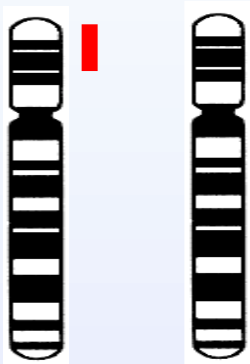
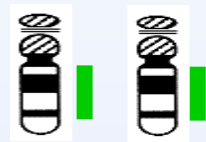


*Structure and Function of  
Fusion Gene Products in  
Childhood Acute Leukemia*

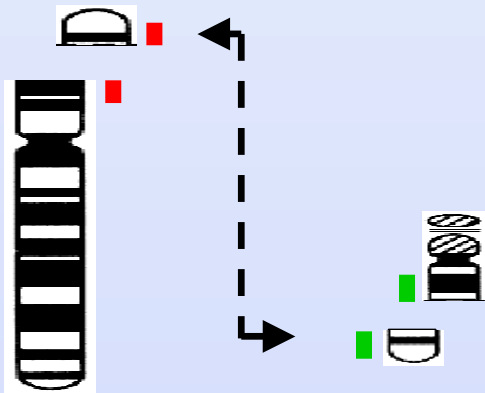
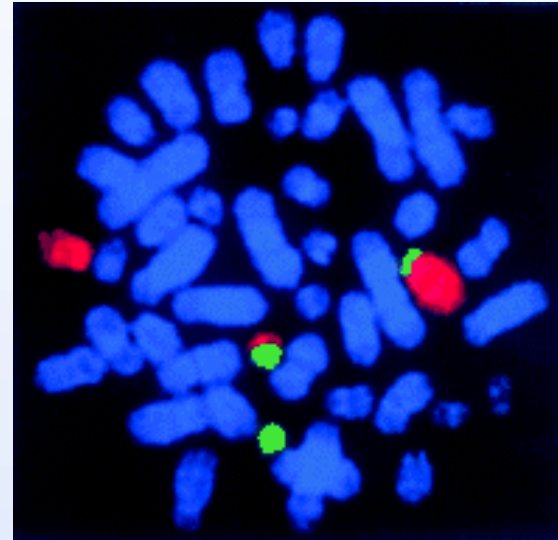
# Chromosomal Translocations



Chr. 12



Chr. 21

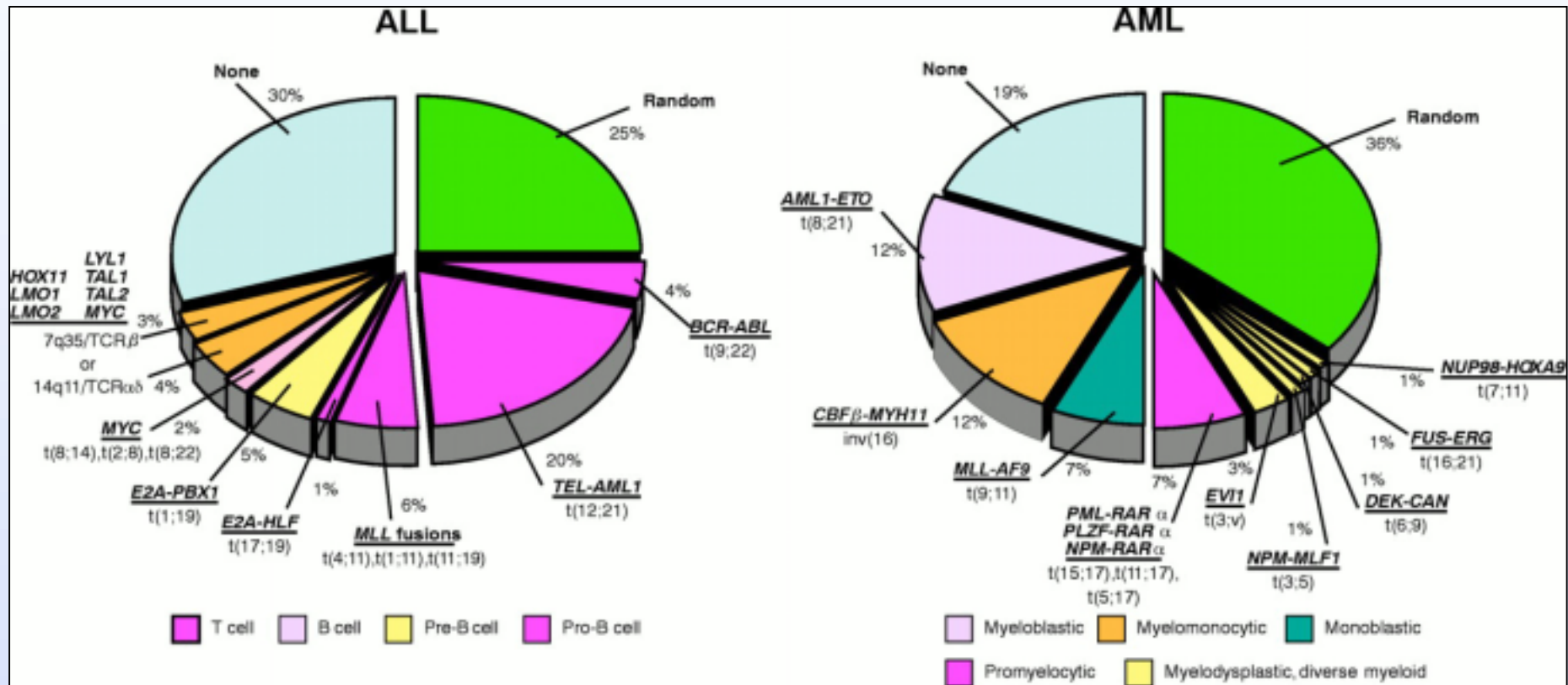


der(12)



der(21)

# Distribution



A.T. Look, Science 278 (1997)

Charisi

# Childhood ALL

- TEL-AML1 t(12;21) 20%

*Transcription factors*

- E2A-PBX1 t(1;19) 5%

*Transcription factors*

- MLL fusions 6%

*MLL-AF4* t(4;11)

*MLL-AF9* t(1;11)

*MLL-ENL* t(11;19)

