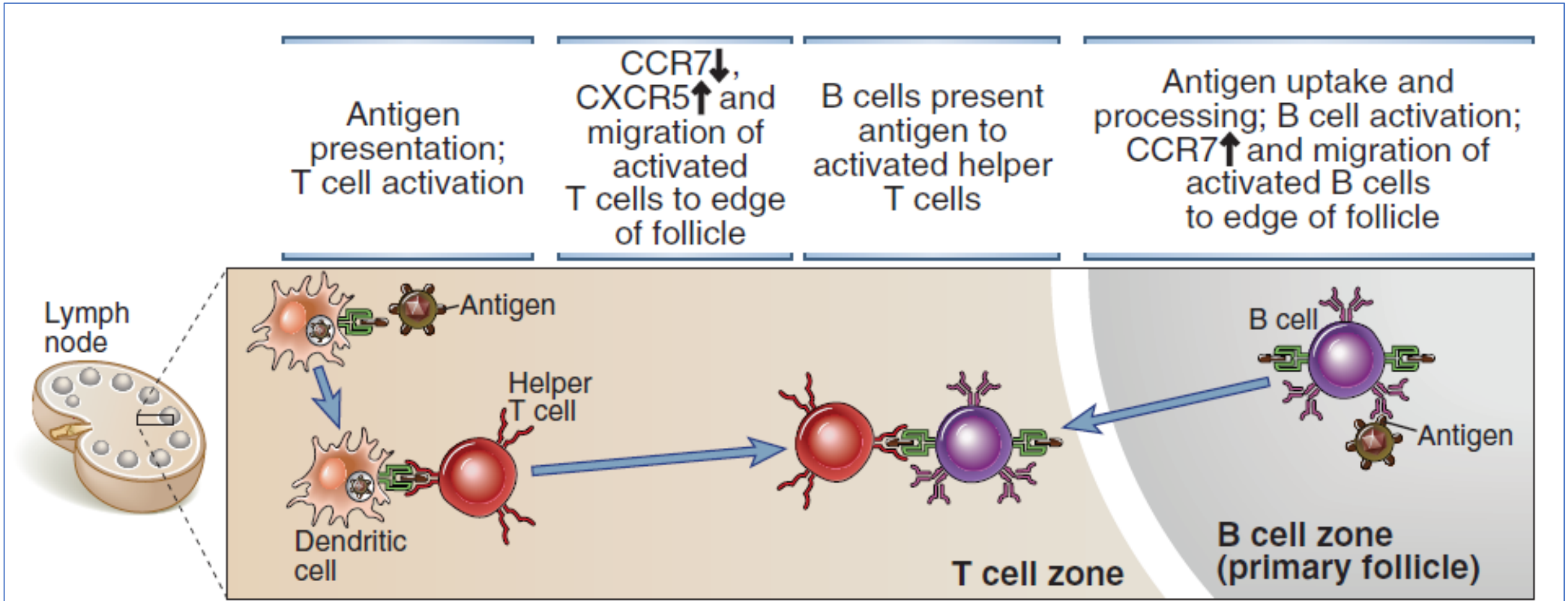
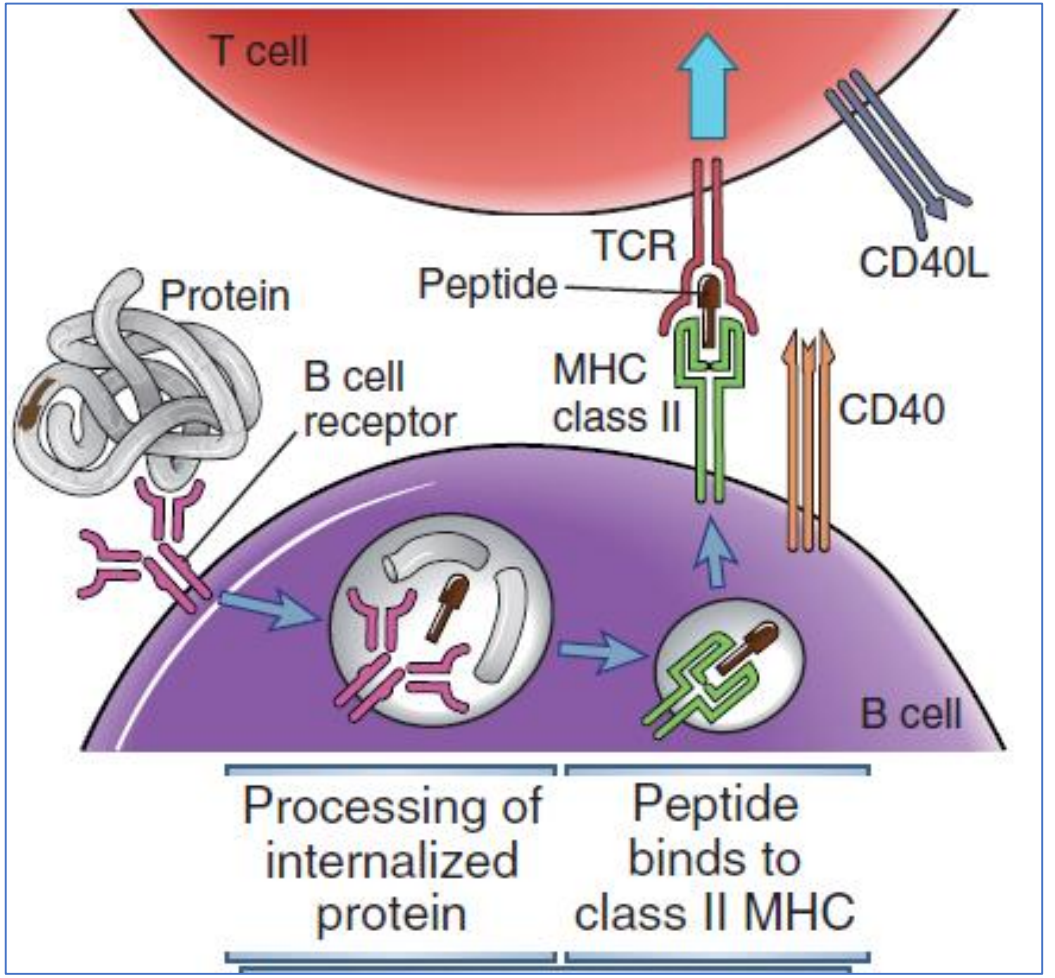


FIGURE 11–8 Migration of B cells and helper T cells and T-B interaction. Antigen-activated helper T cells and B cells move toward one another in response to chemokine signals and make contact adjacent to the edge of primary follicles. In this location, the B cell presents antigen to the T cell, and the B cell receives activating signals from the T cell.

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

- A protein antigen that elicits a T-dependent B cell response therefore makes use of at least two epitopes when activating specific B cells. A surface epitope on the **native protein** is recognized with **high specificity by a B cell**, and an **internal linear peptide** epitope is subsequently released from the protein, binds class II MHC molecules, and is **recognized by helper T cells**.

- The antibodies that are subsequently secreted are usually **specific for conformational determinants of the native antigen.**

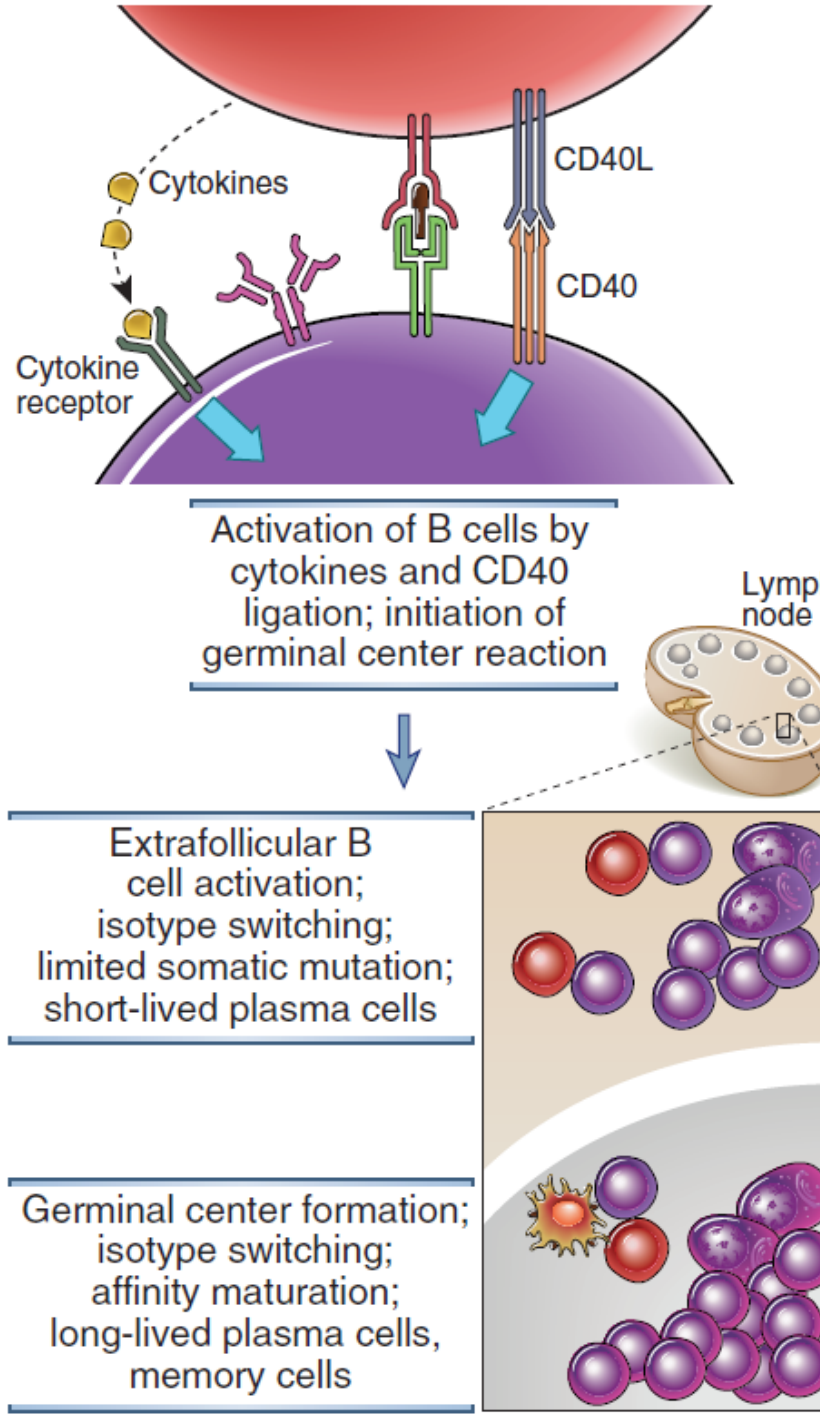


B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

- On activation, helper T cells express CD40 ligand (CD40L), which engages its receptor, CD40, on antigen-stimulated B cells at the T-B interface and induces subsequent proliferation and differentiation **initially in extrafollicular foci** and later **in germinal centers**.

