

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 V₀ domains (subunits in the membranes) and V₁ 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).

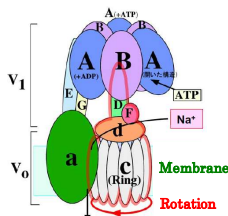


Fig. 1. Schematic Model of V-ATPases

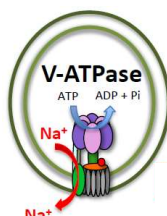
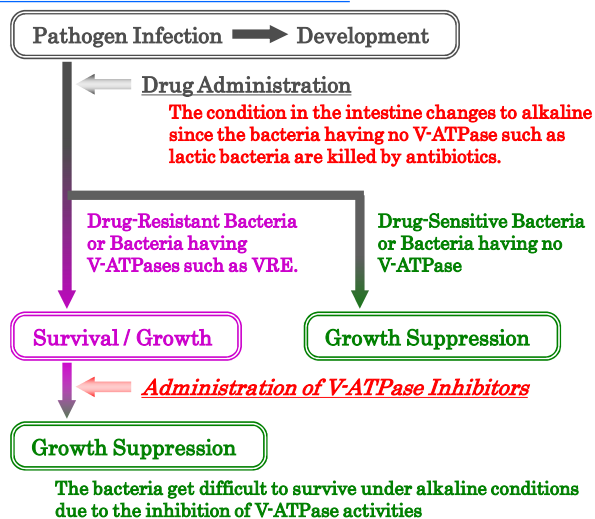


Fig. 2. Mechanism of Na⁺ Draining

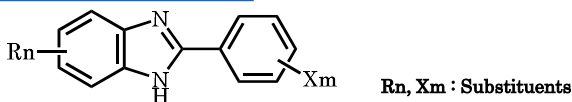
Role of V-ATPase Inhibitors



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

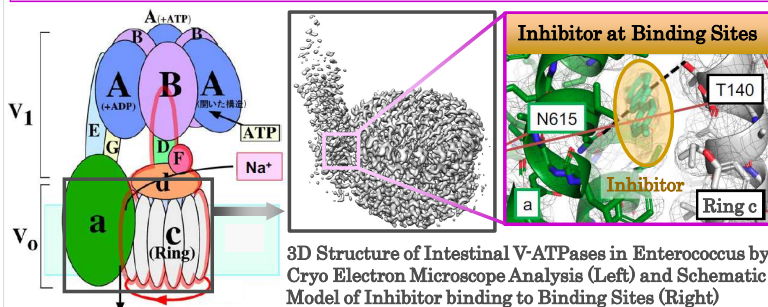
EFFECT of INVENTION

V-ATPase Inhibitors



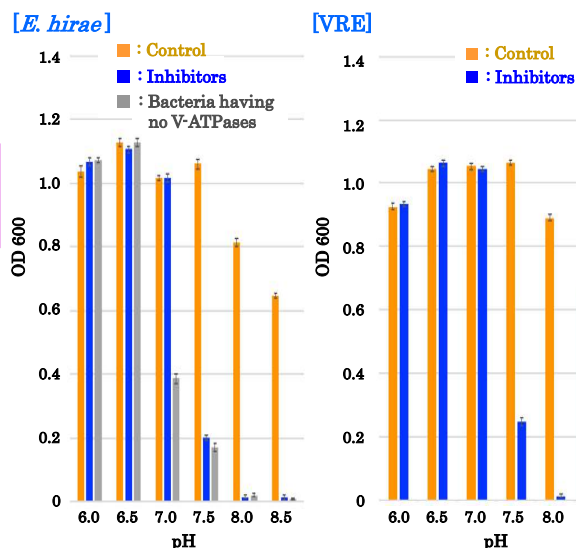
2-Arylbenzimidazole Derivatives

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.



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

Representative Inventor:

Takeshi Murata (Professor, Chiba University)

Licensable Patent

Title of Invention:

Inhibitor for V-ATPase Activity, Antibacterial Agent, Medicine, Antibacterial Method and Screening Method

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Contact:

IP management & Licensing Group, Department of Intellectual Property Management, JST
 TEL) +81-3-5214-8486 email) license@jst.go.jp URL) www.jst.go.jp/chizai

