

New way to target an old foe: Malaria

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Although malaria has been eradicated in many countries, including the United States, it still infects more than 200 million people worldwide, killing nearly a million every year. In regions where malaria is endemic, people rely on preventive measures such as mosquito netting and insecticides. Existing drugs can help, but the malaria parasite is becoming resistant to many of them.

Scientists working to develop new drugs and vaccines hope to target the parasite in the earliest stages of an infection, when it quietly reproduces itself in the human [liver](#).

In a major step toward that goal, a team led by MIT researchers has now developed a way to grow [liver tissue](#) that can support the liver stage of the life cycle of the two most common species of malaria, *Plasmodium falciparum* and *Plasmodium vivax*. This system could be used to test drugs and vaccines against both species, says Sangeeta Bhatia, the John and Dorothy Wilson Professor of Health Sciences and Technology and Electrical Engineering and Computer Science at MIT.

Bhatia is the senior author of a paper describing the liver-tissue system in the July 17 issue of the journal *Cell Host & Microbe*. The paper's lead author is Sandra March, a research scientist in Bhatia's lab, and scientists from the Broad Institute, Sanaria Inc. and the University of Lisbon also contributed to the research.

Reproducing infection

The malaria life cycle has several stages. Once the parasite infects a human victim, through a mosquito bite, it takes up residence in the liver. The parasite spends about a week in the liver, producing tens of thousands of copies that eventually burst free to infect blood cells. After this initial infection, *P. vivax* can lurk for weeks, months or even years, reactivating to cause another malaria bout.

So far, researchers have been able to grow *P. falciparum* in human blood and, to a certain extent, in its liver stages, but they have not been able to reliably grow *P. vivax* in either stage. *P. falciparum* has the highest malaria mortality rate, but *P. vivax* can cause debilitating, long-term infections. To eradicate malaria, drugs and vaccines that target both species will probably be needed, Bhatia says.

Bhatia—who is also a senior associate member of the Broad Institute and a member of MIT's Koch Institute for Integrative Cancer Research and Institute for Medical Engineering and Science—has previously created micropatterned surfaces on which liver tissue can be grown, surrounded by supportive cells. These engineered cells survive for up to six weeks and mimic most of the functions of liver cells in the body, including drug metabolism and production of liver proteins.

Using unique, frozen samples of *P. falciparum* obtained in collaboration with Stephen L. Hoffman and his team at Sanaria, the researchers infected healthy liver cells and observed the development of liver-stage parasites using an automated imaging system designed in collaboration with Anne Carpenter's group at the Broad Institute. This system allows them to quickly evaluate not only how much infection has occurred, but also the effects of potential drugs. They can also measure how weakened forms of the parasites, which could be used as vaccines, perform in the liver.

To test the system's usefulness, the researchers studied a *P. falciparum*

vaccine that is now in clinical trials. For a weakened, or attenuated, parasite to succeed as a vaccine, it must infect the liver and progress enough to raise an immune response, but then arrest and not reach the blood stage. The researchers showed that the [vaccine](#) now in trials does follow that trajectory.

The new system could also be used for larger-scale drug studies than previously possible, Bhatia says. Researchers now use liver cancer cells grown in the lab to study *P. falciparum* infection, but those cells have deficient drug metabolism and keep growing instead of providing a quiet home for the parasite to persist.

Seeking *P. vivax*

Obtaining enough *P. vivax* samples to test the system took several years, but the team eventually acquired samples, flown in from Thailand, India and South America. Using these samples, they were able to grow *P. vivax* in liver tissue and show that it produces small persistent parasites that appear to be dormant forms called hypnozoites.

"We don't want to call them hypnozoites yet, because nobody has a gold-standard marker for them, but we have persistent small forms that live for three weeks. So we are optimistic and doing more to wake them up again. Reactivation would be the ultimate confirmation," Bhatia says.

The researchers are now working on confirming that the *P. vivax* they grew in the liver tissue really did create hypnozoites. Once this is confirmed, they plan to start testing some candidate drugs, now in development, against *P. vivax*.

Provided by Massachusetts Institute of Technology

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