# Leukaemia and lymphoma

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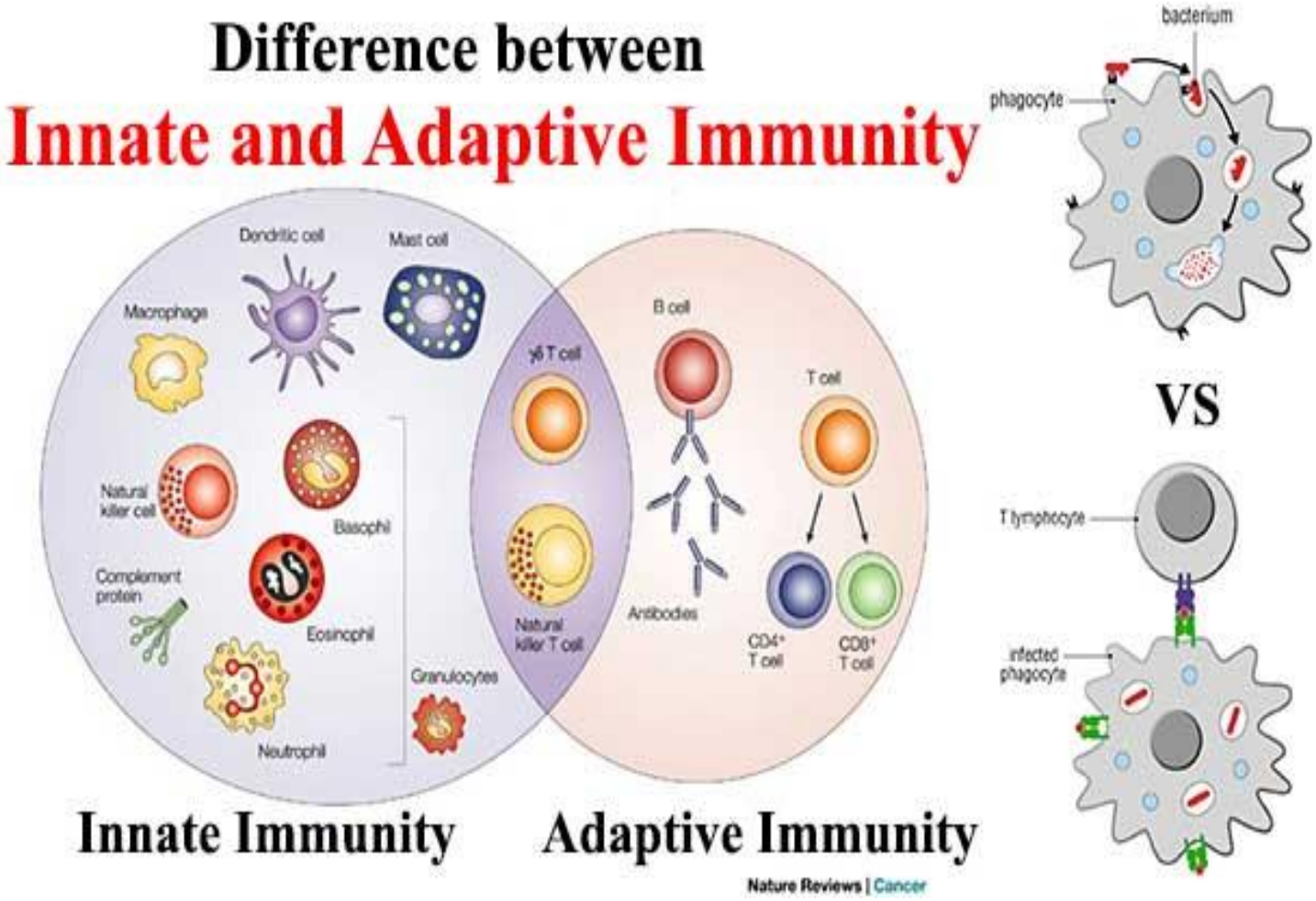
With thanks to Dr Nick Rooney

# Tumour of immune system

# Nature of immunity



# Objectives

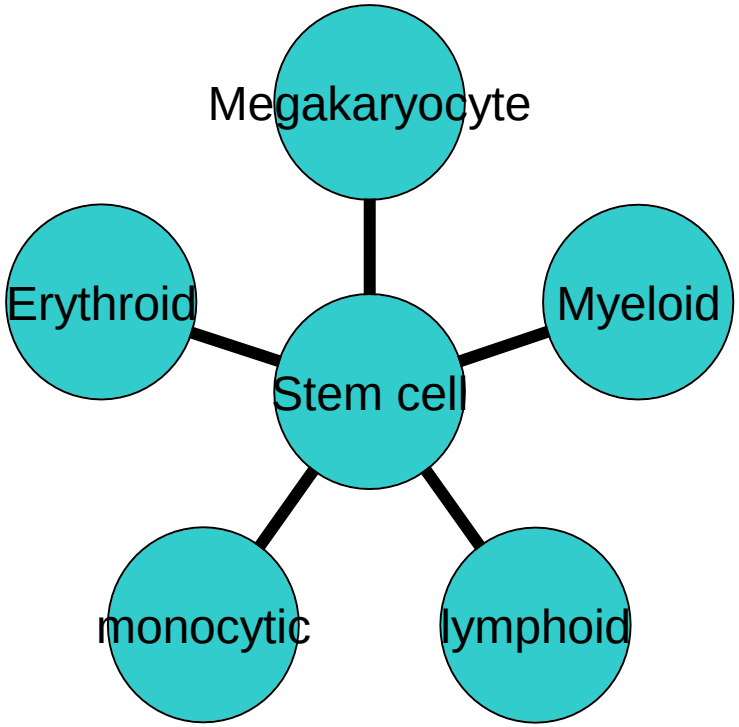
- To understand morphological aspects of immune system
- Relationship between development of lymphoid cells with nature of lymphoma
- Understand principles of lymphoma classification
- Relationship between immunity and lymphoma
- Role of virus and infections

# Immune system

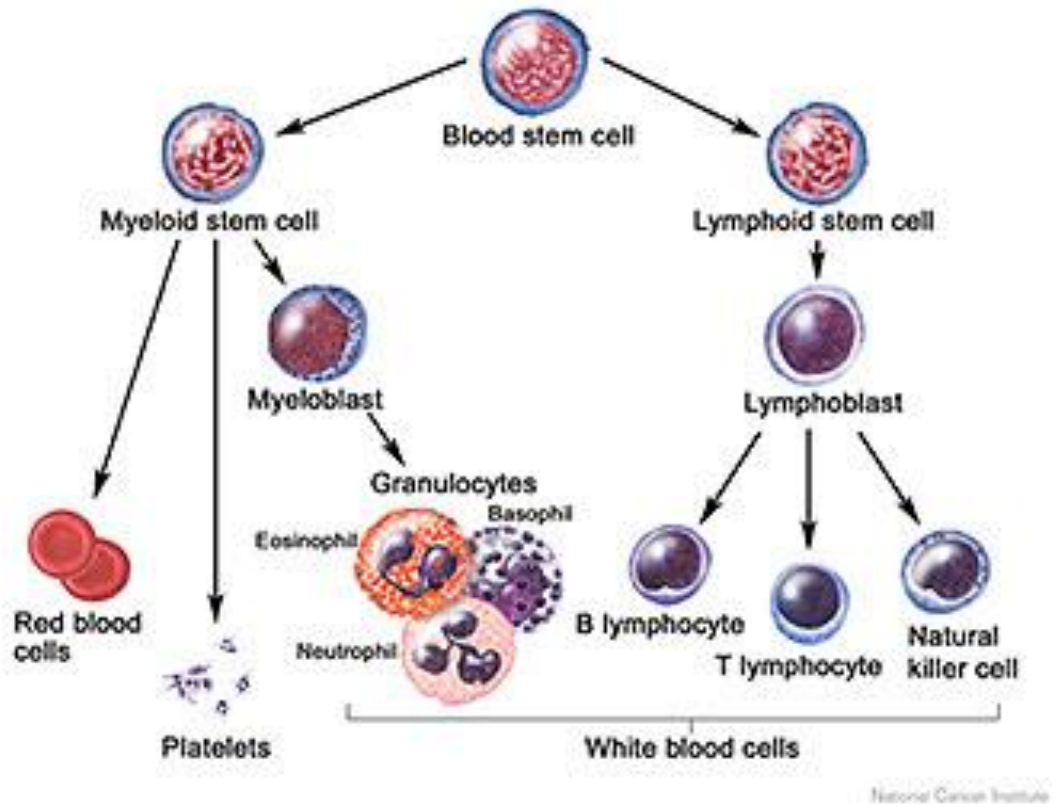
- Primary immune system- Bone marrow and Thymus, where lymphoid precursors are generated.
- Secondary immune system- lymphoid follicle and T zone in lymph nodes, spleen, G I Tract- Where lymphocytes are introduced to antigens
- Tertiary immune system- genital tract, skin- Where lymphocytes respond to antigens

