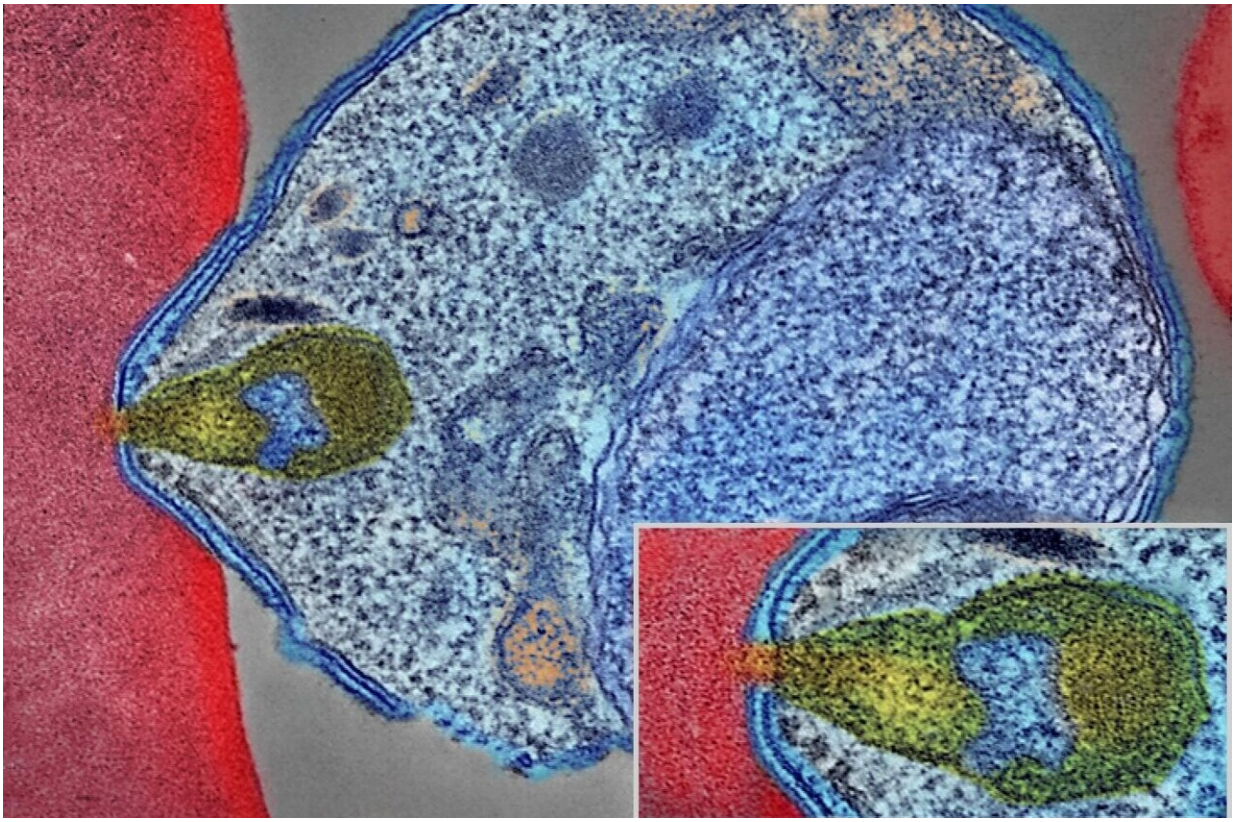
How a cancer drug could be repurposed to fight malaria-causing parasites

October 13 2022, by Mohamed-Ali Hakimi



Colorized electron micrograph showing malaria parasite (right, blue) attaching to a human red blood cell. The inset shows a detail of the attachment point at higher magnification. Credit: NIAID

Malaria is caused by the parasite Plasmodium falciparum, which is transmitted by mosquitos. The World Health Organization (WHO)

estimates that in 2020, there were 241 million cases and 627,000 deaths worldwide, 94% of cases and 96% of deaths occur in sub-Saharan Africa. Tragically, malaria claims the life of a child under the age of five every minute.

As mosquito habitats have expanded with global warming, people are more likely to contract the malaria parasite. The WHO advises vector control to reduce the number of mosquitos and so lessen the likelihood of mosquito bites, as well as chemoprevention to prevent illness in the absence of an effective vaccine.

