ACS Infectious Diseases

In This Issue

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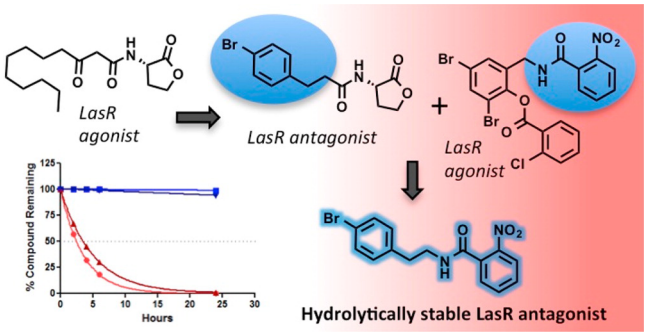
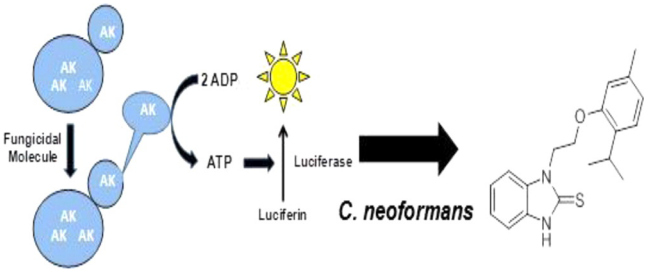
PROBING THE GROUP



Cell-to-cell communication among bacteria is commonly carried out by diffusible chemical signals in a process known as quorum sensing. Many pathogenic species use quorum sensing as a mechanism to regulate virulence at high cell densities allowing the pathogen to effectively coordinate virulence at the group level rather than at the individual cell level. In the laboratory, the development of small molecules capable of modulating quorum sensing presents an opportunity to better understand bacterial virulence. Furthermore, as targeting bacterial virulence gains popularity as a strategy for the development of novel therapeutics, quorum sensing modulators present potential beyond the laboratory setting. At present, the utility of many of the most potent quorum sensing modulators is limited by hydrolytic instability and nonspecific activity.

In this issue, O'Reilly and Blackwell (DOI: 10.1021/acsinfecdis.5b00112) develop quorum sensing modulators with potent antagonistic activity against the *Pseudomonas aeruginosa* quorum sensing receptor LasR. Using a structure-based scaffold hopping approach, the authors provide a new scaffold for the development of optimized quorum sensing probes that overcomes the limitations of previously reported probes.

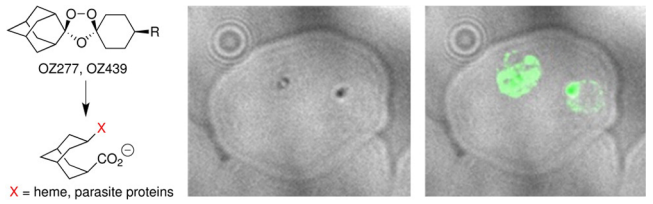
BREAKING THROUGH WALLS



Cryptococcal meningitis is a life-threatening fungal infection of the central nervous system that predominantly affects individuals living with HIV. The successful treatment of cryptococcal meningitis requires the use of antifungal drugs that directly kill the fungus, as agents exhibiting only static antifungal activity fail to clear the pathogen from the cerebrospinal fluid. Although the development of antifungal agents has been a relatively neglected area of pharmaceutical research, antifungals targeting the fungal cell wall have recently been introduced to the market. Unfortunately, these newer agents are ineffective against the causative agent of cryptococcal meningitis, *Cryptococcus neoformans*, and no new drugs have been developed to treat these infections in more than 50 years; the currently prescribed regimen poses many difficulties to effectively administering treatment to the affected population. The cell wall is crucial to fungal cell viability, particularly at human body temperature, and thus presents an ideal target for the development of novel anticryptococcal therapeutics.

In this month's *ACS EditorsChoice* article, Hartland et al. (DOI: 10.1021/acsinfecdis.5b00111) tackle the neglected area of anticryptococcal research. Here, the authors screen a large library of molecules using an assay that detects only fungicidal molecules and identify a new class, benzothioureas, active against *C. neoformans*. The lead agents are active at concentrations comparable to those of currently used drugs, have low toxicity against human cells, and interfere with the ability of the fungus to maintain an intact cell wall. This work suggests that benzothioureas present a promising new class of molecules for further development as potential anticryptococcal drugs.

UNDERSTANDING DERIVATIVES



The discovery of artemisinin proved to be a significant advancement in the treatment of malaria. Artemisinin inspired a number of semisynthetic and synthetic derivatives that are included in artemisinin-based combination therapies, which are currently recommended by WHO as the first-line treatment for uncomplicated malaria caused by *Plasmodium falciparum*. Recently, two artemisinin derivatives, the synthetic peroxide ozonide antimalarials OZ277 and OZ439, have advanced to clinic, with the latter currently in phase IIb clinical trials as a single-dose oral cure. Despite the success of artemisinin-derived antimalarial agents in the clinic, the precise mode of action of these agents remains unclear.

Here, Jourdan et al. (DOI: 10.1021/acsinfecdis.5b00090) investigate the mode of action of the antimalarials OZ277 and OZ439. Using newly developed monoclonal antibodies, the authors demonstrate that these agents alkylate accessible proteins in *P. falciparum*, a mechanism that has been proposed for semisynthetic artemisinin-derived agents. Understanding the mode of action of these compounds will aid in the discovery of the next generation of antimalarial agents.

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