Poster 10

Discovery of inhibitors targeting evolutionary conserved influenza A virus proteins

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Influenza A is a prevalent infectious virus capable of causing significant respiratory illness worldwide. The virus genome encodes several proteins and upon infection, antiviral drugs targeting the neuraminidase surface protein and M2 transmembrane protein are the only treatment options available. However, emergence of antiviral resistance due to mutations highlights the requirement of investigating other proteins as targets for antivirals. Therefore, this research aims to identify inhibitors that may bind to conserved regions of internal influenza A proteins through the application of molecular modelling methods.

Sequences of the influenza A non-structural 1 protein (NS1), nuclear export protein (NEP) and basic polymerase 2 (PB2) were aligned and the degree of amino acid conservation was calculated for each protein. Missing parts of the experimental structures were predicted using a state-of-the art protein structure prediction method, and molecular dynamics (MD) simulations to improve the accuracy of the protein models. Potential binding hot spots were identified with computational solvent mapping based on the FTMap algorithm. Selected binding sites were subjected to virtual screening against a library of ~50,000 chemical compounds from the ZINC database using a combination of two docking algorithms, namely AutoDock Vina and AutoDock 4.

Several highly conserved areas that overlap with ligand binding sites were located and mapped onto the protein structures. MD simulations revealed conformationally flexible regions of the NS1 and NEP models, and virtual screening and docking results revealed drug-like molecules with predicted binding affinities of up to -10.0 kcal/mol. Molecules targeting evolutionary conserved regions are less likely to undergo mutations that could render antiviral drugs ineffective. The findings from this work may lead to the discovery of a novel influenza A inhibitor that remains viable long term.