- CD40 is constitutively expressed on B cells, and **CD40L is expressed on the surface of helper T cells after activation** by antigen and costimulators.

- helper T cells also **secrete cytokines** that contribute to B cell responses. The best defined roles of T cell derived cytokines in humoral immune responses are in isotype switching, with roles in differentiation and proliferation as well.



B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

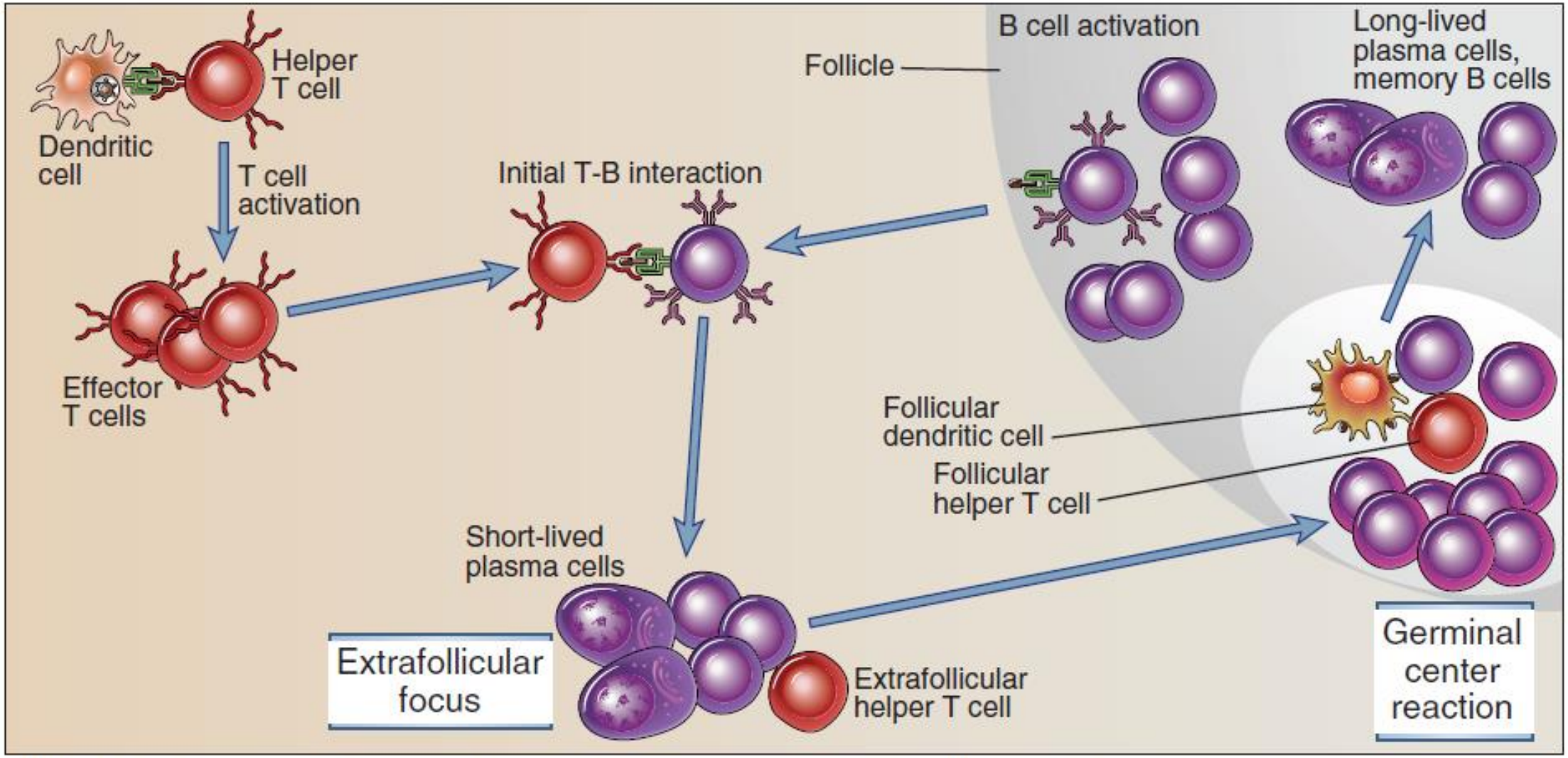


FIGURE 11–7 Sequence of events in humoral immune responses to T cell–dependent protein antigens. Immune responses are initiated by the recognition of antigens by B cells and helper T cells. The activated lymphocytes migrate toward one another and interact, resulting in B cell proliferation and differentiation. Restimulation of B cells by helper T cells in extrafollicular sites leads to early isotype switching and short-lived plasma cell generation. The late events occur in germinal centers and include somatic mutation and the selection of high-affinity cells (affinity maturation), additional isotype switching, memory B cell generation, and the generation of long-lived plasma cells.

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

- **Extrafollicular foci of T-dependent B cell activation** are generated **relatively early** in an immune response**. Germinal centers**, in which specialized **follicular helper T (TFH)** cells trigger B cells to undergo numerous changes, **appear a few days later**.

- The characteristic events of helper T cell–dependent antibody responses, including **affinity maturation**, **isotype switching**, **generation of memory B cells**, and **long-lived plasma cell differentiation**, occur primarily in the **germinal centers** of lymphoid follicles.

- Each fully formed germinal center contains cells derived from only one or a few antigen-specific B cell clones

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

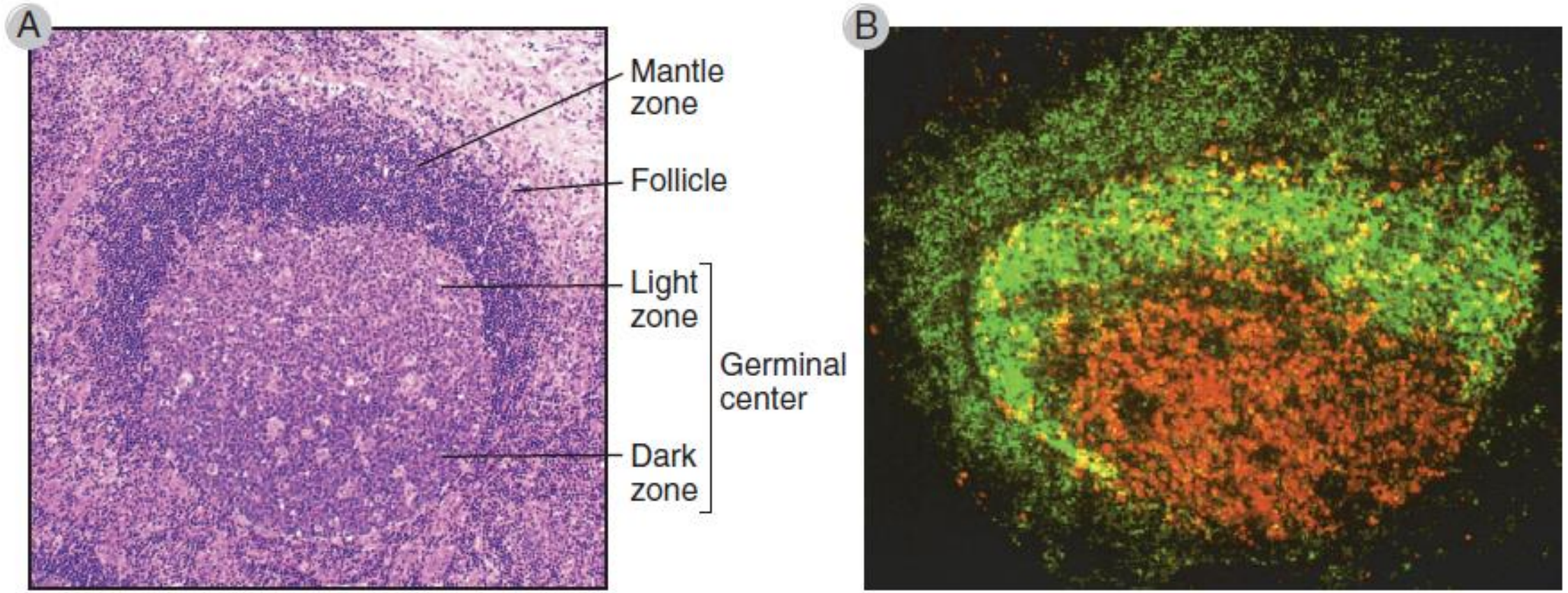


FIGURE 11–11 Germinal centers in secondary lymphoid organs. A, Histology of a secondary follicle with a germinal center in a lymph node. The germinal center is contained within the follicle and includes a basal dark zone and an adjacent light zone. The mantle zone is the parent follicle within which the germinal center has formed. *(Courtesy of Dr. James Gulizia, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)* **B,** Cellular components of the germinal center. A secondary follicle has been stained with an anti-CD23 antibody (green), which brightly stains follicular dendritic cells in the light zone and dimly stains naive B cells in the mantle zone. Anti-Ki67 (red), which detects cycling cells, stains mitotically active B cell blasts in the dark zone. *(Modified from Liu YJ, GD Johnson, J Gordon, and IC MacLennan. Germinal centres in T-cell–dependent antibody responses. Immunology Today 13:17-21, Copyright 1992, with permission from Elsevier.)*

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

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- **follicular dendritic cells (FDCs).** FDCs are found only in lymphoid follicles and express complement receptors (CR1, CR2, and CR3) and Fc receptors. These molecules are involved in displaying antigens for the selection of germinal center B cells

