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BCR:ABL1 FUSION GENE: A LANDMARK DISCOVERY IN CANCER BIOLOGY AND TARGETED THERAPY

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ABSTRACT
One of the landmark achievements in cancer biology is the discovery of the BCR::ABL1 fusion gene, which remarkably advanced the understanding, diagnosis, and treatment of leukemia. BCR::ABL1 arises from a reciprocal translocation t(9;22)(q34;q11), between chromosomes 9 and 22, resulting in the formation of the Philadelphia chromosome (Ph) - the first chromosomal abnormality associated with a human malignancy. The BCR::ABL1 fusion gene encodes a constitutively active tyrosine kinase that propels uncontrolled cellular proliferation, enhances cell survival, and leads to leukemogenesis. BCR::ABL1 is the hallmark genetic lesion of Chronic Myeloid Leukemia (CML) and is also reported in a subset of Acute Lymphoblastic Leukemia (ALL) cases. Over the past decades, extensive investigations of BCR::ABL1 have provided a deep understanding of the molecular mechanisms underlying cancer and improved leukemia management. Advances in diagnostic technologies, including cytogenetic analysis, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR), have enabled accurate detection and monitoring of the fusion gene. Furthermore, the development of targeted therapies, particularly tyrosine kinase inhibitors, has transformed patient outcomes and established a paradigm for precision medicine in oncology. This review discusses the discovery, molecular basis, biological functions, clinical significance, diagnostic approaches, and therapeutic implications of the BCR::ABL1 fusion gene, emphasising its enduring impact on leukemia research and modern cancer care.

1. INTRODUCTION

Advances in cancer research have shown that many malignancies arise from genetic alterations that disrupt normal cellular functions. Among these, leukemia is one of the most extensively studied haematological cancers and is characterised by the uncontrolled proliferation of abnormal white blood cells in the bone marrow and blood. The accumulation of these malignant cells disrupts normal hematopoiesis and impairs essential physiological functions. Understanding the genetic basis of leukemia has provided crucial insights into its pathogenesis and has led to significant advances in diagnosis and targeted therapy.

One of the most significant discoveries in cancer biology was the identification of the BCR::ABL1 fusion gene, which resulted from a reciprocal translocation between chromosomes 9 and 22, designated as t(9;22)(q34;q11). This chromosomal rearrangement produces the Ph chromosome, first identified in 1960 and recognised as the first consistent chromosomal abnormality associated with a human cancer. Subsequent studies revealed that the translocation generates the BCR::ABL1 fusion oncogene, resulting from the fusion of the Breakpoint Cluster Region (BCR) gene and the Abelson Tyrosine Kinase 1 (ABL1) gene. The encoded fusion protein possesses constitutive tyrosine kinase activity that drives leukemic transformation[1, 2].

The BCR::ABL1 fusion gene encodes a constitutively active tyrosine kinase that continuously stimulates cellular growth and survival pathways[3]. As a result, affected hematopoietic cells gain a proliferative advantage, leading to the development of CML and a subset of ALL cases. The discovery of BCR::ABL1 not only advanced the understanding of leukemia pathogenesis but also revolutionized cancer treatment by enabling the development of targeted therapies, particularly tyrosine kinase inhibitors.

Today, BCR::ABL1 is regarded as a landmark example of precision medicine, illustrating how the understanding of a specific genetic abnormality can transform disease diagnosis, monitoring, and treatment. Beyond its role in leukemia pathogenesis, the discovery of BCR::ABL1 has profoundly influenced cancer research by establishing a framework for targeted therapeutic interventions. This review provides an overview of the discovery, molecular basis, biological functions, clinical significance, diagnostic methodologies, and therapeutic advances associated with the BCR::ABL1 fusion gene, emphasizing its enduring contribution to leukemia research and modern oncology

2. Leukemia: A Genetic Disease

Leukemia is a group of hematological malignancies characterized by the uncontrolled proliferation of abnormal blood cells, primarily within the bone marrow. It is broadly classified into acute and chronic forms and can affect either myeloid or lymphoid cell lineages[4]. Advances in molecular genetics have revealed that leukemia is driven by various genetic alterations, including chromosomal translocations, gene mutations, and fusion

genes. Among these, the BCR::ABL1 fusion gene is one of the most clinically significant genetic abnormalities, playing a central role in the pathogenesis of CML and a subset of ALL[5]. The identification of BCR::ABL1 has greatly enhanced our understanding of leukemia biology and has led to the development of highly effective targeted therapies.

