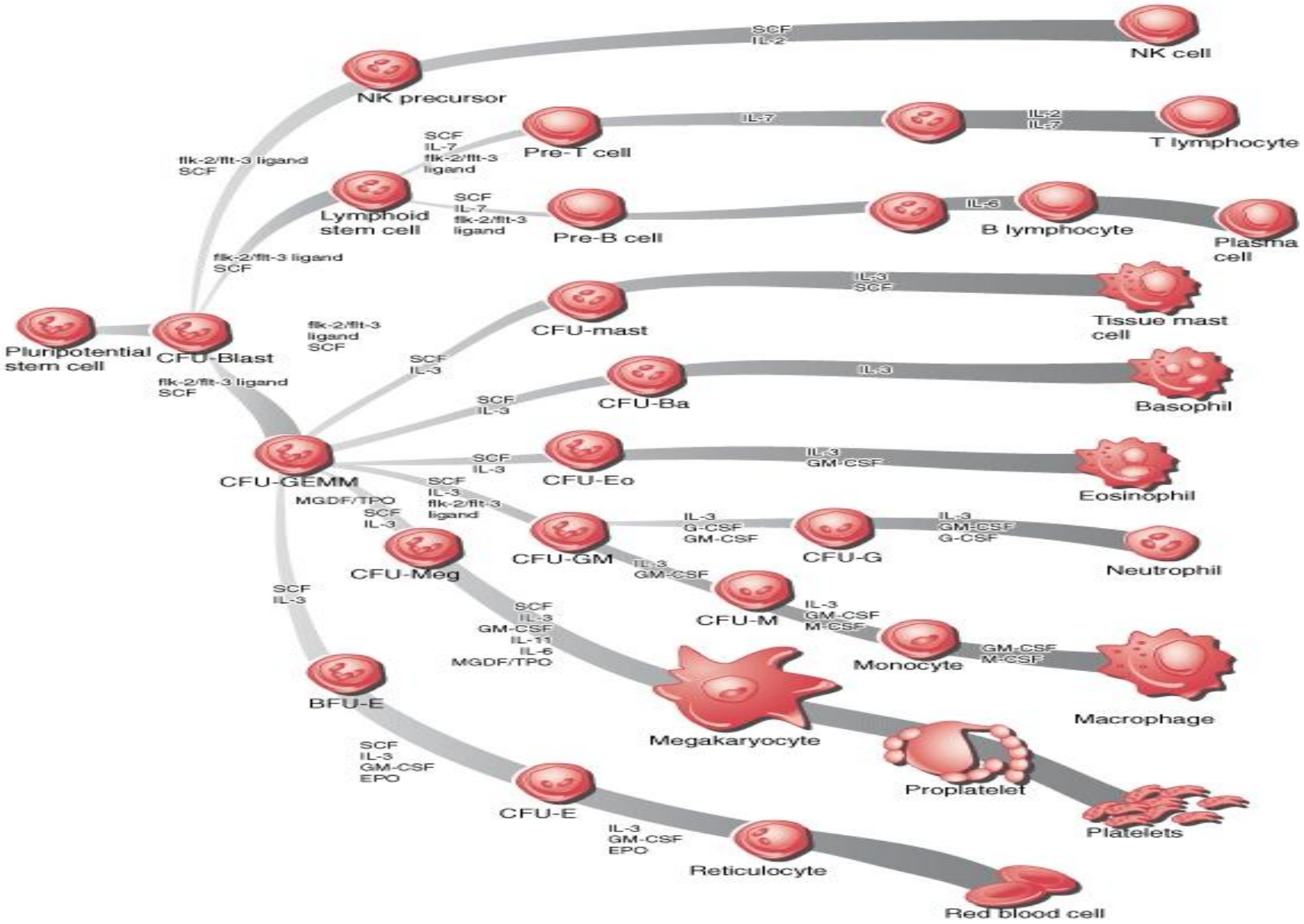
CƠ CHẾ PHÂN TỬ CỦA RỐI LOẠN TĂNG SINH TỦY

TS.BS Phan Thị Xinh
Bộ Môn Huyết Học
Đại Học Y Dược TP HCM

BIỆT HÓA TẾ BÀO HỆ TẠO MÁU



MYELOPROLIFERATIVE NEOPLASMS

(WHO CLASSIFICATION - 2008)

Myeloproliferative disorders/neoplasms (MPD/MPN) are chronic malignant conditions characterized by the clonal expansion of hematopoietic cells from one or more myeloid lineages.

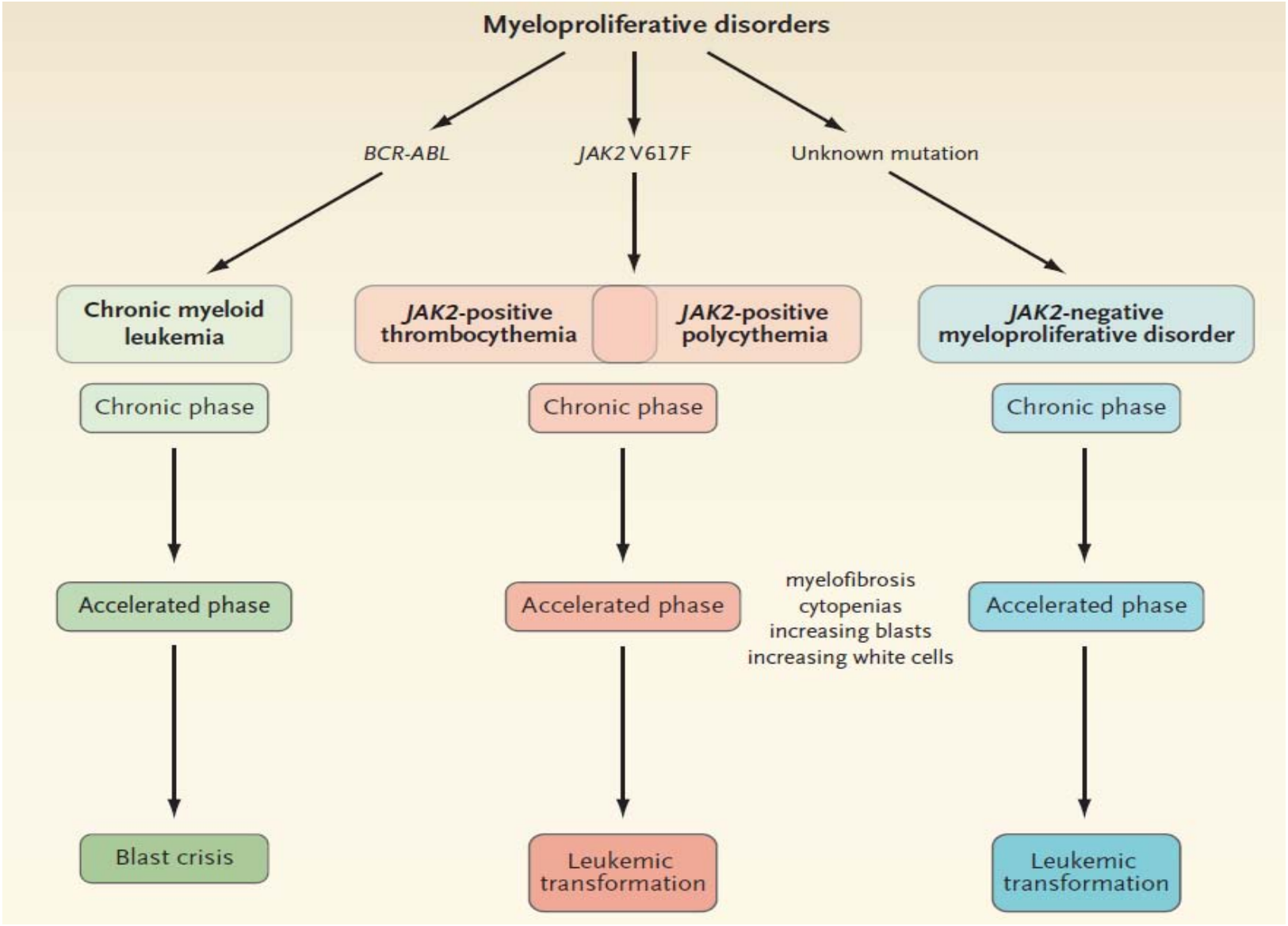
Chronic myelogenous leukemia
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified
Mastocytosis
Myeloproliferative neoplasm, unclassifiable

BẤT THƯỜNG PHÂN TỬ TRONG CÁC RỐI LOẠN TĂNG SINH TỦY

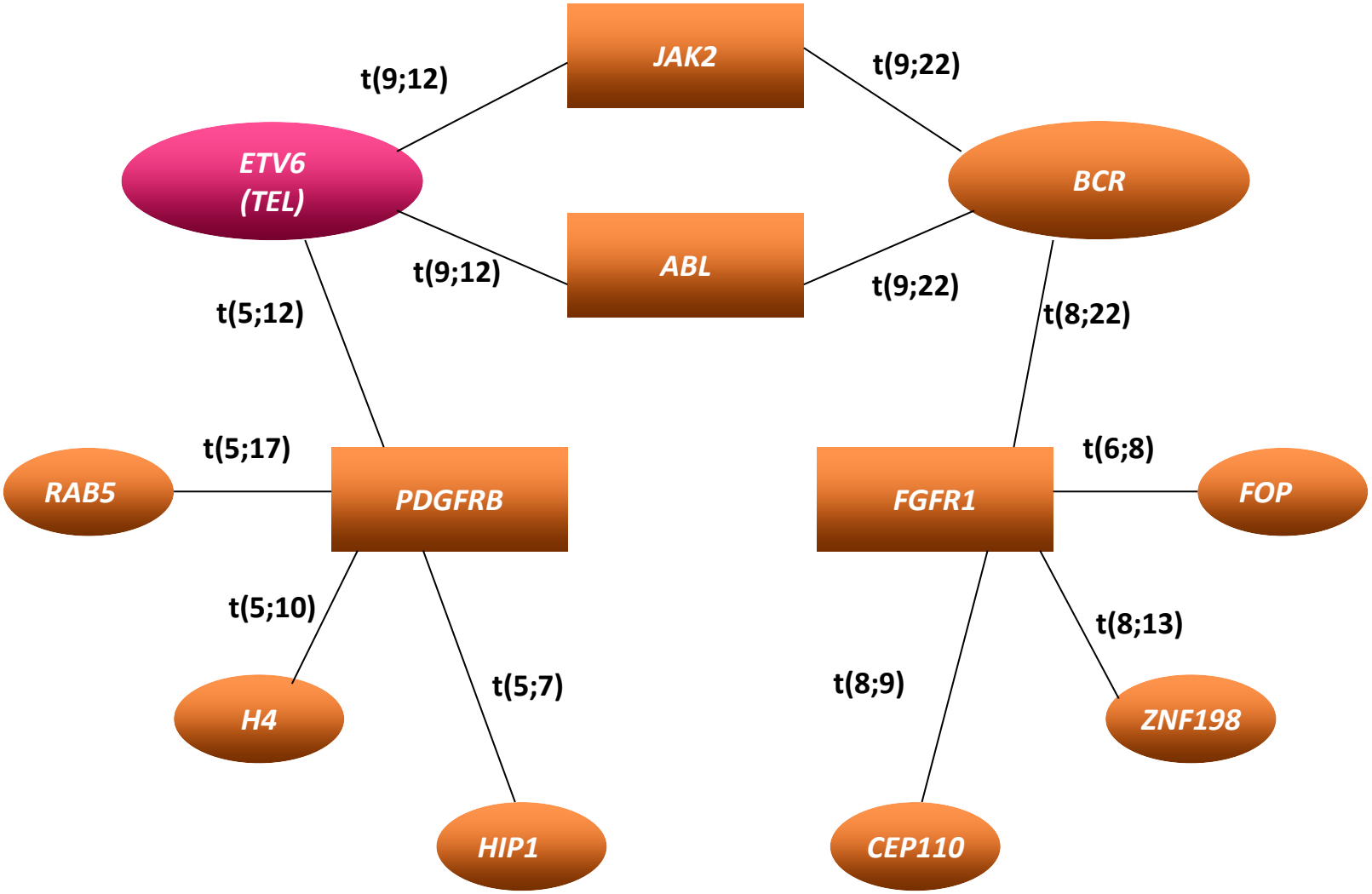
BỆNH LÝ	BẤT THƯỜNG PHÂN TỬ
Chronic myelogenous leukemia	*BCR-ABL*
Chronic eosinophilic leukemia and the hypereosinophilic syndrome	*FIP1L1-PDGFRA*
Chronic neutrophilic leukemia	*BCR-ABL* p230
Chronic myelomonocytic leukemia	*TEL-PDGFRB*
Systemic mastocytosis	*KIT* D816V
Polycythemia vera	*JAK2* V617F (~92% positive) *JAK2* exon 12 mutations (3% positive)
Essential thrombocytosis	*JAK2* V617F (~50% positive) *MPL* W515L/K (~3% positive) *MPL* K39N
Primary myelofibrosis	*JAK2* V617F (~50% positive) *MPL* W515L/K (~14% positive)

