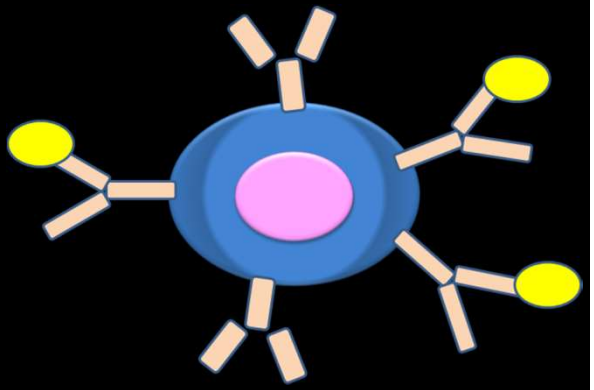
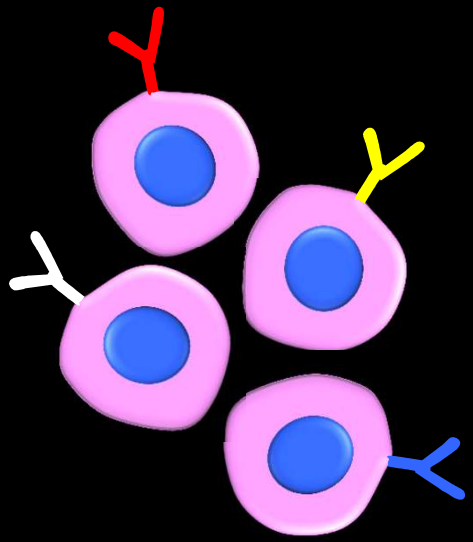


