

Candidiasis drug discovery and development: new approaches targeting virulence for discovering and identifying new antifungal drugs

Jose L. Lopez-Ribot

Targeting pathogenetic mechanisms rather than essential processes represents a very attractive alternative for the development of new antibiotics. This may be particularly important in the case of antimycotics, due to the urgent need for novel antifungal drugs and the paucity of selective fungal targets. The opportunistic pathogenic fungus *Candida albicans* is the main etiological agent of candidiasis, the most common human fungal infection and now the third most common nosocomial infection, threatening an expanding population of immune- and medically-compromised patients. Candidiasis carry unacceptably high mortality rates, a clear reflection of the many shortcomings of current antifungal therapy, including the limited armamentarium of antifungal agents, the toxicity displayed by some of the current therapies, and the emergence of resistance to most classes of antifungals. Moreover the antifungal pipeline is mostly dry. The pathogenesis of *C. albicans* is intimately linked to its ability to undergo morphogenetic conversions between yeast and filamentous morphologies and to its ability to form biofilms. Thus, we posit that filamentation and biofilm formation represent high value targets, yet clinically unexploited, for the development of novel anti-virulence approaches against candidiasis. We have performed high content screenings of over 50,000 small molecules present in commercially-available chemical libraries to identify compounds that inhibit *C. albicans* biofilm formation and filamentation, and conducted a series of follow-up studies to examine the *in vitro* and *in vivo* activity of the identified compounds, as well as their pharmacological properties. Results provide proof of concept for the implementation of anti-virulence approaches against *C. albicans* and other fungal infections that would be less likely to foster the emergence of resistance. Moreover, the top compounds represent advanced candidates for the development of novel antifungal drugs with new chemical structures, new targets and mechanism(-s) of action.