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New drug prospect offers hope against hookworm infections

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A drug candidate that is nearing clinical trials against a Latin American parasite is showing additional promise as a cure for hookworm, one of the most widespread and insidious parasites afflicting developing nations, according to a collaborative study at UCSF and Yale University.

The drug candidate, known by the scientific name K11777, is under development at UCSF and is targeted to enter clinical trials in the next one to two years to treat Chagas disease, a potentially fatal parasitic disease common to Latin America.

In the current study, researchers at the UCSF Center for Discovery and Innovation in Parasitic Diseases and the Yale University School of Medicine tested K11777 both in culture and in hamsters against the parasite *Ancylostoma ceylanicum*, one of several species of hookworm that afflict as many as 1.2 billion people worldwide.

The compound, which works by inhibiting cysteine proteases – key enzymes in the parasite's gut that help digest its blood meal – proved more than 90 percent effective in a single oral dose and completely cured hamsters of hookworm in two doses, according to a paper being published July 3, 2012 in the *Public Library of Science* (*PLoS*) *Neglected Tropical Diseases*.

The studies are the first step in assessing whether this class of drugs could be effective against hookworm in humans, either alone or in combination with current therapies, according to senior author Conor

Caffrey, PhD, a senior scientist at the UCSF center and researcher in the UCSF Department of Pathology.

"The harbinger of concern is that for worm parasites of cattle and sheep, there is rampant resistance to the same or similar drugs that are currently being used to treat humans," Caffrey said. "Up to now, these have performed reasonably well but we're starting to hear reports of lower effectiveness, so we're working hard to identify new drug candidates before the inevitable happens."

Among parasitic diseases, hookworm infection is second only to malaria as a cause of disability worldwide. While not usually fatal, the infection is debilitating, slowing children's development and causing or exacerbating iron-deficiency anemia, which can be serious in young children and pregnant women, especially in those who already are undernourished.

Hookworm spreads when larvae from human waste penetrate human skin via moist soil, most commonly in underdeveloped areas where children go barefoot.

Among the surprises in the study was the potency of the compound against these worms. After starting with multiple doses, the team steadily cut back until they realized they had 90 percent effectiveness in one dose.

Because the current drugs, mebendazole and albendazole, are generally given as a single oral dose to treat the infection in humans, this level of potency was exactly what the researchers needed to consider it as a possibility for humans, Caffrey said.

If it proves safe and effective in humans, that single-dose therapy could be a potent new tool in the arsenal against hookworm and other worm

parasites, providing a new solution that could be delivered using distribution systems already in place in under-developed conditions, according to the paper.

Even if K11777 does not end up as a new therapy, the discovery opens the door to developing cysteine protease inhibitors as a new class of drugs to treat hookworm and, perhaps, other intestinal nematode infections, Caffrey said. This also could have ramifications for treating similar parasites in the animal health industry.

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