Malignant hematopoiesis (1)

Myeloproliferative disorders

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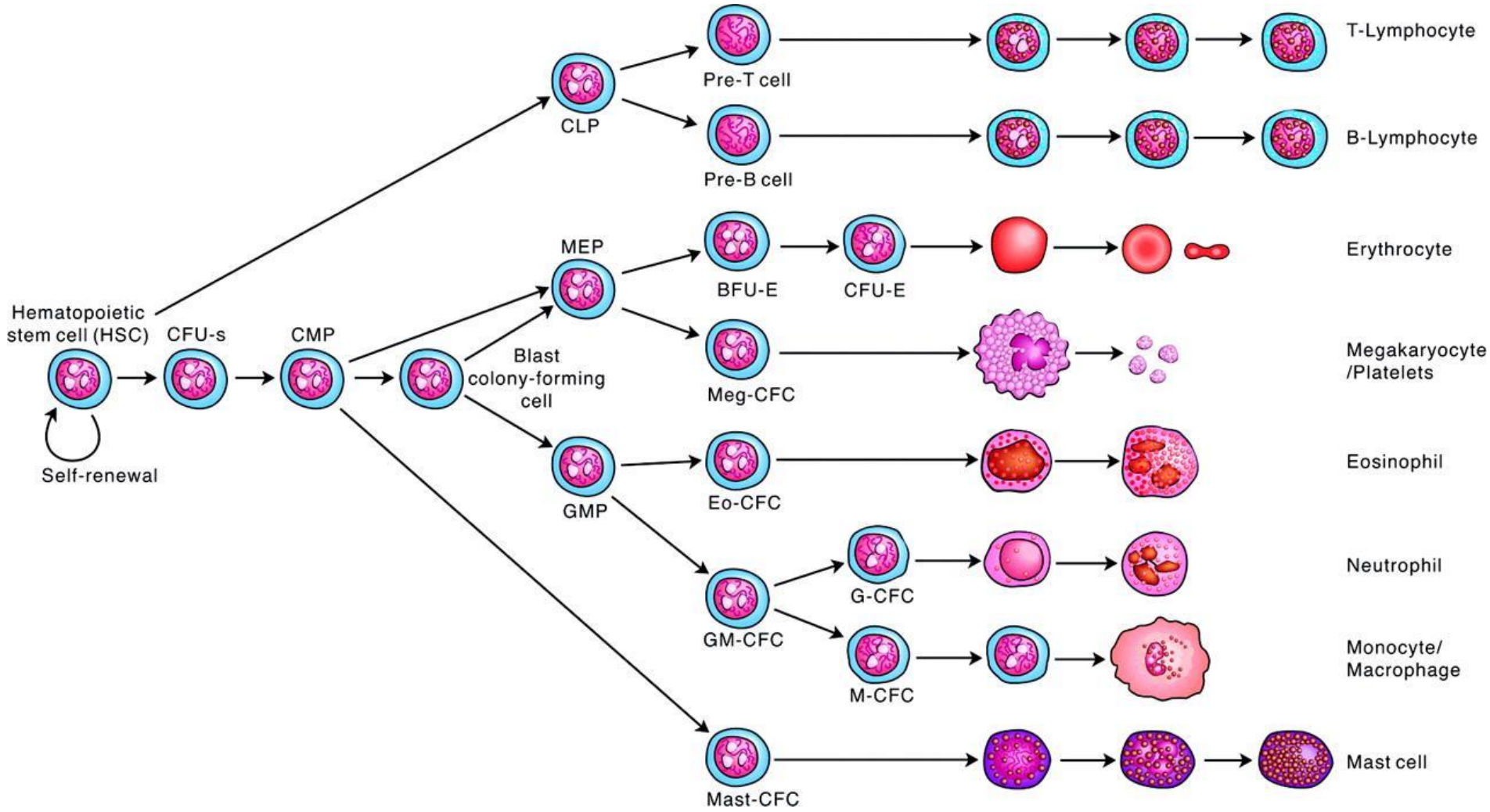
Introduction

Myelopoiesis and Lymphopoiesis



Myelopoiesis and Lymphopoiesis

- **myeloid cells** (erythropoiesis, granulocytopoiesis, monocytopoiesis, thrombocytopoiesis _ megakaryocytes)

- **lymphoid cells** (B-lymphopoiesis, T-lymphopoiesis, NK-lymphopoiesis)

- **Myeloproliferative disorders**
- **Lymfoproliferative disorders**

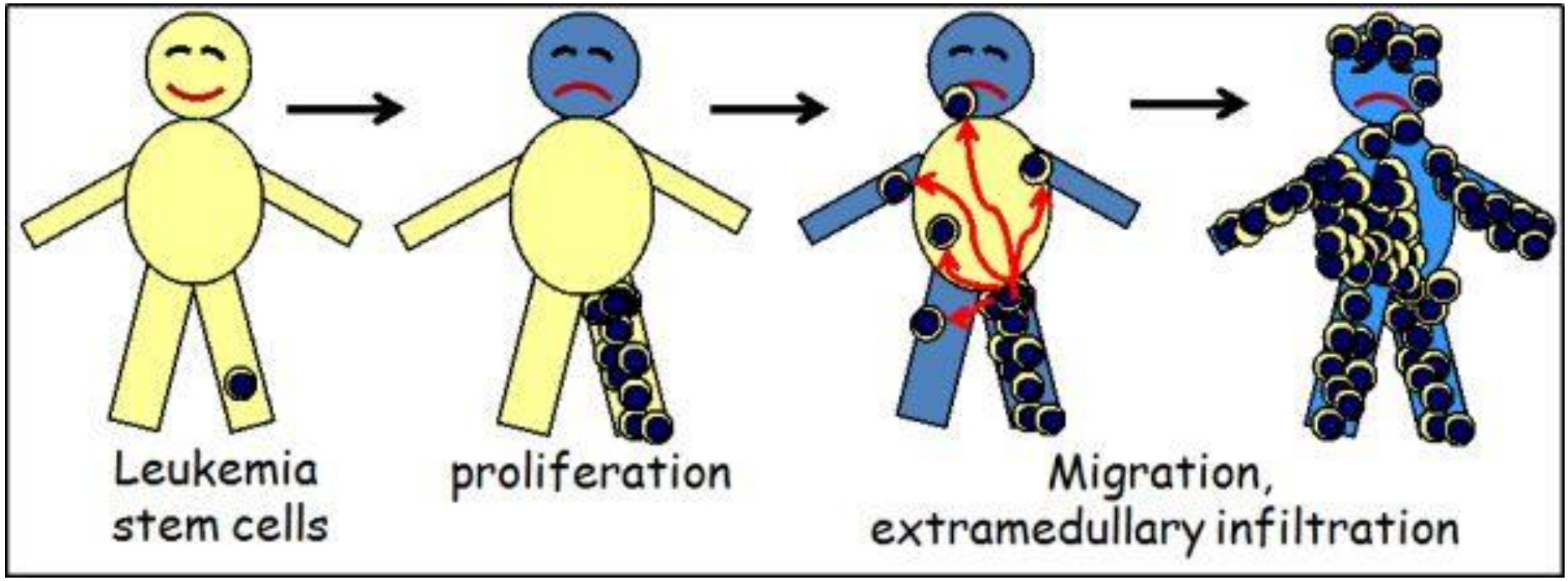
- Myeloproliferative disorders
  - **chronic**
  - **acute**
- Lymfoproliferative disorders
  - **chronic**
  - **acute**

Lymphoproliferative diseases
can also have a form of a solid tumor,
a lymphoma.

Though seemingly localized to a
lymphoid tissue outside the bone
marrow, it is considered to be
a systemic disease involving
(infiltrating) the bone marrow regularly.

A single **leukemic stem cells** starts the disease.

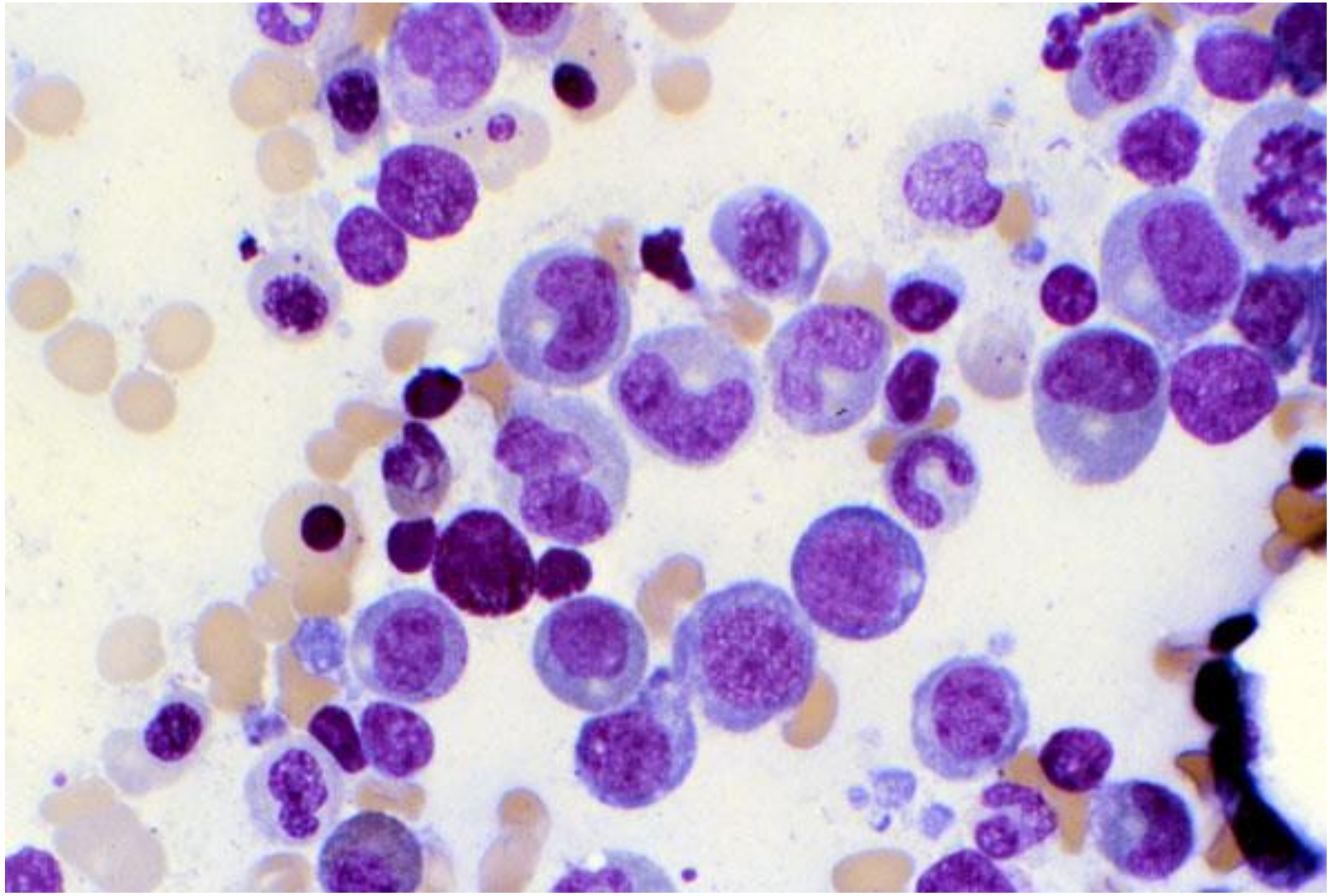
The disease then spreads throughout the body.



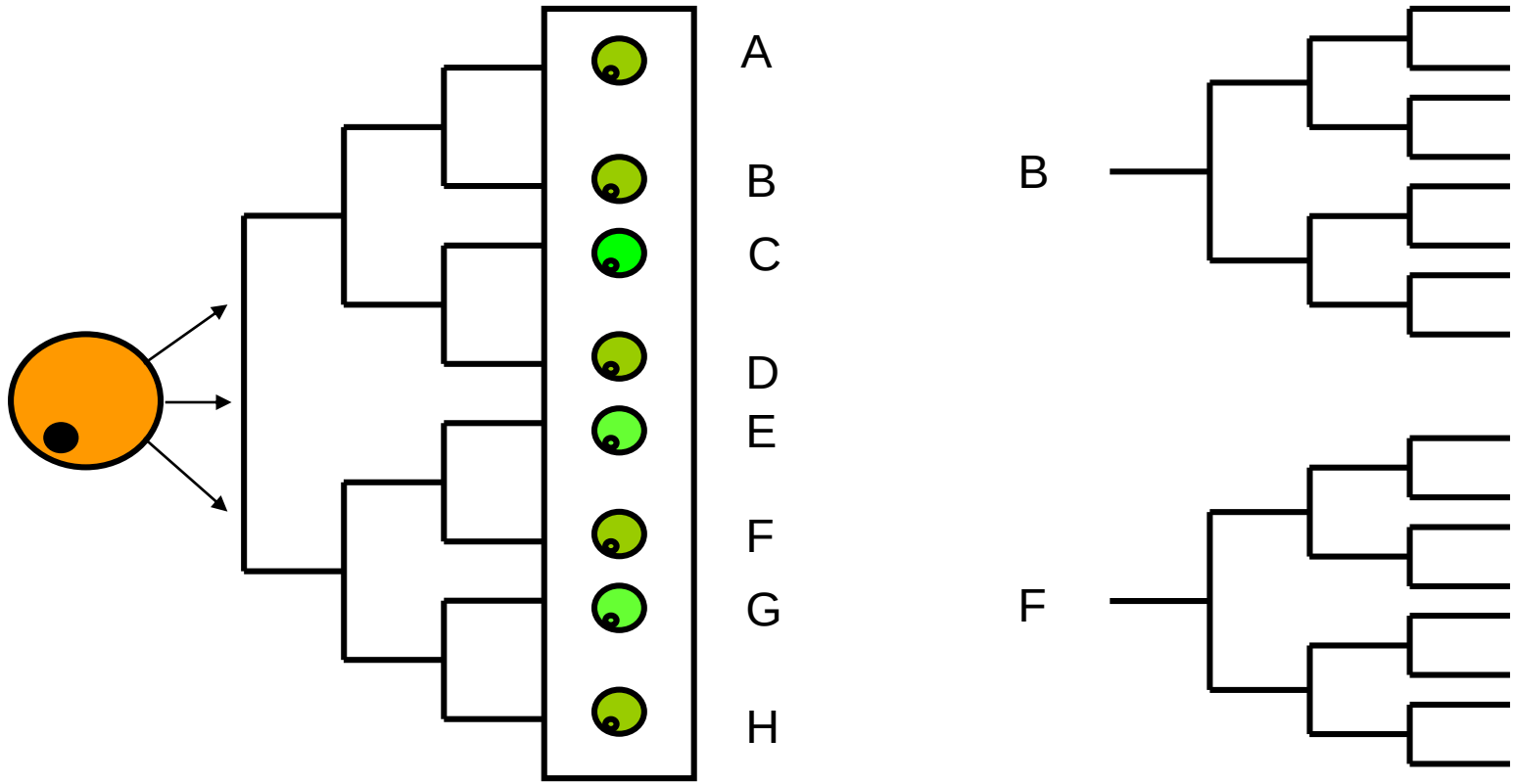
Malignant hematopoiesis

- is usually monoclonal
- is usually systemic

Normal hematopoiesis is **polyclonal**

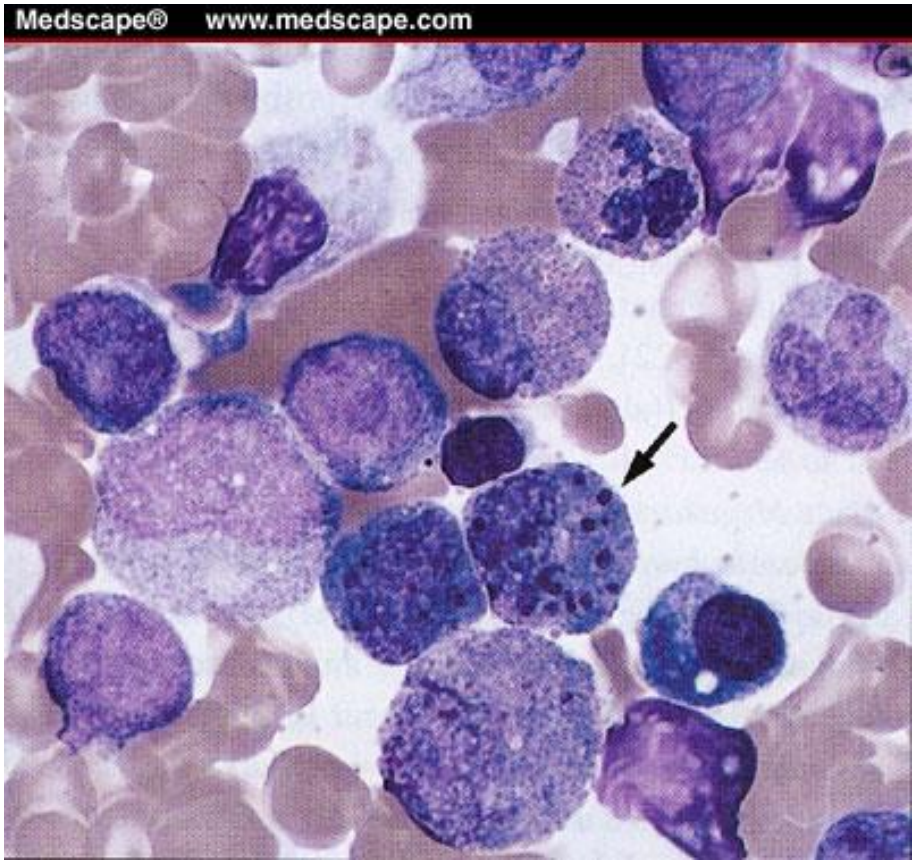


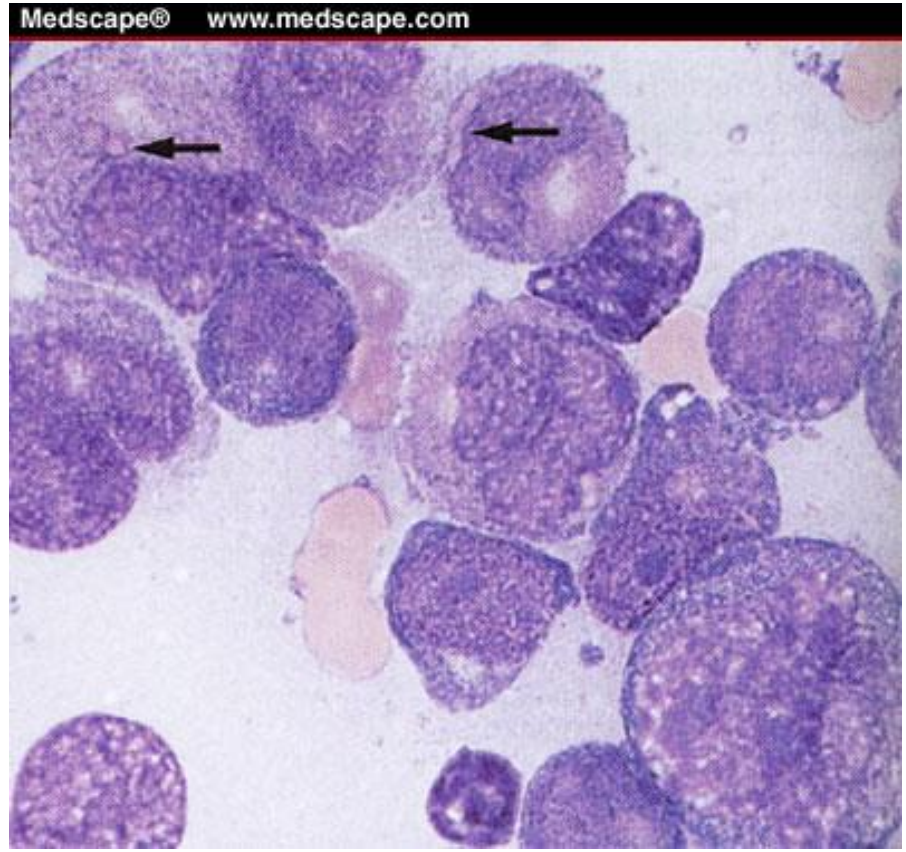
Origin of the normal polyclonal hematopoiesis is in embryogenesis