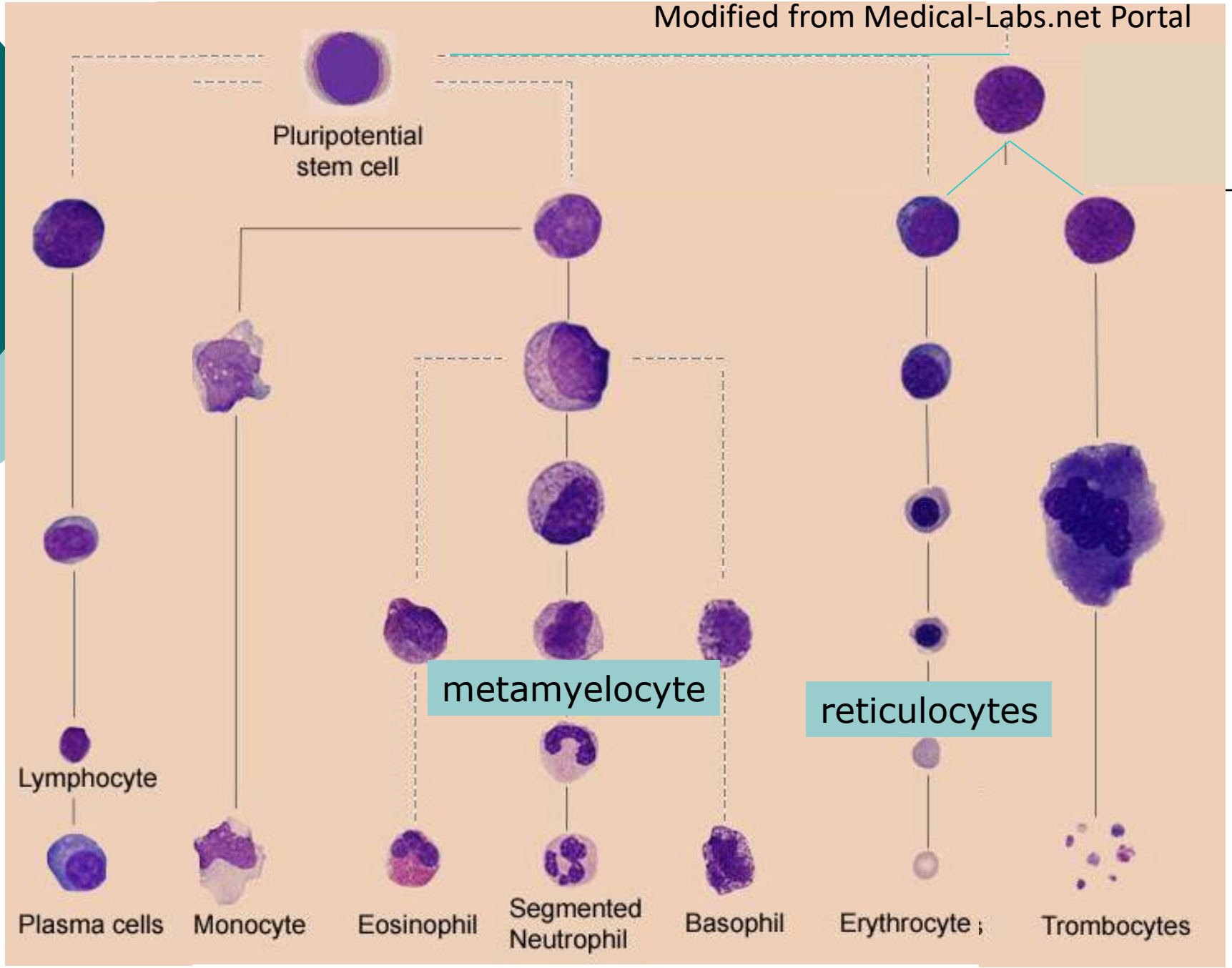
# Bone marrow

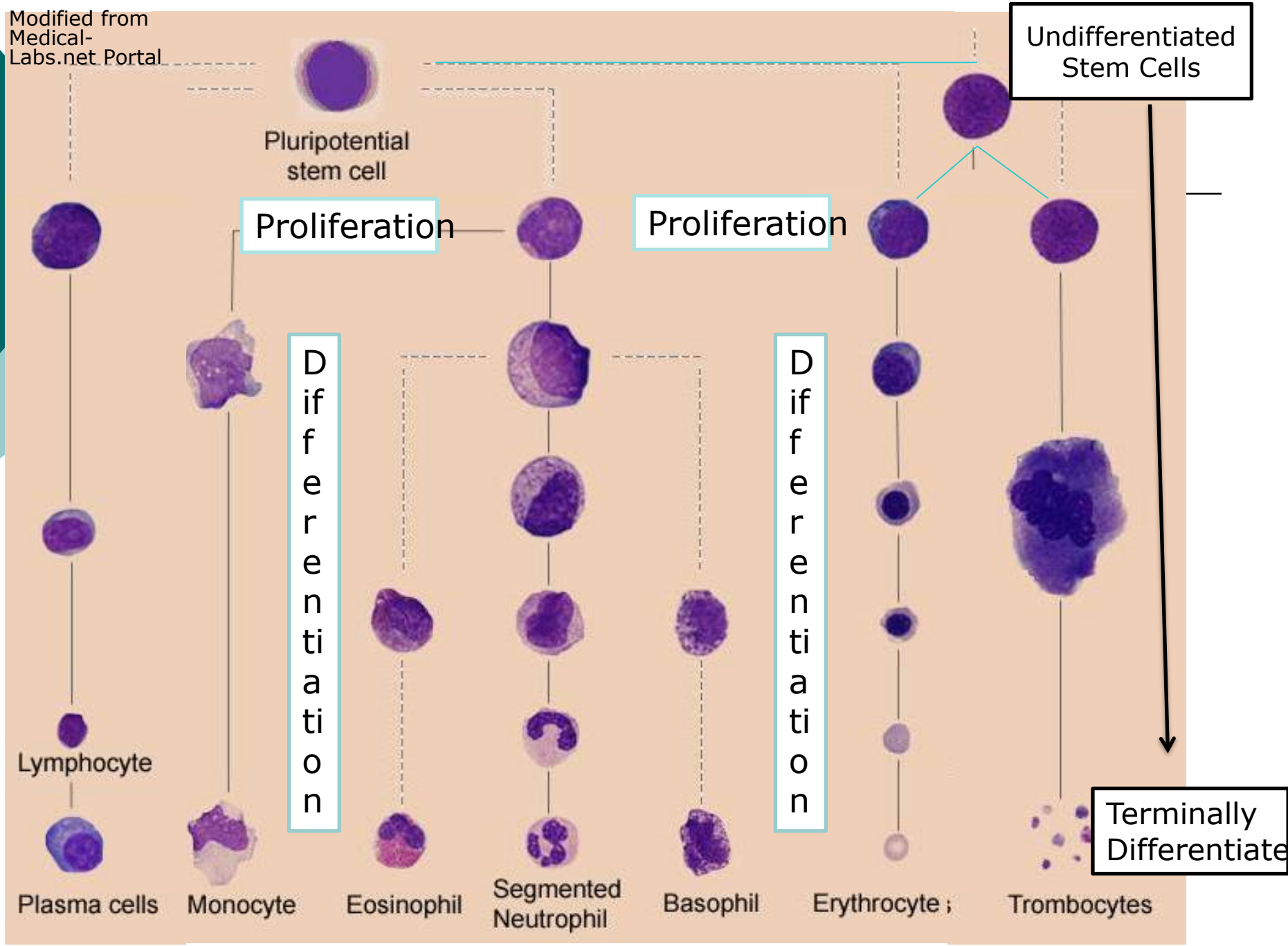
- Stem cell compartment
- Differentiates into erythroid (red blood cell) , myeloid(white blood cell), platelets, histiocytes and lymphoid cells



# Bone marrow


Blood stem cell
Myeloid stem cell
Lymphoid stem cell
Myeloblast
Lymphoblast
Granulocytes
Basophil
Eosinophil
Neutrophil
Red blood cells
Platelets
B lymphocyte
T lymphocyte
Natural killer cell
White blood cells

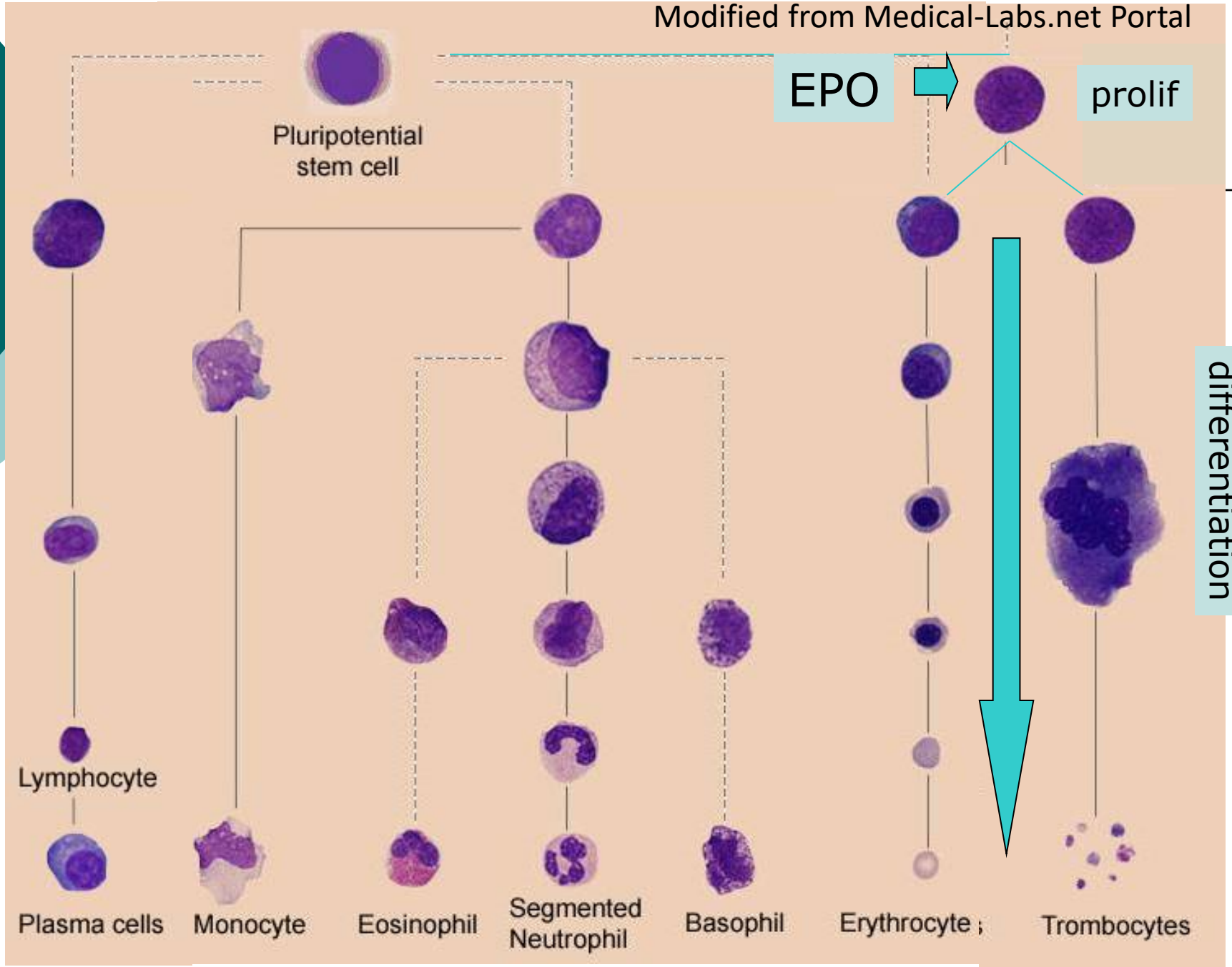

Modified from Medical-Labs.net Portal
Pluripotential stem cell
metamyelocyte
reticulocytes
Lymphocyte
Plasma cells
Monocyte
Eosinophil
Segmented Neutrophil
Basophil
Erythrocyte ;
Trombocytes


Modified from Medical-Labs.net Portal
Undifferentiated Stem Cells
Pluripotential stem cell
Proliferation
Proliferation
Differentiation
Differentiation
Lymphocyte
Plasma cells
Monocyte
Eosinophil
Segmented Neutrophil
Basophil
Erythrocyte ;
Trombocytes
Terminally Differentiate

# What happens to the patients platelets in iron deficiency anaemia?

A it goes up?

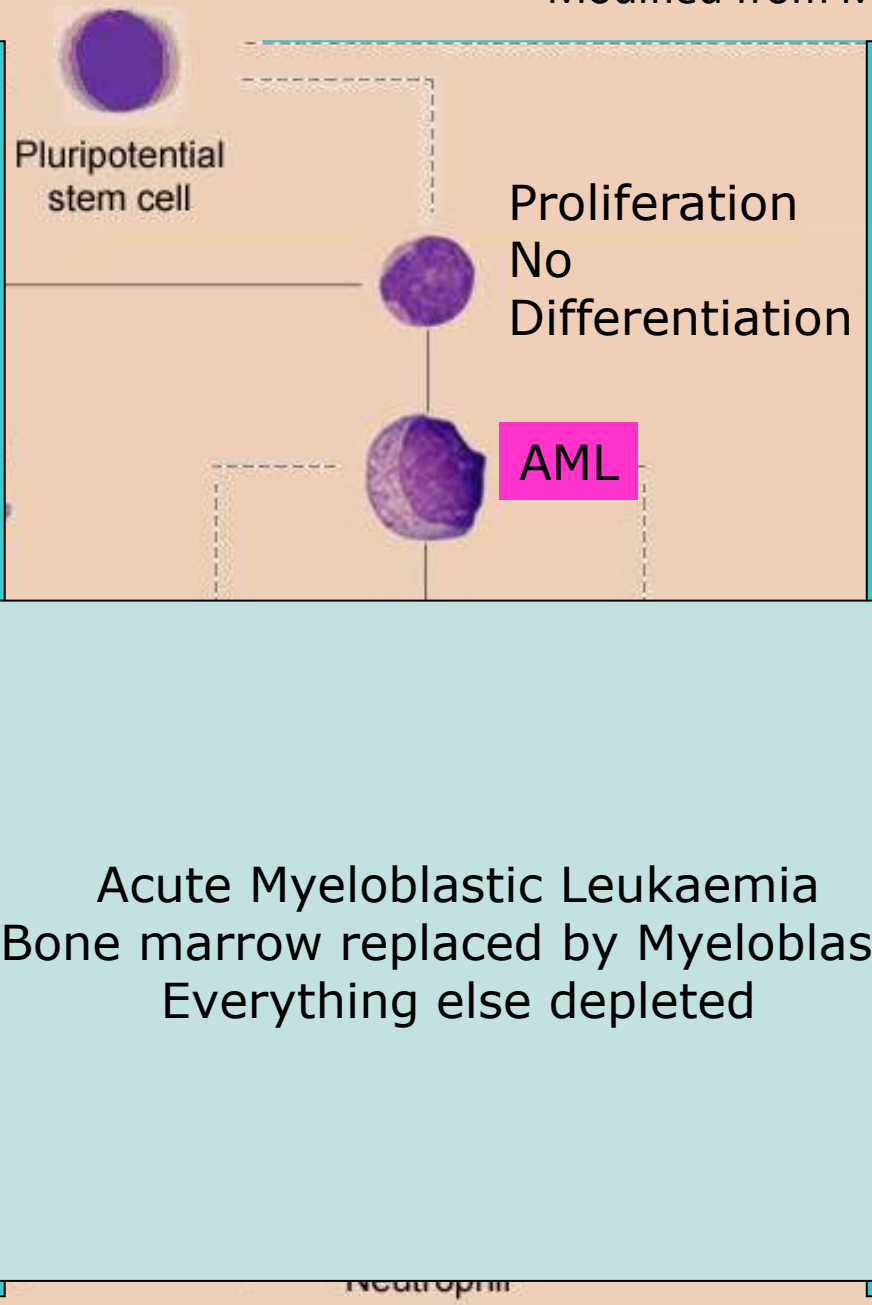
B it goes down?


Modified from Medical-Labs.net Portal
EPO
prolif
Pluripotential stem cell
differentiation
Lymphocyte
Plasma cells
Monocyte
Eosinophil
Segmented Neutrophil
Basophil
Erythrocyte ;
Trombocytes

In acute Myeloid Leukaemia the following cells are found in the blood in increased numbers

