

# Disclosure belangen spreker

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(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen





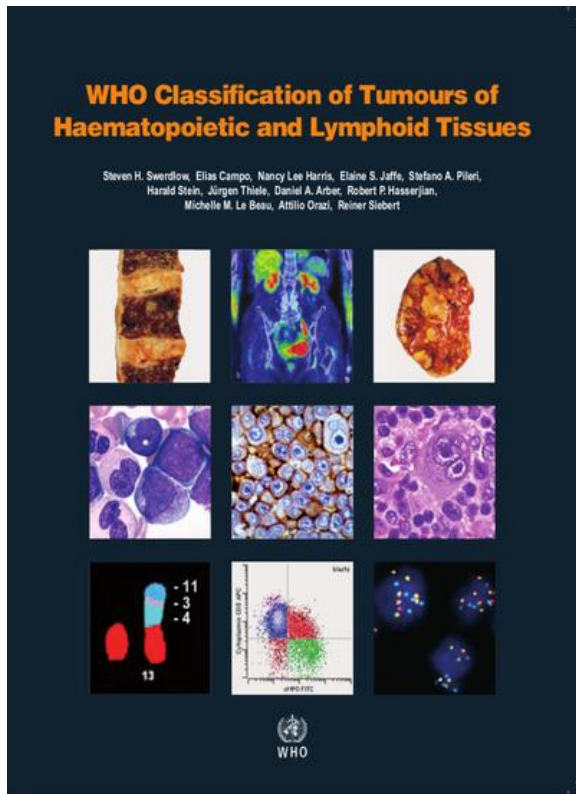
# rijpe T-cel maligniteiten

Classificatie, Cytologie en Flow Cytometrie

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# 2016



# 2022







 **blood** Special Report

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee



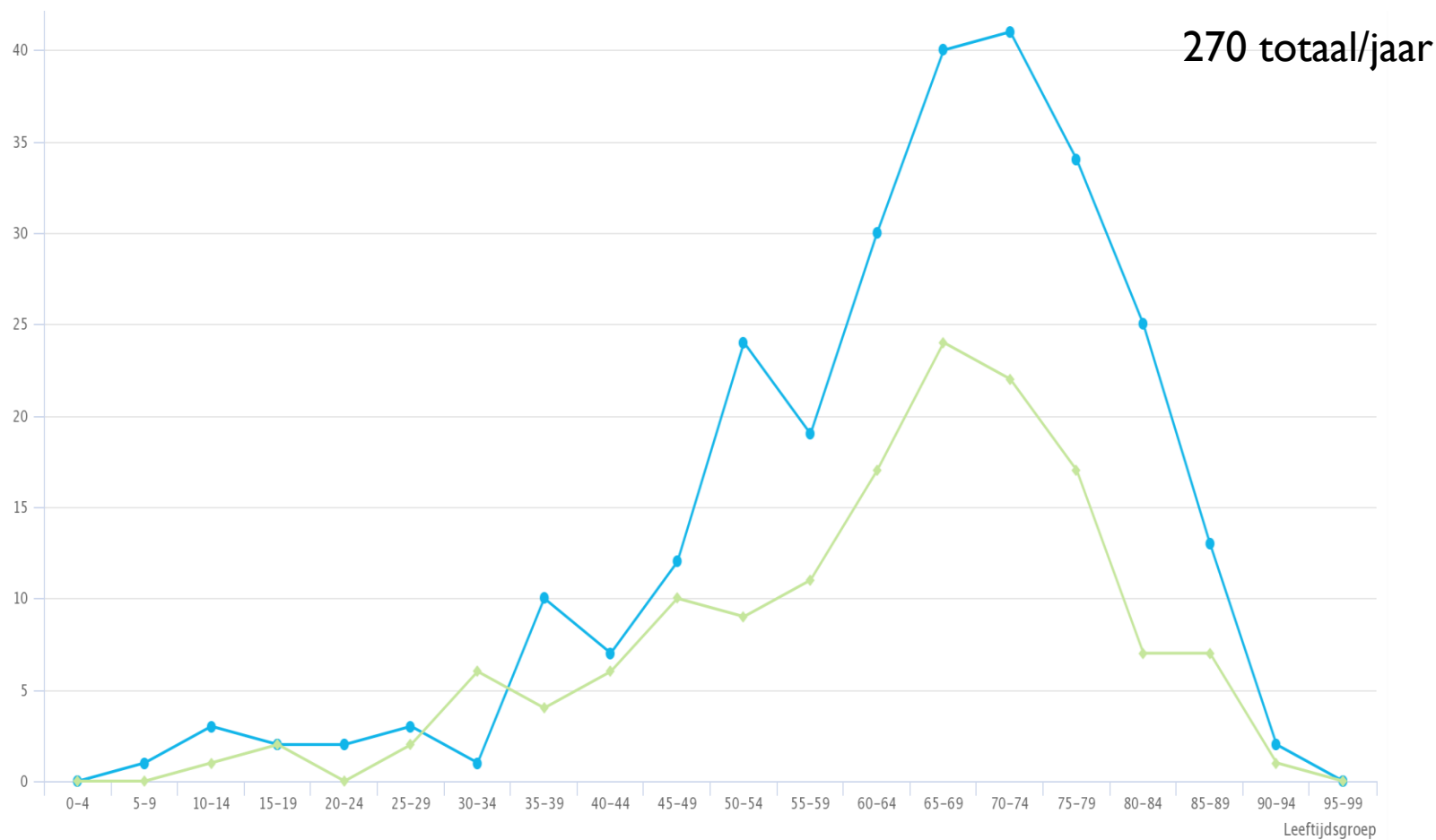
# Indeling WHO 5<sup>e</sup>

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1. Rijpe T en NK cel leukemiën
  2. Cutane T-cel maligniteiten
  3. Intestinale T en NK cel maligniteiten
  4. Anaplastische grootcellige lymfomen
  5. T folliculair helper cel lymfomen
  6. Overige perifere T cel lymfomen
  7. EBV positieve T en NK cel lymfomen (kinderen)
- 



# Cijfers, incidentie 2017

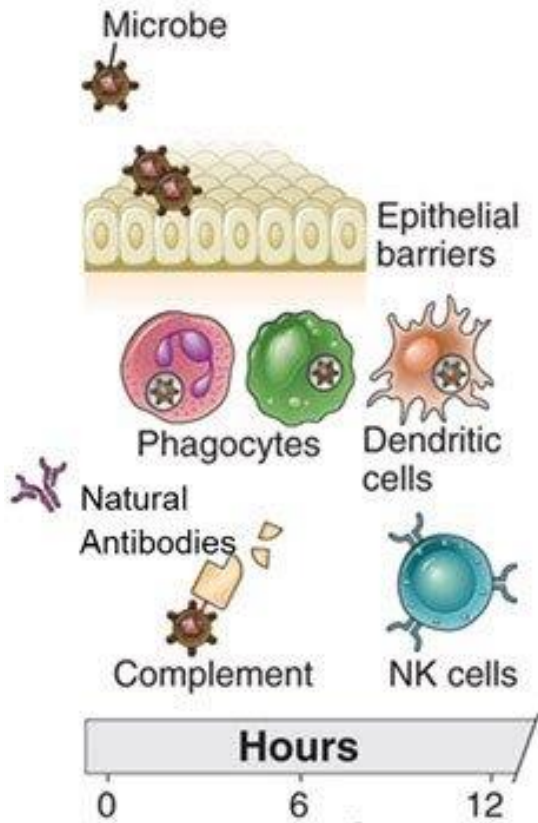


## Kankersoort

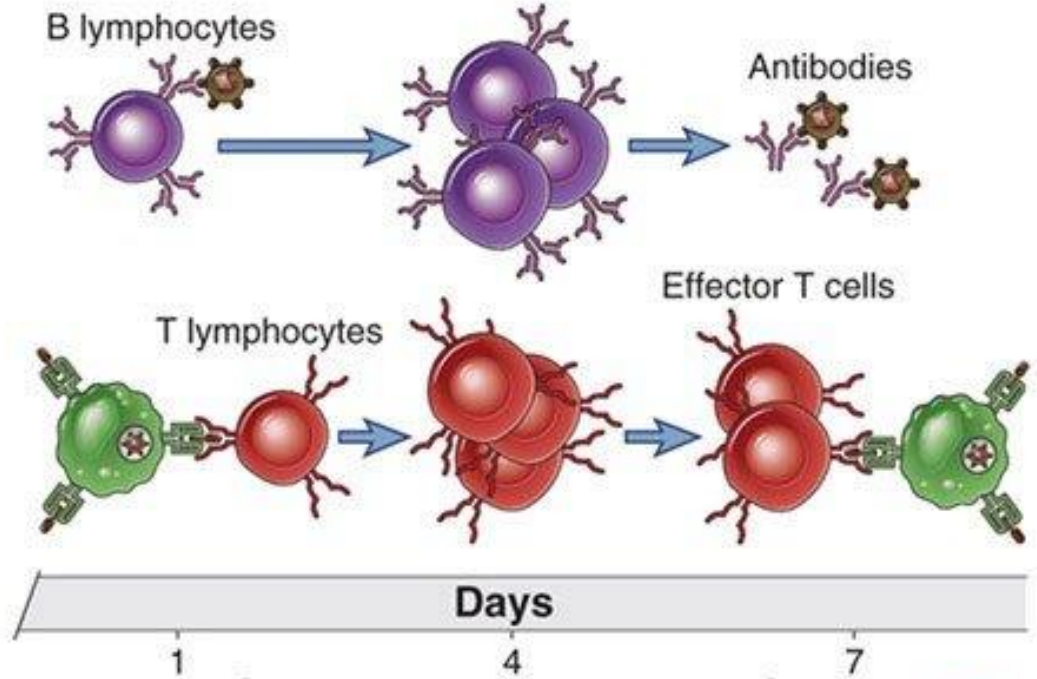
● T- en NK-cellymfoom / -leukemie ● Cutaan T-cellymfoom

# Immuunsysteem

## Innate Immunity



## Adaptive Immunity



Time after infection





# Lymfocyten subsets

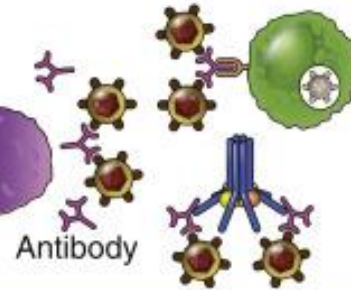
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(A)

CD19  
B  
lymphocyte



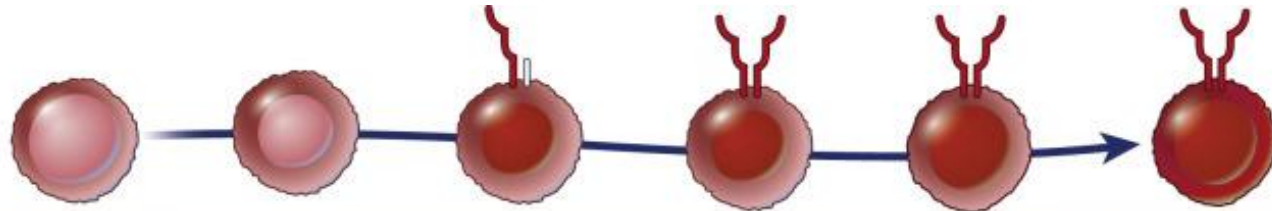
Effector functions



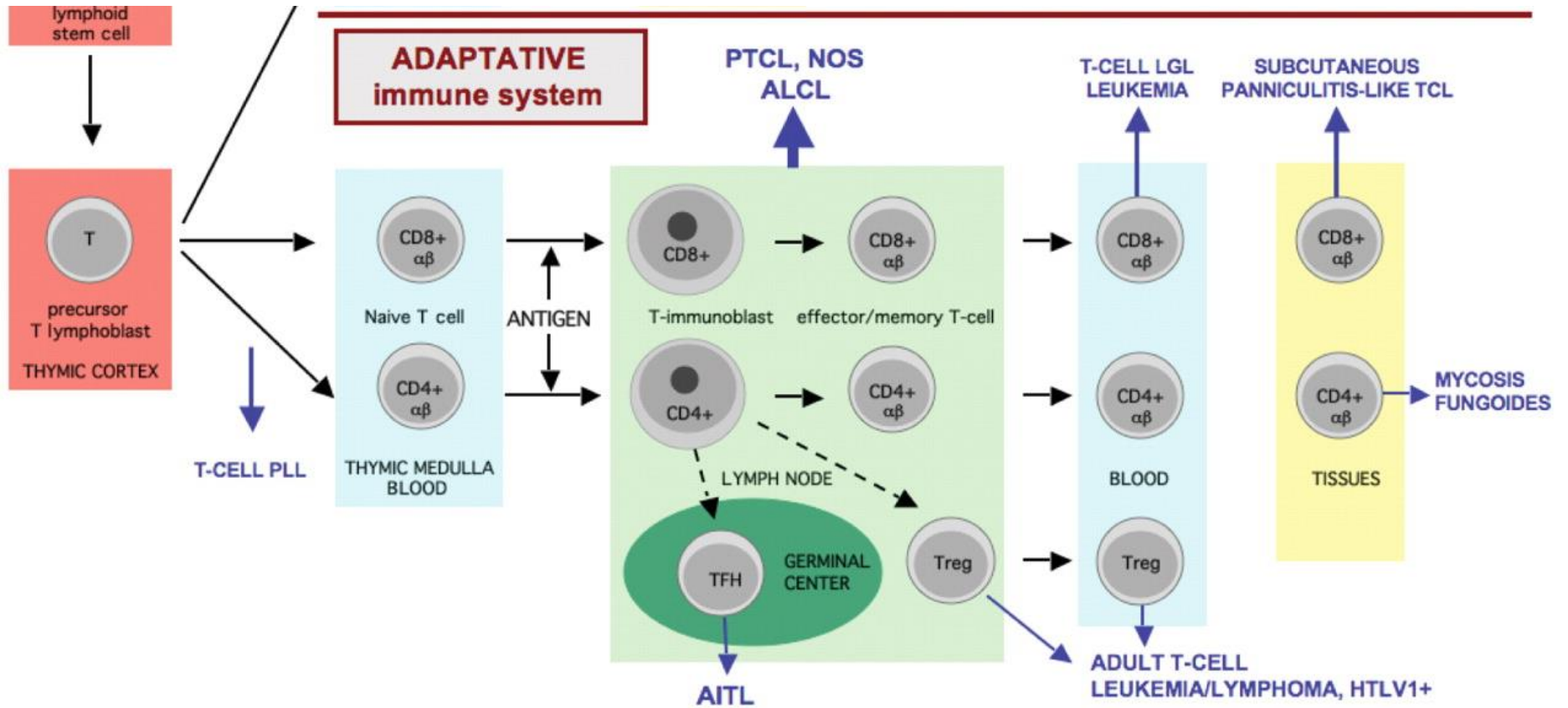
Neutralization  
of microbe,  
phagocytosis,  
complement  
activation

