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# Progress in the Treatment of Chronic Myeloid Leukemia

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Stem Cell Transplantation
Banner MD Anderson Cancer Center

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# Objectives

- Discuss the abnormalities in hematopoiesis found in patients with CML
- Discuss early therapies for CML
- Discuss more recent advances in the biology and treatment of CML

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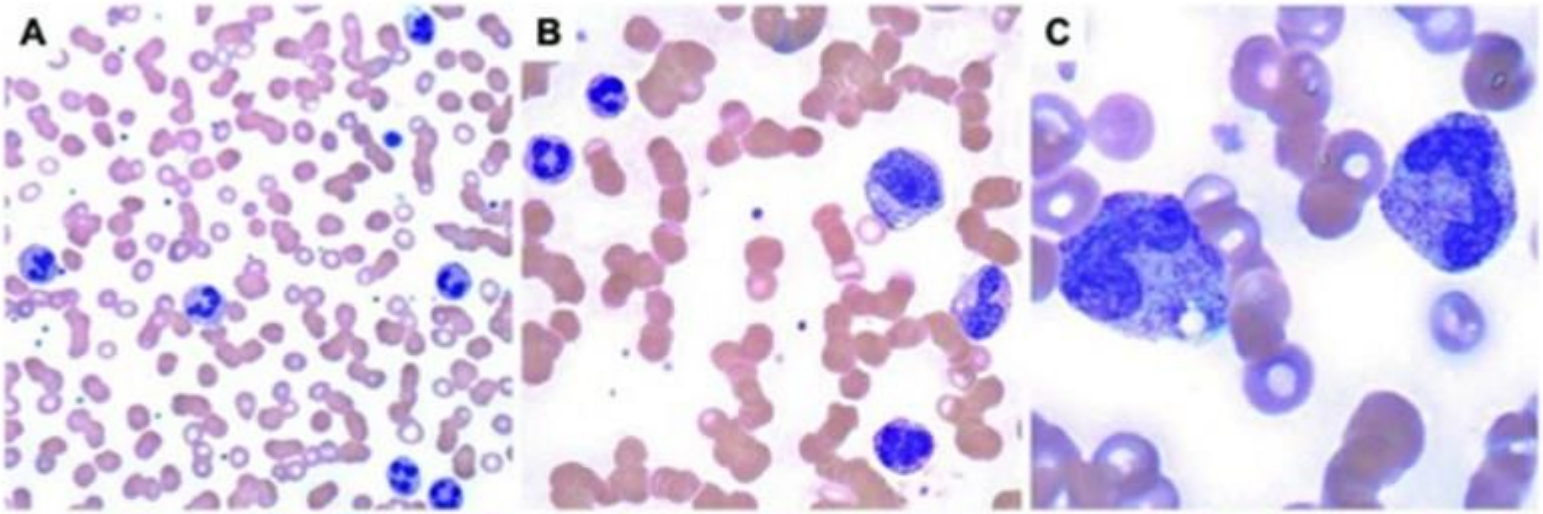
# 56yo man admitted with abdominal pain and leukocytosis

- 4 days of abdominal pain and diarrhea
- Recently discharged from the hospital
- Temp 100.8  HR 110
- Abdomen diffusely tender to palpation




George T I Hematology 2012;2012:475-484

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# What is the most likely diagnosis?

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# 56yo admitted with abdominal pain and leukocytosis

- 3 months of gradually increasing abdominal pain, L>R
- Temp 100.8  HR 110
- Abdomen TTP in the LUQ, spleen palpable 8cm below the costal margin

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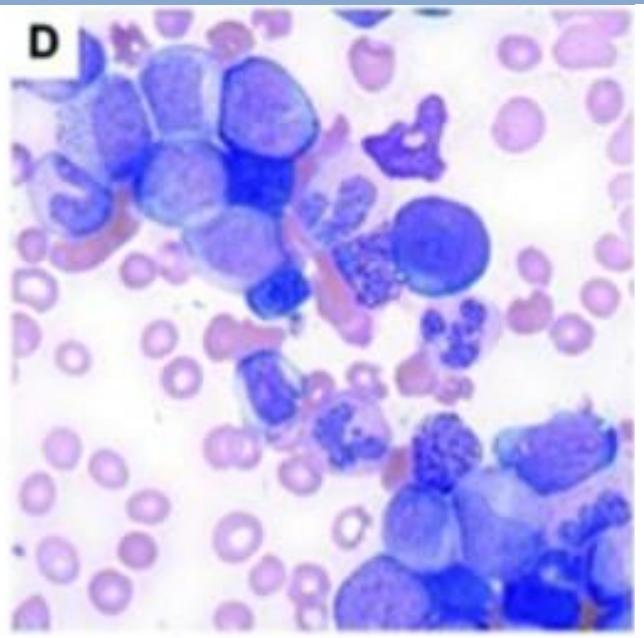
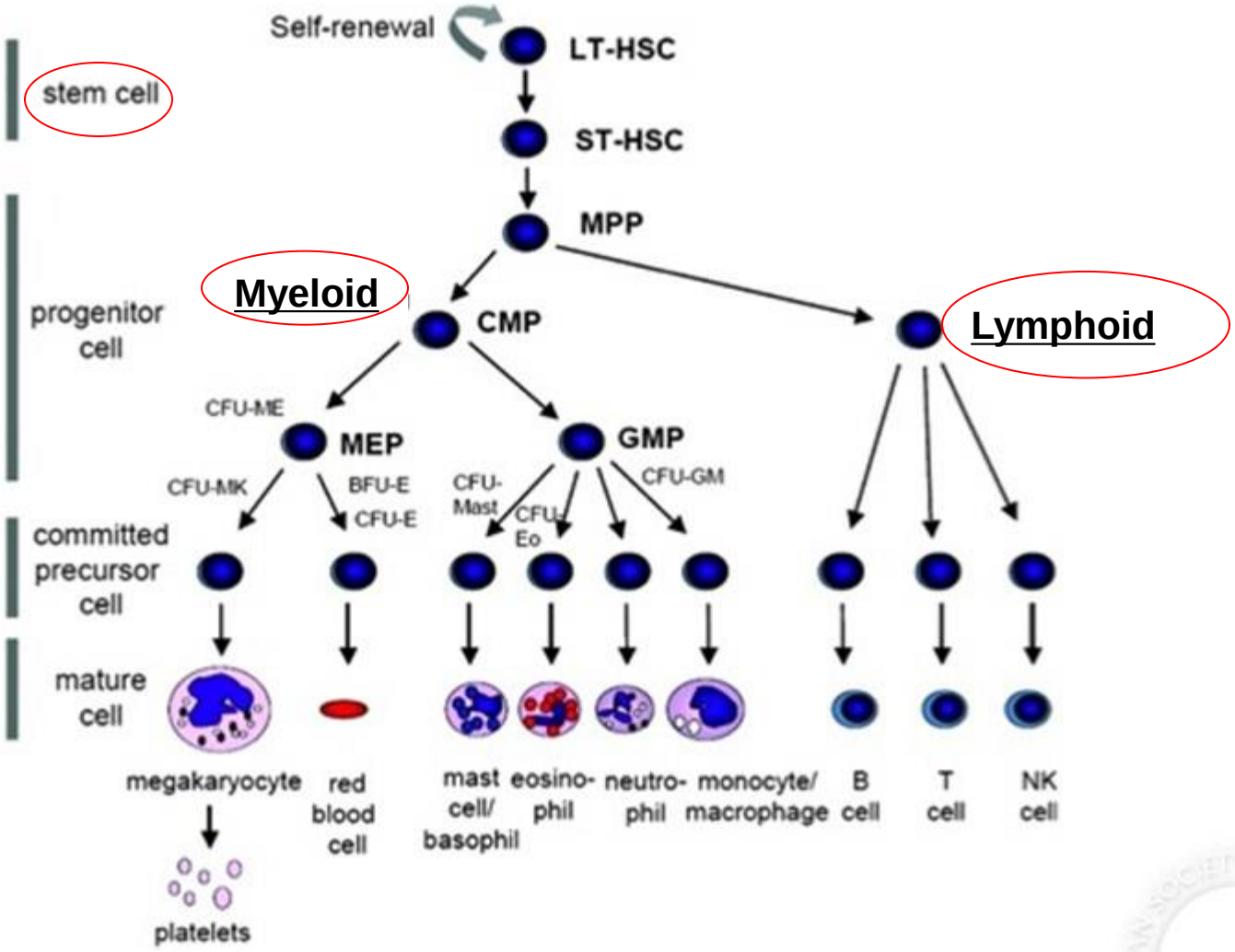
# What is the most likely diagnosis?




George T I Hematology 2012;2012:475-484

# Figure 12-3 Classical hierarchal map of hematopoietic development




Cantor, A. B. et al. ASH-SAP 2010;2010:331-372

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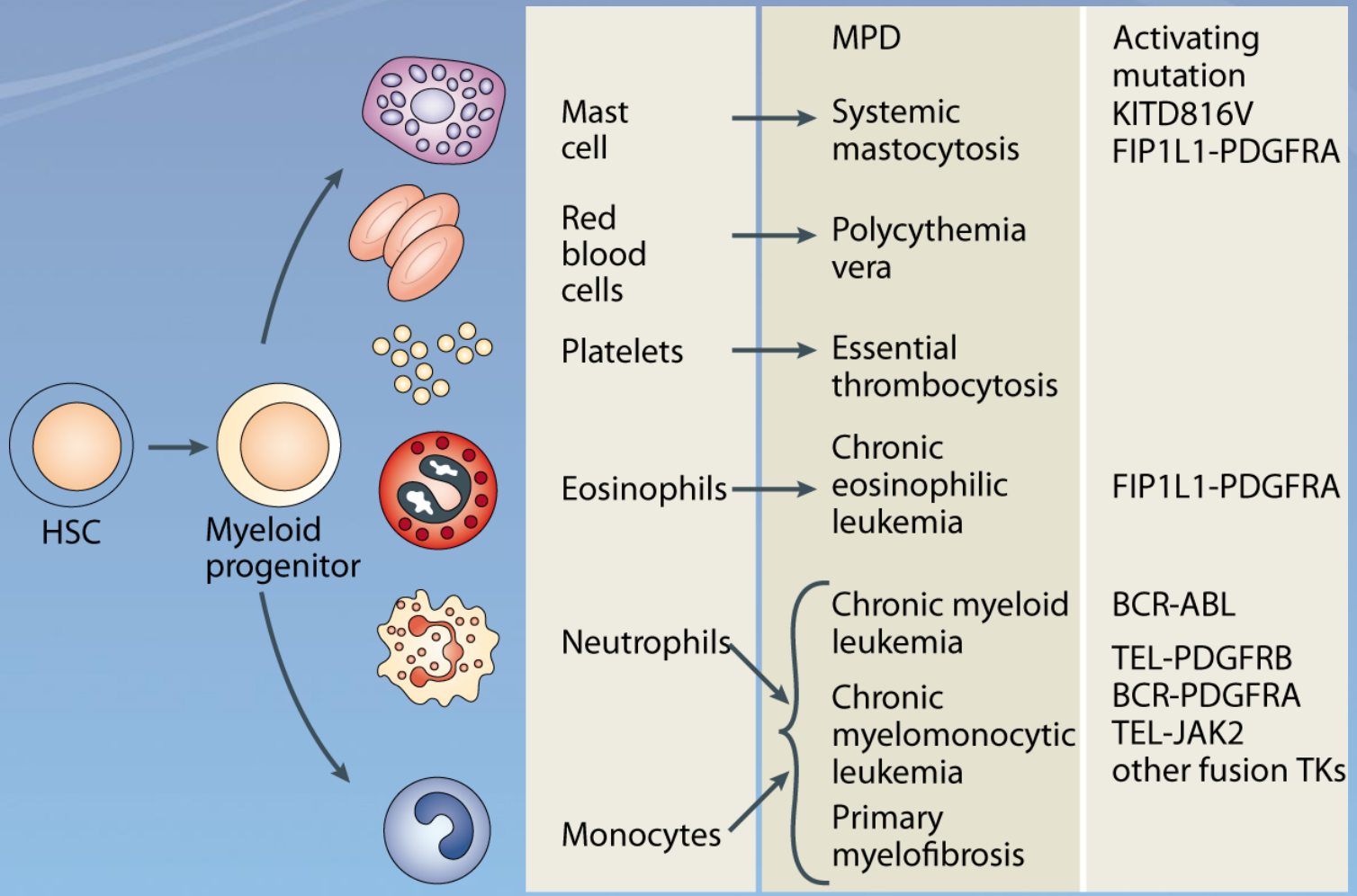
# Myeloproliferative Disorders

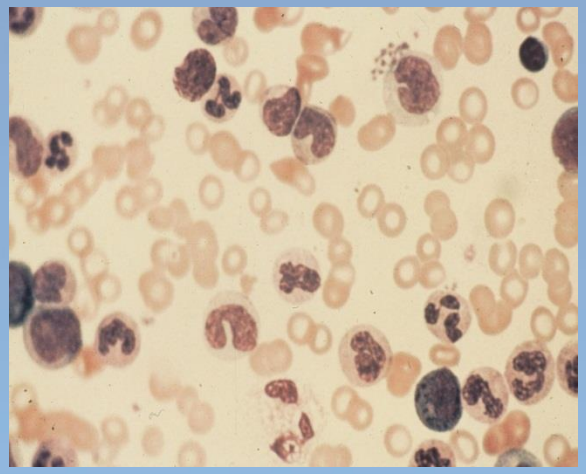



Nature Reviews | Cancer

# Myeloid Malignancies

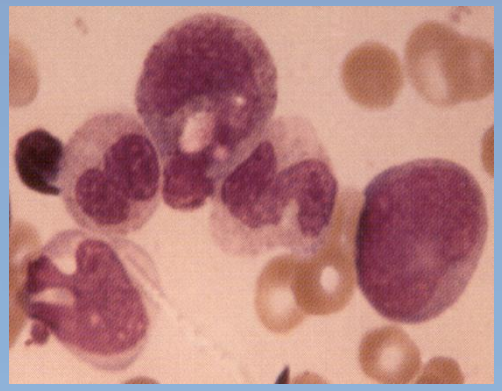
## Myeloproliferative neoplasms

- enhanced proliferation/survival
- normal differentiation
- high white blood cell count
- may progress to AML



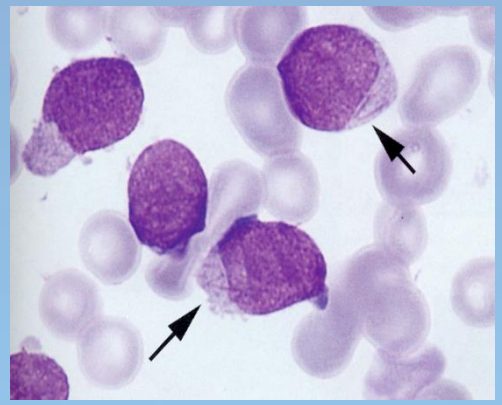
## Myelodysplastic syndrome

- impaired differentiation
- low blood cell counts
- may progress to AML



## Acute myeloid leukemia (AML)

- enhanced proliferation and survival
- impaired differentiation
- limitless self-renewal