*~ 30 diff. translocation partners*

*Transcription factor*

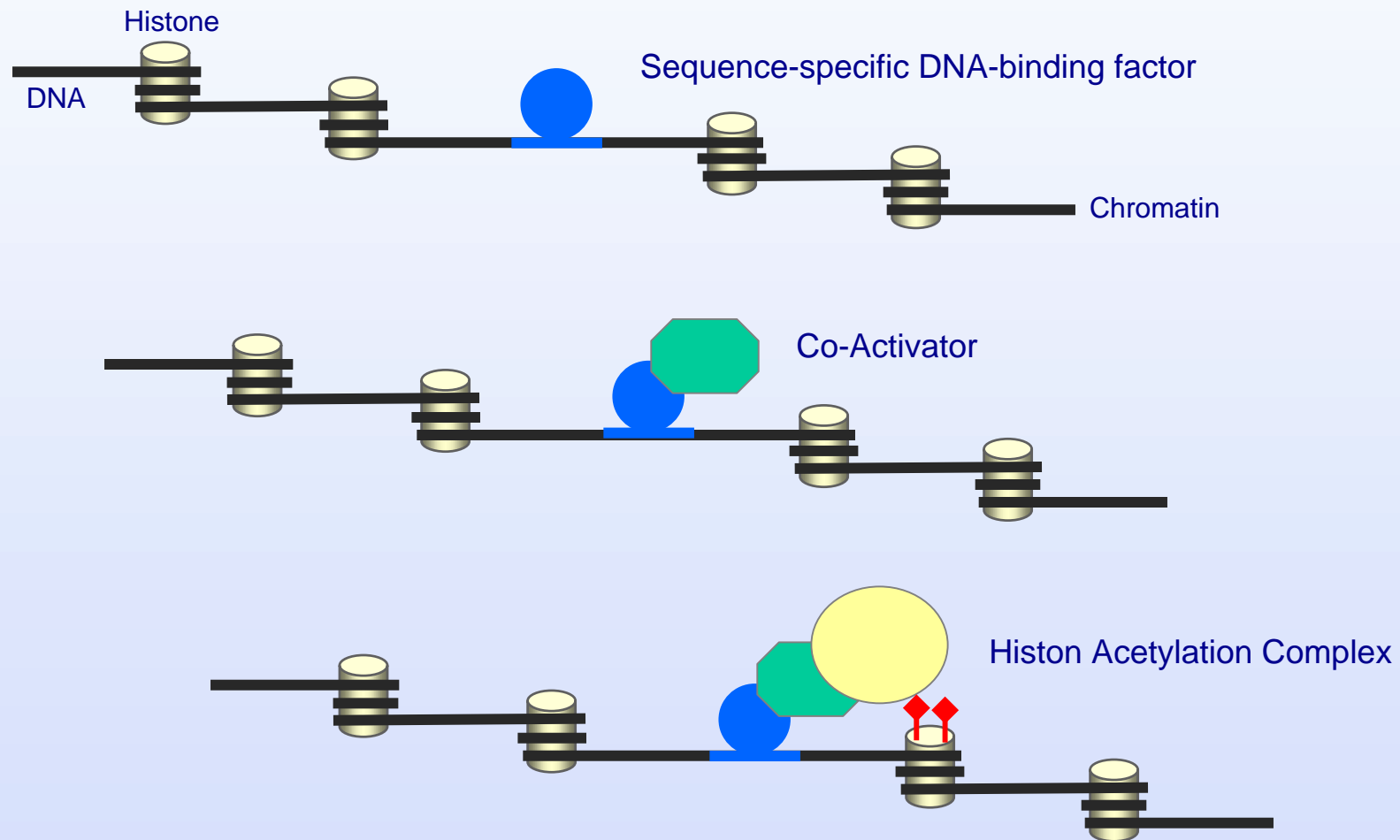
- BCR-ABL t(9;22) 4%

*BCR-ABL* p190 60%

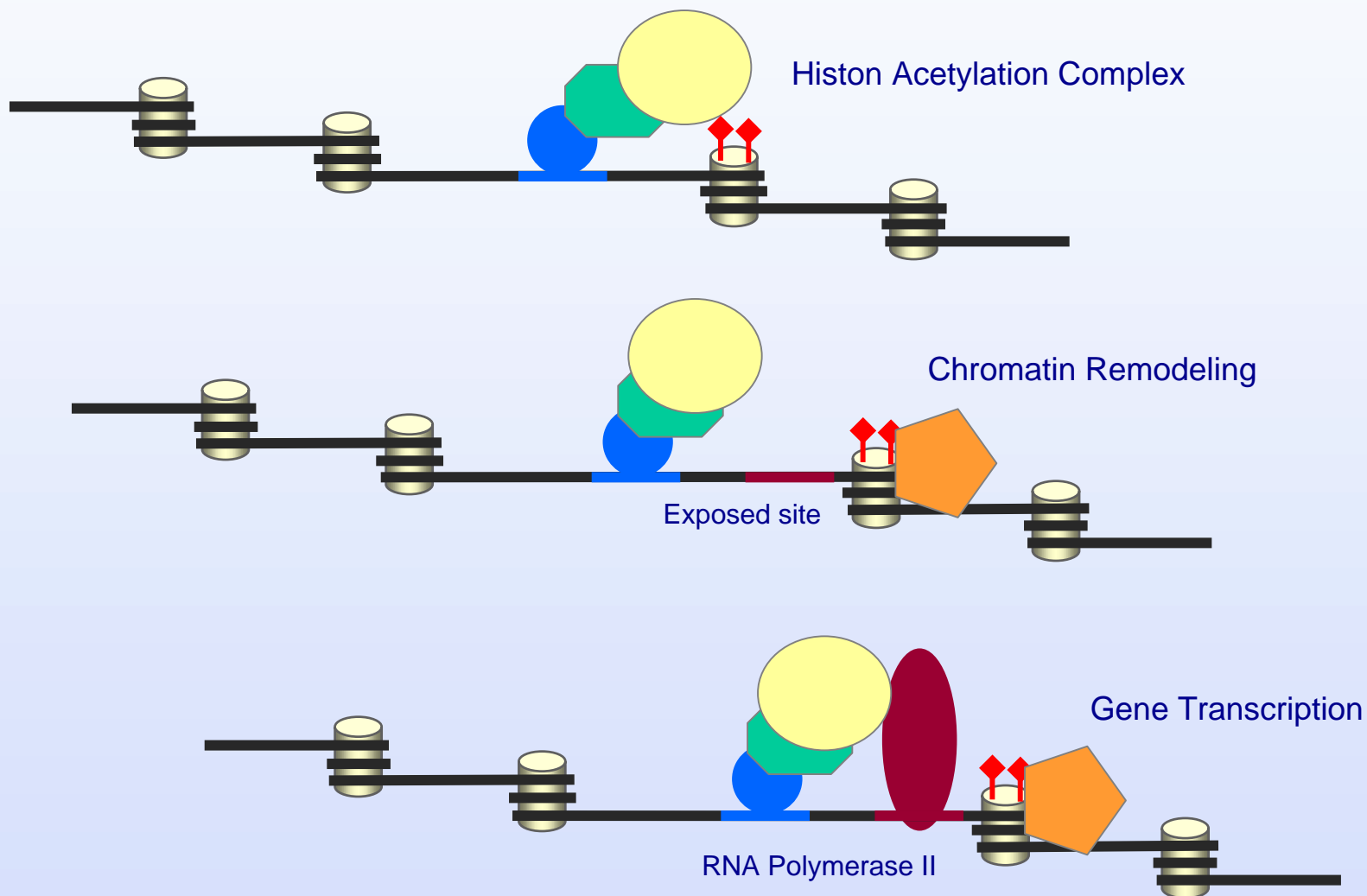
*BCR-ABL* p210 40%

*Protein kinases*

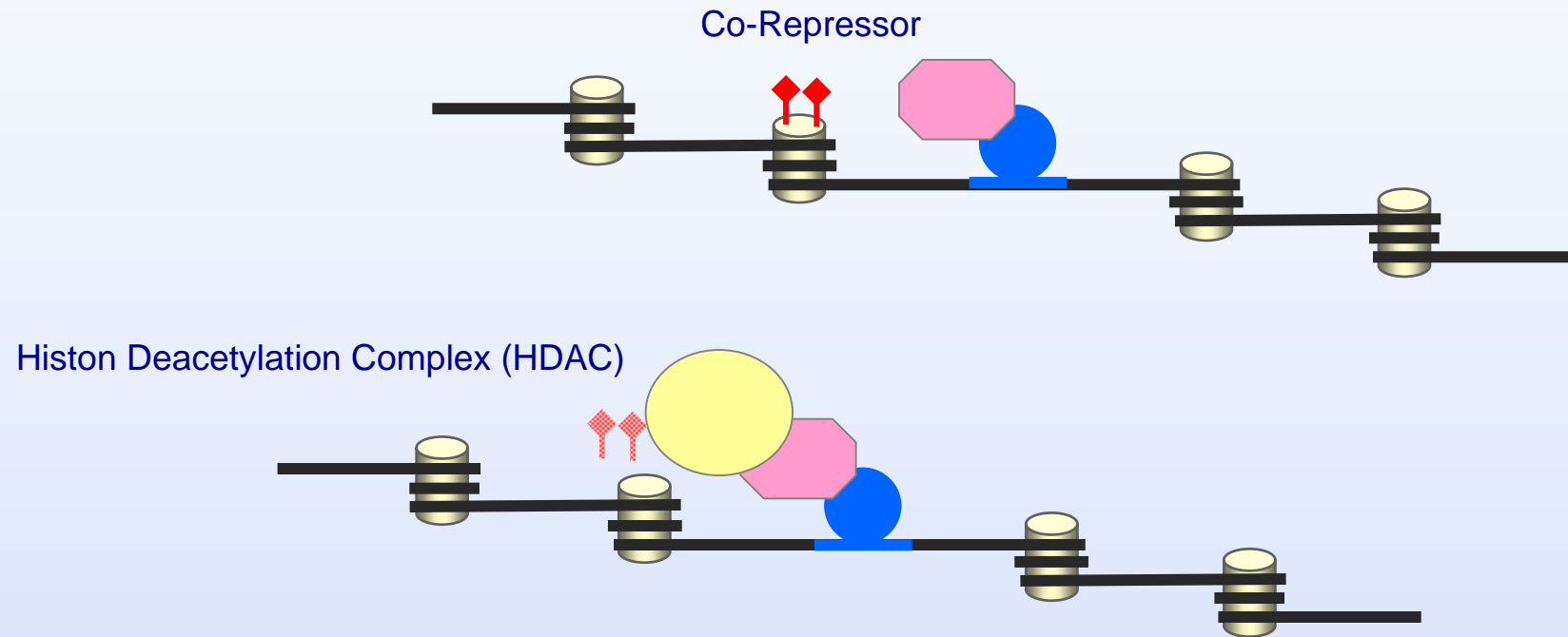
# Transcriptional Activation



# Transcriptional Activation



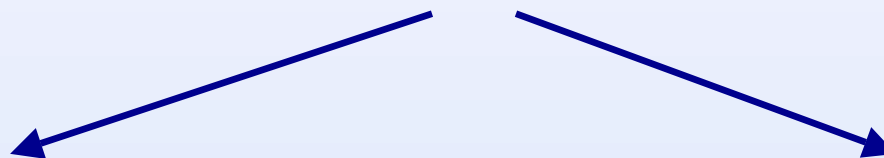
