EXTRA! EXTRA!
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• Learn about the parasite's bizarre life cycle
• Listen to JHMBI director Peter Agre's insights
• Experience the research life in Macha, Zambia
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Resistance to Existing Drugs and New Drug Development
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NEXT ISSUE: MEN AND WOMEN ARE DIFFERENT!
From autoimmune diseases to responses to drugs and vaccines, sex differences play an immense but under-studied role in human health.

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MALARIA

Malaria—the disease that for millennia has filled cemeteries, killed kings, wrecked empires and thwarted human attempts to quash it—begins modestly enough. About 100 parasites swim in the saliva of a female mosquito.

That humble start spawns personal and global misery. The few parasites that invade a person can quickly expand to trillions, overwhelming the human body. The effect manifests in the dulled eyes of blinded children, the paroxysms of fever and chills racking the victim, the deaths of children and pregnant women, and the hobbled productivity of entire nations. Each year, malaria causes nearly 800,000 deaths and 225 million clinical cases.

Were it not such a horror, the Plasmodium parasite would be one of the wonders of the world. The resilient shape-shifter constantly adapts to its surroundings, masters sexual and asexual reproduction, slips past the immunological defenses of the Anopheles mosquito and human beings, rides in the belly of its arthropod ally to new victims…. A testament to evolutionary engineering, the parasite has a solution to every barrier it meets.

And so, Plasmodium has been virtually unstoppable. Humanity’s last global attempt at malaria’s eradication in the 1950s ended in shambles. Bright hopes were extinguished by the parasite’s resilience (and the mosquito’s growing resistance to insecticides).

However, the malaria story does not end there.

We Homo sapiens have our own brand of resilience, innovation and tricks for survival. As the following pages testify, breakthroughs in genetics, parasitology, entomology, drug development, satellite technology and other areas have summoned new hopes against our old enemy.
1. With her recent blood meal, the female Anopheles mosquito consumes dozens of stowaways: gametocytes—male and female forms of the parasite Plasmodium falciparum.

2. In the mosquito’s midgut, male gametocytes produce sperm-like microgametes. The female macrogametes soon are fertilized by the males, transform into zygotes and lengthen into sausage-shaped ookinetes.

3. A few ookinetes pass through the midgut wall and enter the mosquito’s hemocoel.

4. For 8 to 15 days, the oocysts produce thousands of thread-like sporozoites. Perhaps 20% of them reach the mosquito’s salivary glands.

5. As the mosquito bites another person, about 100 sporozoites swim with the saliva into the victim.

6. The sporozoites ride the bloodstream. Only one or two reach their target: the liver. The human victim isn’t yet aware of the enemy within.

7. After infiltrating a liver cell, each sporozoite transforms into a schizont that produces thousands of merozoites, which will invade red blood cells (RBCs).

8. After 5 to 7 days, the merozoites burst from the infected liver cell, enter the bloodstream and invade RBCs. The infected person still doesn’t feel any symptoms.

9. The parasite first takes on a signet-ring shape inside the RBC and later makes knobs on the RBC’s surface, causing it to adhere to blood vessel lining and impede blood flow.

10. The rings and the later form, called trophozoites, feast on the RBC’s cytoplasm and hemoglobin. This RBC stage ends with the formation of a schizont that produces up to 32 new merozoites. These exit in a burst and invade still more RBCs.

11. The parasite’s numbers increase 10-fold every 48 hours. From the one or two sporozoites that entered the liver, trillions of parasites may teem in the body. Two weeks after the mosquito’s bite, the patient experiences fever, headache, malaise and nausea.

12. The knobby RBCs stick like Velcro to the endothelial cells lining the blood vessels of the brain, heart and lungs—and, in pregnant women, the placenta—which often leads to death.

13. During the blood stage, some merozoites develop into yet another form of the parasite: the infective male and female gametocytes—seeds of destruction for malaria’s next victims.
Dancing with the Enemy

The malaria parasite’s life cycle relies on humans and mosquitoes. Could we use the mosquito to stop the parasite?

Story by Christen Brownlee
Illustration by Dung Hoang

The small sign on the door designating the space as the Johns Hopkins Malaria Research Institute’s Core Insect Facility doesn’t do justice to the utter creepiness of what lies waiting inside. Carved into the sterile white walls are doors marked with the names of mosquito species: *A. stephensi*, *A. gambiae*, *A. funestus*. Within these rooms is a disconcerting nursery.

Tiny, tadpole-like larvae float in water in plastic bins on shelves. They are sustained by a single, bloated cat-food pellet. The bins holding older pupa are topped with a layer of mesh held down with lead weights, anticipating their transformation into flying and biting adults. A grad student stands in the corner with an adult-filled bin. Carefully, he uses a vacuum hose to transfer the bugs into mesh-sided cubes, where a dense array of mosquitoes line the walls and buzz around inside. A bug zapper near the ceiling shines blue light—ever ready to catch any escapees.

As an anxious visitor to the *A. stephensi* room, I rub my bare arms and wish I’d worn long sleeves. Warily eyeing the bug-filled boxes, I tell insectarium director Marcelo Jacobs-Lorena, PhD, MS, Molecular Microbiology and Immunology (MMI) professor, that the room’s hundreds of mosquitoes are really disturbing. “That’s okay,” he laughs. “If you feel that way, then it gives you even more pleasure to dissect them.”

It’s the fate that awaits many of these *Anopheles* mosquitoes. That’s because these insects are one of JHMI’s greatest resources in the fight against the disease. The bugs host the malaria parasite, *Plasmodium*. That makes mosquitoes an obvious target for efforts to stop malaria.

Several researchers at JHMI are concentrating on this very goal, focusing on various ways to use the mosquito to block transmission: either by decreasing mosquitoes’ own defenses against *Plasmodium*, shortening their life span so they die before passing on the disease, or developing an innovative vaccine for people that blocks *Plasmodium* infection in mosquitoes. To solve malaria, they say, we have to partner with the very vector responsible for transmitting the disease.

**The Clues Genes Hold**

As I lean back in a comfortable chair in Jacobs-Lorena’s office, warmed by late afternoon sun and safely distant from any six-legged intruders, he explains in a musical accent that reveals his Brazilian heritage that targeting the mosquito is far from a novel idea. As soon as people realized that malaria sprouted from the proboscis of this tiny insect, scientists have been working on strategies to kill off mosquitoes or minimize contact with these bugs to prevent bites. The two most effective strategies for preventing malaria thus far have been widespread use of insecticides and bed nets (both plain and treated with insecticides).

However, these approaches have drawbacks. Heavy use of insecticides, most notably DDT, has led to whole populations of mosquitoes that are resistant to these poisons. Insecticides also aren’t the most eco-friendly of interventions, and they require constant follow-up—often unsustainable in poor locales. Bed nets—which are easily ripped and wear out over time—are also far from perfect.

