Editorial: Antifungal Drug Discovery: New Theories and New Therapies

Chaminda J. Seneviratne 1* and Edvaldo A. R. Rosa 2

1 Faculty of Dentistry, National University of Singapore, Singapore, Singapore, 2 The Pontifical Catholic University of Paraná, Curitiba, Brazil

Keywords: antifungals, Candida albicans, new drug discovery, oral candidiasis, Candida biofilms

The Editorial on the Research Topic

Antifungal Drug Discovery: New Theories and New Therapies

Medically important fungal infections can be broadly classified into superficial surface infections and invasive mycoses (Samaranayake and MacFarlane, 1990; Roemer and Krysan, 2014). Superficial surface infections include mucosal candidiasis, dermatophyte infections whereas invasive mycoses affect sterile body sites such as bloodstream, central nervous system, kidney, lungs, and liver. Rise of fungal infections has caused a substantial morbidity and mortality globally (Vallabhaneni et al., 2016). It is reported that mortality among patients with invasive candidiasis is as high as 40%, even when patients receive antifungal therapy (Kullberg and Arendrup, 2015).

Antifungal drugs are relatively difficult to develop compared to antibacterial drugs owing to the eukaryotic nature of the cells. Only a few classes of antifungal drugs, such as polyenes, azoles, echinocandins, allylamines, and flucytosine, are available to treat the myriad of fungal infections (Sanglard et al., 2009). Of the current antifungal agents, none have all the characteristics of an ideal agent (Wong et al., 2014). Antifungal resistance and host-related adverse reactions further limit the existing antifungal arsenal against fungal pathogens (Chandrasekar, 2011). Rising drug resistance is an inevitable problem, particularly for fluconazole, a drug of choice for candidiasis in AIDS patients (Siikala et al., 2010; Rautemaa and Ramage, 2011). Drug resistance has also been reported for recently introduced echinocandin antifungal agents (Seneviratne et al., 2008a; Ben-Ami et al., 2011; Clancy and Nguyen, 2011). Moreover, some fungal species are inherently resistant to existing antifungals (Sanglard; Kołaczkowska and Kołaczkowski, 2016). In addition, biofilm mode of fungal growth is known to be highly resistant to antifungal agents (Chandra et al., 2005; Seneviratne et al., 2008b). Hence, the development of more effective and safe antifungal agents is a top priority in the health care field. Therefore, this special research topic aimed to address the new theories and therapies pertaining to antifungal drug discovery, covering aspects of clinical relevance and novel antifungal strategies.

Majority of the articles published under this research topic belongs to the Candida species, which is a group of major fungal pathogens in humans. Candida species are commensal fungi that inhabit various niches of the human body, including the oral cavity, gastrointestinal tract, vagina, and skin (Samaranayake and MacFarlane, 1990; Mayer et al., 2013). However, under certain circumstances, Candida can cause infections, or candidiasis, ranging from superficial mucous membrane infections to life-threatening systemic diseases. Candida albicans is the most prevalent fungal pathogen in lethal blood stream infections of humans (Seneviratne et al., 2011). C. albicans infections are a significant clinical problem especially in compromised host populations undergoing HIV/AIDS treatment, chemotherapy or organ transplantation. Moreover, sharp increase in aging populations which are susceptible to fungal infections is expected in the next few decades. The currently available antifungal agents are not always effective against C. albicans, which remains a ubiquitous pathogen in nosocomial diseases, causing severe mucosal infections such as oral
candidiasis, onycomycoses, vulvovaginal candidiasis, and systemic mycoses with high mortality rates (Kojic and Darouiche, 2004; Zaoutis et al., 2005; Concia et al., 2009).