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

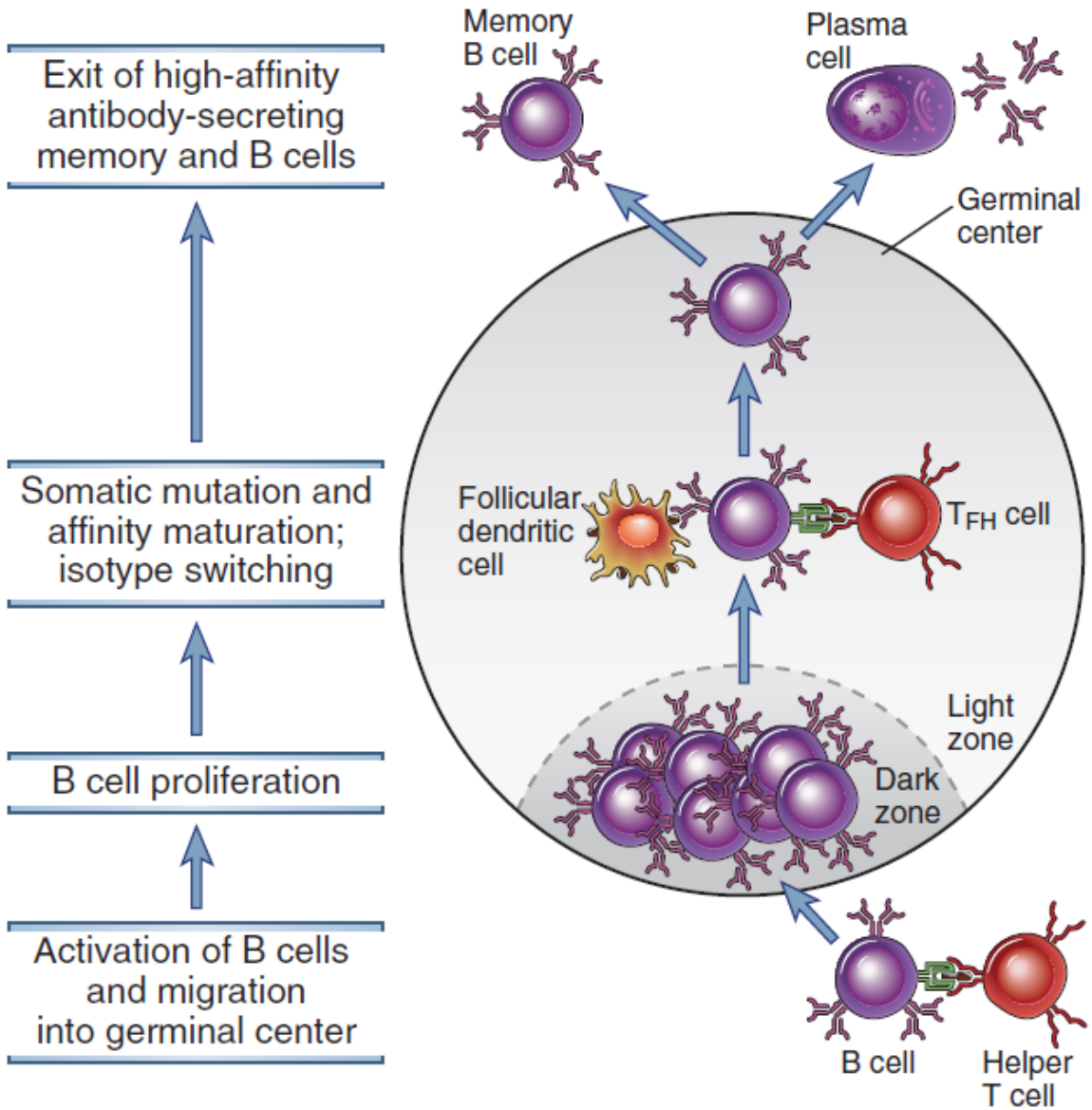


FIGURE 11–12 The germinal center reaction in a lymph node. B cells that have been activated by T helper cells at the edge of a primary follicle migrate into the follicle and proliferate, forming the dark zone of the germinal center. Germinal center B cells undergo extensive isotype switching. Somatic hypermutation of Ig V genes occur in these B cells, and they migrate into the light zone, where they encounter follicular dendritic cells displaying antigen and T_{FH} cells. B cells with the highest affinity Ig receptors are selected to survive, and they differentiate into antibody-secreting or memory B cells. The antibody-secreting cells leave and reside in the bone marrow as long-lived plasma cells, and the memory B cells enter the recirculating pool.

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

TABLE 11–1 Extrafollicular and Germinal Center B Cell Responses

Feature	Follicular/Germinal Center	Extrafollicular
Localization	Secondary follicles	Medullary cords of lymph nodes and at junctions between T cell zone and red pulp of spleen
CD40 signals	Required	Required
Specialized T cell help	T_{FH} cells in germinal center	Extrafollicular T helper cells
AID expression	Yes	Yes
Class switching	Yes	Yes
Somatic hypermutation	High rate	Low rate
Antibody affinity	High	Low
Terminally differentiated B cells	Long-lived plasma cells and memory cells	Short-lived plasma cells (life span of ~3 days)
Fate of plasma cells	Bone marrow or local MALT	Most die by apoptosis in secondary lymphoid tissues where they were produced
B cell transcription factors	Bcl-6	Blimp-1

AID, activation-induced cytidine deaminase; Bcl-6, B cell lymphoma 6; Blimp-1, B lymphocyte–induced maturation protein 1; IL-21R, interleukin-21 receptor; MALT, mucosa-associated lymphoid tissue; T_{FH}, follicular helper T cell.
Data from Vinusa CG, I Sanz, and MC Cook. Dysregulation of germinal centres in autoimmune disease. Nature Reviews Immunology 9:845-857, 2009.

B cell response/ Isotype switching

- **Isotype switching** in response to **different types of microbes** is regulated by cytokines produced by the helper T cells that are activated by these microbes.

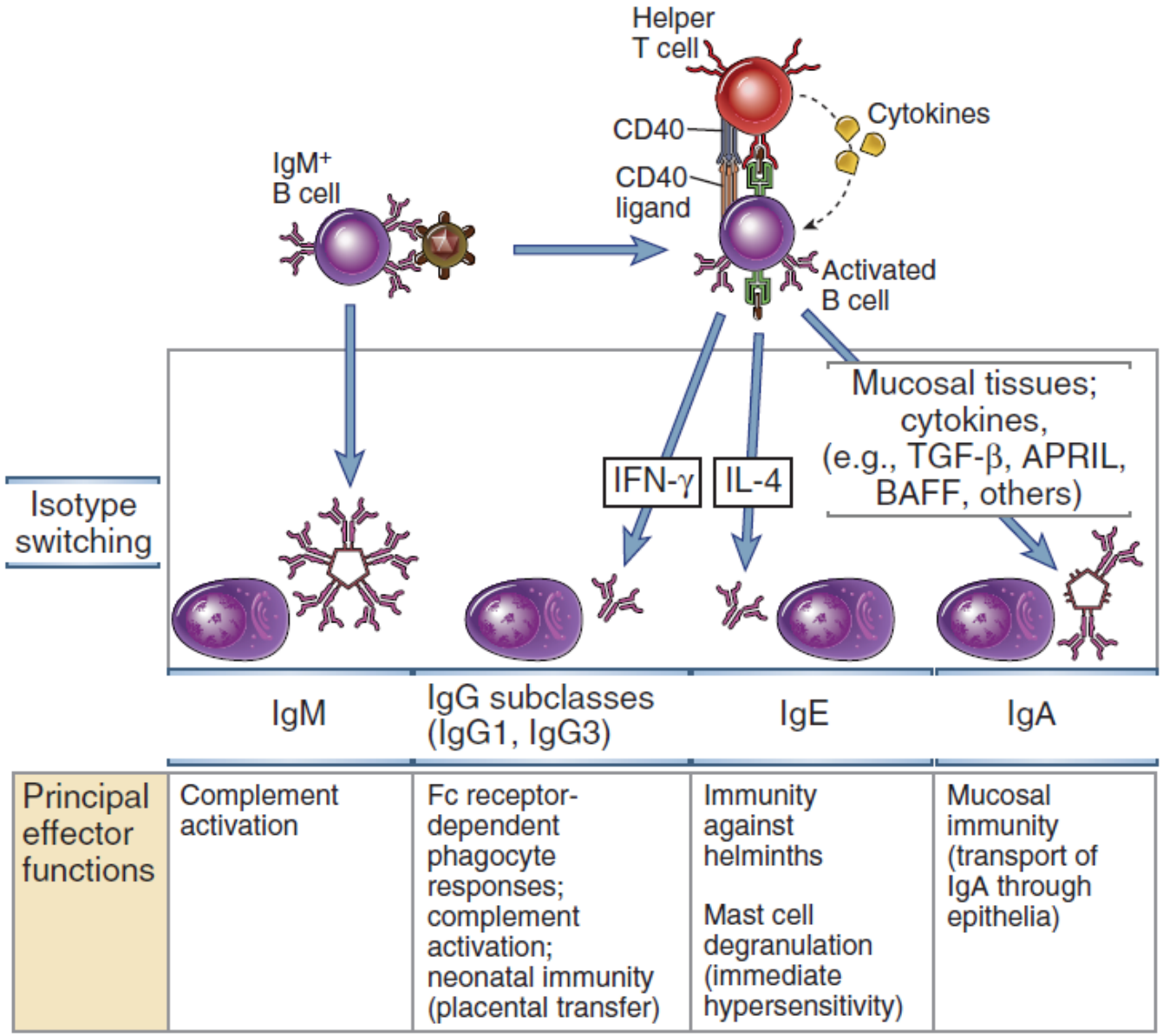
- Polysaccharide antigens, which do not elicit T cell help, stimulate mainly IgM antibodies, with little if any isotype switching to some IgG subclasses

- Viruses and many bacteria activate helper T cells of the TH1 subset, which produce the cytokine IFN-γ.

- Helminths activate the TH2 subset of helper T cells, which produces IL-4, the cytokine that induces switching to IgE.

- **B cells in different anatomic sites switch to different isotypes.** Specifically, B cells in mucosal tissues switch to IgA, which is the antibody class that is most efficiently transported through epithelia into mucosal secretions, where it defends against microbes that try to enter through the epithelia

B cell response/ Isotype switching



	IgM	IgG subclasses (IgG1, IgG3)	IgE	IgA
Principal effector functions	Complement activation	Fc receptor-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)

FIGURE 11–14 Ig heavy chain isotype switching. B cells activated by helper T cell signals (CD40L, cytokines) undergo switching to different Ig isotypes, which mediate distinct effector functions. Selected examples of switched isotypes are shown. The role of IFN-γ in directing specific isotype switching events has been established only in rodents.

B cell response/ Affinity Maturation

- **Affinity maturation** is the process that leads to **increased affinity of antibodies** for a particular antigen as a T-dependent humoral response progresses and is the result of **somatic mutation of Ig genes** followed by **selective survival of the B cells** producing the antibodies with the highest affinities.

