Project Proposal

Project Title: Drug Resistance in the Cancer Kinase BCR-ABL regarding Chronic Myeloid Leukemia

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Project Description:

This project aims to investigate drug resistance mechanisms in Chronic Myeloid Leukemia (CML), focusing on mutations within the BCR-ABL kinase domain. Through computational modeling and structural analyses using PyMOL, specific mutations associated with resistance to tyrosine kinase inhibitors (TKIs) will be identified and characterized. The study will delve into the three-dimensional structural alterations induced by these mutations, exploring their impact on kinase function and the efficacy of TKIs such as imatinib. By elucidating the intricate relationship between structural changes and functional alterations leading to drug resistance, this research seeks to contribute valuable insights into the development of more effective treatment strategies for CML.

Background:

Chronic Myeloid Leukemia (CML) stands as an example of how targeted therapies have revolutionized cancer treatment. Characterized by the presence of the Philadelphia chromosome, resulting from a reciprocal translocation between chromosomes 9 and 22, CML is driven by the constitutively active BCR-ABL tyrosine kinase (Deininger et al., 2000). The advent of tyrosine kinase inhibitors (TKIs), notably imatinib, has transformed the prognosis of CML from

a dire diagnosis to a manageable chronic condition (Druker et al., 2011). However, despite the remarkable success of TKIs in inducing deep and durable responses in the majority of patients, the emergence of drug resistance remains a significant clinical challenge. Resistance to TKIs can arise through various mechanisms, including point mutations within the BCR-ABL kinase domain, alterations in drug efflux pumps, and activation of alternative signaling pathways (Jabbour et al., 2019). Among these mechanisms, mutations within the BCR-ABL kinase domain constitute a major mechanism of acquired resistance, compromising the efficacy of TKIs by altering the conformation of the kinase domain and hindering drug binding (Gorre et al., 2007). Of particular concern is the T315I mutation, which confers resistance to all currently approved TKIs, posing a formidable challenge to effective CML therapy (Redaelli et al., 2012). Understanding the structural and functional consequences of BCR-ABL kinase mutations is therefore of paramount importance in elucidating the mechanisms of drug resistance in CML and developing strategies to overcome this clinical hurdle. This project aims to address this critical gap in knowledge by employing advanced structural biology techniques, such as PyMOL, to decipher the complex interplay between BCR-ABL kinase mutations and TKI resistance. Through comprehensive structural analyses and correlation studies, this research endeavor seeks to unravel the molecular underpinnings of drug resistance in CML, paving the way for the development of novel therapeutic approaches and personalized treatment strategies.

Experimental Design/Research Plan Goals:

The experimental design and research plan for this project are structured to systematically investigate the role of BCR-ABL kinase mutations in drug resistance in Chronic

Myeloid Leukemia (CML). The initial phase involves comprehensive familiarization with PyMOL software, which will be utilized for structural analysis. This includes learning the software interface, navigation tools, and basic functions necessary for protein structure manipulation and visualization. Following software orientation, efforts will focus on identifying and characterizing BCR-ABL kinase mutations associated with drug resistance. This will involve an extensive review of literature to compile a comprehensive database of known mutations, their genomic locations, and documented effects on drug response. With a curated mutation dataset in hand, structural analyses will be conducted using PyMOL. Three-dimensional structures of the BCR-ABL kinase domain, both wild-type and mutant variants, will be visualized and analyzed to discern conformational changes induced by mutations. Subsequent steps will involve correlating structural alterations with functional changes in kinase activity and drug binding affinity. This will entail integrating structural data with available functional assays, such as enzyme kinetics or binding affinity assays, to validate the impact of mutations on kinase function and drug response.

The required materials for this project include PyMOL software, a molecular visualization software used for the analysis and manipulation of protein structures as well as a computer with the ability to run PyMOL smoothly is essential for conducting structural analyses and visualization tasks. Software programs such as Microsoft Excel, Prism, and statistical analysis tools will be required for organizing experimental data, generating graphs, and performing statistical analyses to interpret results.

Risk/Safety Concerns:

Risks/safety concerns do not apply, this project will entirely be done using computational software.

Data Analysis:

Data analysis in this project will involve several steps aimed at interpreting experimental results, identifying patterns, and drawing conclusions regarding the impact of BCR-ABL kinase mutations on drug resistance in Chronic Myeloid Leukemia (CML). Utilizing PyMOL software, three-dimensional structural models of the BCR-ABL kinase domain will be analyzed to identify specific mutations and their spatial location within the protein structure. Structural alterations induced by mutations will be visually inspected to understand their potential impact on the kinase's function and drug binding affinity. Statistical analyses, including one-way ANOVA tests, may be employed to compare means of IC50 values or other quantitative measurements between different groups of mutations. These tests will help assess the significance of observed differences and determine the statistical validity of experimental findings.

Timeline:

- Familiarize myself with the software program, likely PyMOL, understanding its functionality and application to the project.
- Identify and characterize BCR-ABL kinase mutations linked to drug resistance in CML.

- Utilize imagery software to perform structural analyses, examining the mutations' effects on kinase function
- Consider structural elements and interactions hindering kinase activation.
- Investigate the correlation between structural changes and functional alterations contributing to drug resistance.

References:

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