Molecular design of fusion inhibitors for flaviviruses

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Flaviviruses comprise a large group of related viruses, significantly threating human health over the world. However, effective specific anti-flaviviral therapies do not exist yet. The entry of flavivirus into a host cell by pH-dependent endocytosis is mediated by its major envelope (E) protein that possesses a hydrophobic pocket occupied by a detergent molecule (n-octyl-β-D-glucoside) in one of the dengue E protein crystal structures [1]. Potential inhibitors of low-pH-induced membrane fusion can interact with this pocket. This opens an avenue for identifying anti-flaviviral agents active in early steps of viral infection [2]. In this work homology model of 'closed' conformation (corresponding to the resting state) of Powassan virus (POWV) E protein have been constructed using crystal structures of dengue serotype 2 and tick-borne encephalitis virus (TBEV) E proteins as templates (PDB IDs 1OAN and 1SVB, respectively). To obtain 'open' POWV and TBEV E protein models required for docking (corresponding to fusion-inactive state), the structure of dengue E protein in a complex with n-octyl-β-D-glucoside (PDB ID 1OKE) was utilized along with closed forms. The docking-based virtual screening of chemical databases revealed several putative hit compounds against both, POWV and TBEV. Preliminary *in vitro* assays results were obtained for identified substances.

[1] Y. Modis, S. Ogata, D. Clements, S. C. Harrison, *PNAS USA*, **2003**, *100(12)*, 6986-6991.
[2] J-M. Yang, Y-F. Chen, Y-Y. Tu, K-R. Yen, Y-L. Yang, *PLoS ONE*, **2007**, *2(5)*, 1-10.