

Nonreceptor Tyrosine Kinases

Oncogenic activation, BCR::ABL, JAK2, and clinicopathologic consequences

Molecular basis of neoplasia

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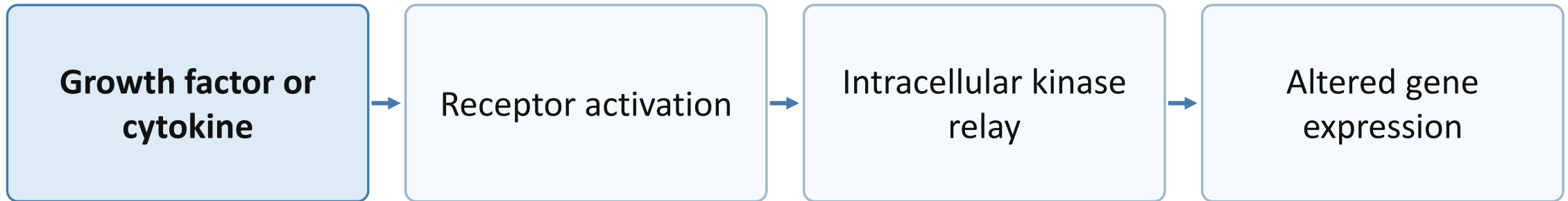
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Learning objectives

- Distinguish nonreceptor kinases from receptor tyrosine kinases and explain their normal signaling role.
- Trace how BCR::ABL fusion and JAK2 point mutations produce persistent mitogenic signaling.
- Relate kinase lesions to CML, Philadelphia-positive ALL, and JAK2-associated myeloproliferative neoplasms.
- Explain molecular diagnosis, targeted inhibition, and the persistence of residual disease.

A cellular growth signal must be transmitted



- Normal signaling is temporally controlled by upstream ligand availability.
- Cancer-associated kinase lesions uncouple signaling from that restraint.

The location of the kinase does not determine whether it can drive growth.

Receptor and nonreceptor tyrosine kinases

Receptor tyrosine kinase

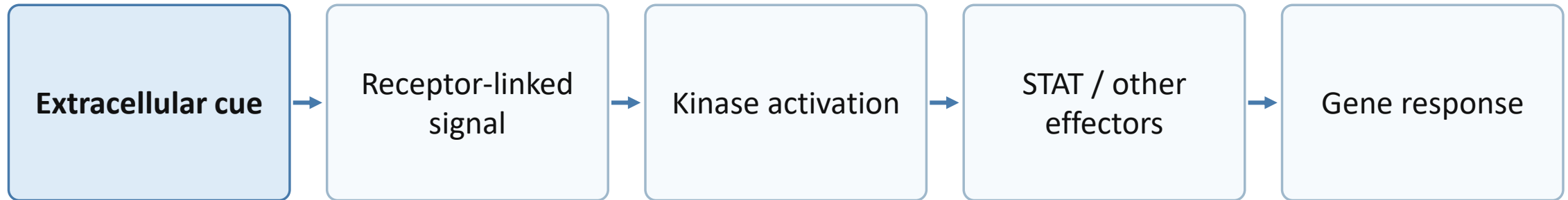
- Contains a membrane-spanning receptor component.
- Extracellular ligand binding normally initiates activation.
- Mutations may constitutively activate receptor signaling.

Nonreceptor tyrosine kinase

- Typically operates in cytoplasm or nucleus.
- Associates with upstream receptors or signaling complexes.
- Fusions or point mutations can create persistent activity.

Both kinase classes can activate overlapping progrowth signaling routes.

Normal intracellular signaling is conditional



- Protein phosphorylation relays growth information across compartments.
- Removal of the initiating signal helps terminate the response.

On–off control versus kinase autonomy

Physiologic control

- Kinase activity is limited by receptor and regulatory inputs.
- Progrowth gene programs respond to cellular context.
- Signal amplitude and duration are restricted.

Oncogenic kinase activity

- A genetic alteration permits activation without normal input.
- Downstream pathways remain persistently engaged.
- Proliferation and survival become abnormally favored.

Two mechanisms of autonomous kinase activation

**Nonreceptor tyrosine kinase
oncogene**

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graph TD; A[Nonreceptor tyrosine kinase oncogene] --> B[Chromosomal rearrangement]; A --> C[Activating point mutation]; B --> D[Fusion partner drives self-association; Prototype BCR::ABL.]; C --> E[Negative autoregulatory restraint is lost; Prototype JAK2.]; D --> F[Distinct DNA lesions converge on excessive kinase signaling.]; E --> F;
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Chromosomal rearrangement

Fusion partner drives self-association; Prototype
BCR::ABL.

Activating point mutation

Negative autoregulatory restraint is lost;
Prototype JAK2.

Distinct DNA lesions converge on excessive kinase signaling.

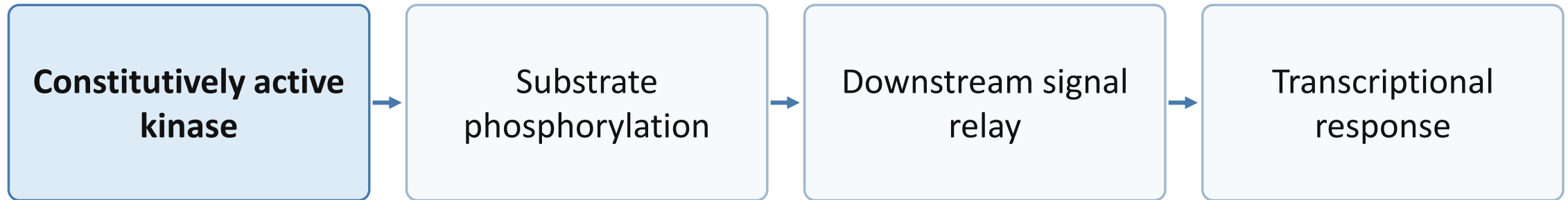
Why a kinase fusion is more than a translocation

- The driver lesion is the new fusion gene—not merely the visual chromosome rearrangement.
- The chimeric protein retains an enzymatically active tyrosine kinase component.
- A nonkinase fusion partner can promote constitutive self-association.
- Sustained kinase activity activates growth and survival signaling without normal regulation.

