About B–Cell Lymphomas

Groupmeeting Klipp/Spang, December 09 2002

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– Computational Molecular Biology –
Berlin

Overview

- **Short History of Lymphoma Classification**

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- **About Healthy B–Cells**
  - Blood Cells
  - Immune System
  - Immunoglobulins
  - Lymphatic System
  - B–Cell Differentiation

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- **WHO Classification**

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- **WHO Classification**

- **Microarrays**
  - Alizadeh *et. al.*
  - Shipp *et. al.*

Short History of Classification

- $>$ 1970's
  Henry Rappaport

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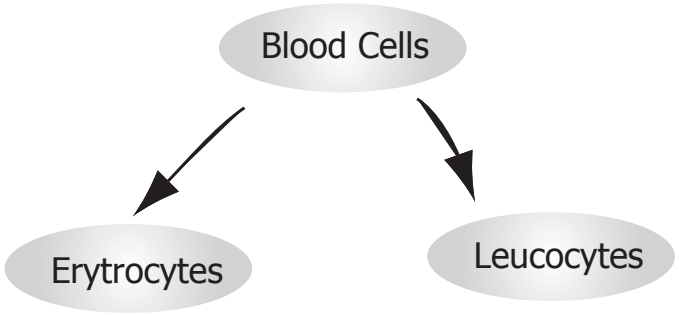
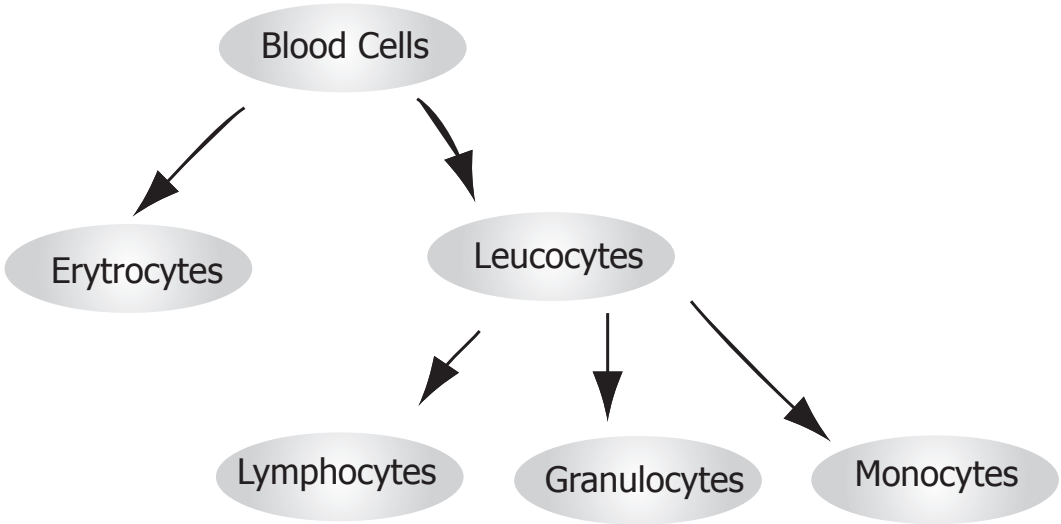
- 2001
  WHO comprehensive classification of neoplasms of haematopietic and **lymphoid** tissues

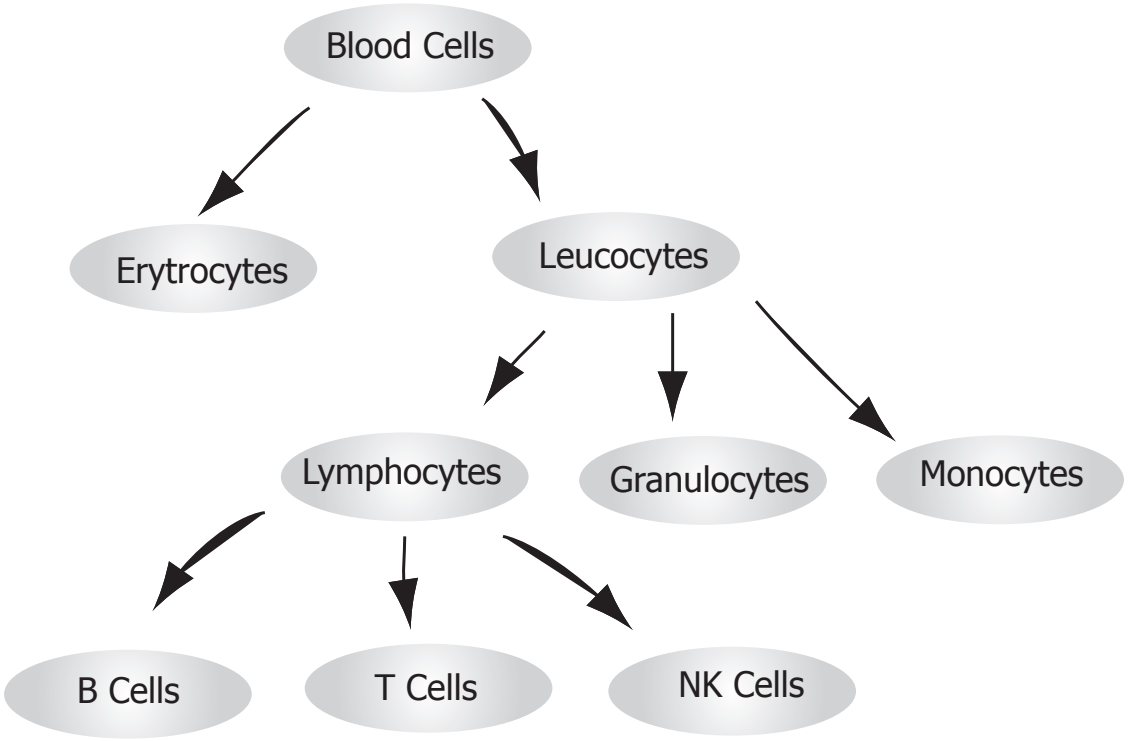
Blood Cells



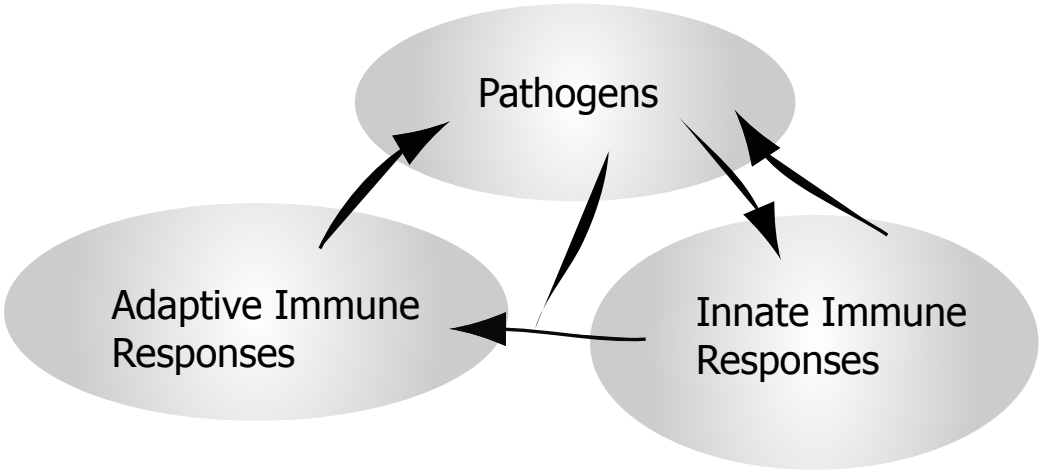
Blood Cells


Blood Cells
Erytrocytes
Leucocytes
Lymphocytes
Granulocytes
Monocytes

Blood Cells

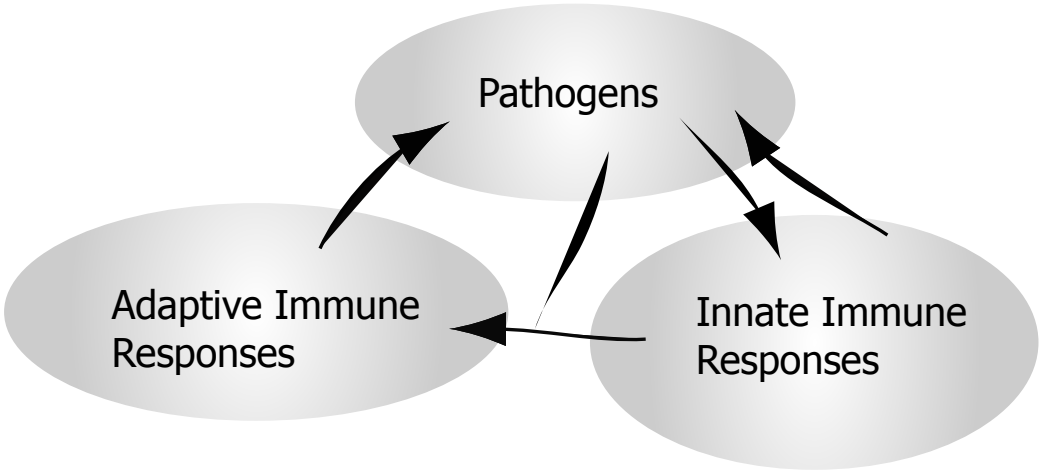

Blood Cells
Erytrocytes
Leucocytes
Lymphocytes
Granulocytes
Monocytes
B Cells
T Cells
NK Cells

