Editorial: Antifungal Pipeline: Build It Strong; Build It Better!

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Editorial on the Research Topic

New Antifungal Drugs

The global burden of fungal infections remains unclear but there are estimates that they infect over a billion people with 150 million having serious fungal diseases and invasive fungal infections (IFIs) killing more than 1.5 million each year globally (Bongomin et al., 2017). More precise data has been reported that IFIs are associated with approximately 7.2 billion dollars in direct costs to the USA Healthcare System alone in 2017 (Benedict et al, 2019). Clearly, IFIs are common, deadly and costly.

Although there are reported to be more than 5 million fungal species worldwide, approximately 300 fungal species are implicated directly in human disease. Only a fraction (between 20-30 species) consistently produce disease. The mortality rates from IFIs remain high and drug- resistant molds (i.e.azole-resistant Aspergillus fumigatus) or yeasts (i.e. Candida auris) have appeared globally and are spreading worldwide. Furthermore, the IFI onslaught has been accelerated by an enlarging global immunocompromised population resulting from persistent untreated HIV infections and ICU care as well as cancer and its new and old therapies. The “perfect storm” has arisen worldwide for the emergence of IFIs. Unfortunately, the medical community is armed with only four classes of antifungal agents for IFIs: the polyenes, azoles, echinocandins, and a pyrimidine analogue for fighting invasive fungal complications. In all these classes there has been success in IFI management but also occurrence of substantial defects and failures. Clearly, the numbers and outcomes for IFIs speak to the urgent demand for development of new effective antifungal agents.

However, there are a variety of important issues and potential roadblocks associated with the current state of antifungal development. First, the Gain Act and the Orphan Drug Act and Fast Track designation by USA FDA have provided a favorable climate for investment into antifungal agents. Unfortunately, antifungal drugs are unlikely to be “block busters” for pharmaceutical sales. Second, diagnosis has always been a challenge but new culture, serologies, genomic techniques, and biomarkers have improved the early diagnosis of IFIs but more improvements need to be made to facilitate the timely and accurate diagnosis of IFIs. Third, attributable mortality for IFIs with present antifungal agents remains too high (10-40% depending on the fungus in the best healthcare systems). Fourth, there needs to be an emphasis on antifungal agents that produce rapid fungicidal activity particularly in the context of reduced host immune functions. Furthermore, long-term treatment regimens interfere and complicate the treatment of
underlying diseases; reduce compliance; increase drug toxicities; and amplify drug resistance pressures. Fifth, finding broad-spectrum antifungal agents are desirable because they allow less precise early diagnosis of a specific fungus and support their use in prevention strategies. However, the question remains how wide-spectrum and what fungi will be left out? Sixth, the concept of optimized combinations of antifungal agents may improve antifungal spectrum and potency by attacking multiple fungal targets. Although this strategy has been widely studied in the pre-clinical settings, its translation to patient care has lagged considerably due to challenges in both drug development and analysis. Seventh, the development of drug resistance in the fungal kingdom is present and measurable. There are no fungal drug-resistance transposons or plasmids that easily pass resistance between isolates, but all of our antifungal agents have been in use for at least twenty years; consequently, we are beginning to see the clinical impact of drug selection for resistance. Eighth, it is important to find new antifungal drugs with novel mechanism(s) of action that avoid targeting highly conserved eukaryotic proteins and processes because impacting human targets with cross-species target inhibition may add toxicity challenges in both drug development and analysis. Seventh, the development of drug resistance in the fungal kingdom is present and measurable. There are no fungal drug-resistance transposons or plasmids that easily pass resistance between isolates, but all of our antifungal agents have been in use for at least twenty years; consequently, we are beginning to see the clinical impact of drug selection for resistance. Eighth, it is important to find new antifungal drugs with novel mechanism(s) of action that avoid targeting highly conserved eukaryotic proteins and processes because impacting human targets with cross-species target inhibition may add toxicity challenges in both drug development and analysis. Seventh, the development of drug resistance in the fungal kingdom is present and measurable. There are no fungal drug-resistance transposons or plasmids that easily pass resistance between isolates, but all of our antifungal agents have been in use for at least twenty years; consequently, we are beginning to see the clinical impact of drug selection for resistance. Eighth, it is important to find new antifungal drugs with novel mechanism(s) of action that avoid targeting highly conserved eukaryotic proteins and processes because impacting human targets with cross-species target inhibition may add toxicity.
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