At the start of the research topic, clinical relevance of oral candidiasis has been discussed in order to provide a glimpse of human fungal infections (Patil et al.). Biofilm formation of the fungal pathogen is a significant problem in medical-device associated infections and directly related to therapeutic failure (Williams and Ramage, 2015). As conventional antifungal agents are ineffective against fungal biofilms, alternative strategies are needed. Novel antifungal compounds that target fungal biofilm formation and the host inflammatory response such as myriocin, fulvic acid, and acetylcholine have been discussed in the research topic as candidate dual action therapeutics to treat opportunistic fungal infections (Borghi et al.). Microbial biotransformation has emerged as an important tool for obtaining novel substances which possess antifungal activity. Implication of endophytic fungi as cell factories for producing new antifungal molecules and in silico approach using databases of 3D molecular structures are also discussed (Bianchini et al.). Oshima and colleagues introduce an interesting concept of biogenics for oral candidiasis. Biogenics advocates the use of beneficial bioactive substances produced by probiotic bacteria, whose activities are independent of the viability of probiotic bacteria in human bodies. Ravikumar and colleagues examine various immune-enhancing strategies for the invasive fungal diseases caused by Candida and Aspergillus species. These novel approaches include cytokine therapy, granulocyte transfusion, antibody-based therapy, natural killer cell treatment and adoptive T cell transfer. Molecules such as phenolic compounds, derived from natural sources and exhibiting considerable antifungal properties are a source for the development of novel anti-candidal therapy (Teodoro et al.). Therefore, potential use, proposed mechanisms of action and limitations of phenolic acids have been discussed.

Candida bloodstream isolates derived from Hong Kong have shown to possess virulence attributes such as biofilm formation, hemolysin production, proteinase activity as well as perturbations in their antifungal sensitivity in the presence of serum, which may contribute to treatment resistance in candidemia (Seneviratne et al.). One of the major mechanisms contributing to multi-drug resistance in C. albicans is the plasma membrane drug-efflux system. Therefore, application of inhibitors of drug-efflux pumps has been suggested as a strategy to increase the susceptibility of C. albicans to antifungals. Szczepaniak et al. developed a new fluorescence method that allows in vivo activity evaluation of compounds inhibiting C. albicans transporters. They demonstrated that fluorescence labeling with diS-C3(3) potentiometric dye enables a real-time observation of the activity of C. albicans Cdr1 and Cdr2 transporters. The new method was able to demonstrate the different specificities of enniatin A and beauvericin toward drug-efflux pumps. In another study investigators have developed three structurally related chemo-sensitizers i.e., oxathiolute fused chalcone derivatives to successfully restore the sensitivity of fluconazole resistant C. albicans strains. The mechanism of action is a possible non-competitive inhibition of drug-efflux pumps Mdr1, Cdr1, and Cdr2. However, more research is warranted in this area to fully establish the role of chemo-sensitizers in clinical use.

Antimicrobial peptide isolates from various sources are also a promising source to develop novel antymycotic agents. A study under this research topic has shown anti-Candida activity of antimicrobial peptide produced by Enterococcus faecium (Roy et al.). It appears to target chitin in the cell wall of Candida species. Host derived molecules like histatin 5 protects human oral mucosa against the transformation of commensal C. albicans into a pathogenic invader. A work by Moffa and colleagues demonstrated that coating with histatin 5 reduces C. albicans colonization of epithelial cell surfaces and also protects the basal cell layers from undergoing apoptosis. Hence, there is a possibility of using host derived antifungal molecules to prevent Candida infections, which may be a useful strategy in compromised host populations.

Candida glabrata is an emerging human fungal pathogen. A study examined the role of glucose sensing mechanism in C. glabrata using SNF3 (Sucrose Non Fermenting 3) knockout strains. Mutation results in higher susceptibility to amphotericin B in low glucose environment (0.1%), but showed no effect on biofilm formation capability. Going beyond Candida species, a study of dermatophyte fungus Trichophyton rubrum investigated the role of Hsp90 in its pathogenicity and drug susceptibility. Chemical inhibition of Hsp90 resulted in increased susceptibility of the fungus to itraconazole and micafungin. The synergism observed between the inhibition of Hsp90 and the effect of itraconazole or micafungin in reducing the fungal growth is of great interest as a novel and potential strategy to treat dermatophytoses.

This specific research topic on antifungal drug discovery provides a detailed overview of potential novel antifungal strategies, promising new discoveries and their clinical implications, particularly that of Candida species.

**AUTHOR CONTRIBUTIONS**

CS and ER contributed to the Editorial.