Immune System



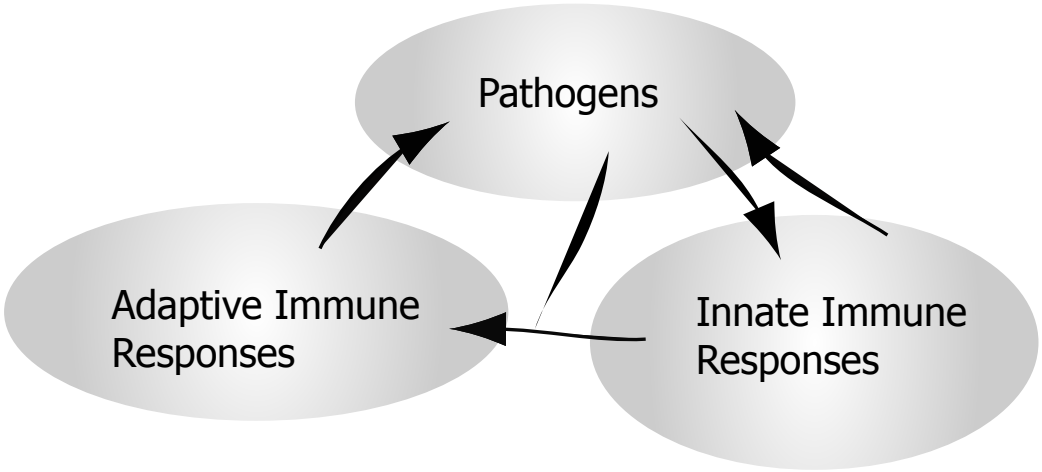
- innate response
- adaptive response

Immune System



- innate response
- adaptive response
  cellular mediated

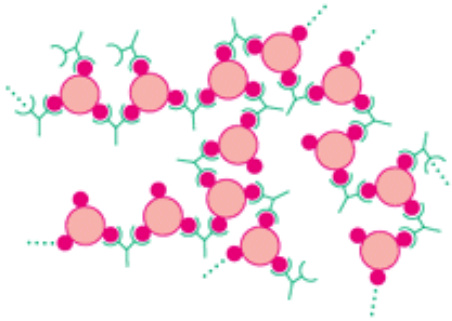
Immune System

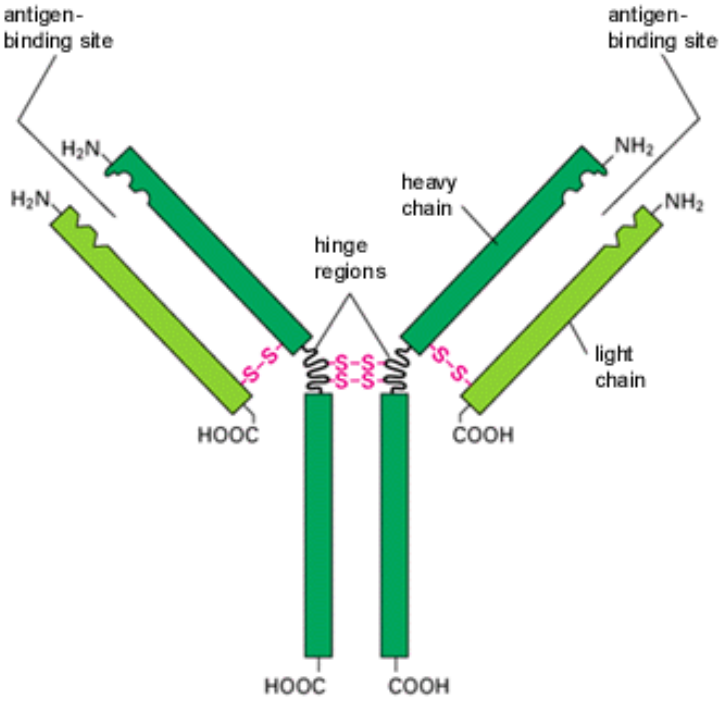


- innate response
- adaptive response
  cellular mediated
  antibody mediated

Antibodies

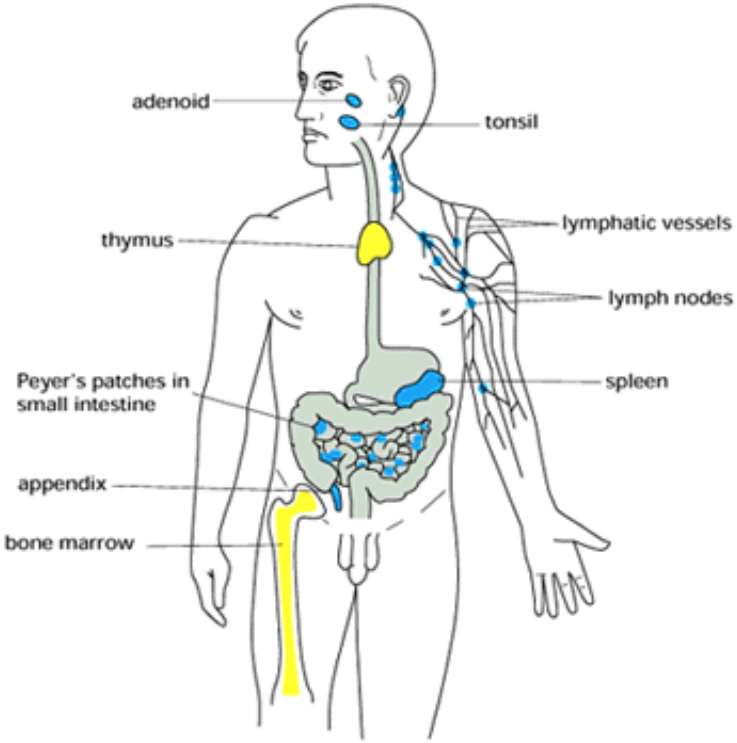
how they work





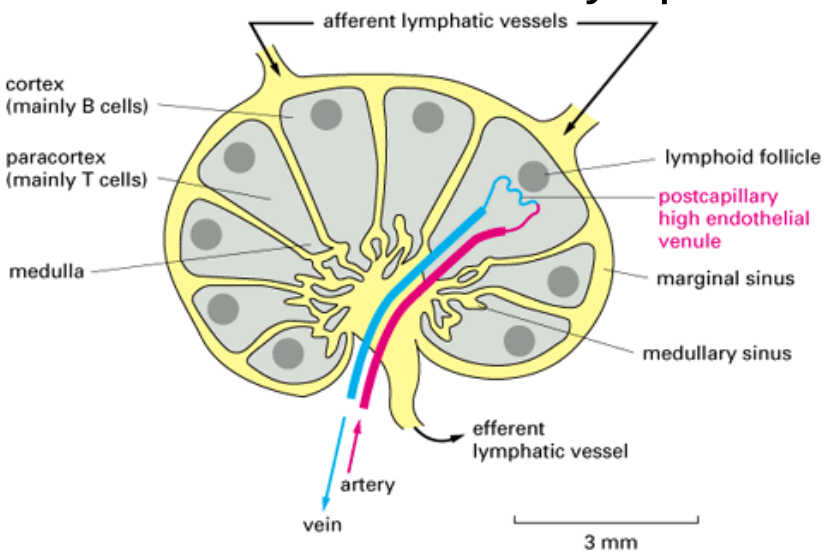
how they look like

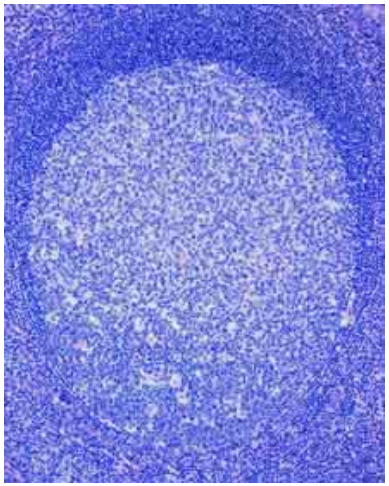
The Lymphatic System



Human Lymphoid Organs

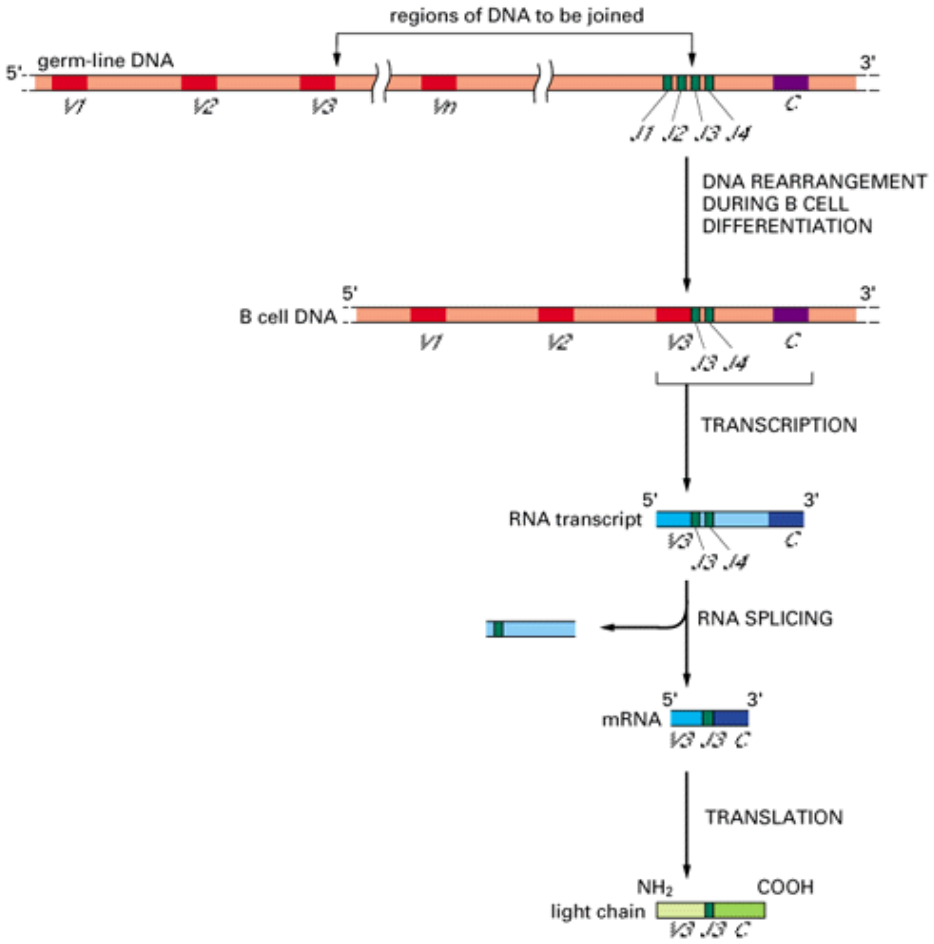
Lymphnode

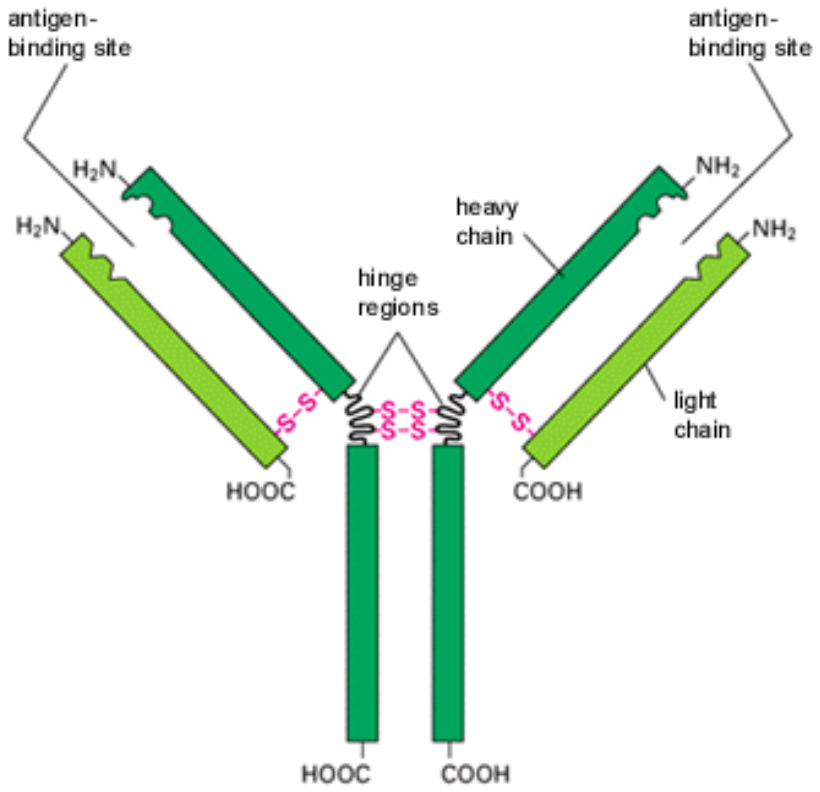




Secondary Follicle

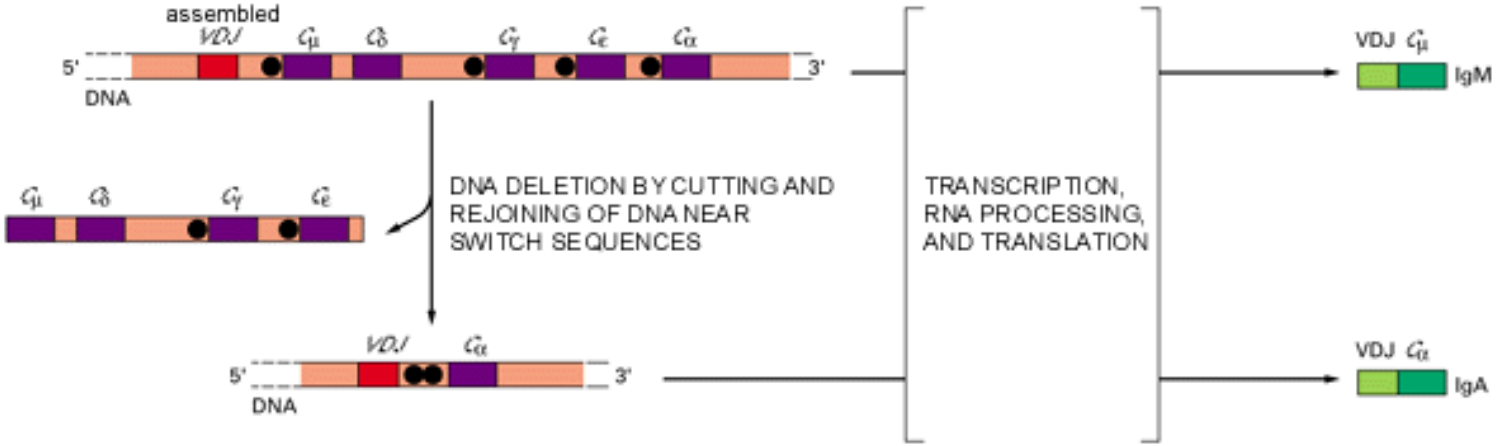
V(D)J – Joining


regions of DNA to be joined
germ-line DNA
5'
3'
V1
V2
V3
Vn
