The rapid emergence of antifungal resistant pathogens has become a global threat to human health, resultantly increasing mortality rates and healthcare costs worldwide. *Cryptococcus neoformans*, an opportunistic yeast-like fungal pathogen, has demonstrated resistance to all major classes of antifungals used to treat cryptococcosis. Specifically, resistance is most commonly observed against fluconazole, the mainstay treatment of cryptococcosis in resource-limited settings. Following dissemination to the central nervous system, this leads to the clinical manifestation of cryptococcal meningitis and meningoencephalitis — two leading causes of morbidity and mortality in immunocompromised individuals. The limited repertoire of antifungals in clinical use has heightened the need to investigate the mechanisms underlying resistance and to identify novel strategies to combat its occurrence. However, a lack of research addressing the molecular mechanisms that give rise to fluconazole resistance in *C. neoformans* remains. My research project will use mass spectrometry-based proteomics to identify proteins that are correlated with antifungal resistance. First, fluconazole-resistant cultures of *C. neoformans* will be established in vitro. Next, a proteomic analysis on fluconazole-resistant isolates will be conducted to identify significant differences in protein abundance between fluconazole-resistant and fluconazole-susceptible isolates of *C. neoformans*. Genes encoding proteins of interest will be knocked out or overexpressed using electroporation combined with double joint homologous recombination and an inducible *C. neoformans* promoter, respectively. Finally, mutant strains displaying overexpression or single knockouts of antifungal resistant-associated genes will be phenotypically characterized to determine patterns of cellular regulation, protein function, and involvement in antifungal resistance. This research will elucidate the molecular mechanisms underscoring fluconazole resistance in *C. neoformans*, with the aim of identifying potential targets for designing novel interventions to inhibit and even reverse the occurrence of antifungal resistant pathogens.