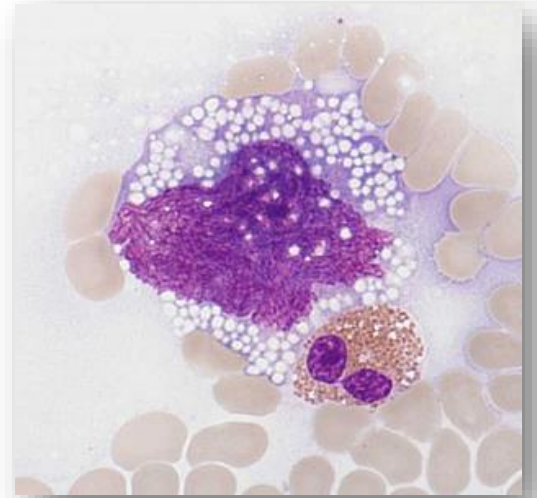
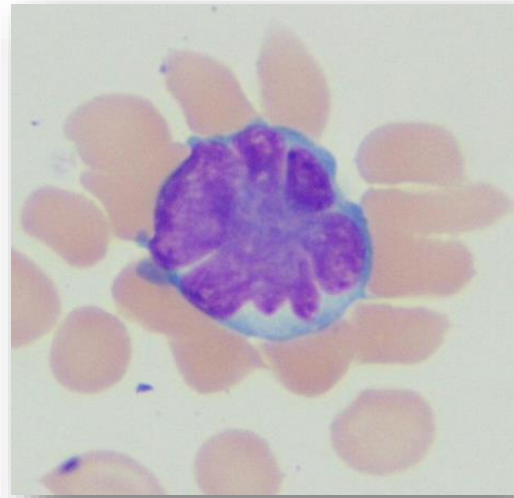
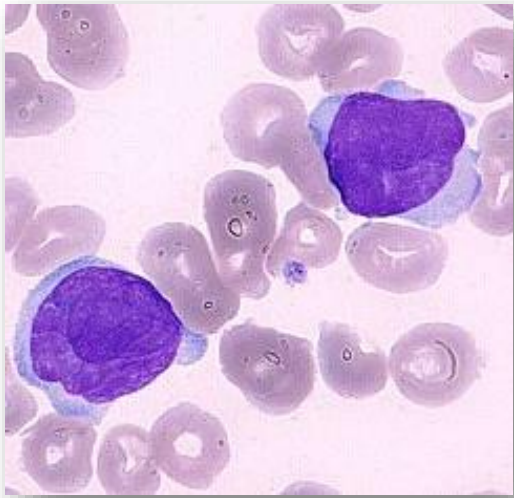
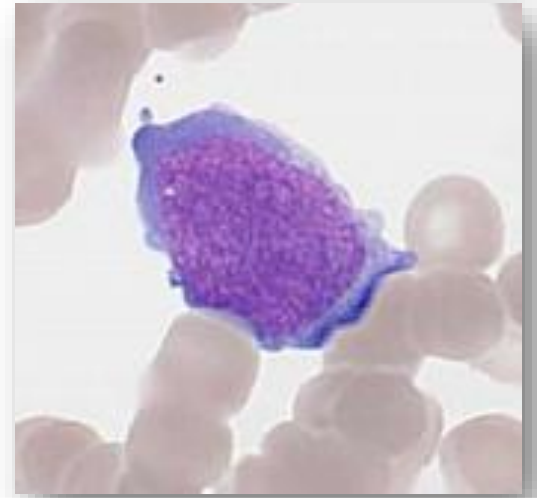
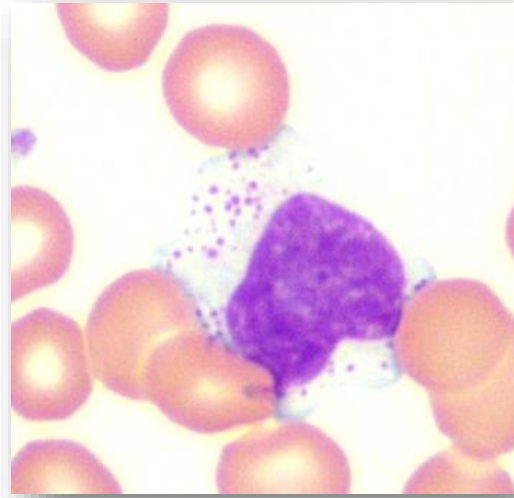
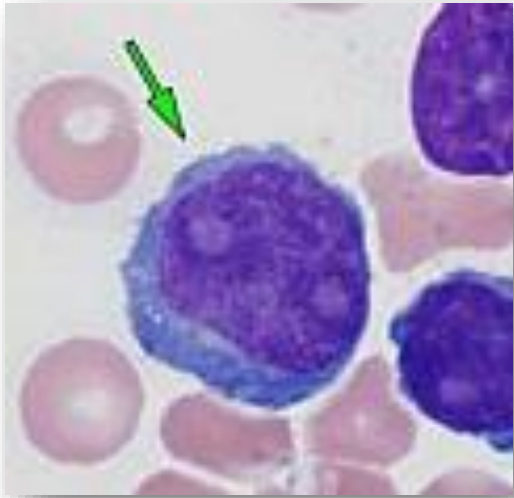


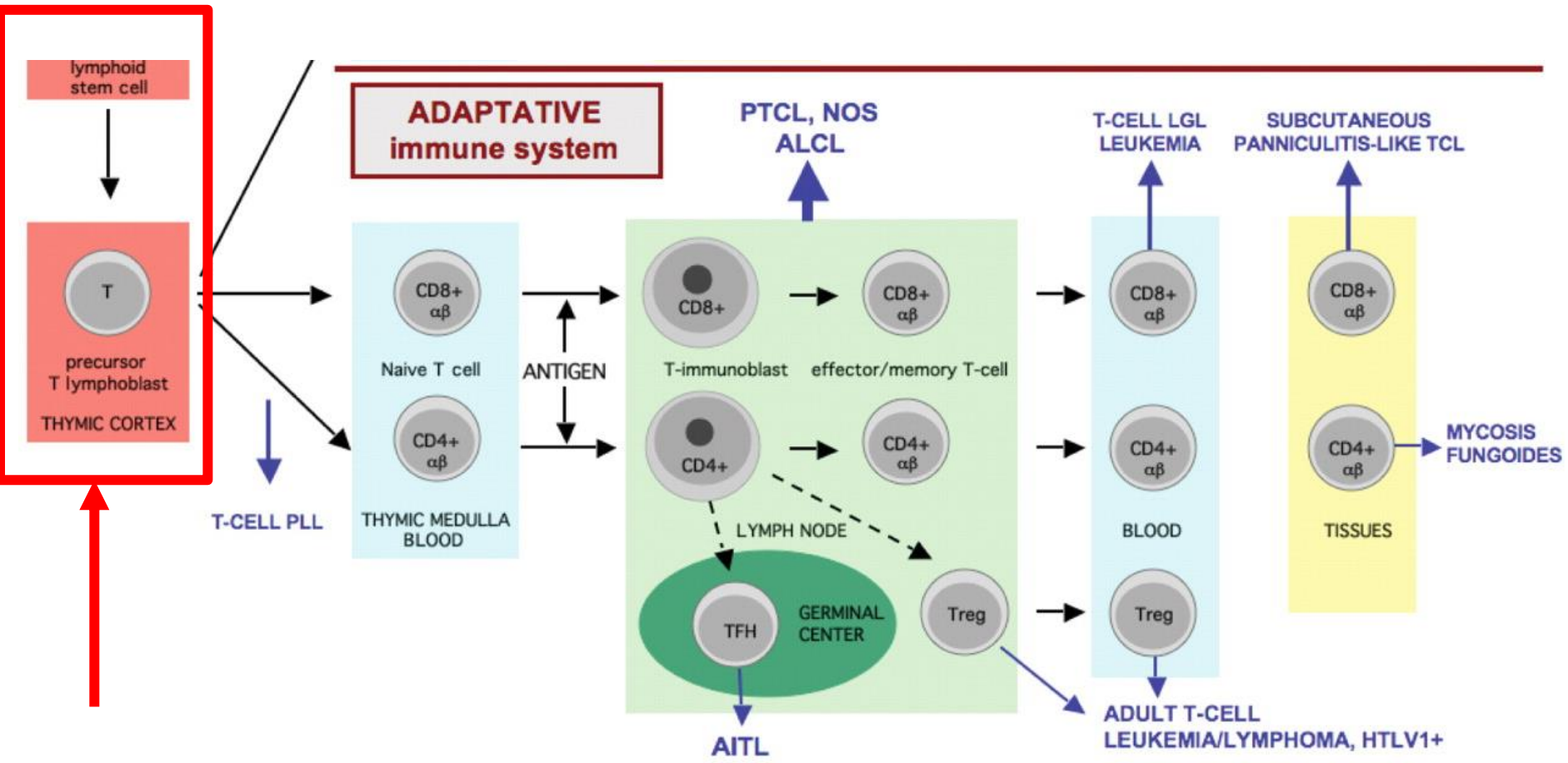
# Ontwikkeling T-cellen



Stage of maturation	Stem cell	Pro-T	Pre-T	Double positive	Single positive (immature T cell)	Mature T cell
Proliferation	█		█			
RAG expression			█	█		
TdT expression		█				
TCR DNA, RNA	Unrecombined (germline) DNA		Recombined $\beta$ chain gene [V(D)J-C]; $\beta$ chain mRNA		Recombined $\beta$ and $\alpha$ chain genes [V(D)J-C]; $\beta$ and $\alpha$ chain mRNA	
TCR expression	None	None	Pre-T receptor ( $\beta$ chain/pre-T $\alpha$ )		Membrane $\alpha\beta$ TCR	
Surface markers	$c\text{-kit}^+$ $\text{CD44}^+$ $\text{CD25}^-$	$c\text{-kit}^+$ $\text{CD44}^+$ $\text{CD25}^+$	$c\text{-kit}^+$ $\text{CD44}^-$ $\text{CD25}^+$	$\text{CD4}^+\text{CD8}^+$ $\text{TCR}/\text{CD3}^{\text{lo}}$		$\text{CD4}^+\text{CD8}^-$ or $\text{CD4}^-\text{CD8}^+$ $\text{TCR}/\text{CD3}^{\text{hi}}$
Anatomic site	Bone marrow	Thymus				Periphery

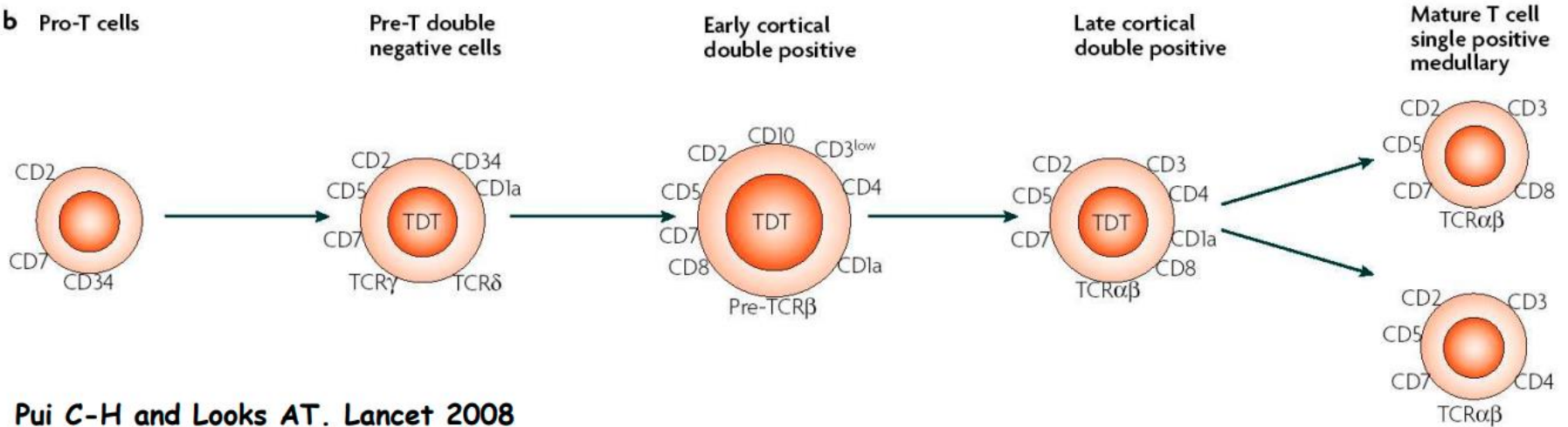






# Flowcytometrie

b Pro-T cells



Pui C-H and Looks AT. Lancet 2008

	cCD3	CD7	CD2/CD5/ CD8	CD1a	sCD3/CD1a-
<b>T1</b>	+	+	-	-	-
<b>T2</b>	+	+	+	-	-
<b>T3</b>	+	+	+	+	-
<b>T4</b>	+	+	+	-	+

T1 = Pro-T-ALL, T2 = Pre-T-ALL, T3 = cortical T-ALL, T4 = mature T-ALL

# T-ALL Not Otherwise Specified

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## ▶ Prevalentie

- ▶ c.a. 15% van de volwassenen met ALL

## ▶ Presentatie

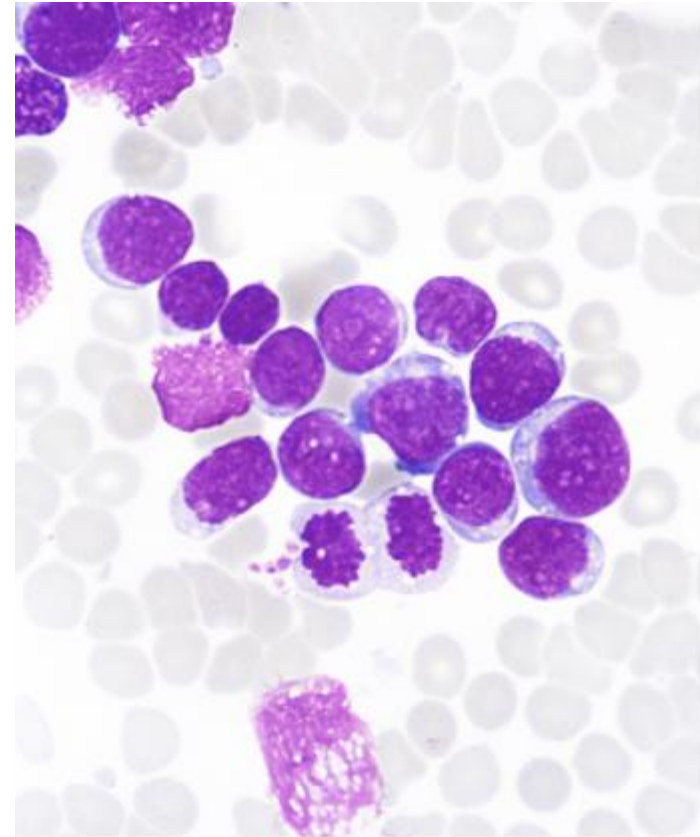
- ▶ Leukocytose, mediastinale massa
- ▶ Rest hematopoëse relatief gespaard

## ▶ Morfologie

- ▶ Klein tot Middelgrote blasten, weinig cytoplasma
- ▶ Soms onderscheid rijp lastig

## ▶ Flowcytometrie

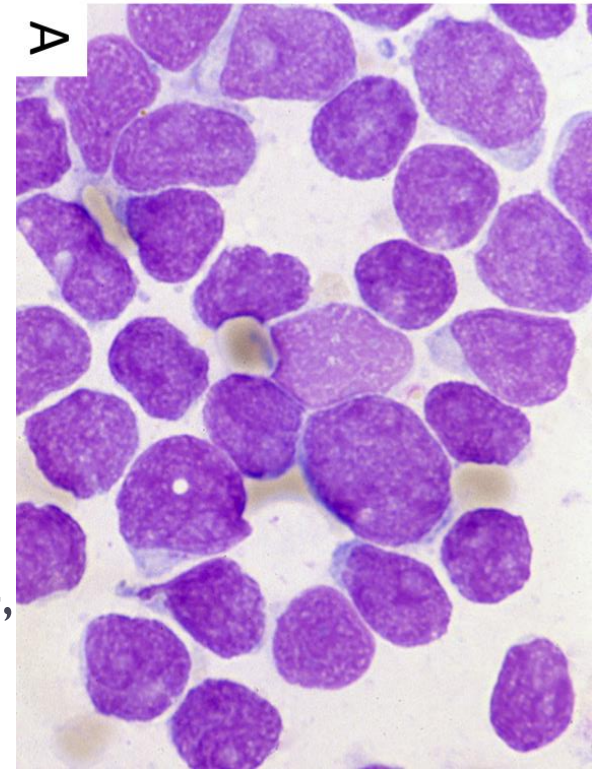
- ▶ cyCD3, meestal TdT en CD7
- ▶ Soms cyCD79a (10%), CD13 en CD33 (30%)



