

# **Cytologie van rijpe lymfatische B-cel maligniteiten**

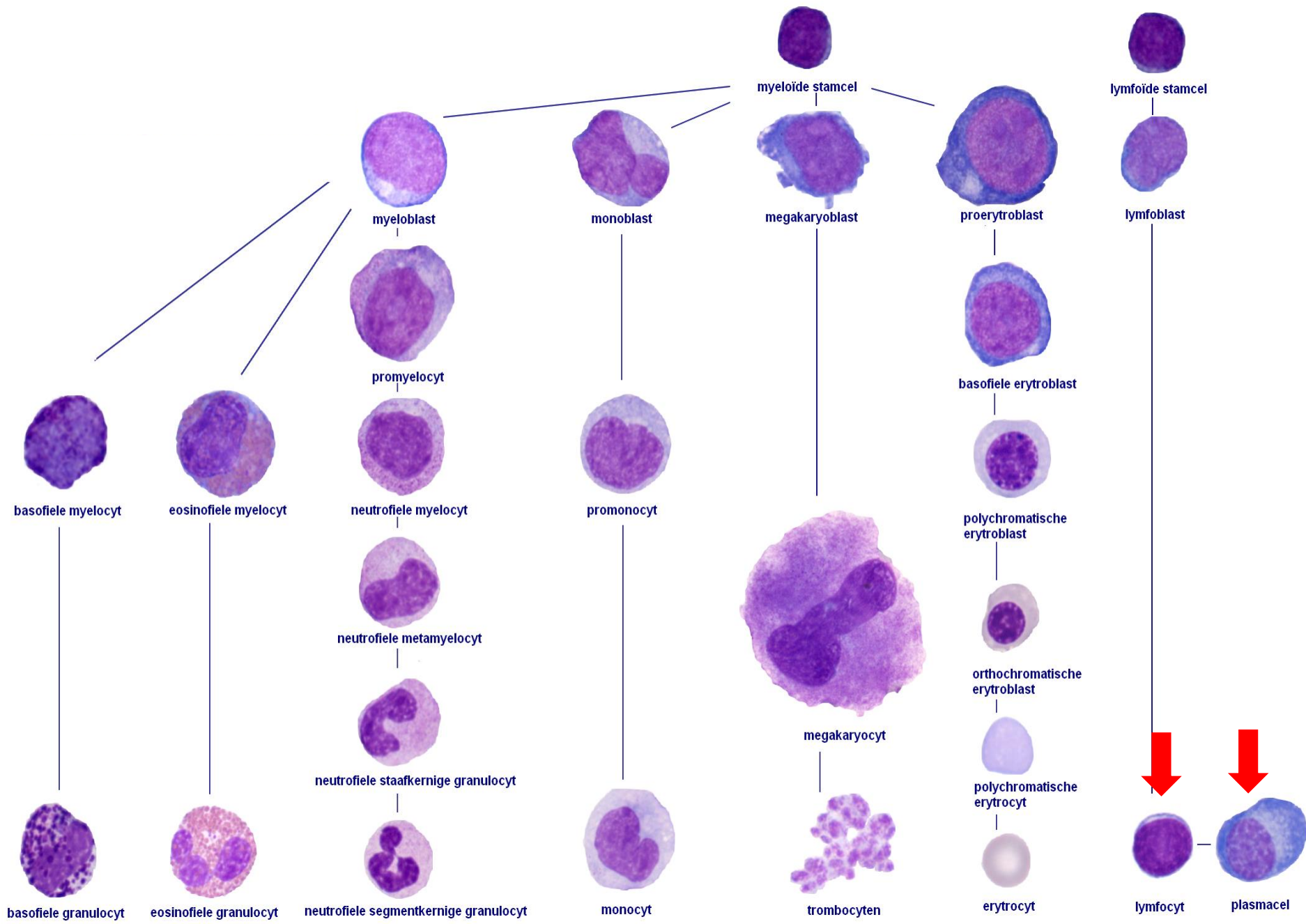
**André Mulder**

Arts klinische chemie/klinisch chemicus

UMCG

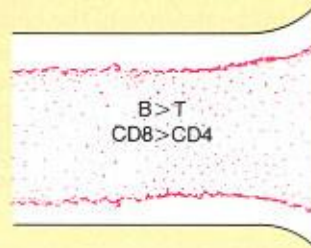
# Disclosures

Type van verstrengeling / mogelijk (financieel) belang	Naam van commercieel bedrijf
<i>Ontvangst van subsidie(s)/research ondersteuning:</i>	Geen belangen
<i>Ontvangst van honoraria of adviseursfee:</i>	Geen belangen
<i>Lid van een commercieel gesponsord 'speakersbureau'</i>	Geen belangen
<i>Financiële belangen in een bedrijf (aandelen of opties)</i>	Geen belangen
<i>Andere ondersteuning (gelieve te specificeren):</i>	Geen belangen
<i>Wetenschappelijke adviesraad:</i>	Geen belangen



### Primary lymphoid organs

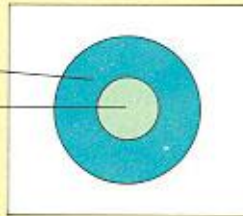
Bone marrow



Thymus

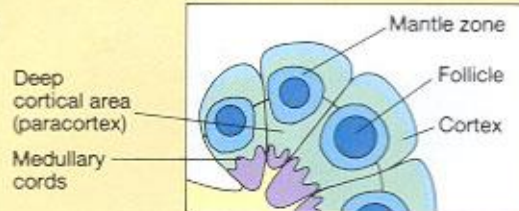
Cortex Td $\alpha$ T<sup>+</sup>

Medulla Td $\alpha$ T<sup>-</sup>

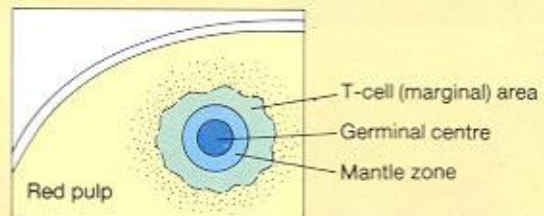


### Secondary lymphoid organs

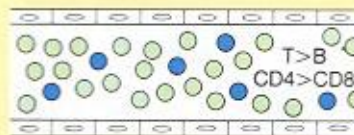
Lymph node



Spleen



Blood

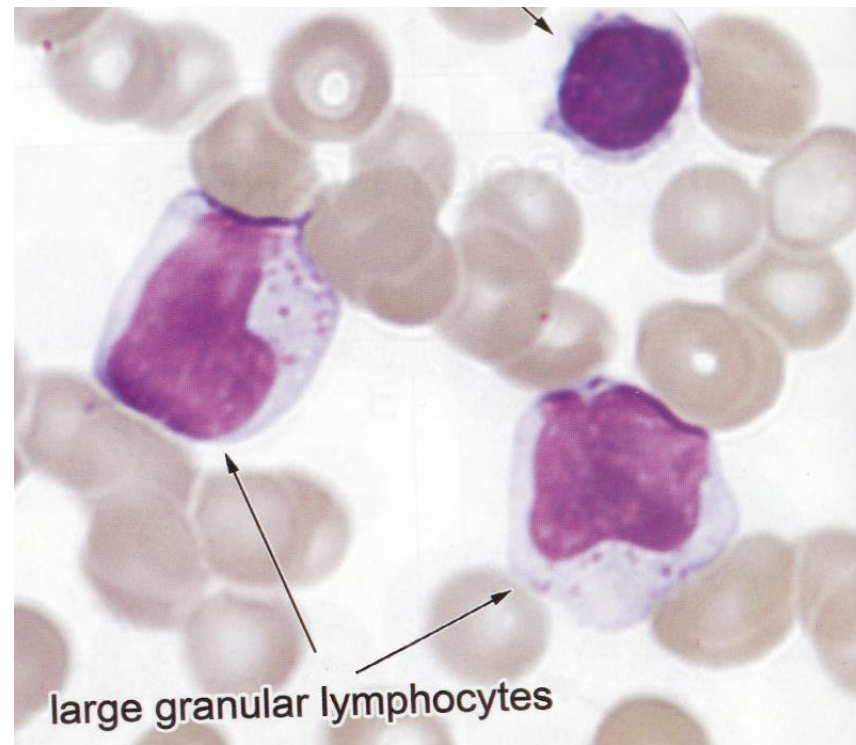
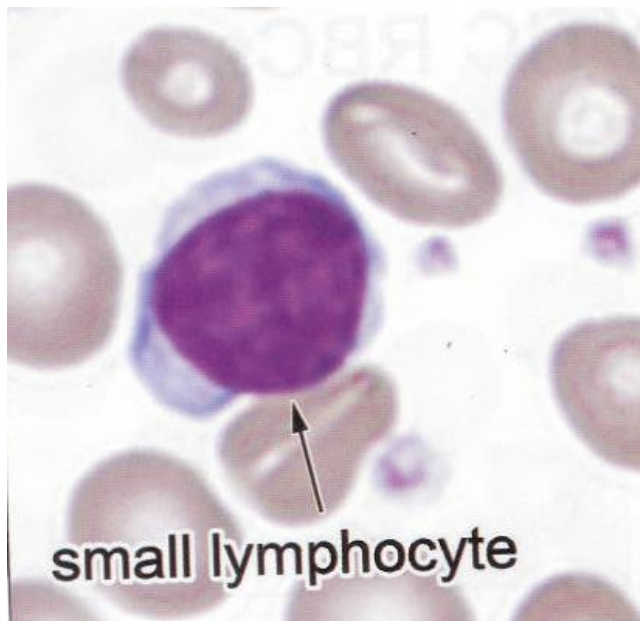


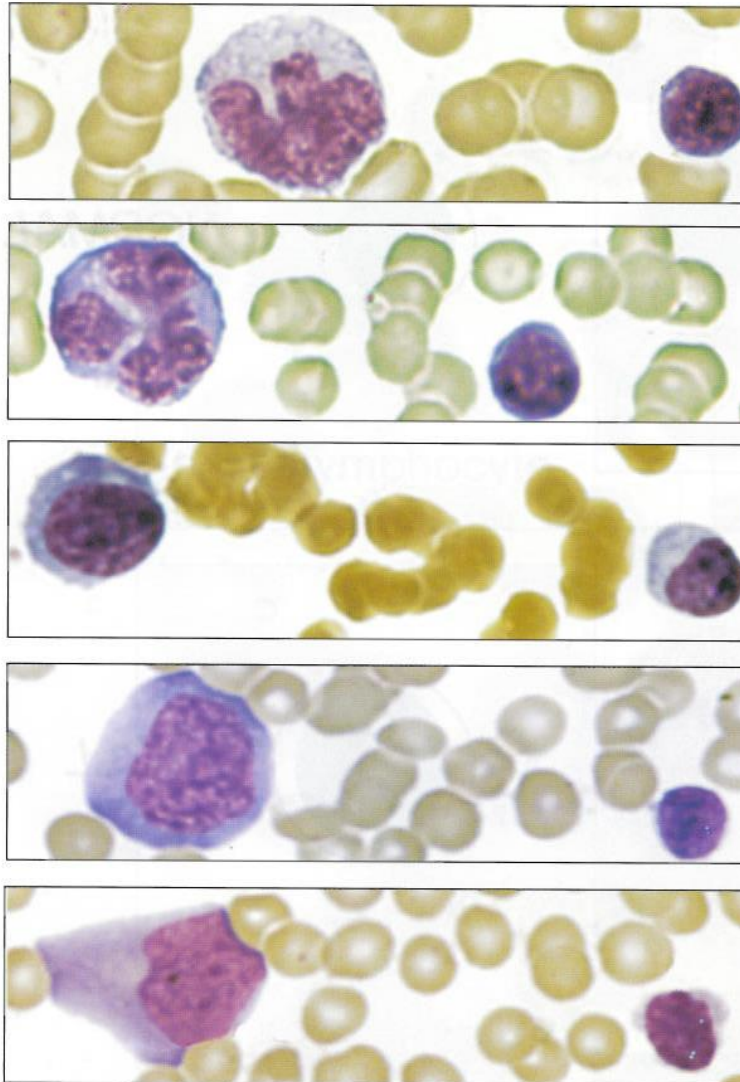
B-cell areas

T-cell areas

# Bloed: lymfocyten ( $< 4 \times 10^9/L$ )

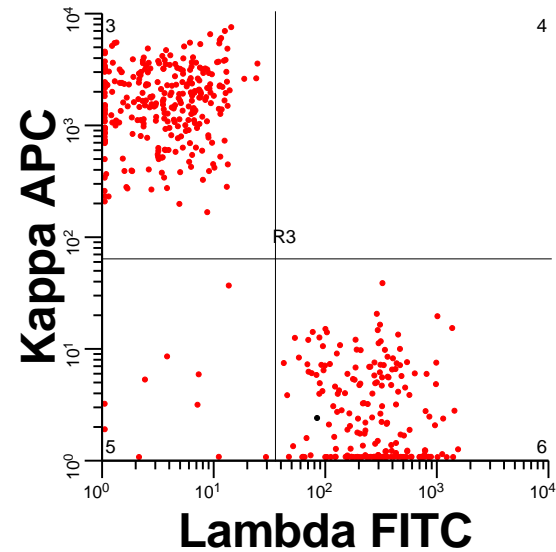
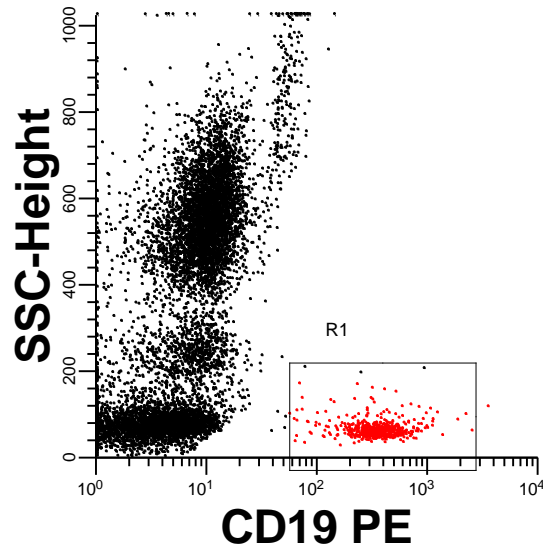
T-lymfocyten (CD4>CD8) > LGL cellen (T/NK, < 20%) > B-cellen (K>L)





**Reactief beeld: atypische lymfocyten: EBV infectie**

# Polyklonale B Lymphocyten



*Pro-B-cell*

CD34  
TdT

CD22



*Pre-B-I cell  
(Pre-pre-B-cell)*

CD34  
TdT  
CD10<sup>bright</sup>  
CD19

CD22  
CD45<sup>dim</sup>



*Pre-B-II cell  
(Pre-B-cell)*

(TdT)  
CD10  
CD19  
CD20<sup>het</sup>  
CD22  
CD45  
Cylg $\mu$



*Immature B-cell  
(tr. Pre-B-cell)*

CD10<sup>dim</sup>  
CD19  
CD20  
CD22  
CD45<sup>bright</sup>  
Cylg $\mu$   
SmlgM



*Mature B-cell*

CD19  
CD20  
CD22<sup>bright</sup>  
CD45<sup>bright</sup>

SmlgM

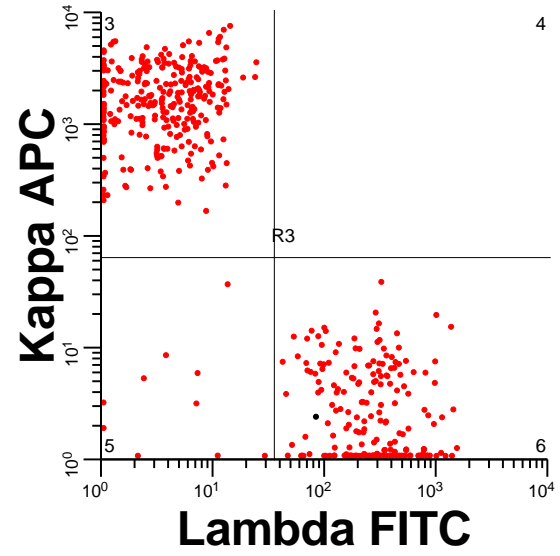
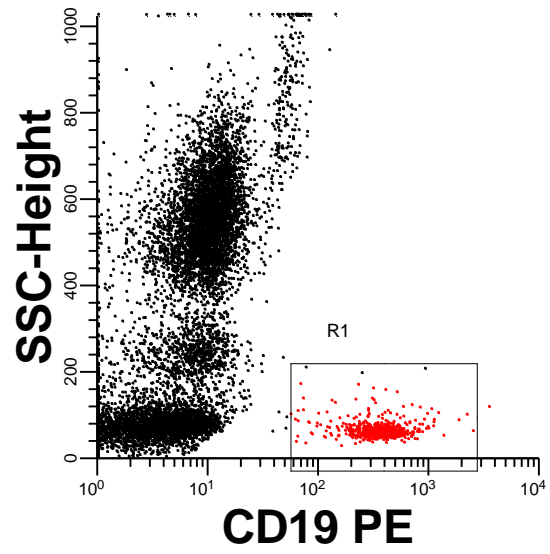


*Plasma cell*

CD19  
  
CD45  
Cylg





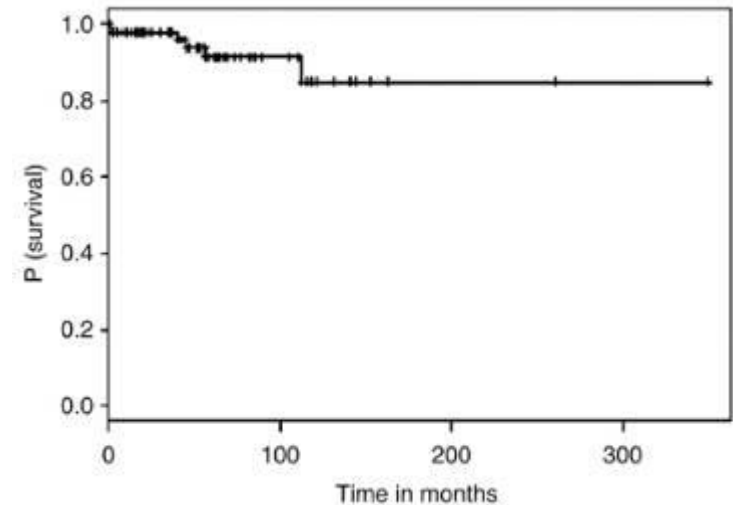


# Long-term follow-up of 111 patients with persistent **polyclonal B-cell lymphocytosis** with binucleated lymphocytes

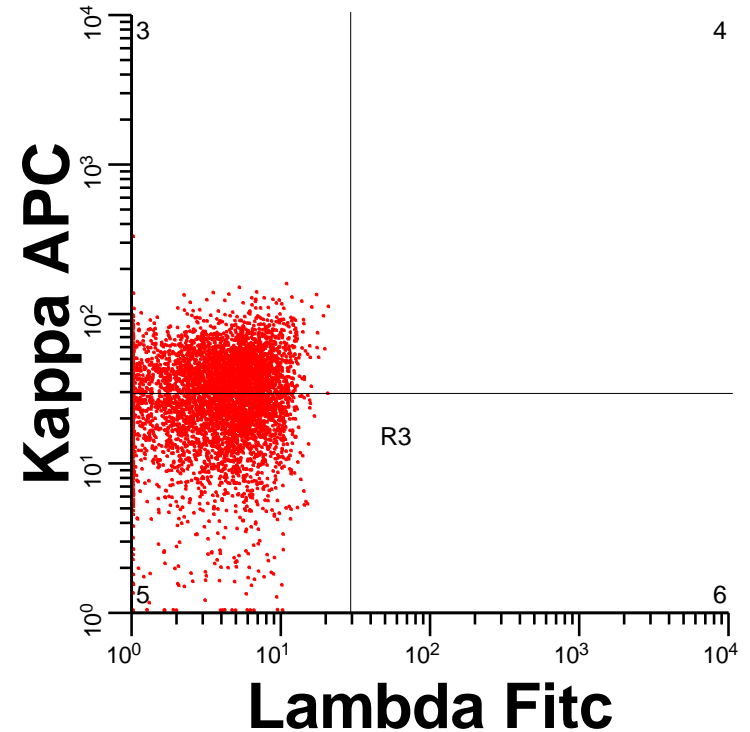
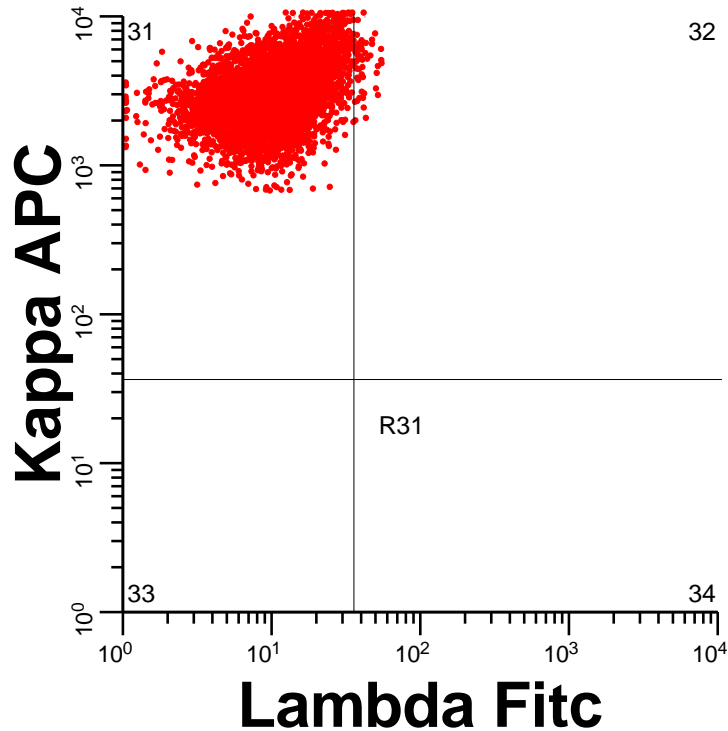


*Edouard Cornet et al, Leukemia 2009;23:419-22*

- n = 111, 82% **female**
- **age: median 40** (19-66)
- **98% smoking**
- 10% spleen enlarged
- IgM median 6 g/l (1.2-17.3)
- Outcome median f.u. 4 yr (0.5-29 yr): 6 died
- 3 x DLBCL, 1 x SMZL, 4 x MGUS (IgM)
- FISH 71% i(3q)

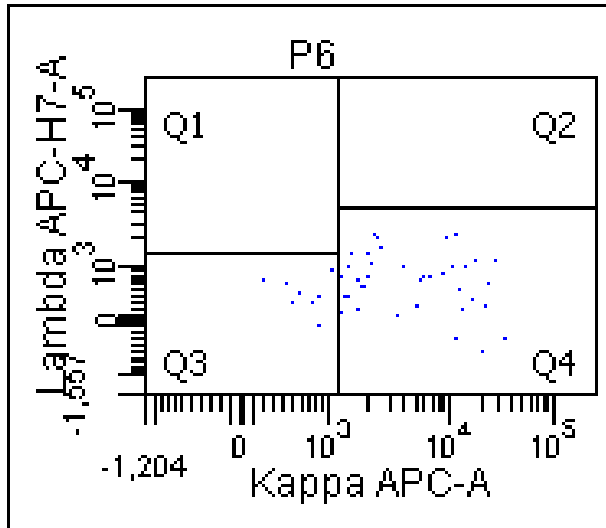
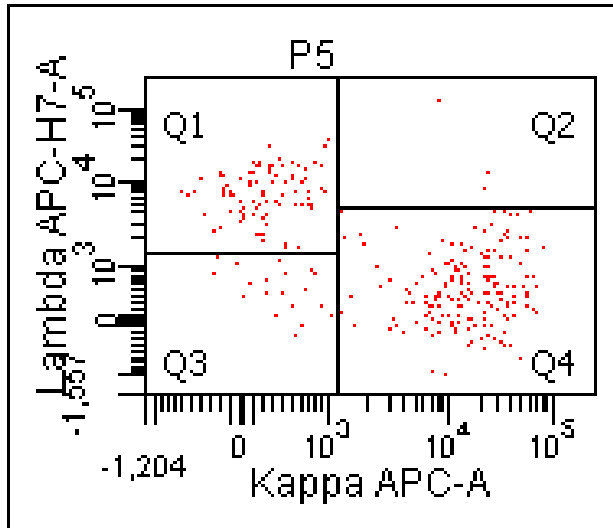
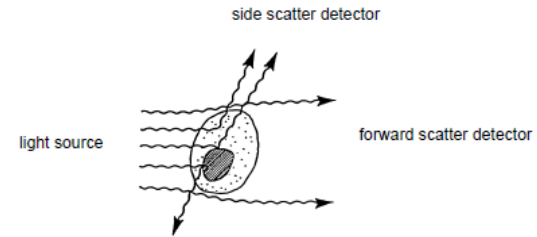
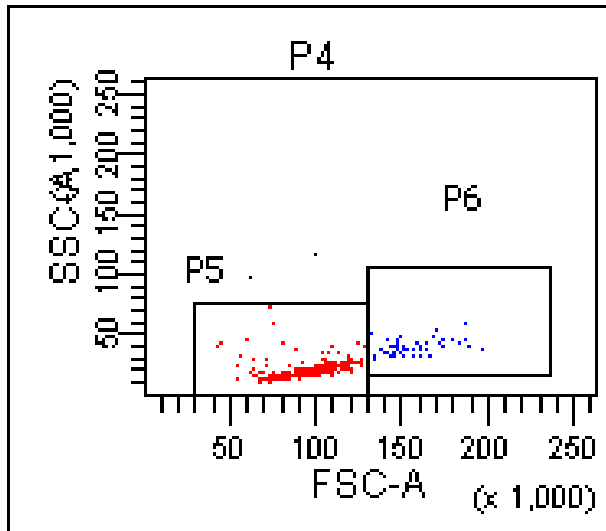
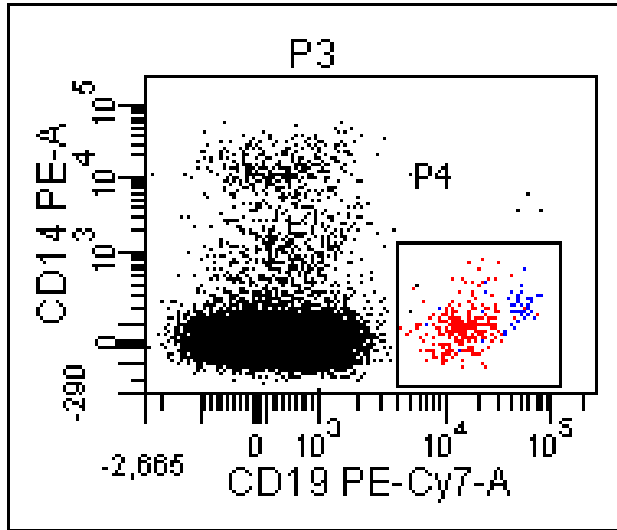


# Rijpe monoklonale B-cel maligniteiten



WHO: monoklonaal:

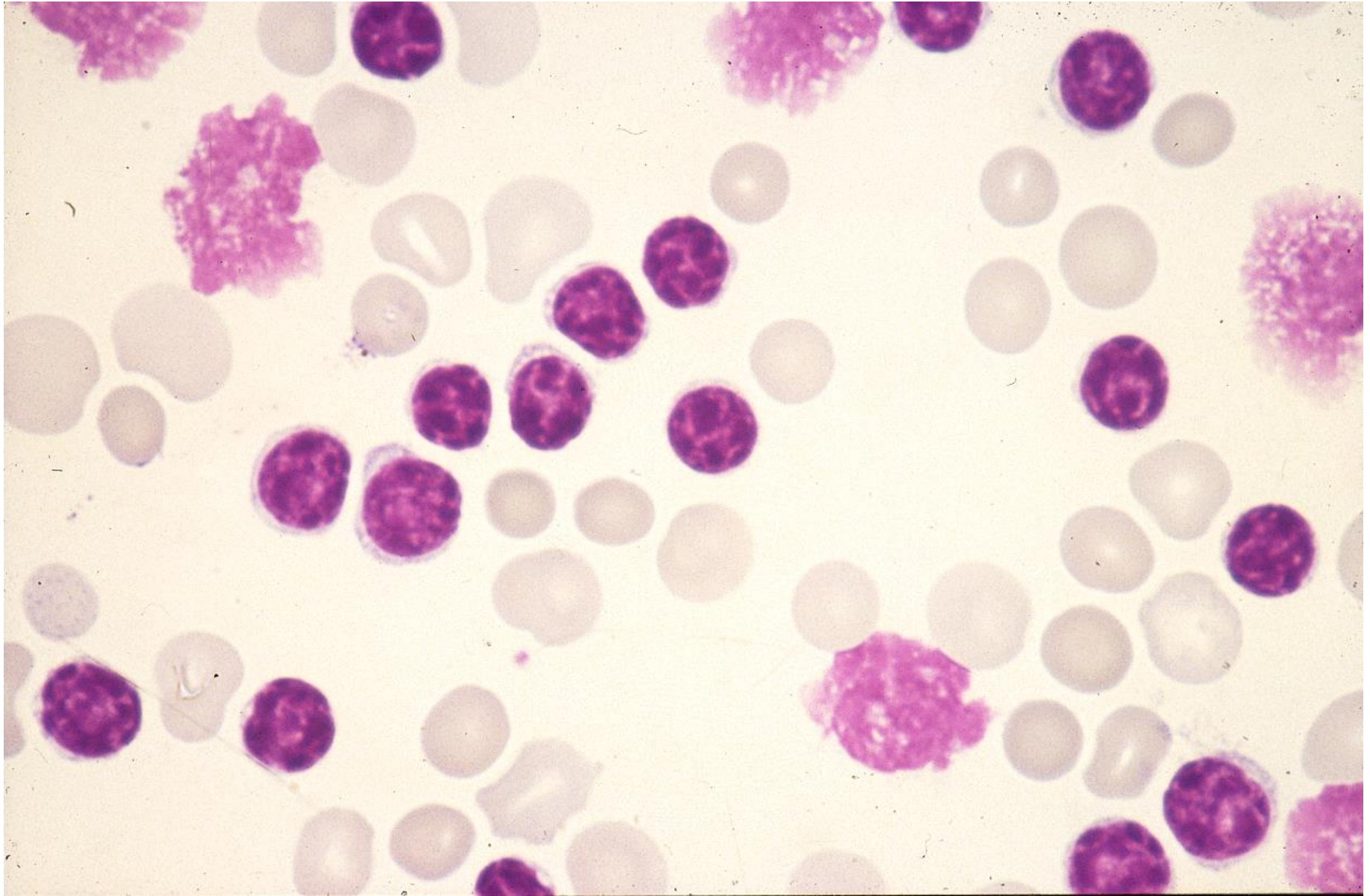
- K/L-ratio:  $> 3$  of  $< 0,3$
- of  $> 25\%$  zonder expressie van Smlg: dubbel-hit lymfomen (dd: blasten/hematogonien)



# Cytologie van rijpe lymfatische B-cel maligniteiten

Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
Smlg-expressie	++ <sup>w</sup>	++ <sup>s</sup>	++	++	++	++	++
Cylg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ, μδ, δ	μ, μδ	μ, μδ, γ, α	γ	μ, μδ, γ	μ, μδ	μ, μδ, γ
CD19	++	++	++	++	++	++ <sup>w</sup>	++
CD20	++ <sup>w</sup>	++	++ <sup>s</sup>	++	++	++ <sup>s</sup>	++
CD21	+	±	±	—	±	±	±
CD22	+ <sup>w</sup>	++ <sup>s</sup>	++ <sup>s</sup>	++	++ <sup>s</sup>	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	± <sup>p</sup>	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	+ <sup>w</sup>
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	++	+	±	—	—
(FMC7)	±	++ <sup>s</sup>	++	++	++	+	++
CD138	-	-	-	-	-	-	-

?



