Exploration of the Binding Kinetics of Zanamivir to WT Neuraminidase via MM/GBSA Analysis of Molecular Dynamics Simulations

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Neuraminidase (NA), a homotetrameric glycoside-hydrolase located on influenza's viral envelope, is essential to the virus' replication cycle. NA facilitates nascent viral release through the recognition, binding, and cleavage of terminal sialic acid (SA) moieties of host cell glycoproteins. Zanamivir (ZAN), an orally administered FDA approved NA inhibitor, has been established as an effective treatment that diminishes the infectivity of the influenza virus by slowing the release of newly-formed virions. Even with the significant structural and compositional similarities between SA and ZAN, NA has displayed resistance to ZAN and other NA inhibitors. To investigate the displayed selectivity of NA for SA, we have explored the binding kinetics of several NA inhibitor-NA systems—one of which is the ZAN-wild-type NA pair. To this end, we have employed a multi-scale methodology comprising multiple computational methods: Brownian Dynamics (BD), which simulates the diffusional approach of ZAN to NA, molecular dynamics (MD), which samples proximal protein-ligand motion, and free energy analysis (Molecular Mechanics/Generalized Born Surface Area—MM/GBSA), which allows for the qualitative interpretation of MD simulations through the generation of a heat map displaying regions of favorable or unfavorable protein-ligand interactions along the protein's surface. Together, this approach elucidates the binding pathway of ZAN, providing information that may allow us to determine factors that contribute to wild-type NA's displayed selectively for SA.

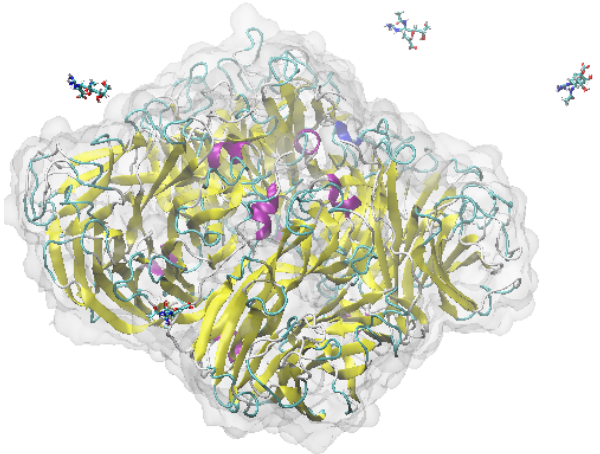

Figure 1: Snapshot of MD simulation displaying homotetrameric NA and four ZAN ligands.