- Helper T cells and CD40:CD40L interactions are required for somatic mutation to be initiated, and as a result, affinity maturation is observed only in antibody responses to T-dependent protein antigens.

- This rate is estimated to be 1 in 1000 V gene base pairs per cell division, which is about a thousand times higher than the spontaneous rate of mutation in other mammalian genes. The mutations are clustered in the V regions, mostly in the antigen-binding complementarity-determining regions.

B cell response/ Affinity Maturation

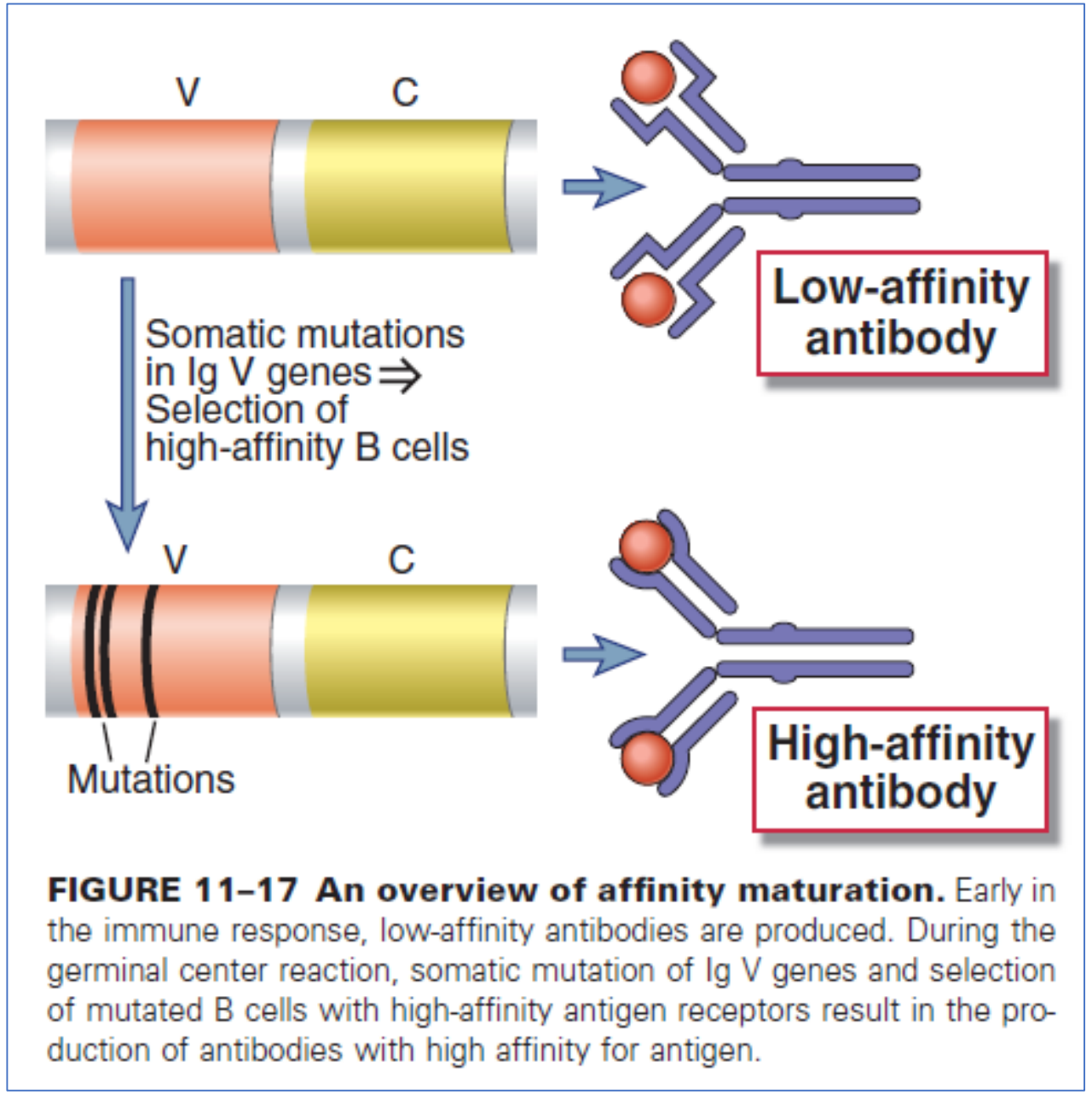
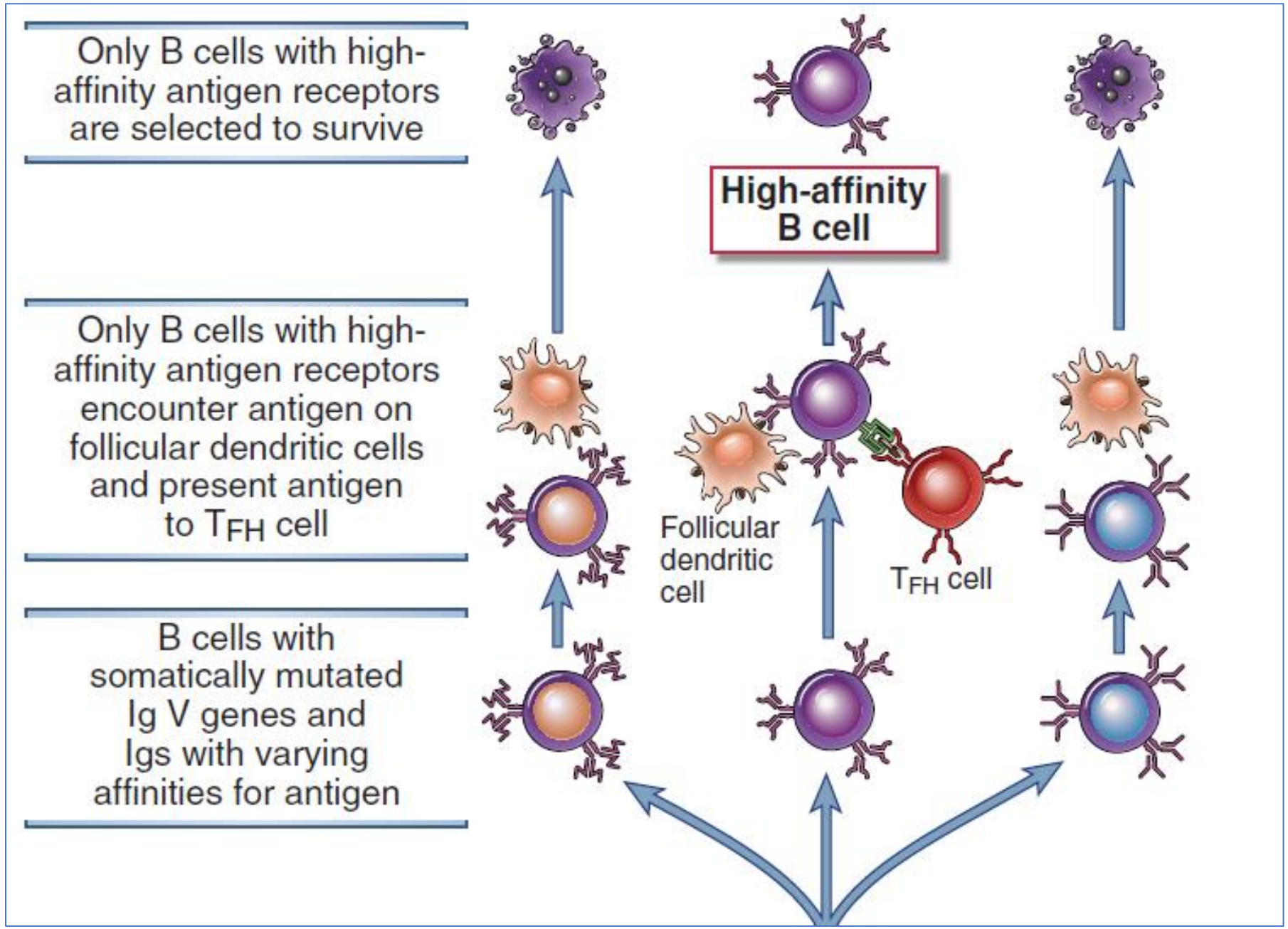


FIGURE 11–17 An overview of affinity maturation. Early in the immune response, low-affinity antibodies are produced. During the germinal center reaction, somatic mutation of Ig V genes and selection of mutated B cells with high-affinity antigen receptors result in the production of antibodies with high affinity for antigen.

B cell response/ Affinity Maturation

- germinal center B cells that have undergone somatic mutation migrate into the FDC-rich light zone of the germinal center. In germinal center B cells, **IL-21 secreted by TFH cells induces the expression of proteins that induce apoptosis and reduces the expression of proteins that prevent apoptosis**. Therefore, these **B cells die by apoptosis unless they are rescued by recognition of antigen**. B cells with high-affinity receptors for the antigen are best able to bind the antigen when it is present at low concentrations, and these B cells survive preferentially because of several mechanisms