# Cytologie:

- Morfologie: monotone **lymfocytose**
- kleine cellen (6-10 um), smalle cytoplasmazoom, zeer **grof kernchromatine** (grumelee), **kapotte cellen** (Gumprechtse schollen)
- flow: **monoklonale** B lymfocyten

**Table 1**

**WHO Classification of Haematolymphoid Tumours, 5<sup>th</sup> edition: B-cell lymphoid proliferations and lymphomas**

**WHO Classification, 5<sup>th</sup> edition**

***Tumour-like lesions with B-cell predominance***

***Precursor B-cell neoplasms***

***Mature B-cell neoplasms***

**Pre-neoplastic and neoplastic small lymphocytic proliferations**

**Monoclonal B-cell lymphocytosis**

**Chronic lymphocytic leukaemia/small lymphocytic lymphoma**

(Entity deleted)

**WHO Classification, revised 4<sup>th</sup> edition**

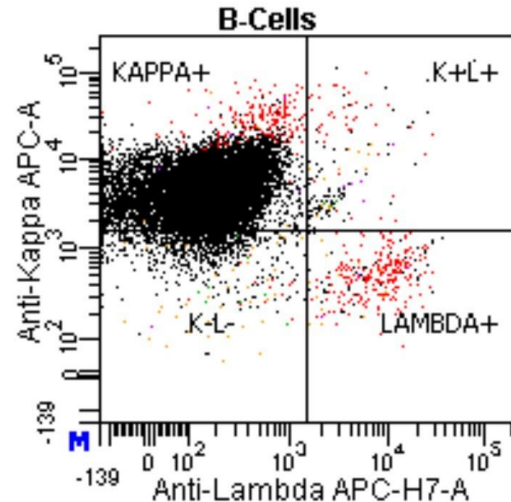
(Same)

(Same)

B-cell prolymphocytic leukaemia



# Monoclonale B cel lymfocytose (MBL)



## Symptomen:

- asymptomatisch (toevalsbevinding)
- vage B-symptomen (moeheid, gewichtsverlies, nachtzweeten)
- Soms toegenomen infectiekans/suboptimale response op vaccinaties
- **geen lymfadenopathie**
- **geen organomegalie**
- **geen andere tekenen van een hematologische maligniteit (cytopenie)**

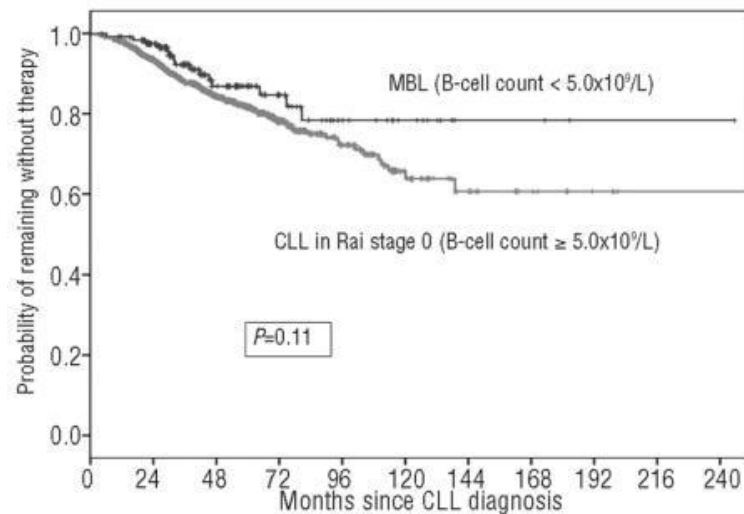
Bloed (beenmerg, secundaire lymfoide organen)

Flowcytometrie: **monoklonale B-cellen:  $< 5 \times 10^9/L$**

# Monoclonale B cel lymfocytose (MBL)

## 1. MBL, low-count

- Monoklonaal CLL/SLL fenotype  $< 0.5 \times 10^9/L$
- **CD5+/CD23+/Smlg zwak+/CD10-**
- 40-50 jr: 1-5%
- 65-80 jr: 5-25%
- $> 90$  jr: 50-75%
- **Zeer weinig kans op progressie naar CLL/SLL**



## 2. MBL, CLL/SLL-type: CD5+

- **Monoklonaal CLL/SLL fenotype  $0.5 - 5 \times 10^9/L$**
- **0,5-2% per jaar over in CLL**
- Genetische predispositie: multiplere SNPs (familiestudies)
- Moleculaire afwijkingen conform CLL/SLL (o.a. 13q14 deleties)
- Soms TP53 mutaties/deleties: niet per definitie uiting van progressie

## 3. MBL, non-CLL/SLL-type: CD5-

- **Monoklonaal non-CLL/SLL fenotype (MZL of LPL fenotype): CD5-**
- **Uitgebreid stadieringsonderzoek nodig!!**

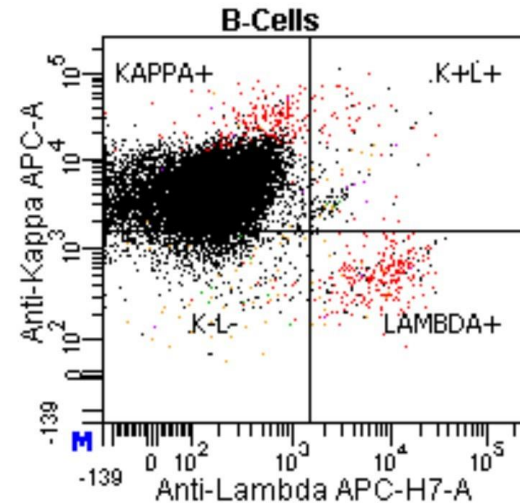
Rawstron. *N Engl J Med* 2008;359:575-83.

Molica. *Haematologica* 2011;96:277-83.

# MBL

- **Belangrijke betekenis: het vinden van een kleine subpopulatie monoclonale B cellen is niet altijd een uiting van een maligniteit!**

# CLL/SLL



## Symptomen:

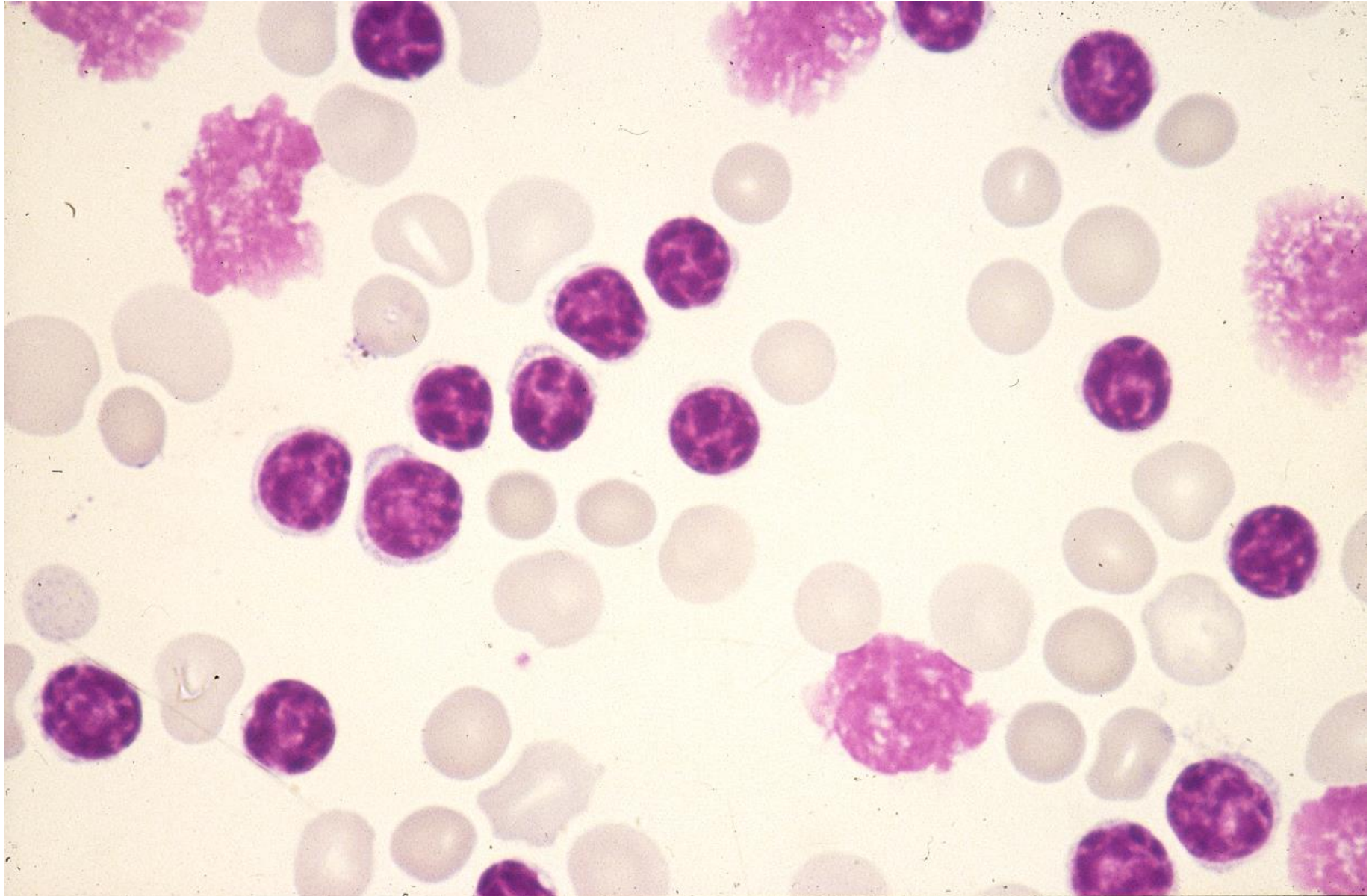
- asymptomatisch (toevalsbevinding)
- vage B-symptomen (moeheid, gewichtsverlies, nachtzweeten)
- Soms toegenomen infectiekans/suboptimale response op vaccinaties
- **lymfocytose**
- **lymfadenopathie**
- **Organomegalie (milt)**
- **andere tekenen van een hematologische maligniteit (cytopenie e.a.)**

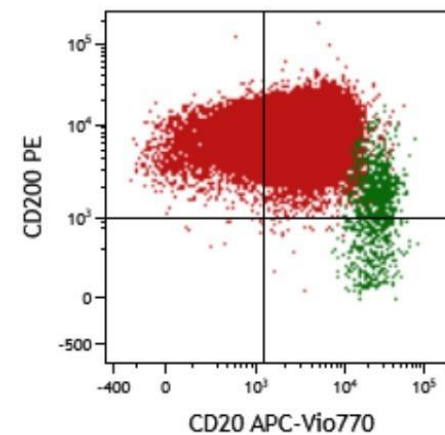
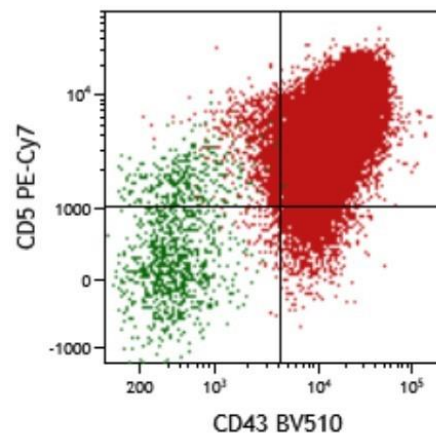
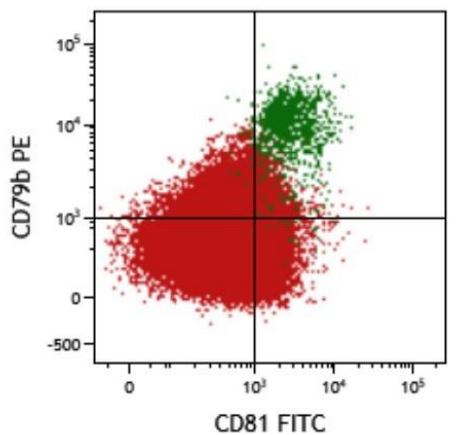
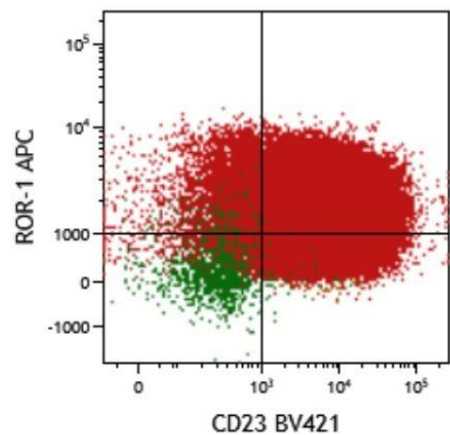
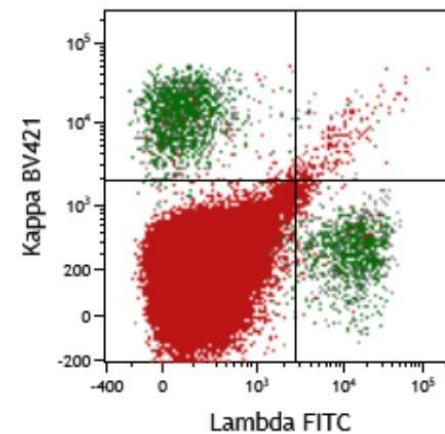
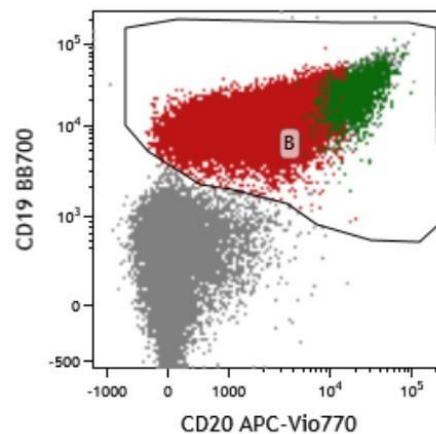
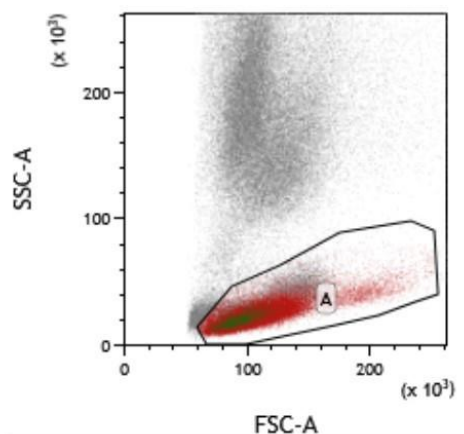
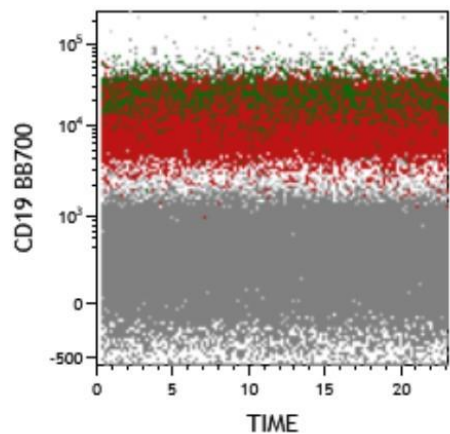
Bloed (beenmerg, secundaire lymfoide organen)

Flowcytometrie: monoclonale B-cellen in bloed:

- **< 5 x 10<sup>9</sup>/L: Small Lymphocytic Lymphoma (SLL)**
- **> 5 x 10<sup>9</sup>/L: CLL**

# + flowcytometrie nodig





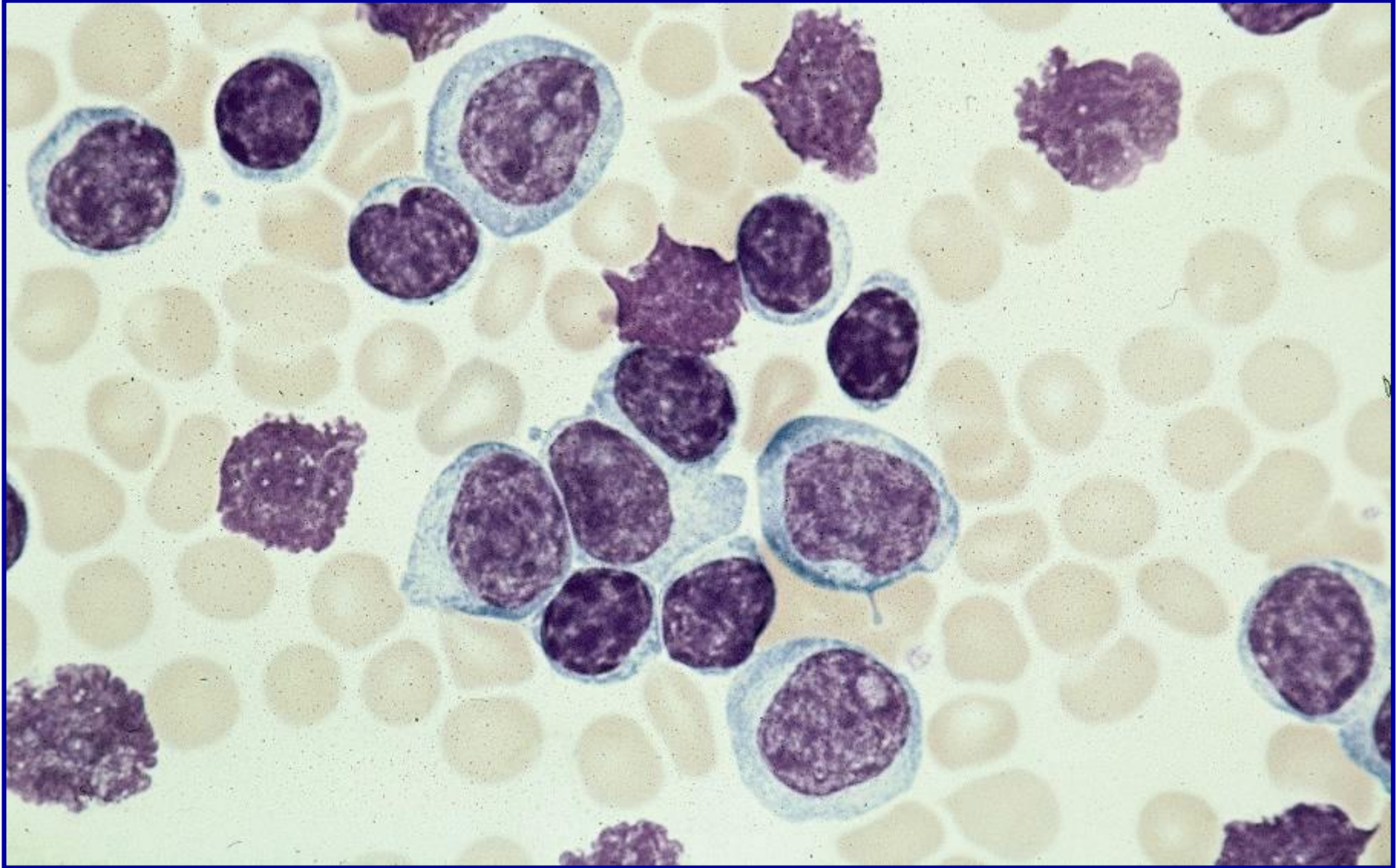
CLL : CD19+ CD20<sup>(wk)</sup> CD5+ CD23+ sIg<sup>-/wk</sup> (κ-λ-) CD79b<sup>-/wk</sup> CD81<sup>-/wk</sup> CD200+ CD43+ ROR1+



Polyclonal mature B-cells

**Immunohistochemie:** MUM1+ (proliferatiecentra)/CD10-/SOX11-

Wat zijn dit?



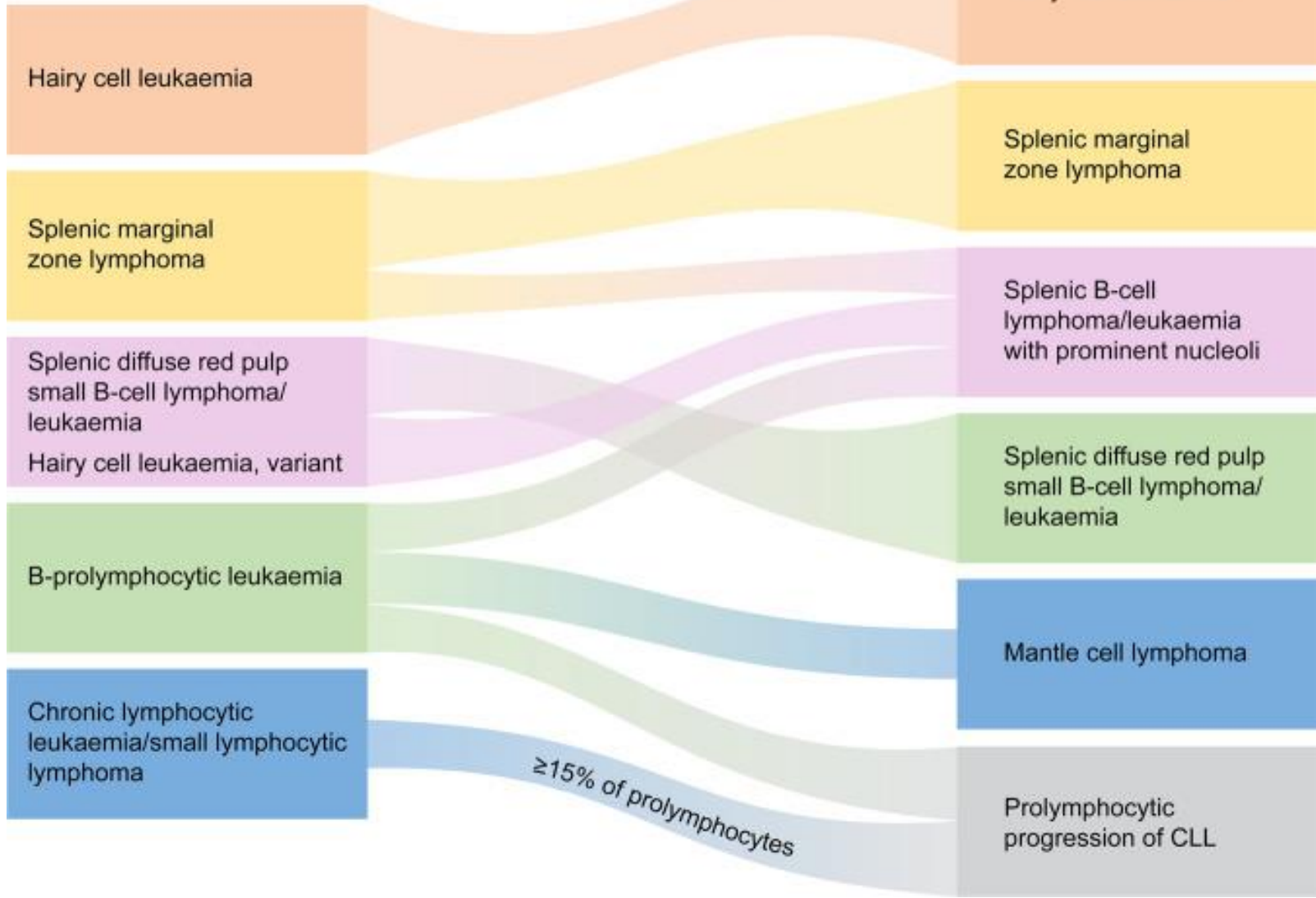
# CLL: evolutie

- Progressie/transformatie
  - **prolymfocyttaire progressie ( $\geq 15\%$ )**
  - **Richterse transformatie** (agressief grootcellig non-Hodgkin's lymfoom):
    - TP53, NOTCH1, SF3B1, deletie CDKN2A, translocatie MYC
    - Deleties 11q (ATM, BIRC3) en 17p (itt deletie 13q14)
    - Trisomie 12
    - LDH verhoogd