# Early T-cell precursor ALL (~~provisional~~)

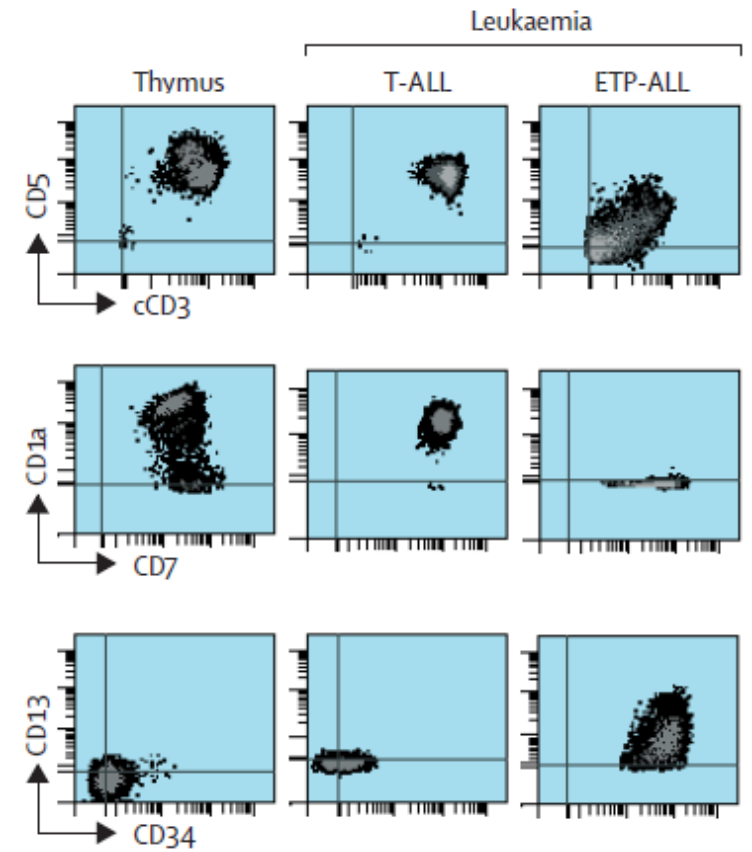
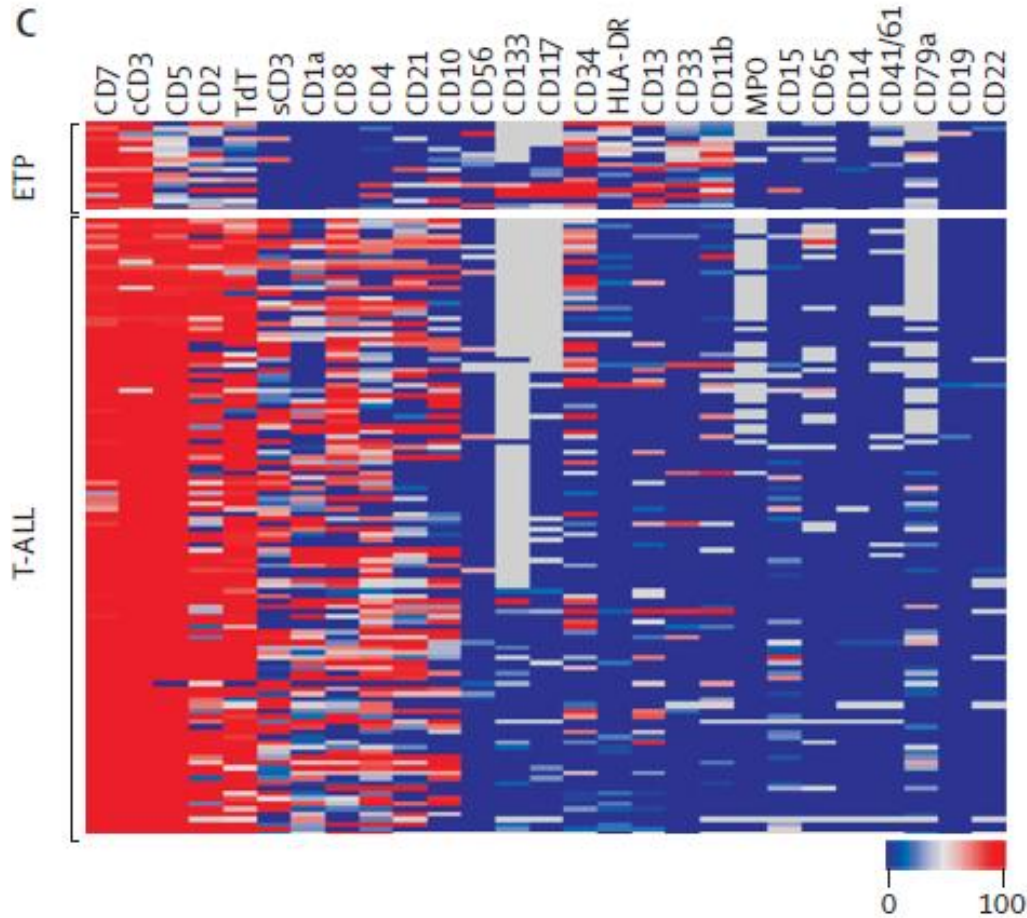
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- ▶ **Prevalentie**
  - ▶ c.a. 5-10% van de volwassenen
- ▶ **Blast met minimale T cel differentiatie met myeloïde/stamcel kenmerken**
- ▶ **Immunofenotype**
  - ▶ Positief CD7 en cyCD3
  - ▶ Negatief CD8 en CD1a
  - ▶ Positief voor stamcel/myeloïde markers CD34, CD117, CD13, CD33
- ▶ **Genetisch myeloïde mutaties**
  - ▶ FLT3, NRAS/KRAS, DNMT3A, IDH1 en IDH2

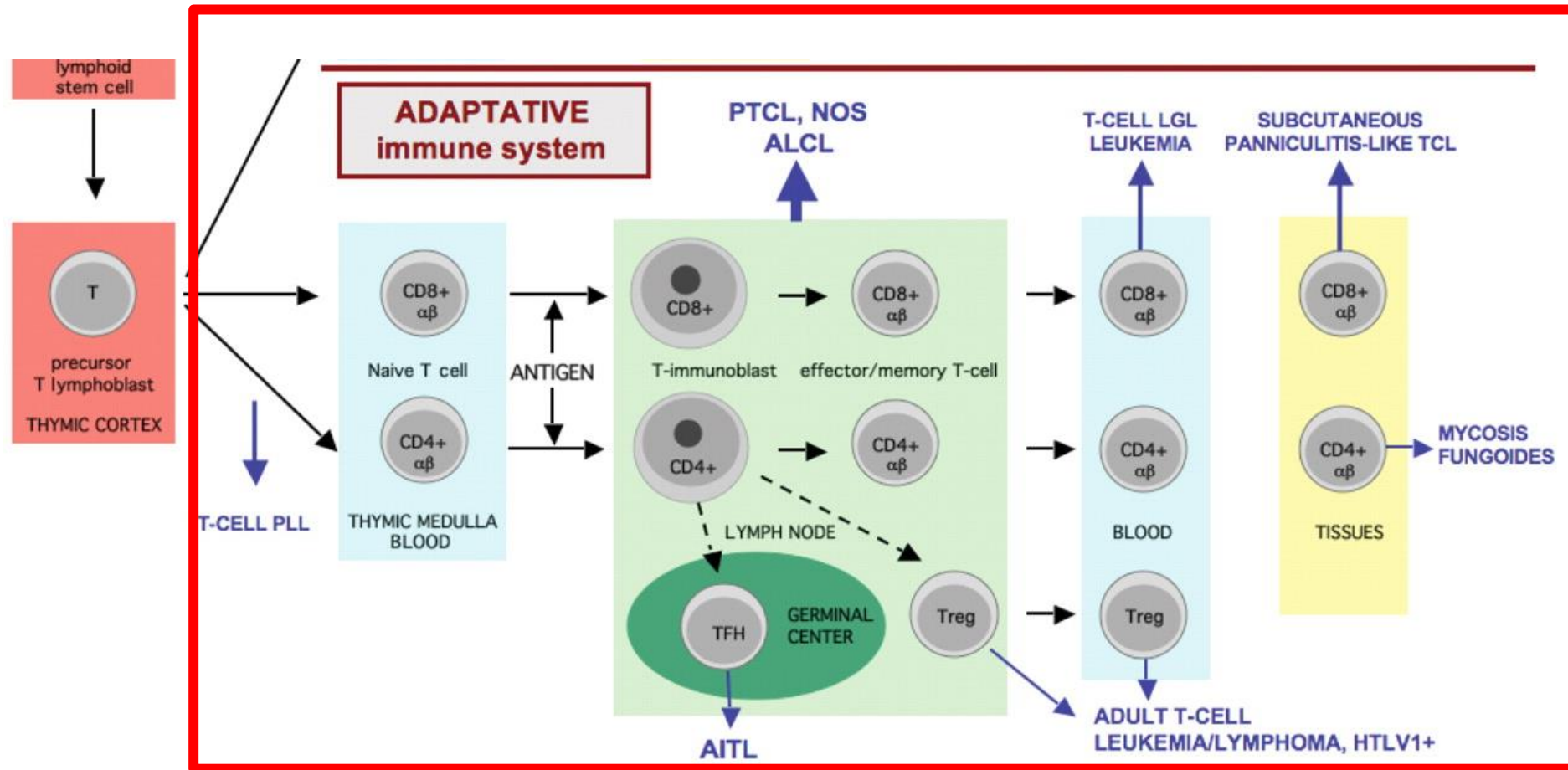




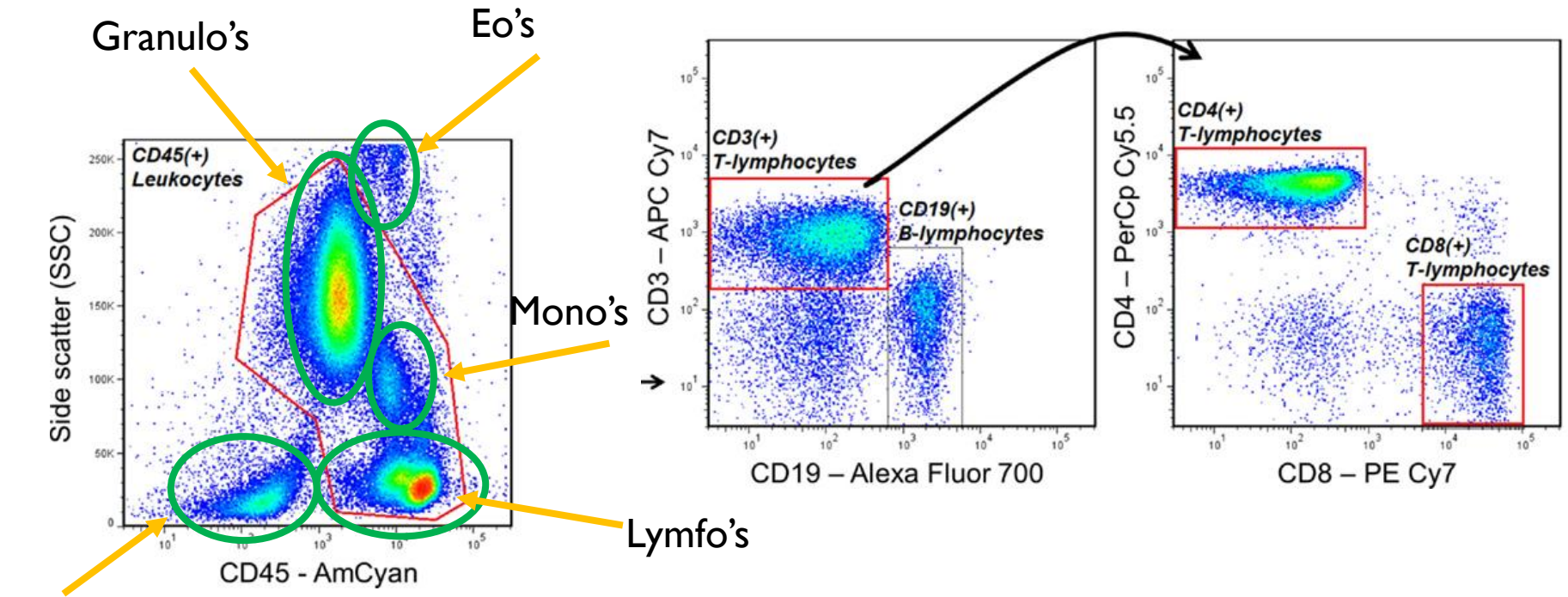
# ETP-ALL



# Rijpe T-cel maligniteiten



# Principe rijpe T-cel Flow cytometrie



T-cel definiërend: **CD3**

▶ Alleen cytoplasmatisch, geen oppervlakte expressie = **onrijp**

**(CyCD3+ SmCD3-)**

▶ Zowel cytoplasmatisch als oppervlakte: = **rijp**

**(CyCD3+ SMCD3+)**

# Vervolg typering

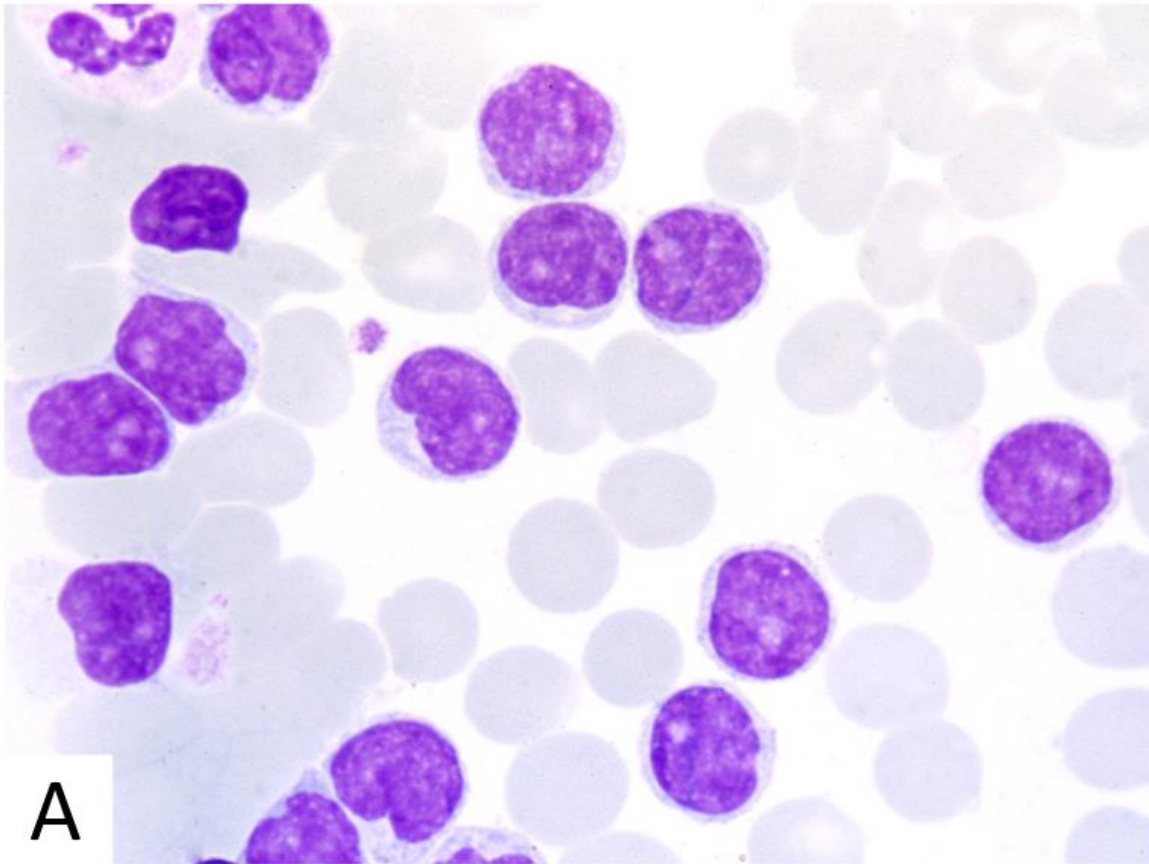
**Table 17.** Utility of T-CLPD markers

Tube	Target antigen	Identification of T-cells and T-cell subsets	Diagnostic level		Sub-classification
			1st	2nd	
BB markers	CD3	X			
	CD4	X			X
	CD8	X			X
	CD45	X			
Tube 1	CD7		X		
	CD26		X		X
	CD2		X		X
	CD28		X		X
Tube 2	CD27			X	
	CD197 (CCR7)		X		X
	CD45RO			X	
	CD45RA		X		
Tube 3	CD5		X		
	CD25			X	X
	HLADR			X	
	CyTcl1		X		X
Tube 4	CD57		X		X
	CD30		X		X
	CD11c		X		X
Tube 5	CyPerforin			X	X
	CyGranzyme B			X	X
	CD16		X		X
	CD94			X	
Tube 6	CD279		X		X
Other	TCR V $\beta$ families		X		

Abbreviations: BB, backbone; CLPD, chronic lymphoproliferative disorders; Cy, cytoplasmic.

