Ferromilab: Quantum Molecular Dynamics-Derived Biclonal Antibodies Modulating Hepcidin-Ferroportin Interfaces to Mitigate Iron Dysregulation and Ferroptosis in Alzheimer's Disease

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Alzheimer’s Disease (AD), a neurodegenerative disorder linked to pathologies characterized with neural cognitive decline, has recently been connected to iron dysregulation and ferroptosis in its pathology. Amyloid-beta has also been shown to aggregate from different forms of iron inclusion due to disturbance of iron homeostasis, thus proving the significance of ferroptosis in AD pathology. This study presents a novel therapeutic approach targeting the hepcidin-ferroportin interaction to mitigate iron accumulation in AD. This study utilizes a framework to develop accurate monoclonal antibodies (mAb) that target and inhibit ferroportin-hepcidin interactions, preventing ubiquitination of the complex and restoring iron efflux. This computational framework initially employs a multi-iterative modeling process based on MODELLER frameworks; DOPE scores and RMSF values are relayed through an algorithm that selects residues and correlative PDB files for the generation of the most accurate protein-structure of a target sequence. Molecular Dynamics was implemented to optimize such models, improving dihedral angle populations with Ramchandran calculations coupled with organization of residual stability. Low-resolution docking of candidate antibodies using the ProABC-2 led to the identification of a high-affinity mAb targeting the ferroportin-binding site, providing an initial model for antibody development. Preliminary results demonstrated effective disruption of hepcidin-ferroportin interactions and restoration of ferroportin functions showcased by HADDOCK docking formulas. Such studies are effective in proving that the amyloid hypothesis is not a singular option for AD pharmaceutical development. Future work involves implementing QMD and in-vitro antibody development.

Awards Won: