



What is the Real Cure? Is Stopping Really a Feasible Approach?

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What is the Real Cure?

- **Medieval Latin *cura*=care**
- A **cure** is the end of a medical condition
 - **Operational Cure** (Prof. John Goldman): "If a treatment is sufficient to prevent the progression of CML to the advanced phase and to prevent the emergence of resistance, then the treatment can provide an "operational cure"
 - Killing the last leukemic cell

Operational Cure Advantage

- **Continuation of treatment is safer ~60% relapse after stopping TKI treatment**

Operational Cure Disadvantage

- If TKI therapy is required indefinitely to maintain the operational cure of CML, then this ongoing drug exposure raises its own problems:
 - There may be chronic toxicity
 - As long as there is residual disease there is at least a theoretical risk of emerging resistance
 - There is a financial cost to the individual and the community

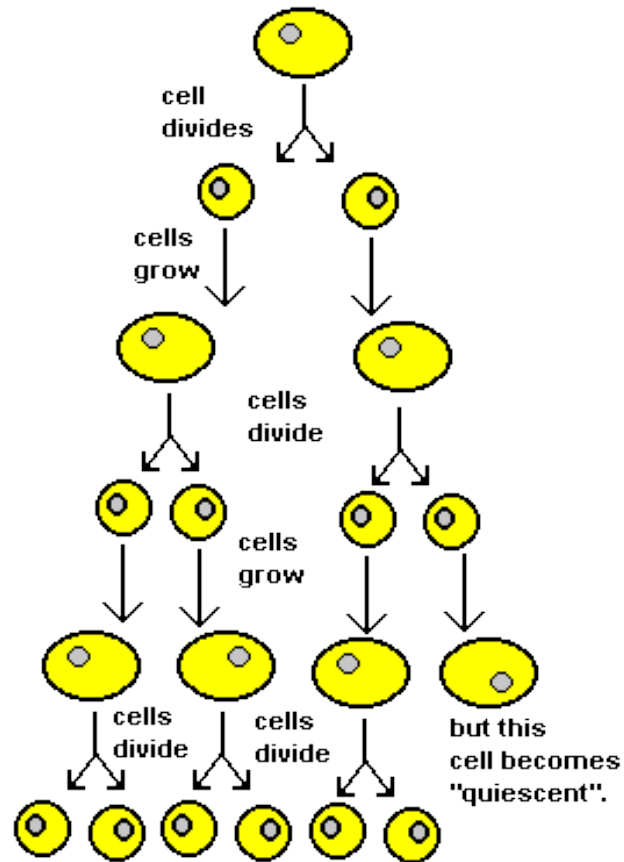
Killing the Last Leukemic Cells

- Allogeneic stem-cell transplantation
 - Reserved for young patients with compatible donor
 - Morbidity and mortality
 - Relapses even after more than decade
- Interferon
 - Patients who stopped IFN after achieving a deep molecular response have been reported in stable minimal residual disease for more than 9 years
 - Much more rarely, in a stable CMR

