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Team to study drug-resistant malaria in Myanmar

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University of Maryland School of Medicine researchers have launched groundbreaking research into the spread of potentially deadly drug-resistant malaria in the developing Southeast Asian nation of Myanmar, also known as Burma. The scientists, working as part of a large international team coordinated by the World Health Organization (WHO), have identified several promising genetic markers that could be used to develop tests to identify and track the spread of the newest type of drug-resistant malaria in Southeast Asia, including Myanmar. The scientists describe these new candidate markers in an article published online Dec. 17 in the journal the *Proceedings of the National Academy of Sciences* (*PNAS*). Additionally, two new National Institutes of Health awards to the University of Maryland School of Medicine are some of the first U.S. federal funds to support the study of malaria in Myanmar. Myanmar, long an isolated sovereign state, ended military rule last year and is gradually opening its doors to the rest of the world. In November, President Obama became the first sitting U.S. president to visit the country.

The University of Maryland School of Medicine researchers will use the new funding to track the spread of artemisinin-resistant malaria and train local investigators in cutting-edge molecular and pharmacology lab practices to help their country cope with the problem. Artemisinin-resistant malaria is a new type of resistant malaria that reacts slowly to the first-line treatment against the deadly disease, the artemisinin group of drugs. Malaria is caused by a parasite transmitted in the bite of a mosquito. The disease causes fevers and other symptoms that can lead to

coma and even death. There were 216 million cases of malaria in the world in 2010, according to the WHO, and 655,000 deaths, most of them children in Africa. In Africa, a child dies every minute from malaria, also according to the WHO.

"Myanmar has about three percent of the Southeast Asian population, but about 20 percent of the region's malaria," says principal investigator Christopher Plowe, M.D., professor of medicine, epidemiology and public health and microbiology and immunology, a Howard Hughes Medical Investigator and leader of the Malaria Group at the University of Maryland School of Medicine's Center for Vaccine Development. Dr. Plowe will work with scientists from the Johns Hopkins Bloomberg School of Public Health on this research. "Artemisinins are our newest group of effective anti-malaria drugs, having replaced older drugs that are no longer useful because the malaria parasite developed resistance to them. Artemisinin is our first line of defense against this parasite, representing a huge global investment in the fight against the disease. This emerging form of artemisinin-resistant malaria, while it's still relatively rare, is already causing treatment failures where it first appeared, in Cambodia. The concern is that we'll lose this drug, at an immense cost of human life."

Both new awards from the NIH fund Dr. Plowe's research. One R03 grant from the National Institute of Allergy and Infectious Diseases (NIAID) provides $50,000 each year for two years (NIAID Award Number 1R03AI101680-01). A second, one-time supplement to existing funding from the NIH's Fogarty International Center, is for $50,000 and will support research training on bioethics, pharmacology and molecular lab techniques (FIC Award Number 2D43TW001589). On both projects, Dr. Plowe works closely with subcontractor Myaing Myaing Nyunt, M.D., Ph.D., a Myanmar native and assistant professor of International Health and Clinical Pharmacology at the Johns Hopkins Bloomberg School of Public Health. Dr. Nyunt, who is married to Dr.

Plowe, is working in Myanmar currently under an Open Society Institute grant to initiate research and teaching collaborations between the Myanmar Ministry of Health and Johns Hopkins University.

The paper published in *PNAS* – with Dr. Plowe as senior author, and lead author Shannon Takala Harrison, Ph.D., assistant professor of medicine and epidemiology and public health at the University of Maryland School of Medicine—is a collaboration with University of Maryland, College Park, scientist Michael Cummings, Ph.D., associate professor in the Center for Bioinformatics and Computational Biology, and other scientists from the United Kingdom and Southeast Asia. The work was funded by the Bill and Melinda Gates Foundation through a grant to the WHO.