B-Cell Tolerance



PROF. ANAND PRAKASH

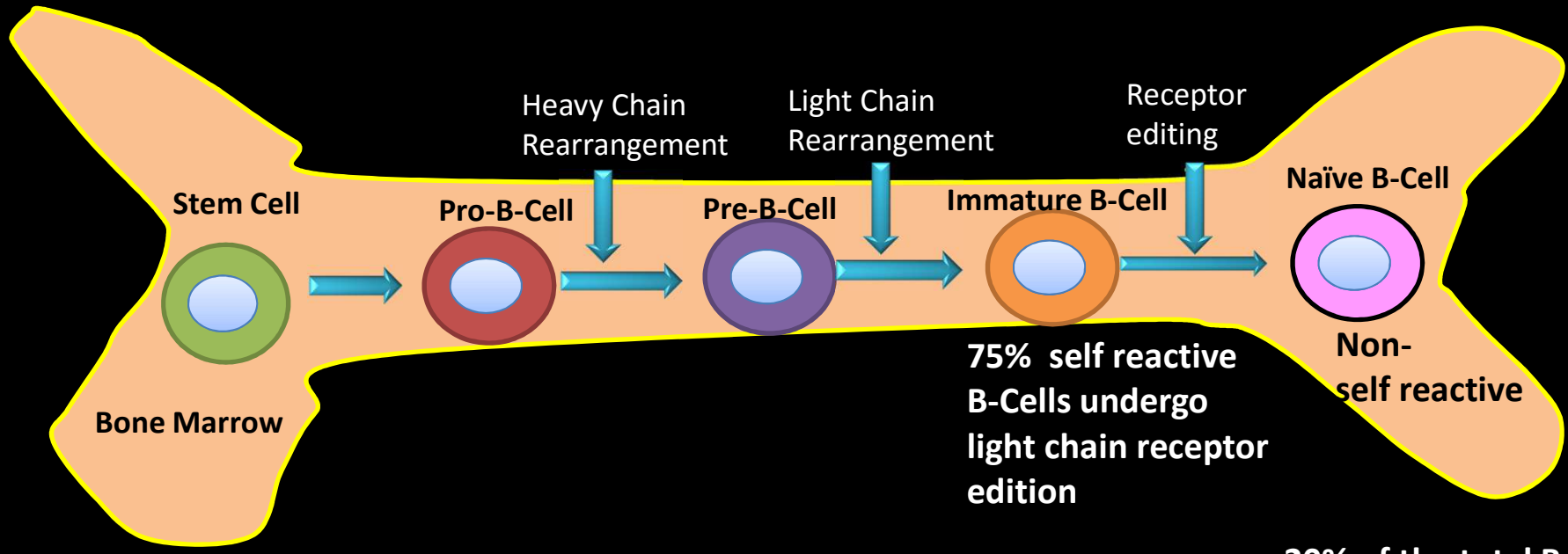
Department of Biotechnology

Mahatma Gandhi Central University

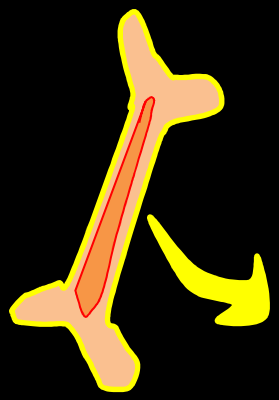
Motihari

Bihar

BONE MARROW IS THE PRIMARY LYMPHOID ORGAN WHERE THE B-CELLS ORIGINATE AND MATURE



20% of the total B-Cells going out of bone marrow are self reactive

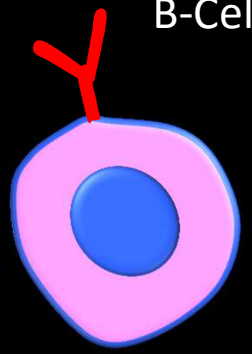


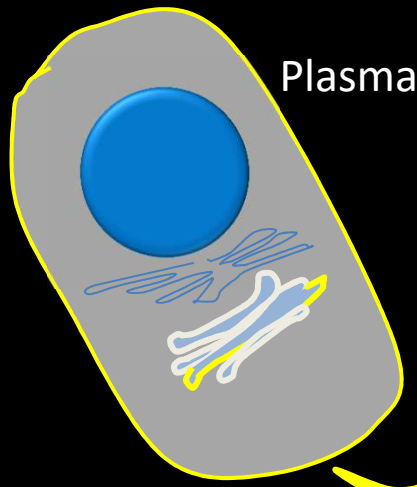
The B-Cells originate and mature in the Bone marrow (primary lymphoid organ)

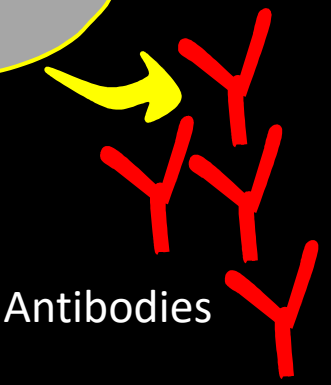
B-Cells after their maturation in the bone marrow move to spleen and lymph nodes (secondary lymphoid organs)

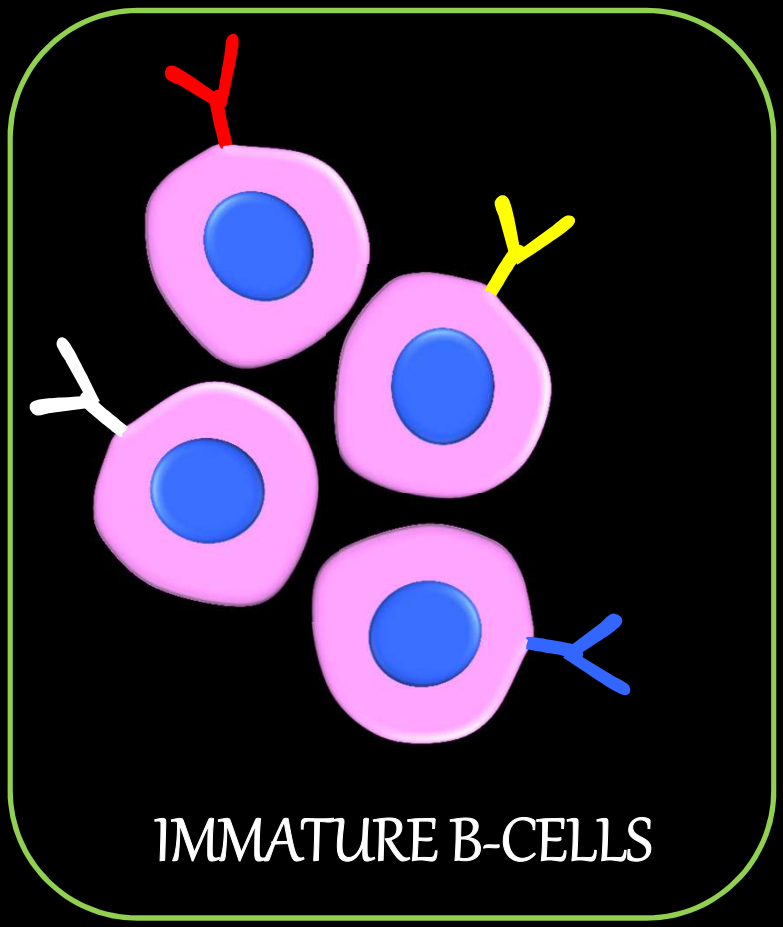
Overthere they encounter with specific antigens to get activated

Once activated the particular clone of B-Cell differentiates into plasma cell and proliferates









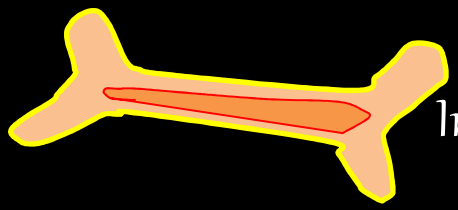
IMMATURE B-CELLS

Immature B-Cells are formed in the bear a vast repertoire of receptors having antigenic specificity to any antigen

A few of these B-Cells may be bearing auto-reactive or self antigen binding receptors

