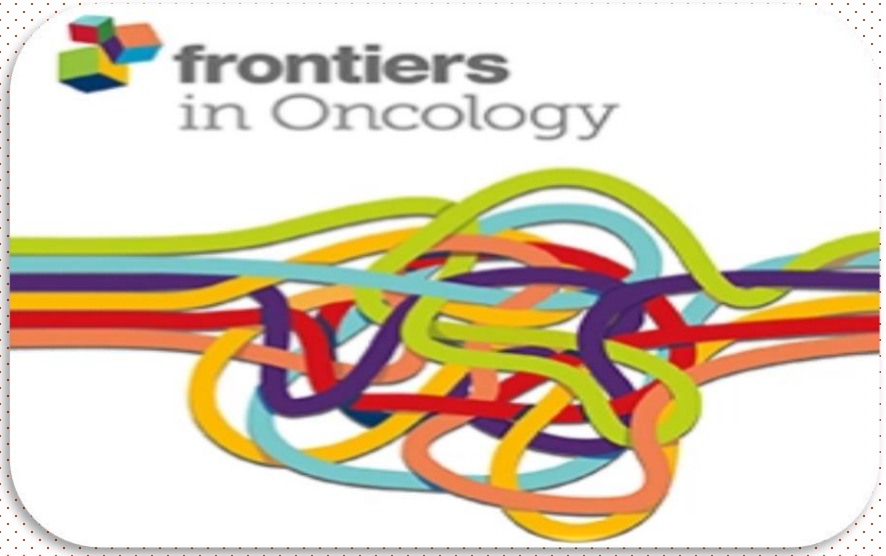
BCR-ABL INDEPENDENT MECHANISMS OF RESISTANCE IN CHRONIC MYELOID LEUKEMIA

Advisor:
Dr Roohollah Mirzaee
Dr Hajar Mardani

Presented by:
Sahar Mostajeran

LEUKEMIA



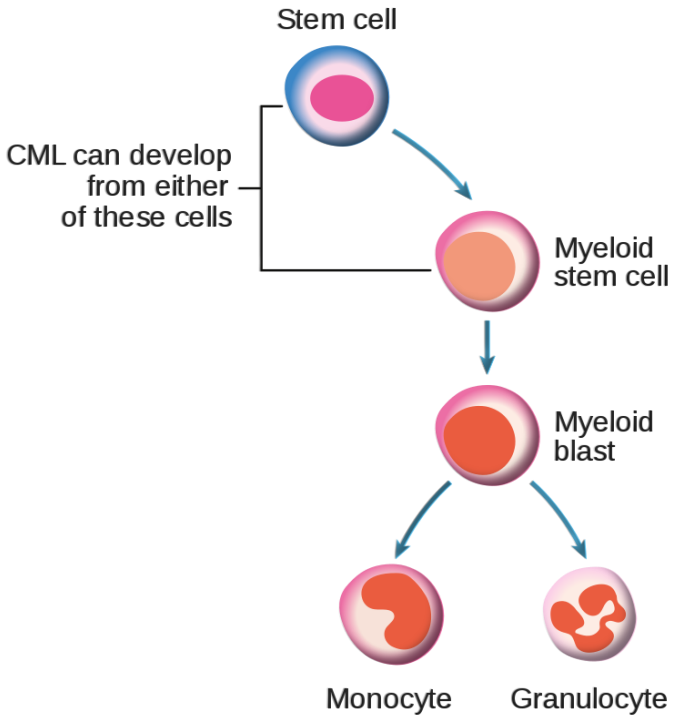
IMPACT FACTOR : 4.8

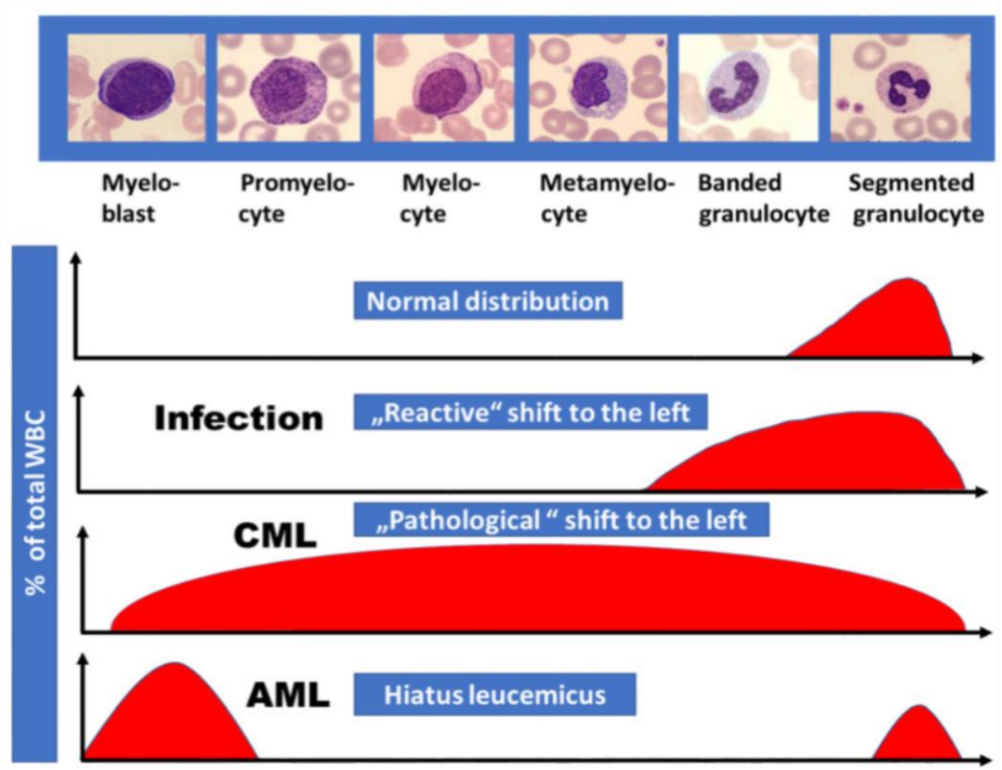
Article content :

