

Meghan Breen Research Group

The Breen lab studies the mechanisms that control drug resistance in fungi. Drug resistant fungal infections are a growing public health concern, especially among immuno-compromised populations. *Candida* species are the most common cause of opportunistic fungal infections, and in 2013 nearly 12% of *Candida glabrata* clinical isolates were resistant to first line therapies.

One way fungi develop drug resistance is through increased transcription of drug efflux pump proteins. These proteins sit within the cell membrane and expel drugs that get into the cell. As a result, the drug does not accumulate to a therapeutic level within the cell and the organism becomes drug resistant. In the human pathogen *C. glabrata* and the model organism *Saccharomyces cerevisiae* (baker's yeast), the process of making these drug efflux proteins is initiated by a transcription factor protein called Pdr1 (Figure 1). Developing drugs that disrupt the function of Pdr1 has been proposed as a way to re-sensitize drug resistant *C. glabrata* infections to existing therapeutics, but accomplishing this goal will require a detailed understanding of how Pdr1 function is controlled.

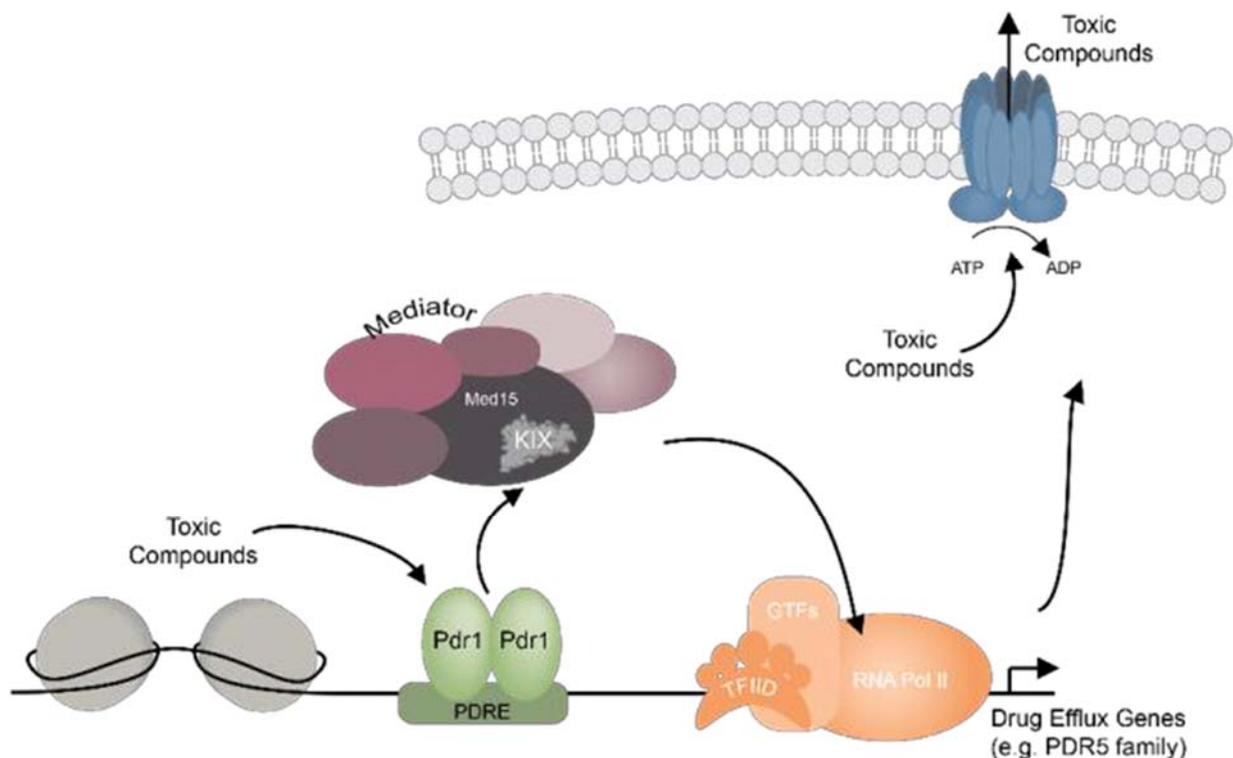


Figure: In the presence of antifungal drugs, Pdr1 binds to the DNA and turns on genes for drug efflux pump proteins.

Previous studies have shown that several phosphate groups are added to the Pdr1 protein. Adding a phosphate group to an amino acid side chain in a protein is a common way cells control the stability, location, or activity of a protein. At this point, the purpose of the phosphate groups added to Pdr1 is not known. During Summer 2020, the Breen lab will focus on two projects aiming to better understand how Pdr1 function is controlled by phosphorylation:

- 1) Evidence in the literature suggests that a protein called Pho85/Pho80 adds some of the phosphate groups to Pdr1. We will express and purify the Pho85/Pho80 protein complex, and then we will use the purified protein in enzyme kinetics assays to determine if it can add phosphate groups to short segments of the Pdr1 protein.
- 2) *S. cerevisiae* will be used as a model system to determine if certain phosphate groups are required for the Pdr1 protein to be active and initiate drug resistance. We will generate strains of *S. cerevisiae* that have a mutation in the Pdr1 gene that prevents one of the phosphate groups from being added. Then, each strain will be grown in the presence of antifungal drugs and evaluated for the drug resistance phenotype.