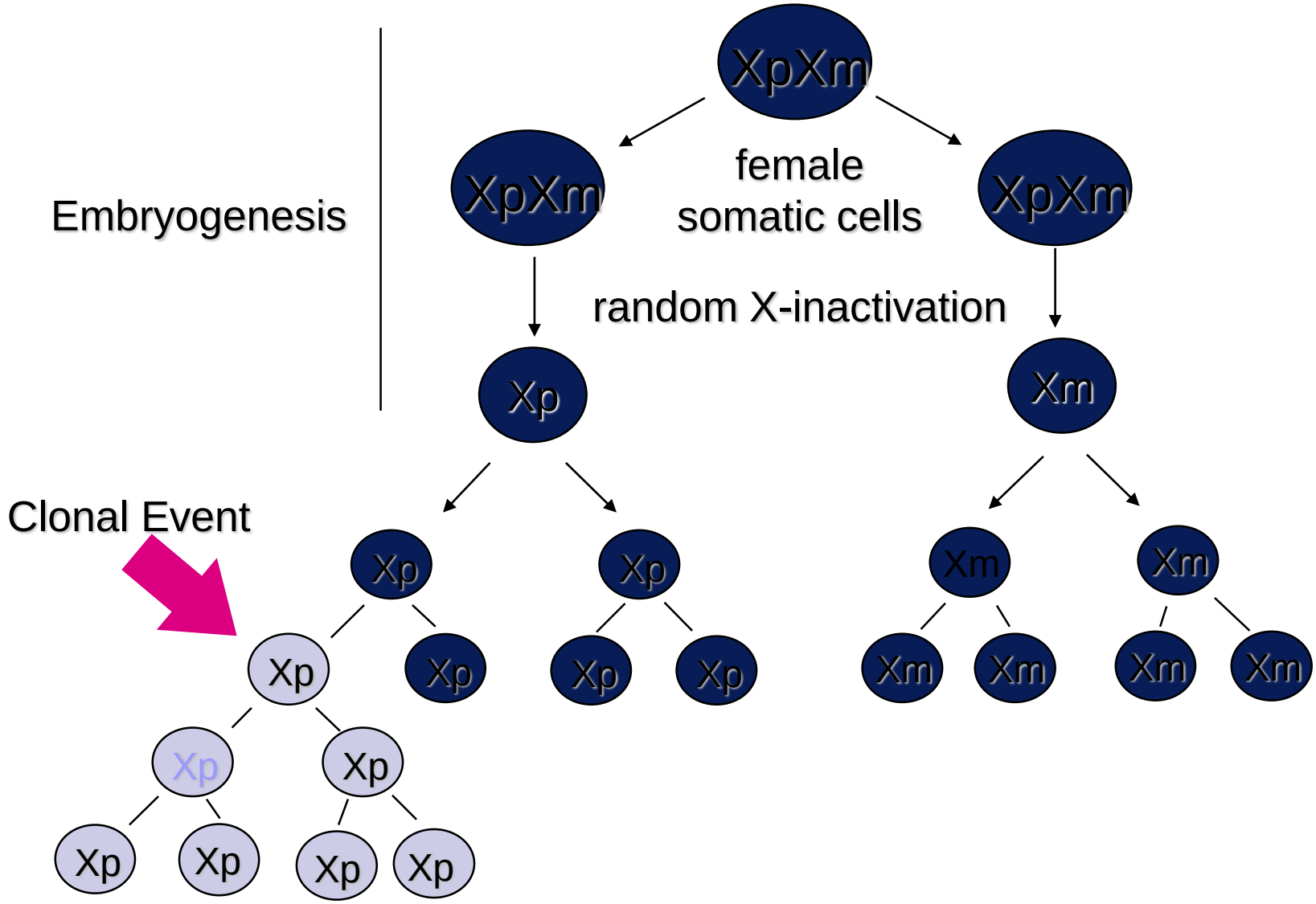


Malignant hematopoiesis is **monoclonal**

(examples: acute myeloid leukemia; AML)






XpXm
Embryogenesis
XpXm
female
somatic cells
XpXm
random X-inactivation
Xp
Xm
Clonal Event
Xp
Xp
Xm
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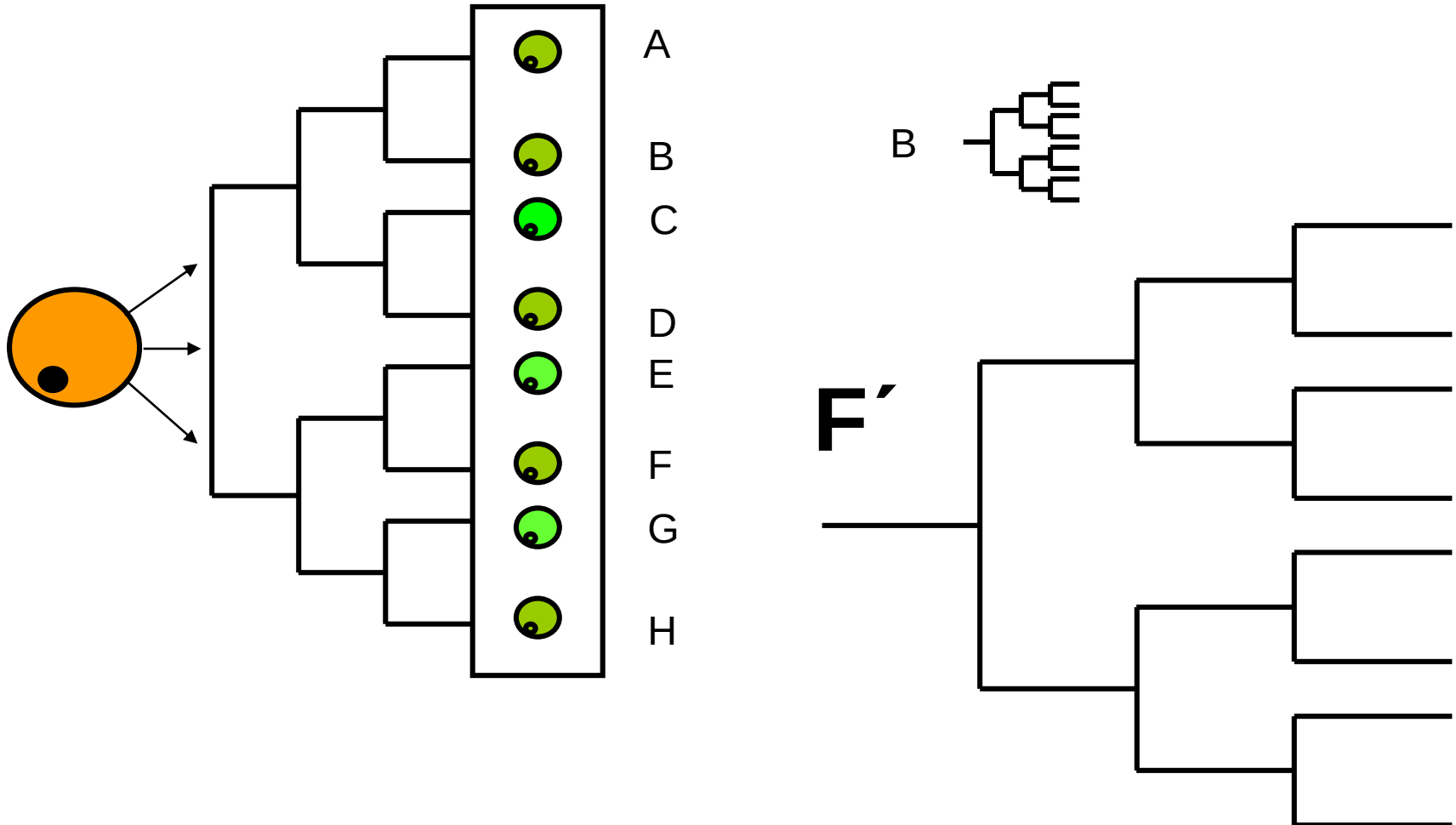
Malignant monoclonal hematopoiesis is caused by mutations (F´cell clone)



Treatment eliminates or supresses the malignant clone and normal polyclonal hematopoiesis usually resumes

Possible therapy outcomes

- remission
- successful treatment (complete remission)
- residual disease
- relaps

A pathological dominant clone may start from

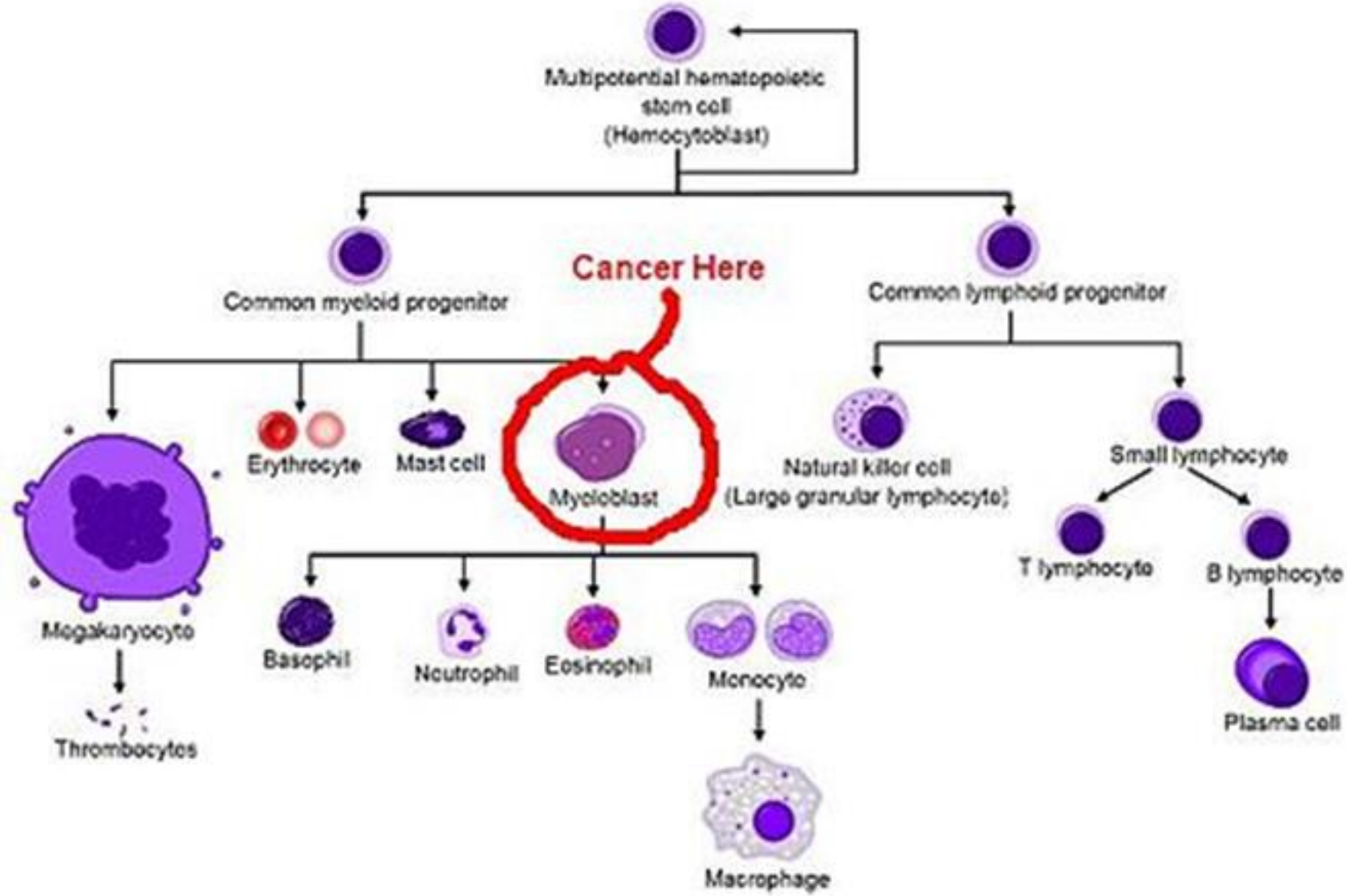
a mutated hematopoietic stem cell

but not necessarily.

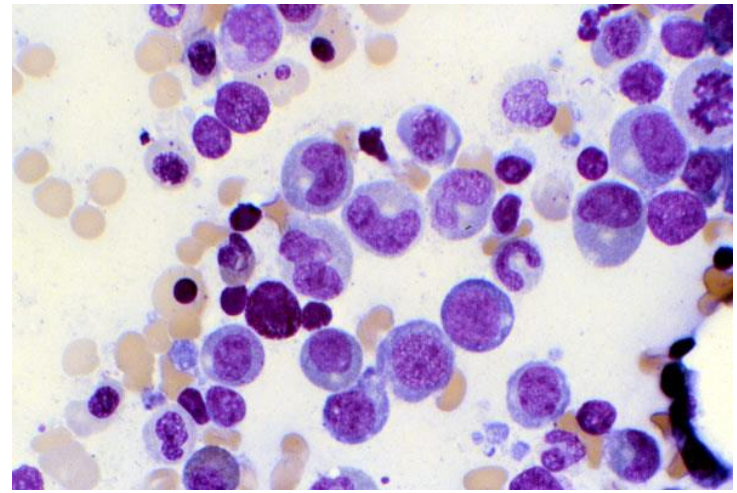
A mutated progenitor cell

may be a source of

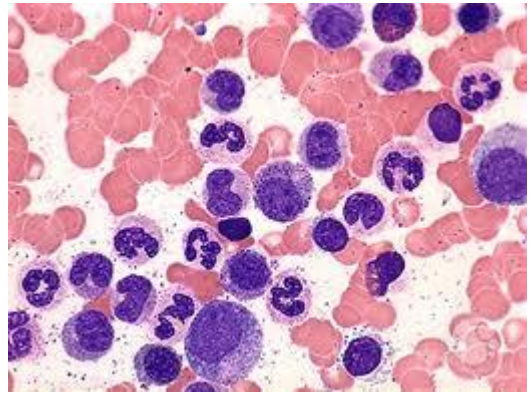
a dominant malignant clone as well.


Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Cancer Here
Common lymphoid progenitor
Erythrocyte
Mast cell
Myeloblast
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
Megakaryocyte
Basophil
Neutrophil
Eosinophil
Monocyte
T lymphocyte
B lymphocyte
Thrombocytes
Plasma cell
Macrophage

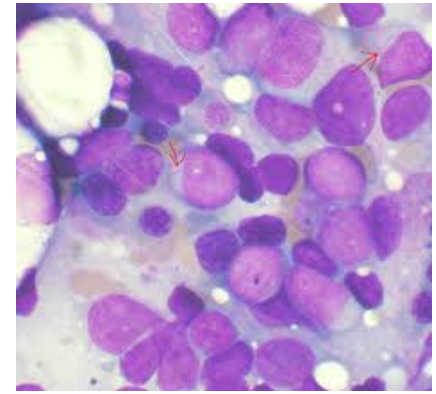
Normal bone marrow and CML, AML, CLL



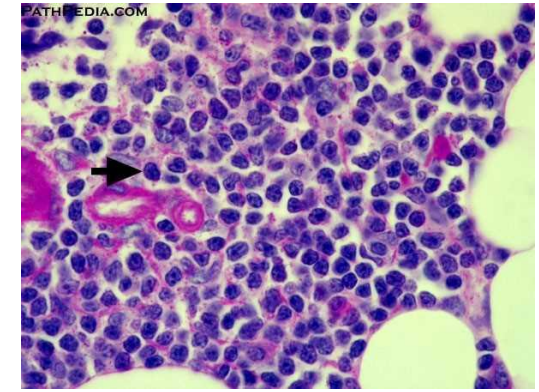
CML



AML



CLL



Chronic myeloproliferative disorders

Chronic myeloproliferative diseases

- Myelodysplastic syndrome (MDS)
- Polycythemia vera rubra
- Chronic myeloid leukemia (CML)
- Essential throbocythemia
- Idiopathic Myelofibrosis/or Agnogenic Myeloid Metaplasia

- Chronic lymphocytic leukemia (CLL) …is lymphoproliferative disease

Myeloproliferative Disorders

(Chronic) Myeloproliferative Disorders – common features

- Acquired mutation in a hematopoietic stem cell
- Clonal hematopoiesis
- Proliferation of granulocytes, red cells and/or platelets
- Splenomegaly (variable)
- Bone marrow fibrosis (variable)

Myelodysplastic syndrome (MDS)

MDS and Leukemias: Annual Incidence (U.S.)

Type	Adults	Children	Total
AML	9,300	1,020	10,320
ALL	1,300	2,900	4200
CML	4,380	120	4500
CLL	10,800	0	10,800
MDS	14,000	1,000	15,000
TOTAL	37,780	5,040	44,820

Myelodysplastic syndrome (MDS)

MDS is a myeloproliferative disease,

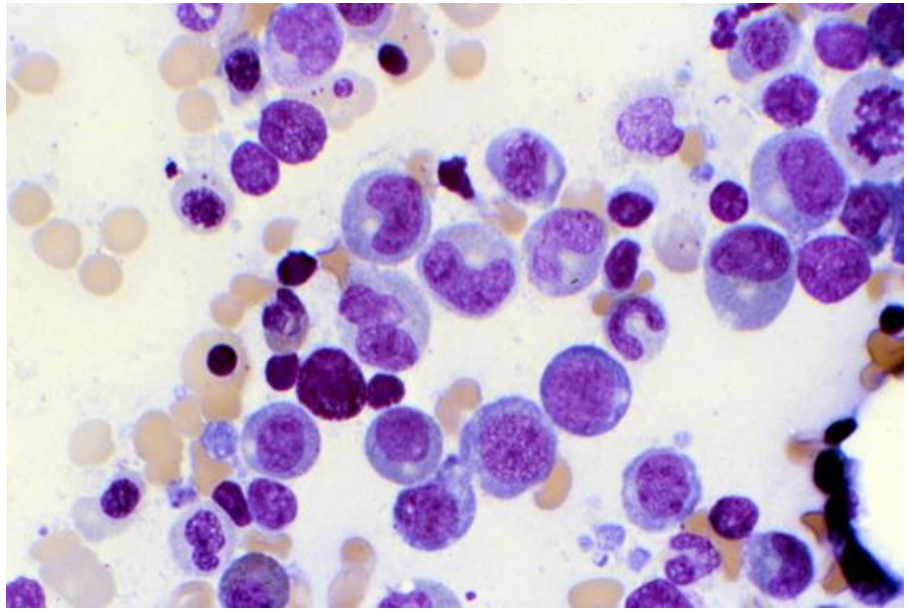
used to be called „preleukemia“

It has several forms.

