Chun-Yeung Lo et al., J Biotechnol Biomater 2016, 6:3 (Suppl)
http://dx.doi.org/10.4172/2155-952X.C1.056

In silico screening for inhibitors blocking the assembly of influenza A virus polymerase complex

Chun-Yeung Lo[1], **Y H Yang**[1], **L M Poon**[2] and **P C Shaw**[1]
[1]The Chinese University of Hong Kong, China
[2]The University of Hong Kong, China

Influenza virus has always been a major threat to humankind, causing sporadic pandemics and recurrent annual epidemics. Moreover, as influenza virus is developing resistance to existing anti-virals, it is essential to design new drugs against it. The influenza RNA-dependent RNA polymerase consists of three subunits: PA, PB1 and PB2. By blocking the protein-protein interactions among these subunits, the viral RNA polymerase complex would fail to assemble, thereby inhibiting influenza virus replication. The co-crystal structure of PA-C terminal and PB1-N terminal was resolved in 2008. It was shown that PB1 binds to PA by inserting a short helix into a hydrophobic core of PA and the residues at the interacting interface are well conserved within type A Influenza. We employed *in silico* screening to identify small molecules that most likely would block the PAPB1 interaction. Compound databases were archived from zinc (UCSF) and commercial vendors (e.g., SPECS) and then virtually docked to the PA hydrophobic core by Autodock 4.0. Top results were then subjected to post-screening evaluation, including visual inspection by molecular visualization software (e.g., Pymol) and prediction of drug-likeness by Lipinski's rules. After post-screening analysis, we selected ~150 potential hit compounds for primary screening, which involves cytotoxicity assay and ribonucleoprotein (RNP) activity assay. Two hit compounds, compound 221 and 312, were able to inhibit influenza RNP activities and attenuate viral growth. Compound 312 also delayed the death of influenza virus PR8 infected mice. The identification of hit compounds provides the basis for future optimization and lead compound development against influenza virus.

Biography

Chun-Yeung Lo has obtained his BSc degree in Biochemistry at the Chinese University of Hong Kong in 2010 and he is currently a PhD student at the Chinese University of Hong Kong. His research is on the screening of inhibitors against influenza virus. He has also obtained several lead compounds that inhibit influenza virus through interacting with the viral nucleoprotein and the work has been published in *Biodesign* in 2015.

locyedwin@gmail.com

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