In the paper, researchers working in Bangladesh, Western Cambodia and areas of northern Thailand near the border with Myanmar conducted clinical trials of artemisinin efficacy, providing samples and data to Dr. Plowe's team. The samples allowed the team to identify four promising molecular markers in hopes of one day developing a test to quickly and accurately identify artemisinin-resistant malaria. The markers were found by testing mutations throughout the malaria genome to see if they were associated with clinical resistance.

"Standard drug susceptibility tests used in the laboratory are not predictive of the slow parasite clearance observed in patients who are infected with drug resistant parasites in Southeast Asia," says Dr. Takala Harrison, who led the genomic analyses for the *PNAS* study. "In this study, we were able to correlate the parasite markers with clinical resistance, measured as the amount of time it took patients to clear their infections following treatment with artemisinins."

Using the R03 funding, researchers in Myanmar, led by Dr. Plowe, already are further exploring the two most promising markers identified

in the paper, one on chromosome 10 and one on chromosome 13. These scientists are examining samples from previous efficacy studies of artemisinin drugs, testing them for the two markers to see if the results correlate with drug resistance. In another project, researchers have undertaken an international study to see if it is possible to replicate the *PNAS*-published results on a far larger scale.

"This research is providing us with candidate molecular markers for drug resistance," Dr. Plowe says of the *PNAS* study. "We are now trying to validate these markers in our research in Myanmar, in part using our R03 funding from NIAID. If these markers turn out to be predictive, we can use them to track the spread of drug resistance and to help guide the malaria control program in affected countries. We want to focus limited resources on artemisinin resistance to try to stop it in its tracks before it spreads."

"The University of Maryland School of Medicine and its Center for Vaccine Development have a strong global research presence, with scientists in dozens of countries," says E. Albert Reece, M.D., Ph.D., M.B.A., vice president for medical affairs at the University of Maryland and John Z. and Akiko K. Bowers Distinguished Professor and dean of the University of Maryland School of Medicine. "Dr. Plowe's exceptional studies in tracking resistant malaria and developing vaccine candidates to prevent it are representative of the mission of the Center for Vaccine Development and the entire School of Medicine—to bring groundbreaking scientific discoveries from the laboratory to the clinic, impacting human health in Baltimore and worldwide."

Myanmar is particularly significant in the study of drug-resistant malaria because malaria cases are found throughout the country, unlike in Thailand, where the center of the nation is malaria-free, forming a potential barrier against the disease's spread. Myanmar's high rate of infection paves a path for resistance to spread to and from neighboring

nations, Dr. Plowe explains.

"Our main goals are both to track resistance and also to understand the parasite population structure," says Dr. Plowe. The researchers will examine whether there are populations of the malaria parasite that interbreed or reproduce only with themselves in a given region, but do not spread to other regions. Studying the genetic make-up of those parasites can help scientists understand how resistance spreads to new regions and maybe even how to stop it. The race against the spread of resistance is crucial, he says.

"The artemisinin resistance that we're seeing now is slowing how long it takes to clear the parasite—the infection eventually clears in most cases, it just takes longer," explains Dr. Plowe. "But if artemisinin resistance reaches the stage that resistance to other drugs has—which is to say, total resistance, rendering the older drugs useless—we would expect the same to happen to artemisinins. In addition to a loss of human life, if we lost this most important tool against malaria, the recent momentum for global malaria eradication could quickly evaporate. It takes a long time to develop a drug, and we have nothing on the shelf to replace this class of drugs."

The new awards are particularly significant as some of the first U.S. funds to support health research in Myanmar now that the nation is opening up, Dr. Plowe adds. "Part of the purpose of this grant is to see what the challenges are to doing federally-funded research in Myanmar," he says. The scientists, including Dr. Nyunt, will learn how to navigate the nation's government and bureaucracy to make their research happen.

"These awards are like ice-breakers," says Dr. Plowe. "As we learn, we hope to follow them with more funds and training to increase our work in Myanmar."

More information: "Genetic loci associated with delayed clearance of Plasmodium falciparum following artemisinin treatment in Southeast Asia," by Shannon Takala Harrison et al. *PNAS*, 2012.

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