Consequently, scientists will need to find new ways to interact with the other half of malaria’s host dyad to slow or prevent infection rates. But before we form a close relationship with an arthropod, it will be crucial to know exactly who we’re working with, says Douglas Norris, PhD, MS, MMI associate professor.

In many places in which scientists would like to target mosquitoes, they’re still pondering lots of basic questions: Which species are actually present in a region? Do they bite just humans, or do they take their meals primarily from other animals? If humans are their food source of choice, are they biting many people sequentially, or do they get a full meal from just one at a time? How many of these human blood suckers are infected with *Plasmodium* and currently infectious?

To address such questions, Norris and his colleagues are going straight to the insect
source, using high-tech genetic methods to derive answers. They have partnered with colleagues in Macha, Zambia, and elsewhere to gather mosquitoes for study. These collaborators ensnare mosquitoes using a variety of methods—one of the most popular is installing a light trap right above a sleeping human, who’s safely covered with a bed net—then freeze them for later study.

Potentially important species are identified through a number of steps, first of which is visual inspection under the microscope. Then, the scientists pop off the insects’ head and thorax (which have salivary glands that contain infectious Plasmodium parasites) and their abdomens (which may contain blood if a mosquito has recently fed) and place them in a small tube with a dollop of silica gel and a cotton plug. Norris explains the procedure as he hands me a tiny plastic tube rattling with dried insect pieces mummified by the silica gel.

When the researchers are ready, they can run a variety of tests on the heads and thoraces. Since many mosquito species and subpopulations look alike, researchers can examine the mosquito’s own genetics to determine exactly which one is in the tube. Such knowledge aids efforts to create and disseminate genetically altered mosquitoes—which requires transformed lab mosquitoes carrying the “anti-Plasmodium” genes to breed with existing populations.

“Researchers working on genetically altered mosquitoes are operating on the assumption that the target population for each species is one big, happy breeding population. But what if, instead, this group is structured into subpopulations that don’t breed with each other?” Norris asks. For example, he says, work with his collaborators at the University of California-Davis has shown that a population of Anopheles arabiensis in central Africa is separated into groups that don’t interbreed. “If the subpopulations don’t interact, then you’ll only get your new gene into one population. That one subpopulation will be converted, but you’ll still potentially have malaria transmission by the other populations—if they’re not interbreeding or the gene isn’t introduced to each population, your whole strategy may fail.”

Understanding if mosquito populations are interbreeding can also tell you whether or how speedily they could be swapping genes, Norris adds. That’s particularly important for strategizing against insecticide resistance, a trait that mosquitoes can acquire through random genetic mutations. If mosquito subgroups are heavily interbreeding, then it’s practically a given that the mutation for insecticide resistance will sweep through the population quickly. However, if the subgroups are giving each other the cold shoulder, then researchers may have more time to develop an action plan to control insecticide resistance.

The desiccated insect body parts can yield answers to other basic questions as well. Any blood that remains in a mosquito’s abdomen from a recent meal can tell researchers which animal it’s recently fed on. If it’s human, Norris’ group can also search deeper to see if multiple people’s blood is present in the same insect. Moreover, they can look for Plasmodium genes or antigens in the mosquito’s salivary glands, a dead giveaway that the insect was infectious at the time of its death.

Gaining such genetic information has already proved useful, Norris says. In a recent study, he and his colleagues examined human blood isolated from mosquitoes caught in Macha to see whether it came from male or female victims. Sex markers in the blood showed that women were bitten most often—perhaps because they get up earlier and go to bed later than men in this particular area, leaving them vulnerable during mosquitoes’ prime biting hours. This information could help researchers target an education plan to encourage women and others to protect themselves from mosquitoes if they’re awake while the insects are active.

Building “Super Immunity”

Protecting humans from malaria is the obvious goal here. But, says George Dimopoulos, PhD, MBA, protecting mosquitoes from malaria accomplishes the same goal. If researchers could successfully create a mosquito that is immune to Plasmodium, then these insects would be unable to continue the parasite’s life cycle and pass it back to humans.

One way to shield mosquitoes from Plasmodium is to bump up the power of their own immune systems. Any normal, healthy mosquito already has the capability to kill off the parasite once it gets infected, explains Dimopoulos, MMI associate professor. “Susceptible mosquitoes that get Plasmodium activate their immune system and kill off large numbers of parasites, but a small number [of parasites] make it through,” he says. That small number eventually becomes the population that gives people malaria.

If only researchers could make mosquitoes’ immune systems stronger and more resistant to Plasmodium, then the insects could kill off all the invading parasites and have complete immunity. Making these super-immune mosquitoes is a major focus for Dimopoulos and his lab.

Last year, he and his colleagues discovered a network of genes that are part of the immune deficiency (IMD) pathway and allow mosquitoes to fight off Plasmodium. This pathway (so-named for the fly in which it was discovered, which had an immune deficiency) controls a protein called Rel2. When the parasite-fighting IMD pathway is turned on, Rel2 binds to a mosquito’s DNA and activates production of parasite-killing molecules. Experiments show that’s what seems to happen during a natural malaria infection—albeit too late and too weak to catch all the parasites before an infection
takes hold. This pathway doesn’t stay running all the time, explains Dimopoulos, since it would take too much of a mosquito’s resources to maintain.

He and his team also discovered Rel2’s shutdown valve, a gene called caspar, which they manipulated to show that strong activation of the IMD pathway can give mosquitoes Plasmodium resistance. Knowing the components that go into running the IMD pathway allowed them to use genetic engineering to construct an elaborate system in which they linked Rel2 to the gene for a digestive enzyme. That means that once mosquitoes take a blood meal and get to work on digesting it, Rel2 is activated, which jumpsstarts the malaria-fighting pathway. “Once the parasite tries to infect the mosquito, it will encounter a very hostile environment,” Dimopoulos explains.

He and his colleagues are currently studying the genetically engineered strain of mosquitoes they created with this modification to better understand exactly where, when and how Plasmodium is killed and to see whether they can optimize this process. In the meantime, they’re also examining a different system that mosquitoes use to fight off malaria: their gut bacteria. “Mosquitoes have a significant population of symbiotic microbes in their intestine that play an important role in fighting off infectious invaders. Humans also have an intestinal ‘microbiome,’” which fulfills the same function, explains Dimopoulos.

Dimopoulos’ lab has painstakingly searched through the various species that inhabit mosquitoes’ guts to see if any has especially good Plasmodium-fighting power. They recently discovered one that seems to possess significantly more parasite-inhibiting power than the others. They are currently delving into how this microbe species battles Plasmodium, efforts that could lead to using this bacterium, or the strategy it employs against the parasite, as a key warrior in the fight against malaria.

