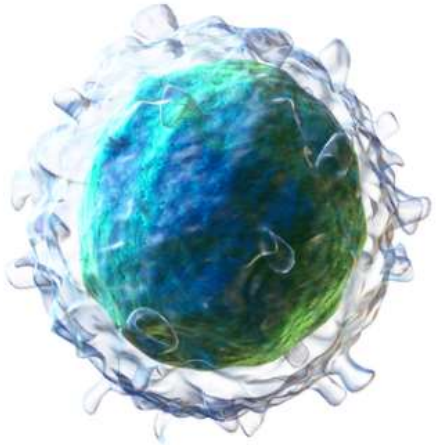
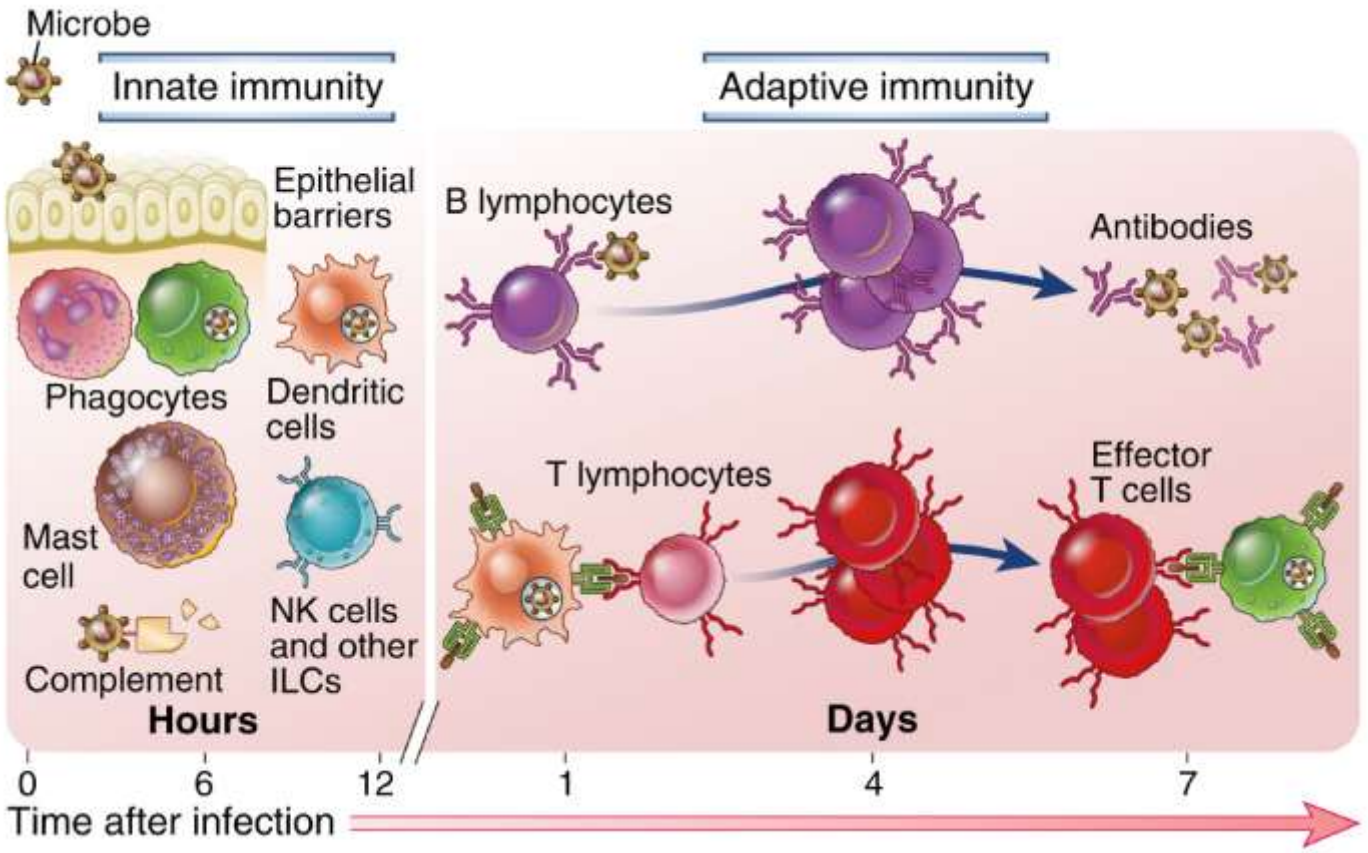


Βιολογία Β - λεμφοκυττάρων

Σωτήρης Τσιόδρας

Innate vs adaptive immunity



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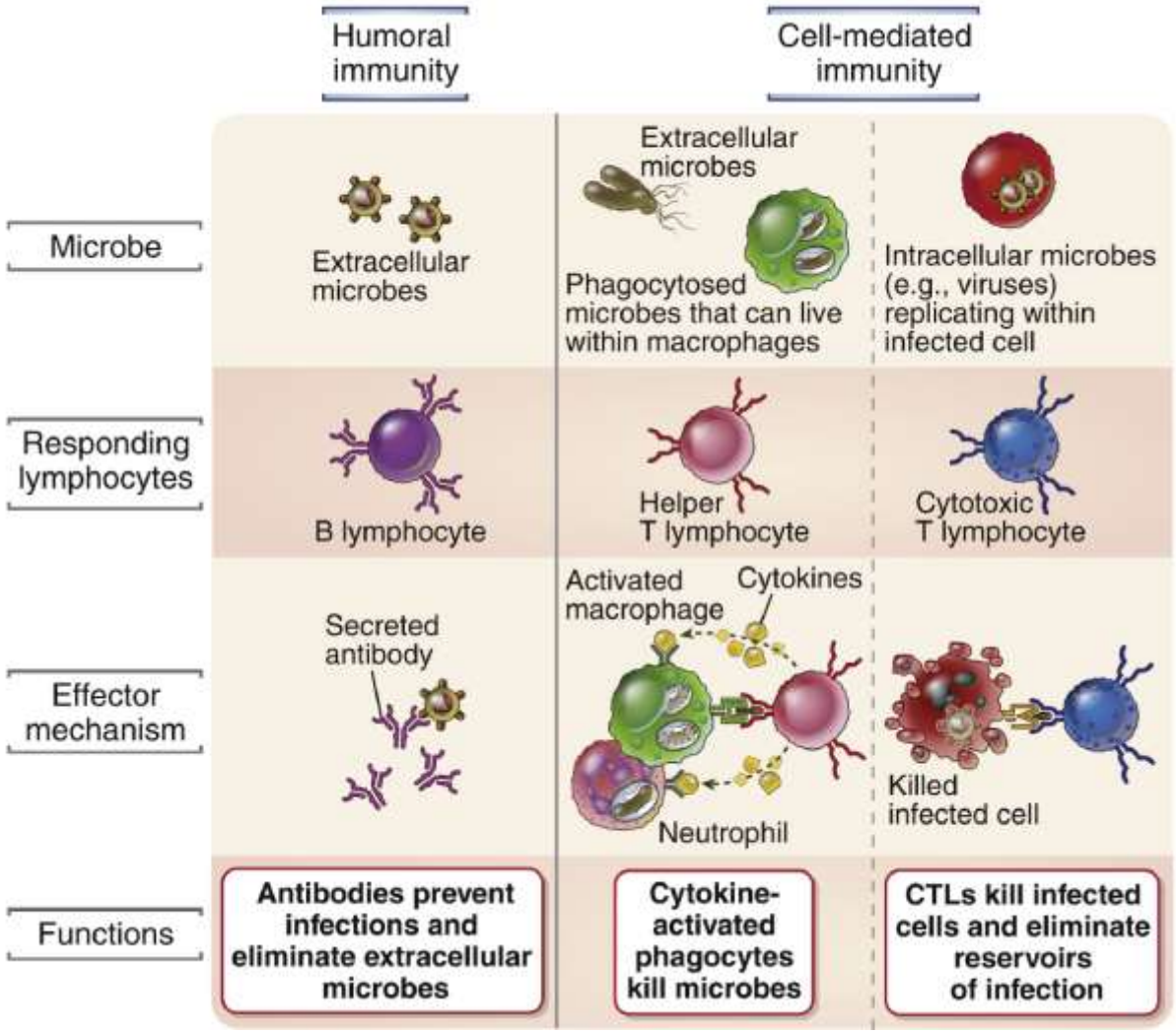
Β λεμφοκύτταρα – Adaptive immune system

Adaptive immunity is systemic, both humoral & cell mediated



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Β λεμφοκύτταρα – Adaptive immune system

Ο ένας εκ των δύο τύπων λεμφοκυττάρων

- B lymphocytes -> **υπεύθυνα για την παραγωγή αντισωμάτων**
  - **κατά των αντιγόνων που εισβάλλουν στο σώμα**
    - ιοί, βακτήρια και άλλες ξένες ουσίες
    - **Marking them for destruction by other immune cells**
- B lymphocytes -> **role in Ag presentation** - interaction w other immune cells
  - **T cells**, to coordinate a more effective immune response.

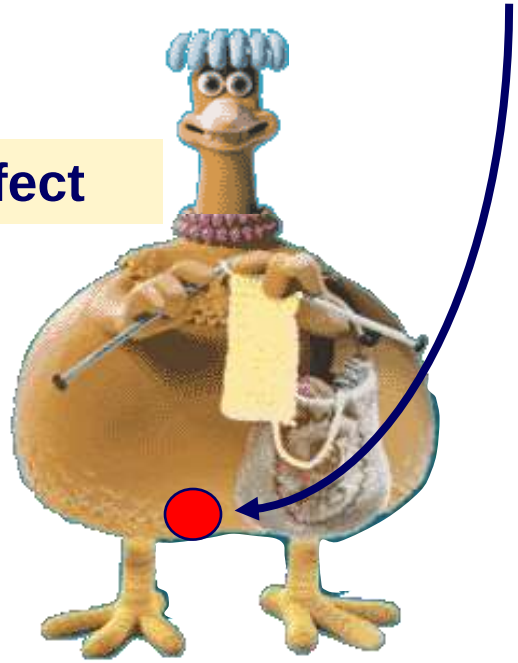
The discovery of B cell immunity

1954 - Bruce Glick, Ohio State University

bursa of Fabricius, a lymphoid organ in the cloacal region of the **chicken**

Bursectomy – no apparent effect

Bursectomised chickens were later used in experiments to raise antibodies to *Salmonella* antigens

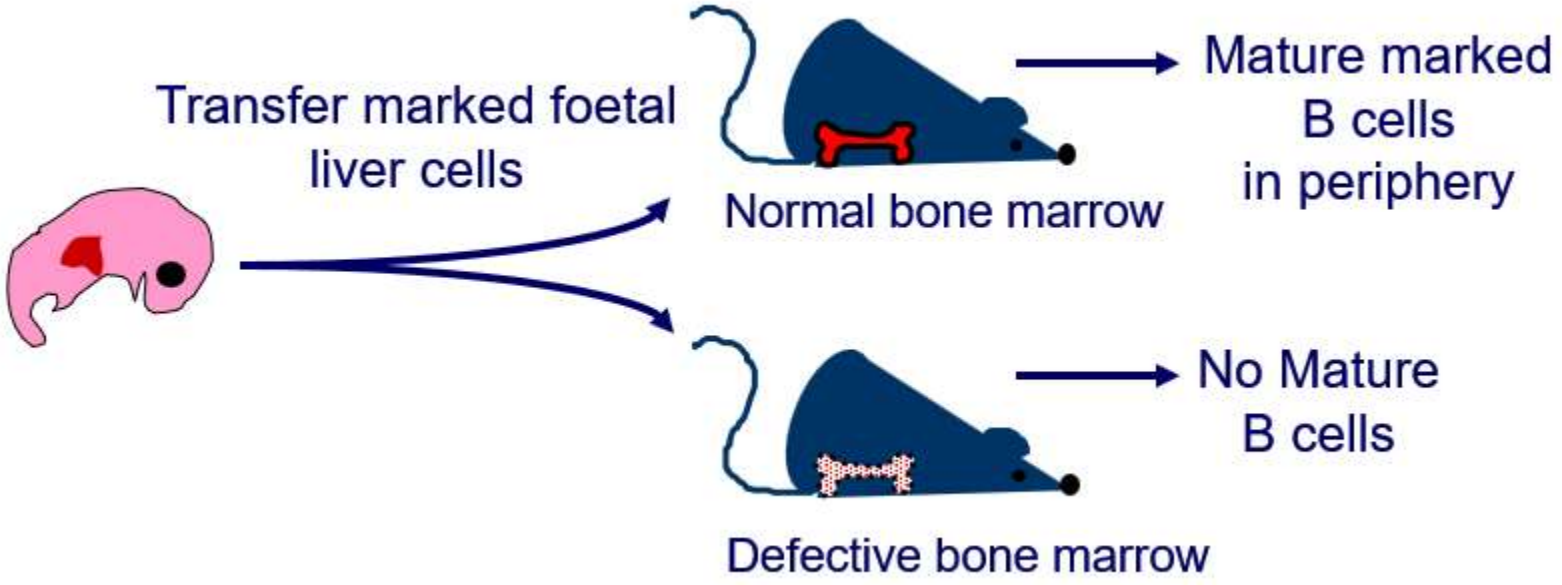


None of the bursectomized chickens made anti-Salmonella antibodies

Bursa was later found to be the **organ in which antibody producing cells developed**
antibody producing cells were thereafter called B cells

Mammals do not have a bursa of Fabricius

Origin of B cells & organ of B cell maturation



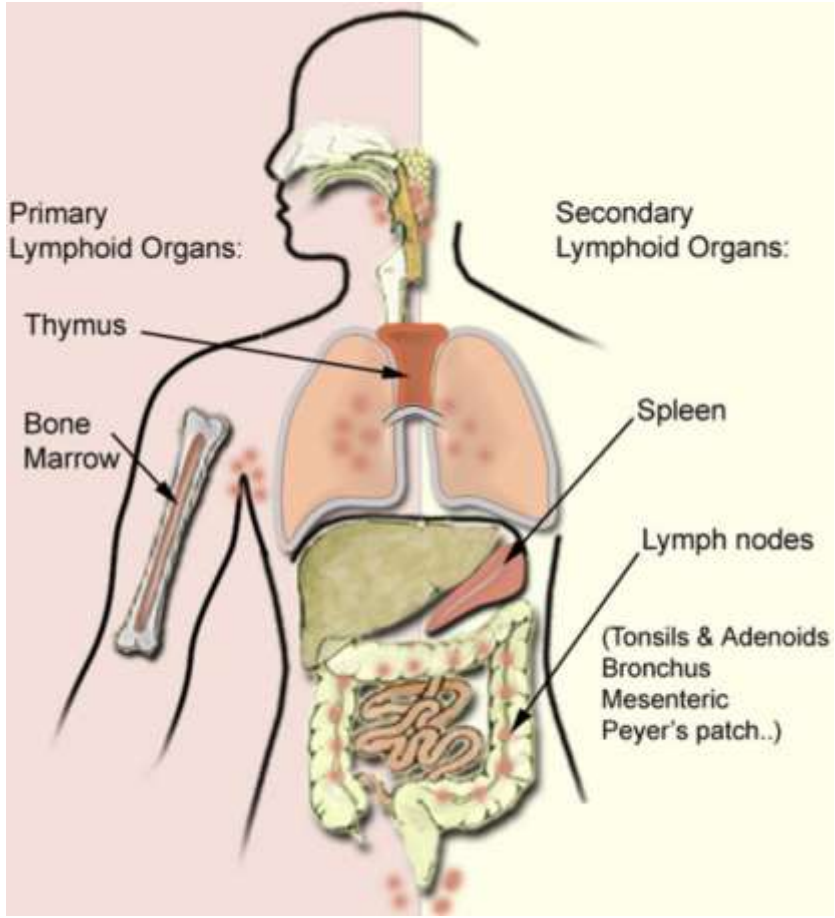
B cell development starts in the **foetal liver**