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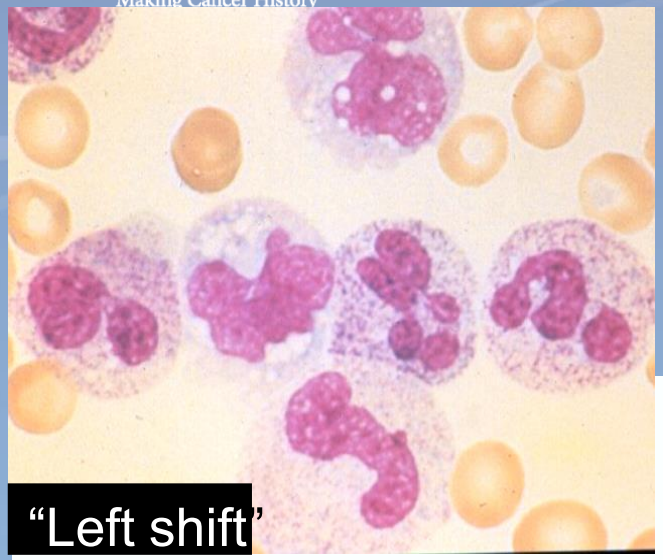
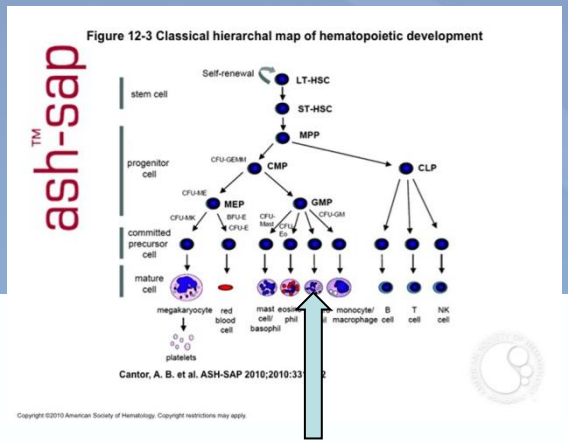
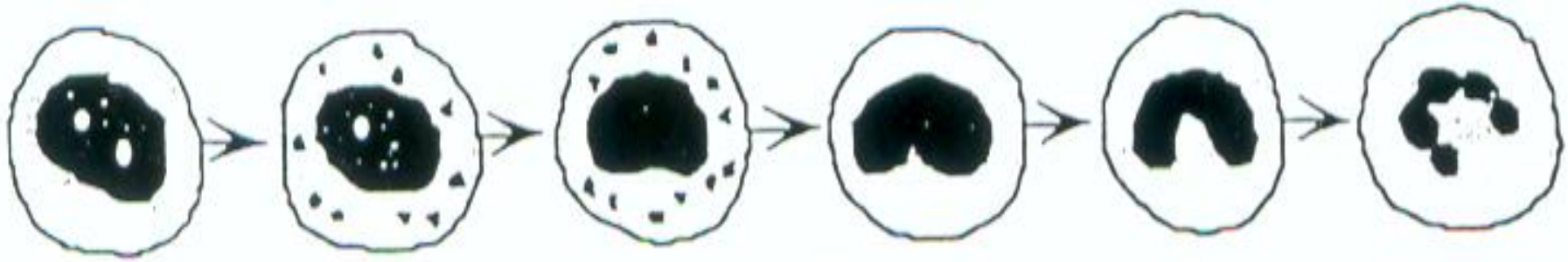
# Myeloid Precursors



"Left shift"



**Myeloblast Promyelocyte Myelocyte Metamyelocyte Band Neutrophil**

**"Left Shift"**

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# CML clinical features

- ~4500 new US cases per year
- Median age at presentation: 53 years
- 60% men
- Disease is clinically divided into three phases
  - Chronic phase
  - Accelerated phase
  - Blast crisis (lymphoid (ALL) or myeloid (AML))

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# CML Clinical Features

- **Disease is clinically divided into three phases**
  - **Chronic phase – can be managed/controlled**
- **Life-threatening**
  - **Accelerated phase**
  - **Blast crisis (lymphoid or myeloid)**
- **Goal of treatment is to prevent transformation/progression**

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# CML Clinical Features

- Approximately 50% have no symptoms at diagnosis, just abnormal counts
- If present, common symptoms include fatigue, night sweats, weight loss, abdominal discomfort, fullness after a small meal
- Uncommonly, symptoms related to increased blood viscosity (headache, shortness of breath)

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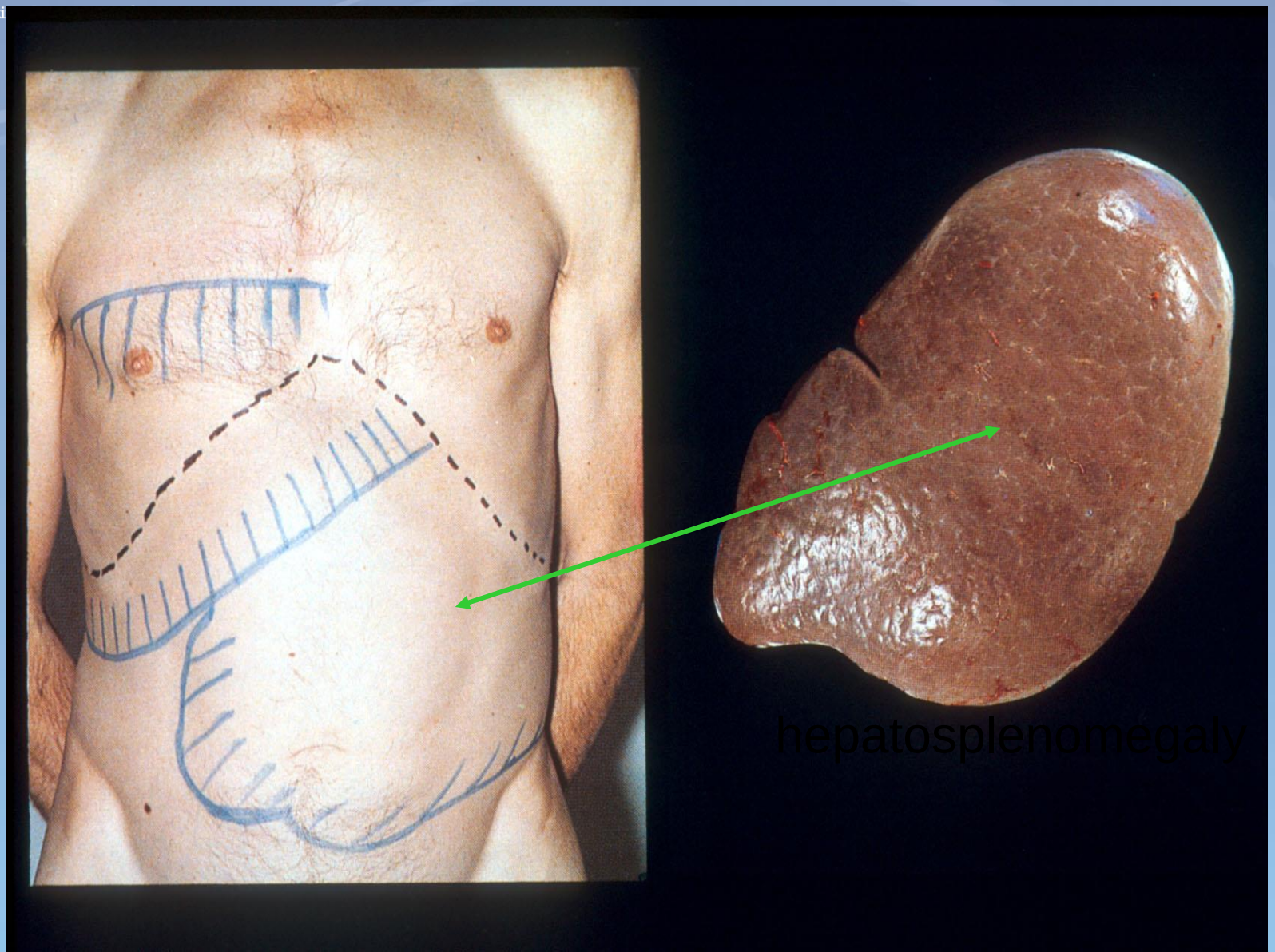
# Hepatosplenomegaly



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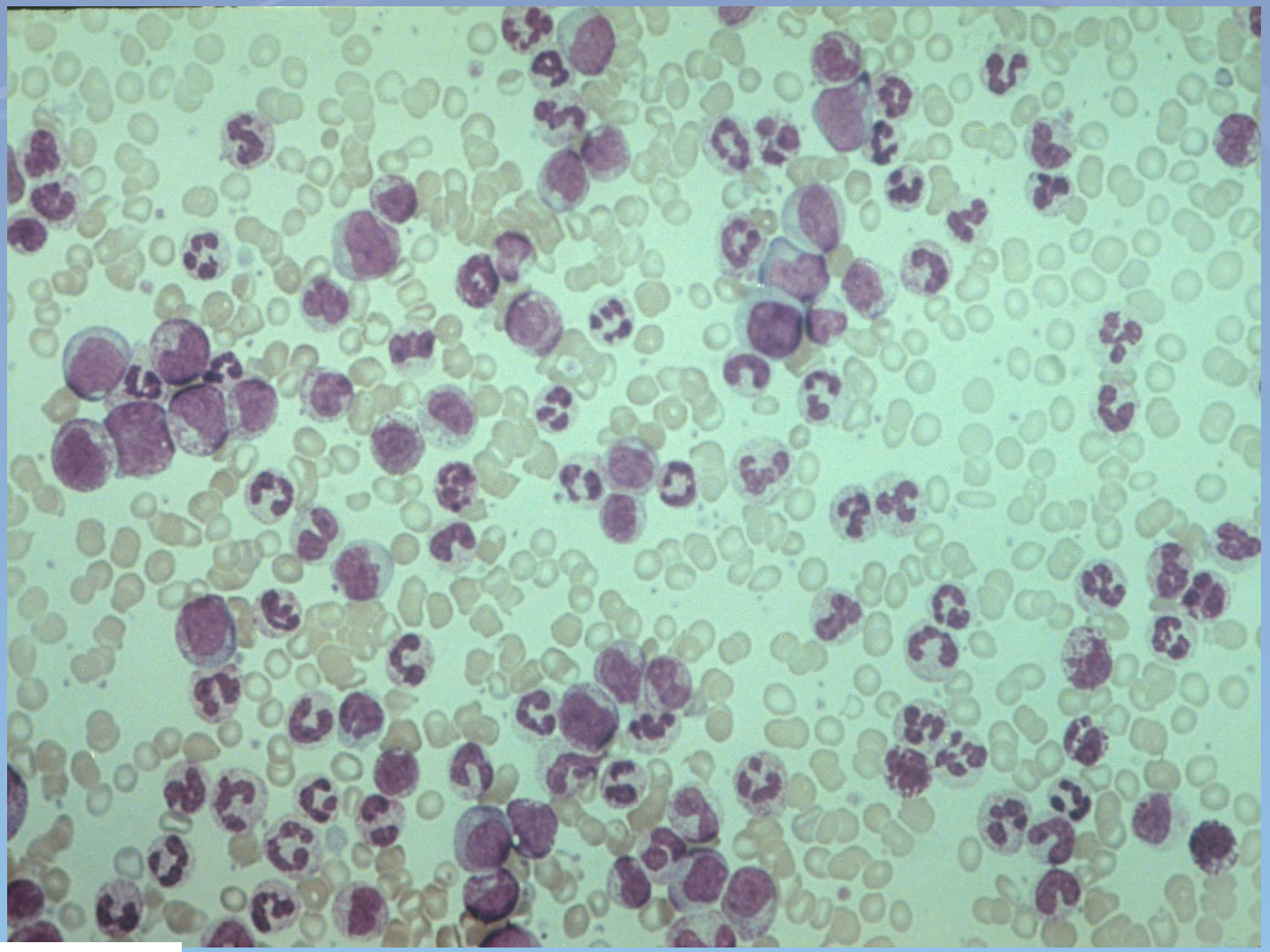
# Chronic Myeloid Leukemia

## Peripheral blood smear



American Board of Internal Medicine®

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# CML - blast phase

- failure of normal blood cell development
- responds poorly to medical intervention
  - bleeding, infections, anemia common
- median survival historically 3-9 months

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# CML - chronic phase

- 85-90 percent of newly diagnosed CML patients are in chronic phase
- Prior to 2000, median duration of chronic phase was ~4-6 years
- Interventions can lead to durable responses in chronic phase

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# CML – How is the Diagnosis Made?

- Distinguish from other causes of a Leukocytosis
  - Neutrophilia - infection, myelofibrosis, CML
  - Lymphocytosis – CLL
  - Monocytosis – CMML
  - Blasts – AML, ALL
  - Basophilia – CML
  - Eosinophilia – CTD, allergic

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# CML – How is the Diagnosis Made?

- Distinguish from other causes of a Leukocytosis
  - Must identify that it is clonal

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# Detecting Mutations: Karyotype Analysis

Direct inspection of the chromosomes achieved by staining.
(arrested metaphase cells)

## Good for:

Gross chromosomal abnormalities such as massive amplifications, deletions, translocations, inversions, or numerical aberrations.