**Gut-Level Investigations**

Jacobs-Lorena and MMI assistant professor Jason Rasgon, PhD, are also hoping to capitalize on mosquitoes’ gut bacteria, though in completely different ways.

Jacobs-Lorena led one of the first teams working to genetically modify mosquitoes to make them resistant to malaria. He’s since switched tactics, focusing now on genetically modifying the gut bacteria instead. This strategy might solve one of the most puzzling problems of genetic modification in general: how to get the desired gene into the target population. Rather than taking a roll of the dice on mosquitoes’ somewhat puzzling sex lives, Jacobs-Lorena notes that getting the target genes inside mosquitoes, packaged inside bacteria, could be a significantly easier exercise. Since all mosquitoes eat—and supplement their blood meals with carbohydrates—mixing some modified bacteria with sugar could be enough to do the trick. Some gut bacteria are passed on from mother to offspring, so starting the process with one generation could keep it going indefinitely.

His lab is currently working on perfecting the right mix of anti-Plasmodium genes in gut bacteria. It’s important to have several genes that fight the parasite in different ways, he explains: “You can never rely only on one. Then you’d have the same problem that you’d have with antibiotics on bacteria that make people sick—with time, the parasite becomes resistant.”

He and his team recently tested this approach in live mosquitoes from the insectaries he directs, infusing them with bacteria whose new genes produced a variety of malaria-combating proteins. For example, some block the parasite from passing into a mosquito’s midgut through a mechanism the scientists still don’t understand. Regardless, these useful bacteria reduced by 80 to 90 percent the formation of oocysts, pouches filled with the precursors of Plasmodium’s motile form that eventually infects humans. The researchers are optimizing those numbers through further modifications.

Rasgon’s work with bacteria aims to shorten the insects’ life spans so that they don’t live long enough to pass on the parasite. His main focus is a genus of bacteria known as Wolbachia. Researchers have long known that these microbes infect insects, with about 70 percent of species affected. More specifically, Wolbachia infects nearly every genus of mosquito—that is, except for...
The lab is currently working on using the virus AgDNV, doesn’t appear to affect the mosquitoes’ cells or bodies is a doable feat. However, unlike other insect species, female Anopheles mosquitoes don’t transfer Wolbachia to their offspring, making the process of sustaining the infection through successive generations impossible.

After nearly a decade of trying to make sustainable Wolbachia infection a reality for Anopheles, Rasgon is expecting success in a couple of years. “We’ve been at this a long time—it’s become personal now,” he says, with a look that combines both hardened determination and a murderous glint, presumably geared toward mosquitoes.

In the course of working on Wolbachia, Rasgon and his colleagues—by accident—found a virus living in a line of mosquito cells. In live mosquitoes, this virus, called AgDNV, doesn’t appear to affect the insects in any way, but tests show that it peaks in reproduction right before the insects are old enough to pass on the malaria parasite. His lab is currently working on using the virus to express some kind of mosquito toxin that could work in a similar way to Wolbachia, by shortening the insects’ life spans before they can infect people with malaria.

Toward a Transmission-Blocking Vaccine
In contrast, Rhoel Dinglasan, PhD, MMI assistant professor, has developed a unique strategy with an intervention that isn’t administered directly to mosquitoes. Instead, it targets mosquitoes indirectly through their food source: humans. He’s creating a new vaccine that imbues mosquitoes with malaria-fighting power through antibodies in human blood. One blood snack would lead to Plasmodium protection for the insects, as well as protection for the next person that a mosquito bites.

Dinglasan’s vaccine isn’t the only “transmission-blocking” vaccine in development. Several research groups, including one led by former JHMI Professor Nirmhaya Kumar, PhD, have worked on similar approaches for decades. However, Dinglasan’s methodology has quickly gained the backing of the malaria community, including the PATH Malaria Vaccine Initiative, which funds other promising malaria vaccine initiatives. The recent stir over Dinglasan’s work is due to its unique success in attacking the two most common human malaria parasite species in all the species of mosquitoes tested thus far.

While completing his PhD, Dinglasan had become interested in the various naturally occurring sugars that attach to proteins present throughout mosquitoes—sugar-coated proteins known as glycoproteins. At the time, little was known about these glycoproteins. However, previous research had shown that glycoproteins in the mosquito’s midgut in particular appear to play a key role in Plasmodium’s ability to invade mosquito cells and set up an infection.

Dinglasan hatched the idea as a postdoc in Jacobs-Lorena’s lab. There, he identified a key midgut glycoprotein called aminopeptidase 1 (APN1) that’s present in all mosquitoes. This protein is a digestive enzyme that’s always present in the mosquito midgut, ready to digest a blood meal as soon as the insect consumes one.

However, this protein also appears to play another role: It’s necessary for Plasmodium infection. Dinglasan and his colleagues found that when antibodies to a portion of this protein are present in an infectious blood meal, mosquitoes were 100 percent protected from the parasite.

To get these antibodies efficiently into mosquitoes, Dinglasan relied on the same strategy used by the creators of other transmission-blocking vaccines: creating antibodies in the people that mosquitoes bite. When mosquitoes take a blood meal, they pick up the antibodies.

So far, Dinglasan and his collaborators have produced the protein fragment that serves as an antigen that spurs people to make antibodies to the APN1 protein. In the next two years, they hope to test this vaccine in clinical trials.

To eradicate a disease, Dinglasan says, its cycle of transmission must be broken—that strategy worked for smallpox.

“Malaria researchers have real opportunities to include new approaches to break the cycle of malaria transmission,” Dinglasan says. “We have to take them.”
On an autumn morning in his lab at the Johns Hopkins Malaria Research Institute, Jürgen Bosch gets down to work.

He removes a pencil-sized metal wand from its case and places it on his lab bench to the left of a light microscope. He hoists a heavy container of liquid nitrogen and pours some into a foam dish. Fog billows from the frigid liquid. Then he sets a plastic laboratory dish underneath the microscope’s lens. The dish is divided into 96 wells.

Bosch takes a seat, interlaces his fingers and stretches out his arms so that his knuckles crack. “Okay,” he says. “Now comes the fun part.” He wheels his chair in close to the lab bench, picks up the wand and peers into the microscope.

The object of his attention?

A protein crystal, about one ten-thousandth of a meter long, delicate and brittle. The protein comes from the malaria parasite *Plasmodium*. Bosch, PhD, an assistant professor of Biochemistry and Molecular Biology, is studying the structure of this protein and others like it to design new malaria drugs. This work involves growing crystals in laboratory dishes, and then plucking individual crystals from the dishes and flash freezing them in liquid nitrogen.

Through the lens, two crystals come into view, floating in their salt/sugar bath. They resemble rectangular blocks but with more sides. Bright streaks of green and red light reflect off their mirrored surfaces.