Where nonreceptor kinases act

- They usually do not contain the extracellular ligand-binding structure of receptor tyrosine kinases.
- Nonreceptor kinases may localize to cytoplasm or nucleus.
- They integrate signals from surface receptors and intracellular protein complexes.
- Their oncogenic effects can converge on transcriptional programs promoting proliferation.

Persistent phosphorylation reaches the nucleus



- JAK signaling engages STAT transcription factors.
- BCR-ABL activates multiple progrowth and prosurvival cascades, rather than just one pathway.

A fusion oncogene begins with DNA breakage

01

DNA breaks

Chromosomal breaks affect the partner loci.

02

Abnormal joining

DNA ends rejoin into derivative chromosomes.

03

Fusion gene

Coding regions become linked in a new arrangement.

04

Chimeric protein

The novel product acquires oncogenic activity.

The biologic driver is the fused protein encoded after rearrangement.

Two consequences of oncogenic translocation

Fusion protein: BCR::ABL

- Parts of two coding sequences combine.
- A novel chimeric kinase is synthesized.
- Constitutive enzymatic activity is the driver.

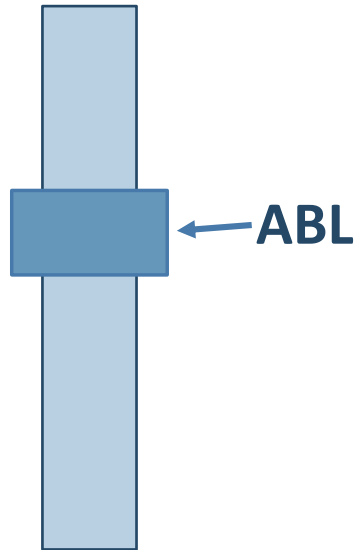
Deregulated expression: MYC example

- Regulatory DNA changes raise MYC expression.
- The principal consequence is oncogene overexpression.
- The coding product need not be a chimeric kinase.

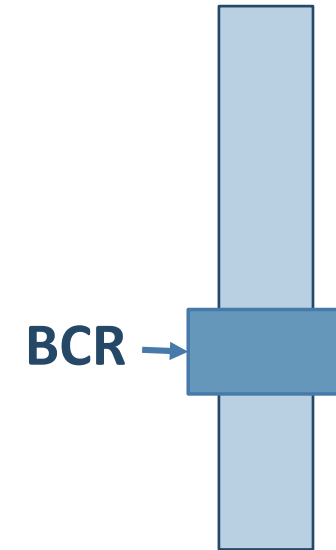
A chromosomal translocation does not always create the same type of oncogene.

BCR and ABL arise on different chromosomes

Chromosome 9



Chromosome 22



BCR resides on chromosome 22; ABL resides on chromosome 9.

The t(9;22) translocation generates BCR::ABL

Chromosome 9: ABL

Chromosome 22: BCR

Reciprocal exchange at t(9;22)(q34;q11)

Derivative chromosome 22: BCR::ABL

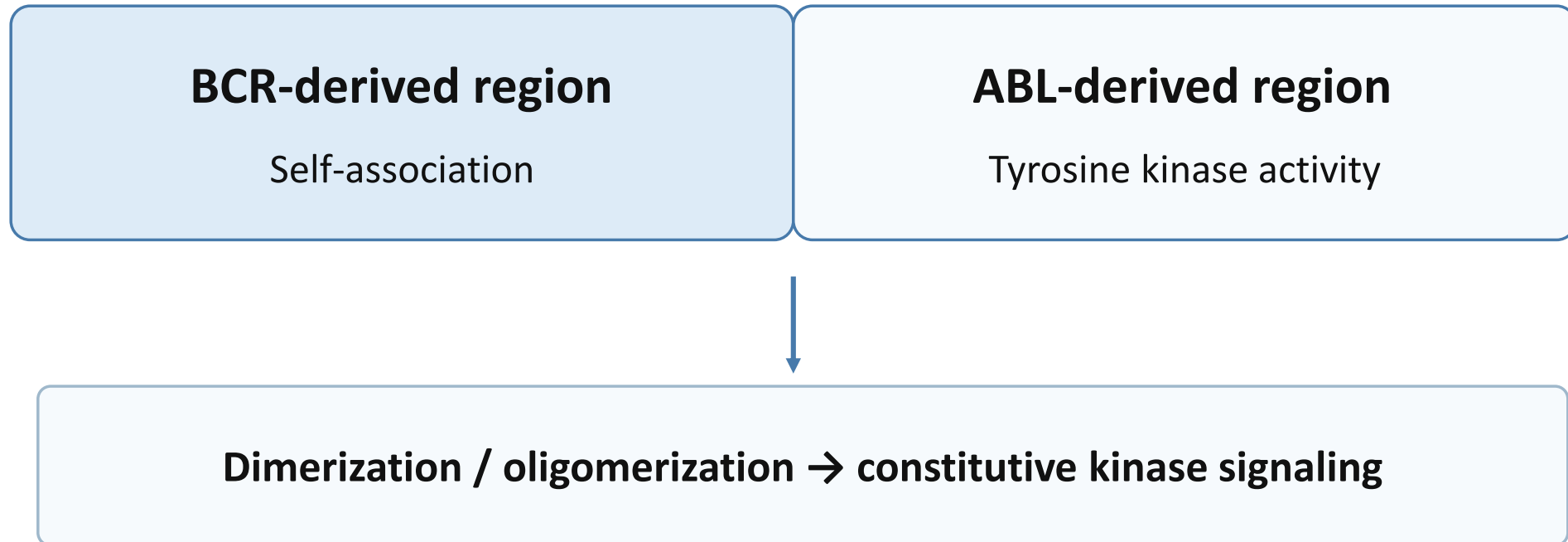
The oncogenic BCR::ABL fusion resides on derivative chromosome 22.

The Philadelphia chromosome: Interpret carefully

- The Philadelphia chromosome is the derivative chromosome 22 resulting from t(9;22).
- BCR::ABL encodes the critical chimeric tyrosine kinase; The karyotypic finding is a way to recognize the lesion.
- A cryptic or complex rearrangement may create BCR::ABL without a conventional visible Philadelphia chromosome.
- Therefore molecular evidence of the fusion can be more informative than conventional karyotype alone.

