V-ATPase Inhibitors

~ Novel Antimicrobial Agents targeting Na^+ Pumps ~

KEY INVENTION

The inhibitors for V-ATPases which are the membrane proteins draining Na^+ using ATP hydrolysis energy have been developed.

➡ **These are expected to be applied as novel mechanism antimicrobial agent for the inhibitors against drug-resistant bacteria such as Vancomycin-Resistant Enterococcus (VRE).**

What are V-ATPases ?

- These are the rotating molecular motors activated by the ATP in the cell membranes of eucaryotic organisms or bacteria, and generally transport H^+.
- The enterococci have V-ATPases and are also survivable under alkaline conditions by draining Na^+.
- The eukaryotic cells, lactic bacteria and bifidobacteria are difficult to survive under alkaline conditions due to no V-ATPase.

SUMMARY of INVENTION

Characteristics of V-ATPases

These are the membrane proteins which consist of V_o domains (subunits in the membranes) and V_1 domains (hydrophilic subunits) and drain Na^+ using ATP hydrolysis energy (Fig. 1).

➡ **The bacteria having V-ATPases such as drug-resistant enterococci are survivable under alkaline conditions caused by the administration of antibiotics (Fig.2).**

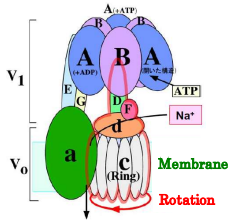


Fig. 1. Schematic Model of V-ATPases

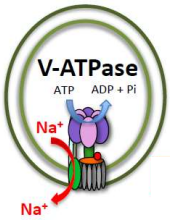
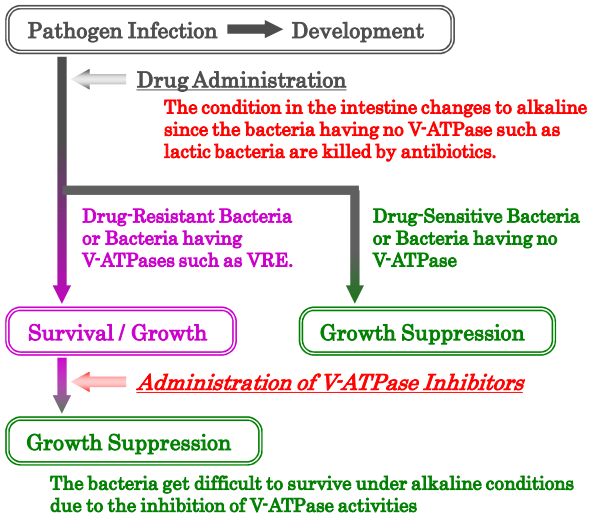


Fig. 2. Mechanism of Na^+ Draining

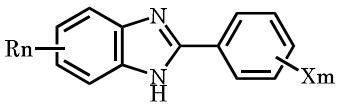
The growth suppression of drug-resistant enterococci is expected by the inhibition of V-ATPases.

Role of V-ATPase Inhibitors



EFFECT of INVENTION

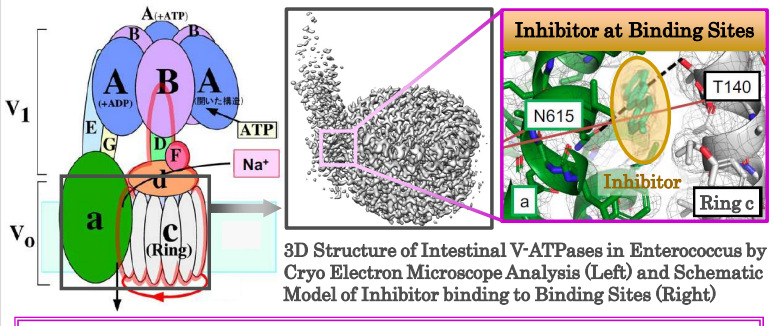
V-ATPase Inhibitors



Rn, Xm : Substituents

2-Arylbenzimidazole Derivatives

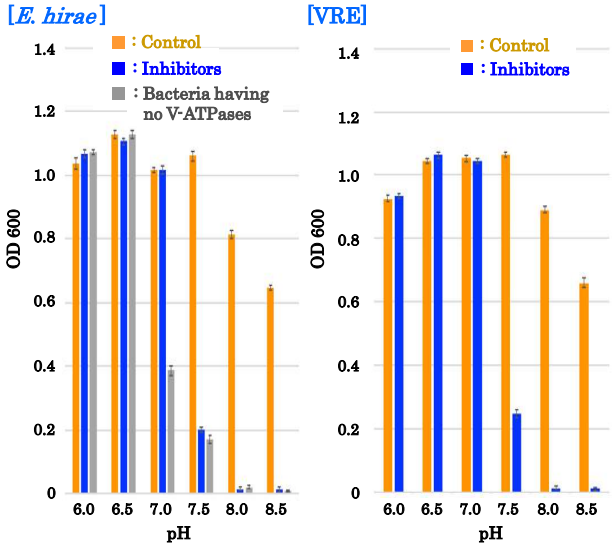
2-Arylbenzimidazole derivatives have been confirmed to bind to the binding sites of the membrane subunits in V-ATPases (the boundary surface of Subunit a and Ring c) and inhibit the V-ATPase activities.



3D Structure of Intestinal V-ATPases in Enterococcus by Cryo Electron Microscope Analysis (Left) and Schematic Model of Inhibitor binding to Binding Sites (Right)

The inhibitors have been confirmed to bind to the two bases both in Subunit a and Ring c which are important for Na^+ transporting.

Efficacy of V-ATPase Inhibitors (*in vitro*)



The inhibitors have been observed to strongly inhibit the growth of *E. hirae* and VRE at pH 7.5 or higher.

APPLICATION expected

◎ Application as new antimicrobial agents against the drug-resistant enterococci having V-ATPases

◎ Application as broad-spectrum antimicrobial agents in combination with other agents

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Licensable Patent

Title of Invention: Inhibitor for V-ATPase Activity, Antibacterial Agent, Medicine, Antibacterial Method and Screening Method

International Publication No.: WO2020149295

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