

Inhibitors of the σE Virulence Pathway as Novel Antibiotics

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Intellectual Property:

Issued Patent:
- US 8,962,550

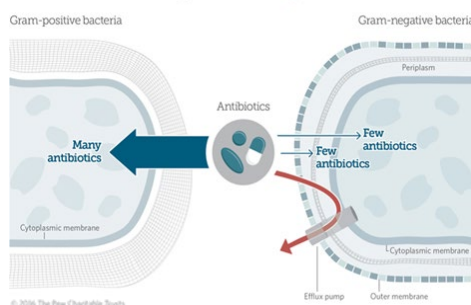
Pending Applications:
- US Provisional: 63/030,673

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Barriers to Antibiotic Entry Into Gram-Negative Bacteria



Clinical Need:

There is a critical need for new drugs to treat infections of Gram-negative antibiotic-resistant bacteria. The problem is especially urgent in hospital settings where resistance to multiple antibiotics is found in approximately 20% of infections caused by Enterobacteriaceae, predominantly *Escherichia coli* and *Klebsiella pneumoniae*, and in 13% of infections caused by *Pseudomonas aeruginosa*.

Value Proposition:

To reduce the incidence of hospital-associated infections caused by antibiotic-resistant bacteria through use of a novel drug that inhibits a virulence pathway not targeted by existing antibiotics and may be used as a stand-alone therapy or in combination with existing drugs.

Technology Solution:

The σE pathway is critical for virulence in tested Enterobacteriaceae and is essential in *E. coli*. Inhibition of this mechanism is novel because no existing drugs target σE or other components of the envelope stress response pathway. Using a patented high-throughput screening system, researchers at Penn State's Eberly College of Science identified several novel σE inhibitors exhibiting antibiotic activity and drug-like physical properties. Structure-activity relationship (SAR) studies assessed the importance of different functional groups for approximately 50 analogs. Compounds from the lead series show MIC levels of 1-3 $\mu\text{g}/\text{mL}$ in *E. coli*, no cytotoxicity and no CYP450 inhibition. Drugs that emerge from these compounds have the potential to be used as stand-alone treatments or as supplements to traditional antibiotics.

Market Opportunity:

Gram-negative bacilli are the most common cause of hospital-acquired infection and the most common causes of infection in the ICU. By 2026, global sales for therapeutics to treat hospital-acquired Gram-negative infection are expected to exceed \$3.5 billion, with the US representing half of global sales. New antibiotic treatments, such as antivirulence factors, are needed as only four new antibiotics have been approved since 2014.

Path Forward:

Continue lead optimization studies with focus on potency, ADME-tox and demonstration of efficacy in an animal model system.



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