Fish may provide key to stopping disease spread, researcher says

December 12 2011

A small fish may prove useful to understanding a worldwide health problem, if a Wayne State University researcher is correct.

Jeff Withey, Ph.D., assistant professor of immunology and microbiology in WSU's School of Medicine, recently received two grants from the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, to use zebrafish to study the spread of cholera and characterize signals that induce the disease in humans.

Cholera, which has been studied for nearly 150 years, strikes about 5 million people annually, causing 100,000 deaths. It's caused by the ingestion of the Vibrio cholerae bacteria (*V. cholerae*), usually through drinking untreated water. *V. cholerae* occurs naturally in the environment and normally doesn't cause problems unless consumed by humans, when it then colonizes the upper small intestine.

There the bacteria become pathogens, causing severe diarrhea that can result in the loss of up to a liter of body fluid an hour and rapid death through dehydration. Once *V. cholerae* passes through a human host, it can spread rapidly in its more virulent form, often causing epidemics or pandemics.

Withey's first study will attempt to establish zebrafish as a functional natural animal model for *V. cholerae*. Researchers recently have found that the bacteria, which often live on shellfish, insect egg masses and plankton, also colonize the intestinal tracts of vertebrate fish.

With a grant of $418,000, Withey's group will try to induce *V. cholerae* to colonize inside zebrafish, either by injecting it directly into the digestive system after administering a small dose of anesthetic, or by adding it to the water in which the fish live. Researchers then will try to determine which parts of the fish become colonized, how long the process takes and how much of the bacteria must be present to cause infection and death.

Early research has shown that zebrafish whose digestive systems are injected with *V. cholerae* are colonized but do not develop disease, Withey said, but that when the bacteria is added to the water in which the fish live, it secretes a substance known as cholera toxin (CT) that can kill the fish.

"We will look at the best ways to do experiments and see what parts of fish bacteria colonize," Withey said. "That will lead to future studies where we determine what colonization factors might be."

The zebrafish model, he said, is less expensive, simpler and more biologically relevant than existing *V. cholerae* models using mice or rabbits, neither of which is a natural host for the bacteria. Withey believes a zebrafish model should enable future researchers to identify the elusive signals for inducing *V. cholerae* virulence in humans.

"Identifying these signals should uncover new components of the virulence pathway, as well as new therapeutic targets," he said.

The second study, funded by a $361,000 grant, will focus on the bacteria itself, attempting to determine how *V. cholerae* senses and responds to signals to activate its expression of CT and other virulence factors that cause the symptoms of cholera. Withey also will try to track the complex regulatory cascade as the bacteria shuts down its virulence gene expression before escaping the host and returning to the environment.

In humans, bicarbonate is a major inducer of *V. cholerae* virulence and is found in high concentrations in the upper small intestine. Bile, also present in the small intestine, is another regulatory signal. Withey's studies are aimed at learning the mechanisms by which such signals cause *V. cholerae* to secrete CT and become toxic.

"Regulation of virulence gene expression is a common theme among bacterial pathogens, including well-known ones like salmonella or E. coli," he said. "These studies will significantly increase our understanding not only of *V. cholerae* pathogenesis, but of bacterial pathogens as a whole."

Provided by Wayne State University