B cell response/ Affinity Maturation



Vaccination/ overview

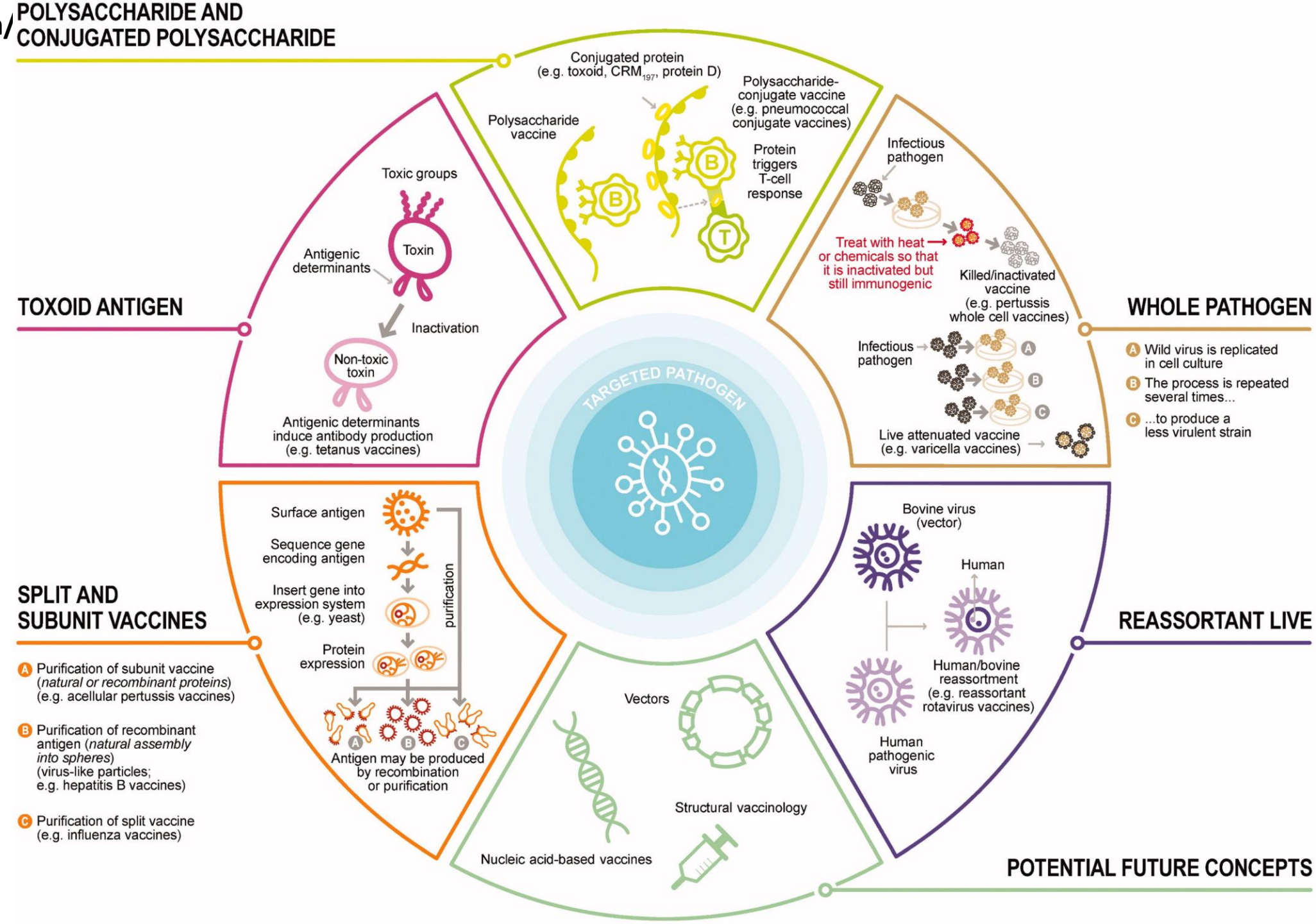
- The aim of vaccination is to **induce a protective immune response** to the targeted pathogen **without the risk** of acquiring the disease and its potential complications.

- Each pathogen (or vaccine) expresses (or contains) antigens that induce **cell-mediated immunity** by activating highly specific subsets of **T lymphocytes** and humoral immunity by stimulating **B lymphocytes** to produce specific antibodies.

- After elimination of the pathogen, the adaptive immune system generally establishes immunological memory.

- Vaccines may contain **live-attenuated pathogens**, **inactivated pathogens**, or only **parts of pathogens** and may also contain **adjuvants** to stimulate the immune responses.

Vaccination/



Vaccination/ Live attenuated vaccines

- **Live attenuated vaccines** contain pathogens that have been **weakened**, **altered** or **selected** to be less virulent than their wild-type counterparts. In their altered form, they cannot cause the actual disease or only mimic the disease in a very mild way.

- They are generally produced **from viruses rather than bacteria** because viruses contain fewer genes and attenuation can be obtained and controlled more reliably. The most **common method** to obtain live attenuated vaccines is to **pass the virus** through a series of in vitro cell cultures (e.g. in chick embryo cells). At each “passage”, the selected viruses **become better at infecting and replicating in cell cultures** but progressively **lose their ability to infect** and replicate in their **original human host**.

- These vaccines induce robust cell-mediated and antibody responses and **often confer long-term immunity** after only one or two doses. Although rare, clinical disease can occur after vaccination, but vaccine-induced symptoms are typically much milder than after natural infection. However, live attenuated vaccines **are often contraindicated** in **immunocompromised** individuals

Vaccination/ Live attenuated vaccines

- Classical examples of live attenuated vaccines produced by serial passage are those against **measles, mumps, rubella** and **varicella**, which are usually combined into trivalent or tetravalent vaccines

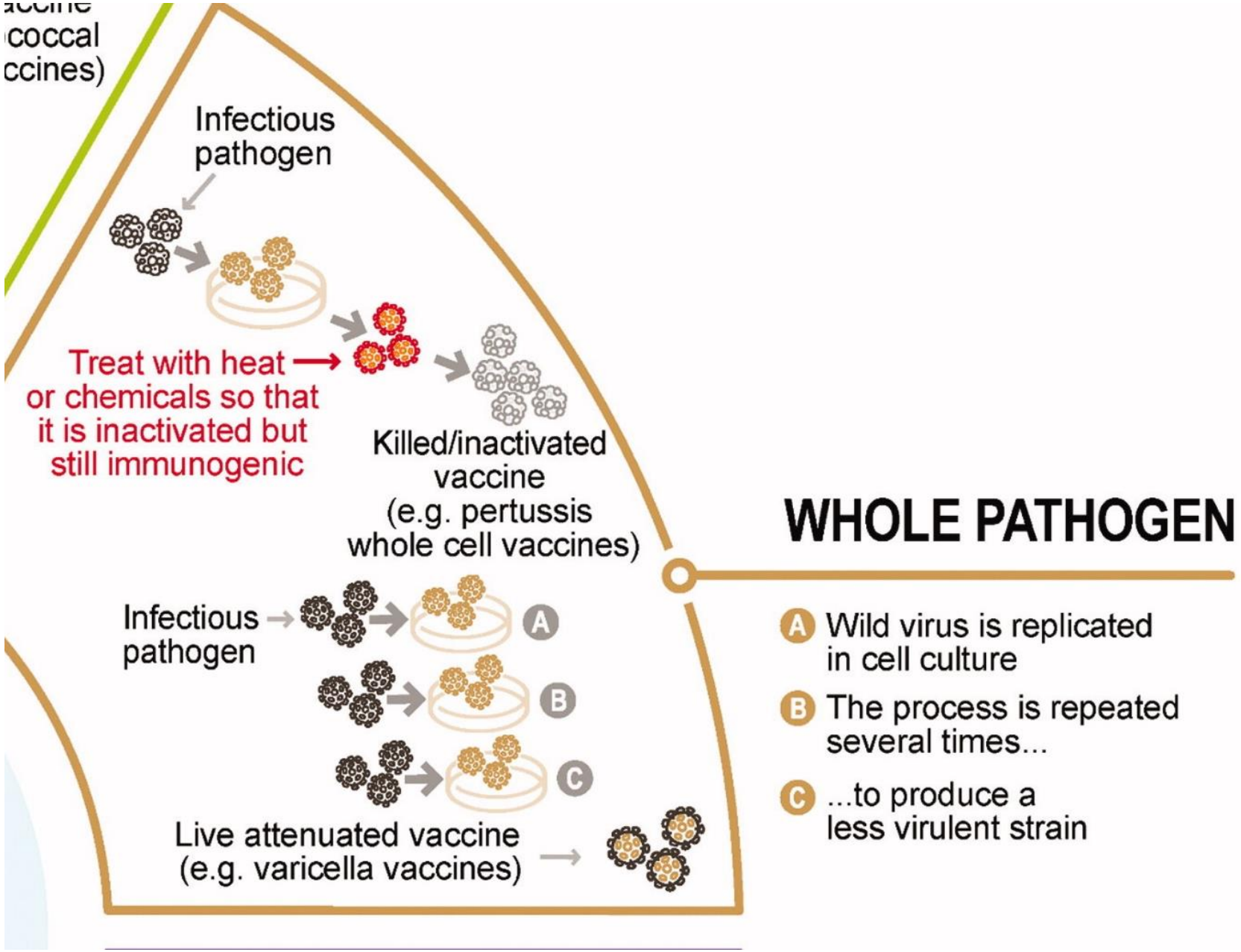
- The **only live attenuated bacterial** vaccine currently in use is the bacillus Calmette-Guérin **(BCG) vaccine**, which was developed almost a century ago

- **Oral polio vaccine (OPV)** is a live attenuated vaccine that was obtained through serial passages in non-human cells, OPV is easily administered through oral drops, inexpensive, and effective at inducing intestinal mucosal immunity.

- However, in very rare cases (one case per million doses), OPV can mutate into a virulent form and induce very rare cases of vaccine-associated paralytic poliomyelitis.

- **OPV** should be stopped after wild poliovirus transmission has been controlled. For this reason and to maintain population immunity, OPV has been replaced by an **inactivated polio vaccine (IPV)** in an increasing number of countries worldwide.

Vaccination/ overview



Vaccination/ Non-live vaccines

- **Non-live vaccines** do not contain any living or infectious particles, so they cannot cause disease and cannot reactivate. Therefore, they generally have a good safety profile, even in immunocompromised individuals.

- However, a **drawback** of these vaccines is that **immunogenicity** and **duration** of **protection** tend to be less than for live vaccines, and they may require several doses or adjuvants to improve immunogenicity.

- Therefore, these vaccines are usually given repeatedly based on the prime-boost principle to induce long-term immunity.

