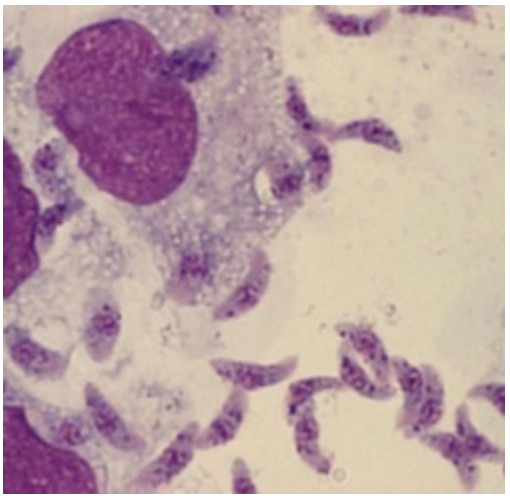
Beating a Parasite At Its Own Game

Posted on August 15, 2012 by John Easton in Infectious Disease, Microbiology



Toxoplasmosis is a parasitic disease caused by *Toxoplasma gondii*, one of the most common parasites in the world. It's often carried by cats, and people sometimes get it after cleaning out a litter box. But it can also come from eating meat from an animal that was infected. The parasite hitches a ride on our dinner and starts to do its damage inside our bodies before we know it. Treatments for toxoplasmosis can cause nasty side effects, so scientists are still looking to develop a better approach. Now researchers at the University of Chicago Medicine have figured out a way to beat the parasite at its own game by slipping a bit of DNA inside to knock it out before it knows what hit it.

This targeted approach to treating toxoplasmosis 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, the researchers report in the Proceedings of the National Academy of Sciences (http://www.pnas.org/content/early/2012/08/08/1208775109.abstract?sid=3b61340e-7595-4f6a-9750-4251feff022e).

The new 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 (http://www.uchospitals.edu/physicians/rima-mcleod.html), 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.

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Bo-Shiun Lai, William H. Witola, Kamal El Bissati, Ying Zhou, Ernest Mui, Alina Fomovska, & Rima McLeod (2012). Molecular target validation, antimicrobial delivery, and potential treatment of Toxoplasma gondii infections *Proceedings of the National Academy of Sciences* DOI: 10.1073/pnas.1208775109 (http://dx.doi.org/10.1073/pnas.1208775109)

- toxoplasmosis

4 Comments on Beating a Parasite At Its Own Game

1. *Sara* // *August 16, 2012 at 11:24 am* //
   The studies are good, but people like Dr. Hulda Clark have already proven the connection between parasites and all diseases like cancer. If researchers were just able to come the realization that not all the answers lie in drugs and chemicals in treating human beings.
   Would you right about some of the natural cures and remedies for disease?
   Thanks Matt!

2. *Sara* // *August 16, 2012 at 11:25 am* //
   Sorry Matt… I meant WRITE… (I feel like I'm texting…)

3. *Matt Wood* // *August 16, 2012 at 2:29 pm* //
   Here's one you might like then, using an extract from beehives to treat cancer:

   https://sciencelife.uchospitals.edu/2012/05/04/from-beehives-to-prostate-cancer-treatment/

4. *hitbadly* // *August 17, 2012 at 6:07 pm* //
   a couple of years ago, when I would't know about Toxoplasmosis I underwent a iodine-131 (radioiodine) therapy for thyroid treatment. It helped so much, but after a few weeks the effect was gone.

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