Using Brewers Yeast to Fight Malaria

Jacques Kessl, Benjamin Lange, and David Blank, working in the research laboratory of Professor Bernard Trumpower in the Biochemistry Department of Dartmouth Medical School, are using brewers yeast in a research project aimed at developing new treatments for malaria. Up to half a billion people in the world suffer from malaria with various degrees of severity. The disease kills more than 2.7 million people a year, most of them children under 5 years old in sub-Saharan Africa (1). During the past 3 decades, Plasmodium falciparum, the mosquito-borne parasite that causes malaria, has developed resistance to almost every commonly available antimalarial drug, including chloroquine, pyrimethamine, cycloganil, and sulfadoxine. Because some of these molecules are now almost useless in many parts of the world, the rapid spread of resistant parasites is a serious global health problem in endemic countries. The urgent need for new antimalarial drugs for treatment and prophylaxis has led to the development of atovaquone (Fig. 1).

![Figure 1: The anti malaria drug atovaquone.](image)

In a recently published article that was featured on the cover of the Journal of Biological Chemistry, Dr. Kessl and his colleagues have described how atovaquone is a potent and specific inhibitor of the cytochrome $bc_1$ complex (2). The $bc_1$ complex is an
essential respiratory enzyme present in mitochondria, an organelle responsible for energy production in cells. This drug was FDA approved in 1995 and is now distributed by GlaxoSmithKline under the trade name of Malarone®. Unfortunately, there is recent evidence that malarial parasites may develop resistance to this drug by mutations in the cytochrome b gene that prevent atovaquone from acting on the bc₁ complex (3).

It is not possible to grow malaria parasites in the large quantities necessary to isolate and study the cytochrome bc₁ complex, and even if possible, it would be dangerous to do so. The cytochrome bc₁ complex of brewer's yeast is also inhibited by atovaquone and the yeast cytochrome b is very similar to that of the malaria parasite. The Trumpower research group reasoned that it might be possible to use yeast as a surrogate in which to study the mutations that confer atovaquone resistance in malaria.

Figure 2: Atovaquone (ATV) bound to the yeast cytochrome bc₁ complex.
The researchers were able to transfer genetically into the yeast cytochrome \( b \) mutations like those found in the atovaquone resistant parasites. They found that these mutations caused the yeast to acquire resistance to atovaquone like the malaria parasites. This allowed them to isolate the cytochrome \( bc_1 \) complex with the mutations from the genetically modified, atovaquone resistant yeast. Using the known structure of the yeast cytochrome \( bc_1 \) complex it was possible to apply computerized modeling techniques to show how atovaquone interacts with the cytochrome \( bc_1 \) complex (Fig. 2). The DMS researchers were thus able to visualize the molecular changes in the malaria parasites that counter the effects of this new drug. The ability to visualize the interaction of the anti-malarial drug with its target allows the Trumpower research team to understand how the resistance mutations change the interaction of the drug with the parasite target. As the genetically modified yeast strains now display atovaquone resistance identical to that found in malaria, these yeast can be used to design new anti-malarial drugs with features making the appearance of resistance more unlikely.