Analysis of the Binding Pathways of Neuraminidase through MM/GBSA Post-Processing of Equilibrium Molecular Dynamics Trajectories

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Neuraminidase (NA) is essential to the proliferation of the influenza virus. The homotetrameric enzyme cleaves terminal sialic acid moieties from host cell surface receptors enabling nascent viral release. Small molecules that act as NA inhibitors, including the widely prescribed oseltamivir (Tamiflu®), effectively prevent proliferation of the wild type influenza virus. However, an influenza strain with a mutated NA (H274Y) has displayed resistance to oseltamivir and other NA inhibitors. To better understand how these ligands interact with NA, we simulated the complete binding trajectories of both sialic acid and oseltamivir to the wild-type NA. The pathways were sampled using a multi-scale methodology utilizing Brownian Dynamics (BD) for the diffusional approach, and Molecular Dynamics (MD) to investigate the close-range motion. Post-processing of the trajectories using Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) free energy calculations was employed in order to identify specific binding pathways and areas of binding favorability for both complexes. Additional trajectory-specific analysis further elucidated the ligand-residue interactions that enable the pathways. This analysis revealed a set of six residues that form a channel-like structure that interacts with hydroxyl groups on sialic acid's aliphatic chain, thus orienting the ligand so that the carboxylate can form salt bridges with active site residues. The lack of this same functionality on oseltamivir's aliphatic chain possibly results in oseltamivir taking alternate pathways to achieve its final bound configuration.

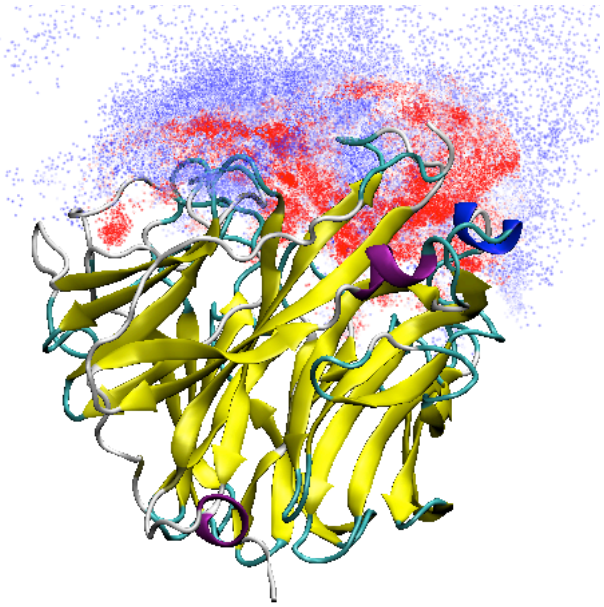

Figure 1. Wild-type NA monomer with MM/GBSA map of sialic acid binding favorability (red points indicate relatively favorable energies)