

Johns Hopkins Malaria Research Institute

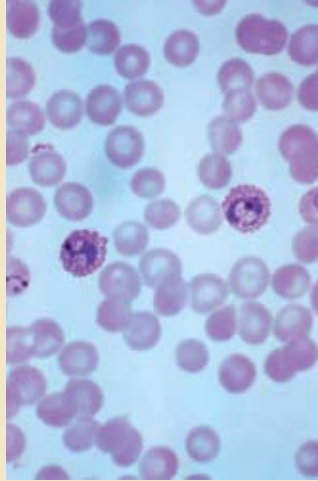
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**JHMRI**

JOHNS HOPKINS  
MALARIA RESEARCH  
INSTITUTE





## A New Approach to Malaria

The Johns Hopkins Malaria Research Institute is one of the Bloomberg School's greatest research endeavors.

Founded in 2001, the Malaria Research Institute confronts a difficult challenge: to provide the scientific basis to eradicate one of humanity's most persistent and lethal foes—the *Plasmodium* parasite that causes malaria.

From quinine (derived from cinchona bark) to today's artemisinin-combination therapy, antimalarial treatments have saved many lives, but the parasite has always found a way to adapt, thrive and threaten more people. Today four of every ten people in the world are at risk. And more than one million people—mostly children—die from malaria each year.

New approaches are needed.

The Institute embodies the Bloomberg School's strengths: world-class researchers, community-based research in an international setting, and a spirit of interdisciplinary investigation that leads to transformative scientific insights.



**“Discoveries, insights and achievements by the Johns Hopkins Malaria Research Institute signal great hope.”**

Since its inception, the Institute has done all the right things. It has drawn together the best people, the best technology and the best research to probe the *Plasmodium* parasite's complex life cycle in *Anopheles* mosquitoes and in humans.

As you will see, Johns Hopkins Malaria Research Institute researchers have already exposed weak points in the parasite, proposed radical new ways of containing malaria and deepened basic scientific understanding essential to developing new strategies that will one day eradicate the parasite.

In epidemiology, we place great emphasis on incidence—the number of new occurrences of a condition or disease over a period of time. Measurement of incidence over time makes us aware of trends that help predict the future. In the case of the Johns Hopkins Malaria Research Institute, the incidence of discoveries, insights and achievements signals great hope for the ultimate success against our ancient enemy, malaria.

Michael J. Klag, MD, MPH  
Dean  
Johns Hopkins Bloomberg School  
of Public Health

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**ISABELLE COPPENS, PHD**, is researching ways to prevent the *Plasmodium* parasite from leaving the liver and causing clinical disease.

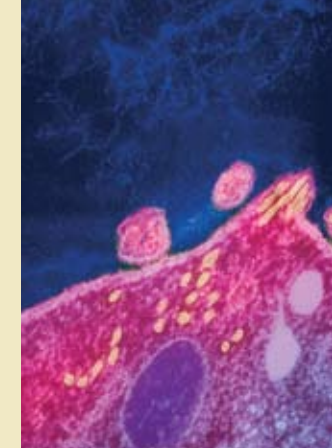
Cover photo: Malaria-stricken children are treated in Kalene Mission Hospital in northwestern Zambia. (John Stanmeyer / VII)



**EVERY YEAR MALARIA KILLS MORE THAN ONE MILLION PEOPLE—MOSTLY CHILDREN.**

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## Saving Lives Through Basic Science



At the beginning of a new century, we surveyed the state of malaria science and found great opportunities to make a difference. Malaria was widespread (it threatens 40 percent of the world's people), widely ignored (at least by the fortunate, malaria-free developed countries) and extremely complex (the parasite needs to infect both *Anopheles* mosquitoes and humans).

The small community of scientists who had devoted themselves to malaria was researching mostly familiar approaches. The main financial resources devoted to malaria were largely spent on applying traditional solutions such as bed nets and antimalarial drugs discovered 50 years ago. Those efforts are still important, but we founded the Johns Hopkins Malaria Research Institute (JHMRI) in 2001 with a different vision. In 10 years or 20 years, we wanted to live in a world that had rid itself of malaria. We knew that would require new knowledge and new tools. We believed—and still believe—our greatest contributions to malaria research would be advances in basic science that would shed light on all aspects of the disease and provide new approaches for control.

We launched JHMRI at a propitious time. With the sequencing of the genomes of humans, the *Anopheles* mosquito and the *Plasmodium* parasite, science had a completely new base from which to forge novel discoveries. The human immune



system might be primed against the parasite, or the mosquito's own genes might be tweaked to make it less hospitable to *Plasmodium*. New molecular approaches might speed diagnosis of malaria in the field.

To achieve our paradigm-changing discoveries, we established state-of-the-art core laboratory and computing facilities, and we recruited new faculty in a wide variety of areas. (You will see many of their stories in the pages that follow). We believed it was critically important to bring together more scientists from different fields to work on malaria. Our pilot grant program has attracted many investigators with no previous malaria experience. Our most illustrious pilot grant recipient is Peter Agre, who extended to malaria his Nobel Prize-winning insights into aquaporins and earned his first NIH malaria grant before succeeding me as JHMRI's director. Peter shares his story and his vision for the Institute's future on page 24.

We also founded JHMRI with the conviction that malaria research could not be done exclusively in Baltimore. We committed ourselves to studying and combating the disease in an endemic country. As a result, we have built an advanced research facility in Macha, Zambia, where we can pursue promising investigations and apply new diagnostic tools, treatments and interventions.

I am pleased to report that our broad-based, basic science approach to malaria is already having real impacts. From a powerful, new artemisinin-derivative treatment to a promising, easy-to-use diagnostic test, to advances in a transmission-blocking vaccine and the development of transgenic mosquitoes, JHMRI is capitalizing on its early investments in people and technological resources. Life-saving discoveries have been made and will continue to be made.