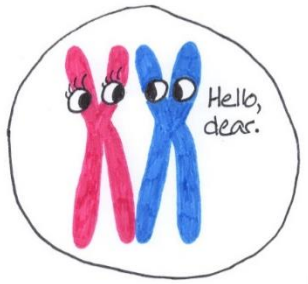
Introduction

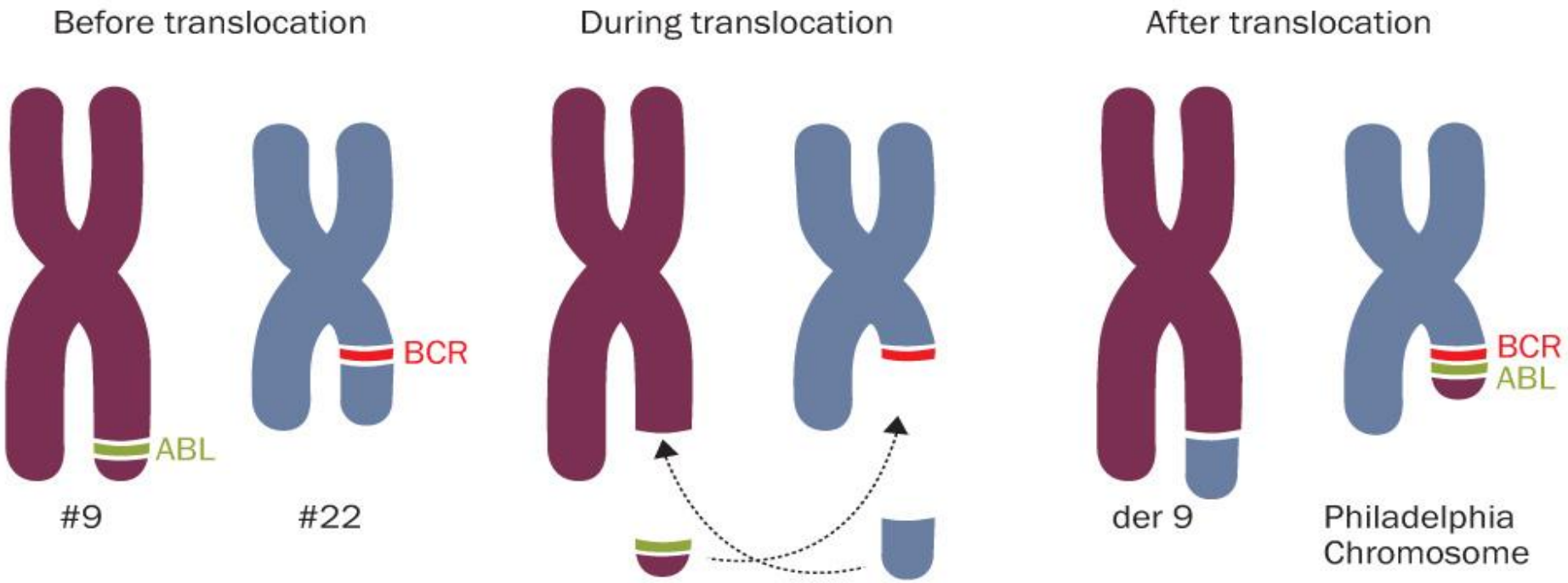
CONCLUSIONS

INTRODUCTION :

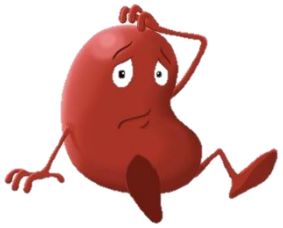




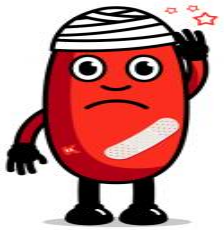

Hello,
dear.


