

# Antisense approach promising for treatment of parasitic infections

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A targeted approach to treating toxoplasmosis, a parasitic disease, shows early promise in test-tube and animal studies, where it prevented the parasites from making selected proteins. When tested in newly infected mice, it reduced the number of viable parasites by more than 90 percent, researchers from the University of Chicago Medicine report in the *Proceedings of the National Academy of Sciences*.

This precisely focused therapy combines short strands of "antisense" nucleic acid-like material with a small peptide that can transport those strands through cell membranes and into [parasites](#), where they disrupt genetic signals. A similar approach from a team at Yale, published in April, showed comparable promise as a treatment for the parasites that cause malaria.

"This was [proof of concept](#)," said study author Rima McLeod, MD, a toxoplasmosis expert and professor at the University of Chicago Medicine. "We were able to cross multiple membranes, to insert the antisense strands into parasites living within cells and prevent them from making several different proteins. We now think we can shut down any of this parasite's genes."

"This approach may even have a role in non-parasitic diseases," she added. It is currently being tested in [drug-eluting stents](#), as a treatment for bacterial or [viral infections](#), including [Ebola](#), and in patients with Duchenne muscular dystrophy, where it can block production of the defective segment of a dysfunctional gene.

The parasite McLeod and colleagues focused on, *Toxoplasma gondii*, is "probably the most common [parasitic infection](#) in the world," she said. "It infects as many as one-third of all humans, about two billion people worldwide." *T. gondii* causes disease in those who have immature immune systems, particularly those infected in utero. It also can be devastating for those who are immune-compromised and when it causes [eye disease](#).

"New medications are urgently needed," she said. The standard treatments can cause side effects and patients may become hypersensitive to them. There are no medicines that can eliminate certain latent stages of the parasite's life cycle. There is no vaccine for humans.

The new treatment consists of a phosphorodiamidate morpholine oligomer (PMO), a short DNA-like molecule that binds to messenger RNA, preventing it from being translated into protein. This is conjugated to a "transductive peptide," a small molecule that can ferry the PMO across cellular barriers. The combination is known as a PPMO. An earlier study from the McLeod lab showed that such transductive peptides could bring small molecules into the untreatable dormant phase of the parasite.

The researchers tested this system in infected cells in tissue culture and in live, recently infected mice. It was able to knock down production of several distinct proteins.

They first tested their PPMO against easily detectable biomarkers by inserting genes for yellow fluorescent protein and for luciferase, a protein responsible for fireflies' glow, into parasites. Then they exposed parasite-infested cells to low levels of a PPMO targeting one piece of those genes. This reduced yellow fluorescence or dimmed bioluminescence by 40 to 60 percent.

Next, they tested its ability to block production of an enzyme, dihydrofolate reductase (DHFR), that the parasite needs to make folate and to replicate. After 48 hours, DHFR production of intracellular parasites was markedly reduced. Antisense oligomers targeting another enzyme and factors that direct the activity of many genes, called "transcription factors," associated with parasite replication, "also were successful," the authors note, "reducing parasite replication."

When they tested the anti-DHFR PPMO in newly infected mice, the results were dramatic. Within 96 hours, treatment reduced the number of parasites by 83 percent to 97 percent, depending on the measurement technique.

This approach is "paradigm shifting," McLeod said. "It has the potential to abrogate any molecular target and underscores the variety of diseases for which such an approach might apply."

The technology still has a few problems, she said. These PPMOs have a narrow therapeutic index; they can be toxic at a little more than the lowest effective dose. And we have not yet developed a way to eradicate latent stages of *T. gondii*, which can lie dormant in retina or brain cells for years, but such studies are underway. The researchers hope to use this technique to awaken dormant parasites, and then use drugs or PPMOs that target replicating parasites to kill them or eliminate both active and dormant parasite stages by targeting their plant-like transcription factors and other proteins unique to the parasites that humans don't have.

Much of the credit for developing and testing this system should go to the study's lead author, McLeod said.

Bo-Shiun Lai, a 20-year-old rising fourth-year college student at the University of Chicago, stumbled into his research position in McLeod's

laboratory but adapted quickly. "Although it was difficult at the outset," he said, "everyone in the lab helped me develop the project and hone my laboratory techniques along the way."

It paid off. He completed his senior thesis as a junior, with honors, and will be applying for PhD programs.

Provided by University of Chicago Medical Center

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