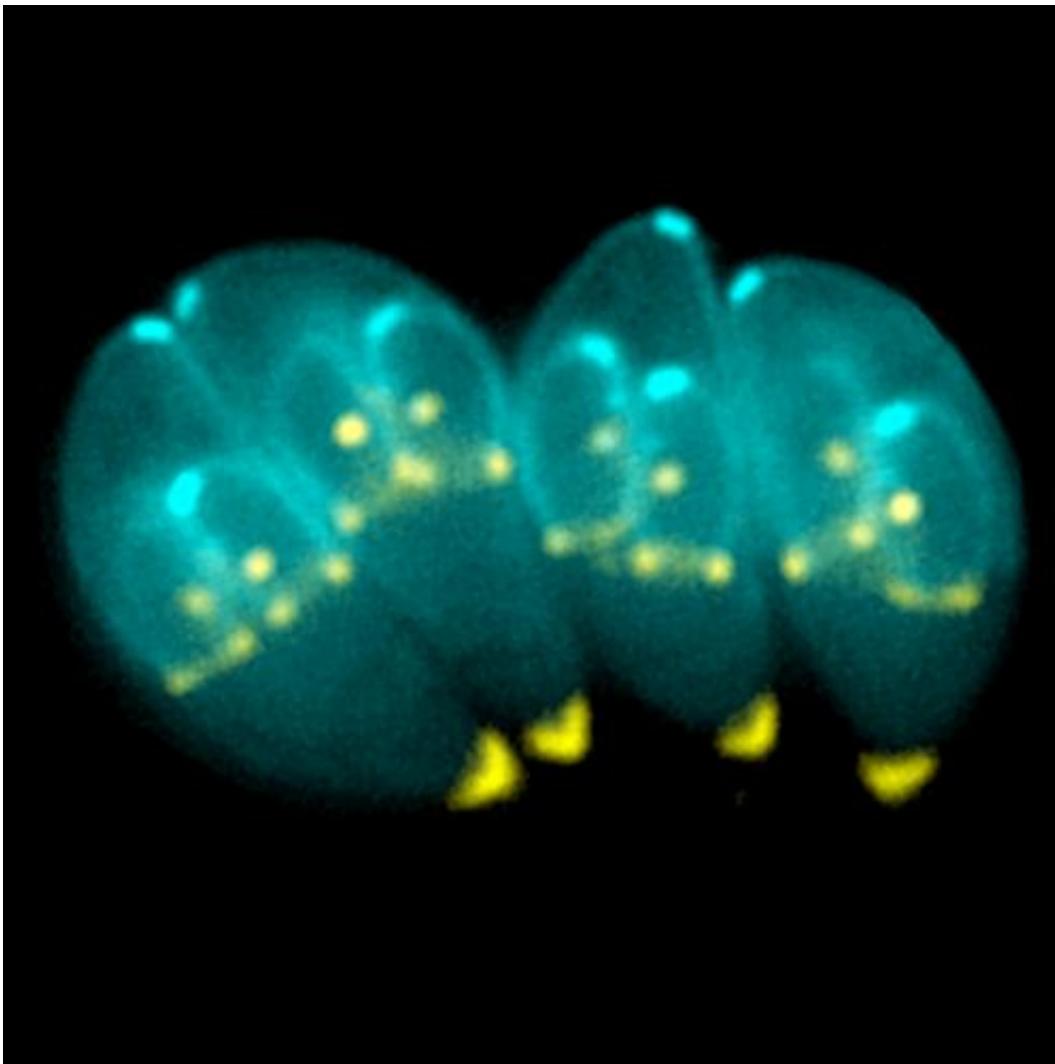


Potent tetrahydroquinolone can eliminate parasites that cause toxoplasmosis and malaria

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Toxoplasma gondii. Credit: Wikipedia

Toxoplasma gondii infection is one of the most frequent parasitic infections of humans. This parasite is present in the brain of an estimated two billion people—about 40 percent of all humans on earth. It is endemic throughout the world, causing water and food-borne epidemics that result in toxoplasmosis.

This neglected, often mistreated or untreated [infection](#), is transmitted to humans when a person eats infected undercooked meat, drinks contaminated water or is exposed to parasites in soil, usually from cat feces. Few victims recognize the exposure immediately, but the parasite causes life-long infection. It cannot presently be cured.

This disease can begin before or after birth. It can permanently damage the eyes and the brain during the initial active infection. Dormant infections can re-activate, causing severe illness or death, especially in immuno-compromised patients with cancer, autoimmune disease, AIDS or transplantation. There is no preventive vaccine.

The related tropical parasitic disease, malaria, caused by plasmodia, kills one child every 11 seconds, or about 500,000 children each year. Malaria remains an ongoing threat for travelers who visit endemic areas. Drug resistance is a significant clinical problem.