## Typical Protocol:

- Treat white blood cells with a mitosis stimulating agent (phytohemagglutinin)
- After cells begin to divide, arrest cells with Colcemid
- Lyse cells with a hypotonic solution of KCl
- Spread chromosomes onto a microscope slide and apply fixative
- Stain with Giemsa and visualize

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# Metaphase Spread

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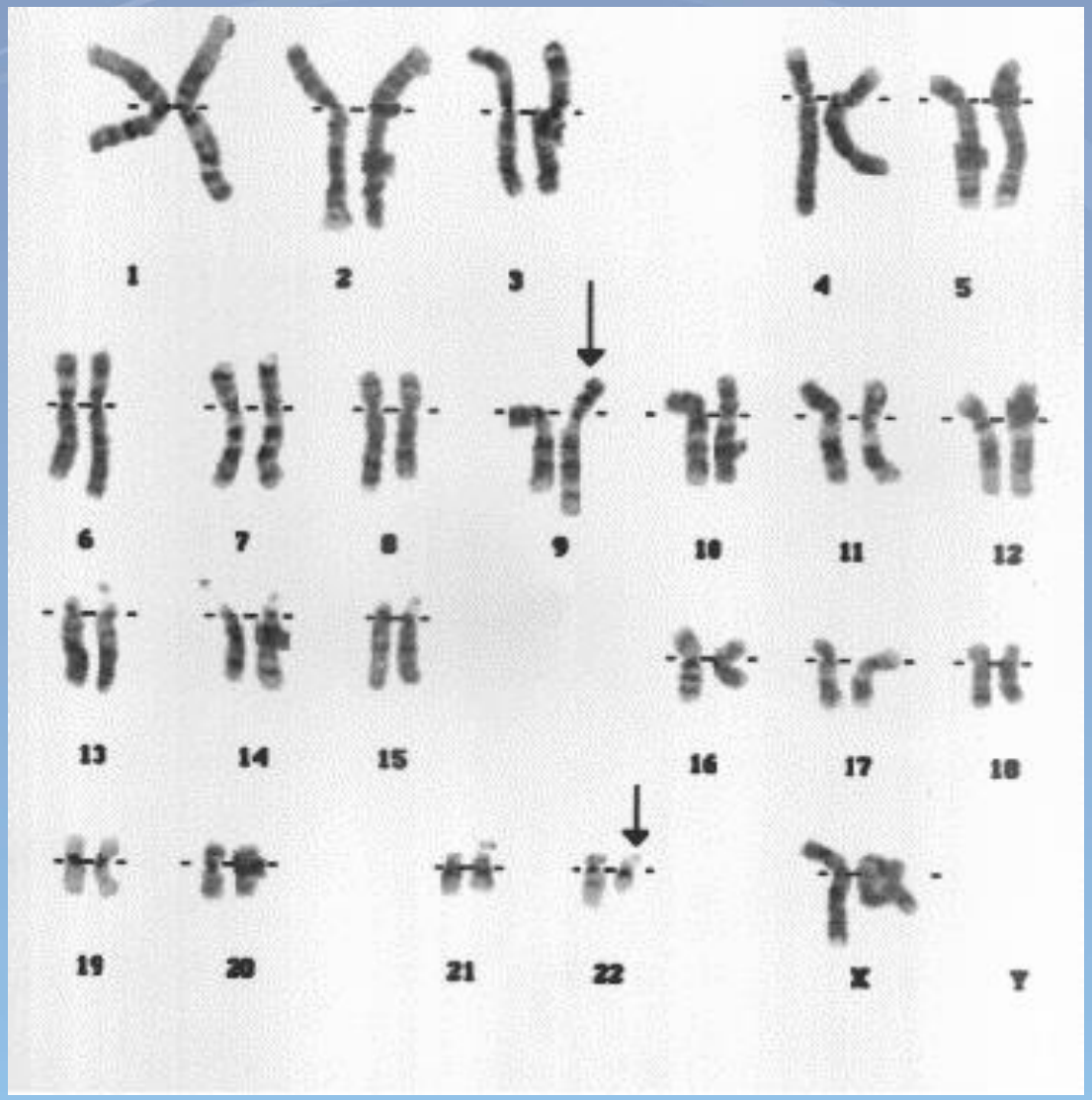
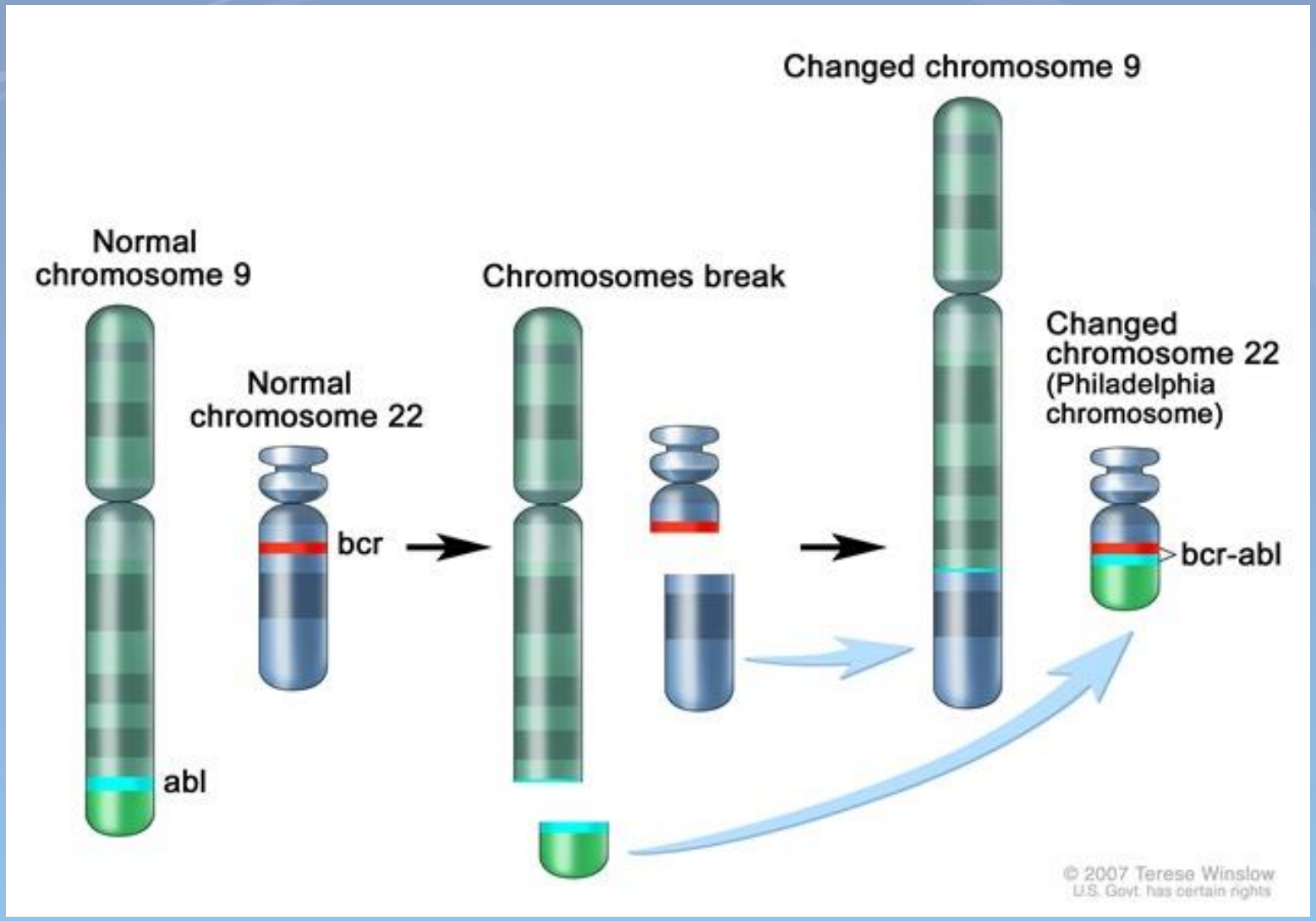
# First hint at the cause of CML:




46,XX,t(9;22)(q34;q11.2) a.k.a. “the Philadelphia chromosome”

Forrest et al, 2008; Bakshi et al, 2008; Image courtesy of Larry Beauregard, Jr., PhD.

# CML BCR/ABL1 fusion gene, the result of a genomic rearrangement



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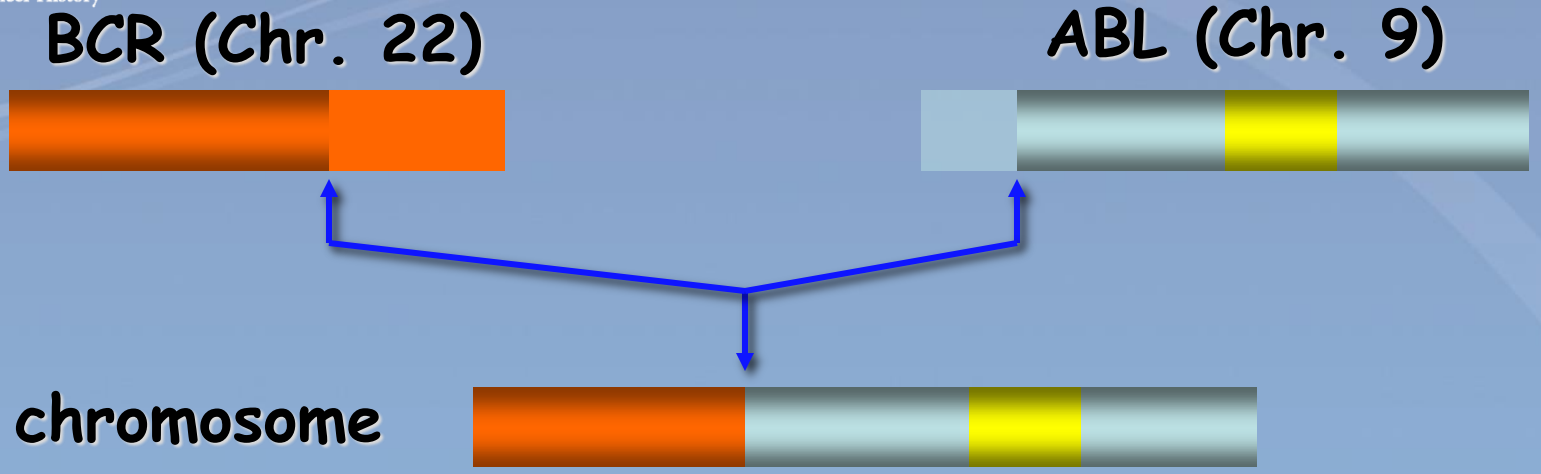
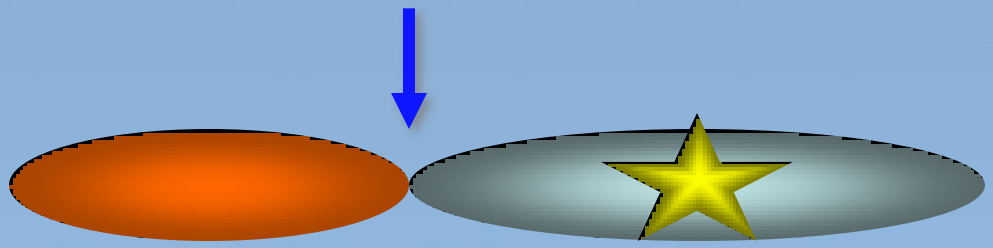
# The Philadelphia Chromosome Results in the Fusion of Two Genes and Leads to CML



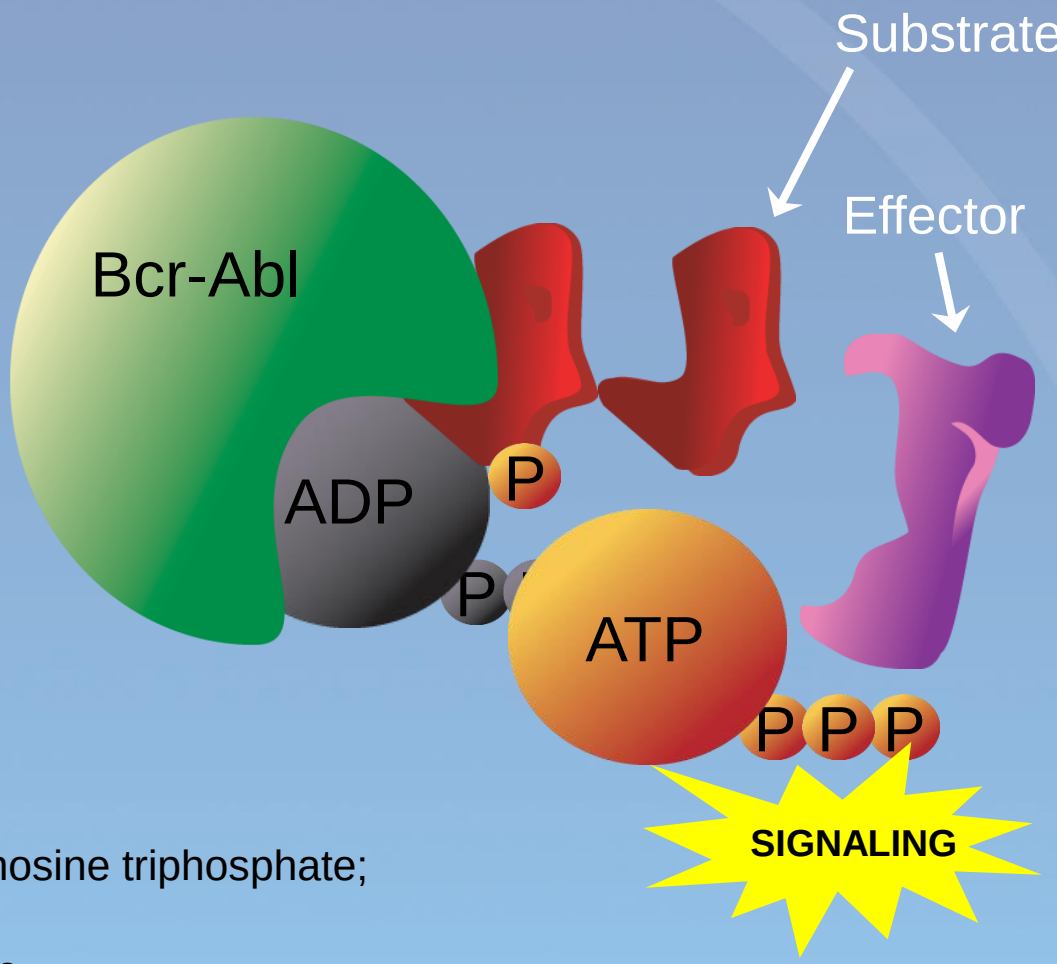

BCR-ABL (activated tyrosine kinase)