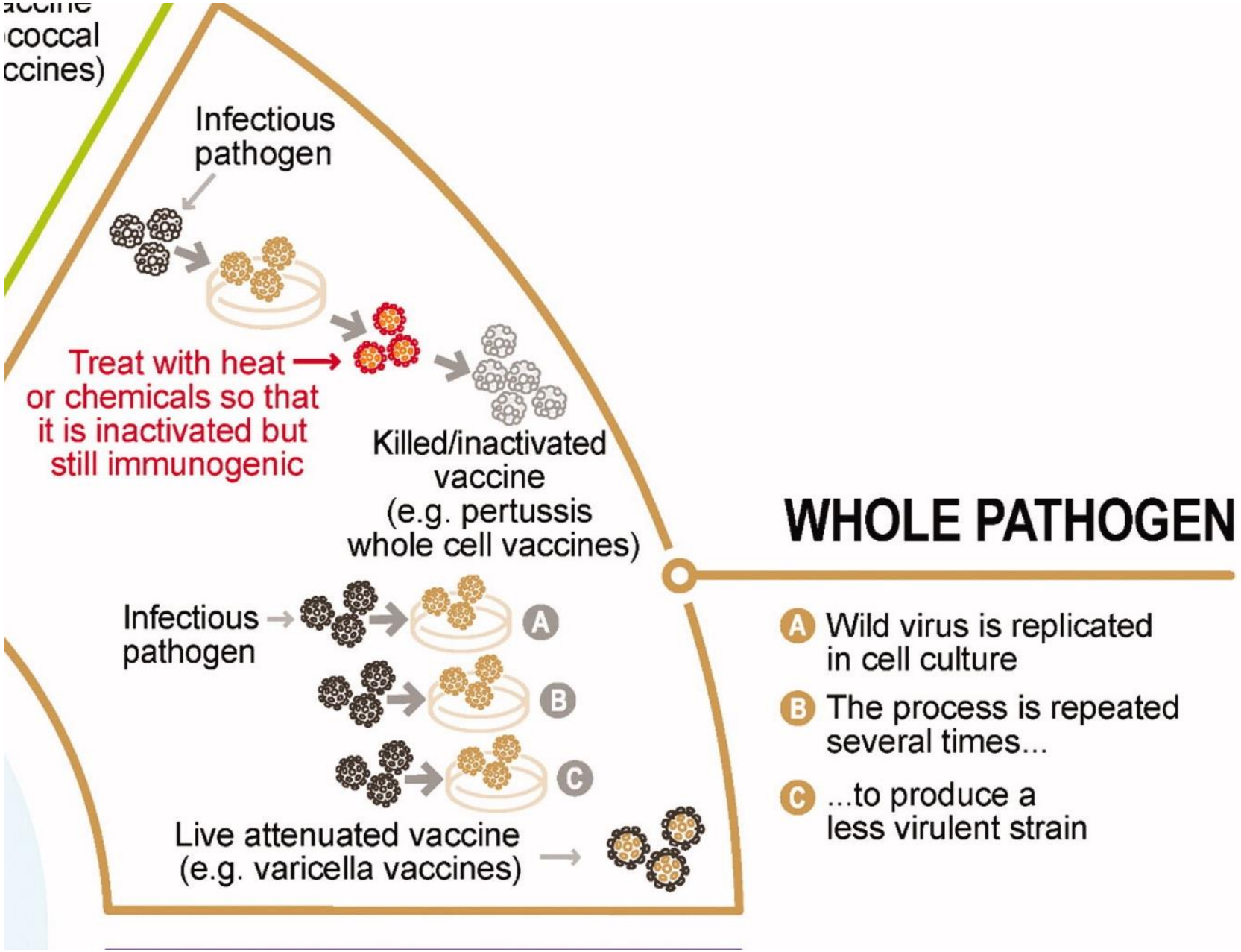
- Non-live vaccines can contain inactivated **whole pathogens** or **only parts of them** such as **proteins** or **polysaccharides** (**subunit vaccines**).

Vaccination/ Non-live vaccines / whole pathogen

- Vaccines based on inactivated pathogens are produced by inactivating preparations of whole pathogens by **heat, radiation, or chemicals** such as formalin or formaldehyde.

- Current examples of inactivated vaccines include the previously mentioned **IPV**, **whole-cell pertussis**, **rabies** and **hepatitis A vaccines.**

Vaccination/ overview



Vaccination/ Non-live vaccines/ Subunit vaccines

- Subunit vaccines contain selected fragments of the pathogen as antigens instead of the whole pathogen. These fragments can be **proteins**, **polysaccharides**, or parts of a virus that may form **virus-like particles (VLPs).**

- Subunit vaccines generally cause less adverse reactions than live or inactivated whole-organism vaccines, but they may be less immunogenic because they contain fewer antigens and the purification process often eliminates components that trigger innate immunity.

- Examples of subunit vaccines include **tetanus toxoid**, inactivated split and subunit seasonal **influenza**, **acellular pertussis** and **pneumococcal polysaccharide vaccines**.

Vaccination/ Non-live vaccines/ Subunit vaccines

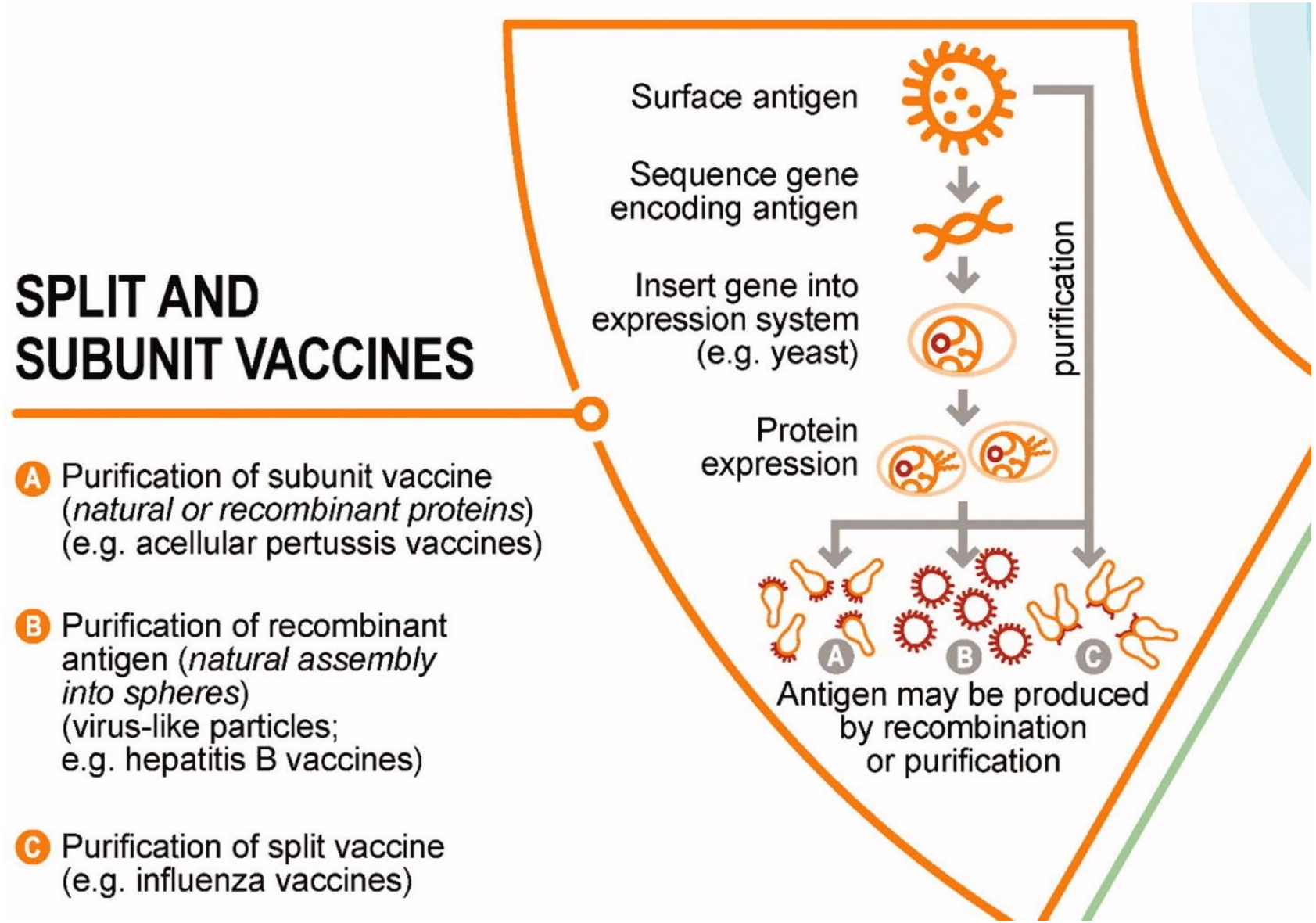
- Antigenic proteins can be **purified** from preparations of the whole pathogen, as for the acellular pertussis vaccines, or can be **produced by recombinant genetic engineering**.

- **Acellular pertussis vaccines** are other examples of **purified antigenic proteins**. These vaccines contain between one and five highly purified pertussis antigens, compared to more than 3000 antigens for whole-cell inactivated pertussis vaccines.

- An example of **recombinant protein vaccine** is provided by the widely used hepatitis B vaccine in which the gene of the **hepatitis B surface antigen (HBsAg)** has been inserted into appropriate vectors for production in yeast.

- The concept of combining recombinant proteins helped to develop the first malaria vaccine. In this vaccine, the gene of a **surface protein** of the infectious form of **Plasmodium falciparum** is fused to the **HBsAg gene**, and the resulting recombinant fusion protein is expressed in yeast with free recombinant HBsAg.

