Breakthrough research turns the tide on water-borne pathogen

January 25 2008

Cryptosporidium parvum is a tiny yet insidious waterborne parasite that wreaks havoc worldwide. This parasite is a major cause of diarrhea and malnutrition in small children in developing countries, and causes severe disease in AIDS and other immune compromised patients in the developed world. Cryptosporidium is resistant to water chlorination and has caused massive outbreaks in the U.S., which has led to the concern that the parasite could be used as a bio-terrorism agent. There are neither vaccines nor effective drugs available to respond to these multiple threats to human health.

In this week's issue of *Chemistry and Biology*, researchers at Brandeis University and the University of Georgia report they have identified lead compounds that inhibit Cryptosporidium's parasitic punch, paving the way for an effective antibiotic treatment. In all, scientists identified ten new compounds, four of which are better at fighting Cryptosporidium than the antibiotic paromomycin, the current gold standard for evaluating anticryptosporidial activity.

"These are promising new compounds and this research provides an avenue of much needed therapy for this disease," said Brandeis biochemist Lizbeth Hedstrom, whose lab identified the compounds together with parasitologist Boris Striepen of the University of Georgia.

While there are many drugs to treat bacterial infections, it has been very difficult to find drugs against pathogens like Cryptosporidium because the proteins of these parasites are actually very similar to those of their

human host. Scientists have been further thwarted because little was known about Cryptosporidium metabolism. This situation recently changed dramatically when genome sequencing provided a genetic blueprint of Cryptosporidium.

In work leading up to the current study, Hedstrom and Striepen used this blueprint to show that Cryptosporidium has a very simple process to produce the building blocks of DNA and RNA. Surprisingly, the researchers also discovered that Cryptosporidium stole a critical gene in this pathway from intestinal bacteria. This unusually large evolutionary divergence between parasite and host proteins provides an unexpected platform for novel drug design.

The stolen bacterial gene encodes a gatekeeper protein, known as IMPDH, which is essential for parasite growth. Hedstrom and her colleagues set out to find compounds that bind to the part of the parasite's IMPDH that is most different from human IMPDH. They tested 40,000 compounds using the facilities of the National Screening Laboratory for the Regional Centers of Excellence in BioDefense and Emerging Infectious Disease (NSRB/NERCE) at Harvard Medical School, and identified ten compounds that inhibited the parasite protein, but not the human counterpart. Four of these compounds are effective in stopping Cryptosporidium infection in the laboratory.

"The quest to develop drugs to treat this debilitating disease has been almost futile," said Hedstrom. "We are still a long way from an actual anticryptosporidial drug, but we are very encouraged by these results."

Source: Brandeis University