# Transcriptional Repression



Chromatin Condensation and Gene Silencing

# Combinatorial Control

Transcription factors build up  
activating or repressing protein complexes



*Differential effects depending  
on molecular environment*

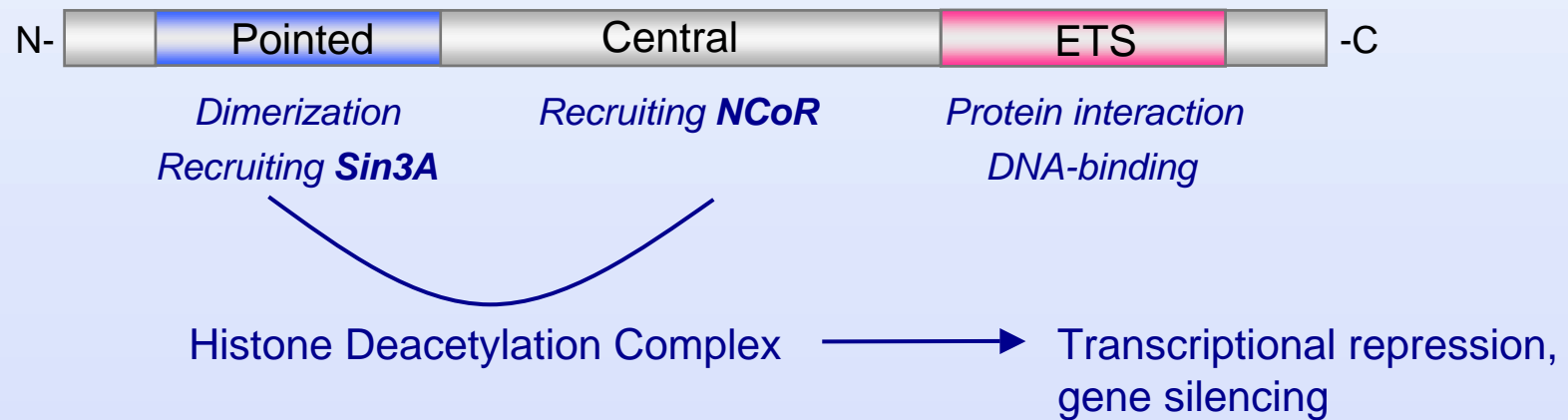
*Cross talk between  
signaling pathways*