a) neutrophils
b) lymphoblasts
c) myeloblasts
d) metamyelocytes
e) erythroblasts

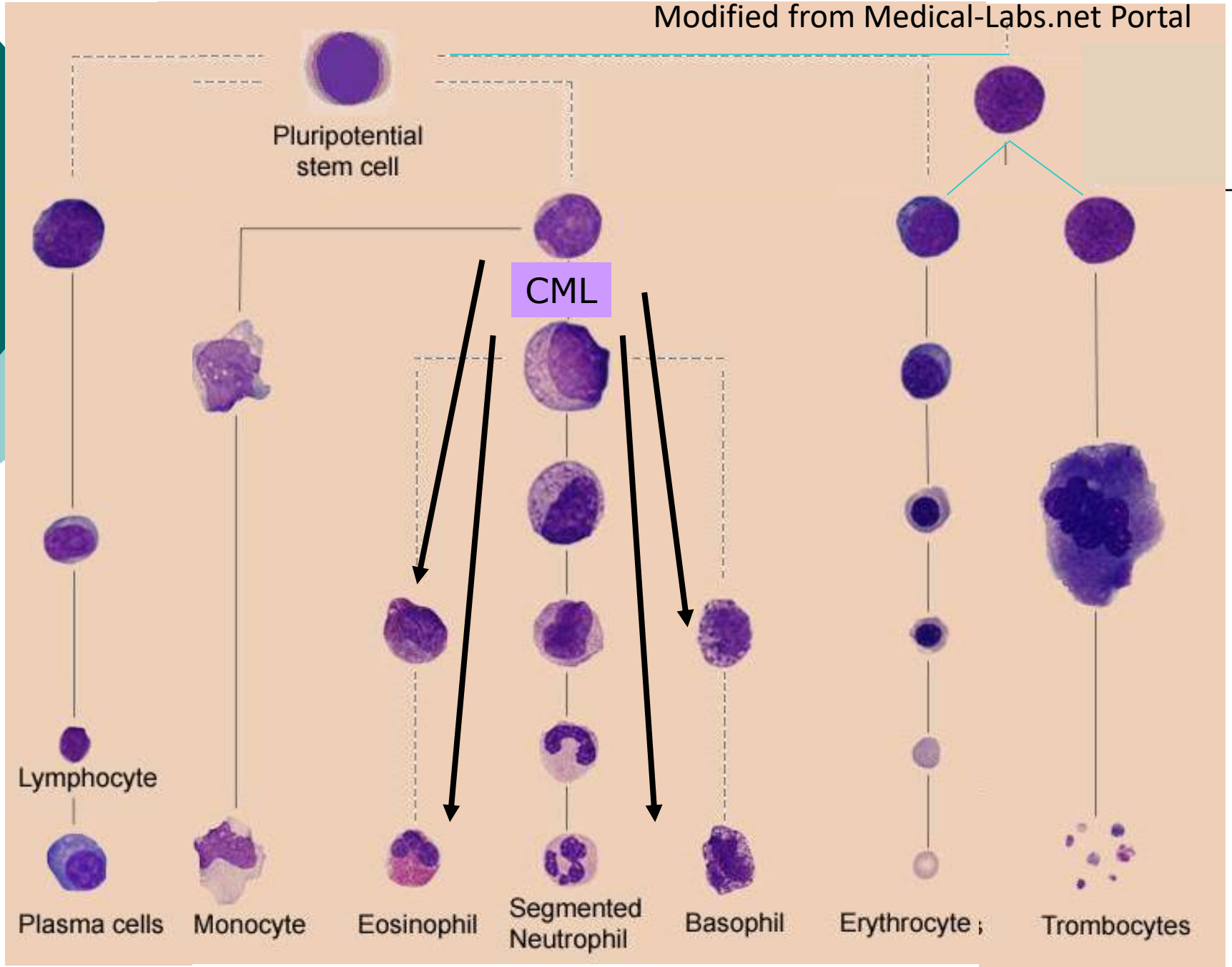
Modified from Medical-Labs.net Portal

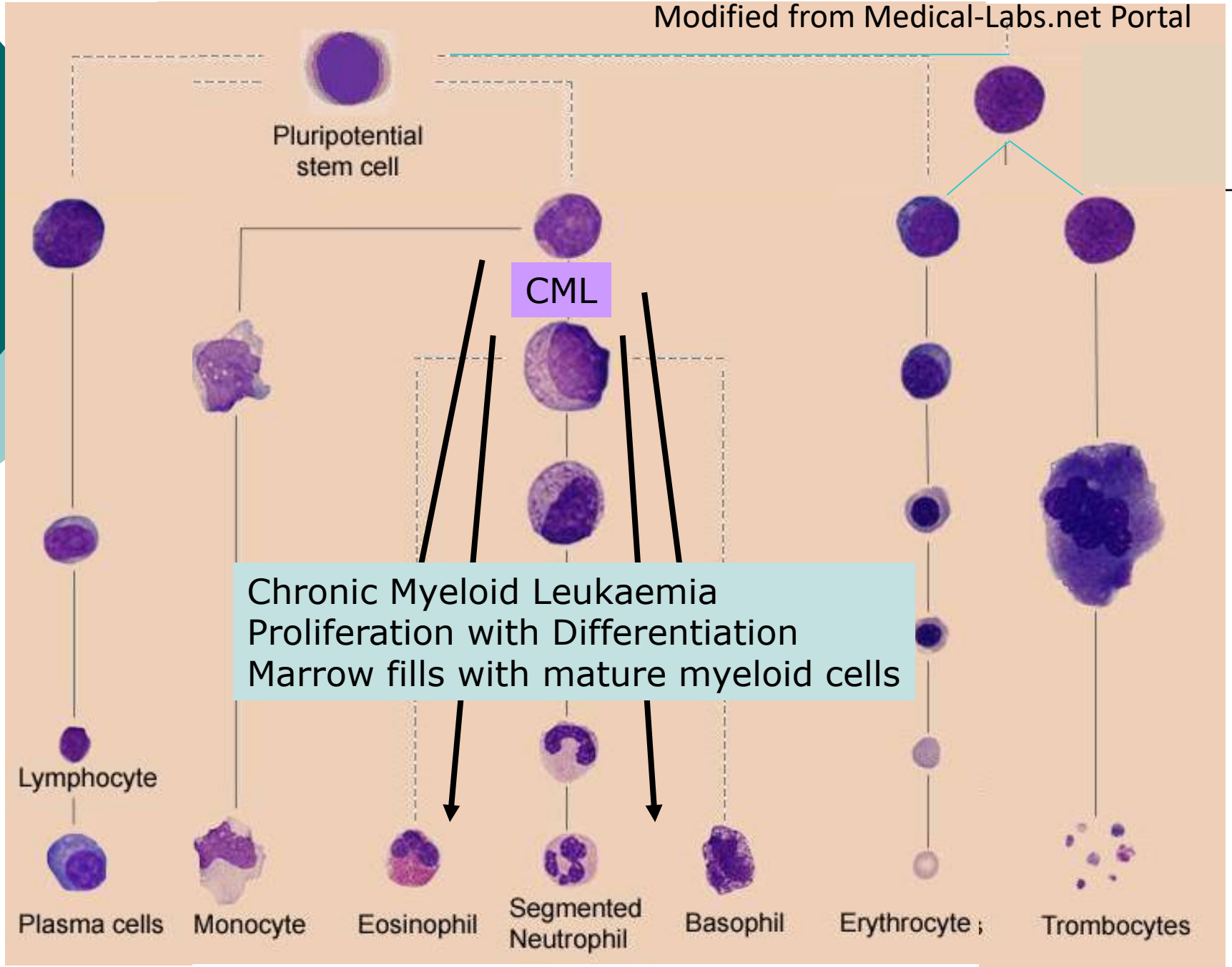


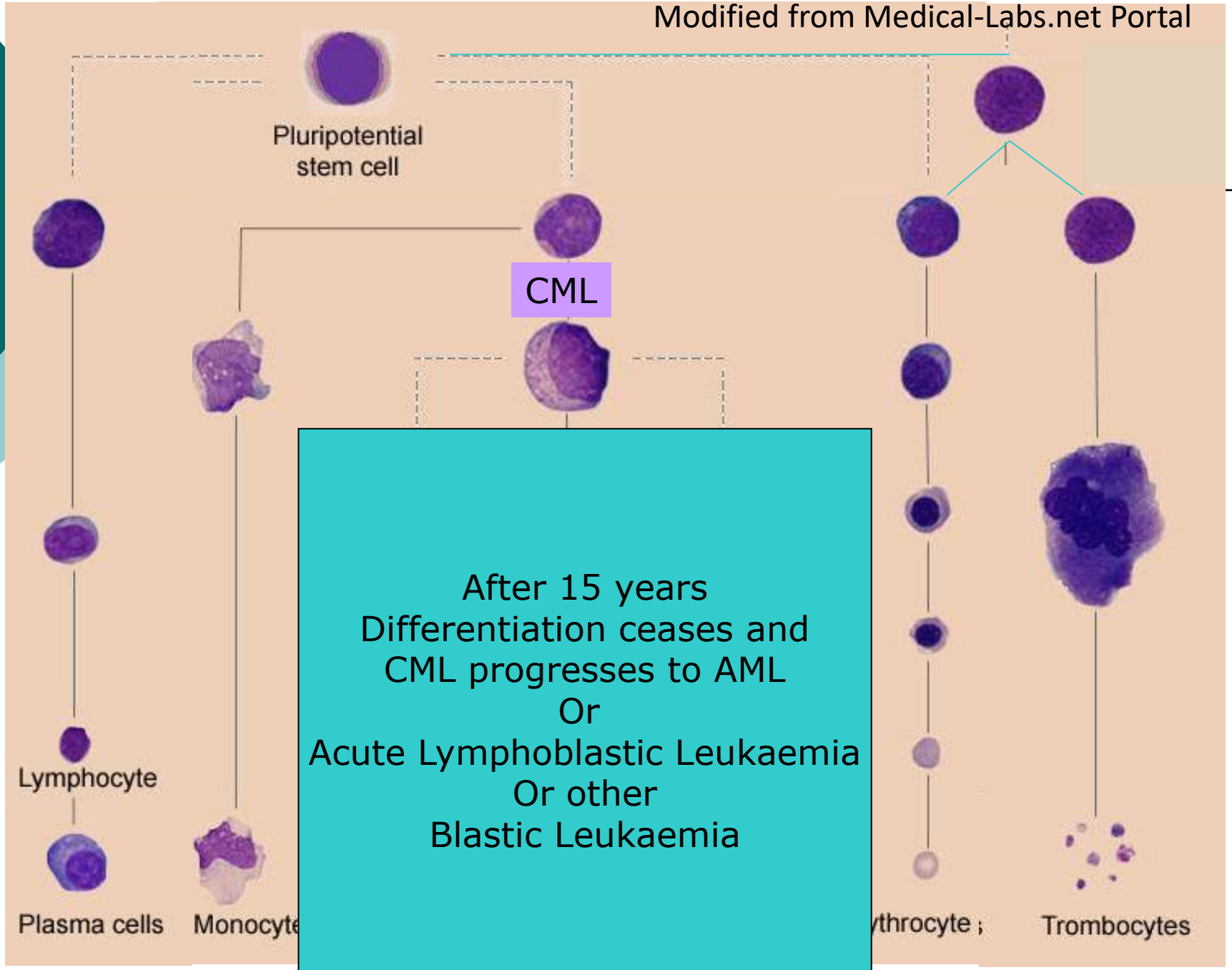

Acute Myeloblastic Leukaemia
Bone marrow replaced by Myeloblasts
Everything else depleted

# In chronic myeloid leukaemia the following cells are found in the blood in increased numbers

- neutrophils
- lymphoblasts
- myeloblasts
- metamyelocytes
- erythroblasts


Modified from Medical-Labs.net Portal
Pluripotential stem cell
CML
Lymphocyte
Plasma cells
Monocyte
Eosinophil
Segmented Neutrophil
Basophil
Erythrocyte ;
Trombocytes


Modified from Medical-Labs.net Portal
Pluripotential stem cell
CML
Chronic Myeloid Leukaemia
Proliferation with Differentiation
Marrow fills with mature myeloid cells
Lymphocyte
Plasma cells
Monocyte
Eosinophil
Segmented Neutrophil
Basophil
Erythrocyte ;
Trombocytes


Modified from Medical-Labs.net Portal
Pluripotential stem cell
CML
Lymphocyte
Plasma cells
Monocyte
ythrocyte ;
Trombocytes
After 15 years
Differentiation ceases and
CML progresses to AML
Or
Acute Lymphoblastic Leukaemia
Or other
Blastic Leukaemia

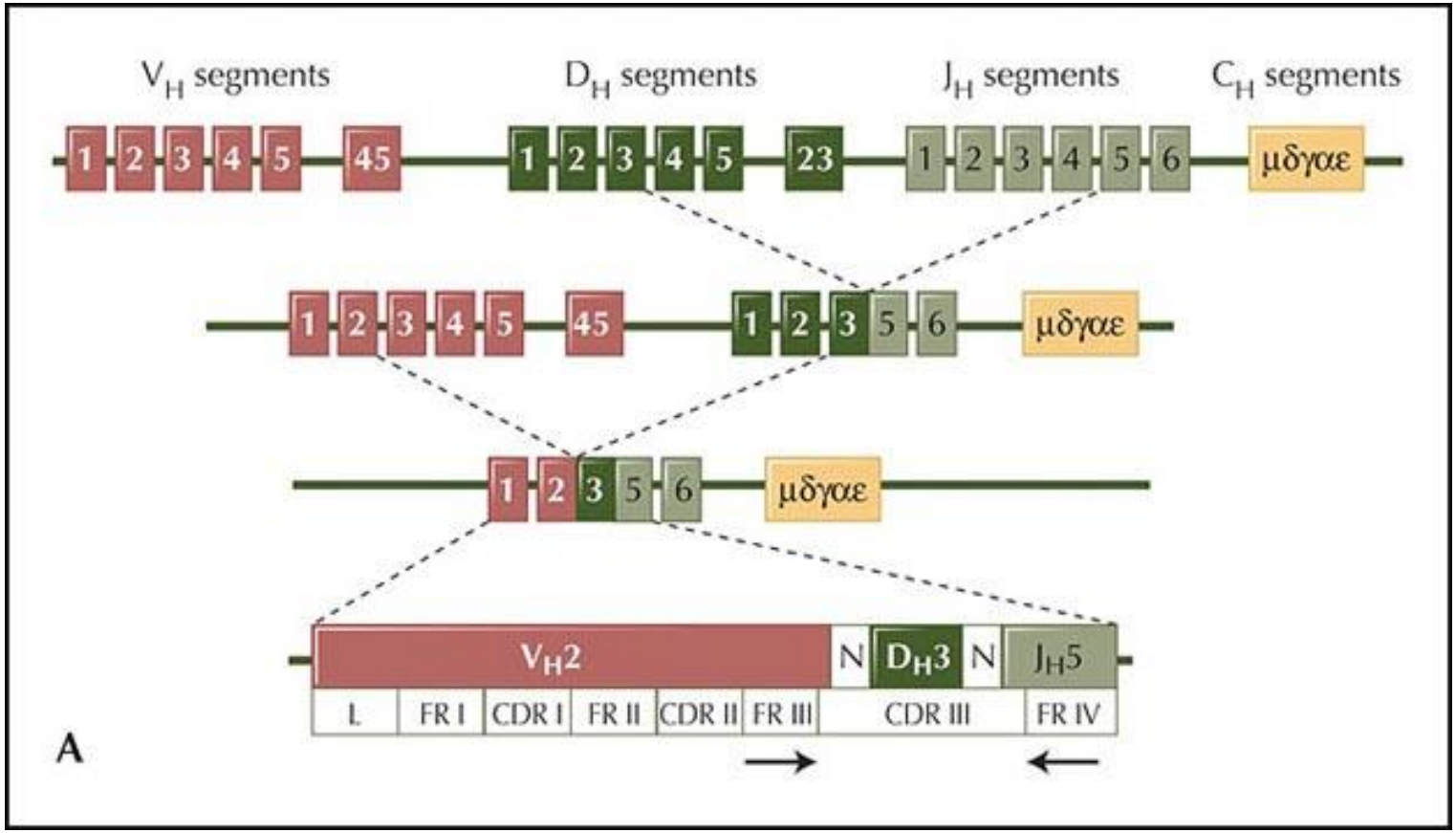
# In chronic myeloid leukaemia the following cells are found in the blood in increased numbers

