B cell development and antibody production

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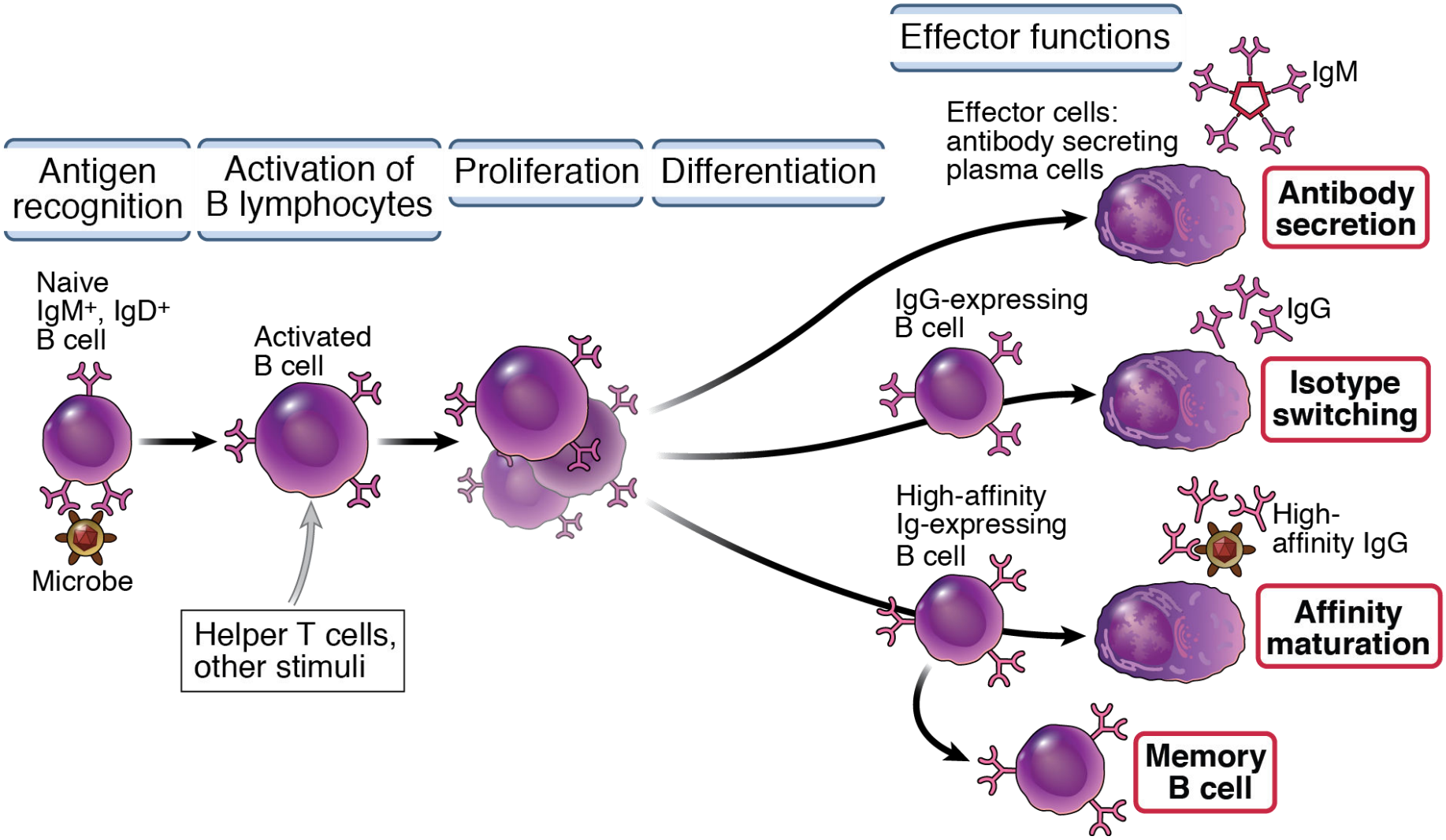
Lecture outline

- B cell activation; the role of helper T cells in antibody production
- Therapeutic targeting of B cells

