Bacterial Protein Shows Promise in Treating Intestinal Parasites

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Scientists at the University of California, San Diego and Yale University have discovered that a natural protein produced by *Bacillus thuringiensis,* a bacterium sprayed on crops by organic farmers to reduce insect damage, is highly effective at treating hookworm infections in laboratory animals.

Their discovery, detailed in this week's early online edition of the *Proceedings of the National Academy of Sciences,* could pave the way for the development of more effective treatments for hookworm and other soil-transmitted nematode infections, which are a major global health problem in developing countries. Many of the nearly two billion people worldwide infected with these intestinal parasites are children, who are at particular risk for anemia, malnutrition and delayed growth.

The UCSD-Yale team found that a protein produced by the bacterium *Bacillus thuringiensis,* or Bt , given orally to laboratory hamsters infected with hookworms was as effective in eliminating the parasites, curing anemia and restoring weight gain in the hamsters as mebendazole, one of the drugs currently recommended to treat infections in humans. The scientists also discovered that this protein, called Cry5B, targets both developing, or larval, stages and adult parasites, as well as impairs the excretion of eggs by female worms.

Hookworms cause anemia by attaching to the intestine and feeding on their host's blood and nutrients, causing anemia and weight loss. The researchers said in their paper that because this naturally-produced protein is safe to humans and other vertebrates and can be produced inexpensively in large quantities, it has the potential to substantially improve this global health problem.

"Our ability to control parasitic nematode infections with chemotherapy on a global scale is dependent on the availability of medicines that are safe, effective, and inexpensive to manufacture," said Michael Cappello, one of two principal authors of the study and a professor of pediatrics and epidemiology & public health at Yale School of Medicine. "We believe that Bt crystal proteins not only meet, but exceed these essential criteria."

The discovery is particularly relevant to global health, because of concerns about the potential emergence of resistance in human intestinal nematodes to currently available medicines.

"There are only a few new agents under development for the treatment of hookworm and other intestinal parasite infections," said Raffi Aroian, an associate professor of biology at UCSD and co-principal author of the study. " Crystal toxins are safe to humans, mammals and other vertebrates. And it might be possible to improve the efficacy of current treatments by giving a drug like mebendazole and Cry5B simultaneously."

Other authors of the study are Richard Bungiro and Lisa Harrison of the Yale medical school and Larry Bischof, Joel Griffitts and Brad Barrows of UCSD.

Aroian and his UCSD colleagues discovered five years ago that the roundworm *C. elegans* and other nematodes are susceptible to the effects of Cry5B, then known primarily as an insecticide. The toxin forms tiny

holes in the membranes of the cells of nematodes and insects. However, since the toxin can't bind to the cells of mammals or other vertebrates, Cry proteins can't hurt humans.

"Crystal proteins had been used for decades to kill insects by organic farmers who sprayed their crops with Bt ,"said Aroian. "Until now, however, no one has used a purified Cry protein to treat a parasitic nematode."

Aroian met Cappello, a pediatric infectious diseases specialist who studies hookworm, at a meeting of the Burroughs-Wellcome Fund and decided to collaborate on a project to see if crystal proteins could be effective against hookworm infections. Three years ago, Aroian and his colleagues purified Cry5B toxin and sent it to Cappello, who then tested the compound in a laboratory model of hookworm infection.

"It worked on the first day," said Aroian. "Laboratory animals treated with Cry5B survived a lethal hookworm infection, and showed no side effects from the medication."

Colleagues in Cappello's lab then carried out additional experiments that demonstrated that Cry5B was comparable to mebendazole for treating hookworm infection in laboratory animals. Additional studies also determined which life cycle stages of the parasite were most susceptible to Cry5B and at what concentrations.

"These experiments confirmed that the mechanism of action of Cry5B in *Ancylostoma* hookworms appears to be identical to that for other nematodes, including *C. elegans*," said Cappello. "This suggests that crystal proteins will likely have activity against a broad range of nematodes, and could be used to treat children who are often infected with multiple intestinal parasites. Studies are underway to fully define the spectrum of activity of Cry5B as part of its preclinical development as a human therapeutic."

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Control **Cry5B**