After birth, development continues in **the bone marrow**

Β λεμφοκύτταρα – Adaptive immune system

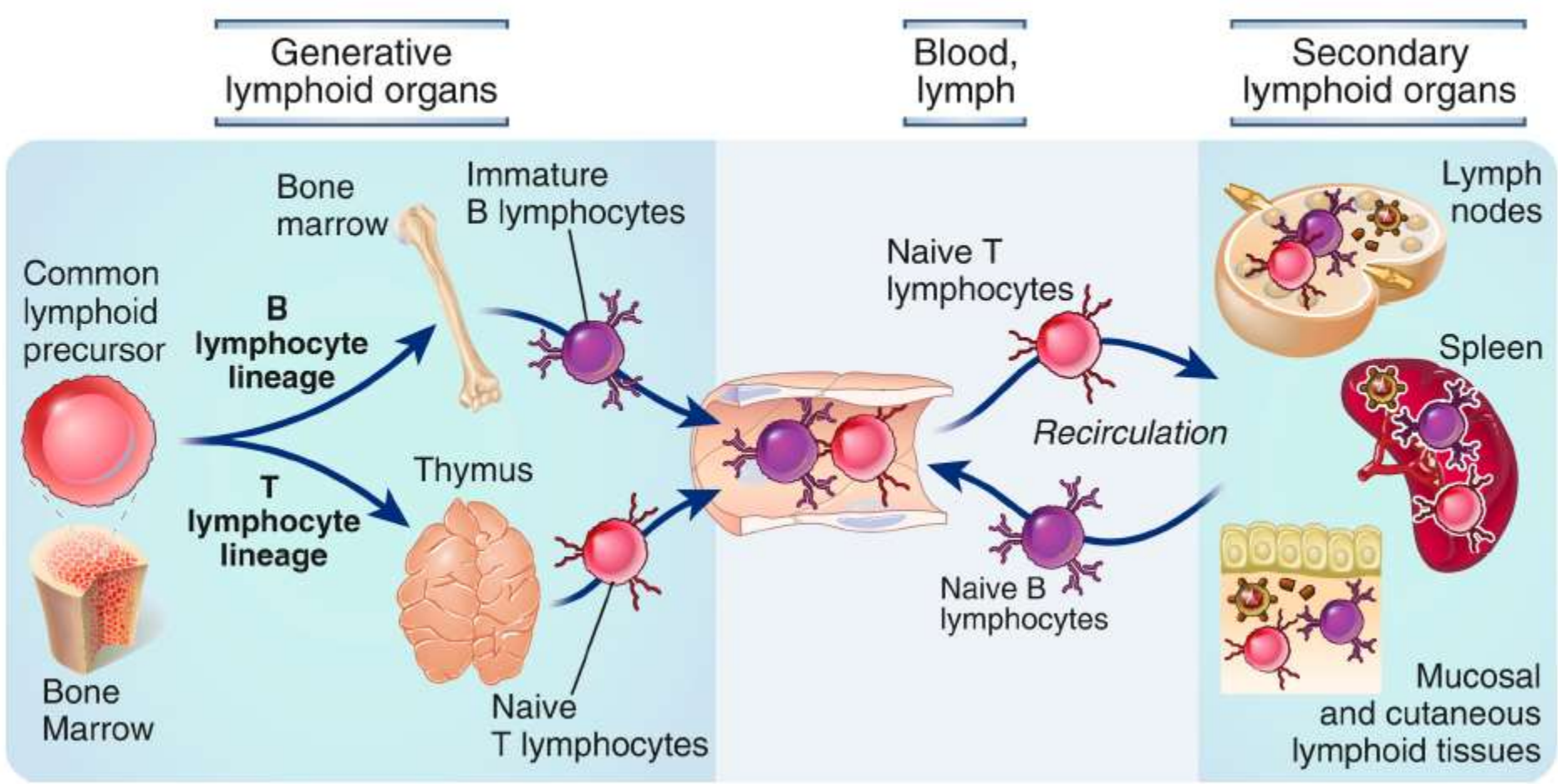
Ο ένας εκ των δύο τύπων λεμφοκυττάρων

- B cells are *produced* in **the bone marrow**
- *mature* in the **secondary lymphoid organs**
  - such as the **spleen and lymph nodes**



Maturation of lymphocytes

B vs. T lymphocytes



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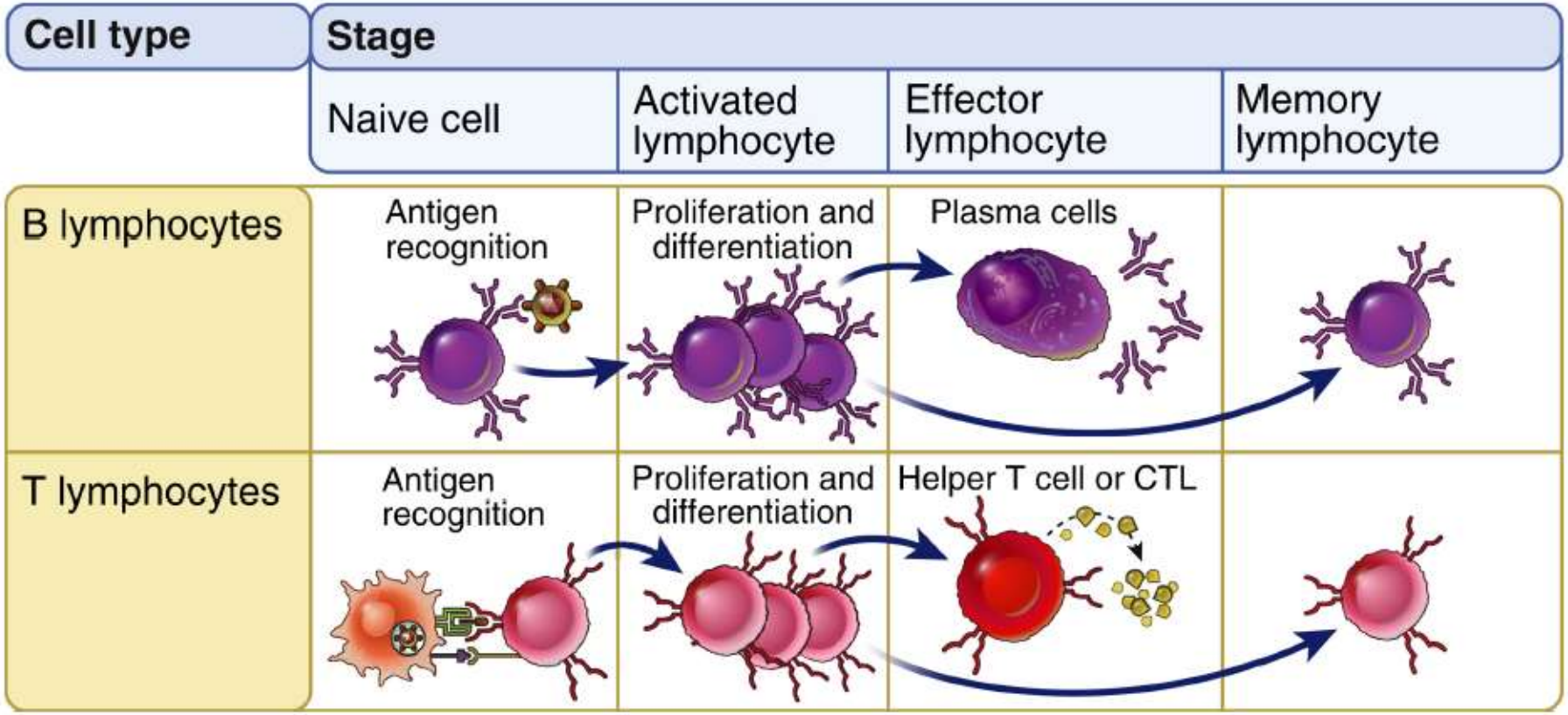
Stages in life history of lymphocytes

B vs. T lymphocytes



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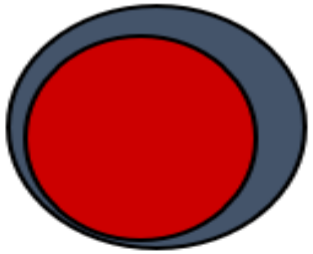
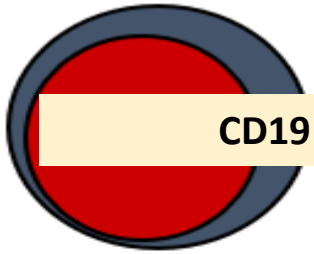
B cell development

several stages, rearrangements of IgH/IgL

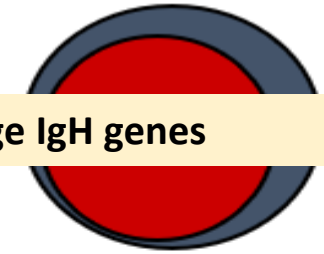


Stem Cell



Early pro-B cell

CD19 & rearrange IgH genes



Late pro-B cell

CD19 & CD20 & rearrange IgH genes

Large pre-B cell

Not yet rearranged IgL genes

Small pre-B cell

CD19 & CD20, IgM & rearrange IgH/IgL genes, Not yet undergone selection

Immature B cell

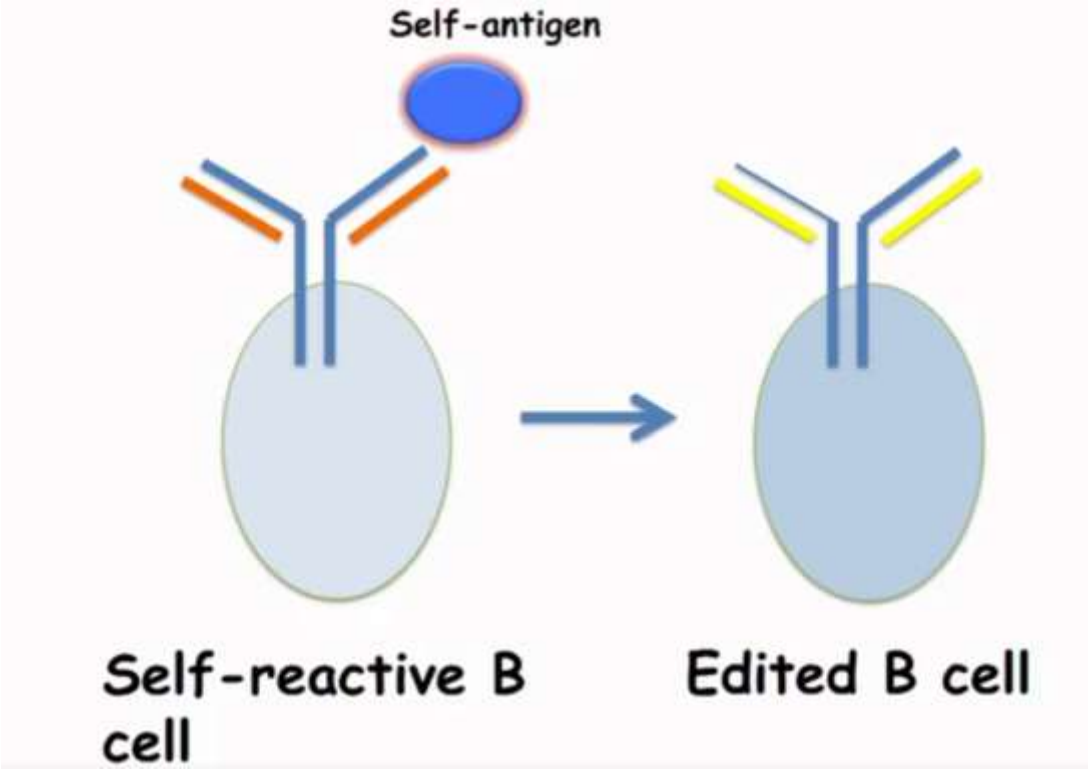
CD19 & CD20, IgM, IgD, capable of recognizing foreign Antigens

Each stage of development is defined by **rearrangements of IgH chain genes, IgL chain genes, expression of surface Ig,** expression of adhesion molecules and cytokine receptors

Receptor editing occurs in the BM

avoid apoptosis -modifying sequence of light chain V & J genes

- When the B cell receptor (BCR) on an immature B cell recognizes self Ag -> **receptor editing** occurs
  - **Ig light chain rearrangements** continue
  - in order to change the BCR specificity



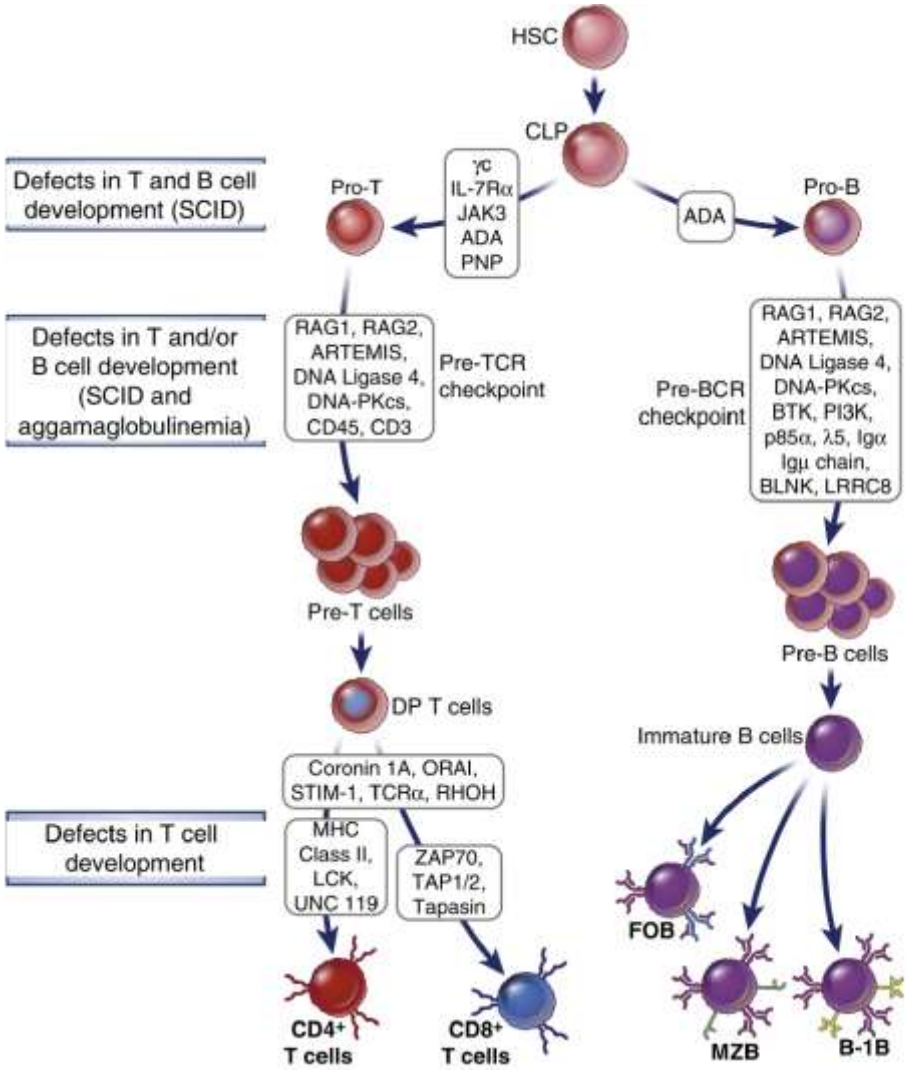
B-cell tolerance, 20-50% of all naïve B cells!