**Why with TKIs we kill
the last leukemic cell
only in the minority of
our patients?**

It is all Because of Daddy

Cells Multiply by Division



Normal Organ

**Cell
Division**

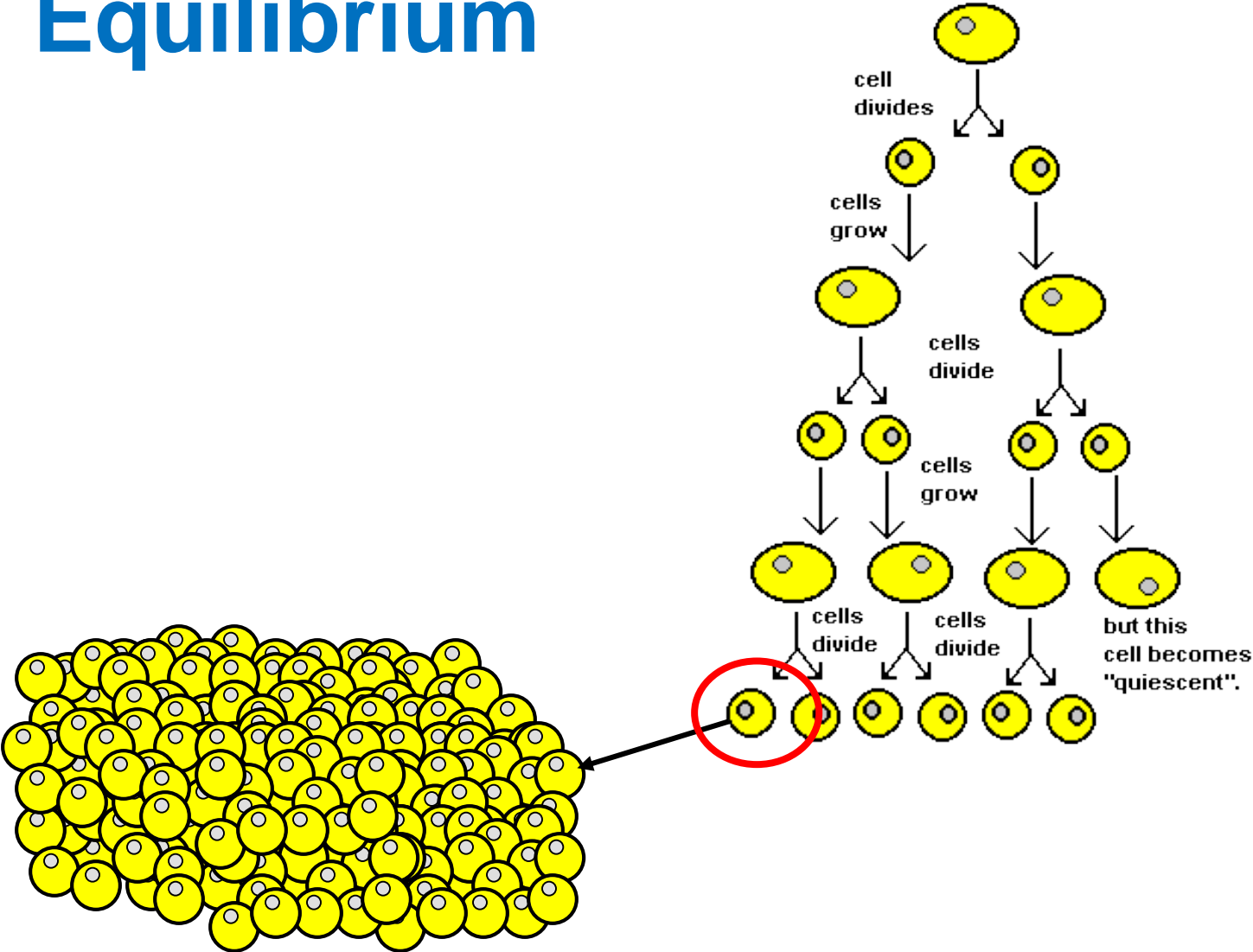