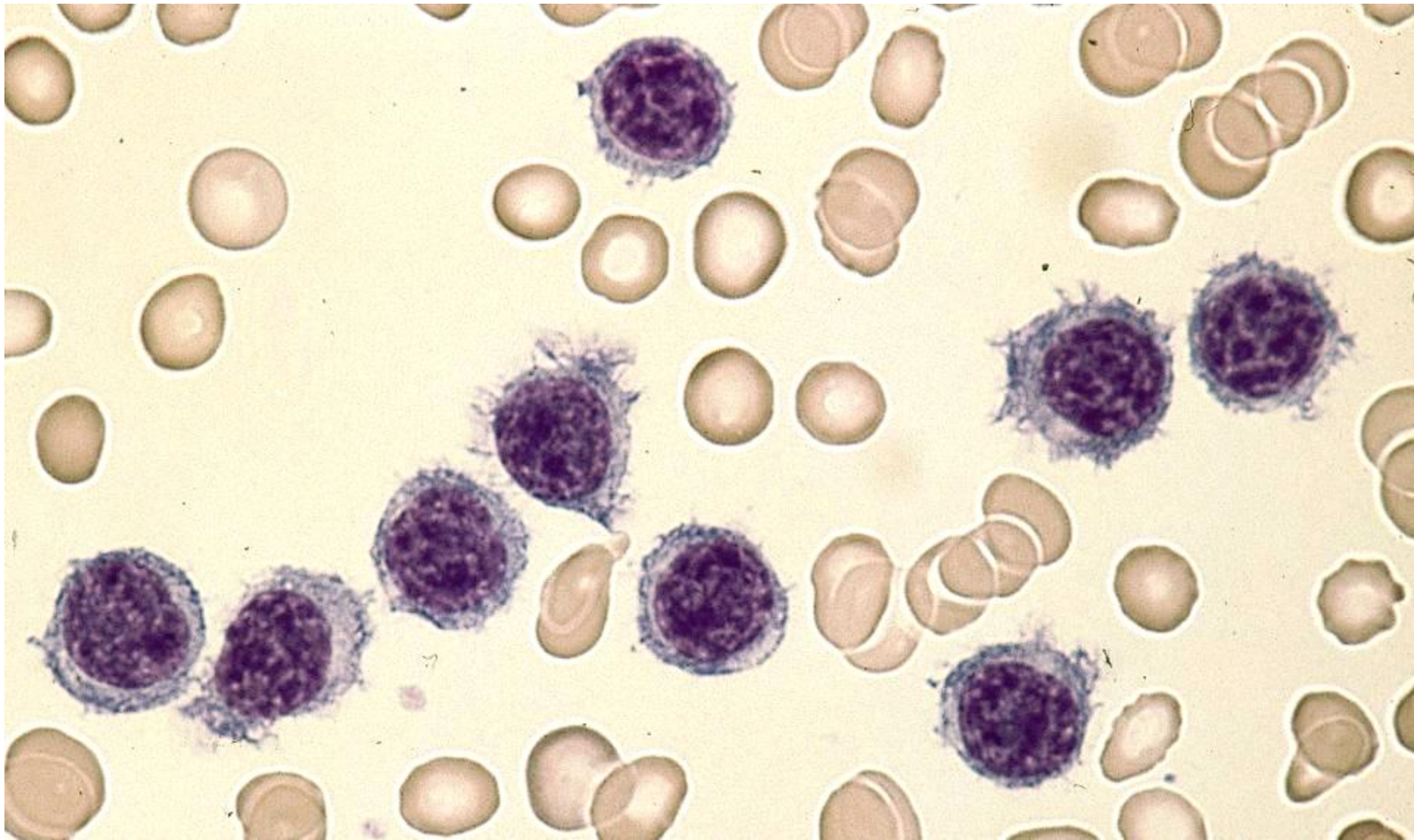


# WHO-HAEM5

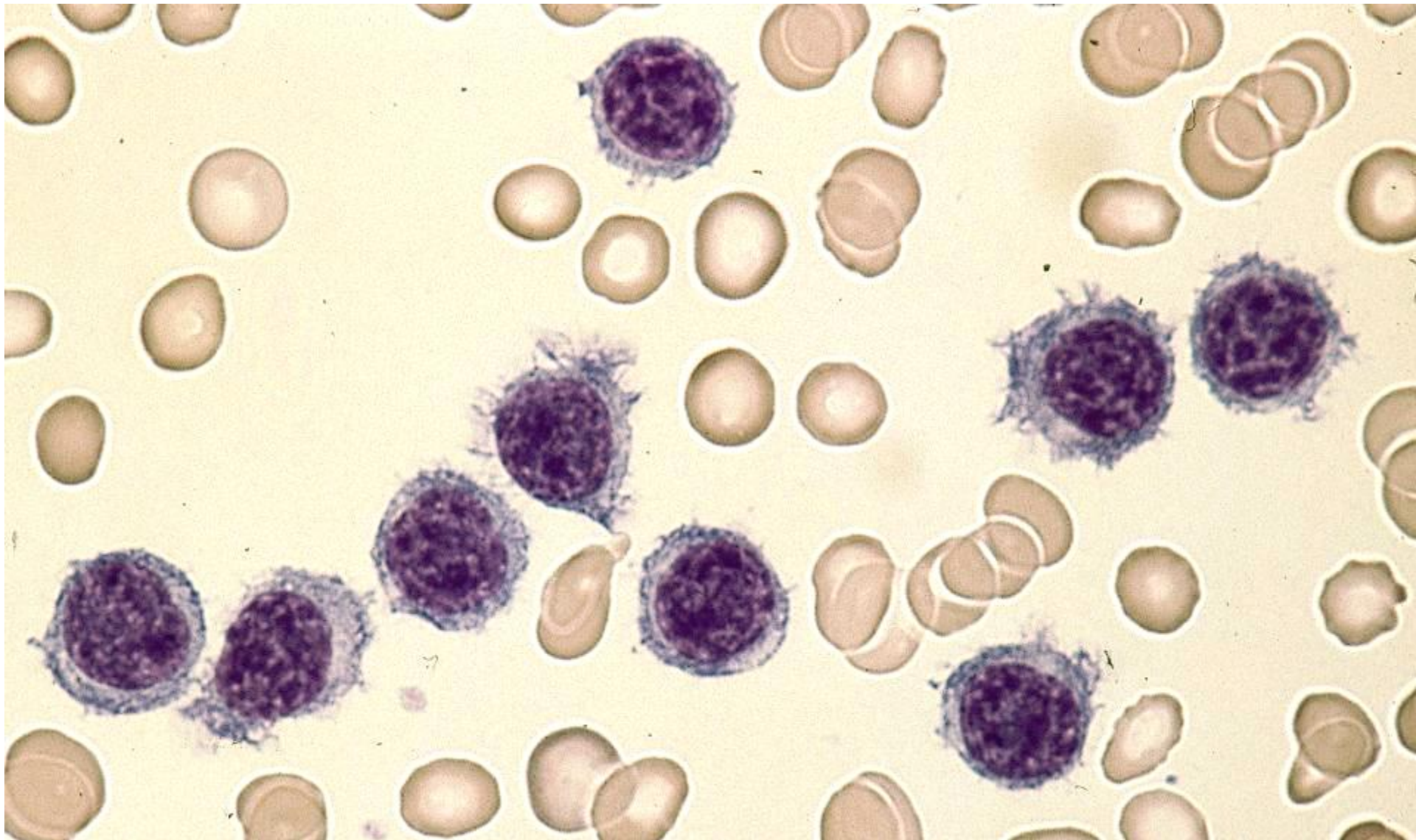
## WHO-HAEM4R



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# Leukemisch mit marginale zone lymfom (**SMZL**)



# WHO: splenic marginal zone lymphoma (SMZL)

(obsoleete naam: Splenic lymphoma with villous lymphocytes; SLVL)

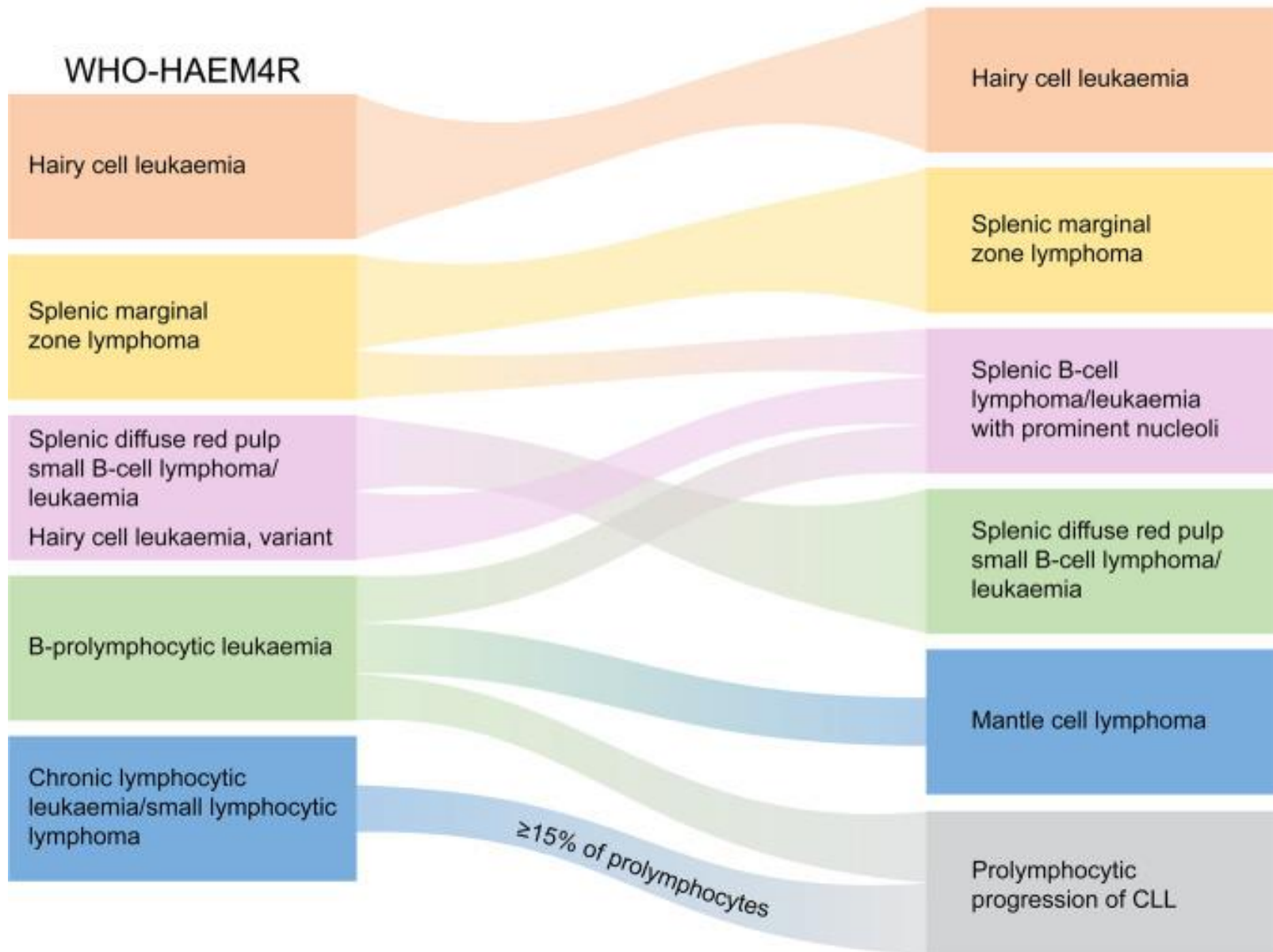
- **bloed**  
Middelgrote lymfocyten met karakteristieke **polaire villi**
- **beenmerg cytologie**  
Idem als bloed
- **Splenomegalie**
- **Specifiek: del 7q31-32 (en o.a. NOTCH2 mutaties)**
- **DD: CLL, HCL, leukemisch rijpe B-NHL**

SMZL: **CD5 meestal neg., CD23-, CD43-, CD200+, CD10-, CD11c+, CD103+/-, cyclin D1-, SOX11-**

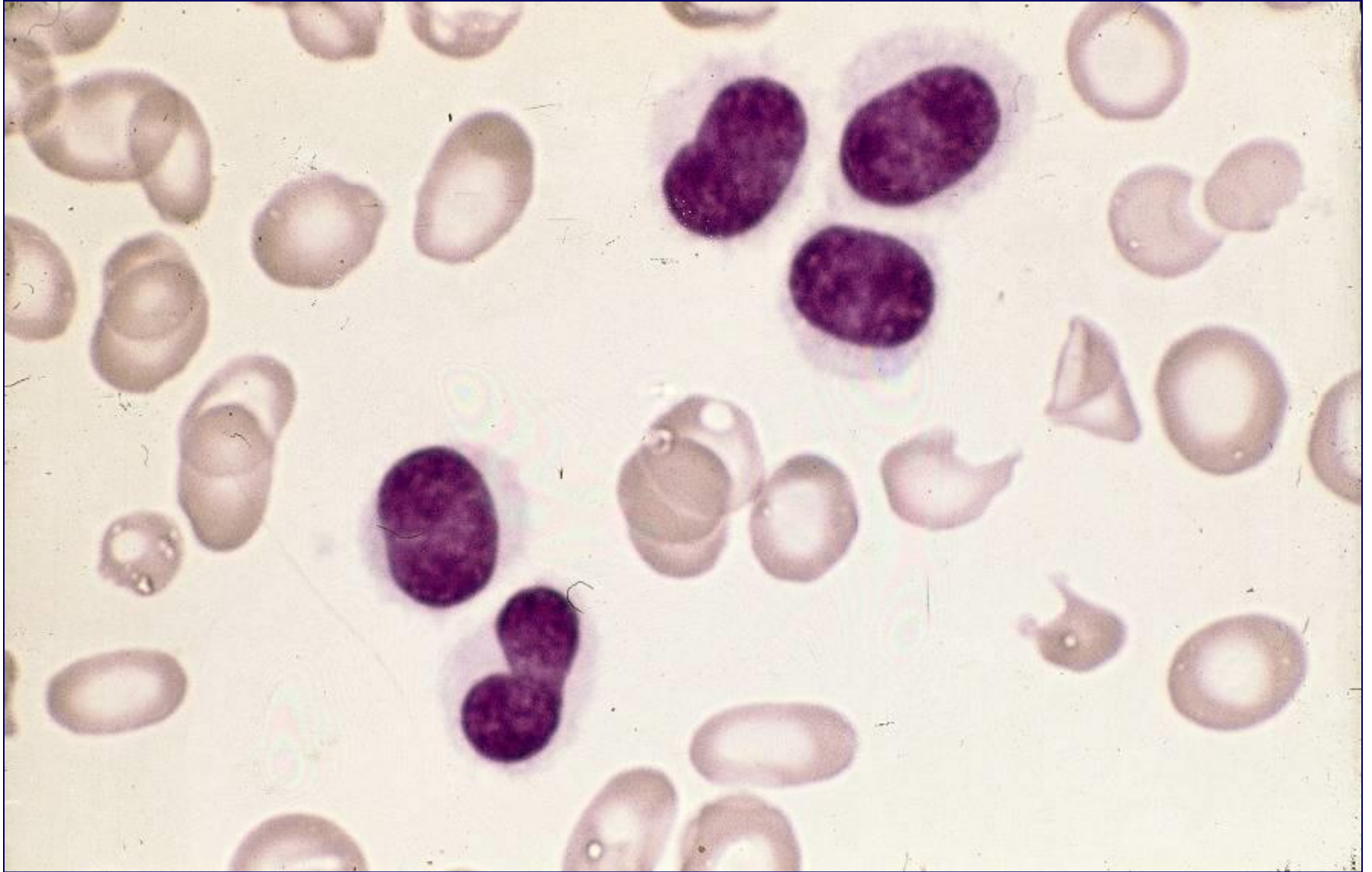
Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
Smlg-expressie	++ <sup>w</sup>	++ <sup>s</sup>	++	++	++	++	++
Cylg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ,μδ,δ	μ,μδ	μ,μδ,γ,α	γ	μ,μδ,γ	μ,μδ	μ,μδ,γ
CD19	++	++	++	++	++	++ <sup>w</sup>	++
CD20	++ <sup>w</sup>	++	++ <sup>s</sup>	++	++	++ <sup>s</sup>	++
CD21	+	±	±	—	±	±	±
CD22	+ <sup>w</sup>	++ <sup>s</sup>	++ <sup>s</sup>	++	++ <sup>s</sup>	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	± <sup>p</sup>	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	+ <sup>w</sup>
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	<u>++</u>	+	±	—	—
(FMC7)	±	++ <sup>s</sup>	++	++	++	+	++
CD138	-	-	-	-	-	-	-

# WHO-HAEM5

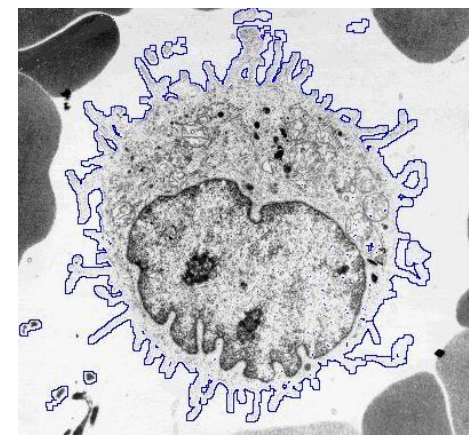
# WHO-HAEM4R



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# Hairy cell leukemia



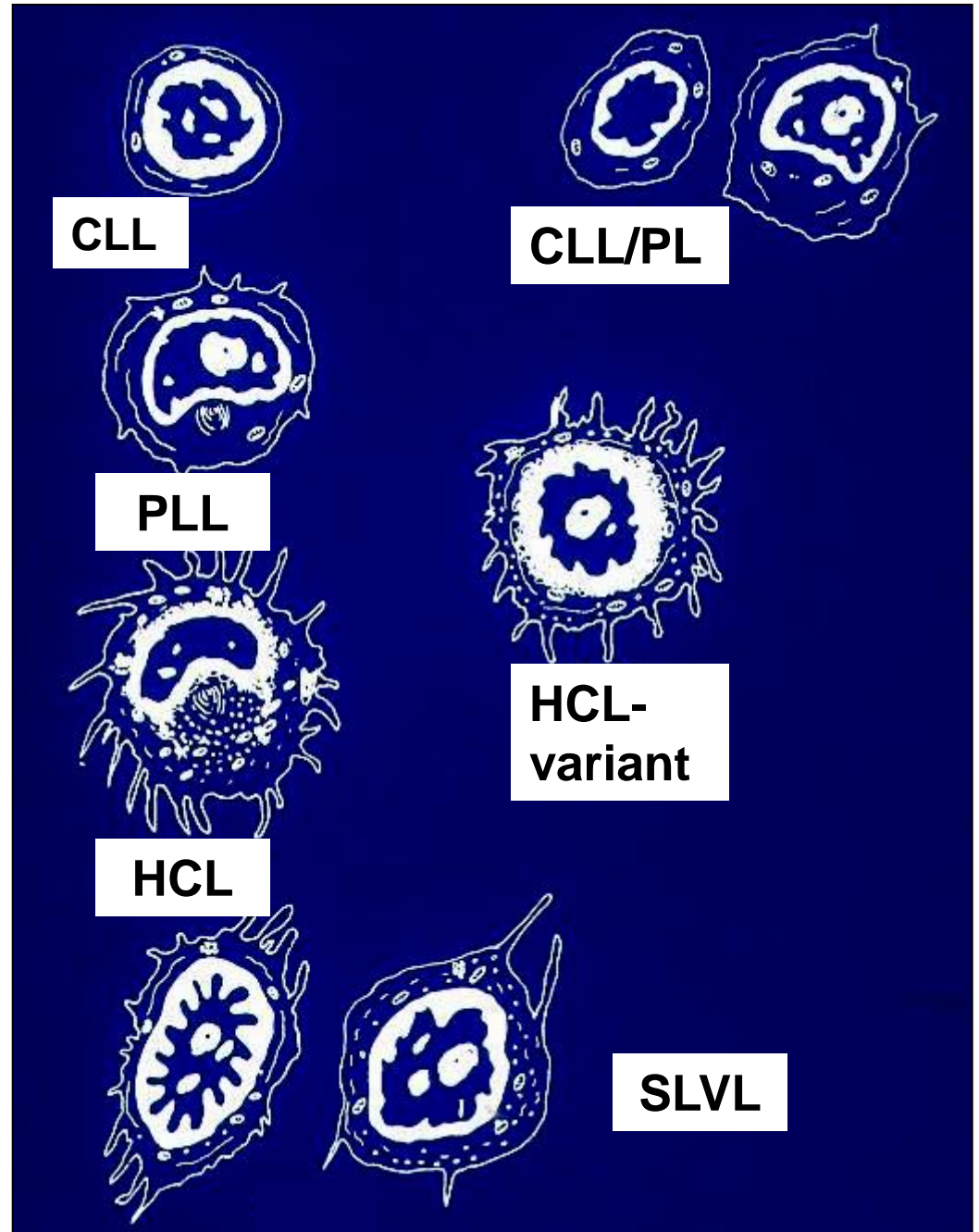
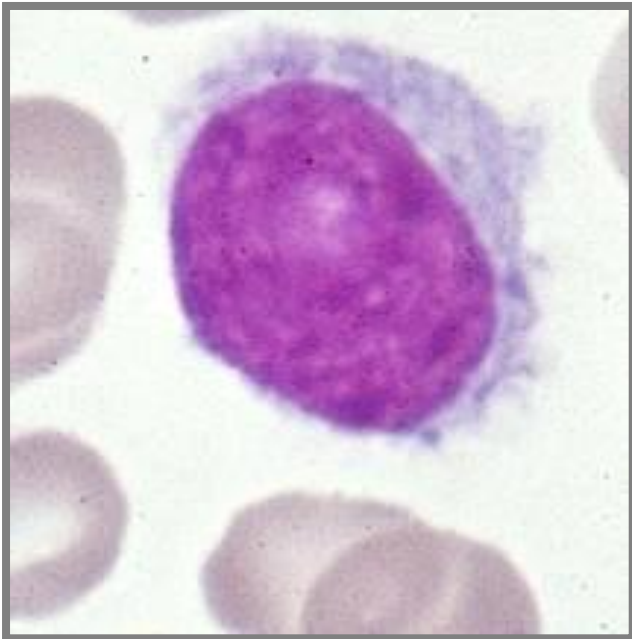
- **Bloed**
  - cytopenie, met name **monocytopenie**
  - circulerende hairy cellen vaak zeldzaam
  - middelgrote lymfatische cellen, ovale kern, fijn chromatine, **bleek ruim cytoplasma** met harige uitlopers
- **Beenmerg cytologie**
  - vaak “dry tap”, altijd is een biopsie vereist
- **Genetica**
  - BRAF V600E mutatie (80-100%), dd: 4% PCM, 3% ander B-NHL (andere mutatie)



HCL: Smlg sterk, **CD25+**, **CD24-**, CD11c+, **CD103+**,  
 CD5-, Annexin A1+, Cycline D1+

Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
Smlg-expressie	++ <sup>w</sup>	++ <sup>s</sup>	++	++	++	++	++
CyIg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ,μδ,δ	μ,μδ	μ,μδ,γ,α	γ	μ,μδ,γ	μ,μδ <sup>w</sup>	μ,μδ,γ
CD19	++	++	++	++	++	++ <sup>w</sup>	++
CD20	++ <sup>w</sup>	++	++ <sup>s</sup>	++	++	++ <sup>s</sup>	++
CD21	+	±	±	—	±	±	±
CD22	+ <sup>w</sup>	++ <sup>s</sup>	++ <sup>s</sup>	++	++ <sup>s</sup>	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	± <sup>p</sup>	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	+ <sup>w</sup>
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	++	+	±	—	—
(FMC7)	±	++ <sup>s</sup>	++	++	++	+	++
CD138	-	-	-	-	-	-	-

???



CLL

CLL/PL

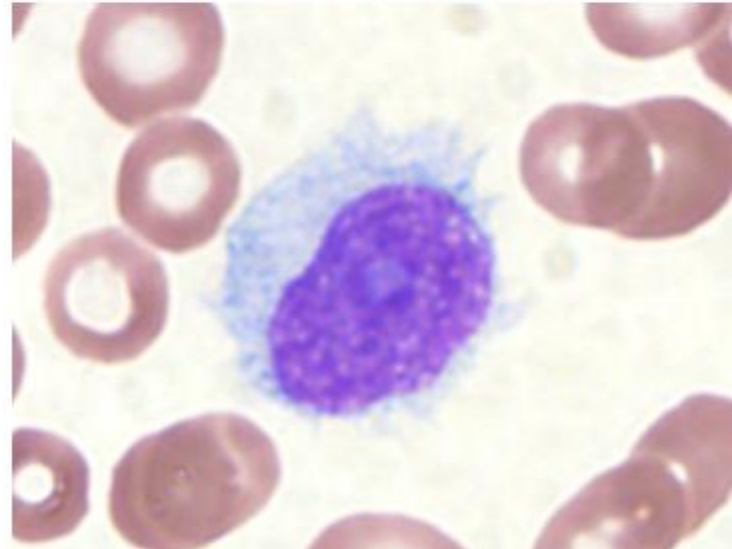
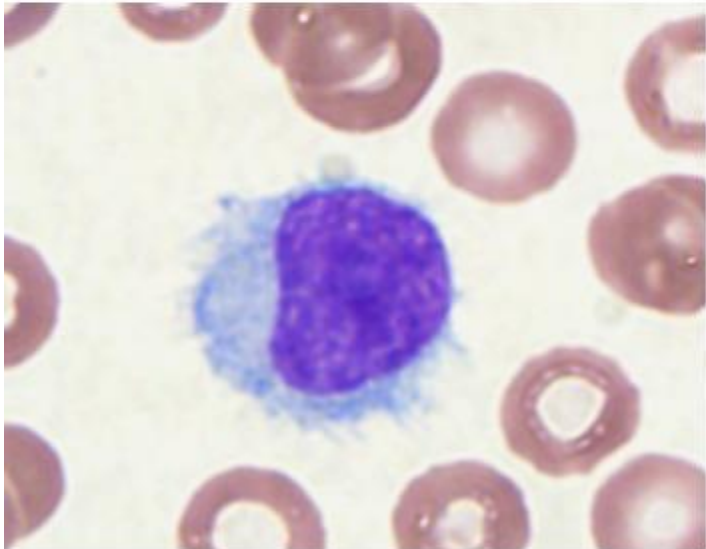
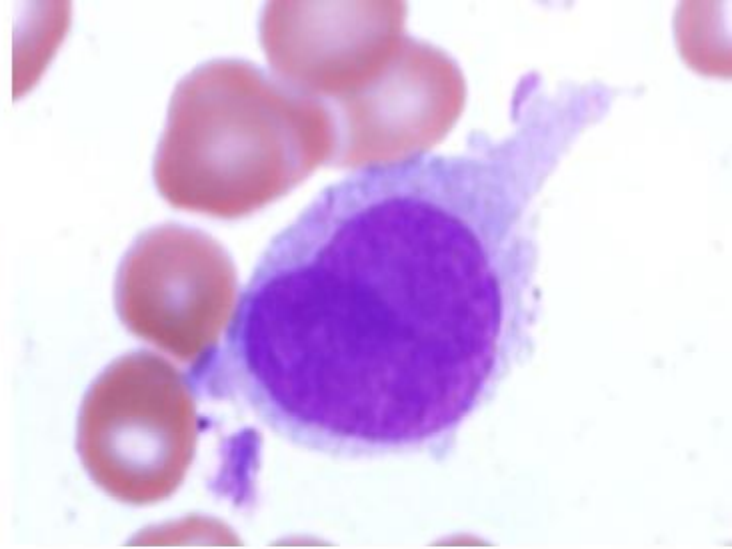
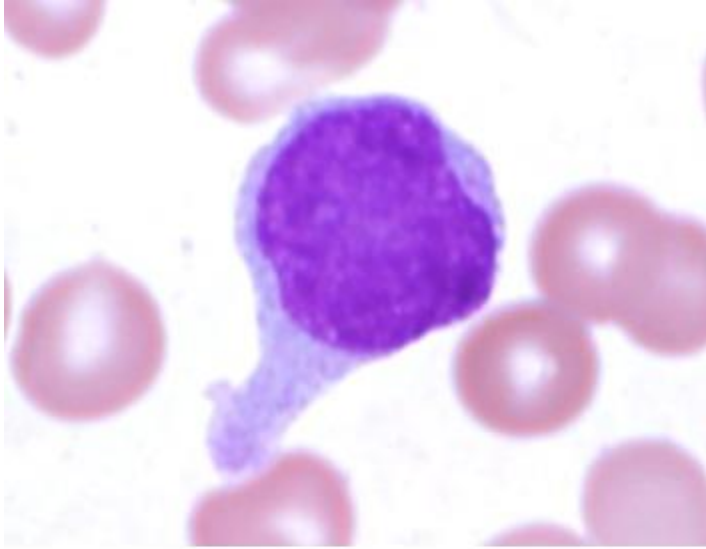
PLL

HCL-variant

HCL

SLVL

# HCLvariant: obsolete

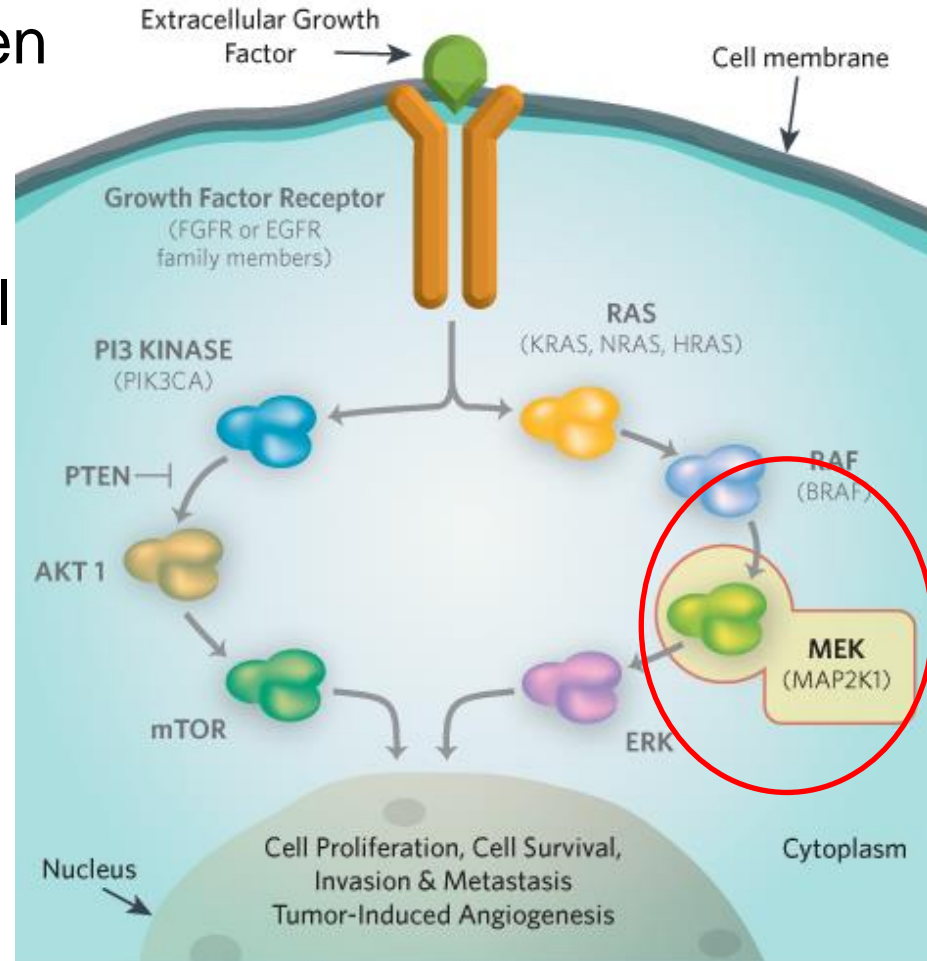
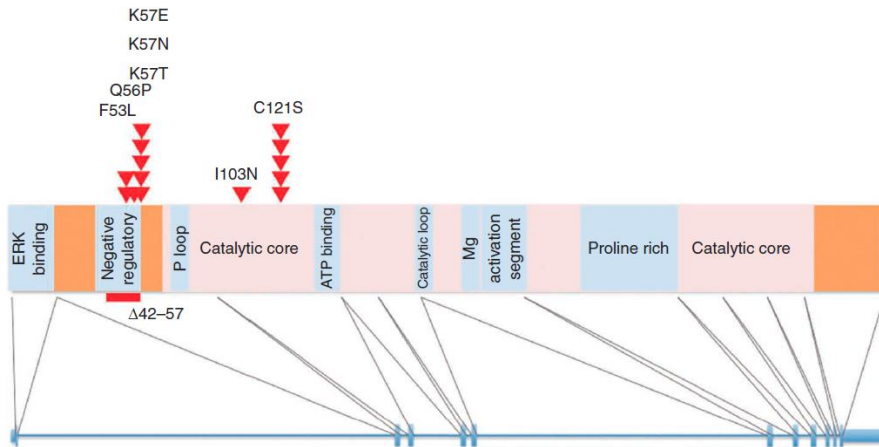


