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## Design of inhibitors targeting *Coronavirus* main proteases

**Introduction:** *Coronavirus*es (*CoVs*) infection causes various diseases in human and animals, including severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS). *Human Coronavirus NL63 (HCoV-NL63)* was found to cause upper and lower respiratory tract infection worldwide. *Porcine epidemic diarrhea virus* (*PEDV*) infects the gastrointestinal tract in feeder pigs and fattening swine and causes porcine epidemic diarrhea. Feline infectious peritonitis virus (FIPV) leads to lethal systemic granulomatous disease in cats. No approved specific drugs or vaccinations are available to treat their infections.

**Materials & Methods:** The synthesized compounds were evaluated for the inhibition of multiple *CoV* proteases and their crystal structures were determined.

**Results:** (1) Structural analysis of the *HCoV-NL63* main protease compelx was determined, consistent with biochemical inhibition results, reveals the molecular mechanism of enzyme inhibition at the highly conservative substrate-recognition pocket. We show such molecular target remains unchanged across 30 clinical isolates of *HCoV-NL63* strains. (2) We solved the structure of *PEDV* main protease complexed with peptidomimetic inhibitor N3 carrying a Michael acceptor warhead, revealing atomic level interactions. We further designed a series of 17 inhibitors with altered side groups. Inhibitors M2 and M17 demonstrated enhanced specificity against *PEDV* main protease. (3) We demonstrated that zinc ion and a Michael-acceptor based peptidomimetic inhibitor synergistically inactivate FIPV main protease. We also solved the structure of FIPV main protease complexed with two inhibitors, delineating the structural view of dual inhibition mechanism.

**Conclusion:** Our study provides new insight into the pharmaceutical strategy against *CoV* main proteases through design of irreversible peptidomimetic inhibitors combinded with an adjuvant therapy to enhance the efficacy.

### Biography

Haitao Yang has received his PhD in the year 2006 from Tsinghua University. His current focus is on antibiotics and antivirals Discovery in ShanghaiTech University in China. He is working as Research Professor in Shanghai Institute for Advanced Immunochemical Studies (SIAIS), at ShanghaiTech University. He has published more than 50 papers in reputed journals.

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