Β λεμφοκύτταρα – development
non reactivity to self (tolerance)

- respond & eliminate non-self Ags **while not reacting harmfully to individual's own (self) Ags**
- Positive (BCR editing) & negative (apoptosis in spleen & BM) selection
- Immunologic unresponsiveness is also called **tolerance.**
  - **Eliminate lymphocytes expressing receptors for self Ag, suppress these w reg cells - If failure -> autoimmunity**

Defects in B & T cell maturation

1ry immunodeficiencies, mutations in genes encoding listed proteins



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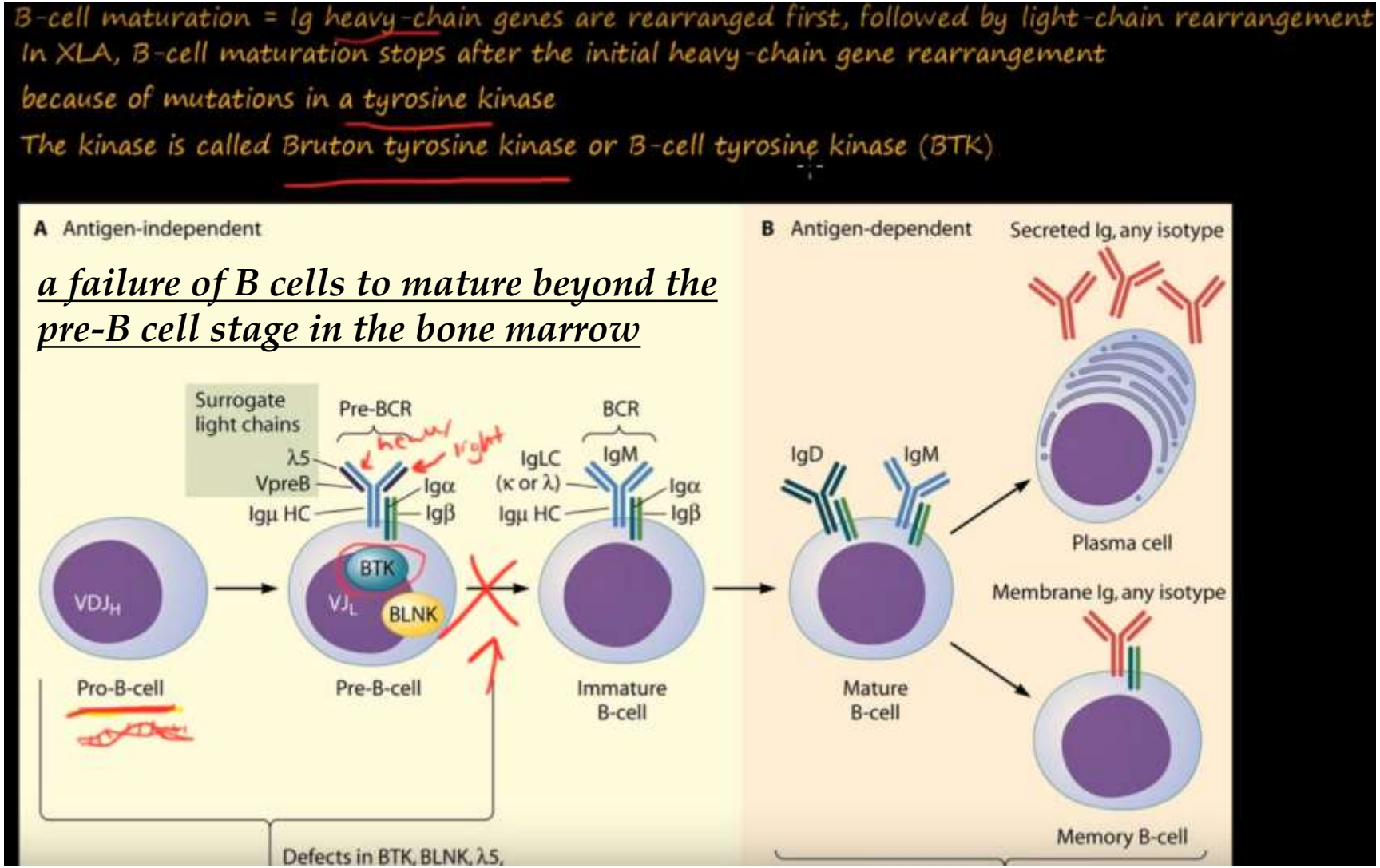
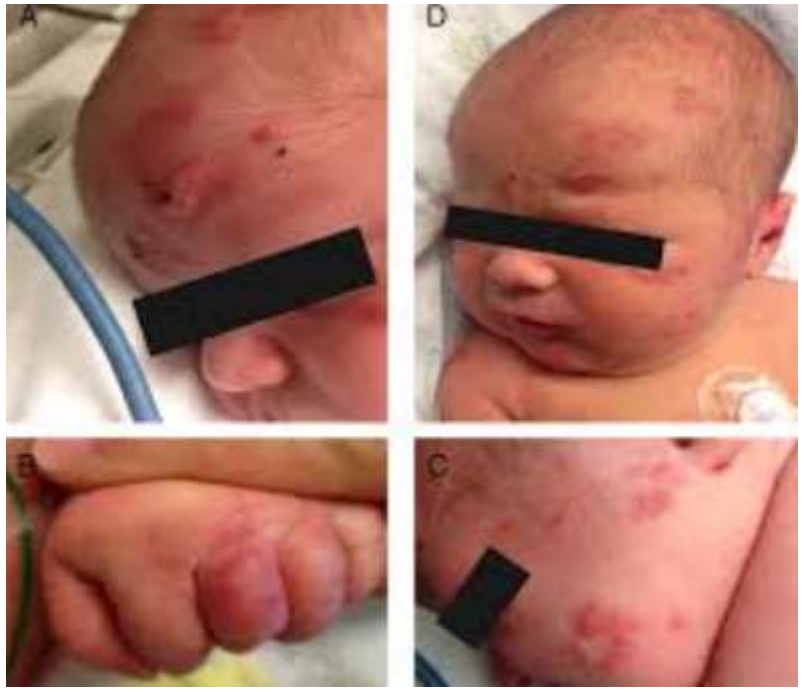
Φυλοσύνδετη αγαμασφαιριναιμια-XLA, Brutons disease

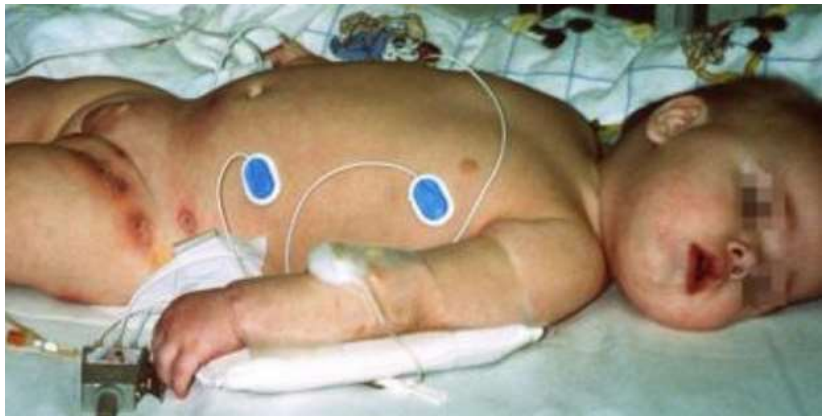
maturation stops after HC rearrangement due to tyrosine kinase mutations (BTK)

B-cell maturation = Ig heavy-chain genes are rearranged first, followed by light-chain rearrangement
In XLA, B-cell maturation stops after the initial heavy-chain gene rearrangement
because of mutations in a tyrosine kinase
The kinase is called Bruton tyrosine kinase or B-cell tyrosine kinase (BTK)



XLA Brutons disease



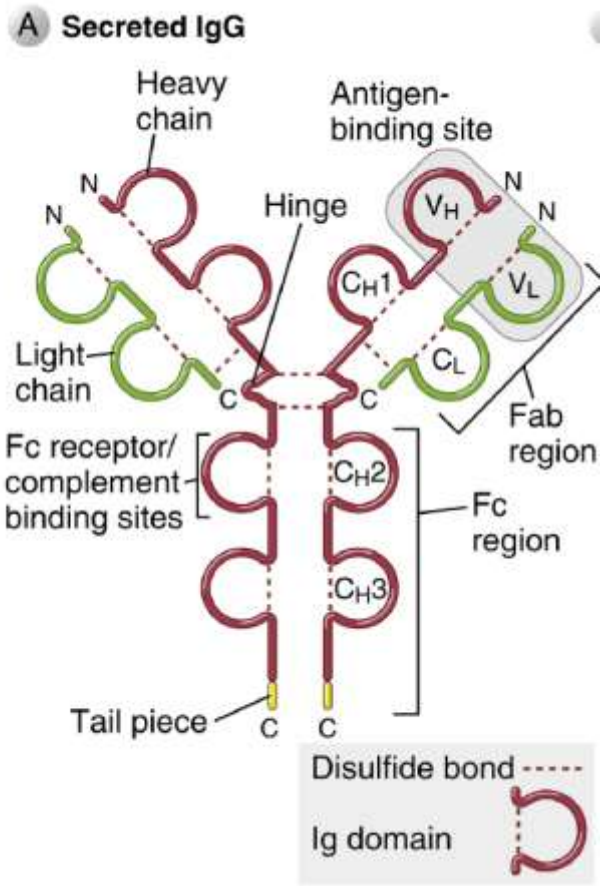


Diagnosis? Low Igs, Lymphocyte phenotyping->> absent B-cells, genetic testing -> BTK mutation

Β λεμφοκύτταρα -> Ab structure & function

Y-shaped structure -> 2 H & 2L chains, variable / constant regions

- **Variable region** bind to specific antigens
- **Constant region** mediates effector functions
  - complement activation
  - antibody-dependent cellular cytotoxicity



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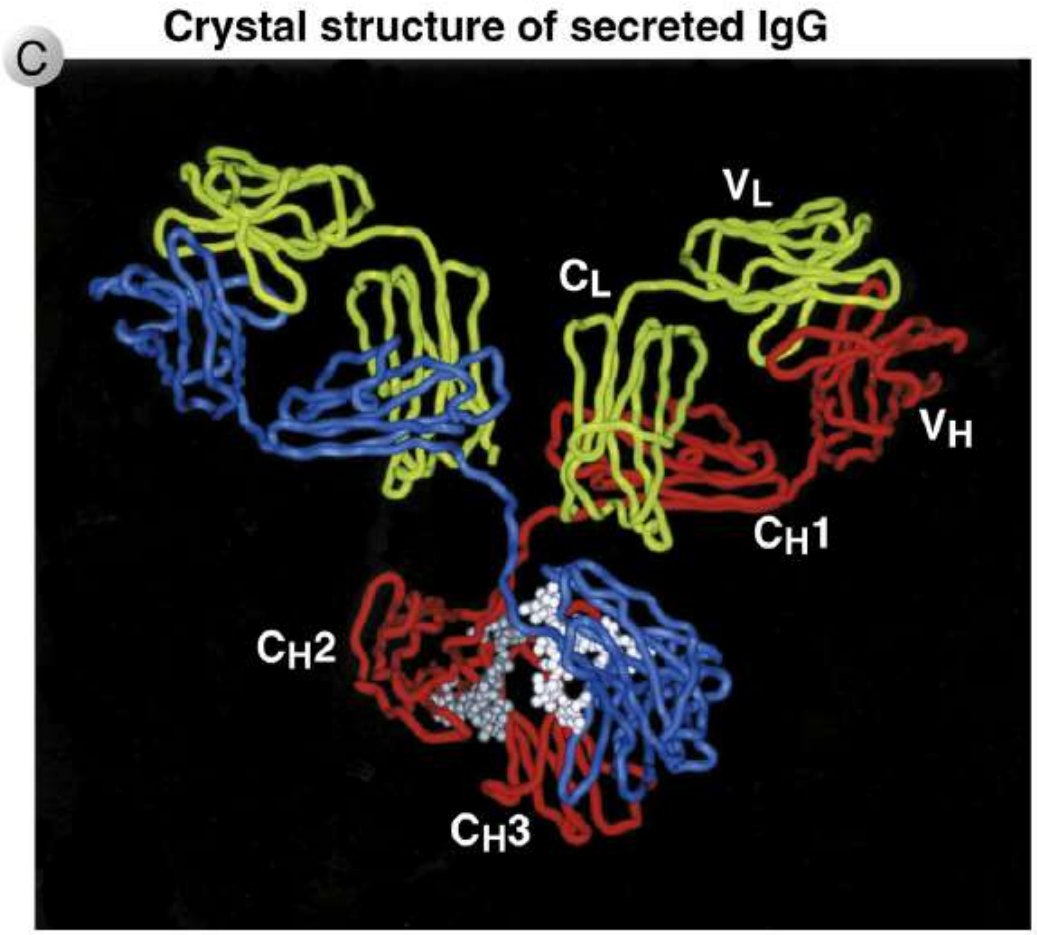
Β λεμφοκύτταρα -> Ab diverse repertoire

somatic recombination of immunoglobulin genes

- Identical heavy chains ->blue & red
- Light chains -> green
- Carbohydrates bound to IgH -> grey



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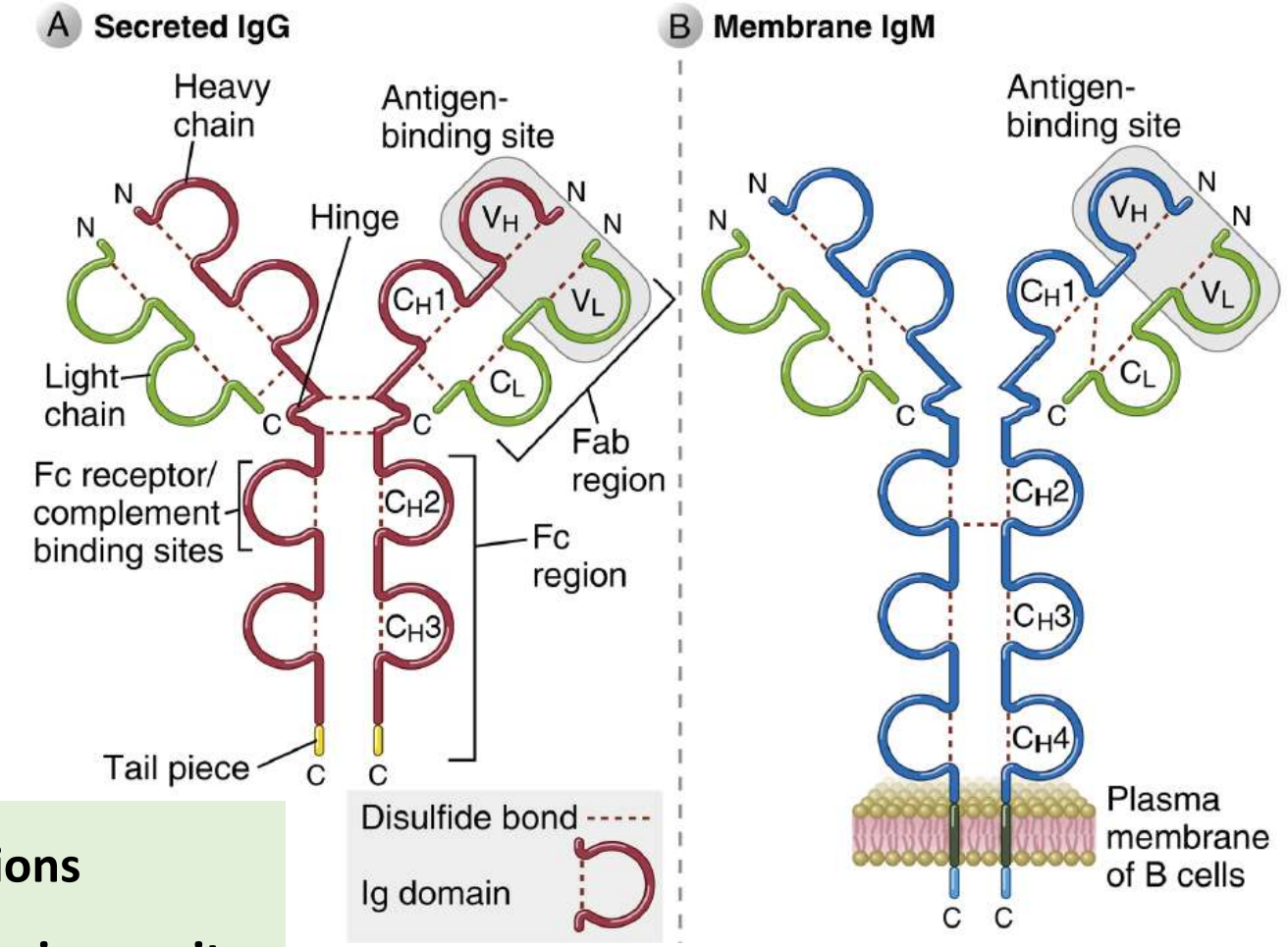
Antibodies

diversity through various mechanisms

- **Ab diversity**
  - Combinatorial diversity
  - Junctional diversity &
  - Somatic hypermutation