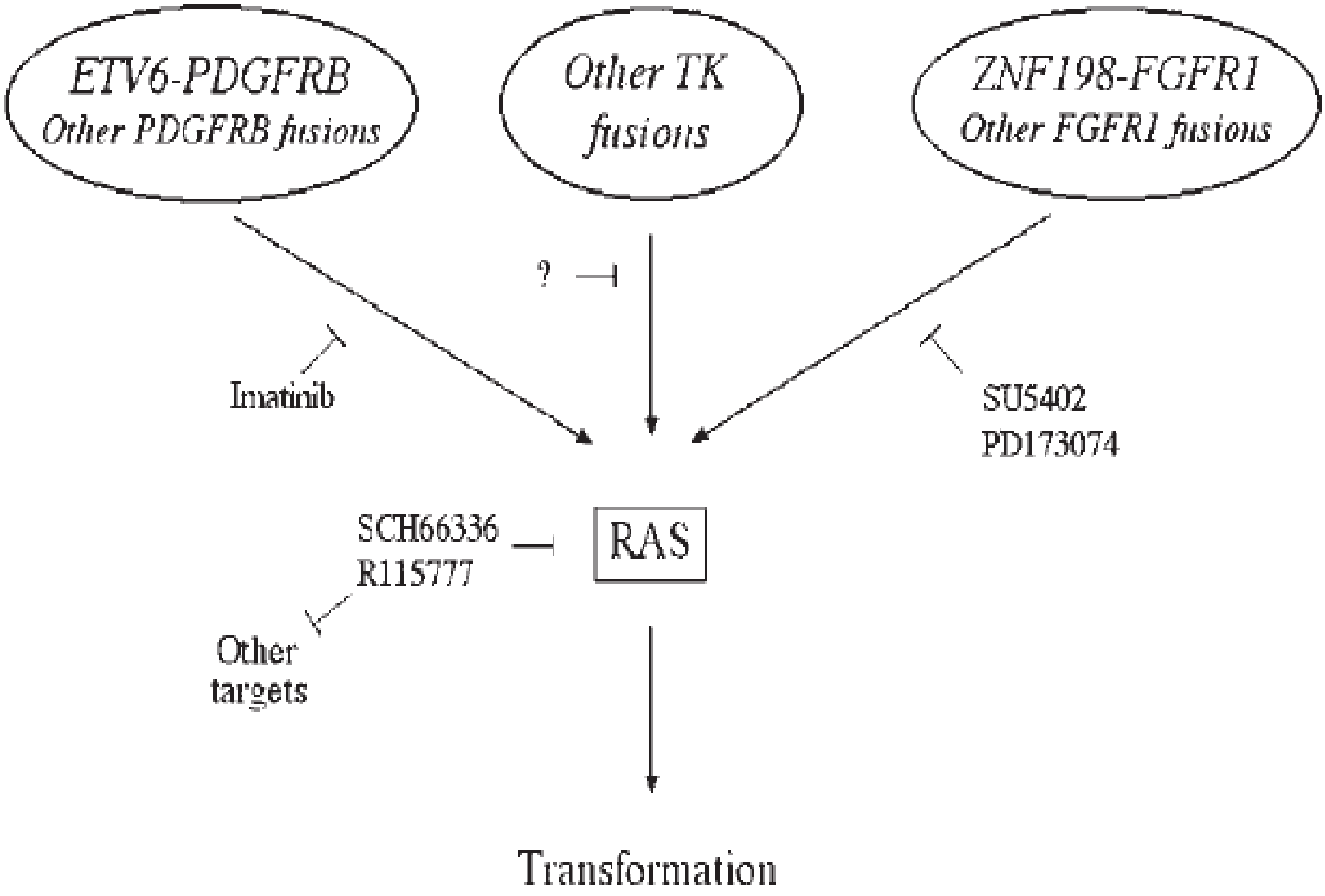
(Spivak JL, *Ann Intern Med* 2010)

CLASSIFICATION OF THE MYELOPROLIFERATIVE DISORDERS ON THE BASIS OF MOLECULAR PATHOGENETIC CHARACTERISTICS

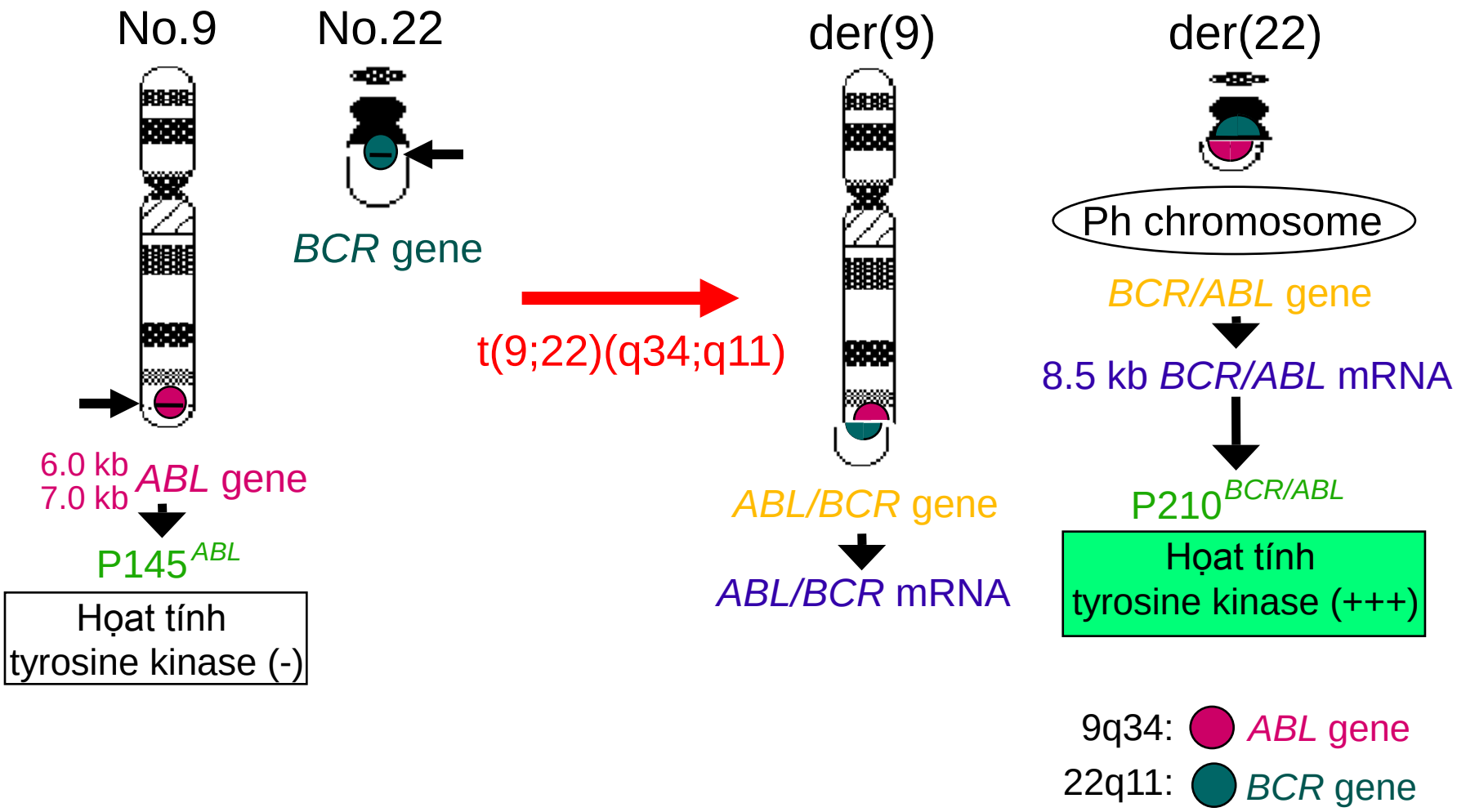


Tyrosine kinase fusion genes in chronic myeloproliferative diseases

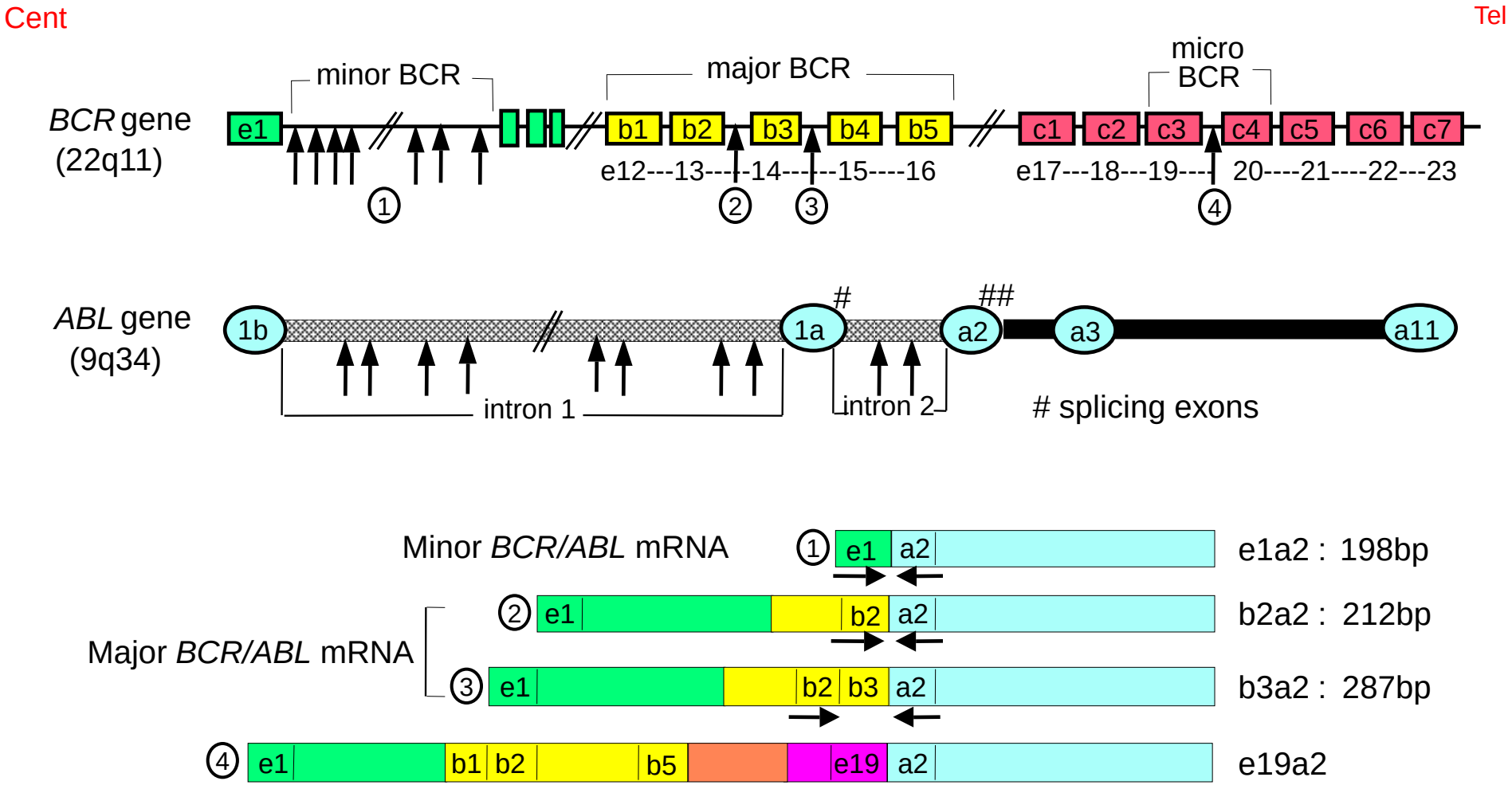



ETV6-PDGFRB
Other PDGFRB fusions
Other TK fusions
ZNF198-FGFR1
Other FGFR1 fusions
?
Imatinib
SU5402
PD173074
SCH66336
R115777
RAS
Other targets
Transformation

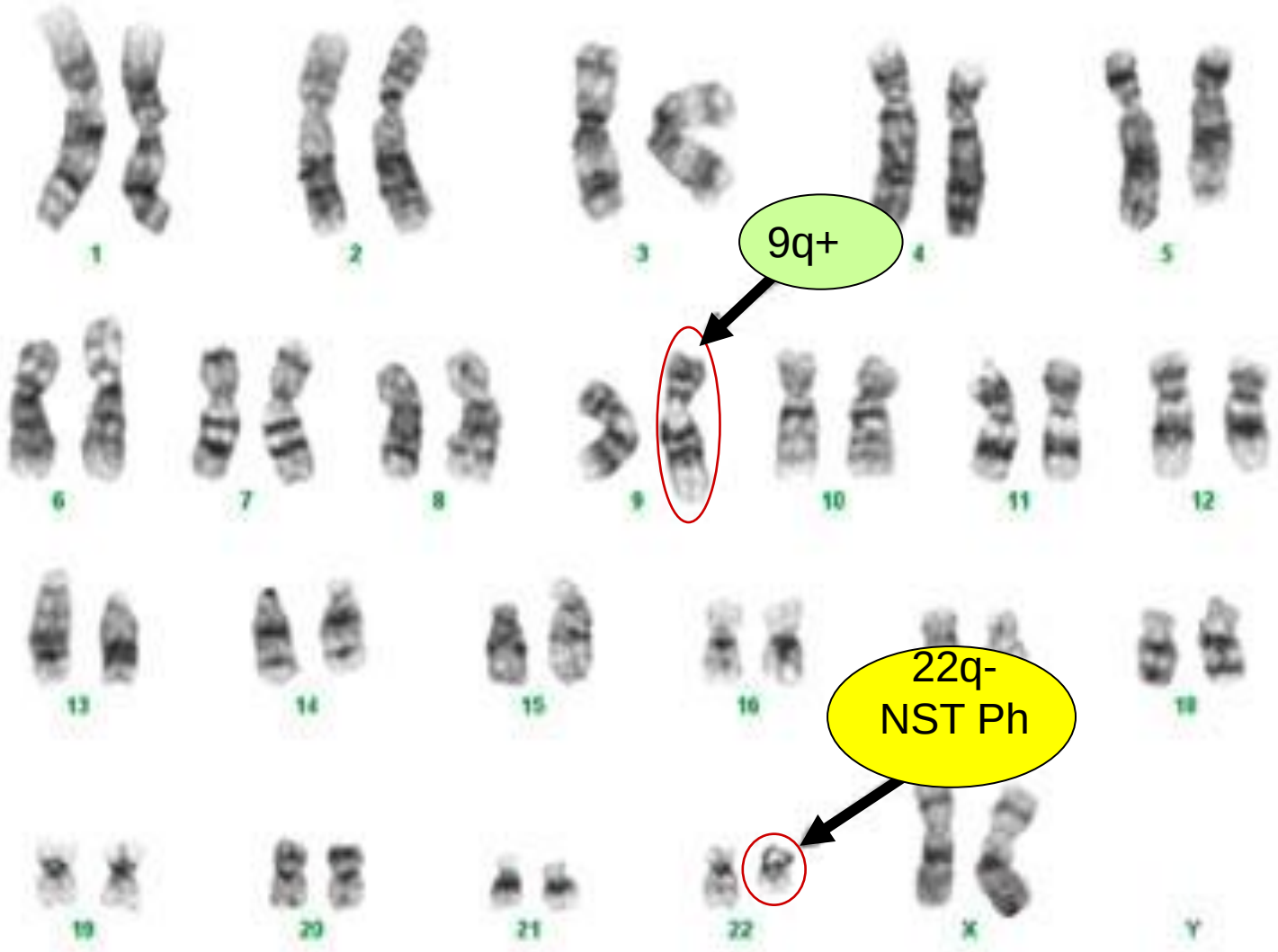
Sinh học phân tử của t(9;22)(q34;q11)