# TEL

Synonym: ETV6

Ets-like transcription factor

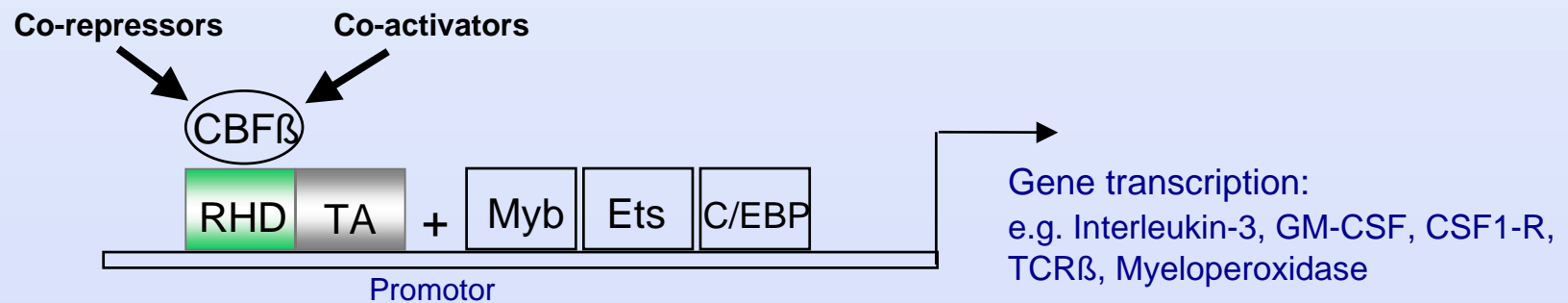
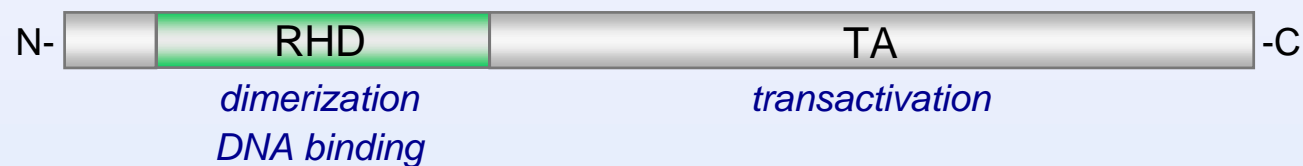
Widely expressed in all normal tissues, frequently lost in tumors



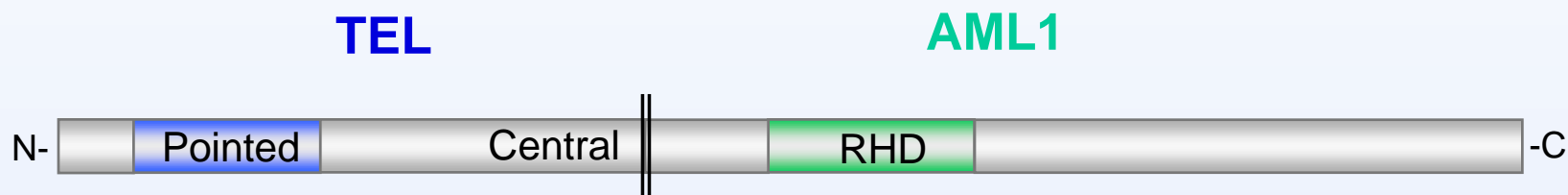
# AML1

Synonyms: RUNX1 / CBFA2 / PEB2 $\alpha$ B

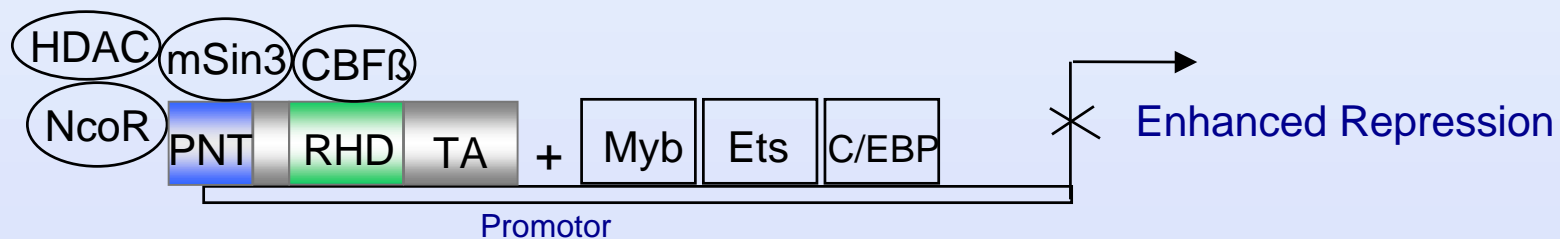
Gene family, homologous to *Drosophila runt*