- **different isotypes based on HC constant regions**
- **distinct effector functions & different roles in immunity**

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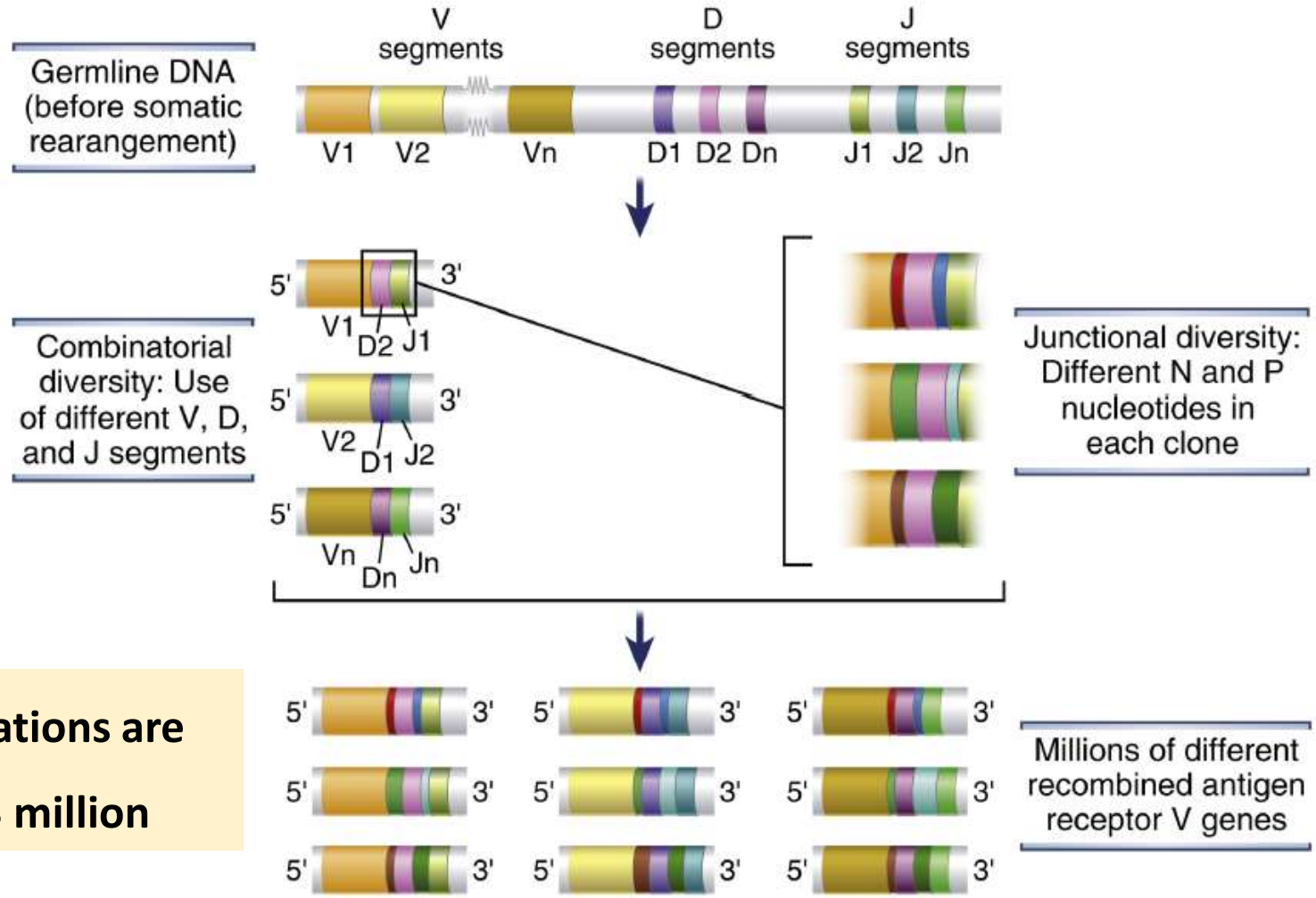
Antibodies & human immunoglobulin genes

combinatorial & junctional diversity of Ag receptor genes



possible n of combinations are

on the order of 1 to 3 million

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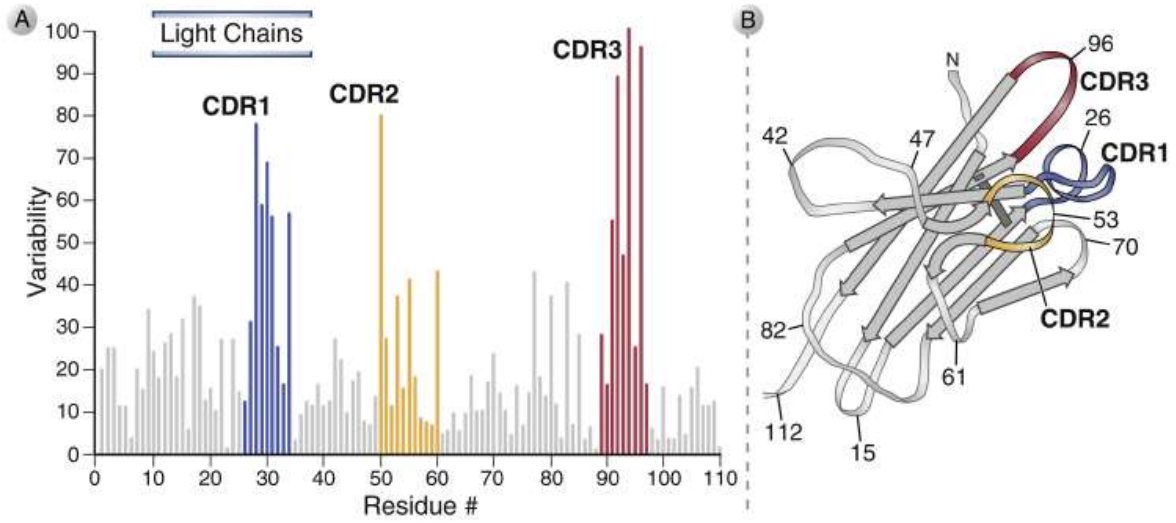
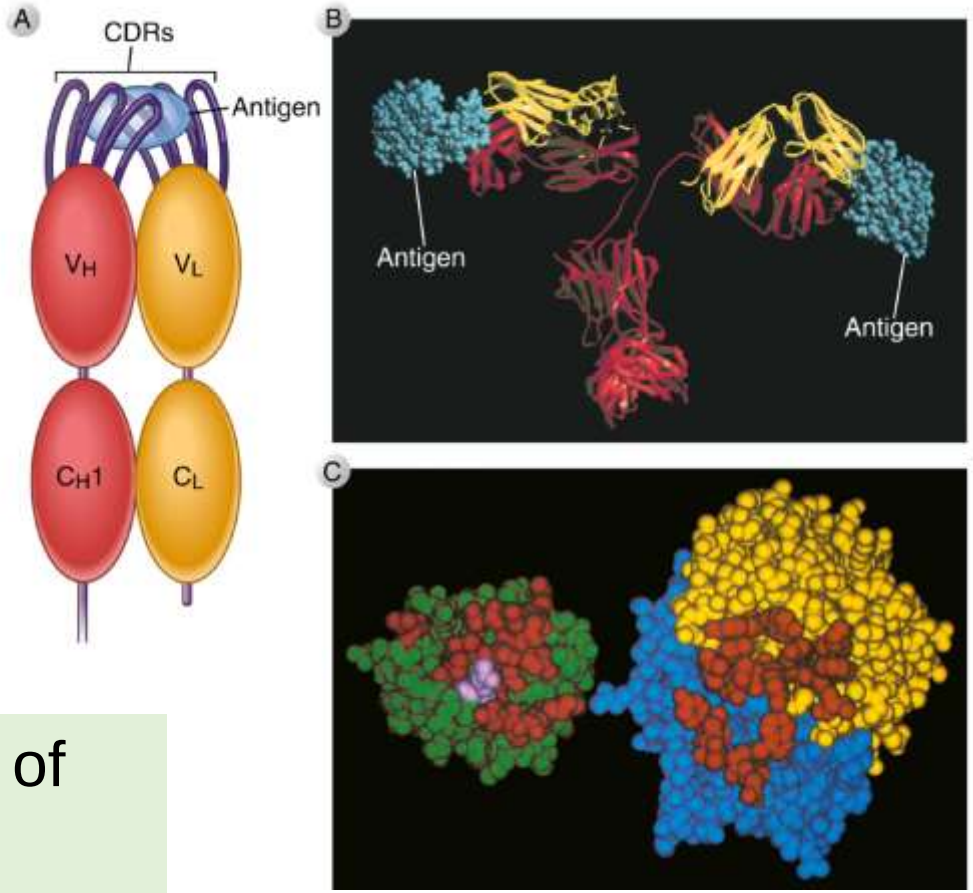
Β λεμφοκύτταρα -> Ab diverse repertoire

CDRs & Ag binding site – κλειδί και κλειδαριά





CDR: Loops that protrude from the surface of the two immunoglobulin V domains and in combination create an antigen-binding surface.

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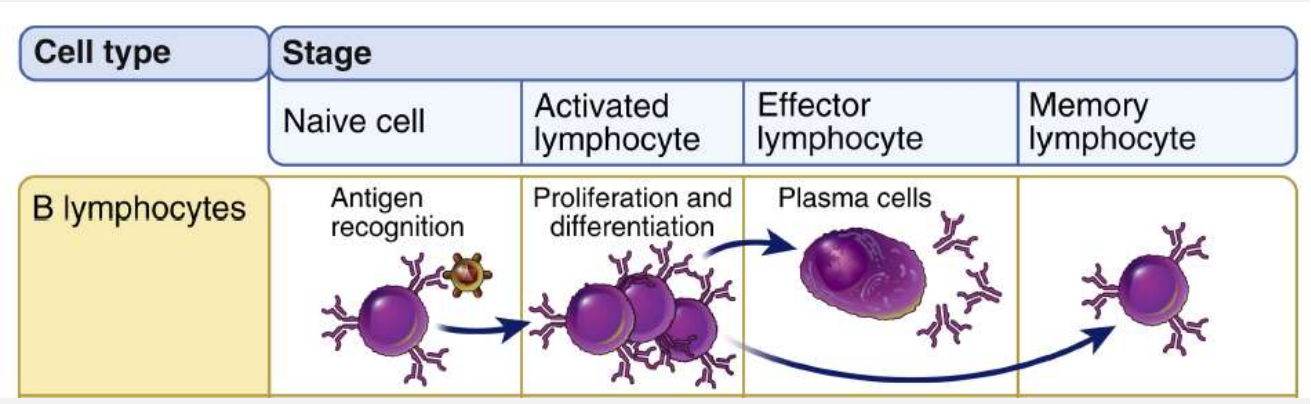
B-cell activation

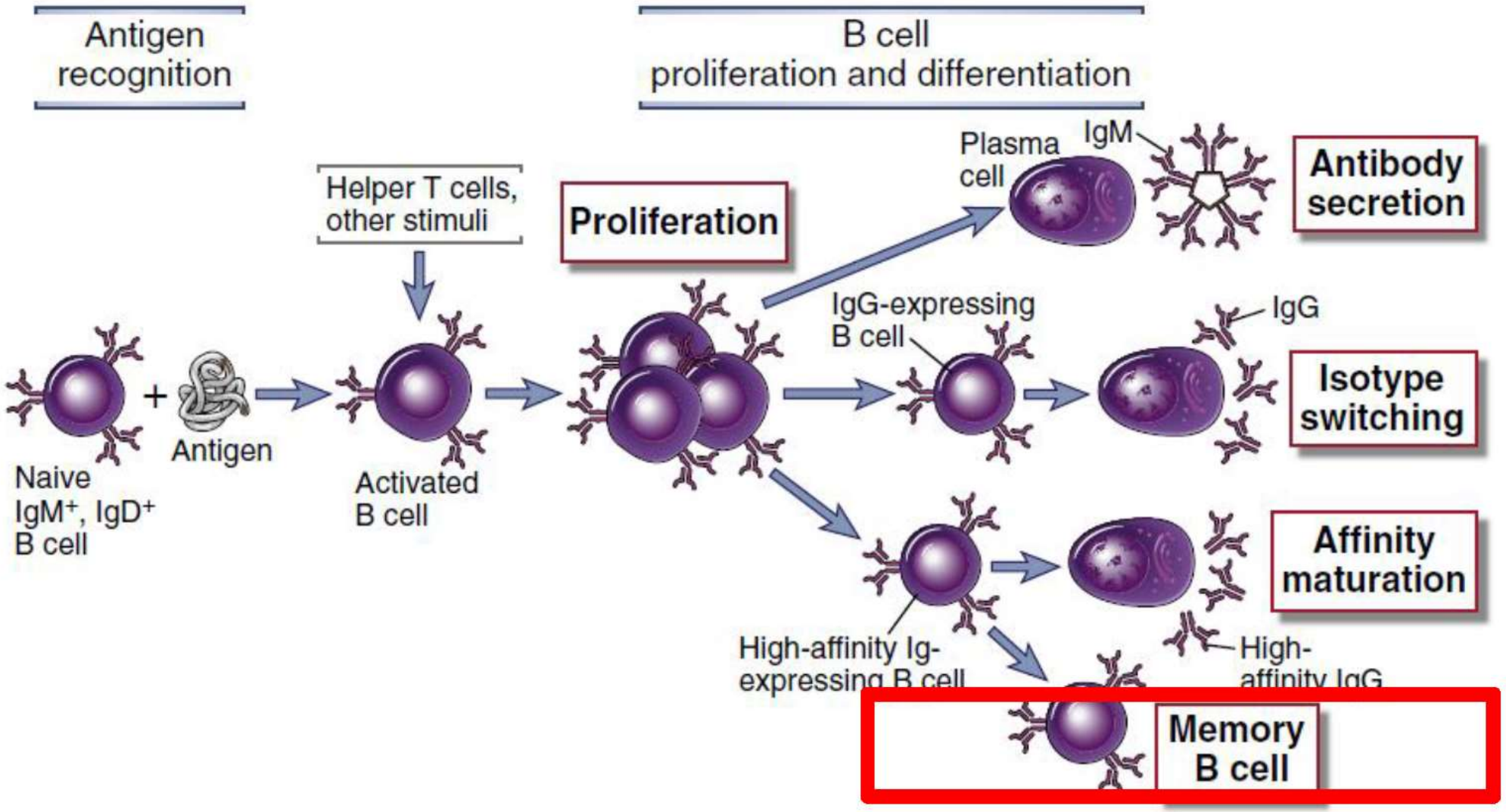
upon encountering an Ag, cytokine interactions, T helper cells

- B cells can be activated by **a variety of stimuli when they encounter an Ag that matches their surface Ig receptors -> series of intracellular signaling events ->**