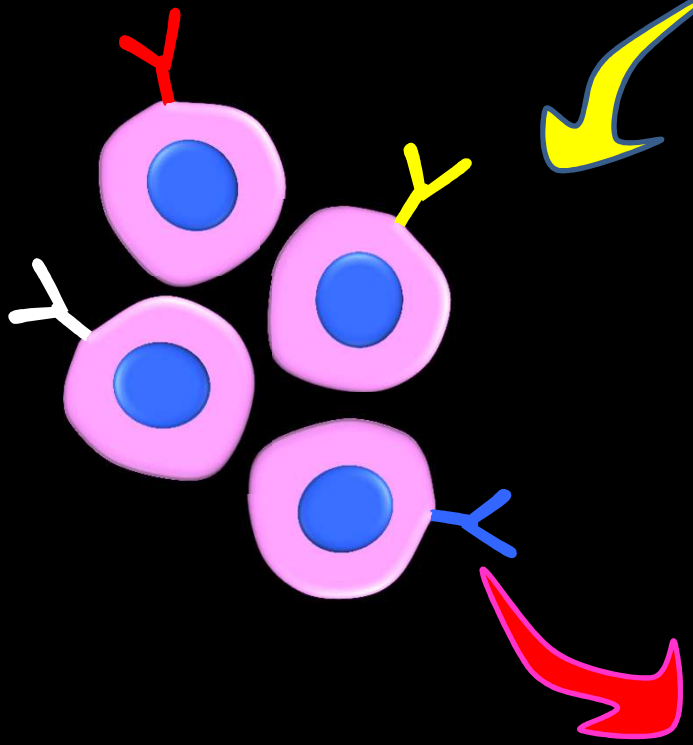
These self antigens recognising B-cells may harm the body cells and organs

These if activated will produce auto-reactive antibodies and can result in auto immune diseases



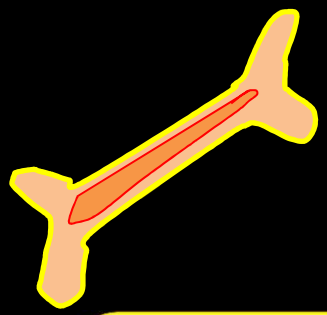
In Bone Marrow

Immature B-Cells having receptors both for self and non-self antigens undergo screening process



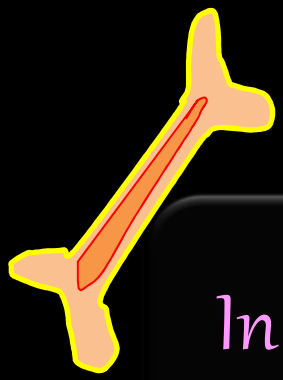
NEGATIVE SELECTION

During the screening process the B-cells bearing self reactive receptors are either inactivated or filtered out.



Exppression of self antigens bone marrow and it's source ?

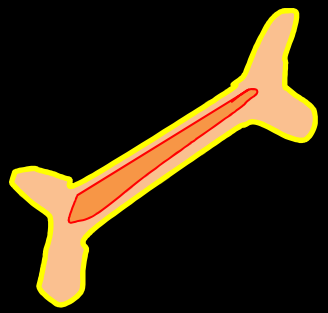
What is the mechanism operative in the bone marrow that facilitates recognition of auto reactive B-Cells ?



SOURCE OF SELF ANTIGENS

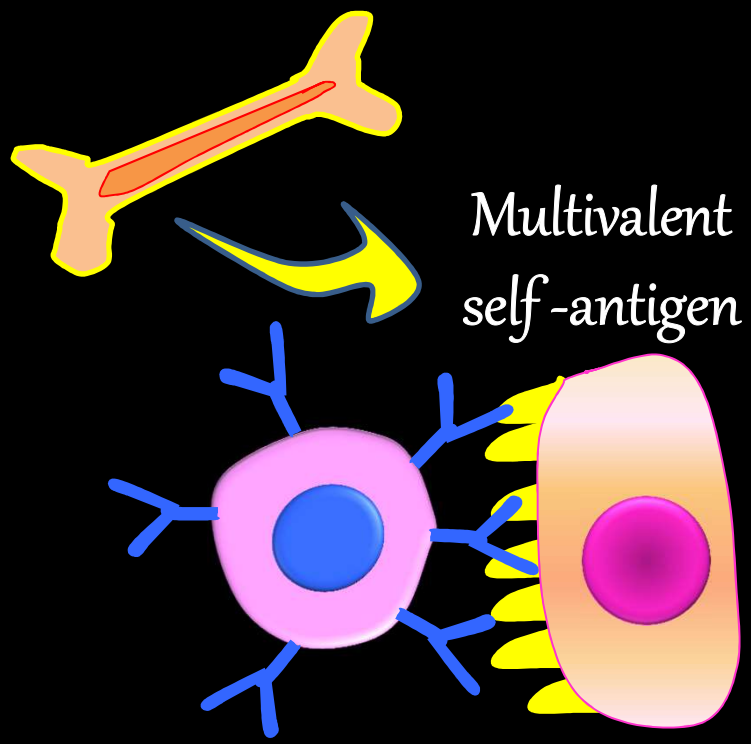
In Bone Marrow self antigens are expressed and are encountered by developing B-Cells

