Researchers design new strategy to find drugs to treat neglected infection

November 3 2009

Using an unconventional approach that they designed, University of Pittsburgh drug discoverers and their collaborators at Walter Reed Army Institute of Research have identified compounds that hold promise for treating leishmaniasis, a parasitic infection that many consider one of the world's most overlooked diseases. The findings are available online today in *PLoS Neglected Tropical Diseases*.

These drug candidates, which are able to disrupt the growth of a certain stage in the life cycle of the parasite, were found by screening nearly 200,000 chemical compounds and then regrouping them into chemotypes or chemical classes, both new and known, explained senior investigator John S. Lazo, Ph.D., director of Pitt's Drug Discovery Institute and Allegheny Foundation Professor in the Department of Pharmacology and Chemical Biology, Pitt School of Medicine. One of the most potent compounds was further tested in a mouse model of leishmaniasis to confirm it could be effective against the infection.

"We are making real progress in our effort to find new drugs to treat what I'd call the most neglected of the neglected diseases," Dr. Lazo said. "And the method we've developed could be applied to find treatments for other parasitic infections, which are an enormous global health burden."

According to the U.S. Centers for Disease Control and Prevention, each year worldwide, there are about 1.5 million new cases of cutaneous leishmaniasis skin infections, which lead to ulcers, and about 500,000

visceral infections, which lead to fever, weight loss and enlargement of the spleen and liver,. There is no vaccine or drug to prevent the parasitic infection, which is transmitted through sandfly bites.

Interest in developing new treatments for leishmaniasis has grown because of the military presence in Afghanistan and Iraq, where the infection is common, said co-investigator Col. Alan Magill, M.D., director of the Division of Experimental Therapeutics at the Walter Reed Army Institute of Research, Silver Spring, Md.

"Our soldiers are at risk for becoming infected with the Leishmania parasite, but the treatments we have can produce serious side effects," he said. "Also, the organism is becoming resistant to those agents, which haven't changed in 50 years."

For the new study, lead investigator Elizabeth R. Sharlow, Ph.D., a research assistant professor in Pitt School of Medicine's Department of Pharmacology and Chemical Biology, took unconventional approaches to find drug candidates. First, she developed an assay based on the promastigote, the Leishmania life cycle stage that infects the sandfly, to measure the candidate's ability to inhibit the parasite's growth.

"Another unusual step we took was to screen compounds at relatively high concentration, which would make them more likely to affect promastigote growth," Dr. Sharlow said. "The aim was to maximize the diversity of the active compounds, which we then clustered into similar chemotypes with powerful computational methods to make further testing more manageable."

The researchers have dubbed this process "HILCES" for high throughput, low-stringency, computationally enhanced small molecule screening. Low stringency is the drug discovery term for high concentration.

A promising anti-leishmanial compound they found turned out to be disulfiram, or Antabuse, a drug that causes an acute sensitivity to alcohol and that is sometimes prescribed to discourage drinking among patients with chronic alcoholism. Testing in a mouse model of the infection showed that it could slow promastigote growth in a living organism, further demonstrating that the HILCES strategy can reveal effective, as well as unexpected, drug candidates.

"In a million years, we wouldn't have thought about using a compound such as disulfiram for leishmaniasis," noted Dr. Lazo. "It has appeal because it has already been widely used and is inexpensive, but in its current form, it might not be the best option to treat the infection. We plan to develop it further with our colleagues at Walter Reed to improve the compound's potency and efficacy."

All of the primary and confirmation screening data has been made available online, "so it can be data mined by medical researchers and industry anywhere in the world to identify and refine other anti-leishmanial drug candidates," Dr. Lazo added. "And, the same screening techniques could be invaluable to find compounds to treat other parasitic infections."

Source: University of Pittsburgh