- **PRODUCTION OF ANTIBODIES**

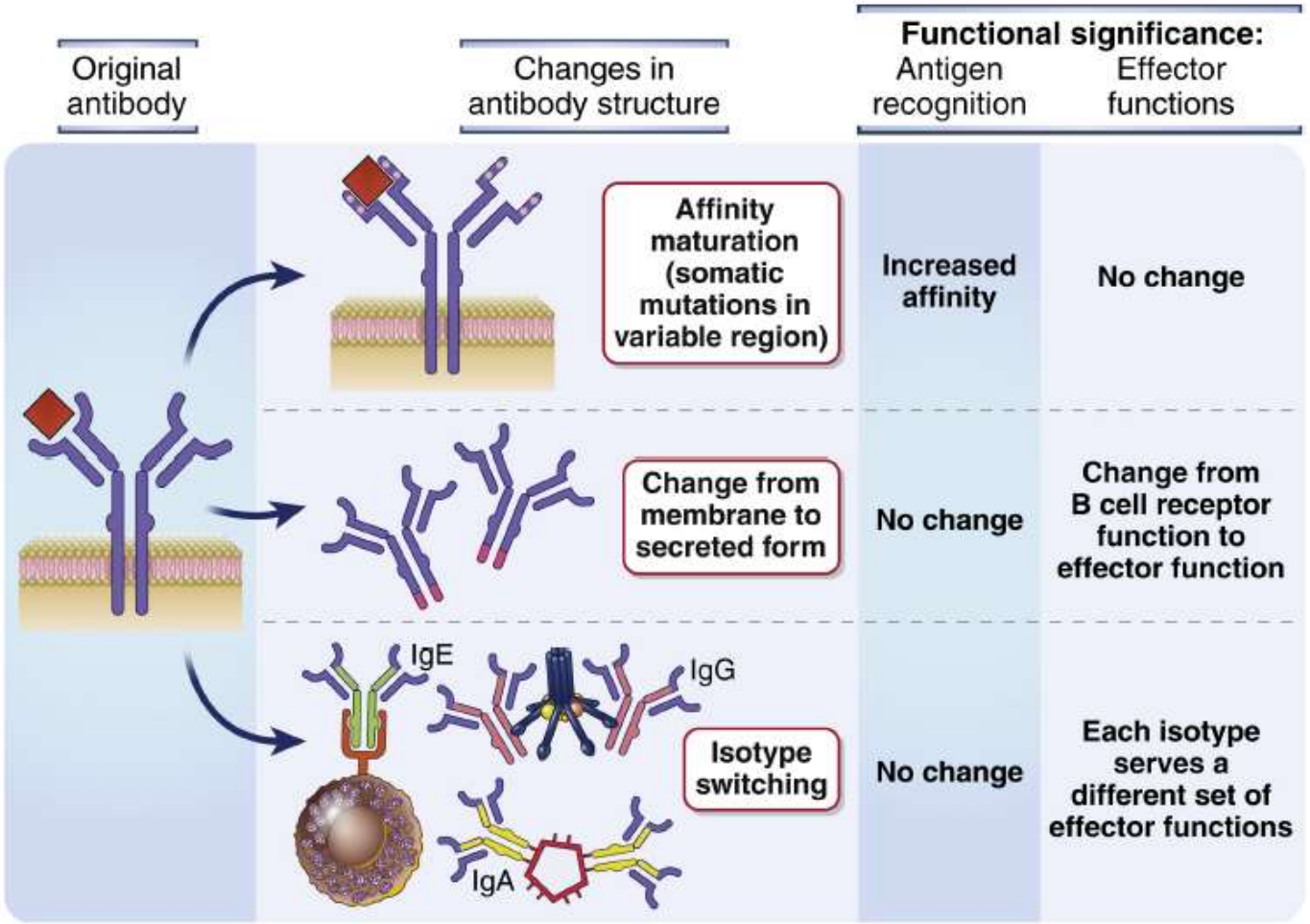


B-cell activation



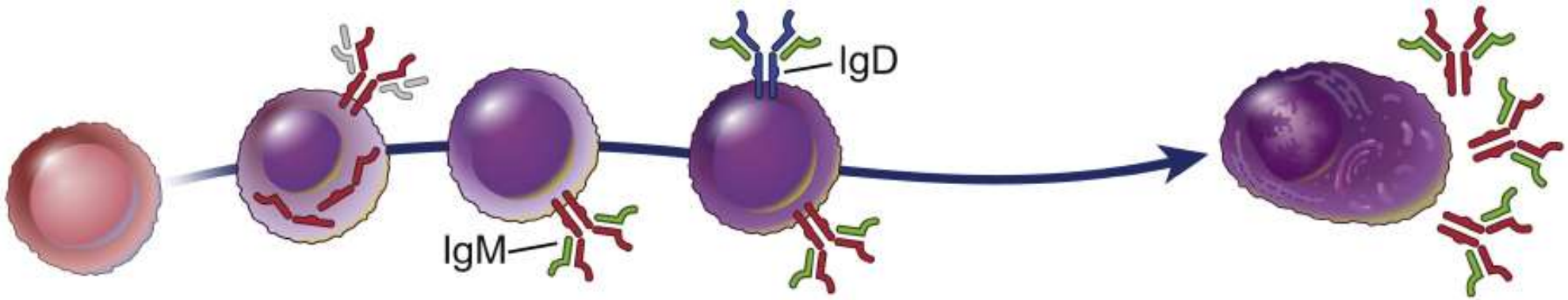
Affinity maturation & isotype switch

C regions change (IgM, IgD -> IgG/IgA/IgE)



Maturation of lymphocytes

B lymphocytes



Stage of maturation	Stem cell	Pre-B cell	Immature B cell	Mature B cell	Activated B cell (plasmablast)	Plasma cell
Pattern of immunoglobulin production	None	Cytoplasmic μ heavy chain and pre-B receptor	Membrane IgM	Membrane IgM, IgD	Low rate Ig secretion; heavy chain isotype switching; affinity maturation	High rate Ig secretion; little or no membrane Ig

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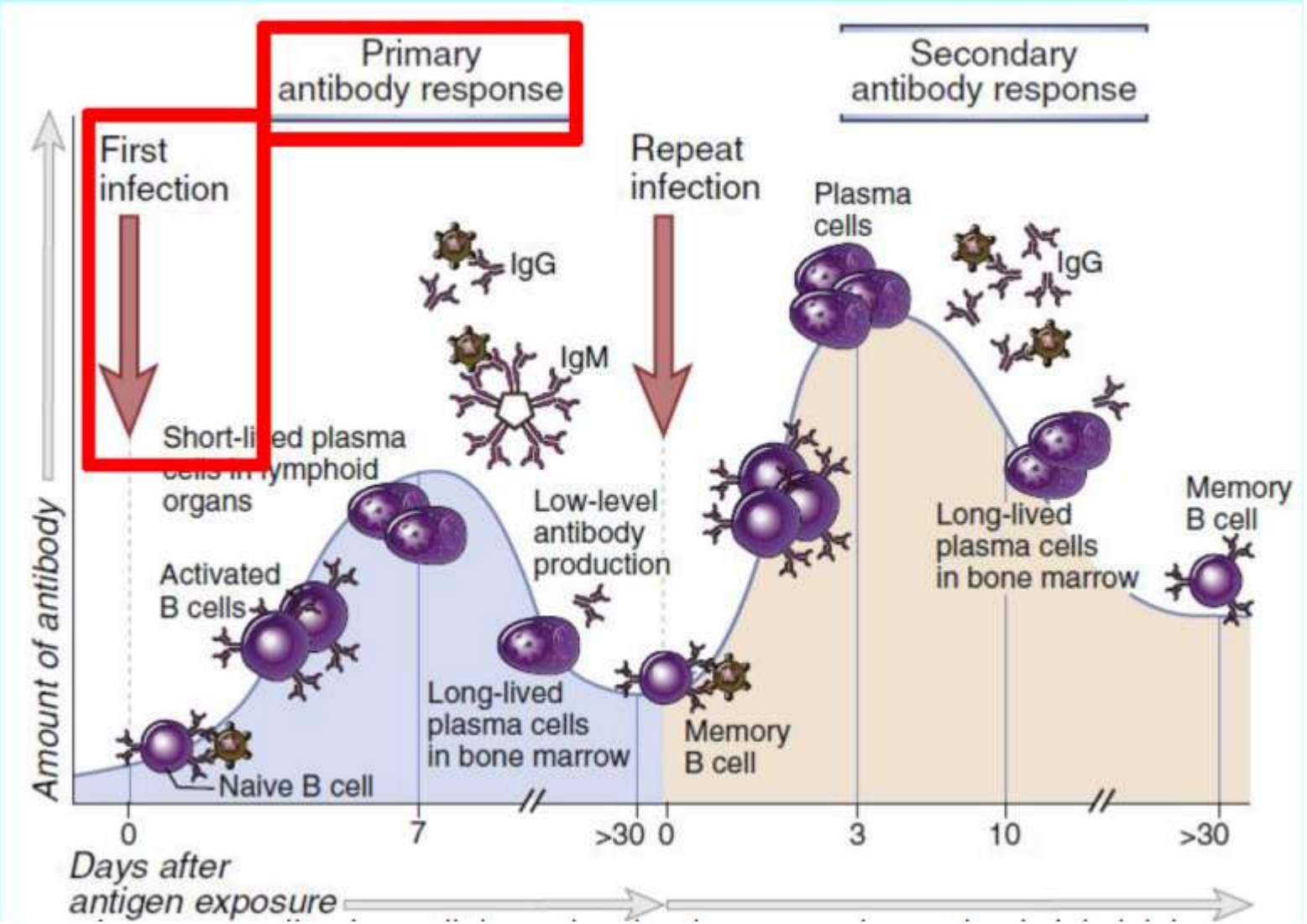
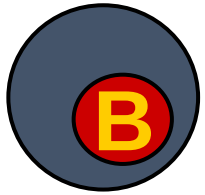
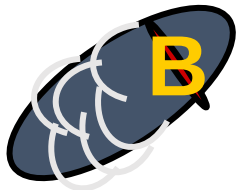
Overview of B-cell activation



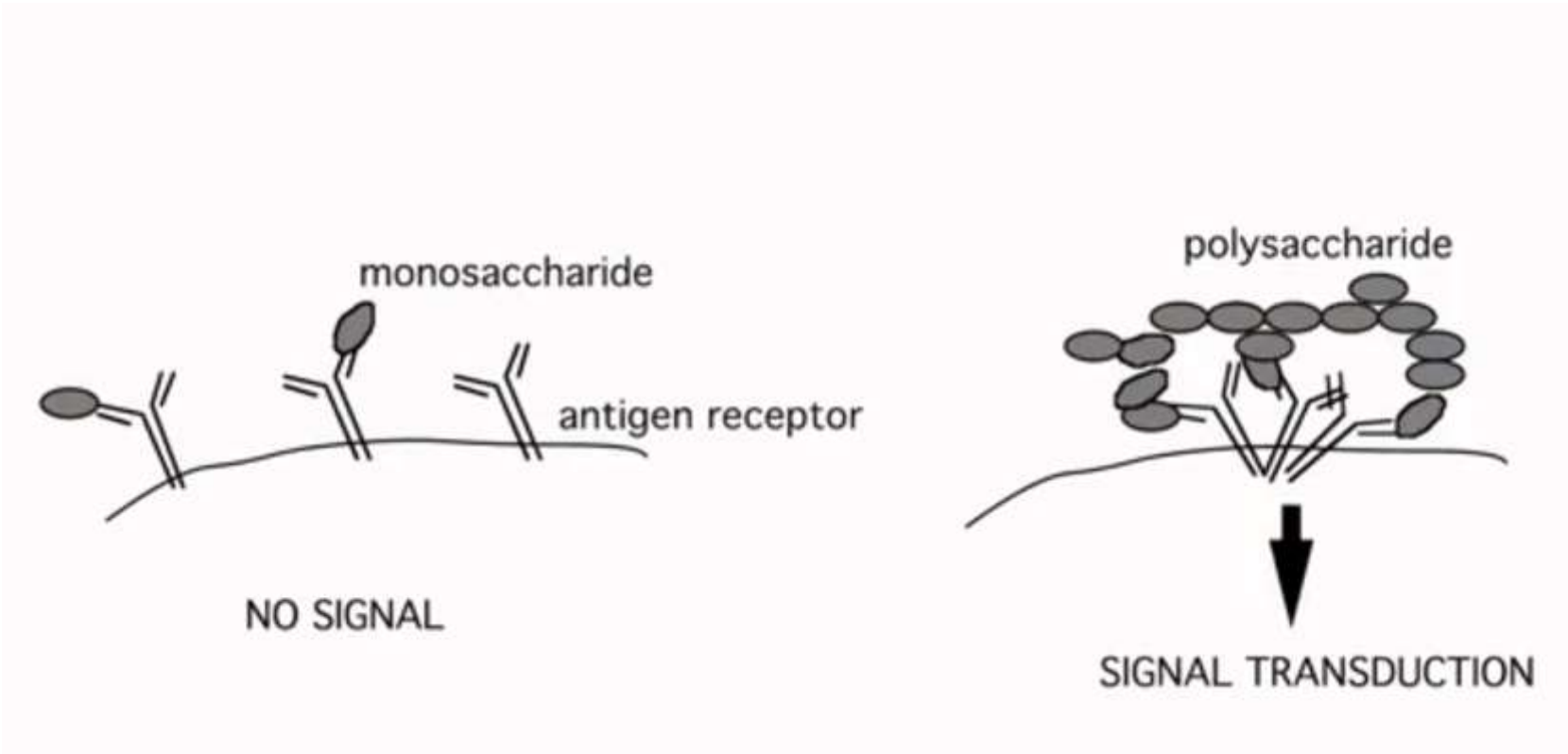
1ry vs 2ry Response

Feature	Primary response	Secondary response
Peak response	Smaller	Larger
Antibody isotype	Usually IgM > IgG	Relative increase in IgG and, under certain situations, in IgA or IgE
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)
Induced by	All immunogens	Mainly protein antigens

Plasma cells

	Surface Ig	Surface MHC II	High rate Ig secretion	Growth	Somatic hypermut'n	Isotype switch
 Mature B cell	High	Yes	No	Yes	Yes	Yes
 Plasma cell	Low	No	Yes	No	No	No

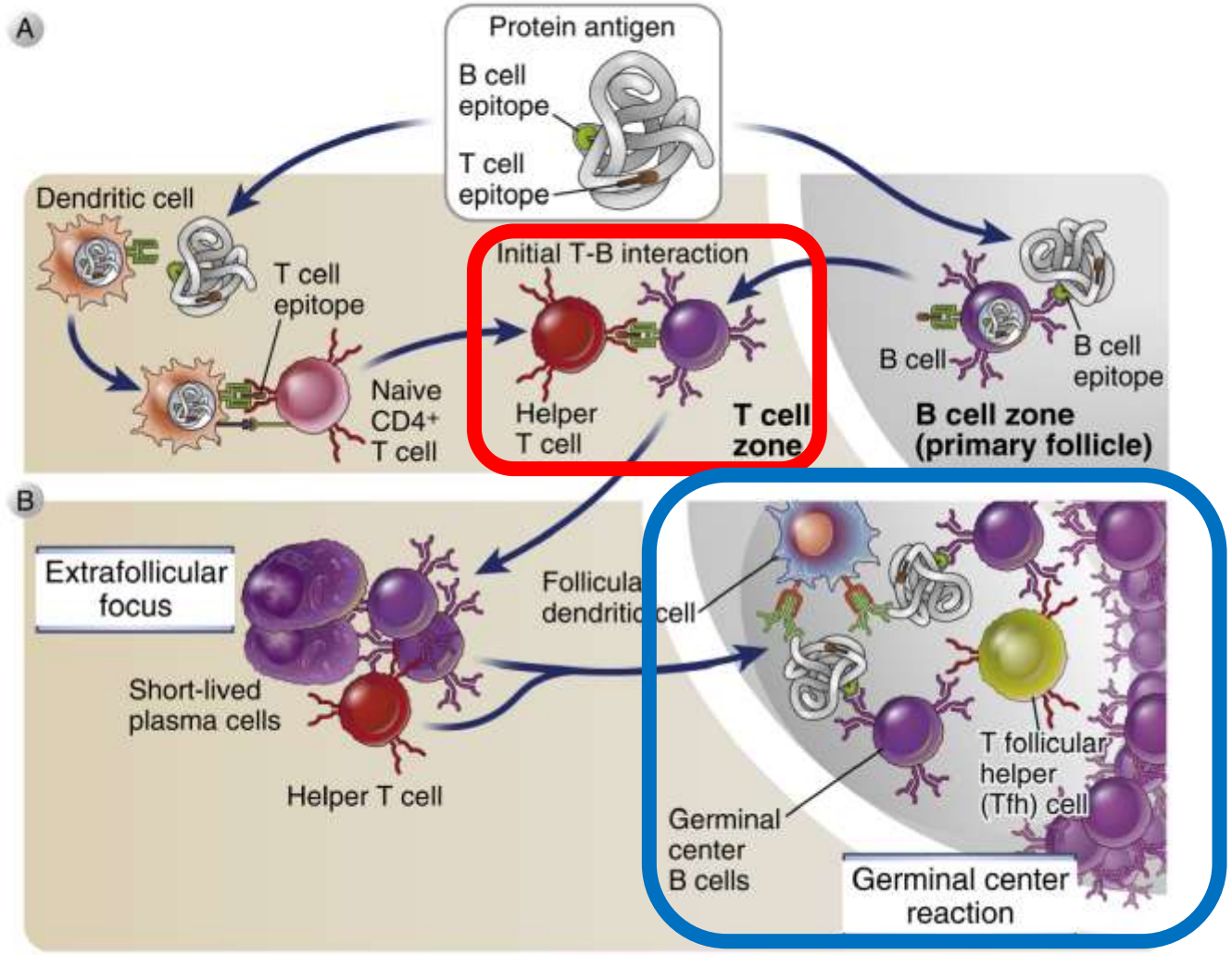
T independent B cell activation
in the absence of T cell help