- Stromal cells
- Hematopoietic cells
- Antigens circulating in the blood plasma

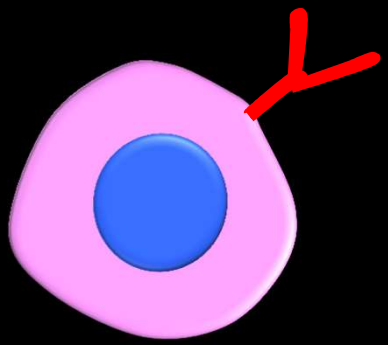


The recognition of Self reactive B-Cells depends on the affinity of BCR for the antigens expressed in the bone marrow

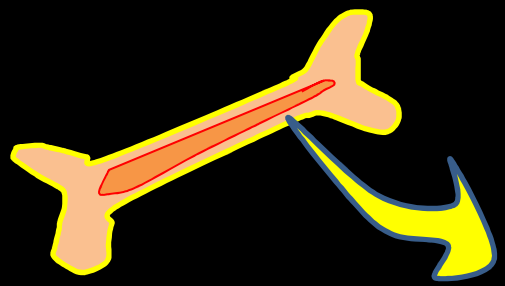
The antigens expressed in bone marrow are multivalent.



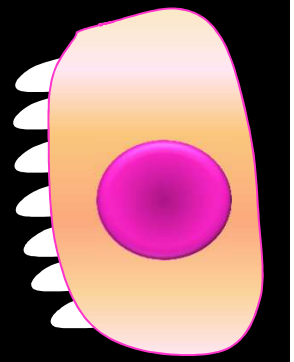
These multivalent antigens can efficiently bind the BCRs expressed on immature B-Cells.



Immature B-Cell



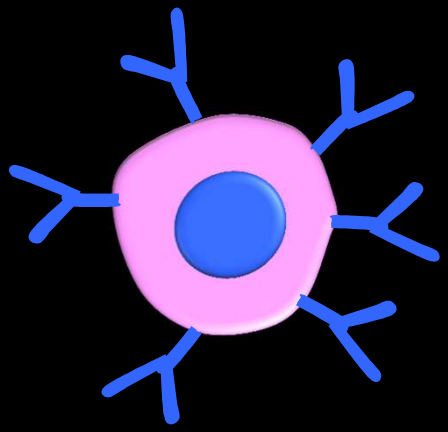
Multivalent self-antigen



If there is No Interaction

If there is Weak Interaction

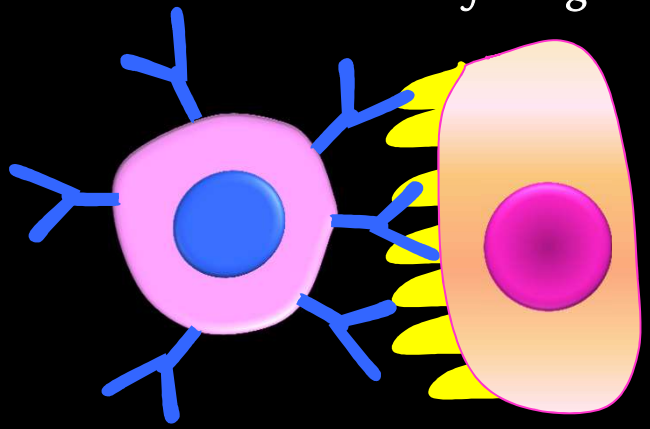
Such B-Cells escape to the secondary lymphoid organs



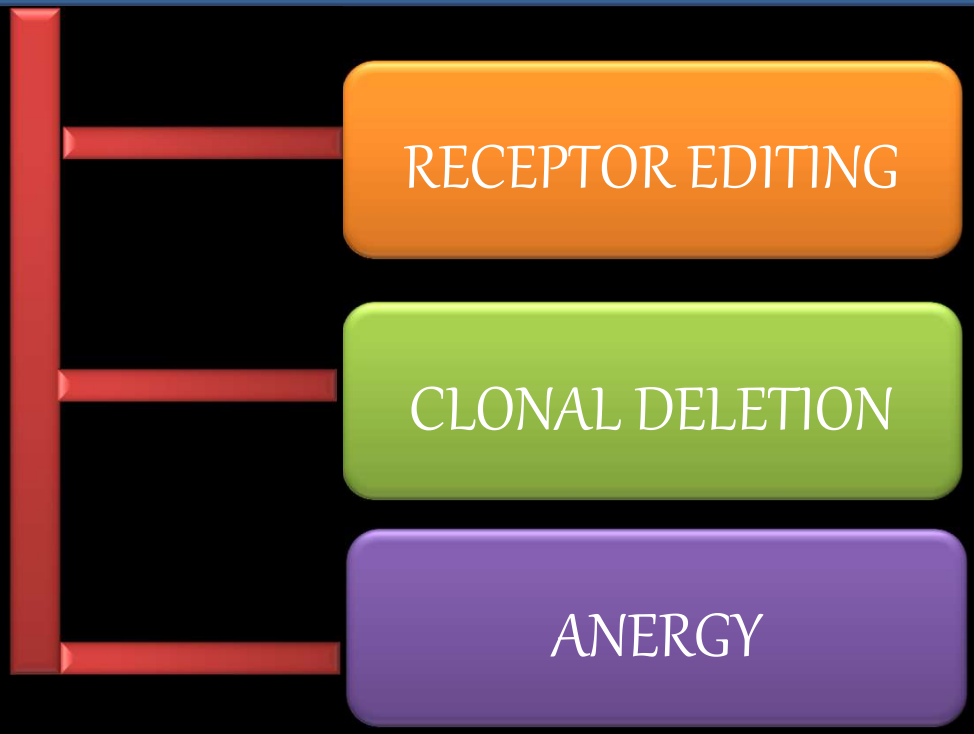
If the Immature B-Cells interact very strongly with the multivalent antigen