- neutrophils
- lymphoblasts
- myeloblasts
- metamyelocytes
- erythroblasts

# B lymphoid cell

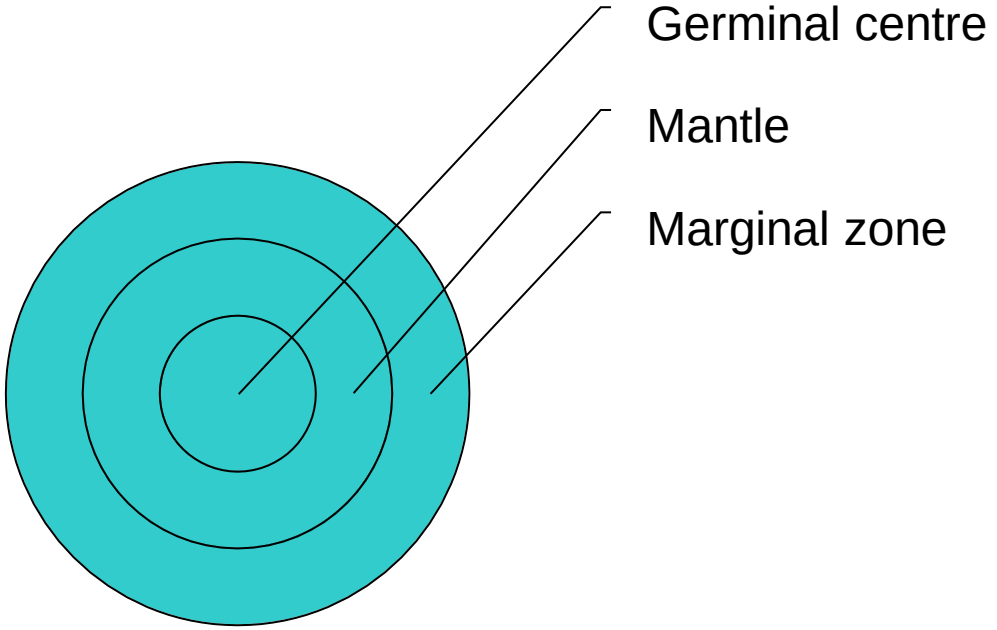
- B lymphoblast- rearrangement of immunoglobulin gene
- Matures into B lymphocytes – naïve cell exits bone marrow to enter blood and secondary lymphoid follicles. Expresses on surface Immunoglobulin as part of B cell receptor

# Immunoglobulin gene rearrangement

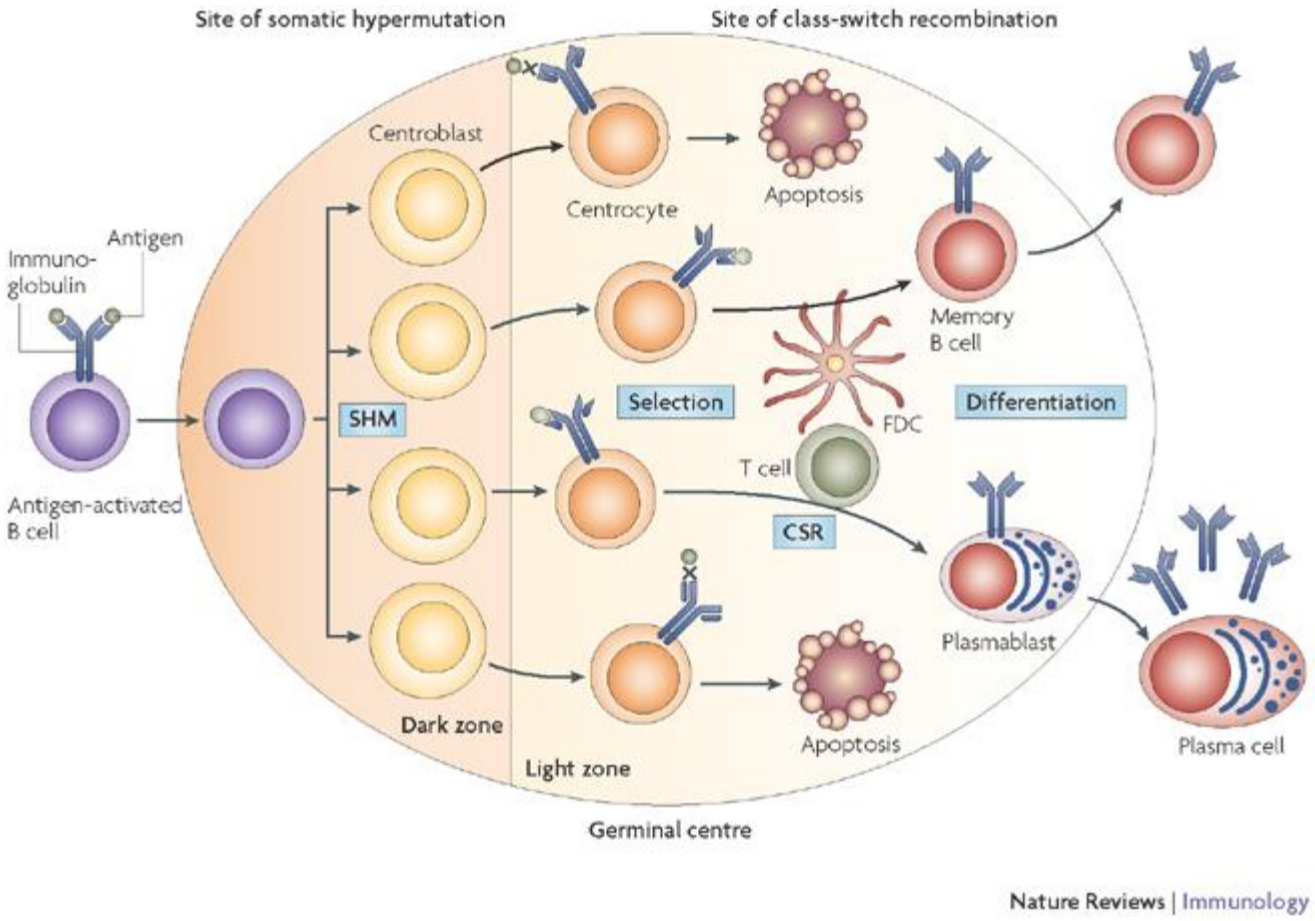


# Secondary-B lymphoid follicle

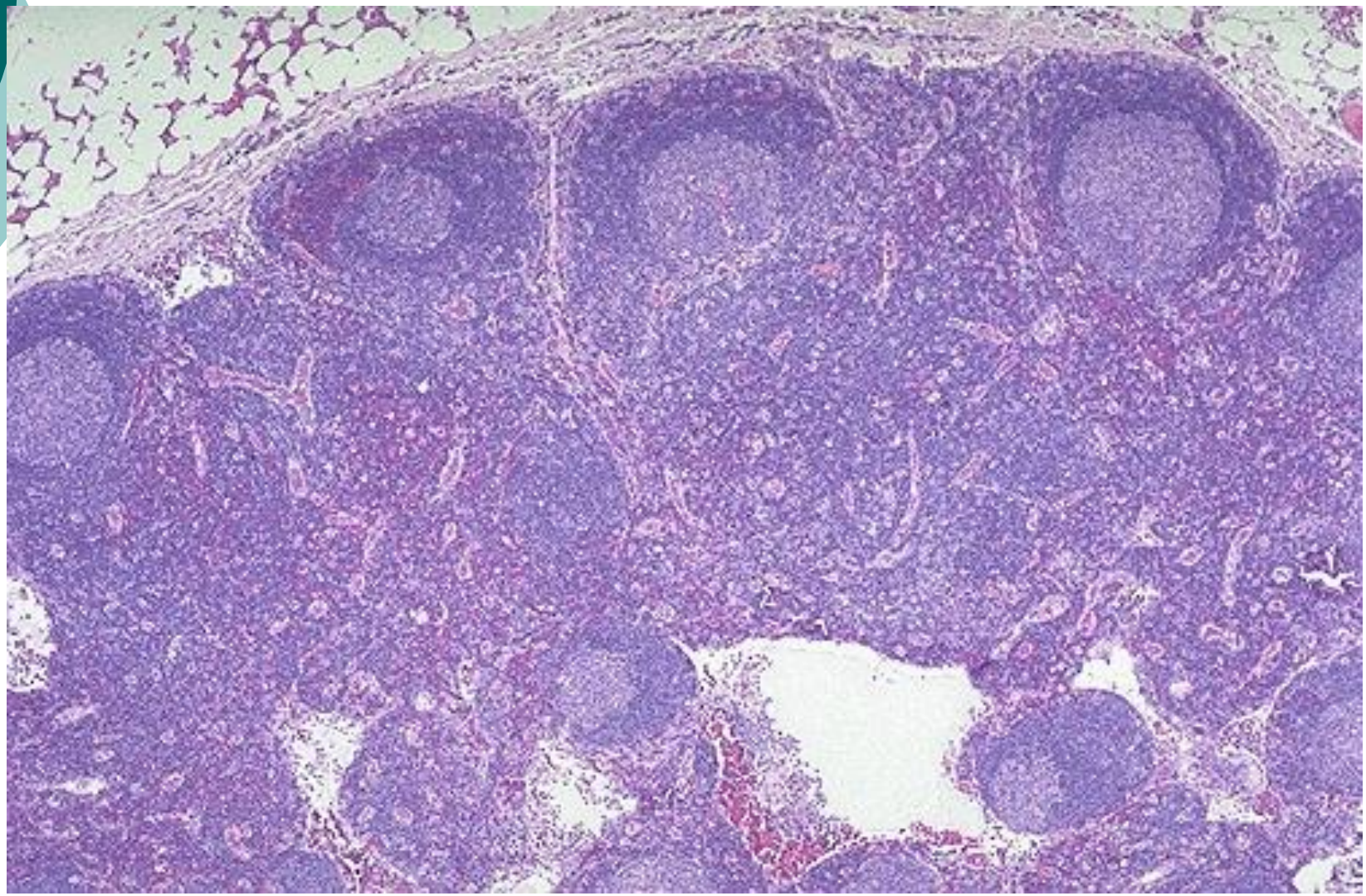
- T cell dependant B cell proliferation
- Antigen dependant
- Organised into 3 compartments
- Present in secondary immune system
- B cells transform to centroblasts
- Centroblasts produce centrocytes, plasma cells and marginal zone B cells