HCLv: CD200-, CD5 meestal neg., CD23-, CD10 (10-20%),  
**CD24-, CD103+, CD25-, CD11c+, Annexin A1-, cyclin D1+**

Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
Smlg-expressie	++ <sup>w</sup>	++ <sup>s</sup>	++	++	++	++	++
Cylg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ,μδ,δ	μ,μδ	μ,μδ,γ,α	γ	μ,μδ,γ	μ,μδ <sub>w</sub>	μ,μδ,γ
CD19	++	++	++	++	++	++ <sup>w</sup>	++
CD20	++ <sup>w</sup>	++	++ <sup>s</sup>	++	++	++ <sup>s</sup>	++
CD21	+	±	±	—	±	±	±
CD22	+ <sup>w</sup>	++ <sup>s</sup>	++ <sup>s</sup>	++	++ <sup>s</sup>	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	± <sup>p</sup>	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	+ <sup>w</sup>
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	++	+	±	—	—
(FMC7)	±	++ <sup>s</sup>	++	++	++	+	++
CD138	-	-	-	-	-	-	-

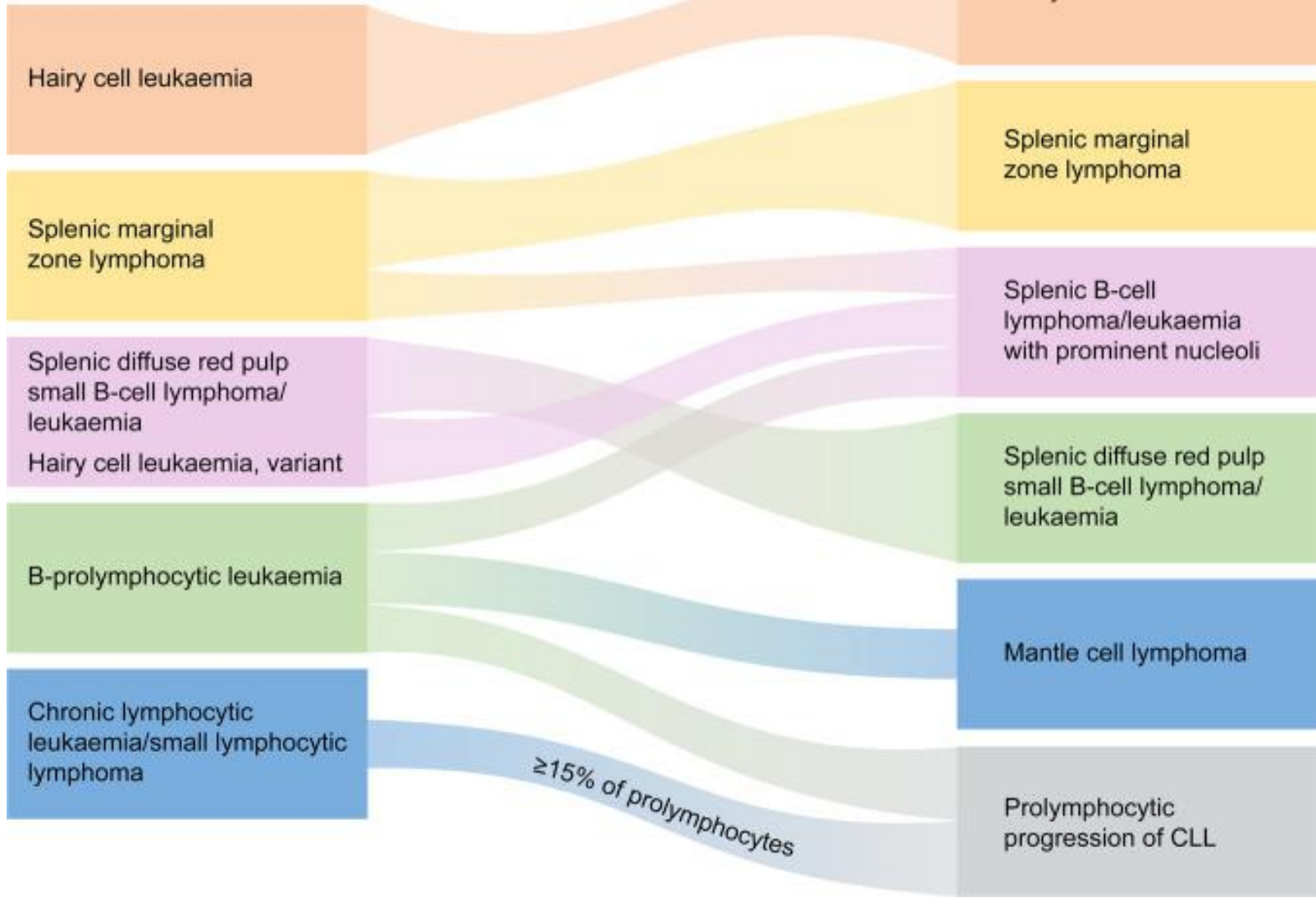
# HCL variant

- Monoklonale B-cellen met expressie van CD11c, CD103 en **negatief voor CD25**
- **Geen monocytopenie**
- **Geen BRAF mutatie**, maar wel MEK/MAP2K1 mutaties



# WHO-HAEM5

## WHO-HAEM4R



$\geq 15\%$  of prolymphocytes

**Table 1**

**WHO Classification of Haematolymphoid Tumours, 5<sup>th</sup> edition: B-cell lymphoid proliferations and lymphomas**

**WHO Classification, 5<sup>th</sup> edition**

**Mature B-cell neoplasms**

***Splenic B-cell lymphomas and leukaemias***

Hairy cell leukaemia

Splenic marginal zone lymphoma

Splenic diffuse red pulp small B-cell lymphoma

**Splenic B-cell lymphoma/leukaemia with prominent nucleoli**

**WHO Classification, revised 4<sup>th</sup> edition**

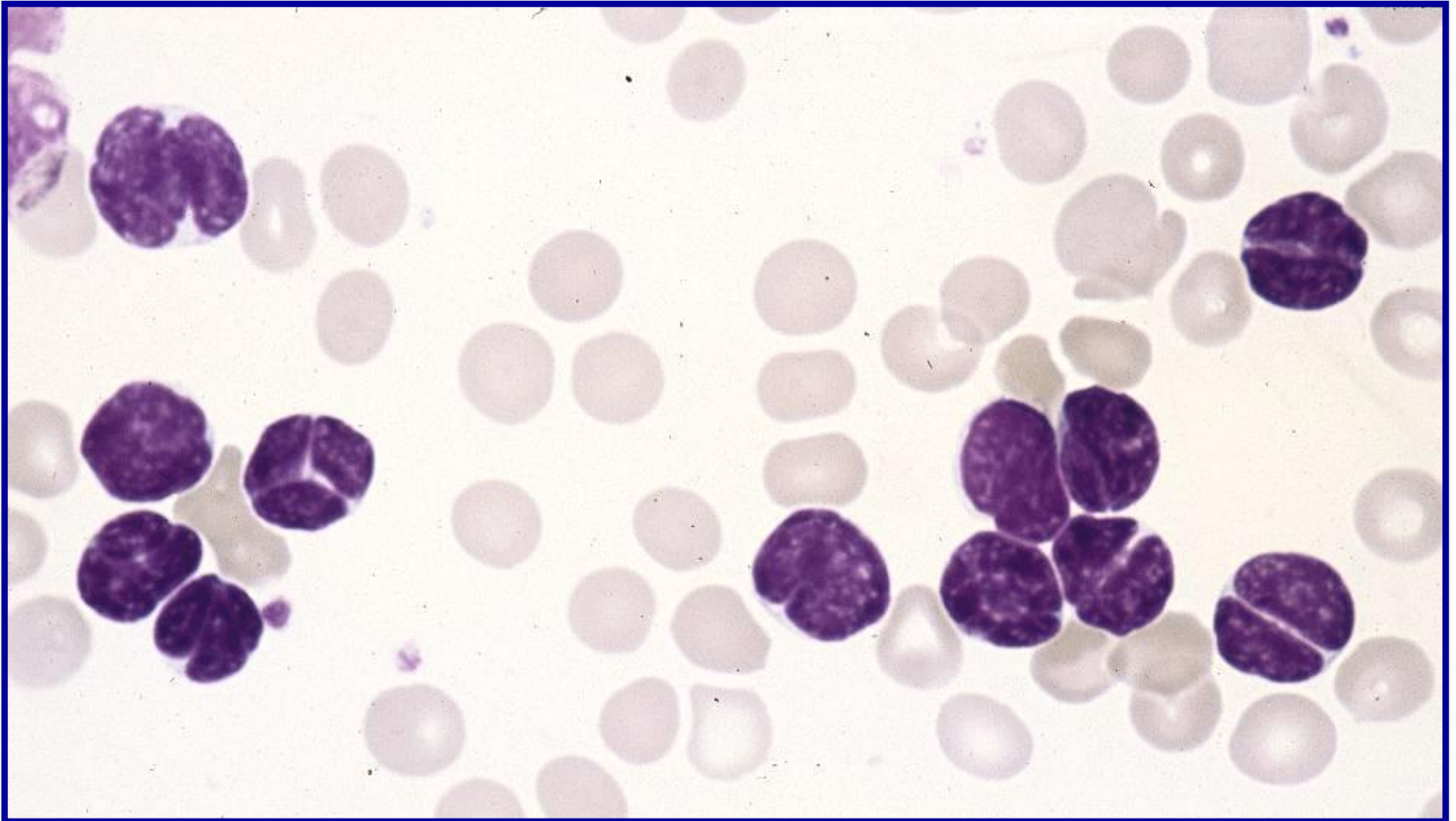
(Same)

(Same)

(Same)

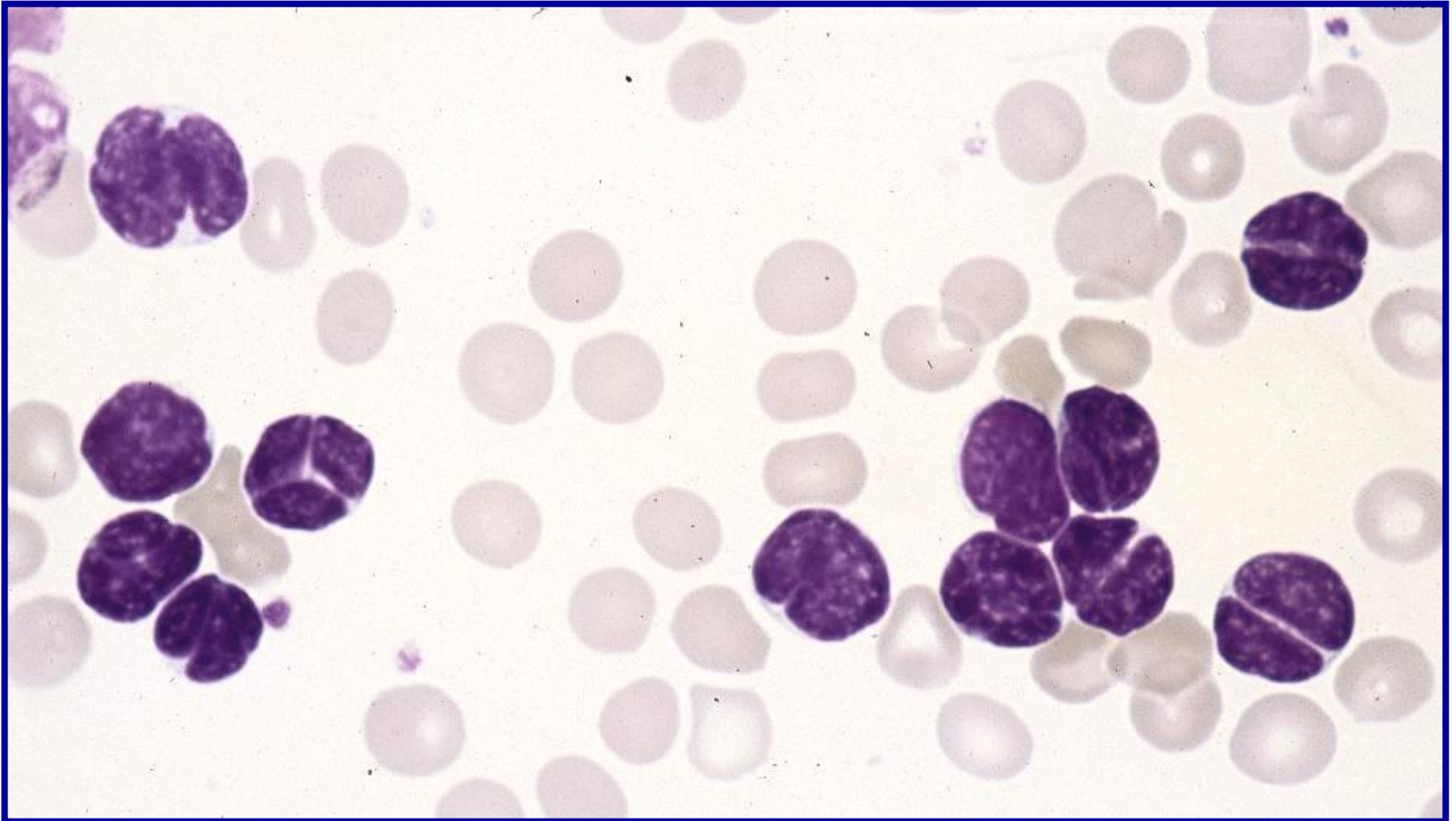
*Not previously included* (encompassing **hairy cell leukaemia variant** and some cases of B-cell prolymphocytic leukaemia)

?

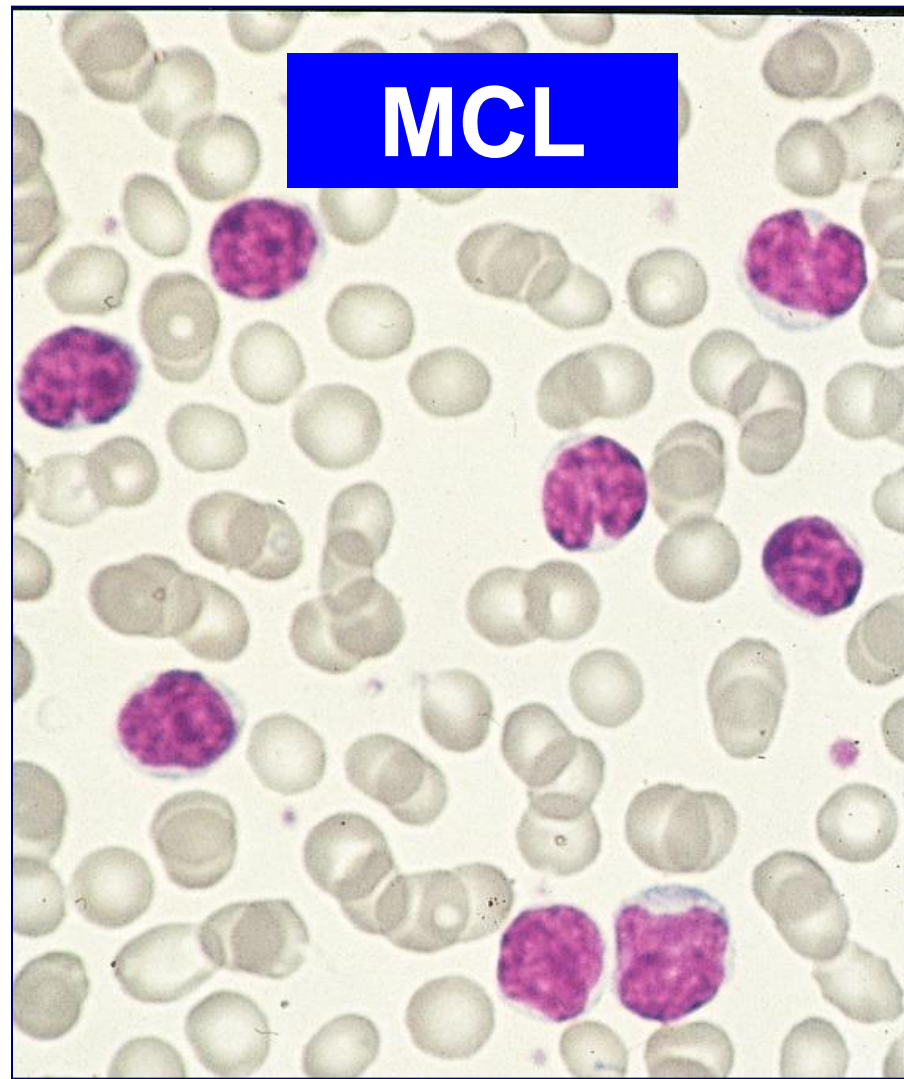
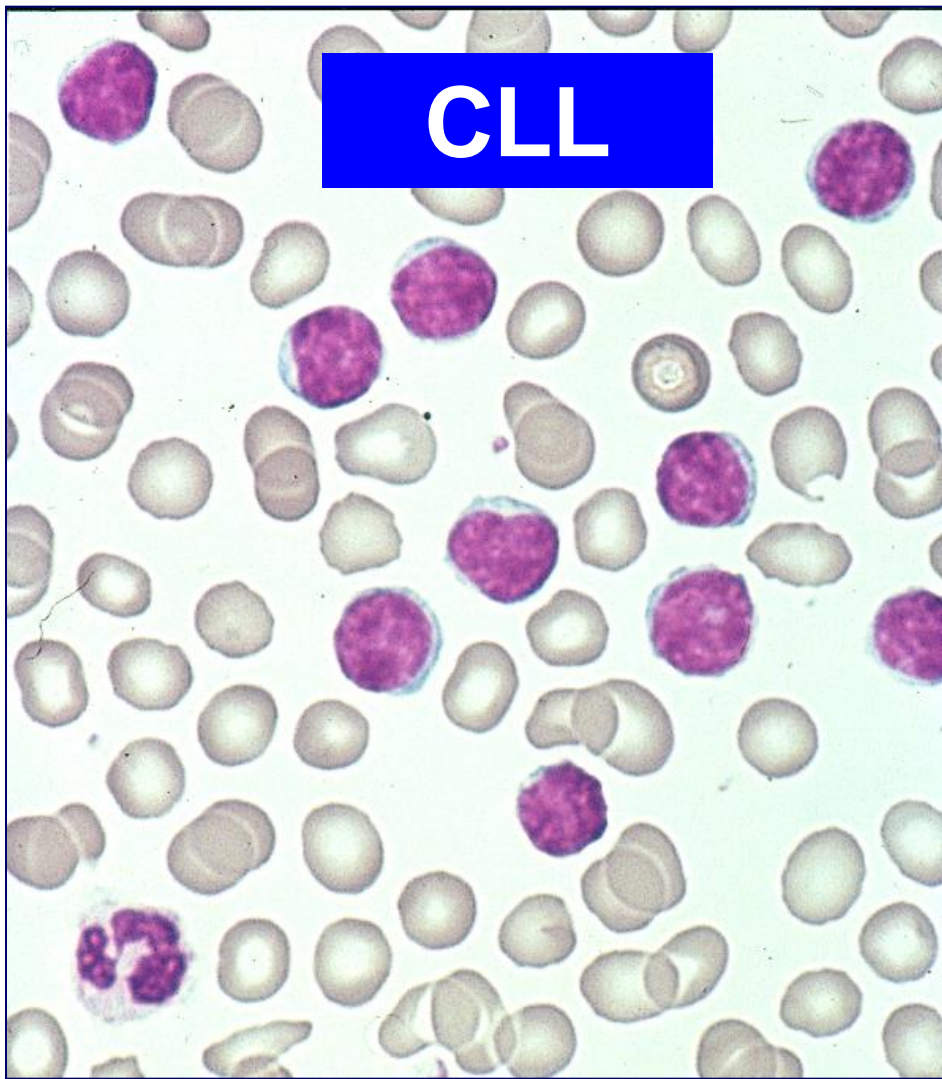




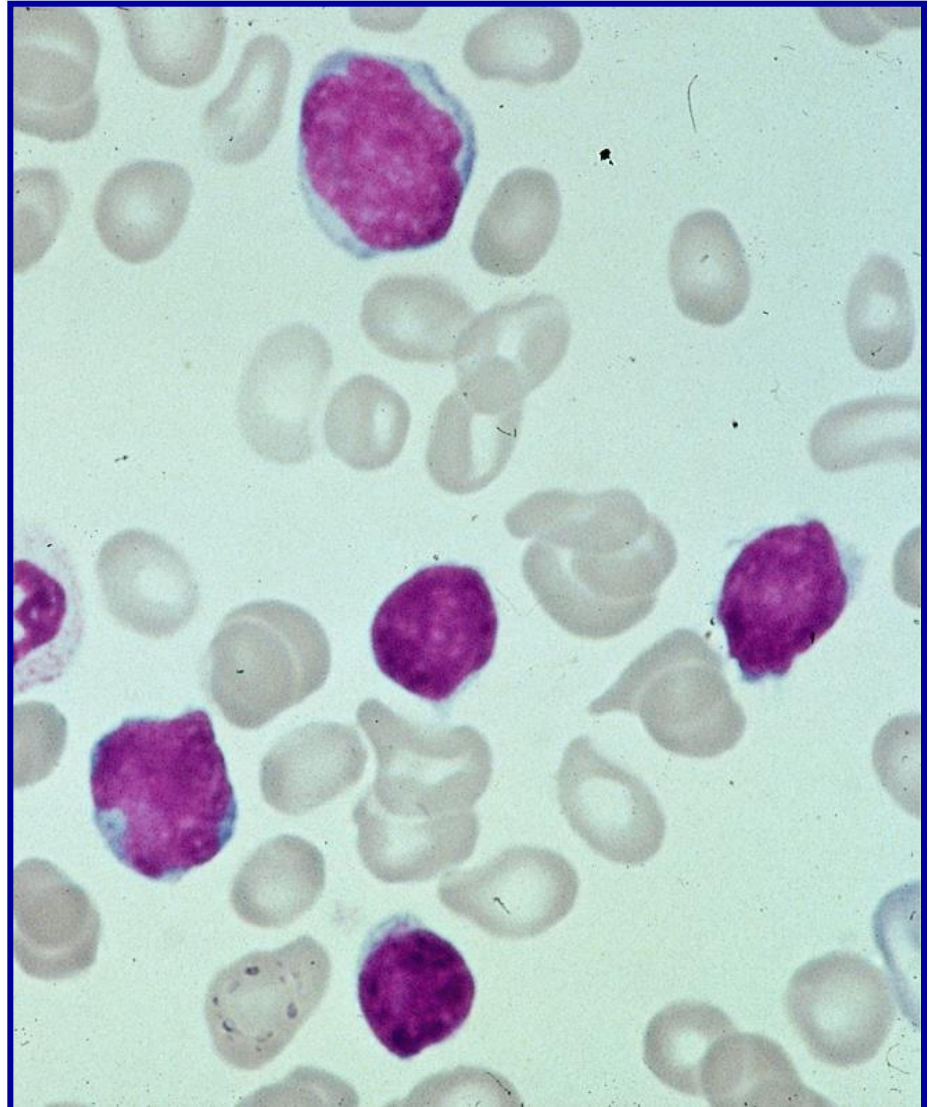
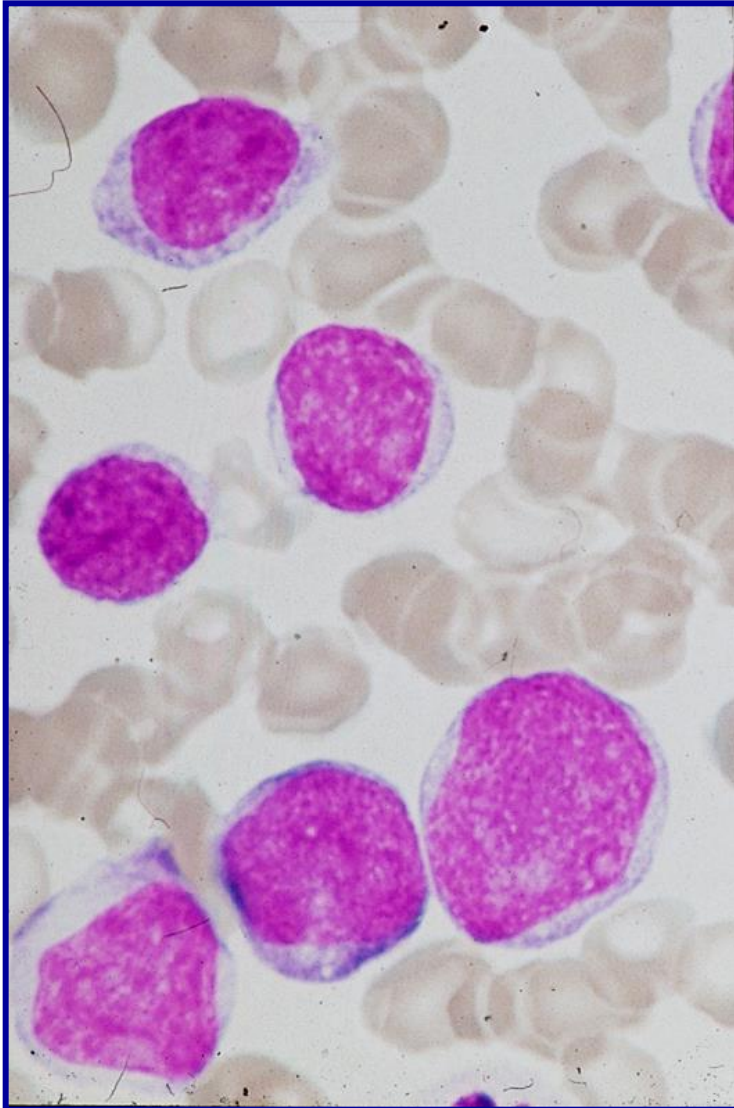
# Leukemisch mantelcel lymfoom



# atypische CLL versus MCL

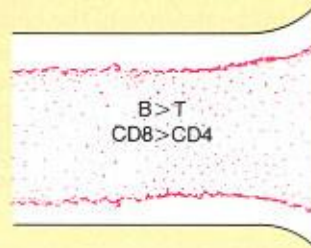


# Mantelcel lymfoom: blastaire of anaplastische variant



### Primary lymphoid organs

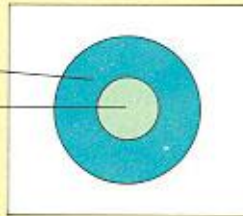
Bone marrow



Thymus

Cortex Td $\alpha$ T<sup>+</sup>

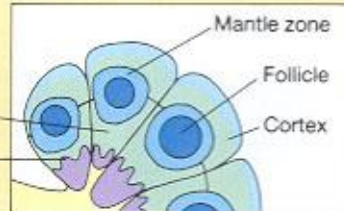
Medulla Td $\alpha$ T<sup>-</sup>



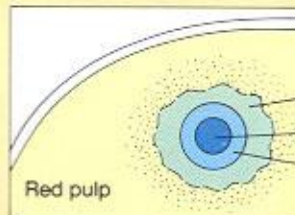
### Secondary lymphoid organs

Lymph node

Deep cortical area (paracortex)  
Medullary cords

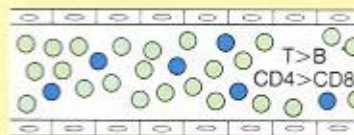




Spleen



T-cell (marginal) area  
Germinal centre  
Mantle zone

Blood



 B-cell areas  
 T-cell areas

# MCL: CD19+, SmlgM/D sterk, CD20 sterk, CD5+, CD23-, CD200-, cycline D1+

Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
Smlg-expressie	++ <sup>w</sup>	++ <sup>s</sup>	++	++	++	++	++
Cylg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ,μδ,δ	μ,μδ	μ,μδ,γ,α	γ	μ,μδ,γ	μ,μδ	μ,μδ,γ
CD19	++	++	++	++	++	++ <sup>w</sup>	++
CD20	++ <sup>w</sup>	++	++ <sup>s</sup>	++	++	++ <sup>s</sup>	++
CD21	+	±	±	—	±	±	±
CD22	+ <sup>w</sup>	++ <sup>s</sup>	++ <sup>s</sup>	++	++ <sup>s</sup>	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	± <sup>p</sup>	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	+ <sup>w</sup>
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	++	+	±	—	—
(FMC7)	±	++ <sup>s</sup>	++	++	++	+	++
CD138	-	-	-	-	-	-	-