Multivalent self-antigen

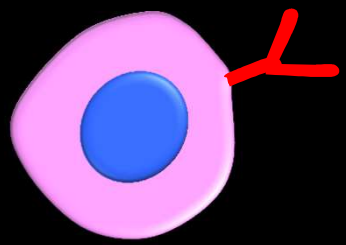
Such B-Cells stay back in bone marrow and their development is arrested



Three mechanisms are operative in the bone marrow towards CENTRAL B-CELL TOLERANCE



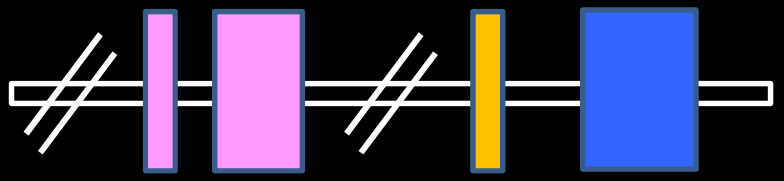
RECEPTOR EDITING



Antigen Receptor of the immature self reactive cell is modified.

Immature B-Cells can rearrange their immunoglobulin genes.

Light chain gene locus



RECEPTOR EDITING IN B- CELLS

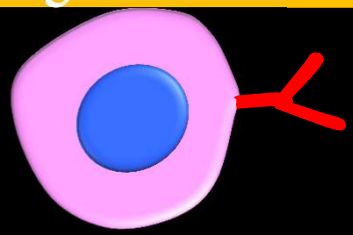
- Immature B cells encounter multivalent self-antigens in bone marrow.
- Self reactive one's revert back to the small pre-B stage, rearrange kappa and lambda light chain genes, and new B cells are generated.
- These newly formed B cells have a new BCR with novel light chains which may not self reactive any more.
- Such B cells exit from bone marrow to the peripheral lymphatic tissue as mature B cells.

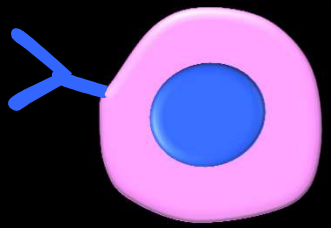
RECEPTOR EDITING

OLD light chain is replaced by NEW light chain

Self Reactive

Non Self Reactive





APOPTOSIS

CLONAL DELETION

Non-reactive B-Cell matures and migrates to secondary lymphoid organs

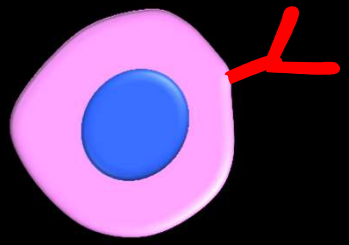
ANERGY

Monovalent Antigens mostly in form of soluble proteins are also present in bone marrow

Auto Reactive B-Cell get bond by these monovalent antigens

Anergic B-Cells enter peripheral circulation

PERIPHERAL B-CELL TOLERANCE



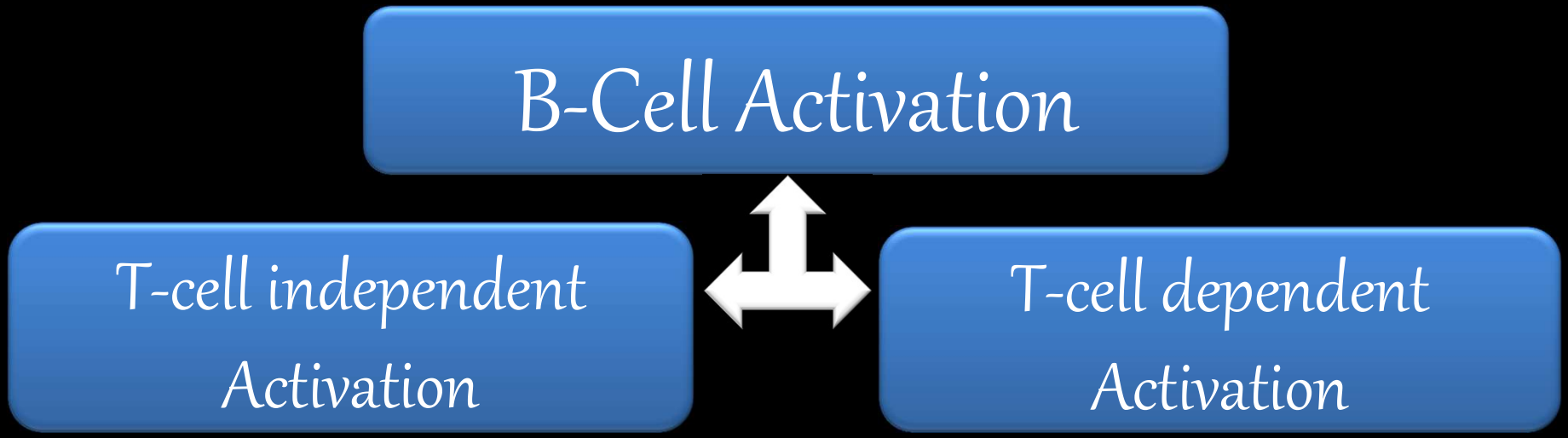
B-Cells are not exposed to all auto antigens in bone marrow.

