Humoral Immunity

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Introduction

- Arise and mature in the red bone marrow
- Found primarily in the spleen, lymph nodes, and MALT
- Small percentage of B cells circulates in the blood
- Major function is the secretion of antibodies

* MALT : Mucosa Associated Lymphoid Tissue
* The biggest percentage of B-cells are found in the lymphatics & lymph nodes.

Importance

- Humoral immunity helps cellular immunity to perform action through interaction of T helper cells with B cells
- Is the arm of adaptive immunity in killing extracellular microbes and microbial toxins
- Important in defending against microbes with capsule ; which is the most specific point of importance.

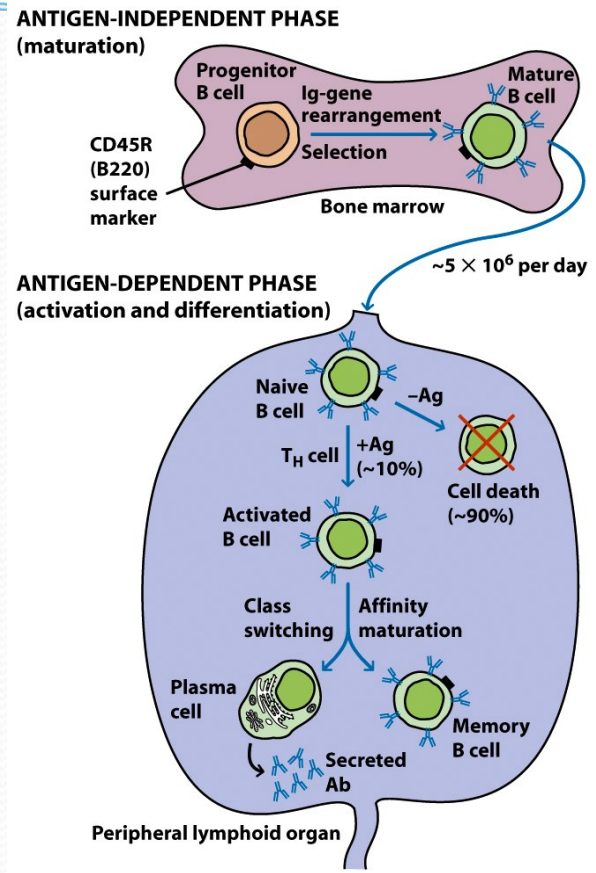
B Cells Maturation

- B cells matures in **bone marrow** independent of antigen, then continue to maturate in **peripheral lymphoid organs** with the presence of antigen
- Three main steps of maturation:

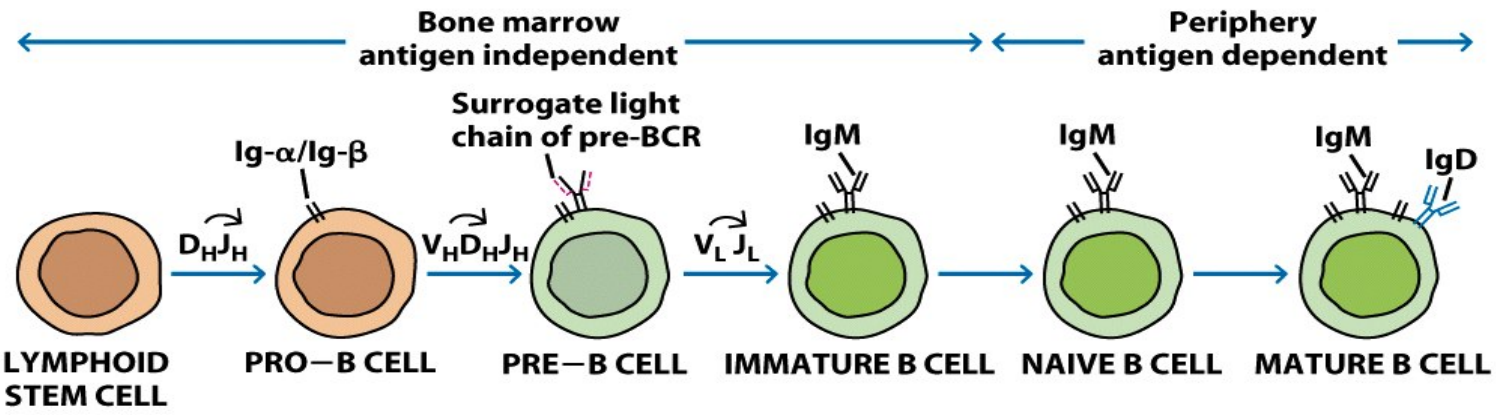
1. Progenitor- Ig alpha and beta- for signal transduction (long tails)
2. Pre-B cell- IgM heavy chain, and light chain
3. "mature"- IgD

* IgM & IgD are the antibodies which is found on the B-cell surface initially

* Naïve : the cell did not encounter an antigen yet !
* A totally mature B-cell is known when an IgD is deticted on its surface !