**Table 6.13** Summary of the immunophenotype and clinical features of CD4 positive T-cell LPD.

Antigen	Sezary	T PLL	ATLL	ALCL	AITL
CD2	Pos	Pos	Pos	Pos	Pos
CD3	Pos	Pos	Pos	Pos/neg	Pos
CD5	Pos	Pos	Pos	Pos/neg	Pos
CD7	Often neg	Pos	Neg	Pos/neg	Neg/dim
CD25	Rare pos	Neg	Pos	Neg	Neg
CD30	Neg	Neg	Neg	Pos	Neg
CD10	Neg	Neg	Neg	Neg	Pos
Myeloid	Neg	Neg	Neg	Wk pos	Neg
Skin	Erythema	Variable	Variable	Variable	Rashes
Nodes	Yes	Yes	Yes	Yes/no	Yes
Blood	Yes	Yes	Often	Rare	Rare
Extranodal	No	No	Yes	Yes	Yes
BM disease	Yes	Yes	Yes	Variable	Yes
Other	Pruritis Nails Alopecia	Effusions Organomegaly	High Ca <sup>+</sup> HTLV <sup>+</sup>	High LDH Stage IV	Fever Organomegaly Arthralgias

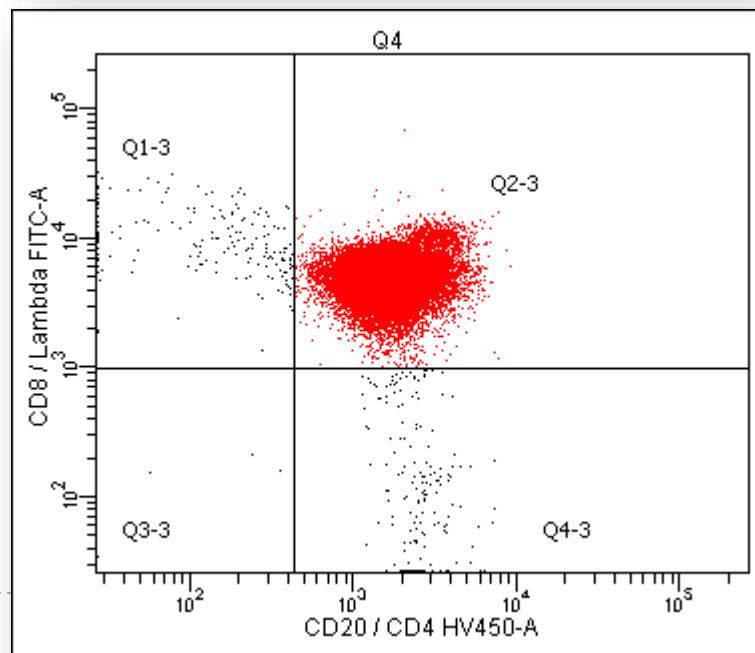
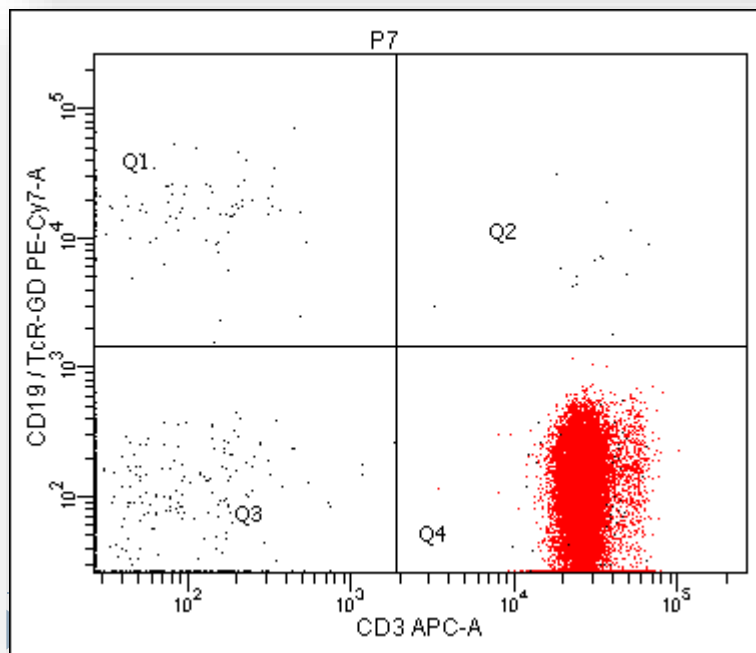
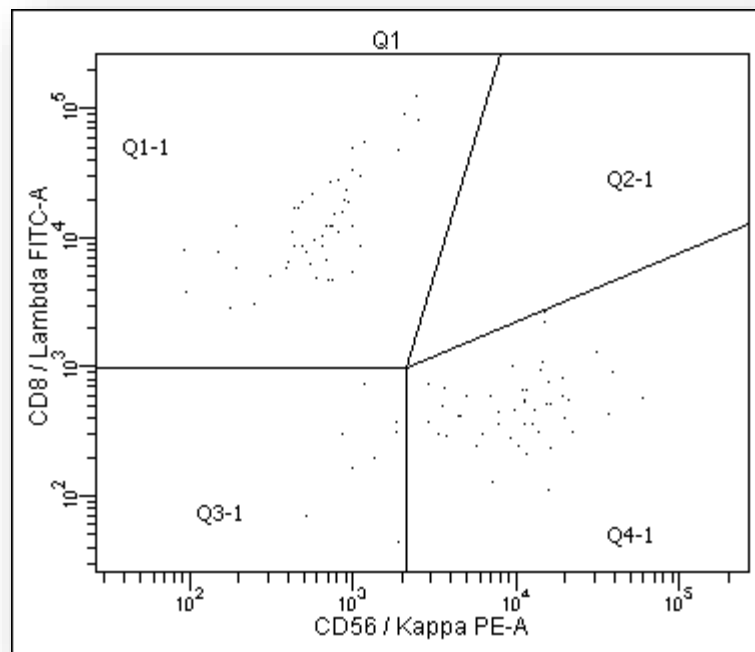
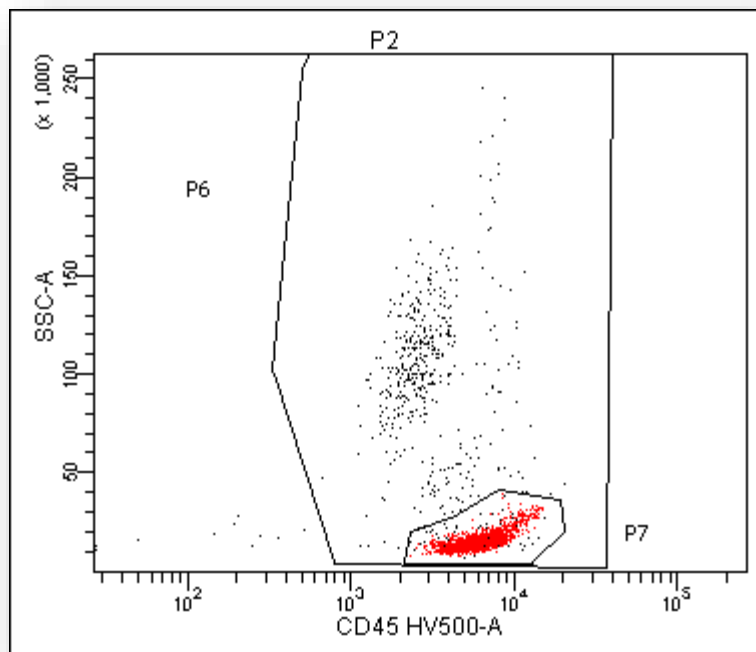


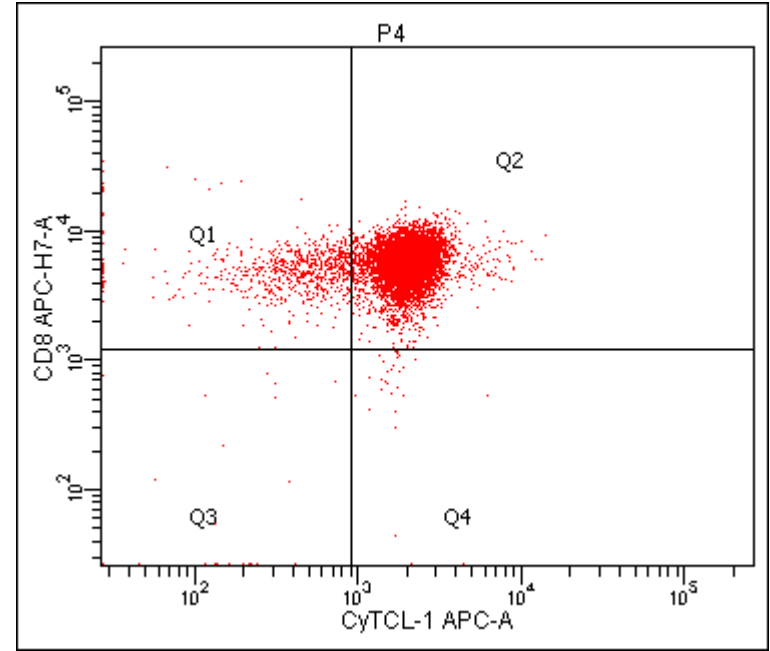
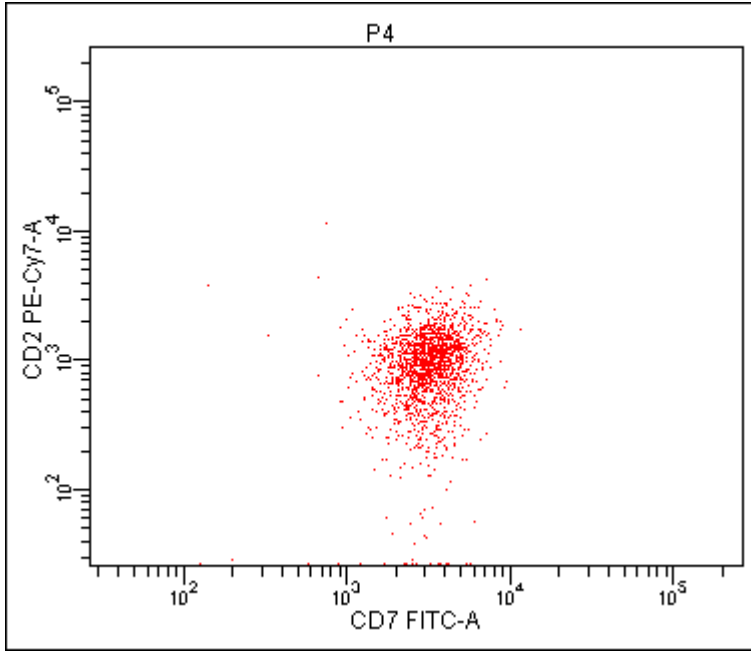
## Vrouw 65jr

- Hb 6,0
- Plt 65
- WBC  $165 \times 10^9/l$

Splenomegalie en  
lymfeklieren









# T-cel prolymfocyten leukemie

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## ▶ Karakteristieken

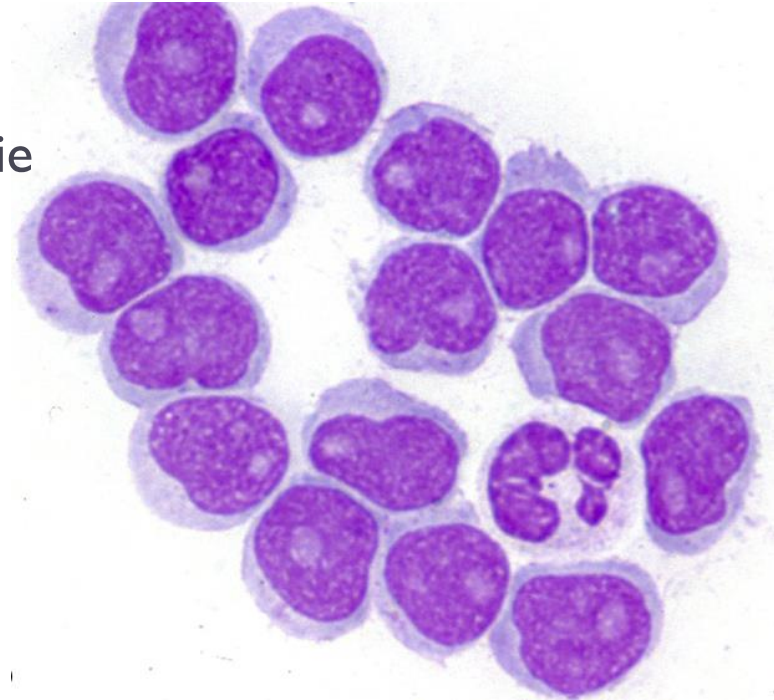
- ▶ Zeldzaam 2% van alle lymfomen
- ▶ Leeftijd >30jr, gem 65jr
- ▶ Hepatosplenomegalie en lymfadenopathie
- ▶ Leucocytose  $>100 \times 10^9/l$