We have known since the beginning that there would never be one solution to malaria. Controlling this disease will require a combination of approaches. As JHMRI enters a new era, we will persevere in our goal to discover entirely new solutions.

Diane E. Griffin, MD, PhD  
Founding Director, Johns Hopkins Malaria Research Institute  
Alfred and Jill Sommer Professor and Chair in Molecular Microbiology and Immunology  
Johns Hopkins Bloomberg School of Public Health



By genetically modifying the mosquito, **MARCELO JACOBS-LORENA, PHD**, and his team investigate multiple approaches to thwarting the *Plasmodium* parasite's reproduction.



By studying local mosquito populations, **DOUGLAS NORRIS, PHD**, provides data that can help officials to gauge the most effective measures for specific regions.



**GEORGE DIMOPOULOS, PHD**, researches ways to use the mosquito's immune system to resist the malaria parasite more efficiently.



**JASON RASGON, PHD**, and his team search for genetic markers in mosquitoes with the goal of creating mosquito populations less likely to transmit malaria to humans.

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## Winged Misery: Malaria's Essential Vector

Six legs. Two wings. And a taste for blood. The female *Anopheles* mosquito is the essential vector of malaria. Without it, the *Plasmodium* parasite would languish in one victim, unable to infect the next person. Its complicated life cycle would stall. Disabling the winged transporter of *Plasmodium* would score a great victory in the war against malaria. Yet, for the most part, the mosquito has proved as wily a survivalist as the parasite.

So JHMRI scientists are scrutinizing the mosquito—from its life in the field to the genes of its immune system—to find ways of interrupting or eliminating its parasitic passenger's travels. "The key to controlling is understanding," says Douglas Norris, a Molecular Microbiology and Immunology (MMI) assistant professor who does research in Macha and Baltimore. This quest leads researchers down several promising avenues of research:

**Turning the mosquito's immune system against the malaria parasite.** Some strains of *Anopheles* completely resist infection by the malaria parasite, while others become infected. Whatever their degree of resistance, however, the mosquitoes use the same immune factors against *Plasmodium* as they do against bacteria, according to recent research by MMI assistant professor George Dimopoulos and his team. That knowledge creates opportunities to manipulate a mos-

quito's exposure to bacteria that can boost its immune system's ability to resist parasites. But since parasites can also use evasive tactics against the mosquito's defenses, the team is exploring ways that the mosquito can mount multiple and more efficient immune attacks, says Dimopoulos, PhD.

**Preventing the parasite from reproducing.** *Plasmodium* reproduces inside the mosquito's midgut. In order to reproduce successfully, it must lock onto a receptor on the midgut wall and then penetrate it. But now MMI Professor Marcelo Jacobs-Lorena and his group have found an antibody that blocks the parasite from making that crucial connection. This offers two possibilities: one, developing a vaccine that might keep *Plasmodium* out of the midgut, and, two, altering expression of the receptor to prevent infection, says Jacobs-Lorena, PhD. But, he adds, defeating the clever parasite most likely will require multiple approaches. As another possible means of eliminating the parasite, his team is developing a way to modify the microbes that occur naturally in the midgut.

**Mapping the behavior and genetics of Macha-area mosquitoes.** Malaria specialists often say "all malaria is local," since the habits and genetics of local mosquito populations vary greatly and dramatically affect the infection risk in a given area. Around Macha,

the risk can differ by a factor of 18 between villages just 10 kilometers apart, says Douglas Norris, PhD. So his team is conducting a detailed investigation of where and how the area's mosquitoes live, how often they bite, how many are infected with the parasite, and so on. At the same time, they are also studying mosquito genetics, with an emphasis on finding out how local mosquito populations differ. Combining the information from these studies may explain both why some mosquitoes are more susceptible to parasite infection and which control measures could work best in a specific area.

**Discovering how genetic variation in mosquitoes is related to their ability to transmit pathogens.** Jason Rasgon, an MMI assistant professor, is searching for genetic markers in mosquitoes that are correlated with their ability to become infected with, and transmit, malaria parasites. Some mosquitoes have genetic factors that give rise to resistance to malaria, says Rasgon, PhD. His team is also working on techniques to introduce genes into mosquito populations that inhibit their ability to transmit malaria to humans. The team is studying a bacterium and a virus that infect mosquitoes in order to determine if, once suitably modified, these agents can be used to interrupt transmission.

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## When is a Fever Caused by Malaria?

Imagine you're a mother in an isolated African village, and your child is sick. Maybe the fever and malaise are caused by a virus and will pass in a day or two. Or, perhaps they are early signs of malaria requiring prompt medical attention. Should you and your child start the two-hour walk to the nearest clinic, or gamble that she'll soon be feeling better?

Now, imagine that you can avoid the dilemma altogether. From your cupboard, you take a cardboard strip and dip it in a tablespoon of your child's urine. If a line on the strip changes color, you know instantly that the infection very likely is malaria and you need to start walking.

MMI associate professor David Sullivan, a biochemist and physician, has pursued the idea of a reliable home diagnostic test for years. The goal is not to replace the gold-standard diagnostic (blood smear microscopy), but to make diagnosis more accessible, he says. Today, only a laboratory blood test can diagnose malaria, and that requires clean needles to draw the blood and equipment and trained personnel to do the analysis—all in short supply in many malaria-affected areas. The arduous examination of a blood smear for malaria can take up to 20 minutes. In many places, clinicians treat first for malaria and

then see what happens—wasting precious time if the patient's fever is actually due to pneumonia, bacterial meningitis or other infection.