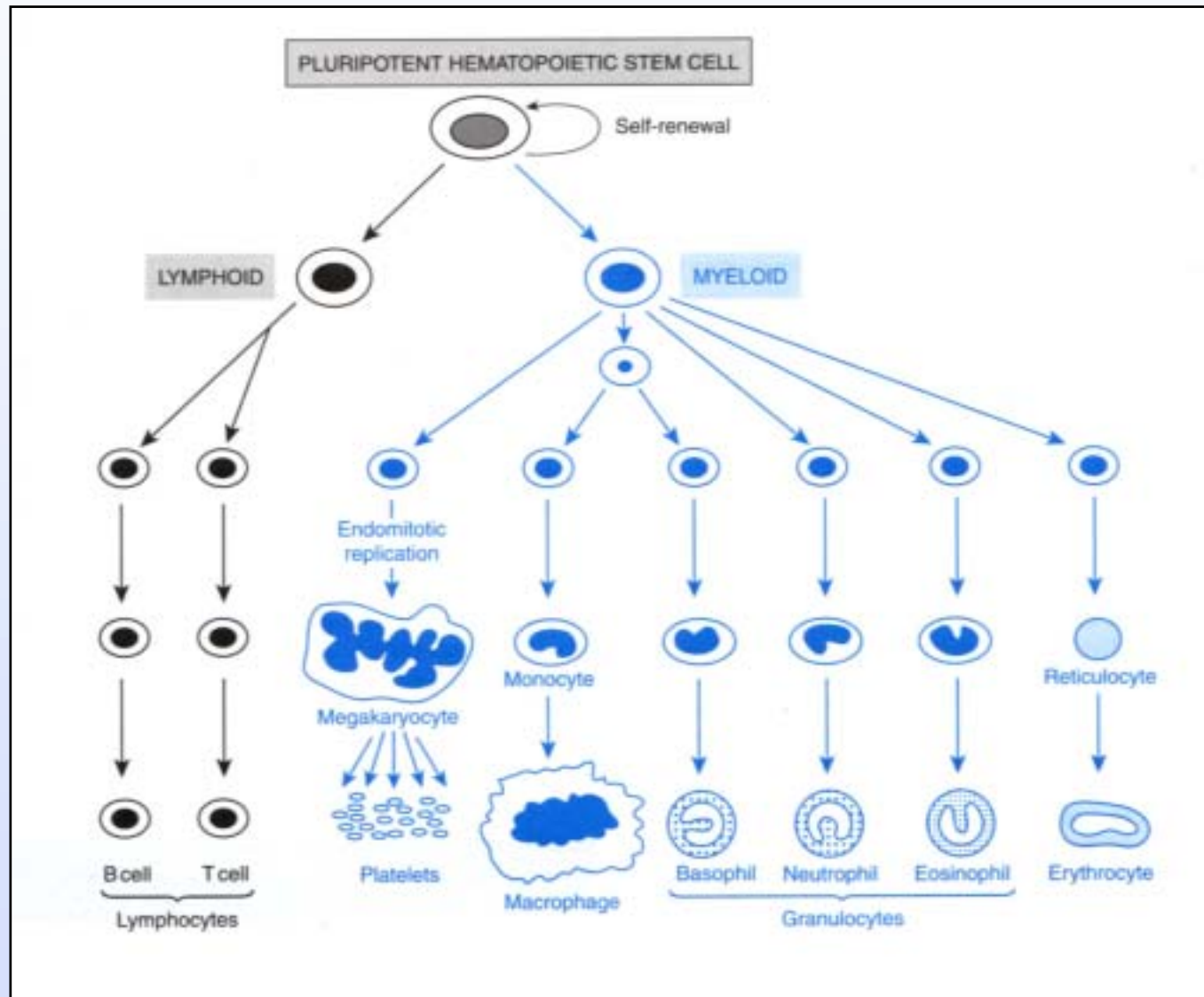
# TEL-AML1



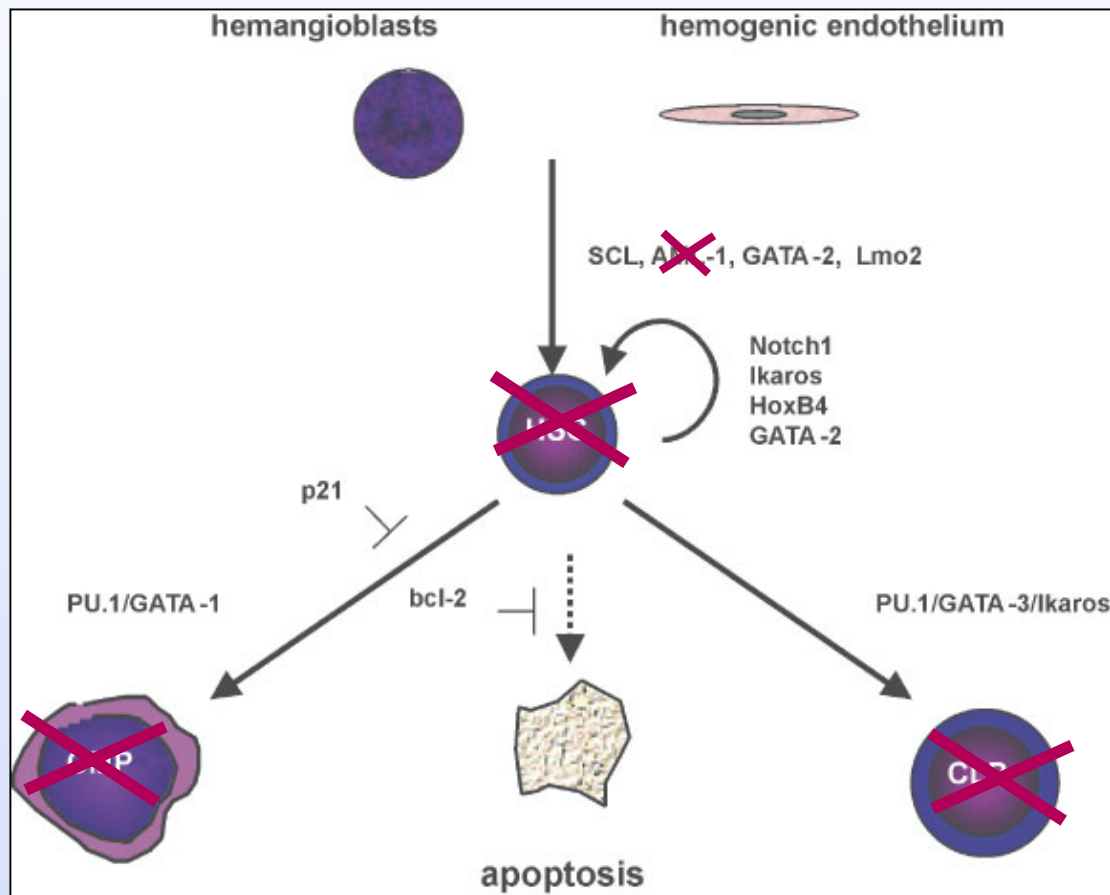
## Deregulation of AML1 target genes



# Hematopoiesis



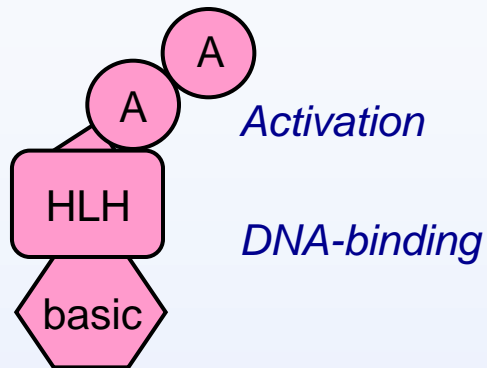
# TEL-AML1



J. Zhu et al., *Oncogene* 21 (2002)

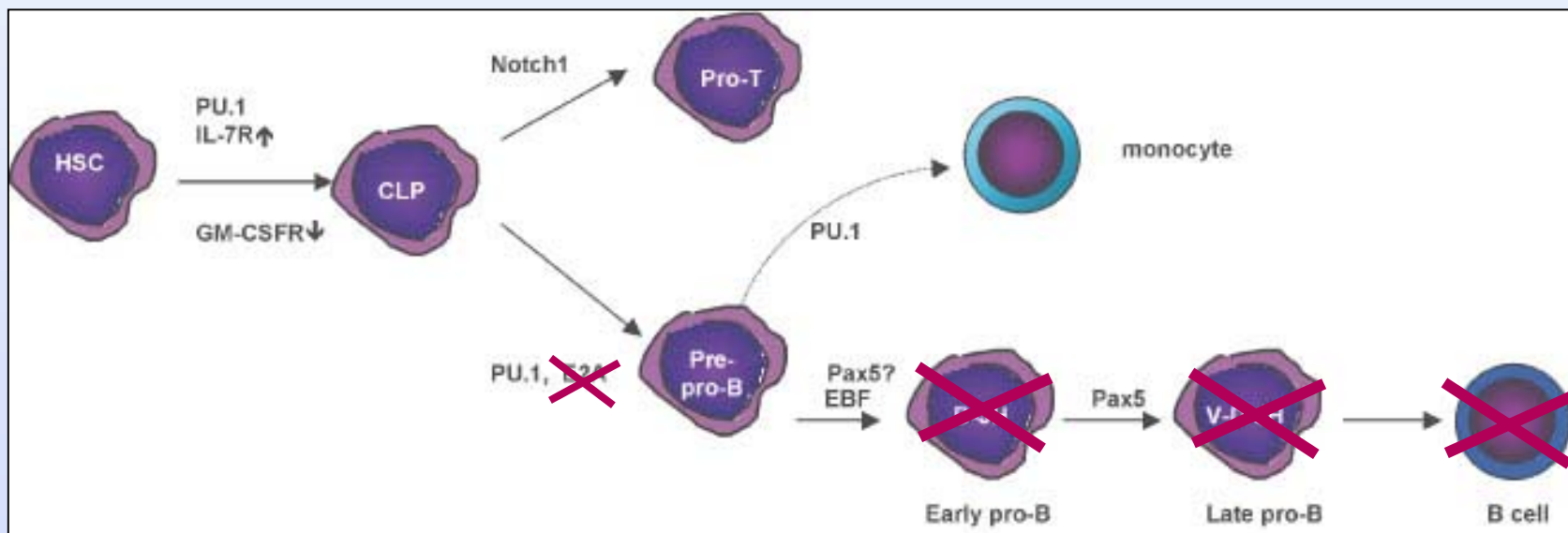
- WT AML1:  
necessary for hematopoietic stem cells
- TEL-AML1:  
generation of a pre-leukemic cell population
- Secondary genetic lesions  
necessary for transformation