# Mantelcel lymfoom

- **Bloed**
  - vaak leukemisch met monotone kleine tot middelgrote lymfocyten, smalle cytoplasmazoom, fijn tot grof chromatine
  - **kern vaak een klief**, soms ook blastair!
- **Beenmerg cytologie**
  - hetzelfde als het bloed, vaak sterk geïnfilteerd
- **t(11;14)(q13;q32): IGH::CCND1: overexpressie van Cycline D1**
  - >95%
  - Soms cryptisch (FISH)
- **High risk:**
  - Blastaire morfologie
  - Ki67 proliferatie index
  - TP53 mutatie

**Table 1**

**WHO Classification of Haematolymphoid Tumours, 5<sup>th</sup> edition: B-cell lymphoid proliferations and lymphomas**

**WHO Classification, 5<sup>th</sup> edition**

**WHO Classification, revised 4<sup>th</sup> edition**

**Mature B-cell neoplasms**

***Mantle cell lymphoma***

In situ mantle cell neoplasm

In situ mantle cell neoplasia

Mantle cell lymphoma

(Same)

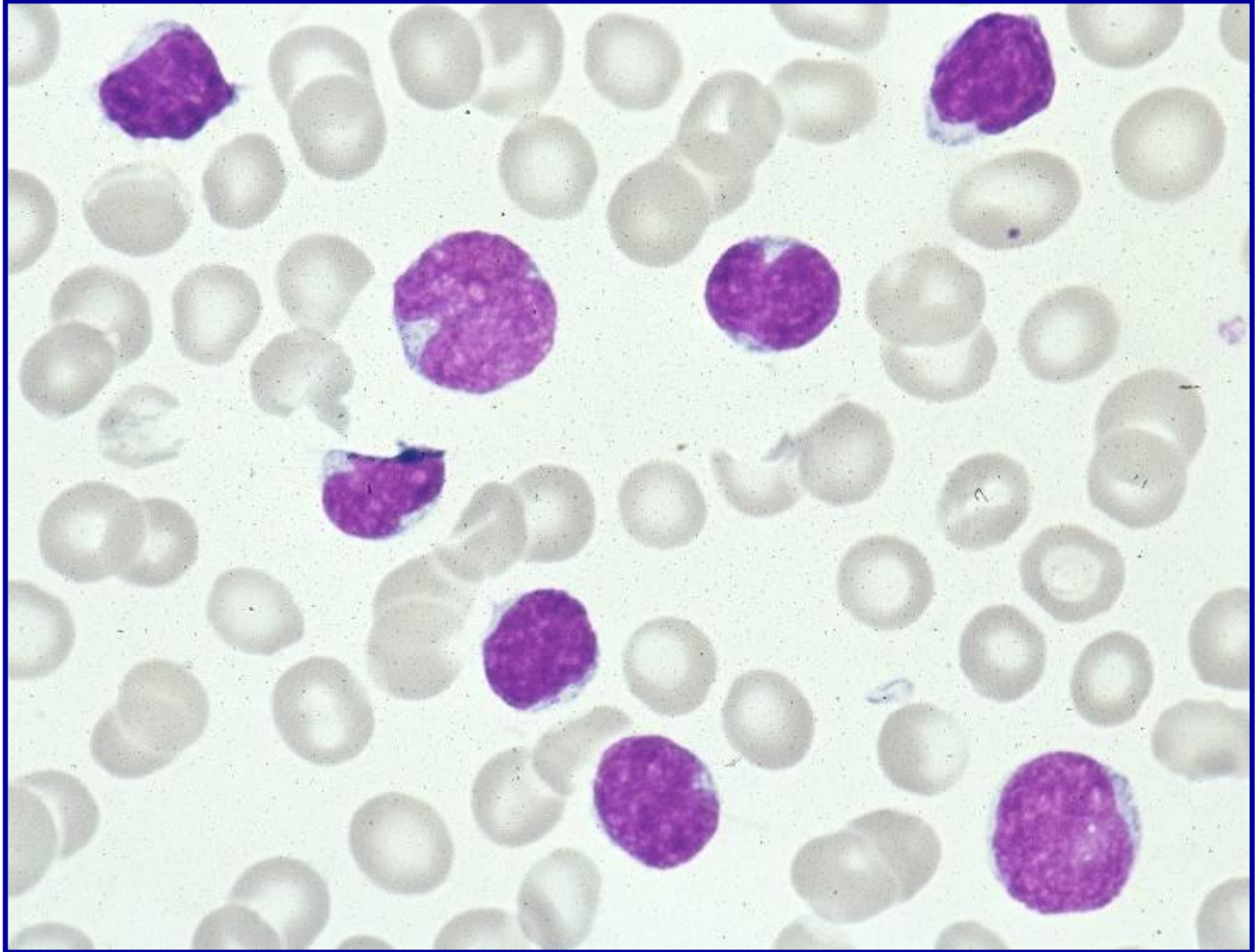
Leukaemic non-nodal mantle cell lymphoma

(Same)

**Leukemisch non-nodaal MCL:**

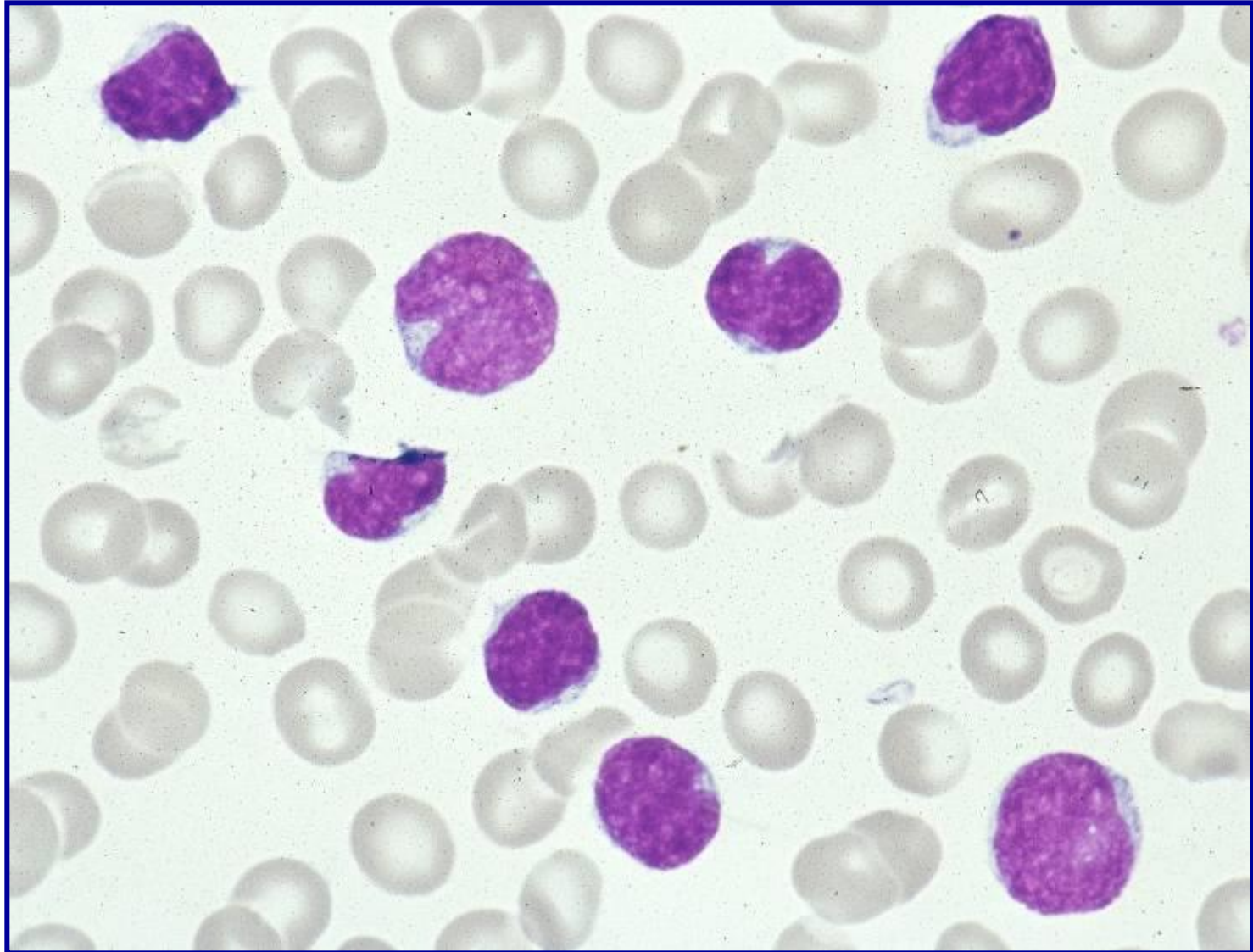
- **Bloed, beenmerg, milt**
- **SOX11-, CD5+/-, low Ki67 index**
- **Indolenter beloop**

?

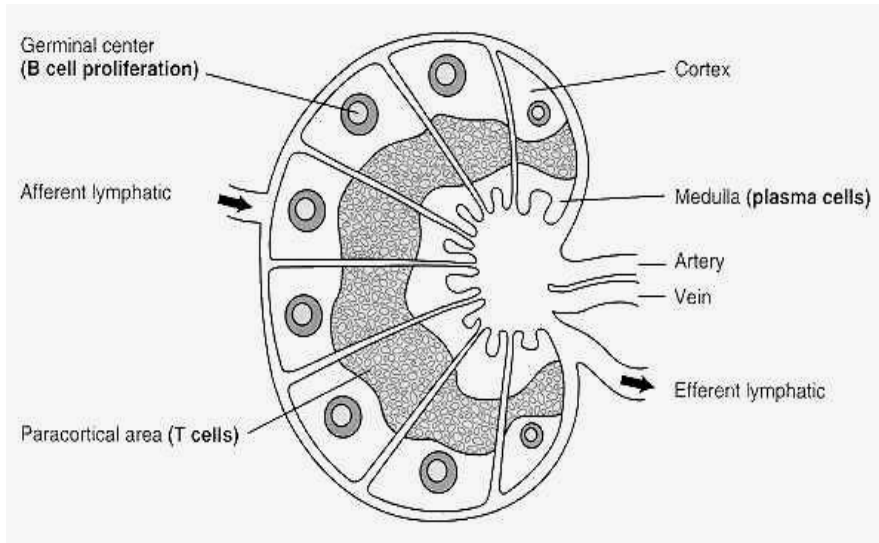




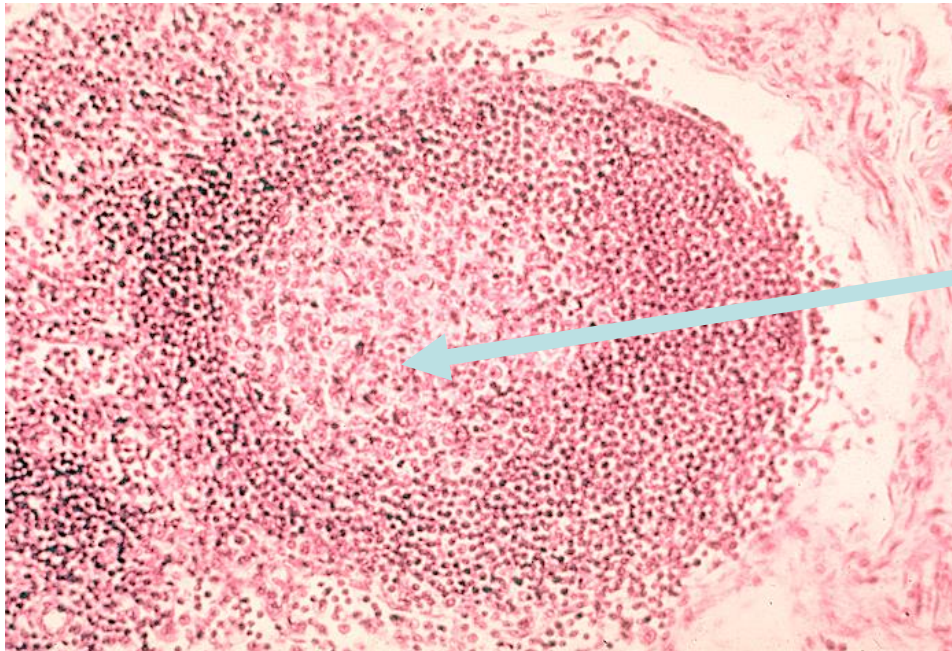
# Leukemisch folliculair NHL



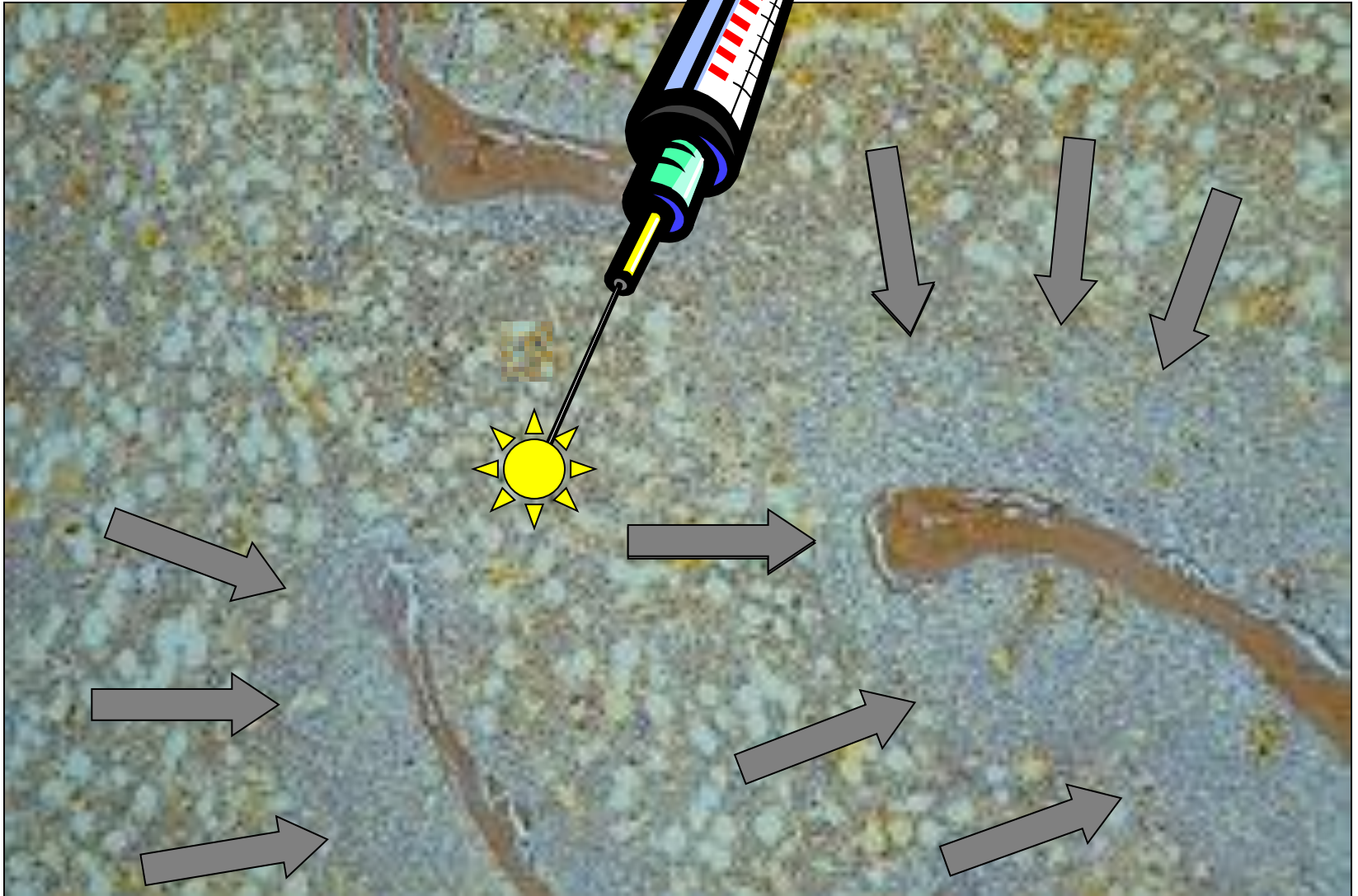
# Folliculair lymfoom



**Lymfeklier  
overzicht**



**Follikel  
centrum**



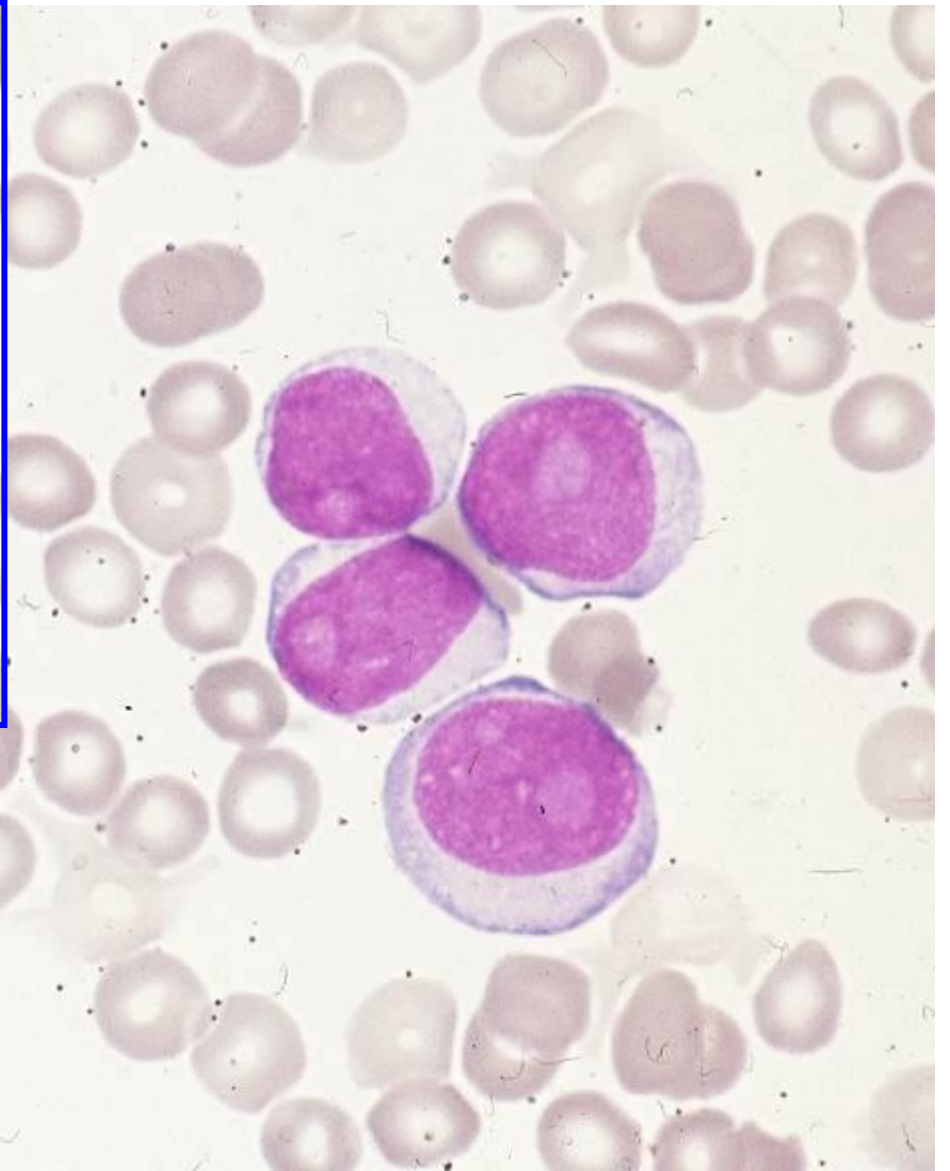
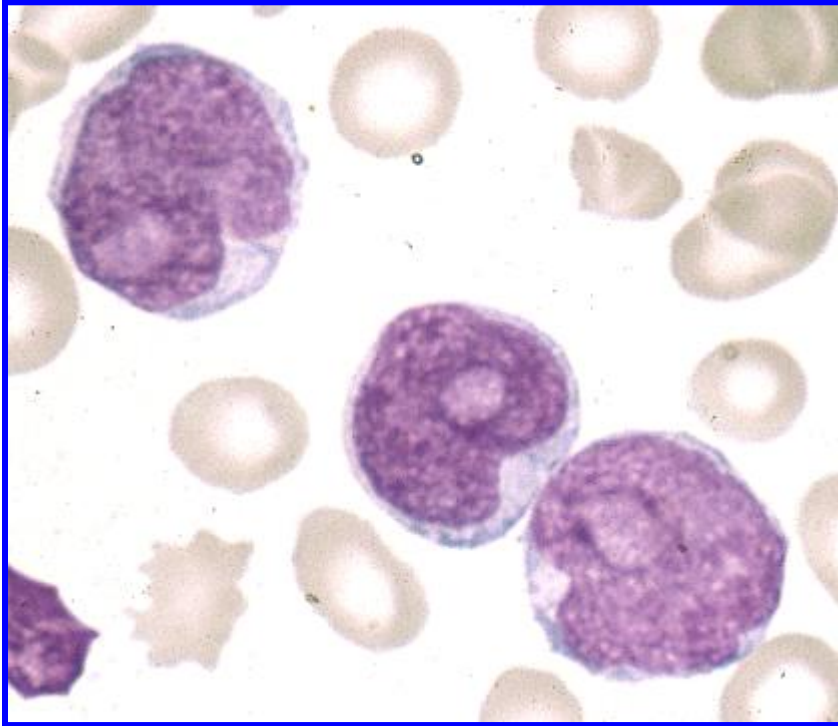
# FCL: CD19, SmlgM/D/G, CD20, **CD10+**, **CD5-/zwak**, CD23-/zwak

Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
Smlg-expressie	++ <sup>w</sup>	++ <sup>s</sup>	++	++	++	++	++
Cylg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ,μδ,δ	μ,μδ	μ,μδ,γ,α	γ	μ,μδ,γ	μ,μδ	μ,μδ,γ
CD19	++	++	++	++	++	++ <sup>w</sup>	++
CD20	++ <sup>w</sup>	++	++ <sup>s</sup>	++	++	++ <sup>s</sup>	++
CD21	+	±	±	—	±	±	±
CD22	+ <sup>w</sup>	++ <sup>s</sup>	++ <sup>s</sup>	++	++ <sup>s</sup>	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	± <sup>p</sup>	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	+ <sup>w</sup>
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	++	+	±	—	—
(FMC7)	±	++ <sup>s</sup>	++	++	++	+	++
CD138	-	-	-	-	-	-	-

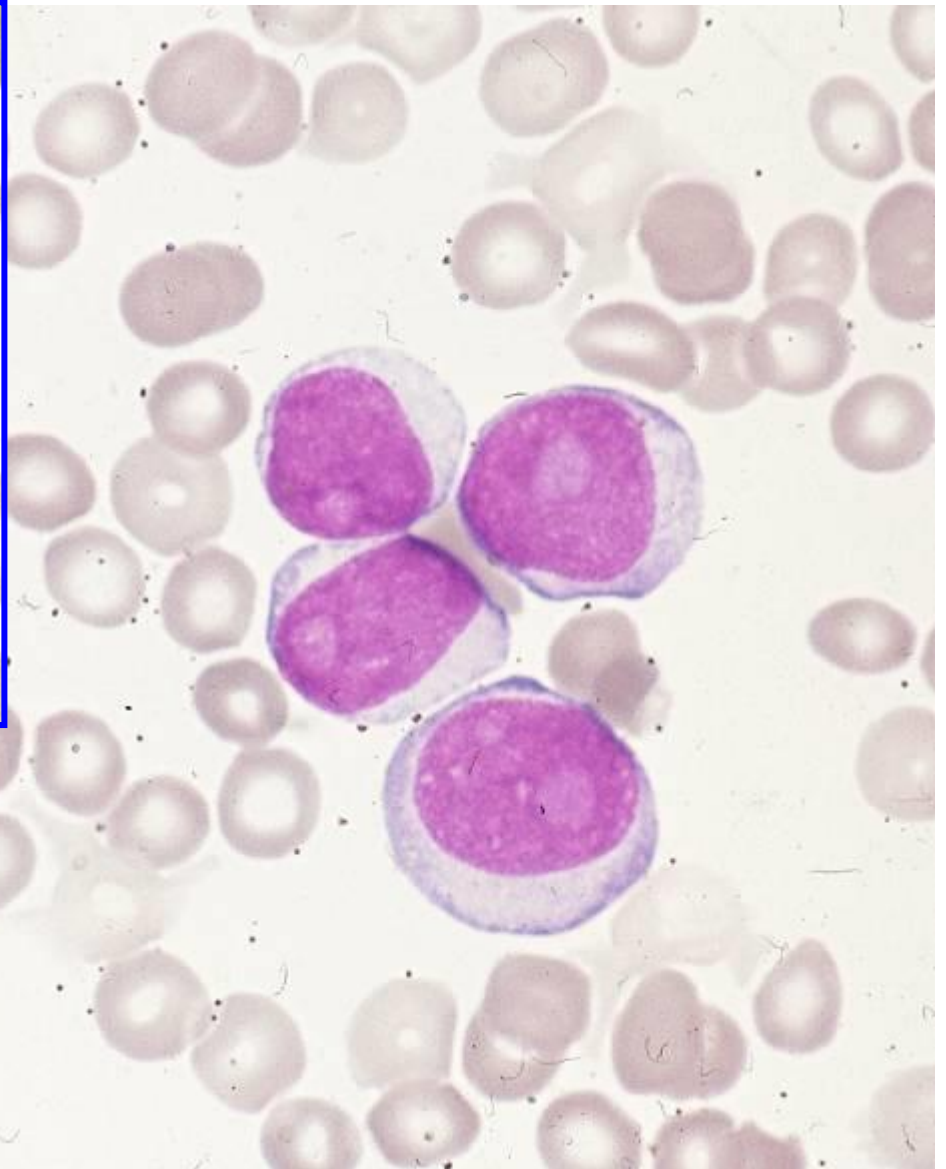
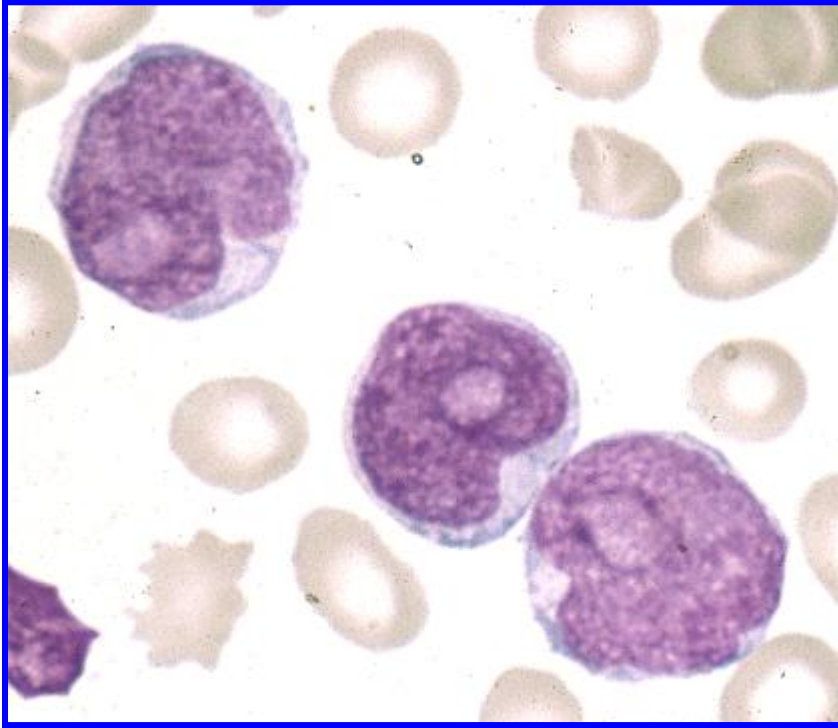
# Folliculair lymfoom (FL)

- **Bloed**
  - meestal normaal leukocytengetal,
  - soms wisselend percentage afwijkende lymfocyten, met **gekliefde kern**,
  - **wandstandige nucleoli**
- **Beenmerg cytologie**
  - vaak normaal, terwijl het BLOPT dan positief is, tgv paratrabeculaire lokalisatie
  - NB: rolpreparaat bekijken!
- $t(14;18)(q32;q21)/IGH::BCL2$ : 85%
- Centrocysten/**centroblasten**, onderscheid met **DLBCL** soms moeilijk
- **WHO2022:**
  - **Klassiek** folliculair lymfoom: graad 1, 2, 3A
  - Folliculair **grootcellig** B-cellymfoom: graad 3B

?



