POLSKY Center for Entrepreneurship and Innovation
THE UNIVERSITY OF CHICAGO

Small Molecule Potentiators of Antibiotics for Treatment of Methicillin-Resistant Staphylococcus Aureus (MRSA)

SUMMARY

Beta-lactam antibiotics work by disrupting bacterial cell wall synthesis and represent the first-line therapy for patients infected with methicillin-resistant Staphylococcus aureus (MRSA) – however, an increasing number of MRSA strains that are resistant to these antibiotics are emerging. The Staphylococcus aureus vraSR operon is a highly conserved cell wall stress-sensing and signaling system, and expression from the operon allows for activation of genes that enable MRSA bacteria to adapt to cell wall stress and resist antibiotic treatment. Researchers at the University of Chicago have identified compounds that inhibit expression from the vraSR operon to potentiate antibiotic treatment of MRSA, thereby rescuing the first-line therapy.

KEY RESULTS

Compounds were identified that demonstrated efficacy in potentiating two different antibiotics, reducing the concentration of the antibacterials required to inhibit the growth of bacteria. These compounds have been shown to reduce expression from the vraSR operon via RT-PCR. The molecules have further been demonstrated to have effects in a variety of MRSA strains and to act synergistically with oxacillin.

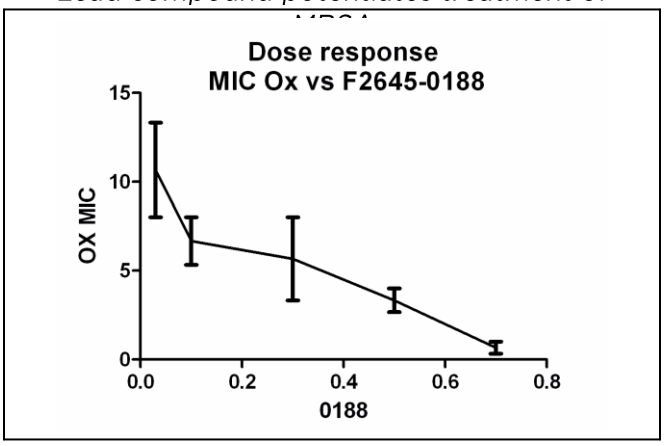
ADVANTAGES

- Rescues first-line therapy for a significant medical problem.
- Targets a highly conserved antibiotic resistance mechanism.
- Prevents development of an antibiotic-resistant population of bacteria.
- Small molecule approach.

APPLICATIONS

- Combinational therapy to potentiate treatment of MRSA with beta-lactam antibiotics.

Lead compound potentiates treatment of



Dose response of small molecule antibiotic potentiator and its reduction of the minimal inhibitory concentration of oxacillin (OX MIC). Courtesy of Daum Lab.

TECHNICAL DESCRIPTION

The vraSR operon system comprises genes, and regulates over 45 downstream genes, some of which are involved in fundamental processes that modulate the development of resistance to antibiotics. These researchers have identified compounds that inhibit expression of the vraSR operon. Lead anti-MRSA compounds were identified based on their ability to enhance oxacillin-mediated inhibition of MRSA growth and inhibit vraSR operon gene expression. The molecules were tested for efficacy against multiple MRSA strains, their ability to potentiate a second antibiotic (vancomycin), and their binding to the operon. Lead molecules were able to decrease the minimum required antibiotic concentration by at least a factor of 16. Researchers are currently testing these compounds in a soft-tissue model of MRSA infection and exploring chemically optimizing the lead molecules.

REFERENCE
UCHI 2145, 2215

DEVELOPMENT STAGE
Research/ animal studies

THERAPEUTIC AREAS
MRSA

PUBLICATION
Boyle-Vavra, et al. VraT/YvqF Is Required for Methicillin Resistance and Activation of the VraSR Regulon in *Staphylococcus aureus*. Antimicrob Agents Chemother. 57(1):83-95, 2013.

INTELLECTUAL PROPERTY
PCT/US2013/068085

PCT/US2014/029237
(Both now pending in US, Europe, and Japan)

INVENTOR(S)
Dr. Robert Daum, MD is a pediatric infectious disease physician and head of the University of Chicago's MRSA Research Center. He serves on the US Food and Drug Administration's Vaccine and Related Biological Products Advisory Committee (VRBPAC) and is the Chair of the Immunization Advisory Committee with the Illinois Department of Public Health. Dr. Daum has consulted for several large pharmaceutical companies regarding development of MRSA vaccines.

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