Vaccination/ Non-live vaccines/ Subunit vaccines



Vaccination/ Non-live vaccines/ Toxoid vaccines

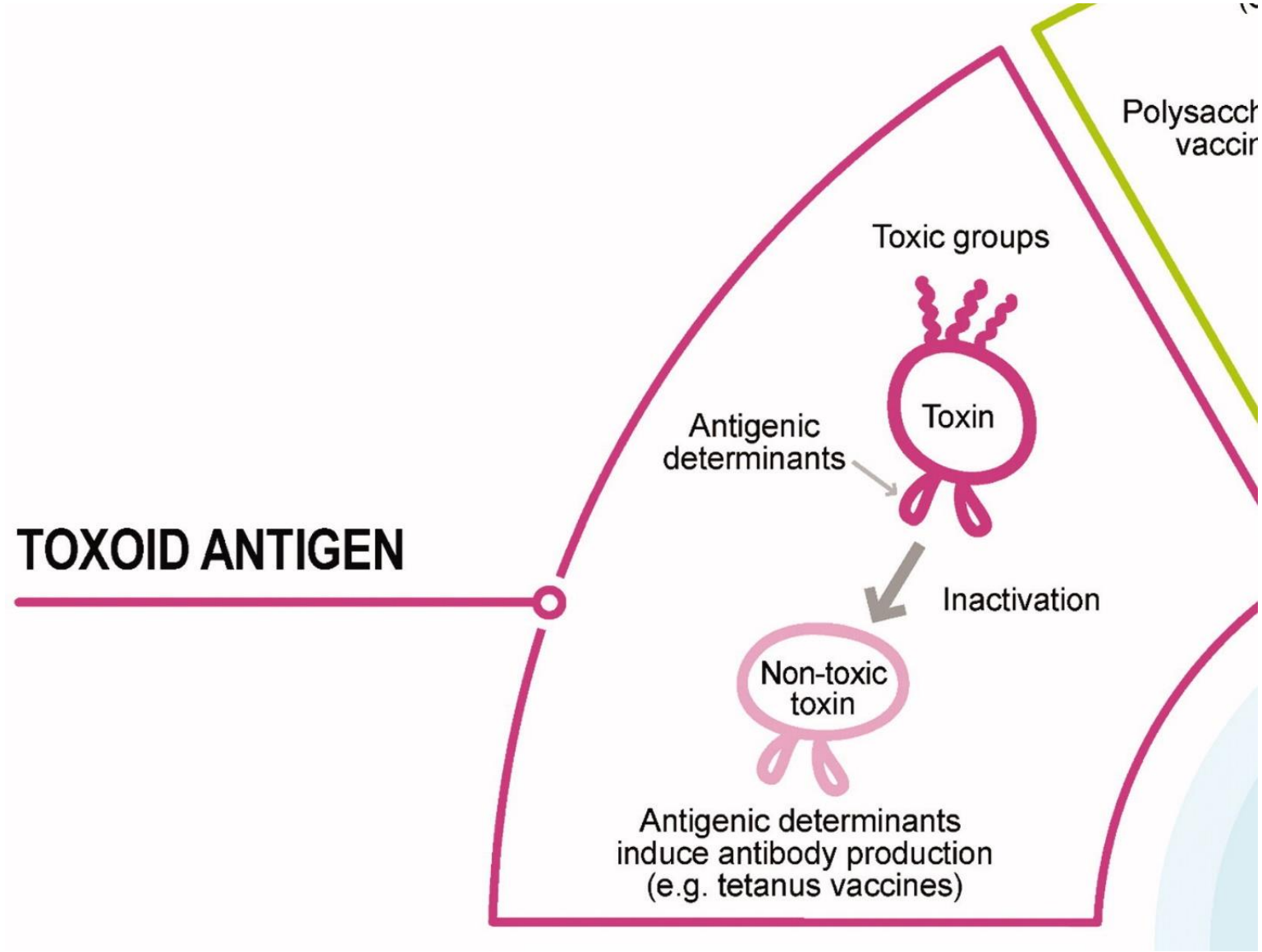
- Some bacteria such as **Clostridium tetani**, Clostridium difficile or **Corynebacterium diphtheriae** cause disease by releasing **pathogenic toxins**. Vaccines against these diseases are produced by **detoxifying the toxin** using heat, chemicals (e.g. formaldehyde) or both.

- The inactivated toxins, called **toxoids**, are no longer pathogenic but retain their ability to induce toxin-neutralizing antibodies. Classical examples of toxoid vaccines are those against diphtheria and tetanus, which have been used since their discovery in the 1920s

- However, toxoids **protect** only against disease pathogenesis in **vaccinated individuals** but **do not prevent infection or transmission.**

- Therefore, high vaccination coverage does not provide **herd protection** and unvaccinated or individuals not receiving regular booster doses are potentially at risk.

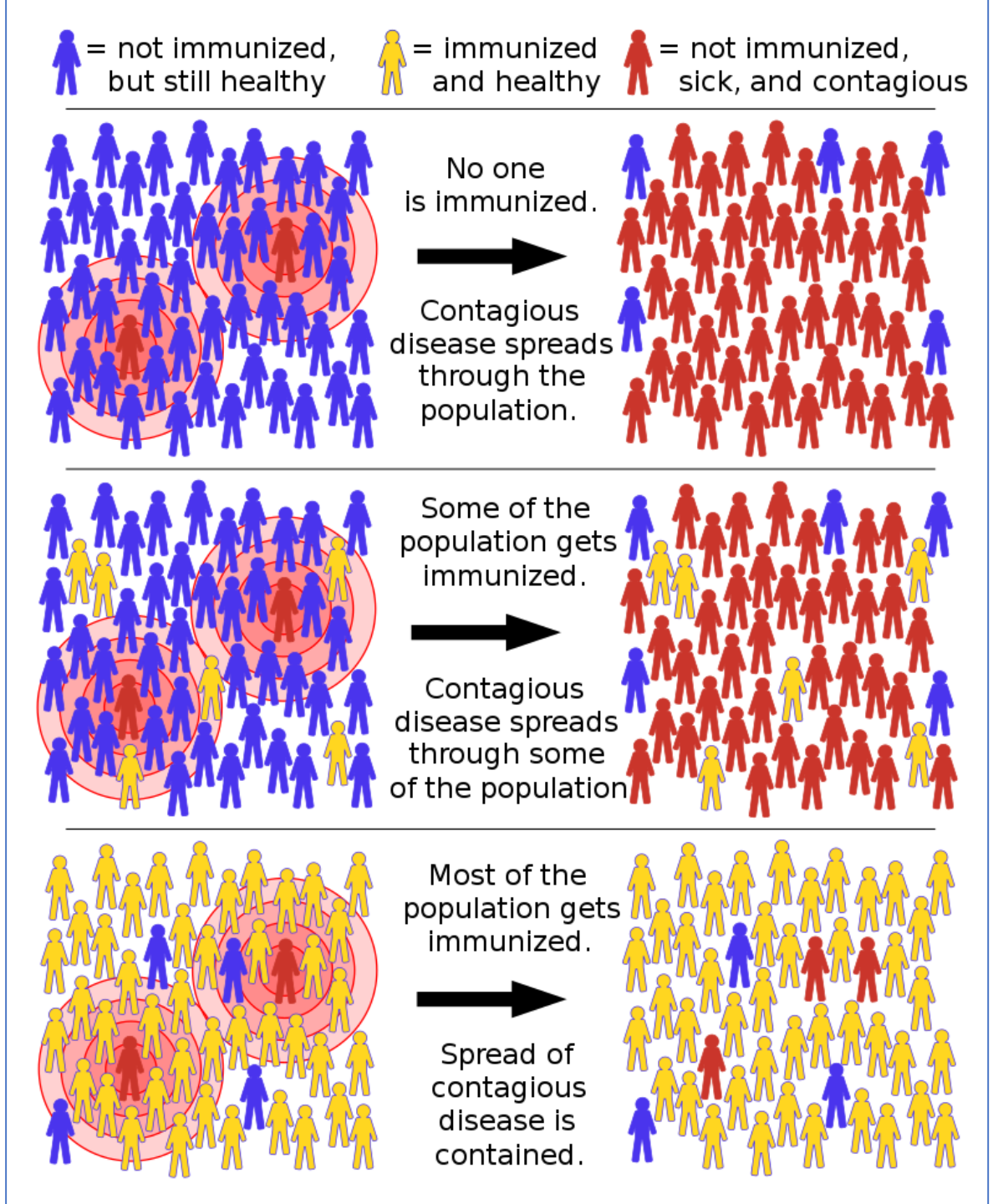
Vaccination/ Non-live vaccines/ Toxoid vaccines



Vaccination/ Herd immunity

- Herd immunity is a form of **indirect protection from infectious disease** that occurs when a **large percentage** of a population has become immune to an infection, **thereby providing a measure of protection for individuals who are not immune.**

- The greater the proportion of individuals in a community who are immune, the smaller the probability that those who are not immune will come into contact with an infectious individual.



Vaccination/ Non-live vaccines/ Polysaccharide and conjugate vaccines

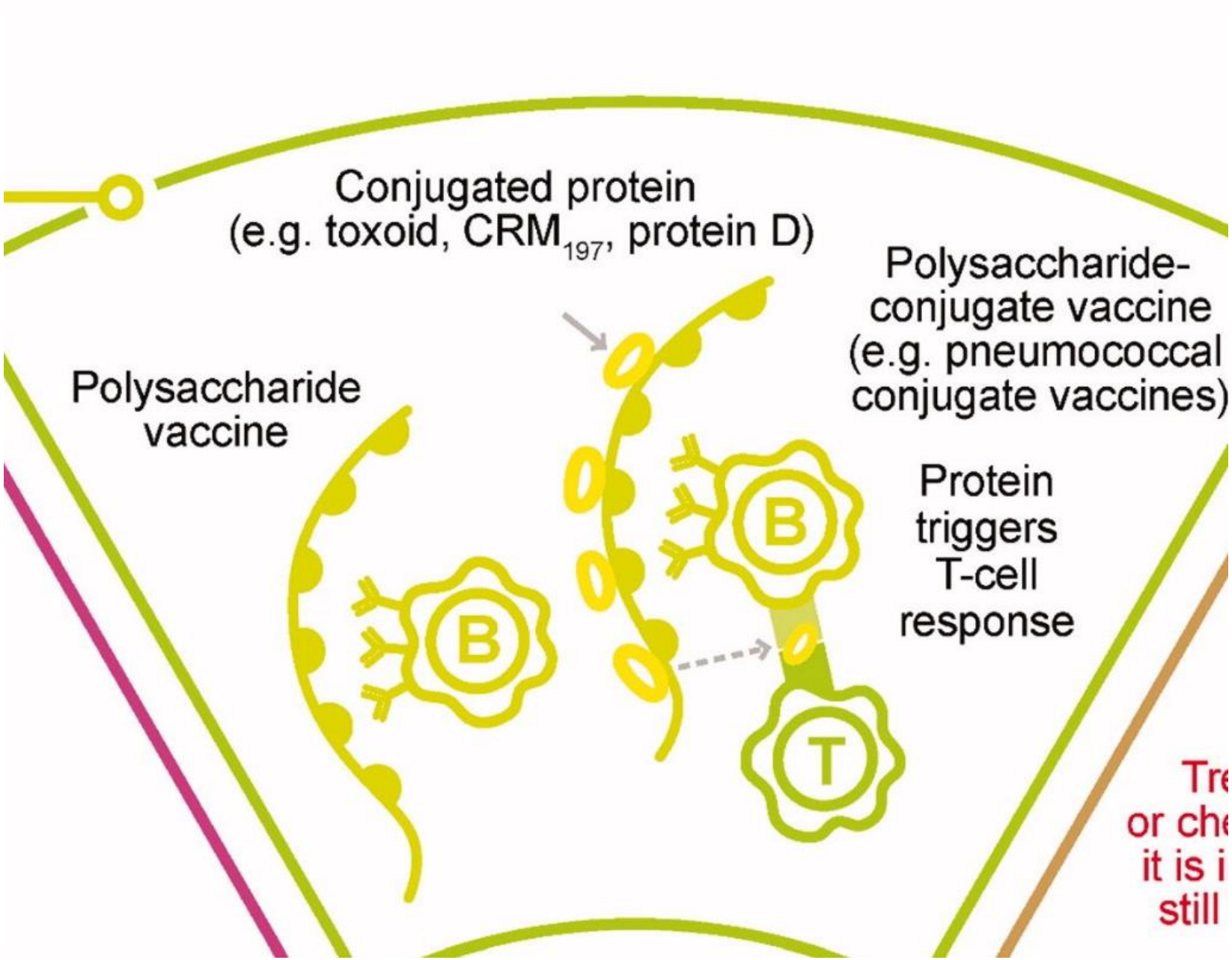
- **Streptococcus pneumoniae**, **Haemophilus influenzae type b** and **N. meningitidis** are three **encapsulated bacteria** that cause severe invasive disease. They possess **polysaccharide capsules** that **facilitate bacteria's survival** when carried in the **nasopharynx** and in the **blood** during disease pathogenesis.