The parasite Toxoplasma gondii, a close cousin of Plasmodium, infects 2 billion people worldwide and is the cause of the foodborne illness toxoplasmosis. Babies and persons with compromised immune systems, such as those with AIDS or cancer, are more vulnerable to the disease. Studies also suggest that Toxoplasma parasites have long-term effects on a person's personality and behavior due to their ability to nest in the human brain, and they may play a role in schizophrenia and bipolar disorder.

Despite the tireless efforts of scientists to eradicate these two parasite-borne diseases, the drugs currently available to treat them are suboptimal, and few alternatives exist, if any.

Undesirable side effects

Treatment for toxoplasmosis often has serious side effects such as liver toxicity and suppression of the bone marrow, which is involved in the production of blood cells, putting immunocompromised individuals at even greater risk. In addition, there are no drugs that can kill Toxoplasma when the parasite establishes itself as a latent infection in the muscle and brain. Even when drugs do exist, cost can be a factor—one option, Daraprim, made news in 2015 after Turing

Pharmaceuticals hiked the price from $13.50 to $750 per tablet in the United States, threatening access for vulnerable patients.

In places where malaria is endemic, artemisinin-based combination therapies (ACTs) are now the first-line treatments. Artemisinin is a plant extract that originated in traditional Chinese herbal therapy and was first synthesized by Dr. Tu Youyou, who received the 2015 Nobel Prize. However, a major worry is the spread of resistance to both artemisinin and alternative drug combinations, initially in south-east Asia and recently in Rwanda and Uganda. Resistance occurs when a medication loses its potency and can no longer completely cure the infection it was designed to treat.

A drug-development strategy that can save significant time and money in the "repurposing" of treatments initially approved for other illnesses or conditions. A well-known example is Sildenafil, originally developed to treat chest pain caused by coronary artery disease. While it failed clinical trials, scientists discovered that one of the drug's side effects was erection, and it was purposed as Viagra, which treats erectile dysfunction. As researchers raced to develop COVID-19 therapies, drug repurposing received a lot of attention.

Fighting parasites with a new drug

Our team just achieved a scientific breakthrough with the discovery of a new drug against parasites, altiratinib. Originally developed to treat glioblastoma, an aggressive brain cancer, we determined that altiratinib has potent parasiticidal activity against toxoplasma. Altiratinib is also active against Eimeria and Neospora, two parasites of veterinary importance that cause significant economic losses in livestock.

When discussing drugs, scientists often use the term "mechanism of action" (MOA) to describe what the drug actually does in the body. To

better understand how altiratinib works in the parasite, identifying its "target" is the holy grail. Using cutting-edge genetics, we determined that altiratinib's main target was a kinase—an enzyme that chemically modifies other molecules and in doing so regulates their biological activity. In Toxoplasma, the kinase is known as PRP4K, while in Plasmodium it's referred to as CLK3.

Most cell functions are performed by proteins, which are large and complex molecules. The information that allows cells to manufacture proteins is contained in the DNA. The production of a given protein starts with the transcription (i.e., the "copy") of the corresponding gene into an immature messenger RNA molecule (mRNA).

Immature mRNA is a "work in progress," similar to a rough sketch that needs to be polished. In a second step, the mRNA will undergo a process named "splicing." Enzymes will remove the unnecessary parts of the immature mRNA molecule, like tailors touching up a piece of clothing. The resulting "matured" mRNA can be seen as the "final sketch" that will be used for protein production. If something goes wrong during splicing, the resulting protein may not work as intended, or may not work at all.

The kinase PRP4K is one of the "tailors" involved in this splicing step. Its inhibition by altiratinib disrupts the splicing of the parasite on a genome-wide level, leading to chaos in protein production and death of the parasites.

Identification of regions of interest

Some regions of proteins interact with molecules in their environment and so are essential to their functioning. Using state-of-the-art methods, we were able to determine the region of PRP4K where chemical reactions occur and to which altiratinib binds. If the binding site is better

defined, more effective compounds can be made.

We also learned more about the multispecies malaria drug TCMDC-135051, which is not yet commercially available. It too can bind PRPK4, and because TCMDC-135051 and altiratinib have such dissimilar chemical spaces and likely work in different ways, therapies could be developed based on a combination of the two, which could theoretically limit the occurrence of resistance.

Our discovery highlights the importance of the kinase PRP4K/CLK3 as a drug target in parasites and makes altiratinib, originally developed for cancer treatment, a therapeutic option not only for the treatment of malaria, but also toxoplasmosis and parasite-prone animal diseases.

Provided by The Conversation