J1 J2 J3 J4
C
DNA REARRANGEMENT DURING B CELL DIFFERENTIATION
B cell DNA
TRANSCRIPTION
RNA transcript
RNA SPLICING
mRNA
TRANSLATION
NH2
COOH
light chain


antigen-binding site
antigen-binding site
H2N
NH2
heavy chain
hinge regions
light chain
HOOC
COOH

Class Switch / Somatic Hypermutation

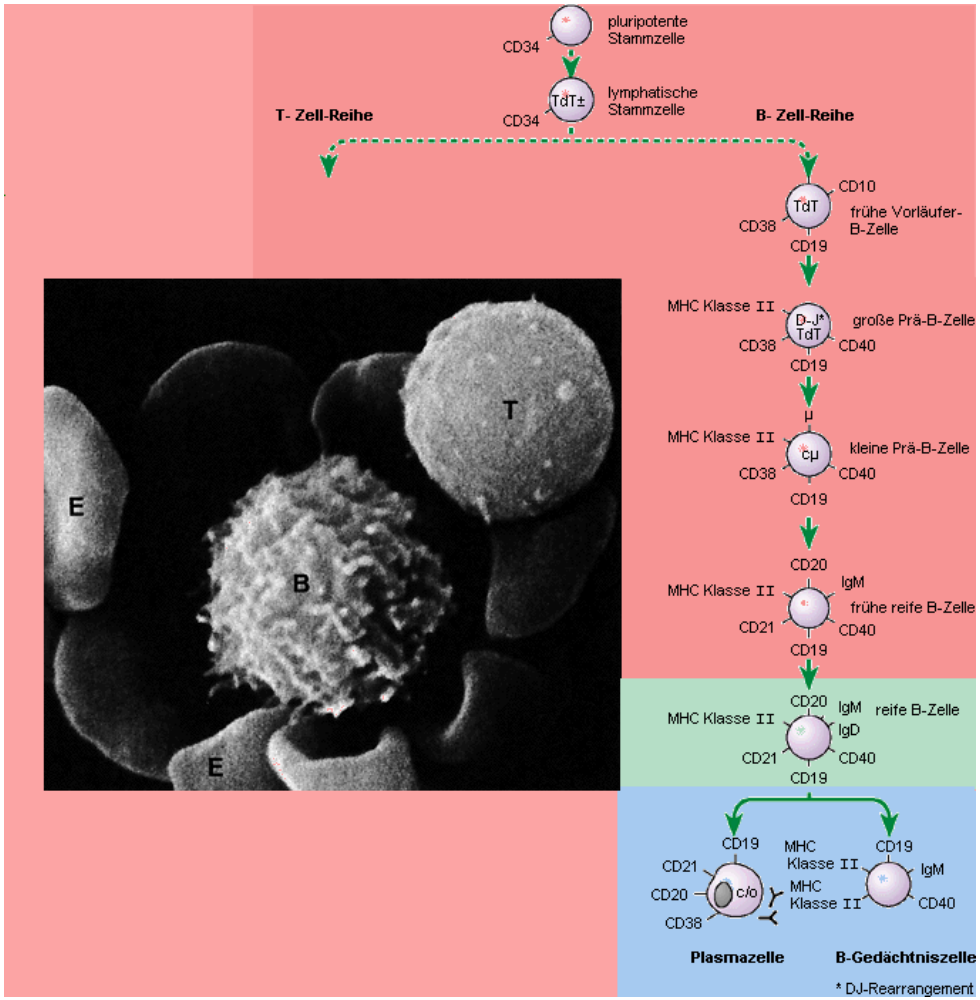
Class Switches



Somatic Hypermutation

- 1 / V region coding sequence / generation
- aim : enlargen affinity to antigen
- place: germinal center

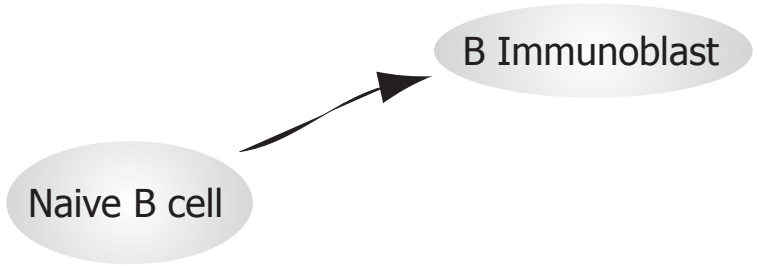
B Cell Differentiation



B Cell Differentiation ctd.

Naive B cell

B Cell Differentiation ctd.



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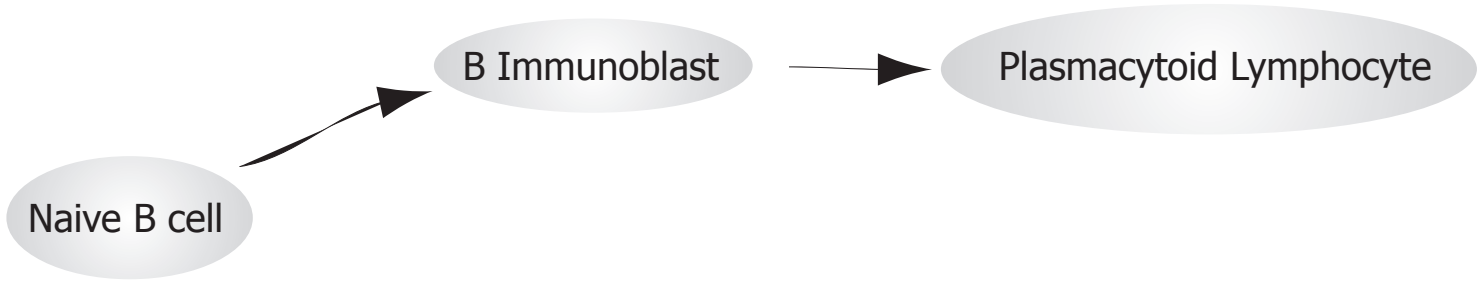

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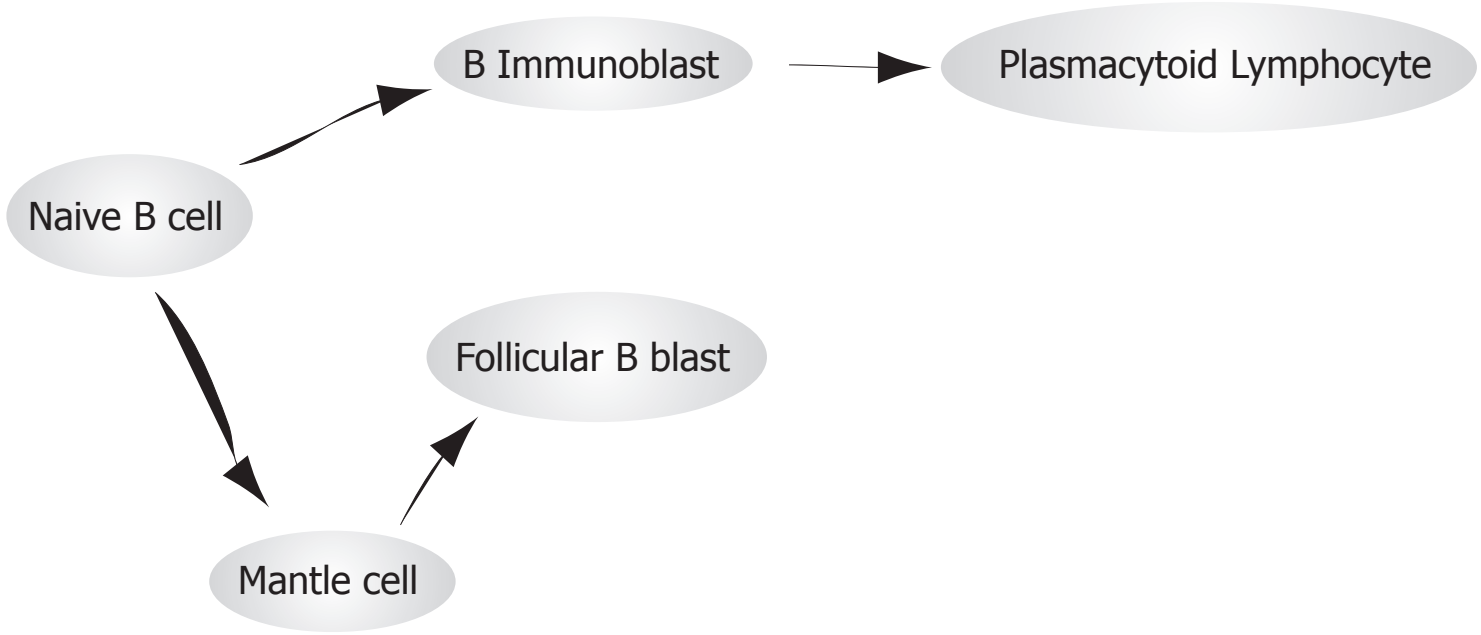

