Chronic myeloid leukemia (CML) is a hematological malignancy characterized by the uncontrolled proliferation of myeloid cells in the bone marrow. The disease arises from a genetic abnormality known as the Philadelphia chromosome, resulting from a reciprocal translocation between chromosomes 9 and 22, leading to the formation of the BCR-ABL fusion gene (Deininger et al., 2000). The BCR-ABL fusion protein possesses constitutive tyrosine kinase activity, driving the malignant transformation of hematopoietic stem cells and the development of CML.The creation of tyrosine kinase inhibitors (TKIs), such as imatinib, revolutionized the treatment landscape of CML. By targeting the aberrant signaling of the BCR-ABL tyrosine kinase, TKIs disrupt downstream signaling cascades involved in cell proliferation and survival, leading to remarkable clinical responses and prolonged survival in patients with CML (Druker et al., 2011). However, despite the initial success of TKIs, the emergence of drug resistance remains a significant challenge in the management of CML.

While TKIs have undeniably transformed the CML landscape, the specter of drug resistance lurks around every corner, significantly impacting long-term treatment success and posing a major obstacle to achieving a complete cure. The emergence of resistance underscores the dynamic nature of cancer, characterized by genomic instability, clonal evolution, and selective pressure exerted by therapeutic interventions (Braun, 2020).Resistance to TKIs can manifest through various mechanisms, including point mutations within the BCR-ABL kinase domain, amplification or overexpression of the BCR-ABL gene, activation of alternative signaling pathways, and alterations in drug pharmacokinetics and pharmacodynamics (Chen, 2017; Hanfstein, 2014). These adaptive responses contribute to the survival and proliferation of leukemic cells despite continued TKI therapy, leading to disease progression and clinical relapse. Understanding the intricate mechanisms underlying these diverse resistance pathways is crucial for developing next-generation strategies to combat CML and pave the way for a definitive cure. By elucidating the role of BCR-ABL kinase mutations in this complex phenomenon, researchers aim to shed light on the intricate dance between CML and targeted therapy, ultimately contributing to the development of more effective and personalized treatment approaches.

The BCR-ABL kinase domain serves as a critical therapeutic target in CML therapy. This highly conserved region harbors a precise pocket where TKIs bind, competitively inhibiting its

signaling and disrupting downstream oncogenic pathways (Deininger et al., 2000). However, the adaptability of CML cells can lead to mutations within the kinase domain, reshaping the TKI binding pocket and diminishing its efficacy. The T315I mutation represents one of the most notorious mechanisms of TKI resistance in CML. This single amino acid substitution within the catalytic cleft induces a conformational change, essentially remodeling the keyhole, that renders first-generation TKIs like imatinib ineffective (Gorre et al., 2007). Moreover, recent studies have identified additional mutations which confer resistance to multiple TKIs and pose significant clinical challenges (Redaelli et al., 2012). Understanding the relationship between BCR-ABL kinase mutations and TKI resistance necessitates a detailed understanding of their three-dimensional (3D) structural alterations.

This is where computational tools like PyMOL come into play. PyMOL facilitates the visualization and analysis of protein structures, enabling researchers to explore how specific mutations affect the BCR-ABL kinase domain's conformation and TKI binding interactions (Laskowski et al., 2011).Recent advancements in structural biology have provided unprecedented insights into the molecular mechanisms of TKI resistance.

High-resolution crystal structures of BCR-ABL kinase mutants have revealed subtle conformational changes within the ATP-binding pocket, sterically hindering TKI binding and facilitating the emergence of drug-resistant clones (Liu, 2022). .The possible connection between BCR-ABL kinase mutations and drug resistance in CML represents a complex and evolving challenge in cancer treatment. By leveraging advances in structural biology and understanding the intricate mechanisms underlying resistance pathways, researchers can pave the way for more targeted and personalized therapies, ultimately improving outcomes for patients with CML.