Design of Inhibitors for *Trypanosoma cruzi*'s Trans-sialidase from Molecular Docking and Molecular Dynamics Studies

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Trypanosoma cruzi is the protozoan responsible for Chagas' disease, a lethal disease that affects millions of people in Central and South America and is considered one of the fourteen neglected tropical diseases by the World Health Organization. *T. cruzi*'s trans-sialidase (TcTS), an enzyme vital to the life cycle of *T. cruzi*, catalyzes the transfer of sialic acids from mammalian host cells to parasitic cell surfaces in order to mask the infection from the host's immune system. Trans-sialidase is not expressed by humans, and thus makes an attractive option for drug design and discovery. Unlike for related sialidases, it has been difficult to design or synthesize a strong, specific inhibitor of TcTS. Thus, the need exists for new, specific inhibitors to be designed to help in the treatment of Chagas' disease.

The proposed research aims to validate a method for docking compounds to *T. cruzi* trans-sialidase, and then use that method to successfully identify strong inhibitors of TcTS. Schrodinger's Glide was used to dock libraries of compounds to trans-sialidase structures. Potential inhibitors have been designed based on the known transition state for TcTS and also screened from small molecule databases. Core scaffolds were also used as input with LigBuilder to create new molecules with strong binding affinity for TcTS. All potential inhibitors were docked to structures of TcTS obtained from a 50 ns molecular dynamics (MD) simulation of the holo structure of TcTS. Obtaining snapshots from an MD simulation provides an ensemble of snapshots that more appropriately represent the structure *in vivo* than a single Protein Databank (PDB) structure, and thus should result in a more accurate binding affinity from the docking program. MD simulations have been performed using AMBER 11 on the top ranking inhibitors from the docking analysis to fully characterize the interactions that govern the binding of the inhibitor to TcTS. Finally, Molecular Mechanics Generalized-Born/Surface Area (MM-GBSA) post-production analysis has been used to more accurately calculate the free energy of binding for the inhibitors. Several novel ligands have shown very favorable interactions with TcTS, including one molecule from LigBuilder that has a significantly stronger MM-GBSA binding affinity than the substrate.