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## Proteins Take on New Roles in Malaria Parasite

While searching for new targets for malaria drugs and vaccines, a team including a Howard Hughes Medical Institute (HHMI) medical student fellow reached a fundamental insight about evolution: different species make use of similar sets of proteins in different ways.

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"We've observed that organisms may share many similar proteins and yet retain very little parallel function among them," said Taylor Sittler, a medical student at the University of Massachusetts Medical School in Worcester, Massachusetts. "For instance, *Plasmodium falciparum* —the parasite that causes malaria—shares with its human host many proteins involved in forming chromosomes during cell division, but those proteins may interact in different ways, creating different cellular pathways and even entirely different functions. This contradicts the currently accepted paradigm that shared proteins interact simply because their genes are conserved. It was quite unexpected," he added.

Malaria is the third leading cause of infectious disease death in the world, after tuberculosis and AIDS. The World Health Organization estimates the parasite causes acute illness in some 300 million people each year, resulting in about 2.7 million deaths.

Sittler, who conducted the research during his HHMI fellowship year at the University of California at San Diego (UCSD), is co-first author on a paper published in the November 3, 2005, issue of the journal *Nature*. The paper was co-authored by two UCSD colleagues, Silpa Suthram, a Ph.D. candidate in bioinformatics, and Trey Ideker, an assistant professor of bioengineering.

The team made the discovery while comparing protein networks of *P. falciparum* to protein networks in four model organisms: yeast, fruit flies, roundworms, and *Helicobacter pylori*, the bacteria that causes stomach

ulcers. Their analysis drew on data developed by HHMI investigator Stanley Fields, a professor of genetics and yeast genome expert at the University of Washington in Seattle, and published in the same issue of *Nature*.

The discovery showcases the burgeoning power of proteomics, the systematic study of proteins. If the genes of an organism comprise its blueprint, then proteins are the lumber, shingles, and other building materials. Proteomics researchers study how proteins—which are the largest biological molecules—hold the cell together, communicate with other cells, process nutrients into energy, and carry out various other jobs. By comparing proteins in different organisms, researchers can identify each protein within cellular pathways. In the case of disease-causing organisms, this can lead to new ideas about how to disarm the pathogen.

Sittler and colleagues at UCSD, where he earned a master's degree in bioengineering, developed a data-mining tool called PathBlast to help speed up the comparison of proteins. Instead of comparing single proteins from different organisms, PathBlast compares entire networks of proteins. While single proteins perform specific tasks, organisms need networks of proteins to accomplish complicated jobs, such as cell division or, in the case of the *Plasmodium* parasite, host invasion.

Sittler explained the value of protein network analysis: “If you know certain proteins are involved in the invasion of red blood cells”—something that *Plasmodium* excels at in humans—“you can surmise that proteins interacting with those proteins are also involved in invading red blood cells.”

Or, as co-first author Suthram put it: “Protein interaction analysis gives you a second source of information about the organism. Now you can compare both the DNA sequence and the protein networks. That's what PathBlast does.”

Scientists understand the function of very few protein networks, in part because proteomics is a relatively new field. Sittler and his colleagues developed PathBlast to help fill some of the gaps. As it sifts through thousands of protein interactions, PathBlast highlights the networks in one organism that appear similar to those of another. Researchers call these “conserved networks.”

Using PathBlast, Sittler and his colleagues looked for conserved networks between *P. falciparum* and the four model organisms, expecting to find hints about how the parasite operates. “We were hoping to find some proteins that would be excellent targets for vaccines or new pharmaceuticals,” said Sittler.

Instead, they discovered that *P. falciparum* is very different from the other organisms. It shares only three protein networks with yeast and none with the fruit fly, roundworm, or ulcer-causing bacteria. In contrast, yeast and the fruit fly share 61 protein networks.

“What this points to is that protein function can change, sometimes dramatically, with a relatively small change in DNA sequence,” said Sittler. “You can change a few base pairs, and the protein might take on an entirely

different role.” Or, expanding on the construction analogy, “a nail simply has to develop a bend, and all of a sudden you have a hook.”

“This is an important paper,” said Joseph Vinetz, a systems biologist at UCSD and former HHMI-NIH research scholar who studies malaria in the lab and in the field, in Peru. “It shows that *Plasmodium* can be used to learn about underlying biological mechanisms, just like other model organisms.”

From earlier studies that compared the genome of *P. falciparum* to that of other species, scientists already knew that the parasite is an evolutionary oddball—more than 60 percent of its 5,334 proteins are not found in other organisms. But, Sittler found, the degree of protein network conservation is even smaller. “We expected *Plasmodium* to be different. It's part of a group of organisms, obligate parasites, that are different from bacteria and from all other multi-cellular organisms,” he said. “But statistically speaking, when we started looking at the protein networks, the degree of dissimilarity went far beyond what we expected.”

However, one of the protein networks that *P. falciparum* does share with yeast—a complex involved in cell invasion—may, in the end, help the team reach their original goal. “We identified one *Plasmodium* complex that may be pivotal for a better understanding of the mechanism of action of drugs that treat malaria and provide protein targets for new pharmaceuticals,” said Sittler.