Sullivan, MD, has developed a dipstick that indicates the presence of a protein specific to the malaria parasite and found in the urine of infected people. He's optimistic that the technique, now in early clinical experimentation, will prove useful as a first-line screening test. Such low-tech tests, says Sullivan, could let people know earlier that they have malaria, helping them to have both better access to malaria treatment and greater peace of mind.

Sullivan is also collaborating with Sungano Mharakurwa, PhD, scientific director of JHMRI's field research site in Zambia, on a very different diagnostic test. They are exploring whether it's possible to use polymerase chain reaction technology to detect the presence of a fragment of the malaria parasite's DNA in a person's saliva.



Low-tech tests would let people know earlier that they have malaria.



DAVID SULLIVAN, MD, hopes that a new dipstick test for malaria will prove useful as a first-line screening test.

## Vaccinating a Village

For eons, the *Plasmodium* parasite has exploited the female *Anopheles* mosquito's appetite for human blood, infecting one person and then the next with the mosquito's help. But molecular parasitologist and immunologist Nirbhay Kumar has a novel plan for stopping malaria transmission.

During each bite, the female *Anopheles* injects her anticoagulant-rich saliva into her victim's blood to keep it from clotting. Any parasites in the mosquito's salivary glands go along for the ride. And as the mosquito sucks out blood for her meal, she ingests any parasites present in the victim as well. But Kumar, an MMI professor, hopes that mosquitoes will soon pick up something extra as well.

Kumar, PhD, is developing a malaria transmission-blocking vaccine that could protect entire communities. Instead of preventing vaccinated individuals from being infected, it blocks transmission of the parasite by the mosquito.

Traditional vaccines induce immune systems to produce a substance known as an antibody. But

in Kumar's transmission-blocking vaccine, the antibody doesn't have an effect in humans. When an *Anopheles* mosquito bites the vaccinated person, she slurps up the antibody along with the blood. Once inside the mosquito, the antibody goes into action, blocking a process essential to the parasite's sexual reproduction.

If a significant number of people in a community had this vaccine—even those already infected with malaria—disease transmission could not occur. Trials in baboons will soon test the vaccine's efficacy. Kumar hopes that human trials eventually will follow.

Efforts to eradicate malaria-bearing mosquitoes have thus far failed, Kumar says, but he hopes that this “community-based approach” can turn a former insect enemy into an unwitting ally in the fight against malaria.

**NIRBHAY KUMAR, PHD**, is developing a malaria transmission-blocking vaccine that could protect entire communities.



A new vaccine brings a community-based approach.

## Wanted: A Knockout Punch

A stealthy invader, the *Plasmodium* parasite survives in people by attracting little attention from the human immune system.

With each bite from a malaria-infected mosquito, a few hundred parasites find their way into the victim's bloodstream. The individual's immune system spots the unwanted parasites and mounts a defense, but not one strong enough to defeat the invaders. Turning that feeble response into a knockout punch is the goal of MMI professors Fidel Zavala and Richard Markham.

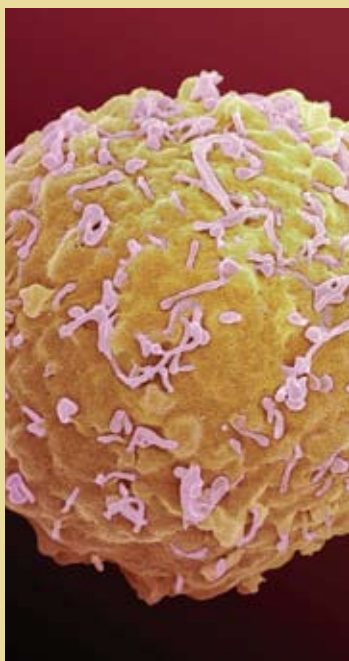
Zavala, MD, wants to improve on the effective but temporary immune defense that had been triggered experimentally by injecting people with large numbers of irradiated parasites. But procuring and irradiating the quantities of parasites needed to immunize a human population at risk for malaria may be logistically unmanageable, Zavala says. So he is working on another method to produce the response without such huge numbers of parasites, and also on ways to keep the resulting immune cells active over the long term.

He's already seen progress. An antigen—a part of the malaria parasite that alerts a person's immune system—has been identified, and Zavala is working on a vaccine that will combine that antigen with either a synthetic protein or a harmless virus to trick the immune system into seeing a massive *Plasmodium* invasion. If that works, and a way is also found to keep large numbers of the immune cells active over the long term, vaccines could protect people by producing large armies of “constantly surveilling” CD8+ immune cells, Zavala says.

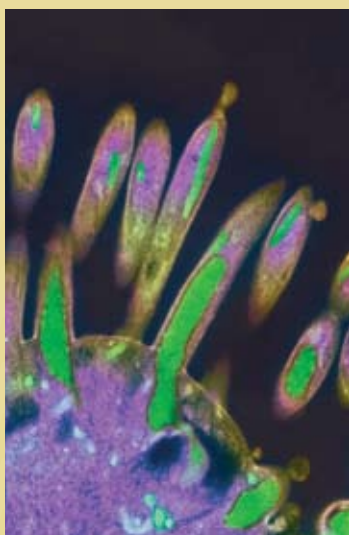
Meanwhile, Markham, MD, is researching how to boost the immune response to malaria with a DNA vaccine that has already succeeded in sparking a greatly enhanced response in mice. This type of vaccine uses genetically engineered DNA from the malaria parasite as the antigen that can be recognized by the immune system, which then triggers the defense. Markham will soon test the vaccine in monkeys, a critical step on the path toward a vaccine for humans.



**FIDEL ZAVALA, MD**, is working on a vaccine that will trick the immune system into seeing a massive *Plasmodium* invasion.



A new DNA vaccine could trigger an enhanced immune response.