# E2A



- bHLH transcription factor
- Regulates B-cell lineage genes, e.g. immunoglobulins, transcription factors EBF-1, Rag-1

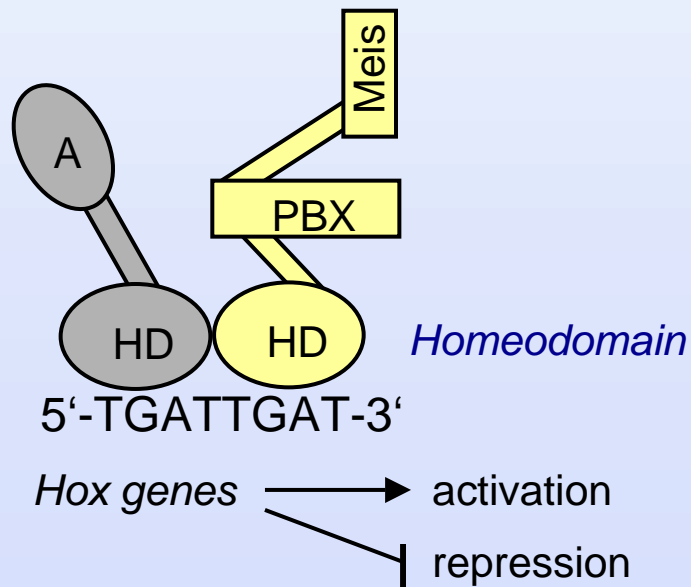
- Regulator of **lymphocyte differentiation**



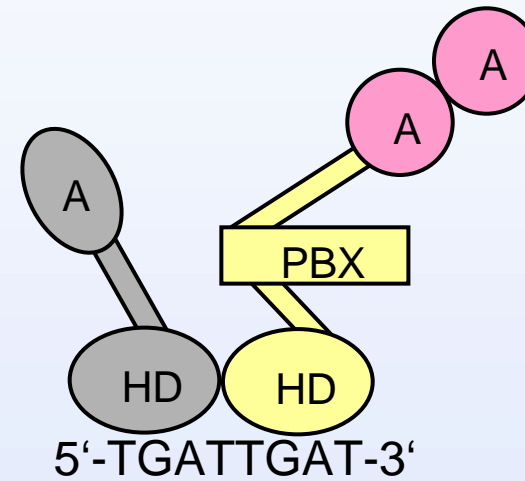
# E2A-PBX1

- PBX1

- homologous to *Drosophila extradenticle (exd)*
- normally not expressed in lymphoid cells
- Cofactor for HOX proteins



- E2A-PBX1

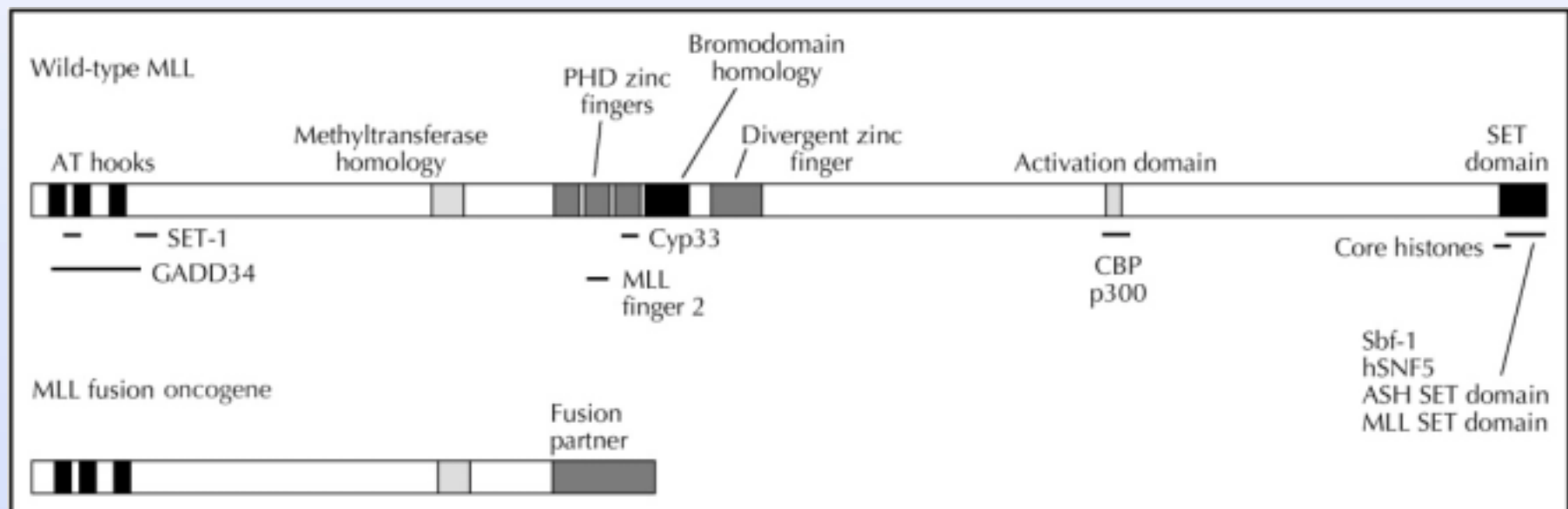


*Hox genes* → activation

- aberrant *Hox* gene activation
- Disturbance of lymphoid differentiation
- Promotion of uncontrolled cell division

