Sticky Problem

Exploring the mysteries of the malaria parasite

JOHN ABBOTT

Kirk Deitsch, PhD

Each year, 350 million to 500 million people are infected with malaria and more than a million die from it—most of them African children under five. "It's a devastating disease," says Kirk Deitsch, PhD, associate professor of microbiology and immunology, "and to fight it we need a better understanding of the basic molecular and cellular biology of malaria parasites and how they interact with their human and insect hosts."

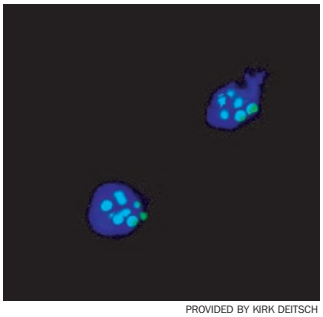
Deitsch has devoted his career to studying how *Plasmodium falciparum*—the protozoan parasite that causes most severe malaria infections—dodges the human immune response. In collaboration with colleagues in pharmacology and microbiology, he also investigates mechanisms of drug resistance and works to develop new antimalarials.

The *P. falciparum* parasites are transmitted to humans via the bite of an infected mosquito. After they first multiply in the liver, the parasites invade and destroy red blood cells, causing symptoms such as anemia and fever. The parasite places a protein called PfEMP1 on the surface of the infected red cells so they become cytoadherent (or "sticky") and cling to the walls of blood vessels; this prevents the bloodstream from carrying the infected cells to the spleen, where they'd be filtered out.

With time, the immune system begins producing antibodies against the protein and destroying the parasites—but a small number of them change the sticky protein they're placing on the surface of infected cells. This process, known as antigenic vari-

ation, lets them avoid the immune response and maintain infection. "Over the length of an infection, you'll see waves in which parasites are getting wiped out and then new populations are arising that express a different protein on the surface," says Deitsch, winner of a 2002 Presidential Early Career Award in Science and Engineering.

The parasite owes its ability to outsmart the immune system to a family of genes called *var*. Within its genome, each parasite contains up to sixty *var* genes. Only one is expressed at a time, determining which protein is displayed on the surface of the infected red blood cell. Deitsch's research focuses on how the parasite coordinates that expression. "It's one of the most fascinating puzzles in all of genetics," he says.



PROVIDED BY KIRK DEITSCH

Gene pool: *Var* genes are highlighted within the nuclei of two malaria parasites.

After completing his doctorate in genetics at Michigan State in 1994, Deitsch spent five years as a postdoc under Thomas Wellems, MD, PhD, in the Laboratory of Parasitic Diseases at the National Institutes of Health. Wellems and his team had recently discovered *var* genes, and his work with Deitsch resulted in the discovery of the two primary DNA elements that control their regulation. In a paper published in *Nature* in 2001, they described how one of the elements sits upstream of each gene along the chromosome and the other sits in the intron (or non-coding section) of each gene; they work together to silence expression of all but one *var* gene at a time. Since joining the Weill Cornell faculty in 2001, Deitsch has continued to explore how those elements interact.

Deitsch and his team have created transgenic parasites that have several *var* genes "on" at one time, as well as parasites with *var* genes that do not encode for the sticky protein. This has allowed them to identify many of the DNA sequences that control how parasites express only a single *var* gene at a time. "By continuing to dissect this regulatory process, we might be able to discover ways to disrupt it," says Deitsch, "and ultimately interfere with the parasite's ability to cause disease." Recently, Deitsch published a paper on a new methodology for controlling the level of expression of a gene that is inserted into the parasite. With colleagues at Weill Cornell and Notre Dame, he is using this technique to find out if over-expression of particular genes plays a role in drug resistance. "Since malaria parasites develop resistance to antimalarial drugs over time and effective vaccines have yet to be developed, we'll always need new drugs in the pipeline," says Deitsch.

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Pharmacology professors Lonny Levin, PhD, and Jochen Buck, MD, PhD, are working with Deitsch to develop inhibitors of an enzyme that the parasite uses to sense changes in pH and carbon dioxide levels; when the enzyme is inhibited, the parasite fails to replicate and eventually dies. Deitsch is also collaborating with associate professor of pharmacology Anthony Sauve, PhD, to investigate proteins that modify the structure of chromatin (the combination of DNA, RNA, and proteins in the cell's nucleus) and are important for *var* gene regulation. Deitsch cloned the version of the protein found in malaria parasites and gave it to Sauve, who is using it as a target for drug development.

Deitsch is also interested in strategies to prevent malaria during pregnancy. Expectant mothers are particularly vulnerable to the disease, which increases risk of premature delivery, miscarriage, stillbirth, and low birth weight. A gene called *var2csa* is present in all malaria parasites but is expressed only by those infecting pregnant women, adhering to the placenta. Scientists had long wondered why the gene is never expressed in men or in women who are not pregnant. Recently, Borko Amulic, PhD '09, and Deitsch found that *var2csa* has an extra level of regulation; when the parasite is not infecting a pregnant woman, this regulatory element prevents expression of the gene. "If we could work out the mechanism for keeping that gene silent when you're not pregnant," Deitsch says, "perhaps we could switch it 'on,' so women could make natural immunity and would never get placental malaria." He notes that several groups are currently working on developing a vaccine against pregnancy-associated malaria that is targeted to the protein encoded by this gene.

In the future, Deitsch hopes to study gene regulation in other protozoan parasites such as toxoplasma, cryptosporidium, and babesia. "These important pathogens share many basic biological processes," he says, "so discoveries we make while studying malaria parasites are likely to be applicable to them as well."

— Jen Uscher