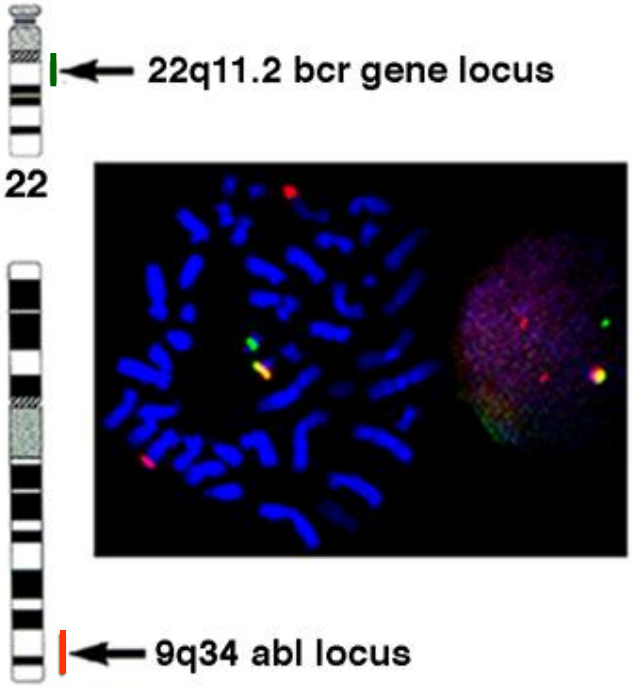
Những tổ hợp gen *BCR/ABL* thường gặp trong CML

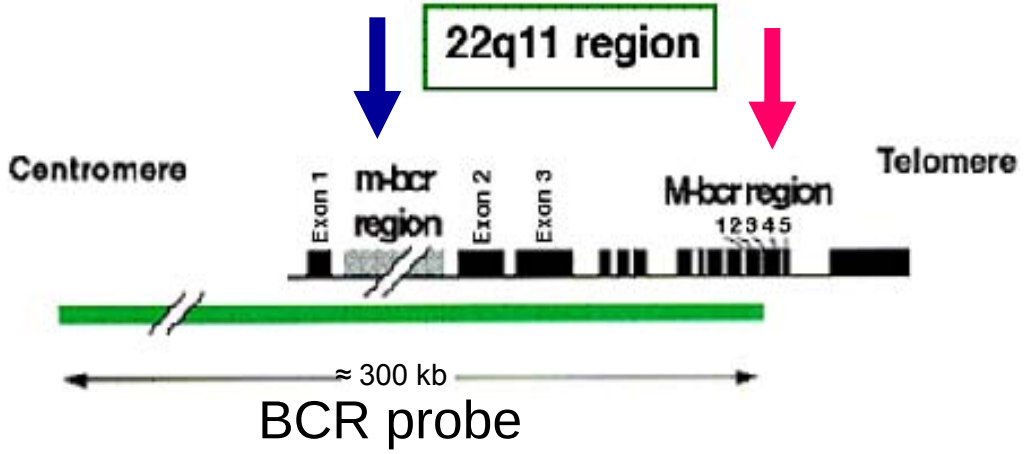


t(9;22)(q34;q11)

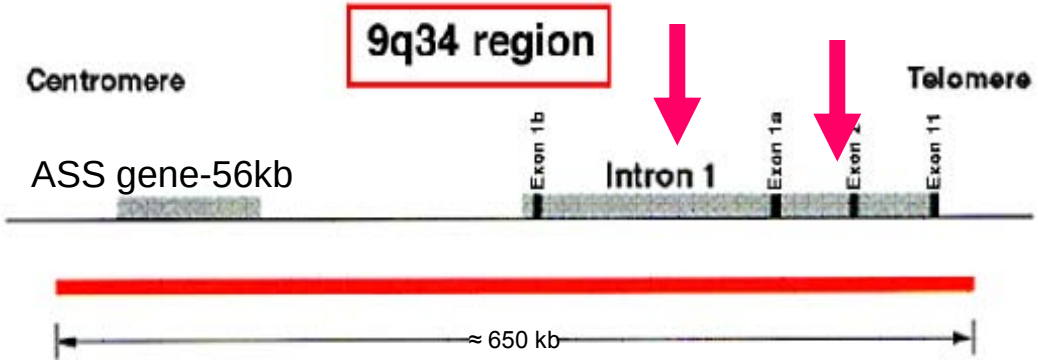


Vysis LSI *BCR/ABL* ES Dual Color Translocation probes



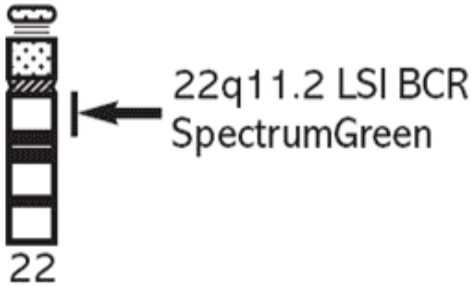


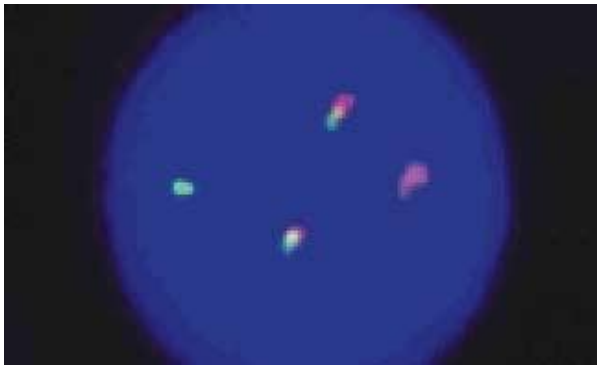
BCR probe

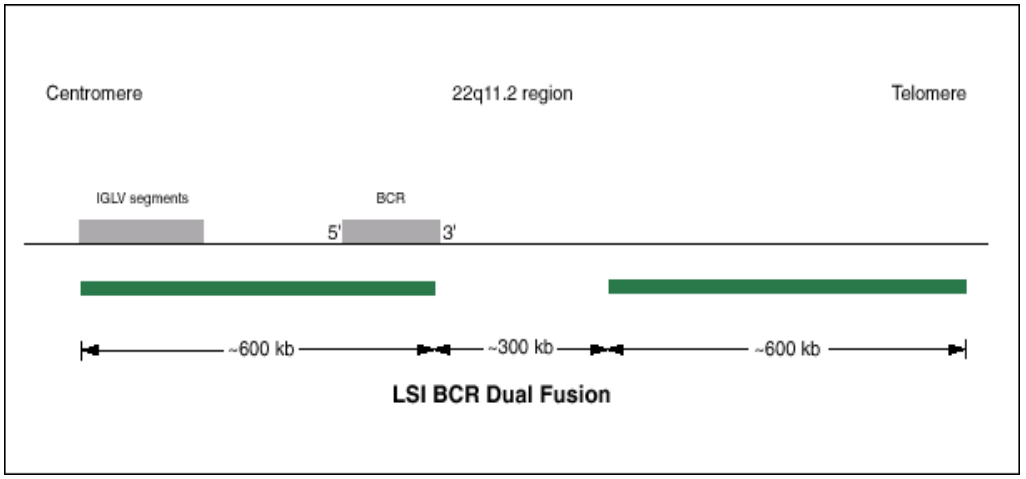


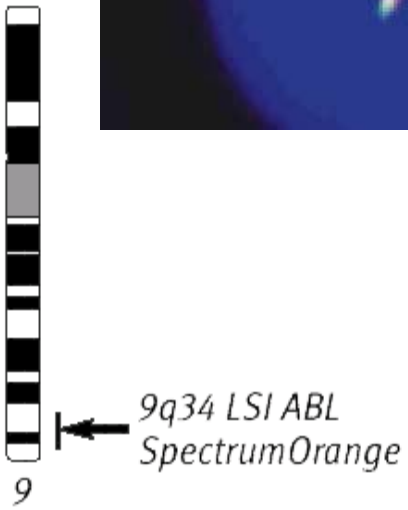
ABL probe

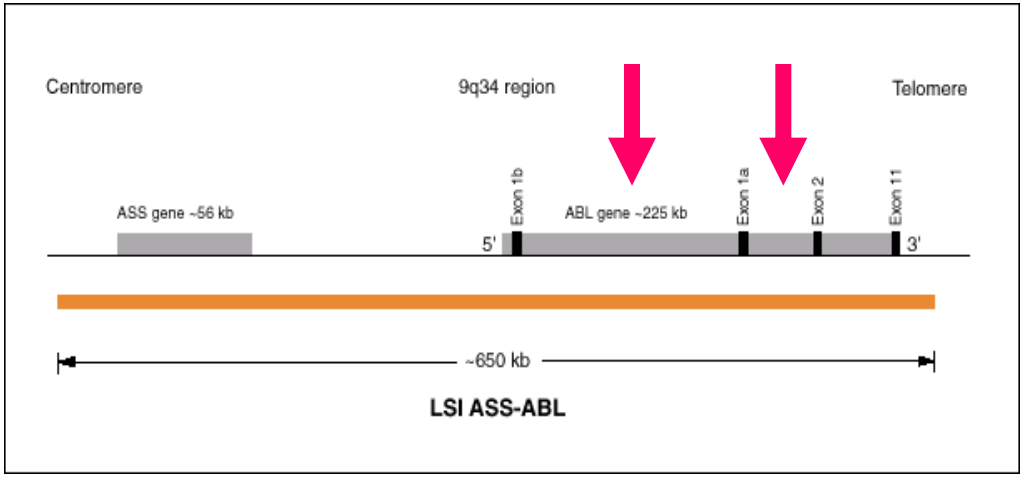
Vysis LSI *BCR/ABL* Dual Color, Dual fusion translocation probes