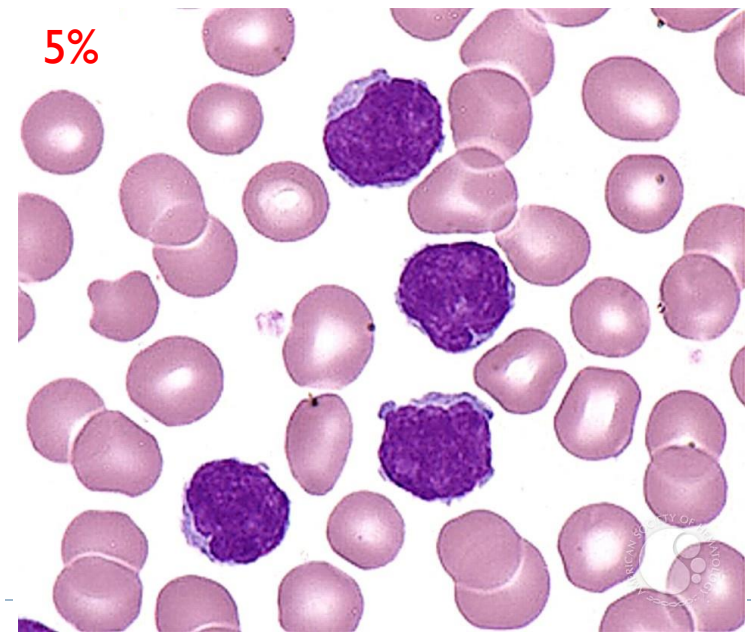
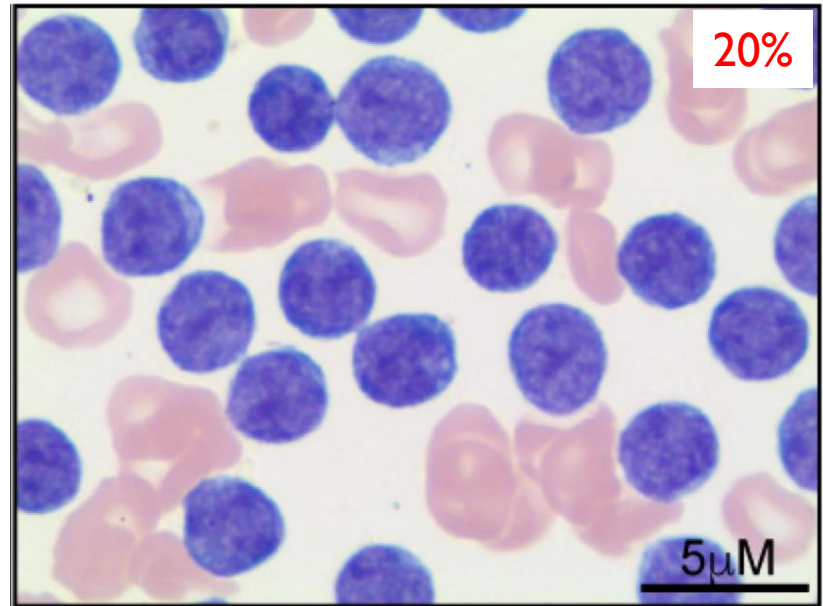
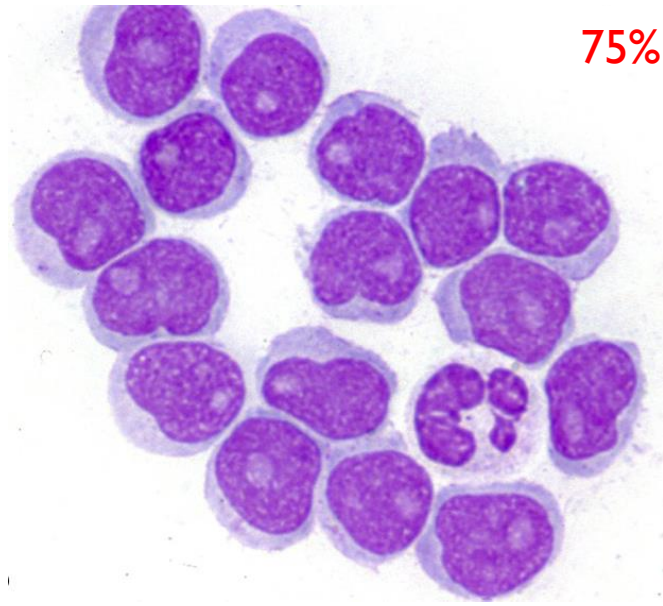
## ▶ Morfologie

- ▶ Kleine/middelgrote lymfocyten met prominente nucleolus

## ▶ Moleculair

- ▶ Inversie chromosoom 14 (80% van de gevallen)





# T-cell prolymfoctyten leukemie criteria

## Major criteria

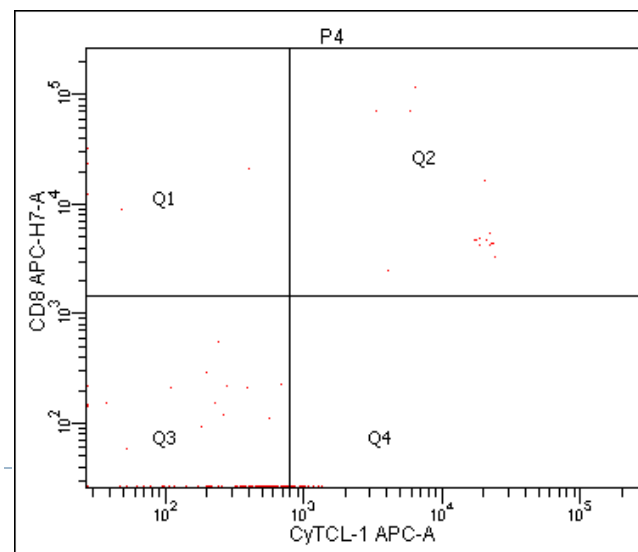
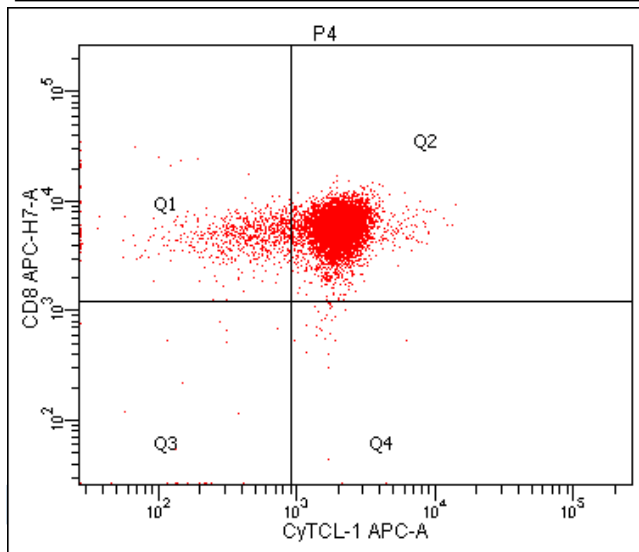
- $>5 \times 10^9/L$  cells of T-PLL phenotype in peripheral blood or bone marrow
- T-cell clonality (by PCR for TRB/TRG, or by flow cytometry)
- Abnormalities of 14q32 or Xq28 OR expression of *TCL1A/B*, or *MTCP1\**

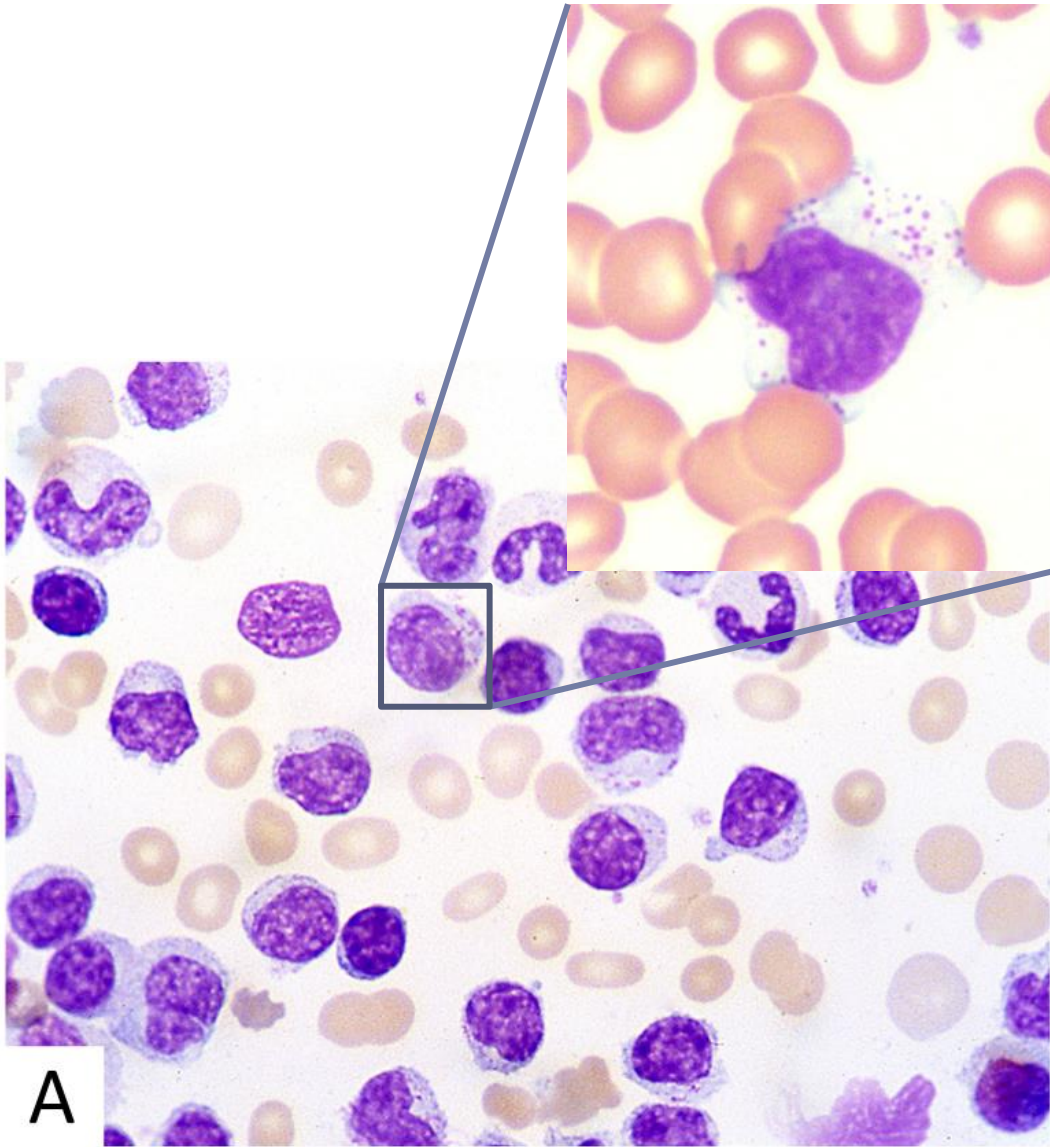
## Minor criteria (at least 1 required)

- Abnormalities involving chromosome 11 (11q22.3; *ATM*)
- Abnormalities in chromosome 8: *idic(8)(p11)*, *t(8;8)*, trisomy 8q
- Abnormalities in chromosome 5, 12, 13, 22, or complex karyotype
- Involvement of T-PLL specific site (eg, splenomegaly, effusions)

# Flowcytometrie T-PLL en MRD

Differential diagnosis	Immunophenotype
T-PLL	cyTCL1+ (>90%), CD3+ (>80%), CD4+(60%), CD5+ (100%), CD7+ (>90%), CD8+(15%), CD4+CD8+(25%)
T-ALL	Tdt +, CD1a+
Leukemic PTCL	cyTCL1-
T-cell large granular lymphocytic leukemia	CD8+, CD57+, CD16+
Sézary syndrome	CD7-, CD4+, CD25+
Adult T-cell lymphocytic leukemia	CD4+, CD25+, HTLV1+





## Man 65jr

- Hb 7,5
- Plt 265
- WBC  $5,5 \times 10^9/l$
- Neutro  $0,6 \times 10^9/l$

> 6 maanden deze cellen in de diff

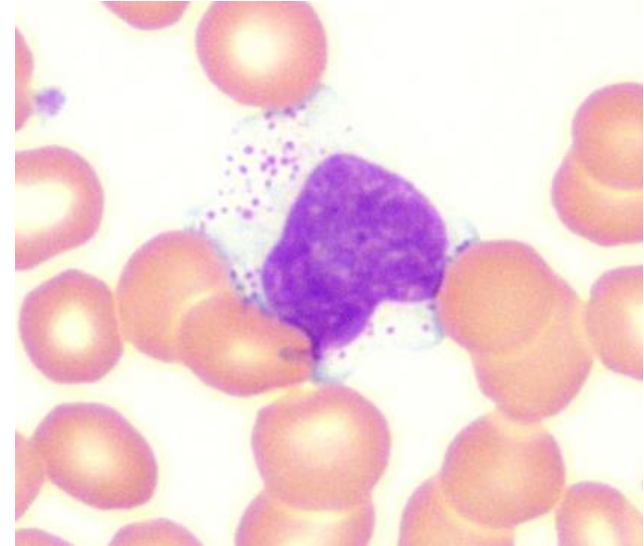
# T-cell Large Granular lymphocytic leukemia (T-LGL)

## ▶ Karakteristieken

- ▶ 2% van alle lymfomen
- ▶ Beenmergfalen en cytopenie en auto-immuun verschijnselen