# MLL Fusions

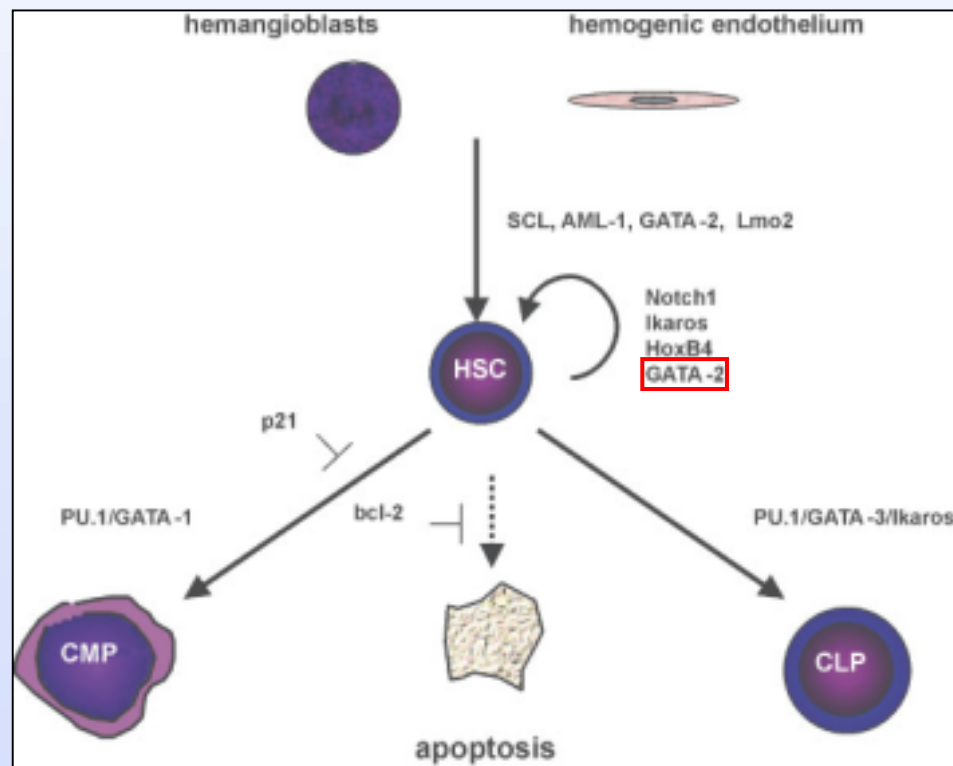
- MLL gene
  - *Mixed Lineage Leukemia*
  - homologous to *Drosophila trithorax (trx)*
- MLL fusions



P. Ernst et al., *Curr. Opin. Hematol.* 9 (2002)

# MLL Function

- maintenance of *Hox* gene expression
- loss of MLL leads to severe developmental defects in mice
- Role in hematopoiesis: downstream or parallel of *GATA-2*



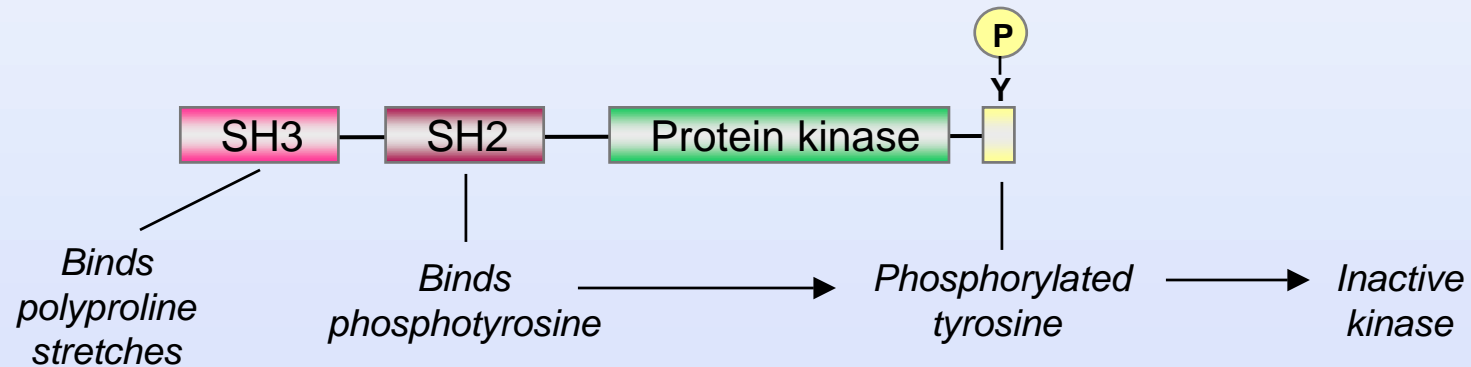
J. Zhu et al., *Oncogene* 21 (2002)

# Protein Kinases

- Phosphorylation of *serine & threonine* or *tyrosine* residues
  - Serine-threonine kinases
  - Tyrosine kinases
- Phosphorylation is a common mechanism to regulate protein activity
- Protein phosphatases reverse the effects of protein kinases

# Tyrosine Kinases

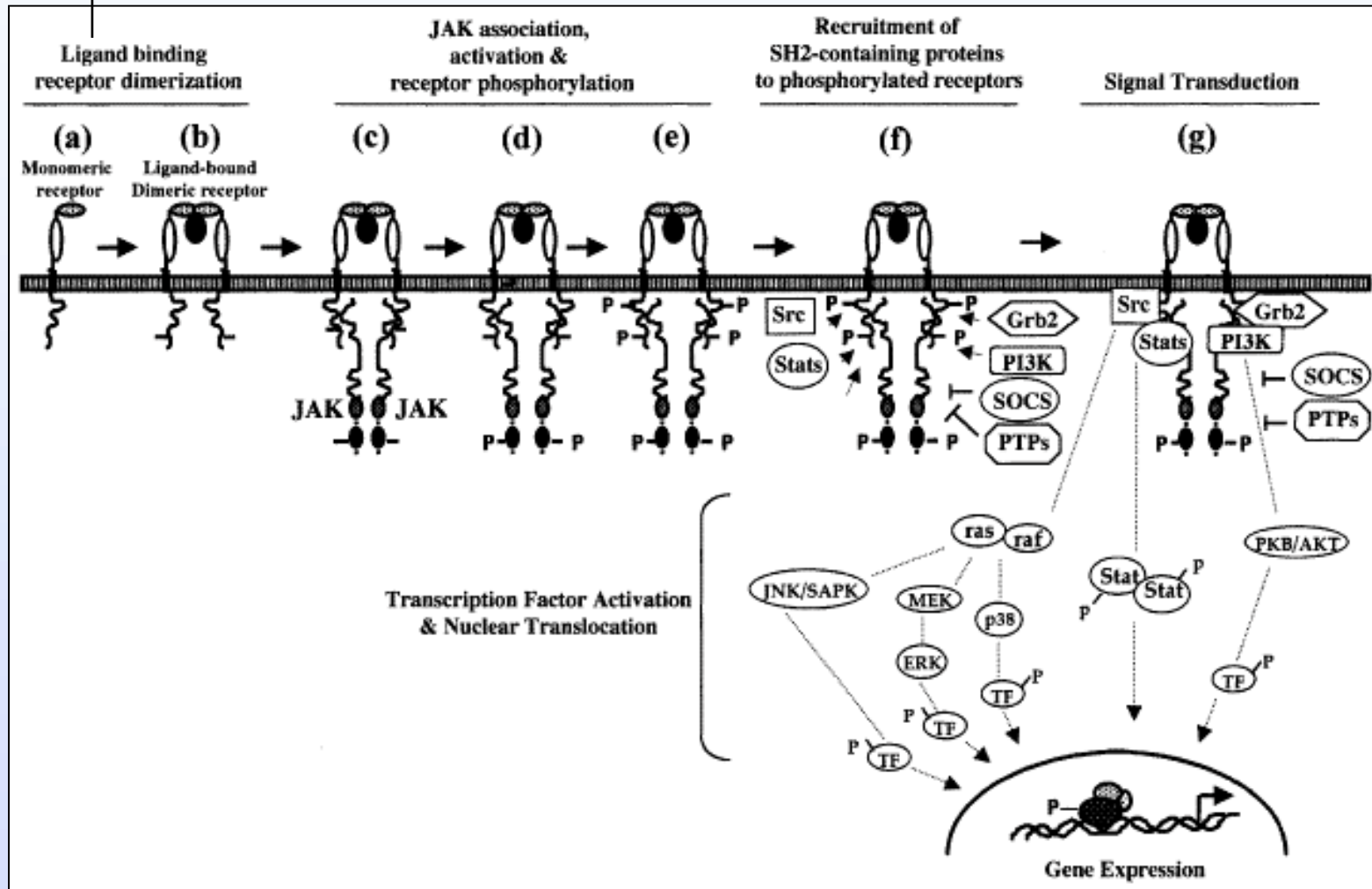
- Receptor tyrosine kinases (membrane bound)
- Non-receptor tyrosine kinases (cytoplasmic)  
*e.g. Src family of kinases*