# Germinal centre



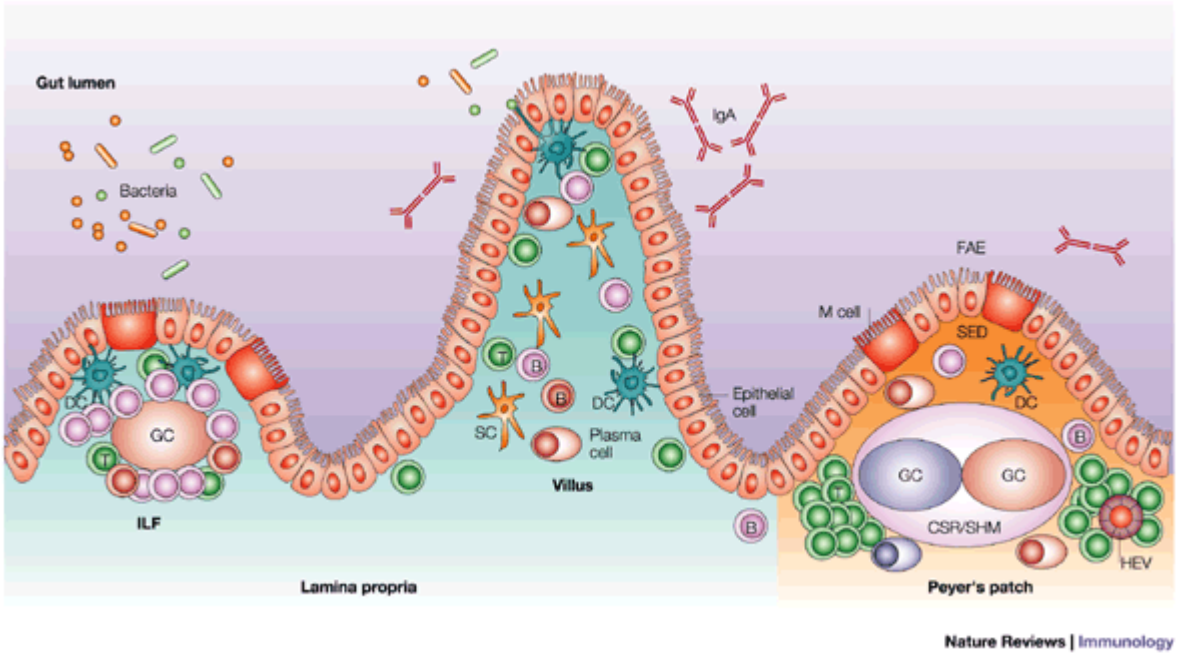
# Reactive lymph node

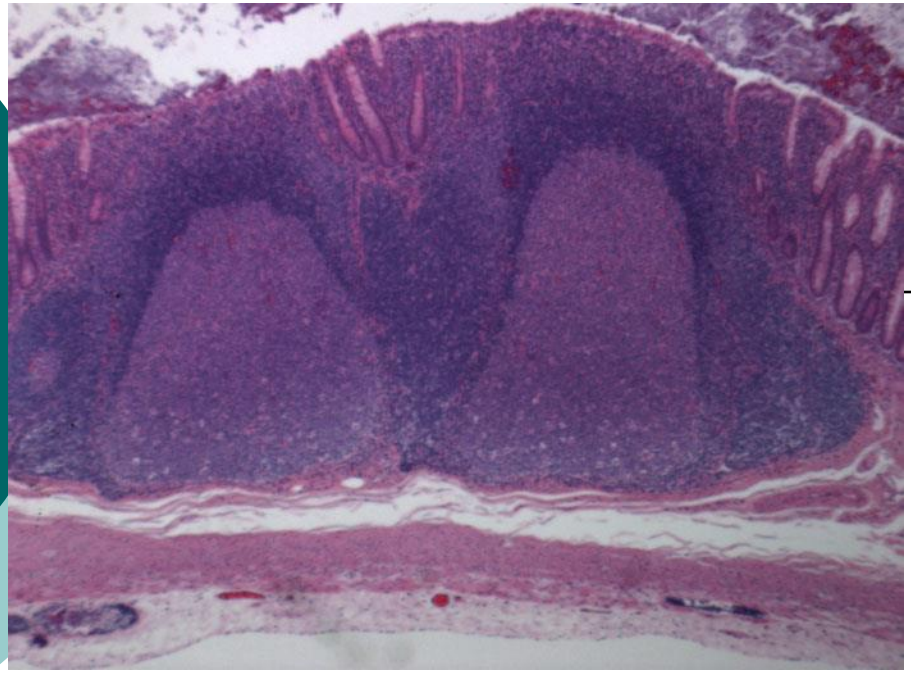


# Mucosa associated lymphoid tissue MALT

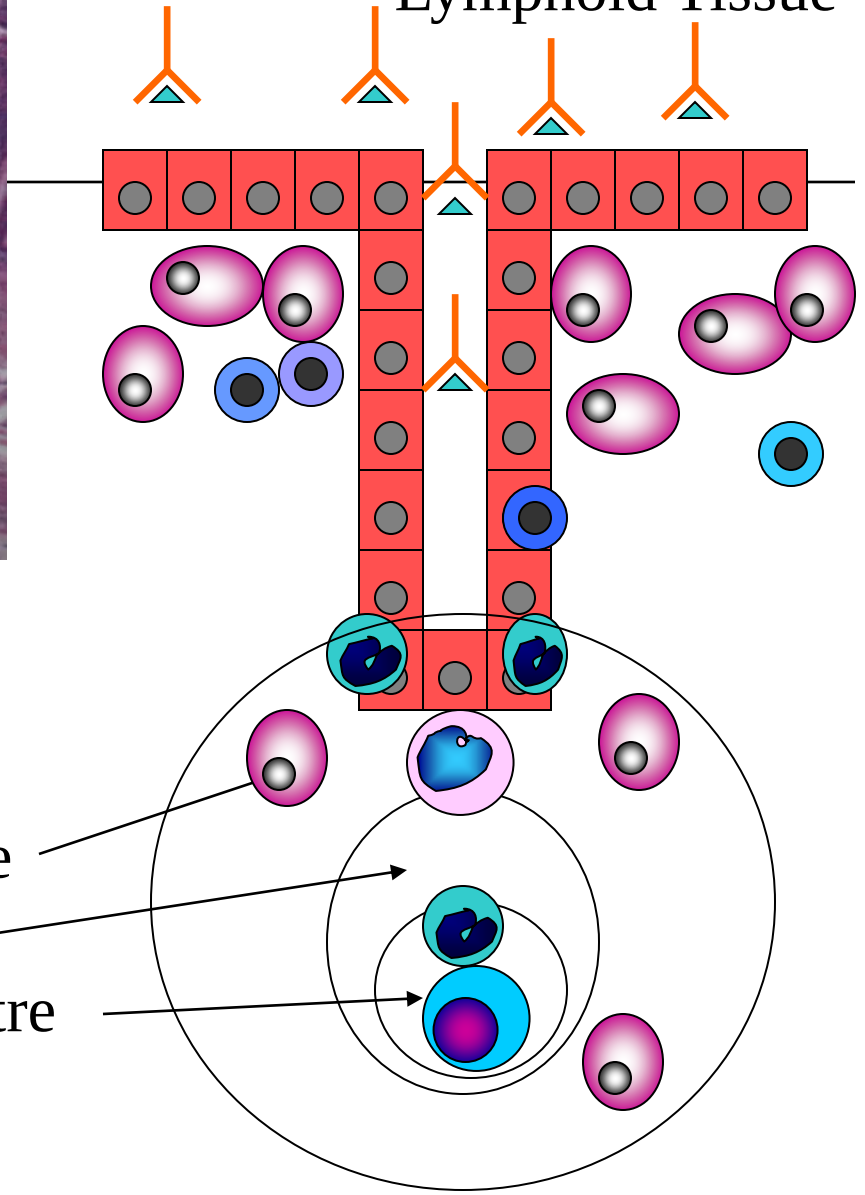
- Largest secondary lymphoid organ committed to local immunity
- First and best described in the Peyer's patches in ileum
- Comprises surface epithelium, underlying lymphoid follicle and T zone
- The lymphoid follicle has a well developed marginal zone .
- Both B and T lymphocytes infiltrate the surface epithelium

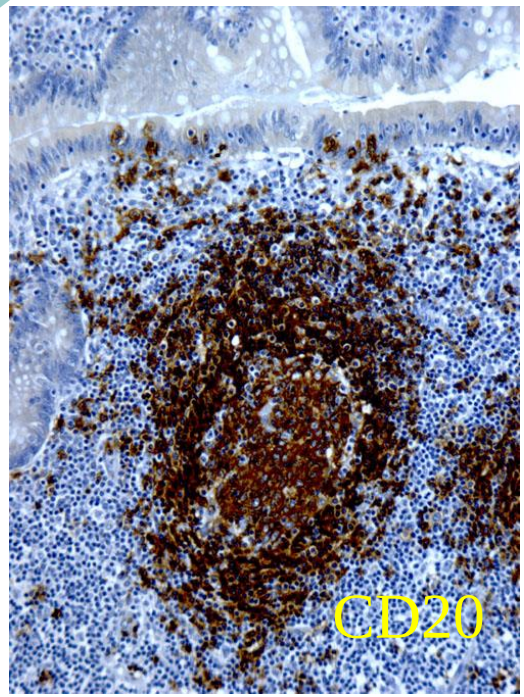
# MALT


Gut lumen
Bacteria
IgA
FAE
M cell
SED
DC
GC
T
B
DC
Epithelial cell
SC
Plasma cell
Villus
ILF
Lamina propria
GC
GC
CSR/SHM
HEV
Peyer's patch
Nature Reviews | Immunology



