Repurposing FDA-approved drug disulfiram plus zinc supplement for treatment of parasitic infections

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New drugs are urgently needed for parasitic protozoan infections and repurposing drugs is a promising approach for the drug development process. New and emerging data support the repurposing of the FDA-approved drug disulfiram along with zinc supplement as an anti-parasitic agent (Figure 1).

The drug repurposing approach identifies new therapeutic uses for approved drugs outside of their original indication. Drug repurposing is an attractive alternative strategy because of the high failure rate, significant cost, and long time-consuming task for new drug discovery and development (Farha & Brown, 2019). Current therapies for parasitic infections are unsatisfactory due to drug resistance, toxicity, limited treatment options, and poor efficacy (Rycker et al., 2018). Therefore, new drugs are urgently needed for these infections which contribute significantly to global morbidity and mortality, and drug repurposing may help address this need.

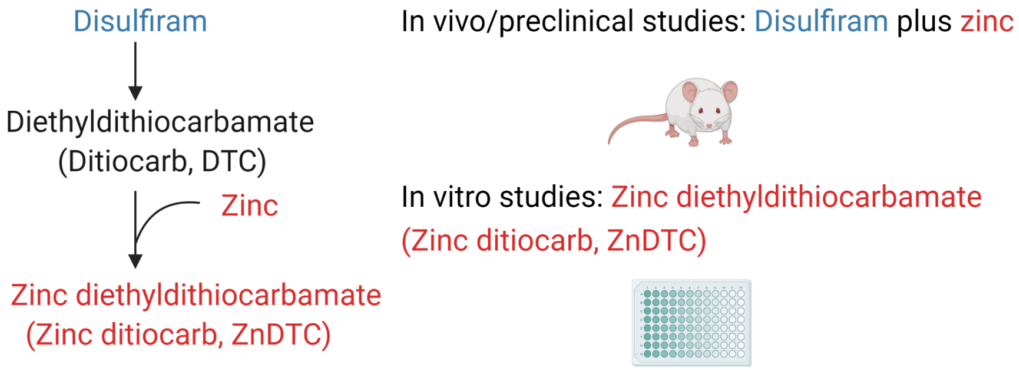

Figure 1: Illustration of how the disulfiram metabolite zinc diethyldithiocarbamate is formed. In vivo, disulfiram is rapidly metabolized to diethyldithiocarbamate (ditiocarb, DTC) which chelates with zinc to form zinc diethyldithiocarbamate complex (zinc-ditiocarb, ZnDTC).

Disulfiram is an inexpensive, globally available, orally administered, FDA-approved drug to treat alcoholism with well-established pharmacokinetic properties, safety, and tolerance. In the body, disulfiram is rapidly metabolized to diethyldithiocarbamate (ditiocarb, DTC) which in the presence of metal ions such as zinc, forms zinc diethyldithiocarbamate (zinc-ditiocarb, ZnDTC). DTC-metal complexes are more stable with a

relatively long half-life, widely distributed throughout the body and are already being repurposed for cancer therapy (Cvek, 2012)(Ekinci et al., 2019).

The ZnDTC disulfiram metabolite was found to be extremely potent against the diarrhea and liver abscess-causing parasite *Entamoeba histolytica* in in vitro studies, demonstrating 1000-fold more potency than the current drug of choice metronidazole (Ghosh et al., 2020). To safely achieve adequate levels of ZnDTC in vivo, it is given as a combination of disulfiram plus zinc. Disulfiram is converted to diethyldithiocarbamate in vivo which then complexes with zinc to generate ZnDTC, therefore, to have sufficient ZnDTC, enough zinc needs to be present to direct the metabolic pathway towards forming ZnDTC. Although in vitro studies have shown direct disulfiram activity in vitro, it is rapidly metabolized and almost does not exist in the body in its original form after ingestion. Therefore, administering disulfiram alone would be less effective. Consistent with the in vitro activity, disulfiram plus zinc gluconate was highly effective in clearing *E. histolytica* parasites in a preclinical animal model that mirrors human amebic colitis (Ghosh et al., 2020).

One drug for many bugs: The anti-parasitic activity of ZnDTC involves blocking the essential proteasomal pathway (Ghosh et al., 2020). Disruption of the proteasomal pathway prevents proteins from being degraded resulting in the accumulation of toxic unwanted protein products ultimately leading to parasite cell death. Given that this pathway is conserved in many parasites, the combination of disulfiram and zinc might have broad-spectrum activity and prove to be effective against a wide number of parasites.

The excellent safety profile, low cost, oral formulation, available worldwide combined with the recent preclinical efficacy supports further studies to explore the repurposing of the old anti-alcoholism drug disulfiram combined with zinc supplement as a new antiparasitic agent.

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