Bleomycin exhibits dual inhibition towards amyloid aggregation in β-amyloid and hIAPP

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Aberrant misfolding and amyloid aggregation, which result in amyloid fibrils, are frequent and critical pathological incidents in various neurodegenerative disorders. Multiple drugs or inhibitors have been investigated to avert amyloid aggregation in individual peptides, exhibiting sequence-dependent inhibition mechanisms. Establishing or inventing inhibitors capable of preventing amyloid aggregation in a wide variety of amyloid peptides is quite a daunting task. Bleomycin (BLM), a complex glycopeptide, has been widely used as an antibiotic and antitumor drug due to its ability to inhibit DNA metabolism, as well as an antineoplastic, especially for solid tumors. In this study, we investigated the dual inhibitory effects of BLM on Aβ aggregation, associated with Alzheimer's disease and hIAPP, which is linked to Type 2 diabetes using both computational and experimental techniques. Combined results from drug repurposing and replica exchange molecular dynamics simulations demonstrate that BLM binds to the β-sheet region considered a hotspot for amyloid fibrils of Aβ and hIAPP. BLM was also found to be involved in β-sheet destabilization and, ultimately, in its reduction [Figure 1]. Further, experimental validation through in vitro amyloid aggregation assays was obtained wherein the fibrillar load was decreased for the BLM-treated Aβ and hIAPP peptides in comparison to controls [Figure 2]. For the first time, this study determines BLM is a dual inhibitor of Aβ and hIAPP amyloid aggregation. In the future, the conformational optimization and processing of BLM may help develop various efficient sequence-dependent inhibitors against amyloid aggregation in various amyloid peptides.

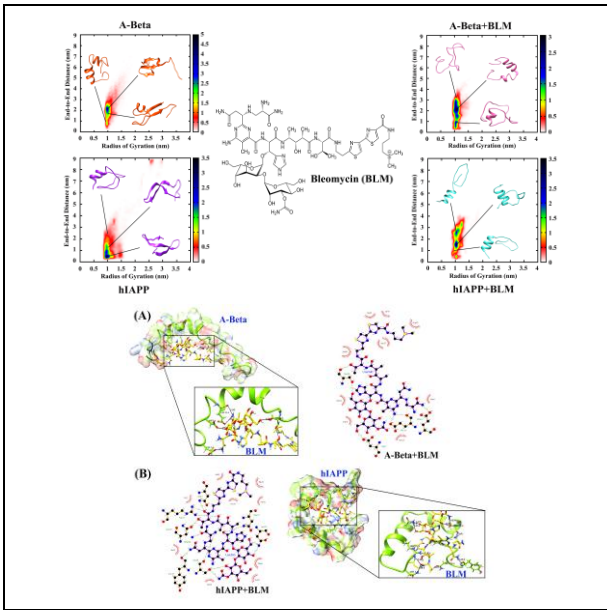

Figure 1: Population density analysis for A-Beta and hIAPP in presence and absence of BLM, peptide end to end distance (Ree) i.e. C to N terminal and radius of gyration (Rg) around its center of mass (above). Protein ligand interaction (2D and 3D) diagram (A) Aβ and BLM (B) hIAPP and BLM (below)

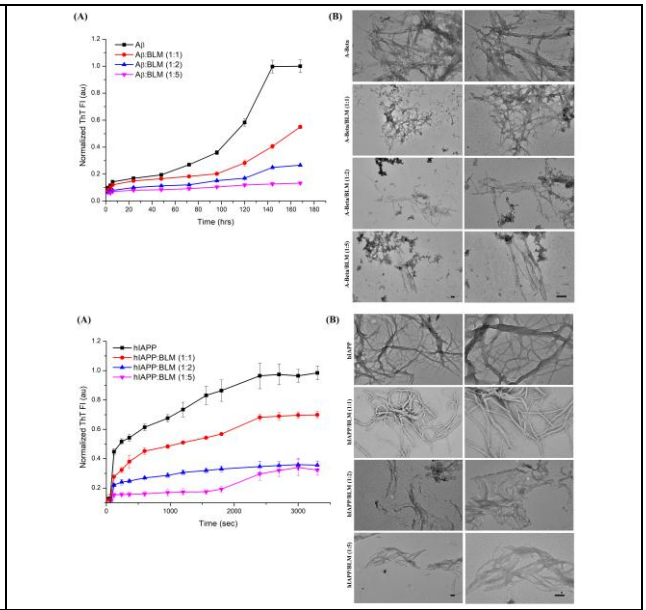

Figure 2: (A) ThioflavinT (ThT) fluorescence monitored showing kinetics mechanism of fibril formation for Aβ and hIAPP in presence and absence of BLM. (B) Transmission electron microscopy 72 showing morphology of Aβ and hIAPP amyloid fibrils stained in uranyl acetate at 25,000 fold magnification and at 20 and 100 nm scale.