Mucosa Associated Lymphoid Tissue





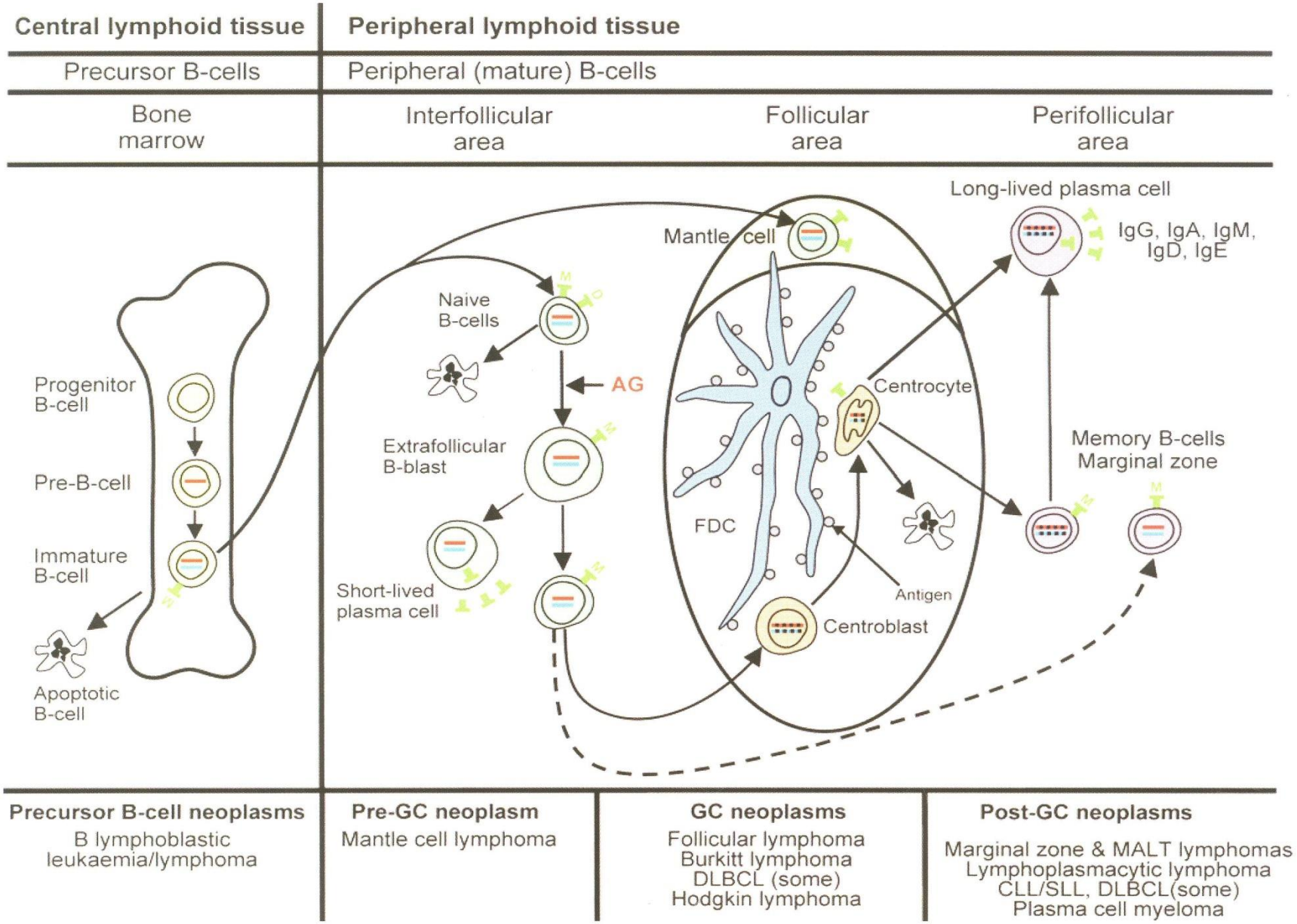

Marginal zone

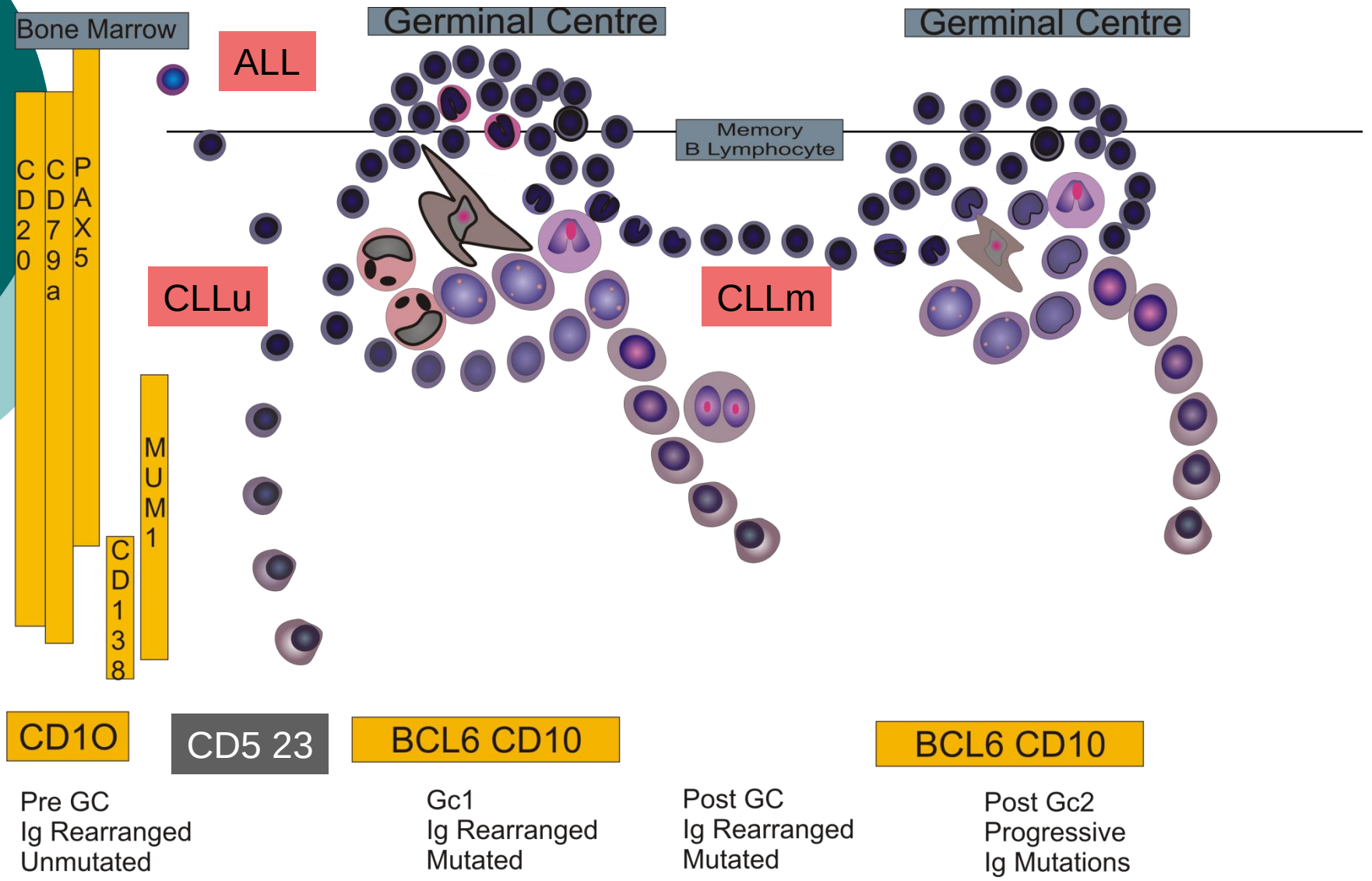
Mantle zone

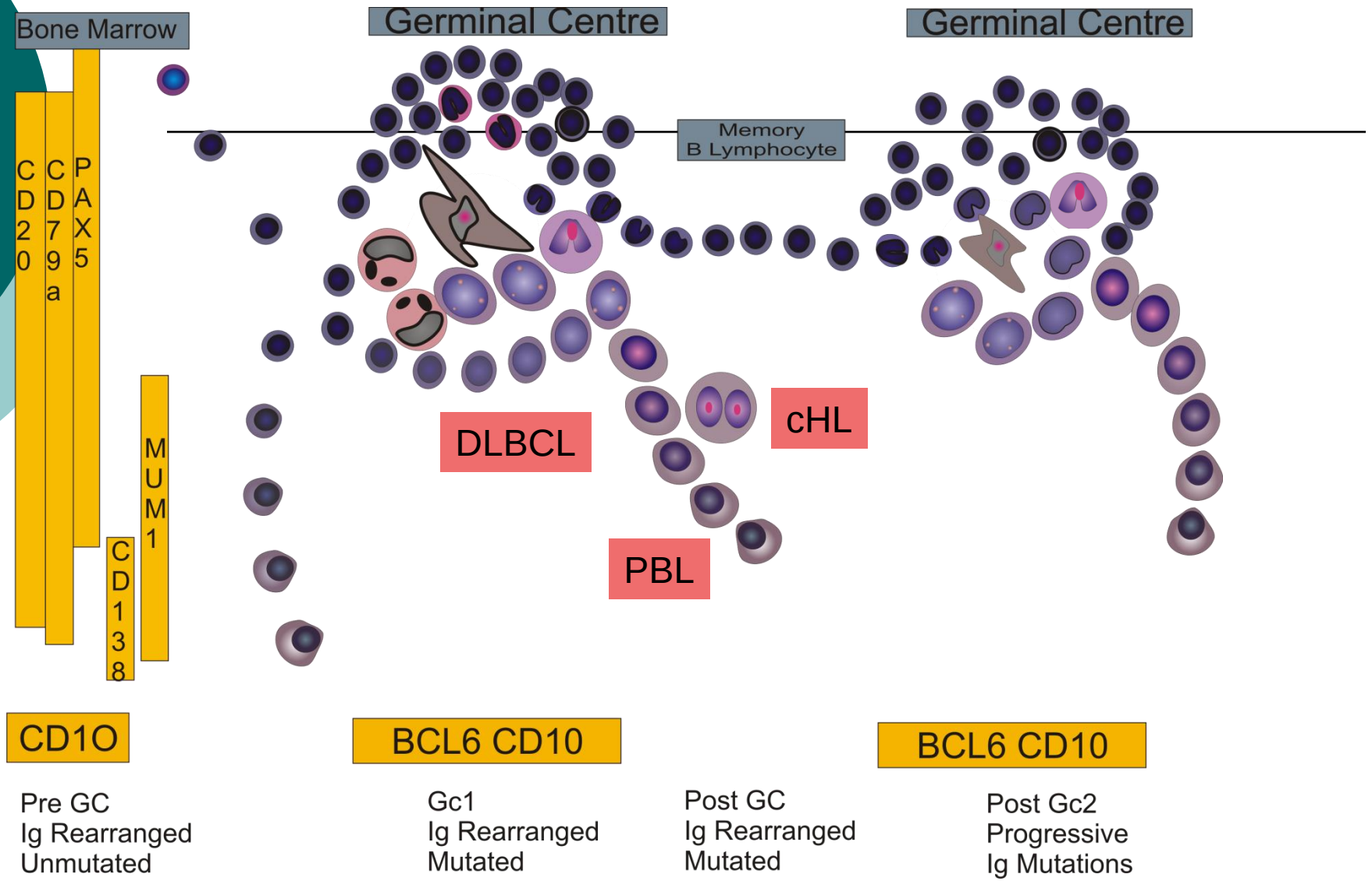
Germinal centre

# Tertiary Immune system

- There are mature lymphoid cells which are immune competent
- Patrol all the surfaces of body in every system


Central lymphoid tissue
Peripheral lymphoid tissue
Precursor B-cells
Peripheral (mature) B-cells
Bone marrow
Interfollicular area
Follicular area
Perifollicular area
Progenitor B-cell
Pre-B-cell
Immature B-cell
Apoptotic B-cell
Naive B-cells
AG
Extrafollicular B-blast
Short-lived plasma cell
Mantle cell
FDC
Centrocyte
Antigen
Centroblast
Long-lived plasma cell
IgG, IgA, IgM, IgD, IgE
Memory B-cells Marginal zone
Precursor B-cell neoplasms
B lymphoblastic leukaemia/lymphoma
Pre-GC neoplasm
Mantle cell lymphoma
GC neoplasms
Follicular lymphoma
Burkitt lymphoma
DLBCL (some)
Hodgkin lymphoma
Post-GC neoplasms
Marginal zone & MALT lymphomas
Lymphoplasmacytic lymphoma
CLL/SLL, DLBCL(some)
Plasma cell myeloma


Bone Marrow
ALL
Germinal Centre
Germinal Centre
Memory
B Lymphocyte
CD20
CD79a
PAX5
CD138
MUM1
CLLu
CLLm
CD1O
CD5 23
BCL6 CD10
BCL6 CD10
Pre GC
Ig Rearranged
Unmutated
Gc1
Ig Rearranged
Mutated
Post GC
Ig Rearranged
Mutated
Post Gc2
Progressive
Ig Mutations


Bone Marrow
Germinal Centre
Germinal Centre
Memory
B Lymphocyte
CD20
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MUM1
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cHL
PBL
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Gc1
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Mutated
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Ig Rearranged
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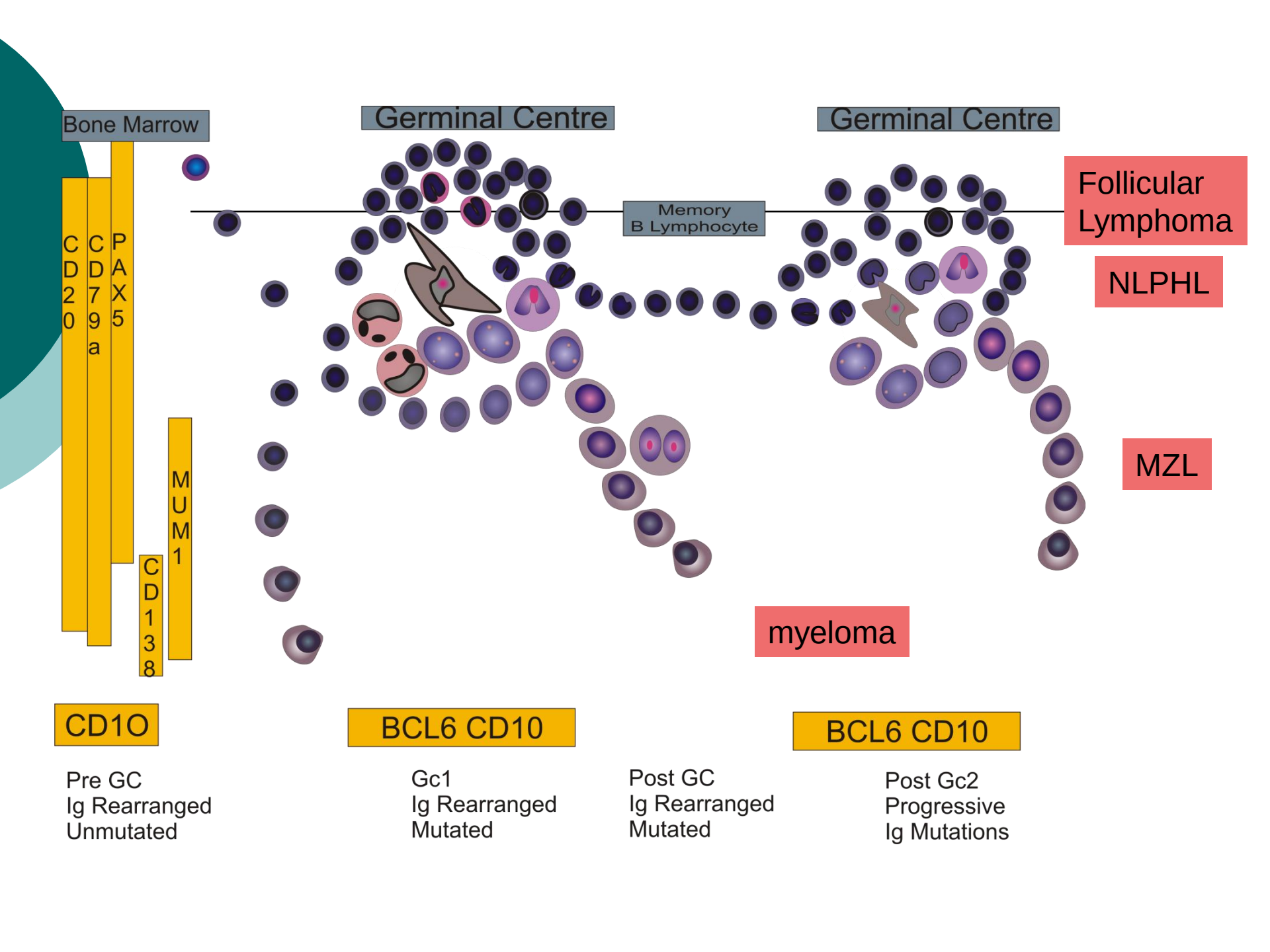
Bone Marrow
Germinal Centre
Germinal Centre
Memory
B Lymphocyte
CD20
CD79a
PAX5
CD138
MUM1
Follicular Lymphoma
NLPHL
MZL
myeloma
CD1O
BCL6 CD10
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Pre GC
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Mutated
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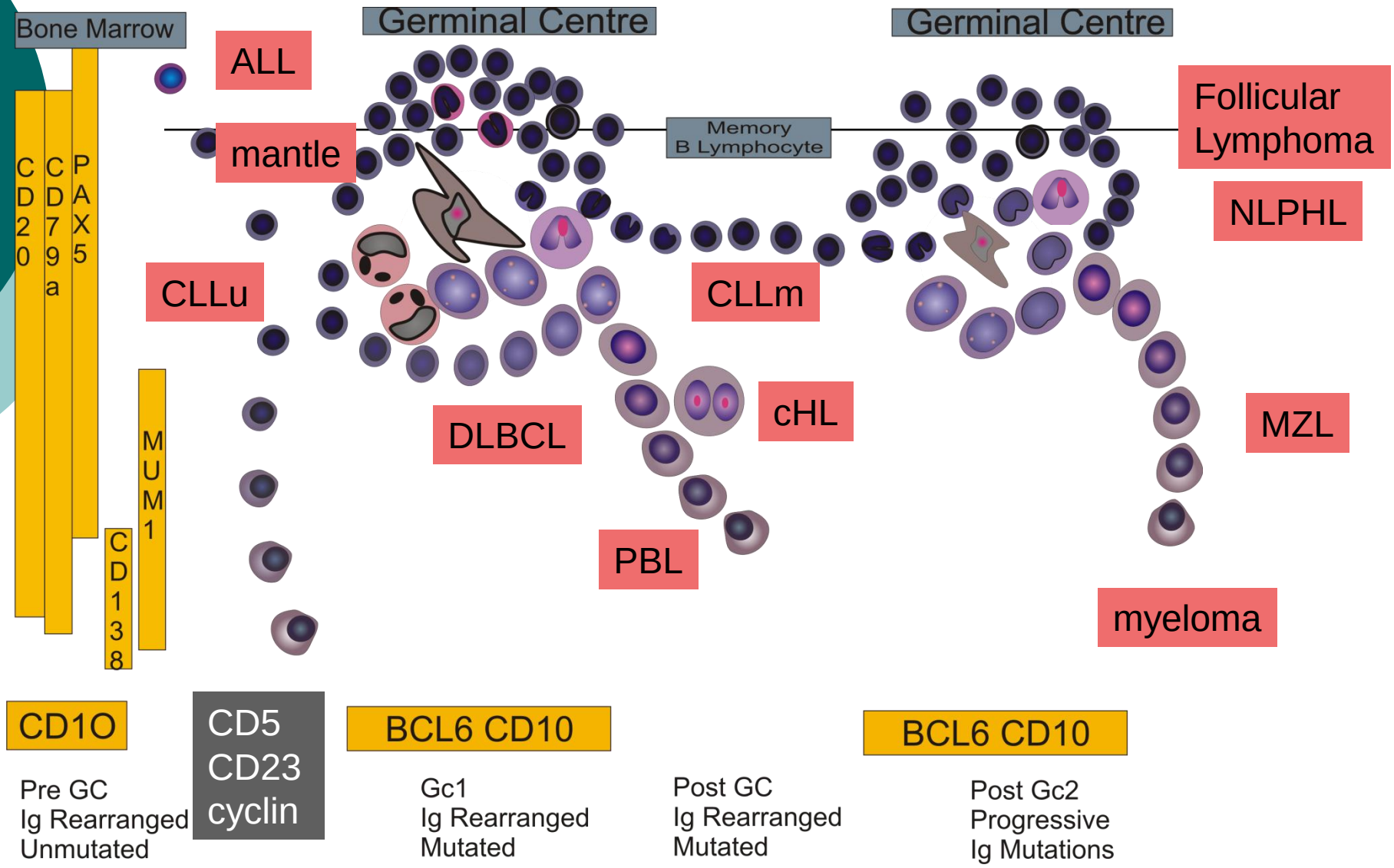
Ig Rearranged
Mutated
Post Gc2
Progressive
Ig Mutations




Adapted from Rooney Foster Byers Diagnostic Histopathology 16: 2 2010

# Malignant lymphoma

- Incidence- a gradual rise over the years of 4 %
- Nodal 60% or extranodal 40% disease
- Leukemia and lymphoma
- Classification-WHO system
- Grading- done on pattern follicular v/s diffuse and dominant cell type -Blastic/cytic
- Staging – distribution in the body
- Secondary to previous chemo or radiotherapy
- Infection/antigen and or autoimmune driven malignancy