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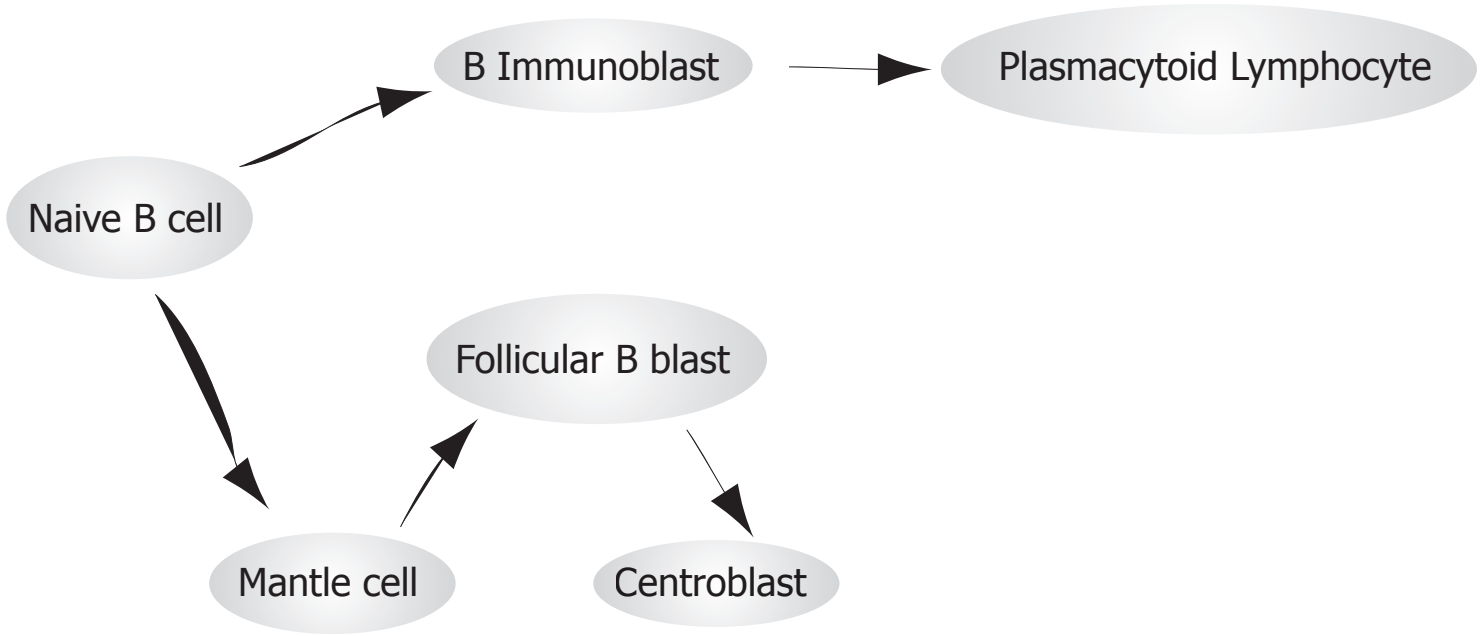

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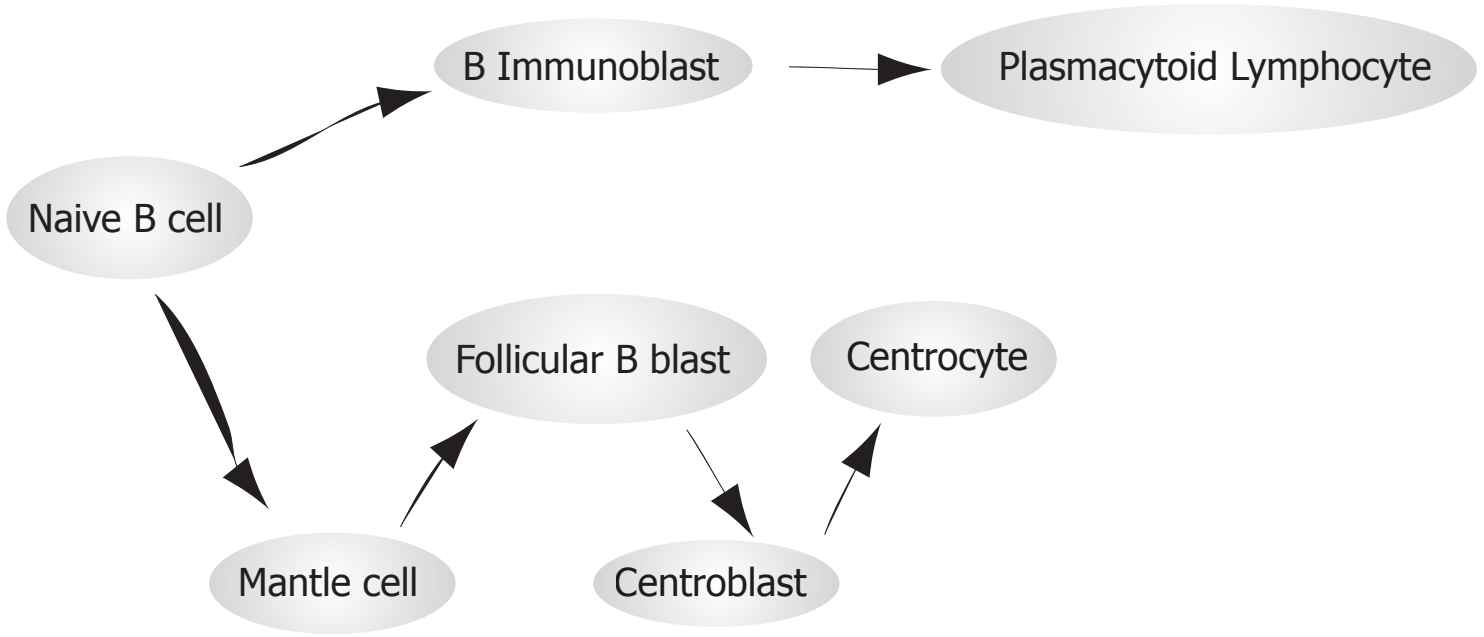

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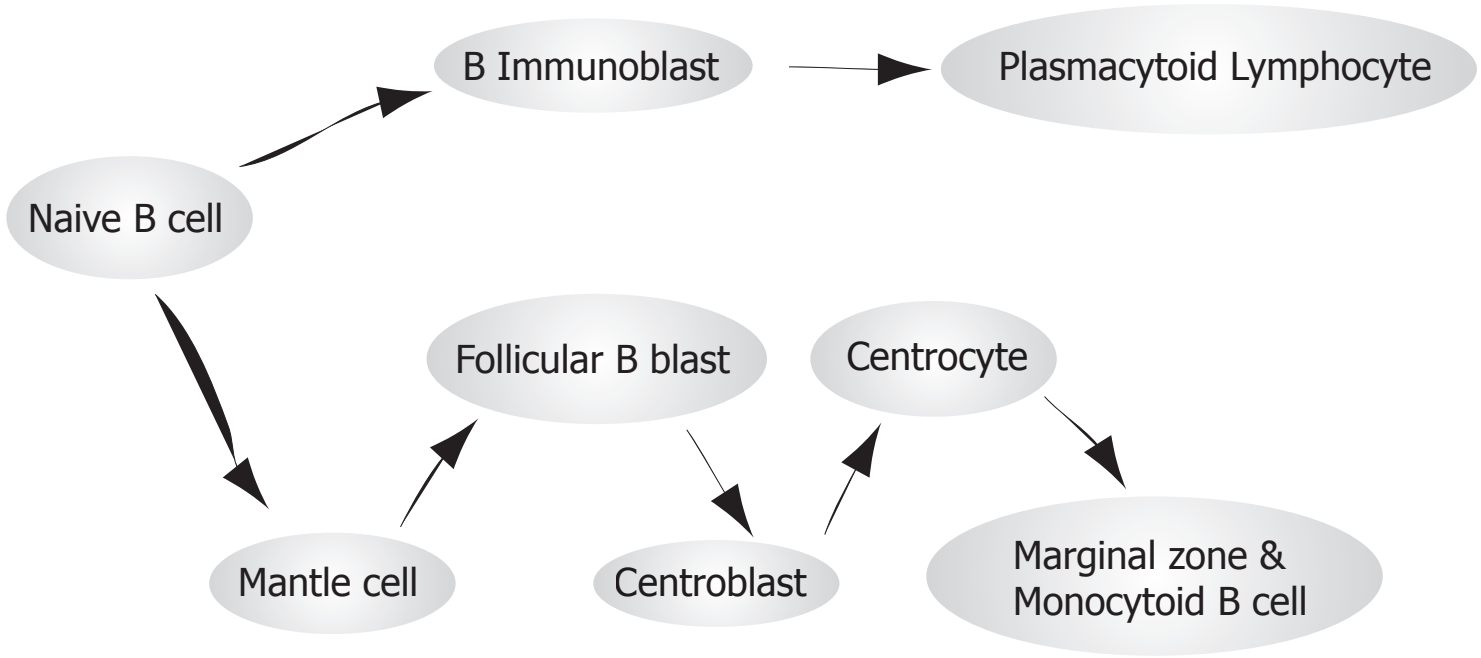