# B-prolymfocyten leukemie (B-PLL): obsoleet



- **Bloed**

- **zeer hoog leukocytengetal**
- **grote cellen, ruim cytoplasma (kern dobbert),**
- **ronde centrale kern met zeer opvallende grote centraal gelegen nucleolus**
- **Valkuil: lijkt op ALL!**

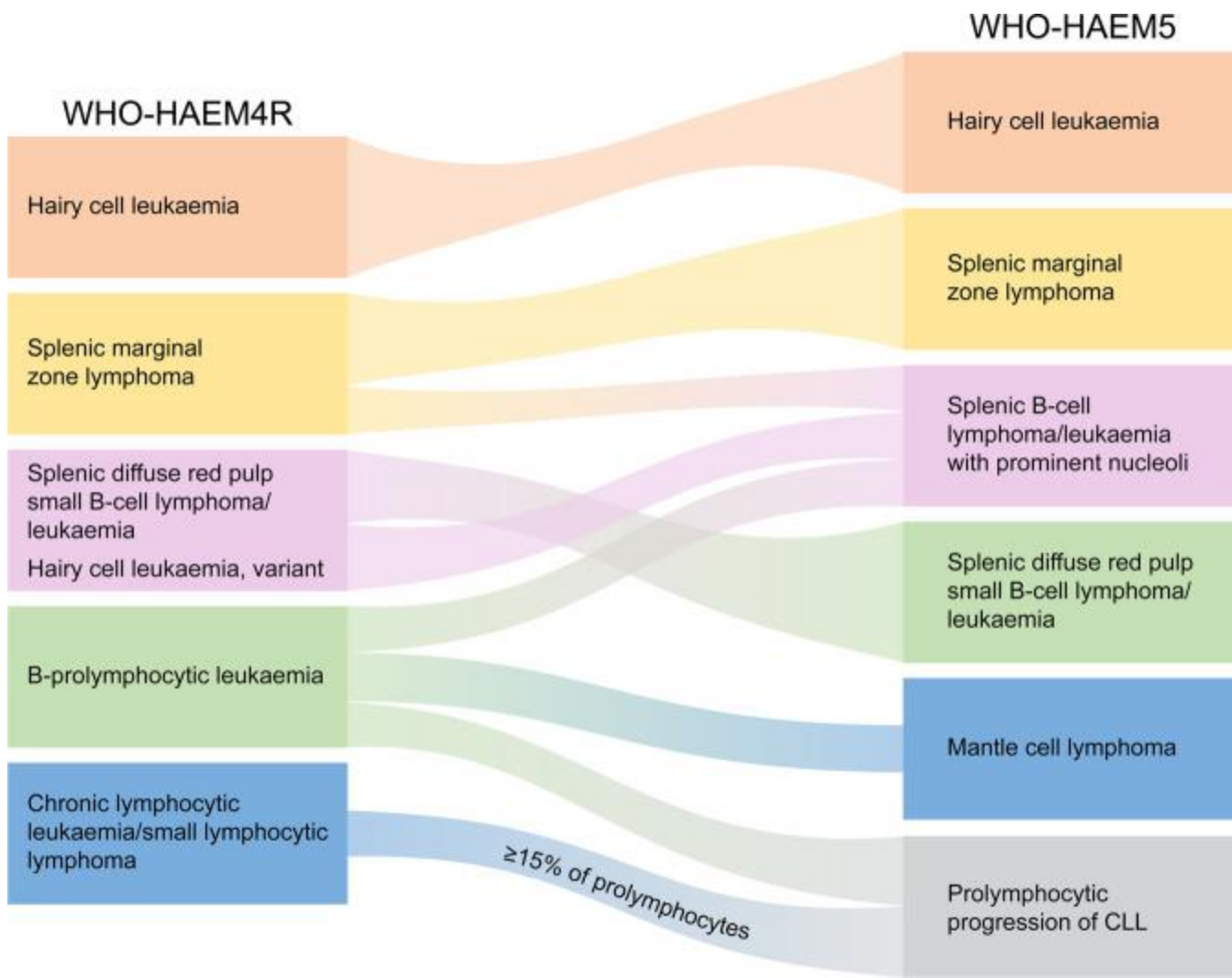
- **Beenmerg cytologie**

- **hetzelfde als bloed, vaak sterke infiltratie**



# B-PLL: Smlg sterk, CD22 sterk, **CD5-/zwak**, CD23-

Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
Smlg-expressie	++ <sup>w</sup>	++ <sup>s</sup>	++	++	++	++	++
Cylg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ,μδ,δ	μ,μδ	μ,μδ,γ,α	γ	μ,μδ,γ	μ,μδ	μ,μδ,γ
CD19	++	++	++	++	++	++ <sup>w</sup>	++
CD20	++ <sup>w</sup>	++	++ <sup>s</sup>	++	++	++ <sup>s</sup>	++
CD21	+	±	±	—	±	±	±
CD22	+ <sup>w</sup>	++ <sup>s</sup>	++ <sup>s</sup>	++	++ <sup>s</sup>	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	± <sup>p</sup>	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	+ <sup>w</sup>
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	++	+	±	—	—
(FMC7)	±	++ <sup>s</sup>	++	++	++	+	++
CD138	-	-	-	-	-	-	-



**Table 1**

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**WHO Classification, 5<sup>th</sup> edition**

**Mature B-cell neoplasms**

***Splenic B-cell lymphomas and leukaemias***

Hairy cell leukaemia

Splenic marginal zone lymphoma

Splenic diffuse red pulp small B-cell lymphoma

**Splenic B-cell lymphoma/leukaemia with prominent nucleoli**

**WHO Classification, revised 4<sup>th</sup> edition**

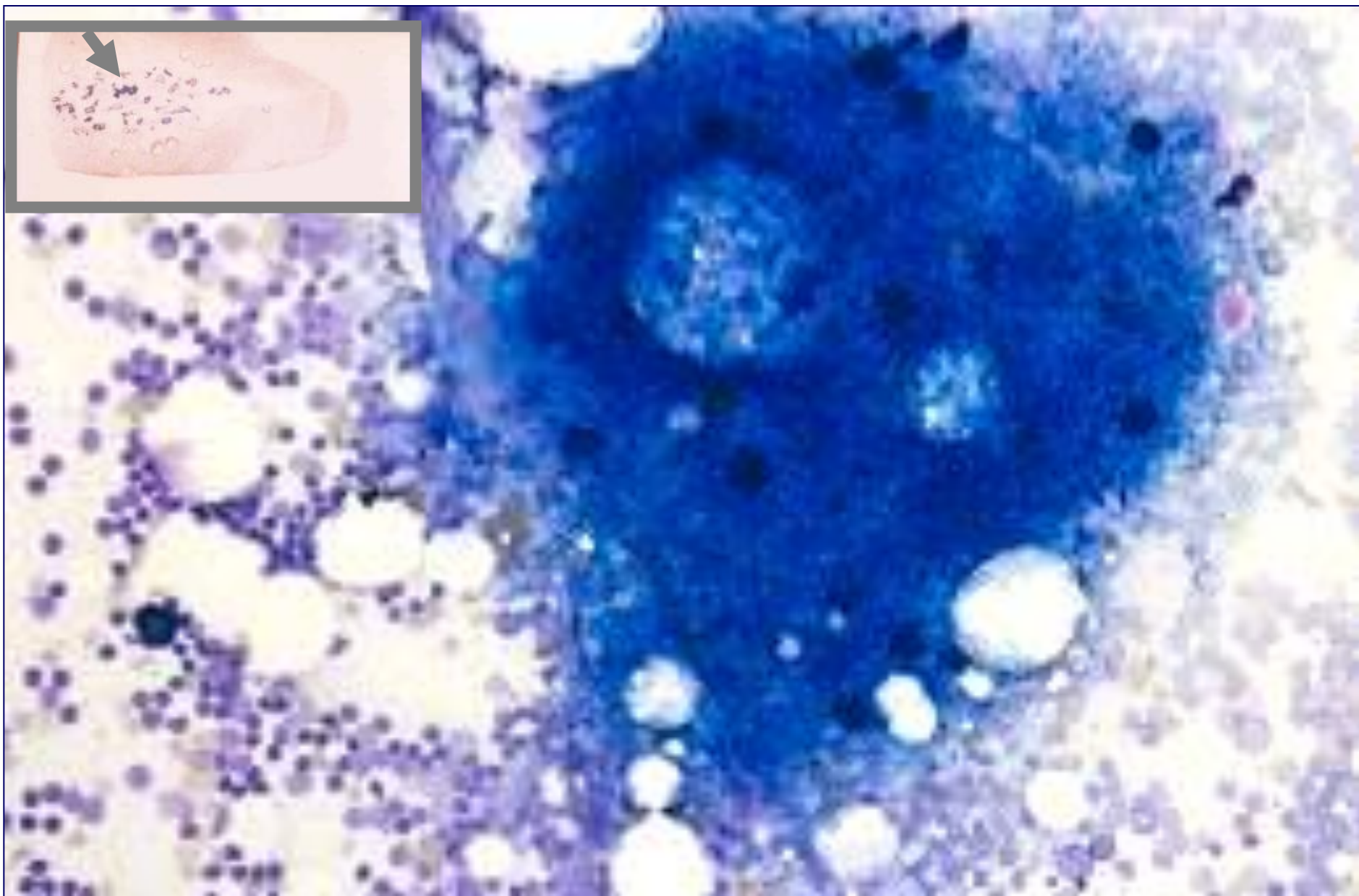
(Same)

(Same)

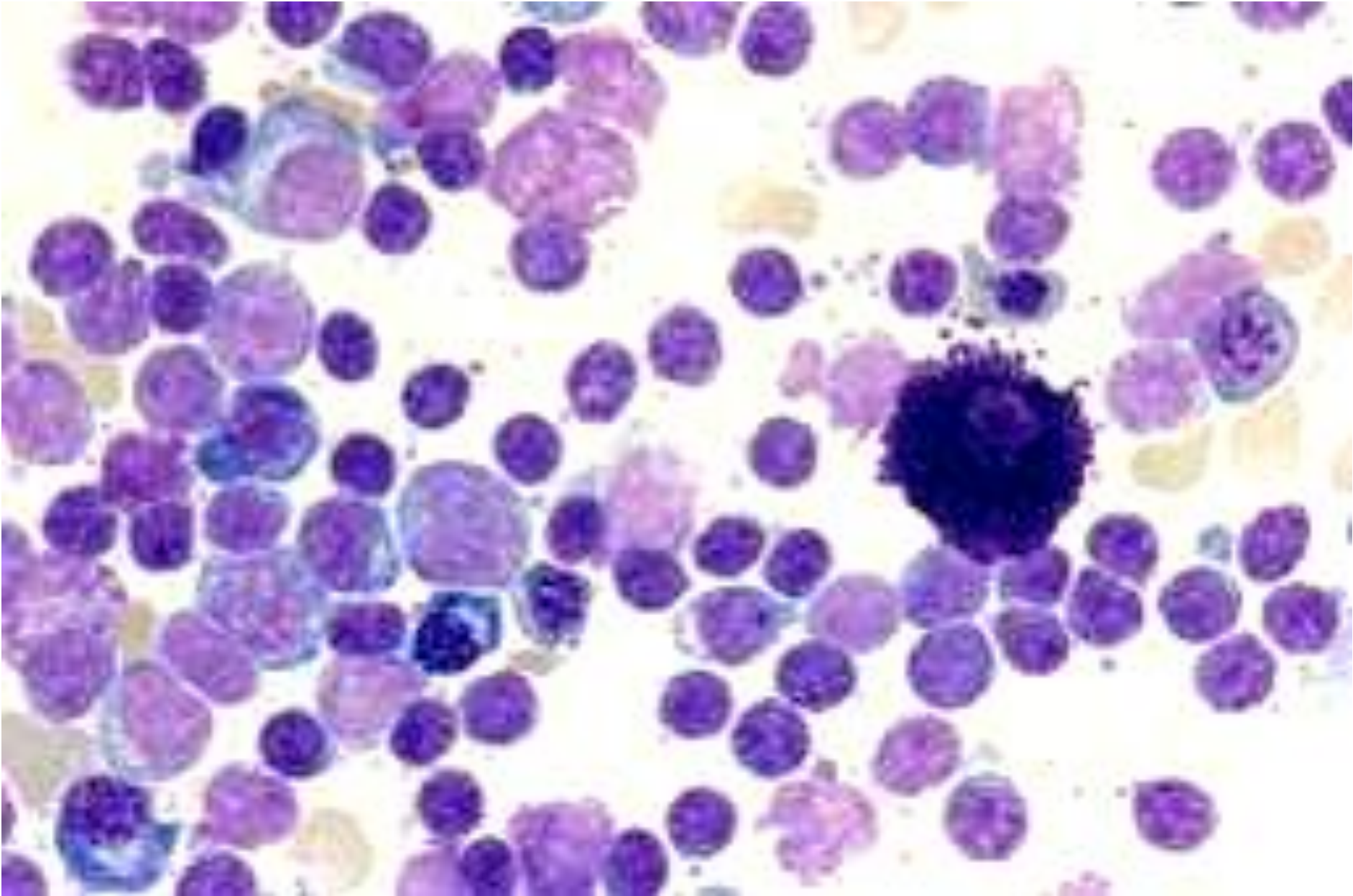
(Same)

*Not previously included* (encompassing **hairy cell leukaemia variant** and some cases of **B-cell prolymphocytic leukaemia**)

?



?



# LPL: Lymfoplasmacytair lymfoom (ziekte van Waldenström)

## **Bloed**

- Vaak normaal of cytopenie of **enkele** lymfoplasmacytoïde cellen
- M-proteïne (meestal IgM type, kan ook IgG, IgA)
- Soms **agglutinatie** van erythrocyten: geldroelvorming

## **Beenmerg cytologie**

- Infiltratie met **lymfoplasmacytoïde cellen: >10% (WHO)**  
plasmacellen, **mestcellen**, vaak **haarden**

**Flow: monoklonale B + monoklonale PC (geen overige afwijkingen)**

**Genetica: MYD88 mutatie (L265P)**

## **Klinisch beeld**

Vaak weinig symptomen, soms echter veel complicaties door **hoog IgM gehalte** (hyperviscositeit)

**Dd: andere plasmacytair uitgerijpte B-cel maligniteit (CLL, MZL, MCL)**

## 1A

Mature B-cell neoplasms	MYD88(L265P) prevalence	MYD88(L265P) incidence	Total sequenced	Range	Number of studies	References
Chronic lymphocytic leukemia/small lymphocytic lymphoma	2.5%	221	8773	0 – 25%	41	18, 22-24, 28, 38-53
Monoclonal B-cell lymphocytosis	0%	0	75	N.A.	2	53, 54
B-cell polyclymphocytic leukemia	Unknown*					
Splenic marginal zone lymphoma	7.0%	59	840	0 – 50%	19	18, 23, 29, 55, 56
Hairy cell leukemia	1.1%	1	89	0 – 8%	5	22, 30, 57-59
Splenic B-cell lymphoma/leukemia, unclassifiable	16.7%	1	6	N.A.	1	60
Lymphoplasmacytic lymphoma	85.5%	337	394	0 – 100%	16	18, 22-30
Non-IgM lymphoplasmacytic lymphoma	55.0%	33	60	42 – 100%	7	18, 23, 31, 33, 61
Waldenström macroglobulinemia	85.3%	1888	2213	57 – 100%	34	18, 22, 23, 31-37
Monoclonal gammopathy of undetermined significance, IgM	52.7%	301	571	0 – 100%	13	18, 22, 23, 62
Monoclonal gammopathy of undetermined significance, IgG/A	0%	0	41	N.A.	3	18, 22, 23, 34
Plasma cell myeloma	1.5%	3	205	0 – 30%	14	18, 22, 23, 30, 43, 63, 106, 107
Solitary plasmacytoma of bone	Unknown*					
Extramedullary plasmacytoma	Unknown*					
Monoclonal immunoglobulin deposition diseases	Unknown*					
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	3.9%	15	383	0 – 13%	9	18, 22, 23, 64, 65
Nodal marginal zone lymphoma	10.3%	16	156	0 – 71%	9	18, 22, 23, 66
Follicular lymphoma	1.9%	5	264	0 – 50%	10	18, 22, 23, 67, 68
Pediatric-type follicular lymphoma	0%	0	27	N.A.	2	69, 70
Large B-cell lymphoma with <i>IRF4</i> rearrangement	Unknown*					
Primary cutaneous follicle center lymphoma	0%	0	60	N.A.	3	71-73
Mantle cell lymphoma	6.7%	2	30	0 – 50%	6	30, 43, 74
Diffuse large B-cell lymphoma (DLBCL), NOS	15.6%	853	5457	0 – 71%	43	3, 18, 22, 23, 67, 75-84, 113
Germinal center B-cell type	5.3%	81	1520	0 – 57%	21	3, 22, 23, 79-81, 85
Activated B-cell type	22.9%	492	2151	8 – 61%	21	3, 22, 23, 79-81, 85
T-cell/histiocyte-rich large B-cell lymphoma	Unknown*					
Primary DLBCL of the central nervous system	60.8%	382	628	33 – 100%	21	18, 22, 23, 86-88, 96
Primary cutaneous DLBCL, leg type	62.2%	138	222	40 – 75%	9	22, 71, 89-91
EBV+ DLBCL, NOS	4.4%	4	90	0 – 22%	4	22, 83, 92
EBV+ mucocutaneous ulcer	0%	0	14	N.A.	1	93
DLBCL associated with chronic inflammation	Unknown*					
Lymphomatoid granulomatosis	Unknown*					
Primary mediastinal (thymic) large B-cell lymphoma	0%	0	68	N.A.	3	2, 3, 94
Intravascular large B-cell lymphoma	44.0%	11	25	N.A.	1	95
ALK+ Large B-cell lymphoma	Unknown*					
Plasmablastic lymphoma	Unknown*					
Primary effusion lymphoma	Unknown*					
HHV8+ DLBCL, NOS	Unknown*					
Burkitt lymphoma	1.5%	1	67	0 – 2%	2	2, 74
Burkitt-like lymphoma with 11q aberration	Unknown*					
High-grade B-cell lymphoma, with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements	11.1%	1	9	N.A.	1	83
High-grade B-cell lymphoma, NOS	Unknown*					
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma	Unknown*					

## 1B

Other mature B-cell neoplasms with	MYD88(L265P) prevalence	MYD88(L265P) incidence	Total sequenced	Range	Number of studies	References
Ocular adnexal marginal zone lymphoma	9.0%	23	255	36 – 71%	6	22, 23, 105
Primary bone DLBCL	5.8%	3	52	0 – 15%	3	100-102
Primary breast DLBCL	54.3%	38	70	35 – 71%	3	22, 99
Primary cutaneous marginal zone lymphoma	2.0%	2	100	0 – 4%	3	103, 104
Primary DLBCL of the thyroid	0%	0	21	N.A.	1	22
Primary testicular lymphoma	68.4%	65	95	14 – 82%	6	22, 23, 96, 108
Vitreoretinal lymphoma	72.7%	88	121	50 – 82%	9	22, 97, 98

\* No data found in a literature search of articles published from January 2011 until August 2019. Terms used: 'WHO terms' (MeSH terms) AND MYD88 | 'WHO terms' (MeSH Terms) AND Genetic. Additionally, all articles found by the 'WHO terms' (MeSH terms) were screened for lymphomas with unknown status of the MYD88 L265P mutation. DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified; EBV: Epstein-Barr virus; ALK: anaplastic lymphoid kinase; HHV8: human herpes virus 8.

**MYD88 mutatie:**

**LPL (IgM): 86%**

**LPL (IgG/IgA): 55%**

**MGUS: 53%**

**CLL: 3%**

**MBL: 0%**

**MZL: 4-10%**

**MCL: 7%**

**DLBCL: 15-23%**

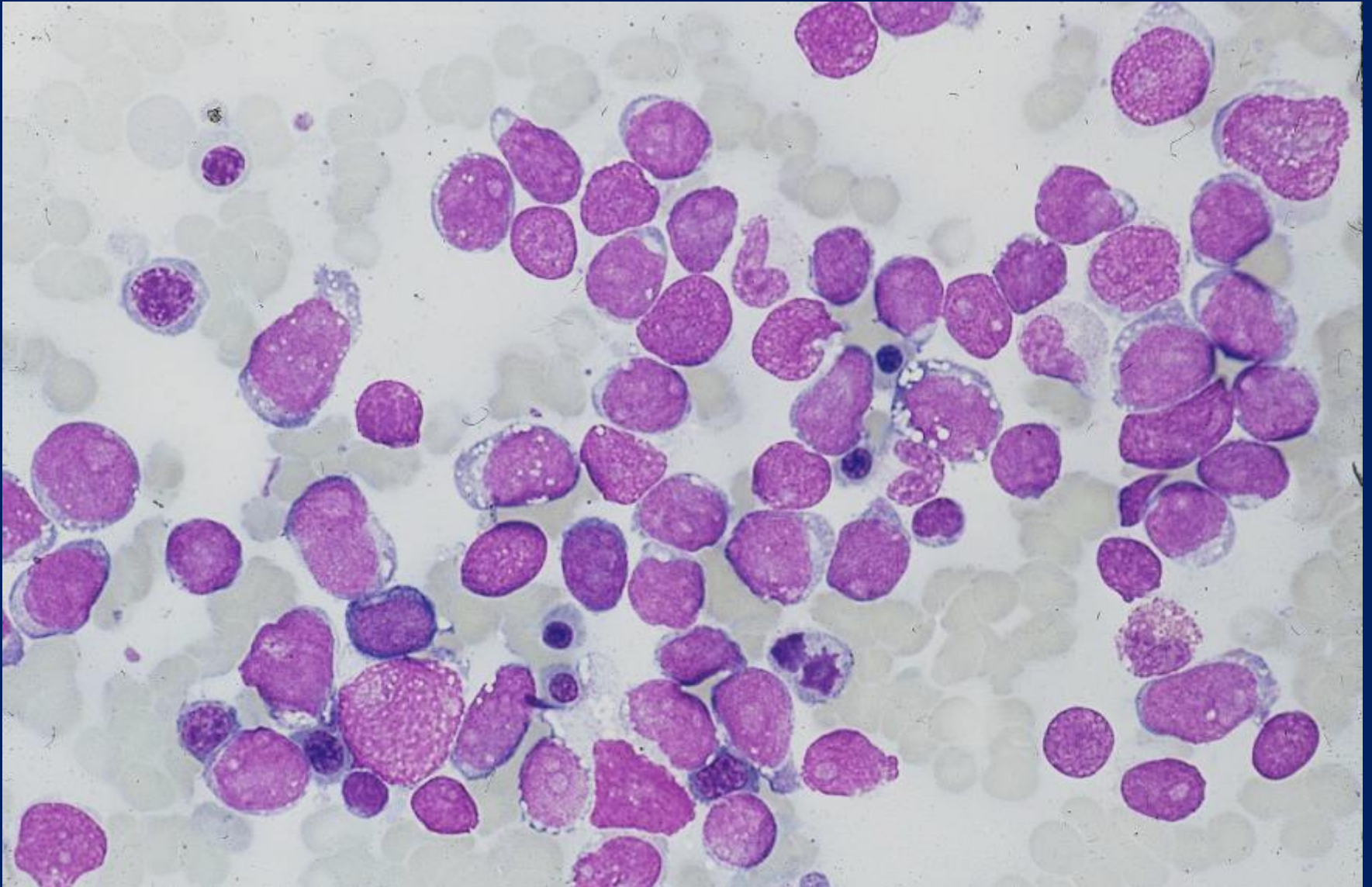
**- CNS: 61%**

**- Leg type: 62%**

Groen et al.,

<https://doi.org/10.3324/haematol.2019.227272>

# BM met DLBCL infiltratie (Burkitt lymfoom?)

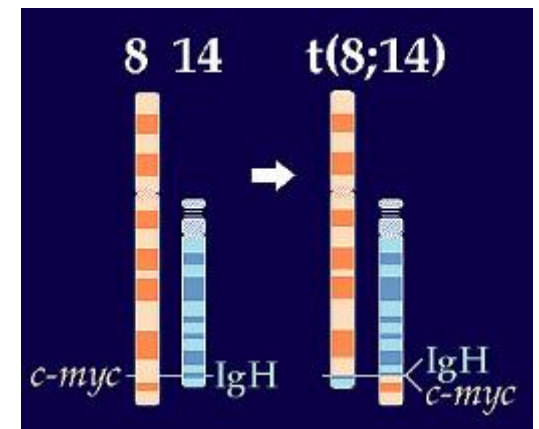
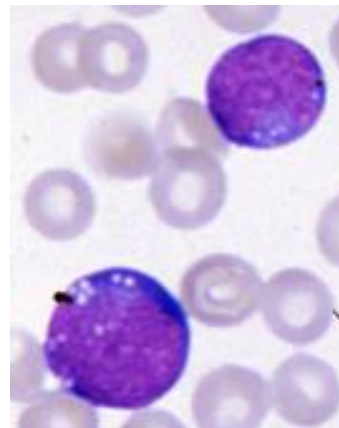
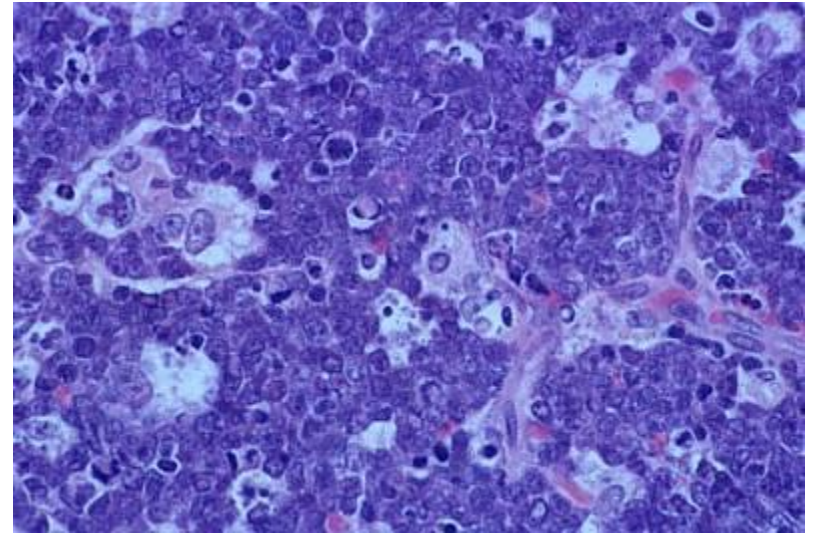
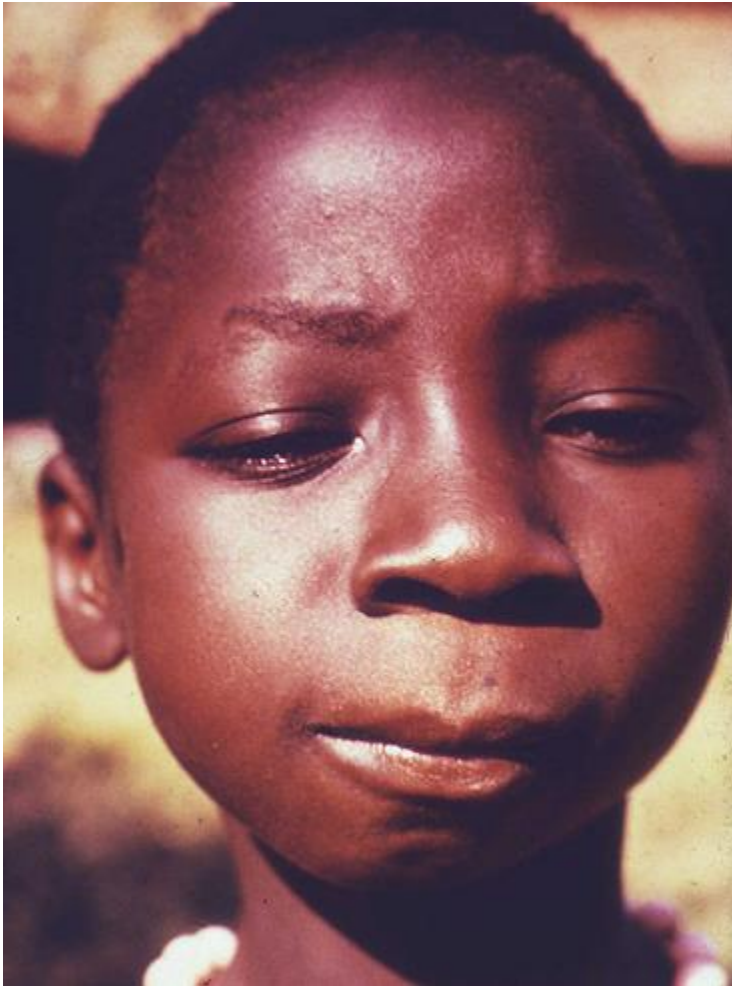