Homeostasis

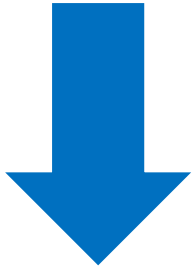
**Cell
Death**



Leukemia is a Disruption of the Equilibrium



The Roads to Leukemia



**Acute
Leukemia**



Cell Division



CML



Cell Death

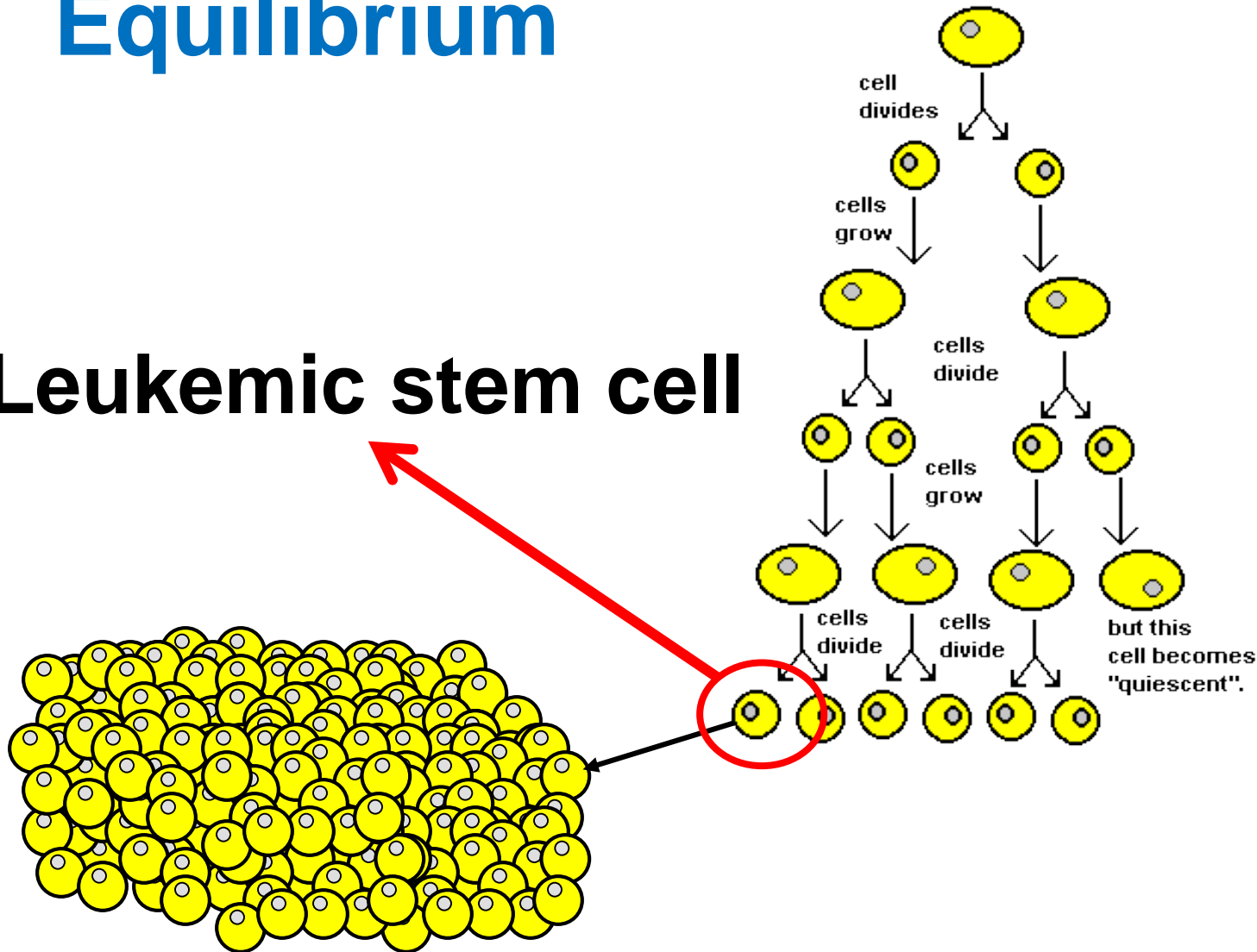


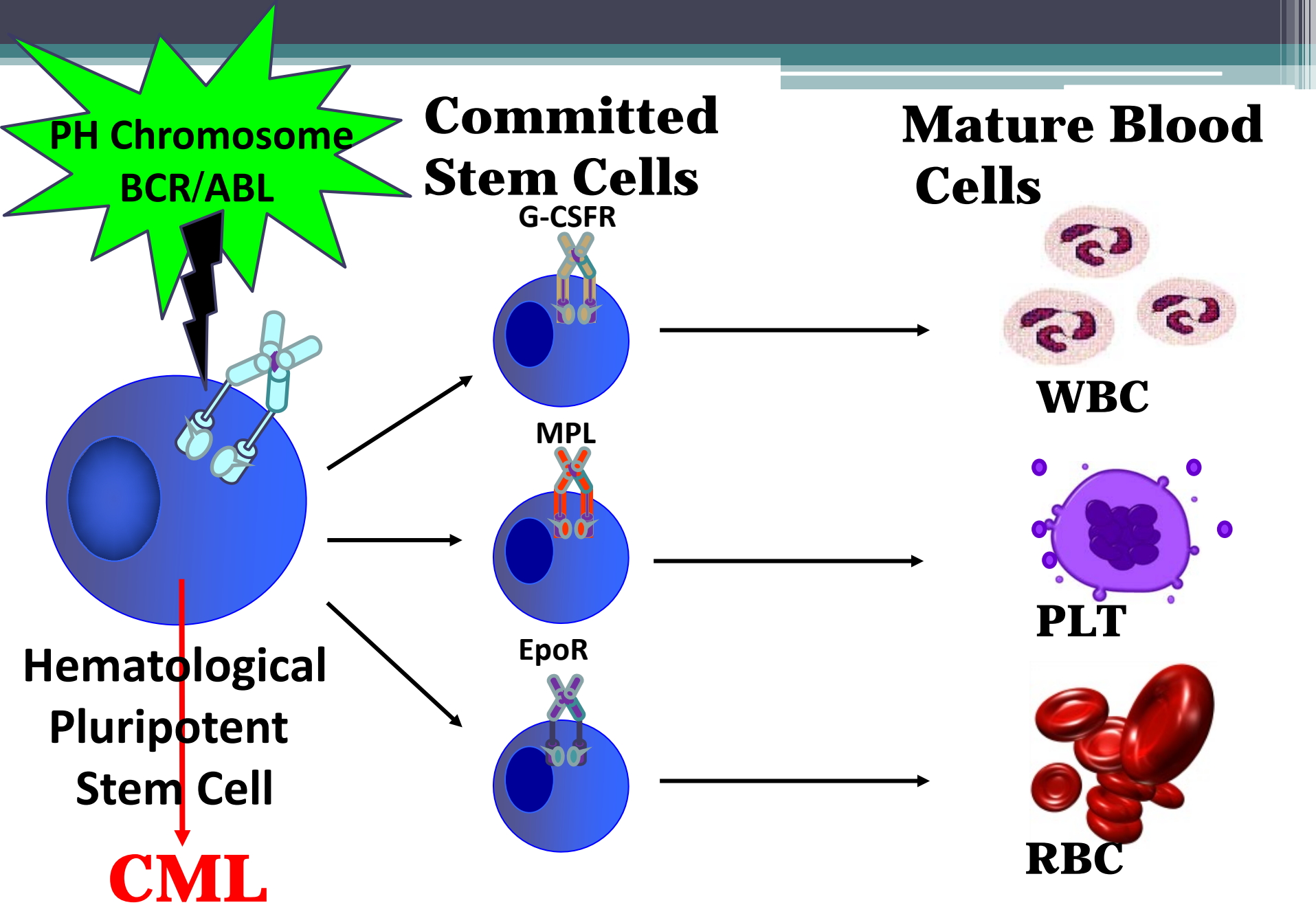
**Chronic
Lymphatic
Leukemia**



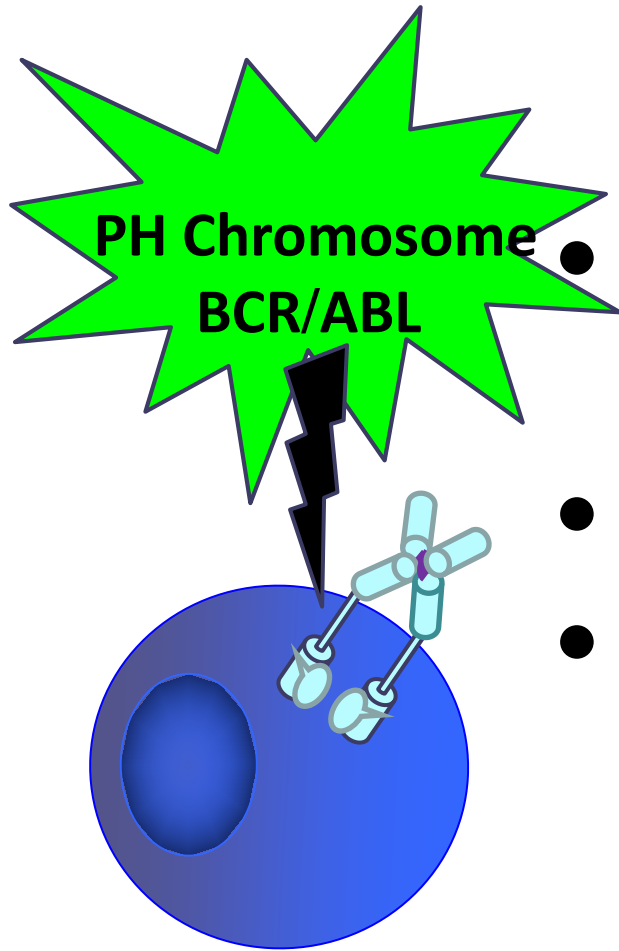
Leukemia is a Disruption of the Equilibrium

