Researchers identify new drug target for Kaposi's sarcoma

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UCSF researchers have identified a new potential drug target for the herpes virus that causes Kaposi's sarcoma, re-opening the possibility of using the class of drugs called protease inhibitors against the full herpes family of viruses, which for 20 years has been deemed too difficult to attain.

The new drug target, which is known as a protease dimer, could serve as a model for developing new therapeutics for diseases ranging from cancer to Alzheimer's, the researchers say. Findings are reported in the Advance Online Publication section of the "*Nature Chemical Biology*" web site and can be found at www.nature.com/nchembio/index.html.

Most current antiviral drugs target the active sites of viral proteins, where enzymes and receptors work in a lock-and-key approach to either activate or deactivate that particular protein, the researchers explained. Traditionally, drug development has focused on inhibiting that lock-and-key action to prevent the enzyme, or receptor from being effective.

Some viral enzymes known as proteases, however, including those for HIV and the herpes virus family, take the form of a dimer, or two identical halves - much like a fully opened clamshell - in their most stable state. Those proteases play an essential role in making the virus infectious, but require the two clamshell halves to bind together to be activated, according to the paper.

The HIV protease was successfully targeted for drug development in the

1980s, by blocking the active site on the surface of the dimer, but the herpes virus protease dimer has consistently eluded efforts to disrupt it at its active site, the researchers said.

The UCSF team set out to find ways to instead prevent the two halves of the dimer from connecting at that clamshell joint, to prevent it from activating. What they found was a new target on the unstable, monomer form of the protease, which responded well to a chemical inhibitor.

"If you disrupt the protein-protein interactions, you don't need the key to a specific lock," said Charles S. Craik, PhD, senior author on the paper and a professor of pharmaceutical chemistry in the UCSF School of Pharmacy. "Instead, we're essentially preventing the lock from being made in the first place."

Craik, who also led a team that identified HIV protease inhibitors in the late 1980s, said the "Nature Chemical Biology" paper validates this new site as a viable option for small-molecule drugs to treat Kaposi's, as well as other members of this viral family.

"All known herpes virus proteases are structurally similar," Craik explained. "The inhibitor we found knocks out not only KS, but also the cytomegalovirus protease, so the site we've identified here could be a target for a broad-acting inhibitor against the entire viral family."

To their knowledge, the researchers said, this is the first small-molecule inhibitor of a herpes virus protease to not only act outside the active site, but also to select for the partially unfolded protein to keep it from forming the dimer interface.

Herpes viruses make up one of the most prevalent viral families, including eight human viruses that cause a variety of devastating illnesses, the researchers said. Those include mononucleosis (Epstein-

Barr virus), shingles (Varicella zoster virus), genital herpes (herpes simplex), retinitis (cytomegalovirus) and cancer (Kaposi's sarcoma). While therapies exist for these viruses, they often have negative side effects and are facing rising viral resistance.

In addition to validating herpes virus proteases as suitable targets, Craik said this research was also among the first to use computational design to identify and create a potential drug to target that protease interface.

Using high-throughput screening, the team screened a library of 182 compounds that it had specifically and rationally designed to mimic the protease interface. The work identified six molecules that inhibited the Kaposi's sarcoma virus protease activity by at least 50 percent, including one that was highly potent.

That discovery potentially opens myriad opportunities for drug discovery, Craik said, by making target receptors that were biologically validated, but then deemed undruggable, more attractive. Protein-protein interactions have been researched as drug targets against a range of diseases, from certain cancers to neurodegenerative diseases. This advance could enable researchers to reconsider those targets, he said.

Source: University of California - San Francisco