Investigating binding pathways to neuraminidase using MM/GBSA free energy 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 (Releza®), and oseltamivir (Tamiflu®). These inhibitors compete with terminal cell-surface receptor sialic acid moieties for access to neuraminidase's binding site. To better understand how these ligands interact with neuraminidase, we employed Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) calculations in order to elucidate specific binding pathways and areas of binding favorability for both the wild-type neuraminidase and sialic acid complex and the wild-type neuraminidase and oseltamivir complex. The MM/GBSA calculations analyzed frames from 194 five-nanosecond close-range molecular dynamics (MD) simulations for the oseltamivir system and 261 five-nanosecond close-range MD simulations for the sialic acid system. After visual comparison of the MM/GBSA free energy maps from both complexes, alanine mutation scanning and residue decomposition calculations were performed in order to better understand specific receptor-ligand interactions.

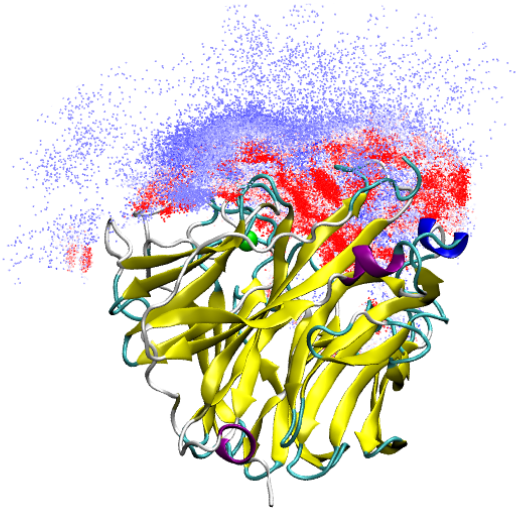

Figure 1. H274Y neuraminidase monomer with MM/GBSA map of oseltamivir binding favorability (red points indicate relatively favorable free energies while blue points indicate relatively unfavorable free energies)