Leukemic stem cell

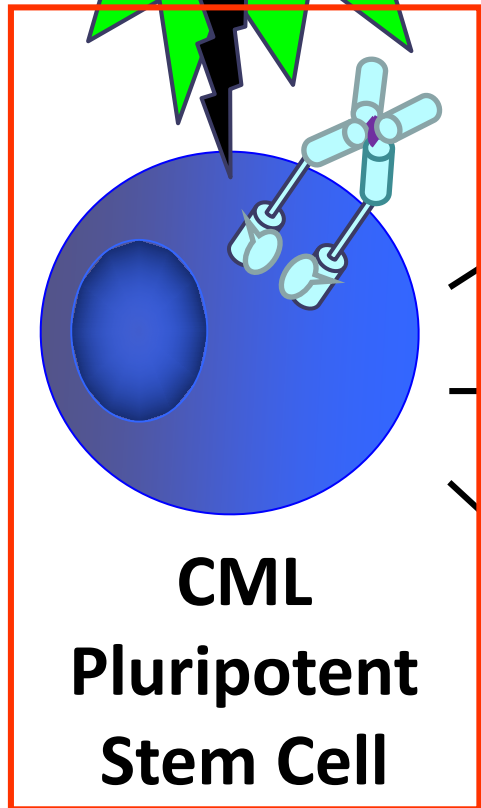
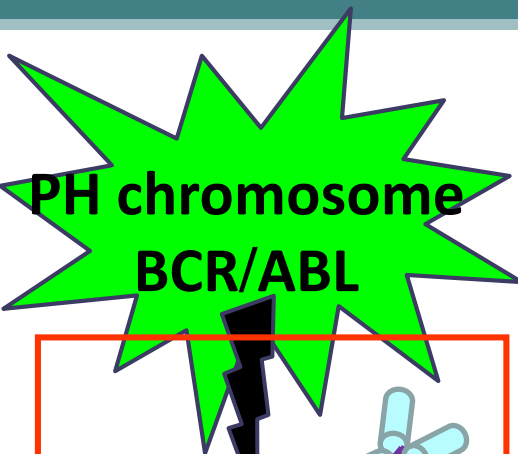




