ELUCIDATION OF PEPTIDE INHIBITORS AGAINST HUMAN BAP1 USING IN-SILICO STUDIES

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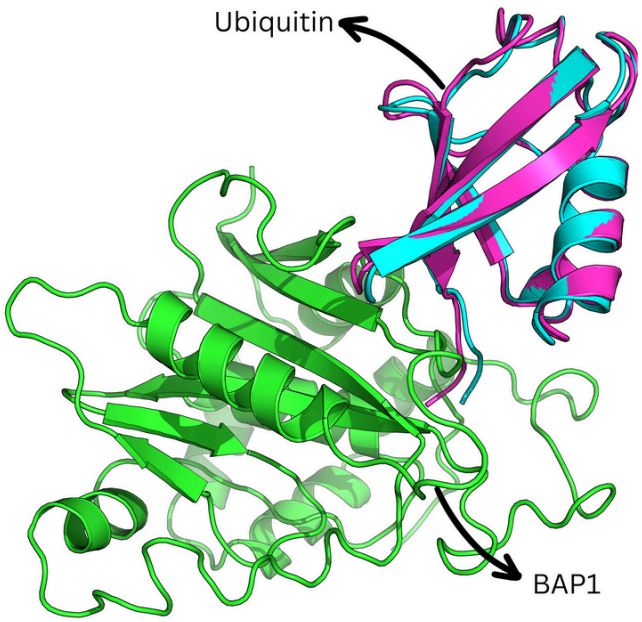
Breast cancer (BC) cases are rising globally at an alarming rate, making BC the leading cause of cancer-related deaths worldwide, including in Malaysia. In 2020 alone, the Global Cancer Observatory recorded 48,639 new cancer cases, with BC accounting for a significant 8,418 of these. Despite advancements in treatment, survival rates remain low due to factors like late detection, diagnostic delays, and limited access to proper treatment. Improving early detection and treatment accessibility is crucial, but given the persistence and severity of BC, new strategies are urgently needed.

Targeting the BRCA1-associated protein 1 (BAP1), a tumour suppressor that regulates essential cellular processes such as cell proliferation, apoptosis, and DNA damage response, emerged as a promising field in treating BC. Studies have suggested that BAP1, which functions as a transcriptional activator and a participant in gene silencing, could serve as a novel therapeutic target in breast cancer treatment (Campagne et al., 2019; Scheuermann et al., 2010).

Mutations in BAP1 have been linked to the development of several cancers, including malignant pleural mesothelioma and uveal melanoma. In estrogen receptor-alpha (Erα)-negative basal subtype BC, it was observed that the highly expressed non-histone Krüppel-like factor 5 (KLF5) protein responsible for the progression of the cancers was protected by the BAP1 from degradation by removing the ubiquitin attached to the KLF5 protein (Jia et al., 2021; Qin et al., 2015). This insight has spurred interest in exploring inhibitors that target BAP1 to disrupt its deubiquitinase activity and consequently slow down cancer growth.

However, currently, no Food and Drug Administration (FDA)-approved drugs specifically target BAP1, leaving a significant gap in treatment. While traditional small-molecule inhibitors have shown promise, peptide-based inhibitors offer highly specific binding due to their structural similarity that mimics native protein-protein interactions. This precise binding capability allows for increased specificity and reduced side effects compared to small molecules. As researchers search for more effective treatments, peptide inhibitors hold the potential to change the landscape of cancer therapy.

Our study aims to design and develop a peptide inhibitor specifically targeting human BAP1 based on the interacting residues of the ubiquitin (Figure 1). By leveraging computational methods such as molecular docking and molecular dynamics simulations, we seek to design and optimize peptide inhibitors that can selectively inhibit BAP1 activity. We hope to open new possibilities in BC treatment. This research supported by the 600-RMC 5/3/GPM (039/2023) from Universiti Teknologi MARA, may lead to a new class of inhibitors with the potential to improve BC outcomes and expand therapeutic options in cancers associated with BAP1 dysregulation.



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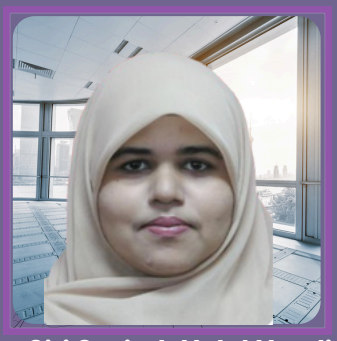

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