BCR::ABL joins self-association and catalytic activity

Fusion polypeptide

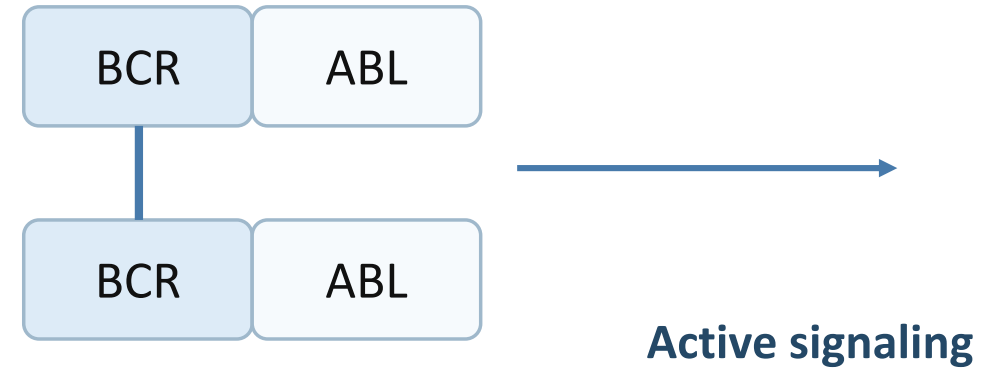


BCR-driven self-association releases ABL activity

Isolated fusion molecules



Self-associated fusion molecules



BCR-mediated association drives activation of the ABL kinase domain.

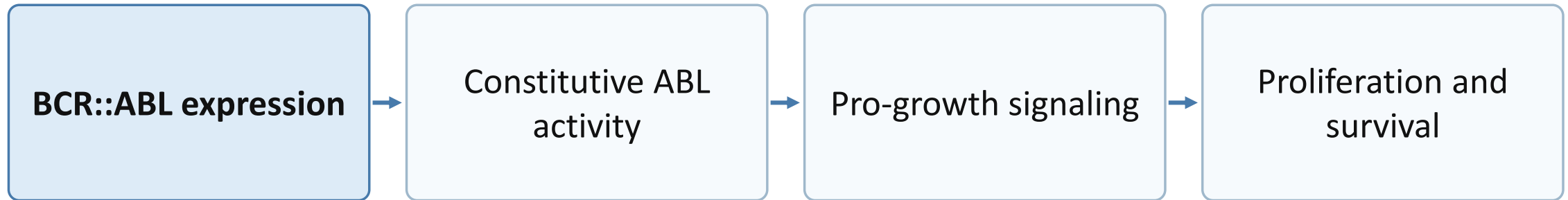
The contribution of the BCR moiety

- BCR provides a self-association function within the chimeric protein.
- Association of BCR-ABL molecules promotes constitutive activity of the ABL kinase component.
- The oncogenic effect is not simply an increased amount of otherwise normally regulated ABL.
- Similar partner-driven association mechanisms recur among other oncogenic kinase fusions.

The contribution of the ABL moiety

- ABL supplies the tyrosine kinase enzymatic activity of the fusion oncoprotein.
- Constitutive activation removes the need for normal upstream triggering.
- The fusion can engage pathways otherwise stimulated by growth factor receptors.
- Inhibiting this kinase activity attacks the causal driver of CML proliferation.

From fusion protein to growth advantage



- The fusion can initiate the disease, but later acquired lesions may alter the course.
- Persistent signaling supports excessive growth without requiring the normal stimulus.

BCR-ABL signals through multiple pathways

BCR-ABL tyrosine kinase

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graph TD; A[BCR-ABL tyrosine kinase] --> B[RAS-associated signaling]; A --> C[JAK / STAT signaling];
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RAS-associated signaling

Downstream progrowth programs support proliferative responses.

JAK / STAT signaling

Transcriptional responses promote growth and survival.

BCR-ABL is an upstream oncogenic node, not a single terminal pathway.

Growth factor dependence in normal and CML cells

Normal myeloid progenitor

- Receives regulated hematopoietic growth signals.
- Growth and survival depend on these extracellular cues.
- Lineage maturation proceeds within controlled hematopoiesis.

BCR-ABL-positive progenitor

- Exhibits kinase signaling without normal ligand dependence.
- Proliferation and survival are constitutively favored.
- Maturation can continue, generating abundant mature cells.

CML: Initiation precedes clonal evolution

01

Initiating lesion

BCR::ABL forms in a hematopoietic stem cell.

02

Clonal expansion

The kinase drives progenitor proliferation.

03

Additional lesions

Selected mutations can complement the original driver.

04

Progression

Some clones acquire aggressive properties / blast crisis.

A founding oncogene is not necessarily the only mutation in advanced cancer.