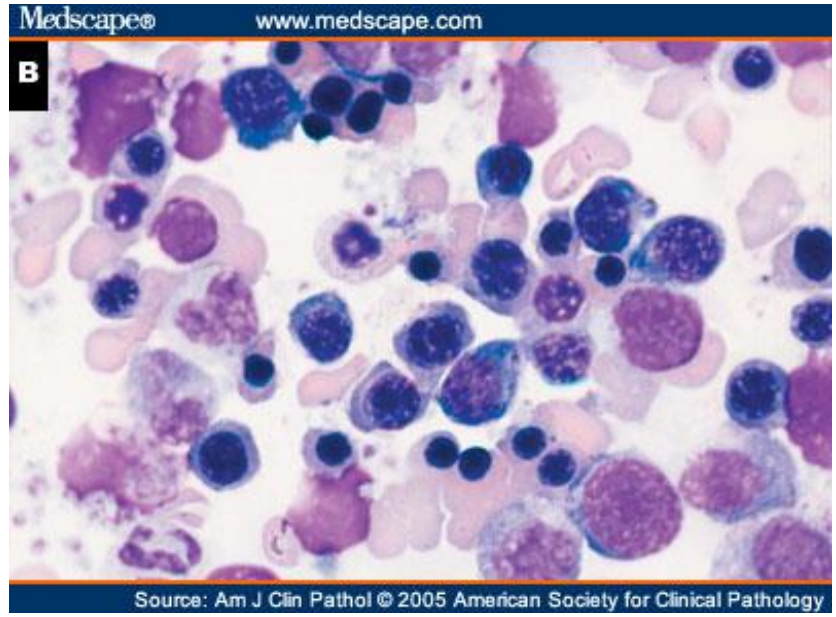
There is decreased number of „myeloid“ cell in the blood (anemia, granulocytopenia, thrombocytopenia = pancytopenia)

Normal and dysplastic (MDS) bone marrow

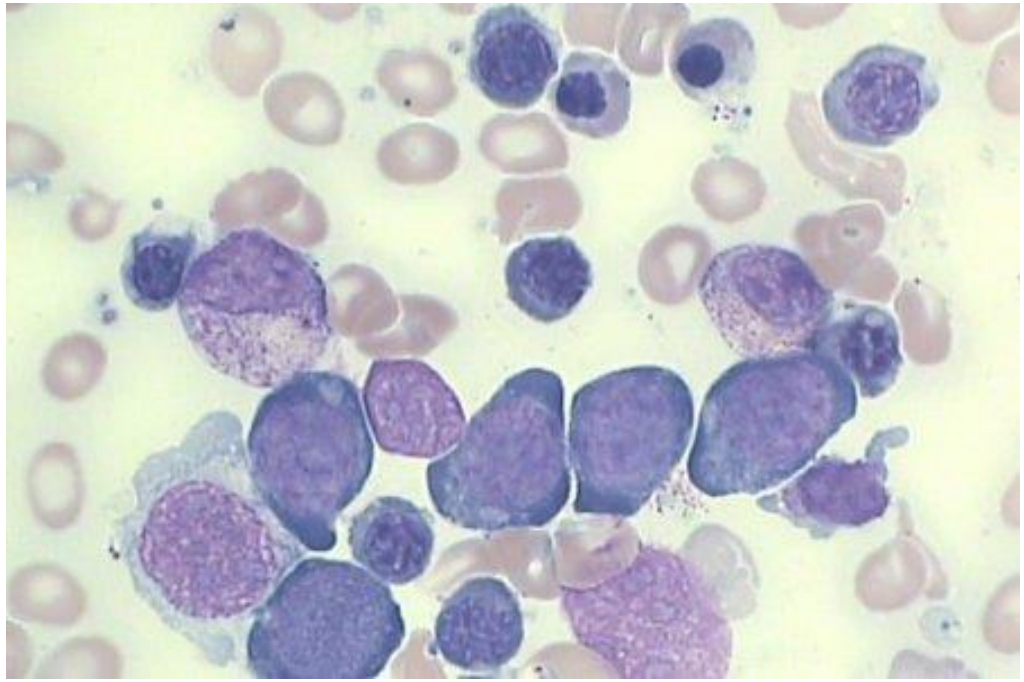
Normal bone marrow

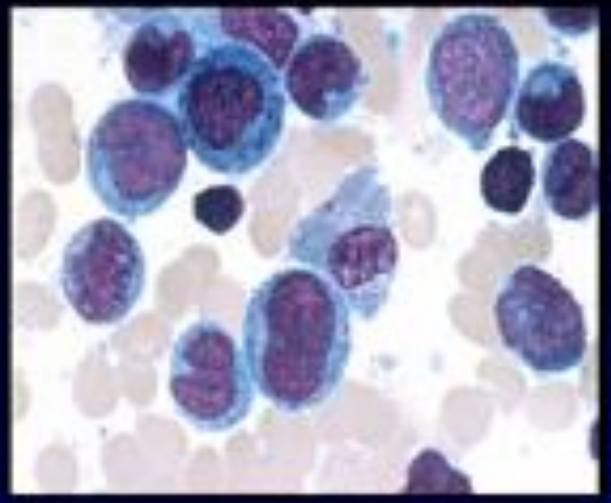


Dysplastic bone marrow



Dysplastic bone marrow in the RAEB (refractory anemia with excess of blasts) a form of the MDS



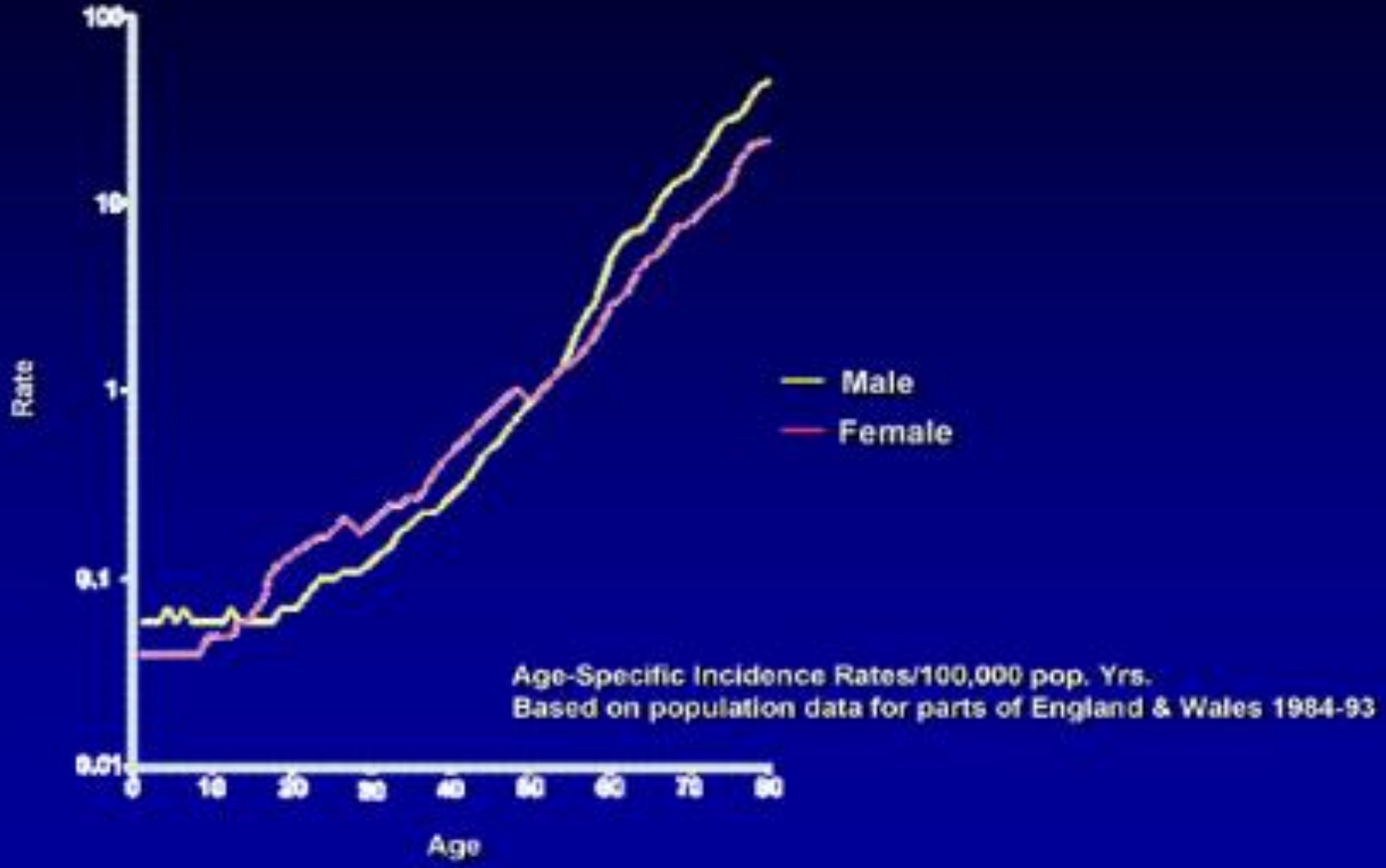


The Myelodysplastic Syndromes

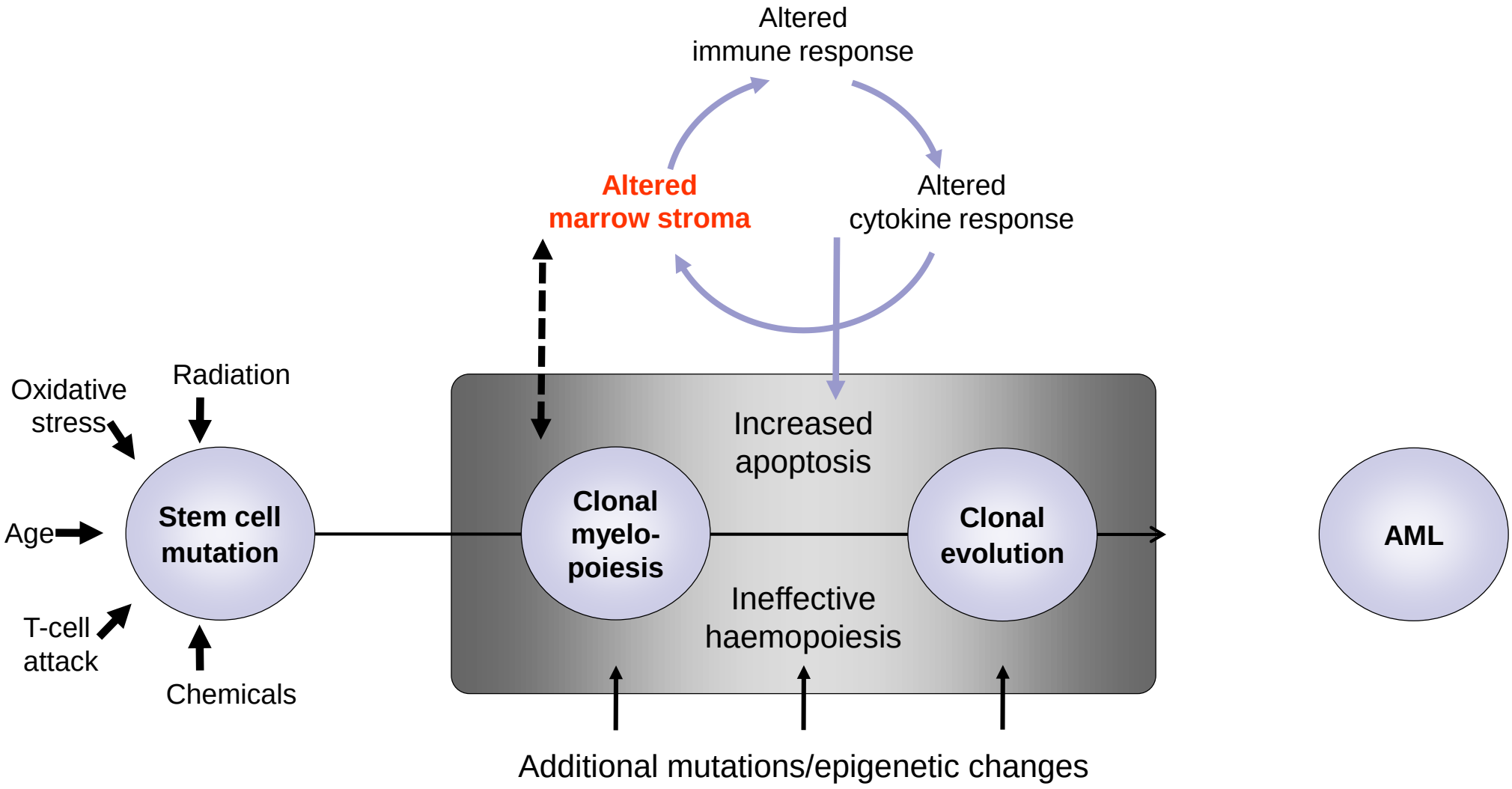
A heterogeneous group of clonal hematopoietic stem cell disorders characterized by:

- Ineffective, dysplastic hematopoiesis
- Peripheral cytopenias
- Variable rates of progression to AML

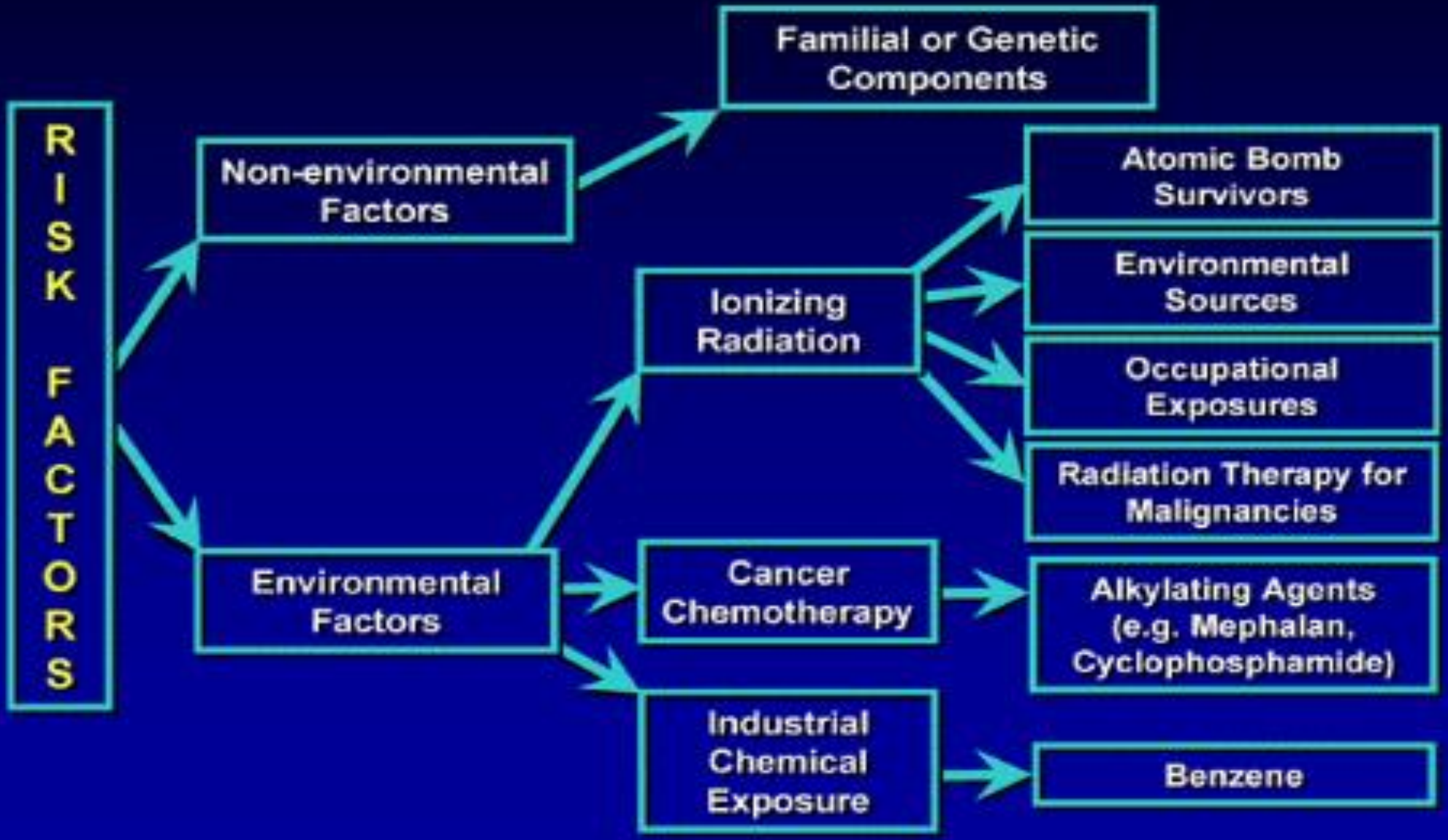
MDS: Incidence by Age



MDS – etiopathogenesis and conversion into AML



MDS: Etiology



FAB Classification System

MDS Subtypes	% Blasts (BM)	% Blasts (PB)
RA	<5	≤1
RARS*	<5	≤1
RAEB	5-20	<5
RAEB-t**	>20-30	≥5
CMML***	<5-30	<5

[AML: >30% BM blasts]

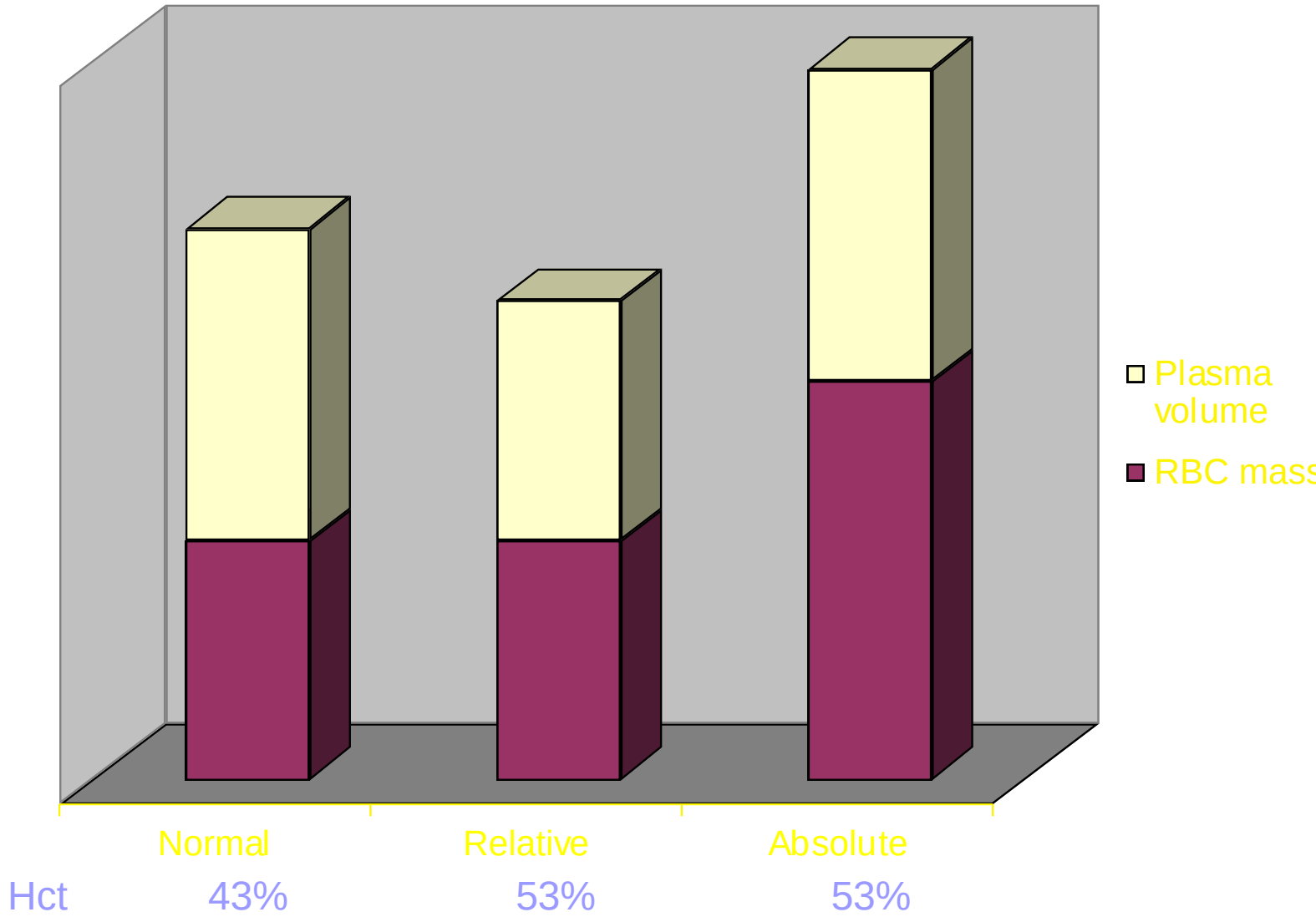
*Ringed sideroblasts >15% of BM blasts

**Auer rods

***Monocytosis (1 x 10^9/L)

Polycythemia vera rubra („primary polycythemia“, Disease Vasquez-Osler)