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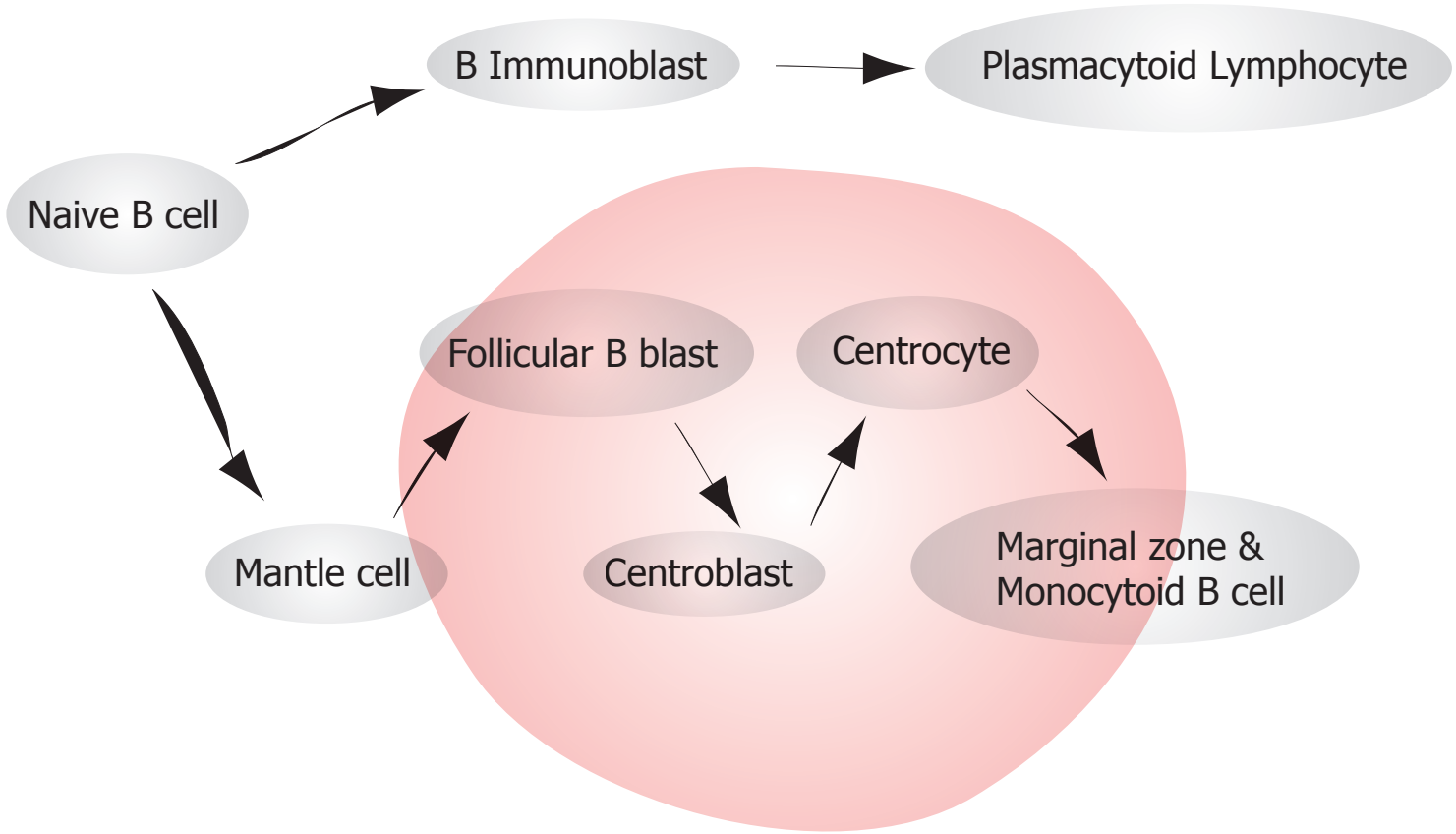

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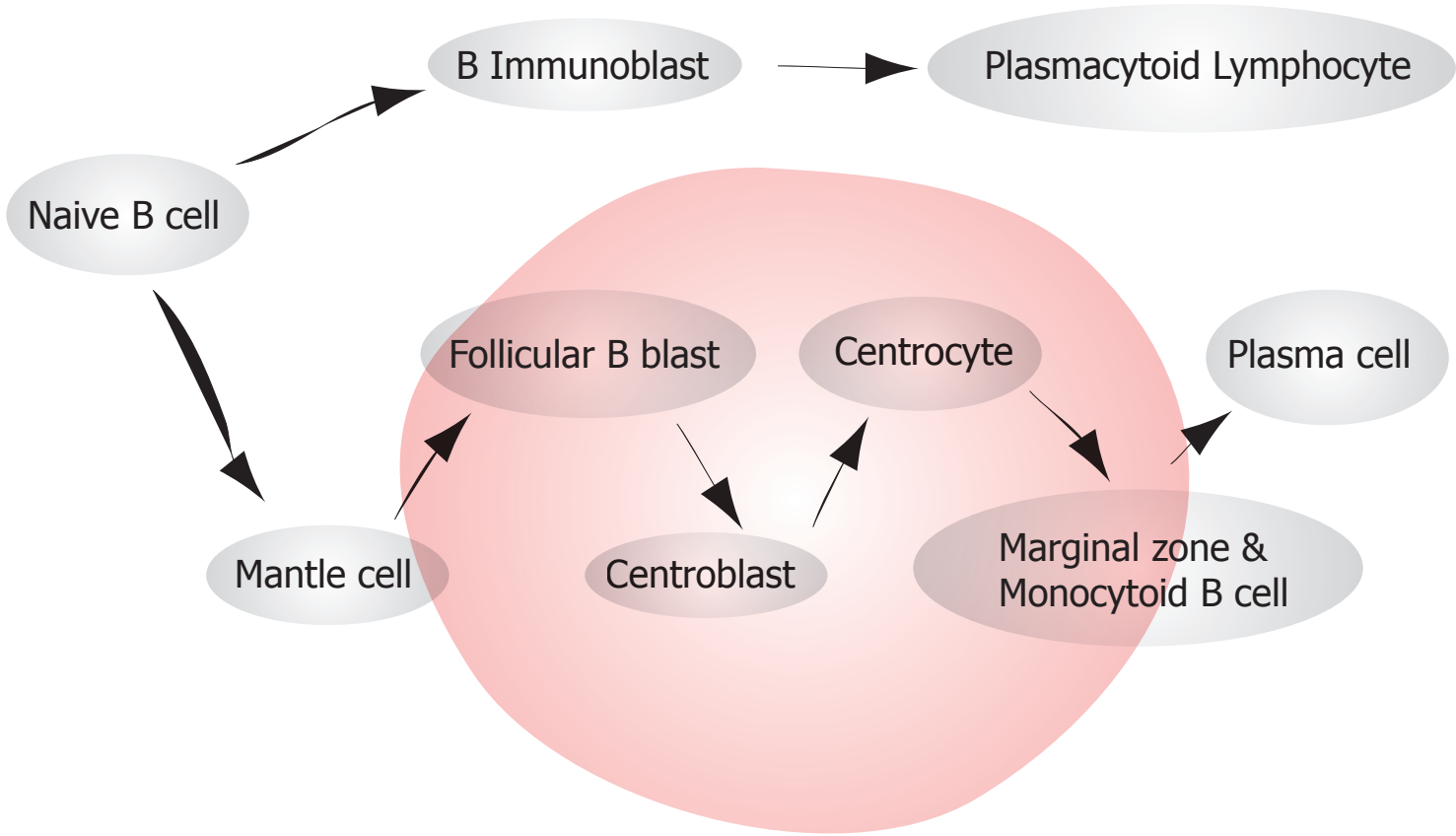
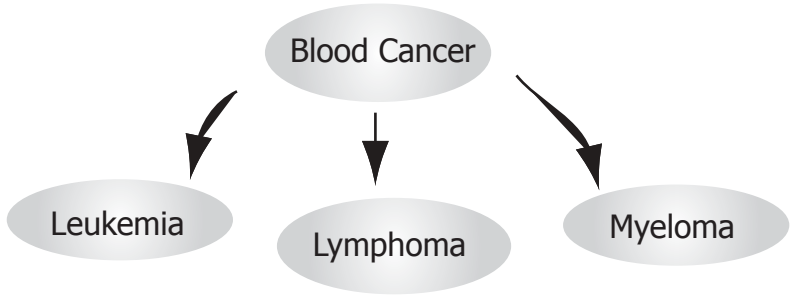


Blood Cancer



CLL can be

Chronic **L**ymphatic **L**eukemia

Small Lymphocytic Lymphoma

ALL can be

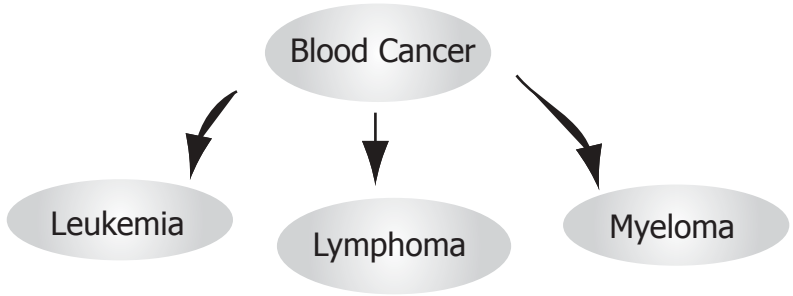
Acute **L**ymphoblastic **L**eukemia (B-ALL)

if $>$25 % Lymphoblasts in bonemarrow

Lympho**b**lastic **L**ymphoma (B-LBL)

else

Blood Cancer



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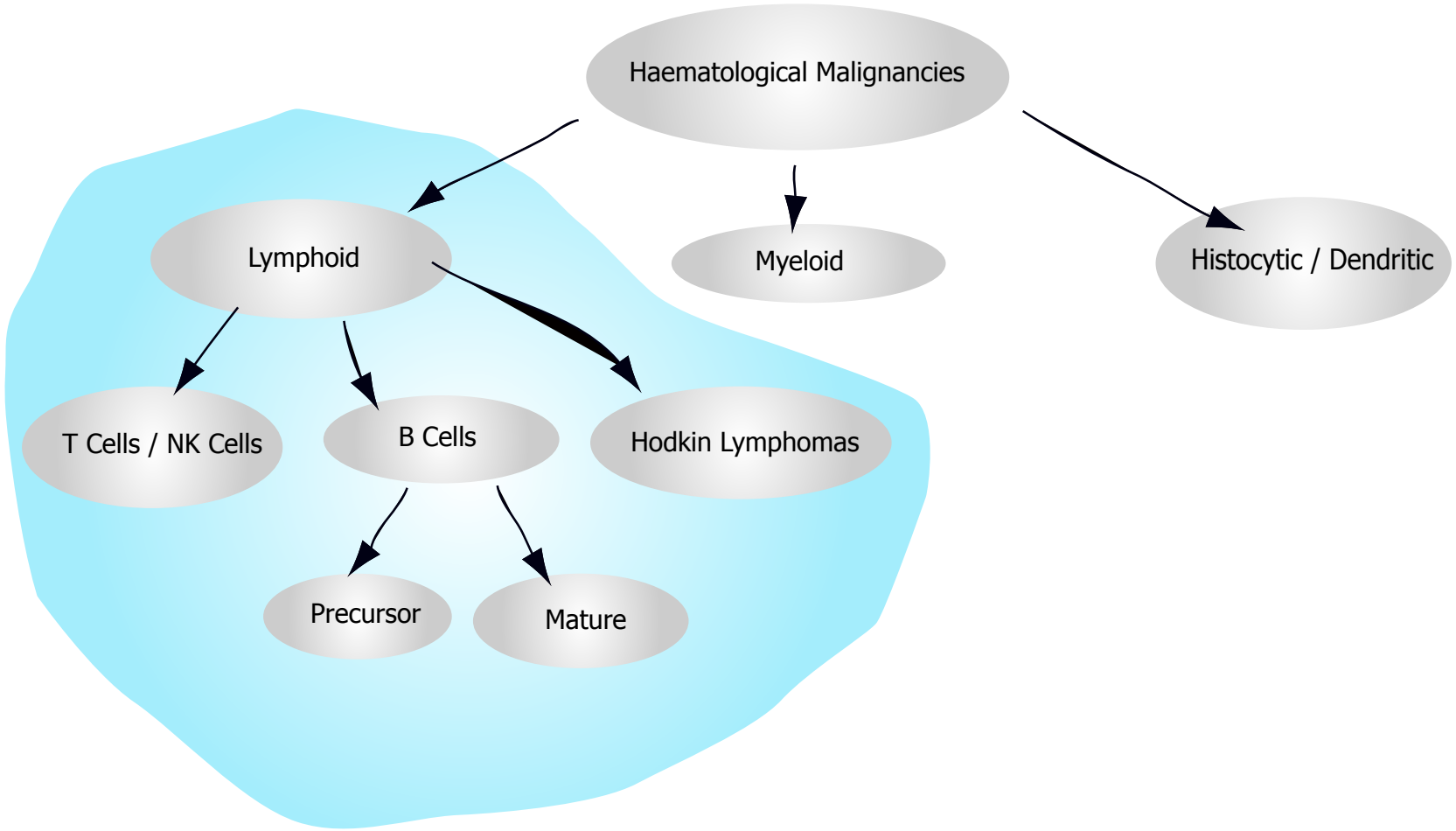
else