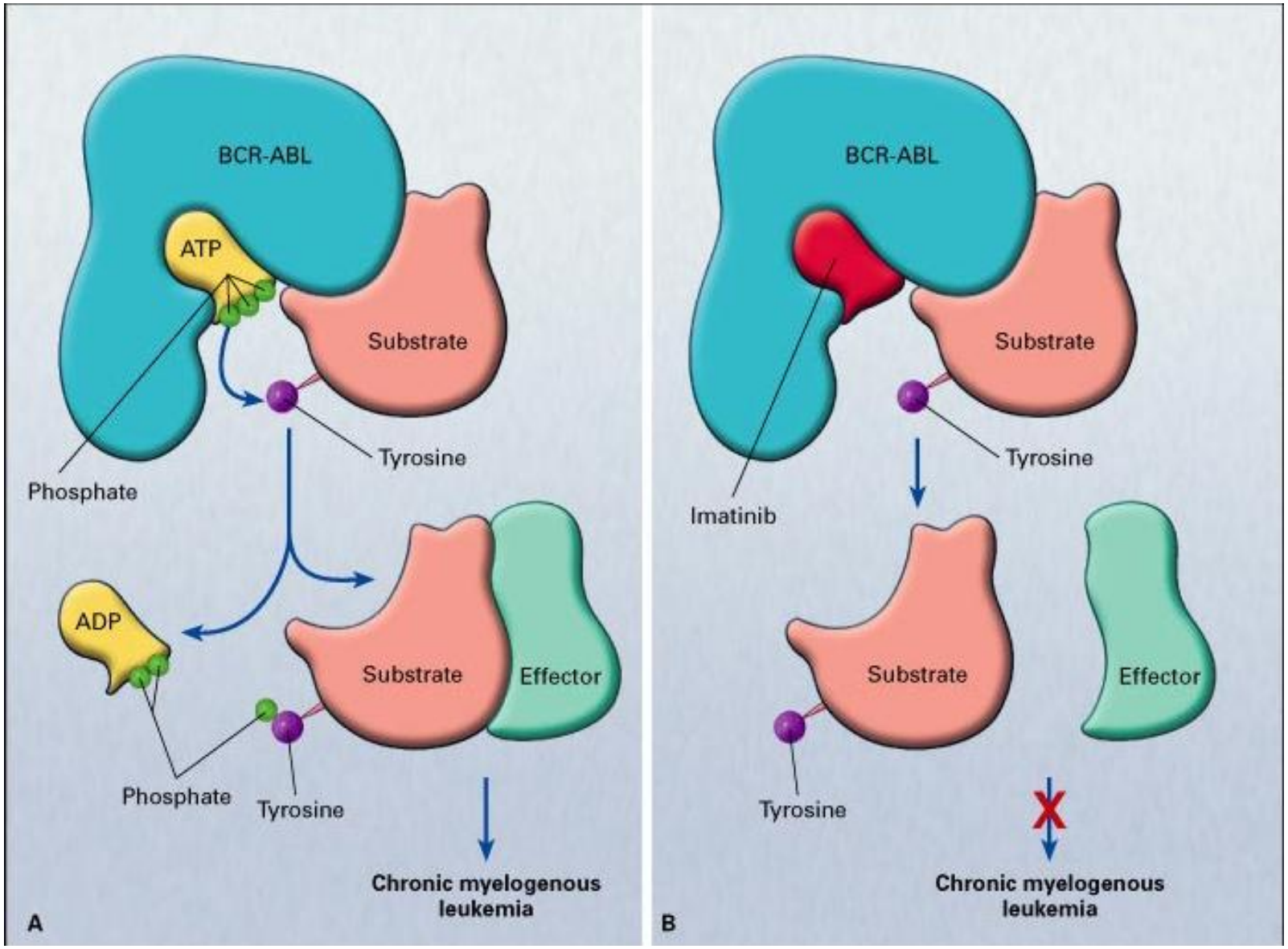


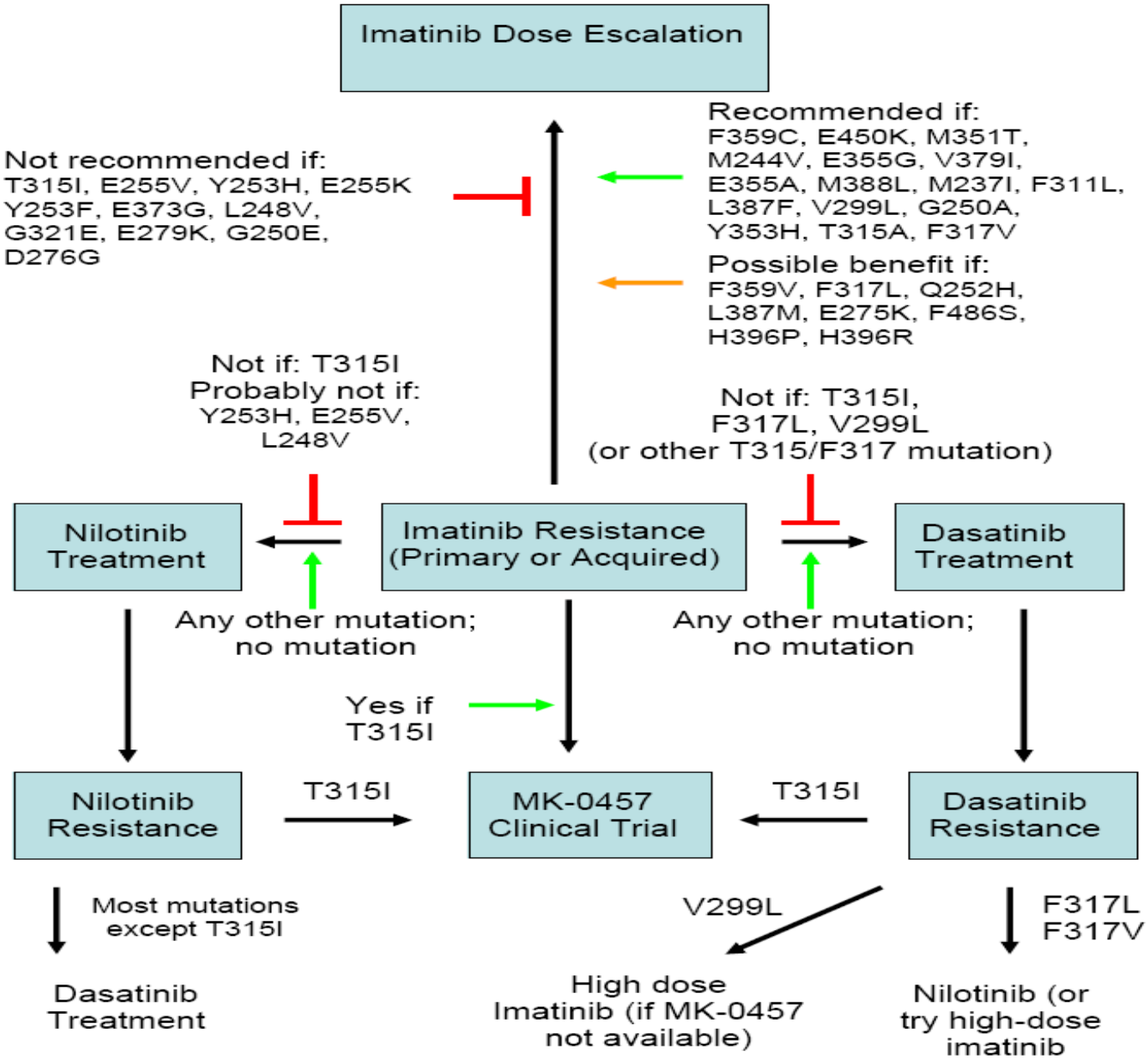
ĐÁNH GIÁ ĐiỀU TRỊ

Phân loại	Tiêu chuẩn
Đáp ứng hoàn toàn về huyết học	Huyết đồ về bình thường
Đáp ứng tối thiểu về di truyền tế bào	66–95% Ph^+
Đáp ứng thấp về DTTB	36–65% Ph^+
Đáp ứng một phần về DTTB	1–35% Ph^+
Đáp ứng hoàn toàn về DTTB	0% Ph^+
Đáp ứng cao về DTTB	0–35% Ph^+
Đáp ứng cao về mặt phân tử	Giảm ≥3-log bản sao *BCR/ABL*
Đáp ứng hoàn toàn về mặt phân tử	Âm tính với RT-PCR

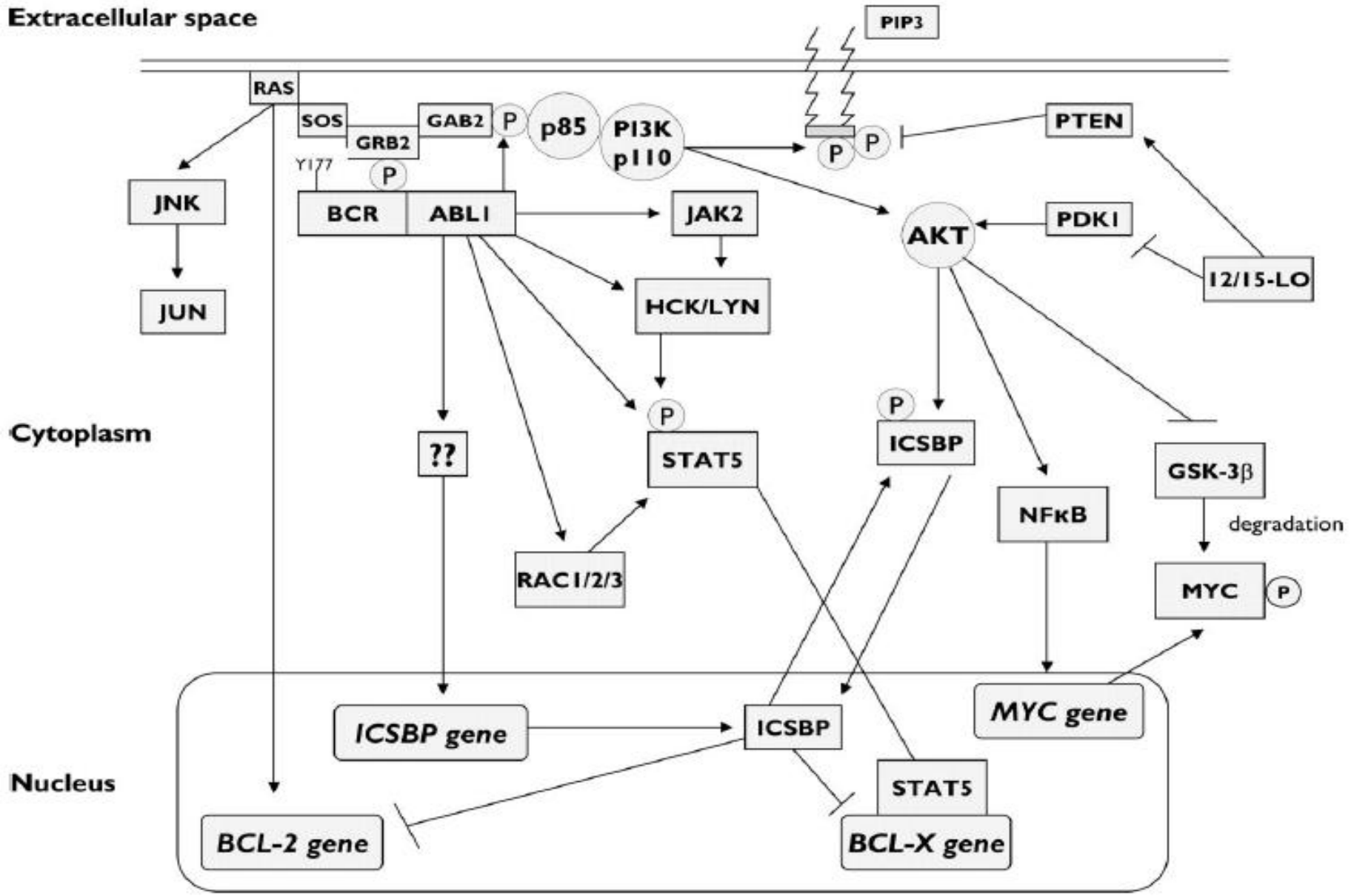
RT-PCR: reverse-transcription polymerase chain reaction

CƠ CHẾ HOẠT ĐỘNG CỦA IMATINIB



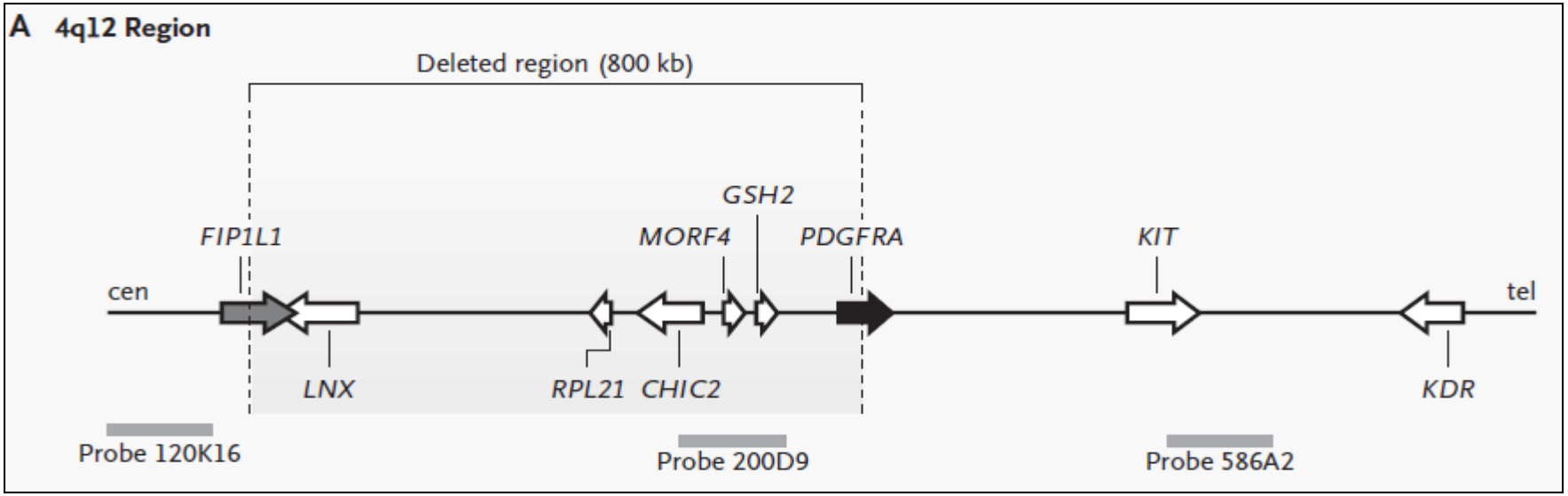

Imatinib Dose Escalation
Recommended if:
F359C, E450K, M351T,
M244V, E355G, V379I,
E355A, M388L, M237I, F311L,
L387F, V299L, G250A,
Y353H, T315A, F317V
Possible benefit if:
F359V, F317L, Q252H,
L387M, E275K, F486S,
H396P, H396R
Not recommended if:
T315I, E255V, Y253H, E255K
Y253F, E373G, L248V,
G321E, E279K, G250E,
D276G
Not if: T315I
Probably not if:
Y253H, E255V,
L248V
Not if: T315I,
F317L, V299L
(or other T315/F317 mutation)
Nilotinib
Treatment
Imatinib Resistance
(Primary or Acquired)
Dasatinib
Treatment
Any other mutation;
no mutation
Any other mutation;
no mutation
Yes if
T315I
Nilotinib
Resistance
T315I
MK-0457
Clinical Trial
T315I
Dasatinib
Resistance
Most mutations
except T315I
V299L
F317L
F317V
Dasatinib
Treatment
High dose
Imatinib (if MK-0457
not available)
Nilotinib (or
try high-dose
imatinib

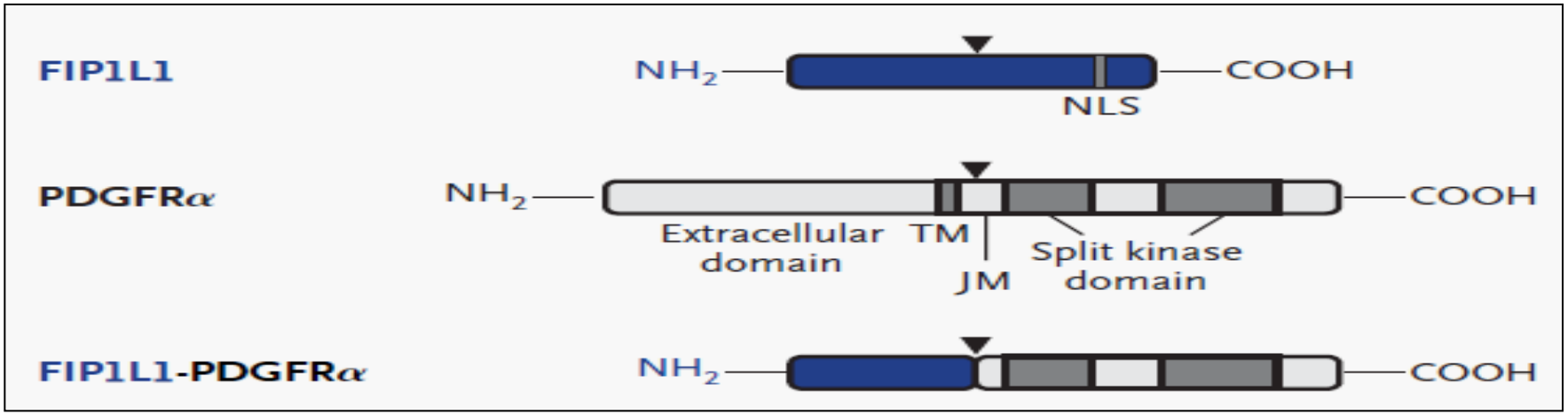
MOLECULAR SIGNALING IN *BCR-ABL1–POSITIVE* MYELOID PROGENITORS.