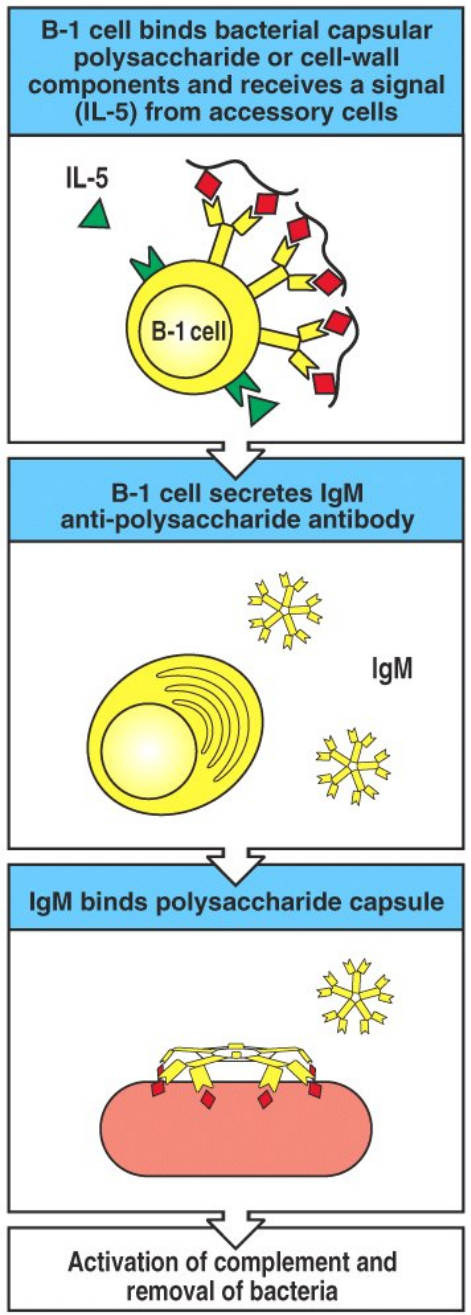


*The cell death occur either because there is no need for the B-cell now , OR to prevent an autoimmune attack.



B-1 B cells

- "Innate-like" subset of B cells; *because it did not encounter an antigen yet.*
- Appear during fetal life and express IgM but little IgD and display CD5. Are also found in peritoneum and pluera.
- Originates from stem cell in bone marrow, but also from proliferation of B-1 cells outside the BM.
- Responds poorly to protein antigen, but **strongly** to carbohydrate antigens.
- Antibodies produced are of low affinity.



VERY IMPORTANT

Attribute	Conventional B cells (B-2 B cells)	B-1 B cells
Major sites	Secondary lymphoid organs	Peritoneal and pleural cavities
Source of new B cells	From precursors in bone marrow	Self-renewing (division of existing B-1 cells)
V-region diversity	Highly diverse	Restricted diversity
Somatic hypermutation	Yes	No
Requirements for T-cell help	Yes	No
Isotypes produced	High levels of IgG	High levels of IgM
Response to carbohydrate antigens	Possibly	Definitely
Response to protein antigens	Definitely	Possibly
Memory	Yes	Very little or none
Surface IgD on mature B cells	Present on naive B cells	Little or none

Figure 11-5
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B cells Clonal Selection

- Self-reactive B cells are eliminated in bone marrow (BM).
- BM produces 5 x 10^7 B cells/day, but only 5 x 10^6 B cells/day or 10% actually enter the circulation.
- **Some of this loss is due to negative selection and elimination or clonal deletion of immature B cells expressing autoantibodies to self-antigens.**
- "Cross-linking" of mIgM by self Ag may lead to cell death or anergy. (Anergy : binding with no activation)
- The clones of lymphocytes that can be interacted with corresponding Ag will be selected and lead to activation, proliferation, produce Ab and specific memory cells.
- (Ag: Antigen .. Ab: Antibody)

Stages of B cells Activation

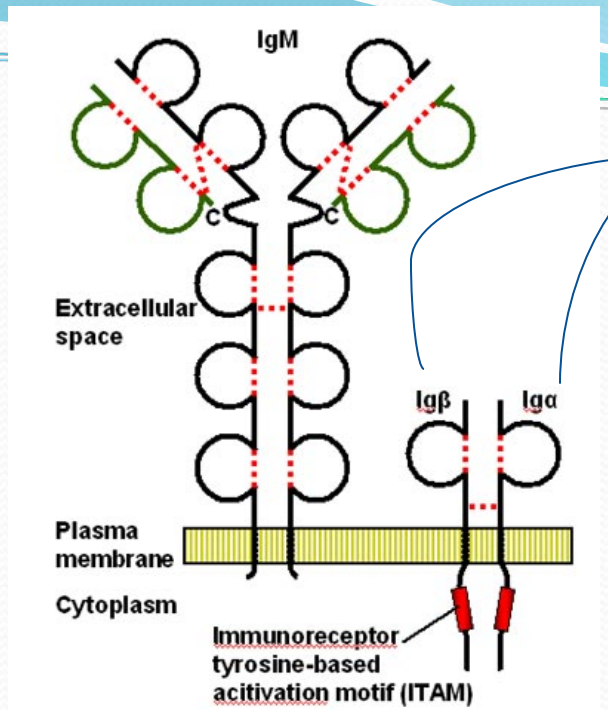
- B cells development involve *five* main stages

1. B cells recognition and binding
2. B cells undergo Ag-induced activation, proliferation and differentiation in the periphery
3. Activated B cells give rise to Ab-secreting plasma cells and memory cells
4. Effector B cells start to function
5. Shut down of immune response

