

Identifying a new target for treating schistosomiasis

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Neglected tropical diseases (NTDs) represent a group of about 20 conditions that affect more than a billion people worldwide. They are diseases of poverty that impact people living in the poorest communities

in terms of wealth, infrastructure, and access to sanitation. They take health away; and for children, their chances of staying in school and earning a living.

One of the most impactful NTDs is schistosomiasis (the 'snail fever', Bilharzia). This disease is caused by infection with [parasitic worms](#) known as schistosomes that live in the blood of their host where they lay eggs that cause tissue damage. Schistosomiasis is treated using a drug called praziquantel, discovered in the 1980s. However, for over forty years, there has not been understanding of how this drug works. This has been a roadblock to designing new therapies for both schistosomiasis as well as other diseases caused by parasitic flatworms.

In work recently published in *Science Translational Medicine*, independent teams from the Medical College of Wisconsin (MCW) and Texas Biomedical Research Institute have finally solved this mystery. Both groups of researchers converged on a protein within these worms that is activated by praziquantel to help eliminate worms from the body.

"Praziquantel is one of the most important clinical drugs that people have not heard about," says Jonathan Marchant, Ph.D., professor, MCW, senior author of one of the studies. "This is because it is a drug used to treat a neglected tropical disease, which unfortunately attracts less research and investment despite its burden on people worldwide."

Marchant's group demonstrated that praziquantel binds with high specificity to a type of ion channel, known as a transient receptor potential (TRP) channel. Activation of this worm TRP channel by praziquantel causes rapid paralysis and damage to the parasite triggering elimination of worms from the body.

By collaborating with scientists from Merck KGaA, Darmstadt, Germany, the company involved in the discovery of praziquantel, the

team mapped the binding site of praziquantel and a detailed model of the molecular interactions necessary for activating the channel was validated in Marchant's laboratory.

"Having a detailed understanding of how this drug engages this target at the molecular level provides new opportunities for drug development to help combat this debilitating disease of children" says Lukas Friedrich, co-first author of this research and scientist at Merck KGaA, Darmstadt, Germany.

This new understanding of praziquantel has already illuminated why some parasitic worms show natural insensitivity to praziquantel, while others are highly sensitive to this drug.

"Tiny variation in this binding pocket stops praziquantel from working," says Sang-Kyu Park, staff scientist, MCW, first author of this research. "We demonstrate that such variation occurs naturally in a type of parasitic flatworm that causes disease of cattle and livestock, and this may occur for schistosomiasis too, causing concern that praziquantel may stop working in the clinic."

This conclusion was reinforced by work co-published in the same issue of *Science Translational Medicine* from Tim Anderson's group from the Texas Biomedical Research Institute. The Texas Biomed group studied a population of worms that showed resistance to praziquantel exposure, applying state-of-the-art genetic analyses to identify regions within the worm's genome that underpinned this insensitivity to drug treatment. Remarkably, their analyses identified the very same TRP channel, providing independent verification of the importance of this particular target.

"We have two independent papers using completely different methods coming to the exact same conclusions," says Tim Anderson, Ph.D.,

professor, Texas Biomed, senior author of the Texas Biomed study.

"Because the papers are being published back-to-back, I think they will be taken very seriously. Research on TRP channels of mammals won the Nobel prize in Physiology or Medicine in 2021. That these channels are also involved in mode of action of a critically important antiparasitic drug is extremely exciting."

"This research will be highly impactful for treating schistosomiasis in the field", adds Thomas Spangenberg, Head of Global Health Open Innovation and Drug Discovery at the Global Health Institute of Merck KGaA, Darmstadt, Germany. "Finally understanding the mechanism of action of praziquantel will help catalyze new research that will support control and elimination programs for schistosomiasis worldwide. This is an important breakthrough."

More information: Sang-Kyu Park et al, Mechanism of praziquantel action at a parasitic flatworm ion channel, *Science Translational Medicine* (2021). [DOI: 10.1126/scitranslmed.abj5832](https://doi.org/10.1126/scitranslmed.abj5832)

Winka Le Clec'h et al, Genetic analysis of praziquantel response in schistosome parasites implicates a transient receptor potential channel, *Science Translational Medicine* (2021). [DOI: 10.1126/scitranslmed.abj9114](https://doi.org/10.1126/scitranslmed.abj9114)

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