CML

# Normal Bcr-Abl Signaling*

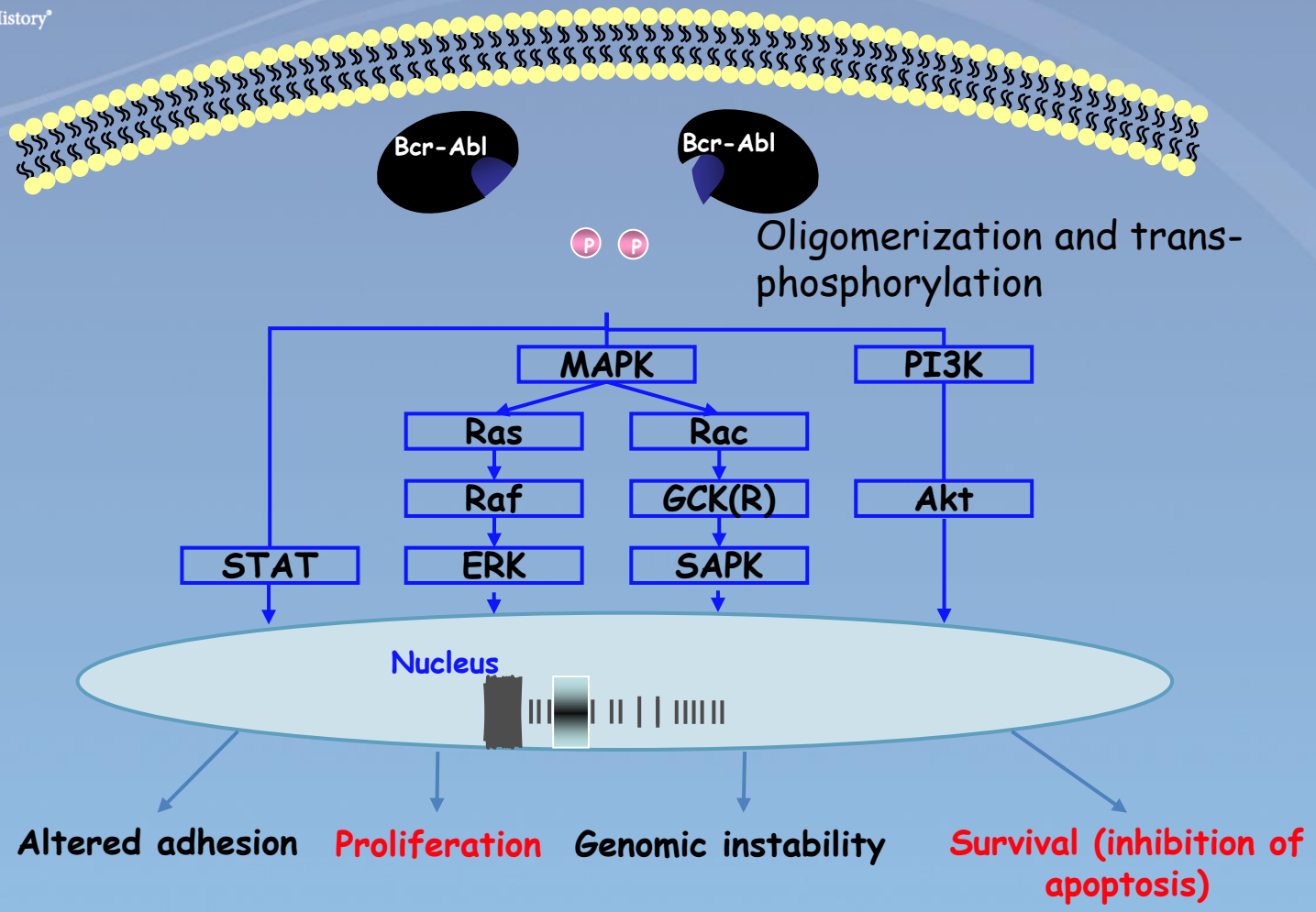
- The kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival




ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Savage and Antman. *N Engl J Med.* 2002;346:683
Scheijen and Griffin. *Oncogene.* 2002;21:3314.

# Downstream Signaling Pathways of Bcr-Abl




ERK=extracellular signal-regulated kinase; GCK(R)=germinal center kinase related; MAPK=mitogen-activated protein kinase; PI3K=phosphatidylinositol 3 kinase; SAPK=stress-activated protein kinase; STAT=signal transducer and activator of transcription.

Adapted from Deininger MWN et al. *Blood*. 2000;96:3343-3356; Smith KM et al. *Mol Cell*. 2003;12:27-37; Johnson FM et al. *Clin Cancer Res*. 2005;11:6924-6932; and Walz C, Sattler M. *Crit Rev Oncol Hematol*. 2006;57:145-164.

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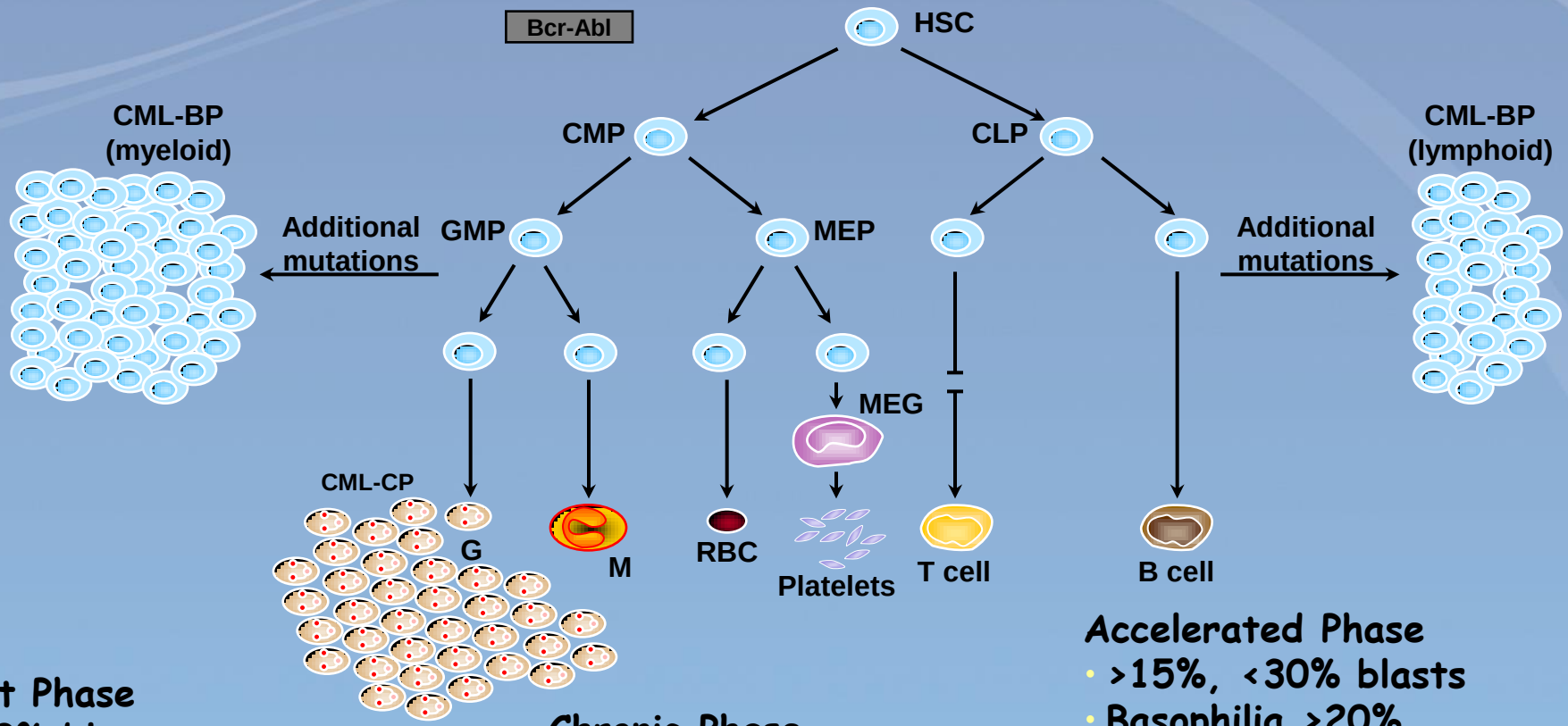
# Progression of CML




**Blast Phase**
- >30% blasts
- ~2/3 of patients have myeloid blast crisis
- ~1/3 have lymphoid blast crisis
- Very poor prognosis

**Chronic Phase**
- Myeloid hyperplasia
- <15% blasts
- Natural history of disease progression, 3-5 years untreated

**Accelerated Phase**
- >15%, <30% blasts
- Basophilia >20%
- New cytogenetic abnormalities in 50% to 80% of patients
- Plt <100k

# Clinical Course: Phases of CML

| Chronic phase | Advanced phases | |
|---|---|---|
| | Accelerated phase | Blastic phase (blast crisis) |
| Median 4–6 years stabilization | Median duration up to 1 year | Median survival 3–6 months |


**loss of p53; trisomy 8; second Ph; PAX5 deletion; others*

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# How can we treat CML?

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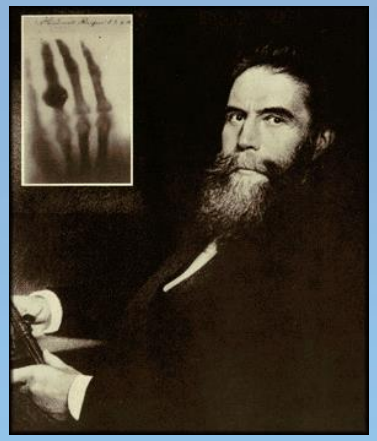
# Very Early Treatment of CML

- "In the hospital he received arsenical treatment (Fowler's solution) and a little Röntgen ray treatment. He was also given calcium lactate against the haemorrhagic tendency."
- Weber, Proc Royal Soc Med 1921. 16-21.



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# Early Treatment of CML

- How can the excessive cell division be slowed?
- Median survival in 1980 = 3 years

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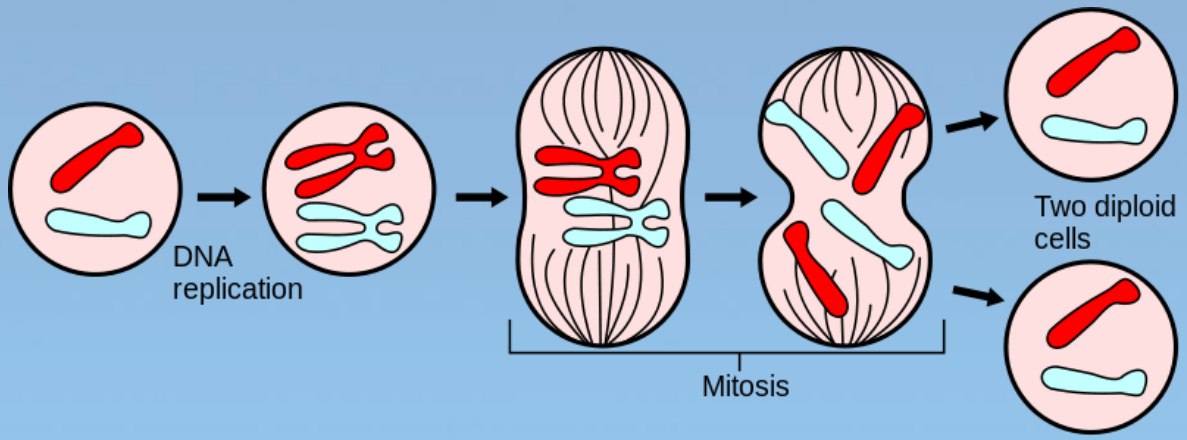
# Early Treatment of CML

- Target: Faster growth
- Hydroxyurea
  - Inhibits DNA synthesis
- Cytarabine
  - Disrupts S phase of DNA replication
- Busulfan
  - Alkylates and damages DNA



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# Early Treatment of CML

- Target: Faster growth

- Hydroxyurea
  - Inhibits DNA synthesis

- Cytarabine
  - Disrupts S phase of DNA replication

- Busulfan
  - Alkylates and damages DNA

But none of them had a significant impact on the overall prognosis of the disease (Koeffler, NEJM 1981. 304: 1269.)

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# Early Treatment of CML

- Interferon
  - Made by Leukocytes
  - Observation that interferon lowered WBC when administered to patients for other reasons

# Interferon Impairs Granulocyte Maturation and Proliferation

- In Vitro

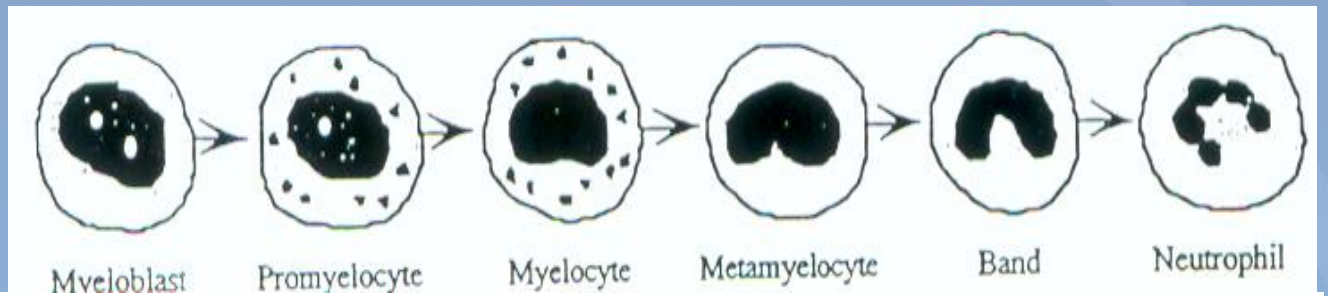


**Table 2. Effect of Human Leukocyte-Interferon on Cell Composition of Aggregates Grown in Agar Culture**

| Interferon Concentration (IRU/ml) | Differential Count of Cells Contained in Clusters (%)* | | | | | |
|---|---|---|---|---|---|---|
| | Myeloblasts | Promyelocytes | Myelocytes | Metamyelocytes | Bands | Polymorphs |
| 0 | 0.0 | 0.0 | 5.7 | 22.8 | 23.0 | 48.5 |
| 10 | 3.0 | 10.0 | 27.0 | 27.2 | 22.4 | 10.4 |
| 100 | 9.6 | 19.2 | 27.0 | 27.8 | 10.6 | 4.8 |
| 1,000 | 6.0 | 12.7 | 37.0 | 30.0 | 9.2 | 4.1 |
| 10,000 | 8.4 | 16.2 | 40.8 | 28.0 | 6.6 | 0.0 |

*Average percentage from 50 clusters examined for morphology. Morphological examination of the colonies from dishes with and without interferon revealed normally differentiating cells.

