Tokyo University of Agriculture and Technology
Institute of Global Innovation Research

グローバルイノベーション研究院　公開セミナー
Institute of Global Innovation Research Open Seminar

New Tricks to Improve Old Antimicrobial Drugs

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言語 / 英語　Language/English

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Lecture Room L1151, 5th Fl., Building 11, Koganei Campus, TUAT

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Treatment of infections is a challenge worldwide. Both fungal and bacterial infections often occur in patients with compromised immune systems, i.e. the mortality rate of HIV-associated invasive fungal diseases likely exceeds that of tuberculosis or malaria. Moreover, cases of drug resistance among major microbial pathogens are on the rise.

We aim to establish novel strategies for design of antifungal and antibacterial agents that interfere with the integrity of the microbial cell membrane either by direct interaction with membrane components or, in the case of fungal pathogens, indirectly by inhibition of the biosynthesis of ergosterol, an essential component of the fungal cell plasma membrane. The direct strategy involves designing cationic amphiphiles that lyse microbial cells through selective interaction with the microbial cell membrane components. Based on our preliminary study, membrane selectivity efficacy can be accomplished by tuning various structural features of the antimicrobial agent.

To indirectly disrupt the fungal membrane, we design novel azole antifungal agents. We recently observed that azole antifungal drugs localize primarily within mitochondria in the first hours following drug uptake and not to the endoplasmic reticulum (ER), which harbors lanosterol 14α-demethylase, the cytochrome P450 that is inhibited by these drugs. We are engaged in the development of antifungal azoles containing molecular features that will direct them to the ER. This should improve activity by enhancing the local concentration near the target enzyme and should therefore reduce the efficacy of efflux pump-mediated resistance.

To enable mechanistic investigation, inherently fluorescent derivatives of each class of antimicrobials were synthesized to allow fluorescent microscopy experiments for determination of subcellular drug distribution and mode of action study.

Molecular design, biological activities and mode of action aspects of the antimicrobial agents developed in our group will be discussed.

■共催 / Co-organized by
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どなたでも、ご聴講いただけます。
Everyone is welcome to attend.

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