- **Multivalent structures can be T independent antigens (polysaccharides, glycolipids, nucleic acids)**
- **Responses generally low affinity w limited class switching-short lived plasma cells**

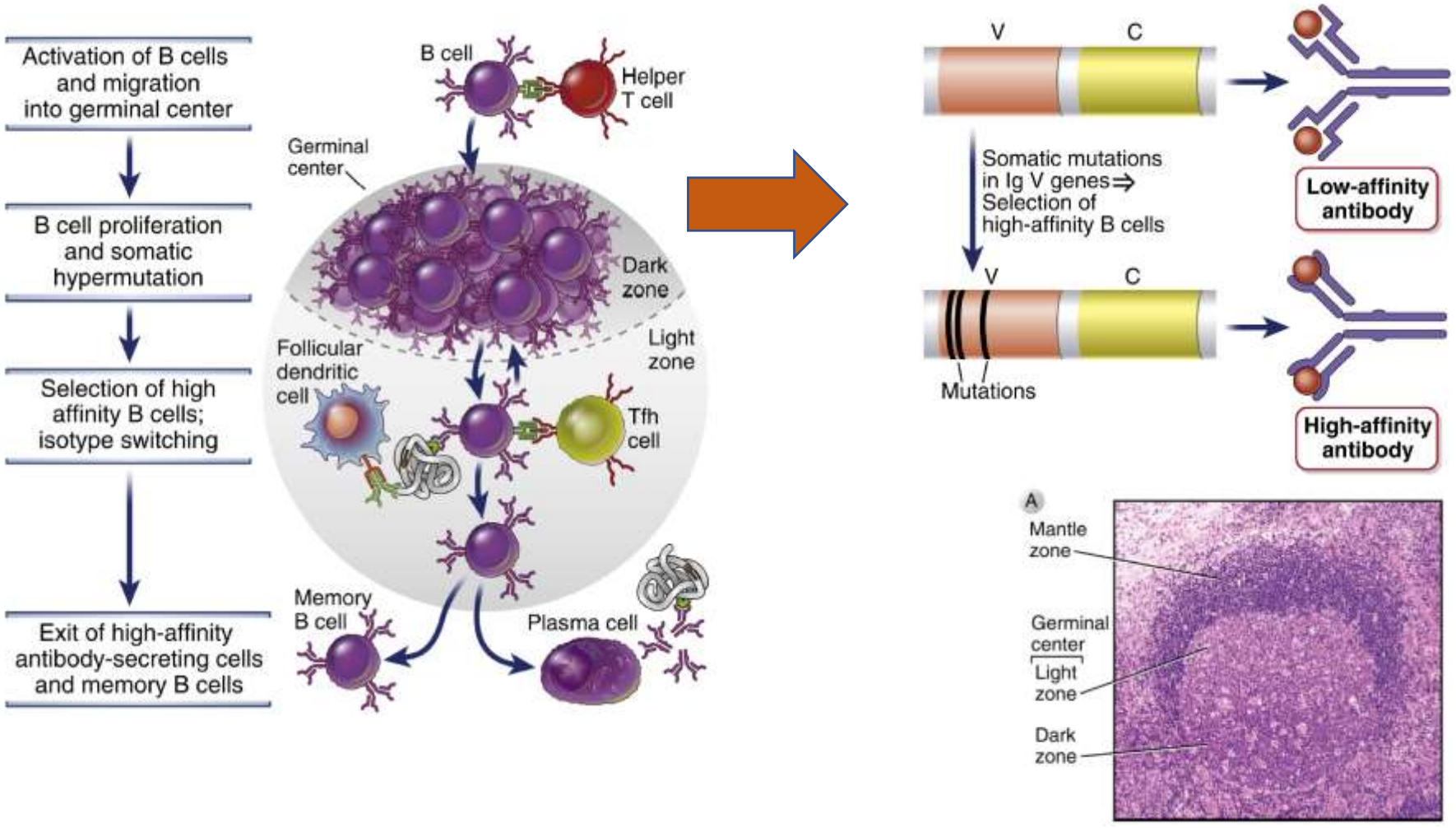
T dependent humoral response

activated lymphocytes migrate toward one another and interact



Activation of B lymphocytes

Germinal center



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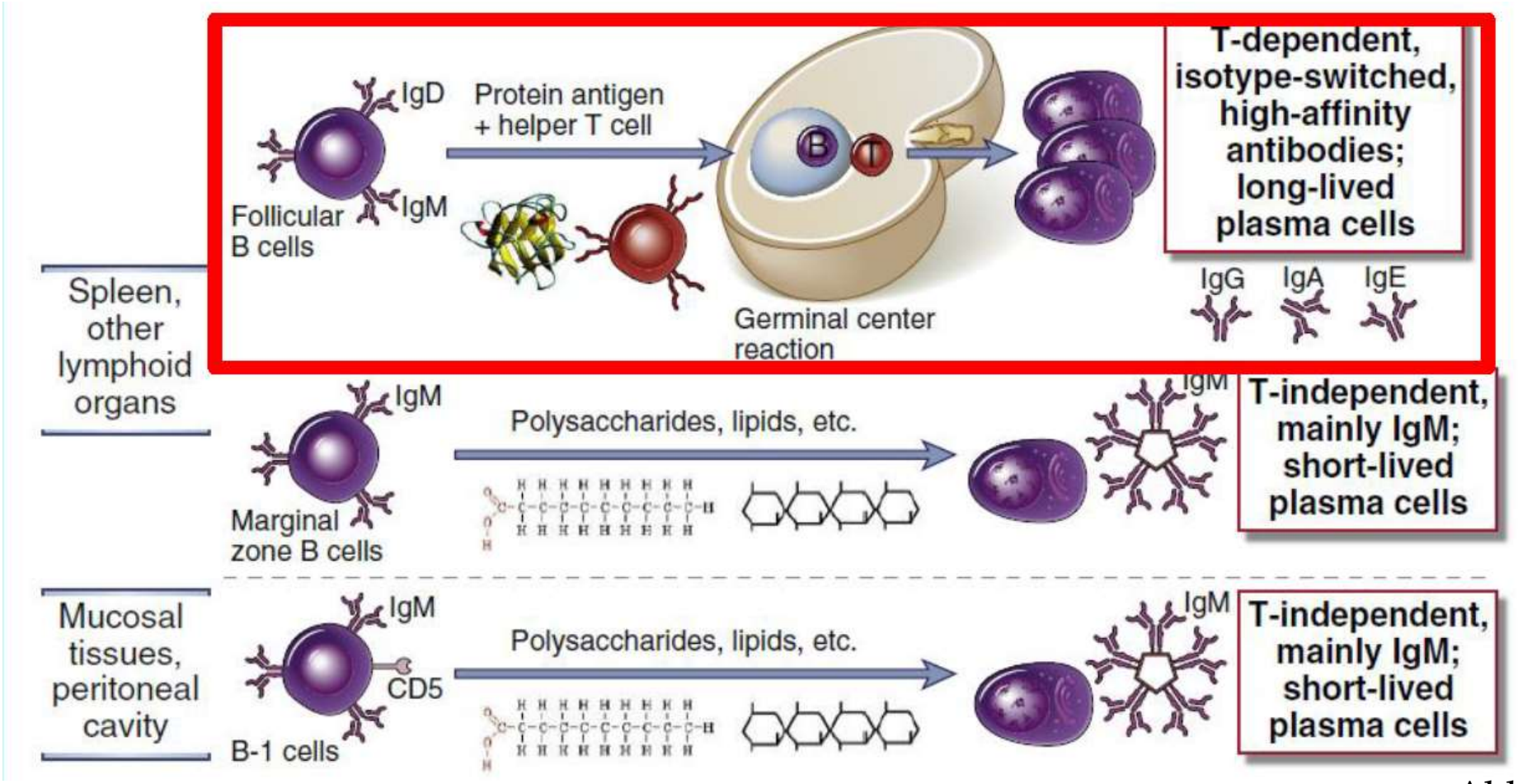
Distinct B cell subtypes mediate different types of Ab responses



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T dependent vs T independent

TABLE 12-2 Properties of Thymus-Dependent and Thymus-Independent Antigens

	Thymus-Dependent Antigen	Thymus-Independent Antigen
Chemical nature	Proteins	Polymeric antigens, especially polysaccharides; also glycolipids, nucleic acids
Features of Antibody Response		
Isotype switching	Yes; IgG, IgE, and IgA	Little or no; may be some IgG and IgA
Affinity maturation	Yes	No
Secondary response (memory B cells)	Yes	Only seen with some antigens (e.g., polysaccharides)

The effector functions of Abs

main mechanisms & interactions with other cells

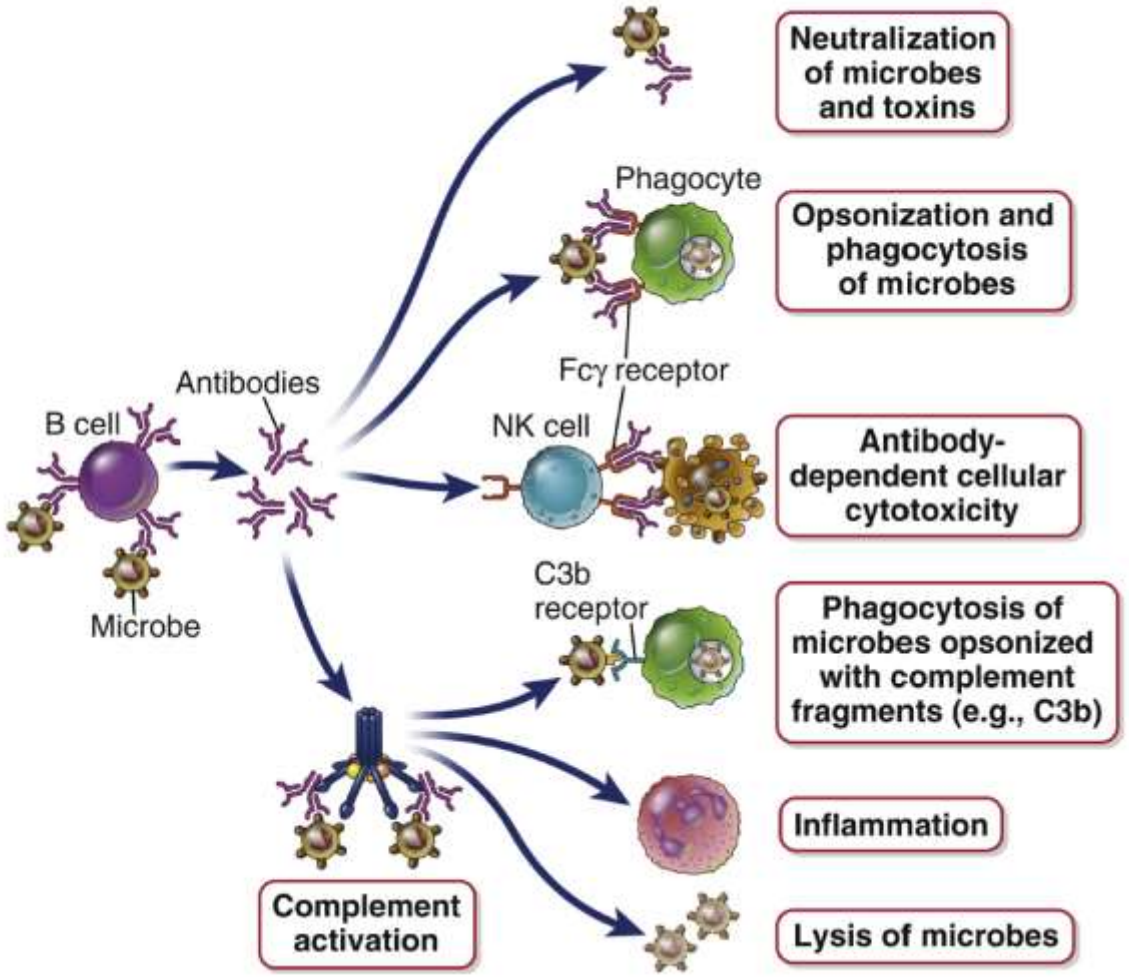
- **extracellular bacteria, fungi**
- **obligate intracellular microbes**, such as

  viruses

  - **targets of antibodies before they infect cells**

  or

  - **when released from infected cells**



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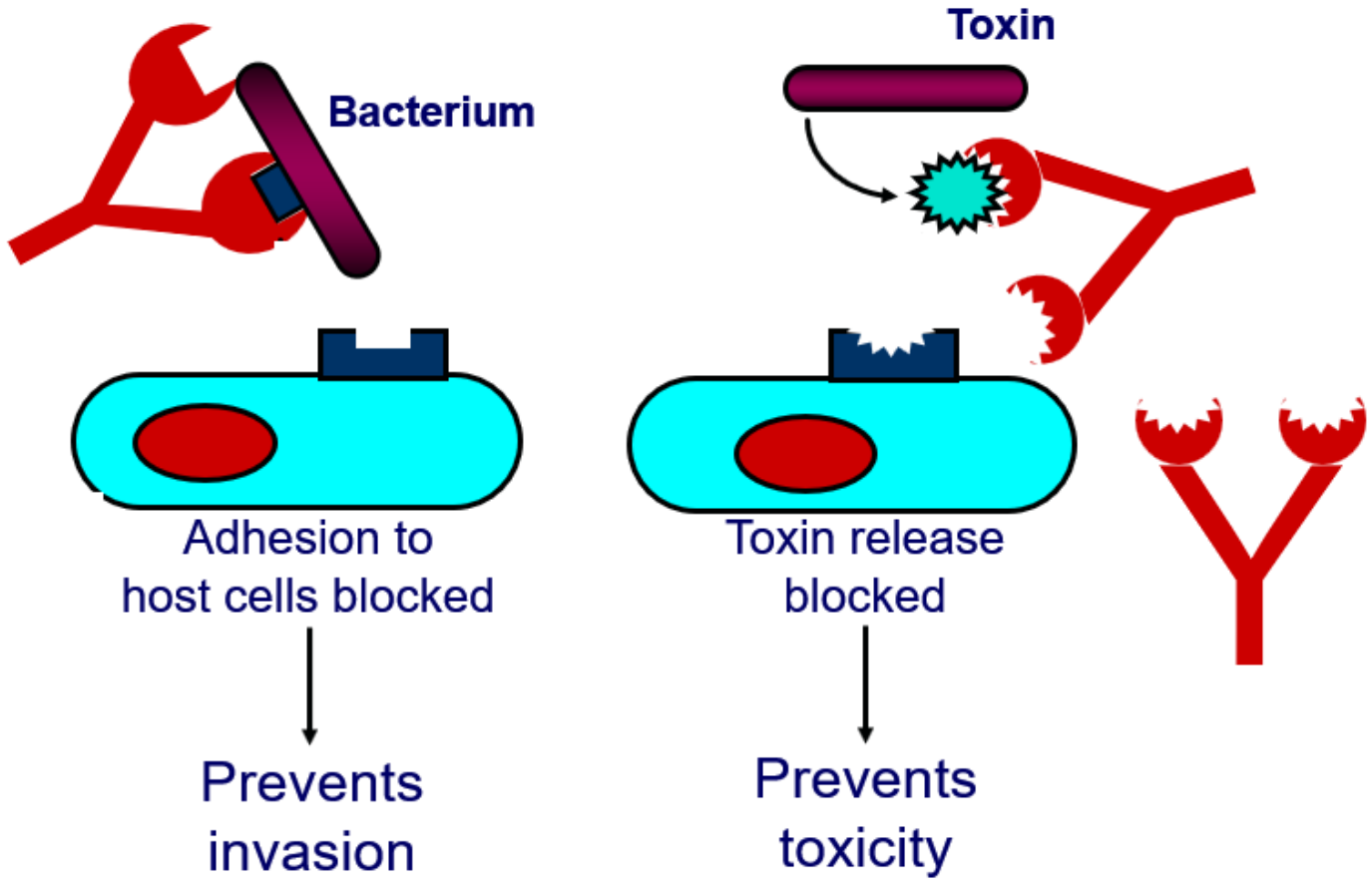
The effector functions of Abs