Verma, Blood 1979. 54:1423

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# Interferon enables temporary control of CML

- Given either in combination with chemotherapy (cytarabine) or as monotherapy
- Very difficult to tolerate
  - Myalgias, fatigue, headache, fever, depression
- Patients lived longer than the prior 3yr average with this therapy
- But no patients were cured
  - ~70% survival at 5yrs
    (Guilhot, NEJM 1997. 337:223)

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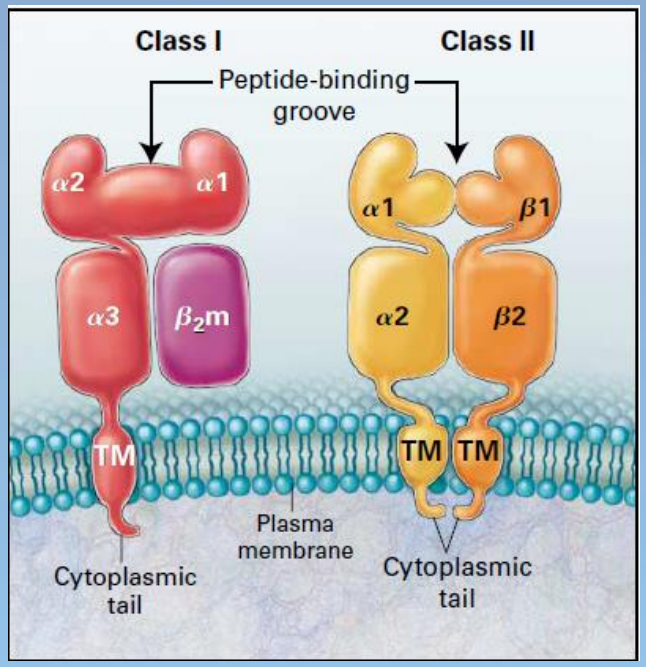
# Immune system control

- Our immune system recognizes disease within the body
- HLA (Human Leukocyte Antigen)
  - Class I (A, B, C)
  - Expressed everywhere (except RBCs, germ cells, neurons)
- Class II (DP, DQ, DR)
  - Only expressed by immune-system cells




Klein. NEJM 2000. 343:702

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# Immune system control

- Our immune system recognizes disease within the body

- Cancer growth is contributed to by the inability of an immune system to recognize the tumor

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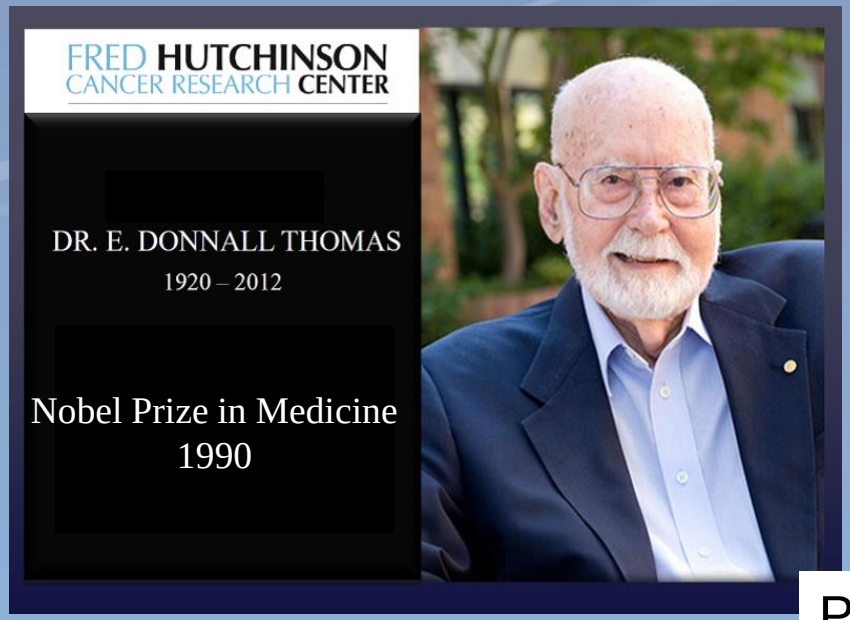
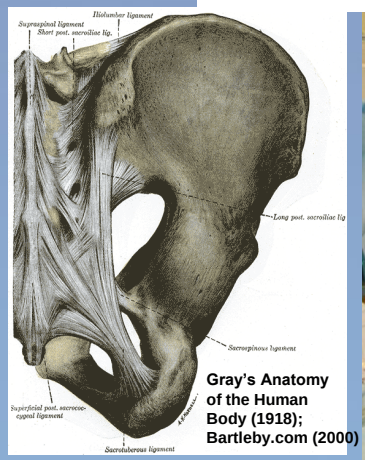
# Immune system control

- Our immune system recognizes disease within the body
- Cancer growth is contributed to by the inability of an immune system to recognize the tumor
- Is there a way to give a patient a ‘new’ immune system that could recognize the cancer?

# Hematopoietic Stem Cell Transplantation



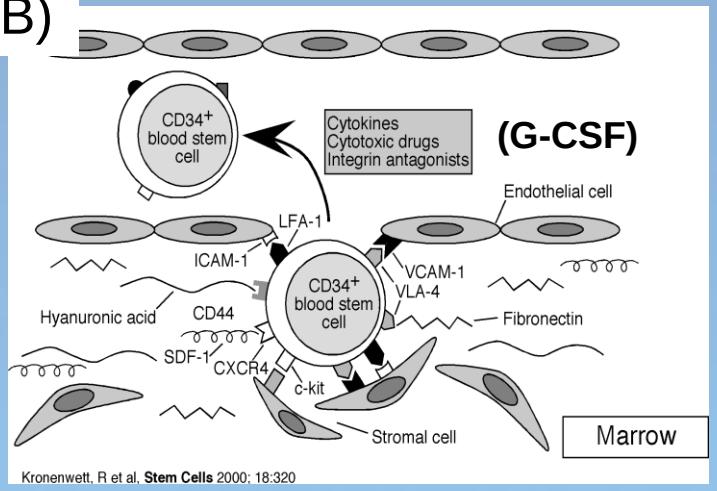

## Bone Marrow



Gray's Anatomy of the Human Body (1918); Bartleby.com (2000)

## Peripheral Blood Progenitor Cells (PBPC)

## Umbilical Cord Blood (UCB)

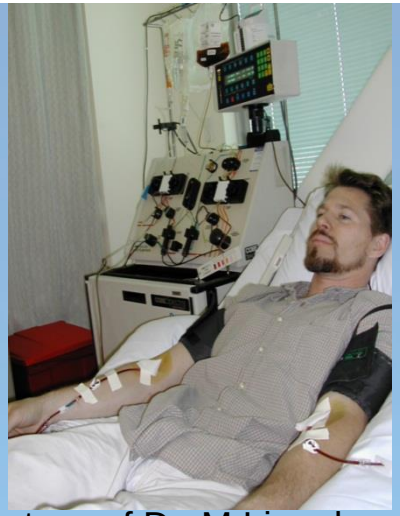



Photo courtesy of Dr. M Linenberger

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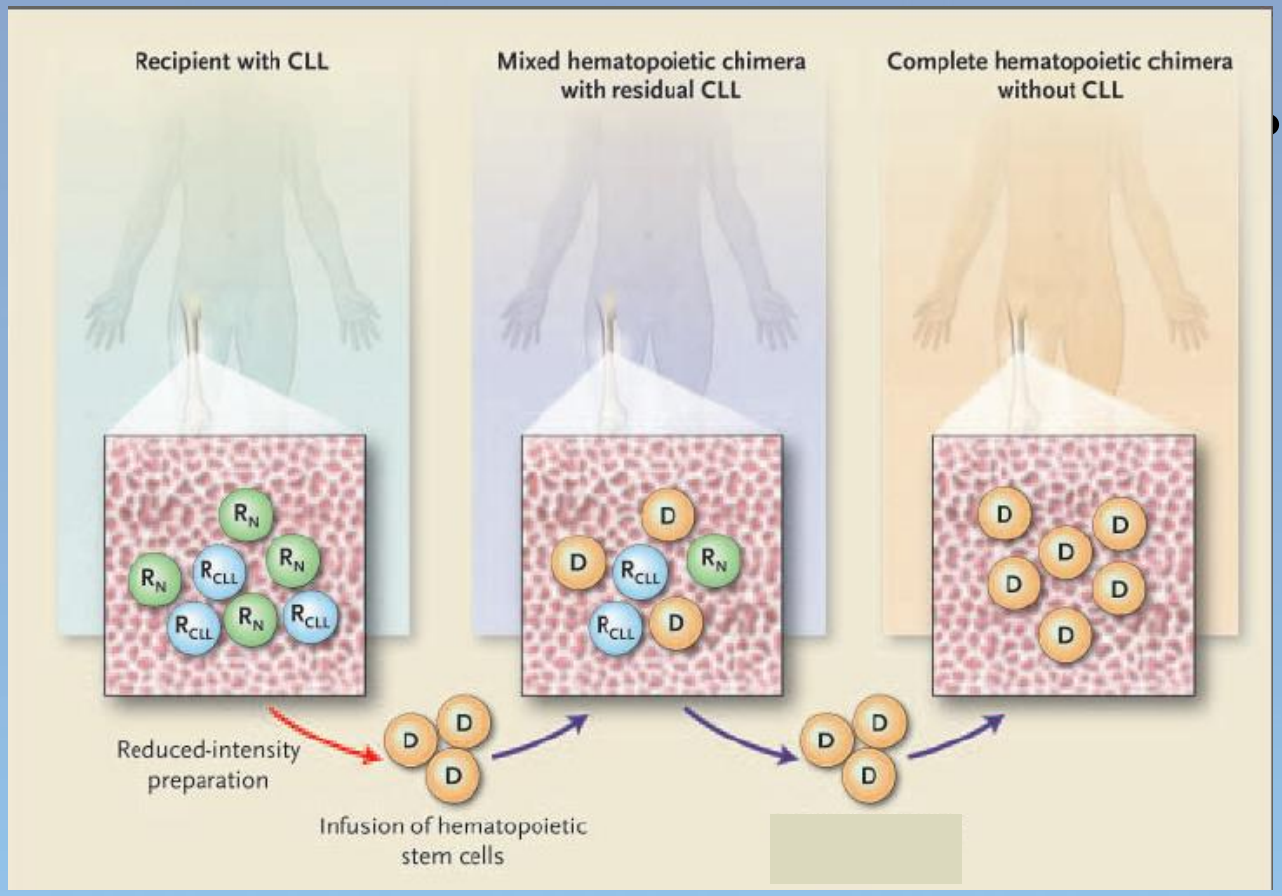
# Hematopoietic Stem Cell Transplantation (HSCT)

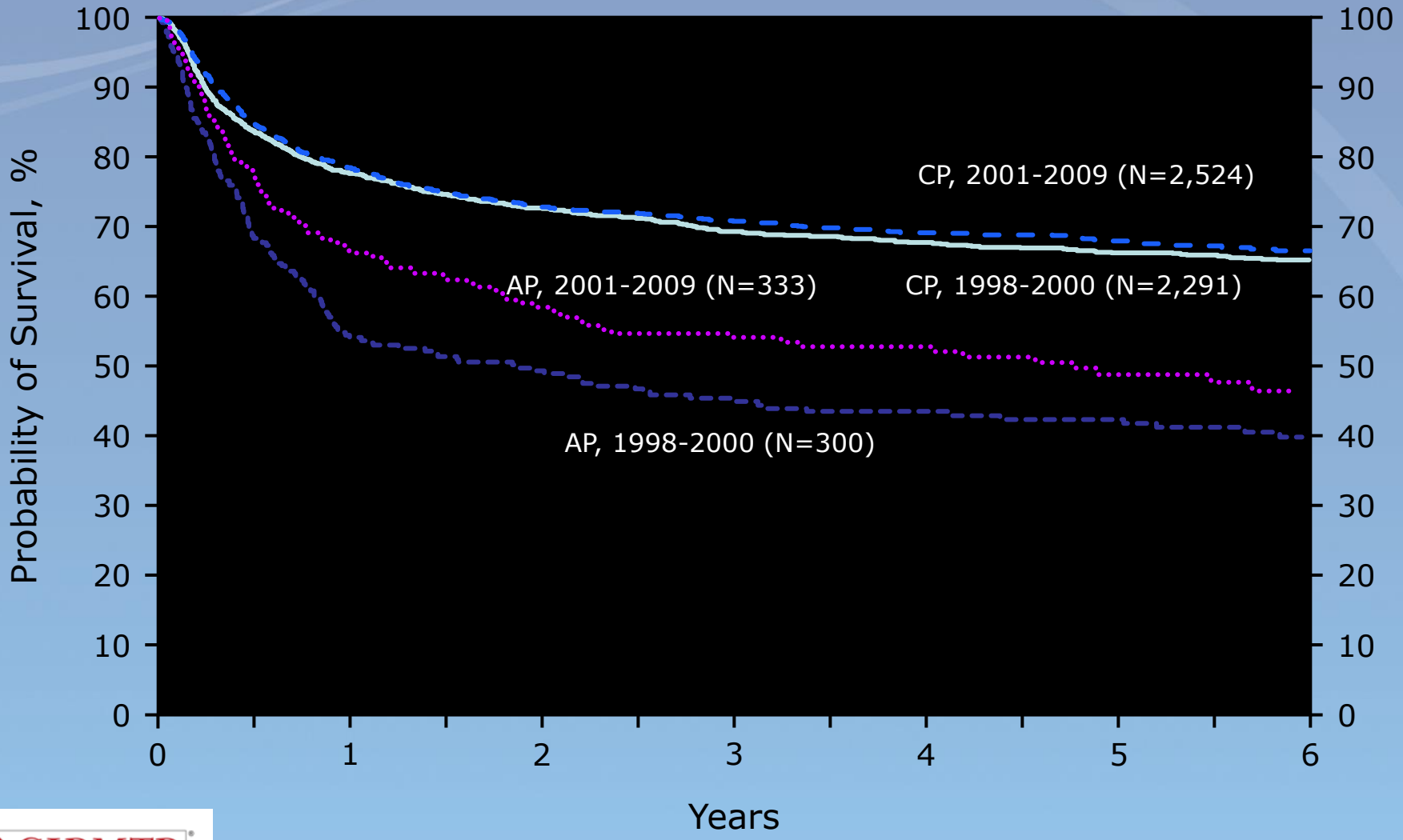



- Graft-versus-leukemia effect

The Chimera of Arezzo

Copelan, NEJM 2006. 354:1813

# Probability of Survival after HLA-identical Sibling Donor Transplants for CML (1998-2009)

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# Limitations to Stem Cell Transplant

