Modelling parasitic worm metabolism suggests strategy for developing new drugs against infection

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Scientists have revealed a way to eradicate parasitic worms by stopping them from using alternative metabolism pathways provided by bacteria

that live within them, according to new findings published today in *eLife*.

The study has identified three potential drugs that are active against the parasitic worm Brugia malayi (B. malayi), a leading cause of disability in the developing world.

Latest figures from 2015 suggest an estimated 40 million people in the world have lymphatic filariasis (elephantiatis) caused by worms such as B. malayi, with an estimated one billion people at risk. Current prevention and treatment efforts rely on a small selection of drugs, but these have limited effectiveness and must be taken for 15 years, and there is an emerging threat of drug resistance.

"One alternative strategy for preventing lymphatic filariasis has been to use traditional antibiotics to target bacteria that live within most filarial worms," explains lead author David Curran, Research Associate at the Hospital for Sick Children (SickKids) in Toronto, Canada. "These bacteria, from the genus Wolbachia, are specific to each worm and are known to be essential for the worms to survive and reproduce."

While targeting the Wolbachia bacteria with antibiotics is a viable strategy, Curran adds that long treatment times and the unsuitability of these antibiotics for pregnant women and children prevent their widespread use, and there remains an urgent need to identify novel targets for treatments. In this study, he and his colleagues looked at targeting both the worm and the bacteria by identifying the essential biological processes provided by the bacteria that the worm depends on.

To do this, they built a model of all the metabolic pathways that take place in the worm and in its resident bacteria. They then systematically changed different components of the model, such as oxygen levels, glucose levels, and which enzymes were activated, to see the effects on

the worm's growth. Their final model included 1,266 metabolic reactions involving 1,252 metabolites and 1,011 enzymes linked to 625 genes.

To cope with the different nutrient conditions, the worm adapted its use of different metabolic pathways—including those provided by the Wolbachia bacteria—throughout the different stages of its lifecycle. To see which of the metabolic reactions were critical for survival and reproduction, the team removed some of the possible pathways from the model. They identified 129 metabolic reactions that slowed the growth to less than 50% of the baseline level. Of these, 50 were metabolic processes provided by the Wolbachia bacteria.

Having identified these essential metabolic reactions, the team searched for drugs that could block crucial molecules involved in activating these reactions, using databases of existing drugs and their targets. They identified three drugs: fosmidomycin, an antibiotic and potential antimalarial drug; MDL-29951, a treatment being tested for epilepsy and diabetes; and tenofovir, which is approved for treating hepatitis B and HIV. These drugs reduced the numbers of Wolbachia bacteria per worm by 53%, 24% and 30%, respectively.

"We also found that two of the drugs, fosmidomycin and tenofovir, reduced the worm's reproductive ability," explains co-senior author Elodie Ghedin, previously Professor of Biology and Professor of Epidemiology at New York University, and now Senior Investigator at the National Institutes of Health, Maryland, US. "Fosmidomycin also appeared to affect movement in the worms."

"All three of the drugs tested appear to act against adult B. malayi worms by affecting the metabolism of the worms themselves or their resident bacteria," concludes co-senior author John Parkinson, Senior Scientist, Molecular Medicine program, SickKids, and Associate Professor, Biochemistry & Molecular and Medical Genetics, University of Toronto.

"This validates our model as a realistic construction of the metabolic processes in these debilitating parasites, and suggests that its use may yield further therapeutic targets with more research."

More information: David M Curran et al, Modeling the metabolic interplay between a parasitic worm and its bacterial endosymbiont allows the identification of novel drug targets, *eLife* (2020). DOI: 10.7554/eLife.51850

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