## Rx for Malaria

In recent decades, pharmaceutical companies have had few incentives to invest research funds in new antimalarial drugs. They can make a greater return on their investment by rolling out therapeutics for chronic illnesses common in wealthy countries.

JHMRI researchers, however, are filling this critical gap.

Gary Posner, Scowe Professor of Chemistry in Hopkins' Krieger School of Arts & Sciences, and Theresa A. Shapiro, Wellcome Professor of Medicine, and of Pharmacology and Molecular Sciences at Hopkins School of Medicine, have cured malaria in mice with a single dose of a new version of an ancient malaria remedy.

For centuries, Chinese herbalists have treated malaria with artemisinin, derived from the wormwood shrub *Artemisia annua*. Posner, PhD, and Shapiro, MD, PhD, developed an improved version that lasts longer and acts more quickly to cure malaria in mice. They created the drug through a process called rational design, using a chemical process suitable for large-scale manufacture.

Also striving to expand the arsenal of antimalarial therapeutics is MMI associate professor David Sullivan. But he is taking a very different approach.

Sullivan and his team are not trying to develop new drugs, but rather to exploit the antimalarial potential of existing ones. Bringing a new drug to market costs up to \$800 million, but getting approval for a new use for an existing drug slashes costs by 40 percent, he says.

“Repurposing is an old idea,” explains Sullivan, MD. “Viagra was originally designed to treat angina, but doctors noticed another effect.” Sullivan’s team has already identified an antihistamine that shows antimalarial activity and a pinworm medicine that is effective against malaria’s close cousin, *Cryptosporidium*, a parasite that causes diarrheal disease.

There are probably only a limited number of drug compounds that are both safe and capable of effective action in humans. None should go to waste in the fight against malaria, says Sullivan.

Repurposing  
existing  
drugs to  
fight  
malaria  
slashes  
costs by  
40 percent.



GARY POSNER, PHD, and THERESA SHAPIRO, MD, PHD, are developing improved versions of the anti-malarial drug artemisinin.



## Nurturing New Ideas

New methods to battle malaria must be bolder and more original than those of the past.

After all, many treatments and preventions—from witchcraft to quinine—have been tried over the years, but none has enjoyed long-term success.

Sadly, the most creative ideas with the greatest potential benefits are often considered too risky to warrant research grants. Even scientists successful in other fields can find it difficult to secure malaria funding.

To spawn innovation, JHMRI has awarded pilot grants for preliminary work that might lead to fruitful lines of investigation. Any Johns Hopkins researcher, with or without previous experience in malaria, can compete for awards of up to \$100,000 annually for up to two years. The pilot grant money could allow these scientists to discover new approaches and garner sufficient data to apply for long-term support from NIH or other funding agencies.

“This has been an excellent way to increase the numbers of people studying malaria and to encourage new types of projects,” says Diane E. Griffin, MD, PhD, JHMRI’s founding director. “The program has made it possible for 25 new investigators to start work on malaria. There have been 33 publications from pilot grant work and 9 extramural grants funded so far.”

Recent pilot grants include:

**Using “jumping genes” to modify the *Anopheles* genome.** Nancy L. Craig, PhD, a professor of Molecular Biology and Genetics at Hopkins School of Medicine, is using mobile genetic elements called transposons found in the genome of the *Aedes aegypti* mosquito to modify the genome of two species of *Anopheles* in an attempt to interrupt malaria transmission.

**Producing a new anti-parasite antibiotic.** Jun Liu, PhD, a professor of Pharmacology and Molecular Sciences at the School of Medicine, is working on a new fumagillin—an antibiotic first used to control infections in honeybees—designed to attack the *Plasmodium* parasite by interfering with the action of an enzyme it needs for cell growth.

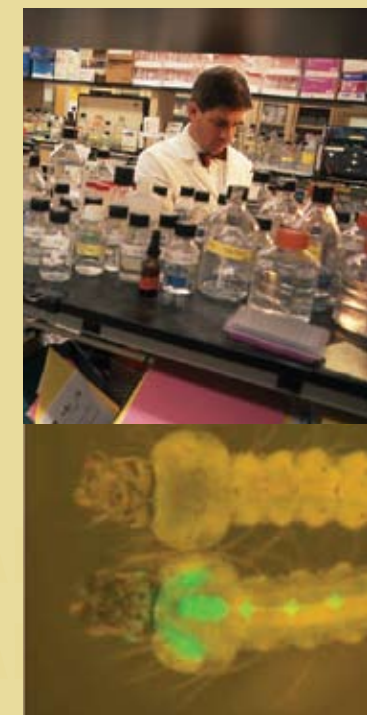
**Targeting the parasite.** Caren Freel Meyers, PhD, an assistant professor of Pharmacology and Molecular Sciences, is developing new methods for inhibiting a metabolic pathway important to many processes in the *Plasmodium* parasite’s cells.

**Finding targets in the mosquito midgut.** Akhilesh Pandey, PhD, an associate professor at the Institute of Genetic Medicine of the School of Medicine, is looking for proteins in the *Anopheles* midgut that might serve as targets that can be used to block the mosquito’s ability to transmit the parasite to people.

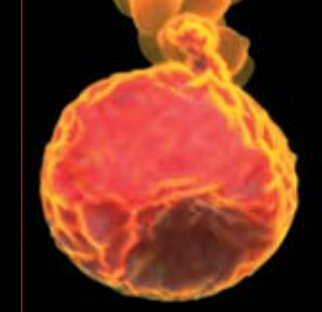
### Pilot Grants by the Numbers

59	Pilot grants awarded
25	Investigators new to malaria
\$9,219,935	Awarded for pilot grants
33	Publications generated
9	Extramural grants generated

Pilot grants support creative ideas with the greatest potential benefits.