Slowly, Bosch angles the end of the wand toward the crystal. At the end of the
wand is a fine nylon loop visible only under magnification. Bosch gingerly moves the wand to bring the loop directly over one crystal. He allows it to hover there a moment, until the surface tension of the fluid in the loop sucks up the crystal.

“Got one.”

AN ELUSIVE FOE

Antimalarial drug research has had lifesaving success stories. Scientists have generated several highly effective agents for treating or preventing the disease—including chloroquine and pyrimethamine-sulphadoxine, and, most recently, chemical derivatives of the plant-based drug artemisinin.

However, resistance to popular antimalarials such as chloroquine has rapidly spread worldwide, and there have been reports in some regions that the artemisinin derivatives are taking longer to clear the parasite from the body (not true resistance but enough to vex health officials). And no one has produced and marketed a new class of antimalarial in 15 years.

There are 225 million clinical cases of malaria each year. The most deadly parasitic disease, it causes nearly 800,000 deaths per year—and the majority of those deaths occur in young African children. Malaria accounts for approximately one out of five child deaths there.

With the looming specter of drug resistance reducing treatment options even further, scientists are seeking new drugs to add to the malaria medicine chest.

At the Bloomberg School, two scientists are employing radically different strategies. Jürgen Bosch is using a relatively new strategy called structure-based drug design. He makes crystals of different protein components of Plasmodium and uses a technique called X-ray crystallography to determine their structure. Using the structure as a sort of cast for a mold, he then designs small molecules that will fit in certain gaps, grooves or crevices of the proteins, bind there and inhibit the parasite.

His colleague David Sullivan, MD, associate professor of Molecular Microbiology and Immunology (MMI), is using more of a brute-force approach: Pull a drug off the shelf, aim it at the parasite and see if it kills.

While the two schemes differ significantly, they also have something in common: Both look great on paper, but neither comes with a guarantee that it will work against an opponent that has eluded medicine time and time again.

FINDING THE PERFECT FIT

Bosch’s first encounter with malaria came when he was a child. He lived first in South and Central America, and then spent 11 years in Nigeria, where his father worked for a multinational corporation. Malaria was pervasive there, and young Jürgen was struck with the disease several times. Fortunately, he says, “it was always a mild case, like a flu, the same type of symptoms.” He also had
access to good health care and medications, he notes, which cleared up his infection in two or three days. Many in Nigeria weren’t so lucky—including the thousands of Nigerian children who succumbed to the disease each year.

A friend of Bosch’s became one such victim. The boy, another member of the expat community, had come down with malaria while on a trip to Germany. “He didn’t come back,” says Bosch. “That’s how we learned.” The boy’s doctors did not recognize the disease until the infection had become severe. By then, it was too late.

Bosch’s firsthand view of malaria stimulated his interest in tropical diseases; he went on to earn a PhD at the Max Planck Institute in Germany and to specialize in using crystallography to study tropical diseases.

Crystallography is like an art, says Bosch. It also is a skill that comes with its own challenges, number one being constraints imposed by the simple laws of physics: Delicate crystals break easily. Not only that, says Bosch. “Even if you only bend a crystal, you can disrupt its lattice structure.” Growing crystals is also tricky; some require exact temperatures or acidity. And the pace of formation is crucial.

“If a crystal forms too fast, mistakes will happen and the crystal will be more fragile,” says Bosch. All of this, he says, “requires tremendous patience and endurance.”

One recent day in his office, Bosch calls up on his computer screen a brilliantly colored image of a protein called aldolase—a complex protein that Bosch calls part of the Plasmodium’s “invasion machinery,” the molecular apparatus that the parasite uses to enter and invade the liver and red blood cells of its human hosts.

On the screen, aldolase looks something like a lumpy catcher’s mitt. Bosch points to a crevice. “We want a drug that will fit into this crevice and touch this particular area,” he says, pointing. An effective drug would slip into this space the way a baseball flies into the palm of a catcher’s glove. That interaction, Bosch posits, will knock out the parasite’s invasion machinery—and, therefore, prevent Plasmodium from entering a host cell.

“If you want to develop a new drug, you’re going to fail more than 90 percent of the time. That’s the reality of the process.”

—David Sullivan

Bosch clicks some keys and a green sausage-shaped molecule appears on the screen, seated within the crevice. He has already designed 60 small molecules that he hopes will bind to parts of the invasion machinery, including this one. To examine the extent of binding, he mixes a candidate drug with aldolase or another part of the invasion machinery. He then crystallizes that complex, freezes the crystals and sends them to a synchrotron facility in California. At the facility, X-rays are fired at the crystals, and the diffraction of those beams is used to generate images of the complex’s structure.

“We can see the space in the cavity where the compound binds,” says Bosch. “Then we can ask, do we want to make [the drug] larger, or a different shape? You know which chemical group will fit where and you can rationally make decisions” to build a more effective drug.

It’s an elegant approach. Bosch is not aware of anyone who has ever designed a malaria drug this way. Still, he says, “I’m positive we’ll find something.” In the best-case scenario, that “something” will be a cure. But if not a cure, the experiments, he says, will at least provide new avenues to pursue in the search for a cure.

“OLD” DRUGS, NEW TRICKS

Three flights down from Bosch’s lab, David Sullivan takes a very different tack. Rather than design a malaria drug from scratch, like Bosch, he is looking for one that already exists but has been used for a different purpose.

The current total pharmacopoeia of approved or experimental drugs contains about 10,000 items, says Sullivan. And within that enormous trove, he believes, there surely reside drugs that have as yet unrecognized powers to kill Plasmodium. To identify such hidden pearls, he advocates screening massive collections of drugs. Since the compounds in such drug libraries have already ascended the arduous FDA approval process or been approved for clinical trials, the approach can save enormous amounts of time and money. (Scientists will not waste time on a drug that is toxic or has serious adverse effects.)

“If you want to develop a new drug, you’re going to fail more than 90 percent of
the time,” says Sullivan. “That's the reality of the process.”

It can take 10 to 15 years and cost hundreds of millions of dollars to move a drug from bench to bedside, he explains. Most of the candidate malaria drugs do not make it that far.

“Look at the odds,” he says. A scientist might mix a certain drug with an enzyme used by Plasmodium and show that the drug inhibits the enzyme. However, the drug might not be able to penetrate the parasite. Or, if it can get into the parasite, it may not work in an animal model. Then, he says, “the biggest hurdle is taking [drugs] that work in mice and pushing those forward to be drugs that work in humans. We have many agents that work beautifully in mice,” he notes, that don’t cure malaria in people.

So he'd rather seek from among those drugs that are already approved for human use. Recently, for example, he has been conducting studies on FBS0701. The drug is an iron chelator; it binds and removes excess iron from the body, and it is currently in clinical trials as a possible treatment for iron overload (a condition that can occur in certain diseases that require repeated blood transfusions). But Sullivan believes it also has potential as an antimalarial. Plasmodium requires iron to reproduce. So by binding up free iron, FBS0701 would cut off the supply of an element essential to the parasite's survival.

