UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Amanda Siegfried
214-648-3404
amanda.siegfried@utsouthwestern.edu

Researchers gain ground in efforts to fight parasite infection

DALLAS – May 26, 2009 – New findings by researchers UT Southwestern Medical Center are accelerating efforts to eradicate worm infections that afflict a third of the world's population.

The new findings, available online and in an upcoming issue of the *Proceedings of the National Academy of Sciences,* demonstrate that a biochemical system that controls development and reproduction of *Caenorhabditis elegans*, a common research worm, also provides the same function in several parasitic nematodes, including hookworm.

In these parasitic organisms, the activating molecule, called dafachronic acid, sends the necessary signals for the worms to mature from the stage in which they infect a host to the stage in which they start feeding on the host, which is what makes the host sick. In 2006 UT Southwestern scientists led by Dr. David Mangelsdorf, chairman of pharmacology at UT Southwestern and senior author of the new study in *PNAS*, had made the discovery in *C elegans*, a nematode about the size of a pinhead.

In the new study, the UT Southwestern researchers treated hookworm parasites pharmacologically at the infective larval stage with dafachronic acid, causing them to pass into the "feeding" larval stage outside a host, where they had no food supply and died. Treatment of other infectious species had similar effects.

"We essentially coaxed them to mature before a food source – the host – is available," Dr. Mangelsdorf said.

Many infectious nematode larva live in the soil, often in areas where proper sanitation is lacking. According to the World Health Organization, parasitic nematodes infect about 2 billion people worldwide and severely sicken some 300 million, at least 50 percent of whom are school-age children.

The results point to a promising therapeutic target for the infectious nematodes, said Dr. Mangelsdorf, an investigator with the Howard Hughes Medical Institute at UT Southwestern.

"What keeps these parasites infectious is the lack of production of dafachronic acid," he said. "Once they get inside the host, however, something switches them on to begin making this compound. We can interrupt the worm's life cycle just by giving it this compound when it's in the

(MORE)

infectious state, before it enters a host."

The nature of that switch is still under investigation. It may be that the parasite itself somehow senses it is inside the host and begins making the compound, or the parasite could receive a signal from the host to begin production, Dr. Mangelsdorf said. There also is the possibility that the parasite receives the dafachronic acid, or its precursor building blocks, from the host, he said.

Whatever the source of dafachronic acid, the researchers are confident that the compound is worth pursuing as a possible therapeutic target. In the study, the researchers present additional details about the nature of different forms of dafachronic acid and how they function in specific nematodes.

Dr. Mangelsdorf said the next step in the research is to screen large libraries of chemicals to search for compounds that behave like dafachronic acid and that could possibly be developed into pesticides that could be spread in high-infection areas.

The research study is Dr. Mangelsdorf's inaugural publication in *PNAS* as a member of the National Academy of Sciences. He was elected to the organization in 2008.

Other UT Southwestern researchers involved in the study were lead author and pharmacology graduate student Zhu Wang; former graduate student Daniel Motola; Dr. Kamalesh Sharma, research scientist in internal medicine; Dr. Richard Auchus, professor of internal medicine; and Dr. Steven Kliewer, professor of molecular biology and pharmacology. Researchers from the Van Andel Research Institute, Argonne National Laboratory, George Washington University Medical Center and the University of Pennsylvania also participated.

The research was funded by the Howard Hughes Medical Institute, the National Institutes of Health, the Welch Foundation, and the Jay and Betty Van Andel Foundation.

###