"New and improved medicines are urgently needed to prevent and cure both toxoplasmosis and malaria," said the study's senior author, Rima McLeod, MD, professor of pediatrics (infectious diseases) and ophthalmology/visual sciences at the University of Chicago Medicine and an authority on the parasite and the care of patients with toxoplasmosis.

"Many people suffer and quite a few die from these infections," she said. "Until now, no medicine has been able to eliminate the chronic, encysted form of *Toxoplasma*. But we may soon have medicines that can make a

real difference in preventing and treating active and dormant infections."

This remarkable study, "Potent Tetrahydroquinolone Eliminates Apicomplexan Parasites," to be published June 9, 2020, in the journal *Frontiers in Cellular and Infection Microbiology*, focused on the discovery and development of new, highly effective [compounds](#) against both *T. gondii* and *P. falciparum*. The researchers discovered a lead compound that can significantly reduce or eliminate toxoplasmosis as well as malaria. These compounds are highly effective against multiple drug-resistant strains of plasmodia in vitro.

The researchers were able to dramatically improve outcomes for both diseases in mouse models. There is a relatively close phylogenetic relationship. The parasites share similarities in a molecule, known as cytochrome bc1, important for energy production.

In developing this new series of compounds, "we aimed to identify a mature lead compound with both anti-plasmodium and anti-*T. gondii* activity," said organic chemist Martin McPhillie, Ph.D., at the University of Leeds (UK). His team focused on molecules with an increased percentage of 'sp³ character.' These tend to be more three-dimensional than the more rigid 'sp²-rich' counterparts. Those with greater sp³ tend to be more specific for their protein targets. They have better physicochemical properties and can accommodate bulkier substituents (atoms taking the place of another atom or group) to minimize the effects on the human enzyme.

The scientists used enzymatic, crystallographic, cryoelectron microscopy and other in vitro and in vivo conclusive empiric studies with parasites, as well as a simple but novel nano-formulation method to find compounds that reduce or eliminate toxoplasmosis and malaria. They created and tested their lead anti-apicomplexan compound, which showed promise for treatment of these infections. This led to

characterization of this compound, which revealed drug-like chemical properties. If utility and safety are retained and no toxicity appears in next-stage studies, this lead compound, known as JAG21 (named for James A. Gordon who synthesized it as a [graduate student](#)), "may be able to treat both *T. gondii* and *P. falciparum* human infections," said McLeod.

Colin Fishwick, Ph.D., dean of the Leeds School of Chemistry, and McPhillie led the team of medicinal chemists who created JAG21. Fishwick found it "absolutely stunning," that following a single, oral, low dose of JAG21, there were no surviving malarial parasites and no death of mice with otherwise lethal plasmodia infections. Mark Hickman, Ph.D., at Walter Reed Army Institute of Research, noted that JAG21 "has the potential to prevent and cure all three life-cycle stages of malaria."

Teams from The University of Strathclyde and UChicago found that their compound eliminated 100 percent of the active form and more than 95 percent of the previously untreatable encysted *Toxoplasma* parasites in mice. They also found another compound that improves efficacy of JAG21.

A few residual organisms remained after JAG21 treatment of long-established infections. UChicago scientists, working with Hernan Lorenzi at the J. Craig Venter Institute, probed for mechanisms that could eliminate potential remaining organisms. They found that different "persister stasis-like organisms" of *T. gondii*, grown in human brain stem cells, use a distinct genetic pathway to survive. This pathway has similarities to one recently identified in hypnozoites, a form of dormant plasmodia.

Such critical differences in gene expression sustain these novel life-cycle stages of *Toxoplasma*, which JAG21 can only partially inhibit in an

immune-compromised mouse model. These studies point to genes that are molecular targets for new methods to eliminate the few remaining dormant organisms. Targeting these can form the basis of a companion medicine for JAG21. "The impact of these findings will be felt," said the U.Kentucky's Anthony Sinai.

Robert Prud'homme and graduate student Kurt Ristroph at Princeton University developed a method to make an oral formulation of JAG21 that is stable for months. Ying Zhou, in the McLeod group, found that this formulation of JAG21 given orally to mice—once daily for 3 days—is highly effective, even against large amounts of extremely virulent Toxoplasma.

"JAG21," the authors agree, "has the potential to become an orally administered medicine, or part of a combination, that is curative for toxoplasmosis and is a single-dose prevention and cure for malaria." If utility and safety are retained and no toxicity appears in the next series of studies, this compound may become suitable for treatment of T. gondii and P. falciparum infections. "JAG21," the team added, "has real promise."

Provided by University of Chicago Medical Center

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