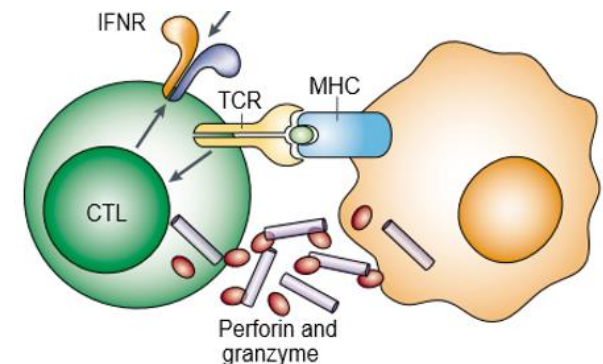
## ▶ Morfologie

- ▶ Relatief grote cellen met prominente granula



## ▶ Flow cytometrie

- ▶ CD3/CD8/CD56/CD57/GranzymeB en Perforine
- ▶ Cytotoxisch T-cel fenotype

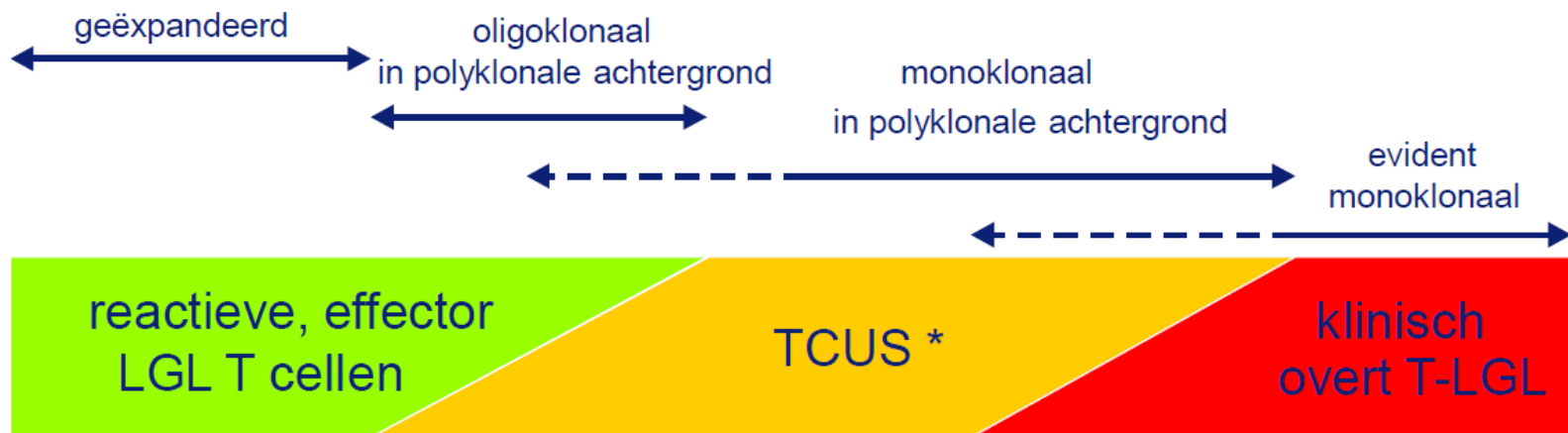


# T Large Granular lymphocytic leukemia (T-LGL)

## Diagnostische criteria

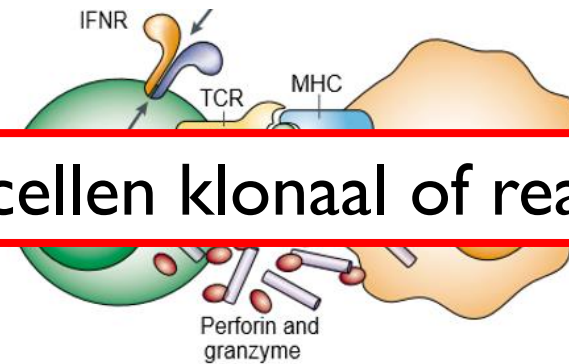
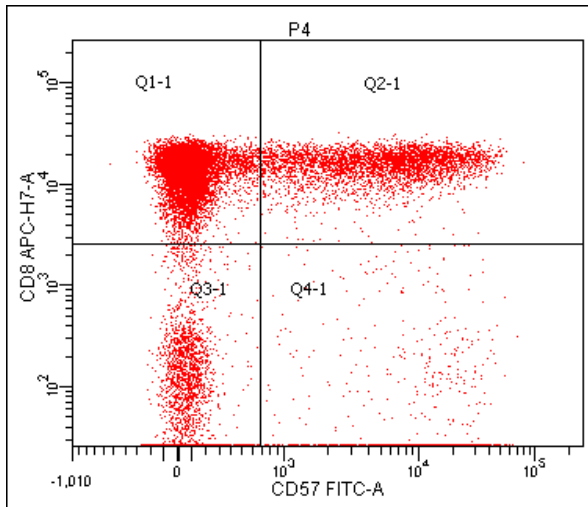
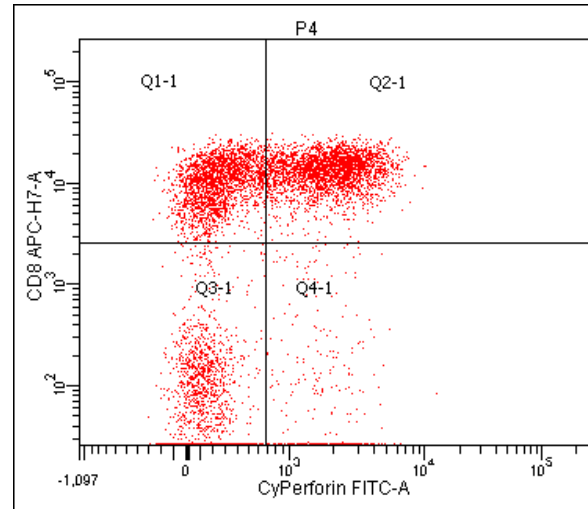
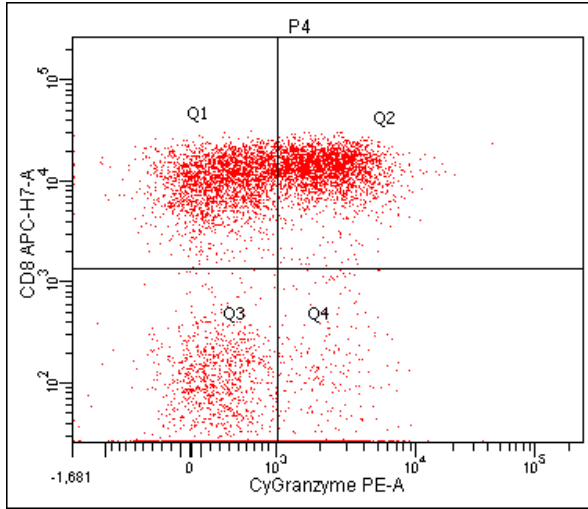
- lymfocytose ( $>2 \times 10^9 / L$ ; updated criteria  $> 0.5 \times 10^9 / L$ )
- $> 6$  maanden
- monoklonaliteit
  - T-cel type: TCR genherschikkingsanalyse
  - NK-cel type : skewed X inactivatie (vrouwen)
- discrete celpopulatie

*Semenzato, Loughran et al., Blood 1997*



\* T-cell clonopathy of undetermined significance

# Flowcytometrie T-LGL



T-cellen klonaal of reactief ?



# T-cell receptor

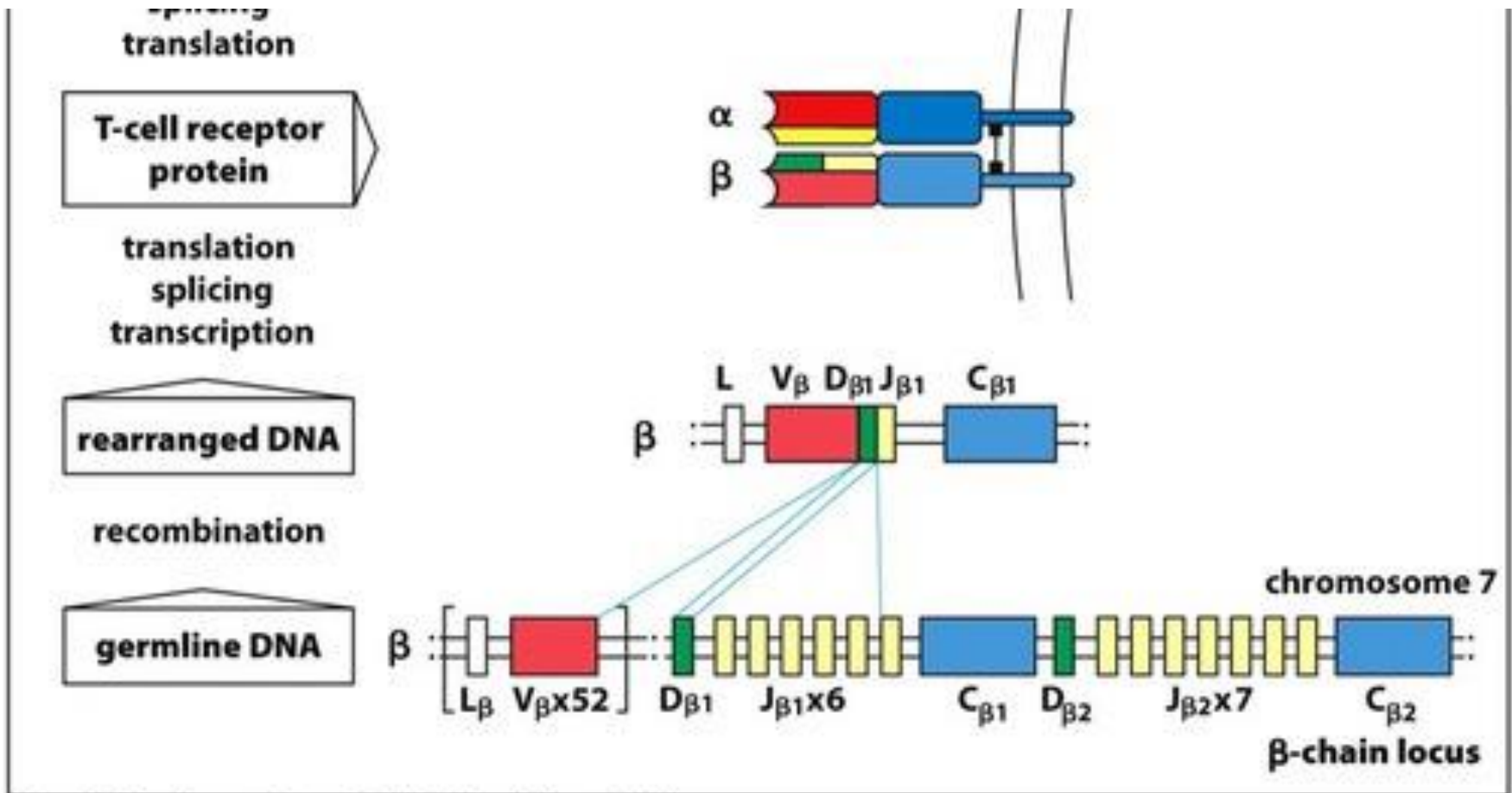
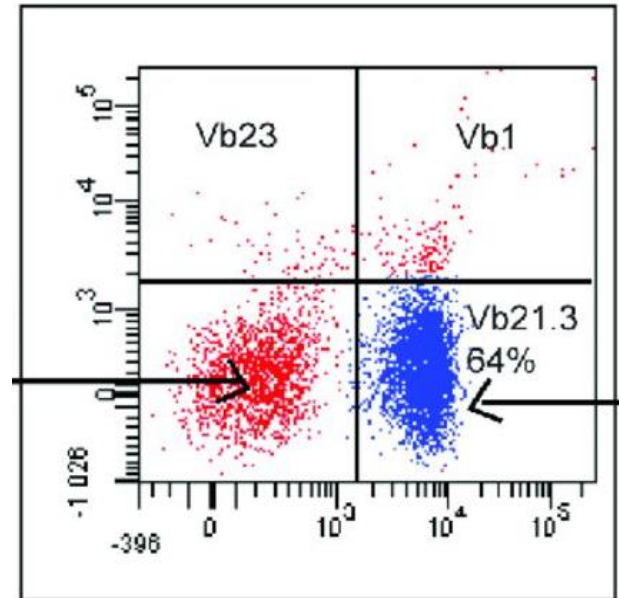
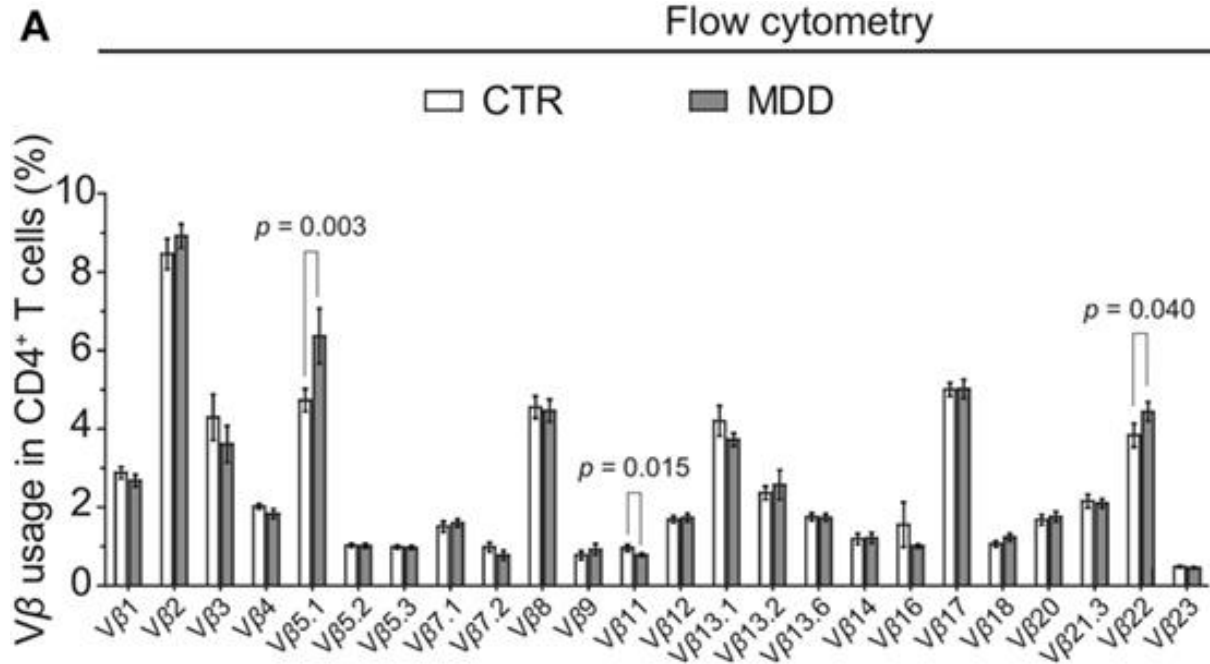
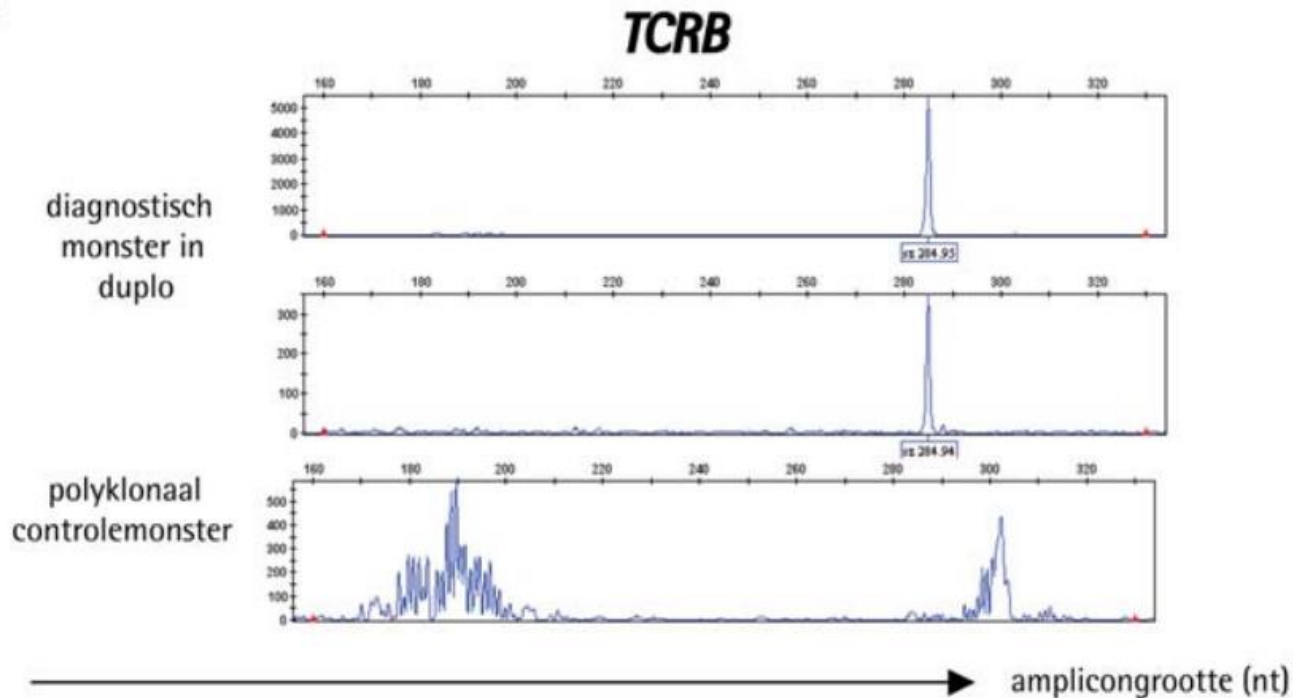
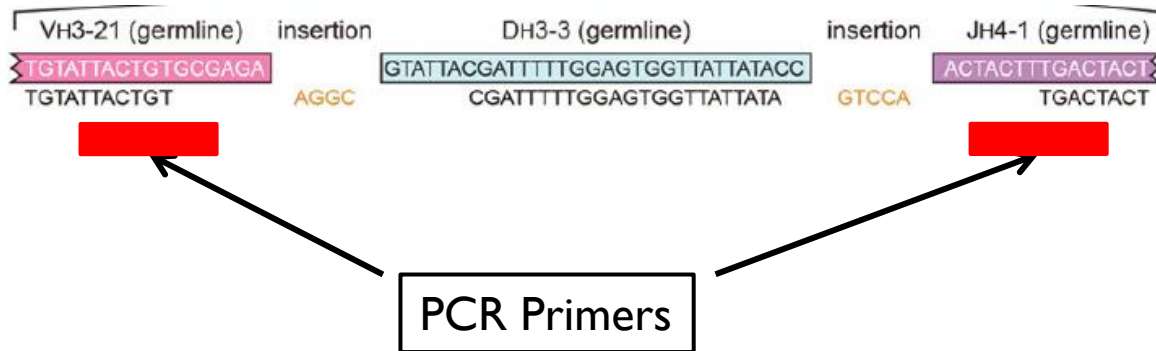