Polycythemias



Polycythemia Vera

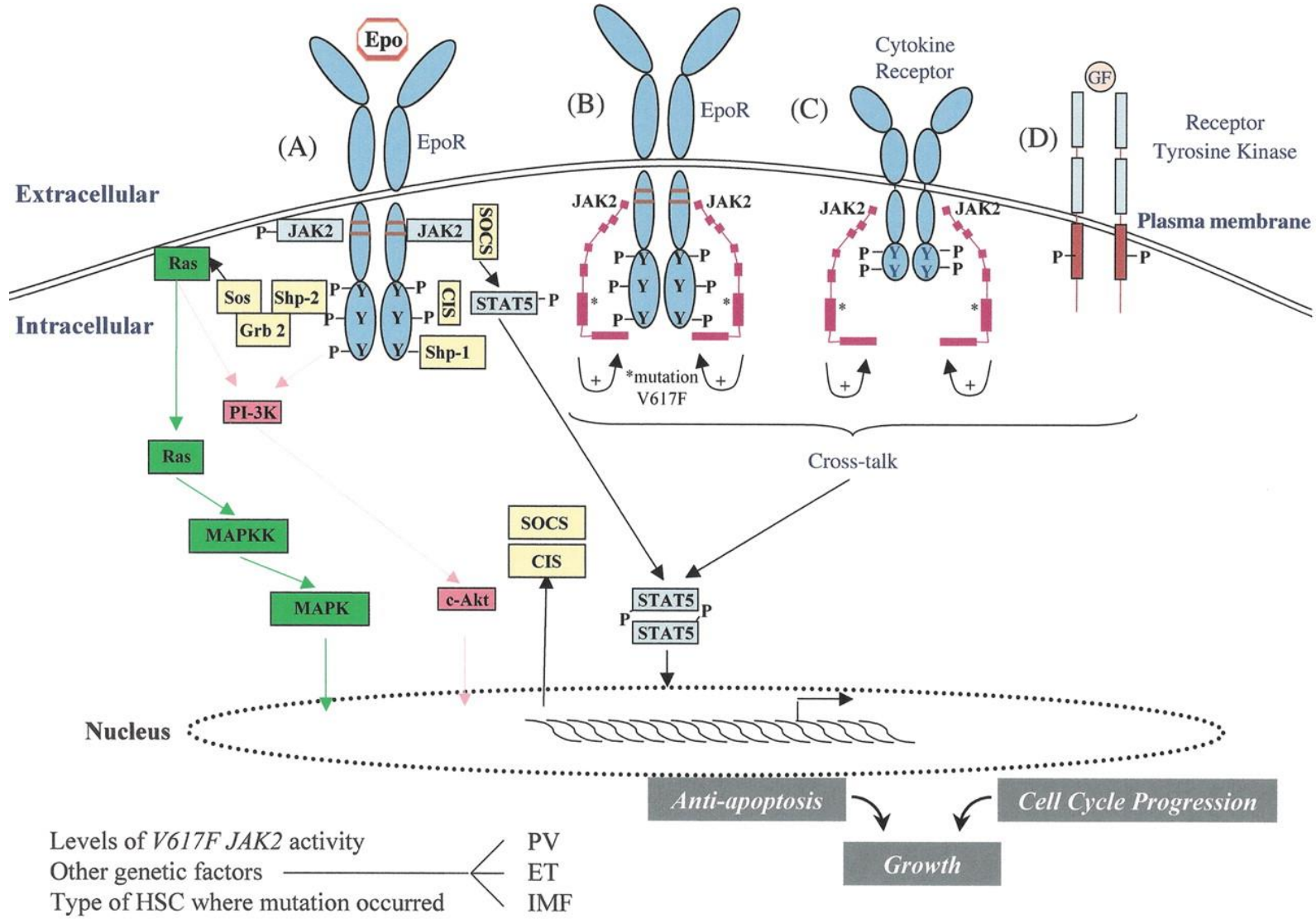
- **An acquired mutation of hematopoietic single stem cell**

- **The nature of the disease causing mutation not known till 2005**

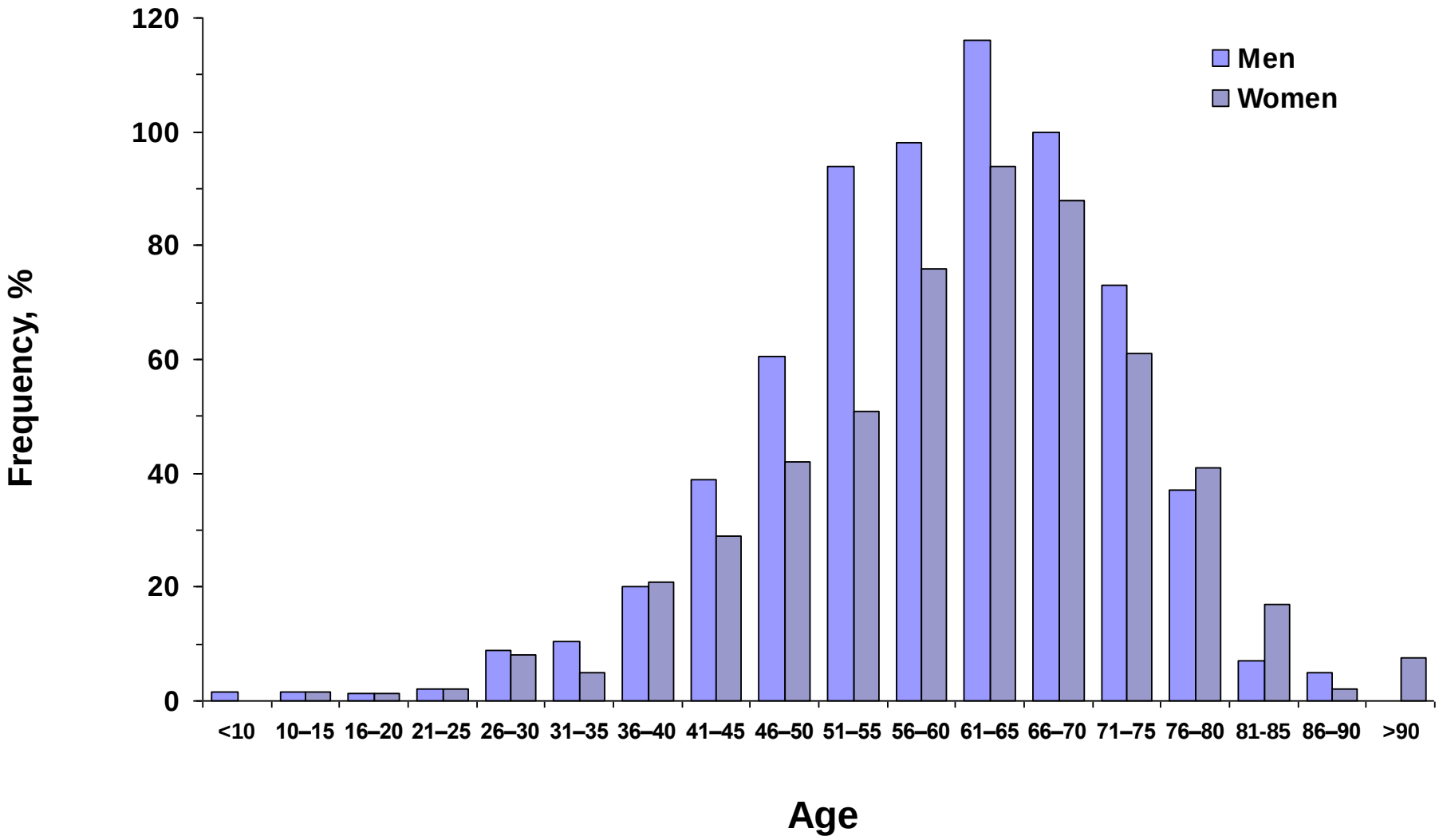
– most cases have mutation in

the JAK2 tyrosinkinase

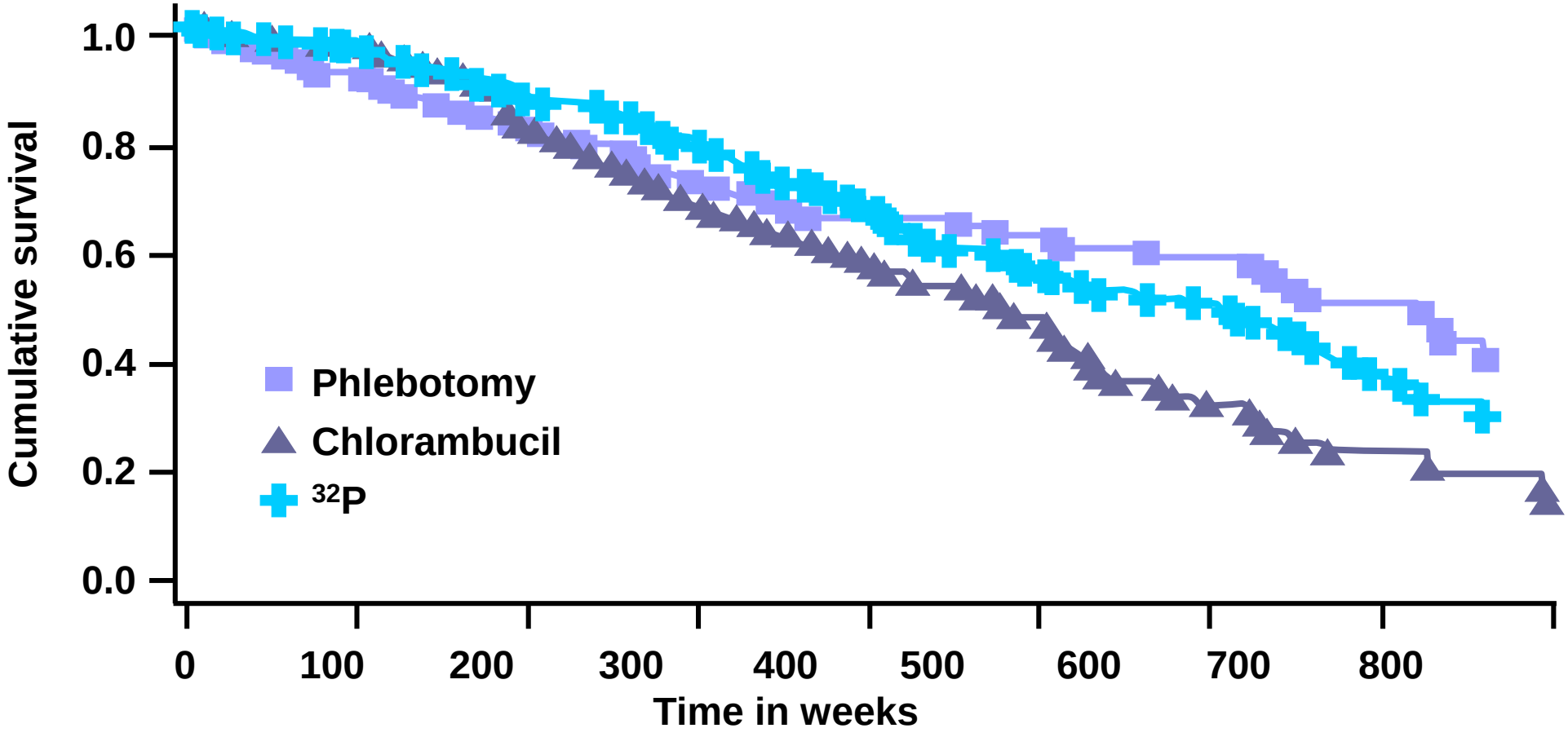
Polycythemia vera, Essential trombocythemia, Idiopathic myeolofibrosis



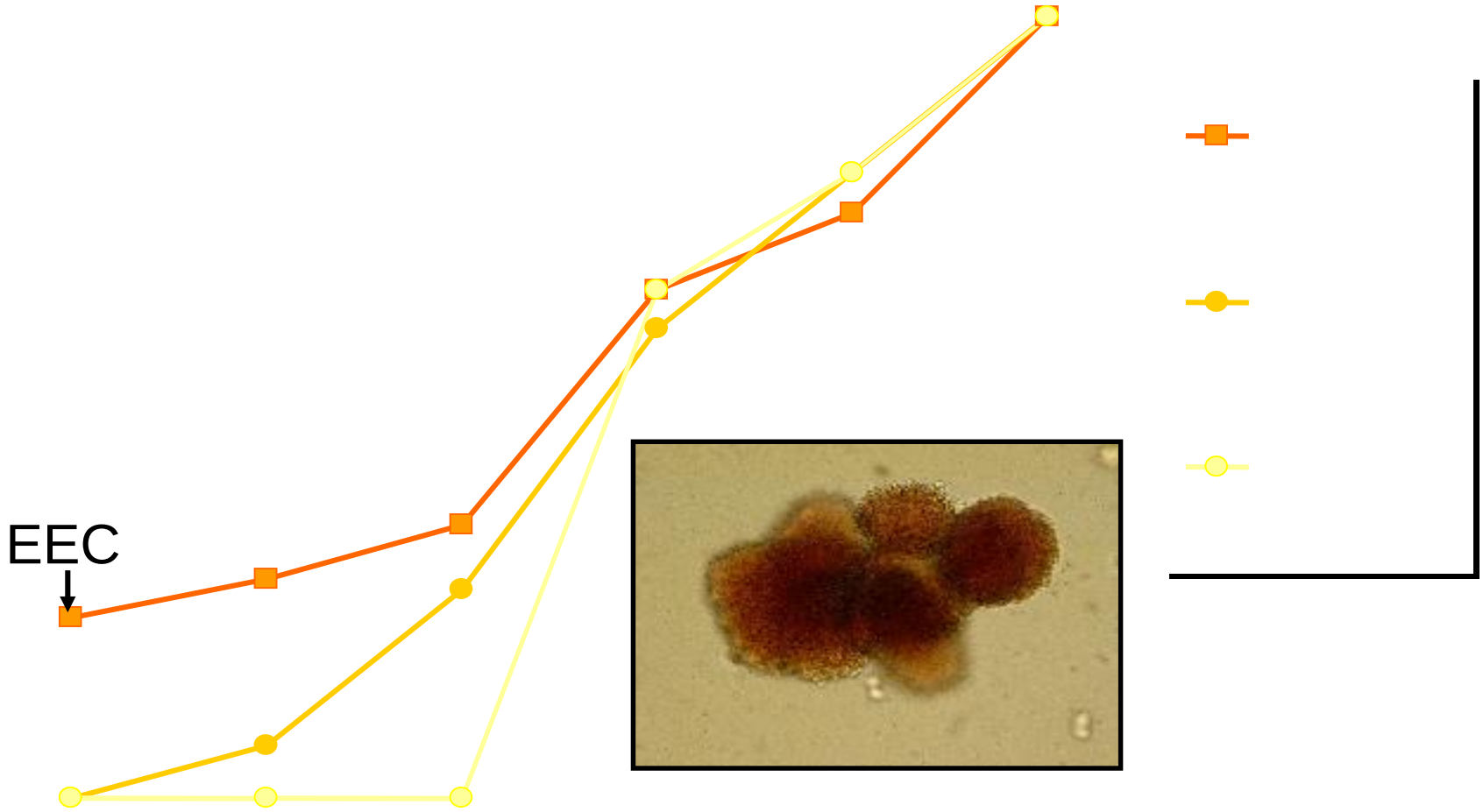
Incidence of Polycythemia Vera



Cumulative Survival on Study (PV)



Sensitivity of BFU-E to Epo



Essential thrombocytemia

Essential Thrombocythemia

- Platelet count in excess of 600,000 per mm3
- Marked megakaryocytic hyperplasia
- Abundant platelet clumps

Essential Thrombocythemia

- No cytogenetic abnormalities
- Splenomegaly seen in fewer than 50%
- Morbidity: Thrombotic and/or bleeding problems

Essential Thrombocythemia

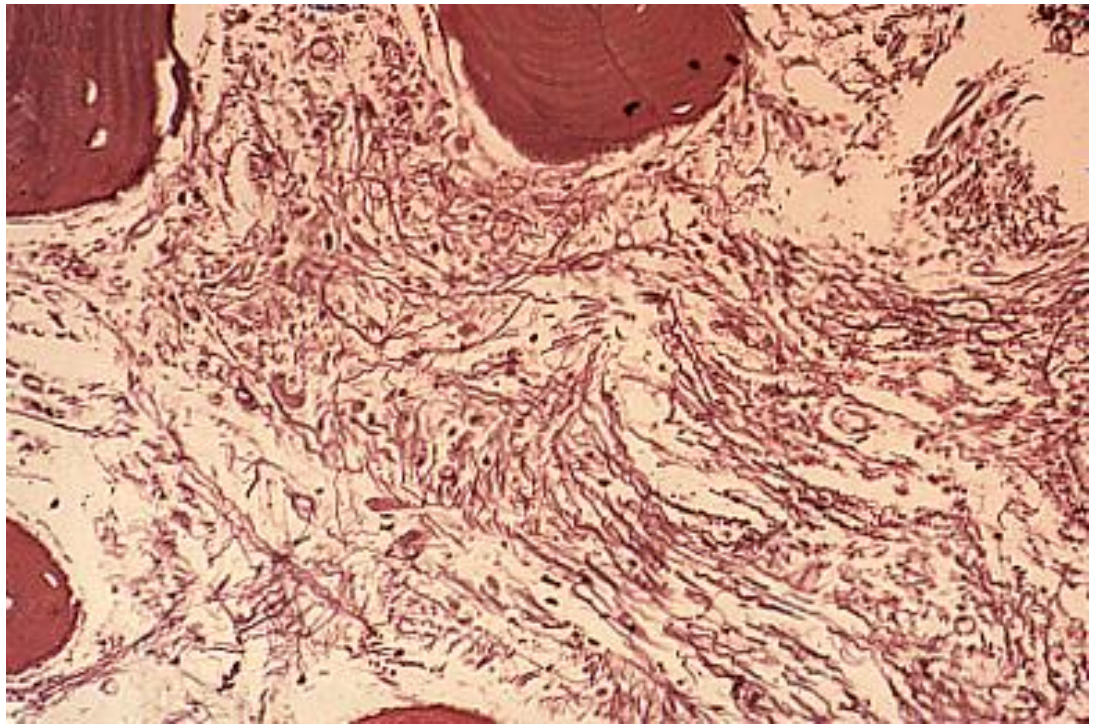
- No cytogenetic abnormalities
- The same

mutation in the JAK2 kinase

as causes Polycythemia vera is present in some patients

Myelofibrosis/ Agnogenic Myeloid Metaplasia

Idiopathic Myelofibrosis/ Agnogenic Myeloid Metaplasia (AMM)

