Advances in malaria research show promise for fight against one of the world's deadliest diseases

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In a novel approach at disseminating scientific research, the Johns Hopkins Malaria Research Institute (JHMRI) will hold a web summit to release the latest breakthroughs in malaria research, including new approaches to boosting mosquito immunity to malaria, mapping mosquito migrations, and the promise of a rapid sputum test that could revolutionize the way malaria is tracked and tested for in rural areas, which are hotbeds for the disease.

Each year more than 300 million malaria cases occur worldwide. Nearly one million people die of malaria every year, most of them children. In Africa, malaria is responsible for one in five childhood deaths.

"Many young people today are passionate about global health issues. We want to engage them to pursue scientific careers in the battle against malaria," says Peter Agre, MD, Nobel Laureate, Director of the JHMRI, and current president of the American Association for the Advancement of Science (AAAS).

Mosquito Immunity to Malaria

George Dimopoulos, PhD, Associate Professor of Molecular Microbiology and Immunology at the JHMRI, will discuss new ways to make mosquitoes' immune systems resistant to the malaria-causing parasite, *Plasmodium falciparum*.

"The mosquito is the most dangerous organism in the world after humans. It has killed more than any other higher organism, which is why vector biology and vector research are incredibly important in controlling diseases in developing countries," says Dimopoulos.

Earlier this year, Dimopoulos' group identified a molecular pathway that triggers an immune response in multiple mosquito species capable of stopping the development of *Plasmodium falciparum*. By silencing the gene, caspar, the researchers were able to block the development of the parasite in *Anopheles gambiae*, *A. stephensi* and *A. albimanus* mosquitoes—three mosquito species that spread malaria in Africa, Asia and the Americas.

The process relied on a technique called transient gene silencing, which means that they didn't make lasting changes to the DNA of a mosquito. Now, Dimopoulos and his team are using genetic modification (GM) to permanently manipulate this particular molecular pathway so that mosquitoes' bodies will attack, rather than host, the malaria-causing parasite. So far they have successfully produced two lines of GM mosquitoes that work. In one line, the immune pathway gene was expressed in the mosquitoes' gut tissue (where the parasite enters). in the other line, it was expressed in the organ that functions like a liver, the 'fat body.' They now hope to create a strain of GM mosquitoes that will express the immune pathway gene in the gut and the fat body tissue simultaneously, and maximize the potency of this immune response.

"This kind of work is pioneering for malaria," says Dimopoulos. "These are the first genetically modified mosquitoes that are resistant to the *Plasmodium* parasite that causes human malaria because of a modification in their immune systems."

Dimopoulos stresses that as promising as this line of research is, "We still need an arsenal of several control strategies to contain malaria because different tactics will work in different scenarios. In some places, a vaccine may work best, in more remote places, other low cost, low tech approaches will work better. You can't win a war with the Air Force alone—you need all the branches."

Marcelo Jacobs-Lorena, PhD, Professor of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health, is also working on modifying the mosquito in order to make it a poor vector for the parasite. His lab was the first to introduce genes into the mosquito genome which caused the mosquito to express a *Plasmodium*-repelling peptide. But spreading these genes into wild populations of mosquitoes has proven challenging. Even though several breeds of mosquitoes can transmit malaria, they don't cross-breed, so just because researchers can introduce a gene into one population of mosquitoes, it doesn't mean that another population in the same area will also get that gene.

Now, Jacobs-Lorena is taking a new approach to creating a malaria-resistant mosquito by tinkering with the bacteria that occur naturally in mosquitoes' guts.

"The idea we are now exploring is how to genetically modify this bacteria so it secretes a substance that is lethal to the *Plasmodium* parasite, but not to the mosquito," he explains.

The benefit of cultivating GM bacteria is that it's much easier to grow large amounts of bacteria than to grow large numbers of mosquitoes. Jacobs-Lorena is currently looking at ways to spread GM bacteria in the wild by creating artificial refuges for mosquitoes containing cotton balls impregnated with sugar and GM bacteria. The theory is that mosquitoes will be drawn to the dark, humid, artificial refuges and get a helping of *Plasmodium*-killing bacteria while they eat the sugar.