# Hodgkin v non-Hodgkin Lymphoma

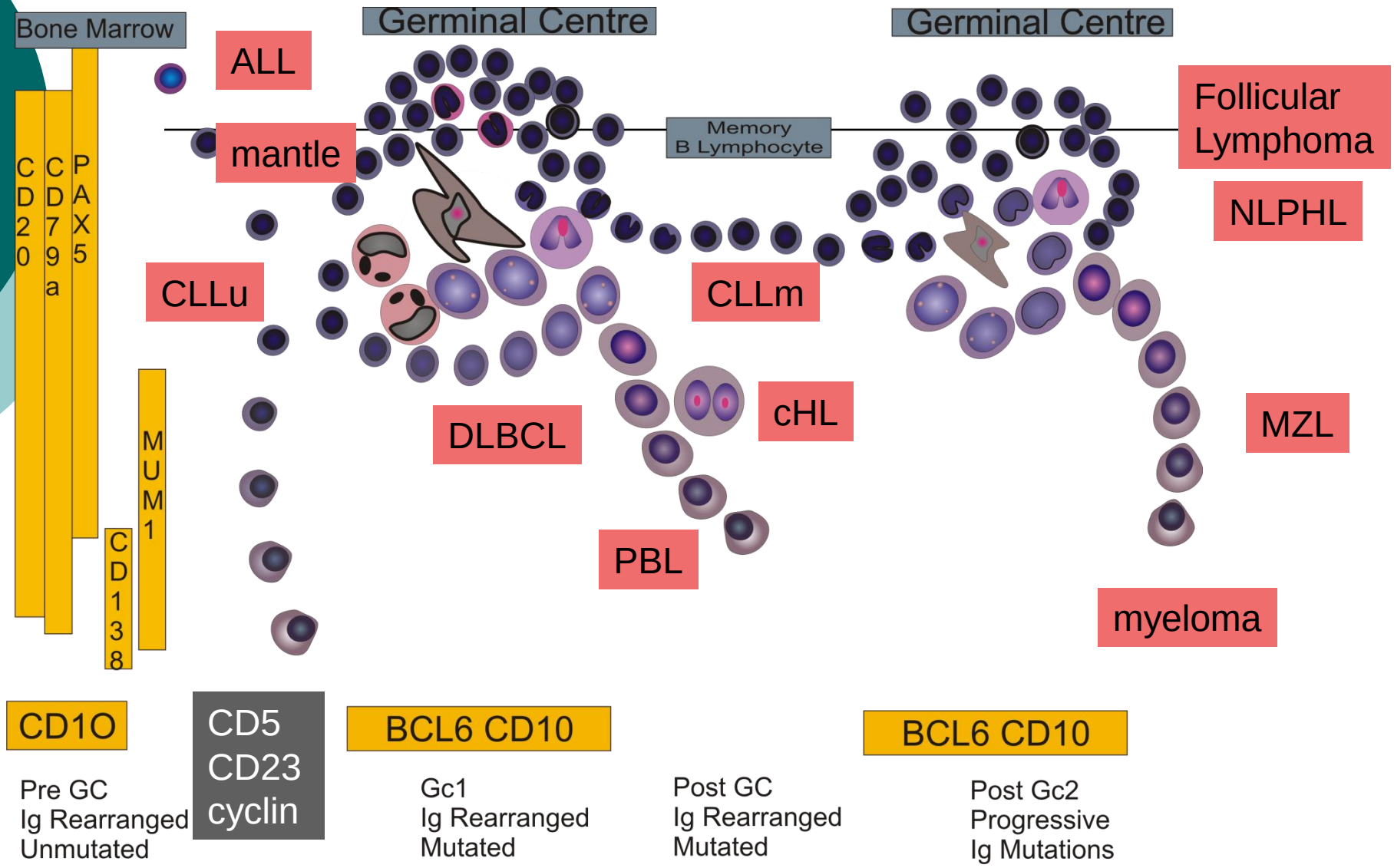
- Confusing!
- High grade lymphomas are stuck in proliferation with out differentiation
- Low grade lymphomas are differentiating and therefore are a mixture of blasts and cytes and resemble normal ie follicles or MALT
- HL are B blast cells (reed-sternberg cells) stuck and unable to undergo apoptosis

# High grade lymphomas

- Aggressive like acute leukaemia
- Progress rapidly
- Often B symptoms because of cytokine released
- Require high grade chemo

# Low grade lymphomas

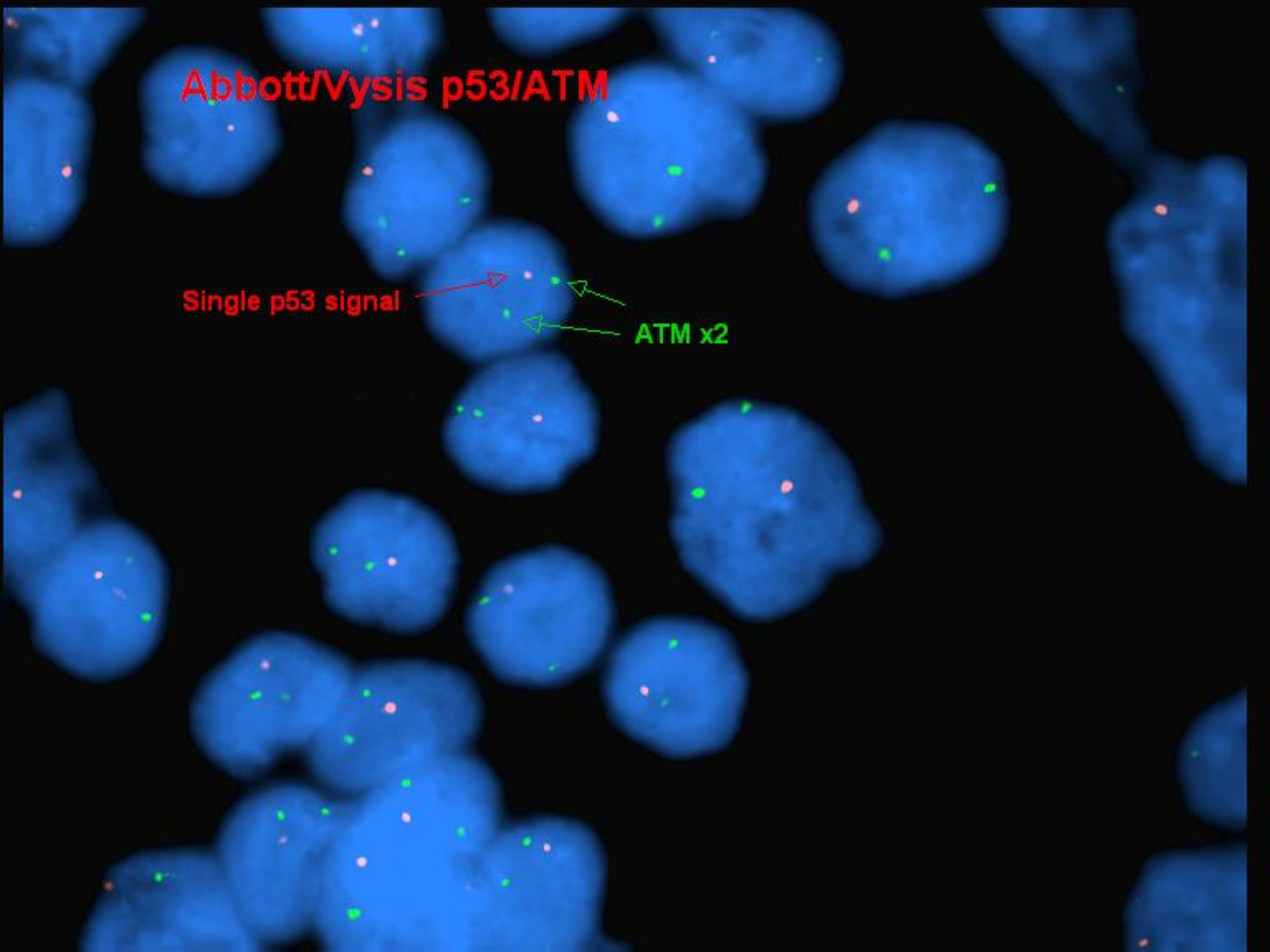
- Slow progression
- Often insidious onset
- Often present at high stage
- Low grade chemotherapy
- After several years stop differentiating and transform to high grade lymphoma
- This may be the first presentation




Adapted from Rooney Foster Byers Diagnostic Histopathology 16: 2 2010

# Chromosomal abnormalities

- Specific translocations in most entities
- Useful for diagnosis and monitoring

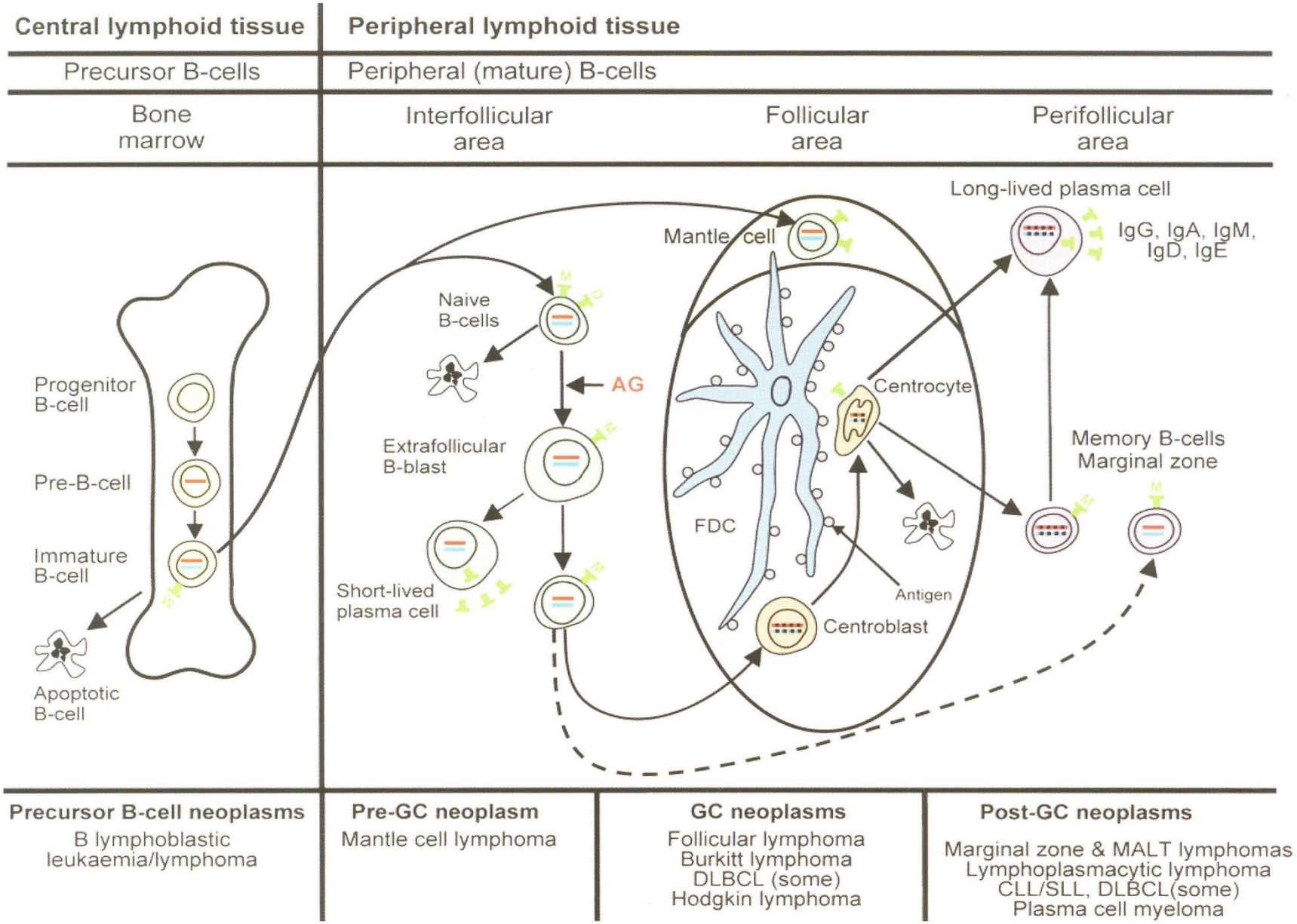

Abbott/Vysis p53/ATM
Single p53 signal
ATM x2

# Role of virus

- Epstein Barr virus- first identified in Burkitt lymphoma, also associated with Hodgkin lymphoma and post transplant and AIDS related lymphoma
- HTLV1- associated with T cell NHL
- Hepatitis C and low grade B cell NHL
- Human Herpes virus 8 or Kaposi sarcoma virus associated with plasma cell malignancy