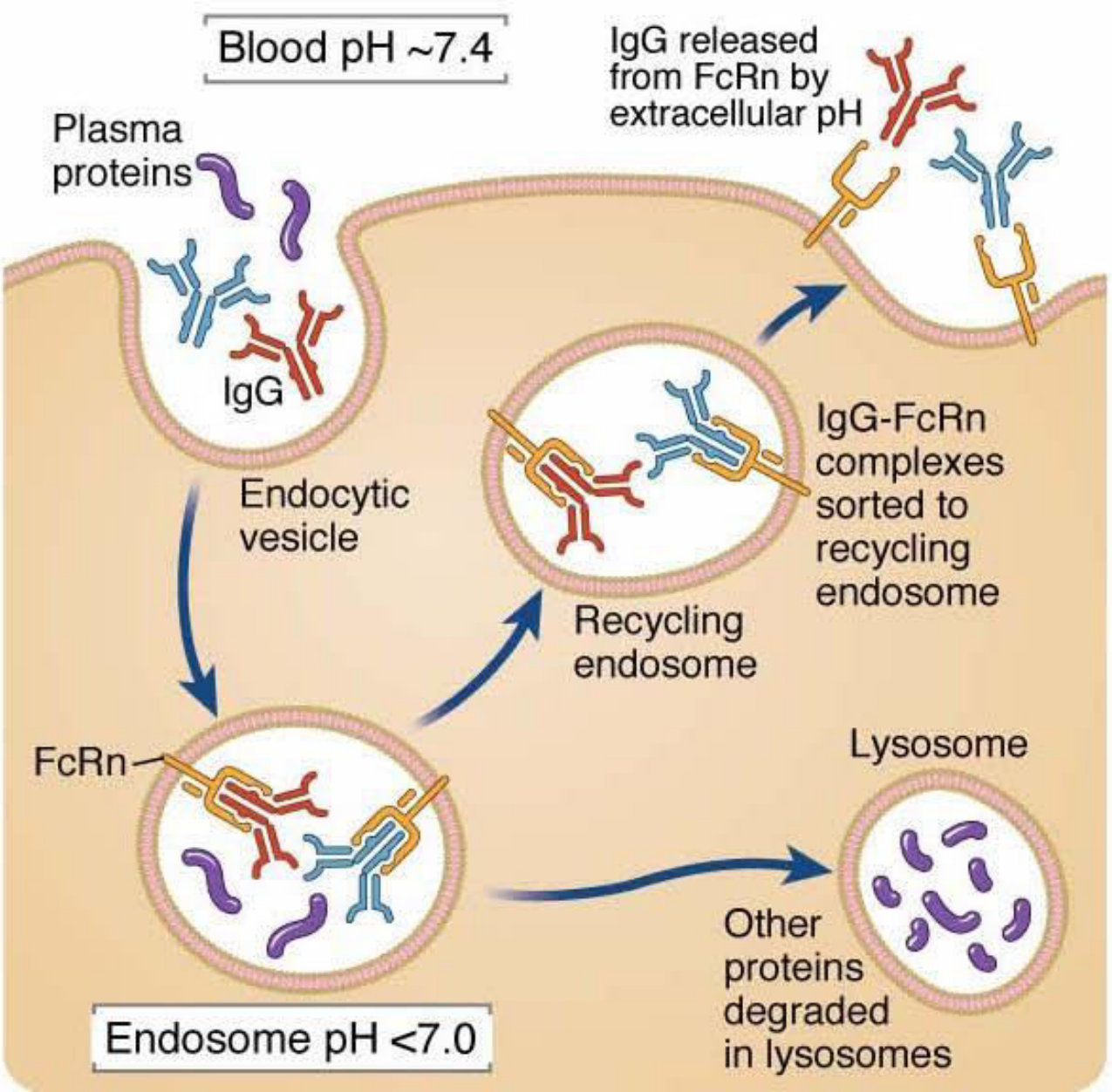
Principles of humoral immunity

- Antibodies are produced only by B lymphocytes.
- Humoral immune responses are initiated by binding of antigen to membrane bound antibody on B cells.
- Activated B cells secrete soluble antibodies of the same specificity as the membrane receptors.
- Antibody responses are specialized and enhanced by signals from helper T cells.

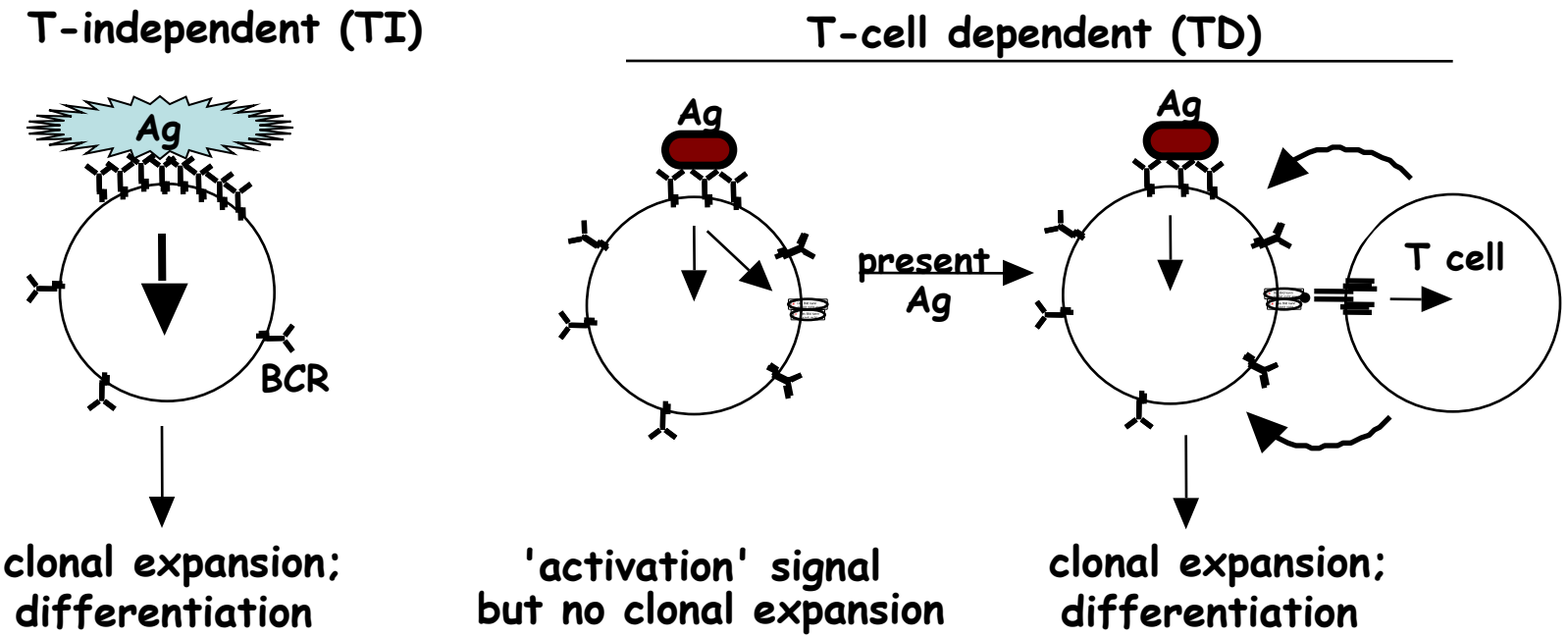
B cell activation and antibody production



IgG recycling by "neonatal" FcR (FcRn)



