Examining the Binding Pathways of Oseltamivir to H274Y Neuraminidase via Molecular Dynamics Simulations and MM/GBSA Analysis

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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, effectively prevent proliferation of the wild type influenza virus. However, a strain of mutated influenza (H274Y) has displayed resistance to oseltamivir. In order to fully understand the molecular basis of this resistance, we analyzed the complete binding trajectories of oseltamivir and H274Y NA. Pathways were sampled using a multi-scale methodology utilizing Brownian Dynamics (BD) for the diffusional approach, and Molecular Dynamics (MD) to examine the close-range interactions. Molecular mechanics/generalized Born surface area (MM/GBSA) free energy calculations were employed to analyze the favored binding pathways.

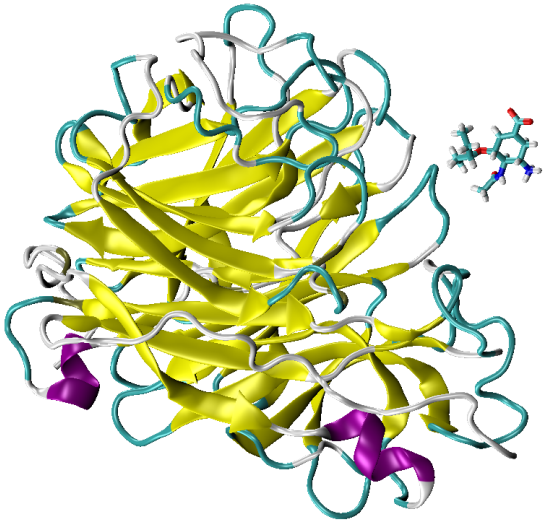

Figure 1. Neuraminidase monomer and oseltamivir ligand.