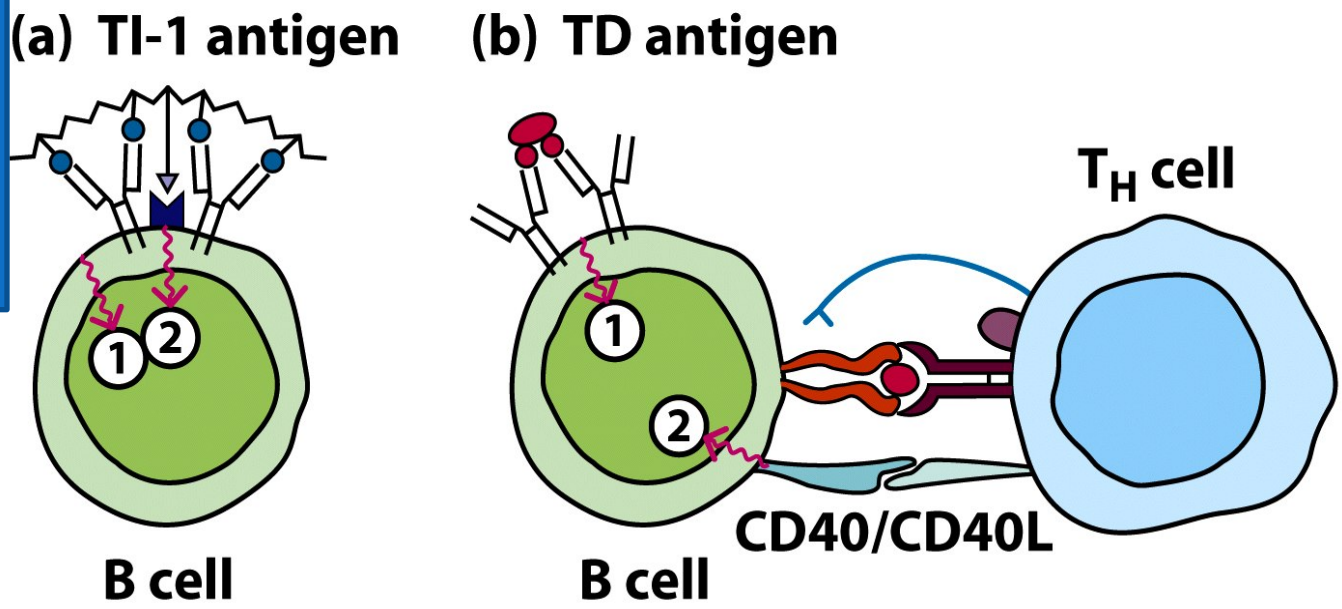
1. Antigen Recognition

- Naieve B lymphocyte two express membrane bond antibodies IgM and IgD that function as antigen receptors (B cells receptors – BCR)
- **Protein antigen** only processed by APCs and recognized by helper T cells that play important role in B cells activation this is referred to as **T dependent B cell activation**
- **Non protein antigen** including lipids and polysaccharides activate B cells directly without involvement of helper T cells (**T-independent activation**). B cells in return can activate T helper cells

* In T-cell-Dependent ; we need co-stimulation through CD40/ CD40L .
* In T-cell-Independent ; cross-linking plays a role in activation.

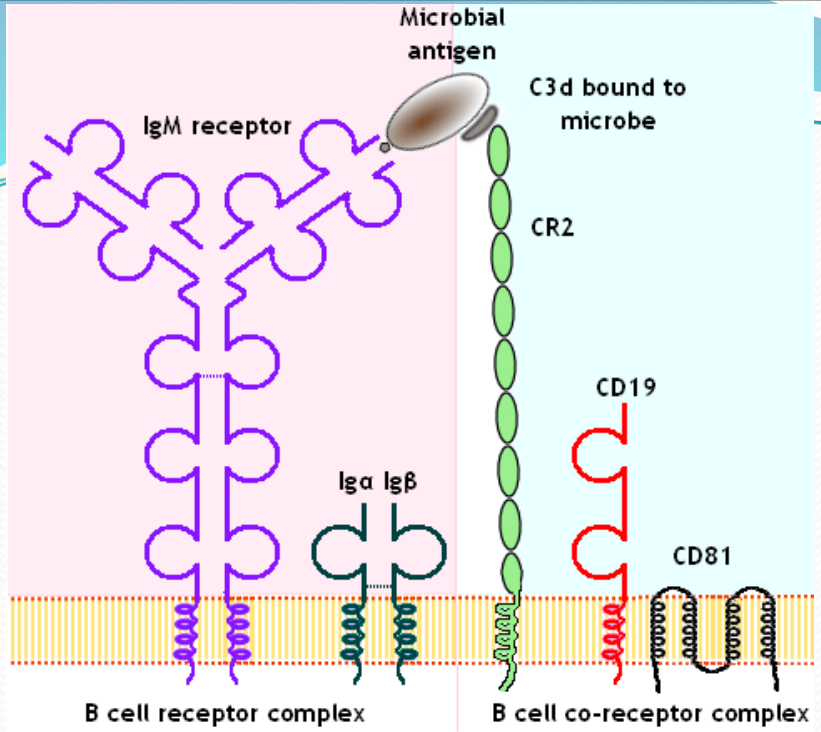


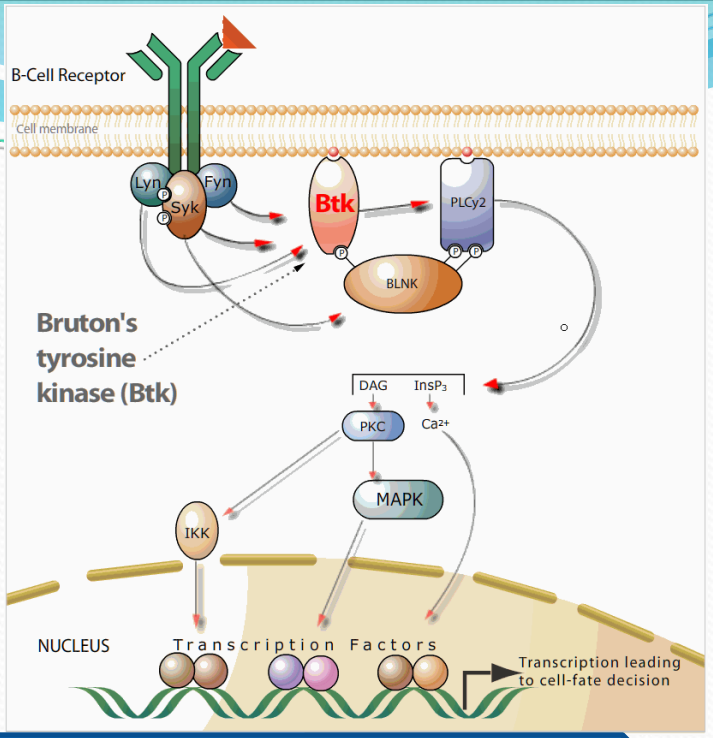
* Their function is for signal transmission !
* They are loaded on the B-cell surface before IgM & IgD !