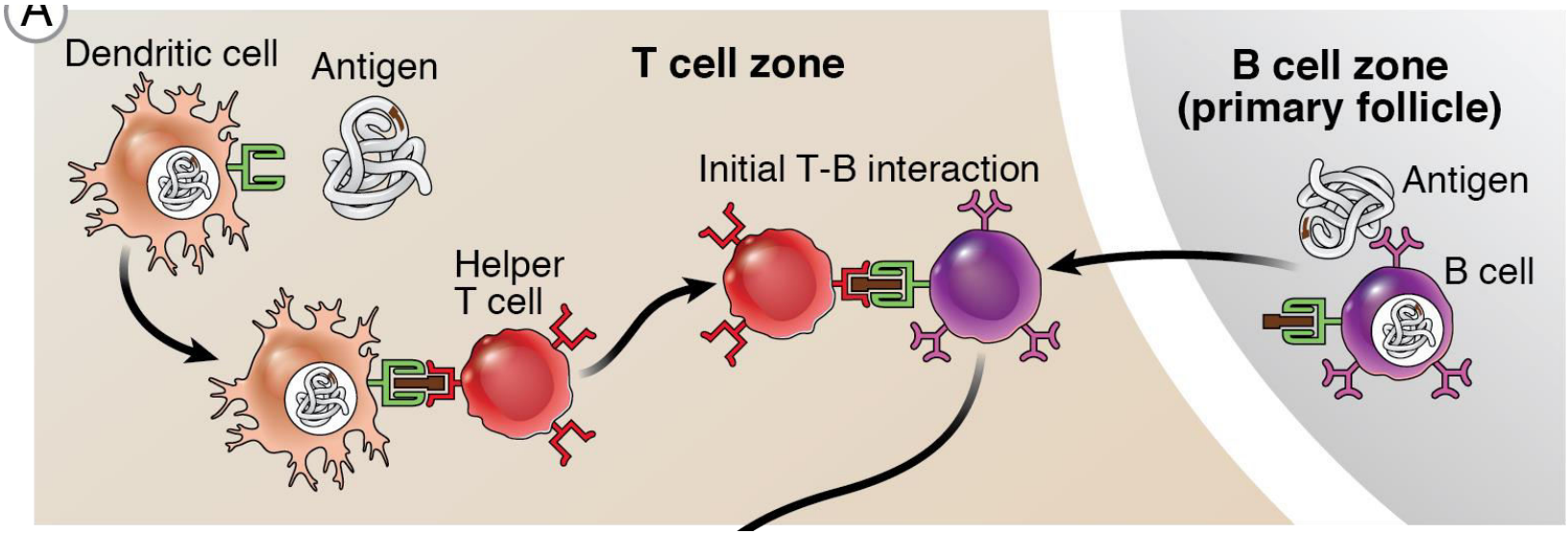
T-independent and T-dependent antibody responses



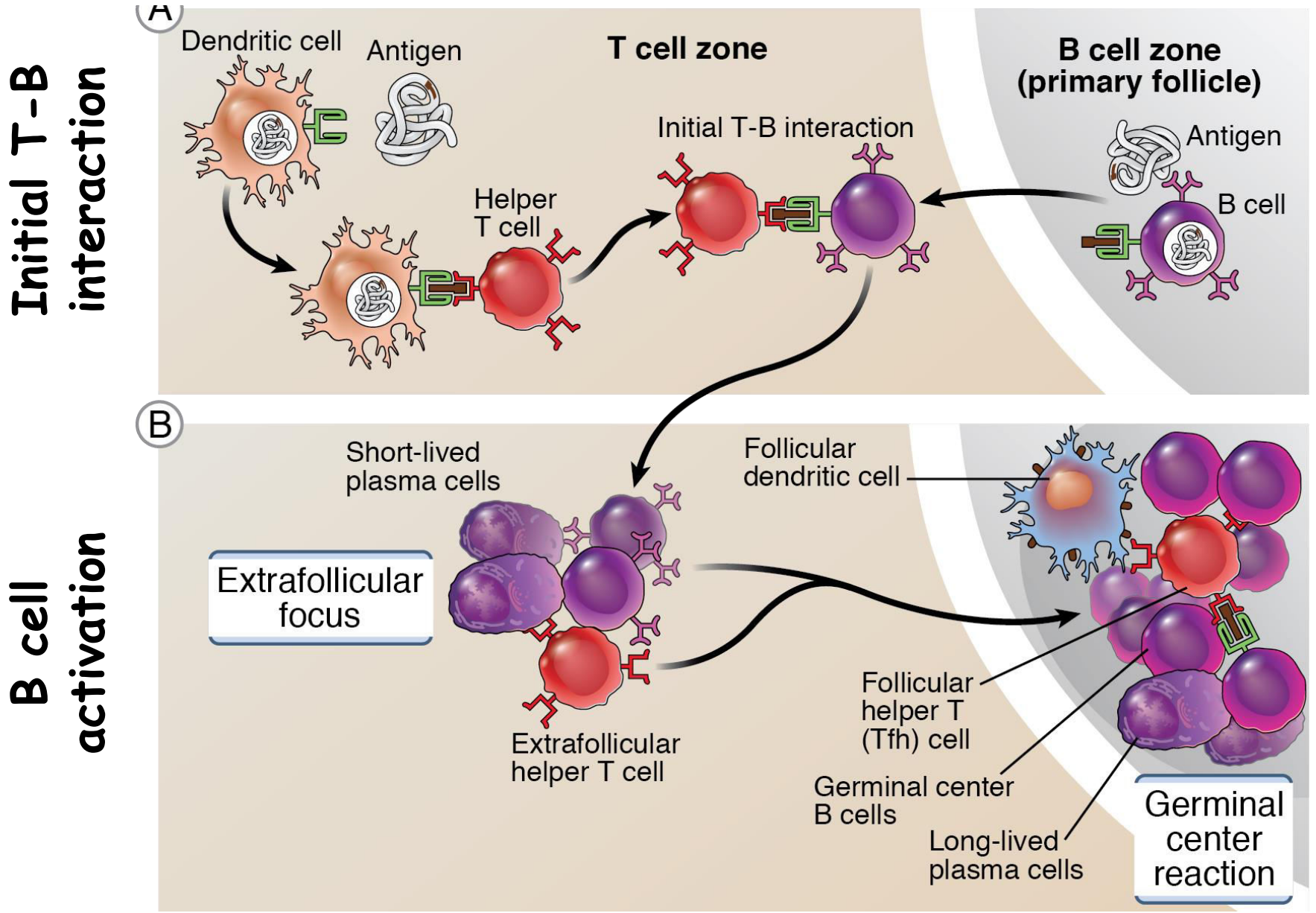
- **T-independent** antigens are multivalent (e.g. bacterial polysaccharides or repeating determinants on the surface of viruses)
  - responses are fast (within 1-2 days) and predominantly IgM
  - weak in infants and young children
- **T-dependent** antigens must contain a protein component (true of most antigens) so that T cell help can be received
  - responses slower (several days), produce all Ig isotypes (IgM, IgG, IgA, IgE)
  - stronger and can lead to antibody affinity maturation and memory