CML originates in a multipotent stem cell

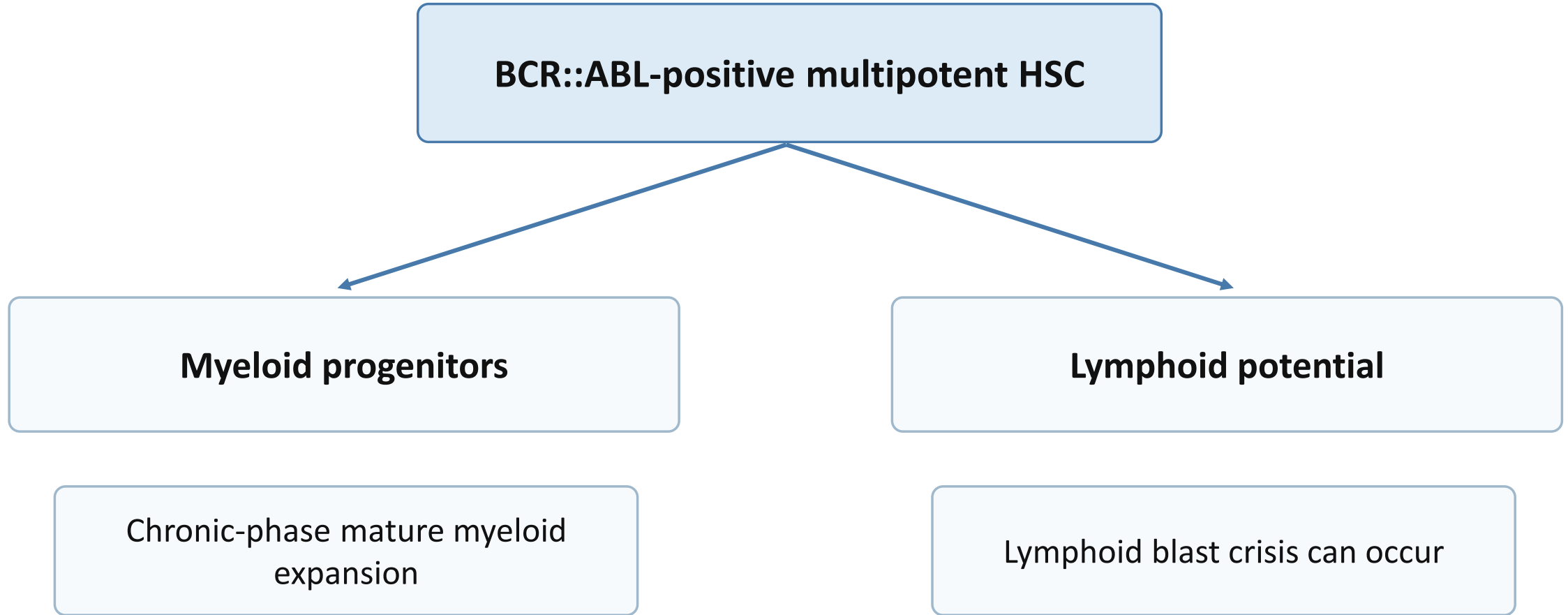
BCR::ABL-positive multipotent HSC

Myeloid progenitors

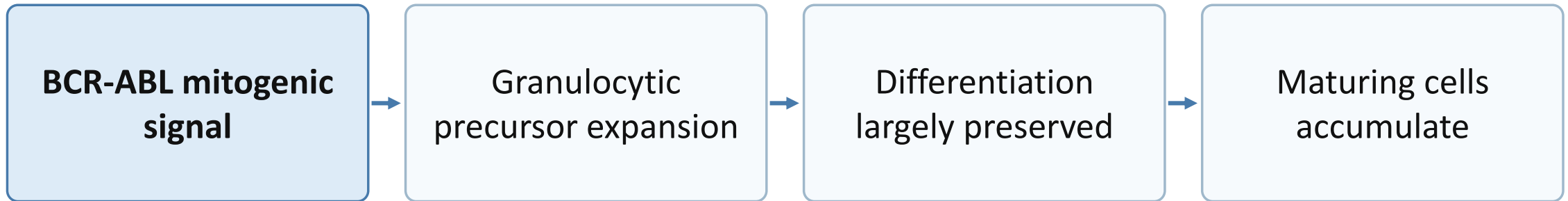
Chronic-phase mature myeloid
expansion

Lymphoid potential

Lymphoid blast crisis can occur



Why mature granulocytes predominate in CML



Increased proliferation need not imply a complete differentiation block.

Characteristic CML blood and marrow phenotype

- Marked marrow hypercellularity with expansion of maturing granulocytic precursors.
- Peripheral blood shows leukocytosis spanning neutrophils and immature granulocytic stages.
- Basophils and eosinophils may be increased; Platelets are often elevated.
- Splenomegaly reflects prominent extramedullary hematopoiesis.

CML marrow: Which lineages expand?

Predominant expansion

- Granulocytic precursors at several maturation stages.
- Basophil and eosinophil components are often increased.
- Megakaryocytes may be numerous, including small forms.

Other changes

- Erythroid precursors are normal or mildly reduced.
- Reticulin deposition can be increased.
- Sea-blue histiocytes may be observed in marrow.

CML peripheral blood: A maturation spectrum

01

Myelocytes

Immature circulating granulocytic precursors.

02

Metamyelocytes

Further maturation is visible.

03

Band forms

Still maturing neutrophils.

04

Segmented forms

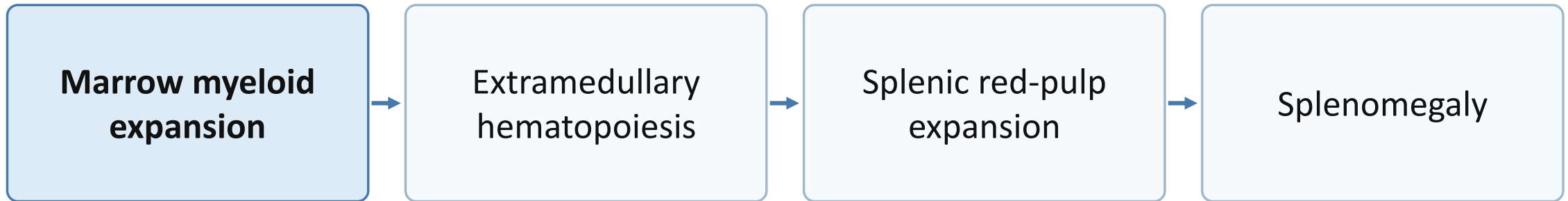
Mature neutrophils coexist with precursors.

The hallmark is a broad granulocytic maturation spectrum, not uniform blasts.

CML megakaryocytes, platelets and fibrosis

- Megakaryocytes are typically increased; Small atypical forms may be present.
- Thrombocytosis can accompany the prominent granulocytic expansion.
- Reticulin increase is characteristic, yet overt fibrotic replacement is uncommon at presentation.
- These findings help build a pattern but do not replace fusion-gene testing.

Why the CML spleen enlarges



- A markedly enlarged spleen may cause abdominal fullness.
- Splenic infarction can produce acute left upper-quadrant pain.

Symptoms of CML follow the disease biology

High cellular turnover

- Fatigue, weakness and constitutional symptoms.
- Anemia can accompany neoplastic hematopoiesis.
- Hypermetabolism contributes to weight loss.

