ACS Infectious Diseases

In This Issue

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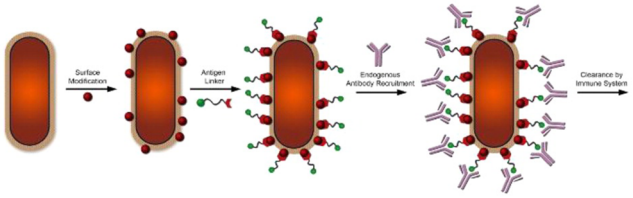
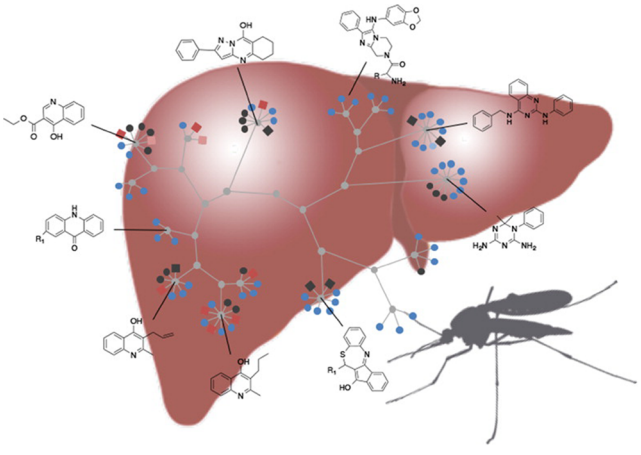
PROMISCUOUS BACTERIA MEET THEIR DEMISE



Traditional antibiotic therapies kill or inhibit bacterial growth by directly targeting essential cellular processes. As increasing rates of antibiotic resistance continue to threaten the utility of the current arsenal of antibacterial agents, novel antibacterial strategies are being investigated. Immunomodulatory approaches present promise either as primary therapeutics or as supplements to traditional antibiotic therapies. One proposed immunomodulatory strategy involves enhancing antibody-mediated clearance of bacterial cells by labeling bacterial cell surfaces with haptens.

In this ACS Editor's Choice article by Fura et al. (DOI: 10.1021/acsinfecdis.6b00007) a novel strategy takes advantage of the inherent promiscuity of Gram-positive bacteria to metabolically incorporate D-amino acid-based dipeptides into their peptidoglycan. The authors established that installation of unnatural epitopes onto the fourth position within the peptidoglycan stem peptide led to greater retention and improved labeling relative to the terminal position. The surface remodeling and labeling strategy employed here, which shows improved recruitment of endogenous antibodies, demonstrates a promising synthetic immunology approach to complement antibiotic therapy.

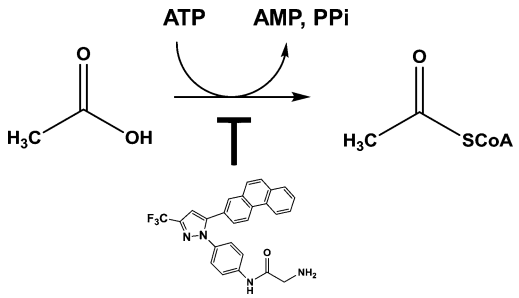
ACCELERATING AN END TO MALARIA WITH ULTRAHIGH-THROUGHPUT PARASITE SCREENING



Therapeutic development for malaria has recently taken center stage with the 2015 Nobel Prize in Physiology or Medicine being awarded in part for discoveries that led to the development of effective antimalarial drugs based on artemisinin. Despite the prior success in the field of antimalarial development, the disease burden remains high, and resistance has emerged to all currently available therapies. As this vector-borne parasite goes through a number of distinct stages in its life cycle, eradication of malaria relies on the development of therapeutics able to target multiple stages of the life cycle. Most current therapeutics target the symptom-causing erythrocytic stage of the parasite. Therapeutics targeting the exoerythrocytic stage present the advantage of being able to prevent the establishment of infection. Identifying novel antimalarial compounds with stage-specific activity presents an enormous undertaking that would be greatly facilitated by ultrahigh-throughput screening methods.

The article by Swann et al. (DOI: 10.1021/acsinfecdis.5b00143) reports the development and evaluation of a 1536-well format luciferase-based phenotypic screen for small molecules active against the exoerythrocytic stage malaria. Using this screen, the authors identified a number of small molecules that could serve as starting points for the development of long-acting compounds that could prevent the development of malaria, effectively opening the stage for the creation of a chemical vaccine for malaria.

FINDING PURPOSE IN AR-12: FROM ANTITUMOR AGENT TO ANTIFUNGAL



As antimicrobial drug resistance develops and new infectious diseases emerge, there is a continued need for the discovery of new anti-infective agents, yet drug development for infectious diseases can take decades to get a new drug to market. Investigations aimed at repurposing existing approved drugs for treatment of infectious diseases have garnered much interest as this approach has the potential to expedite the drug development process. The development of new and effective antifungal agents has been an area of infectious disease research that has been especially slow and could benefit from drug-repurposing efforts.

In this issue, Koselny et al. (DOI: 10.1021/acsinfecdis.5b00134) investigate a celecoxib derivative, AR-12, a molecule that has been in phase I clinical trials as an anticancer agent, for its potential as an antifungal agent. Having previously identified AR-12 as exhibiting potent antifungal activity, the authors conduct a chemical-genetic analysis of AR-12 to elucidate its mechanism of action. These investigations identify AR-12 as an inhibitor of acetyl-CoA synthetase, an enzyme essential to most yeast that is not used by mammals as a significant source of acetyl-CoA, thus presenting acetyl-CoA synthetase as a new antifungal drug target.

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