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EDITORIAL

The unmet clinical need of novel antifungal drugs

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The global impact of fungal infections on human health has recently been highlighted by several important publications,[1,2] and advocacy groups.[3] Although several factors undoubtedly contribute to the estimated 1.5 million deaths due to fungal disease each year,[2] the relative paucity of antifungal drugs is likely to play a significant role. The goal of this special issue of Virulence is to highlight recent developments in the effort to address this unmet clinical need.

Since the dawn of the age of anti-infective drugs early last century, only 3 classes of antifungal drugs have been developed for the treatment of life-threatening, invasive fungal infections[4]: polyenes (e.g., amphotericin B); azoles (e.g., fluconazole), and echinocandins (e.g., micafungin). As a comparison, 5 distinct classes of drugs are currently used to treat HIV and 2 of these agents have been developed since the introduction of the most recently introduced antifungal class, the echinocandins.[5] Amphotericin B was developed in the late 1950s and remains part of the treatment of choice for the treatment of cryptococcal meningitis, the fungal infection that kills more people on this planet than any other.[6] Additionally, it remains the only treatment option for some types of mold infections that are emerging in severely immunocompromised patients. Consequently, the state-of-the-art therapy for some of the most severe fungal diseases faced by our patients has not changed in over 50 y.

This is not to say that the field has been entirely static. Most importantly, on-going efforts toward extending the spectrum of azole antifungals to include non-Aspergillus molds represent clinically significant progress[7]; these and other developments within the existing classes of antifungal drugs are discussed by Chen and co-authors.[8] Despite these improvements, the need for truly novel agents is undeniable. Indeed, the development of novel chemical and mechanistic classes of anti-infective agents is a critical goal for nearly every area of infectious diseases. The need, however, is especially acute for the field of antifungals given the small number of available classes. The urgency of this endeavor is underscored by the recent emergence of multi-drug resistant *C. glabrata*[9] and *C. auris*.[10] In the example of *C. glabrata*, patients who are infected with azole- and echinocandin-resistant isolates must be treated with amphotericin B-based regimens and, as discussed above, are essentially being treated as if they contracted their infection in 1962. Given the slow pace of novel antifungal drug development (30 y elapsed between the discovery of the echinocandins and their introduction into clinical practice), the combination of adjuvant agents with currently used drugs to overcome resistance must be consider an important option to addressing this problem. Precedence for this strategy comes from the addition of β-lactamase inhibitors to β-lactams to block resistance in bacteria. In separate contributions, Wright[11] and Rogers[12] discuss progress in approaches to the rationale development of effective antifungal combinations. In addition, Chen discusses the efforts to exploit synergistic interactions between currently used antifungals as part of their broader discussion of new developments associated with established antifungal drugs.[8]

Although combination therapy has been widely applied to other areas of infectious disease, including HIV, TB and malaria treatment, such approaches would ideally also involve the development of agents with novel mechanisms of action. In this issue, Perfect,[13] Steinbach,[14] and Li[15] discuss developments toward exploiting trehalose, calcineurin, and the mitochondria as the target of novel small molecules with antifungal activity. If ever there was a time for "outside-the-box (OSTB)" thinking, it has arrived for the discovery of novel antifungal agents and these researchers are venturing into box-free zones to find new treatments. One of the most vexing problems of traditional approaches to antifungal drug discovery is that they frequently lead to the repetitive re-discovery of the same chemical matter or slightly different

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chemical matter targeting the same fungal processes.[16] OTSB-approaches like these should circumvent the convergent chemical evolution that has emerged from the previously pursued approaches.

Another OSTB approach is to break with the traditional notion of killing the pathogen and develop agents that, instead, prevent it from cause disease. This trend has also emerged in other areas of infectious disease but, as described by Wiederhold and Lopez-Ribot, it appears to be quite applicable to fungal infections in the form of filamentation-preventing agents.[17] *C. albicans* is the most common human fungal pathogen and, as has been extensively demonstrated, filamentation is required for its ability to cause disease in mammals. Although filamentation is not required for all fungi to cause disease, it is important to consider that focusing our efforts only on broad spectrum agents is extremely stringent and likely to prevent development of potentially useful agents. This is particularly germane when one also considers the evolutionary and biologic distance that separates the fungal species that cause disease. With this in mind, Rappleye and co-authors[18] provide a perspective on the treatment of dimorphic fungi, a class of pathogens that are very distinct from the others and which are able to cause disease in immunocompetent people.

Finally, the repurposing of drugs that are approved for other uses to new indications and diseases has emerged in many areas of medicine as an expedient approach to the development of new therapies. This has been explored in the antifungal space as well, most successfully with respect to the treatment of cryptococcal meningitis.[19] Here, Lopez-Ribot and co-authors[20] describe the antifungal activity of the rheumatoid arthritis therapy auranofin as a potentially repurposable agent.

We hope that the articles in this issue will inspire others to explore new approaches to the identification of new therapies for fungal infections. As Big Pharma continues to de-emphasize anti-infective drug discovery as part of its strategic plans, it will be up to academic laboratories and small firms to take up this crucial task. As with any drug discovery effort, the risks are relatively high because it is unlikely that any one group will develop the next new drug. However, as with any science-based endeavor, the progress made by the collective contributions of a research community that is focused on a shared goal will eventually lead to success. The only certain outcome is that we will fail, if no one tries.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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