A Tyrosine Kinase Created by Fusion of the *PDGFRA* and *FIP1L1* Genes as a Therapeutic Target of Imatinib in Idiopathic Hypereosinophilic Syndrome

N Engl J Med 2003;348:1201-14

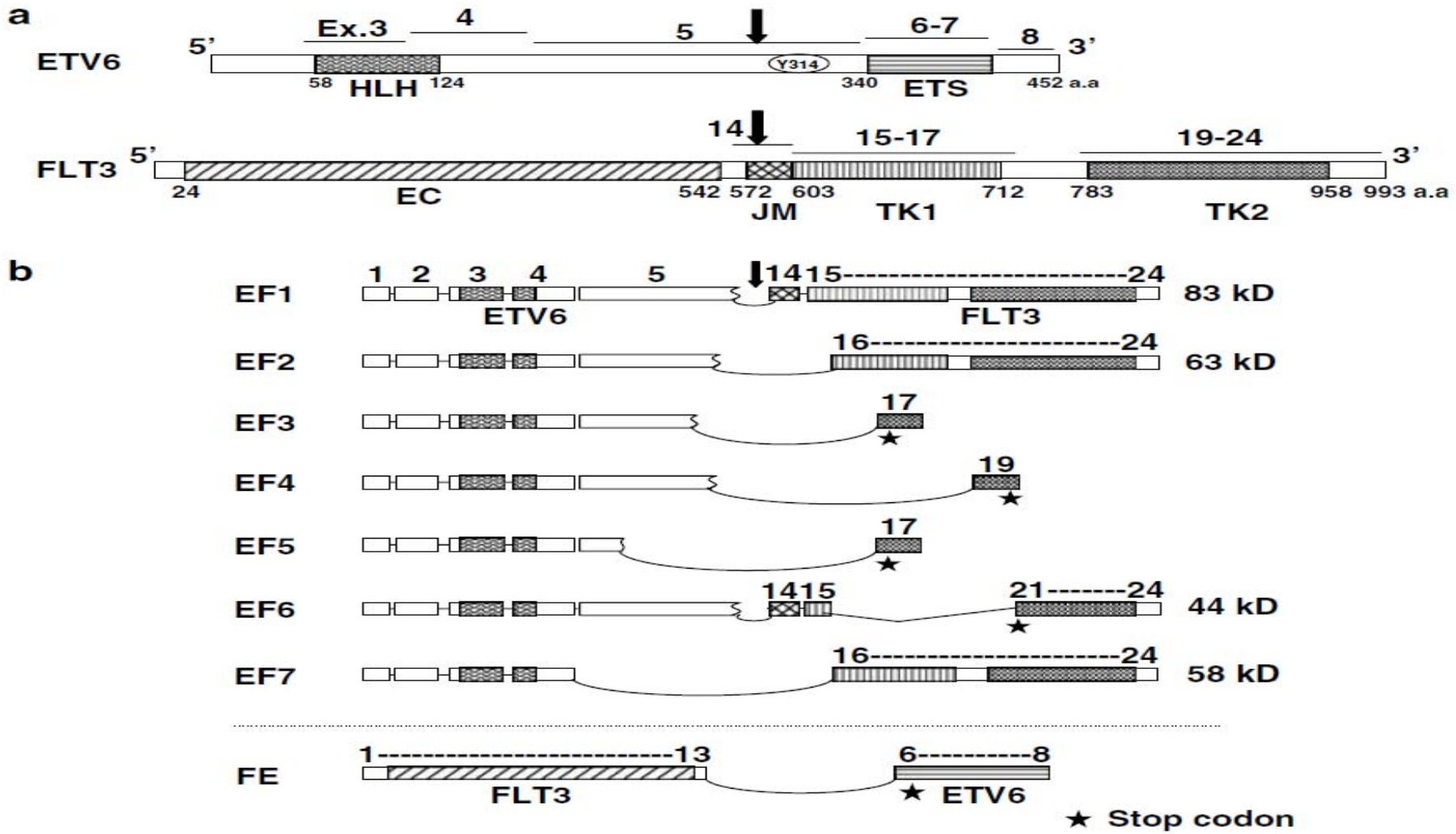


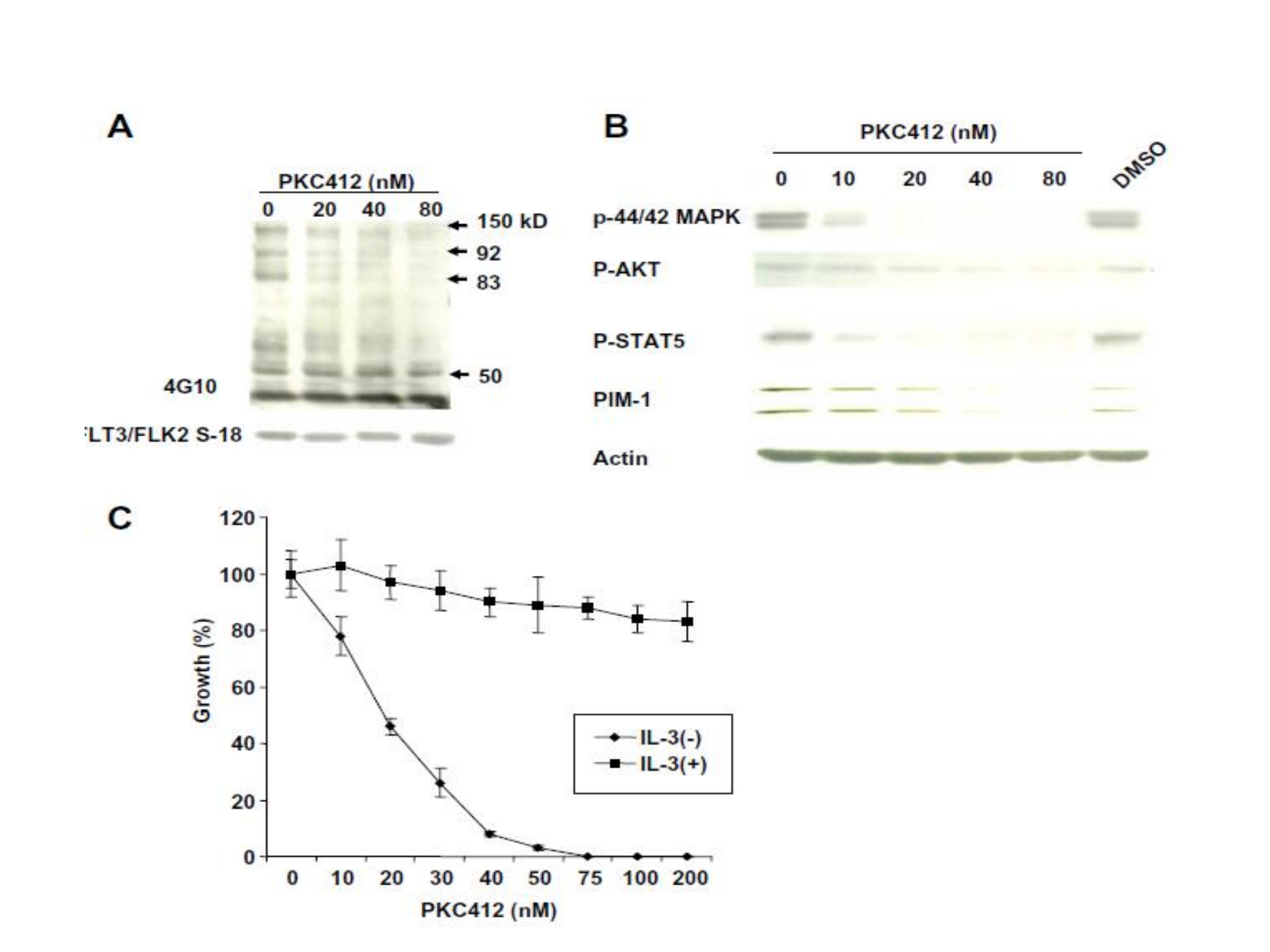


FLT3 is fused to *ETV6* in a myeloproliferative disorder with hypereosinophilia and a t(12;13)(p13;q12) translocation

HA Vu[1,2], PT Xinh[1,2], M Masuda[3], T Motoji[3], A Toyoda[4], Y Sakaki[4], K Tokunaga[2] and Y Sato[1]

