Researchers hunting drugs for devastating parasitic disease

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Hundreds of millions of people, mainly in developing countries, are disabled by infectious diseases, according to the World Health Organization.

More than 12 million people in 88 countries are infected with leishmaniasis, a parasitic disease spread by the bite of infected sand flies. Nearly 2 million new cases are reported and about 70,000 people die from the disease annually.

Researchers at the University of Illinois at Chicago have discovered that compounds derived from a natural product can be used in developing a new drug to treat the disease.

Despite a worsening global impact of this disease, little progress has been made toward the development of new chemotherapeutics against it, says Alan Kozikowski, professor and director of UIC's Drug Discovery Program and coordinator of the project.

Drugs compounded from the toxic metal antimony have been the first-line therapeutic option for more than 50 years.

"But antimonials may cause acute pancreatitis and cardiac arrhythmia and can sometimes lead to death," Kozikowski said. Only recently, he said, have novel agents been added to the therapeutic arsenal.

Leishmaniasis can be cutaneus, which causes skin sores that leave ugly

scars, or visceral, which is 100 percent fatal if left untreated.

Visceral leishmaniasis has increased in recent years due to emerging co-infections with HIV, spreading the disease to the developed countries in North America and southern Europe, Kozikowski said. The disease is normally found in tropical regions, from the rain forests in Central and South America to deserts in West Asia.

To find a starting point from which to develop a better drug, UIC postdoctoral researchers Suresh Tipparaju and Marco Pieroni synthesized a chemical "library" of more than 100 diverse compounds and screened them for biological activity against the Leishmania parasite. They observed high antiparasitic activity in a compound first isolated from streptomyces bacteria more than 20 years ago. That compound, Tipparaju said, could potentially be modified to treat leishmaniasis. It was already three times more active than miltefosine, a drug in current use, he said.

Miltefosine is the first oral drug to cure both visceral and cutaneus leishmaniasis. Despite the drug's efficacy, Tipparaju said, miltefosine is limited by its persistence in the bloodstream and long-term side effects. It is also not effective when given to patients co-infected with HIV.

The UIC researchers are attempting to develop an antiparasitic agent that is less toxic than miltefosine and that can kill the parasite inside blood cells. In addition, the researchers are investigating the mechanism of action of the new candidate compounds through a collaboration with Manlio Tolomeo of the Center for Parasitic Diseases in Palermo, Italy. Mechanistic studies could lead to further improvement of promising agents, Tipparaju said.

The research appears in the current issue of the *Journal of Medicinal Chemistry*.

Source: University of Illinois at Chicago