εξω-κυττάρια παθογόνα & τοξίνες -> NEUTRALIZATION



ΕΞΟΥΔΕΤΕΡΩΤΙΚΑ ΑΝΤΙΣΩΜΑΤΑ

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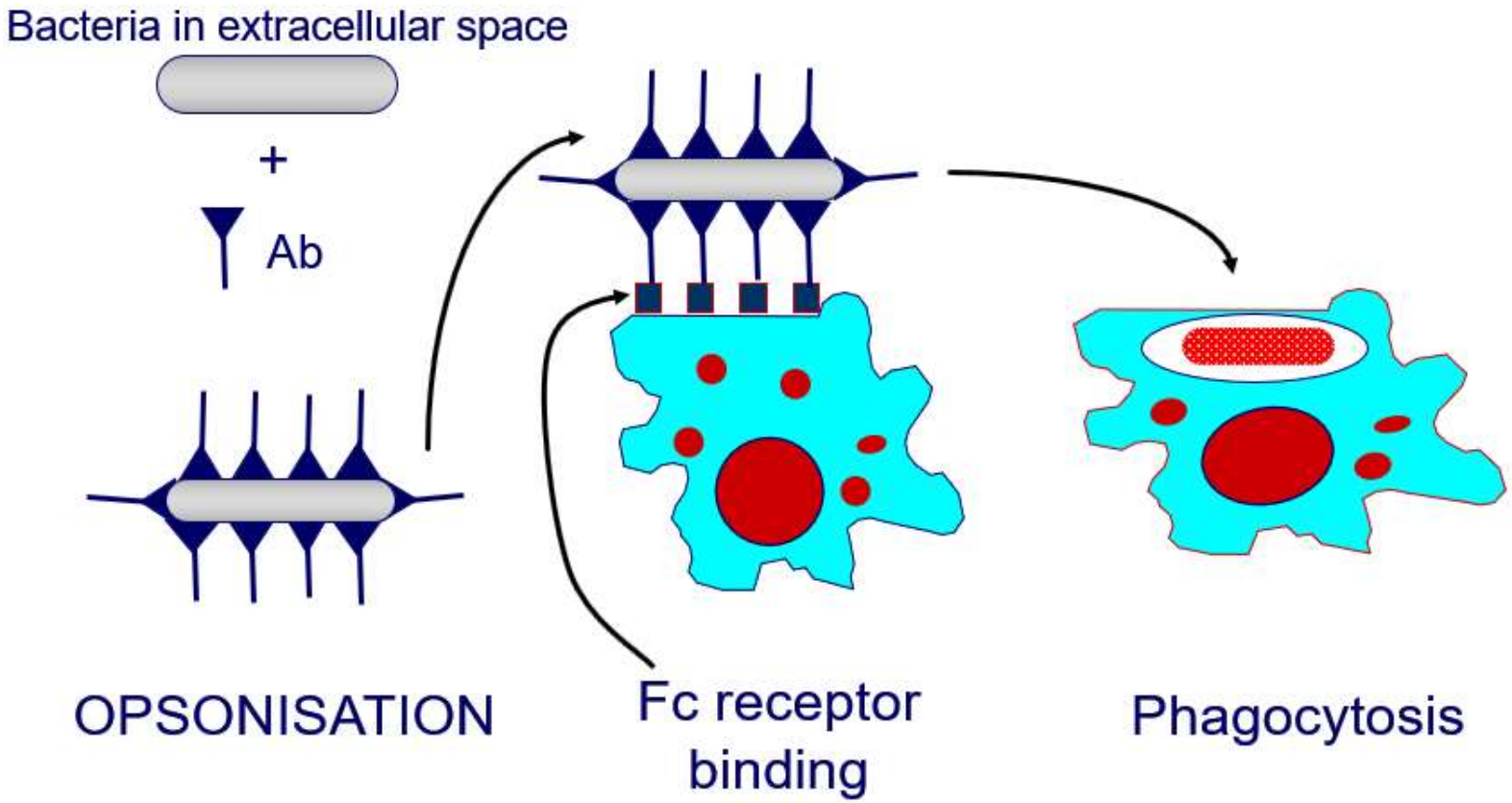
The effector functions of Abs

εξωκυττάρια παθογόνα -> OPSONIZATION



Opsonization -> Phagocytosis

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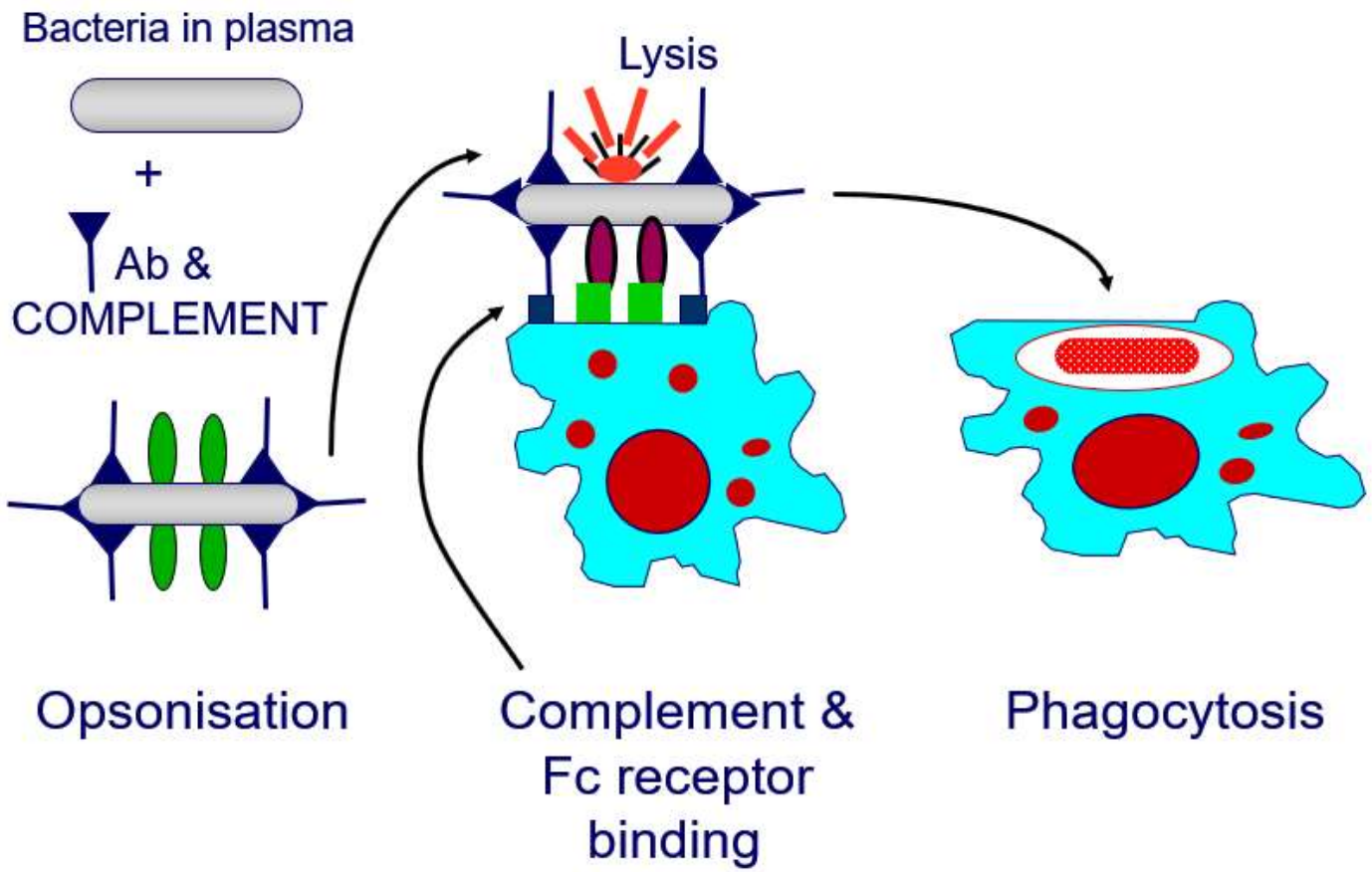
The effector functions of Abs

εξωκυττάρια παθογόνα -> Ενεργοποίηση συμπληρώματος



Complement activation

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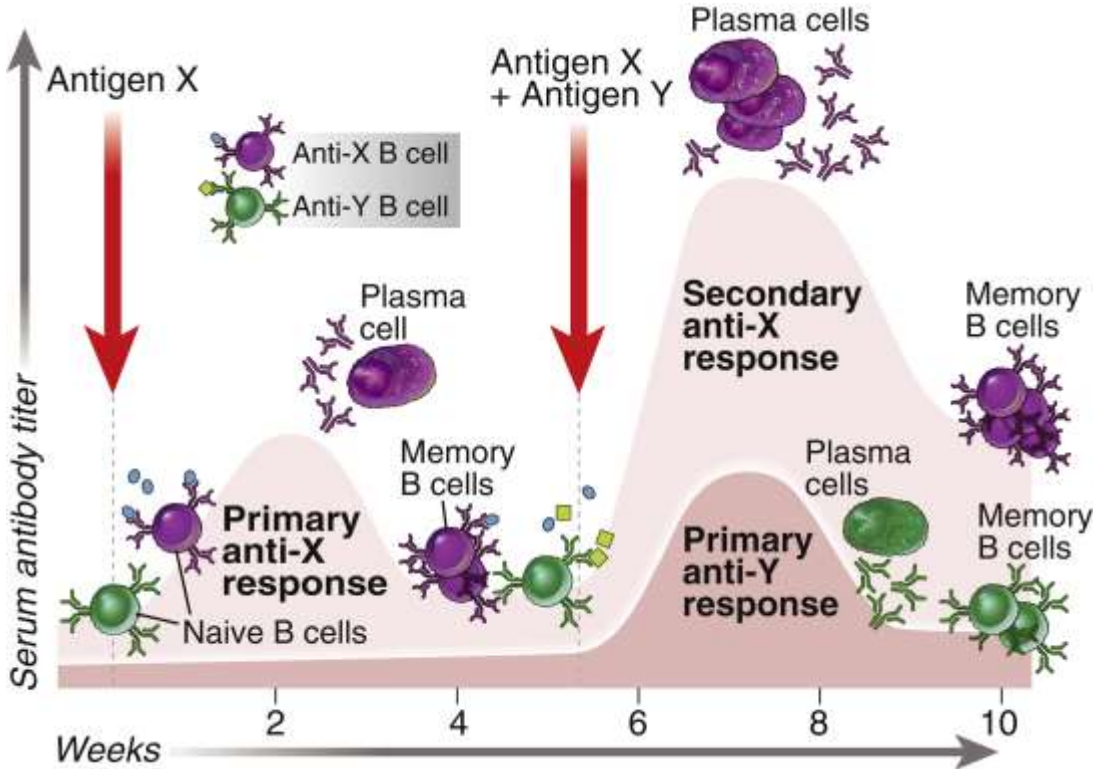
Adaptive immune system
specificity, diversity, contraction memory

- **Specific immune responses**
  - often for different portions of a single complex protein, polysaccharide or other macromolecule
  - **determinants or epitopes**



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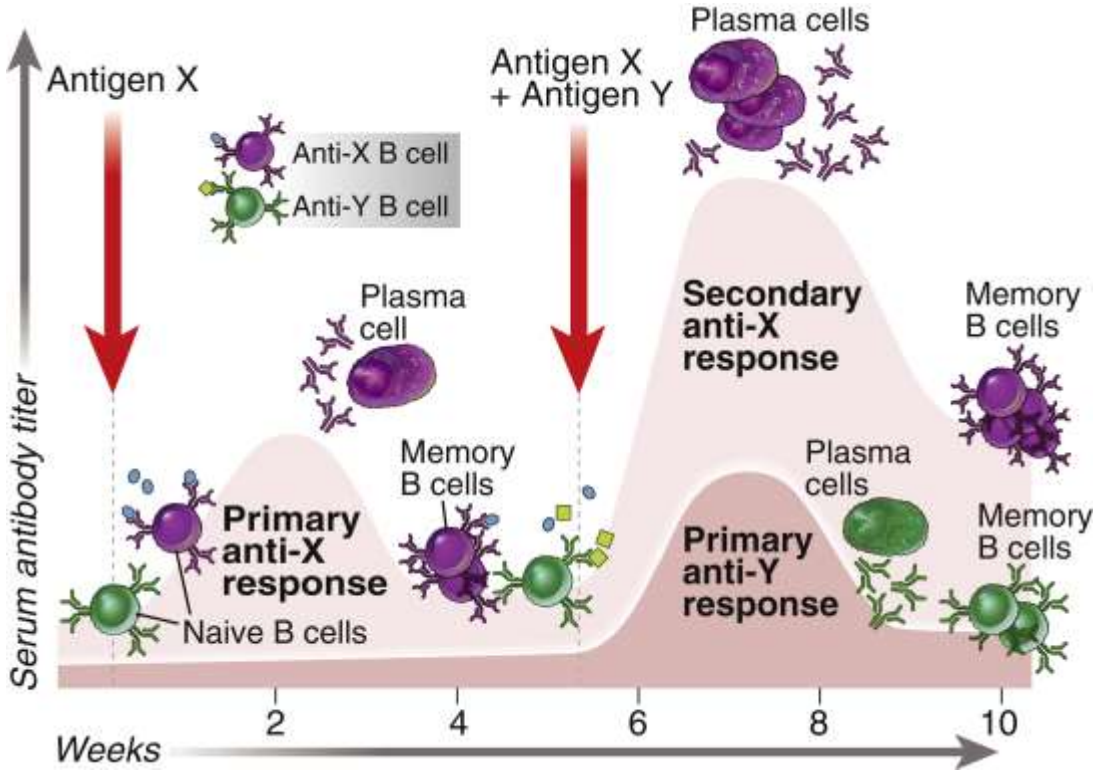
Adaptive immune system
contraction maintains homeostasis

- **Contraction**
  - Antibody levels decline with time after each immunization



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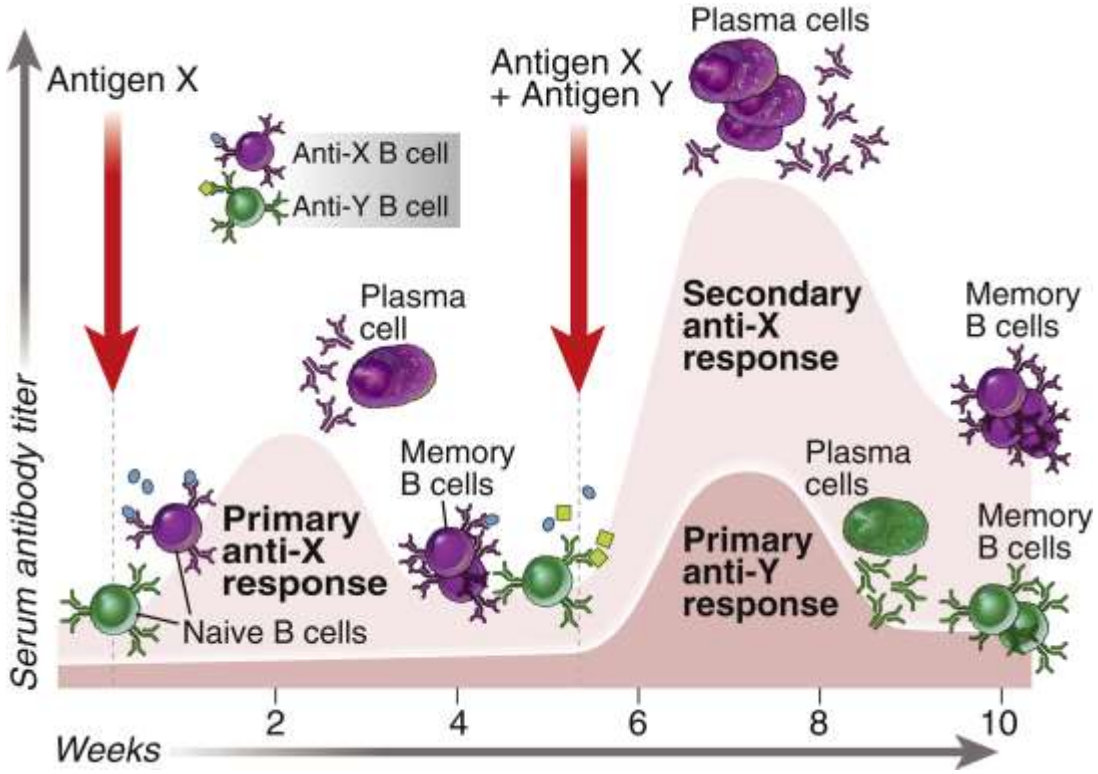
Adaptive immune system

memory cells, 2ry immune responses

- **Exposure** of the immune system to a foreign Ag **enhances its ability to respond again** to that Ag