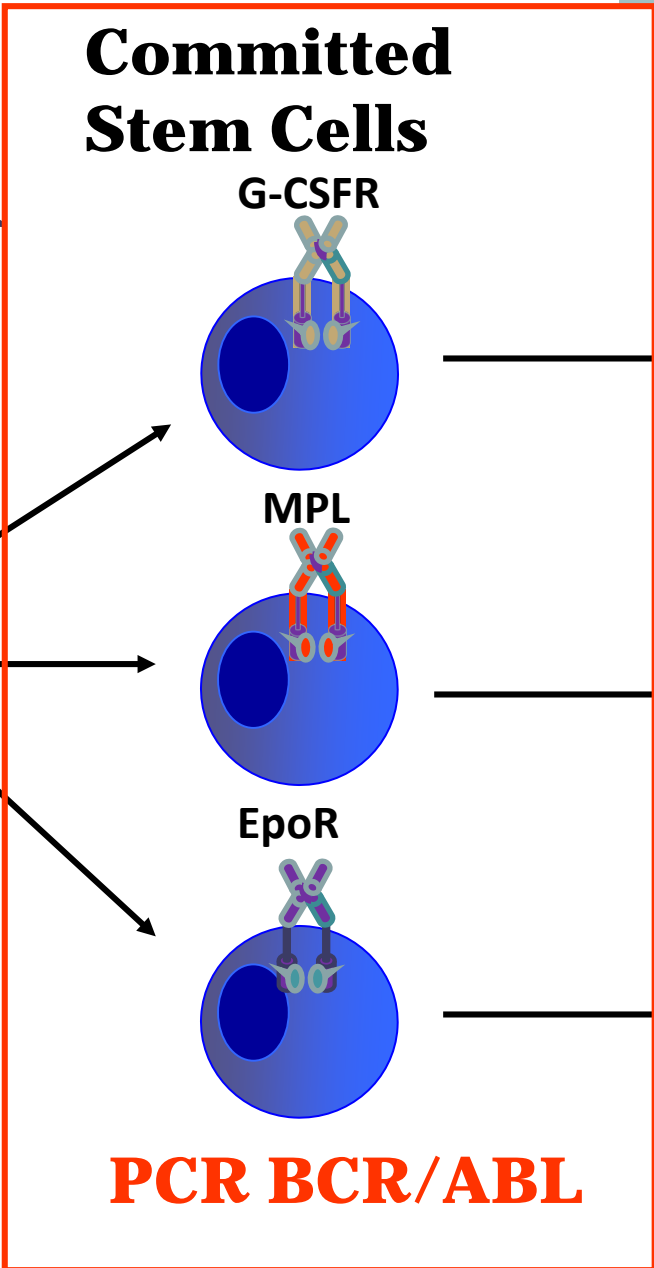
CML Stem Cells



- **More efficient DNA repair**
- **Lives longer**
- **Dormant (sleeping) Cell**

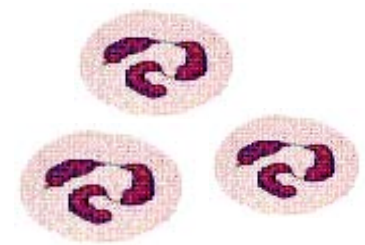


~~PCR BCR/ABL~~



PCR BCR/ABL

Mature Blood Cells



WBC



PLT

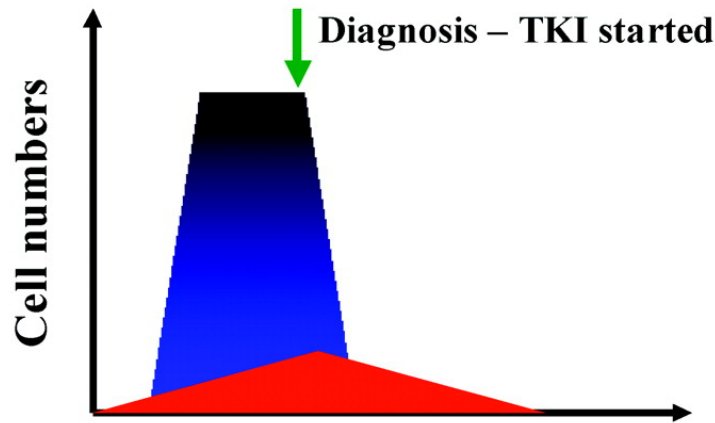


RBC

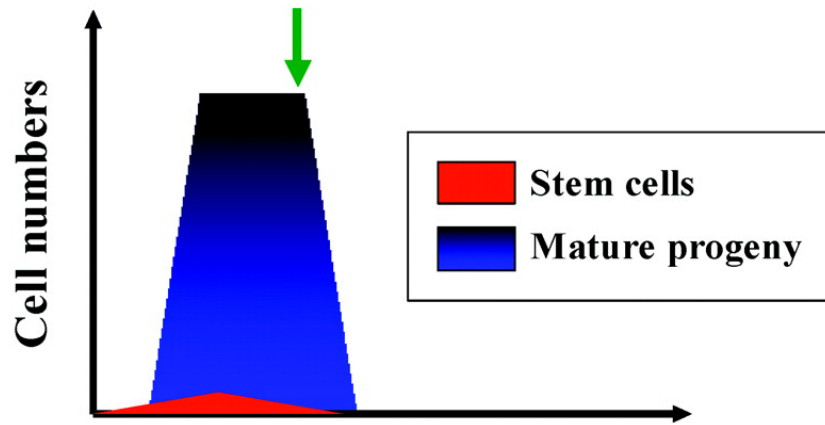
In search of the original leukemic clone in CML patients in complete molecular remission Melo et al Blood 2010