Before translocation
During translocation
After translocation
ABL
BCR
BCR
ABL
#9
#22
der 9
Philadelphia
Chromosome

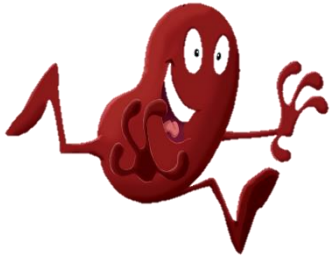
TREATMENT :



Chemotherapy



HSCT



TKI

REASONS FOR RESISTANCE TO TKI :

Primary

- Lack of response to treatment
- from the beginning

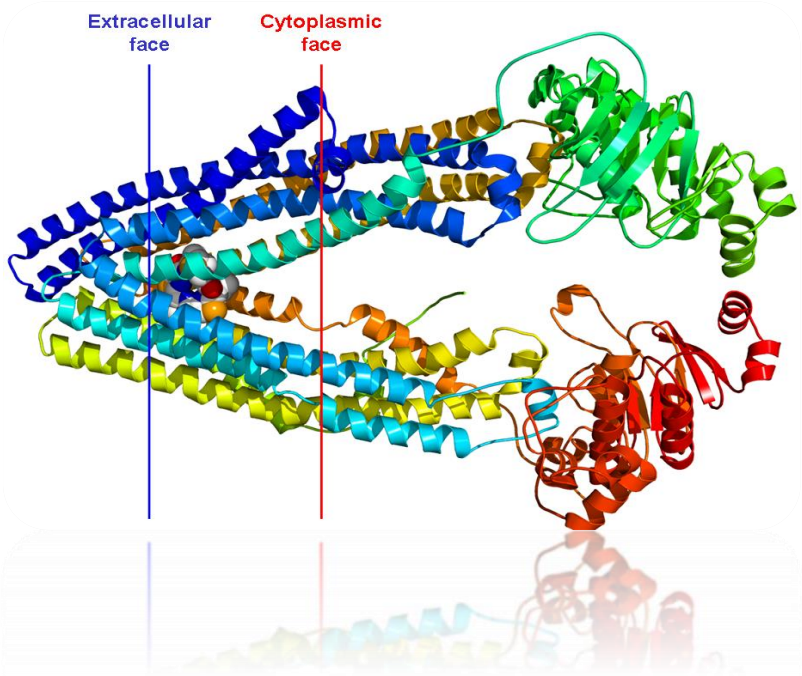
Acquired

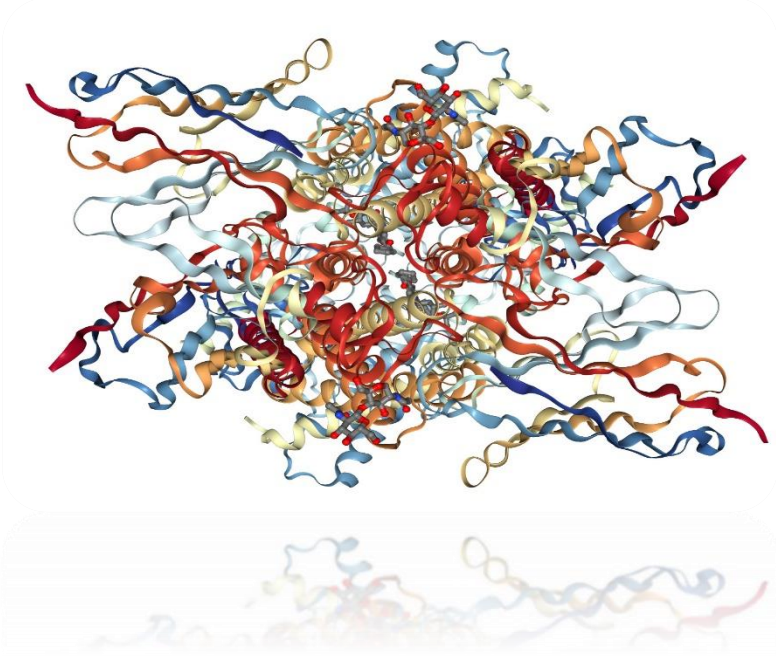
- Disease progresses after an initial response to therapy
- Develops during treatment

Primary resistance:

The overexpression of ATP-binding cassette (ABC) transporters :