B-lymphocytes in the secondary lymphoid organs and circulation (periphery) encounter

Tissue specific cell surface antigens antigens

Secreted proteins

When there is infection in the body



This is decided by the type of antigen B-Cell is exposed to...

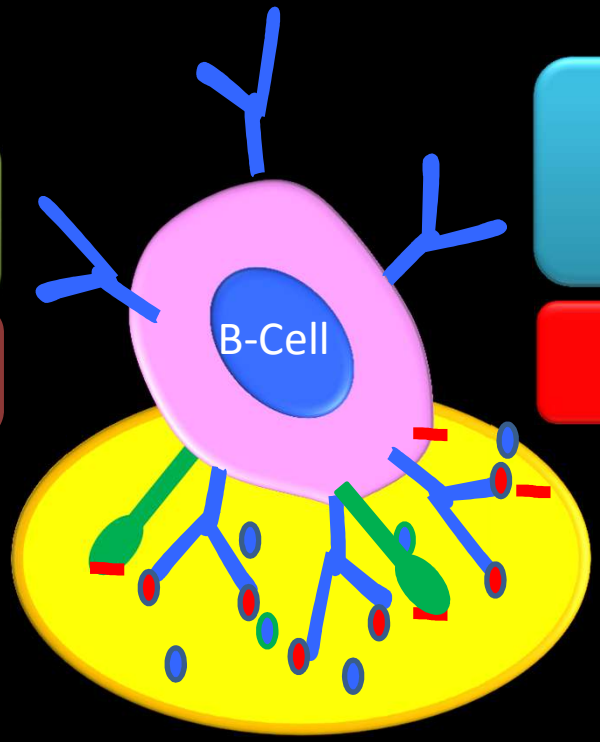
T-CELL INDEPENDENT ACTIVATION

CLUSTERING OF BCRs

SIGNAL 1

RECOGNITION OF DANGER SIGNALS SUCH AS PAMPS

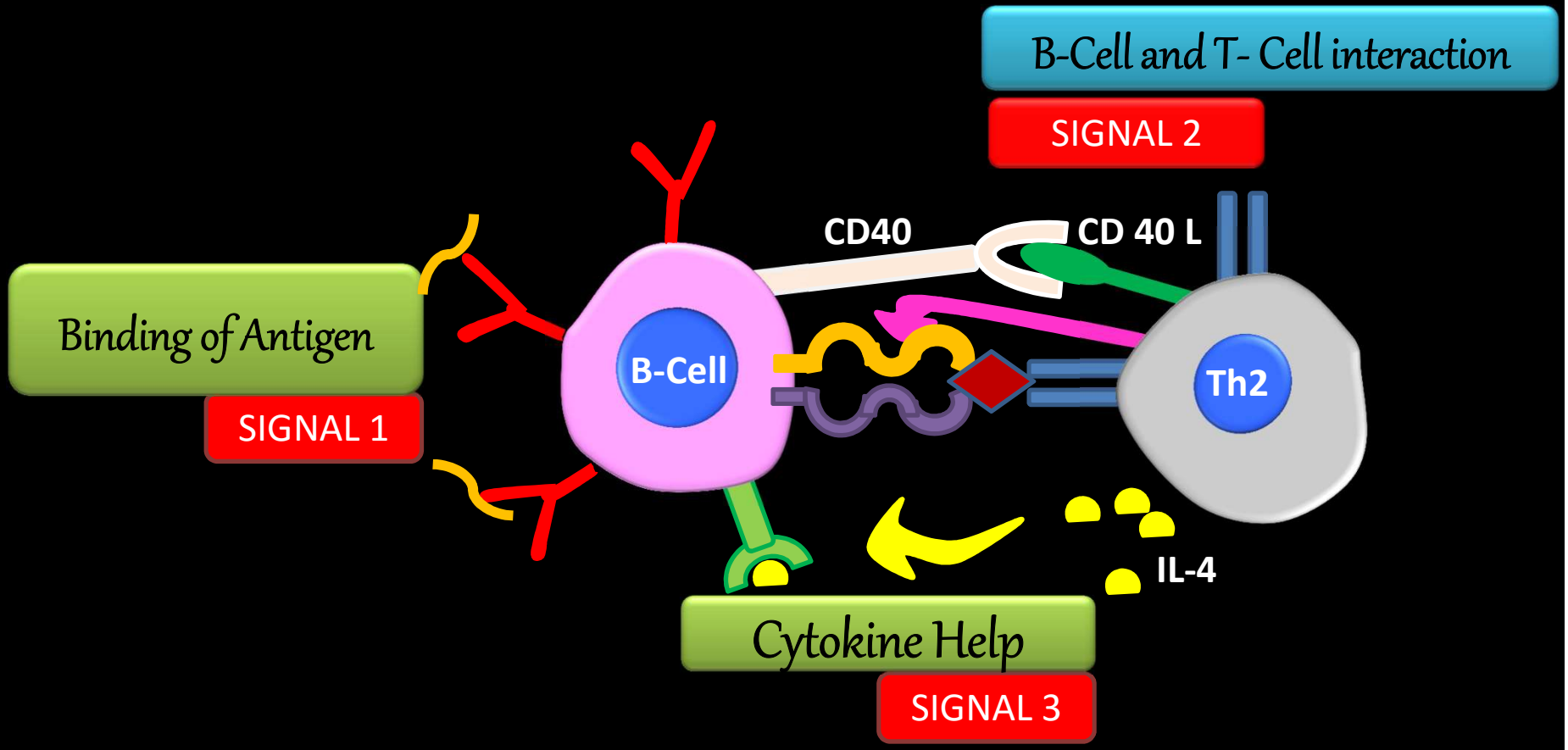