3. The Philadelphia Chromosome: A Landmark Discovery in Cancer Genetics

3.1 Discovery of the Philadelphia Chromosome

A breakthrough in cancer research occurred in 1960 when Peter Nowell and David Hungerford identified an unusually small chromosome in the leukemic cells of patients with CML[6]. This abnormal chromosome, later named the Philadelphia chromosome after the city where it was discovered, was the first chromosomal abnormality consistently associated with a human cancer. Initially, the nature of this genetic alteration was unclear; however, advances in cytogenetic techniques later revealed that it resulted from a reciprocal translocation between chromosomes 9 and 22, designated as t(9;22)(q34;q11). This translocation gives rise to the BCR::ABL1 fusion gene, which plays a central role in leukemogenesis[7].

3.2 Significance of the Discovery in Cancer Research

The discovery of the Ph chromosome fundamentally changed the understanding of cancer by providing the first direct evidence that specific genetic abnormalities can cause human malignancies. It established a clear link between chromosomal alterations and disease development, paving the way for the field of cancer genetics. Subsequent identification of the BCR::ABL1 fusion gene provided critical insights into the molecular mechanisms underlying leukemia and facilitated the development of highly sensitive diagnostic tools. Furthermore, the discovery laid the foundation for targeted cancer therapy, culminating in the development of tyrosine kinase inhibitors that transformed the treatment of CML. As a result, the Ph chromosome remains one of the most influential discoveries in modern oncology.

4. Molecular Origin of the BCR::ABL1 Fusion Gene

4.1 Translocation and Formation of the Philadelphia Chromosome

The BCR::ABL1 fusion gene arises from a reciprocal translocation between the long arms of chromosomes 9 and 22, designated as t(9;22)(q34;q11.2). This chromosomal rearrangement results in the transfer of the ABL1 proto-oncogene from chromosome 9 to the Breakpoint Cluster Region (BCR) gene on chromosome 22, generating the shortened Philadelphia chromosome (Ph chromosome), which harbours the BCR::ABL1 fusion gene (Fig.1). The reciprocal ABL1::BCR fusion is also formed but is generally not considered a major contributor to disease pathogenesis[2].

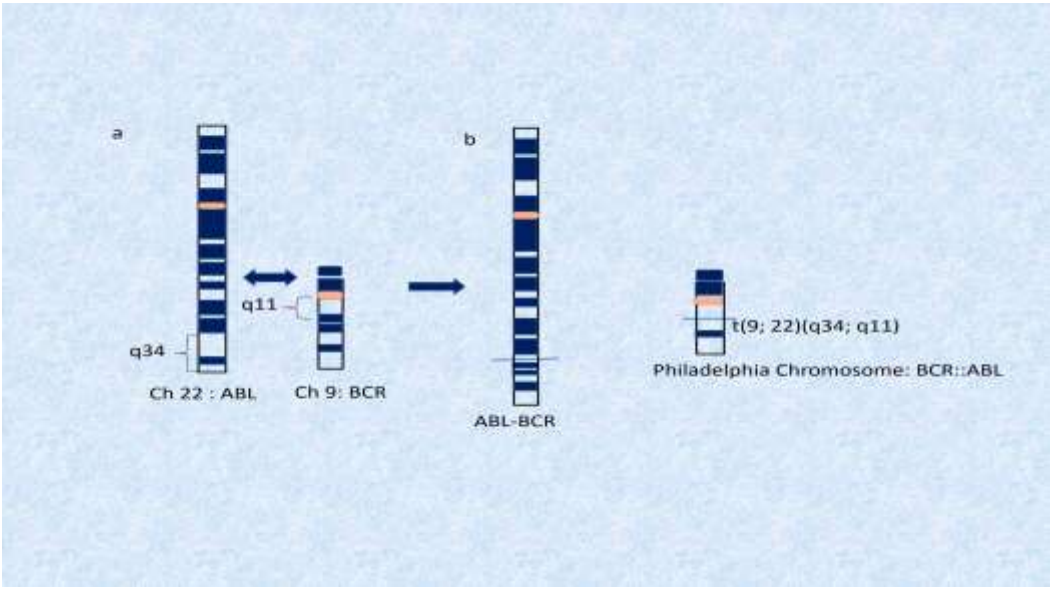

Fig.1. a. **Normal chromosome 22 and 9 with ABL and BCR gene, b. Philadelphia chromosome, Derivative chromosome 9 formation after reverse translocation**.

