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# A novel small-molecule inhibitor of influenza A virus that acts by disrupting PB2 cap-binding of the viral polymerase

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The conserved residues 318-483 in PB2 subunit ($PB2_{cap}$) of influenza A polymerase is an independently folded cap-binding domain that exhibits a distinct binding mode from the cap-binding proteins of host cells, thus it is conceived to be a potential target for the development of new antiviral drugs. We developed an innovative fluorescence polarization assay to identify small-molecule inhibitors that specifically disrupted the interaction between a cap analog ($m^7GTP$) and $PB2_{cap}$. Selected compounds were tested *in vitro* and in vivo for antiviral efficacy. Of these, the best compound PB2-19 was identified as a potent inhibitor against the replication of multiple subtypes of influenza A virus, including H1N1, H3N2, H5N1, H7N7, H7N9 and H9N2, in Madin-Darby canine kidney cell cultures. Combinational treatment of zanamivir and PB2-19 exerted synergistic anti-influenza effect *in vitro*. Intranasal administration of PB2-19 enhanced survival rate and reduced lung viral loads in BALB/c mice challenged with lethal dose of H1N1 virus. Docking analyses predicted the compound interacted with the PB2 cap-binding pocket in a similar manner as m7GTP, suggesting its role as a cap-binding competitor. Our study provides new insights for the development of a new category of influenza therapeutic agents that directly target to PB2 cap-binding domain.

## Biography

Yuan Shuofeng has strong experience in Virology. He did his PhD degree from the University of Hong Kong, studying the anti-influenza drugs development. He has joined HKU Department of Microbiology as a Post-doctoral Fellow since 2015. He has extensive experiences in establishment of drug screening system and animal models. He has also published several papers on the development of antiviral agents that target on the polymerase subunits of influenza virus.

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