“Discovery of novel virulence factors elucidated from Cryptococcus neoformans response to the host environment”

Cryptococcus neoformans, a yeast-like opportunistic fungal-pathogen found ubiquitously within the environment is the leading cause of the dangerous disease cryptococcosis. C. neoformans exploits immunocompromised hosts with an extensive arsenal of virulence factors that modulate the host immune system to promote fungal survival. Without intervention, fungal dissemination may manifest as cryptococcal-meningitis and meningoencephalitis. The global rise of immunodeficiency disorders has demanded a higher use of antifungal agents in which Cryptococcus species have increasingly shown intrinsic resistance towards. To date, a comprehensive investigation of the protein-level interactions between the host cell and C. neoformans has not been extensively described. Using the Geddes-McAlister proteomics platform, my aim is to chronicle the changes in protein abundance during infection to elucidate potential targets for anti-virulence strategies. My research project evolves around the previously profiled in vitro proteome and secretome of wildtype C. neoformans integrated with the infectome of C. neoformans and BALB/c macrophages. From this analysis, 10 candidate fungal proteins are prioritized based on novelty, predicted secretory roles, and abundance. First, a library of novel-virulence associated gene deletion strains will be constructed using electroporation combined with double joint homologous recombination. Next, phenotypic characteristics of each deletion strain will be evaluated for divergences from wildtype C. neoformans classical virulence factor production. I will evaluate the resulting virulence of the gene deletion strains by analyzing fungal-macrophage interactions using cytotoxicity and antifungal protection assays. This research will elucidate the interplay at a host-pathogen interface, offering a unique perspective to characterize secreted fungal proteins critical to virulence.