4.2 Structure and Biological Functions of BCR and ABL1

Under normal physiological conditions, the ABL1 gene encodes a non-receptor tyrosine kinase involved in regulating cellular proliferation, differentiation, DNA damage response, cytoskeletal remodelling, and apoptosis. In contrast, the BCR gene encodes a multifunctional protein containing coiled-coil oligomerisation domains and signalling regulatory regions that participate in intracellular signal transduction[8, 9]. Fusion of these genes disrupts the normal autoregulatory mechanisms of ABL1 and results in the expression of the BCR::ABL1 fusion protein. The coiled-coil domain contributed by BCR promotes oligomerisation and constitutive activation of the ABL1 kinase domain, leading to persistent tyrosine kinase activity that drives leukemogenesis[10].

The molecular characteristics of BCR::ABL1 depend on the location of the breakpoint within the BCR gene. These breakpoints are major breakpoint cluster region (M-BCR), minor breakpoint cluster region (m-BCR), and micro breakpoint cluster region (μ-BCR). Breakpoints within M-BCR generate e13a2 (b2a2) or e14a2 (b3a2) transcripts, which encode the 210-kDa fusion protein (p210 BCR::ABL1) commonly associated with Chronic Myeloid Leukemia (CML) (Fig.1). Breakpoints within m-BCR produce the p190 BCR::ABL1 isoform, which is frequently observed in B-cell Acute Lymphoblastic Leukemia (ALL)[11]. Less commonly, breakpoints within μ-BCR generate the p230 BCR::ABL1 isoform, which has been associated with rare chronic neutrophilic leukemic phenotypes[12, 13].

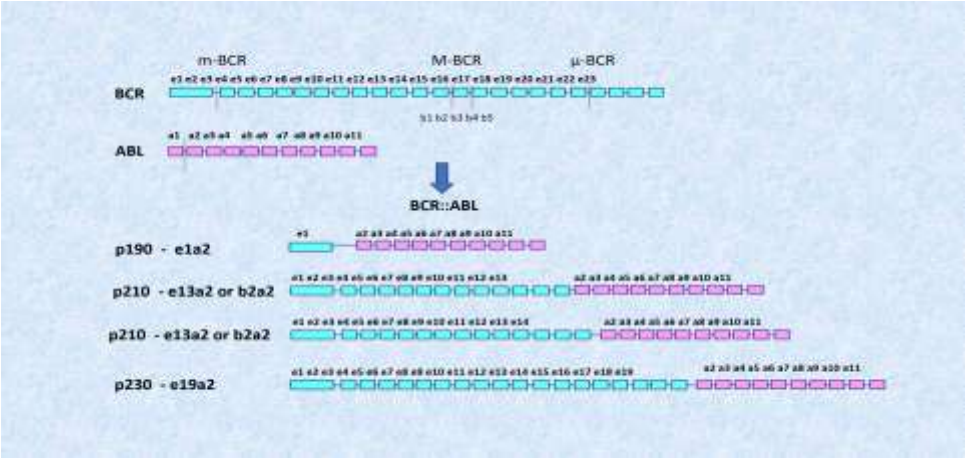

Fig.2. **Schematic of the BCR and ABL gene breakpoints and BCR::ABL fusion proteins:**

The formation of different isoforms of BCR::ABL proteins is due to the breakpoints of BCR (Major (M), Minor(m) and micro (μ)) joined with ABL.

4.3 Molecular Mechanisms of BCR::ABL1-Mediated Leukemogenesis

The fusion of BCR and ABL1 disrupts the normal autoinhibitory regulation of ABL1 kinase activity. The oligomerisation domain contributed by BCR promotes constitutive dimerisation and autophosphorylation of the fusion protein, leading to persistent tyrosine kinase activation independent of physiological signalling cues. Consequently, BCR::ABL1 continuously phosphorylates multiple downstream substrates and activates signalling pathways involved in cell proliferation, survival, adhesion, and genomic instability.