Extramedullary hematopoiesis

- Splenomegaly produces abdominal fullness.
- A splenic infarct may produce pain.
- Spleen size reflects disease burden, not molecular identity.

CML identification: Morphology and molecular tests

Domain	Information supplied	Principal limitation
Blood / marrow	Suggest a myeloproliferative pattern	Cannot establish BCR::ABL identity
Karyotype	May show the Philadelphia chromosome	Cryptic rearrangements can be missed
FISH / PCR	Can detect BCR::ABL rearrangement / fusion	Assay targets and specimen adequacy matter

Conventional cytogenetics in CML

- A classic karyotype reveals t(9;22)(q34;q11), producing the Philadelphia chromosome.
- Cytogenetic analysis depicts the chromosome-level rearrangement.
- Complex or cryptic rearrangements can make the characteristic chromosome change difficult to identify.
- Detection of the BCR::ABL fusion establishes the defining molecular lesion.

FISH and PCR answer related but distinct questions

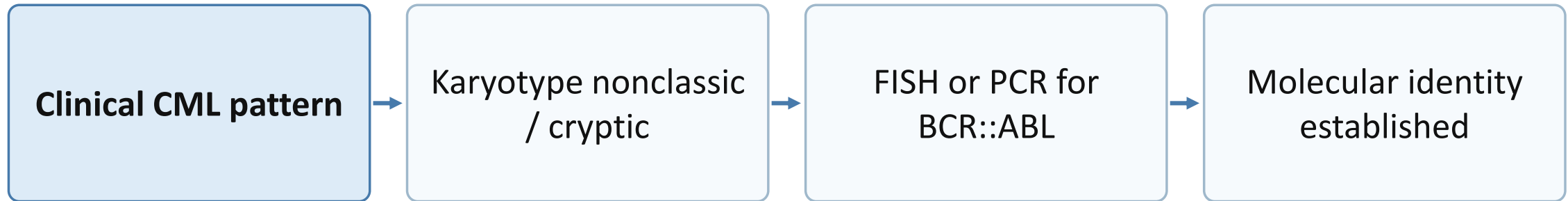
Fluorescence in situ hybridization

- Detects characteristic proximity / rearrangement of gene loci.
- Useful when karyotype fails to show an obvious translocation.
- Provides cell-level localization of probe signals.

PCR-based testing

- Detects fusion-derived sequences or transcripts.
- Can support sensitive molecular monitoring.
- A defined molecular target enables longitudinal disease assessment.

A cryptic fusion may escape a visible karyotype



A negative visible Philadelphia chromosome does not exclude a cryptic BCR::ABL fusion.

BCR::ABL in CML and Philadelphia-positive B-ALL

Chronic myeloid leukemia

- BCR::ABL is a defining initiating lesion.
- Typically produces broad myeloid precursor expansion.
- The prevalent fusion protein is about 210 kDa.

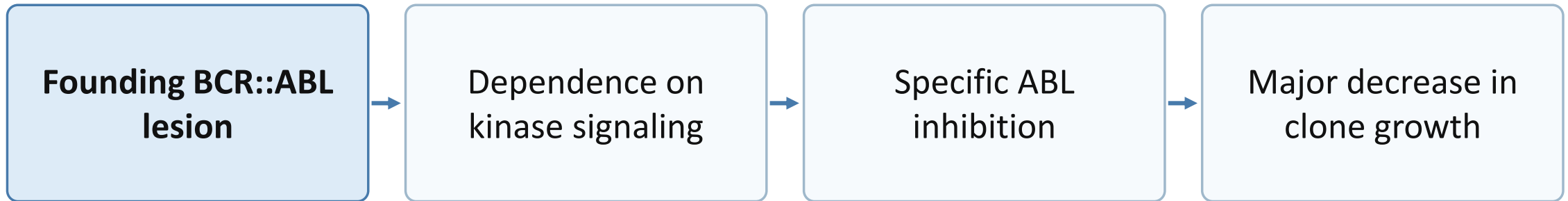
B-cell acute lymphoblastic leukemia

- A subset of B-ALL carries BCR::ABL.
- Immature lymphoid blasts dominate the clinical phenotype.
- The prevalent fusion protein is about 190 kDa.

CML and B-ALL can share a kinase driver

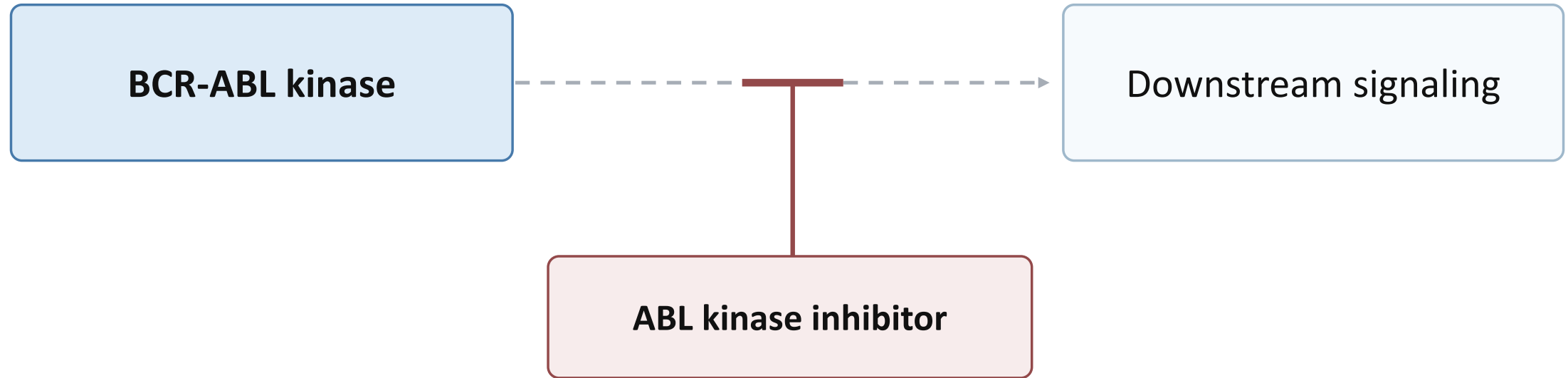
Question	CML	Philadelphia-positive B-ALL
Cell phenotype	Expanded maturing myeloid cells	Immature lymphoblasts
Usual BCR-ABL product	Approximately 210 kDa	Approximately 190 kDa
Clinical model	Myeloproliferation	Acute lymphoblastic leukemia

Oncogene addiction explains targeted vulnerability



- The same driver can initiate disease and become a therapeutic vulnerability.
- Oncogene addiction describes dependence, not universal eradication.