1. P-glycoprotein (ABCB1 = MDR1)
2. Breast cancer resistance protein (ABCG2)



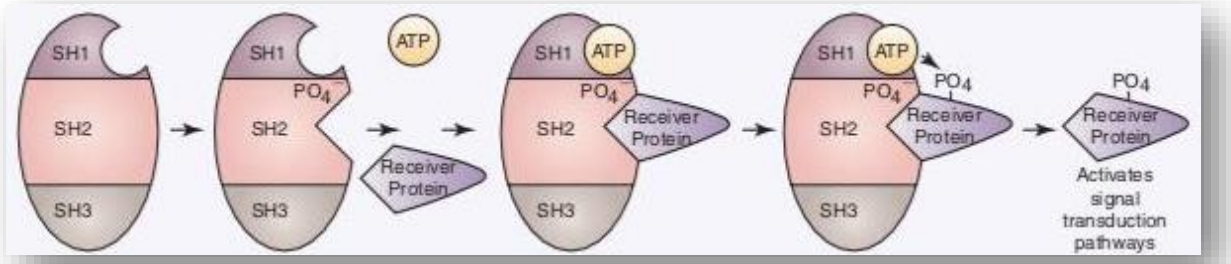


Acquired resistance:

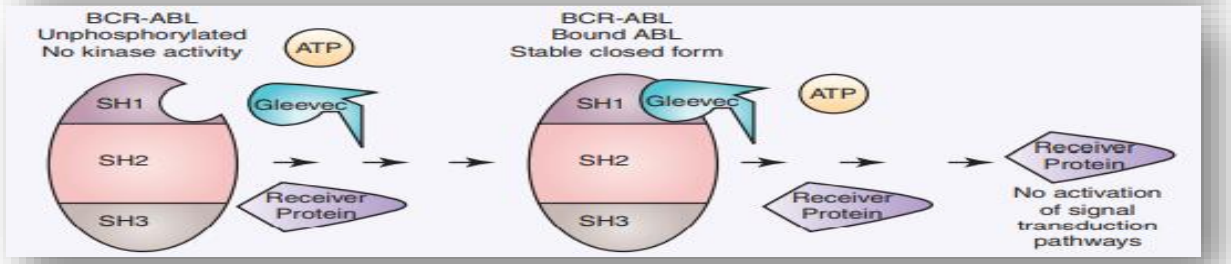
Point mutations in the BCR-ABL kinase domain

- **Mutation at the ATP binding site** → ***T315I***

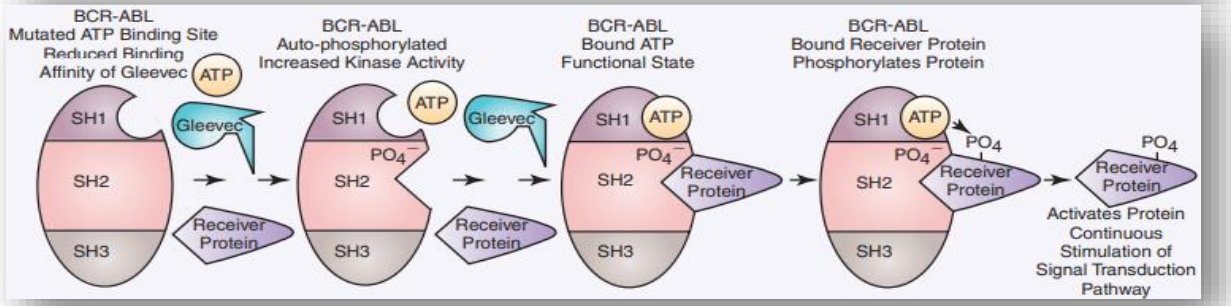
1.

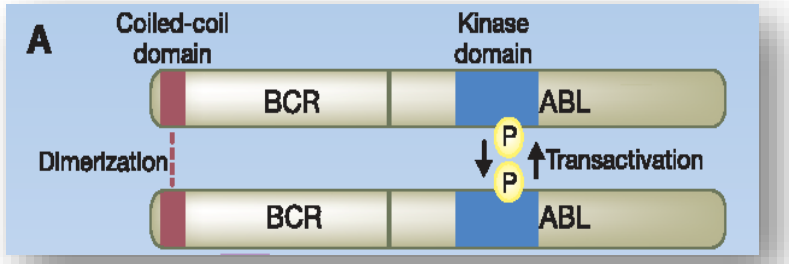


2.



3.