SIGNAL 2



Ti Antigen

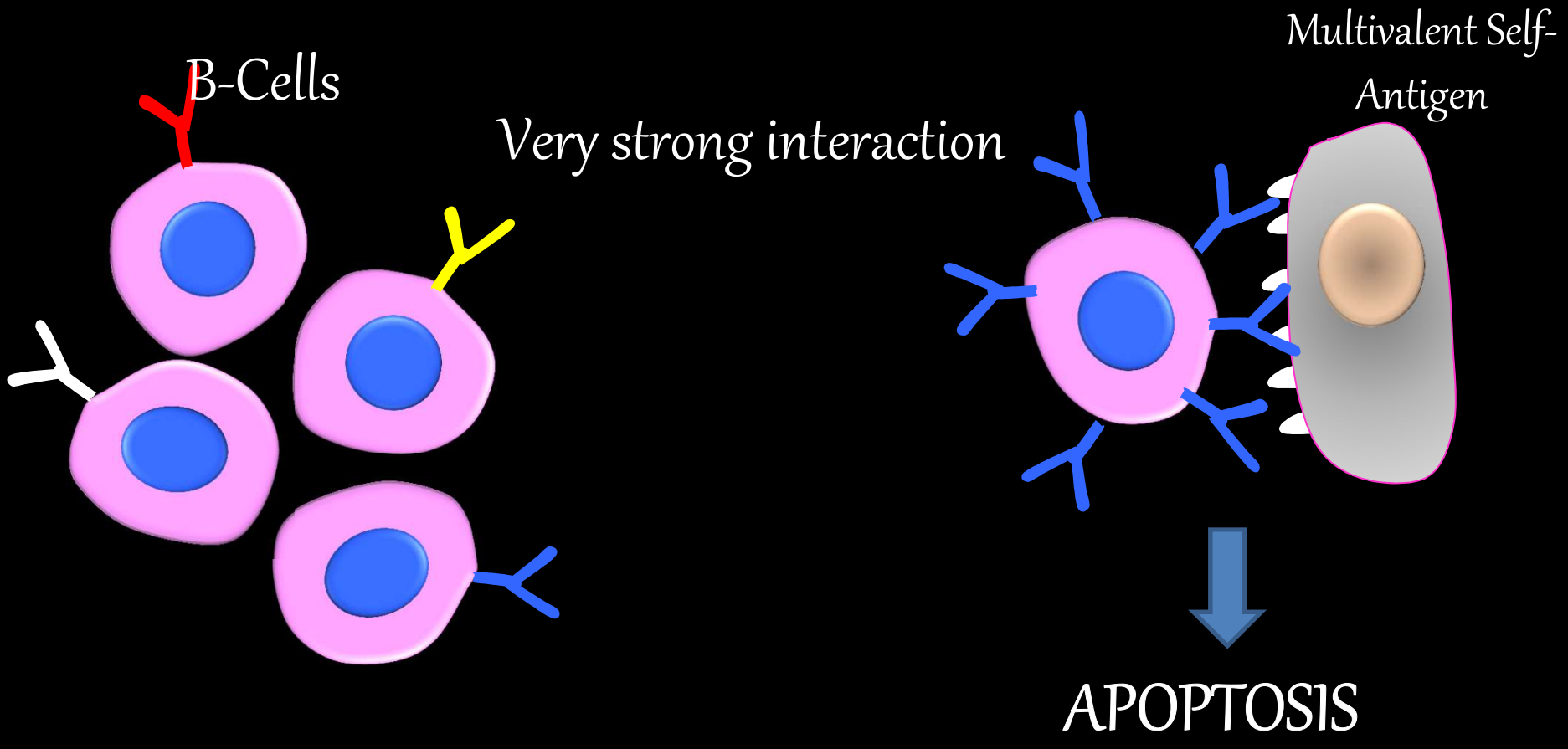
B-CELLS CAN BE ACTIVATED IN A T-CELL INDEPENDENT (Ti) MANNER

T-CELL DEPENDENT ACTIVATION

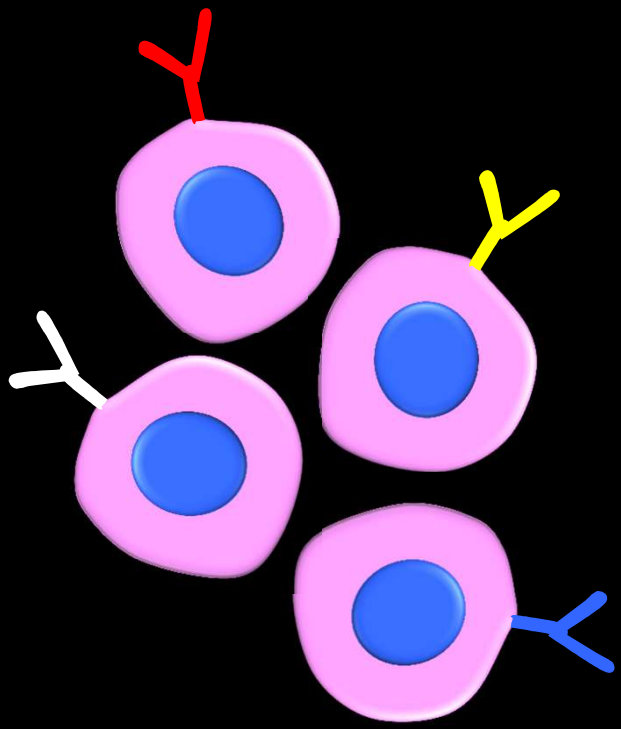


For the B-Cell to get activated require three consecutive signals are required. In absence of any of these signals the B-Cell is not activated

In peripheral Lymphoid organs (Spleen)

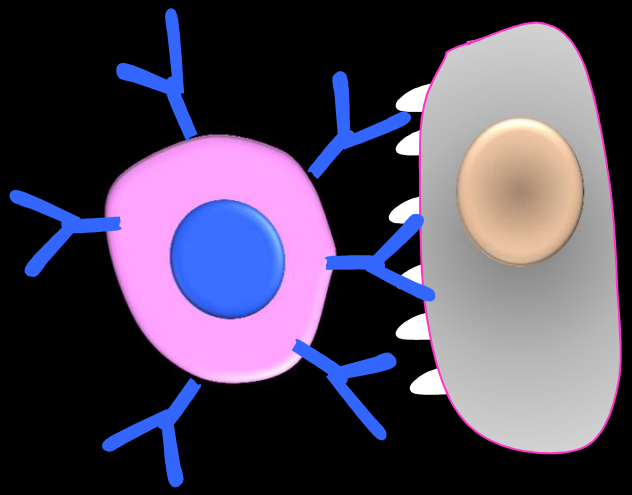