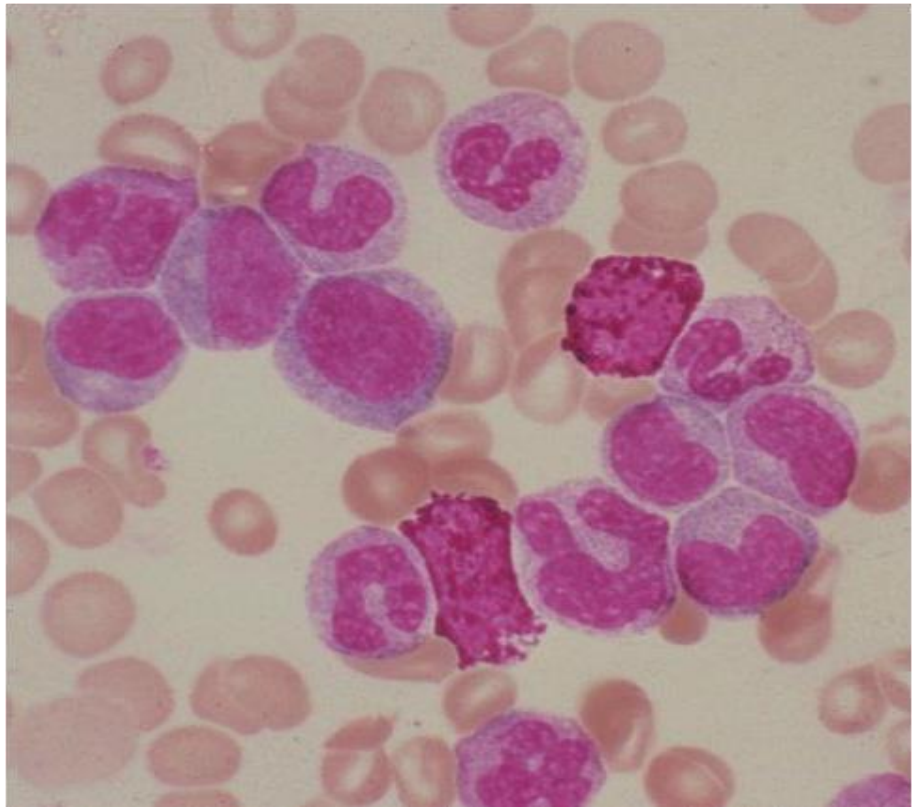


Must exclude other causes of bone marrow fibrosis

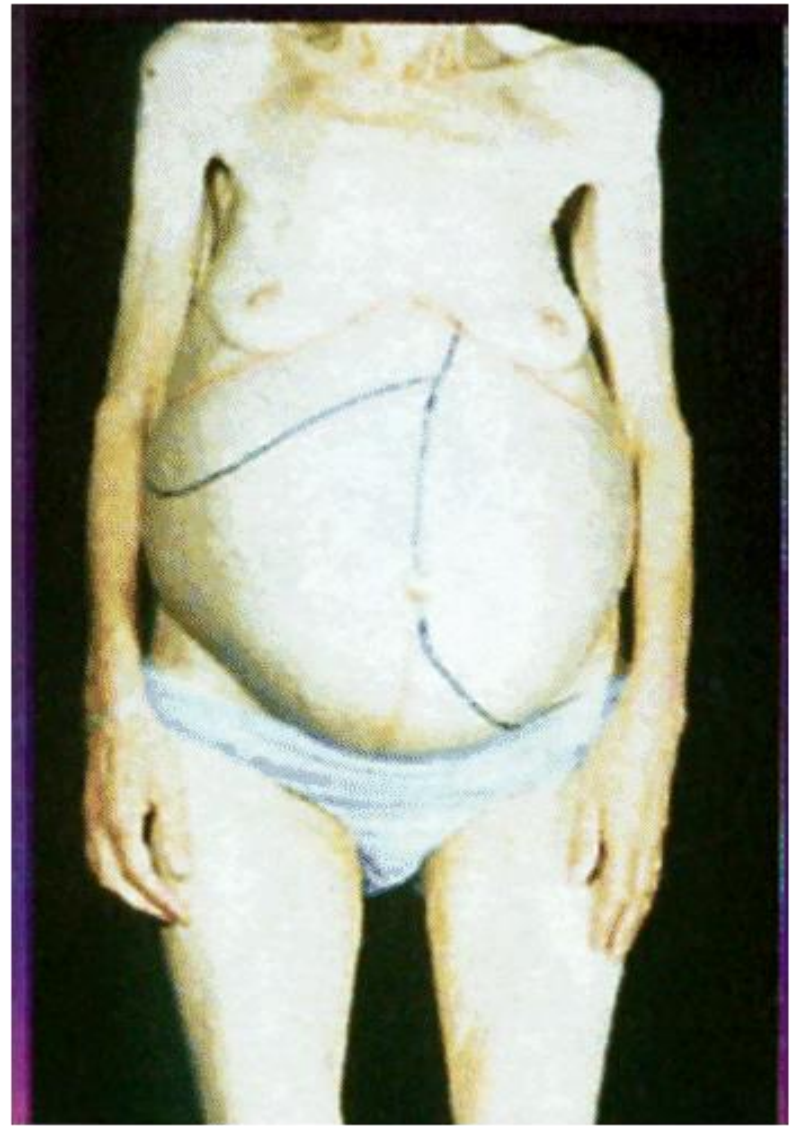
- “Spent phase” of PV or ET
- CML
- Hairy cell leukemia
- Lymphoma
- Metastatic cancer

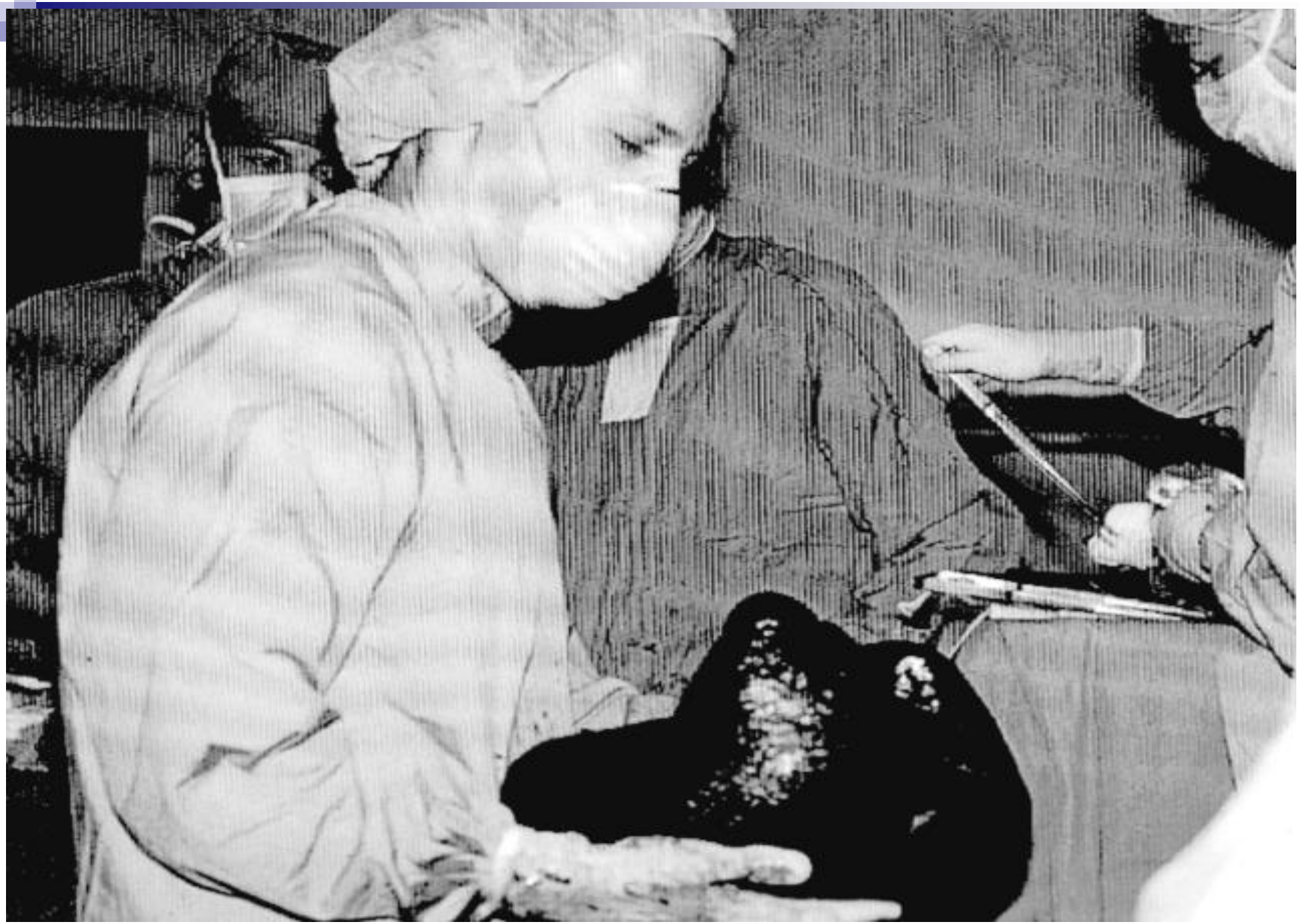
Chronic myleoid leukemia (CML)

Chonic Myelogenous Leukemia

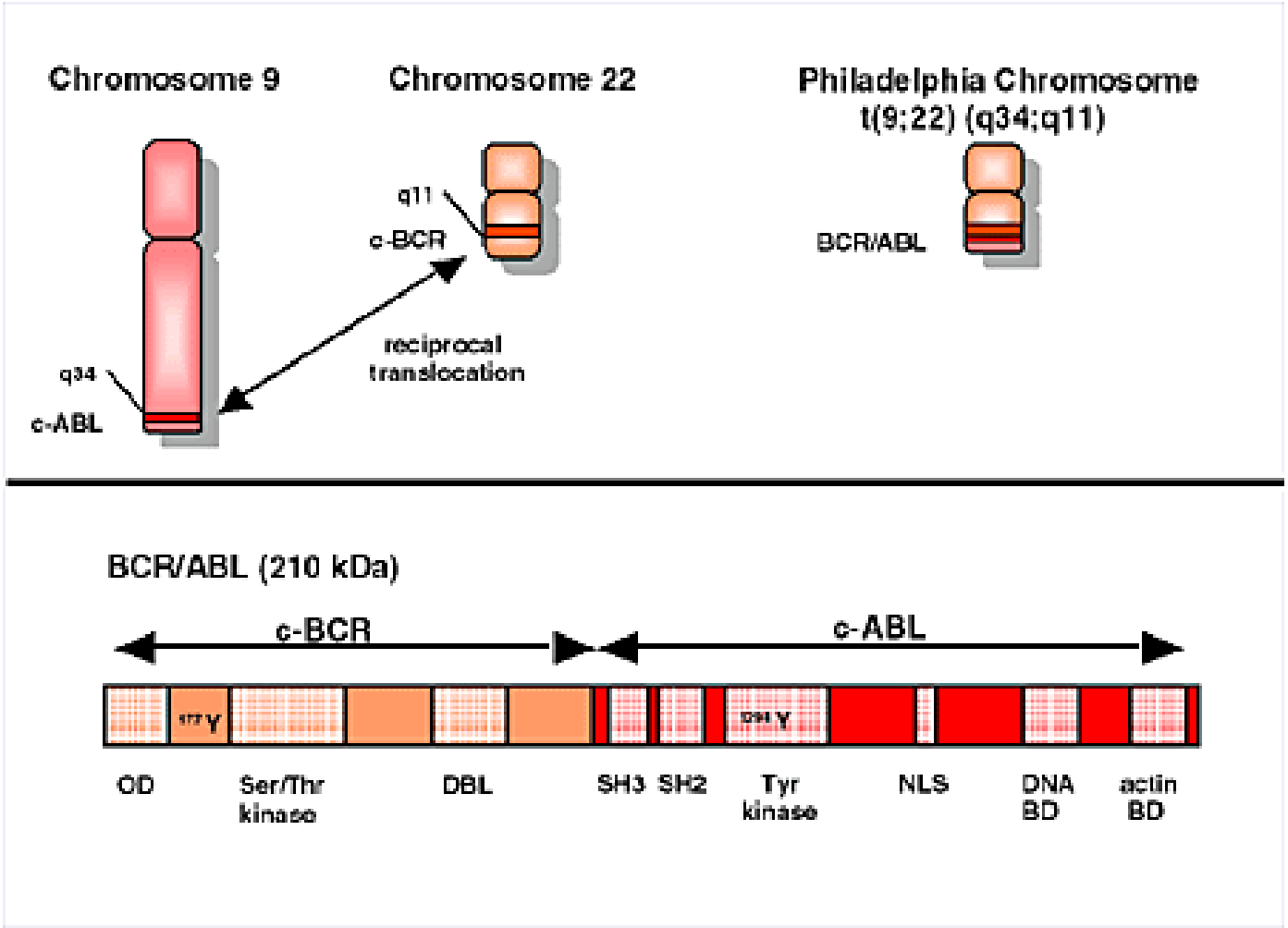


- Proliferation of granulocytes
- All stages of granulocyte maturation in peripheral blood
- Platelets may be elevated
- Polycythemia is rare
- Splenomegaly, may be massive
- Invariable transformation to acute leukemia





Abnormal BCR-ABL fuse gen and BCR-ABL proteinkinase



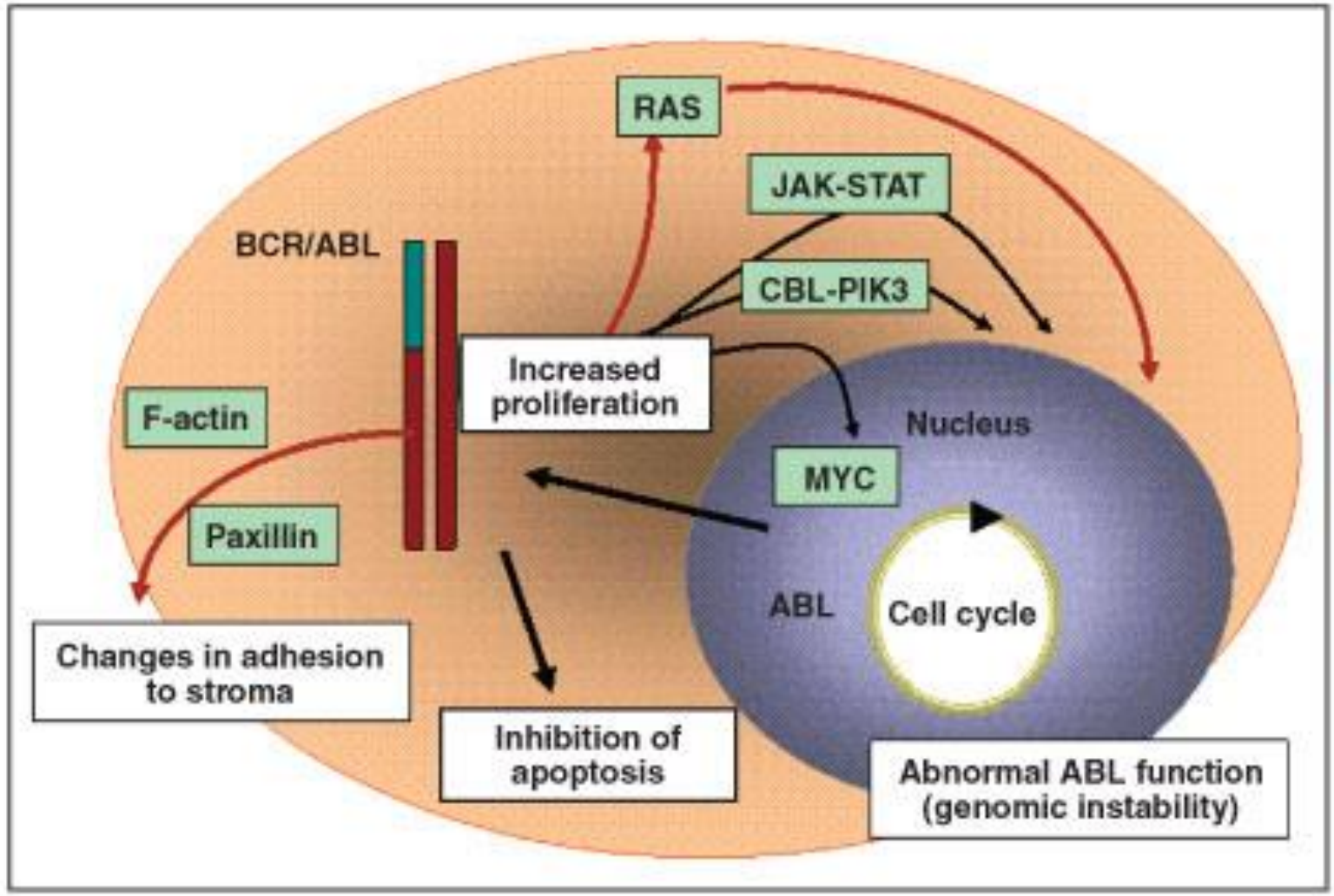
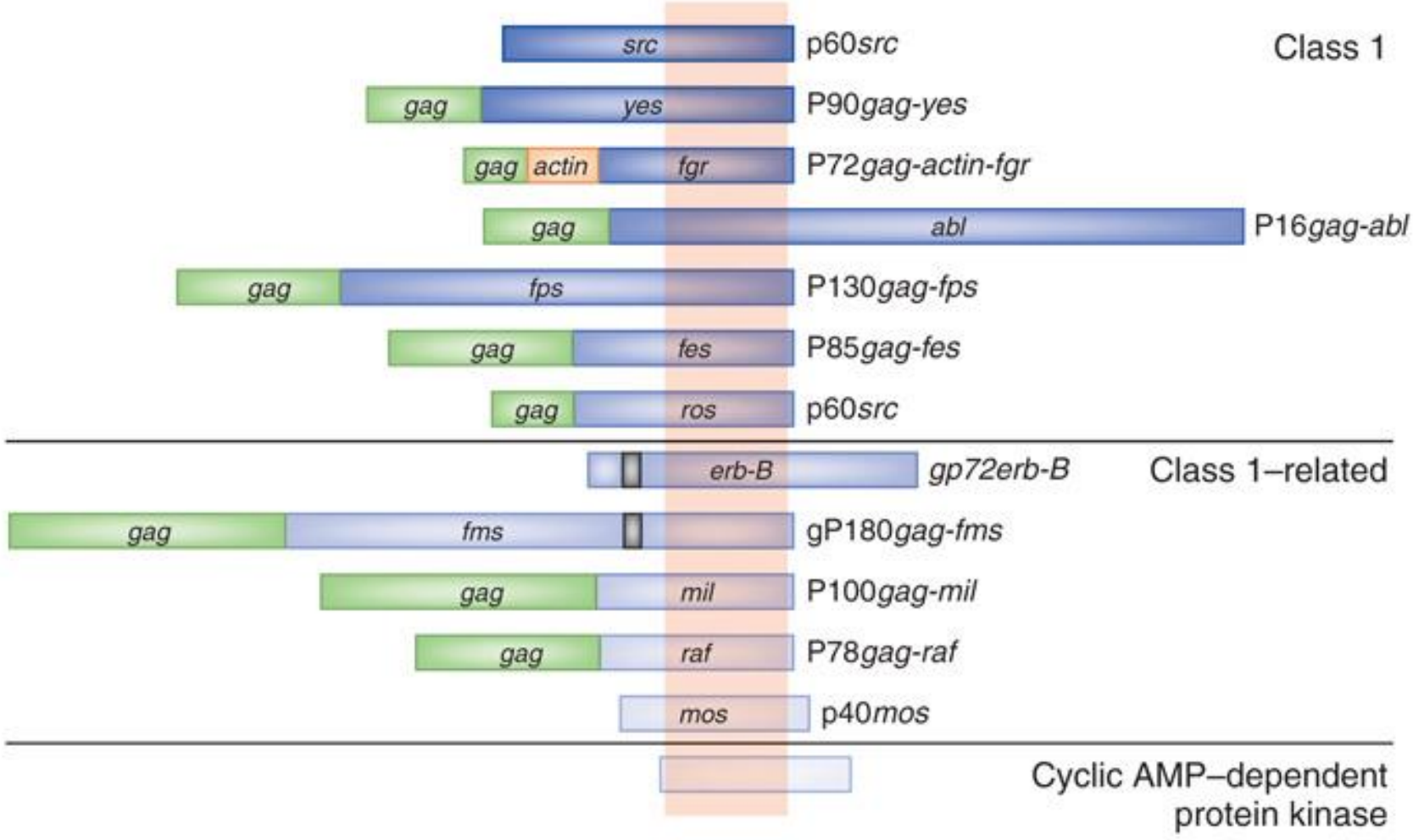
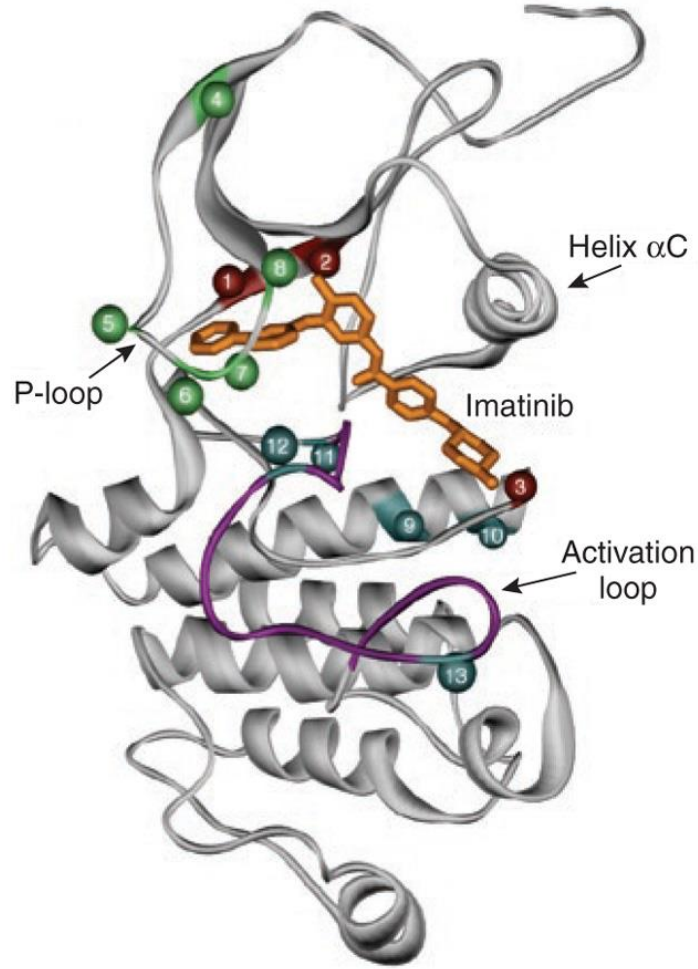


Figure 1: Pathways Activated by Bcr-Abl—Numerous signal transduction pathways are activated by the Bcr-Abl tyrosine kinase. Interrupting these pathways results in uncontrolled cell proliferation and reduced apoptosis. Understanding the pathophysiology of chronic myeloid leukemia has resulted in the development of novel drugs targeting Bcr-Abl tyrosine kinase and its associated pathways.