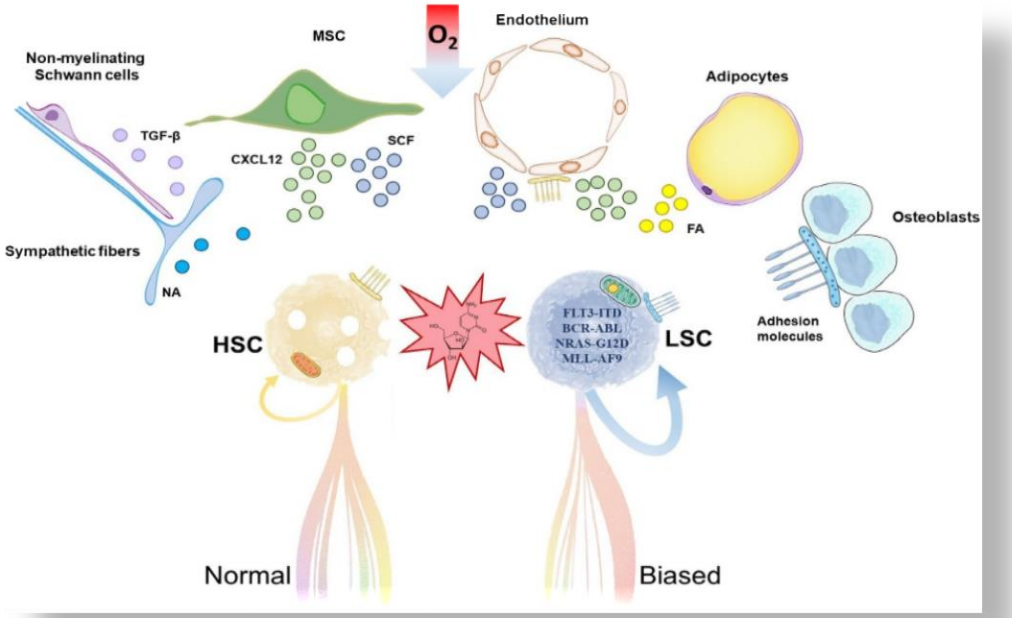


- BCR-ABL independent mechanisms of resistance with a special focus on :

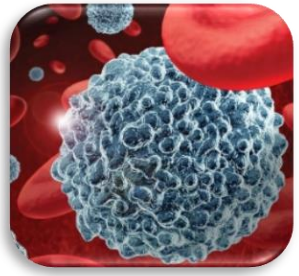
leukemia stem cells (LSCs)

- Interaction, within the hematopoietic niche, between

  LSCs and cells from the microenvironment



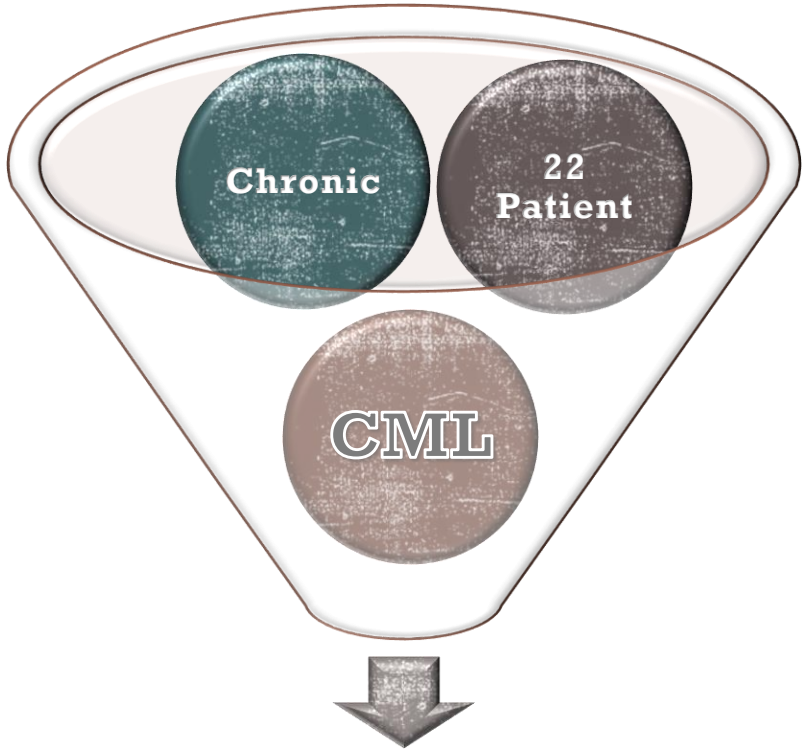
- Minimal residual disease (MRD)



LEUKEMIA STEM CELLS :

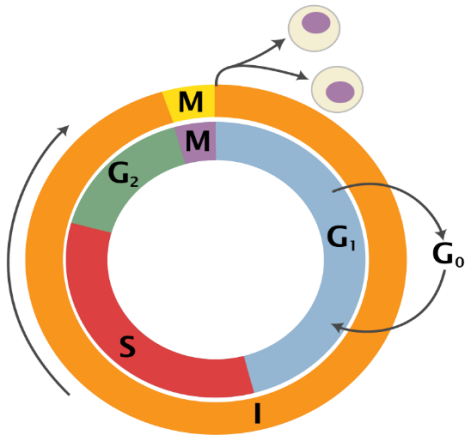
➢Heterogeneity of LSCs :

- ✓LSCs are a reservoir of tumor cells
- ✓Lead to relapse
- ✓CML-LSCs are selectively resistant to TKIs
- ✓Heterogeneity
- ✓It has been very difficult to characterize CML-LSCs