2. B Cell Activation and Signaling

- Antigen induce clustering (cross linking- or bring together) of membrane Ig receptors. Ig clustering occurs when antigen molecules forms aggregates or antigen have repeated epitopes molecules
- Ig clustering induce signaling through Igα and Igβ proteins in the B cell receptor complex
- Furthermore, microbes can activate complement system including C3 to form C3d. C3d can directly bind to B cells through CR2 and other receptors which enhance B cells activation (second signal)
- Later on signal from Ig and CR2 activates many biochemical's and enzymes that ends by formation of different transcription factors





* Just like there is two signals in T-cell-Dependent activation ; cell-Independent has two signals :

1- Through binding to IgM then signal transmission occurs through Igα & Igβ.

2-Through complement system , as the antigen has on its surface C3d that binds to CR2 ‘ Complement Receptor 2’ then signal transmission occurs through CD19 & CD81.

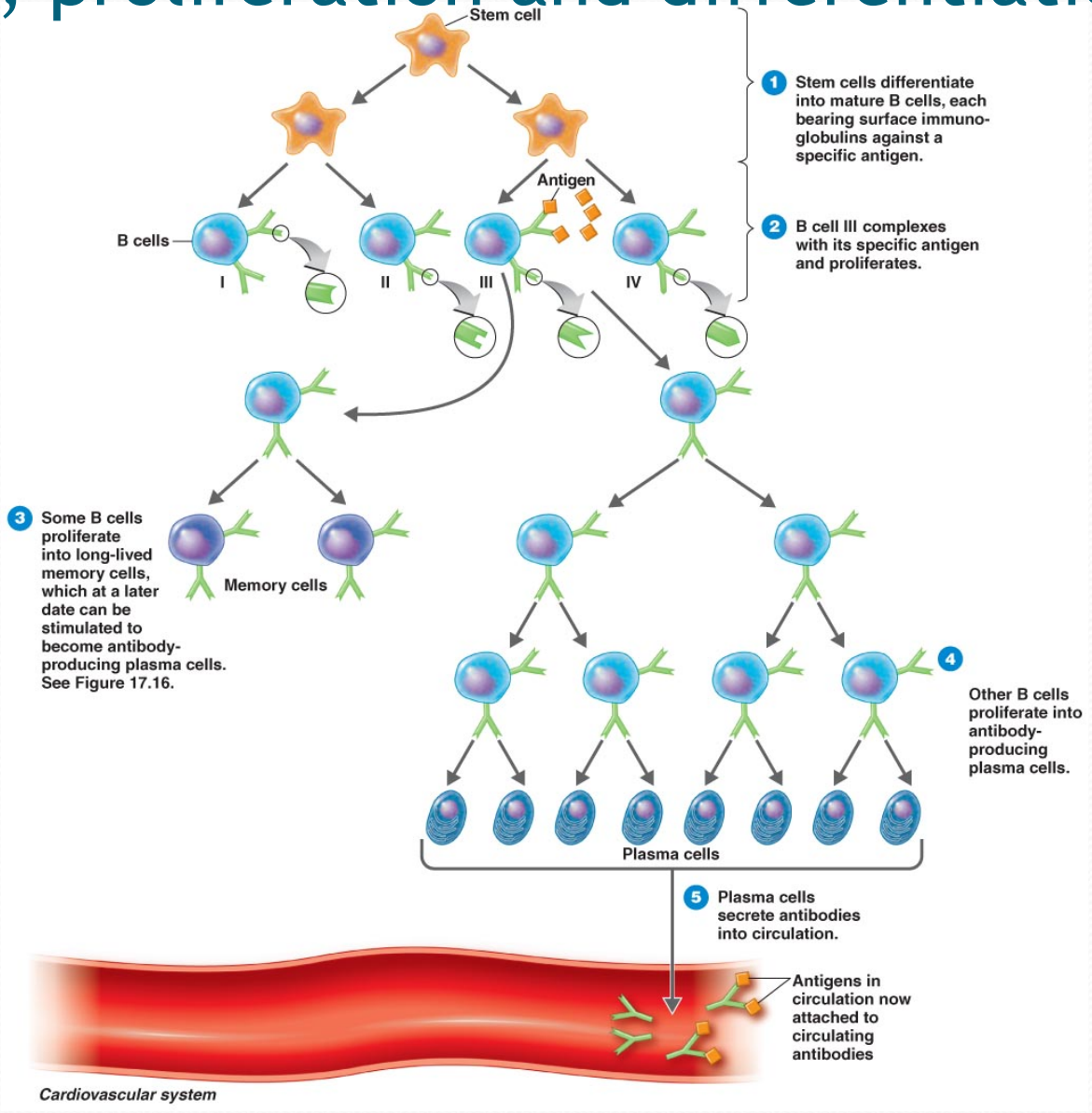
* The main goal of the signal is to reach the nucleus (to synthesize the proteins needed) !