**REFERENCES**

Ben-Ami, R., Garcia-Effron, G., Lewis, R. E., Gamarra, S., Leventakos, K., Perlin, D. S., et al. (2011). Fitness and virulence costs of Candida albicans FKS1 hot spot mutations associated with echinocandin resistance. J. Infect. Dis. 204, 626–635. doi: 10.1093/infdis/jir351

Chandra, J., Zhou, G., and Ghannoum, M. A. (2005). Fungal biofilms and antymycotics. Curr. Drug Targets 6, 887–894. doi: 10.2174/138945005774912762

Chandrasekar, P. (2011). Management of invasive fungal infections: a role for polyenes. J. Antimicrob. Chemother. 66, 457–465. doi: 10.1093/jac/dkq479

Clancy, C. J., and Nguyen, M. H. (2011). At what cost echinocandin resistance? J. Infect. Dis. 204, 499–501. doi: 10.1093/infdis/jir355
Concia, E., Azzini, A. M., and Conti, M. (2009). Epidemiology, incidence and risk factors for invasive candidiasis in high-risk patients. Drugs 69, 5–14. doi: 10.2165/11315500-000000000-00000

Kojic, E. M., and Darouiche, R. O. (2004). Candida infections of medical devices. Clin. Microbiol. Rev. 17, 255–267. doi: 10.1128/CMR.17.2.255-2.2004

Kołaczkowska, A., and Kołaczkowski, M. (2016). Drug resistance mechanisms and their regulation in non-albicans Candida species. J. Antimicrob. Chemother. 71, 1438–1450. doi: 10.1093/jac/dkv445

Kullberg, B. J., and Arendrup, M. C. (2015). Invasive candidiasis. N. Engl. J. Med. 373, 1445–1456. doi: 10.1056/NEJMra1315399

Mayer, F. L., Wilson, D., and Hube, B. (2013). Candida albicans pathogenicity mechanisms. Virulence 4, 119–128. doi: 10.4161/viru.22913

Rautemaa, R., and Ramage, G. (2011). Oral candidosis–clinical challenges of a biofilm disease. Crit. Rev. Microbiol. 37, 328–336. doi: 10.3109/1040841X.2011.585606

Roemer, T., and Krysan, D. J. (2014). Antifungal drug development: challenges, unmet clinical needs, and new approaches. Cold Spring Harb. Perspect. Med. 4:a019703. doi: 10.1101/cshperspect.a019703

Samaranayake, L. P., and MacFarlane, T. W. (1990). Oral Candidosis. London: Wright-Butterworth.

Sanglard, D., Coste, A., and Ferrari, S. (2009). Antifungal drug resistance mechanisms in fungal pathogens from the perspective of transcriptional gene regulation. FEMS Yeast Res. 9, 1029–1050. doi: 10.1111/j.1567-1364.2009.00578.x

Seneviratne, C. J., Jin, L. J., Samaranayake, Y. H., and Samaranayake, L. P. (2008a). Cell density and cell aging as factors modulating antifungal resistance of Candida albicans biofilms. Antimicrob. Agents Chemother. 52, 3259–3266. doi: 10.1128/AAC.00541-08

Seneviratne, C. J., Jin, L., and Samaranayake, L. P. (2008b). Biofilm lifestyle of Candida: a mini review. Oral Dis. 14, 582–590. doi: 10.1111/j.1601-0825.2007.01424.x

Seneviratne, C. J., Wong, S. S., Yuen, K. Y., Meurman, J. H., Parmanen, P., Vaara, M., et al. (2011). Antifungal susceptibility and virulence attributes of bloodstream isolates of Candida from Hong Kong and Finland. Mycopathologia 172, 389–395. doi: 10.1007/s11046-011-9444-4

Siikala, E., Rautemaa, R., Richardson, M., Saxen, H., Bowyer, P., and Sanglard, D. (2010). Persistent Candida albicans colonization and molecular mechanisms of azole resistance in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) patients. J. Antimicrob. Chemother. 65, 2505–2513. doi: 10.1093/jac/dkq354

Vallabhaneni, S., Mody, R. K., Walker, T., and Chiller, T. (2016). The global burden of fungal diseases. Infect. Dis. Clin. North Am. 30, 1–11. doi: 10.1016/j.idc.2015.10.004

Williams, C., and Ramage, G. (2015). Fungal biofilms in human disease. Adv. Exp. Med. Biol. 831, 11–27. doi: 10.1007/978-3-319-09782-4_2

Wong, S. S., Samaranayake, L. P., and Seneviratne, C. J. (2014). In pursuit of the ideal antifungal agent for Candida infections: high-throughput screening of small molecules. Drug Discov. Today 19, 1721–1730. doi: 10.1016/j.drudis.2014.06.009

Zaoutis, T. E., Argon, J., Chu, J., Berlin, J. A., Walsh, T. J., and Feudtner, C. (2003). The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin. Infect. Dis. 41, 1232–1239. doi: 10.1086/496922

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2016 Seneviratne and Rosa. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.