A pilot grant helped DAVID SULLIVAN, MD, develop low-tech diagnostic tests that would provide better access to malaria treatment.



## Achievements

### Field Site Macha

Built the first permanent field research station for clinical, laboratory and epidemiologic research in Macha, Zambia, a malaria-endemic area

### Malaria-Free Mosquito

Developed transgenic mosquitoes and demonstrated they have a "fitness advantage" over unaltered *Anopheles* when feeding on *Plasmodium*-infected blood

### Quick Diagnosis

Developed a simple urine-dipstick test for diagnosing malaria

### Stronger, Better Cure

Developed a faster-acting, longer-lasting artemisinin-based drug treatment that is effective in mice and is promising in humans

### A Library of Drugs

Developed a library of approved drugs to be screened as effective antimalarials and later identified an existing allergy medication as a potential antimalarial

### Attracting New Investigators

Established a successful system of pilot grants and fellowship opportunities that is drawing new scientists from many disciplines to malaria research

### New Vistas in Vaccines

Demonstrated that immune responses against *Plasmodium* are induced in specialized tissues and earlier than previously known, opening new options for vaccine development

### Malaria-HIV Connection

Demonstrated that placental malaria increases mother-to-child transmission of HIV

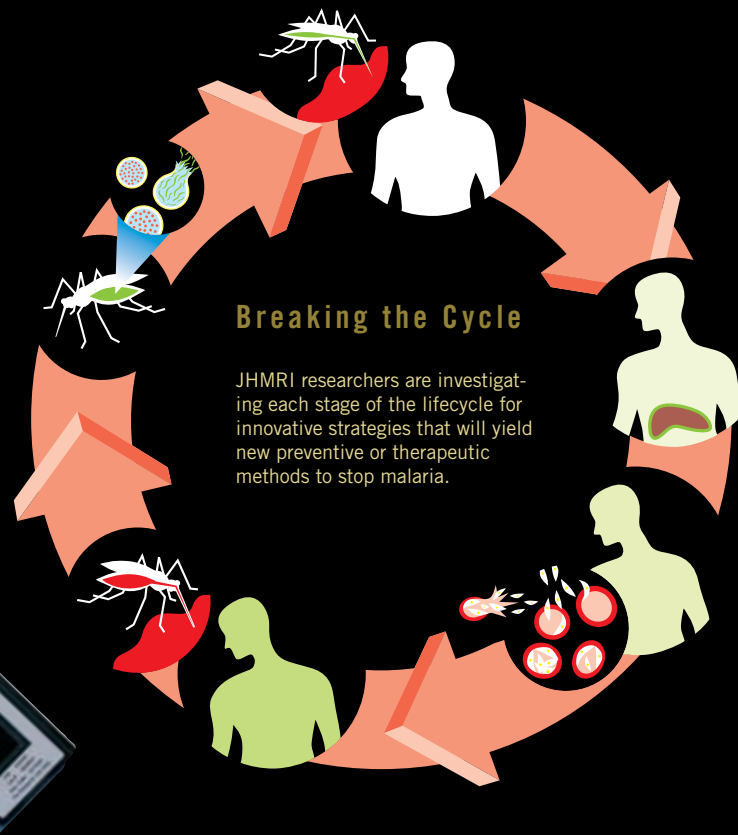
### Tools for Blocking Transmission

Reported several breakthroughs in research of the mosquito's anti-*Plasmodium* defense system, providing several new tools for transmission-blocking interventions

### Gene Chip

Provided intellectual leadership and financial support to develop the first gene chip to contain genes from the *Plasmodium* parasite and *Anopheles* mosquito

# Executive Summary



## JHMRI by the Numbers

**19** JHMRI faculty, including **9** hired since JHMRI's founding **8, 7 and**

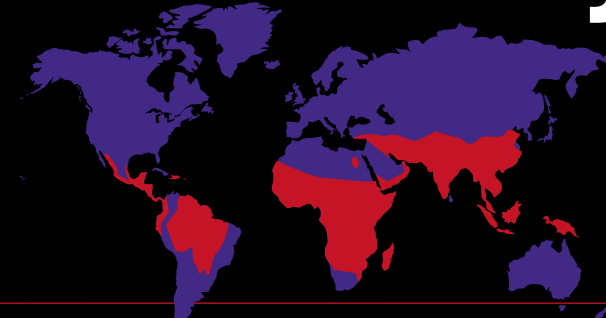
**3** Post-docs, pre-docs and endemic-area fellows supported **171** Peer-re-

viewed publications **7** Years that JHMRI was led by founding director Diane

E. Griffin **7,270,948** Registered U.S. patent awarded to JHMRI and

other researchers for their novel technique that uses a mass spectrometer to

quickly diagnose malaria in multiple blood samples



## JHMRI: A Nexus of Knowledge

### International Malaria Research Conference

A biennial, two-day conference that attracts more than 300 of the world's top malaria experts, including many from Europe and Africa

### Malaria Day

A biennial one-day conference focusing on JHMRI projects that draws more than 200 area researchers

### Baltimore-Washington Quarterly Meeting

A conference of scientists from NIH, Naval Medical Center the Naval Research Institute, and area universities

### Malaria Interest Group Meeting

A biweekly meeting of JHMRI faculty, pilot grant recipients and students through the academic year

### Award-Winning Malariology Course

A free, not-for-credit, online course on malaria is available on the Johns Hopkins Bloomberg School of Public Health's OpenCourseWare site (<http://ocw.jhsph.edu>)

### Publications

<http://malaria.jhsph.edu>

For a list of peer-reviewed publications, go to <http://malaria.jhsph.edu/publications>

## JHMRI's New "Pilot"

Nobel laureate Peter Agre received a JHMRI pilot grant in 2004 to extend his aquaporin research to malaria. His promising work later received NIH funding and inspired him to join JHMRI as its director in January 2008.