Steps in T-dependent B cell activation

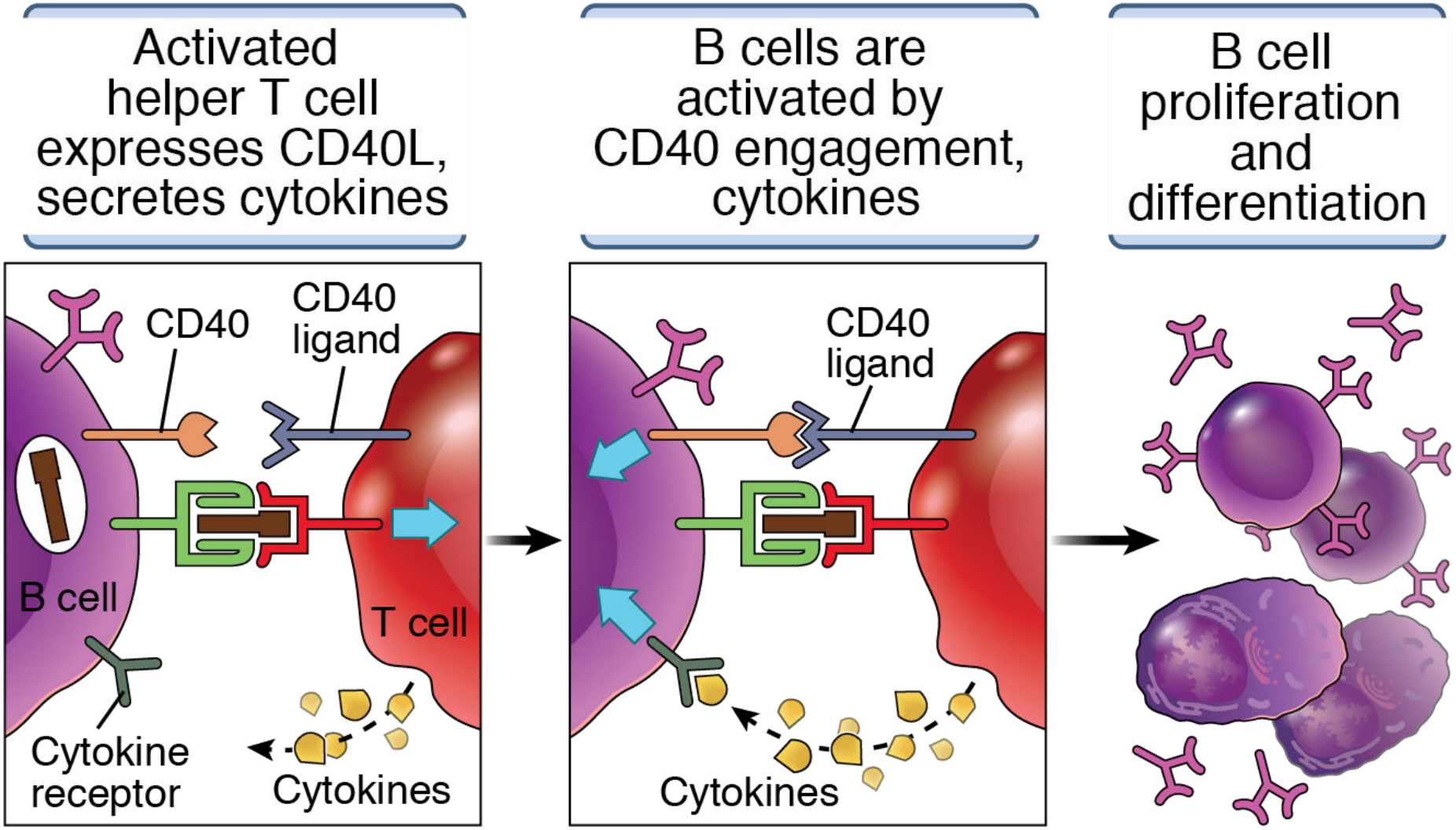
Initial T-B interaction



Steps in T-dependent B cell activation



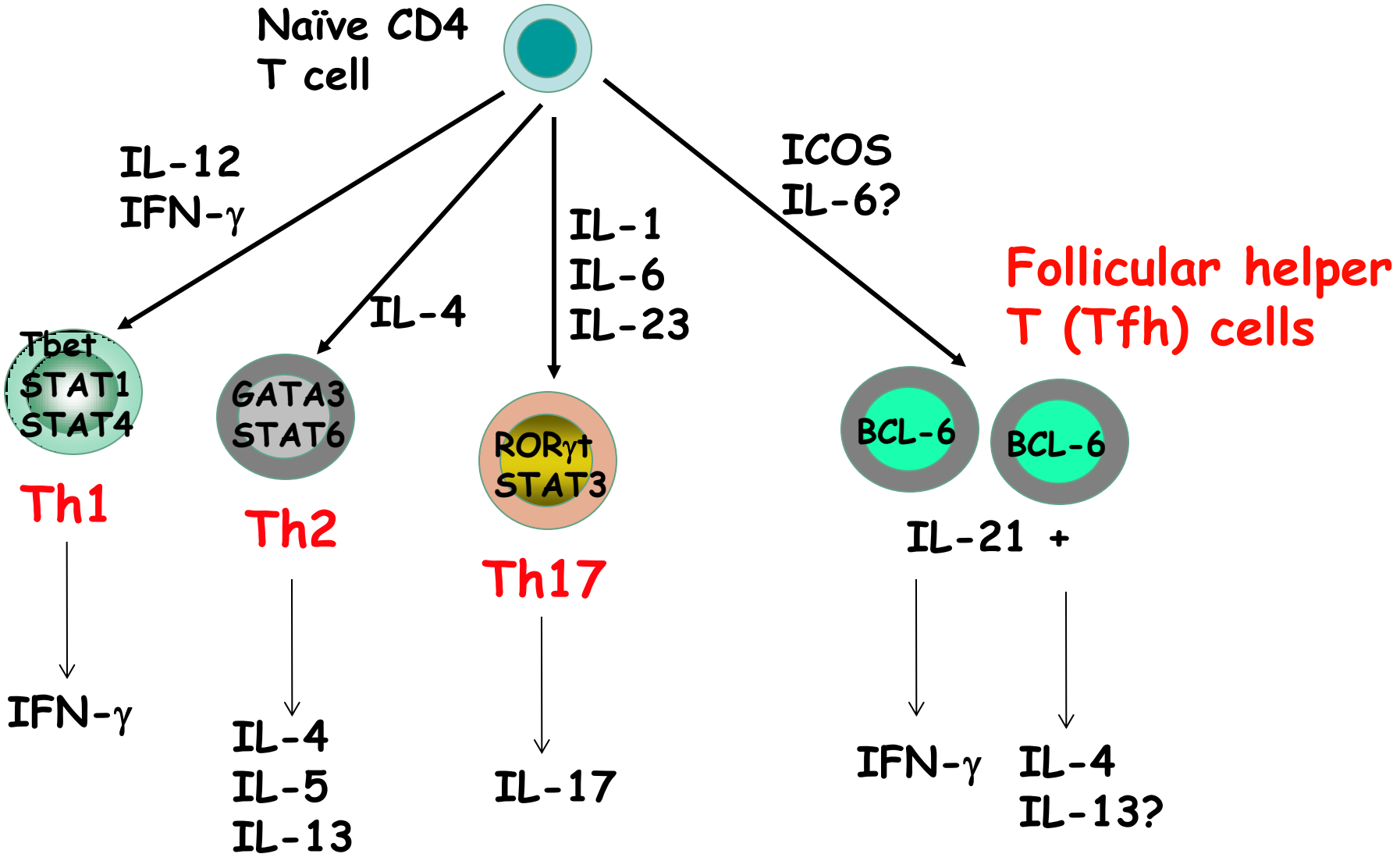
Mechanisms of helper T cell-mediated activation of B lymphocytes



The germinal center reaction

- Some B cells that are activated outside follicles migrate back to form germinal