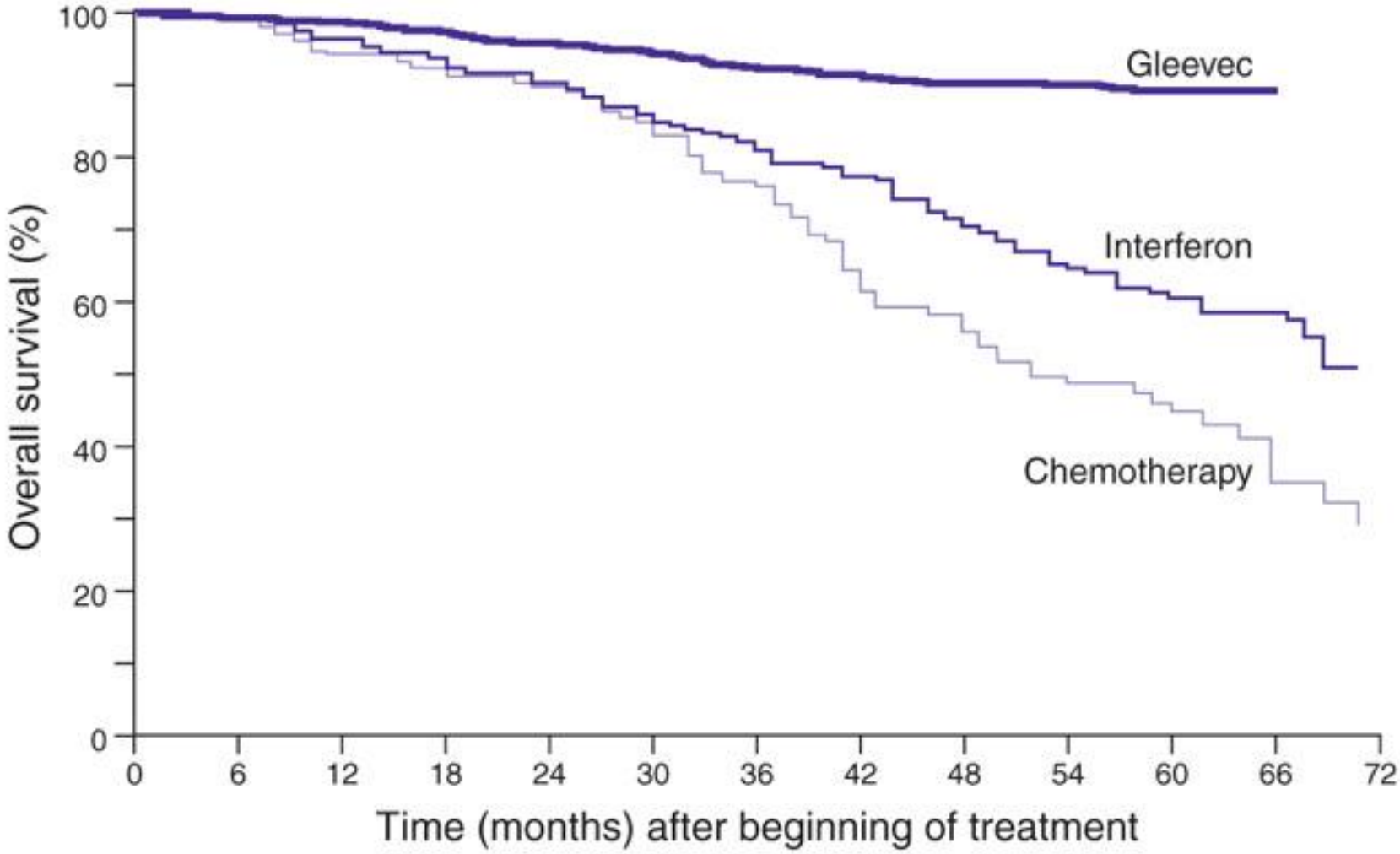
Ciba-Geigy started to develop ***inhibitors of tyrosinkinases*** (≈ 30 years ago)



Imatinib binds to BCR/ABL kinase instead of ATP



Přežití nemocných s CML při různé léčbě



„Targeted“ therapy – aimed at the biological cause of a disease

Imatinibem (Gleevec) suppresses cells belonging to mutated tumor clone – but does not get rid-off the body of the cause (all mutated cells).

Lasker prize for clinical research

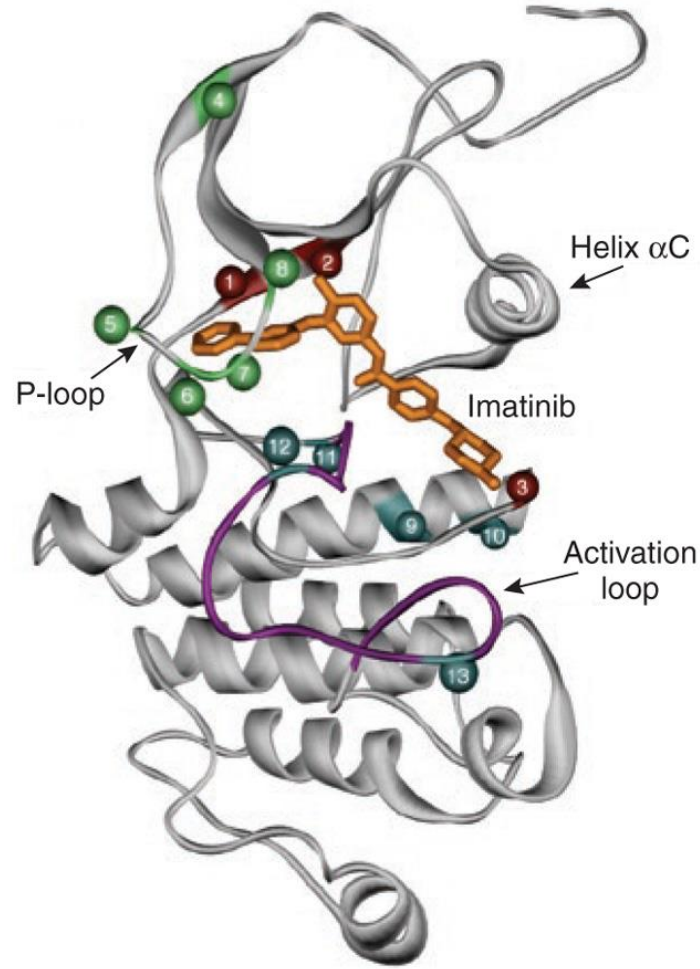
2009

Brian J. Druker

Nicholas Lydon

Charles L. Sawyers

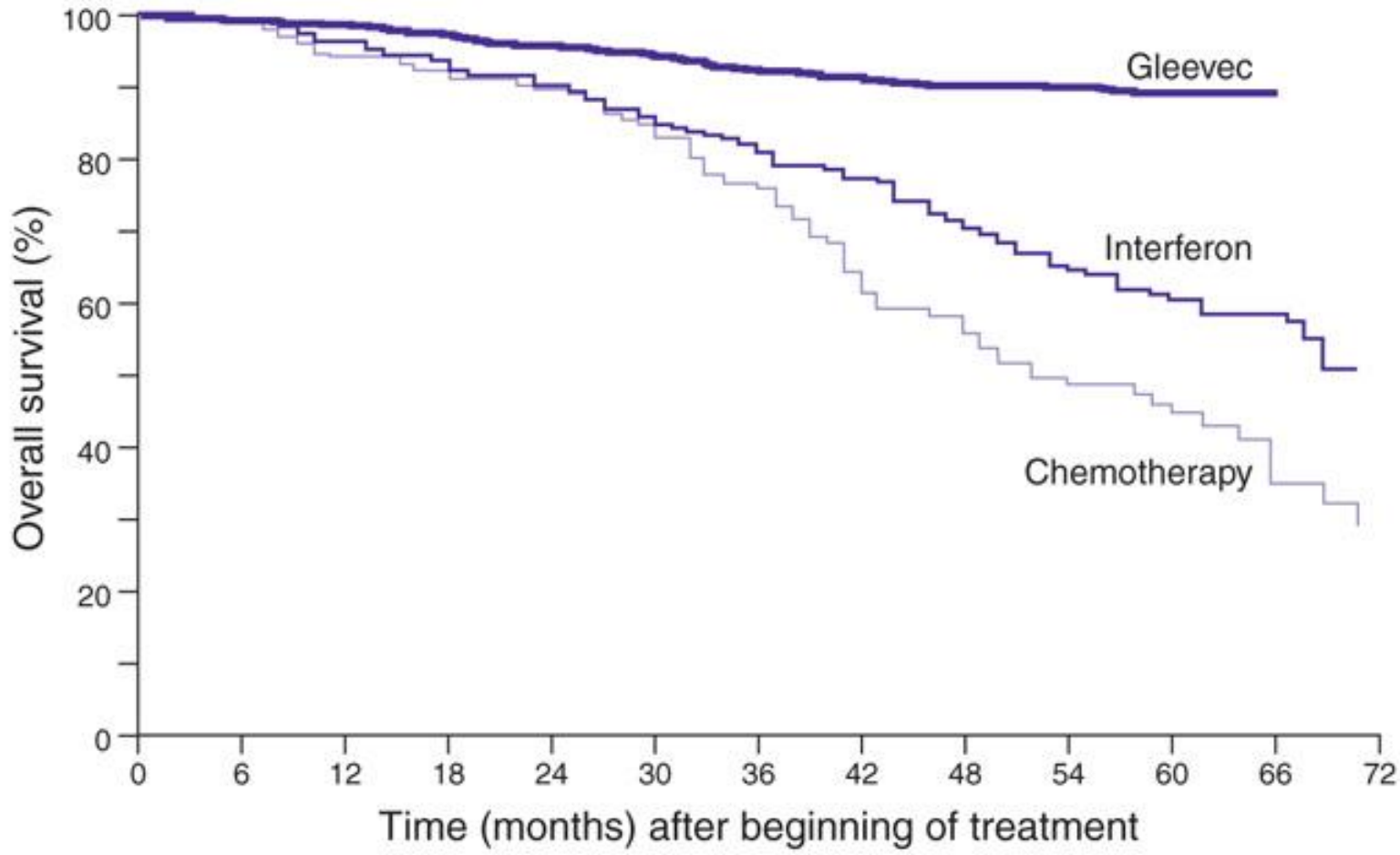
Mutations of the ABL kinase cause resistence against imatinib



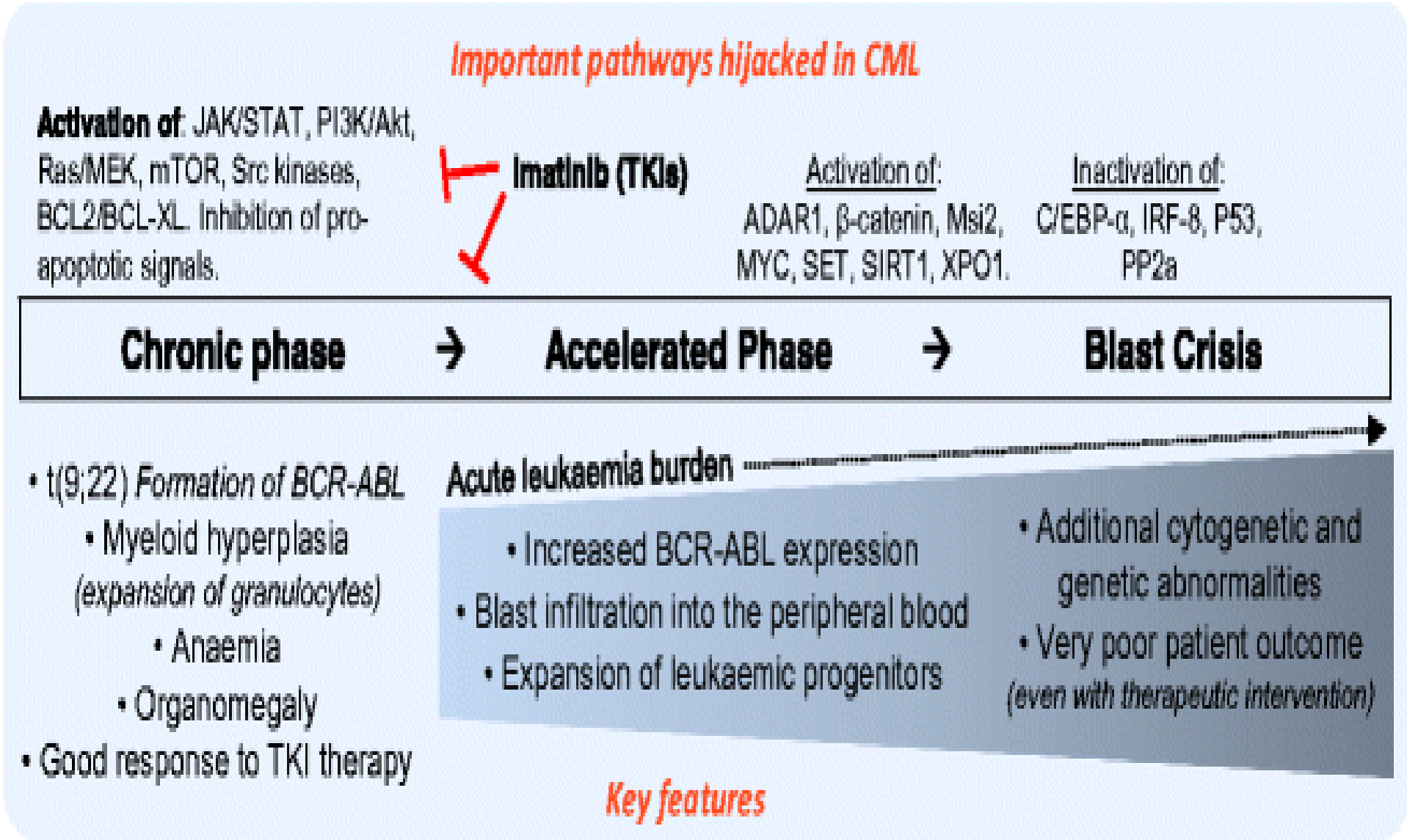
Possible outcomes of CML

- complete remission
- residual disease
- relaps
- resistance to therapy
- blastic conversion (AML)

Targeted therapy with imatinib is very effective



Important events in CML outlined



Acute myeloproliferative diseases

- **Acute myeloid leukemia (AML), several forms**

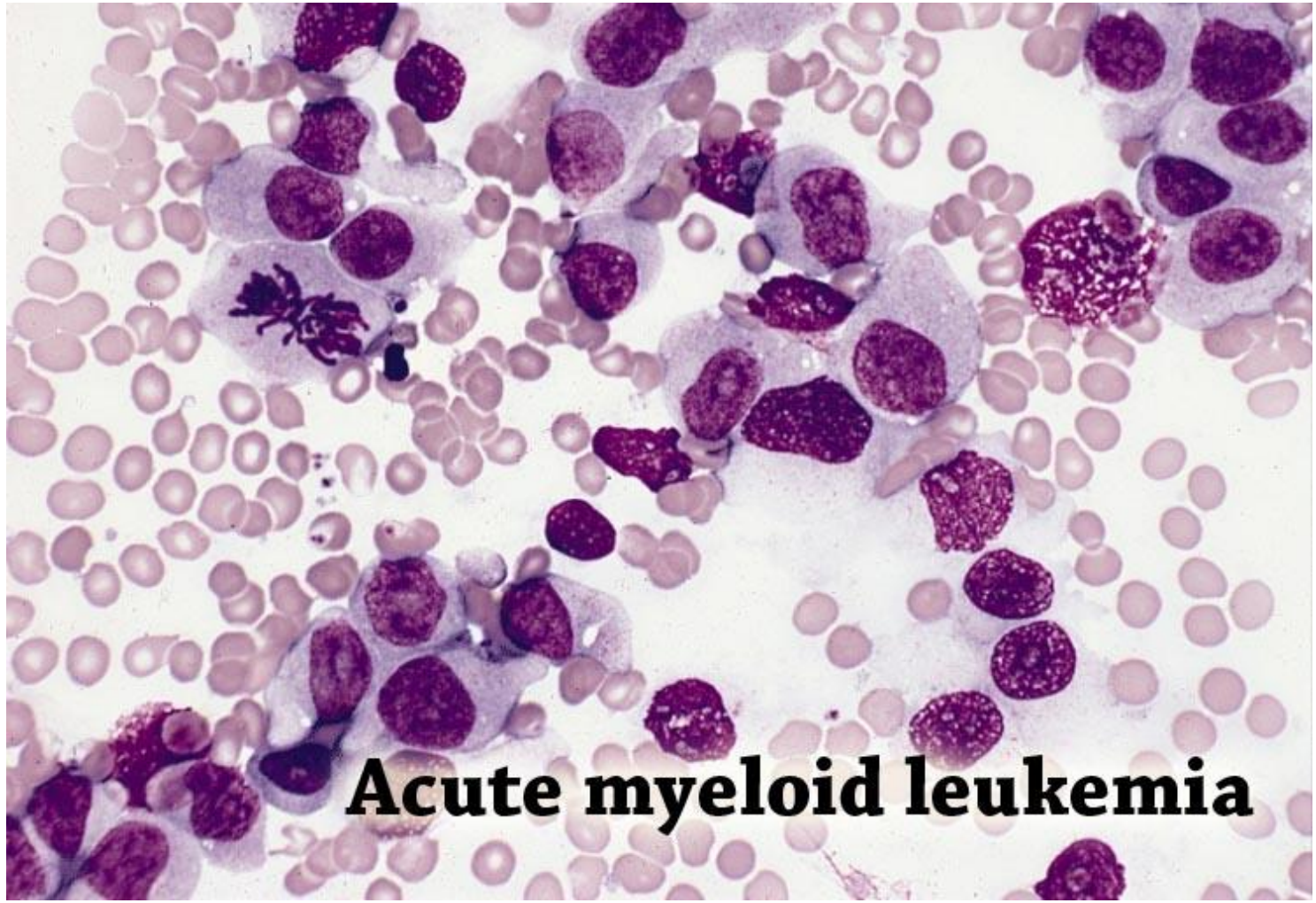
  (myelogenous, myeloblastic are synonyms to **myeloid)**