- In 5 IM-treated patients in CMR, gBCR-ABL was detected in transcript-negative samples; 4 patients became gBCR-ABL-negative with continuing IM therapy
- In contrast, of 9 patients in long term remission (13-27 years) post-SCT, gBCR-ABL was detected in only 1

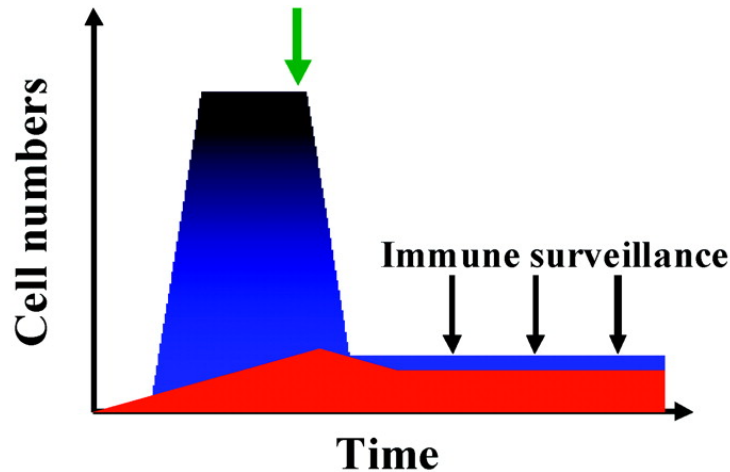
(A)



(B)



(C)



Stem Cell Depletion

The progressive depletion of immature CML cells over years of continued therapy

Stem-cell exhaustion

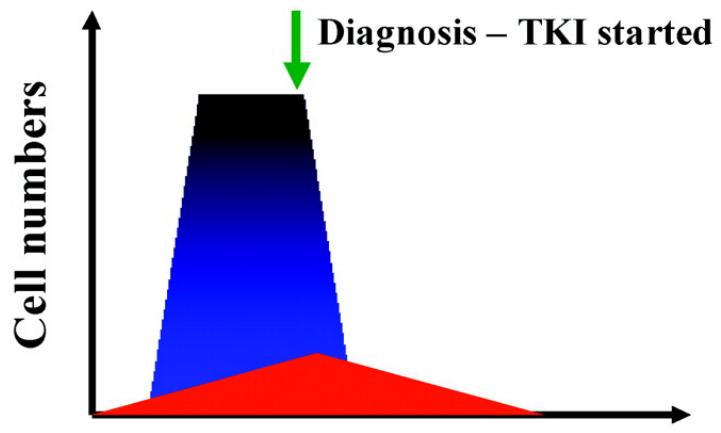
The CML stem-cell pool is relatively small and may become extinct before diagnosis or early in therapy