3. Clonal Expansion, proliferation and differentiatio

Antigen specific B cells expand in numbers to produce specific antibodies

B cells differentiate into
1. Antibody-producing plasma cells
2. Memory cells

* Expansion = Proliferation
* Differentiation means to become a more specific type.



4. Antibodies Production (Affinity Maturation and isotype switching)

- Activated B cells start to produce different classes of antibodies in large amount to eliminate infection
- Antigen stimulated B cells may differentiate into IgM producing antibodies, however, later on, under the influence of CD40L and cytokines; B cells can differentiates into cells producing other classes of heavy chain antibodies (**antibody switching**).
- Repeated exposure to antigen leads to increase the binding abilities of antibodies through affinity maturation, where high affinity B cells are selected to produce antibodies.

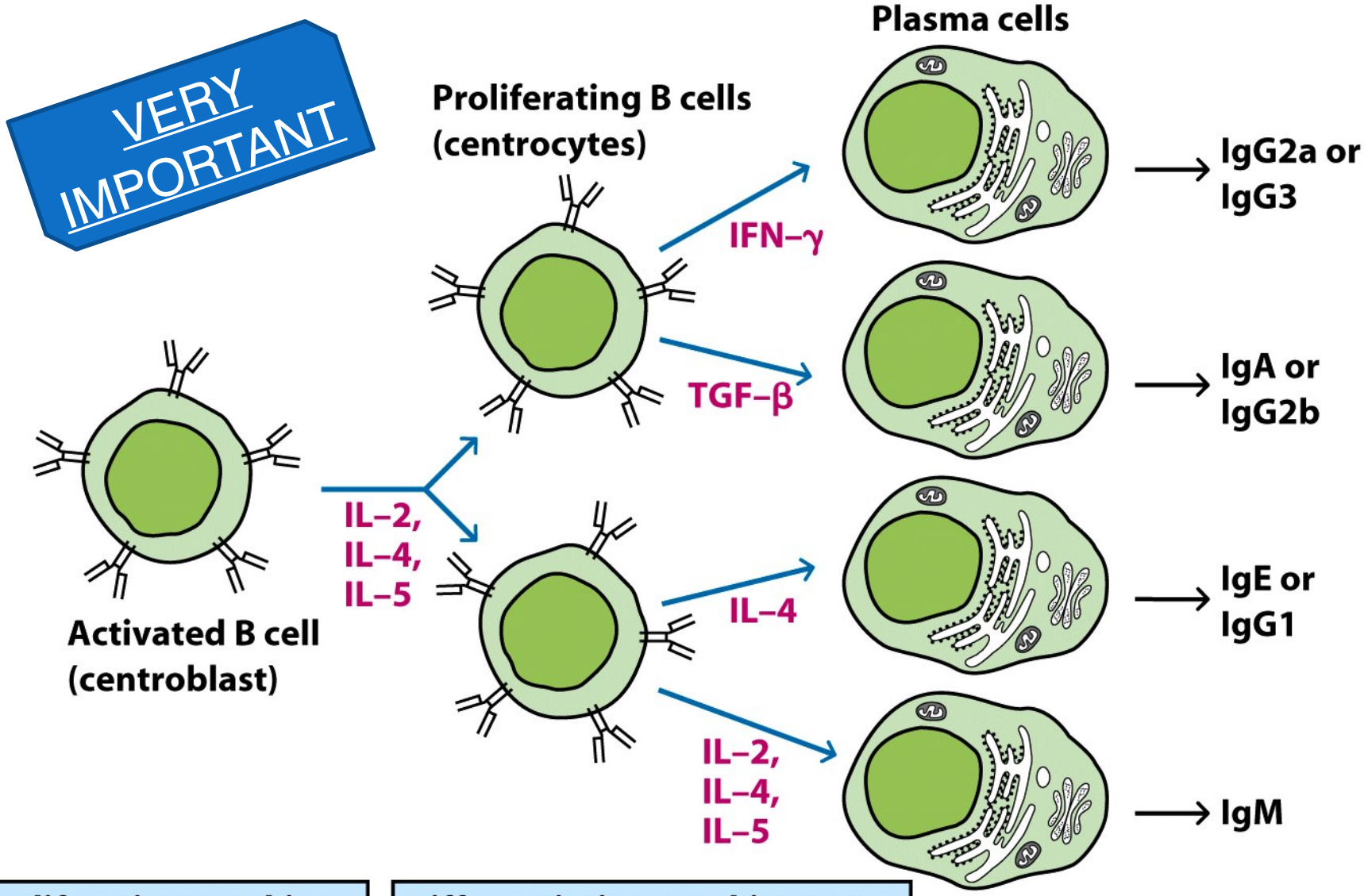


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Figure 11-22
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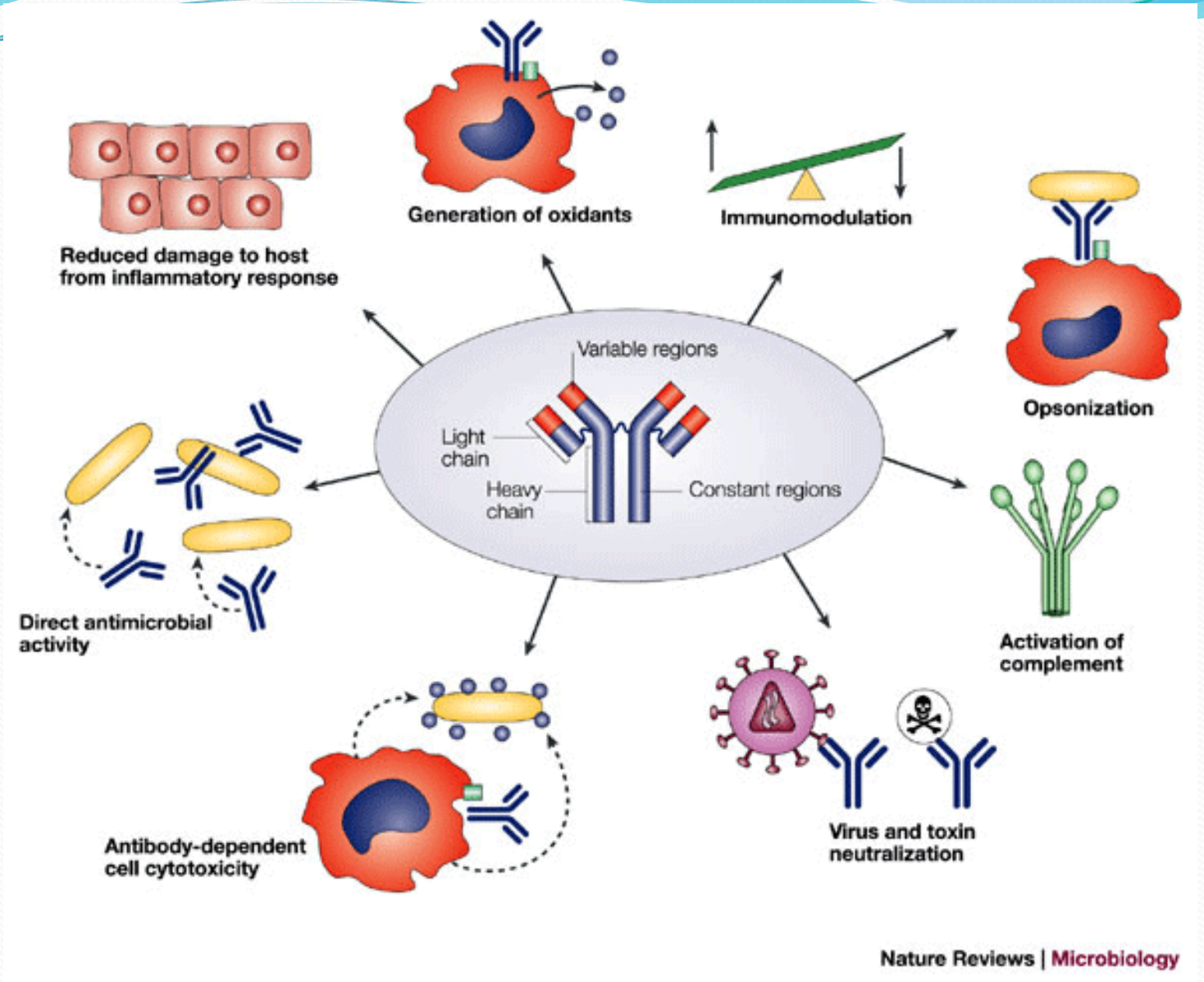
5. Effector Mechanisms

- Neutralization
- Opsonization
- Complement activation
- Antibody dependent cell mediated toxicity (ADCC)
- Transcytosis- movement across epithelial cells

* The details for these mechanisms are already discussed in a previous lecture, so they are required!


Generation of oxidants
Immunomodulation
Reduced damage to host from inflammatory response
Variable regions
Light chain
Heavy chain
Constant regions
Opsonization
Direct antimicrobial activity
Activation of complement
Antibody-dependent cell cytotoxicity
Virus and toxin neutralization
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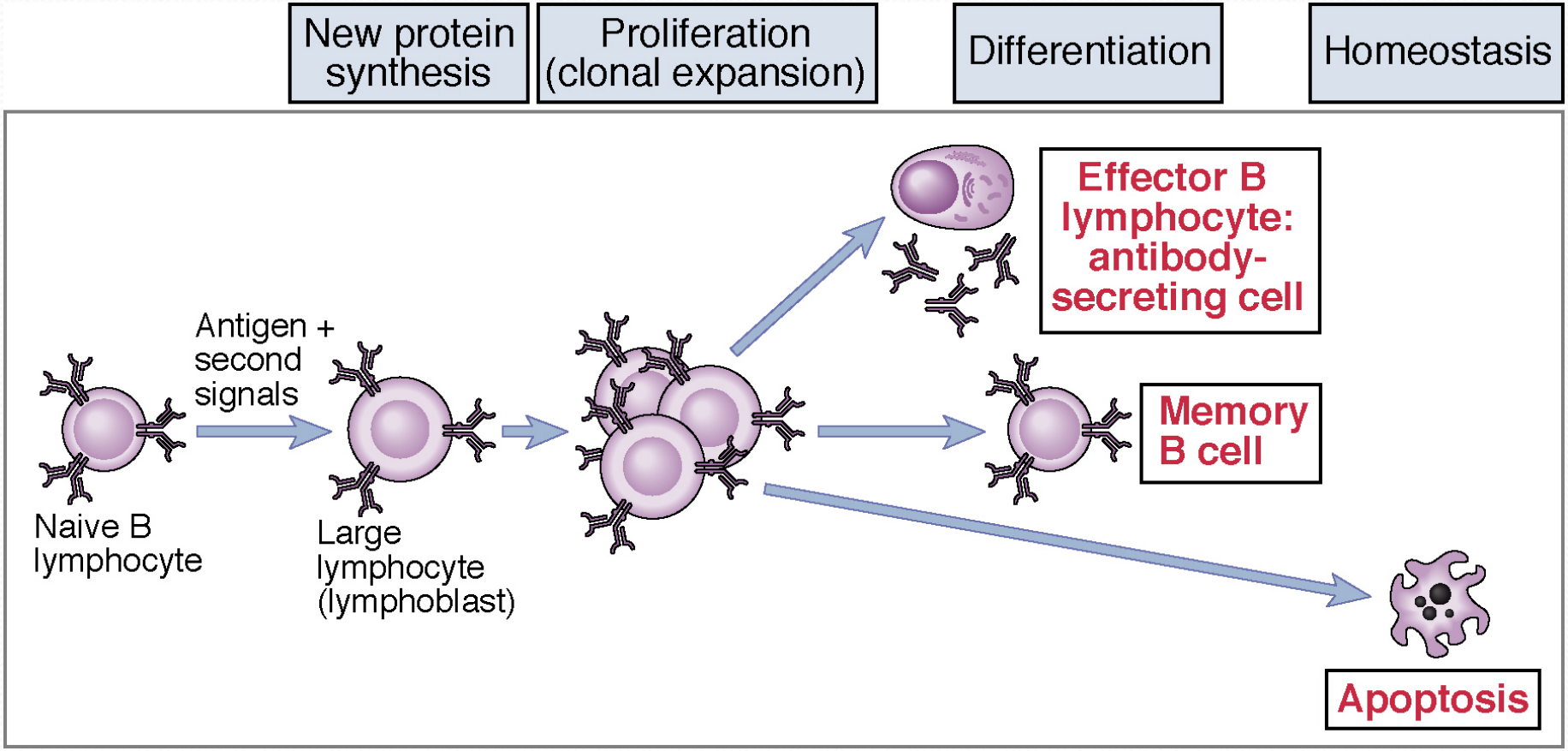
6. Humoral immunity shut down and formation of memory B cells