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## Macha: A Living Laboratory in Zambia

In southwestern Zambia, malaria has long been an inescapable fact of life... and death.

In the small rural community of Macha, people live in scattered clusters of huts connected by dirt roads. In some years, the 208-bed Macha Mission Hospital would treat more than 5,000 outpatients and admit up to 1,000 children with malaria. The youngest patients may suffer the disease's cruelest torments—severe anemia, convulsions and coma—and sometimes death.

But a new neighbor, the Malaria Institute at Macha (MIAM), intends to change this picture with modern malaria control methods and state-of-the-art research. A partnership of JHMRI, the Zambian government, the Macha Hospital and its Macha Malaria Research Institute, MIAM opened in January 2005 as “the only center of its type in central or southern Africa,” says Clive Shiff, JHMRI chief investigator for MIAM. The malaria parasite has adapted so exquisitely to both mosquitoes and humans that to understand the parasite, we first must understand how the people and insects live and interact day to day and season to season. “Malaria is a disease of tropical areas. It is not a disease of ivory towers,” says Shiff, an MMI associate professor, explaining JH-

MRI's mission to bring its research and training resources to an endemic country.

The campus has clinical and research laboratories, satellite communications, a permanent staff of about a dozen, and living accommodations and lab space for visiting researchers. In addition to providing research and training opportunities for scientists and students from Hopkins and other universities, Shiff says, “one of our big objectives is to train Zambians.”

Essential to any success against malaria is a deep understanding of local conditions, says Shiff, PhD, a native of neighboring Zimbabwe (then Southern Rhodesia). He began his career as a malaria-control officer in Zambia. MIAM's executive and administrative director, Philip Thuma, MD, is a Hopkins-trained pediatrician with decades of experience living and working at Macha. (His parents were medical missionaries who founded the Macha hospital.) Scientific director Sungano Mharakurwa, PhD, MSc, was born in Zimbabwe and also resides at Macha. Other key medical and technical staff members come to MIAM from Zambia or other African countries. Students from the University of Zambia's graduate parasitology program regularly do practicums at MIAM.



MIAM's executive director, Hopkins-trained pediatrician **PHILIP THUMA, MD**, has lived and worked in Macha for decades.



**WILLIAM MOSS, MD, MPH**, gathers vital baseline information in malaria in the local population.

To fight malaria we need a deep understanding of local conditions.



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## Macha: Vital Research in an Endemic Area

Research done in just the past few years in Macha has already been reported to the international scientific community via 15 peer-reviewed publications. Entomologist and MMI assistant professor Douglas Norris, PhD, is studying the biology, behavior and genetics of *Anopheles arabiensis*, the dominant vector of malaria in the area, to better understand its population dynamics and devise better ways to control the mosquito. Among the other projects under way is a major research initiative, led by William Moss, an associate professor of Epidemiology, with assistance from Snehal Shah, MD, MPH an MMI research associate. They are gathering vital baseline information on malaria in the local population. The hospital has data on treatment of active cases but not on malaria in the entire community. The survey will provide information on unanswered questions such as where the parasite exists during the dry season when case numbers drop. If we can identify the people harboring parasites at that time and treat them, malaria transmission could be reduced in the rainy season, says Moss, MD, MPH.

“Our grand mission is to identify a set of interventions to eliminate or greatly reduce malaria transmission. MIAM can contribute sophisticated methods for monitoring the interventions,” Moss adds.

Thus, says Shiff, MIAM “serves the needs of the endemic area as well as Johns Hopkins.”

### Macha by the Numbers

- 6** Major studies under way (molecular biology of malaria parasites; molecular drug resistance markers in malaria; epidemiology of community malaria with emphasis on gametocyte carriage; immune response to malarial sexual stage antigens; pharmacokinetics of antimalaria drugs in pregnancy; new diagnostic methods for malaria)
- 3,000** Square feet of lab space
- 120** Square feet of insectary space
- 34** Number of local people employed
- 7** Number of African fellows/scientists
- 1,400** Average number of pediatric admissions for malaria per year at Macha Hospital until recent years
- 300 to 500** Range of pediatric admissions for malaria per year at Macha Hospital in recent years (The decline in admissions is most likely due to drought, fewer mosquitoes and new drugs used to treat infection.)



MIAM's scientific director **SUNGANO MHARAKURWA, PHD, MSC**, is a Zimbabwe native who lives in Macha.



**DOUGLAS NORRIS, PHD**, is studying the biology, behavior and genetics of *Anopheles arabiensis* mosquitoes.



JHMRI chief investigator for MIAM, **CLIVE SHIFF, PHD**, began his career as a malaria-control officer in Zambia.

Malaria is not a disease of ivory towers.





## Hunting Mosquitoes from 126 Miles Up

“Actually, we *do* do rocket science,” says Gregory Glass, an environmental scientist who is using images from the space shuttle to solve a long-standing malaria mystery: Where do African mosquitoes (so ubiquitous during the rainy season) spend the dry season?

Some species survive the annual “tough time” as eggs, but not the malaria-bearing *Anopheles* mosquito, which spends the dry season as an adult, says Glass, an MMI professor. “They must be hiding somewhere, but nobody knows where.” Finding where the insects cluster when their populations are smallest could help to control them and to protect vulnerable people in the seasons when *Anopheles* numbers expand.

An expert in using geographical information systems to analyze risk factors for malaria and other diseases, Glass approaches the mystery of the missing mosquitoes from a slightly different viewpoint than other researchers—from an altitude of 126 nautical miles via the orbiting eye of Space Shuttle Endeavour.