centers, where they undergo isotype switching and affinity maturation, and generate long-lived plasma cells and memory B cells
  - Driven by T cell help (follicular helper T cells)
  - Many of the reactions are dependent on induction of the enzyme **AID** in B cells

TFH cells: a unique helper T cell subset

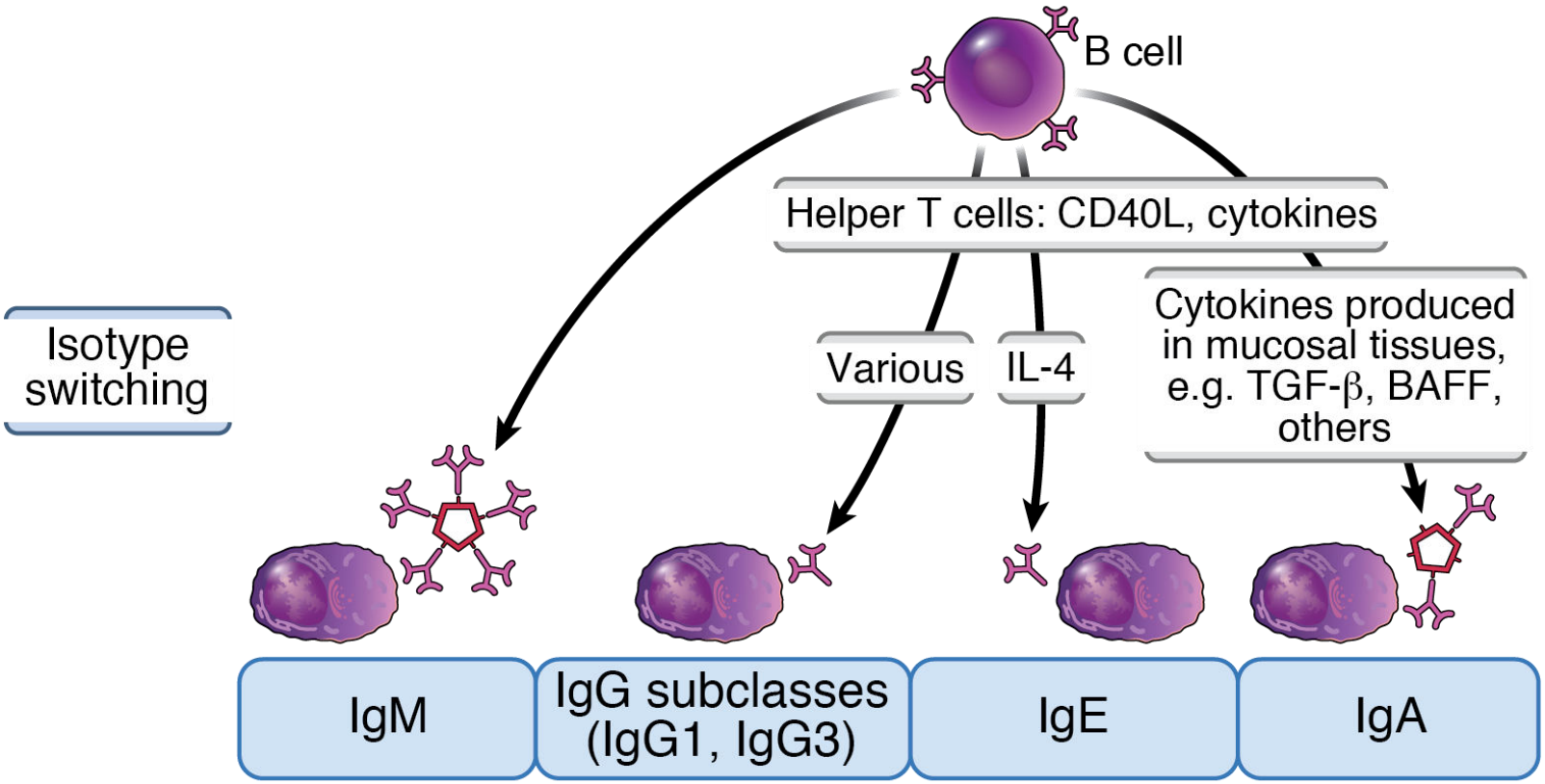


Follicular helper T cells (Tfh)