- **Acute lymphocytic leukemia (ALL) … is lymphoproliferative disease**

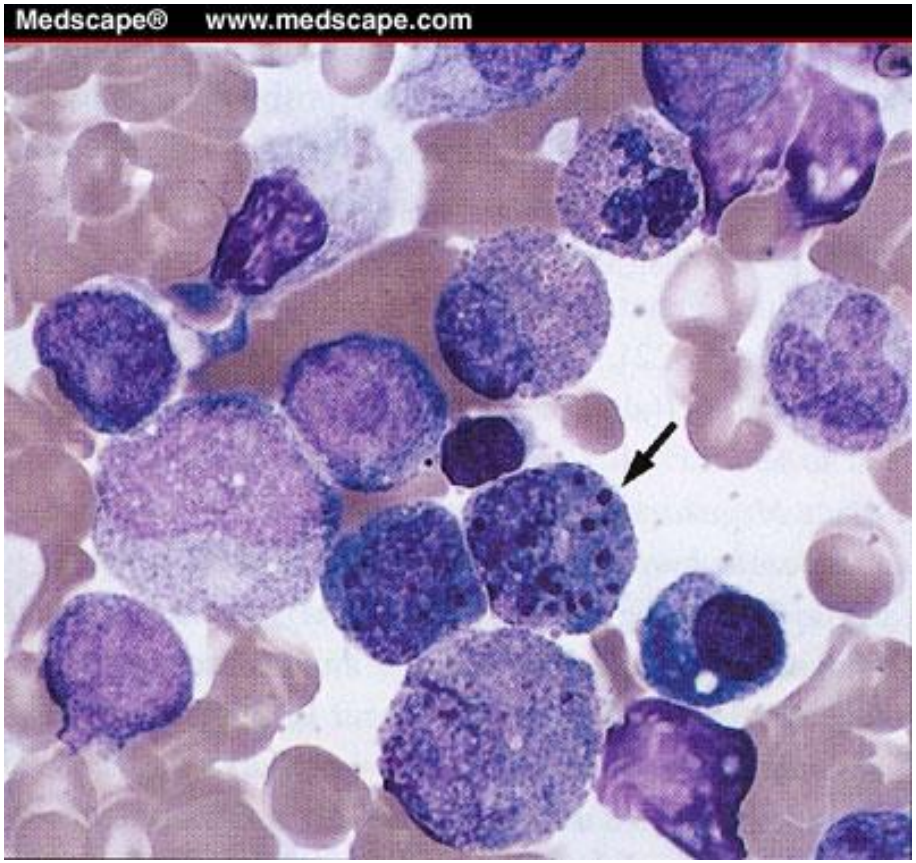
  (lymphoblastic is a synonym to **lymphocytic)**

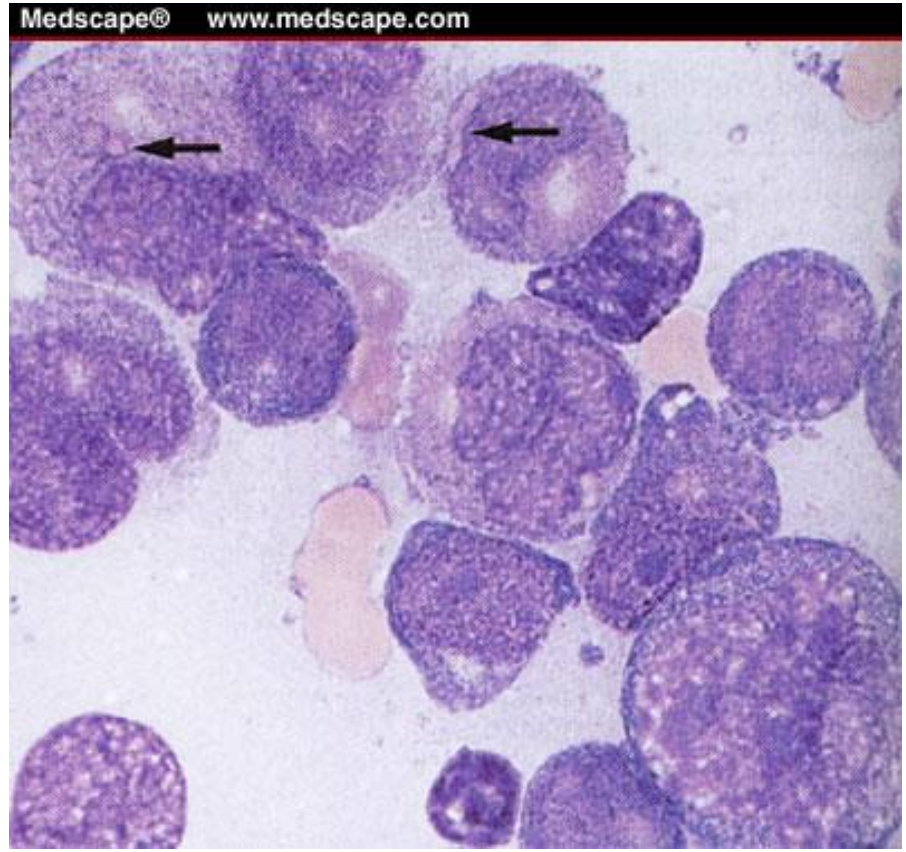
Acute myeloid leukemia (AML)

Leukemic blasts present in blood

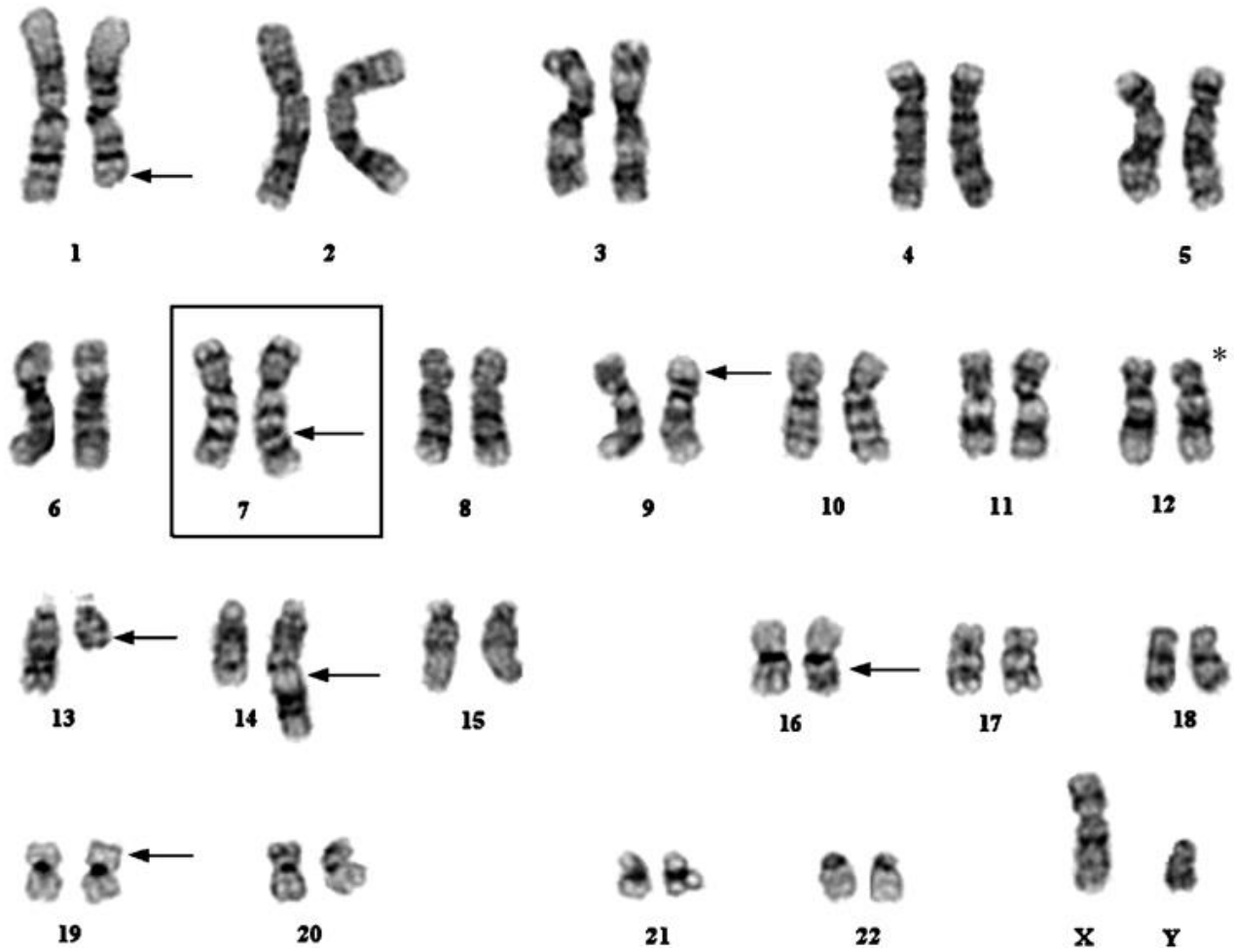


Leukemic blasts are present in bone marrow





Karyotype of the major clone from the relapse **acute myeloid leukemia** (**AML**)



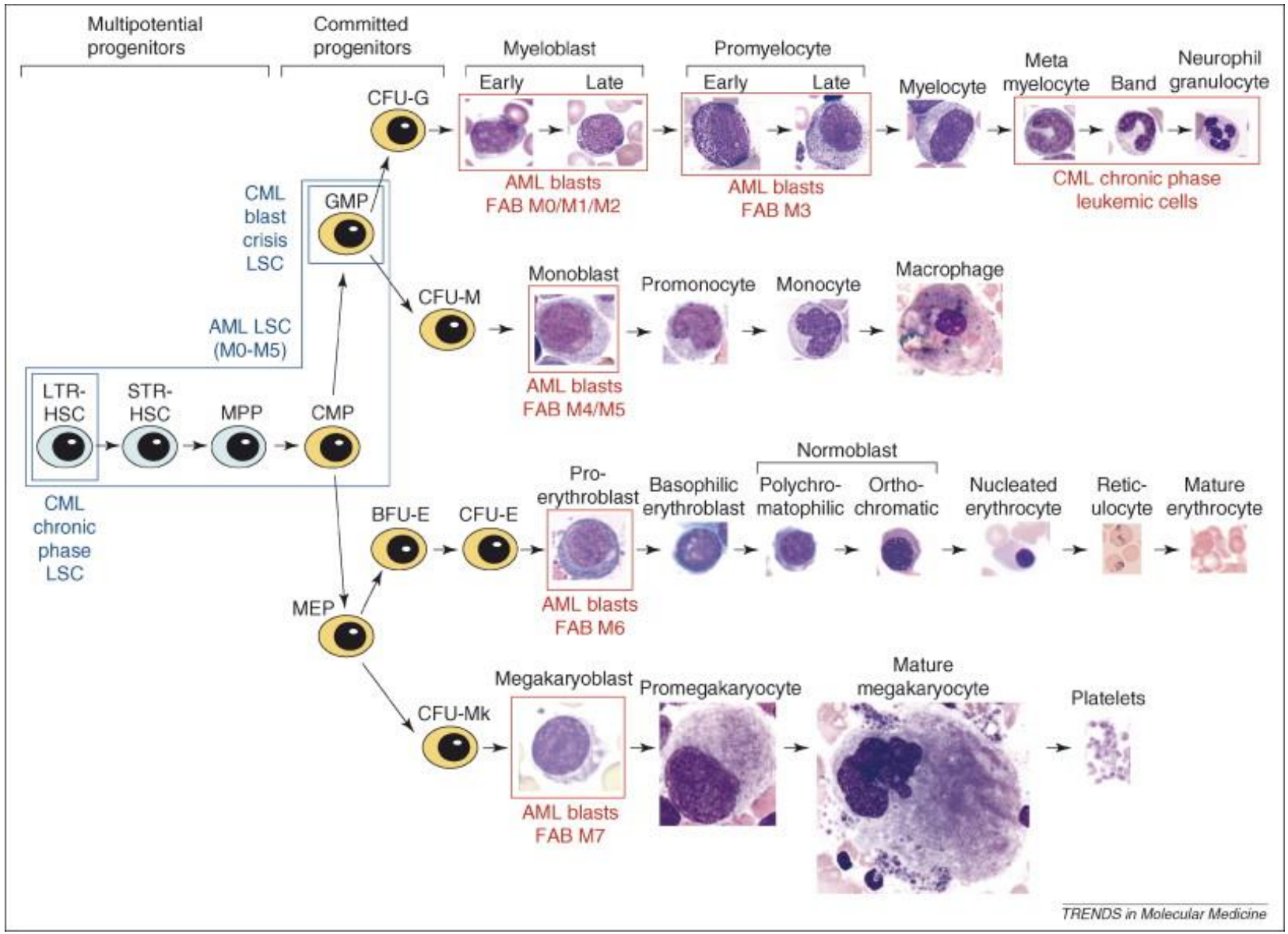
Acute Myeloid Leukemia (AML)- 8 clinical forms

Table 2 | **French–American–British (FAB) classification of AML**

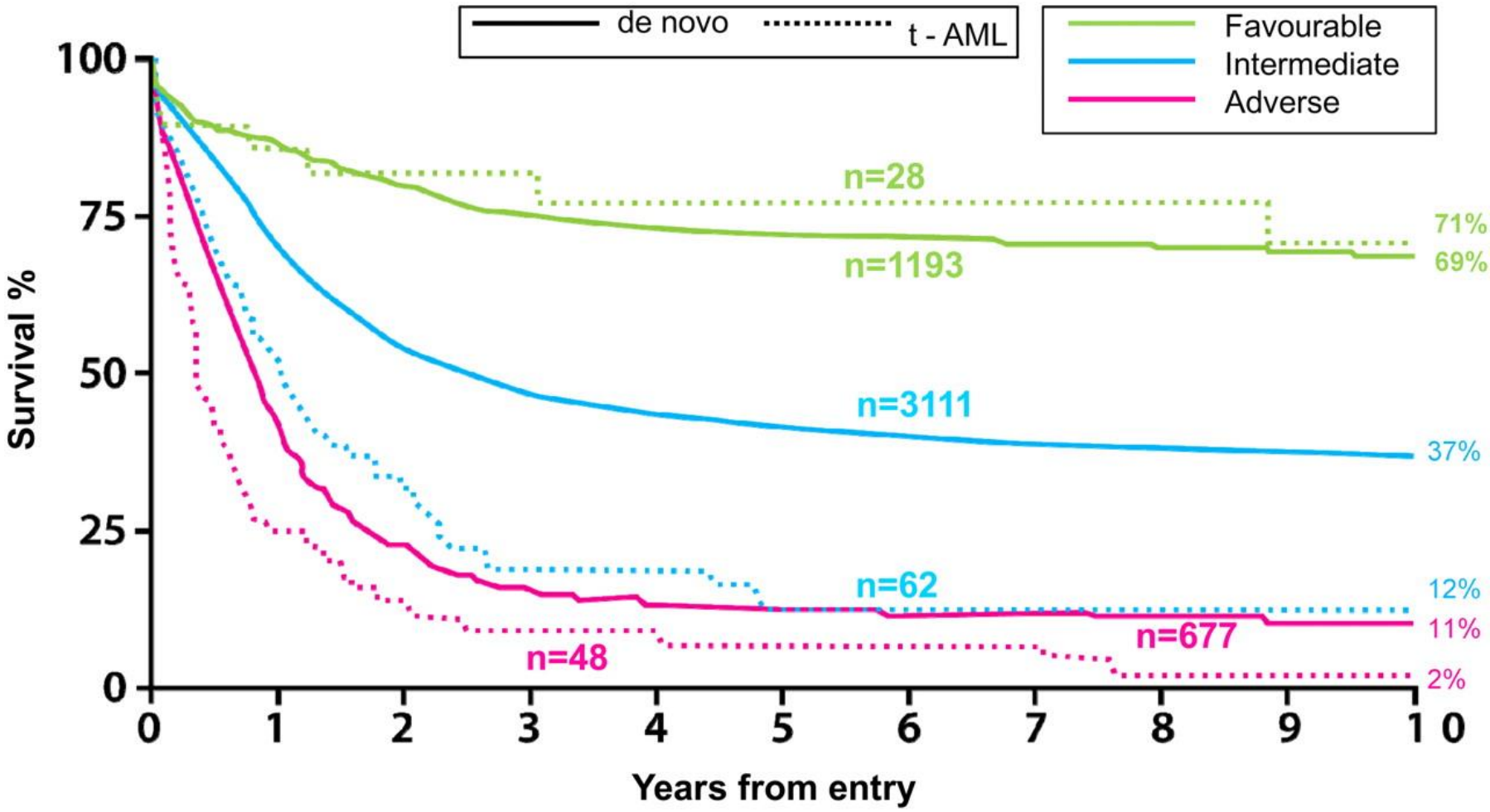
FAB subtype	Description	Comments
M0	Undifferentiated	Myeloperoxidase negative; myeloid markers positive
M1	Myeloblastic without maturation	Some evidence of granulocytic differentiation
M2	Myeloblastic with maturation	Maturation at or beyond the promyelocytic stage of differentiation; can be divided into those with t(8;21) AML1–ETO fusion and those without
M3	Promyelocytic	APL; most cases have t(15;17) PML–RARα or another translocation involving RARα
M4	Myelomonocytic	
$M4_{Eo}$	Myelomonocytic with bone-marrow eosinophilia	Characterized by inversion of chomosome 16 involving CBFβ, which normally forms a heterodimer with AML1
M5	Monocytic	
M6	Erythroleukaemia	
M7	Megakaryoblastic	GATA1 mutations in those associated with Down's syndrome

AML1, acute myeloid leukaemia 1; APL, acute promyelocytic leukaemia; PML, promyelocytic leukaemia; RARα, retinoic-acid receptor-α. Modified from REF. 65.