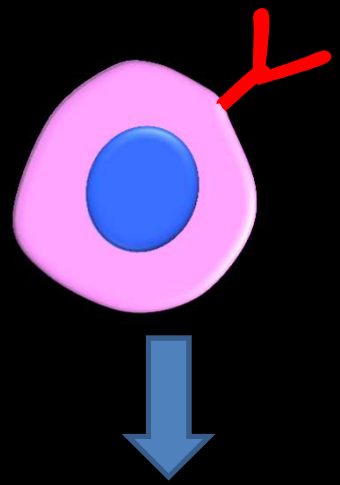
In peripheral Lymphoid organs (Spleen)



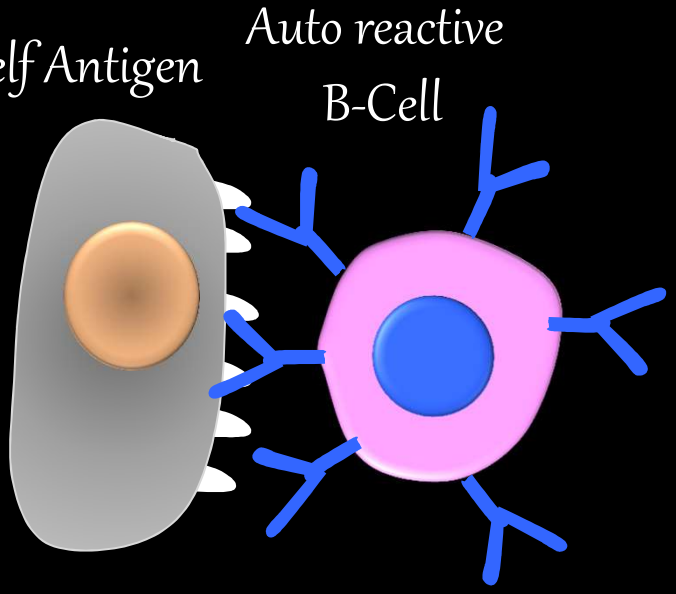
WEAK INTERACTION

NO INTERACTION





SURVIVAL



No Signal 2

B-Cell becomes unresponsive

ANERGY

B-Cells (recognising protein antigens) require T-Cells towards activation

Auto-reactive T-Cells are eliminated by Central Tolerance

Without T-Cell help there is no signal 2 and thus no signal 3

Thank You

To be continued....