In 2002, the Shuttle Radar Topography Mission (SRTM) produced the most extensive and detailed topographic maps of planet Earth ever created. Combining SRTM data with other information on hydrology, topography and vegetation, Glass’s team has mapped where water collects at various seasons in specific African locations—and not just any water, but the specific types of clear pools with sandy bottoms and overhanging trees that *Anopheles* prefers.

Lately the team has been checking the accuracy of their predictions. “We’re really good at finding where this particular species of mosquito lives,” says Glass, PhD. And, because those favored dry-season spots turn out to be near particular houses, Glass already foresees the research producing a down-to-earth result: pinpointing the families that need extra help in controlling the mosquitoes and thereby reducing their exposure to malaria.

Where do African mosquitoes spend the dry season?



GREGORY GLASS, PHD, is using images from the space shuttle to solve the mystery of where the mosquitoes go when the rainy season ends.

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**REBEKAH KENT, PHD,**  
joins Frederick after  
his recovery.

## Saving Frederick

*Entomologist Rebekah Kent's tale of death and life at the end of malaria season*

One morning last April, I was riding shotgun in a truck in southern Zambia. Two Dixie cups of *Anopheles* mosquitoes in my hands and a dying boy in the back seat.

My colleagues and I had been in Mufwafwi village collecting mosquitoes as part of my dissertation research on the dynamics of malaria transmission. Complex and minute, anopheline mosquitoes are fascinating creatures. They also carry the malaria parasite that kills one million children each year in Africa.

As we were jovially piling into the truck to leave the village after a successful morning hunting *monzenyas*, a man came running up to us with a limp child in his arms. A distraught woman followed close behind. Frederick looked about three years old and was completely comatose; only the whites of his eyes showed through partially cracked lids. None of us present was a physician, but the seriousness of his condition was clear. If he was going to have a chance of surviving, he needed a doctor as soon as possible. "Get in," we said. "Let's go."

April is the tail end of malaria season in southern Zambia. I'd seen many children sick with malaria in the Macha Mission Hospital, which is adjacent to the Johns Hopkins Malaria Research Institute's field station where my entomological research was based. Whether Frederick had malaria or some other infectious disease, we were clearly racing against time. Reaching the hospital is a big deal out there. We were a good 45-minute drive away, including 3 kilometers of bush paths leading to the main road. The mother held her sick child in the back seat. His breathing was raspy. I was terrified for him.

The truck bounced as quickly as safety permitted down eroded footpaths through tall grass. In my lap, I cradled the enemy. Topped by mesh held with rubber bands, each cup contained a

dozen or so blood-laden anopheline mosquitoes that we had just collected. Some were from the very house in which little Frederick lived. With each bump the mosquitoes were jostled off their resting place on the side of the cup. Their threadlike hind legs arched up gracefully behind their bodies, and their fine, black and white dappled wings became gray blurs as they struggled to regain their footing. I tried to cushion them as much as possible. Behind me, I heard Frederick alternate from uneven gasps to no sound at all. I gazed out the window and tried to concentrate on the pretty yellow and orange flowers that lined the roadside, on the bright sunlight that had just broken loose from an oppressive cloud cover. I caught a glimpse of the anguished father in the rearview mirror and clenched my jaw and swallowed hard to keep from crying. Please, let us get there on time.

I looked back down at the mosquitoes in my lap and marveled that these tiny, delicate creatures could be the menaces responsible for some of the world's deadliest scourges. Any one of these mosquitoes I held in my hands could be harboring thousands of wriggling, microscopic parasites. When a mosquito takes an infectious blood meal, the parasite burrows into the mosquito's midgut, where it encysts itself for about a week. Seemingly inert inside this oocyst, the parasite is rapidly multiplying into tens of thousands of minute infectious stage parasites called sporozoites. If the oocyst survives attack from the mosquito's immune defenses, it ruptures and releases the sporozoites into the mosquito's body cavity, where they penetrate the salivary glands. From there, they are injected into a host upon the next blood feeding.

Mathematically, it is amazing that malaria transmission happens at all. Assuming the mosquito's very first blood meal was infected, she must live about 16 to 18 days in order to transmit the parasites. (Mosquitoes lucky enough to

escape predation by birds, bats or raptorial insects may live about a month.) In the case of *Anopheles arabiensis*, the critical transmission time is the fourth or fifth blood meal. If this critical meal is taken on a cow, dog or chicken, the transmission cycle is broken. Likewise, if the first blood meal is taken from these animals or an uninfected person, the mosquito might not live long enough to become infectious. But, as Jeff Goldblum's character puts it in *Jurassic Park*, "Nature will find a way." And nature had found its way into the back seat of our 4x4 Toyota Hilux.

*Please, please*, let us get there on time. The road seemed endless. I no longer heard breathing behind me. Finally, we pulled into Macha and stopped at the hospital's front door. Later, Dr. Phil Thuma, a pediatrician and the executive director of the Malaria Institute at Macha, told us that Frederick had cerebral malaria and a +4 malaria smear—a lethal level. "I'm not sure he's going to make it," Thuma told us.

Over the next few days, Frederick responded well to intravenous quinine. He recovered, even managing to avoid the deafness and blindness often caused by cerebral malaria. To my relief and joy, the eyes that were once white slits gazed back at me, suffusing me in their deep brown, captivating warmth.

My happiness over Frederick's recovery was tempered, however, by my knowledge of malaria's grim reality in Africa. On that same April day that Frederick recovered, 3,000 other African children weren't as lucky. The malaria parasite found its way to them, and they died.

We just didn't get to them in time.

*Rebekah Kent, PhD, is a former research fellow with the Johns Hopkins Malaria Research Institute and is now a postdoctoral investigator with the Centers for Disease Control and Prevention.*

## Meet the Next Generation of Scientists

Along with a steady stream of research breakthroughs, JHMRI labs are producing something else vital to success against malaria: the next generation of malaria researchers.