- Some effector T cells express the chemokine receptor CXCR5, migrate to lymphoid follicles, and help B cells (isotype switching, affinity maturation)

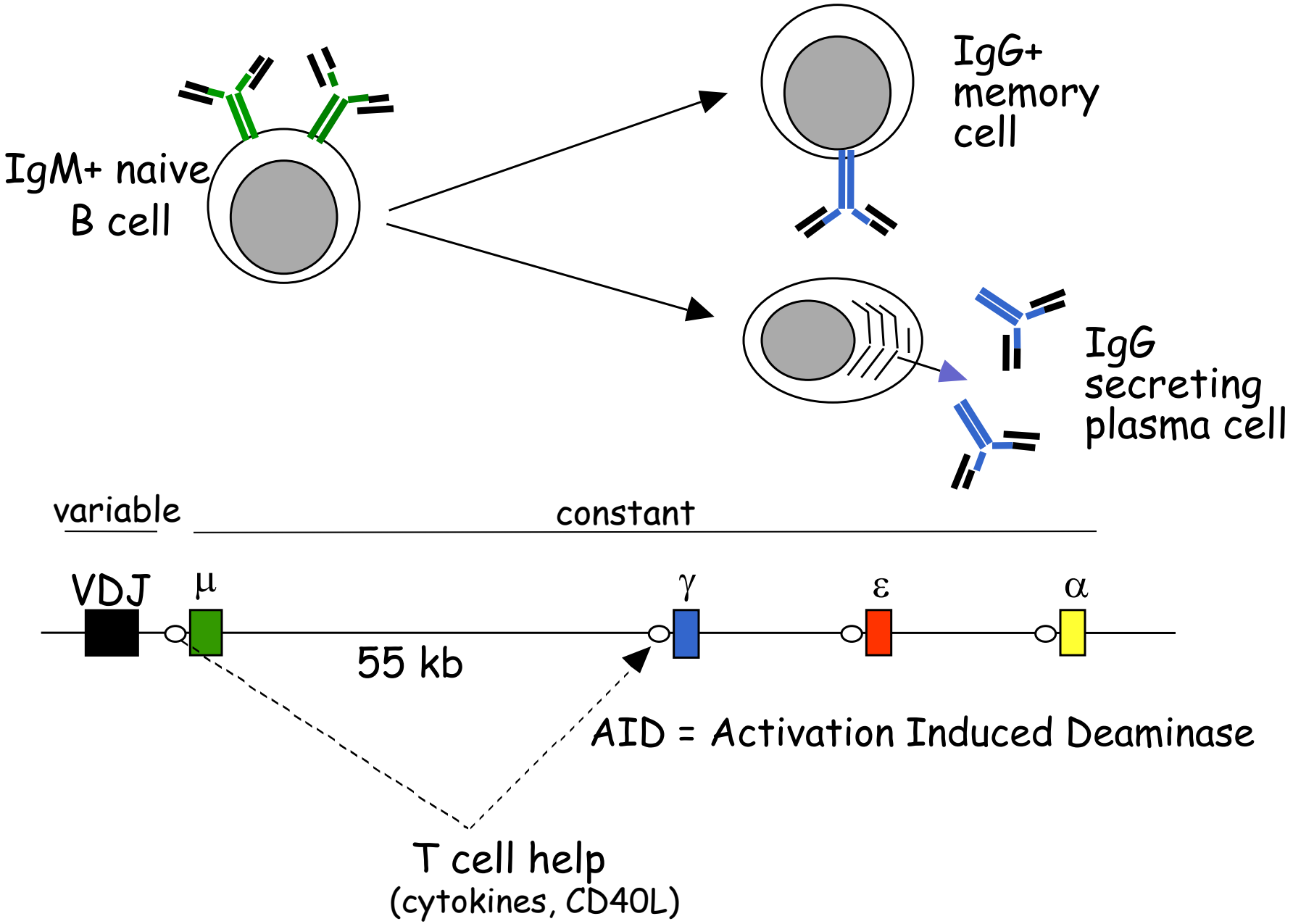
- Characteristics of Tfh:
  - Surface CXCR5, ICOS
  - Transcription factor: BCL-6
  - Cytokines secreted: IL-21 + IL-4 or IFNγ (or IL-17?)

Immunoglobulin (Ig) heavy chain isotype (class) switching



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)