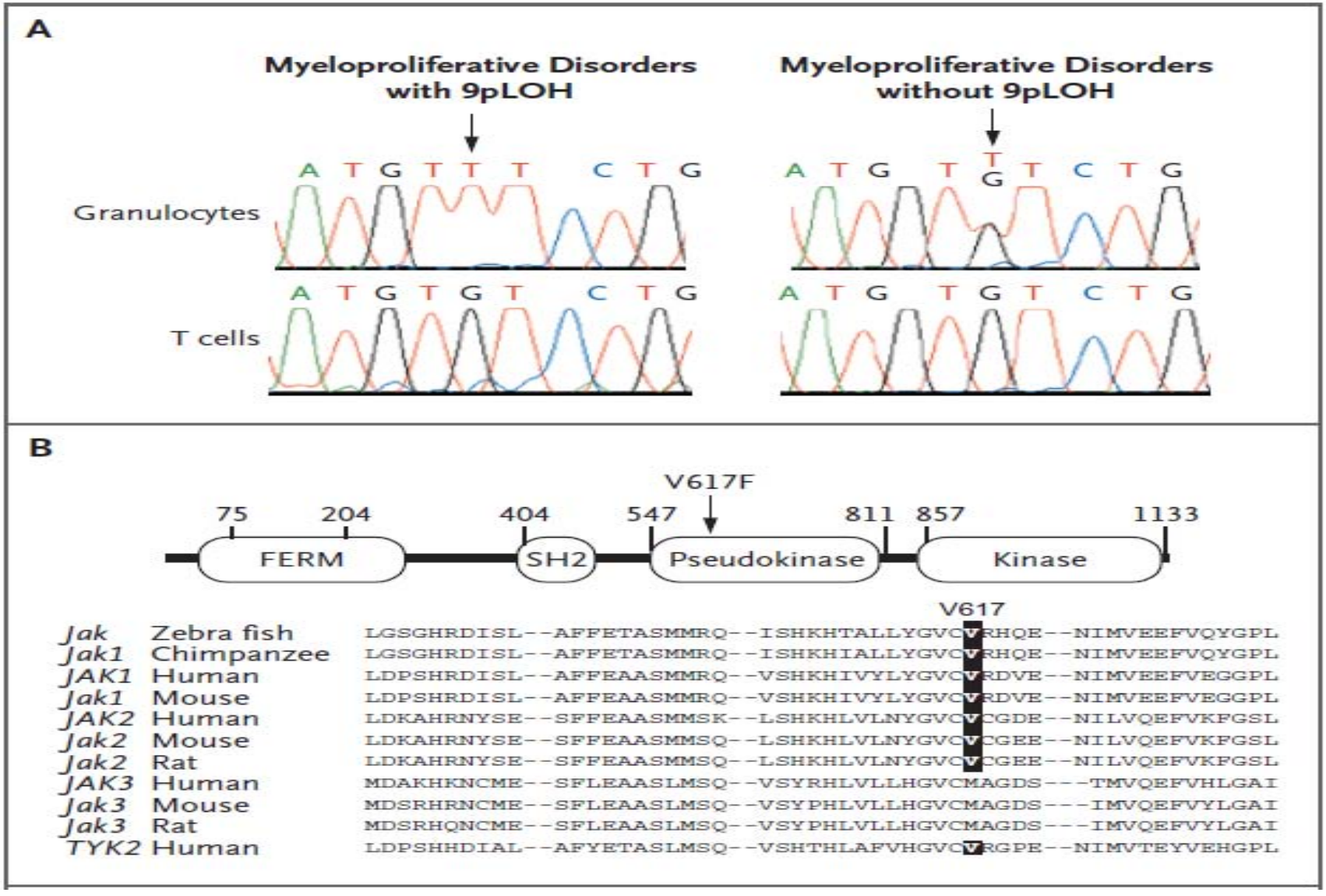
Leukemia (2006) 20, 1414–1421

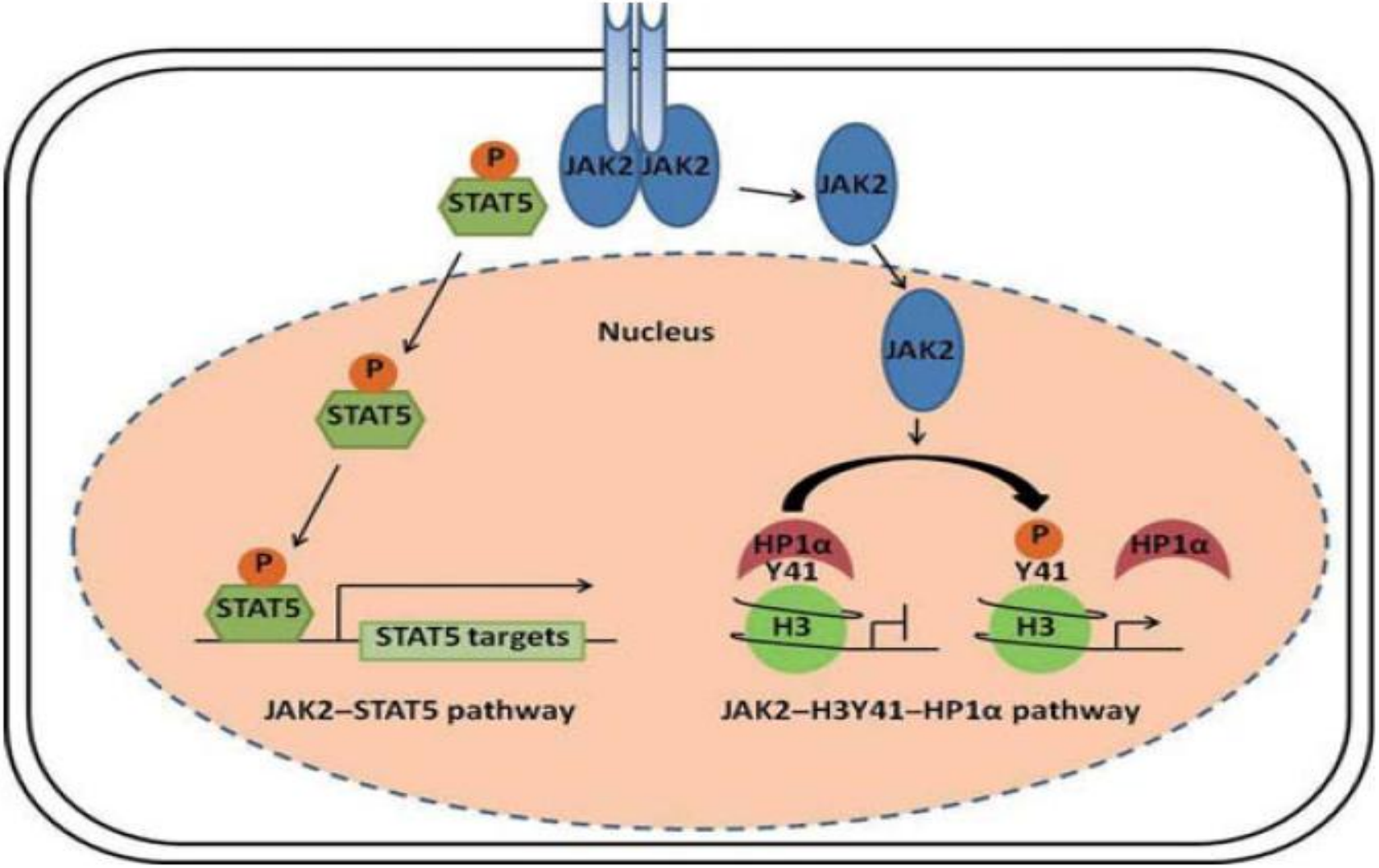



A
PKC412 (nM)
0
20
40
80
150 kD
92
83
50
4G10
LT3/FLK2 S-18
B
PKC412 (nM)
0
10
20
40
80
DMSO
p-44/42 MAPK
P-AKT
P-STAT5
PIM-1
Actin
C
Growth (%)
120
100
80
60
40
20
0
0
10
20
30
40
50
75
100
200
PKC412 (nM)
IL-3(-)
IL-3(+)

A Gain-of-Function Mutation of *JAK2* in Myeloproliferative Disorders

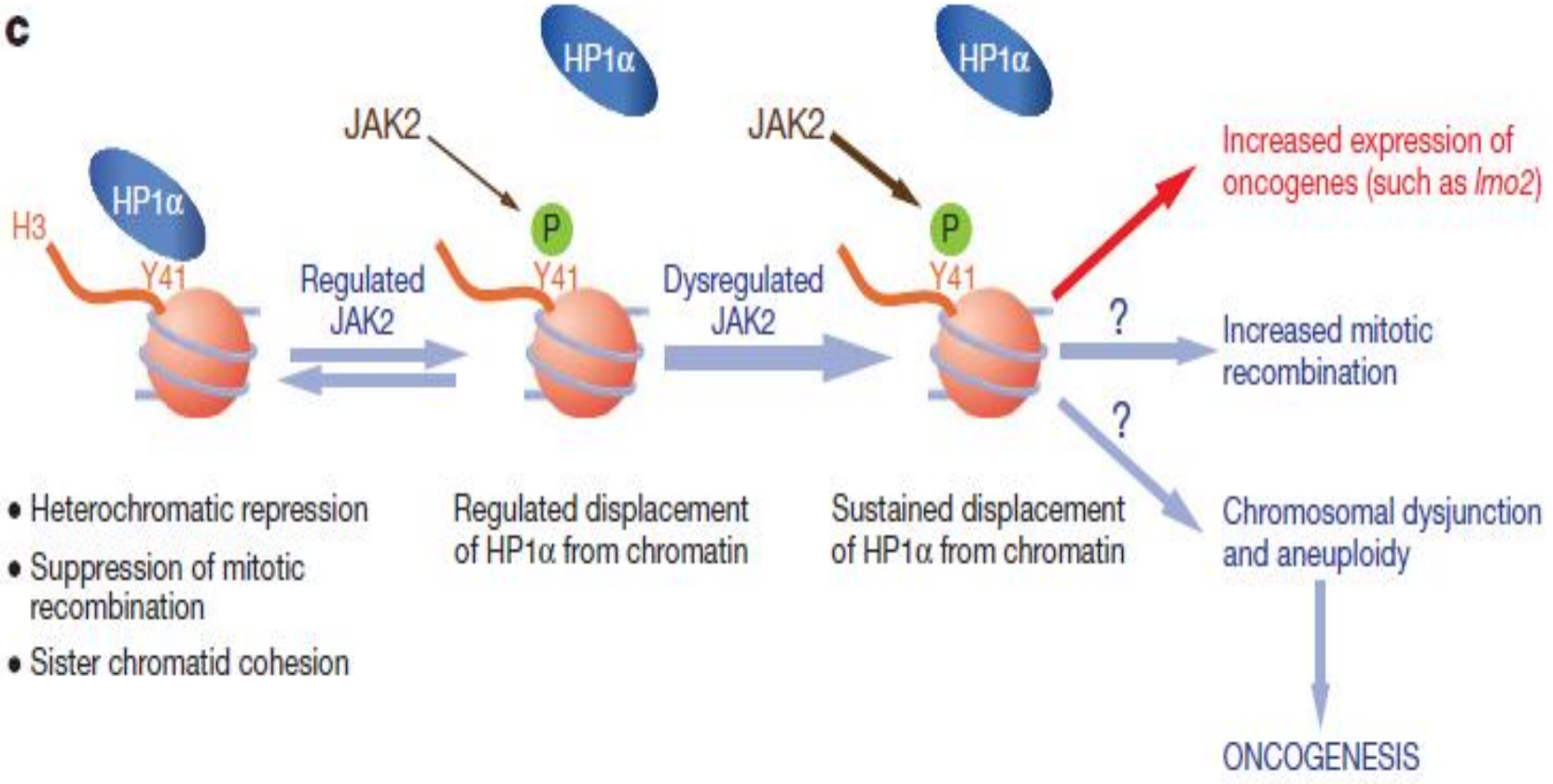
N Engl J Med 2005;352:1779-90.



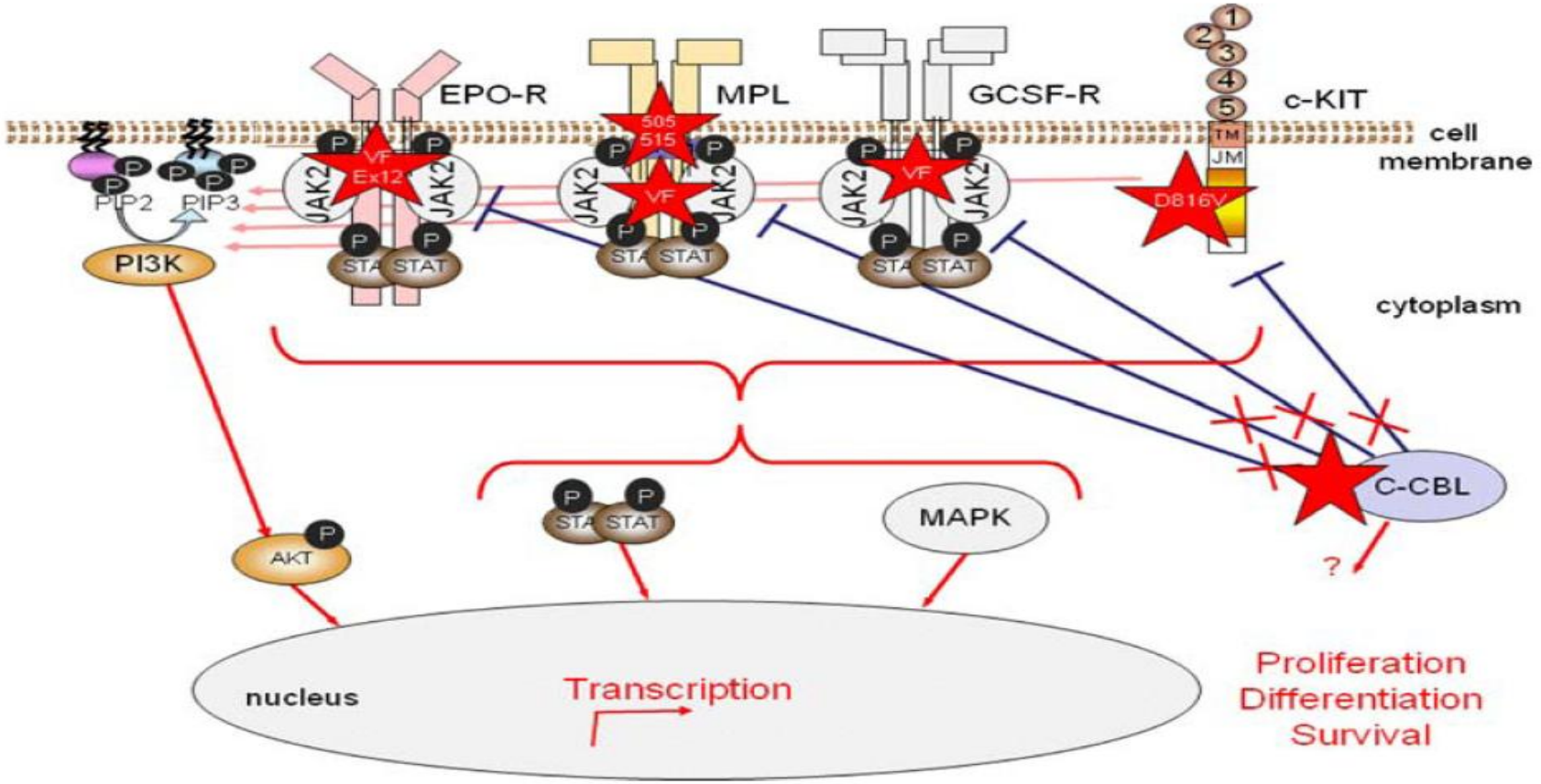


JAK2-mediated transcriptional activation involves two separate pathways. In the canonical JAK2–STAT5 pathway, JAK2 is activated by autophosphorylation upon the association of receptors and their ligands. The active JAK2 further phosphorylates the STAT5, which is translocated into the nucleus to activate its target genes. Alternatively, the active JAK2 enters into the nucleus to phosphorylate histone H3 at tyrosine 41 (H3Y41). H3Y41 phosphorylation disrupts the association of HP1a with chromatin, which leads to the activation of oncogenes such as lmo2