Development of a Non-Invasive Malaria Diagnostic

Sungano Mharakurwa, PhD, Scientific Director of the Malaria Institute at Macha (MIAM) in Zambia, a living laboratory for mosquito and human behavior in malaria-stricken areas, is developing a rapid saliva-based malaria diagnostic test that works without the need for specialized personnel or equipment, and can be used at a grass-roots level.

This new microfluidic device would be affordable to produce in large numbers and would act as a miniature laboratory that could analyze a small spit sample to quickly determine whether or not someone is infected with malaria.

"The safe, affordable, and non-invasive nature of the test would make it an ideal tool for community surveillance and elimination of malaria, especially in children, asymptomatic carriers and communities that have taboos about drawing of blood," says Mharakurwa.

Current diagnostic tests for malaria come with prohibitions. They require trained health workers to take blood samples, which can only be drawn so often, hindering researchers' ability to routinely monitor the efficacy of malarial drugs or vaccines.

"In areas like Southern Africa, we need a test that can cover all communities, particularly those regions where many people don't exhibit symptoms of malaria, even if they carry the disease. These segments can be an inadvertent reservoir for the parasite, and if malaria is pushed down, but not entirely eliminated, it can resurge worse than before," he says.

Phil Thuma, MD, Managing Director of the Malaria Institute at Macha, says that there has been a remarkable decrease in malaria case load in Macha since the research institute has been carrying out research studies.

Thuma believes that credit goes to the remarkable local community cooperation with the research studies and ownership by the community and MIAM staff of the research programs, which has led to a wonderful research working environment. This, coupled with effective tools like insecticide treated bed nets and an effective anti-malarial combination drug based on artemisinin, has helped the fight.

"Malaria control and possible elimination in rural Africa seems very probable, but we need to continue working hard to get there and sustain it. That will take ongoing research studies to better understand the vector and the disease," says Thuma.

Mapping Mosquito Migrations

Gregory Glass, PhD, Professor of Molecular Microbiology and Immunology and Epidemiology with the Johns Hopkins Bloomberg School of Public Health, uses sophisticated satellite imaging to track populations of mosquitoes to help reduce malaria transmission in Africa.

"We study spatial patterns of malaria risk, using new technology like satellite images to target where the mosquitoes are living and breeding in order to get the biggest bang for the buck for our resources," says Glass.

He explains that people differ in their risk for contracting malaria based on their local environment—for example, how close they are to malaria breeding grounds. This is the kind of risk that Glass's group can show with satellite pictures.

In Europe and North America, public health officials control mosquito-borne diseases by carefully monitoring and controlling aquatic breeding sites for mosquitoes. But in sub-Saharan Africa, where there are three vector species and mosquitoes propagate in the likes of watery hoof prints of cattle, controlling mosquito breeding sites is much more difficult.

Satellite images can change this. In Zambia, remote sensing specialists look at satellite data to unearth information about the landscape, like soil moisture, or where water drains to, and bubbles up, in order to identify the most likely breeding places for mosquitoes.

"In Macha, we see some villages where most households are infected with malaria, but six miles away, no one is. Teasing apart this difference will help figure out exactly where to deliver bed nets, medicines and insecticide spray," says Glass.

About the Web Summit

During an interactive web summit, participants from diverse backgrounds, including undergraduate students, journalists and physicians from around the world will be briefed on the latest findings in the fight against malaria from top researchers at JHMRI, and pose questions in real-time via Twitter. In addition, participants will visit (by video) the JHMRI insectary where mosquitoes are bred, raised and studied at the heart of the Institute's scientific operations in Baltimore, MD.

Participants will virtually meet researchers who use NASA data to map the movement of deadly malaria-carrying mosquitoes. They'll also hear from researchers based at the Malaria Institute at Macha.

"The take-home message to students and young scientists is that there's new hope to eliminate malaria. The tools are there and if we use well-investigated approaches, it's possible that in their lifetimes they'll see the end of malaria, at least in certain regions of the world," says Mharakurwa.

More information: To access the Summit, participants will need a computer with high-speed internet access. For more information or to RSVP, visit www.jhsph.edu/malariasummit2009 .

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