Investigating oseltamivir binding pathways to H274Y neuraminidase using molecular dynamics simulations and MM/GBSA analysis

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Influenza neuraminidase is a homotetrameric viral enzyme that is integral to the influenza virus' replication cycle. A successful strategy for combatting the influenza virus has been to inhibit the catalytic activity of this enzyme using such drugs as peramivir, zanamivir (Relenza®), and oseltamivir (Tamiflu®). These inhibitors compete with terminal cell-surface receptor sialic acid moieties for access to neuraminidase's binding site. However, recent studies have shown that a strain of influenza possessing a H274Y neuraminidase mutation demonstrates resistance to oseltamivir. This is problematic as many organizations worldwide have stockpiled oseltamivir for combatting epidemic and pandemic outbreaks. To better understand this resistance, we employed molecular dynamics (MD) simulations to investigate the binding kinetics, spatial binding distribution, and ligand-receptor interactions between H274Y neuraminidase and oseltamivir. These MD simulations were run from various starting points determined by Brownian dynamics (BD) simulations of the ligands diffusional approach. Binding kinetics and spatial distribution data provided by MD were then processed using the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) method in order to elucidate specific binding pathways and areas of binding favorability.

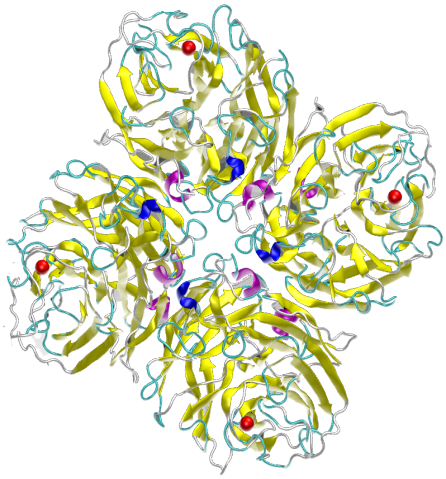

Figure 1. Neuraminidase tetramer with H274Y mutation