- CD26, IL1RAP, CD123, CD33, CD25
- Non-leukemic hematopoietic stem → *TNF-alfa and TNF-beta*
- Targeting inflammatory pathways

➢Quiescence:



✓CML-LSCs cell-cycle quiescence, is mechanism of resistance to TKI

✓BCR-ABL activity is not necessary for quiescent LSCs survival

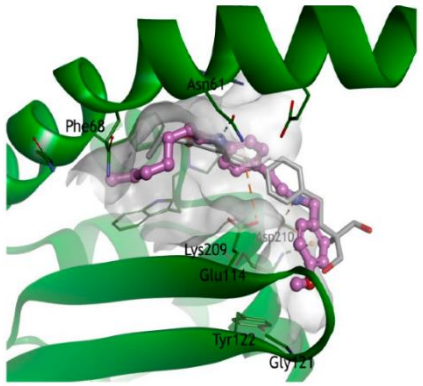
✓TKIs are not able to kill quiescent LSCs. Accordingly, LSCs persistence must be regulated by other aberrant pathways ➡ *JAK-STAT, CTNNB* (Catenin beta-1), *NFKB1A*

✓TGF beta, TNF-alfa

✓Phosphatase 2A (PP2A):

1. A tumor suppressor
2. Decrease survival and self-renewal of CML-LSCs
3. No effect on normal HSCs
4. Inhibition of JAK2 and β-catenin

❖FTY720=Fingolimod

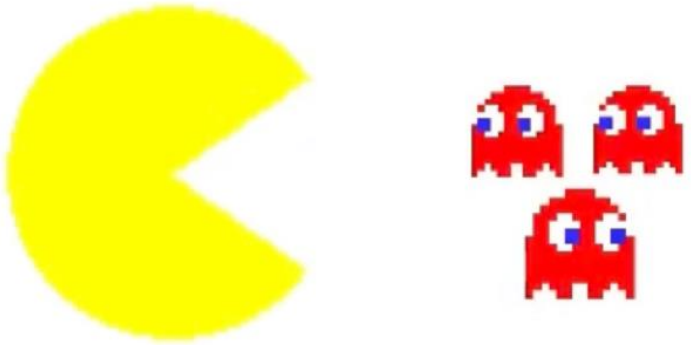


PP2A activator

Ineffective for normal HSCs

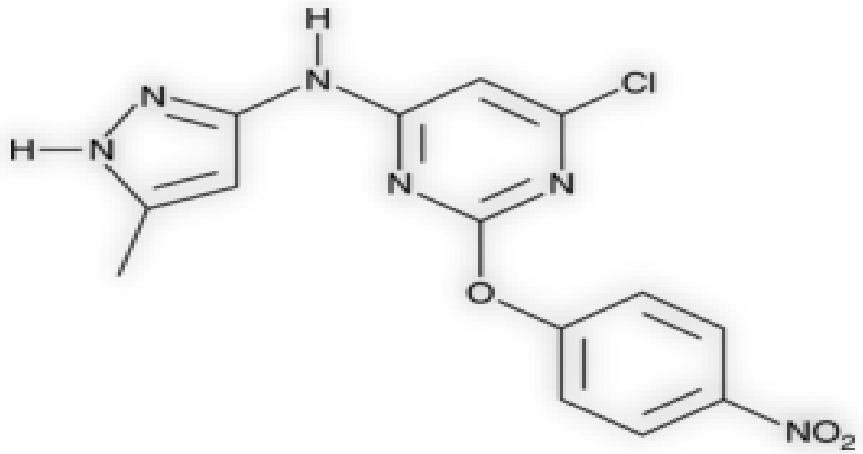
Damaged survival and self-renewal CML-LSCs

Inactivation of JAK2 and β-catenin, and not BCR-ABL1 inactivation

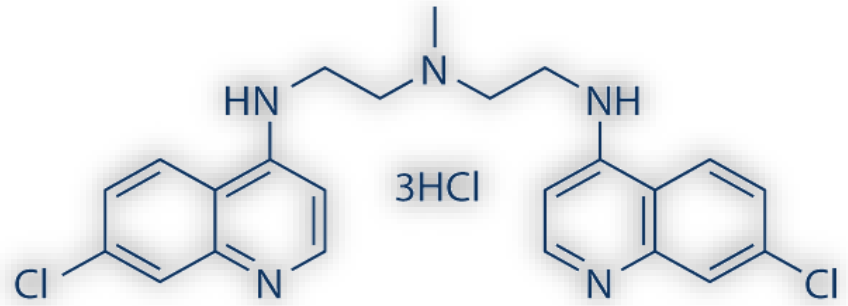


- In CML, TKIs treatment is responsible for the development of autophagy, which favors quiescent LSCs survival and TKI-resistance
- The inhibition of autophagy might revert TKI resistance and by targeting CML-LSCs causes death

