Scientists tap natural extracts in search for malaria drug

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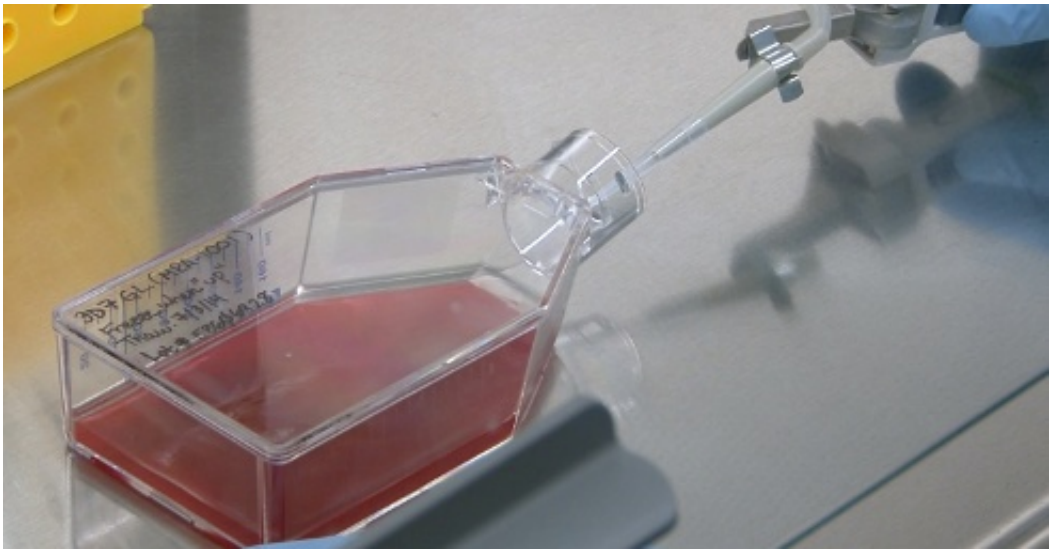

Using malaria-infected red blood cells, scientists test natural product extracts for molecules which may be able to kill the parasite.

Resistance is … inevitable. "We can't afford to have huge gaps between discoveries of new antimalarial products; the pace of innovation is quite literally a matter of life and death," said Virginia Tech's David G.I. Kingston, University Distinguished Professor of Chemistry, director of the Center for Drug Discovery, and an affiliate with the Fralin Life Science Institute.

Despite strong worldwide programs that have eradicated malaria from a number of countries, resistance to current malarial drugs continues and

about 600,000 people a year die from the disease, mostly children. As the disease and carrier mosquitoes build up resistance to the current crop of antimalarial drugs and pesticides, concern is growing that mortality could increase.

As part of a five-year grant worth more than $2 million, Kingston is working with the Natural Products Discovery Institute in an attempt to isolate natural products that can be used to fight malaria.

"When Merck Pharmaceuticals got out of the research and development side of their business, they gave their collection of natural plant extracts to NPDI," said Kingston. "We are working with NPDI to analyze their extracts in an effort to find suitable antimalarial compounds."

Working with Maria Belen Cassera, an assistant professor of biochemistry at Virginia Tech, and also an affiliate of the Fralin Life Science Institute, and Michael Goetz of the Blumberg Institute (formerly the Institute for Hepatitis and Virus Research) in Pennsylvania, Kingston is engaged in what he calls a race to find new drugs.

"As people move around the world and as drugs are used more often, resistance builds up within diseases quickly, forcing us to find alternate means to combat them," he explained. "If we can't secure new antimalarial medications, it's no exaggeration to say millions of people could die."

The effects of malaria were described as early as 2700 B.C. in China and Hippocrates detailed symptoms in the 4th century B.C.

As people become more mobile and allow disease to spread more easily, drugs are used more often to combat the disease, increasing the rate at which resistance evolves.

One of the first antimalarial drugs, quinine, started to be used on a large scale in the 1850s and by 1933 was limited by the League of Nations Malaria Commission.

Proguanil, discovered in 1944, had confirmed instances of resistance by 1949, the same year the United States was declared malaria-free.

Chloroquine, introduced in 1946 saw resistance noted in Africa in 1978. Mefloquine arrived in 1984 and had confirmed instances of resistance by 1991.

The latest drug, Artemisinin, which was deployed on a large scale as part of a combination therapy in 1994, has had reported instances of resistance since 2009.

To combat resistance, researchers are looking for the individual molecules that will kill the malaria parasite.

Using malaria-infected red blood cells, Cassera and her team at the Fralin Life Science Institute prepared plates of natural extracts to try to determine if they have a positive effect on killing the malaria parasite. In all, thousands of extracts will be tested, potentially resulting in many more thousands of screenings as extracts are filtered to find the single molecule responsible for killing the disease.

"Once we prepare and analyze the extracts and if we find one that kills the parasite, we pass along our work to Dr. Kingston's lab," Cassera explained.

The extract is put through a biological guided purification to separate the extract with the goal of isolating the molecule that is killing the parasite. Cassera says this is a process that may be repeated a number of times as researchers continue to narrow their search to ultimately find the

individual molecule they're looking for.

Cassera and her team hope to go through the 22,000 samples of extracts they will need to look at over the course of the next few months. Once active extracts are identified, Kingston will purify them using Cassera's bioassay as a guide. The structures of pure compounds will then be identified using nuclear magnetic resonance spectroscopy and mass spectrometry. Cassera will then work to identify how these new compounds kill the parasite, using mass spectrometry for metabolic studies and other approaches.

It's a big haystack Kingston and Cassera are looking through for a molecule-sized needle, but they are hopeful they can find it. Millions of lives may hang in the balance.

Provided by Virginia Tech