Sullivan has tested the drug in Plasmodium-infected mice and shown that a single dose cures lethal infections. “We can even give the drug a couple of days before we infect the mice, and it works,” he says. Those results are promising, says Sullivan, and he is currently drafting a paper about these findings. Since FBS0701 is already in Phase 2 clinical trials as a treatment for iron overload, Sullivan has a head start on his antimalarial studies.

Despite the apparent promise of FBS0701, Sullivan emphasizes that the drug is still a long way from being ready for human use. “I temper my excitement every day,” he says. “We like to say ‘cautious optimism.’ I’ve seen a lot of promising drugs die on the vine.”

MAKING A GOOD DRUG EVEN BETTER

Artemisinin-combination therapy (ACT) is the first choice for countries experiencing resistance to traditional antimalarials. But recent reports that artemisinin resistance might be appearing along the Thai-Cambodia border are worrying public health experts.

Gary Posner, however, who began synthesizing artemisinin derivatives in the early 1990s, declines to use the term “resistance” quite yet. Posner, PhD, a Chemistry professor in the Johns Hopkins School of Arts and Sciences and a faculty member of the Johns Hopkins Malaria Research Institute, suspects that the Cambodian cases indicate delayed drug “clearance.” The parasite still succumbs to the drug but is acquiring the capacity to survive in its presence for longer, perhaps by entering a dormancy stage.

That’s still a problem: The longer parasites linger in the bloodstream, the more chance they have of spreading the infection. So Posner is designing new artemisinin derivatives. Instead of the six-dose regimen required in current ACT, his new artemisinin derivatives involve just a single dose. For malaria-stricken people in developing countries, “adherence is a big problem,” explains Posner. Patients often take a first dose of a drug but may not take the following doses—ripe conditions for drug resistance.

A single-dose treatment would reduce that risk, and possibly at a fraction of the current cost for ACT.

Last year, Posner, along with Theresa Shapiro, professor of Pharmacology and Molecular Sciences at the Johns Hopkins School of Medicine, and their colleagues reported that a single oral dose of an artemisinin derivative, given in combination with the malaria drug mefloquine, cured malaria-infected mice.

If further funding becomes available, says Posner, he plans to test some of his compounds in monkeys, the next step prior to human testing. —MH
FAST, STRONGER IMMUNITY

The human immune response to malaria is slow and inefficient. The hope is that we can make a vaccine that does better than nature. A mosquito bite injects parasites that make their liver, where they invade its cells. At this stage, the infection is very vulnerable, the numbers of parasites are small, and they can be killed by immune cells called CD8+ T cells. These remarkable cells—which are capable of specifically finding and killing parasite-infected cells—are the focus of my research.

In a normal infection the immune system sends T cells to kill the parasite in the liver—but this natural response is too little, too late. But a vaccine could ensure that enough T cells are in place beforehand to prevent infection from getting established.

So, how do you make enough malaria-specific T cells? We know that if you infect people with irradiated parasites they are protected. People become immune because the irradiated parasites can’t divide, which makes them harmless, but they still manage to induce a good immune response. Immunizing many people with irradiated parasites would be logistically very challenging so it may not be a realistic vaccine, but it gives us clues to how to make one. One thing we’ve found is that even after the irradiated parasite is long gone, the immune system still holds onto proteins from the parasite, stimulating the immune system for months. This helps to generate a robust T cell response. Clearly this would be a good property to engineer into any vaccine we make down the line.

There are a number of promising vaccines under development. They can be made even better as we learn more about the human immune response to malaria.

Ian Cockburn, PhD, is a research associate in Molecular Microbiology and Immunology. He was recently awarded a fellowship from the European Molecular Biology Organization to continue his work in collaboration with the Pasteur Institute in Paris.

About five years ago, with resistance to chloroquine rising, he and a Hopkins MD/PhD student named Curtis Chong decided to search for alternatives to that antimalarial. Their strategy was to do a systematic search—take a whole bunch of already approved drugs and see if any would rid infected cells of Plasmodium. Over two years, the scientists procured 2,687 different drugs (a collection that eventually became the Johns Hopkins Clinical Compound Library) and tested the ability of each to inhibit the parasite.

Sullivan and Chong had some promising leads, in particular an antihistamine called astemizole. In test tube studies it inhibited the growth of chloroquine-resistant Plasmodium and, in infected mice, it significantly reduced the level of infection.

However, there were problems. A dose of astemizole killed only about 100 malaria parasites in a 48-hour period, whereas an equivalent dose of artemisinin could kill 10,000. That’s important, says Sullivan, considering that a malaria patient showing symptoms can harbor about a trillion parasites. So in the end, says Sullivan, “we did not find the pearl.”

Still, Sullivan continues to have faith that "repurposing" old drugs can yield new cures for a raft of diseases, not just malaria. A good portion of the Johns Hopkins Clinical Compound Library, he notes, is available to any scientist who wants to screen it in search of a drug for a particular disease of interest. A sample of each of the available 1,500 drugs can be dispensed into a 96-well laboratory dish and shipped to the requesting scientist. Using the library, colleagues have found leads to diseases ranging from cancer to HIV.

Meanwhile, Sullivan recently took part in an even more ambitious screening project. This time Sullivan and a multidisciplinary team began with almost 310,000 compounds—a wide net that included known drugs but also thousands of trial compounds that companies had produced but that had not yet demonstrated any therapeutic use. That study, which the team reported in the May 20, 2010, issue of Nature, identified many promising leads for fighting malaria, says Sullivan, not necessarily drugs but chemical “scaffolds” that may help steer researchers toward the drug structures most likely to defeat the parasite.

BEST OF BOTH?
The research strategies taken by Sullivan and Bosch could not be more different. But it’s possible that their scientific paths may converge at some point.

While Bosch continues to spend most of his time deducing crystal structures, he has also recently begun to take an interest in drug and chemical collections of the sort that Sullivan uses. This interest began when Bosch read a Nature article by scientists who had screened a GlaxoSmithKline chemical compound library that contains 2 million chemicals. They found several thousand that showed some ability to inhibit Plasmodium growth.

When Bosch looked closely at the results, he became excited. Some of the compounds appeared to strike Plasmodium’s invasion machinery—direct hits to the proteins whose structures he had studied so closely. Bosch immediately emailed the researchers and asked them to send him samples of their compounds.

None of the chemicals is ready to serve as a malaria drug, says Bosch. They inhibit Plasmodium, but only weakly. But the structure of those chemicals could help him improve the potency of his own drug candidates.

