



Novel antimicrobial of new chemical class and new mode of action for therapeutics as monotherapy or in combination with other antibiotics.

Image source: National Institute of Allergy and Infectious Diseases (NIAID), phil.cdc.gov/Details.aspx?pid=18128.

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In vitro and *in vivo*
data available.

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Novel Compounds for Reversing β -Lactam Resistance in MRSA

Abstract

Staphylococcus aureus is the leading cause of both hospital and community-associated infections worldwide and a major cause of morbidity and mortality due to the emergence of methicillin-resistant *S. aureus* (MRSA). The pipeline for innovative antibiotics is insufficient to overcome this healthcare threat and, thus new strategies are urgently needed.

Using a cell-based screen of ~45,000 diverse synthetic compounds, researchers at McMaster University discovered a potent bioactive (MAC-545496) that reverses β -lactam resistance in the community-acquired MRSA USA300 strain. This compound attenuates the MRSA virulence *in vivo* with potency at the low nanomolar range, inhibits biofilm formation, and abrogates intracellular survival in macrophages. Mechanistic characterization through chemical-genomics and biochemical approaches revealed the cellular target to be GraR (glycopeptide resistance associated protein R), an important virulence factor and antibiotic resistance determinant. This newly discovered small molecule bioactive is the first inhibitor against GraR; it can serve as: (i) an antibiotic adjuvant reversing methicillin resistance; and (ii) an anti-virulence agent effective as a monotherapy *in vivo* against MRSA. Together, this work provides a novel antibacterial lead series of new mechanism to combat drug-resistant Staphylococcal infections.

Applications

- Antimicrobial therapy as monotherapy or in combination with other antibiotics

Advantages

- Potent activity against MRSA with potential use as a monotherapy or in combination with other antibiotics
- Reversal of beta-lactam resistance in MRSA
- Prevention of biofilm formation esp. in the presence of anticoagulants commonly used in catheter locks and IV infusion solutions
- Intracellular activity against MRSA
- Definitive infection control of chlamydial infections will likely be achievable through a safe and efficacious vaccine