Bite to the future – studying malaria at Emory

What do time travel, self-repairing homes and Emory's malaria research program have in common? The answer: they're all funded by the US military.

The Defense Advanced Research Project Agency (DARPA) is an agency within the Department of Defense, one that focuses on adapting emerging technologies for the military. It awarded $6.4 million to several Atlanta institutions in 2016 as part of a 3-year contract into understanding malaria resilience.

Malaria research at Emory is focused around the Malaria Host-Pathogen Interaction Center (MaHPIC, pronounced *may-pick*). MaHPIC was established in 2012 with a 5 -year NIH contract. The Center uses systems biology to gather large quantities of data about the progression of malarial infections. Its multidisciplinary investigators come from Emory, Georgia Tech, and the Center for Disease Control (CDC) as well as from universities around the country. Mary Galinski was principal investigator on the initial MaHPIC contract. In addition to her role as center director, she is a Professor of Medicine, Infectious Diseases and Global Health at Emory University.

"Using systems biology approaches we gather all kinds of data in the course of what might be a 100-day infection," she explains. This includes temperature fluctuations and the changing concentration of metabolites and parasites in the blood. "What really makes MaHPIC special in being able to bring all these different kinds of systems data together is the involvement of computational biologists and mathematicians who come up with computer methods and mathematical tools to figure out how to relate all these different kinds of diverse information."

Being supported through a large broadly-defined contract rather than grants allows MaHPIC researchers to explore without feeling to narrow research goals. The MaHPIC website lists 36 peer-reviewed publications resulting from the Center to date.

Postdoctoral scientist Chet Joyner works under the auspices of MaHPIC, looking at the immune responses provoked by malarial infection. There are several malaria species that infect humans and primates. Joyner spent his PhD looking at *Plasmodium vivax*. "When it infects you it goes to your liver like all other malaria parasites do, however unlike the others it can leave the dormant form called hypnozoite. Those hypnozoites are capable of coming out of the dormant state after you've been cleared of your initial infection and caus what we call the relapsing infection." He investigated how relapsing and initial infections produced different immune responses from the host. The presence of non-malaria experts at Emory helped his career almost as much as the experts. "They ask questions that are basic but you didn't think about, and that to me is when you really start to have the great breakthroughs."

Another benefit of MaHPIC is its proximity to the Yerkes National Primate Research Center. Most of the data generated at MaHPIC comes from studying malaria in non-human primates. Although humans and primates get infected by different malaria strains and are therefore not totally comparable, Galinski sees merit in nonhuman primate malaria models. "We would have ongoing infections of nonhuman primates and we would follow those monkeys as if they were human beings, but in humans you have to treat people, you cannot do infections like this." The equivalent human parasites don't last long enough for a comprehensive 100-day study.

What was once 'monkey malaria' can later become 'human malaria'. "Another malaria species we use frequently is called *Plasmodium knowlesi*. And this has been known as a monkey malaria parasite that is naturally found in Southeast Asia. But it's been making its way into the human population," Galinski said.

Long-tailed macaques have evolved resistance to the *P. knowlesi* malaria strain | https://en.wikipedia.org/wiki/Crab-eating_macaque

The mutability of malaria is one reason why the disease is not a 'solved problem'. As Joyner explains, basic research into the mechanics of malaria infection is still needed.

"Malaria is one of the big 3 – HIV, TB and malaria. It gets a lot of attention," Joyner states. "We do have funding, but compared to HIV its minimal."

Galinski agrees with this assessment. "We have to keep beating the drum, making our case because [malaria isn't an epidemic] here in the US, but it certainly is important for people who do leave the country or when people return."

Joyner adds, "The scary thing that's happened now is we've started seeing emergence of resistance - in Southeast Asia what they've called 'superbug malaria' that are resistant to many of the frontline treatments." *(Continued on next page)*

After the NIH contract expired in 2017, MaHPIC secured new funds from DARPA and transmuted in a new direction. The current DARPA-funded project at Emory investigates 'host-directed therapies'. As Galinksi summarizes it: "When someone has malaria what can you give them to make them feel better and function, without necessarily killing off the parasite?"

Such a therapy would allow infected military personnel to continue performing their duties in the field. Civilians could use it to buy time and reach a clinic after the onset of symptoms.

Rhesus monkeys lack resistance to *P. knowelsi* malaria | https://upload.wikimedia.org/wikipedia/commons/thumb/5/5e/

Inspiration comes from comparing two species of monkey – rhesus and long-tailed macaques. Galinski describes how the long-tailed macaque has evolved resilience to *Plasmodium knowlesi* infections, whereas the rhesus monkey becomes very sick because it lacks resilience. "Put the parasite in, do all the systems biology, and see what is the difference in these two monkeys?" Once that difference is characterized, it could be exploited as a therapeutic mechanism.

Although the facilities and institutional knowledge remains constant, there are notable ideological differences in how DARPA and the NIH direct research they fund. And it's not just DARPA's support of projects that appear outlandish to outsiders – efforts towards time-travel, exoskeletons, and self-repairing houses.

"When we go to DARPA for proposals they want to fund research that is close to being ready to something that can get out there in the field. The idea is: they just want it yesterday. It doesn't matter if it's half-baked, or changes the next day," Galinski explains. "They want you driving the car while you're building it! "

Claire L Jarvis PhD, Department of Chemistry

Reference

MaHPIC list of publications, 2018, http://www.systemsbiology.emory.edu/research/Publications/index.html