- Lys05



- PIK-III



SIGNALING PATHWAYS :

- ✓RAF/MEK/ERK signaling
- ✓The increased expression of the protein kinase C (PKC) → sustains the RAF/MEK/ERK signaling → proliferation and inhibition of apoptosis
- ✓Check combining Imatinib and Trametinib (a MEK-inhibitor) in a mice model

TRANSCRIPTION FACTORS :

- ✓97 Differentially expressed genes were found in CML-LSCs vs normal HSCs
- ✓Cell metabolism, cell proliferation, cell surface, self-renewal, differentiation and inflammation

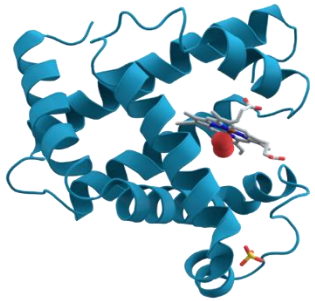
- **cell surface :**

- **CD26 :** *diabetes*
- **CD25 :** *neurological disorders such as multiple sclerosis*
- **IL1RAP :** *several inflammatory disorders*

EPIGENETICS EVENTS:

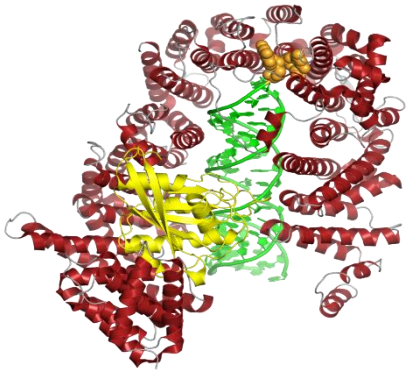
- ✓Resistance to TKI treatment and CpGs islands was recently demonstrated
- ✓Histone acetylase and deacetylase, Methyl transferases
- ✓Transcription factor AP-2 alpha (TFAP2A), early B-cell factor 2 (EBP2), Autophagy related 16-like 1 (ATG16L1)
- ✓SIRT1 deacetylase

- **SIRT1 Deacetylase :**

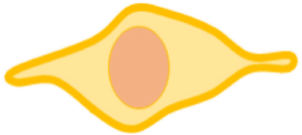


- ✓Expressed is higher in human CML CD34+ cells than in normal CD34+ cells
- ✓Supporter of genetic mutations and critical to keep CML-LSCs alive
- ✓Inhibition of SIRT1
- ✓Promotes CML-LSCs apoptosis
- ✓SIRT1 inhibition had no significant effect on normal CD34+ cells
- ✓As a result, inhibiting SIRT1 is a new frontier

miRNA :



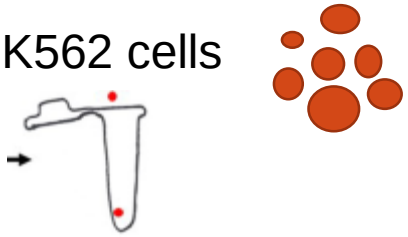
- ✓miRNAs are tumor suppressors at overall level
- ✓miRNAs expression in K562 cell line
- ✓miR-29, miR-23a and miR-451
- ✓Inverse relationship between miR-451 and BCR-ABL1 expression
- ✓miR-126 → *CXCL12/CXCR4*



MESENCHYMAL STEM CELL :

- ✓Recently gained attention
- ✓Difference between MSC gene expression of patients with CML and MSC in healthy individuals → *NANOG*, *MITF*
- ✓Possibility of abnormal MSC gene expression during CML development
- ✓MSCs produce CXCL12
- ✓G-CSF

- K562 cells



- Imatinib

stroma-derived conditioned medium

HS-5 cells

STAT3

Bcl-xl ↑

Mcl-1 ↑

Apoptosis ↓

Survival ↑

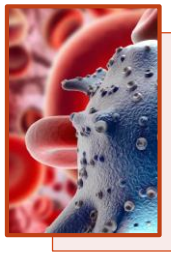
IMMUNE SYSTEM :

- ✓To develop the disease and progress, for prognosis and response to treatment
- ✓The accumulation of immature myeloid cells leads to suppression of the innate immune system
- ✓NK cells and cytotoxic T cell
- ✓PD1, CTLA4, TIM3

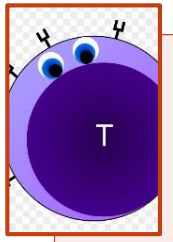
RESPONSE TO TREATMENT :

56 CML patients

14 Healthy controls

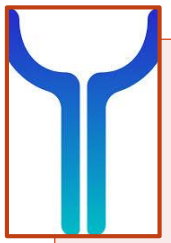


Severe suppression of myeloid immune system and lymphocytes in BM



Low ratio of CD4 T cells to CD8 T cells

High PB Neut



Higher levels of PD-1, TIM3, CTLA4

STRATEGIES TO FIGHT BCR-ABL INDEPENDENT RESISTANCE :