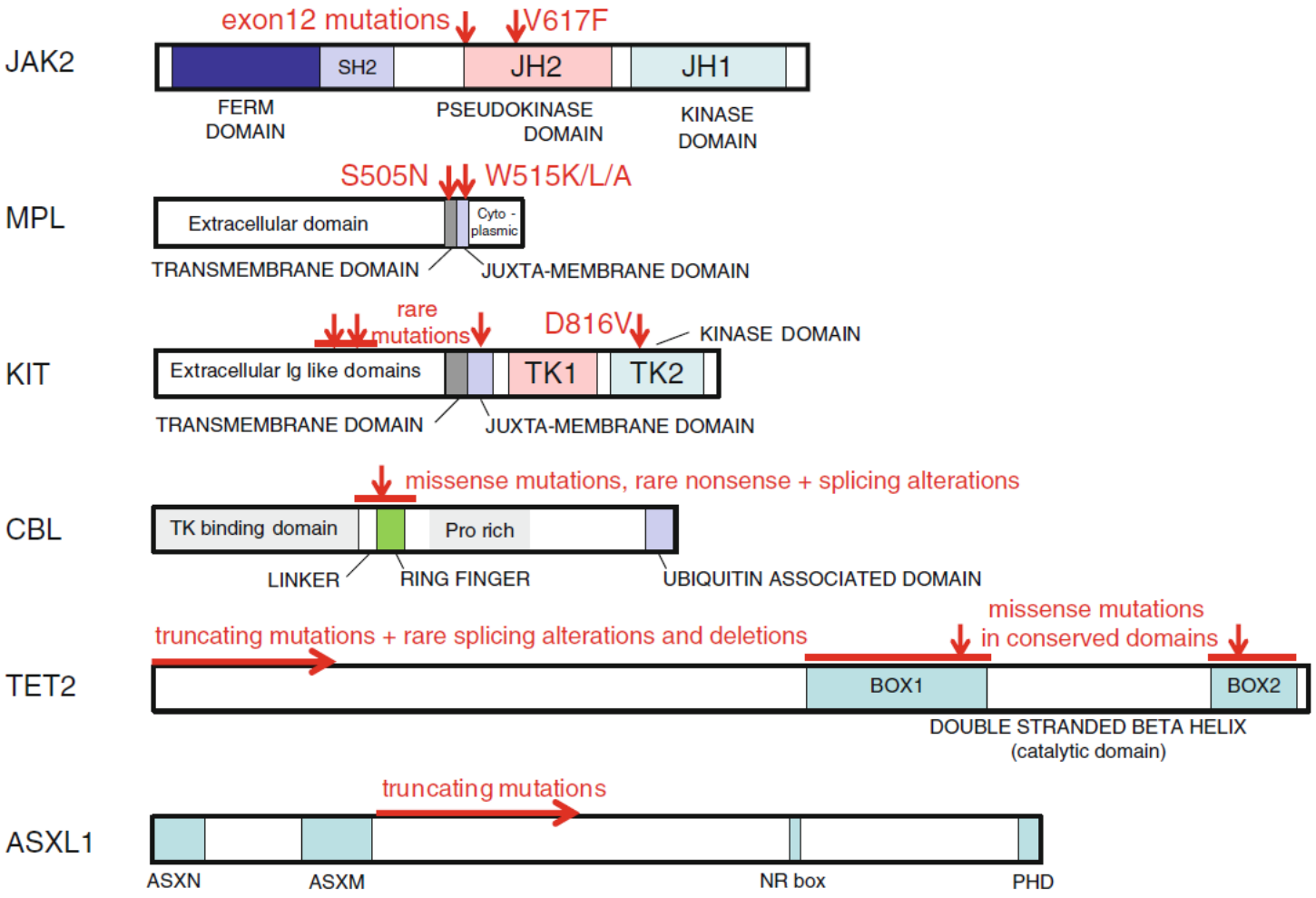
JAK2 PHOSPHORYLATES HISTONE H3Y41 AND EXCLUDES HP1α FROM CHROMATIN



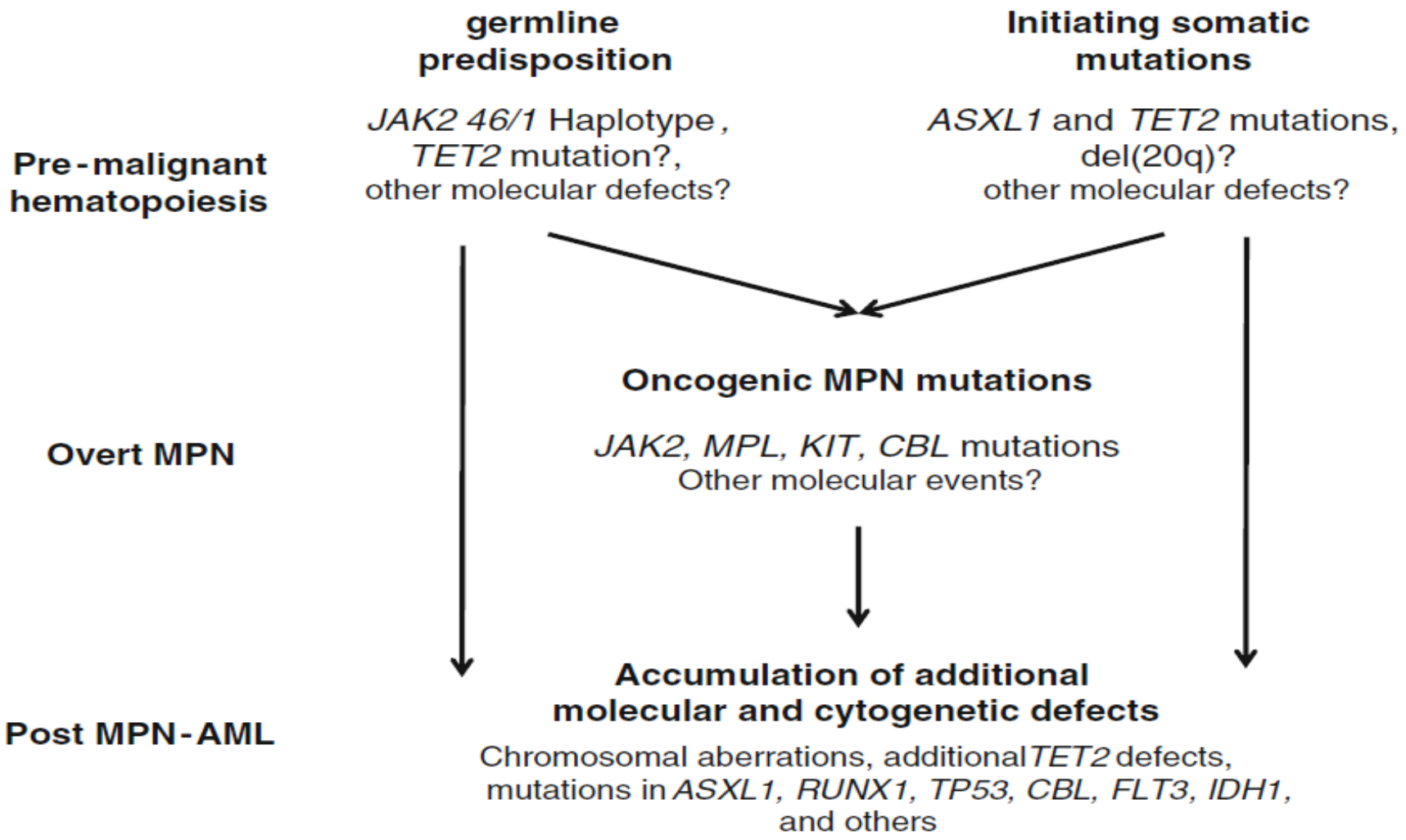
Model depicting the decrease in HP1α binding to chromatin after phosphorylation of H3Y41 by JAK2. On the left are the known functions of HP1α; on the right are the known consequences of dysregulated JAK2 seen as a feature in JAK2-mediated haematological malignancies.



Involvement of the cytokine receptor-tyrosine kinase axis in MPN oncogenesis. The four main myeloid growth factor receptors involved in MPN pathogenesis are represented with their schematic principal downstream signaling involving the binding of JAK2, and the phosphorylation of phosphatidyl-inositol-3-kinase (PI3K), the protein kinase B (AKT), the signal transducers and activators of transcription (STAT), and the mitogen-activated protein kinases (MAPK) (red arrows and brackets). The adaptor and E3 ubiquitinligase C-CBL down-regulates c-KIT and JAK2 signaling (blue bars). Red stars indicate the oncogenic mutations that occur in MPN resulting in a constitutive or enhanced downstream signaling (red) with modulation of transcription and protein levels for cell cycle, proliferation, and apoptosis-related factors. VF, JAK2V617F; Ex12, JAK2 exon 12 mutations; 505 and 515, MPLW515 and MPLS505N mutations, D816V, KITD816V. Several point mutations have been described in C-CBL, resulting in both loss of inhibitory functions (red crosses) and gain of function properties (red arrow)

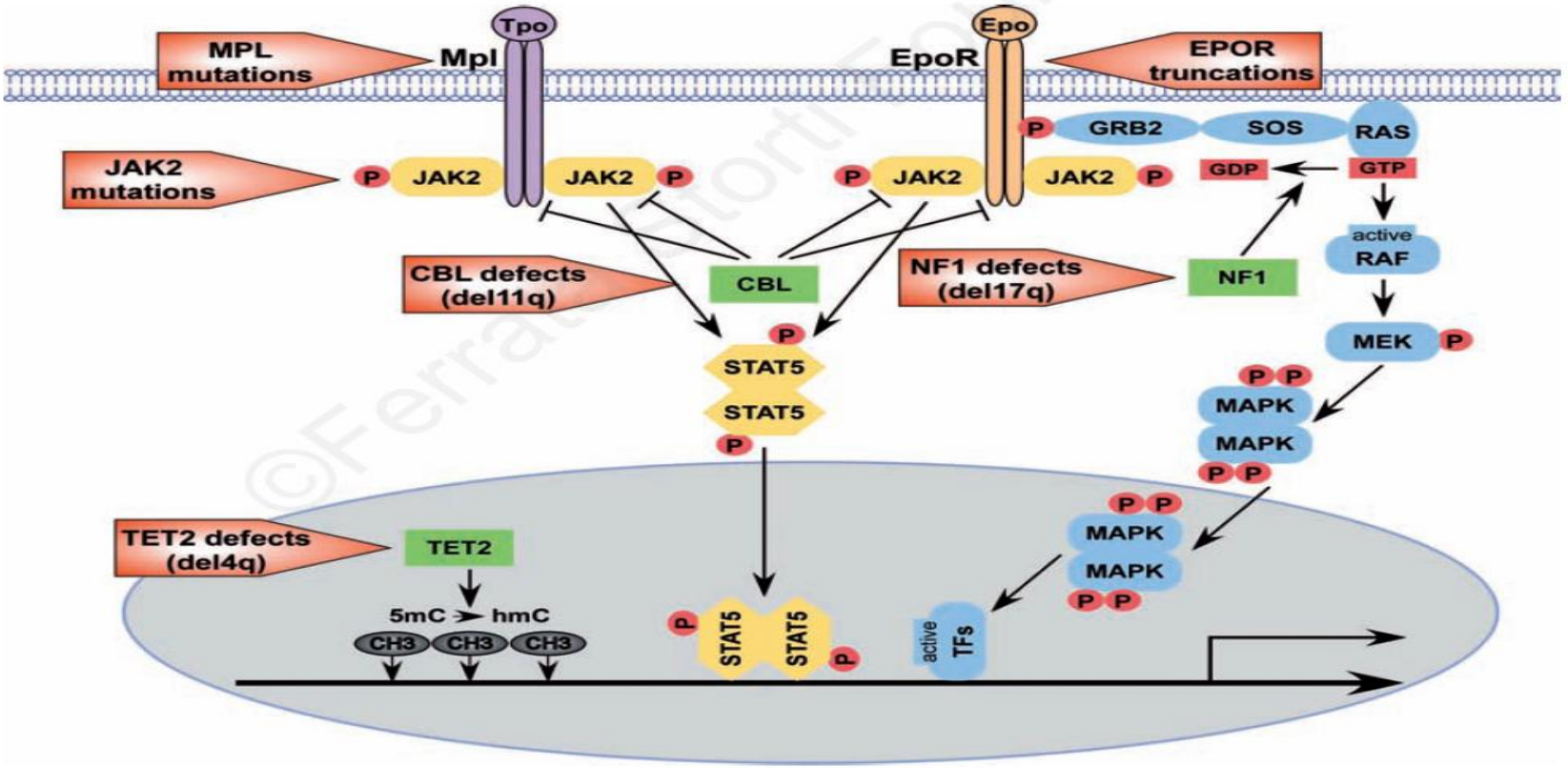


Mutations in myeloproliferative neoplasms. Genes involved in MPN pathogenesis are linearly represented with their principal functional or conserved domains. Molecular defects are shown in red. Point mutations are indicated by vertical arrows, with horizontal bars spanning the domains where multiple mutations have been identified. Horizontal arrows indicate truncating mutations that may occur anywhere in the downstream coding sequence. SH Src homology, JH JAK homology, Ig immunoglobulin, TK tyrosine kinase, Pro proline, ASXN and ASXM ASX conserved domains, NR nuclear receptor, PHD plant homeodomain

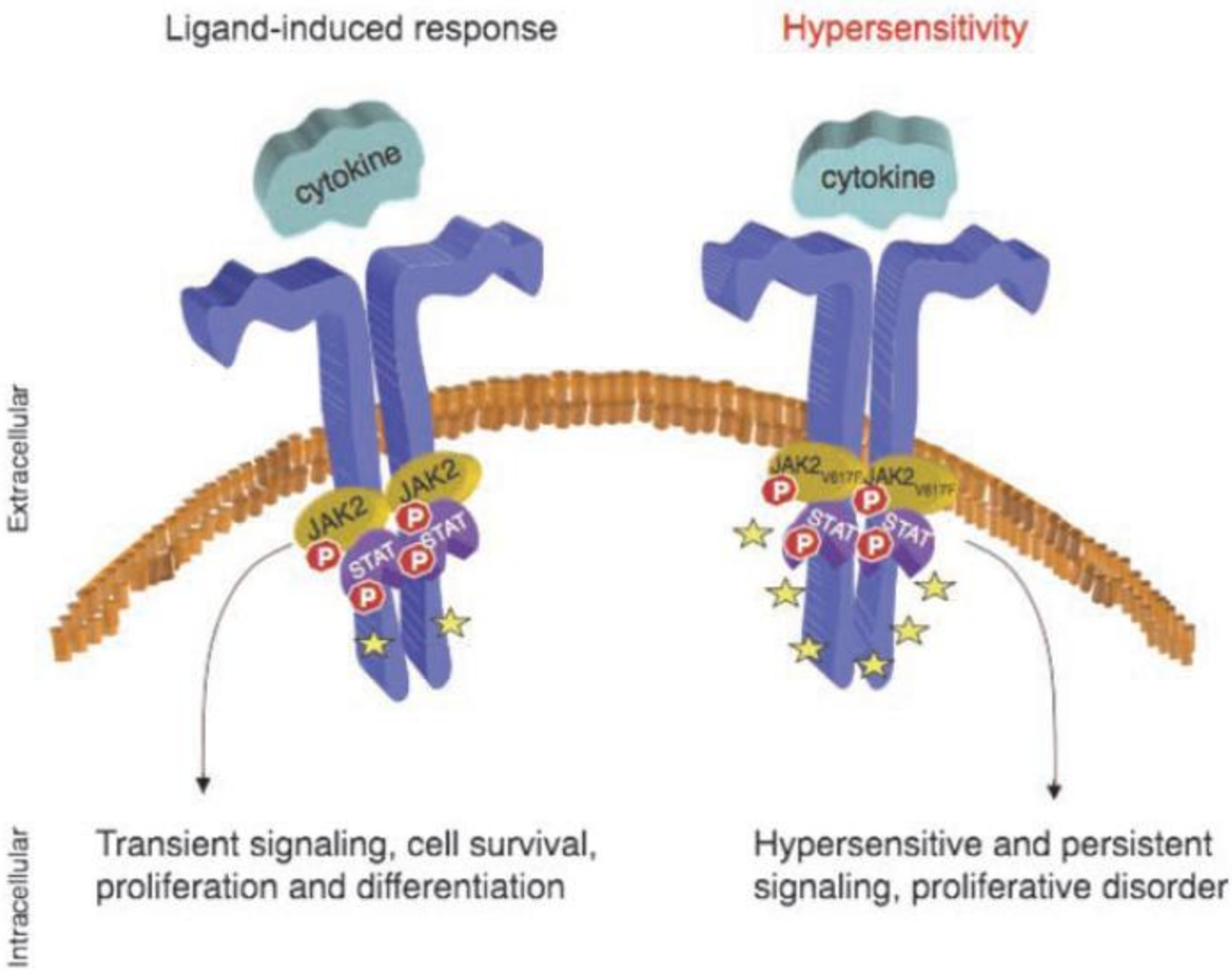


A model for molecular pathogenesis of MPN. The myeloid malignancy is initiated by a polyclonal or clonal premalignant hematopoiesis, depending on the presence of germline or somatic molecular predispositions or defects. Genes whose mutations trigger an overt MPN are indicated. The accumulation of additional events participates in the progression of the disease, which ends with transformation to AML. Left and right vertical arrows indicate that the transformation can occur in cells devoid of the specific MPN oncogenic mutations

