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Global health team pioneers development of a new antimalarial drug screening model

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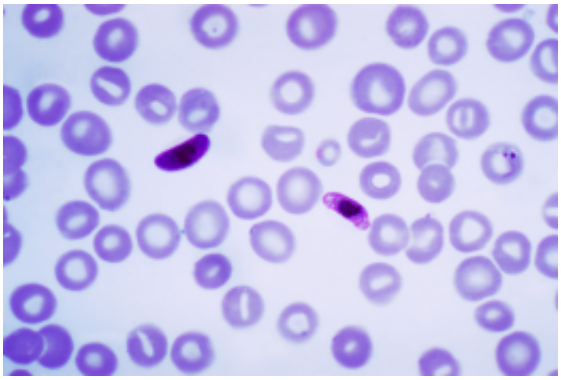

This photomicrograph of a blood smear contains a macro- and microgametocyte of the Plasmodium falciparum parasite. Credit: Wikipedia.

A University of South Florida Center for Global Health & Infectious Diseases Research team has demonstrated a new screening model to classify antimalarial drugs and to identify drug targets for the most lethal strain of malaria, *Plasmodium falciparum*.

The National Institutes of Health-funded study appeared online Nov. 6 in the journal *Scientific Reports*.

The malaria parasite is becoming increasingly resistant to the drug artemisinin as the front-line treatment to combat the mosquito-borne disease, even though artemisinin is given as a combination therapy with another antimalarial drug.

The USF research provides a better understanding how antimalarial drugs work, thus adding ammunition in the race to overcome the spread of multidrug-resistant malaria—a public health threat that could potentially undermine the success of global malaria control efforts.

The global health researchers used a collection of malaria parasite mutants that each had altered metabolism linked to defect in a single *P. falciparum* gene. They then screened 53 drugs and compounds against 71 of these *P. falciparum* piggyBac single insertion mutant parasites. Computational analysis of the response patterns linked the different antimalarial drug candidates and metabolic inhibitors to the specific gene defect.

This novel chemogenomic profiling revealed new insights into the drugs' mechanisms of action and most importantly identified six new genes critically involved *P. falciparum's* response to artemisinin, but with increased susceptibility to the drugs tested.

"That represents six new targets potentially as effective as artemisinin for killing the malaria parasite," said the study's co-senior author Dennis Kyle, PhD, a Distinguished USF Health Professor in the Department of Global Health, USF College of Public Health. "There is definitely a sense of urgency for discovering new antimalarial drugs that may replace artemisinin, or work better with artemisinin, to prevent or delay drug resistance."

The multi-faceted team of USF scientists worked with researchers from the University of Notre Dame's Eck Institute for Global Health to undertake the chemogenomic profiling of *P. falciparum* for the first time.

"The methodology used in the study highlights the importance of team-based interdisciplinary research for cutting-edge scientific innovation by

combining the tools of drug discovery methods with functional genomics and computational biology analysis. We are very happy to have such an important result published in the first year of a five-year NIH grant," said co-senior author John Adams, PhD, professor of global health in the USF College of Public Health. "Equally important are the enormous efforts by the cadre of talented postdoctoral researchers and graduate students who were critical for making this type of challenging scientific study a success."

"That interdisciplinary collaboration is where the power of this work comes to light," Dr. Kyle said. "It helps us develop the tools, the molecular techniques we need to rapidly mine huge amounts of data and to discover new drug targets in ways not previously feasible."

P. falciparum causes three-quarters of all malaria cases in Africa, and 95 percent of malaria deaths worldwide. It is transmitted to humans by the bite of an infected mosquito, which injects the one-celled malaria parasites from its salivary glands into the person's bloodstream.

Half the world's population is at risk of contracting malaria, so any decrease in artemisinin's effectiveness could result in more deaths.

More information: Anupam Pradhan et al. Chemogenomic profiling of Plasmodium falciparum as a tool to aid antimalarial drug discovery, *Scientific Reports* (2015). DOI: 10.1038/srep15930

Provided by University of South Florida