each case: **same biological entity**

WHO Classification



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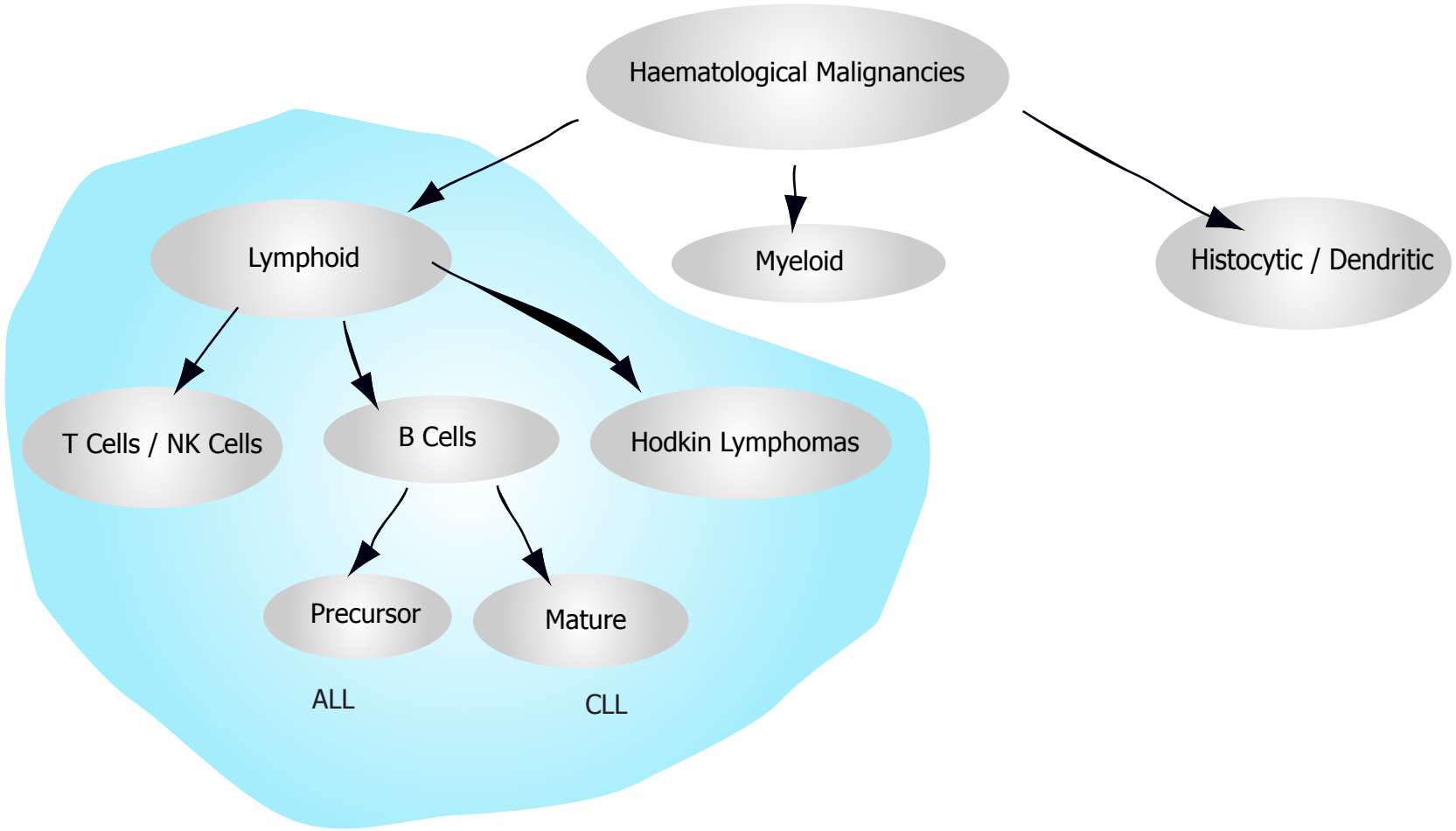

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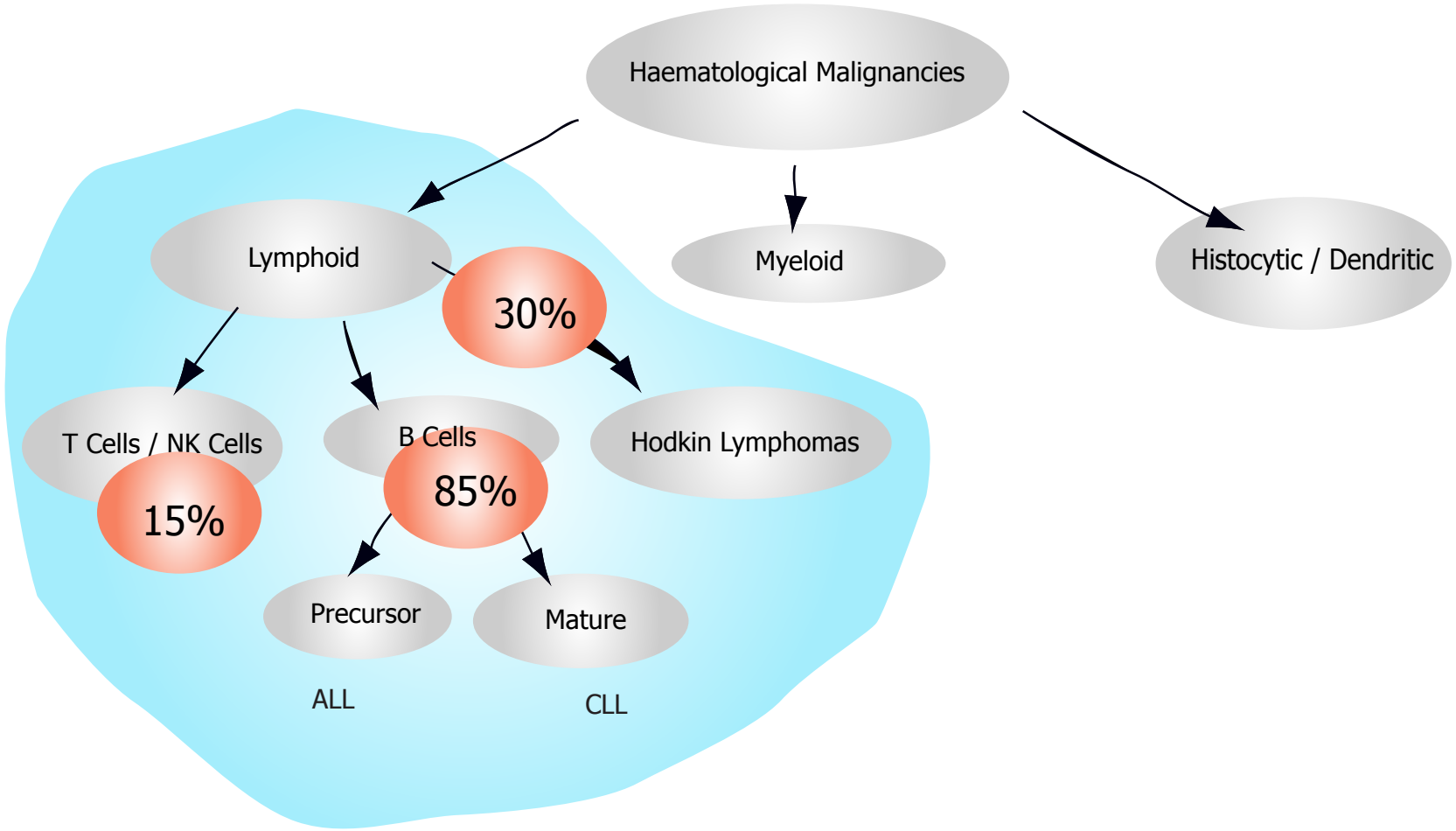
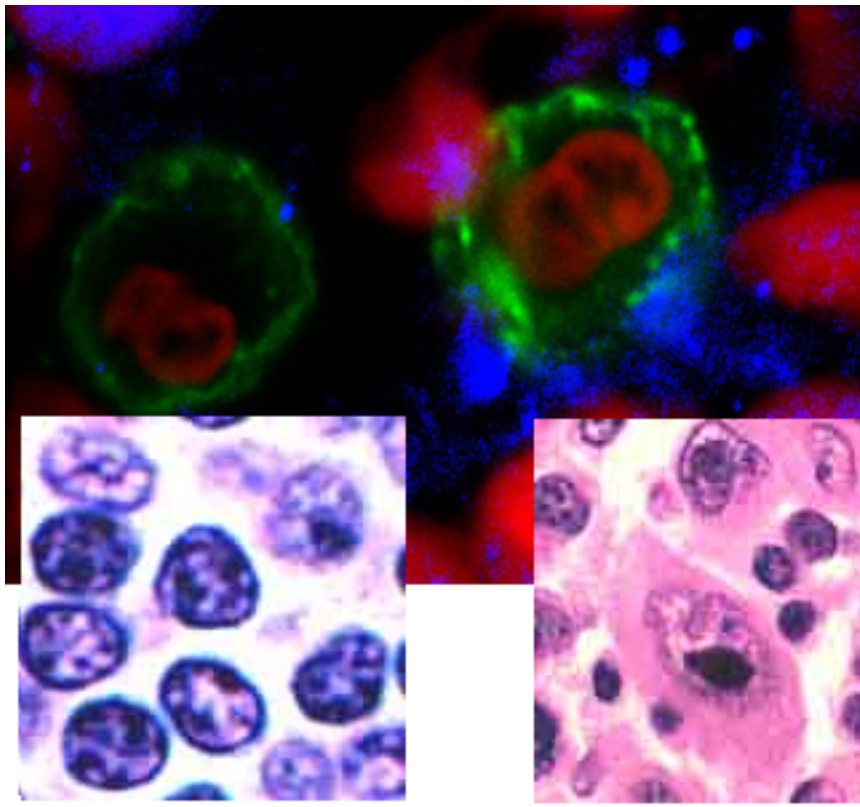