Bosch is also planning to use the Johns Hopkins Clinical Compound Library to search for agents that might bind to aldolase or other parts of the Plasmodium invasion machinery.

“We’ll run through them and see if any might potentially hit,” he says. "

Jürgen Bosch’s drug by design and David Sullivan's brute force approaches could not be more different, but they may soon converge.
Philip Thuma, who grew up in Macha, Zambia, cares for a patient at the hospital his father founded.
The numbers are stark: what they represent, potentially incredible. In a tiny corner of southern Zambia, more than a day’s walk from the nearest hint of a modern town, malaria has gone from a scourge to almost—but not quite—a memory. In fact, the figures coming out of this bush area known as Macha would be unbelievable if they hadn’t occurred elsewhere before. In the 1950s in Sri Lanka, and the 1990s in Zimbabwe, malaria was brought to its knees through massive government control programs. But the moment those efforts ceased, the disease rallied to pre-control heights and far beyond.

By contrast, Philip Thuma and his colleagues have taken malaria from the leading cause of infant mortality in Macha to a place where they’ve reduced its prevalence by 98 percent—and those numbers have held for nearly seven years.

Which begs the question: What’s so special about Macha … and can its success ever be defined, let alone duplicated?

SOFT-SPOKEN by nature, Philip Thuma, MD, is humble in the extreme. It’s hard to get a rise out of the pediatrician. But there is one sure way: Ask him about the skeptics who admit that what’s happened in Macha is an extraordinary feat in malaria control—but dismiss it as a one-off, a statistical anomaly for which, they believe, it’s impossible to separate the scientist—Thuma—from the science. Never mind that the hospital his missionary father, Alvan, founded in 1957, and which runs almost entirely on Zambian government money (there is some church support, along with research dollars), is considered a first-rate institution. Or that during Philip Thuma’s time in Zambia, Macha Hospital, which services some 128,000 residents in a 35-km radius, has grown to 208 beds; and that the research facility he founded in 1997, the Malaria Institute at Macha, published 21 peer-reviewed articles within its first seven years of existence.

Despite these accomplishments, some raise an eyebrow at the fact that Thuma’s resume includes the words “missionary” yet lacks “PhD.” And they claim that Thuma and his work are intertwined beyond the point of unraveling, thus making the Macha experience useless elsewhere in malaria-ravaged, sub-Saharan Africa.

“Funders of malaria control research, a lot of them have come to Macha and they walk away saying, ‘This is great, but we don’t think this is reproducible,’” says the 60-year-old Thuma. “I obviously bristle at that, because I say, ‘we’re scientists. If something seems to work, instead of writing it off, don’t we instead analyze it and ask, ‘What are the key points?’ and then try to see which of those make a difference?’”

To supporters and skeptics alike, one thing is clear: Philip Thuma is inextricably linked with the land and the people he serves. He is a doctor who is revered in his community, as was his father, before him. With a few exceptions—such as when he came to Johns Hopkins to complete his pediatric residency—he has spent the vast majority of his waking moments on these African plains (“Phil is an African. His life’s work is Africa,” says entomologist and Bloomberg School colleague Clive Shiff, who was born in what was then Rhodesia. “He’s as African as me.”)

One measure of Thuma’s connection to Macha is revealed by the pain in his voice as he recounts malaria’s lethal swiftness: “I have seen kids under five who are looking fairly normal one day, fever and headache the next day, by the third day they’re in bed, and by the fourth day they might be dead,” he says.

His lifelong commitment to the community’s health has yielded unprecedented trust in Thuma and his work. In a culture where reverence can be measured by the number of babies named after a local hero, there are enough Thumas in Macha (Philip or Alvan, take your pick) to fill a phone book. “You walk in the bush, or stop by a hut, and everyone knows ‘Thuma,’” says Greg Glass, PhD, a Bloomberg School microbiologist and professor in Molecular Microbiology and Immunology (MMI). “One time my tech, a jogger, got lost in the bush. He bumped into somebody and said, ‘Take me to Thuma!’ Well, they took him to Thuma, but it wasn’t Phil … it was some other guy, even farther out in the bush, named for Phil or Phil’s dad. Fortunately he knew Phil, and got my tech back home.”
Diane Griffin was looking for a very special partner. It was 2001, and Griffin, MD, PhD, chair of MMI and the founding director of the Johns Hopkins Malaria Research Institute (JHMRI), knew that to do the work she envisioned for the Institute, she needed a living, breathing touchstone, an African field site that could serve as a wellspring for investigation, discovery and, ultimately, healing. A place where the presence of a community-oriented researcher would open the door to important projects (especially those that ask African subjects for bodily fluids such as blood) that often run into roadblocks among wary populations.

In Philip Thuma and Macha, she found that match. Alerted by colleague David Sullivan, MD, who had previously met and worked with Thuma, Griffin first met Thuma in Baltimore, during one of Thuma’s stateside trips. She found they shared a mindset for ways of investigating malaria, and soon she visited Macha. Griffin discovered that Thuma’s record keeping of malaria cases that came through his hospital was impeccable, giving her great confidence in his case numbers going back for years. And right next door to the hospital was a fledgling research lab, complete with something Griffin felt was absolutely vital for any sustainable control efforts: Zambian raised and trained technicians.

**THUMA AND GRIFFIN** soon found that, in hoping to better control malaria, they were both headed in the same direction … back into the communities where the disease originated and continued to thrive. “Phil had exquisite records of malaria cases, but it was all hospital based and people were getting malaria out in the countryside,” says Griffin. “The mosquito populations out there were totally unknown. The area hadn’t been mapped. Everything was there to be done.”

Even more enticing was the fact that, from an environmental viewpoint, Macha was virgin territory. While other African sites in Kenya and Mali had been pored over by a plethora of scientists, Macha, says Griffin, “was a brand new type of area of study, with seasonal [non year-round] transmission, no previous DDT spraying, no distribution of bed nets. Nothing had really been done to try and control malaria in the community before.”

But even before JHMRI’s imprint had been felt on Macha, the entire malaria landscape there changed. By 2004 the hospital cases had slowed to a trickle. On the surface, the cause was as simple as looking up at the cloudless skies: A severe drought had wiped out the mosquitoes’ breeding sites. No mosquitoes = no malaria. But theoretically, that respite should only have lasted until the next rainy season. It came and went, but still the malaria stayed away.

Philip Thuma thought he knew why. It had everything to do with what had happened on the ground versus in the skies. Thuma had always sought better drugs for treating malaria. He knew that antimalarial drugs were often problematic, especially in adults who rarely died from the illness.

“In the days when we had quinine, we used to say that you’re supposed to take seven days of it, but by day three, you were so dizzy and your ears rang so much that you usually couldn’t function and you had to go to bed,” recalls Thuma, who has contracted malaria numerous times. “In those early days, it was sometimes hard to separate out the symptoms of the disease from those of the drugs.”