BCR-ABL inhibition blocks the oncogenic relay



Block of phosphorylation / signaling

Treatment response is not equivalent to cure

Proliferating CML compartment

- Strongly depends on active BCR-ABL signaling.
- Usually suppressed effectively by targeted inhibitors.
- Hematologic and molecular responses can be profound.

Persistent stemlike compartment

- Rare fusion-positive cells may remain.
- Can survive with less dependence on BCR-ABL signals.
- May seed recurrence after therapy is stopped.

Residual CML illustrates cellular heterogeneity

01

Large bulk clone

Kinase inhibition sharply reduces proliferating cells.

02

Residual cells

Rare BCR::ABL-positive stemlike cells remain.

03

Dormant reservoir

Some residual cells do not require the driver for survival.

04

Disease recurrence

Regrowth can follow incomplete suppression.

A sensitive target in most cancer cells may be insufficient to remove every malignant cell.

Stopping a kinase inhibitor: Interpret context

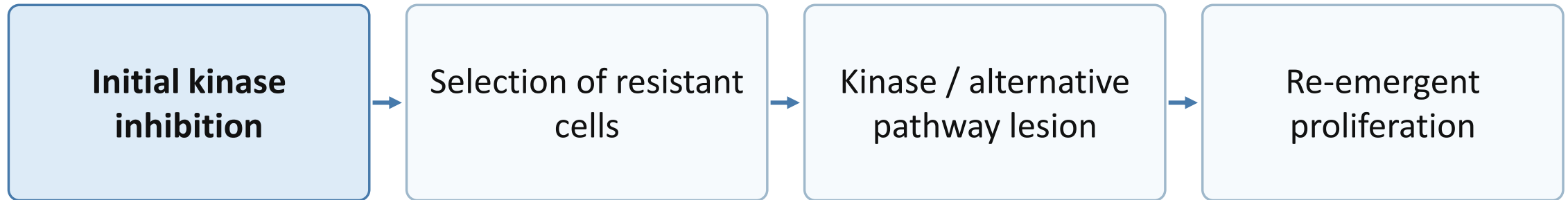
Frequent relapse risk

- Residual fusion-positive stemlike cells may remain.
- Stopping a drug can permit recurrent disease.
- A clinical remission does not prove clone extinction.

Selected deep molecular remissions

- The broader Robbins CML section notes that some patients maintain remission off therapy.
- This requires careful molecular selection and monitoring.
- Do not generalize treatment discontinuation to all patients.

Resistance can restore oncogenic signaling



- Later-generation inhibitors can address some resistant kinase variants.
- Resistance is biologically distinct from persistence of quiescent stemlike cells.

CML evolution may culminate in blast crisis

01

Chronic phase

Myeloid expansion
with preserved
maturation.

02

Additional lesions

Secondary clonal
genetic changes
accrue.

03

Accelerated disease

Increasing cytopenias
or clonal evolution
may emerge.

04

Blast crisis

An acute leukemia-
like phenotype
appears.

The initiating kinase does not fully explain late differentiation arrest.

CML progression and targeted response

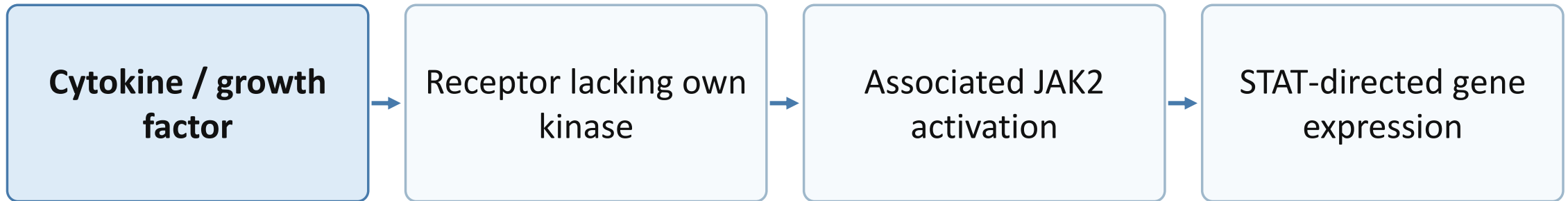
Original initiating oncogene

- BCR::ABL provides sustained mitogenic drive.
- Chronic-phase cells retain differentiation.
- Inhibitors interrupt a major growth dependency.

Secondary molecular evolution

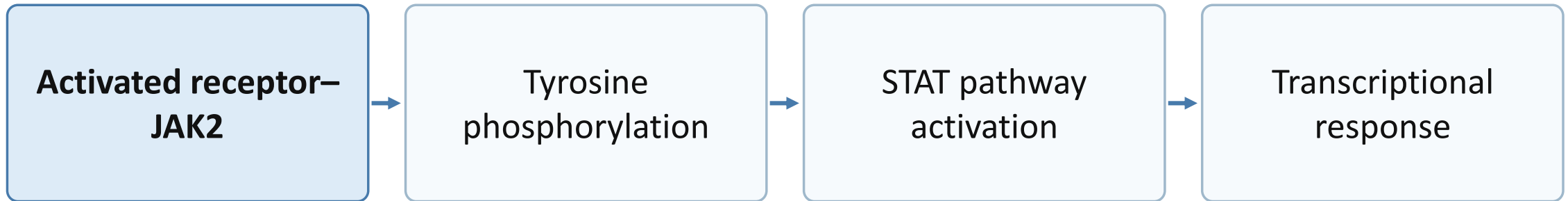
- Other mutations add malignant capabilities.
- Blast transformation can involve differentiation regulators.
- Late lesions complicate disease control.