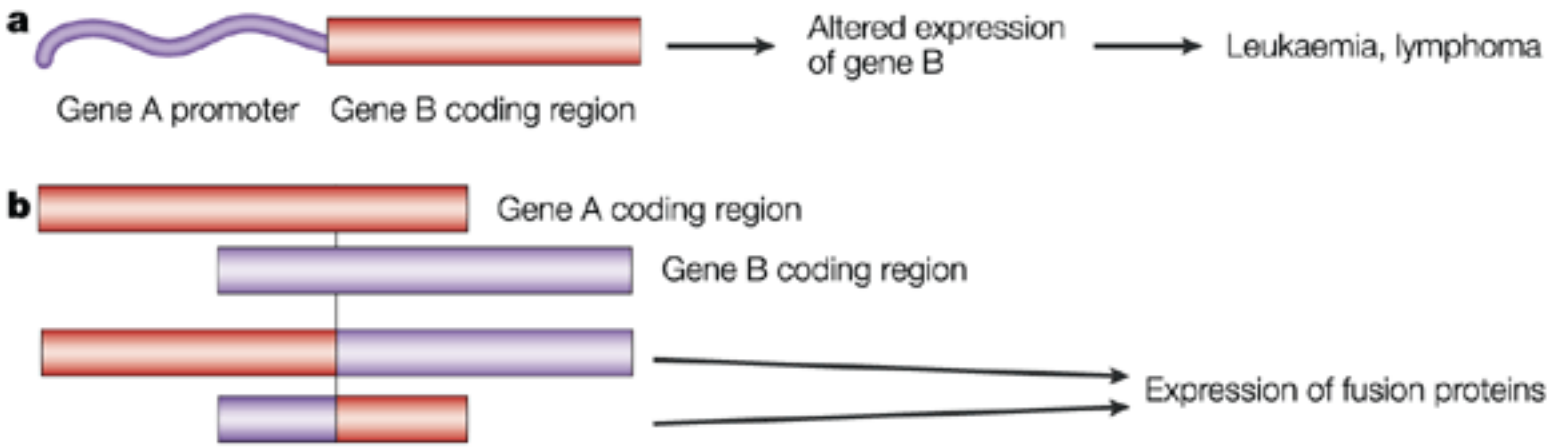
WHO Classification ctd.

Criteria:

- Clinical Presentation
  - dissaminated?
  - leuekemic?
  - extranodal/nodal?
- Morpholgy
  - 'structure' of cells involved
- Immunophenotype
  - CD surface markers, Immunoglobulins
- Cytogenetics
  - translocations



Translocations



- deregulate oncogene by placing it e. g. near IG loci
  oncogenes have been found that way
- create new fusion proteins

WHO B–Cell Neoplasms

I. Precursor B-cell neoplasm:

A. precursor B-acute lymphoblastic leukemia/lymphoblastic lymphoma (B-ALL, LBL)

II. Peripheral B-cell neoplasms

A. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
B. B-cell prolymphocytic leukemia
C. Lymphoplasmacytic lymphoma/immunocytoma
D. Mantle cell lymphoma
E. **Follicular lymphoma (22%)**
F. Extranodal marginal zone B-cell lymphoma of MALT type
G. Nodal marginal zone B-cell lymphoma (+/- monocytoid B-cells)
H. Splenic marginal zone lymphoma (+/- villous lymphocytes)
I. Hairy cell leukemia
J. Plasmacytoma/plasma cell myeloma
K. **Diffuse large B-cell lymphoma (30%)**
L. Burkitt's lymphoma

(subtypes are missing)

Diffuse Large B–Cell Lymphoma

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- Account for about 30% of B–cell neoplasms

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- Two variants (morphological)
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- Highly variable clinical course (independent of subtype)

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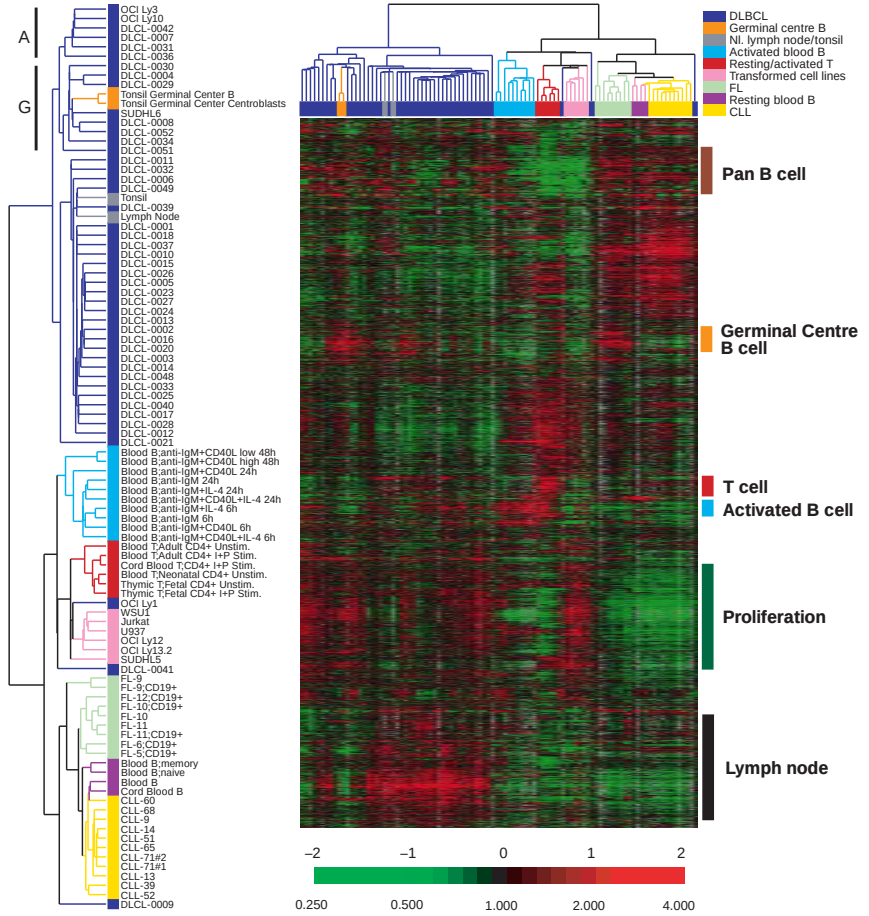
use microarrays for further classification

Microarrays: Alizadeh *et al.*

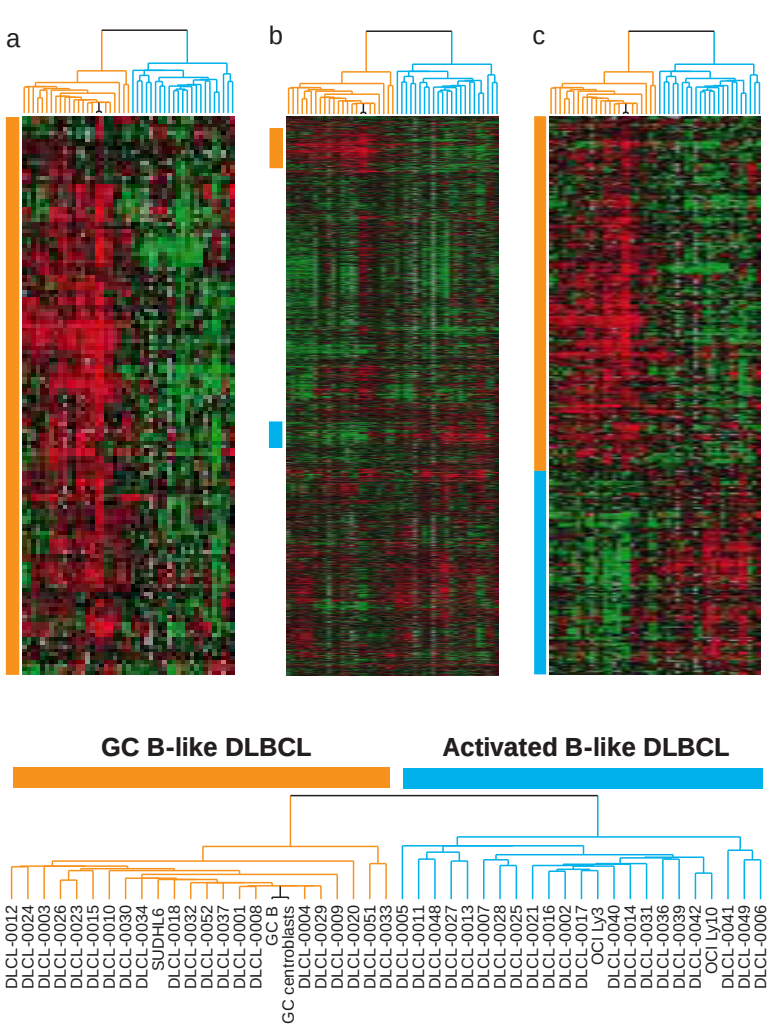
Lymphochip

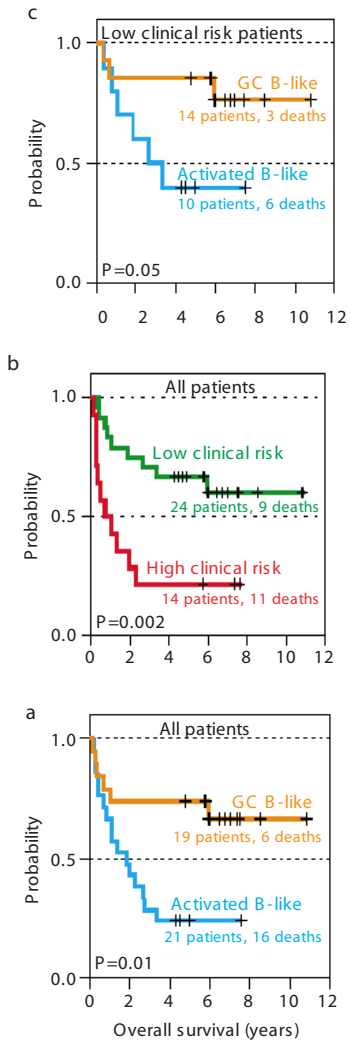
- 17 856 cDNA clones
- 96 tissue-samples
- DLBCL, FL, CLL
- 128 chips

Alizadeh, A. *et.al* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* **4051**, 503-511 (2000)



Alizadeh ctd.