- **Secondary immune responses**, are usually **more rapid**, **greater in magnitude**, and **often qualitatively different** from the 1st, or primary, immune response



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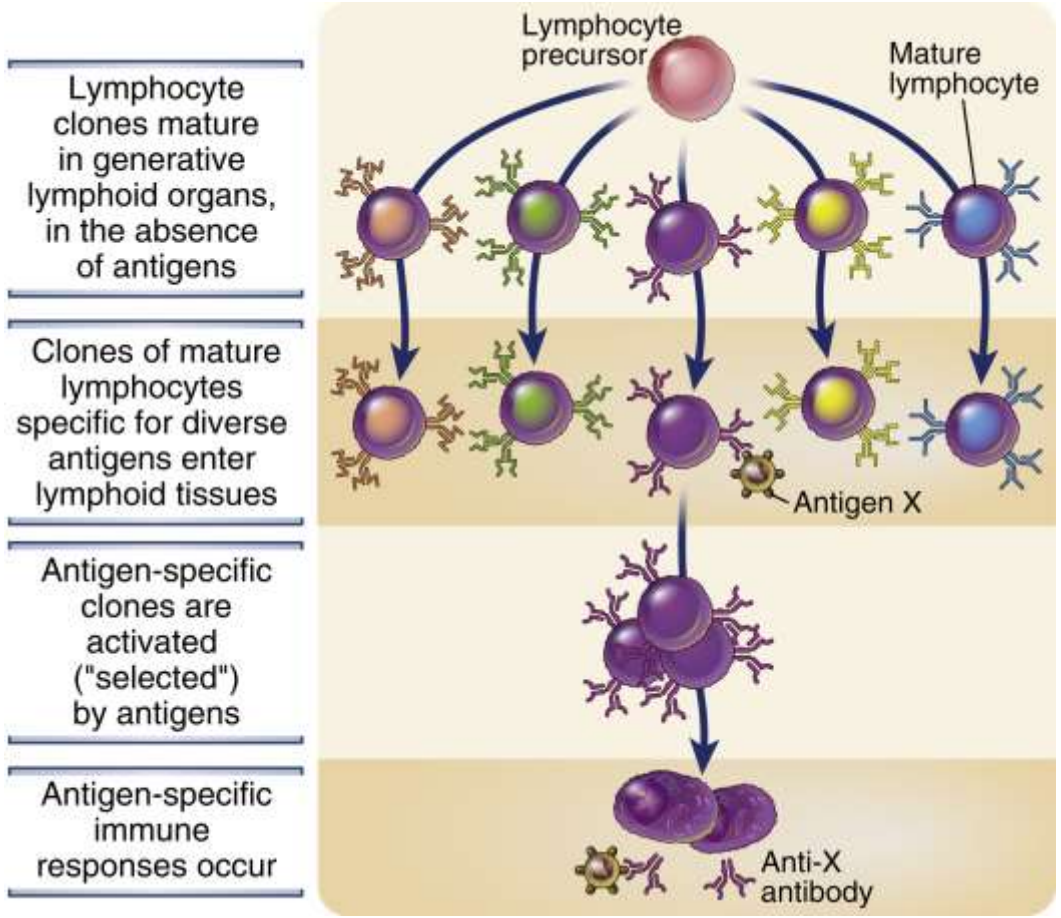
Adaptive immune system
clonal selection

- Clones of lymphocytes w different specificities are present in unimmunized individuals
  - Able to recognize & respond to foreign Ag
- **Clonal selection**



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Β λεμφοκύτταρα – Adaptive immune system

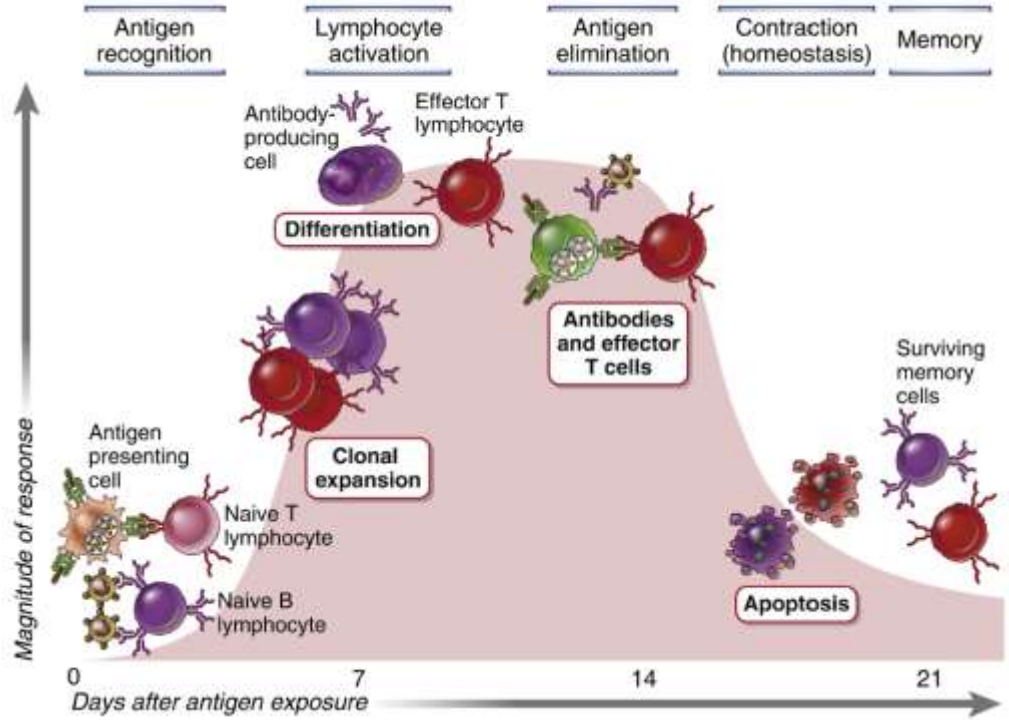
Adaptive immunity is systemic

- Initiated at one site but -> Protection at distant sites
- Essential for vaccination success
    - Administered at sq or muscle tissue in arm -> distant protection

Β λεμφοκύτταρα – Adaptive immune system

Adaptive immunity -> synergy between B & T cells

- Recognition ->
- Lymphocyte activation ->
- Elimination of Ag (effector phase) ->
- Contraction
- Memory



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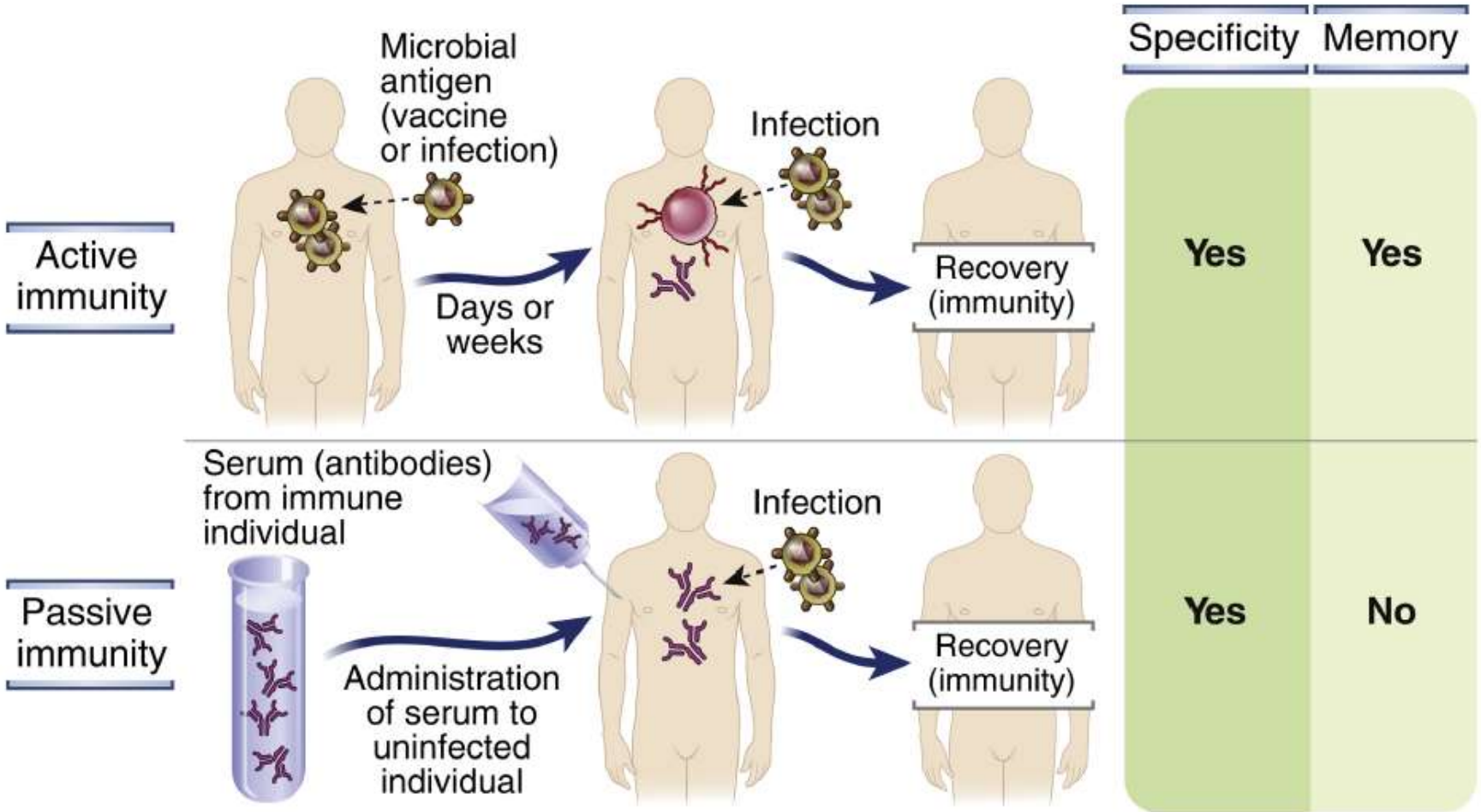
B cells in clinical medicine

- **B cell dysregulation** can lead to a variety of diseases, including autoimmune disorders and B cell malignancies
- **B cell-targeted therapies**, such as rituximab or ibrutinib have been developed to treat these conditions

Β λεμφοκύτταρα

Active vs. Passive immunity



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Β λεμφοκύτταρα
Vaccine immunity

Infectious Disease	Vaccine	Mechanism of Protective Immunity
Polio	Injected inactivated poliovirus (Salk) and oral attenuated poliovirus (Sabin)	Neutralization of virus by IgG or by mucosal IgA antibody
Tetanus, diphtheria	Toxoids (inactivated toxins)	Neutralization of toxin by systemic IgG antibody
Hepatitis A or B	Recombinant viral envelope proteins	Neutralization of virus by mucosal IgA or systemic IgG antibody

Infectious Disease	Vaccine	Mechanism of Protective Immunity
Pneumococcal pneumonia, *Haemophilus influenzae* infections, and bacterial meningitis caused by *Neisseria meningitidis*	Conjugate vaccines composed of bacterial capsular polysaccharide attached to a carrier protein	Opsonization and phagocytosis mediated by IgM and IgG antibodies, directly or secondary to complement activation

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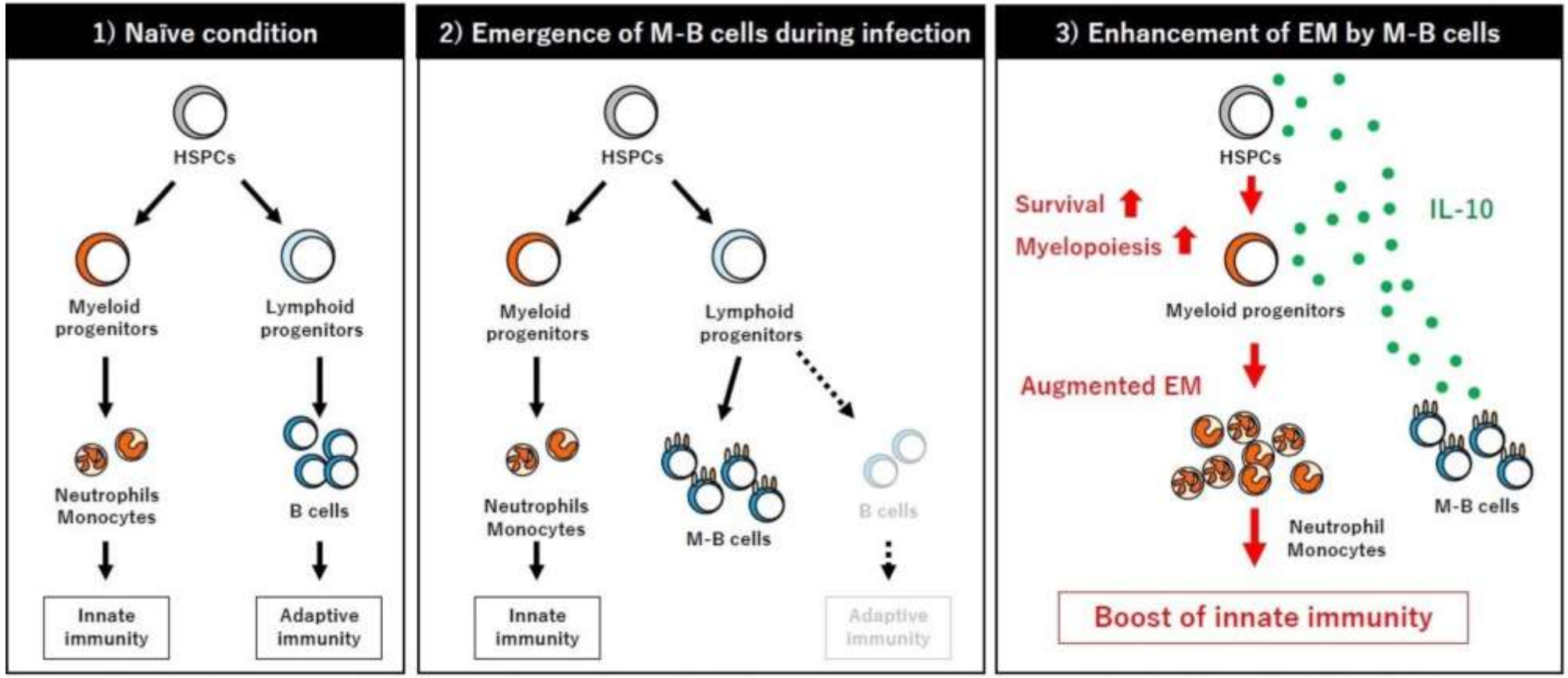
B-cells

- **Important WBC-small lymphocytes**
- **Humoral immunity of adaptive immune system**
- **Express BCR on membrane-bind Ag – initiate Ab response**
- **Can present Ag & collaborate w Tfh cells**

10th edition. Cellular and molecular Immunology Abbas, Lichtman, Pilai. 2021

B-lymphocytes, Research continues

new role discovered in emergency myelopoiesis & innate immunity



HSPCs: hematopoietic stem and progenitor cells, EM: emergency myelopoiesis, M-B cell: myeloid-like B cells

Kanayama M et al. Journal of experimental medicine 2023