Graduate students and postdoctoral fellows working alongside eminent scientists are making original contributions to malaria science via a wide range of studies of the *Plasmodium* parasite, the *Anopheles* mosquito and humans:

**Examining immune response to parasite infection.** Ian Cockburn, PhD, a postdoctoral fellow in the lab of MMI Professor Fidel Zavala, MD, is examining how the immune system gives the first warning signal of the parasite invasion.

Michael Overstreet, a PhD student also in Zavala's laboratory, is "eavesdropping on the crosstalk" between two types of immune cells (CD8+ and CD4+) to learn about the human response to malaria infection, and he is studying how these cells interact in the defense against the parasite.

**Understanding *Plasmodium* metabolism.** Maroya D. Spalding, a PhD student, in biochemistry and Molecular Biology in the laboratory of Sean Prigge, PhD, an MMI assistant professor, is investigating the role of a protein essential to the parasite's metabolism in the hope of finding targets for future antimalarial drugs.

**Stopping the parasite in the mosquito.** Rhoel Dinglasan, PhD, MPH, a postdoctoral fellow in the laboratory of MMI Professor Marcelo Jacobs-Lorena, PhD, is turning recent discoveries (that a sugar and a previously unknown antigen both help the parasite gain entry to the mosquito's midgut) into strategies for blocking disease transmission.

Sung-Jae Cha, PhD, a postdoctoral fellow in Jacobs-Lorena's laboratory, is studying a molecule and a gene that both play important roles in the insect's response to parasite infection.

**Studying transmission-blocking vaccines.** Debabani Roy Chowdhury, PhD, a postdoctoral fellow in the lab of MMI professor Nirbhay Kumar, is examining the effects of worm infestation on the effectiveness of experimental vaccines designed to block malaria transmission and immunological memory. Worm infections are common among children in the developing world and are known to suppress immune response.

Ralph LeBlanc, MD, a PhD student in the lab of Nirbhay Kumar, is studying malaria antigens expressed in mosquito-stage parasites as target antigens for vaccines that block malaria transmission by interfering with mosquito infection.

Students and post-docs work alongside eminent scientists to make original contributions to malaria science.



**RHOEL DINGLASAN, PHD, MPH**, is turning recent discoveries into strategies for blocking disease transmission.

## Faculty



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Ernesto Freire, PhD

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**Bioinformatics Core**  
Fernando Pineda, PhD\*

**Environmental Surveillance Core**  
Gregory Glass, PhD\*  
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**Gene Array and Proteomics Core**  
Alan Scott, PhD\*  
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**Insectary**  
Marcelo Jacobs-Lorena, PhD\*

**Parasite Core**  
Nirbhay Kumar, PhD\*

AI Scott

\* JHMRI faculty

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## Into the Future



Curiosity—that basic quality of science—drives us in new directions. Research is not about plowing the same row repeatedly or resting on your laurels. Research is about looking ahead for new ways to advance science with the goal of improving the well-being of humanity.

In 2004, the Johns Hopkins Malaria Research Institute provided our lab an opportunity to do just that. A pilot grant from the Institute has changed our lab's direction. We had never worked in malaria before, but the Institute saw that our expertise in aquaporin research might offer an innovative way to attack the *Plasmodium* parasite. Our lab had previously discovered aquaporins—proteins that form small water channels in cell membranes throughout nature, including *Plasmodium*. Our initial research revealed an interesting functional role for aquaporins during malarial infection.

Every scientist is looking for a new adventure, and it's a new day for us. We have secured a new five-year NIH grant to study aquaporins in malaria. Science is never predictable, and we are not guaranteed success. But I really think that our lab can now contribute to basic science, which is humanity's greatest hope for eradicating malaria.

It is a heartwarming honor for me to be asked to direct the Johns Hop-

kins Malaria Research Institute. Diane Griffin and her colleagues have built up a top-tier malaria program with a global reach. I am not a lifelong malariologist, and I do not come to this with great malaria expertise. Sometimes I even feel like a fan who's been asked to play with the band. Nevertheless, I feel that I have potentially important expertise. The malaria parasite spends a significant part of its lifecycle in red blood cells, and my background as a Johns Hopkins hematologist and red-blood-cell membrane biochemist will be very useful. I also feel that I have a vision for the science and can contribute in special ways, using the bully pulpit I have been given to advance the prevention and treatment of malaria.

My priorities are to increase the visibility of the Institute and malaria science in general, and to coordinate activities with other malaria research centers. I hope these efforts will lead to new methods of preventing malaria infection and new approaches to treatment of malaria.

On another level, I strongly feel it is time for me to give something back to science and to society. Programs cannot run themselves. Someone has to go to bat for the younger scientists whom we hope will soon be making the big advances. I want to do all I can to help them. For me,

that is what leadership is about. I have been named director, but my job is to serve, not to command. I'm just another scientist—albeit at a senior level—who still hopes to make new discoveries but who also wants to contribute in an organizational way to Johns Hopkins, a very special institution that has always been first in my heart.

To achieve something genuinely significant in medical science, you need that rare constellation of resources, people and good ideas. The Johns Hopkins Malaria Research Institute has them all. I consider myself extremely fortunate to have been given this opportunity. Now, my job is to make sure the bright people here have the resources needed to develop ideas that will one day help us control one of the world's worst scourges.

Peter Agre, MD  
Director, Johns Hopkins Malaria Research Institute, 2008 –  
Professor, Molecular Microbiology and Immunology  
Johns Hopkins Bloomberg School of Public Health

**SEAN PRIGGE, PHD,**  
investigates the role of a protein essential to the parasite's metabolism.

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