The constitutively active BCR::ABL1 kinase drives leukemogenesis through the activation of several oncogenic signalling cascades, including the RAS/MAPK, PI3K/AKT/mTOR, and JAK/STAT pathways. These molecular alterations promote uncontrolled proliferation of hematopoietic stem and progenitor cells, inhibit apoptosis, and confer a selective growth advantage to leukemic clones. Thus, the formation of the BCR::ABL1 fusion gene represents the central molecular event in the pathogenesis of CML and contributes significantly to the development of a subset of ALL cases[14].

5. From Molecular Alteration to Clinical Disease

5.1 Common Symptoms

The clinical manifestations of BCR::ABL1-positive leukemia vary based on the disease stage and leukemia subtype. Many patients with CML are asymptomatic at diagnosis and are identified through routine blood examinations. Common symptoms include fatigue, weakness, fever, night sweats, unexplained weight loss, and reduced exercise tolerance. Enlargement of the spleen (splenomegaly), a characteristic feature of CML, may cause abdominal discomfort, early satiety, or a sensation of fullness in the left upper abdomen. Patients may also experience anaemia, recurrent infections, and easy bruising or bleeding due to impaired normal hematopoiesis.

5.2 Disease Progression

CML is typically a progressive disease that runs through distinct clinical phases if left untreated. The expansion of BCR::ABL1-positive hematopoietic stem cells leads to increasing leukocyte counts and gradual disruption of normal bone marrow function. Over time, additional genetic abnormalities accumulate, promoting disease progression and increasing resistance to therapy. CML progresses through three clinical phases: the initial, most stable stage, Chronic Phase (CP), characterised by the expansion of mature myeloid cells. Most patients are diagnosed during this phase and respond well to tyrosine kinase inhibitor therapy. An intermediate stage, the Accelerated Phase (AP), is marked by increasing disease burden, worsening hematological abnormalities, and reduced treatment response. The most aggressive stage, Blast Phase (BP) or Blast Crisis, is characterised by the rapid proliferation of immature blast cells in the bone marrow and blood (Fig.2). Clinically, this phase resembles AL, associated with poor prognosis if not effectively treated.

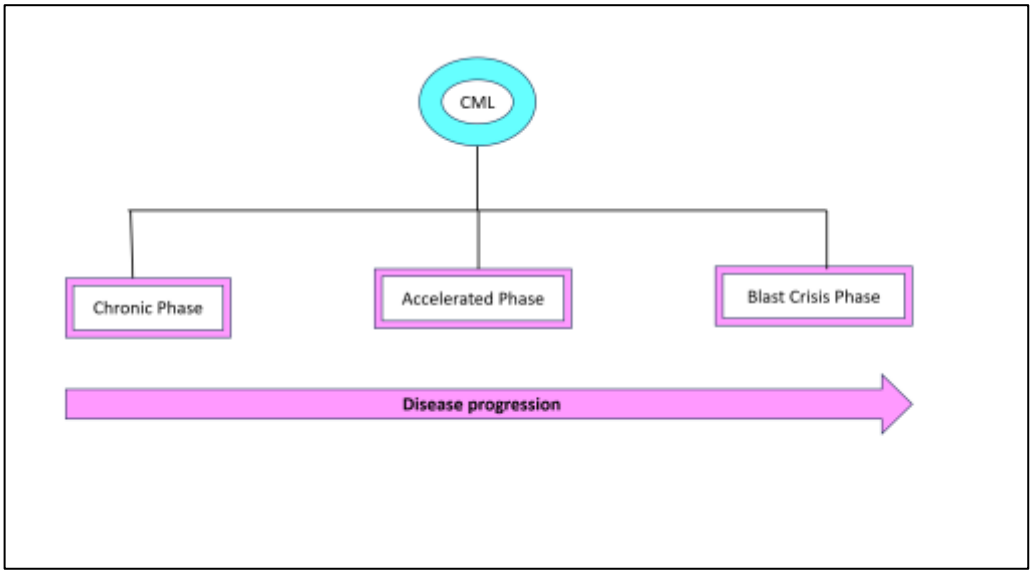

Fig. 2. Different phases of Chronic Myeloid leukemia

6. Detecting the Molecular Signature of Leukemia

6.1 Cytogenetic Analysis (Karyotyping)

Cytogenetic analysis, or karyotyping, is one of the earliest methods used to detect chromosomal abnormalities associated with leukemia. This technique involves examining metaphase chromosomes obtained from bone marrow cells. Bone marrow cells are typically cultured, arrested during metaphase, stained, and analysed under a microscope to identify chromosomal abnormalities[15]. In patients with BCR::ABL1-positive leukemia, karyotyping can identify the Ph chromosome, which results from the reciprocal translocation t(9;22)(q34;q11.2). The presence of the Ph chromosome is a hallmark of CML and is also observed in a subset of ALL cases.