- **Polysaccharide vaccines** are **poorly immunogenic**, provide only **short term protection.**

- **Immunogenicity** of purified polysaccharides **could be enhanced by coupling** (i.e. conjugating) them **to a protein**.

- **Conjugation transforms** the **T-cell-independent** response induced by polysaccharides into a **T-cell-dependent** response that induces high-affinity antibodies and immune memory

Vaccination/ Non-live vaccines/ Polysaccharide and conjugate vaccines



Vaccination/ adjuvants

- **Adjuvants** are substances that can **enhance and modulate the immunogenicity of the antigen**. Adjuvants are usually not needed for live attenuated vaccines because these vaccines actively replicate and self-enhance the immune response.

- Due to their capacity to **activate innate immune responses**, adjuvants can **broaden or extend responses** and improve memory responses

- For almost a century, aluminium salts (also known as alum) were the only adjuvant approved worldwide and they still remain the most widely used.

Vaccination/ conclusion

- Our improved understanding of the immune system and host-pathogen interactions has allowed transition from an empirical to a more rational vaccine design, but progress is still needed to address unmet needs and improve protection induced by current vaccines.

- Like all medicines, vaccines can have adverse events. However, because vaccines are given as preventive measures mostly to healthy individuals, especially infants and children, a highly positive benefit–risk profile is essential. Vaccine safety is evaluated in the preclinical and clinical phases of development but is also continuously monitored after licensure.

- New vaccine designs and concepts are needed to improve existing vaccines or address unmet needs notably for **pathogens with multiple serotypes** (e.g. dengue, S. pneumoniae), **antigenic hypervariability (**e.g. human immunodeficiency virus) or **an intracellular phase that are predominantly controlled by T-cell responses** (e.g. tuberculosis, malaria)

Vaccination/ Vaccine program in Jordan

Motherhood & More

برنامج التطعيم للأطفال / الأردن

أقرب وقت بعد الولادة، يُعطى مطعوم السل (BCG)
على عمر شهرين (٦١ يوم) يُعطى الطفل الجرعة الأولى من مطعوم شلل الأطفال IPV والمطعوم الخماسي الذي يتكون من : المطعوم الثلاثي DPT (الدفتيريا والسعال الديكي والكزاز)+مطعوم المستدمية النزلية نوع (ب) + مطعوم التهاب الكبد نوع (ب)+ الجرعة الأولى من مطعوم الروتافيروس .
على عمر ٣ اشهر (٩١ يوم) يُعطى الطفل الجرعة الثانية ـ مطعوم شلل الأطفال IPV+OPV +المطعوم الخماسي الذي يتكون من: المطعوم الثلاثي DPT (الدفتيريا والسعال الديكي والكزاز) +مطعوم المستديمة النزلية نوع (ب) + مطعوم التهاب الكبد نوع (ب) + الجرعة الثانية من مطعوم الروتافيروس .
على عمر ٤ شهور (١٢١ يوم) يُعطى الطفل مطعوم شلل الاطفال الفموي OPV + المطعوم الثلاثي DPT (الدفتيريا والسعال الديكي والكزاز)+مطعوم المستديمة النزلية نوع (ب)+ مطعوم التهاب الكبد نوع (ب)على شكل رباعي أو خماسي + الجرعة الثالثة من مطعوم الروتافيروس .
على عمر ٩ شهور (بداية الشهر العاشر) يُعطى الطفل ـ مطعوم الحصبة Measles + مطعوم شلل الأطفال الفموي OPV+ فيتامين أ (١٠٠ الف وحدة دولية).
عند بلوغ الطفل عامه الأول يُعطى الطفل الجرعة الأولى من المطعوم الثلاثي الفيروسي MMR (الحصبة والحصبة الألمانية والنكاف)
على عمر ١٨ شهر يُعطى الطفل الجرعة المدعمة من مطعوم شلل الأطفال الفموي OPV والمطعوم الثلاثي البكتيري DPT + الجرعة الثانية من مطعوم الثلاثي الفيروسي MMR + فيتامين أ (٢٠٠ الف وحدة دولية).

Vaccination/ Vaccine program in Jordan

Motherhood & More

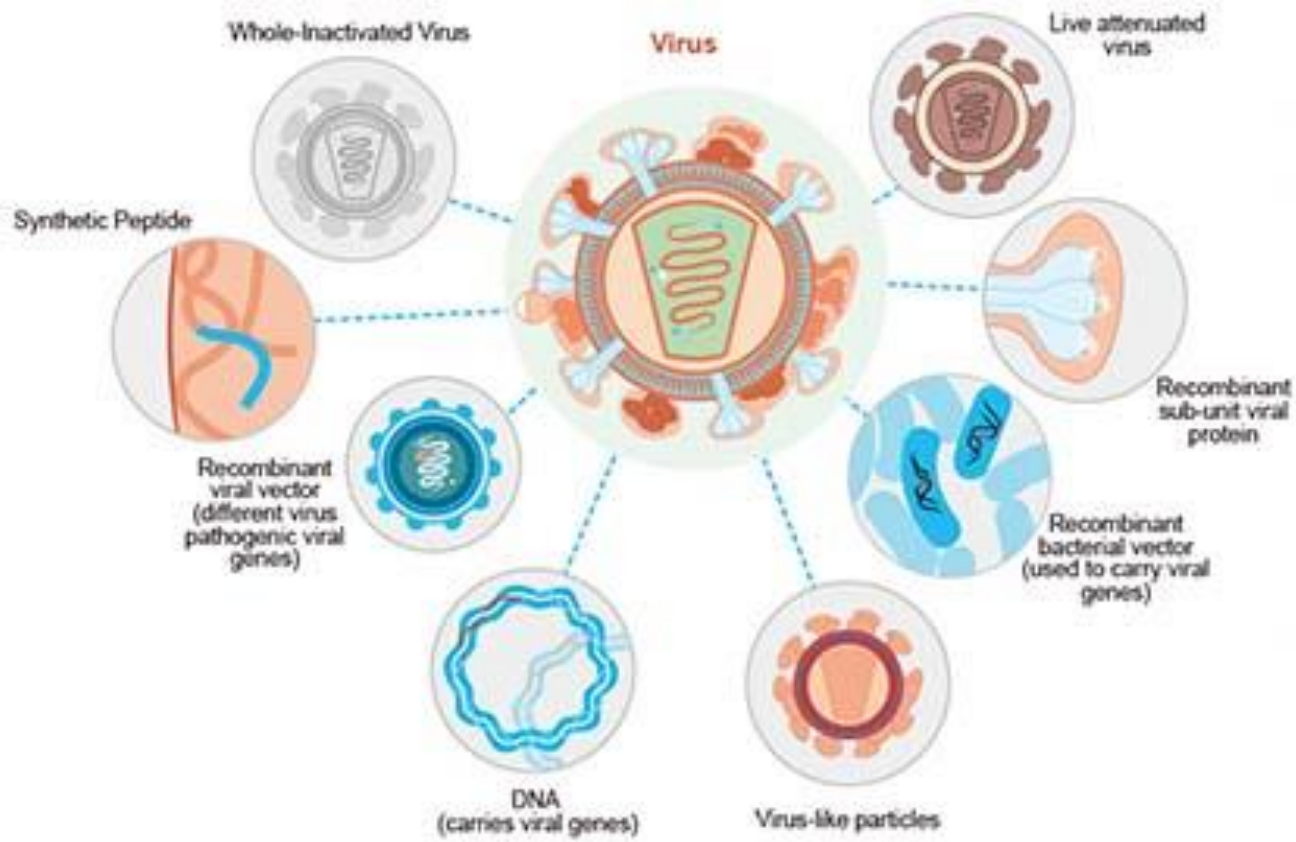
Vaccination Schedule جدول المطاعيم

اسم المطعوم	تاريخ أخذ الجرعات					ملاحظات
	الجرعة الأولى I	الجرعة الثانية II	الجرعة الثالثة III	الجرعة الرابعة IV	الجرعة المدعمة	
التدرن BCG	٨/٧/٢٠١٧					
شلل الأطفال المقتول IPV						
شلل الأطفال الفموي OPV		٦/٩/٢٠١٧	٨/١٠/٢٠١٧	١١/٣/٢٠١٨	٢٩/١٢/٢٠١٧	
الثلاثي البكتيري DPT					٢٩/١٢/٢٠١٧	
الخماسي المحسن DPT IPV +Hib	٥/٨/٢٠١٧	٦/١٠/٢٠١٧	١٨/١٠/٢٠١٧			
الخماسي العادي DPT+BV +Hib						
التهاب الكبد الوبائي HBV	٥/٨/٢٠١٧	٦/١٠/٢٠١٧	١٨/١٠/٢٠١٧			
المستدمية النزلية Hib						
الحصبة Measles فيتامين أ(١٠٠الف وحدة دولية)	١١/٣/٢٠١٨					
الثلاثي الفيروسي MMR فيتامين أ(٢٠٠الف وحدة دولية)	٥/٦/٢٠١٨	١٧/١٢/٢٠١٧				
مطعوم الروتافيروس *						
أخرى Others						
هل تم أخذ عينة المسح الطبي للتحري عن الأمراض الوراثية	☐ نعم ☐ لا					

* ملاحظة: عدد الجرعات يعتمد على الشركة المصنعة للمطعوم

Vaccination

Types of Vaccines



Live attenuated (LAV)

- Tuberculosis (BCG)
- Oral polio vaccine (OPV)
- Measles
- Rotavirus
- Yellow fever

Inactivated (killed antigen)

- Whole-cell pertussis (wP)
- Inactivated polio virus (IPV)

Subunit (purified antigen)

- Acellular pertussis (aP).
- *Haemophilius influenzae* type B (Hib).
- Pneumococcal (PCV-7, PCV-10, PCV-13)
- Hepatitis B (HepB)

Toxoid (inactivated toxins)

- Tetanus toxoid (TT).
- Diphteria toxoid

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 11. B Cell Activation and Antibody Production

- Review Article

Understanding modern-day vaccines: what you need to know