RESEARCH NEWS STORY

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V-161: A Breakthrough in the Fight against Antibiotic-Resistant VRE Infections

V-161 targets a crucial enzyme in VRE, offering promise in combating antibiotic-resistant infections in hospital environments

V-161, a novel compound targeting the Na^+-V-ATPase enzyme in vancomycin-resistant *Enterococcus faecium* (VRE), significantly reduces bacterial growth and colonization. A recent study has demonstrated a promising approach for fighting antibiotic resistance by identifying a compound, V-161, that inhibits a sodium-pumping enzyme critical for VRE survival under alkaline conditions in the intestine while preserving beneficial bacteria. This breakthrough offers hope for treating hospital infections and tackling the global threat of antibiotic-resistant bacteria.

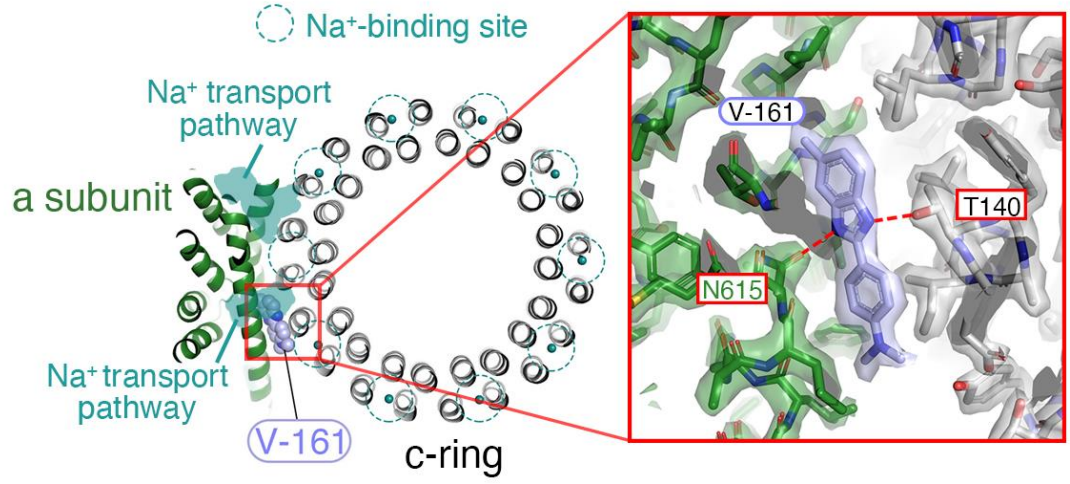

Image title: Structure of the V_O domain in *Enterococcus hirae* V-ATPase enzyme with V-161 inhibitor
Image caption: Researchers from Japan have identified V-161, a compound that inhibits *Enterococcus hirae* V-ATPase activity, disrupting Na^+ transport and effectively inhibiting VRE growth
Image credit: Takeshi Murata from Graduate School of Science, Chiba University, Japan
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The rise of antibiotic-resistant bacteria is a global health concern, with studies projecting over ten million deaths annually by 2050 due to these resistant infections. The World Health Organization (WHO) has identified twelve critical antibiotic-resistant pathogens, including vancomycin-resistant Enterococci (VRE), such as *Enterococcus faecium* (*E. faecium*). VRE causes severe hospital-acquired infections like endocarditis and sepsis and has developed resistance to multiple antibiotics, highlighting the urgent need for new antimicrobial treatments.

In response to this crisis, a team of researchers led by Professor Takeshi Murata from the Graduate School of Science, Chiba University, Japan, has discovered a promising new compound, V-161, which effectively inhibits the growth of VRE. Their research examined a sodium-pumping enzyme found in these bacteria called Na^+-transporting V-ATPase found in *E. hirae*, a close relative of *E. faecium*, used as a safer, more tractable model for studying the enzyme. The team consisted of Assistant Professor Kano Suzuki, first author from the Graduate School of Science, Chiba University; Associate Professor Yoshiyuki Goto from the Medical Mycology Research Center, Chiba University; Professor Toshiya Senda and Associate Professor Toshio Moriya from the Structural Biology Research Center, High Energy Accelerator Research Organization; and Professor Ryota Iino from the Institute for Molecular Science, National Institutes of Natural Sciences. This study, published online in *Nature Structural & Molecular Biology* on November 21, 2024, hypothesized that Na^+-transporting V-ATPase could play a key role in the development of an antibiotic that specifically targets VRE without affecting beneficial bacteria.

Dr. Murata explains, *"This enzyme helps pump sodium ions out of the cell, aiding in the survival of VRE, especially in alkaline environments like the human gut. This enzyme is absent in beneficial bacteria like lactobacilli, and while humans have a similar enzyme, it serves different functions. This makes the Na^+-transporting V-ATPase in VRE an ideal target for selective antimicrobial treatments."* He further states, *"We screened over 70,000 compounds to identify potential inhibitors of the enzyme Na^+-V-ATPase. Among these, V-161 stood out as a strong candidate, demonstrating significant effectiveness in reducing VRE growth under alkaline conditions—an environment critical for the survival of this resistant pathogen."* Following this, further studies revealed that V-161 not only inhibited the enzyme function but also reduced VRE colonization in the mouse small intestine, highlighting its therapeutic potential.

A major finding of this study was the high-resolution structural analysis of the membrane V_0 domain of the enzyme, revealing detailed insights into how V-161 binds to it and disrupts the enzyme function. V-161 targets the interface between the c-ring and the a-subunit of the enzyme, effectively blocking sodium transport. This structural information is critical to understanding the workings of the compound and provides a foundation for developing drugs that target this enzyme.

Dr. Murata explains, *"The findings obtained from the structural analysis could be used for the development of treatments for other refractory bacteria and also form a basis for the development of important guidelines for future drug development."* He further adds, *"We hope that the development of innovative treatments not only for VRE but also a wide range of drug-resistant bacteria will greatly advance the treatment of drug-resistant infections."*

While the results are promising, the study also notes that further research is needed to make V-161 even more effective and improve its efficacy against a broader range of bacterial strains. Despite these challenges, the findings mark a significant advancement in developing new therapeutic agents to combat VRE and other antibiotic-resistant bacteria. As part of ongoing efforts to refine V-161, the research team plans to test it against other bacterial strains to further assess its potential.

Reflecting on these results, Dr. Murata says, *"We hope that these efforts will ultimately yield more effective treatments for infections caused by VRE and other drug-resistant bacteria, making a significant impact on the fields of infectious diseases and public health."* The ultimate goal is to develop a new class of antibiotics that not only complements existing treatments but may also serve as a powerful solution to combat the escalating threat of antibiotic resistance.

About Professor Takeshi Murata

Dr. Takeshi Murata is a Professor at the Graduate School of Science and the Director of the Membrane Protein Research Center at Chiba University, Japan. He earned his Ph.D. in Engineering from the Tokyo University of Science in 2000. With more than 200 publications, Dr. Murata has received numerous honors, including the Young Researcher Presentation Award at the 49th Symposium of the Society for Bioenergy Research. His research primarily focuses on membrane proteins and structural studies, areas in which he continues to make significant contributions.

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