Figure 5.3 The Immune System, 3ed. (© Garland Science 2009)

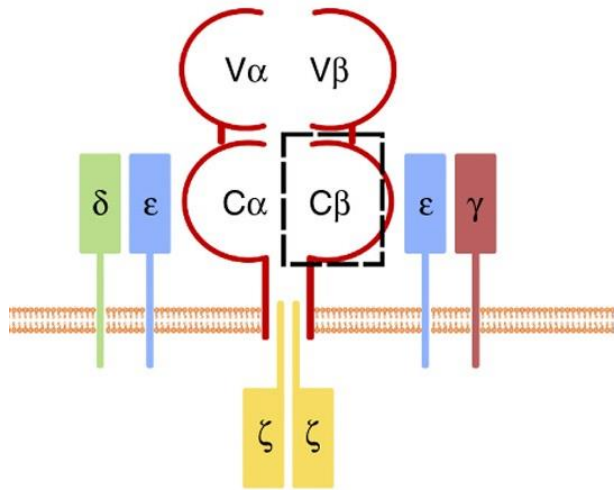
# vBeta repertoire



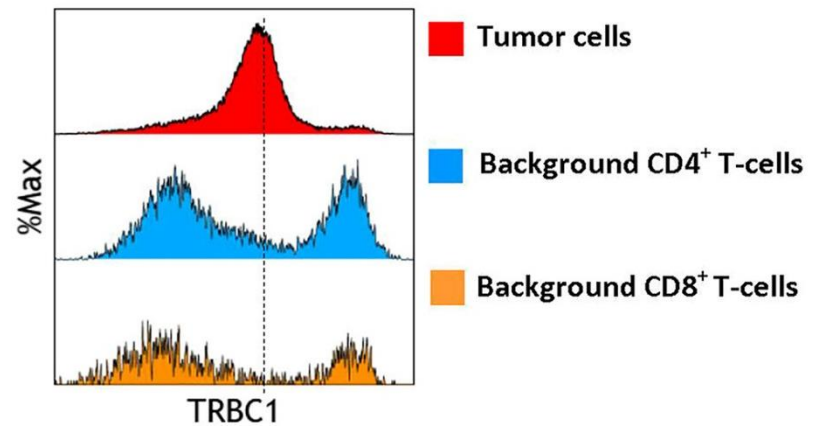
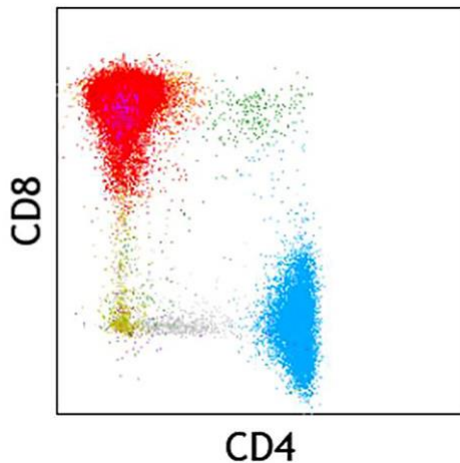
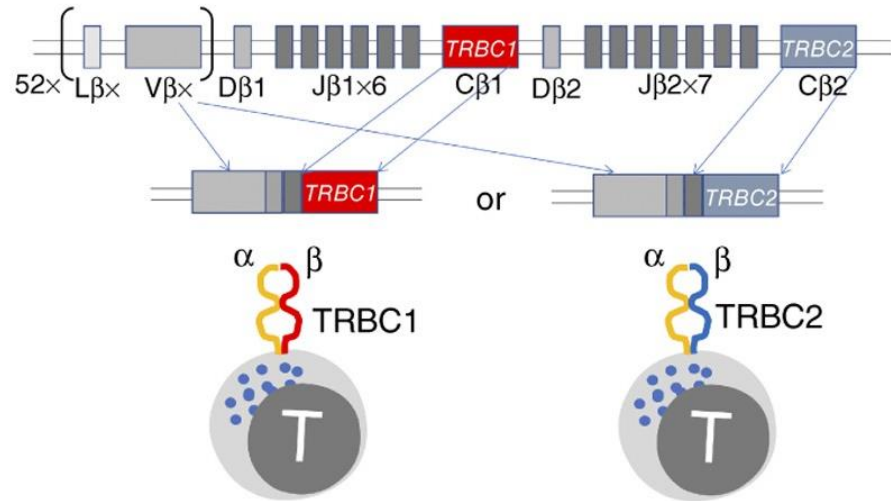
# T cel receptor genherschikking



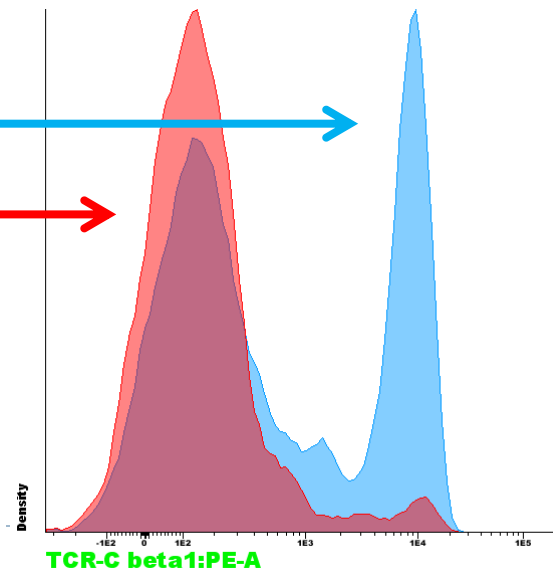
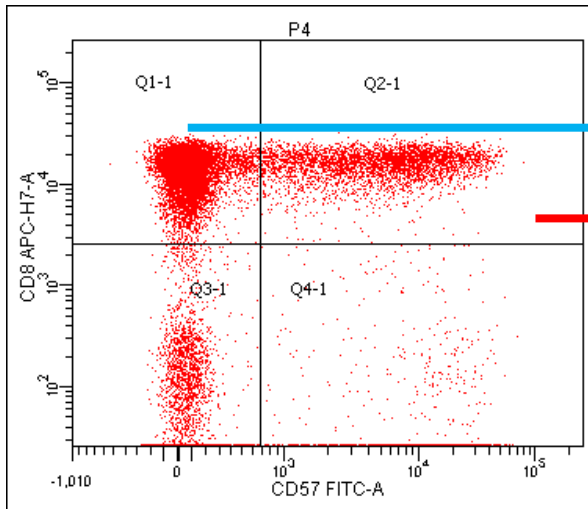
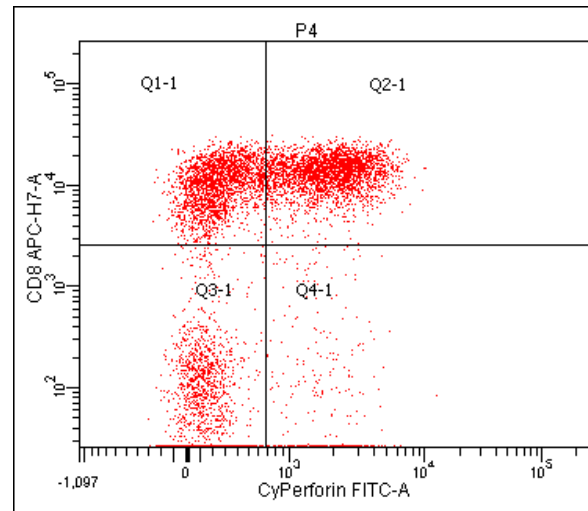
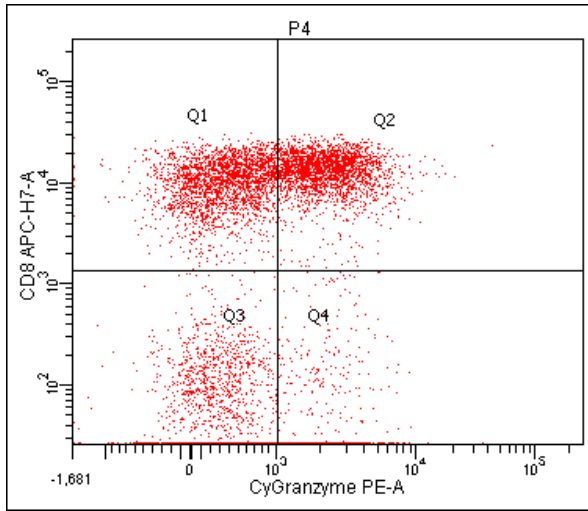
# T-cellen klonaal ?

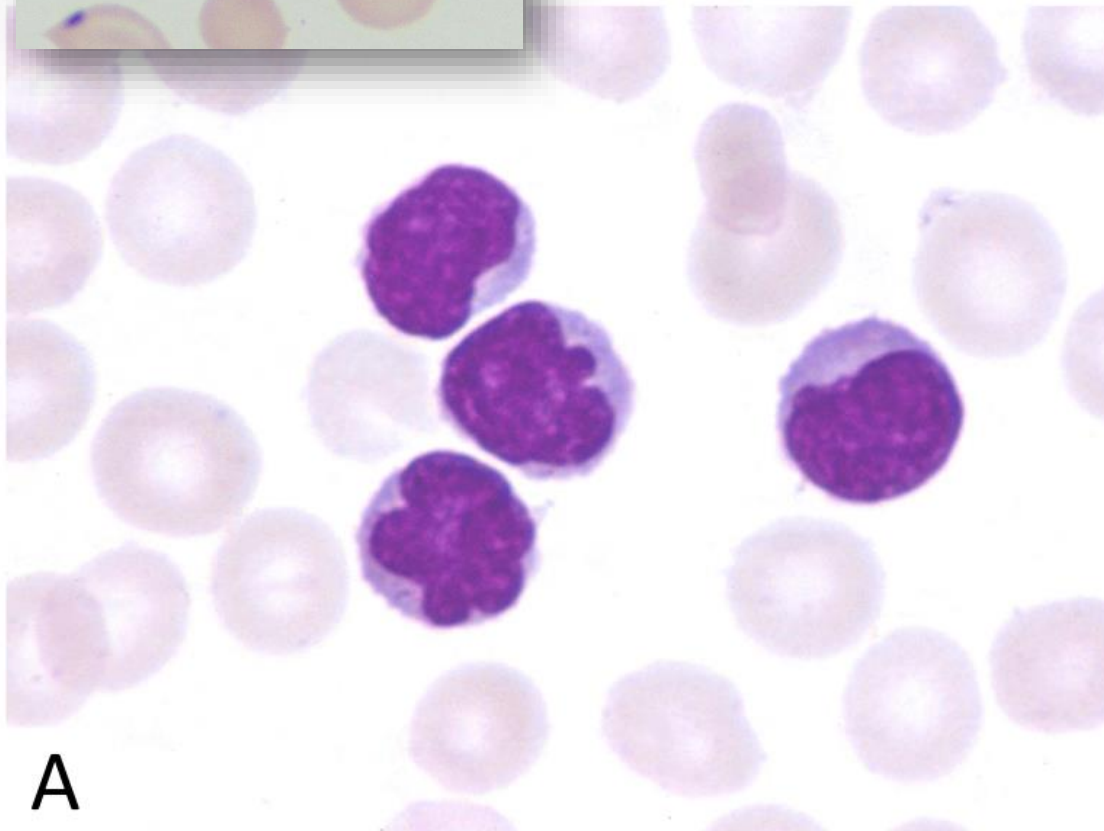


**b**



# Flowcytometrie T-LGL





A

## Man 55jr

- WBC  $25,5 \times 10^9/l$
- Neutro  $0,6 \times 10^9/l$
- Komt uit de Cariben en recent in Nederland
- Antistoffen tegen HTLV-I positief

# Adult T-cell Leukemia/Lymphoma

## ▶ Karakteristieken

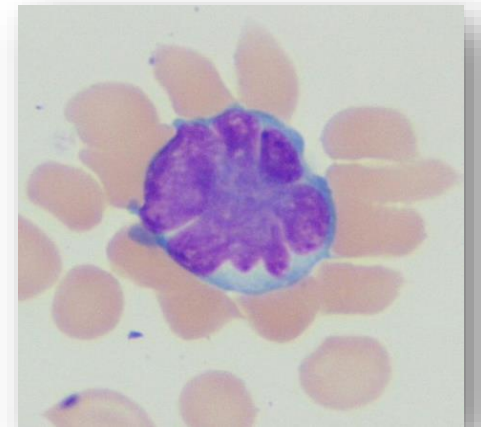
- ▶ Frequent in gebieden waar HTLV-I endemisch is
- ▶ Hepatosplenomegalie en lymfadenopathie

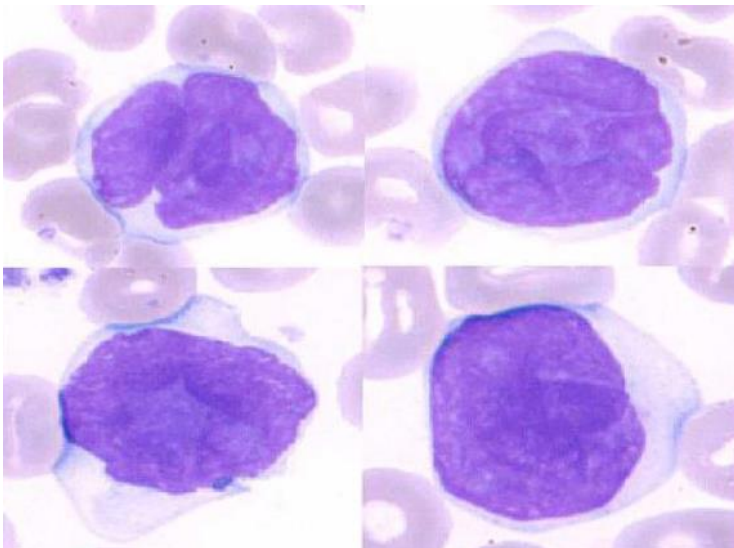
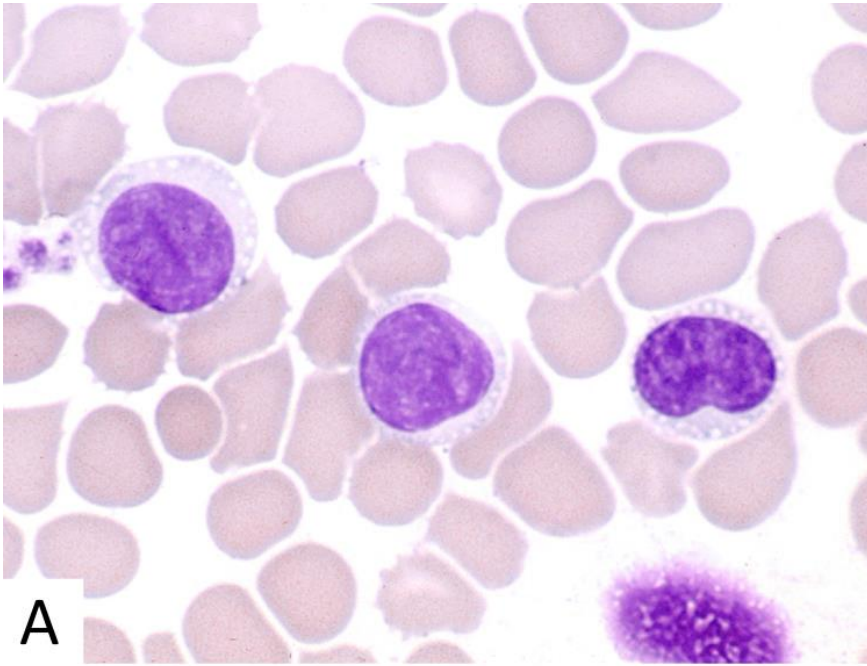
## ▶ Morfologie

