Computational Investigation of the Binding Pathways of Zanamivir to H274Y Neuraminidase

Janice Kang and Adam W. Van Wynsberghe

*Department of Chemistry, Hamilton College, Clinton, NY 13323*

Influenza is a very contagious and common yet deadly viral infection for high-risk groups. It affects between 5-20% of the US population and results in more than 200,000 individuals being hospitalized and 3,000-49,000 deaths due to influenza related complications[1]. The virus' replications is facilitated by Neuraminidase (NA), an envelope protein that cleaves terminal sialic acid moieties from host-cell surface receptors. To slow the spread of influenza infection, NA inhibitors including oseltamivir (Tamiflu), zanamivir, and others, have been used as a post-infection antiviral treatment. However, due to wide-spread use, strains with mutated NAs such as H274Y that show resistance to oseltamivir have emerged. In this research, the binding pathways of zanamivir to H274Y NA have been examined through a multiscale method utilizing Brownian dynamics, molecular dynamics (MD), and Molecular Mechanics/ Generalized Born Surface Area (MM/GBSA) free energy calculations. The representative trajectories of ligand approach were identified using Brownian dynamics. Subsequent MD simulations starting from the initial approach conformations were used to examine more proximal interactions between the protein and ligand. Lastly, MM/GBSA was used to analyze the free energies of individual frames of the MD simulations to determine zanamivir's most favorable binding pathways to H274Y NA.

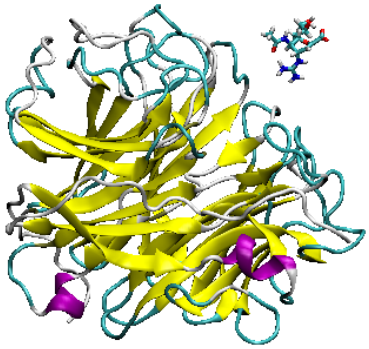

Figure 1. Neuraminidase monomer with zanamivir ligand

[1] http://www.nfid.org/idinfo/influenza