Supplementary Information

An example of computationally docking a compound-polymer complex

Here we demonstrate the second approach that has been proposed in the text, which is aimed at providing systematic guidance in the investigation of the interactions and binding affinity between potential ZIKV inhibitors and a drug delivery system.

Based on Srivastava *et al* (2016) which highlights the role of polymers and their advantages as formulations and in devices [1], an example of transporting potential ZIKV inhibitors, conjugated to a polymer would be an ideal example. Tosi *et al* (2013) has shown that the polymer, poly (D,L-lactide-co-glycolide) (PLGA) has the ability to effectively cross the BBB and can be used as a drug delivery system. [2] The following potential ZIKV inhibitors have been docked to PLGA via molecular docking and the free binding energies of different poses were compared: NITD008, sofosbuvir, sertraline, ribavirin and 2-C-methyladenosine (Table 3). UCSF Chimera and AutoDock Tools were used to dock these compounds and calculate the free binding energies.

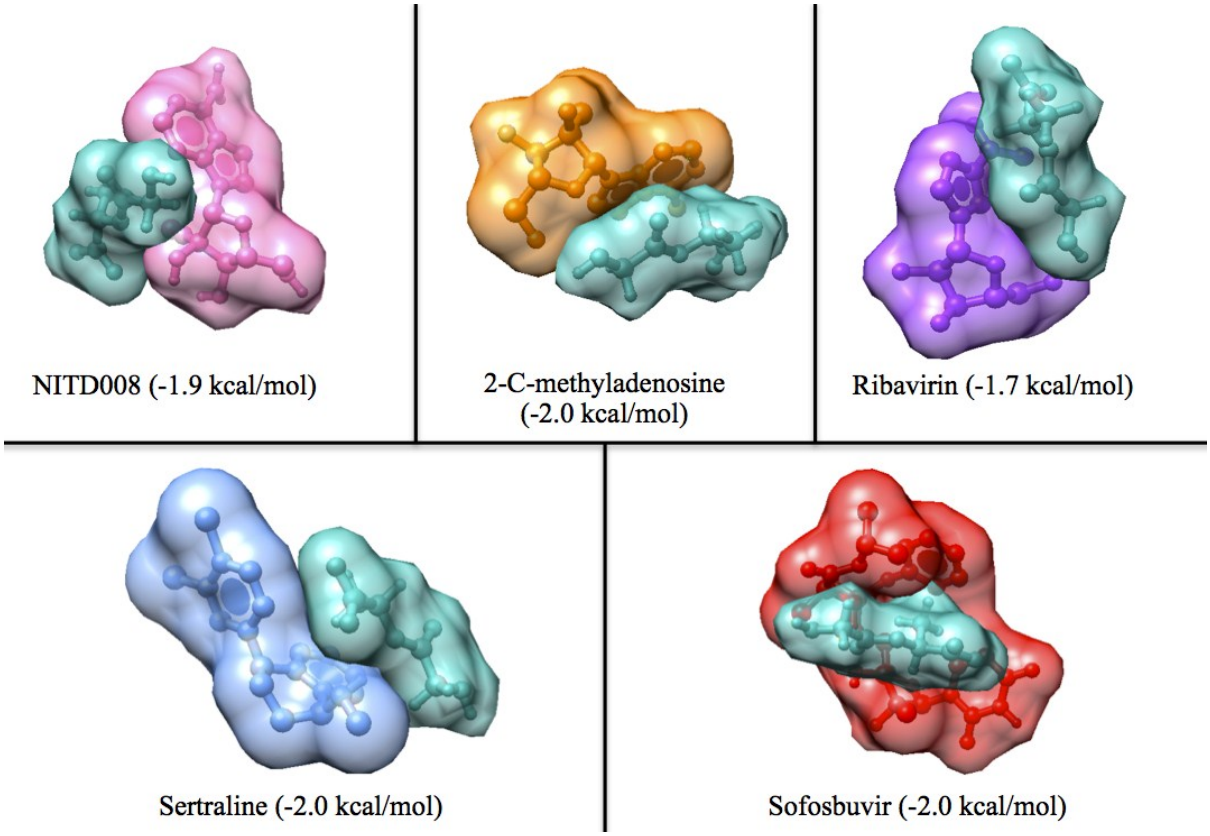

Figure S1: Potential ZIKV Inhibitors docked with a polymer showing the estimated binding affinity of the best compound-polymer pose.

In Figure S1, 2-C-methyladenosine, sertraline and sofosbuvir scored the lowest free binding energy of -2.0 kcal/mol and therefore have stronger binding than NITD008 and ribavirin to the polymer.

Technical Guidelines

A number of tools are available which can be utilized to screen for compounds on chemical databases based on a set of criteria. Structure-based virtual screening will allow searching through combinatorial chemistry libraries for compounds that may be potential inhibitors of a target protein and will rapidly dock them into the 3D target's active pocket.[3,4] Screening of potential compounds can be carried out on ZINC Database [5] or ZincPharmer [6]. Several molecules may have the potential to bind to the

active site of the protein; therefore, the free binding energy of every pose is calculated. Binding affinity estimations may be carried out using molecular docking approaches and free binding energy calculations. This will generate a scoring function to rank the ligands which best suit the target protein.[3] Computational software that can be used to calculate binding affinities include UCSF Chimera [7] and AutoDock Vina.[8] Protein-ligand complexes of lowest free binding energy may be used as inhibitor candidates, which may subsequently be validated via molecular dynamic simulations as binding affinity predictions may not be one hundred percent accurate.[4,9–12]

Molecular dynamic simulations uses Newton's equations of motion to analyze the physical movements that occur between the atoms and molecules involved in a docking pose over a course of time.[13] Force fields are used to calculate potential energies of particles and electrostatic forces that occur between atoms in a system.[14] Some force fields that can be used for molecular dynamic simulations include NAMD [15], Gromacs [16], Amber [17] and Charrm [18]. Complexes can also be simulated through lipid bilayer, in cases where potential compounds need to enter certain target tissues which are surrounded by lipophilic membranes. This can give a prediction as to whether or not the potential compound will be able to pass through the lipid membrane or not. Software that can be used to generate a 3D lipid bilayer model include CHARRM-GUI and Visual Molecular Dynamics (MEMBPLUGIN).[19,20]

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