Ig Heavy chain class (isotype) switching

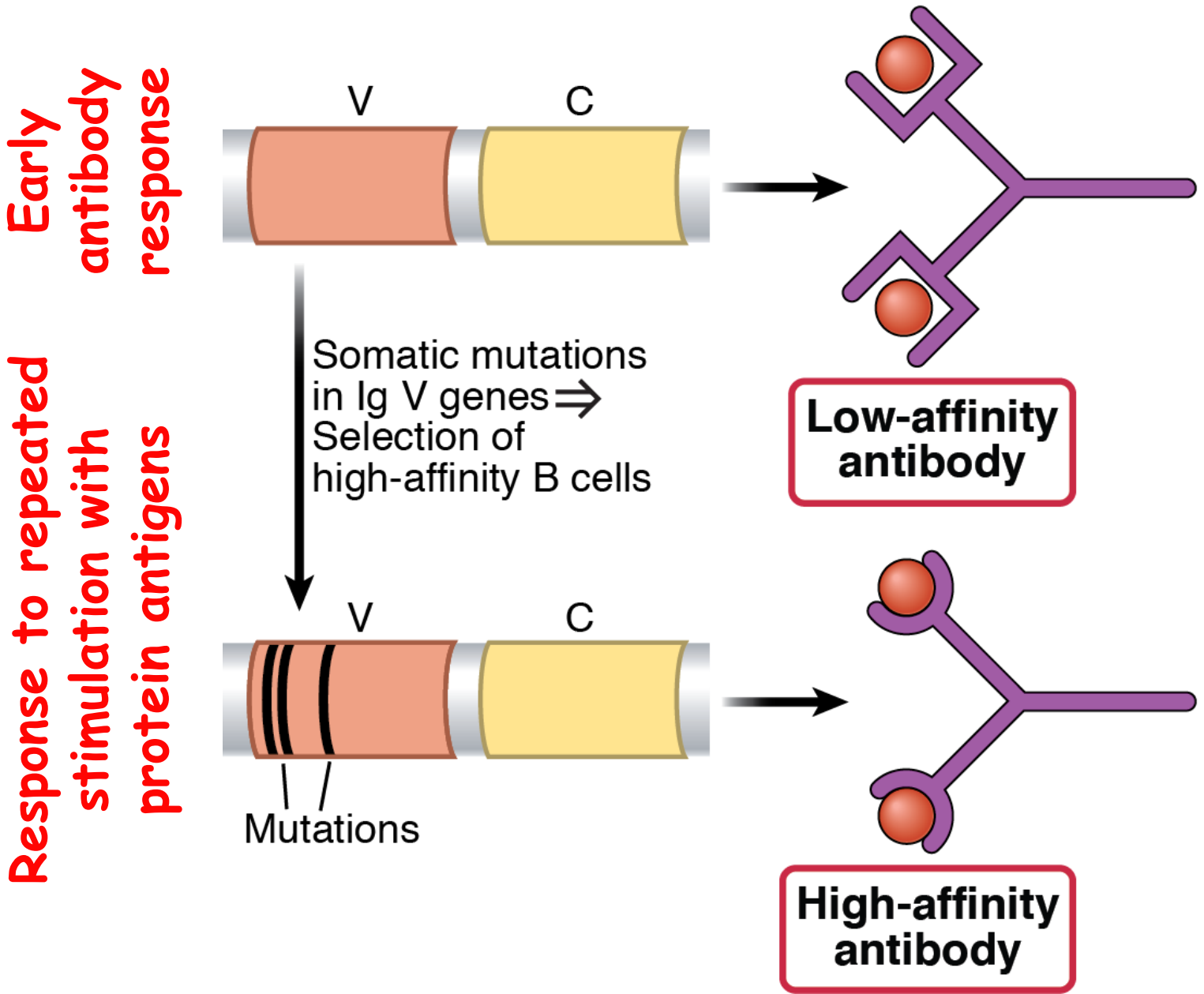


Activation-induced deaminase (AID)

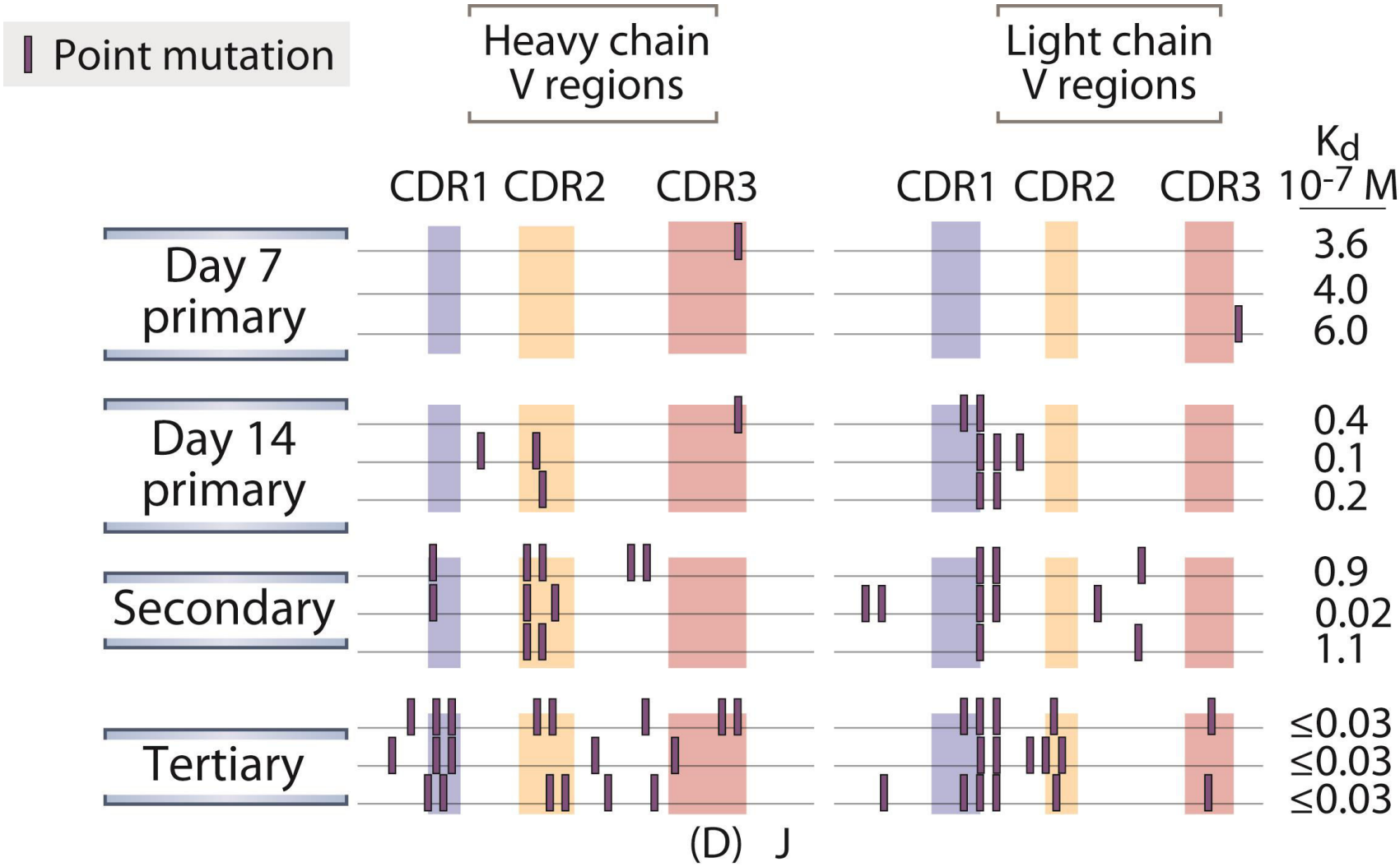
- Enzyme induced in B cells by Tfh signals (mainly via CD40)