Nilotinib

Ruxolitinib

Increased apoptosis

JAK2-STAT3

Imatinib

Pioglitazone

Pulls them out quiescence

Overcoming resistance to treatment

Imatinib

+

Decitabine or Azacytidine

→

Able to generate answers even in advanced stages

Not durable

TKI

TKIs

+

p53 stabilization combined with **BET** inhibitor

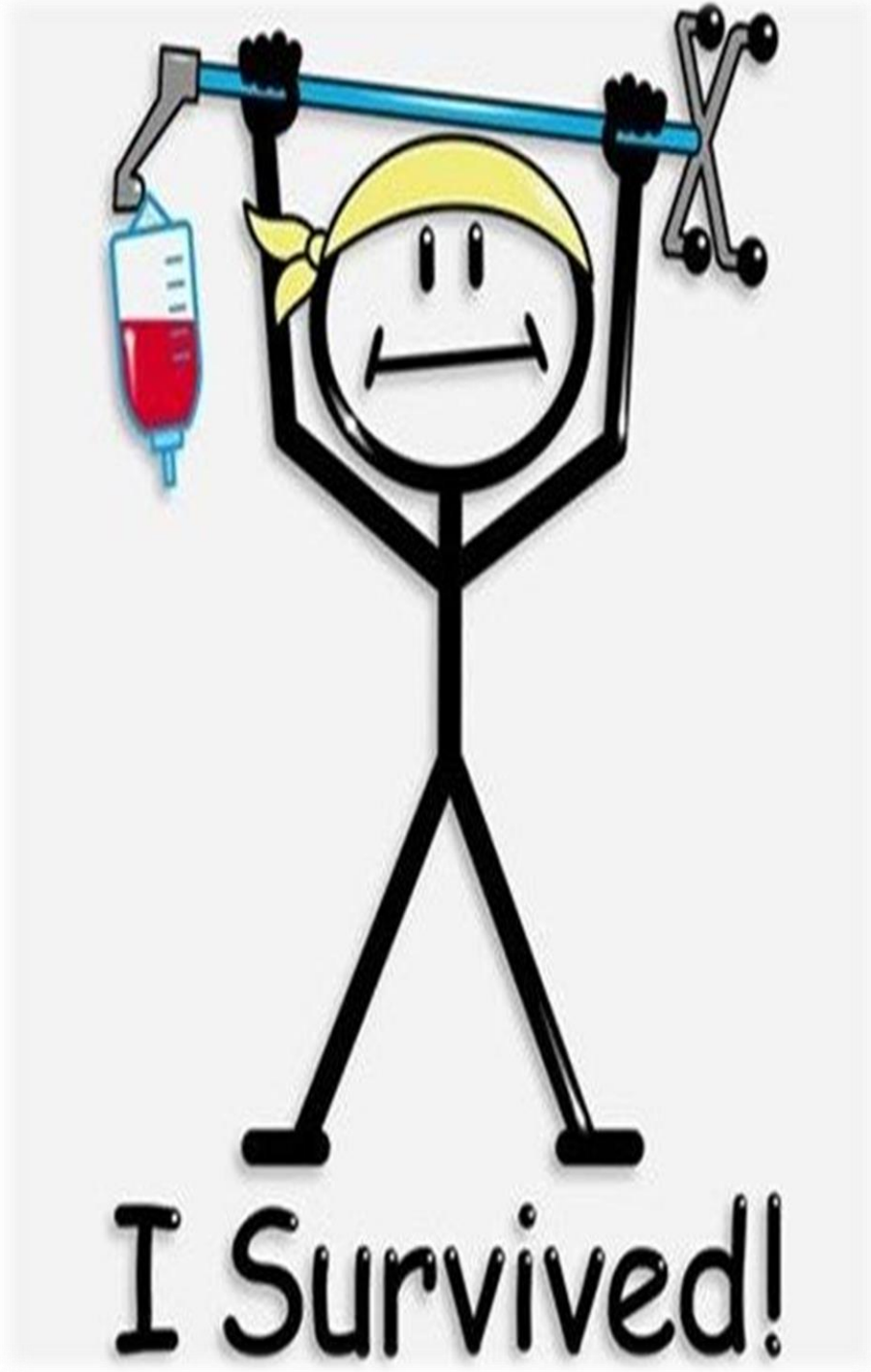
→

Chromatin disruption

Destruction of CD34 + cells

CONCLUSIONS :

- ✓The rate of improvement is still low
- ✓Persistence of MRD in most CML patients
- ✓LSCs in CML
- ✓These mechanisms of resistance, BCR-ABL independent, are responsible for TKI failure
- ✓Therapeutic approach to target LSCs and, consequently, treat a large number of CML patients
- ✓Increase the speed of treatment


I Survived!


I WON