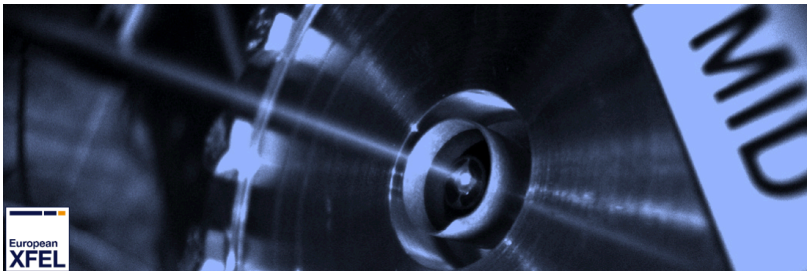

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Development New Generation of Imatinib Using Structural Biology Techniques at Ambient Temperature

Thursday 19 January 2023 19:23 (7 minutes)

Chronic myeloid leukemia (CML) is a kind of blood cancer and most CML patients have associated with a chromosomal anomaly with the BCR-ABL fusion oncogene, which occurs as a result of translocation between the Abelson murine leukemia (ABL1) gene on chromosome 9 and breakpoint cluster region (BCR) gene on chromosome 22. Imatinib mesylate is the first small molecule developed to target the BCR-ABL fusion protein. Imatinib reduces BCR-ABL activity by binding to the inactive conformation of tyrosine kinases. Despite a high response rate in CML patients with imatinib therapy, almost one-third of patients still have an inadequate response to Imatinib. In other words, due to mutations in region of Imatinib binding-pocket or other of the BCR-ABL, resistance to Imatinib has emerged in CML patients. Therefore, there have revealed need to develop a more potent new molecule with an Imatinib function. In this study, ABL kinase domain gene was purchased from Genscript Biotech. The gene was inserted to pET11a vector plasmid constract. The plasmid was transformed into E. coli, strain BL21 (Rosetta-2). Transformed E. coli were grown overnight on agar plates. The colonies were collected from agar plates and started large volume of culture in rich LB media. To be able to procure further purified protein, we were used Ni-NTA affinity chromatography. The purified protein solution was added to crystal screen conditions in Terasaki plates. Then, X-ray diffraction images were collected from the formed crystals in order to acquire the best 3D structure. These diffraction datas were collected from XtalCheck module (Rigaku Oxford Diffraction) at ambient temperature. We will have revealed the structures determined at ambient temperature and high resolution with the help of X-ray crystallography technique. Additionally, we will have re-evaluated structures and designed new target small molecule with approaching from the perspective of integrative structural biology. The results propose that may developed a new generation of imatinib that is more specific, high affinity and resistant to possible mutations to treat CML disease and improve patients'lives.

Primary author: KARAKADIOĞLU USTA, Gözde

Co-author: DEMIRCI, Hasan

Presenter: KARAKADIOĞLU USTA, Gözde

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