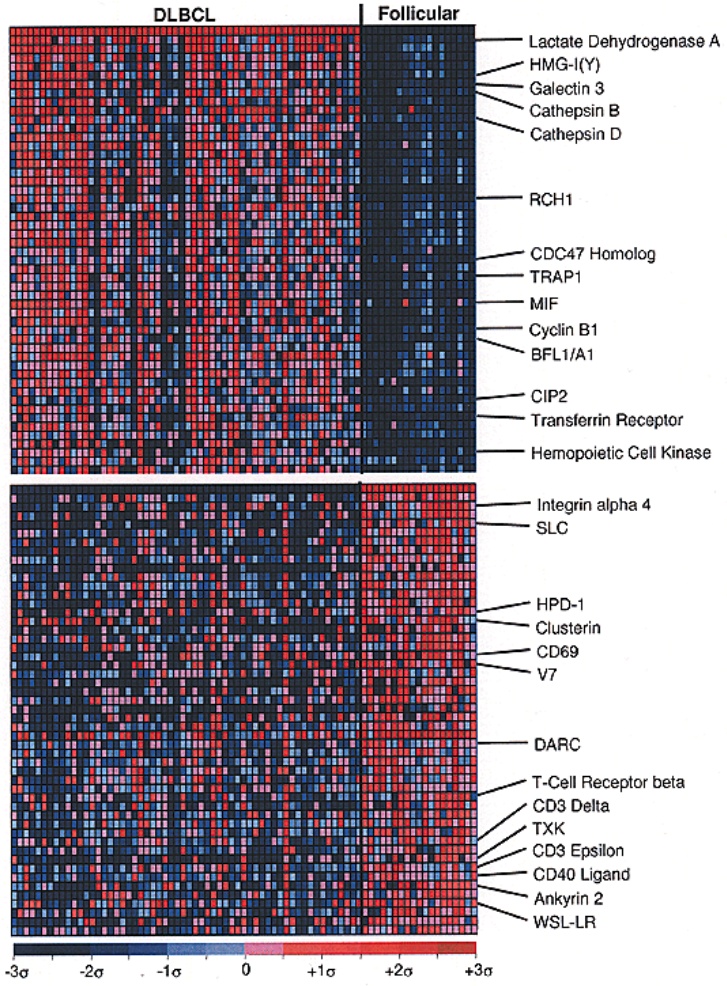


Microarrays: Shipp *et al.*

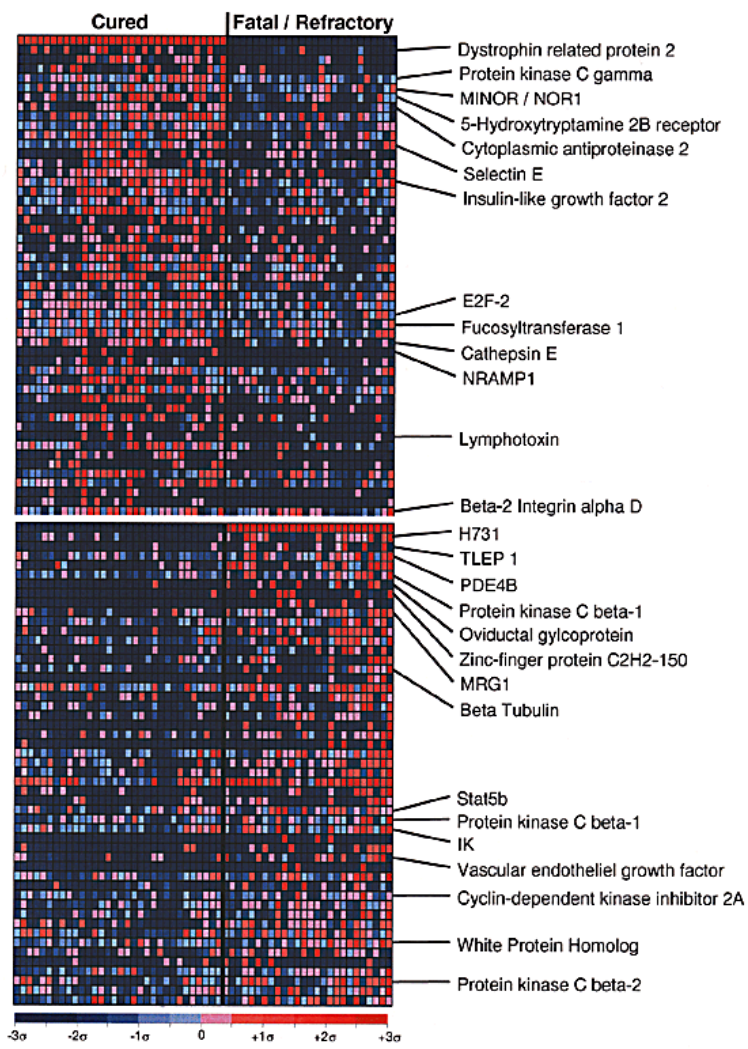
Affy HU 6800

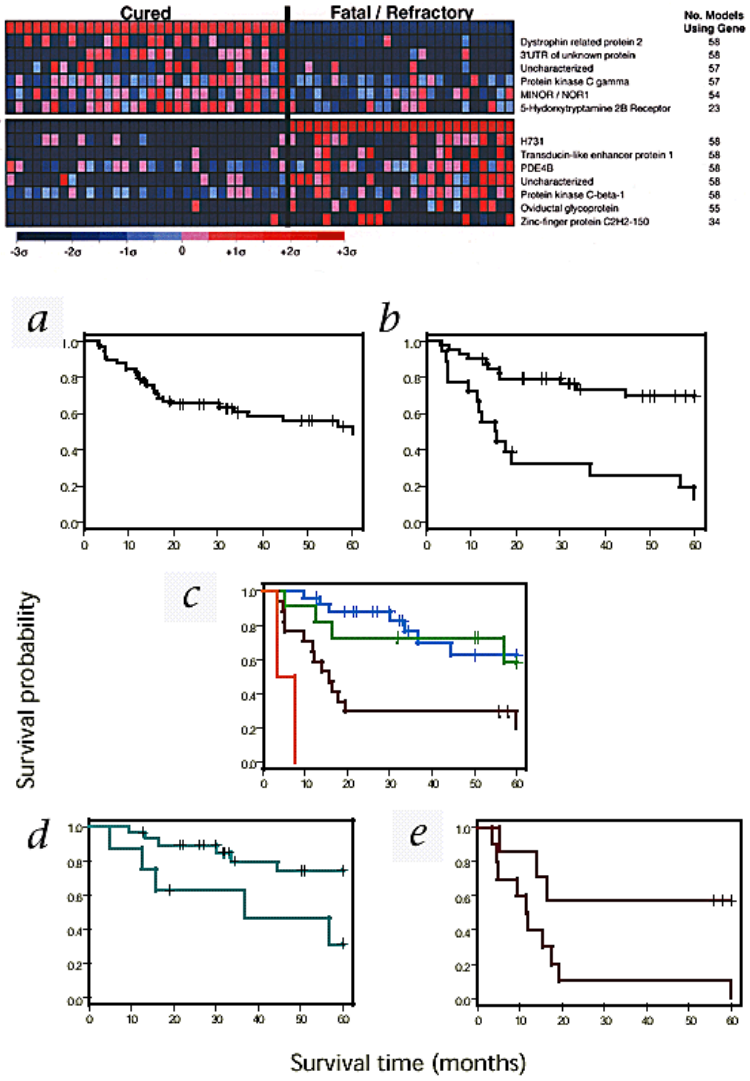
- 6 800 genes
- 77 tissue samples
- DLBCL, FL

Shipp, M.A. *et al.* Diffuse large B-cell lymphoma outcome predition by gene expression profiling using supervised machine learning. *Nature Medicine* **8**, 68-74 (2002)

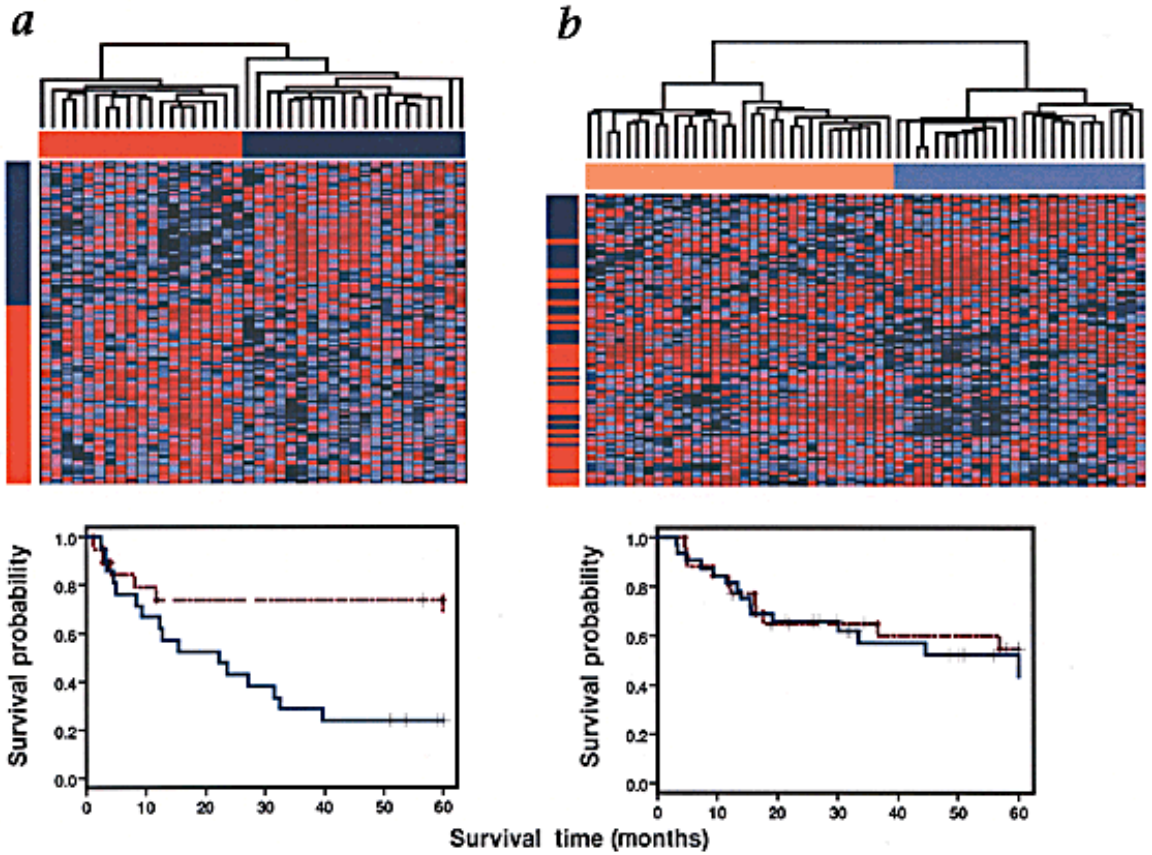


Shipp ctd.


Cured
Fatal / Refractory
Dystrophin related protein 2
Protein kinase C gamma
MINOR / NOR1
5-Hydroxytryptamine 2B receptor
Cytoplasmic antiproteinase 2
Selectin E
Insulin-like growth factor 2
E2F-2
Fucosyltransferase 1
Cathepsin E
NRAMP1
Lymphotoxin
Beta-2 Integrin alpha D
H731
TLEP 1
PDE4B
Protein kinase C beta-1
Oviductal gylcoprotein
Zinc-finger protein C2H2-150
MRG1
Beta Tubulin
Stat5b
Protein kinase C beta-1
IK
Vascular endotheliel growth factor
Cyclin-dependent kinase inhibitor 2A
White Protein Homolog
Protein kinase C beta-2
-3σ -2σ -1σ 0 +1σ +2σ +3σ


Cured
Fatal / Refractory
No. Models Using Gene
Dystrophin related protein 2 58
3'UTR of unknown protein 58
Uncharacterized 57
Protein kinase C gamma 57
MINOR / NOR1 54
5-Hydoxytryptamine 2B Receptor 23
H731 58
Transducin-like enhancer protein 1 58
PDE4B 58
Uncharacterized 58
Protein kinase C-beta-1 58
Oviductal glycoprotein 55
Zinc-finger protein C2H2-150 34
-3σ -2σ -1σ 0 +1σ +2σ +3σ
a
b
c
d
e
Survival probability
Survival time (months)

Shipp ctd.


a
b
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Survival time (months)