JAK2 transmits cytokine receptor signals



- Erythropoietin receptor is a relevant hematopoietic example.
- This pathway helps regulate hematopoietic cell proliferation.

The JAK/STAT pathway couples signals to transcription



- The response is mitogenic in the relevant hematopoietic setting.
- Mutation of the associated kinase may short-circuit receptor dependence.

JAK2 normally requires autoregulatory restraint

Intact regulatory control

- Receptor-linked signaling engages JAK2 when appropriate.
- Autoregulatory regions limit kinase activity.
- Target gene activation follows controlled input.

Autoregulatory failure

- An activating mutation disrupts inhibitory control.
- Kinase activity can become excessive.
- The clone becomes less dependent on ligand supply.

A JAK2 point mutation can unlock kinase activity

Normal JAK2

Autoinhibitory regulation



Kinase restrained

Mutant JAK2

Loss of negative restraint



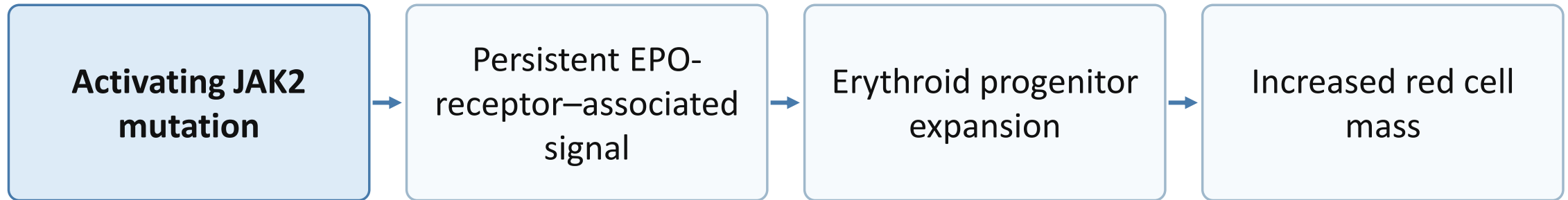
Kinase activated

A point mutation can activate a kinase without creating any fusion protein.

JAK2 V617F is a canonical activating lesion

- Substitution of valine by phenylalanine at residue 617 of JAK2.
- This lesion disrupts normal restraint on JAK2 activity.
- The associated clone shows markedly reduced dependence on hematopoietic growth factors.
- The mutation is strongly associated with polycythemia vera but is not limited to that disorder.

Erythropoietin-independent growth in PV



- The altered kinase is downstream of the erythropoietin receptor.
- Low circulating erythropoietin can coexist with high erythrocyte output.

Polycythemia vera involves panmyelosis

JAK2-activated marrow progenitor

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graph TD; A[JAK2-activated marrow progenitor] --> B[Erythroid]; A --> C[Myeloid]; A --> D[Megakaryocytic]; B --> E[Increased red cell mass]; C --> F[Granulocyte expansion]; D --> G[Platelet expansion];
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Erythroid

Increased red cell mass

Myeloid

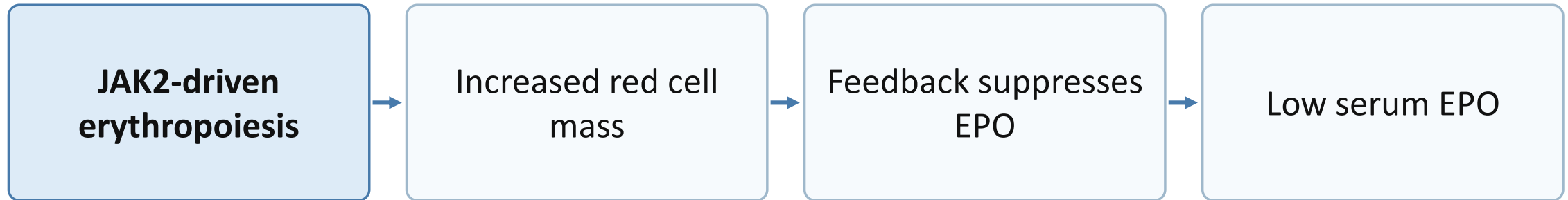
Granulocyte expansion

Megakaryocytic

Platelet expansion

PV increases multiple myeloid lineages; Erythrocytosis drives many symptoms.

Why serum erythropoietin is often low in PV



- This contrasts with erythropoietin-driven secondary polycythemia.
- The abnormality is within hematopoietic signaling rather than a response to hypoxia.

PV: Marrow expansion and clinical consequence

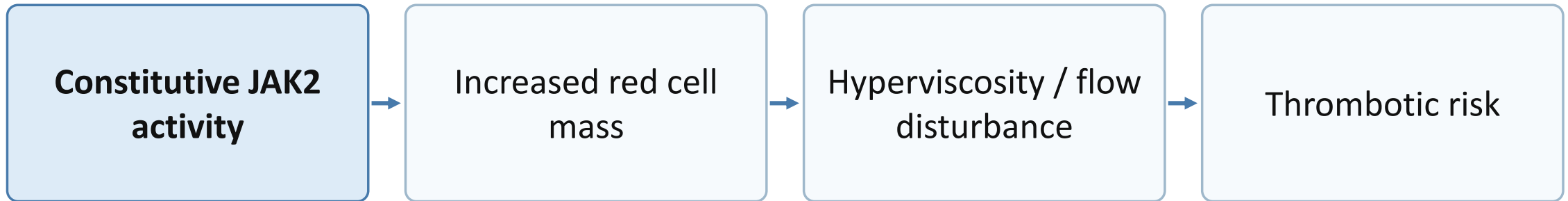
Marrow and blood pattern

- Increased erythroid, granulocytic and megakaryocytic production.
- Marrow hypercellularity with residual fat can be present.
- Platelets may be abnormal in number and function.

Clinical effects

- Increased hematocrit can raise blood viscosity.
- Pruritus, plethoric appearance and organomegaly occur.
- Thrombotic and hemorrhagic events are major hazards.

PV hyperviscosity links signaling to thrombosis



- Vascular complications may precede an obvious hematologic diagnosis.
- Bleeding may coexist because platelet function can be abnormal.

