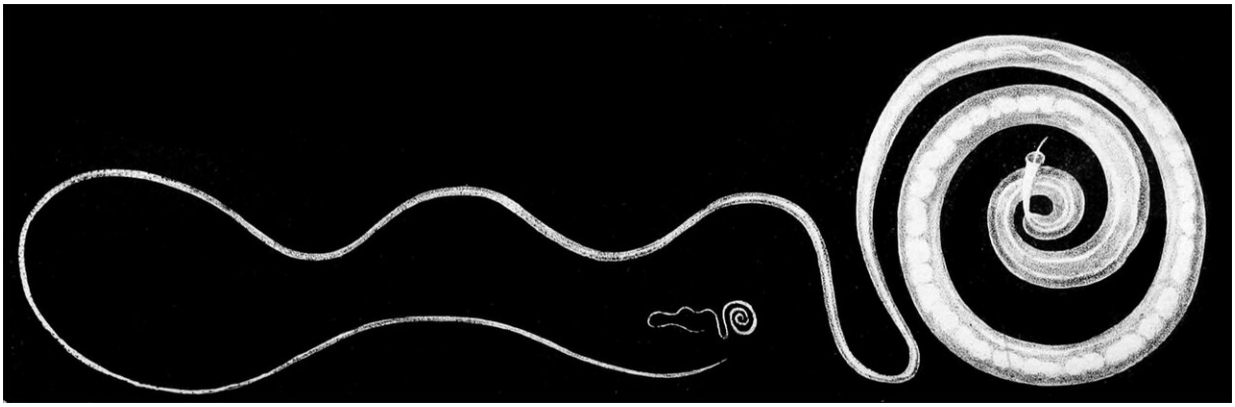
Airless worms: A new hope against drug-resistant parasites

July 2 2019



Parasitic nematodes, such as whipworms and hookworms, disproportionately affect developing nations with more than one billion people suffering from infections that can cause lasting damage and can also be lethal. This illustration of a whipworm is from an 1830 French zoology textbook. Credit: WikiMedia Commons

Over one billion people, including 880 million children, are infected with intestinal nematode worms, such as roundworms, hookworms and tapeworms, according to the World Health Organization. The infections are especially common in the developing world due to a lack of clean water and sanitation. If left untreated, they can leave a lasting mark on health and can also be lethal.

"We serendipitously discovered a new way to kill these parasites without

harming the human host," says Andy Fraser, a professor of molecular genetics in the Donnelly Centre for Cellular and Biomolecular Research at the University of Toronto.

"These parasites pose a major global health burden and as their resistance to the available drugs continues to grow, so does the need to develop new therapies," he says.

The work was led by three graduate students, Samantha Del Borrello, Margot Lautens and Kathleen Dolan, and in collaboration with Amy Caudy, also a professor of molecular genetics in the Donnelly Centre. Their findings are described in a study published online in *eLife*, an open-access journal.

Fraser's team were testing their new method for unpicking how drugs affect the movement of a nonparasitic nematode, *Caenorhabditis elegans*, used as a stand-in for humans by researchers across the world. But a fluke finding prompted them to use this lab worm as a model for parasites instead.

The first drug they tried was cyanide because its effects are well known and they wanted to make sure the new system works. Cyanide blocks respiration and, as expected, when added to the lab dish containing the worms, it quickly paralyzed them. But to the researchers' surprise, the worms did not die. They resumed wriggling about as if nothing happened when the drug was washed out 24 hours later.

"Our worms were clearly doing something very different to everything we knew about respiration in other animals," says Del Borrello.

It turned out that the cyanide made the worms switch to another, unusual form of metabolism that makes energy without needing oxygen. This type of anaerobic metabolism has been known to occur in parasitic

worms, allowing them to survive for long periods of time in the airless confines of the gut. Instead of oxygen, these parasites rewire their metabolism to produce energy using a molecule called rhodoquinone, or RQ.

Crucially, humans do not make RQ. That makes it a perfect target for drug development because the drugs will selectively kill the parasites without touching their human host.

Having tricked the lab worm into making energy like a parasite, the team could now apply all the genetic and molecular tools that have been developed for *C. elegans* to begin to work out how RQ is made. This has remained an outstanding question in a field that has seen little progress since RQ was first discovered 50 years ago in parasitic worms, for which such tools still do not exist.

But first, they needed oysters. Oysters, and other coastal mollusks, are among the few organisms beside the nematodes that produce RQ, probably as an adaptation to changing oxygen levels brought about by tide turns. Because RQ is not commercially available, Dolan had to extract it from the oysters she bought at the store and use it to optimize the mass spectrometry instrument that was later used to detect RQ in worms.

Then began the hunt for the genes responsible. They tested about 80 different mutant worm strains before finding one unable to make the molecule—and thus unable to survive in cyanide— indicating that the mutated gene is required for RQ biosynthesis. The gene, called *kynu-1* (pronounced as 'kai-noo 1') turned out to code for an enzyme that carries out an early step in RQ synthesis. This finding upended widely accepted ideas about how RQ is made. Most importantly, it also showed them clear ways to try to block RQ synthesis with drugs.

Del Borello is now testing thousands of compounds to find candidates that kill *C.elegans* when it's using RQ and which could be developed into new drugs against parasites.

"It's great that we figured out the science behind it, but what I am most excited about is finding drugs that target the RQ-dependent metabolism," she says. "We haven't reached the tipping point quite yet in terms of drug resistance, but we also don't have anything in the pipeline to help out when we do."

They already have several promising candidates, which will next be tested on animals, such as mice and sheep, before moving on to human trials. But even if a drug for livestock could be found, it would help save agricultural industry billions of dollars estimated to be lost from lower productivity that is caused by nematode infections in farm animals.

From testing new equipment to solving parasite metabolism, the way the project turned out took everyone by surprise. "This was not at all what we expected when we started out," says Lautens who credits the whole team for their success. "That we've been able to contribute to a field that has not seen much progress in many years is a testament to how hard everyone's been working on it with a lot of different perspectives."

More information: Samantha Del Borrello et al, Rhodoquinone biosynthesis in C.elegans requires precursors generated by the kynurenine pathway, *eLife* (2019). DOI: 10.7554/eLife.48165

Provided by University of Toronto