Immunological control

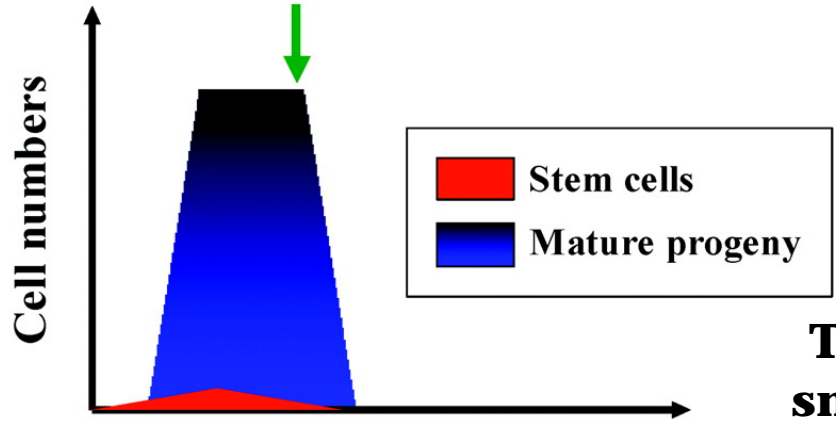
Killing the Last Leukemic Cell

**Detection of minimal residual
disease at the stem cell
levels**

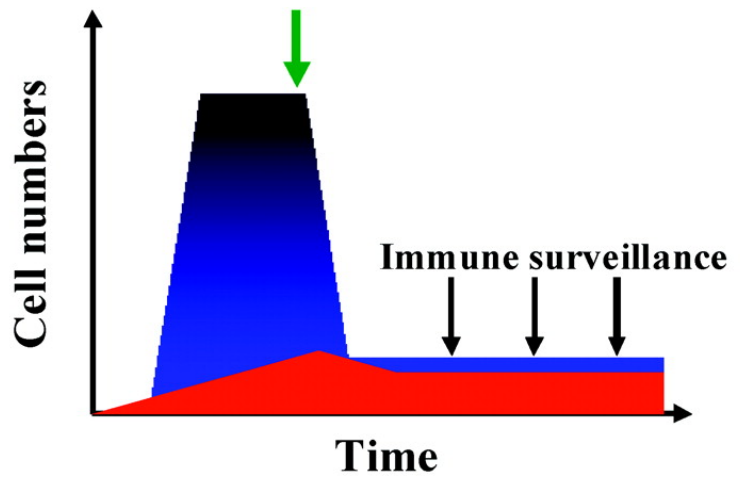
(A)



(B)



(C)



Better drugs
longer time of
therapy

Better parameters
at diagnosis +

Immune modulators
IFN
immunotherapy-
antibodies/Vaccine

Stop

imm

of

s of

Stop

The

small

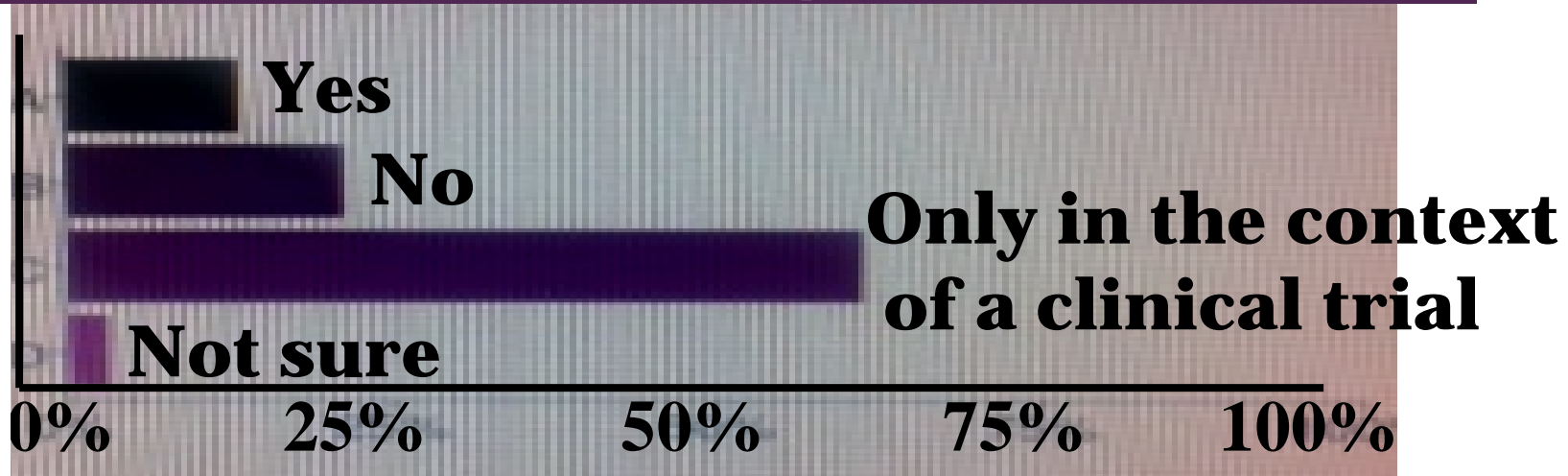
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Im

ASH 2011

Is Stopping Really a Feasible Approach?

Would you consider stopping TKI in patient with CML and a complete molecular response?



When do I Stop TKIs

- As part of clinical trial – one of the few clinical trials I am not encouraging patients to join
- Pregnancy
- Severe side effects in patients in complete molecular response for at least 3 years

Conclusion

- We do have operational cure in the majority of CML patients
- We have non maintained cure only in the minority of patients
- We need to identify and target the leukemic stem cell: new, combinations, immune
- Better selection of patients who can stop therapy

Thank You