No.	K25-3167	
Project Title	Development of viral inhibitors targeting envelope proteins	
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(Form 2)

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IMSUT International Joint Usage/Research Center Project <International>

Joint Research Report (Annual/Project Completion)

Annual Report

Report

Coronavirus disease (COVID-19) is an ongoing infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Besides the significant morbidity and mortality associated with acute infection especially among elderly and immunocompromised patients, post-COVID-19 condition has also been recognized. Previous studies have showed that use of the SARS-CoV-2 antivirals in the acute phase may reduce the risk of post-COVID-19 condition.

One of the major challenges in combating COVID-19 is the emergence of SARS-CoV-2 variants and subvariants that are immunoevasive to previously developed vaccines and monoclonal antibodies. Apart from RdRp and M^{pro}, the S protein is another important antiviral target, given its critical role in virus-host interactions.

We discovered several promising peptides with strong binding affinities to the RBD and broad-spectrum antiviral activities against emerging SARS-CoV-2 variants and subvariants. Structural studies demonstrated that the peptides bind to a conserved non-receptor binding motif (non-RBM) region of RBD, and can form homotrimer to lock the S trimer into a "closed" conformation which prevents binding with ACE2. Structure-guided modifications result in a thermostable and trypsin-resistant peptide, that exhibits prophylactic and therapeutic effects against SARS-CoV-2 infection in a male hACE2 transgenic mouse model after intranasal administration.

Our results provide a drug candidate for the control and prevention of COVID-19 and may stimulate further research on broad-spectrum anti-coronavirus drug development.

Publication:

Wang M[#], Yang J[#], Tan Y[#], Yuan S[#], Shi G[#], Peng Q, Li Y, Poon VK, Chan CC, Xiao N, Zhang AJ, Xie Y, Li J, Luo H, Fu Y, Chen Y, Compton AA, Zhang Y, Yang Y, Gao GF, Hou H, Chan JF*, Yin Y*, Shi Y*. Intranasal administration of broad-spectrum macrocyclic peptide inhibitor protects against SARS-CoV-2 Omicron variants. Nat Commun. 2026 Jan 26;17(1):1753.