Primary JAK2-driven versus secondary erythrocytosis

Feature	Polycythemia vera	Secondary erythrocytosis
Dominant driver	Clonal JAK2 activation	Elevated erythropoietin drive
Serum EPO tendency	Often suppressed	Often elevated
Marrow response	Panmyelosis	Predominantly reactive erythropoiesis

JAK2 alterations span myeloproliferative neoplasms

Entity	Molecular associations	Interpretive point
Polycythemia vera	Usually activating JAK2 alterations	Strong molecular association
Essential thrombocythemia	JAK2, CALR or MPL alterations	Not all cases have JAK2 mutations
Primary myelofibrosis	JAK2, CALR or MPL alterations	Driver class alone does not define morphology

A JAK2 mutation is not a complete diagnostic label

- JAK2 mutations occur in more than one myeloproliferative neoplasm.
- Disease assignment also requires the blood count pattern, marrow findings and clinical context.
- ET and primary myelofibrosis may instead involve CALR or MPL driver alterations.
- Molecular identification must be integrated with phenotype rather than interpreted in isolation.

BCR::ABL and JAK2: The critical contrasts

Feature	BCR::ABL	Mutant JAK2
Molecular alteration	Fusion from chromosome rearrangement	Activating point mutation
Proximal mechanism	BCR-driven self-association	Loss of negative autoregulation
Illustrative disease	CML; Subset of B-ALL	PV; Some ET and PMF
Therapeutic concept	ABL kinase blockade	JAK pathway inhibition

Two driver architectures converge on autonomy

Constitutive fusion kinase

- New DNA junction generates BCR::ABL.
- Fusion partner promotes self-association.
- The kinase becomes constitutively active.
- CML exemplifies oncogene addiction.

Mutated native kinase

- JAK2 coding sequence acquires a point mutation.
- Normal negative regulation is impaired.
- Cytokine responsiveness becomes abnormal.
- PV exemplifies growth factor independence.

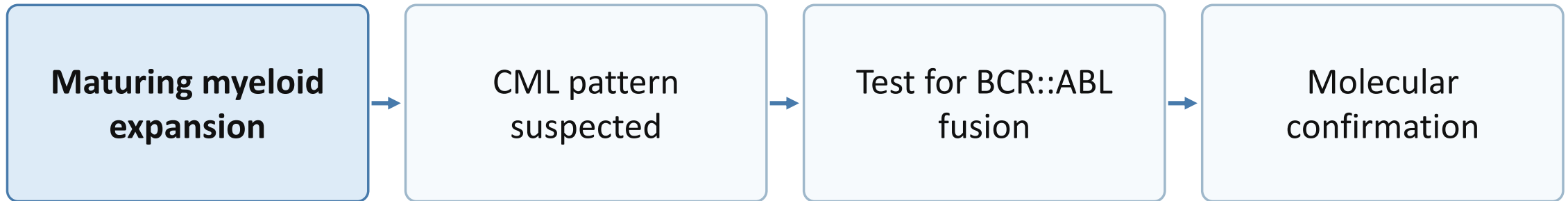
Case application: Marked myeloid proliferation

A patient has persistent marked leukocytosis, circulating granulocytes at multiple stages of maturation, basophilia, and splenomegaly. The marrow is highly cellular.

Which molecular lesion most directly defines the suspected neoplasm?

- A. Activating JAK2 alteration
- B. BCR::ABL fusion gene
- C. IG::MYC translocation

Case interpretation: A BCR::ABL-driven clone



- CML is a disease of hematopoietic stem cells with substantial differentiation.
- The fusion establishes the molecular identity; Morphology supplies context.

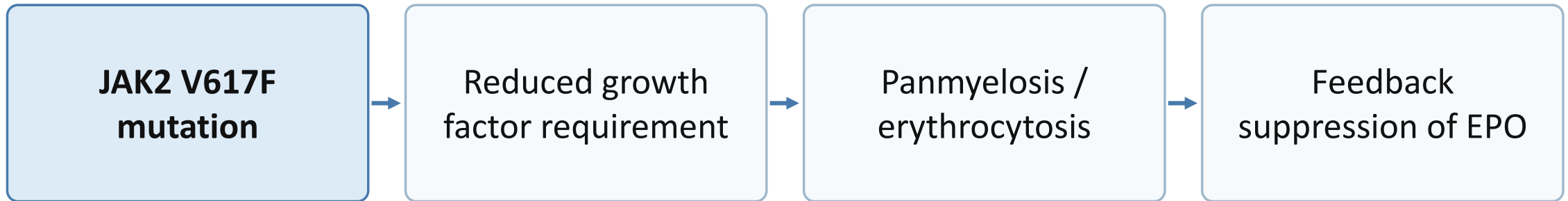
Case application: Erythrocytosis with low EPO

A patient has increased red cell mass, thrombocytosis, low serum erythropoietin, and marrow panmyelosis. Molecular analysis identifies JAK2 V617F.

What mechanism best accounts for the erythroid expansion?

- A. Constitutive signaling despite reduced EPO input
- B. Increased ligand-driven erythropoietin receptor activity only
- C. BCR-mediated ABL oligomerization

Case interpretation: Autonomous JAK2 activity



- PV must be separated from secondary EPO-driven erythrocytosis.
- Low EPO supports the pathophysiologic model but phenotype and molecular results remain important.

Three general lessons from nonreceptor kinases

01

Mechanism

Gene fusions or point mutations can create kinase autonomy.

02

Phenotype

Cell context shapes which hematologic neoplasm develops.

03

Therapy

Targeting the initiating kinase exploits a molecular dependence.

04

Limit

Residual cells and acquired lesions can undermine durable eradication.

Molecular cause, lineage phenotype, and treatment response must be interpreted together.

Primary reading and contextual source sections

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 7, Neoplasia: “Nonreceptor Tyrosine Kinases,” pp. 255–256.
- Chapter 7: chromosomal translocations and fusion oncogenes (BCR::ABL mechanism).
- Chapter 13: chronic myeloid leukemia, polycythemia vera, and associated kinase abnormalities.
- Chapter 13: Philadelphia-positive B-cell acute lymphoblastic leukemia (contextual comparison).