- Role in isotype switching: switch regions are rich in AGCT sequences, sites of double-stranded DNA breaks; repair leads to recombination of different switch regions

Affinity maturation of antibodies



Affinity maturation of antibodies

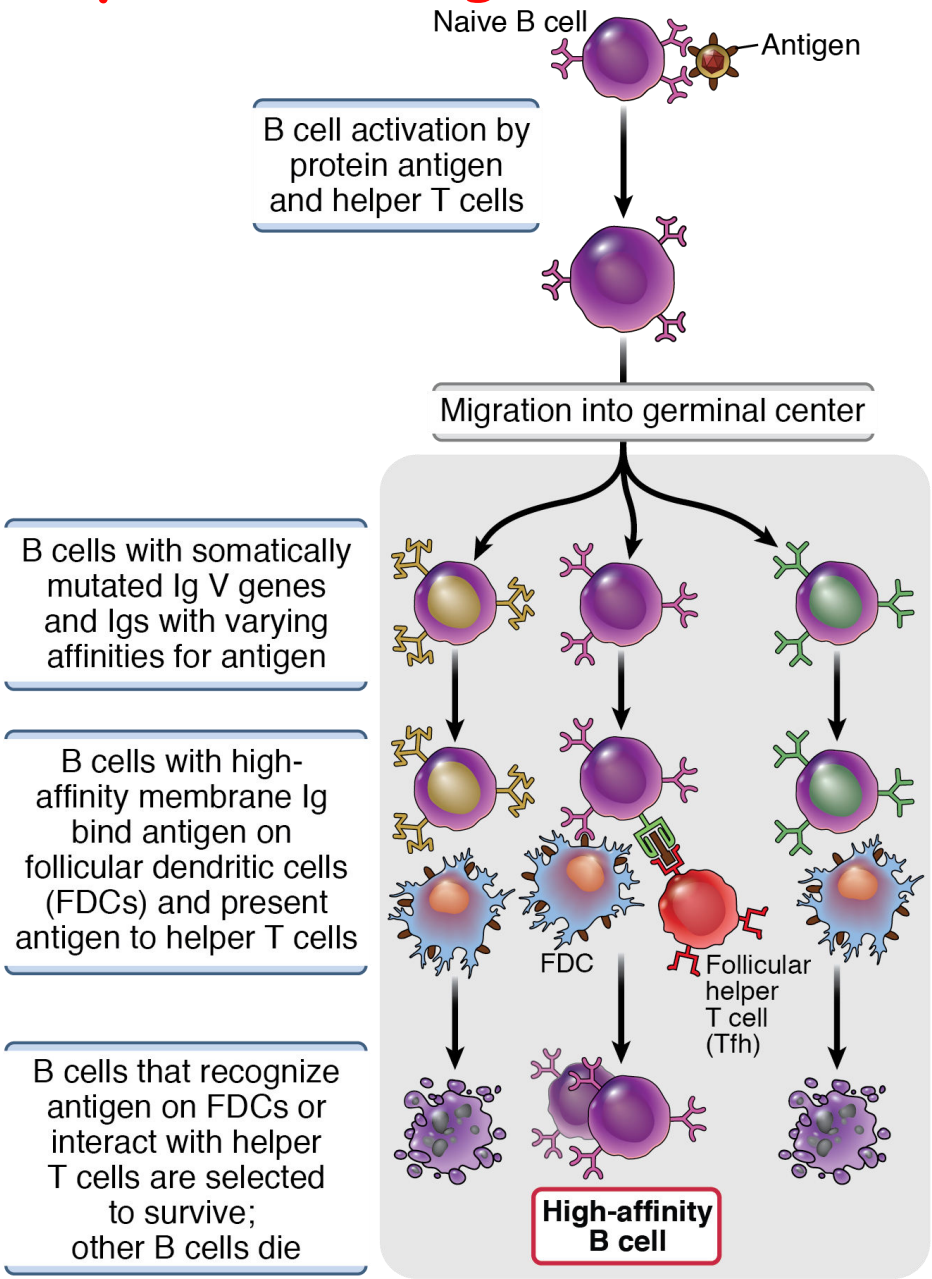


Activation-induced deaminase (AID)

- Enzyme induced in B cells by Tfh signals (mainly via CD40)

- Role in affinity maturation: V region sequences are hotspots for AID-induced mutations; selection increases the frequency of CDR mutations that result in high affinity

"Darwinian" selection of the "fittest" high-affinity B cells in germinal centers



Plasma cells

- Following immunization, serum antibody is detectable for a long time but there are no plasma cells in lymph nodes or spleen
  - Who is making the antibody and where?

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- Plasma cells generated during GC reaction migrate to bone marrow (and mucosal tissues) and survive for years, producing antibody
  - Much of circulating IgG is produced by long-lived plasma cells, provides initial protection

The germinal center reaction

- Site of development of sophisticated antibody responses
  - Isotype switching, affinity maturation, long-lived plasma cells, memory B cells
  - Driven by follicular helper T cells (assays for blood Tfh cells in humans?)
- Need to maximize the reaction for development of effective vaccines
- Does dysregulation of the GC reaction contribute to autoimmune diseases?
  - Strong autoantibody responses
  - Generation of self-reactive B cells?

Therapeutic strategies targeting antibody producing cells

- IVIg (does it act on B cells?)
- B cell depletion: anti-CD20 antibody
- BAFF antagonists
- Anti-CD40, CD40L (trials)
- Depletion of plasma cells: bortezomib (proteasome inhibitor)
- Plasmapheresis (in severe cases of autoimmunity)