# Relationship with immune system

- Produces immune deregulation or incompetence
- Seen in children with inborn immune disorder
- More frequent in patients with an autoimmune disorder
- Complicates immune deficient disease such as AIDS and post transplant immunosuppressed patients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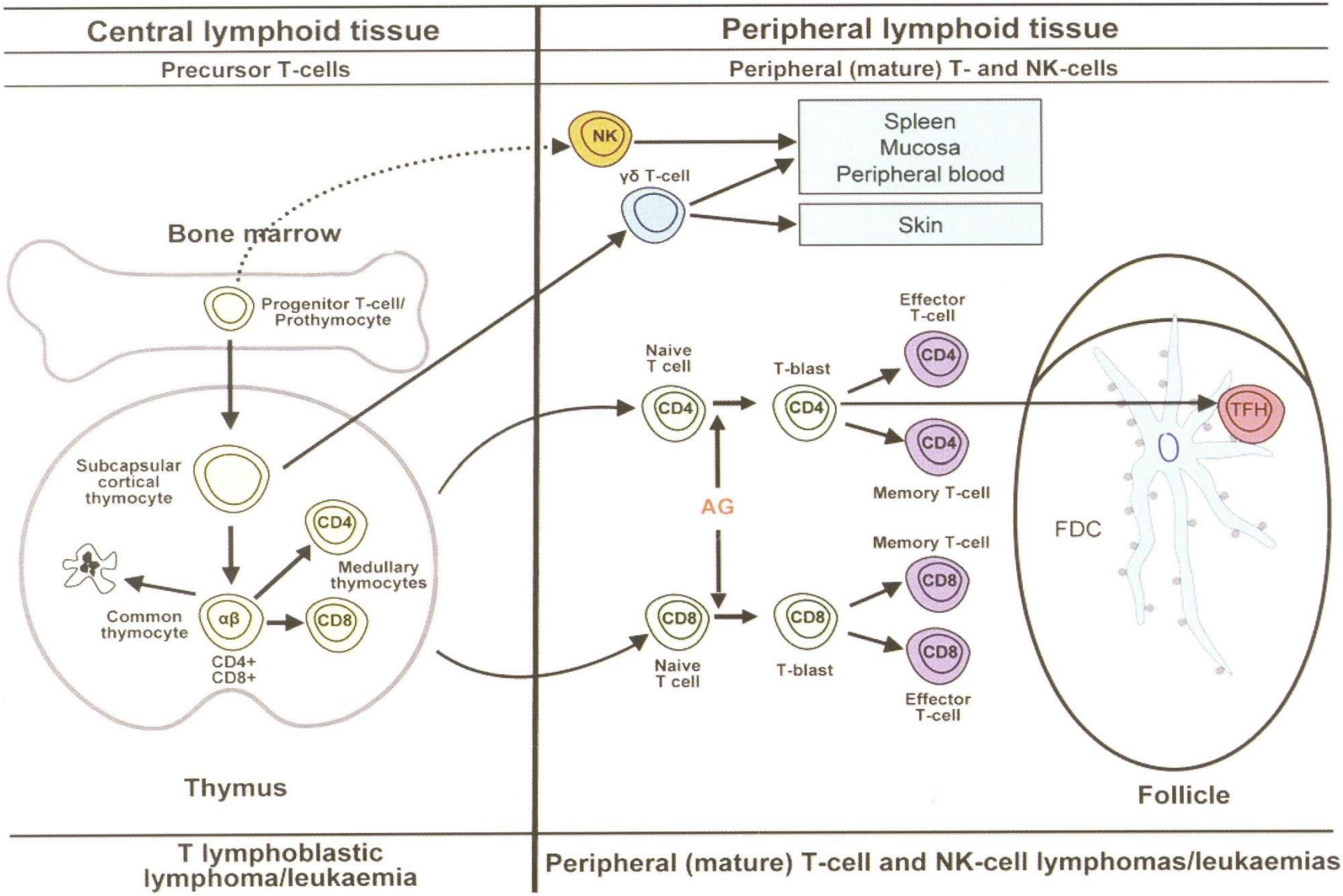

Central lymphoid tissue
Peripheral lymphoid tissue
Precursor T-cells
Peripheral (mature) T- and NK-cells
NK
γδ T-cell
Spleen
Mucosa
Peripheral blood
Skin
Bone marrow
Progenitor T-cell/
Prothymocyte
Effector
T-cell
Naive
T cell
T-blast
CD4
TFH
Memory T-cell
AG
FDC
Subcapsular
cortical
thymocyte
Medullary
thymocytes
Common
thymocyte
αβ
CD4+
CD8+
Memory T-cell
CD8
Naive
T cell
T-blast
Effector
T-cell
Thymus
Follicle
T lymphoblastic
lymphoma/leukaemia
Peripheral (mature) T-cell and NK-cell lymphomas/leukaemias

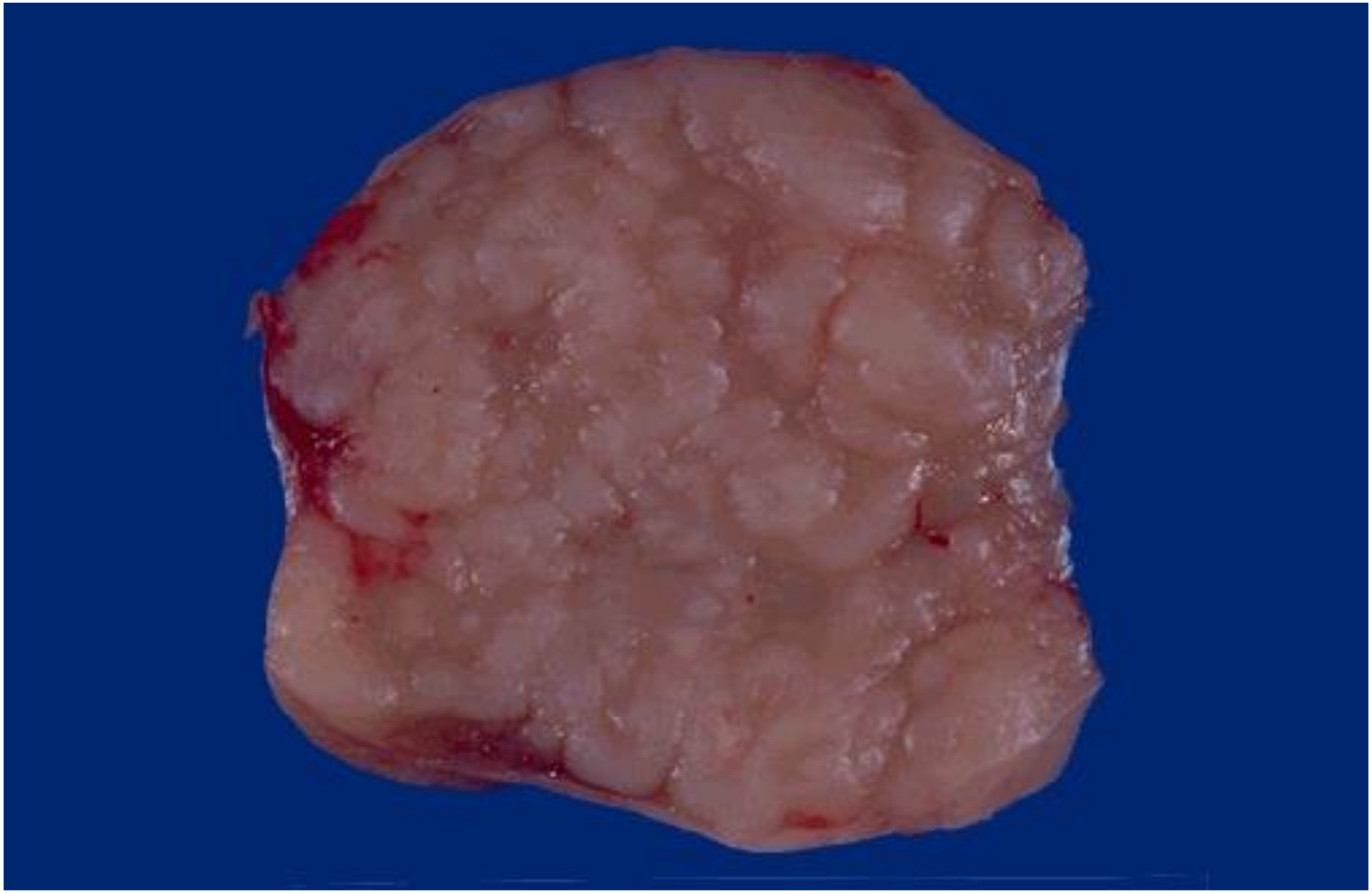
# Classification

- Hodgkin lymphoma and B and T cell lymphoma
- Numerous attempts at classification
- New WHO 2016 classification defines clinico-pathological entities with a recognised morphology, immunophenotype and underlying molecular abnormality with well characterised clinical behaviour. This is therefore ideal for the pathologist and clinician.

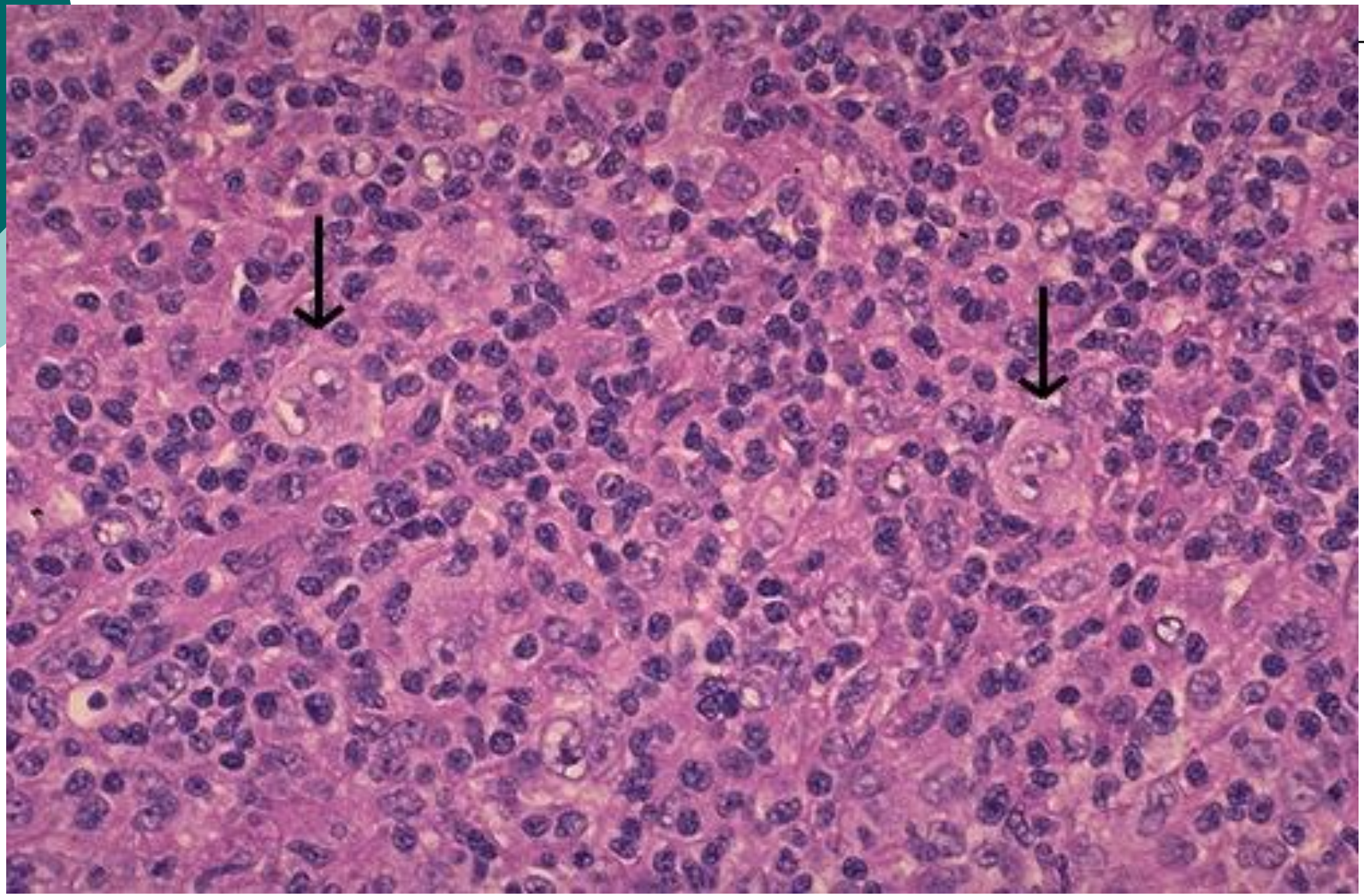
# Hodgkin lymphoma

- Thomas Hodgkin described a disease of young people with nodal enlargement and B symptoms
- Bimodal age distribution
- Nodal disease
- Characteristic clinical B symptoms
- Typical morphology with 1 to 5 % malignant cells seen in a background of inflammatory infiltrate.
- Malignant cells are referred as Reed Sternberg cells and now believed to be of B cell derivation
- Role of EBV virus in 35% cases

# Hodgkin lymphoma



# Morphology of Hodgkin lymphoma



# B and T/NK cell lymphoma

- B cell neoplasm
- Arise from a single malignant cell producing clonal proliferation
- A B cell during its development can transform to a malignant cell and retains morphological and phenotypic similarities to parent cell

- T cell neoplasm
- Arise from a single cell
- TCR rearranged
- Classified according to site and distribution

# Classification of B cell Lymphoma

- **Precursor B-lymphoblastic lymphoma (precursor B-cell acute lymphoblastic leukemia)**

- **Mature (peripheral) B-cell neoplasms**
  **Small lymphocytic lymphoma (chronic lymphocytic leukemia)**
  **Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia**
  **Splenic marginal zone lymphoma**
  **Extranodal marginal zone B-cell lymphoma of MALT**
  **Nodal marginal zone B-cell lymphoma**
  **Follicular lymphoma**
  **Mantle cell lymphoma**
  **Diffuse large B-cell lymphoma**
  **Mediastinal (thymic) large B-cell lymphoma**
  **Intravascular large B-cell lymphoma**
  **Primary effusion lymphoma**
  **Burkitt lymphoma**

# Primary T immune system

- Thymus
- T lymphoblast
- Rearrange T cell receptor (TCR)
- 2 Types of TCR alpha beta and gamma delta
- Mature into CD4 or CD8 positive cells
- Antigen independent process
- Exit thymus as mature T cells

# Secondary immune system- T cell

- T zone of lymph node, MALT, spleen
- Antigen dependant process
- Require antigen presenting cells

# NHL WHO Classification T cell

- **T-cell and NK-cell neoplasms**

- **Precursor T Lymphoblastic lymphoma**
- **Mature T-cell and NK-cell neoplasms**
  Adult T-cell lymphoma/leukemia
  Extranodal NK/T-cell lymphoma, nasal type
  Enteropathy-type T-cell lymphoma
  Hepatosplenic T-cell lymphoma
  Subcutaneous panniculitis-like T-cell lymphoma
  Blastic NK-cell lymphoma
  Mycosis fungoides or Sézary syndrome
  Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
  Angioimmunoblastic T-cell lymphoma
  Peripheral T-cell lymphoma, unspecified
  Anaplastic large cell lymphoma

# Was that all clear?