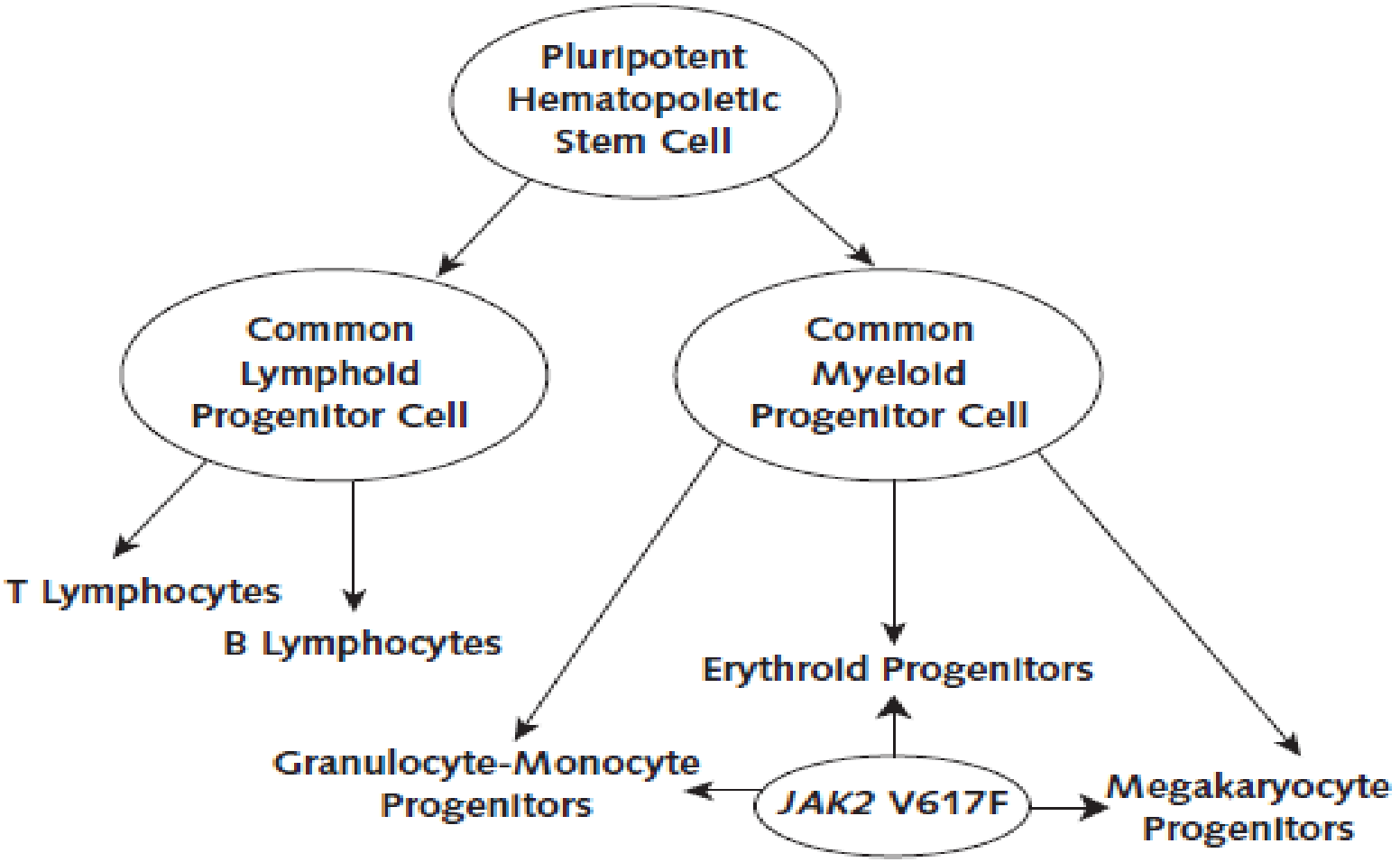
MECHANISMS AND PATHWAYS TARGETED BY MUTATIONS IN MPN



Red boxes summarize germ line and somatic mutations in MPN and MPN-like phenotypes. Clonal advantage based on cytokine hypersensitivity can be triggered by genetic defects directly targeting cytokine receptors, such as MPL mutations and EPO-R C-terminal truncations, as well as mutations affecting elements of downstream signaling cascades. Defects identified so far in MPN predominantly activate the JAK-STAT and the mitogen-activated protein kinase (MAPK) pathways. Gain-of-function mutations in JAK2 (JAK2-V617F and JAK2 exon 12 mutations) directly affect signal transduction, whereas loss of function mutations in CBL and NF1 intervene indirectly. The ubiquitin ligase CBL regulates the degradation of surface receptors and JAK2. NF1, a GTPase activating protein decreases signal potential of Ras, an important protooncogene in the MAPK pathway. Besides defects in cytokine signal transduction, mutations potentially directly affecting gene transcription have been found in TET2. TET2 might be involved in epigenetic transcriptional regulation by enzymatically catalyzing the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, as shown for another TET family member TET1.

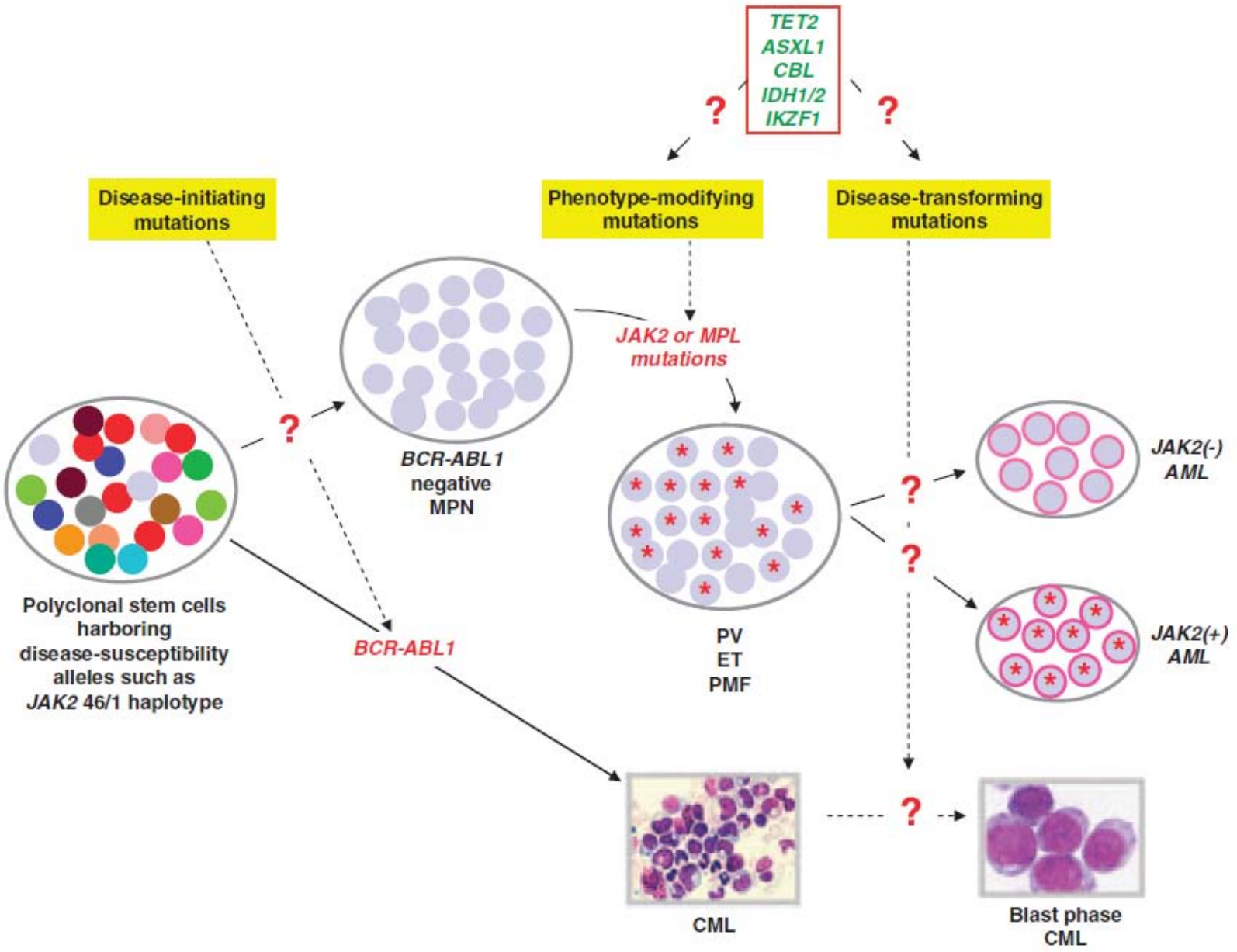

Ligand-induced response
Hypersensitivity
cytokine
cytokine
Extracellular
Intracellular
JAK2
JAK2
JAK2V617F
JAK2V617F
STAT
STAT
STAT
STAT
P
Transient signaling, cell survival, proliferation and differentiation
Hypersensitive and persistent signaling, proliferative disorder

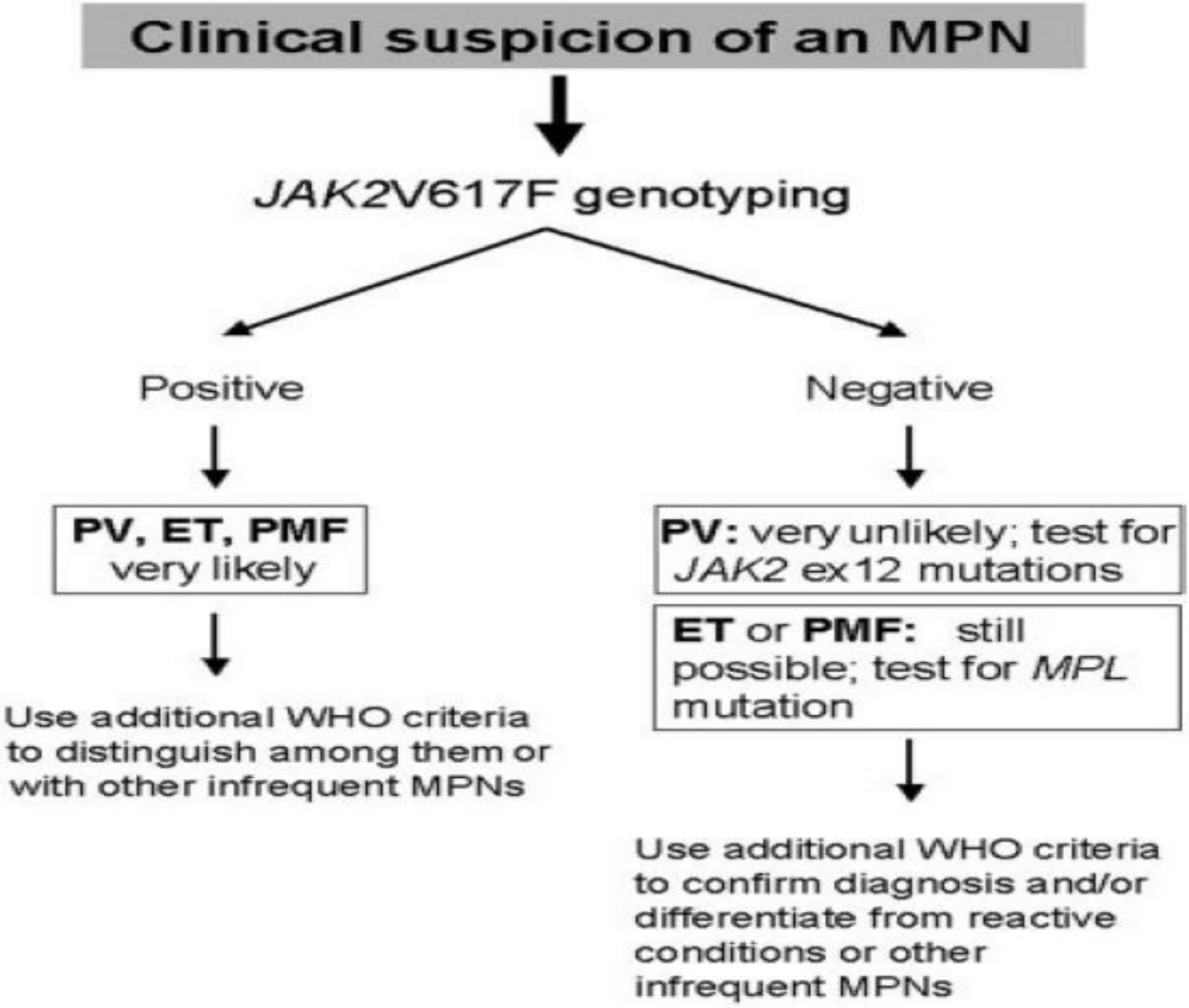
SCHEMATIC REPRESENTATION OF THE PROGENITOR CELLS MOST SENSITIVE TO JAK2 V617F



JAK2 is an obligatory kinase primarily for erythroid and megakaryocytic cell development; granulocytes can also use JAK1, and lymphocytes do not require JAK2. As illustrated, polycythemia vera is the ultimate clinical phenotype that can be caused by constitutive JAK2 activation.

CLONAL ORIGINATION AND EVOLUTION IN MYELOPROLIFERATIVE NEOPLASMS




Clinical suspicion of an MPN
JAK2V617F genotyping
Positive
Negative
PV, ET, PMF very likely
Use additional WHO criteria to distinguish among them or with other infrequent MPNs
PV: very unlikely; test for JAK2 ex12 mutations
ET or PMF: still possible; test for MPL mutation
Use additional WHO criteria to confirm diagnosis and/or differentiate from reactive conditions or other infrequent MPNs