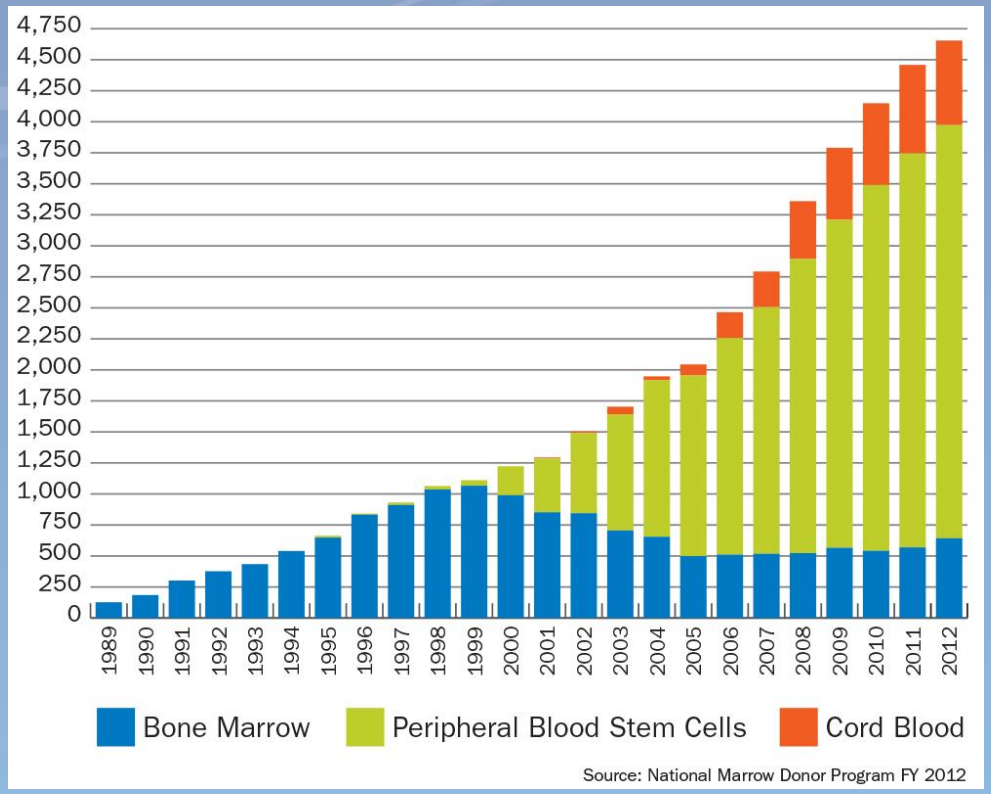
- In 2000, only 25-30% of patients could undergo SCT for CML
  - Transplant-related mortality - risk of dying from allogeneic transplant about 20-30% within the first year, so only young and very healthy patients were candidates
  - Finding HLA-matched donor for ethnic minorities much more difficult

# Improving Transplants (2000-present)

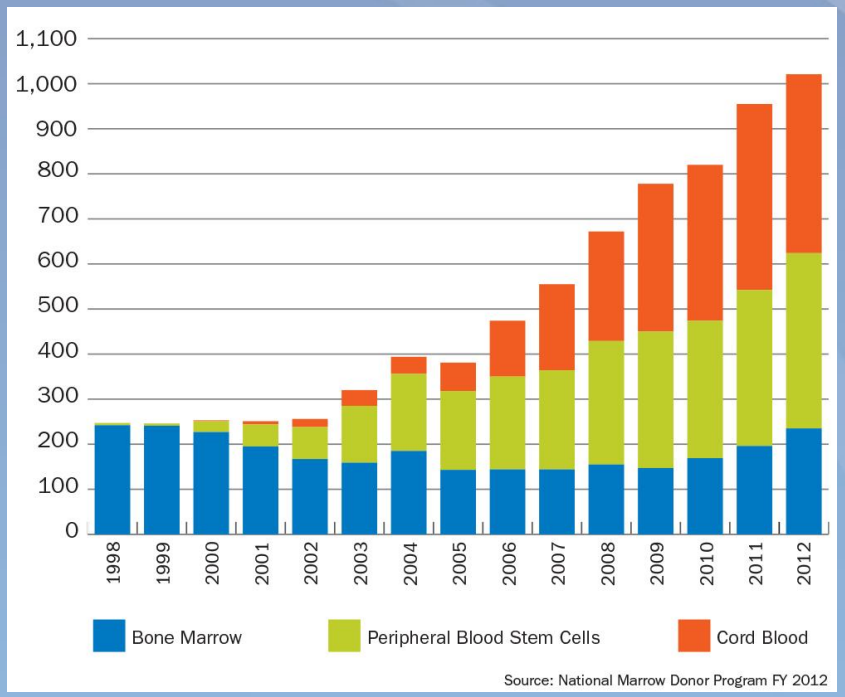
- Reduced-intensity conditioning chemotherapy
  - Older patients and those with other medical conditions are now candidates
- Alternative stem cell sources and expansion of donor registry improves access for non-Caucasians

# Transplants by Cell Source

Adult Recipients (18 years and older)

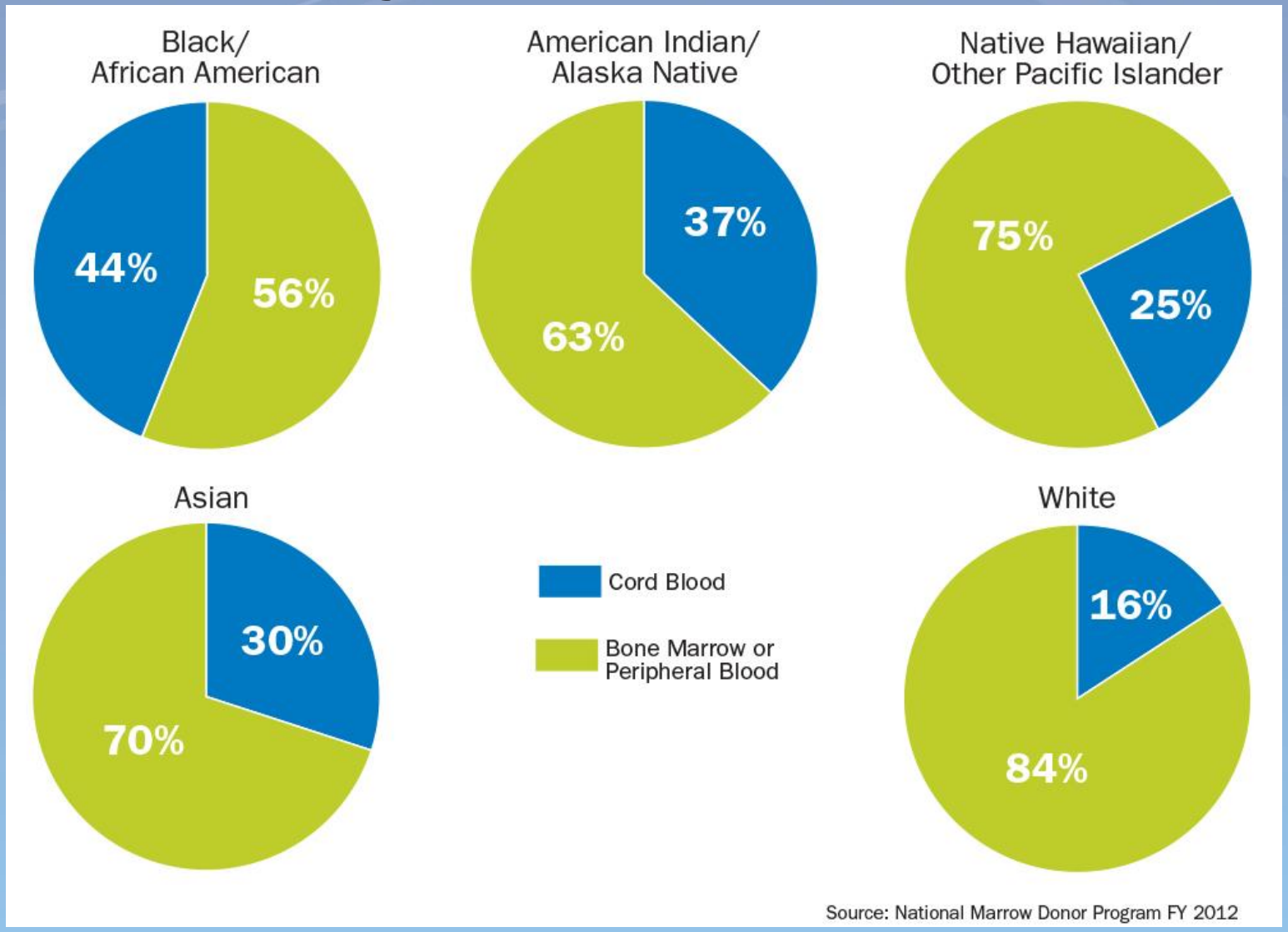



All Patients

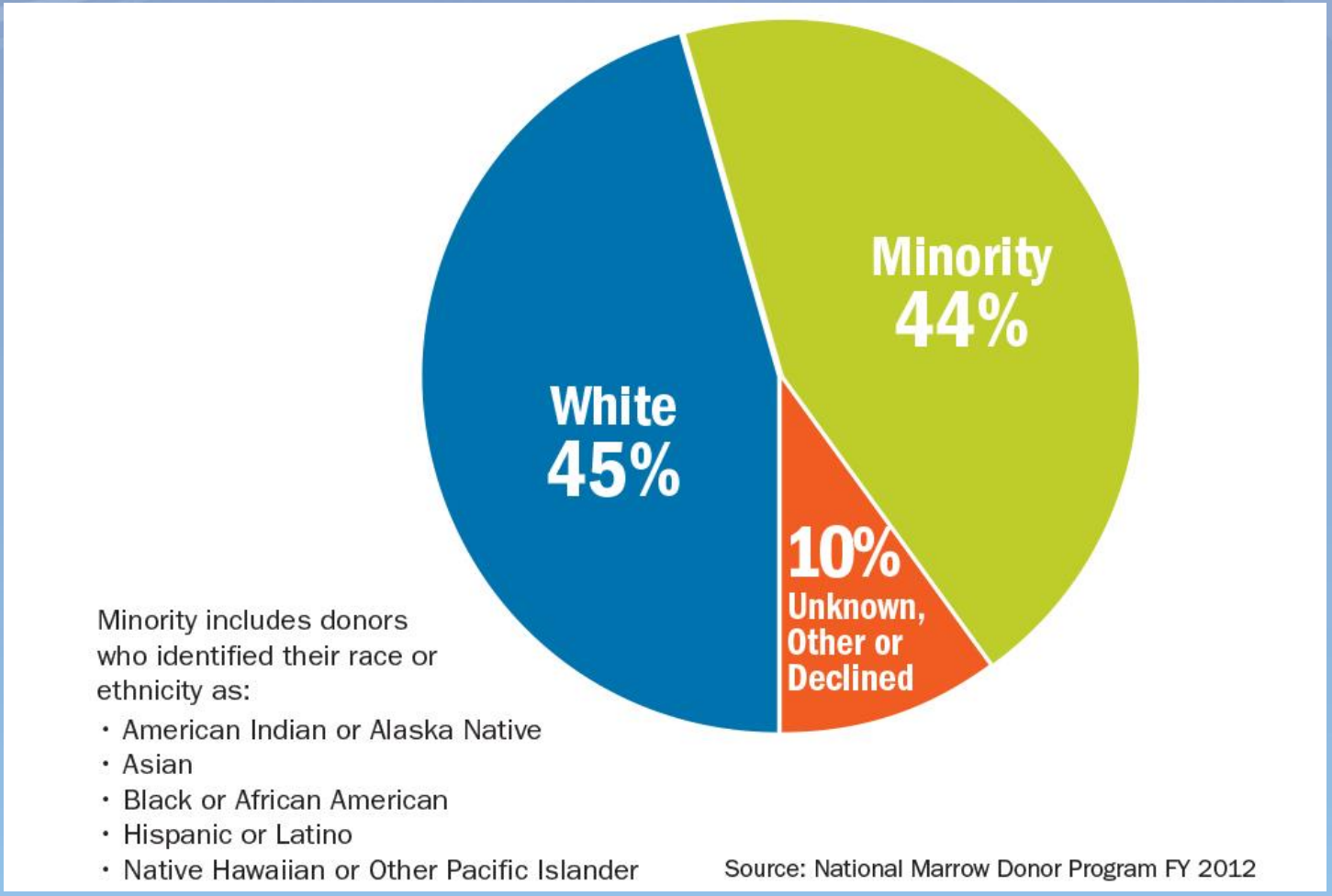



Non-Caucasian patients

# Role of Cord Blood in Transplants by Patient Race



# Diversity of Cord Blood Units on the Be The Match Registry® 2012



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# How you can help

- Become a donor
  - BeTheMatch.org (National Marrow Donor Program)
- Organize a donor drive
- Encourage new parents to donate cord blood at the time of delivery
  - to a Public cord blood bank

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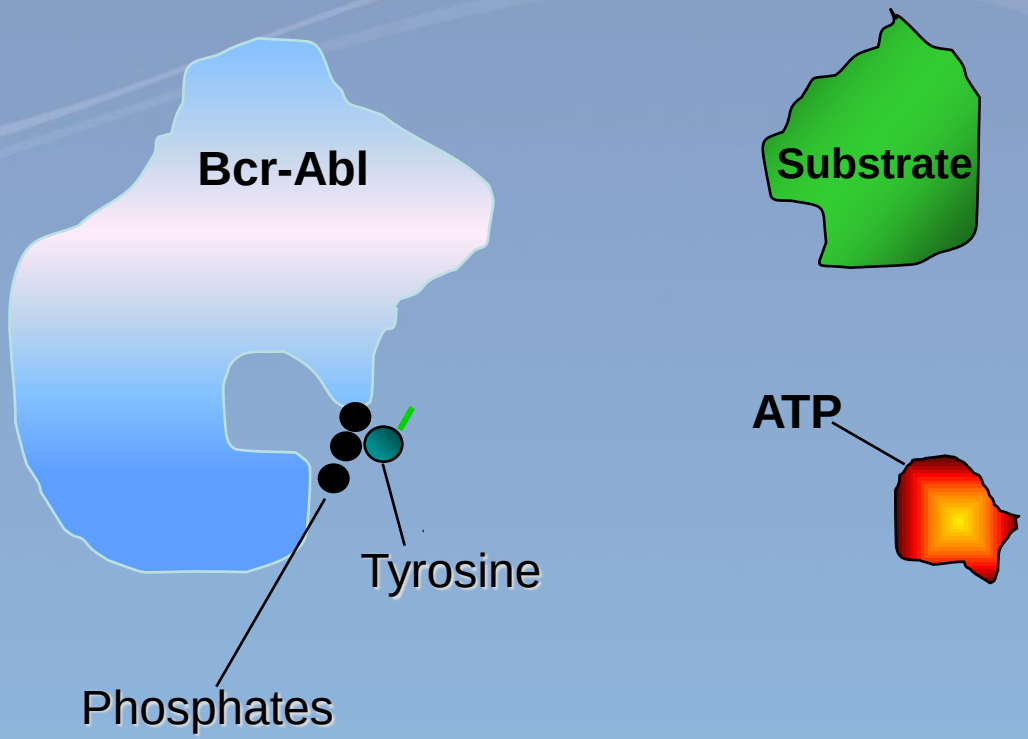
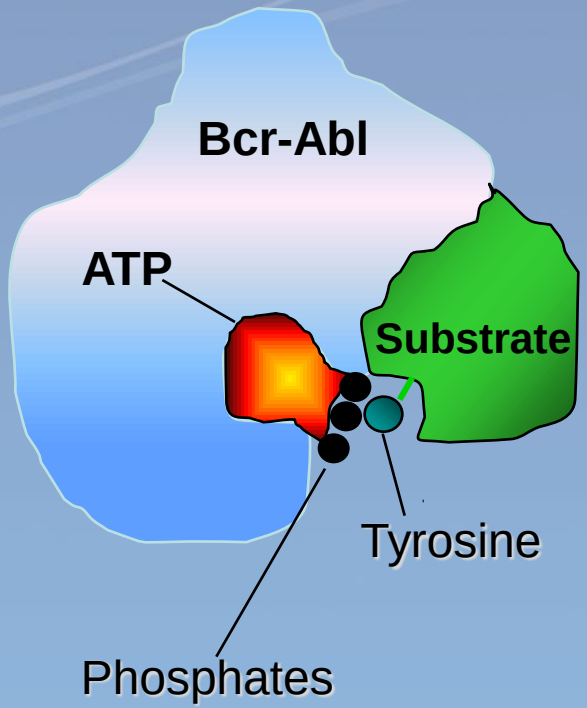
# Let's get more specific

- Specific mutation found in all CML
  - Driver mutation
- Could this be targeted and blocked?