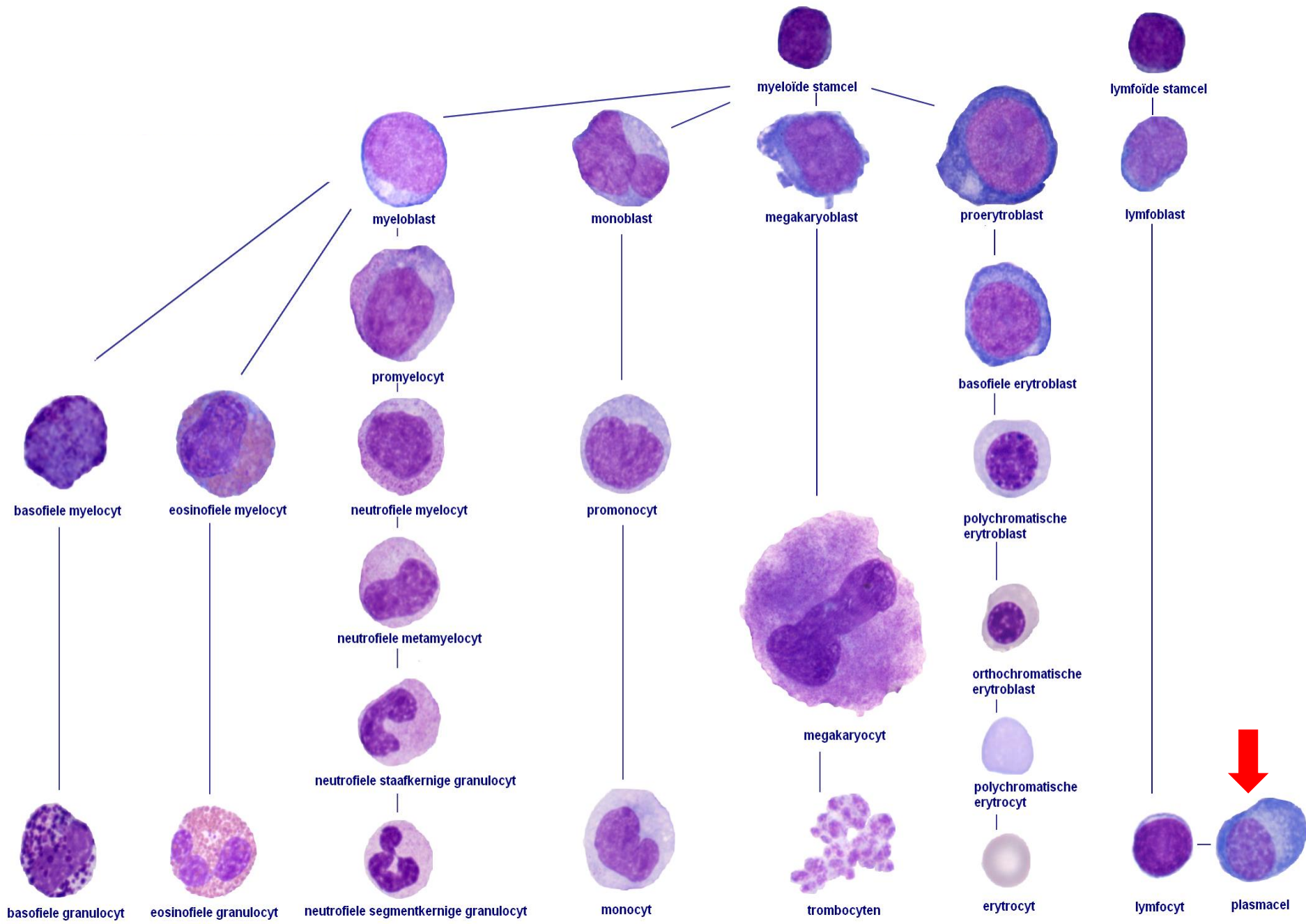


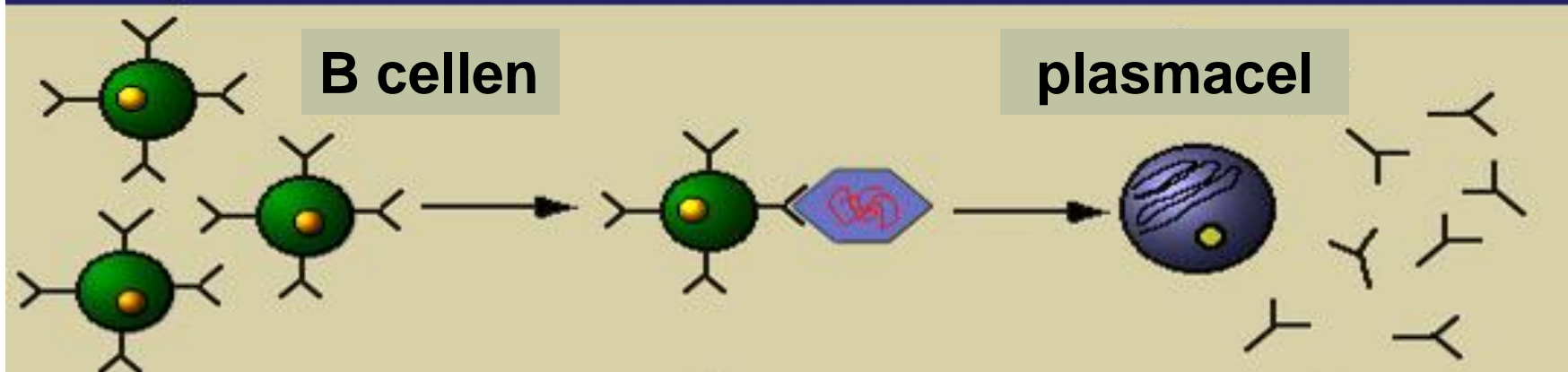
# Burkitt Lymfoom



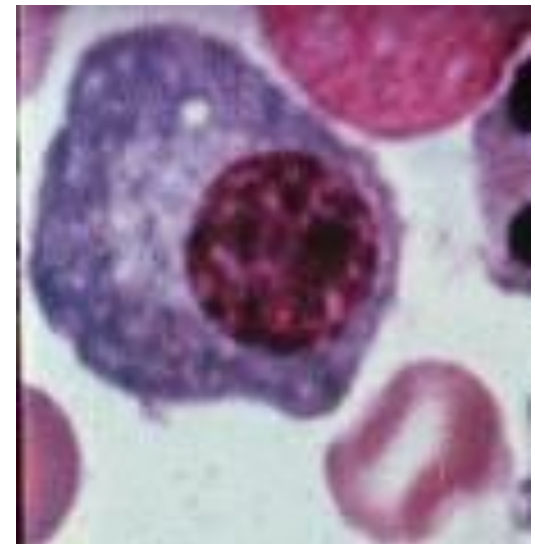
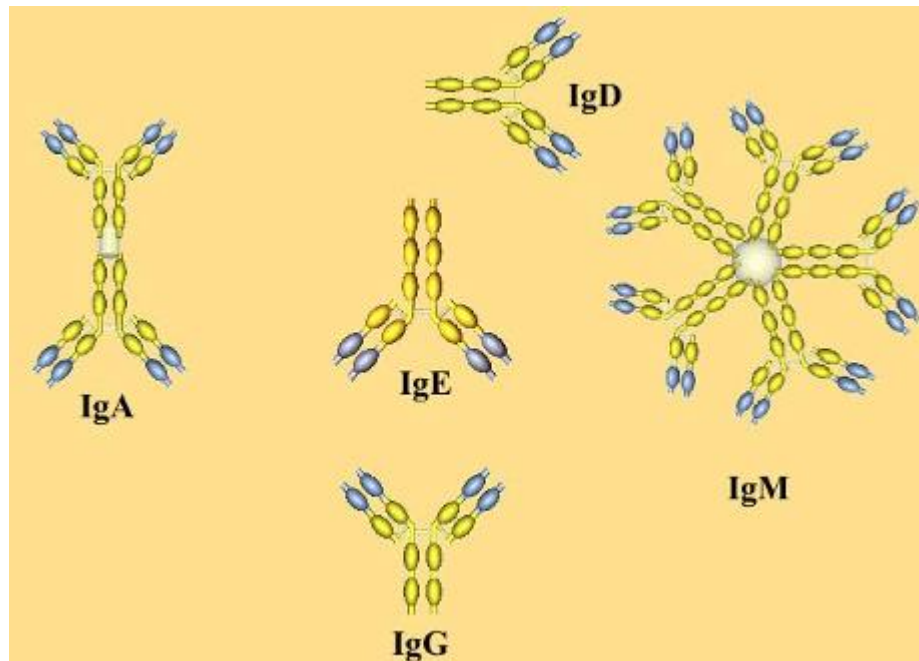
# Burkitt lymphoma



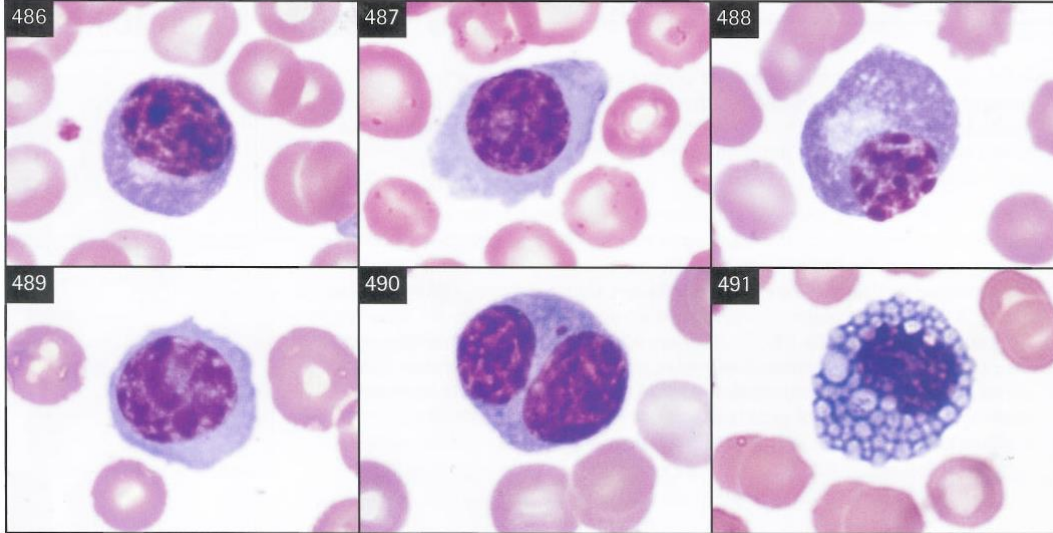




B cellen worden plasmacellen;  
 plasmacellen produceren antistoffen;  
 1 plasmacel maakt 1 soort antistof

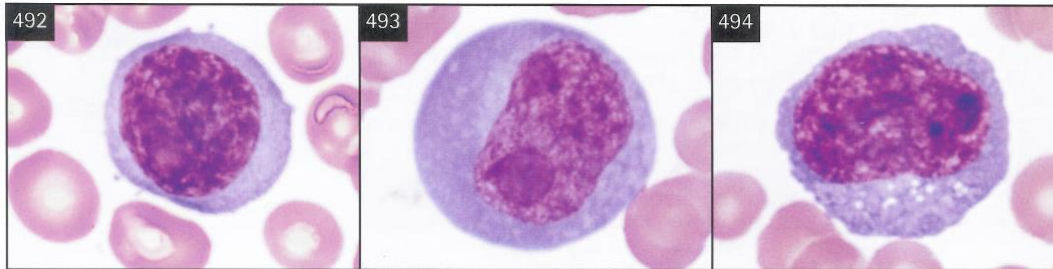


Plasma Cells: Images 486-491

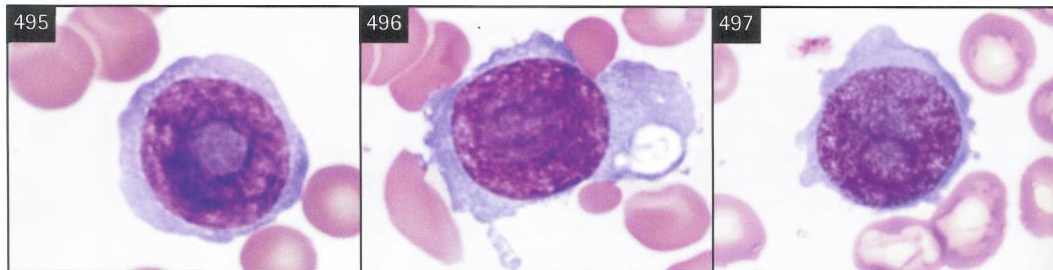


Mature plasma cells ( 491 is also known as a grape cell or Mott cell)

Proplasmacytes: Images 492-494



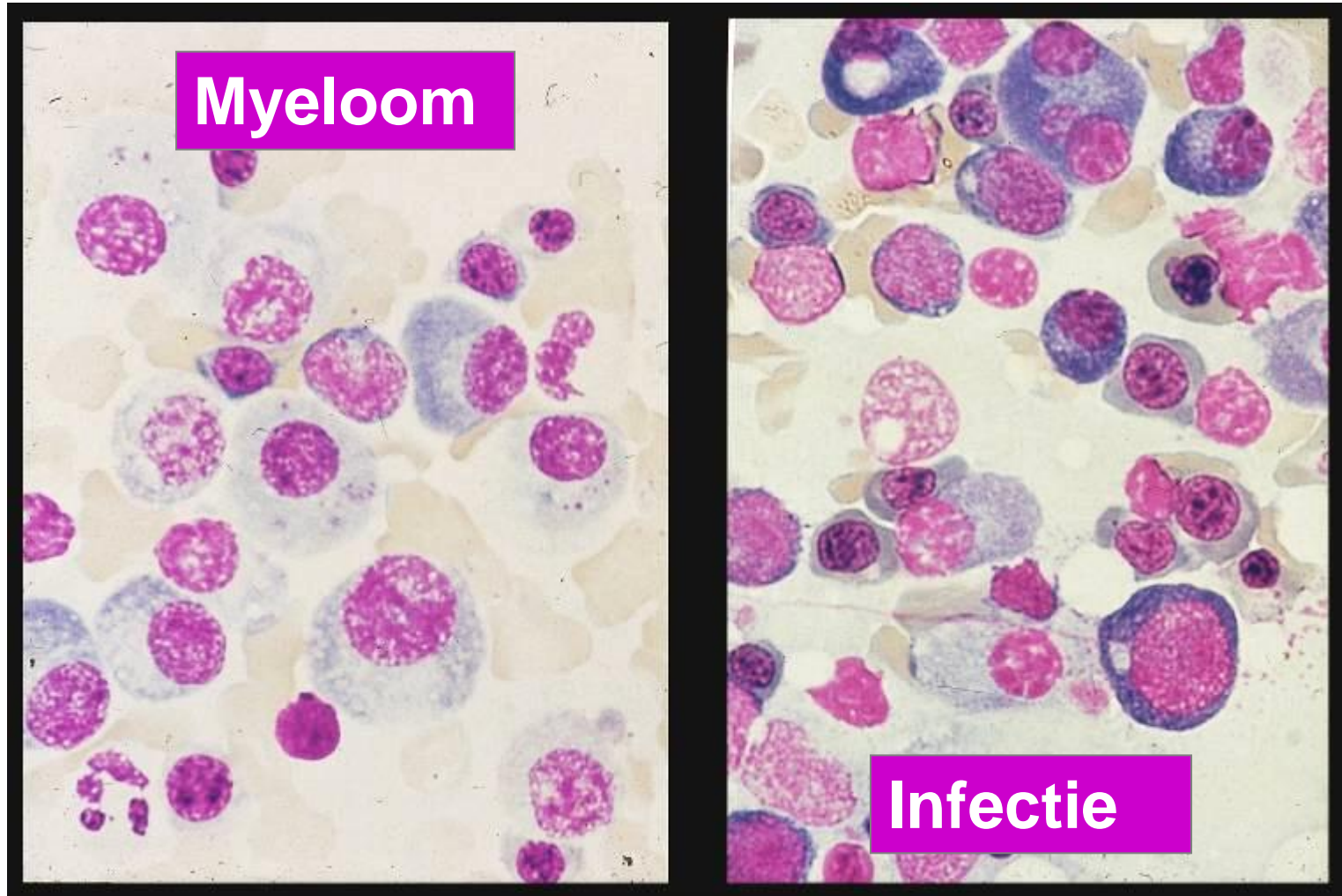
Plasmablasts: Images 495-497



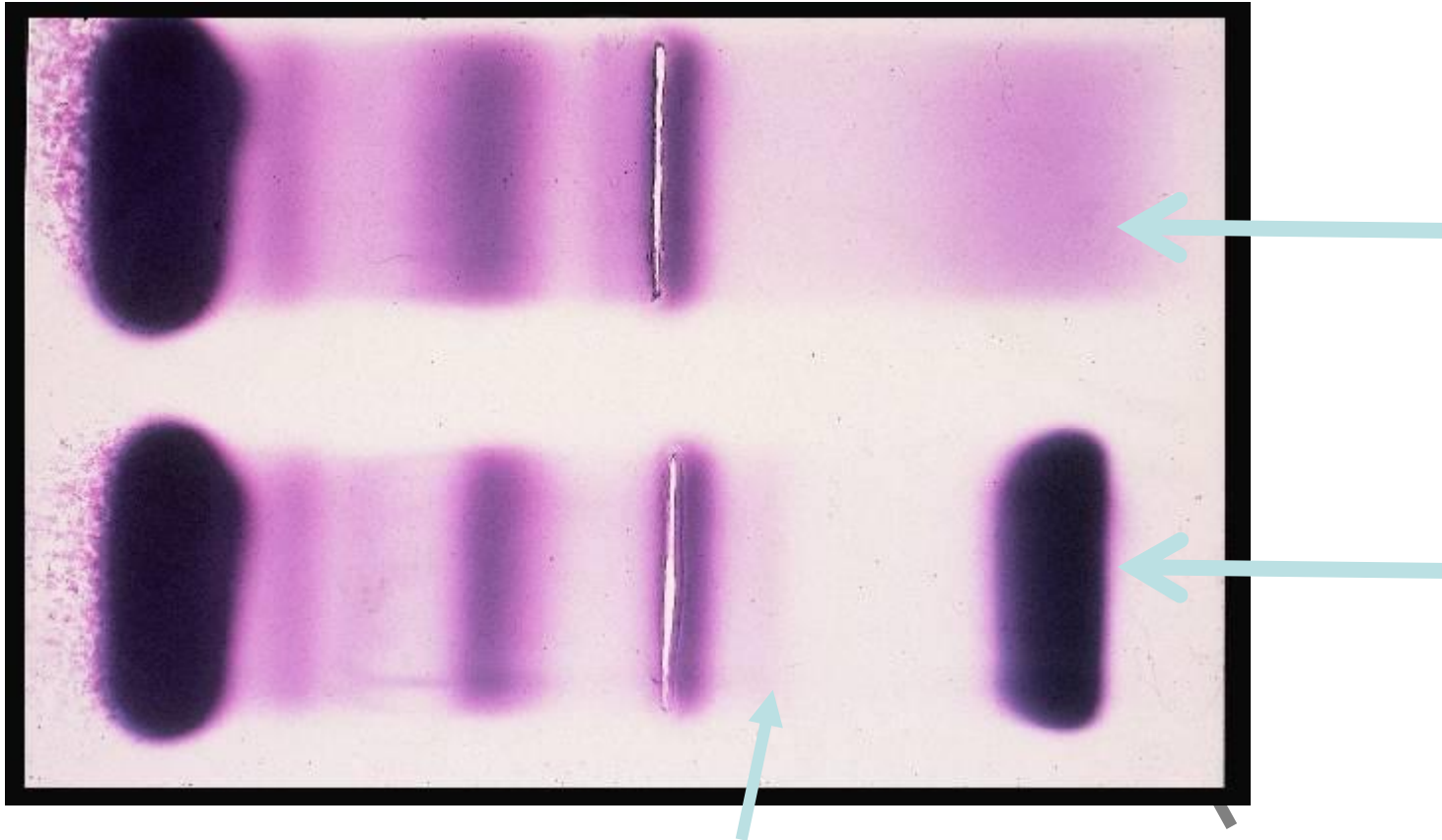
**Russell bodies**

**Dutcher bodies**

Een **toename** aan plasmacellen komt ook bij reactieve aandoeningen voor!



# Eiwitspectrum met monoclonaal M-proteïne

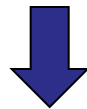




# M-proteïne

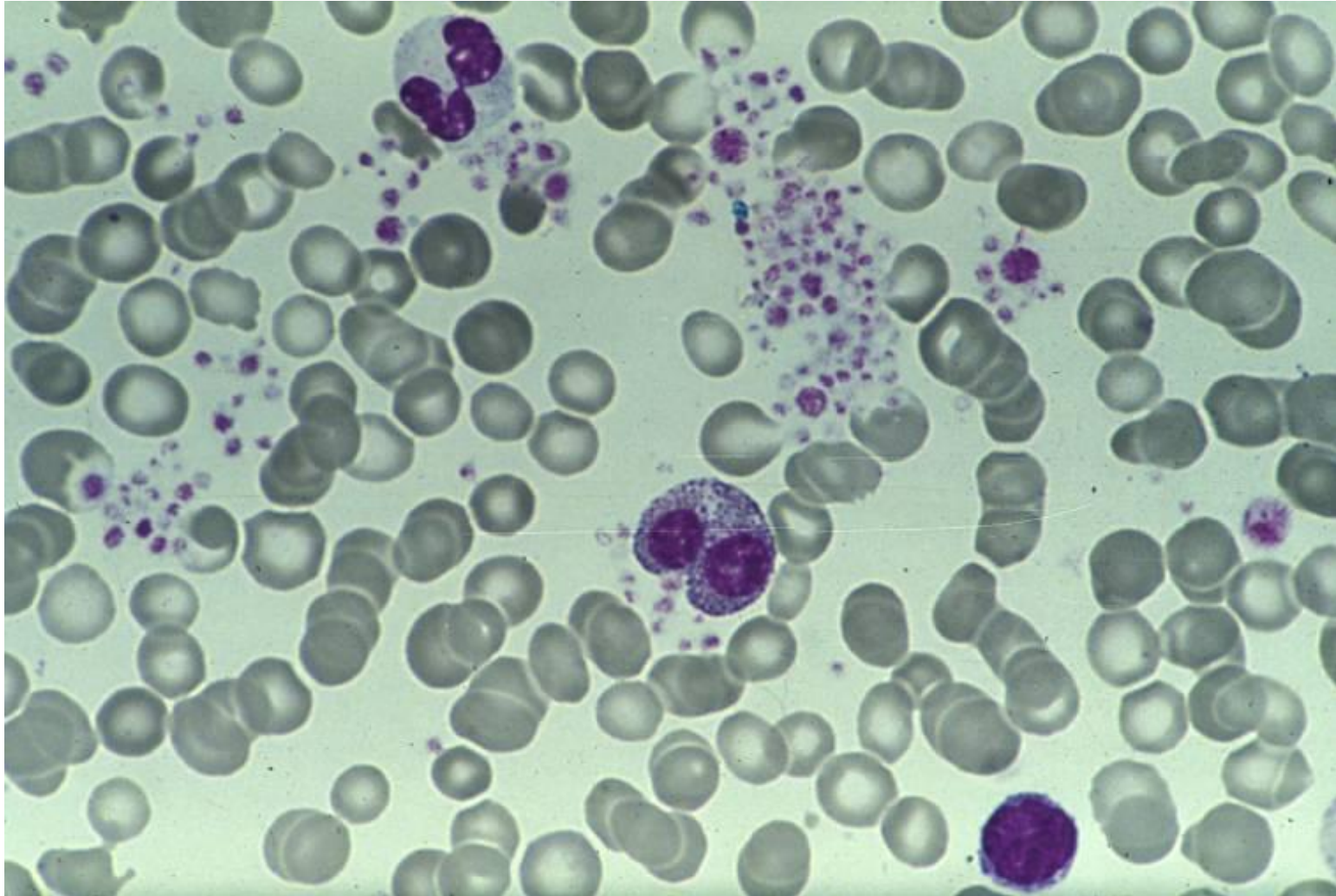
De aanwezigheid van een M-proteïne geeft alleen aanwezigheid van klonale plasmacellen aan.

**M-proteïne ≠ maligne**

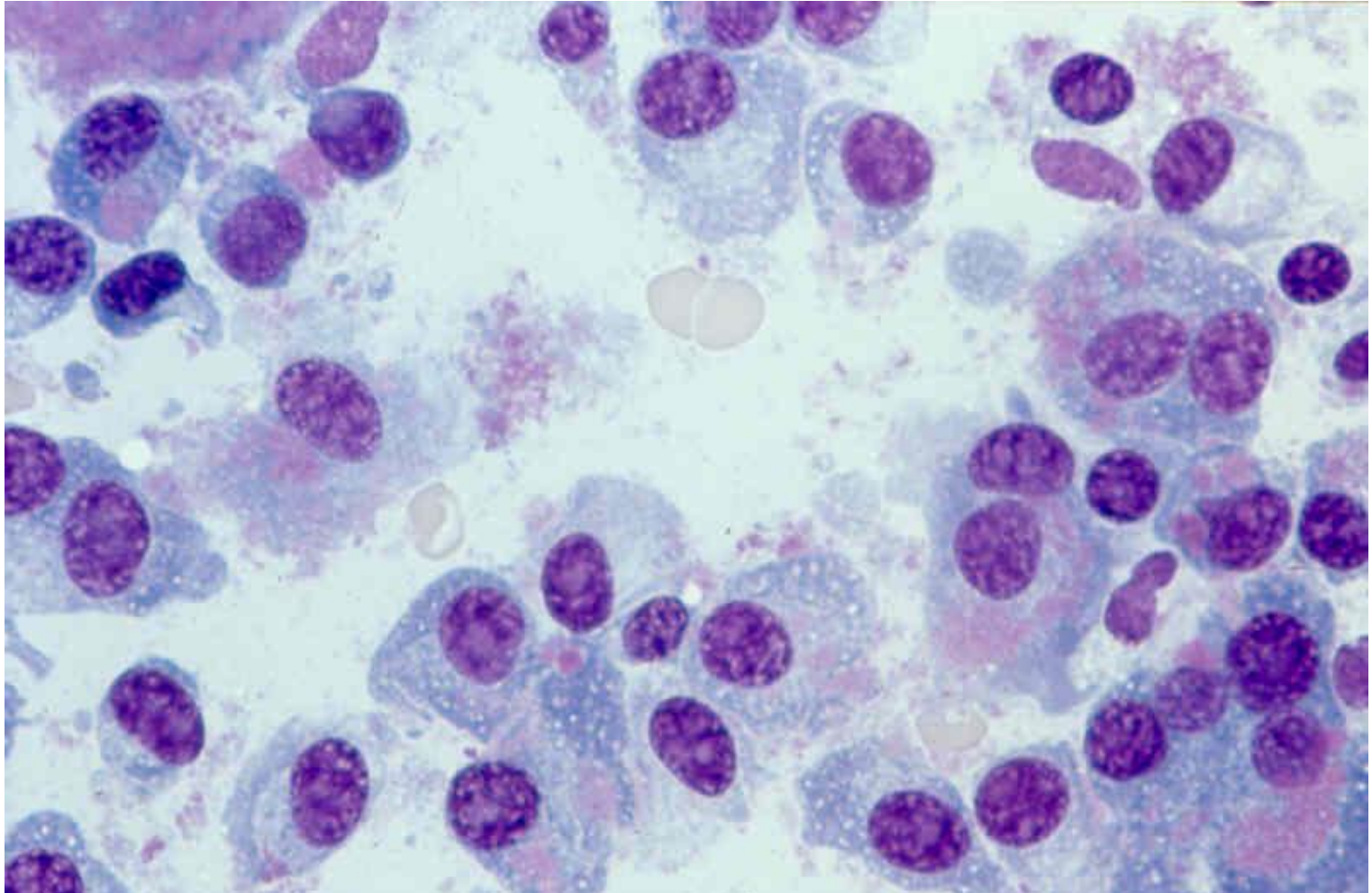


**>80% van de M-proteïnes is MGUS of reactief!**

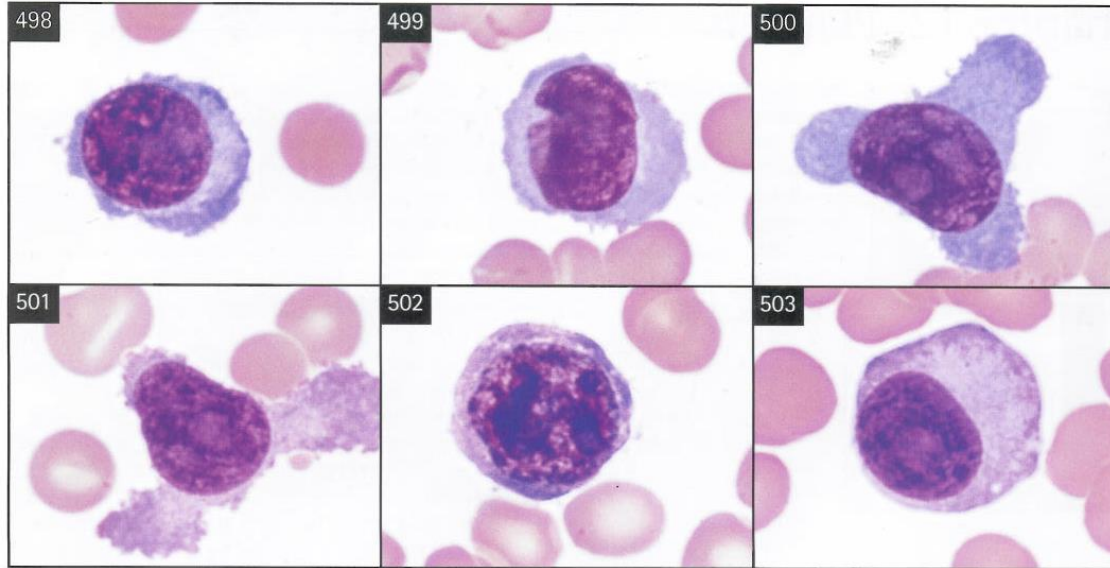
# Geldrolvorming/agglutinatie



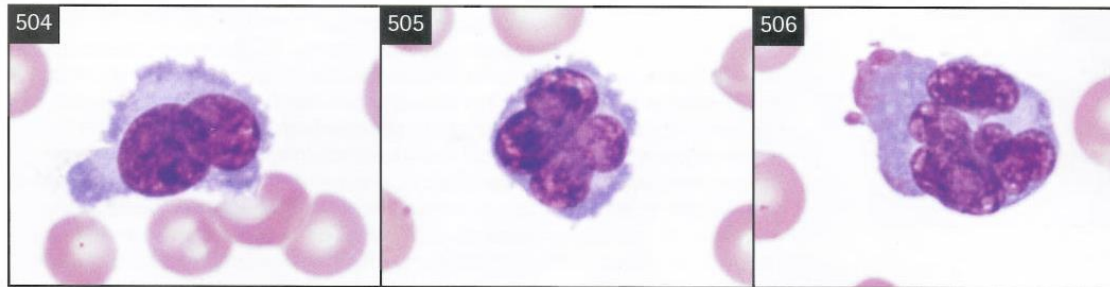
# Plasmacel (multipel) myeloom (PCM)