Karyotyping not only confirms the presence of the Ph chromosome but also detects additional chromosomal abnormalities that may influence disease progression and prognosis. Despite being an important diagnostic tool, its sensitivity is limited, and it requires actively dividing cells for analysis. Therefore, more sensitive molecular techniques such as FISH and PCR are often used alongside cytogenetic analysis for accurate diagnosis and disease monitoring.

6.2 Fluorescence In Situ Hybridization (FISH)

FISH is a widely used molecular cytogenetic technique for the BCR::ABL1 fusion gene. The method employs fluorescently labelled DNA probes that bind to the specific parts of the BCR gene on chromosome 22 and the ABL1 gene on chromosome 9. When the translocation t(9;22)(q34;q11.2) occurs, the probes hybridise in proximity, producing a fusion signal that can be visualised using a fluorescence microscope[16, 17].

FISH offers higher sensitivity compared to karyotyping and can detect the BCR::ABL1 rearrangement in both dividing and non-dividing cells. Thus, particularly useful when metaphase chromosomes are unavailable or rapid confirmation of the Ph chromosome is required[18]. In addition to diagnosis, FISH is valuable for monitoring treatment response and identifying residual leukemic cells following therapy[19, 20]. Although FISH is more sensitive than cytogenetic analysis, it does not provide detailed information about specific BCR::ABL1 transcript variants. Therefore, it is often used in combination with molecular techniques such as reverse transcription polymerase chain reaction (RT-PCR) for comprehensive diagnosis and disease monitoring[21].

6.3 Polymerase Chain Reaction (PCR)

A highly sensitive molecular technique used to detect and quantify BCR::ABL1 fusion transcripts in patient samples with leukemia is the polymerase chain reaction (PCR). Unlike, karyotyping and FISH, which identify chromosomal abnormalities at the DNA level, it detects the messenger RNA (mRNA) produced by the BCR::ABL1 fusion gene. The RNA is first converted into complementary DNA (cDNA) using reverse transcriptase, followed by amplification of specific BCR::ABL1 sequences through polymerase chain reaction.

Reverse Transcription PCR (RT-PCR) single out different BCR::ABL1 transcript variants (e13a2 (b2a2), e14a2 (b3a2), and e1a2), associated with distinct leukemia subtypes[22]. The highly sensitive RT-PCR can pick out very low levels of leukemic cells in comparison to cytogenetic analysis or FISH[23].

Quantitative PCR (qPCR) or real-time PCR is routinely used in patients receiving tyrosine kinase inhibitor therapy. It is an approved and reliable method for monitoring treatment response and assessing minimal residual disease (MRD). It provides valuable information on disease burden, therapeutic effectiveness, and risk of relapse by quantifying BCR::ABL1 transcript levels in real time. Owing to its accuracy, sensitivity, and ability to quantify disease progression, PCR has become the gold standard for molecular diagnosis and monitoring of BCR::ABL1-positive leukemia[24, 25].

7. Targeting BCR::ABL1: Therapeutic Advances

The molecular fingerprints of BCR::ABL1 have divulged targeted therapies in the form of tyrosine kinase inhibitors (TKIs), which inhibit the abnormal kinase activity of the fusion protein. The first BCR::ABL1-targeted TKI, Imatinib, revolutionised the treatment of CML by significantly improving patient survival and quality of life. However, the drug resistance was the major problem in treatment which was consistently tackled by the subsequently developed second and third-generation TKIs, including dasatinib, nilotinib, bosutinib, and ponatinib. These TKIs exhibit greater potency and impact against several resistant BCR::ABL1 mutations. Nowadays, TKI therapy is the framework treatment for BCR::ABL1-positive leukemia. Regular molecular monitoring using quantitative PCR (qPCR) allows assessment of treatment response and early detection of resistance, enabling personalised disease management[26].

