Harnessing Inhibition of Efflux to Reverse Antifungal Resistance

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Fungal pathogens pose an enormous threat to global health, and a growing number of pathogens are developing resistance to our already limited arsenal of antifungals. Overexpression of efflux pumps to expel antifungals from fungal cells is the main mechanism of antifungal resistance. This project successfully repurposed existing underexplored compounds to inhibit efflux in the clinically relevant fluconazole-resistant fungal pathogen Candida albicans, thus reversing antifungal resistance. Fluconazole is the most common antifungal used to treat Candida infections, but its activity is severely inhibited by efflux hyperactivity. This project leveraged the Medicines for Malaria Venture library to identify previously unknown efflux inhibitors to restore fluconazole activity in drug-resistant pathogens. The minimum inhibitory concentrations of promising compounds were identified and their inhibitory effects on fungal efflux were quantified. The compound cytotoxicity in human liver cells as well as activity against filamentous C. albicans to observe bioactivity in yeast and hyphal cellular morphologies were analyzed. The antiparasitic doramectin and the kinase inhibitor URMC-099-C were discovered as potent efflux inhibitors that restore fluconazole's antifungal activity. At low concentrations that still have effective efflux inhibition, doramectin was found to have minimal liver cell cytotoxicity. The compounds enhanced the ability of fluconazole to inhibit filamentation. Doramectin was found to restore fluconazole's antifungal activity in drug-resistant pathogens while maintaining low toxicity to host cells. These findings demonstrate a novel strategy to reverse antifungal resistance and combat fungal pathogens.

Awards Won:
First Award of $6,000