OS04-3 Search for anti-infective antibiotics having novel targets

◯Kazuro SHIOMI[1,2]

[1]Kitasato Univ. Grad. Sch. of Infect. Control Sci., [2]Kitasato Univ. Kitasato Inst. for Life Sci.

Infectious diseases are still a big threat, and antibiotics with new mechanisms of action are urgently required. The screening for anti-infective antibiotics having novel targets and some antibiotics found from the screening are shown below. An aminoglycoside antibiotic, arbekacin (ABK), is active against MRSA, but some MRSA becomes resistant to ABK recently. ABK resistant MRSA has a bifunctional enzyme that modifies ABK by phosphorylation and acetylation. ABK resistant MRSA was cultured with or without ABK, and the sample that showed anti-MRSA activity only with ABK was selected for the screening of the compounds that circumvent ABK resistance. New compounds, biverlactones A-D, were isolated from the culture broth of a fungus, *Penicillium* sp. Biverlactone A is a carboxylic acid having α,β-unsaturated lactone. The MIC value of ABK against ABK resistant MRSA were lowered 32 times by the addition of 16 μg/ml of biverlactone A. Biverlactone A showed the resistance circumvention by inhibiting the phosphorylation activity of the bifunctional enzyme. The type III secretion system (T3SS) is highly conserved in many pathogenic Gram-negative bacteria. T3SS functions as an injector of bacterial proteins (effectors) into host cells and is involved in establishing disease processes. The inhibitors of T3SS are suggested to reduce virulence without causing bacterial death and avoid the emergence of the resistant strains. Aurodox was isolated as a T3SS inhibitor. It inhibited T3SS activity at 30 times lower concentration (1.2 μg/ml) than its antibacterial concentration and cured the bacterial infected mice at low concentration.