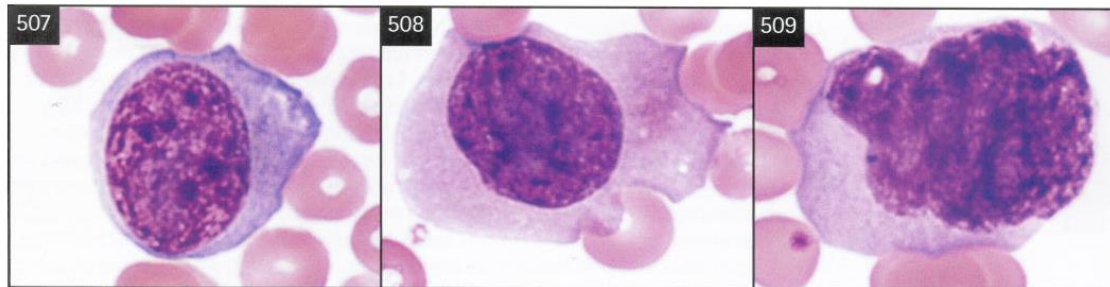
Myeloma Cells: Images 498-509



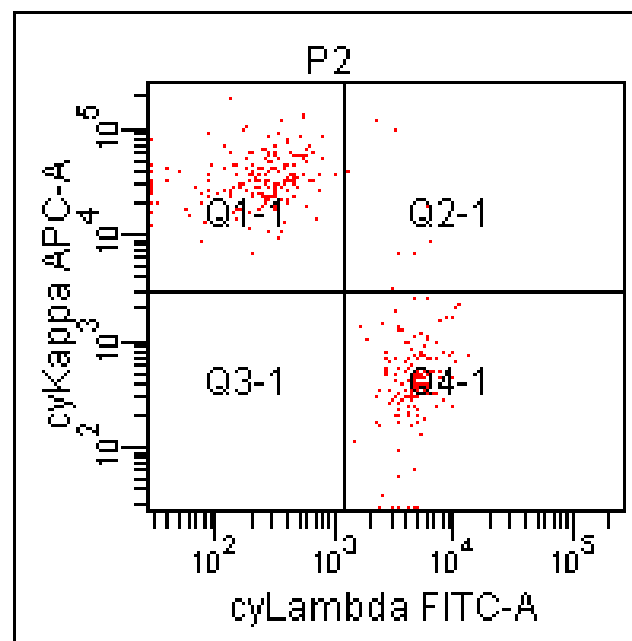
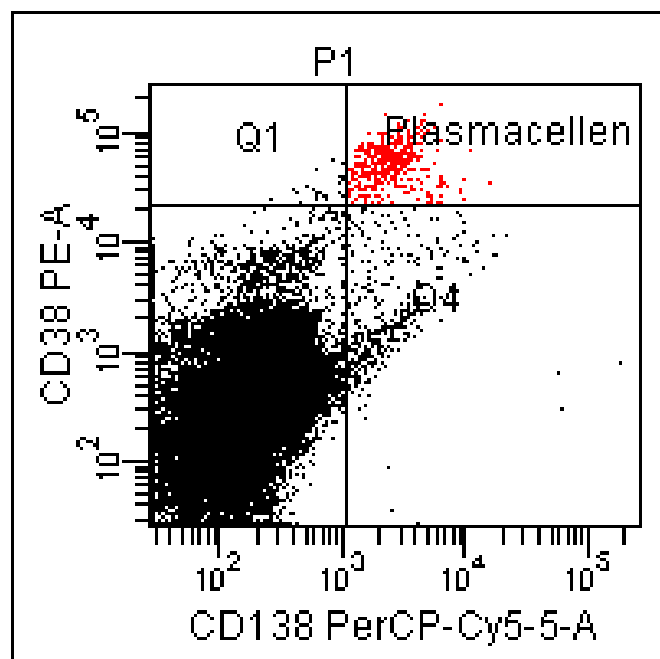
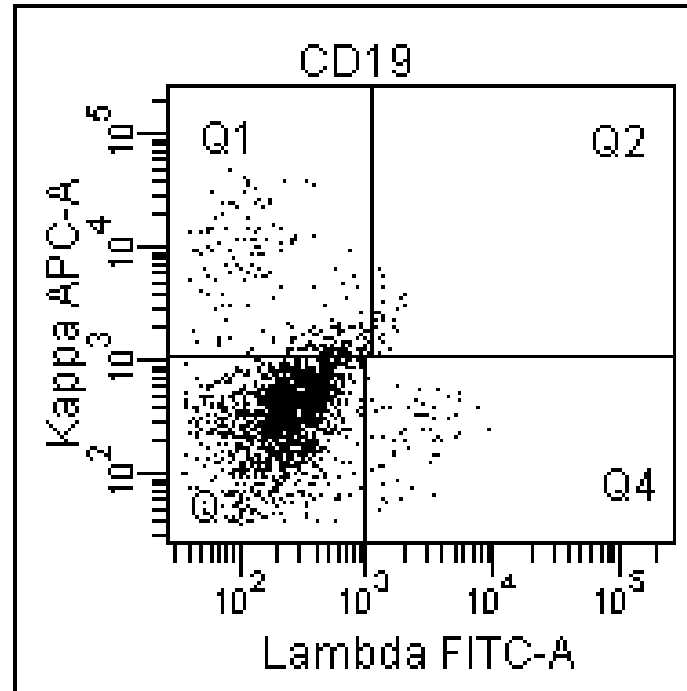
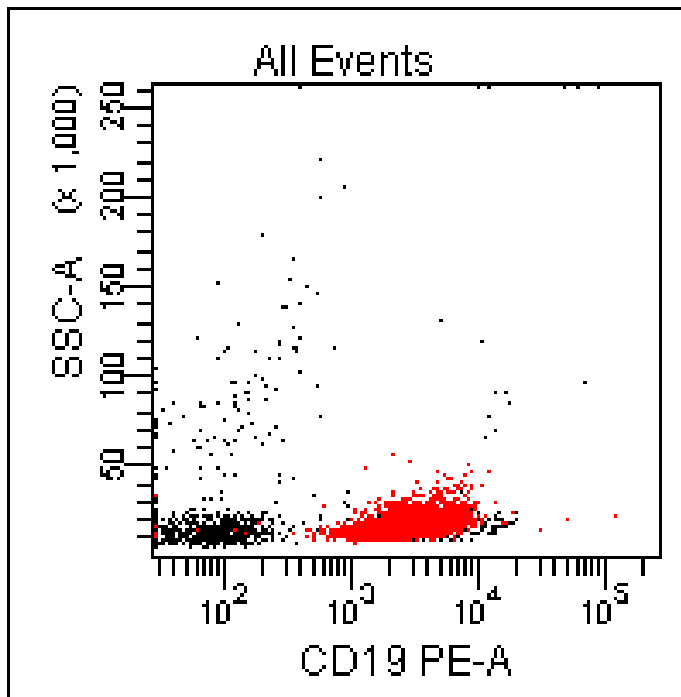
Myeloma cells ( 501 and 503 are flame cells)

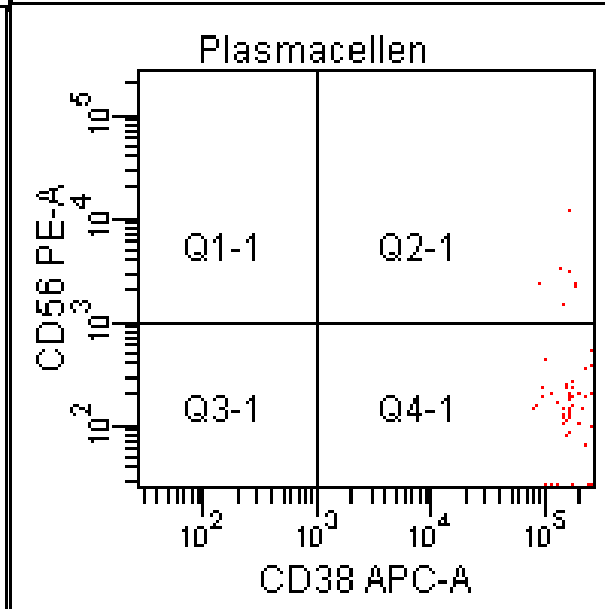
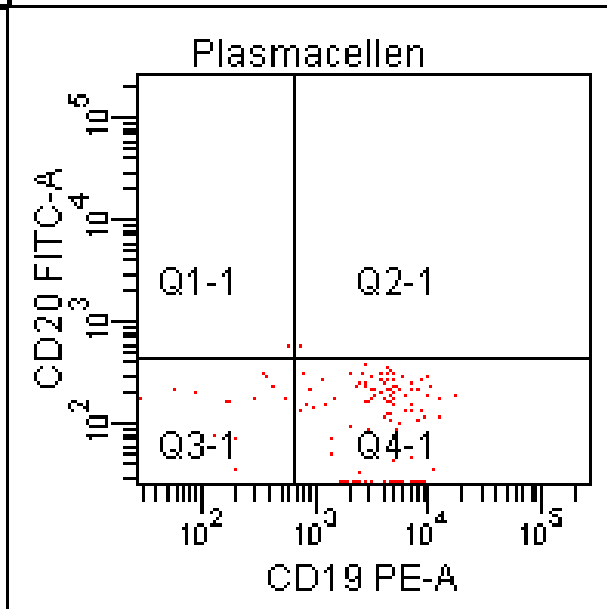
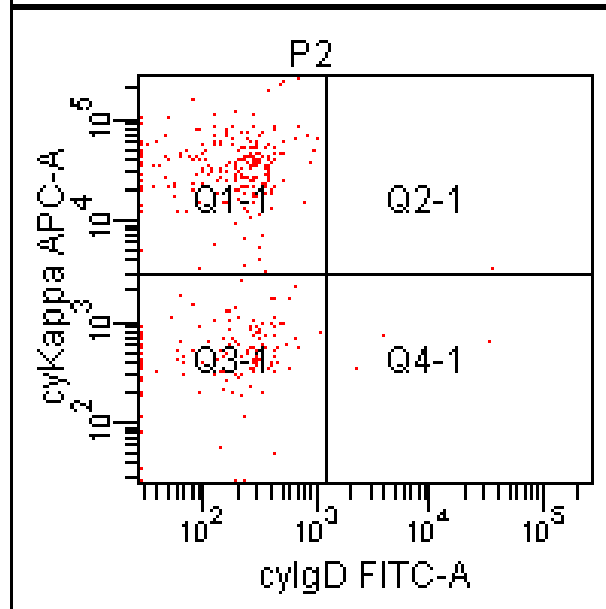
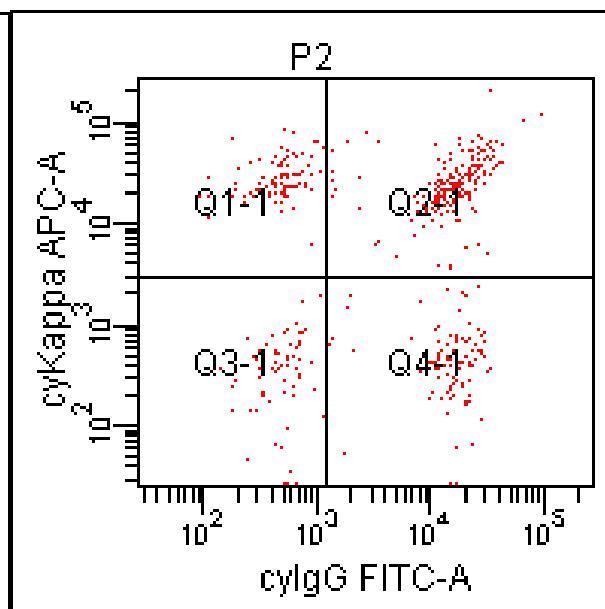
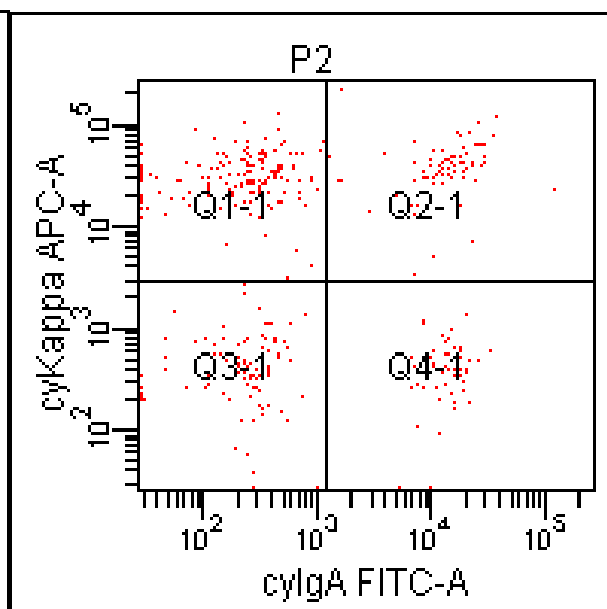
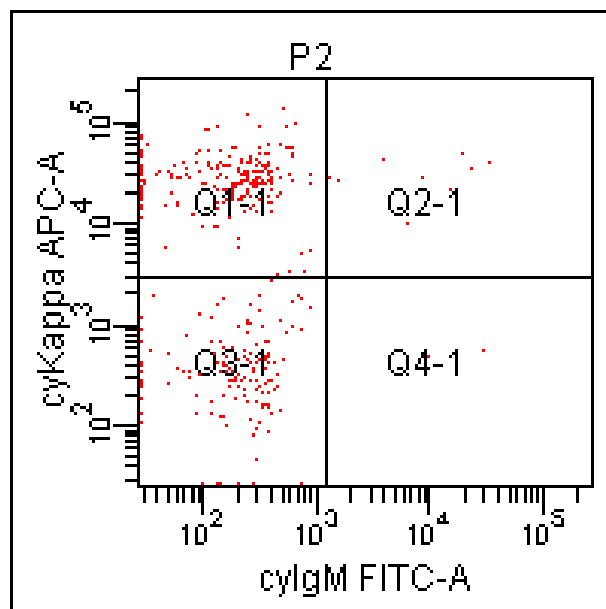


Multinucleated myeloma cells ( 506 is a flame cell)

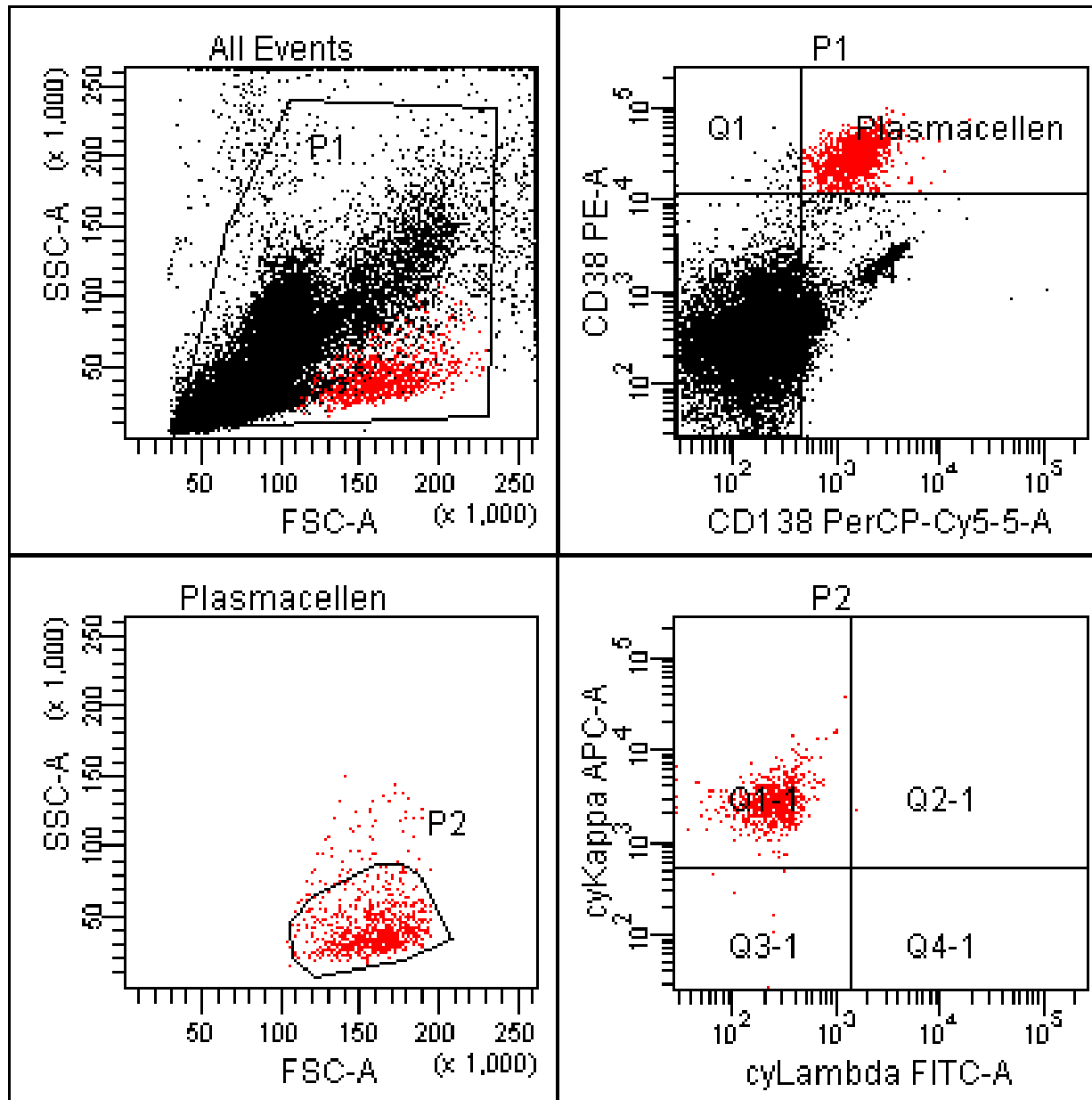


Giant myeloma cells ( 508 and 509 are flame cells)

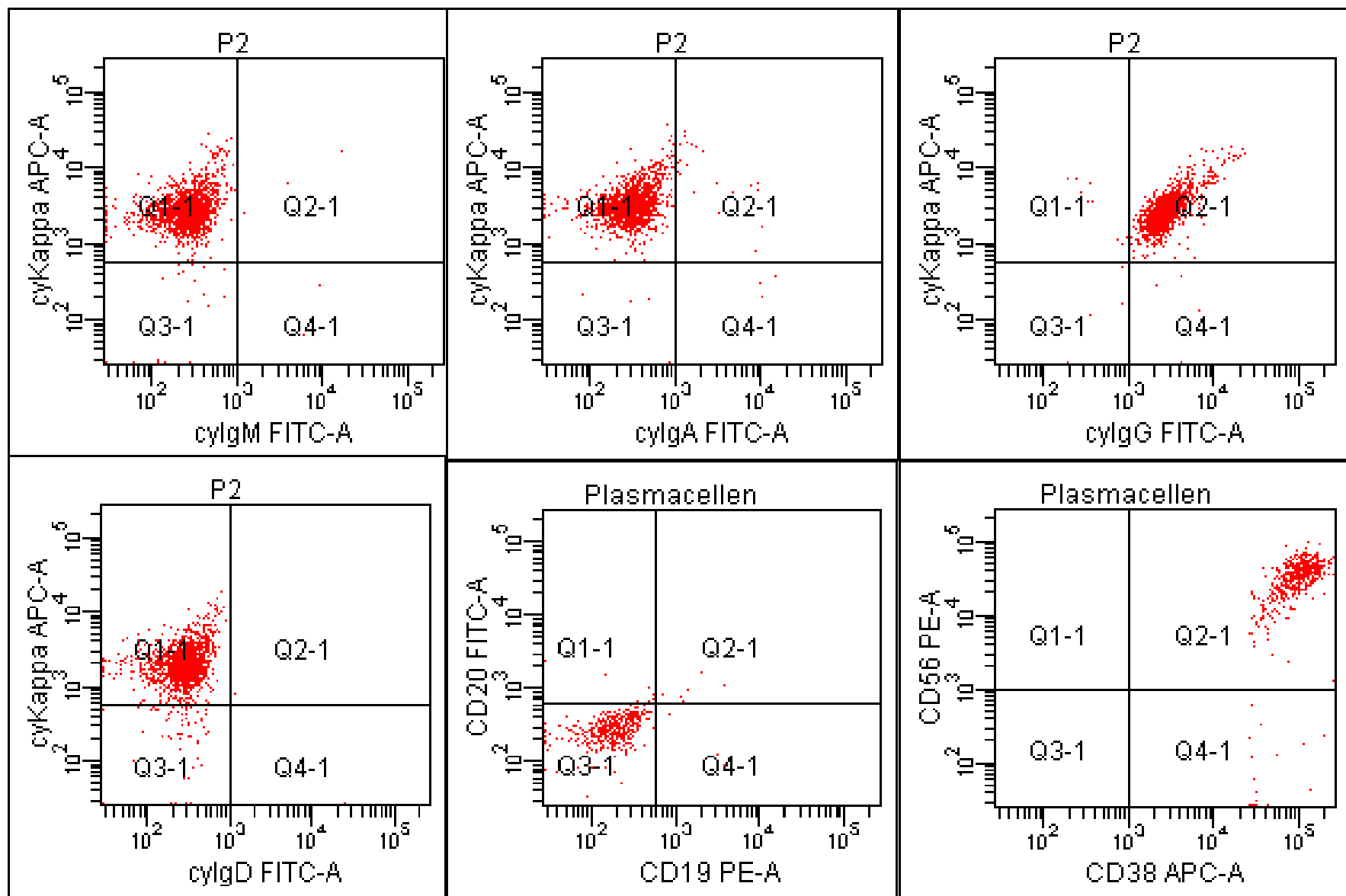




# PCM

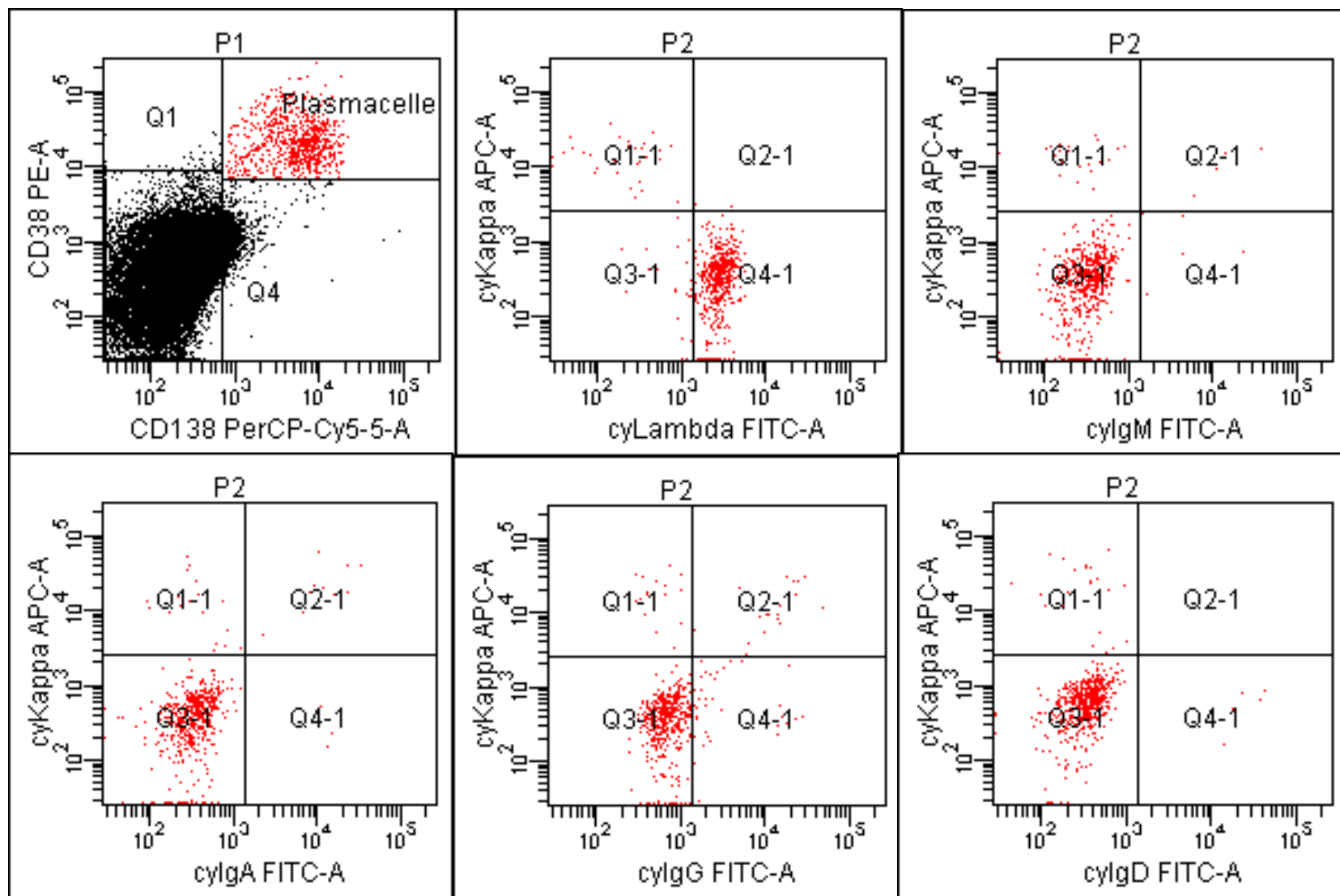


???





???



# Valkuilen bij Plasmaceldyscrasie

- Een toename van atypische plasmacellen door andere oorzaken
- Een M-proteïne door andere oorzaken
- Plasmacellen kunnen zo maligne zijn dat ze nauwelijks meer herkenbaar zijn!
- **In flow van beenmerg vaak hele kleine fractie van de plasmacellen: geen percentage rapporteren!**

**Table 1**

**WHO Classification of Haematolymphoid Tumours, 5<sup>th</sup> edition: B-cell lymphoid proliferations and lymphomas**

**WHO Classification, 5<sup>th</sup> edition**

**Plasma cell neoplasms and other diseases with paraproteins**

***Monoclonal gammopathies***

**Cold agglutinin disease**

IgM monoclonal gammopathy of undetermined significance

Non-IgM monoclonal gammopathy of undetermined significance

**Monoclonal gammopathy of renal significance**

***Diseases with monoclonal immunoglobulin deposition***

**Immunoglobulin-related (AL) amyloidosis**

Monoclonal immunoglobulin deposition disease

***Heavy chain diseases***

Mu heavy chain disease

Gamma heavy chain disease

Alpha heavy chain disease

***Plasma cell neoplasms***

Plasmacytoma

Plasma cell myeloma

Plasma cell neoplasms with associated paraneoplastic syndrome

-POEMS syndrome

-TEMPI syndrome

**WHO Classification, revised 4<sup>th</sup> edition**

*Not previously included*

(Same)

(Same)

*Not previously included*

**Primary amyloidosis**

Light chain and heavy chain deposition disease

(Same)

(Same)

(Same)

(Same)

(Same)

(Same) Except AESOP syndrome *not previously included*



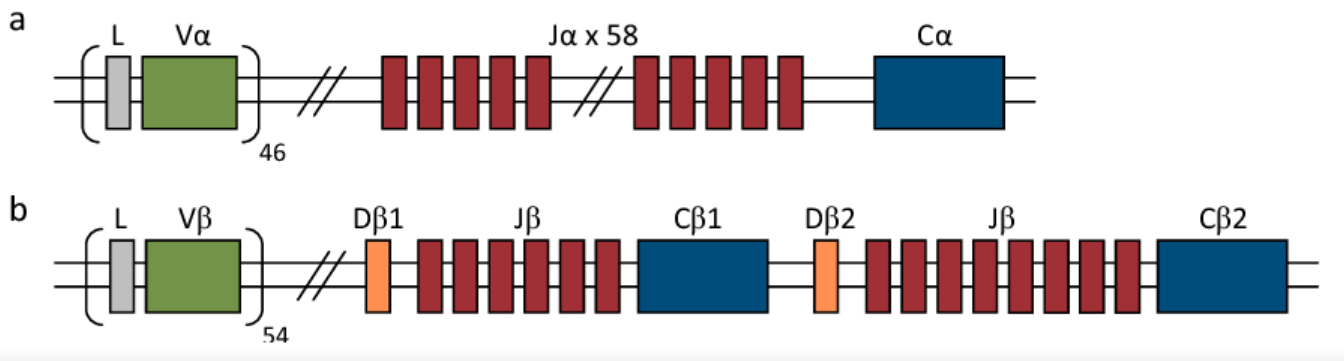
## **Leukemische rijpe T-/NK-cel vormen:**

### Primair leukemisch:

- T-cel prolymphocyttaire leukemie (T-PLL)
- T-/NK-cel large granular lymfocyt leukemie (T/NK-LGL)

### Secundair leukemisch:

- Sézary syndroom uit MF
- Leukemische T-cel lymfomen



## Antistof tegen T-cell receptor $\beta$ chain constant region 1 (anti-TRBC1)