Things only got worse when malaria became resistant to chloroquine in the 1980s and ’90s. Then, in 2003, the Zambian government made a strategic decision to spend big dollars on a new antimalarial medication, artemisinin combination therapy (ACT), which promised fewer side effects and the opportunity for malaria-stricken employees to return to work far sooner.

In Macha, Thuma discovered that ACT also held the potential to stop the disease. He got his Zambian government connections to procure for him large doses of the medication, which he and one of his first Hopkins hires, Zimbabwean Sungano Mharakurwa, PhD, delivered directly into the community. What they found astounded them. Before artemisinin, other antimalarials were capable of killing the parasite that caused the disease and its symptoms. But there’s a stage to which the parasites can mature—a reproductive stage where they become known as gametocytes—that survived such previous treatment. Infectious gametocytes can persist for months in people with asymptomatic parasitemia. Seasonal mosquitoes die off, but come back in the next rainy season, and have a human source of the disease all ready to ingest.
Artemisinin stopped this process, knocking out both the blood-borne form of the parasite that causes clinical symptoms as well as the asymptomatic gametocytes. Aided by a relatively new field technology, rapid diagnostic testing, Thuma and company quickly identify and treat malaria carriers with artemisinin—and do it right in their homes.

“We would take malaria smears every six hours, to count the parasites and quantify them,” says Thuma, who had conducted similar tests during numerous previous drug trials held at his hospital. “Suddenly, with this drug, those parasites melted away faster than anything we’d ever seen.”

Relying on a coterie of chiefs, medicine men and other influential community elders, Thuma and Mharakurwa, along with Zambian field workers they trained, visited every hut they could in 2003, testing asymptomatic people for gametocytes. Screening these unknowing carriers and offering them drug treatment was, by Thuma’s own admission, a controversial choice. Some argued that parasites’ presence in the body offered some immunity against serious cases of malaria. Eliminate the parasites and that potential protection is gone, but so is the chance of reinfection.

“People are taught about Typhoid Mary in medical school,” says Thuma. “I talk about ‘Malaria Mary’—though it’s not just women. [My] example: If there’s a parent in a hut with five or six kids, if the mosquito bites an asymptomatic parent, and then, after the 10- to 14-day incubation period, that mosquito bites their kid and the kid gets sick with malaria, you’ll treat the kid at the hospital, the kid will go home, and the same thing will happen again because you’ve never found the source.”

Thuma had found and treated the source. By 2004, cases at the hospital had plummeted, and malaria was on the ropes. The question for both Thuma and JHMRI had now shifted: What could they do to knock malaria down to the canvas … and keep it there?

SOME OF THE most important translational research in Macha didn’t happen in the lab, or the creeks and huts that dot the countryside, but rather on Philip Thuma’s veranda. It’s there at the end of a hard day’s work that some of the numerous JHMRI researchers and their Zambian counterparts gather. Ostensibly they come to eat—half of Thuma’s house is the communal kitchen for the compound (“My wife is chief cook and I’m head bottle washer,” he laughs)—but a few stragglers usually make their way to the porch as the sun goes down and the enemy, those damned mosquitoes, start pinging off the veranda’s enclosing screens. That’s the kind of omnipresent buzz that can turn thought into action.

And so it has. Over the past six years, JHMRI researchers and postdocs have made numerous trips to Macha. By studying both Thuma’s work and greater Macha, they’re hoping to develop a transferrable one-two punch: Prove that there’s a way to knock down seasonal malaria to just a few cases, and then track those cases back to the homes where the disease was initially transmitted to treat asymptomatic patients who are parasite carriers. In and around this, investigate the effectiveness of control efforts such as insecticide-treated bed nets and mosquito larvae eradication programs.

When I look back, I’m grateful to be alive. I lost my maternal grandmother to malaria. She had confusion and convulsions, which led people around her to suspect she had been bewitched. This may have delayed her referral to a health center.

I also vividly remember myself having malaria at preschool age. I still shudder at the recollection of how bad it was. I no longer wanted food. I had exhausting cycles of feeling very cold, then suddenly feeling very hot. A terrible headache. Finally I got to the hospital where I was born and got effective treatment.

Macha has been extremely well received as a treasured resource for the country, a tremendous help for the malaria control program. The possibility of developing non-invasive ways of testing for malaria, which is novel research, has become a source of pride to the country. Taking blood is often met with suspicion by communities. So we’re working on three approaches for testing saliva, including looking at the nucleic acids of the parasite.

I think what’s happening here has a strong potential to have a ripple effect, convincing governments to put more money into PhD education and research jobs. Tanzania committed 1 percent of its GDP to research. And I understand Uganda is trying to pay its researchers an international salary. And once we do that, it will blossom because there’s no shortage of smart people; it’s only the careers have not been rewarding.

Sungano Mharakurwa, DPhil, MSc, is scientific director for the Malaria Institute at Macha, and a senior research associate in the Bloomberg School’s Department of Molecular Microbiology and Immunology.

After taking blood samples from a village family, Macha field team workers Cornelius Choobwe (left), Clement Mwaanga and Harry Hamupumbu carry out rapid diagnostic tests for malaria.
Thuma says the largest body of publications in the 2004–2007 period came from mosquito vector expert Douglas Norris’s team, including then doctoral student Rebekah J. Kent. Kent collected 31 different mosquito species in Macha, discovering that one, *Anopheles arabiensis*, was the primary vector for transmission. “No one had studied mosquitoes in that part of Africa for many years,” says Thuma.

Thuma and his JHMRI colleagues understand the irony of what’s going on in Macha now. With malaria cases at an all-time low, some researchers and funders might be tempted to shift attention to other diseases. Clive Shiff, an MMI associate professor, says that would be a mistake on several fronts, noting that another mosquito malaria vector, *An. funestus*, was wiped out in the Macha area during the 2003 drought but could return in any given rainy season. On a more practical level, cash-strapped African governments could spend far fewer dollars if they attacked malaria when it was relatively quiescent—if they only knew where to look.

“None of the African countries where malaria is endemic can afford these long-term, high-cost control programs,” says Shiff, of the massive mosquito spraying and drug distribution efforts some health ministries have used in the past when malaria cases soared out of control. Moreover, he notes, “this is not a good time for donor countries to reach into their pockets and come up with another billion dollars.” Shiff’s goal? “[Find ways] of reducing the costs by about 80 percent, so you can focus at specific times of the year on critical parts of the population.”

Working with Thuma and parasitologist Mharakurwa, JHMRI’s faculty and several young Zambian scientists have made significant potential inroads to creating such efficiencies in Macha in just a few short years. Their efforts combine fieldwork with the latest communication and satellite technologies. Amplifying on the work of Doug Norris’ team, Greg Glass and Clive Shiff determined that *An. arabiensis* was particularly fond of breeding in clean streams of slow running water. They also learned *An. arabiensis* could only travel 450 meters from its birthplace to feed, an important factor in targeting control efforts aimed at humans.

