STRONG CHILDREN'S RESEARCH CENTER

Summer 2012 Research Scholar

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ABSTRACT

Title: **Anti-Cryptococcal Molecules alter Vacuolar and Endocytic Membranes**

Background: Cryptococcus neoformans is an opportunistic fungal pathogen. While infections are rare in healthy individuals, it causes meningoencephalitis and pneumonia in people whose immune systems have been compromised by HIV/AIDS or who are receiving immunosuppressant therapies due to cancer, organ transplantation, or immune system disorders (Didone et al. 2010). Almost a million cases of cryptococcal meningitis occur each year, with the majority being in sub-Saharan Africa (Park et al. 2009). Fluconazole is often the only treatment option in resource-limited countries, but it is associated with high rates of relapse and treatment failure, thus the discovery of new antifungal compounds is an important goal (Bicanic et al. 2005).

Objective: The Krysan lab previously identified several compounds with anti-cryptococcal activity. The objective of this project was to further evaluate the activity of these compounds and to characterize their mechanism of action. Because the vacuole in Cryptococcus is essential for cell physiology and is a target for current antifungal drugs such as fluconazole, research focused on changes to vacuole and endocytic physiology in the presence of the compounds individually as well as combined with fluconazole.

Results: Visual analysis of cells with brightfield and fluorescence microscopy showed that several drugs generated higher percentages of cells with brightfield-visible inclusion bodies, punctate fluorescence, abnormal endocytic membrane formation, and additional or fewer vacuoles, which demonstrates that the compounds are affecting the cells' membranes ($P < .05$). Combining drugs with fluconazole resulted in higher percentages of normal phenotypes, but the differences were not statistically significant.

Conclusion: This investigation identified several novel molecules that negatively affect Cryptococcus vacuolar and endocytic membrane structure, and supports prior research that linked several of the drugs to yeast autophagy. Characterizing the effect of these compounds on Cryptococcus suggests that other anti-psychotic, anti-estrogen, and vasodilating drugs are strong potential candidates for therapeutic agents.