8. Drug Resistance and Current Challenges

Despite the remarkable success of TKIs, drug resistance remains a daunting challenge in the treatment of BCR::ABL1-positive leukemia. Resistance can reduce therapeutic effectiveness, leading to disease persistence or progression in a subset of patients. Resistance to TKI therapy may arise from several factors, including poor drug adherence, altered drug transport, activation of alternative signaling pathways, and the persistence of leukemic stem cells. These mechanisms enable leukemic cells to survive despite continued treatment[27].

8.2 BCR::ABL1 Kinase Domain Mutations

Mutations within the BCR::ABL1 kinase domain are the major causes of drug resistance. These mutations, particularly the alteration in the structure of the kinase, can hinder the binding efficiency TKIs to bind effectively. The T315I mutation is particularly important because it confers resistance to several first- and second-generation TKIs, necessitating the use of alternative therapeutic strategies[28].

8.3 Need for Improved Diagnostics and Therapies

Although current diagnostic methods and targeted therapies have upgraded patient outcomes, challenges such as drug resistance, leukemia relapse, and residual leukemia persist. Advancements are needed in developing more sensitive diagnostic tools, combination therapies, and innovative treatment approaches to achieve substantial and more reliable responses in the treatment of BCR::ABL1-positive leukemia[29].

9. Emerging Research and Future Perspectives

The association of molecular biology and biotechnology in the advancement of managing detection and treatment is a prerequisite in BCR::ABL1-positive leukaemia management [30, 31]. Emerging technologies could help in enhancing sensitivity, specificity, and therapeutic efficacy while supporting the transition toward personalised medicine.

9.1 Nanotechnology-Based Detection Methods

Nanotechnology has been a pioneering approach that has advanced the rapid and sensitive detection of leukaemia biomarkers. Various nanoparticles (gold, quantum dots, magnetic, etc.) can be used with nucleic acid, proteins and antibodies for specific biomarker detection with high sensitivity. These platforms have the potential to enable cost-effective, point-of-care diagnostics and earlier disease detection[31, 32].

9.2 Immunodiagnostics and Biosensors

Novel immunodiagnostic assays and biosensors are being developed to improve the detection and monitoring of BCR::ABL1-associated leukemia. Antibody-based biosensors can selectively recognise leukaemia-specific biomarkers and generate measurable signals in real time. Such technologies offer the possibility of rapid, portable, and highly sensitive diagnostic testing, particularly in resource-limited settings[33, 34].\

9.3 Gene-Editing Approaches

Advances in gene-editing technologies, particularly the CRISPR-Cas9 system, have opened new avenues for targeted leukemia therapy. These approaches aim to selectively disrupt or correct disease-causing genetic alterations, including the BCR::ABL1 fusion gene. Although still largely experimental, gene editing holds promise for developing more precise and potentially curative treatment strategies[35, 36].

9.4 Personalized Medicine

Personalized medicine utilizes molecular and genetic information to guide clinical decision-making and optimize treatment outcomes. In BCR::ABL1-positive leukemia, molecular monitoring of fusion transcript levels and mutation profiling can help tailor therapy to individual patients. Continued integration of genomic technologies is expected to improve treatment selection, minimize drug resistance, and enhance long-term disease management[24, 37].

10. CONCLUSION

The discovery of the BCR::ABL1 fusion gene has profoundly influenced the understanding of leukemia and represents one of the most significant milestones in cancer biology. As the molecular hallmark of CML and a subset of ALL, BCR::ABL1 has provided critical insights into the genetic basis of cancer and the mechanisms underlying leukemogenesis. Its identification not only enabled the development of highly sensitive diagnostic techniques but also led to the advent of targeted therapies that have transformed patient outcomes.

Despite remarkable advances in diagnosis and treatment, challenges such as drug resistance and disease persistence continue to drive ongoing research. Emerging technologies, including nanotechnology-based diagnostics, biosensors, gene-editing approaches, and personalized medicine strategies, hold promise for further improving disease detection, monitoring, and therapeutic efficacy. Continued exploration of BCR::ABL1 biology will not only enhance leukemia management but also contribute to the broader development of precision medicine and targeted cancer therapies.

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