

Compound has potential for new class of AIDS drugs

Researchers have developed what they believe is the first new mechanism in nearly 20 years for inhibiting a common target used to treat all HIV patients, which could eventually lead to a new class of AIDS drugs.

Researchers at the University of Michigan used computer models to develop the inhibiting compound, and then confirmed in the lab that the compound does indeed inhibit HIV protease, which is an established target for AIDS treatment. The protease is necessary to replicate the virus, says Heather Carlson, U-M professor of medicinal chemistry and principal investigator of the study.

Carlson stresses this is a preliminary step, but still significant.

"It's very easy to make an inhibitor, (but) it's very hard to make a drug," said Carlson, who also has an appointment in chemistry. "This compound is too weak to work in the human body. The key is to find more compounds that will work by the same mechanism."

What's so exciting is how differently that mechanism works from the current drugs used to keep the HIV from maturing and replicating, she says. Current drugs called protease inhibitors work by debilitating the HIV-1 protease. This does the same, but in a different way, Carlson says.

A protease is an enzyme that clips apart proteins, and in the case of HIV drugs, when the HIV-1 protease is inhibited it cannot process the proteins required to assemble an active virus. In existing treatments, a larger molecule binds to the center of the protease, freezing it closed.

The new mechanism targets a different area of the HIV-1 protease, called the flap recognition pocket, and actually holds the protease open. Scientists knew the flaps opened and closed, but didn't know how to target that as a mechanism, Carlson says.

Carlson's group discovered that this flap, when held open by a very small molecule—half the size of the ones used in current drug treatments—also inhibits the protease.

In addition to a new class of drugs, the compound is key because smaller molecules have better drug-like properties and are absorbed much more easily.

"This new class of smaller molecules could have better drug properties (and) could get around current side effects," Carlson said. "HIV dosing regimes are really difficult. You have to take medicine several times in the day. Maybe you wouldn't have to do that with these smaller molecules because they would be absorbed differently."

Kelly Damm, a former student and now at Johnson & Johnson, initially had the idea to target the flaps in this new way, Carlson says.

"In a way, this works like a door jam. If you looked only at the door when it's shut, you'd not know you could put a jam in it," she said. "We saw a spot where we could block the closing event, but because everyone else was working with the closed form, they couldn't see it."

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