# Mechanism of Activation of Bcr-Abl



# Mechanism of Activation of Bcr-Abl




Signal transduction cascade
uncontrolled activity

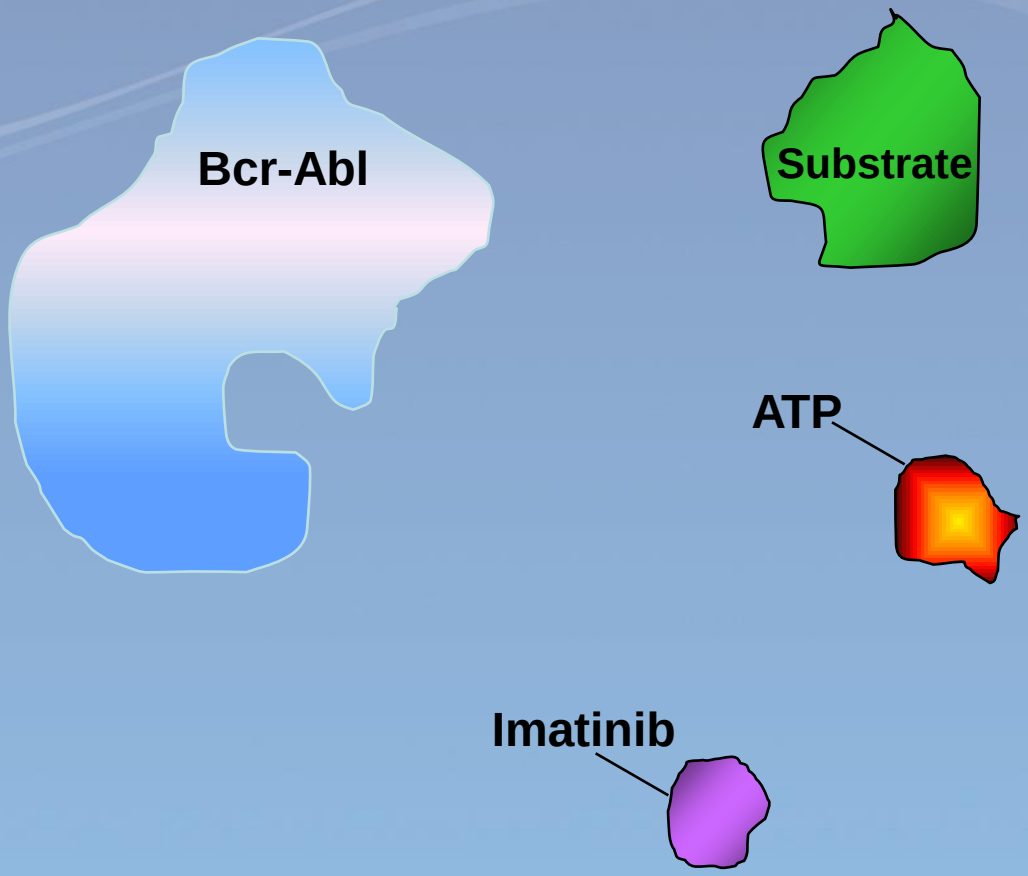
Proliferation

Survival

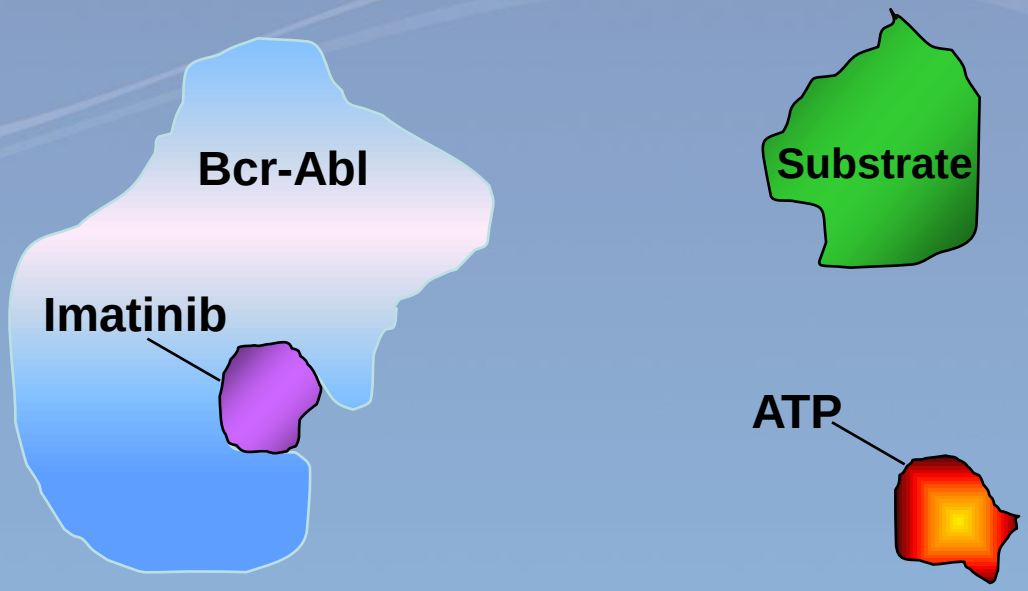
Adherence

Genetic Instability

# Mechanism of Action of Imatinib

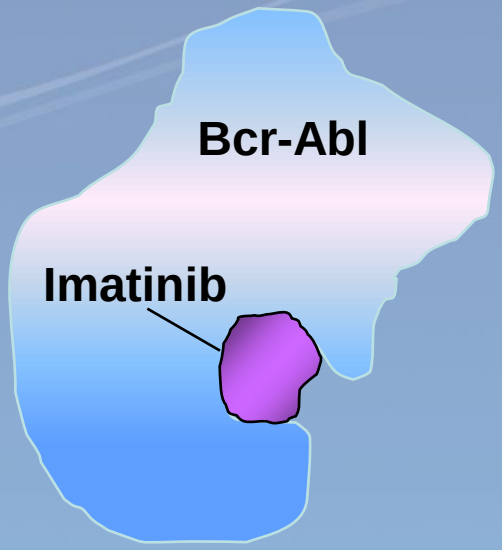


# Mechanism of Action of Imatinib




Adapted from Goldman JM, Melo JV. *N Engl J Med*. 344:1084-1086

# Mechanism of Action of Imatinib




Adapted from Goldman JM, Melo JV. *N Engl J Med*. 344:1084-1086

# Phase I Clinical Trial
# Chronic phase CMLwho failed α-interferon

With imatinib, no dose-limiting toxicity observed (25-1000 mg/daily)

400-600 mg daily- achieved maximal inhibition of BCR-ABL kinase activity; clinical efficacy noted

53 of 54 patients (receiving ≥ 300 mg/day) achieved complete hematologic response (WBC returned to normal).
Some patients also achieved a complete cytogenetic response (Philadelphia chromosome no longer detected in bone marrow)

Side effects: mild bone marrow suppression (21%);
nausea, diarrhea, rashes, cramps

# Imatinib (Gleevec) - *Clinical Efficacy*

## *Phase III Trial (Chronic Phase CML)*

| Treatment | Response Rate (%) | |
|---|---|---|
| | Hematologic | Major Cytogenetic |
| Imatinib | 94 | 83 |
| Interferon + Ara-C | 55 | 20 |

*O'Brien et al, NEJM, 2003*

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# FDA Approval, May 2001

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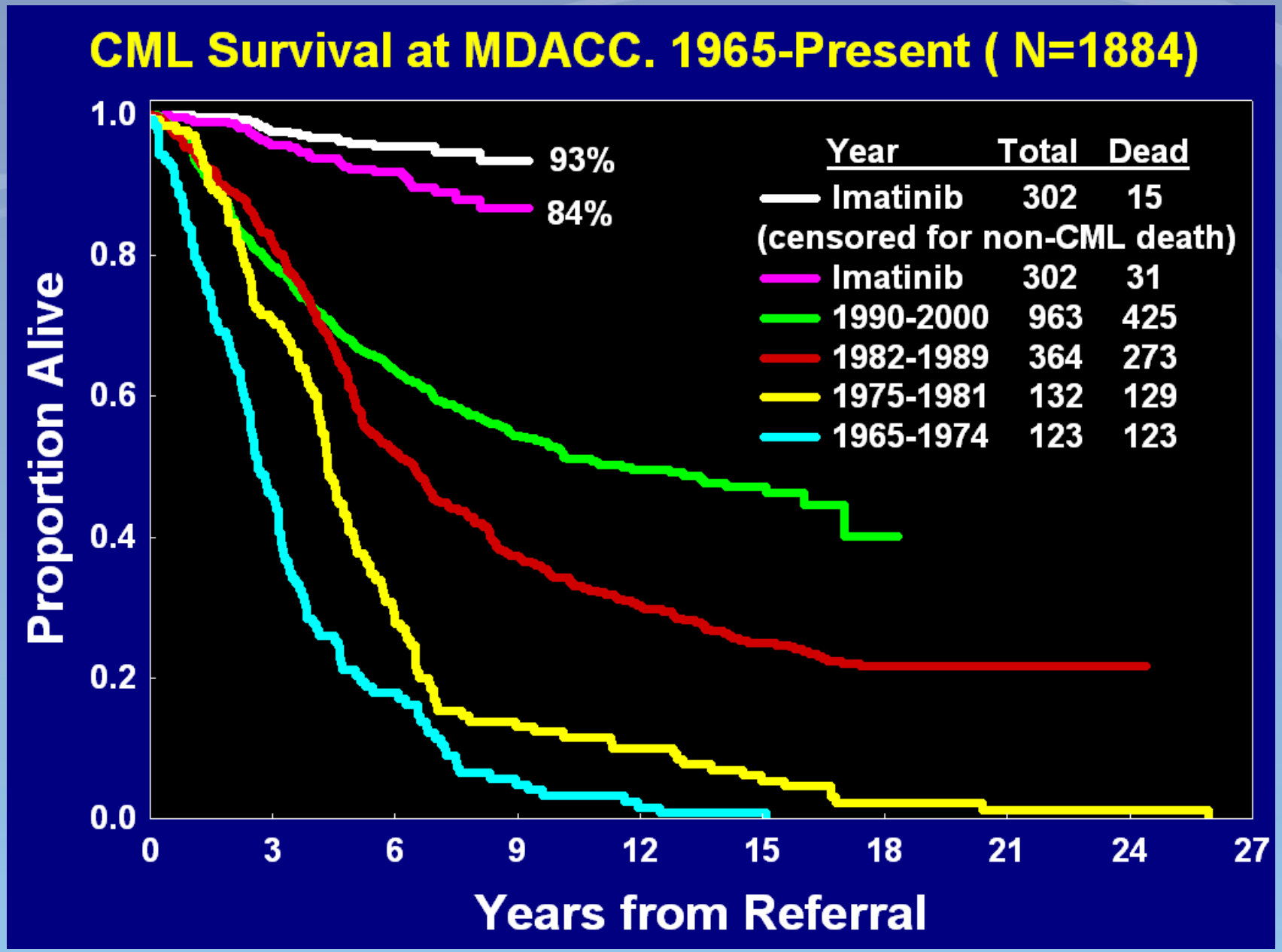
# Imatinib has dramatically improved survival



# Incidence And Mortality Of CML

| Year | Number of Cases | Number of Deaths (%) |
|---|---|---|
| 1997 | 4300 | 2400 |
| 2007 | 4570 | 490 |

Based on current data, median survival is expected to exceed 15-20 years.

Parker et al, 1997; Jemal et al, 2007; Alvarez et al, 2007.

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# Next Generations of TKIs

- Dasatinb – improved responses compared to imatinib (DASISION, Kantarjian *NEJM* 2010 362(24): 2260)
- Nilotinib – improved responses compared to imatinib (ENESTnd, Saglio *NEJM* 2010 362(24)2251)
- Ponatinib – effective against T315I mutations
- Bosutinib

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# Side effects of TKIs

- Commone side effects: edema, myalgias (rhabdo), cytopenias, LFTs, CYP450

- Dasatinb – pleural effusions
- Nilotinib – diarrhea, pancreatitis
- Ponatinib- cardiovascular events
- Bosutinib

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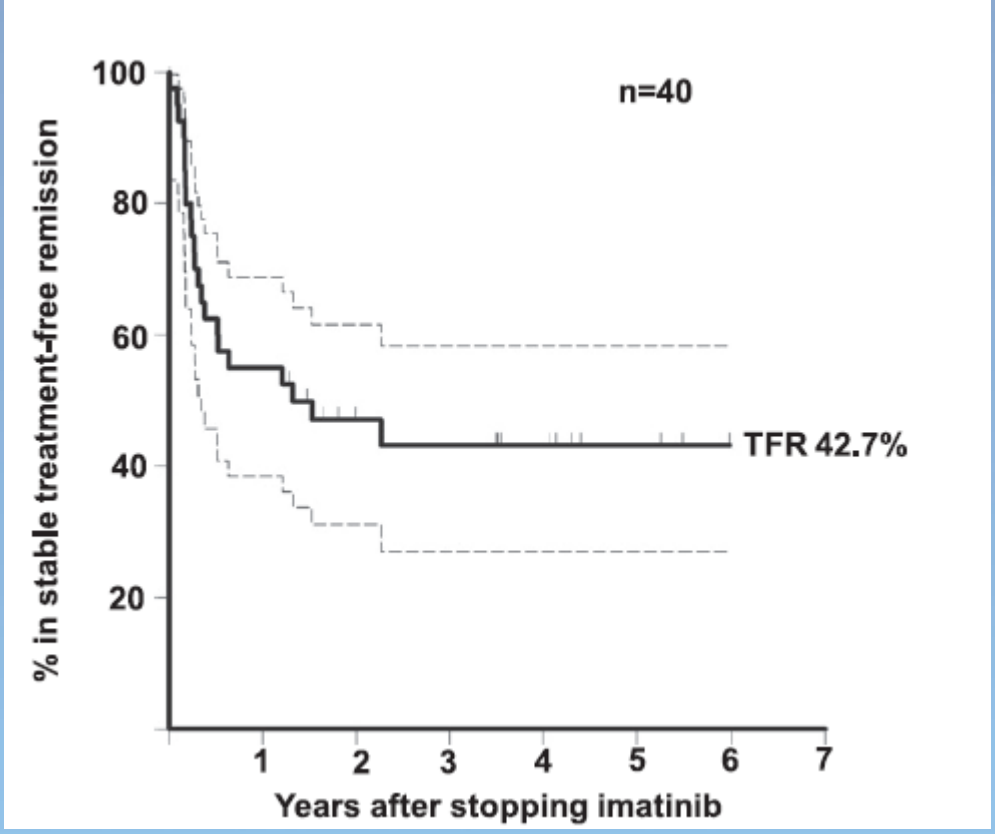
# Can you stop medication?

