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Novel paths to antifungal therapeutics

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Presenter Information
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NOVEL PATHS TO ANTIFUNGAL THERAPEUTICS

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Adhesion to medical device and host cell surfaces are crucial steps during pathogenesis by fungi such as *Candida albicans*, which is especially dangerous to immunocompromised individuals such as AIDS patients. We have identified a small molecule that inhibits adhesion of *C. albicans* to polystyrene and to cultured human epithelial cells. Moreover, this compound is able to coat plastic surfaces and make them resistant to colonization by fungal biofilms. Therefore, this compound has the potential to be widely useful as a novel therapeutic and/or as a coating on medical devices.

Rationale: *C. albicans* is the most widespread fungal pathogen of humans and one of the most frequent hospital-acquired infections. The estimated annual cost of treating nosocomial *Candida* infections exceeds $1 billion per year. As an opportunistic pathogen, it is responsible for common clinical problems including oral thrush and vaginitis, but can also lead to life-threatening systemic infections (candidiasis) in immunocompromised individuals, resulting in 30-50% mortality rates. Contributing to these problems is the ability of *C. albicans* to develop resistance to antifungal drugs. Moreover, most effective antifungal drugs also cause serious side effects, in many cases because of the significant homology between mammalian and fungal drug targets. Therefore, new antifungal drugs are a high medical priority. Surface adhesion, morphological switching, and biofilm formation are interrelated factors that contribute directly to *C. albicans* virulence. Therefore, compounds that impair these processes would have promising properties as first step towards new antifungal therapeutics.

Preliminary Studies: Efficient adhesion is required for formation of aggressive biofilms, which in turn make *Candida* a successful pathogen. Therefore, we identified compounds that prevent adhesion of *Candida albicans* to polystyrene surfaces. Because the assays in this proposal are based on altering the behavior of intact cells, we avoid the complication of compounds unable to cross the cell wall and membranes.

Our initial search for adhesion inhibitors was conceptually simple, based on dye binding to monitor yeast adhesion to surfaces. We identified 41 compounds that reduced adhesion to <25% of the vehicle-

only wells. Retesting these compounds in a secondary assay measuring adhesion of a GFP-expressing *Candida* strain confirmed that most of the reordered compounds indeed inhibit adhesion to polystyrene (**Figure 1**).

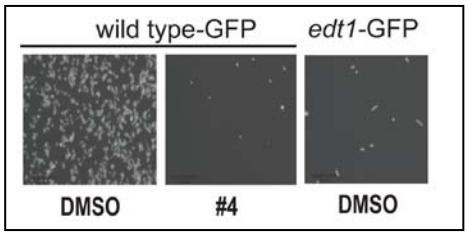

Figure 1. Compound #4 inhibits *C. albicans* adhesion to polystyrene. GFP-expressing wild type or non-adherent *edt1* mutant *C. albicans* cells were plated into 96 well plates with DMSO or 25 μM compound 4 as indicated. Plates were incubated for 4 hours at 37°C. Media was then decanted and plates were washed 3 times prior to fluorescence microscopy.

Human cell adhesion: To determine whether any candidate compounds would affect interactions with biological targets as well as inert surfaces, we also tested how the candidate compounds affect *C. albicans* adherence to human cells, using monolayers of human lung epithelial cells. The GFP-encoding cells allowed us to use both microscopy and fluorescence measurements to detect fungal cells that remained bound after washing. We observed that "compound #4", but not other candidate compounds, reduced the interaction of *C. albicans* with the human cells to background levels. We also verified that compound 4 did not affect the viability of this human cell line, even at concentrations much higher (250 μM) than those used in the adhesion assay (data not shown).

Plastic coating: Compound 4 also inhibits *Candida* adhesion to polystyrene when it is incubated with the plastic prior to the addition of the cells. Therefore, compound 4 not only has effects on *Candida* cell morphology in the absence of surface adhesion, it also renders plastic surfaces resistant to subsequent *Candida* binding. Together, our data suggest that compound 4 may not only be effective at combating fungal infections, but could also have potential use as a compound to prevent multiple types of unwanted microbial colonization.