- ▶ Middelgrote flower cells
- ▶ Heterogeen

## ▶ Flow cytometrie

- ▶ CD4+/CD25 Sterk/CD7 negatief





## Man 47jr

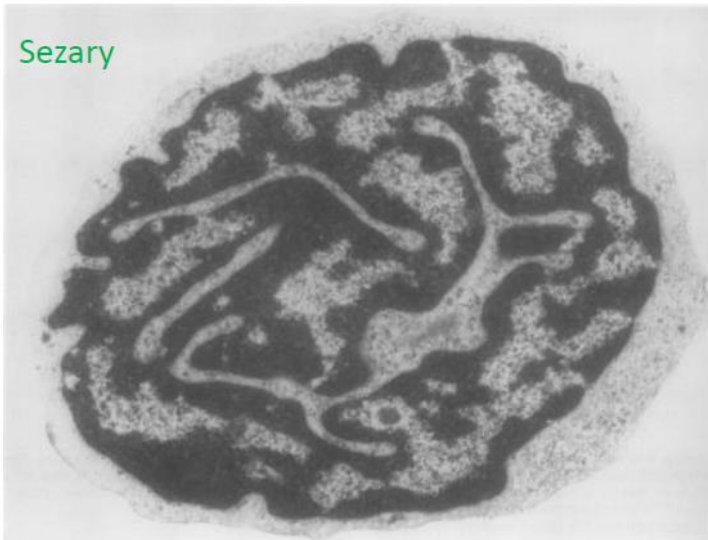
- Opvallende afwijkingen van de huid >80%
- Lymfeklieren



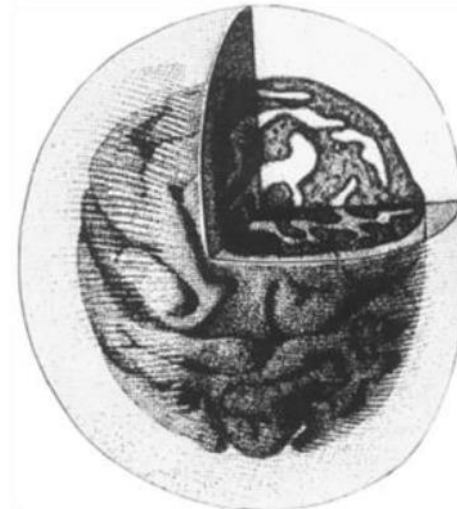


# Sezary & Mycosis Fungoides

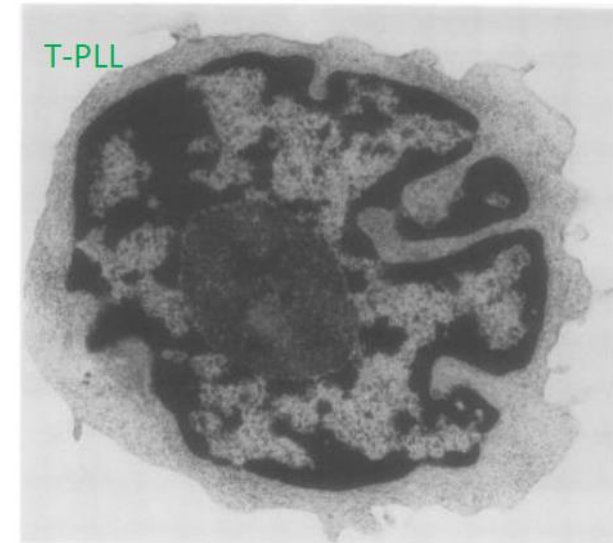
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[Journal of Clinical Pathology](#) 42(6):567-84 · July 1989



The American Journal of Dermatopathology  
August 2006, Volume 28 (4), p 357-367



[Journal of Clinical Pathology](#) 42(6):567-84 · July 1989

## Mycosis Fungoides

- Cutaan T-cel lymfoom van de huid
- Relatief frequent
- In eind stadium ook lokalisatie in bloed

## Sezary Syndroom

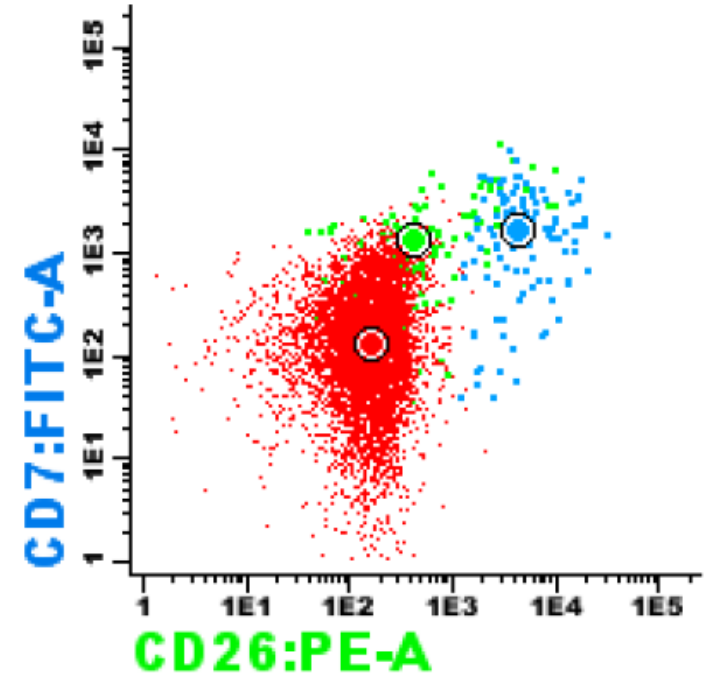
- Perifeer T-cel lymfoom
- Relatief zeldzaam
- Ook lokalisatie in huid

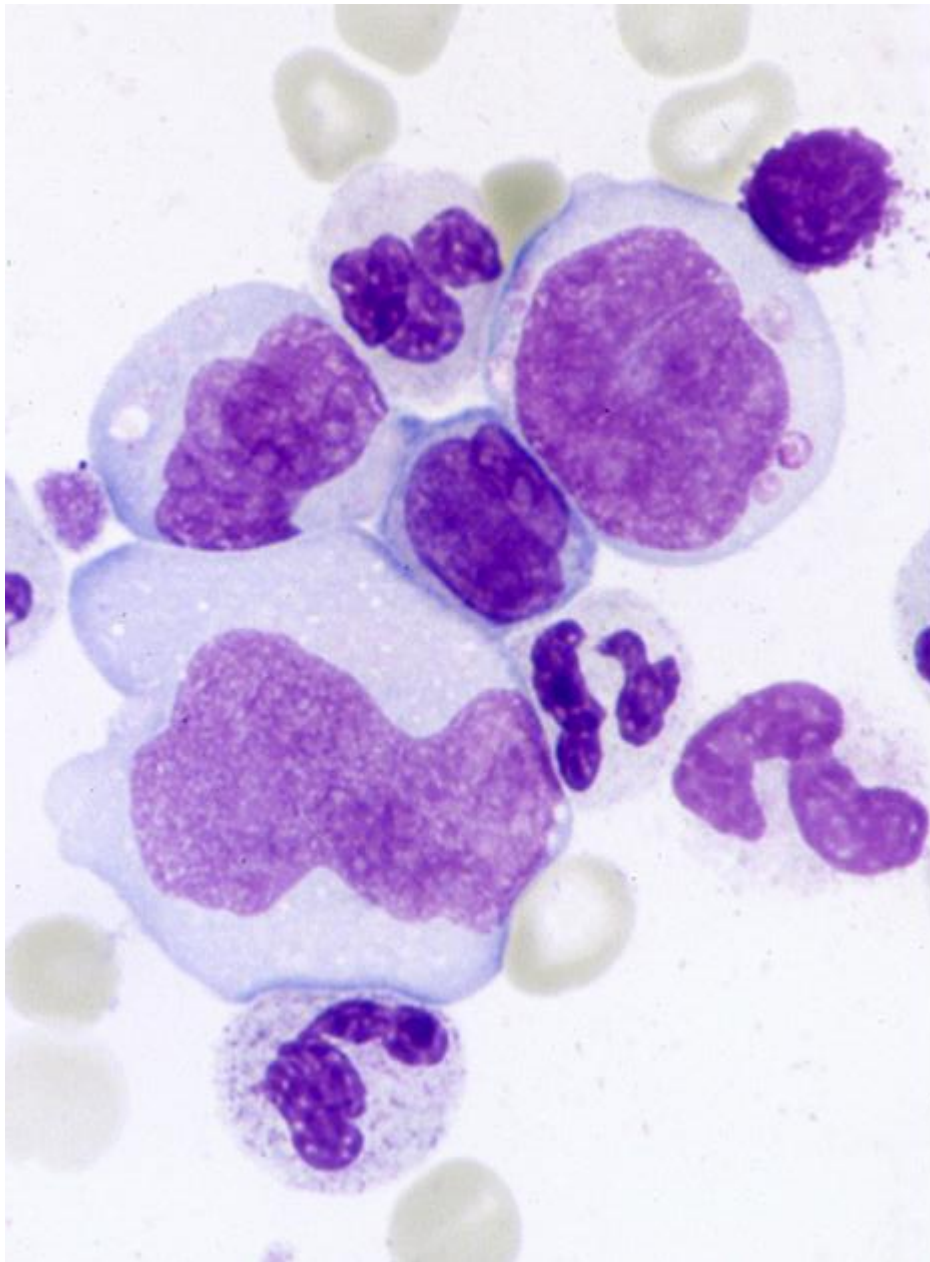


# Sezary

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- ▶ Criteria
  - ▶ >1000 Sezary cellen/ul
  - ▶ Verlies van specifieke antigenen
- ▶ Flow cytometrie
  - ▶ Vaak hogere FSC
  - ▶ CD3+/CD4+/CD7 neg/CD26 neg





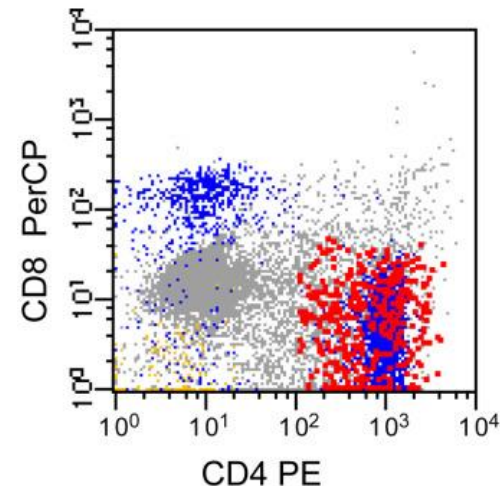
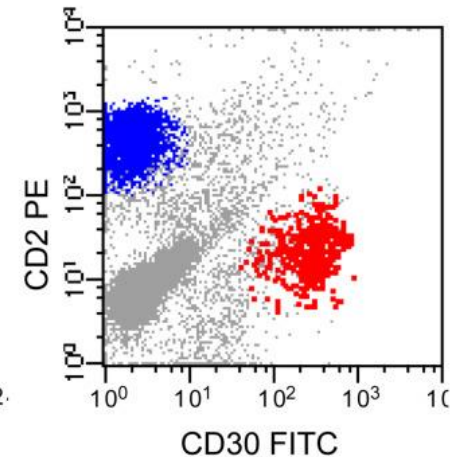
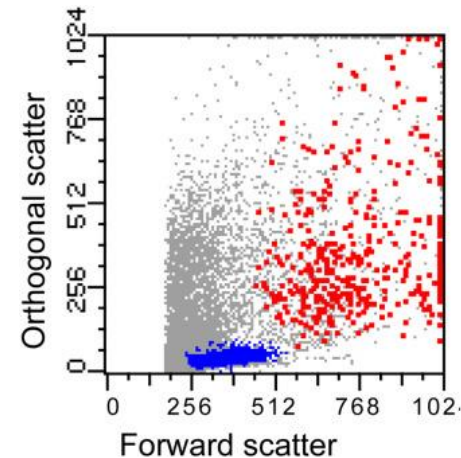
## Vrouw 25jr

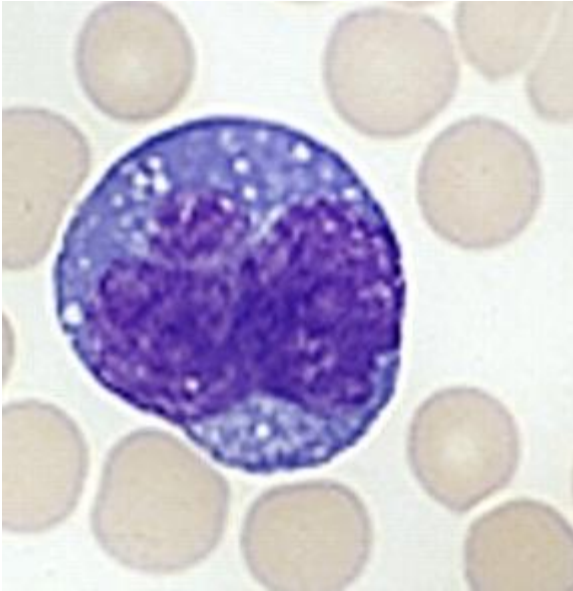
- Koorts
- Lymfeklieren
- Grote afwijkende cellen



# Anaplastisch large cell lymphoma (ALCL)

- ▶ Twee varianten
  - ▶ ALK positief
  - ▶ ALK negatief
  - ▶ **Borst implantaat geassocieerd**
- ▶ Flow cytometrie
  - ▶ CD3+/CD4+/**CD30++**
- ▶ Cytogenetica
  - ▶ Translocatie t(2:5) ALK





## **Vrouw 58 jr**

- Splenomegalie en lymfeklieren
- Auto immuun hemolytische anemie
- Flow cytometrie

CD3/CD4/CD10



# Nodulair T-folliculair helper cell lymfoom

## Angio Immuno blastair type

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### ▶ Karakteristieken

- ▶ Frequent T-cel lymfoom (20-30%)
- ▶ Klieren
- ▶ Auto-immuun fenomenen

### ▶ Morfologie

- ▶ Normaal tot middelgrote cellen
- ▶ Heterogeen

### ▶ Flow cytometrie

- ▶ **CD4+** CD10+ CD3zwak (CD279+)
- ▶ T follicular helper cel fenotype