Glass took the finding one important step further: He used satellite imaging and modeled the hydrology to elegantly map likely breeding sites (see sidebar). Armed with knowledge of the mosquito’s flying range, Glass drew concentric circles around these bodies of water to come up with a relative bull’s-eye of those most likely affected: people who lived or worked inside the ring. Shiff is pulling the treatment net even tighter: He and team members Aniset Kamanga and Gillian Stressman are finding and treating asymptomatic adults.

These findings were an impressive start at establishing some kind of controls that might be reproducible elsewhere. This past July, the National Institute for Allergy and Infectious Diseases (NIAID) designated JHMRI as an International Center of Excellence in Malaria Research (ICEMR), in part because of the Institute’s work with Thuma. Part of the multimillion dollar, seven-year ICEMR grant will strengthen the Macha collaborative, allowing Hopkins researchers to better share and implement their ideas with other ICEMR grantees studying endemic malaria in Asia, Latin America and the Pacific Islands.

JHMRI director Peter Agre says the money may allow the research in Macha to move more quickly into wider practice. “This is, I think, a big story waiting to un-
Anopheles arabiensis

Norris, who helped determine the types of breeding pools and foraging habits. Building on the discoveries of researchers such as entomologist Doug Clennon (now at Emory University), are creating elegant satellite maps that allow researchers to discern and treat the area’s most vulnerable populations.

Utilizing digital technology, Glass and his researchers, notably postdoc Julie iset Kamanga and Petros Moono developed a cell phone text messaging system between mobile field clinics and JHMRI’s Macha data collection center to communicate and record who is diagnosed with malaria and where. After the rainy season, health care workers return to look for and treat carriers.

“This may be the most important advance,” says Agre, a Nobel laureate. While looking for asymptomatic carriers may seem obvious in retrospect, he says, “people hadn’t done it because it required an investment. But now, with modern molecular diagnostic tests, we can identify who is carrying the parasite.”

Agre says that with the ICEMR grant, Macha—and what’s discovered there—will be juxtaposed against two other field sites; Nchelenge, Zambia, just a stone’s throw from the border with Democratic Republic of Congo, an area where epidemic malaria has never been controlled; and Mutasa, an area of Zimbabwe once under control but now devastated by the disease. “Macha is our reference point where malaria is coming under control, and Phil’s a principal in all our international activity [in Africa]. So we have a good series of viewpoints to establish whether the Macha experience can be transferred,” says Agre.

For his part, researcher Bill Moss, MD, MPH, believes that at least part of the Macha model will benefit other areas. Moss, who is investigating the epidemiology of symptomatic and asymptomatic malaria, gametocytemia and changes in immunity in Macha, says that while different regions may have different epidemiological features, the work done in Macha could yield more efficient, exportable control efforts. He points to Doug Norris’ investigations identifying vectors and their behaviors: when they like to feed (day vs. night), where (indoors vs. the fields), on whom (men vs. women, children vs. adults) and for how long (a quick rush at dusk vs. an all-night bite-a-thon). If it’s found that a vector bites during the day and outdoors, Moss says it might be less effective to distribute insecticide-laden bed nets for indoor use. Overall, says Moss, an Epidemiology associate professor, “I don’t think it will be a complete model that’s translatable from one area to another, but I would hope we could understand what the key factors are that you need to know in a particular area”—in order to arrive at the best package of malaria control interventions.

While investigations mature under the ICEMR grant, one thing is already clear to JHMRI’ers and Phil Thuma: The man’s mission can and will go on, perhaps long after he’s hung up his shingle. “He’s created capacity building,” Peter Agre says of Thuma’s little miracle in the middle of nowhere. Agre believes that Thuma’s model may convince Zambian health officials to go where they’ve rarely gone before: accelerating an academic track for homegrown PhD-level researchers—who bring a passion that comes from personal awareness of the devastating disease—and making sure they get paid a reasonable wage.

That’s the type of passion Phil Thuma can understand. Outsiders may see him as unique, but he insists he’s not. Well, maybe a little. “I’m like Don Quixote. I tilt at windmills. If there’s a problem, I’ll invest myself and work hard at it,” says Thuma. “I was raised by my Dad, who said, ‘You need to leave the world a better place.’” Somewhere, you have to believe Alvan Thuma is smiling.

RUNNING RINGS AROUND MALARIA

On the surface, malaria, especially during the southern Zambian rainy season when mosquitoes breed, appears to strike at random.

“There’s so much variability in transmission of malaria in and around Macha,” says Greg Glass, PhD, professor of Molecular Microbiology and Immunology. “In some areas, 20 percent of the people are infected. But if you move a kilometer down the road, maybe only 1 percent are affected.”

Yet it’s by studying that very surface—the topography of Macha—that Glass’ team hopes to show that there are organizing factors behind malaria outbreaks, characteristics that may allow researchers to discern and treat the area’s most vulnerable populations. Utilizing digital technology, Glass and his researchers, notably postdoc Julie Cleennon (now at Emory University), are creating elegant satellite maps that meld the work of several disciplines to create precise zones where malaria-carrying mosquitoes are most likely to reproduce and raise the risk of infection.

Building on the discoveries of researchers such as entomologist Doug Norris, who helped determine the types of breeding pools and foraging habits preferred by Anopheles arabiensis, the dominant malaria mosquito vector in Macha, Glass’ team developed hydrological models to show where water will flow and pool.

By integrating their findings with geographical information system (GIS) data—which show exactly where people live and work in the area, and how far vector mosquitoes are likely to fly to feed on humans (Glass’ group discovered the magic number is approximately 450 meters)—it becomes possible to create concentric rings around the breeding pools.

Glass says these colorful maps and rings can serve two control purposes: On the mosquito front, health ministries can attack breeding pools with targeted, cost-effective spraying programs that eliminate larvae prior to the rainy season. As for treating people, Glass says, “we’re trying to supply researchers with an approach that says ‘here’s a way to do an epidemiological study, integrated with characteristics of the environment, to be able to identify who is likely to be in need of bed nets, ACT (artemisinin-based combination therapy), indoor residual spraying, rapid diagnostic tests,’ and to give administrators the tools to know how many doses of each they’re going to need.”

While the effectiveness of the maps is still being determined, Glass is optimistic about both their effectiveness and the ability of Hopkins to apply them to mosquito-ravaged areas such as the Democratic Republic of Congo.

“One of the great things about this School is that, if we can show that this approach works, there are whole departments here that are designed to scale this up to a point where it can make an impact on a huge portion of the world’s population. To me, that’s intriguing and exciting.”

—ME