- Ross et al. Blood 2013.
- In selected patients – yes, but follow very closely

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# Questions and Thanks

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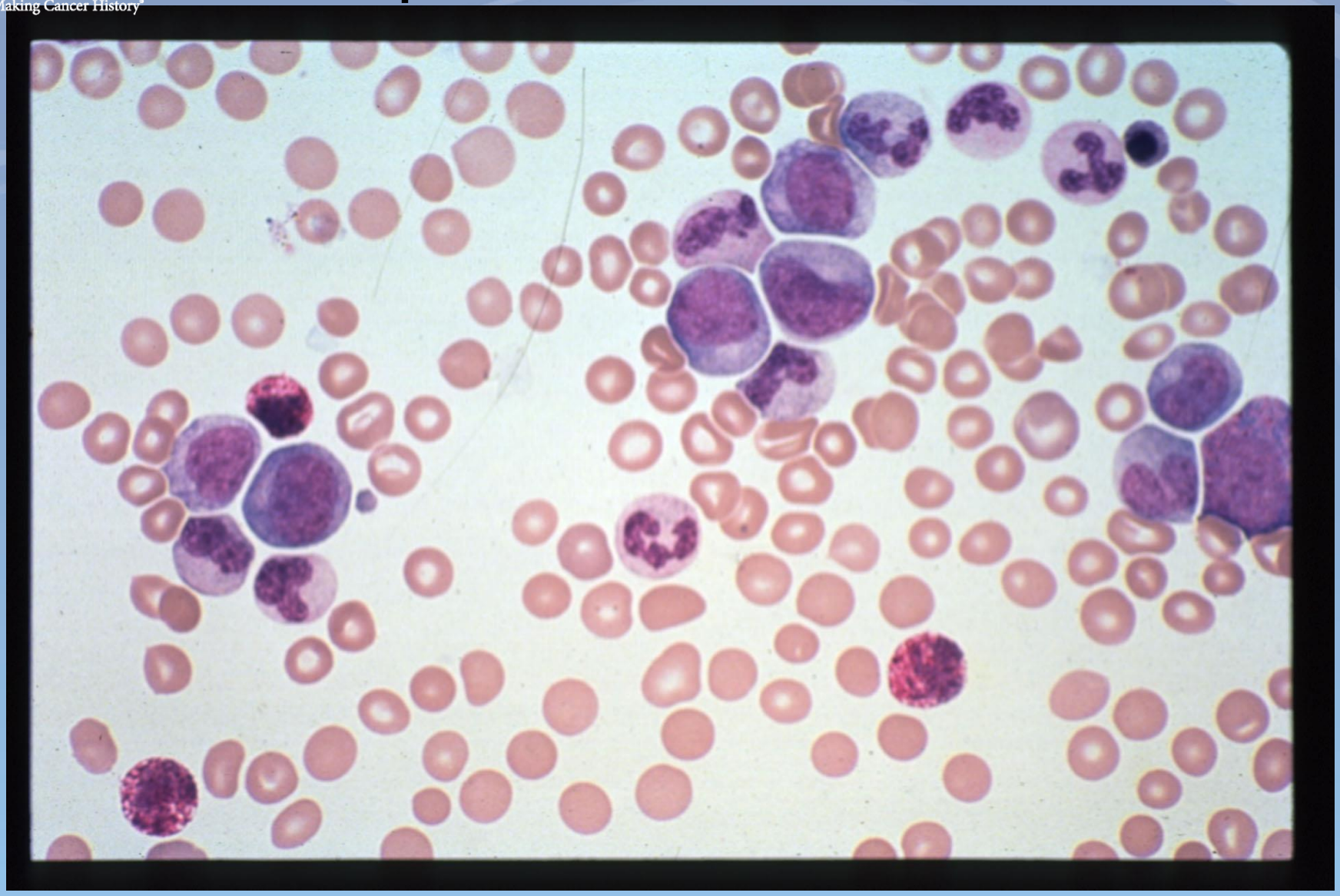
# Peripheral Blood Smear



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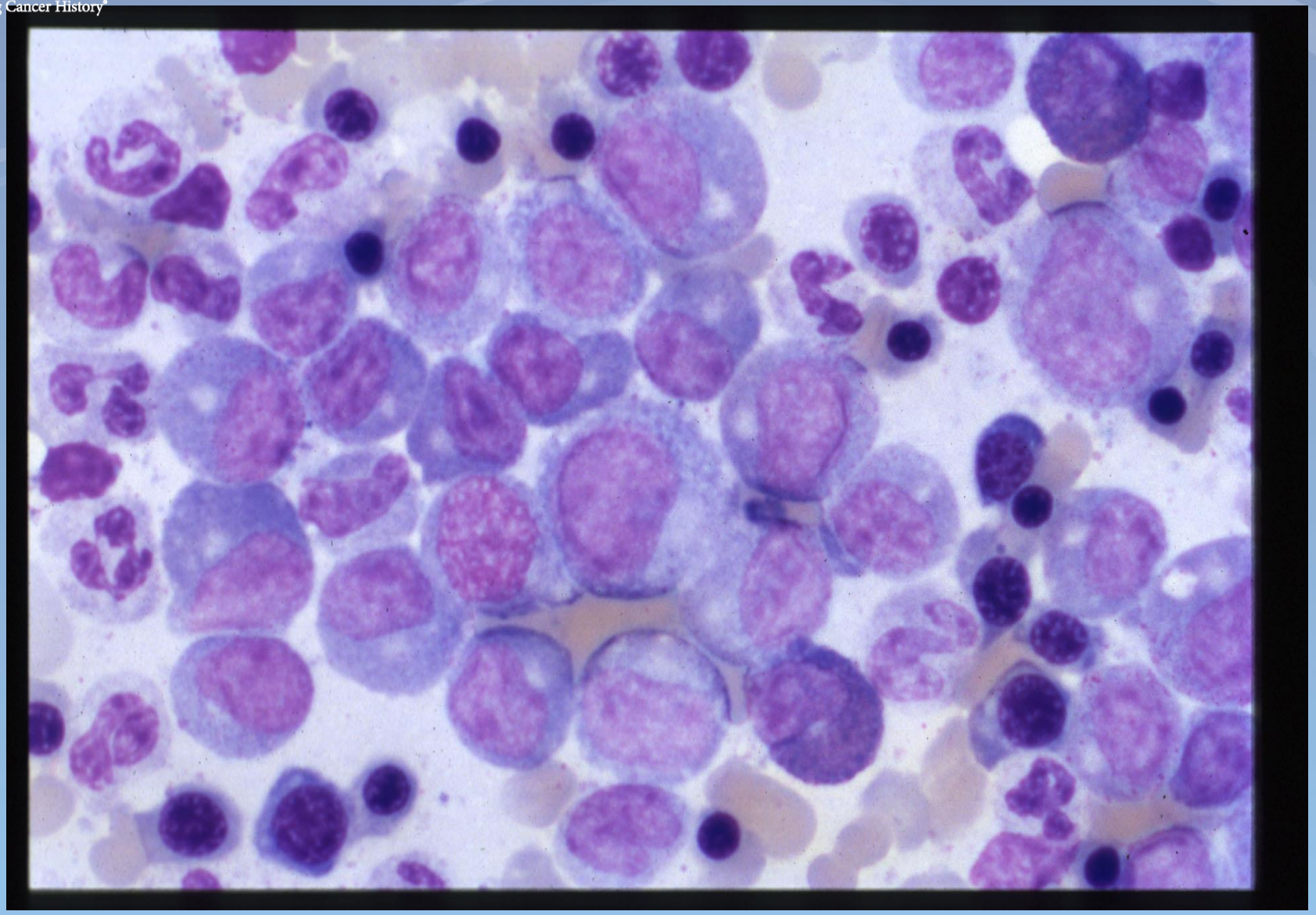
# Bone Marrow Aspirate



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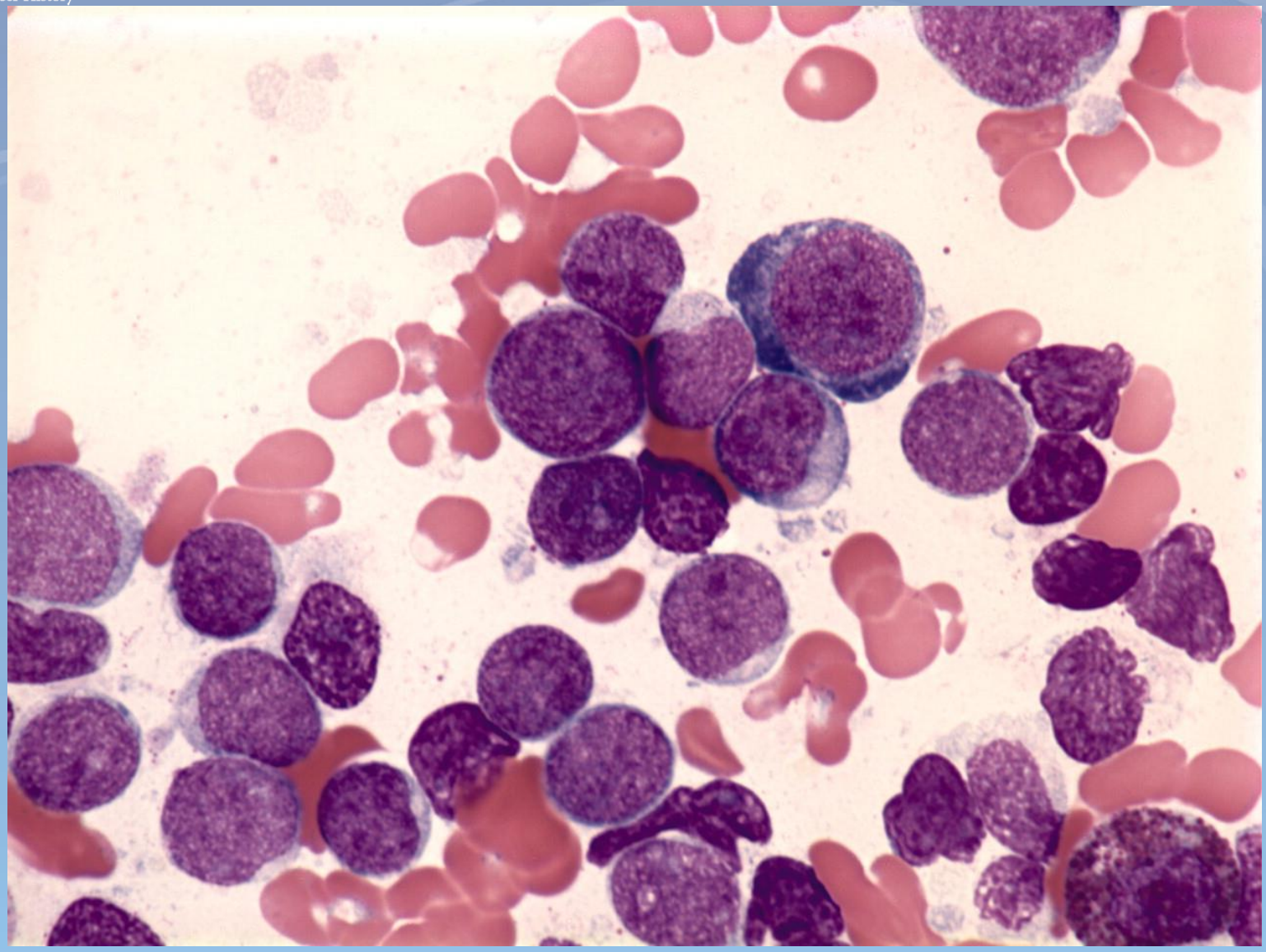
# Bone Marrow Aspirate

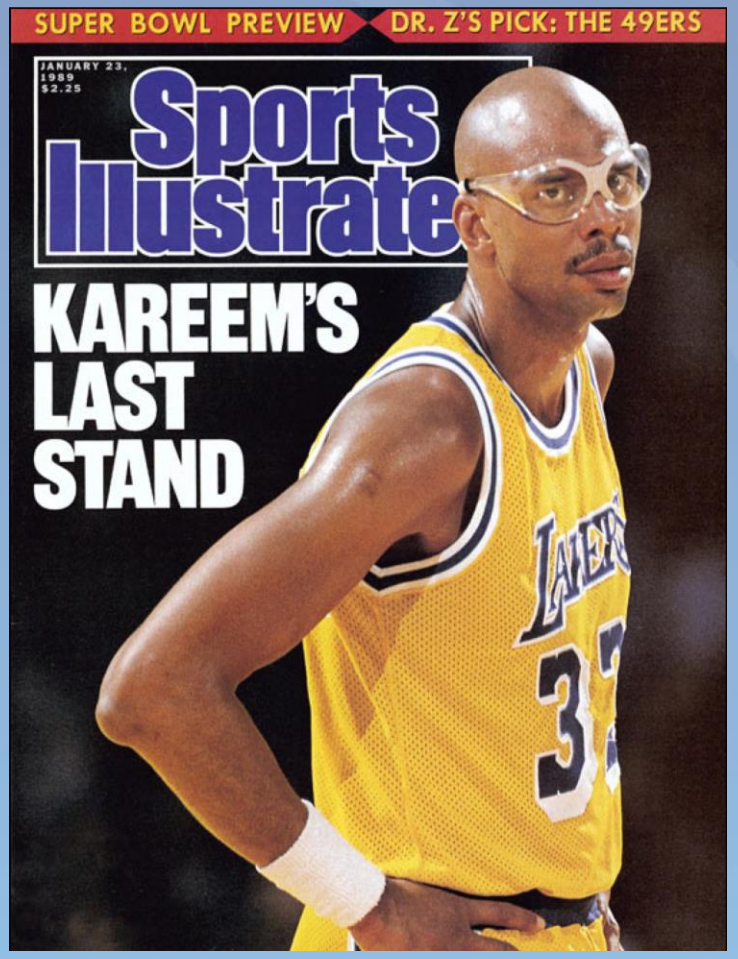




**Maslak, P. ASH Image Bank 2004:101107**

# Some famous people living with CML

Jason Blake




Kareem Abdul-Jabbar