- ***A.*** After antibodies are capable of killing invading microorganisms, most of activated B cells die by programmed cell death ***(Apoptosis)***.
- ***B.*** Furthermore, circulating IgG antibodies that binds to antigen in periphery induce negative feedback mechanism to inhibit further antibody production.
- ***C.*** Memory B cells are formed and stay for long time to facilitate faster antibodies production when the body is exposed to same antigen next time.


New protein synthesis
Proliferation (clonal expansion)
Differentiation
Homeostasis
Effector B lymphocyte: antibody-secreting cell
Antigen + second signals
Memory B cell
Naive B lymphocyte
Large lymphocyte (lymphoblast)
Apoptosis

IMPORTANT

TABLE 11-6 Comparison of naive and memory B cells

Property	Naive B cell	Memory B cell
Membrane markers		
Immunoglobulin	IgM, IgD	IgM, IgD(?), IgG, IgA, IgE
Complement receptor	Low	High
Anatomic location	Spleen	Bone marrow, lymph node, spleen
Life span	Short-lived	May be long-lived
Recirculation	Yes	Yes
Receptor affinity	Lower average affinity	Higher average affinity due to affinity maturation*
Adhesion molecules	Low ICAM-1	High ICAM-1

*Affinity maturation results from somatic mutation during proliferation of centroblasts and subsequent antigen selection of centrocytes bearing high-affinity mIg.

Table 11-6
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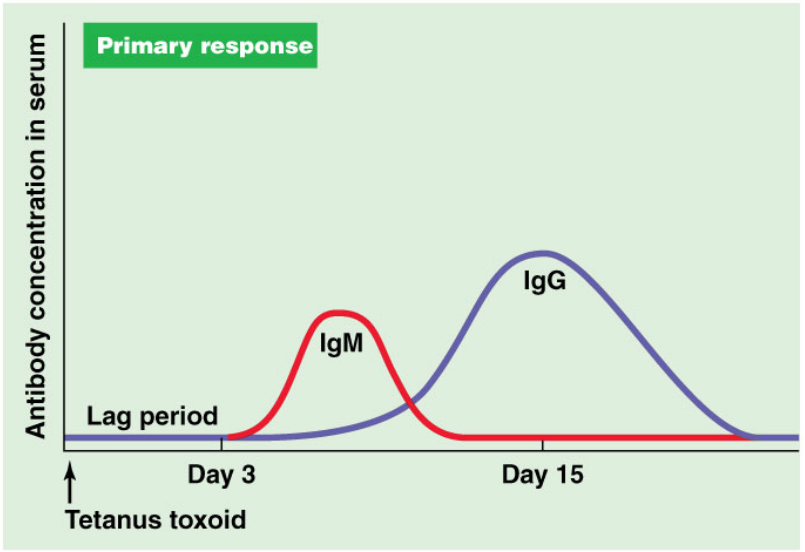
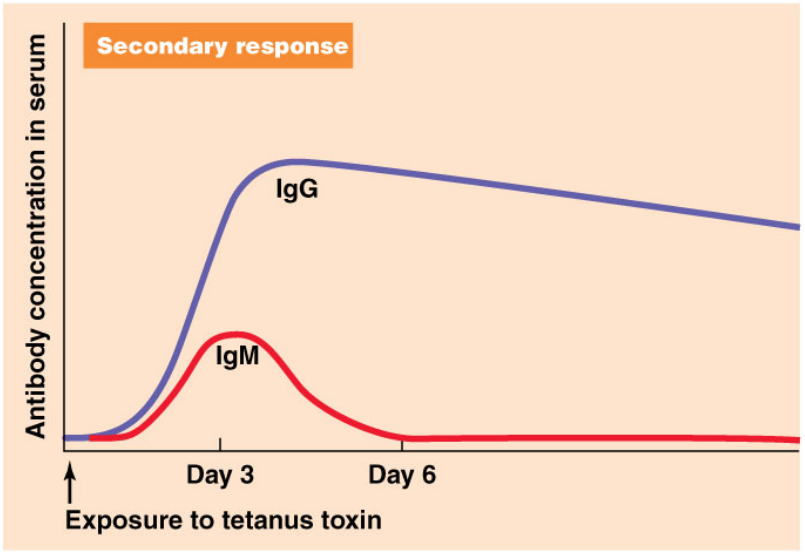
* The presence of Memory B-cell assures a faster and a more potent response in case the antigen came back .
* Memory B-cell stays the way it is and does not proliferate or get activated unless it encounters the antigen again !

