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INFECTION

High-throughput drug screen strikes gold in the search for a new amoebiasis treatment

Auranofin—an FDA-approved gold-containing drug used as a rheumatoid arthritis treatment for 25 years—could be a promising new therapy for amoebiasis.

A collaboration led by Sharon Reed and James McKerrow overcame the challenge of working with the slow-growing anaerobic parasite *Entamoeba histolytica* to develop an automated high-throughput assay capable of screening large, diverse inhibitor libraries for amoebicidal activity.

"We solved the problems with earlier screening methods by using GasPak™ EZ Anaerobe Gas Generating Pouch Systems and an ATP-bioluminescence based assay," explains Anjan Debnath, who made the breakthrough. "Anaerobic conditions were not required during robotic transfers, making this assay fully compatible with workstation-based automation."

Screening a library of 910 FDA-approved and unapproved bioactive compounds identified 11 that were

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active against *E. histolytica*. Auranofin was the most potent (10 times more so than metronidazole).

"Based on a transcriptional profiling study, we hypothesized that *E. histolytica* thioredoxin reductase (*Eh*TrxR) is the probable target of auranofin," says Debnath. Key enzymatic assays performed on recombinant *Eh*TrxR proved the efficacy of auranofin against the enzyme.

Reed and colleagues then confirmed the activity of auranofin in amoebae *in vitro*. Finally, they used a mouse model of amoebic colitis and a hamster model of amoebic liver abscess to show that the number of parasites, host inflammatory response and hepatic damage were all markedly decreased by auranofin (at doses lower than standard metronidazole treatment).

These findings prompted the FDA to give auranofin orphan-drug status as an amoebiasis treatment, so the team will now apply for clinical trial funding from the FDA and NIH. "The ability to take these findings from the laboratory to clinical trials in only a few years would not be possible if auranofin was not a 'reprofiled' drug," concludes Reed.

Natalie J. Wood

Original article Debnath, A. *et al.* A high-throughput drug screen for *Entamoeba histolytica* identifies a new lead and target. *Nat. Med.* doi:10.1038/nm.2758