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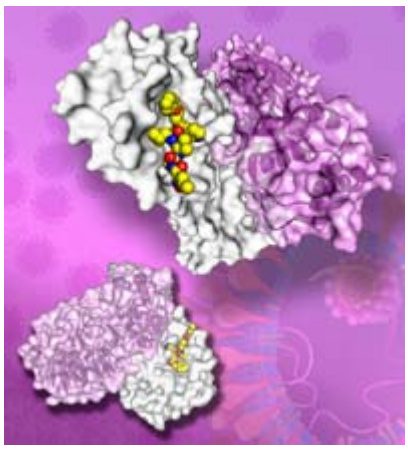
Casting a wide net to fight coronaviruses

Coronaviruses - the family of viruses that causes the common cold - gained widespread recognition when the deadly severe acute respiratory syndrome, familiarly known as SARS, killed at least 800 people in 2003. Research efforts to design antiviral agents to combat coronaviruses intensified after the SARS epidemic and have focused mostly on just this virus. But because coronavirus sequences and structures mutate so quickly, a challenge is to find wide-spectrum vaccines, since a vaccine targeting one strain would likely be ineffective against another.



Caption: A broad-spectrum inhibitor can specifically recognize active site of all coronavirus main proteases, the key enzymes for viral life cycle, which could lead to the discovery of a single agent against all existing and possible future emerging coronavirus-related diseases. The protease structure is shown in ribbon-and-surface representation and inhibitor molecules are shown as CPK models (Yang et al.).
Click here for a high resolution image.

Online this week in the open-access journal *PLoS Biology*, Haitao Yang, Dawei Ma, Zihe Rao, and colleagues report that they have produced an antiviral inhibitor that is active against several coronaviruses. The authors combined structural and biochemical analyses to identify a target in the structurally conserved substrate-binding region of the main protease (Mpro). Since humans and other animals have no proteins similar to Mpro, the likelihood of deleterious side effects is low. The substrate-binding site is especially attractive as a target for drug development because evolutionarily conserved regions do not undergo high mutation rates like the rest of the viral genome, allowing antiviral drugs to maintain their effectiveness.

Yang et al. created a synthetic version of the Mpro substrate - reasoning that if they could inhibit the substrate's access to the binding site by the mimic (known as suicide inhibitors), they should be able to block the protease's activity and maybe halt viral replication. The authors designed a synthetic inhibitor that bound strongly to the protease and used it as a base to design a panel of inhibitors, which allowed them to identify compounds that rapidly blocked proteases from multiple coronaviruses and kept the coronaviruses from reproducing. The compounds caused no obvious damage in human cells in the experiments.

The compounds developed in this study inhibit Mpro from new coronavirus strains that cause conjunctivitis, bronchiolitis, and pneumonia. By identifying promising candidates for drugs capable of targeting the entire Coronavirus genus, Yang et al. have laid the foundation for containing everything from the common cold to the deadly SARS virus. Preclinical and clinical trials will show whether these compounds live up to their promise.

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Citation : Yang H, Xie W, Xue X, Yang K, Ma J, et al. (2005) Design of wide-spectrum inhibitors targeting coronavirus main proteases. PLoS Biol 3(10): e324.

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