Primary and secondary humoral immunity

* IgG is faster in release than IgM in secondary response !
* IgG concentration is higher in secondary response than in the primary response !
* IgM is a bit faster in release in secondary response than in the primary response !



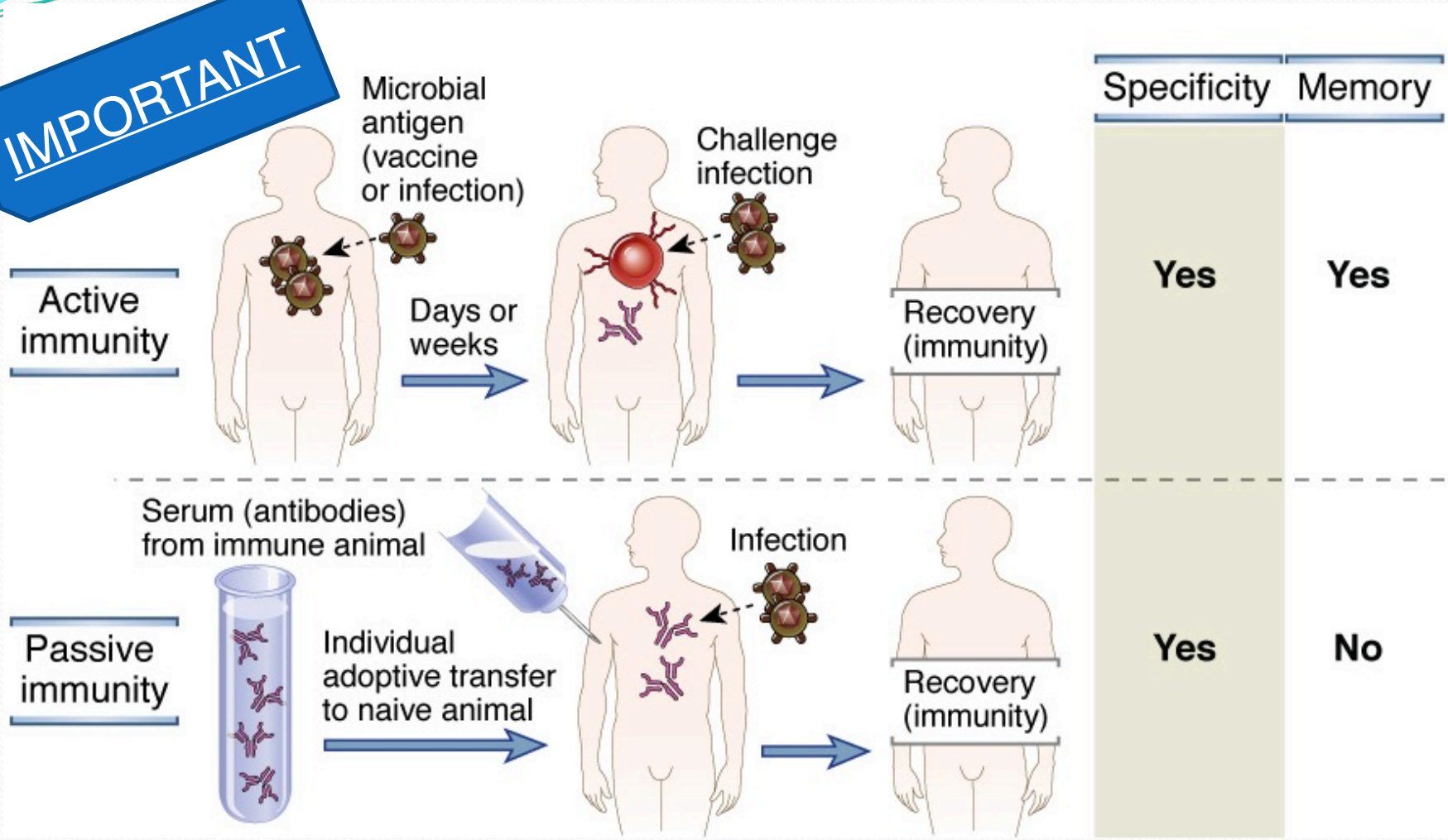
(a)



(b)

Active and Passive Immunity

IMPORTANT



Active immunity: long-lasting protection (memory), multiple effector mechanisms activated, lag time

Passive immunity: rapid protection, short duration

* All what we have discussed through this lecture is known to be an Active immunity (the body encountered an antigen and synthesized an antibody against it ‘an immune reaction had occurred’).

* Passive immunity is marked when the body receives the antibody from outside (not synthesized by his own B-cells) ; just like in cross placenta , breast feeding or through an injection ! * *

Vaccination to be beneficial must work through Active immunity !