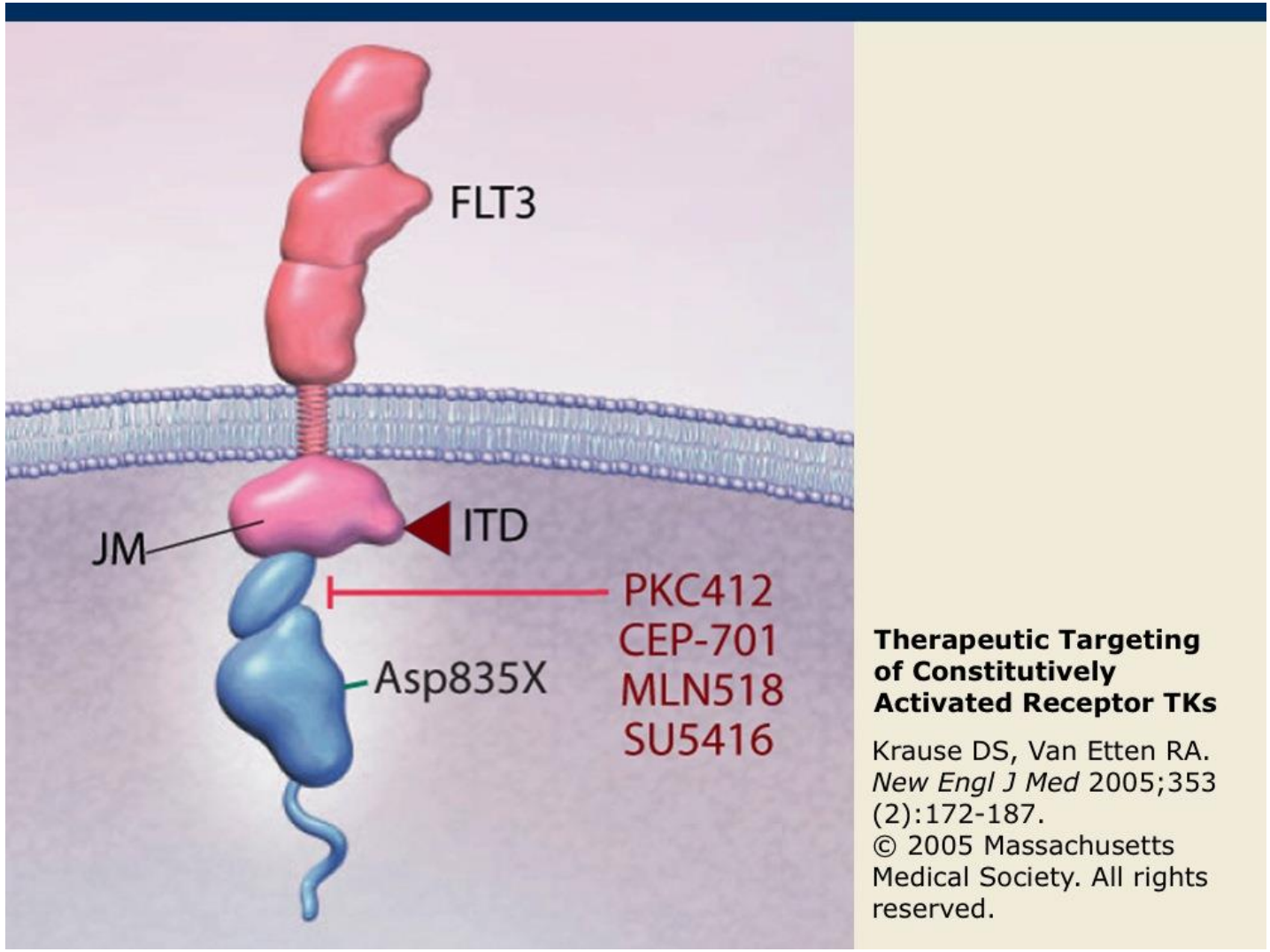
AML subgroups – FAB classification



Different AML types differ in prognosis



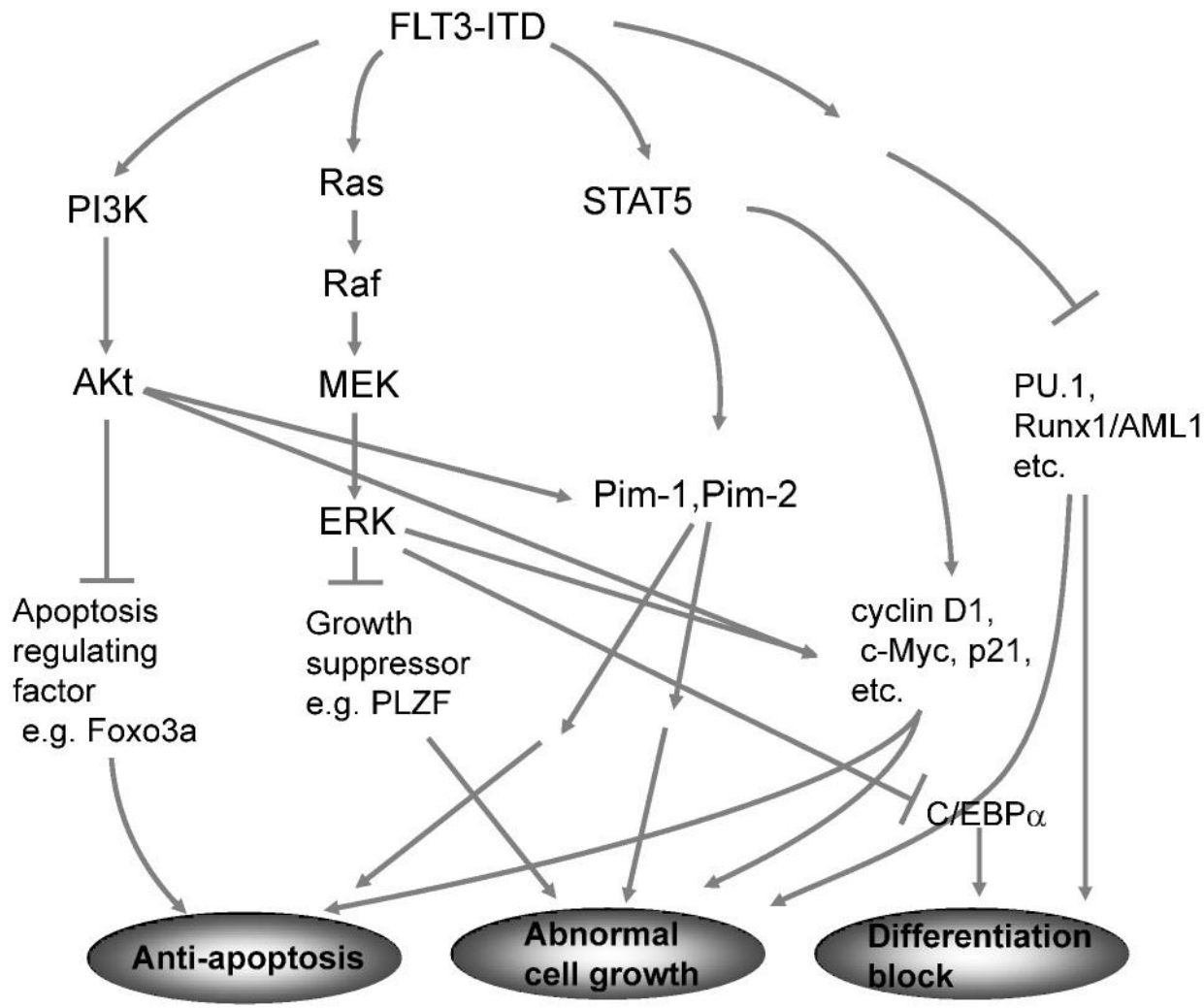
Flt3 receptor mutated in 40% of AML cases



Therapeutic Targeting of Constitutively Activated Receptor TKs

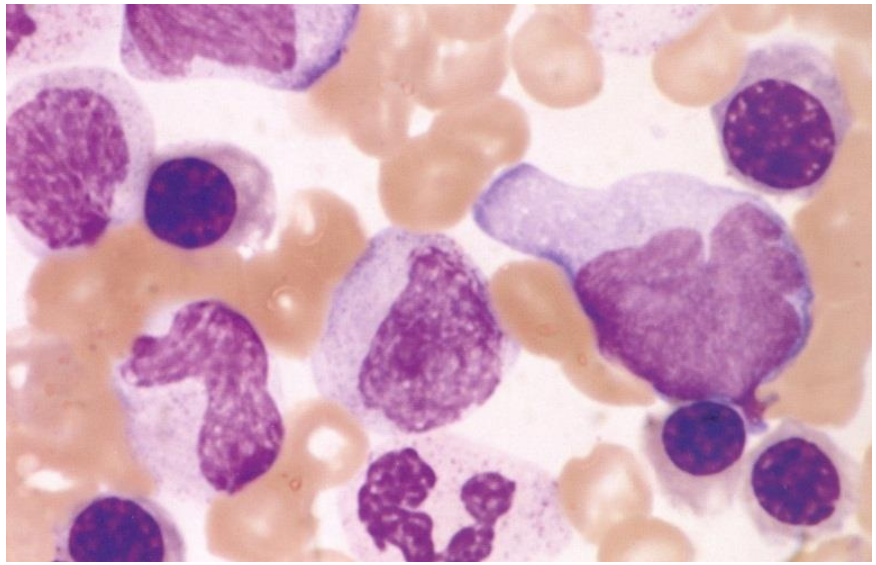
Krause DS, Van Etten RA. *New Engl J Med* 2005;353 (2):172-187.

FLT3-ITD (internal tandem duplication)

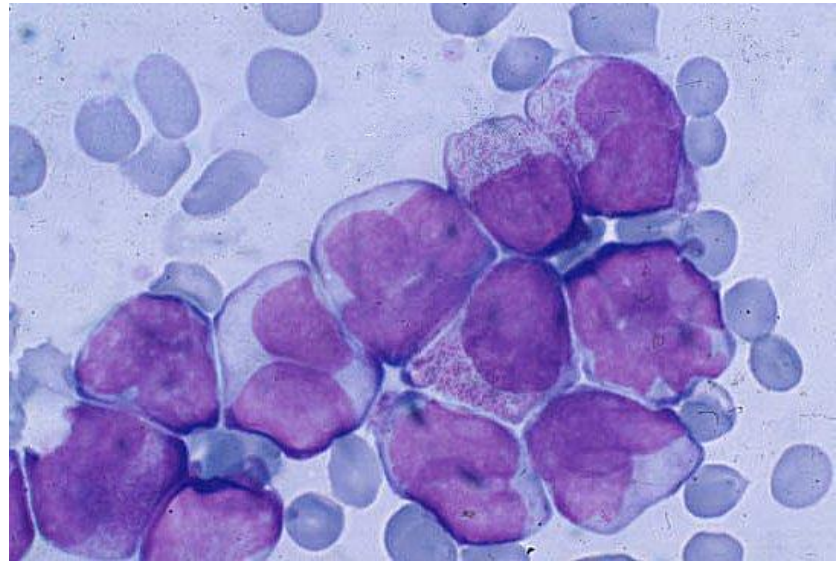


Acute promyelocytic leukemia (APL) _ M3

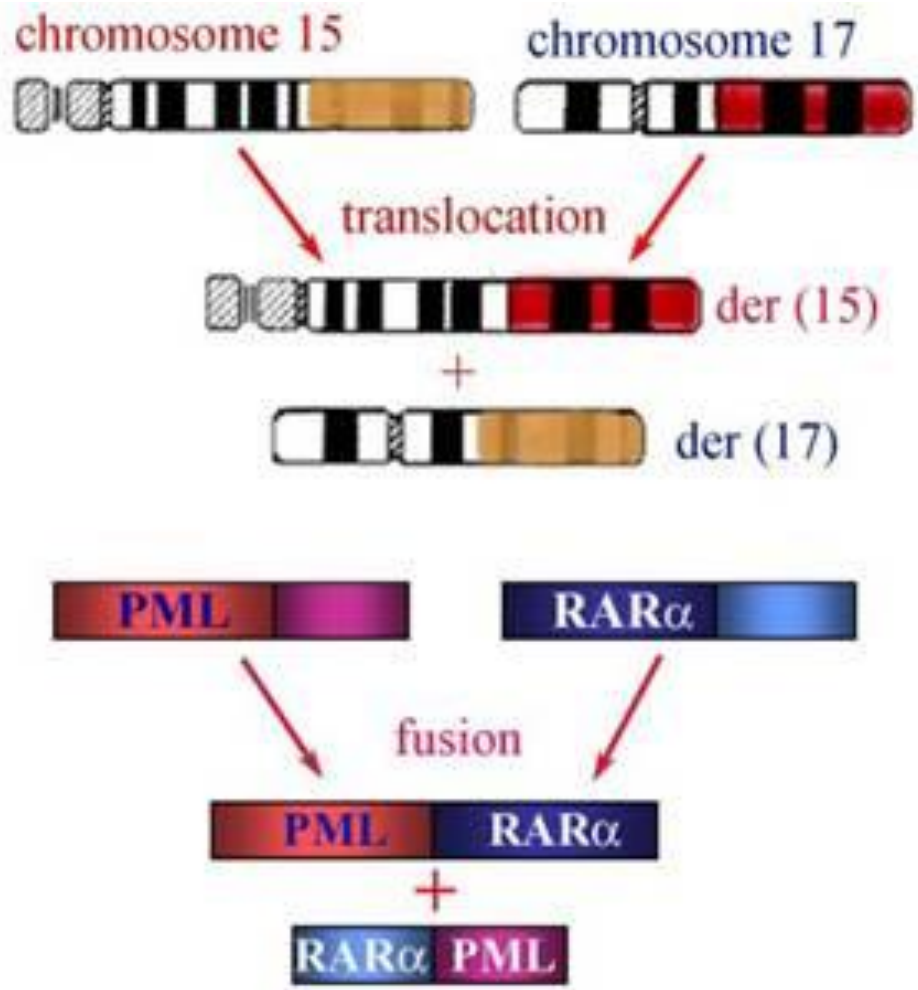
Normal bone marrow



APL – promyelocytes do not mature into granulocytes



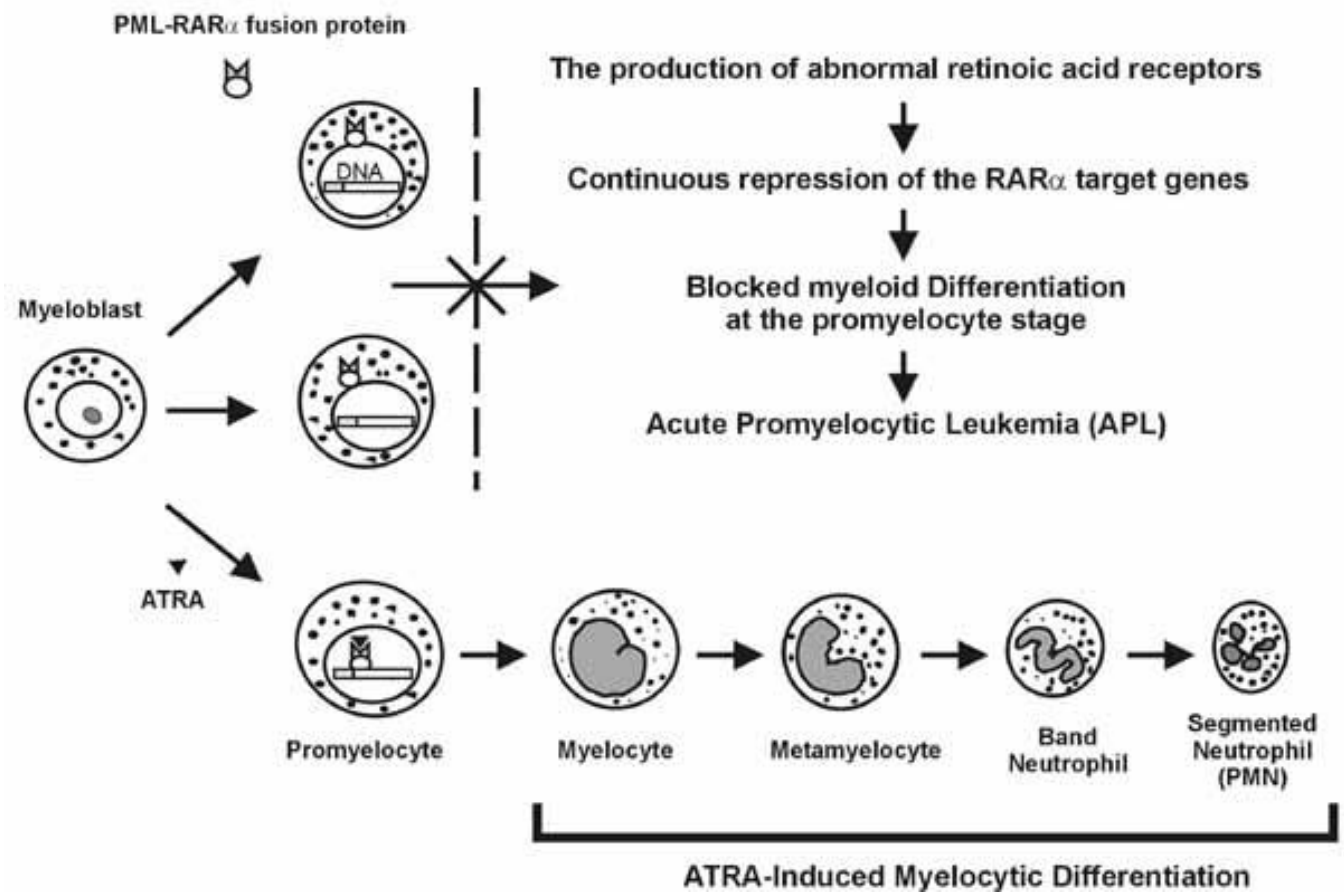
Chromosomal translocation in APL results in abnormal – **PML-RARα protein**



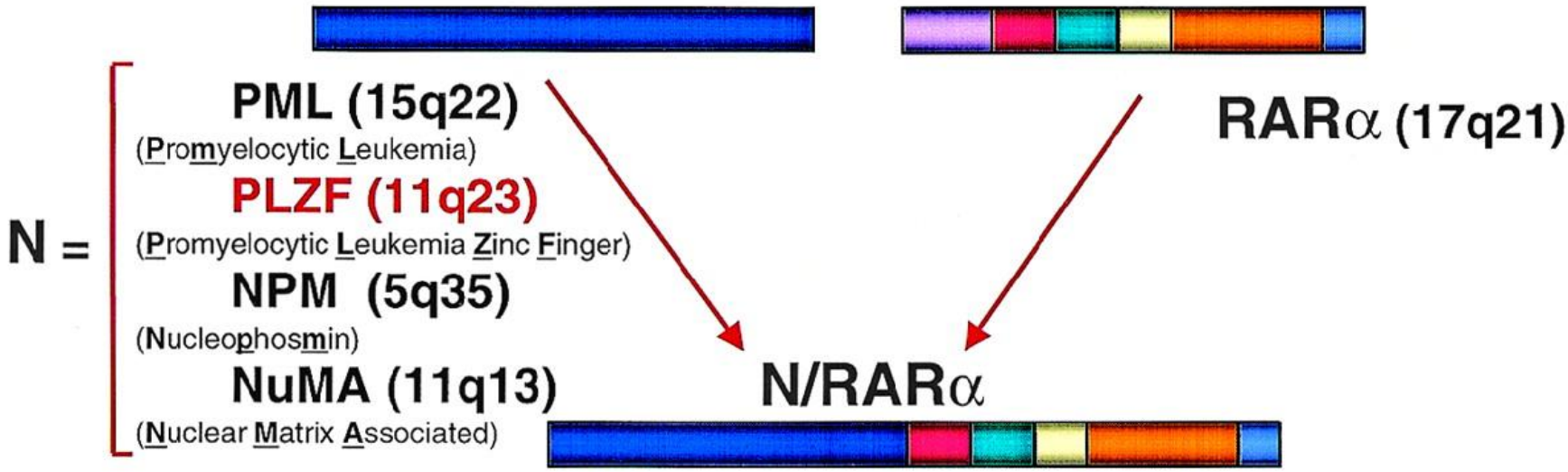
Acute promyelocytic leukemia (APL)_M3

ATRA = all-trans retinoic acid overcomes defect of RARα protein and induces maturation of pathological promyelocytes =

„targeted therapy“ induce remission of the disease



Molecular Pathogenesis of APL



Two Syndromes

- Retinoic Acid Responsive
  PML, NPM, NuMA
- Non-Responsive to RA
  PLZF

Transplantation of hematopoietic stem cells („Bone Marrow Transplantation“)

is the only

„causative therapy“ for AML

END

OF THE LECTURE