# Signal transduction

## Cytokines

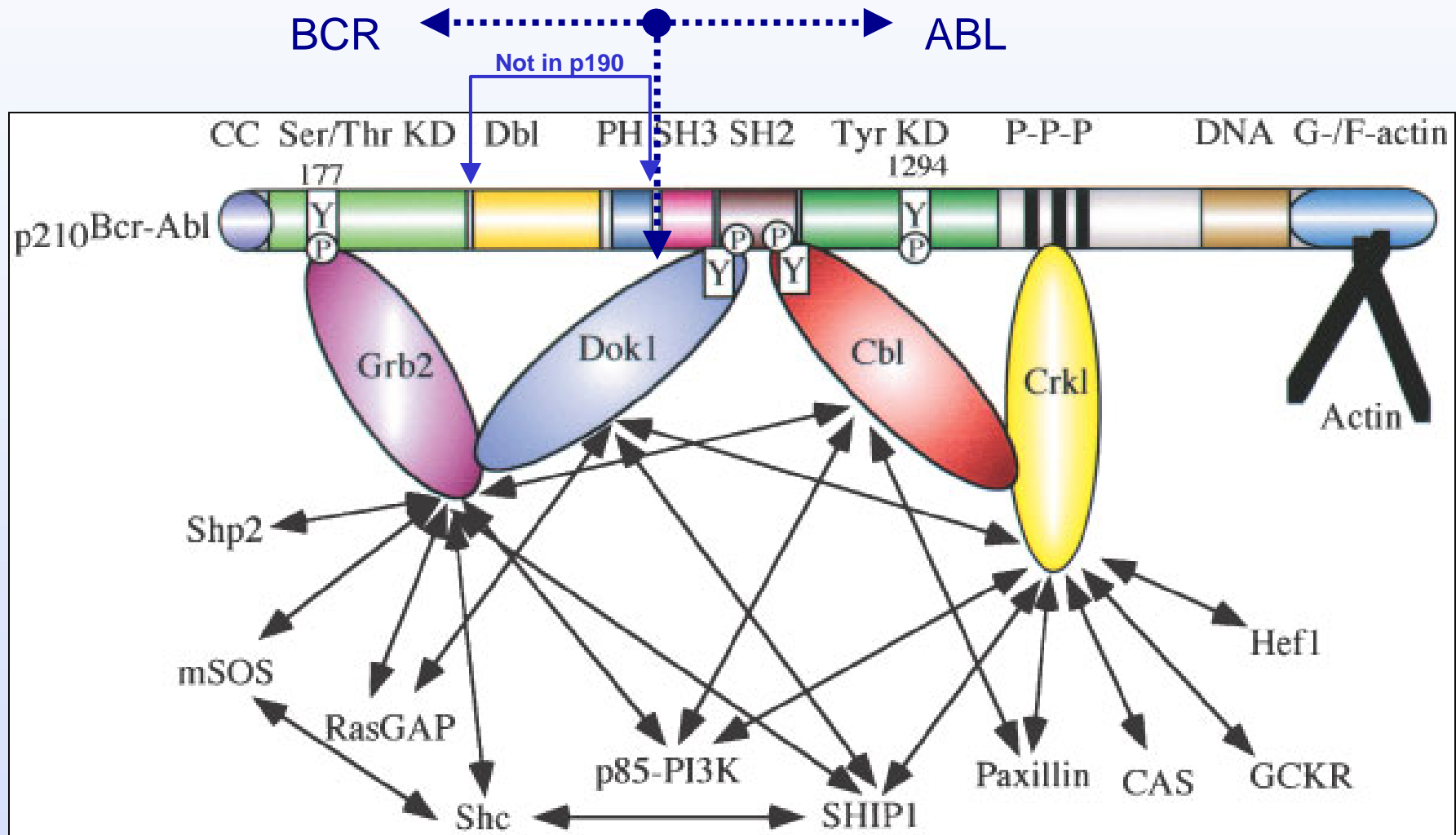
(e.g. Interleukin, Interferon, CSFs, Erythropoietin)



# BCR-ABL

- BCR
  - *Serine threonine kinase*
  
- ABL
  - *Tyrosine kinase, non-receptor type*
  - *Distantly related to Src-kinases, ubiquitously expressed*
  - *Multifunctional kinase acting in different signaling pathways*
  - *Role in cell cycle progression, activation of apoptosis*
  
- BCR-ABL
  - *Oncogenic transformation requires deregulated tyrosine kinase activity*
  - *Causes enhanced proliferation and prolonged viability of cells*

# BCR-ABL



B. Scheijen et al., *Oncogene* 21 (2002)

# Treatment Implications

- Gleevec™ / STI-571
  - *Tyrosine kinase inhibitor, selective for Abl, c-Kit and PDGFR*
  - *Almost no side effects*
  - *Successful in treatment of CML*
  - *Occurrence of resistancy in acute leukemia*
  
- Ras pathway inhibitor
  - *Successful in a murine model of ALL*
  - *Investigated in clinical trials*