Small Molecule Inhibitors of Bacterial CSE for Treatment of Diverse Antibiotic-Resistant Infections

Innovative approache to combat antibiotic resistance and enhance the efficacy of existing antibiotics, particularly against biofilm-encased and persister bacteria

Technology

The Nudler Lab has identified a novel antibacterial target, to which they have discovered small molecule inhibitors that show pre-clinical efficacy against both gram-positive and -negative human pathogens. They identified the enzyme cystathionine γ-lyase (CSE) as the primary generator of hydrogen sulfide (H_2S) in *Staphylococcus aureus* and *Pseudomonas aeruginosa*. H_2S production has been shown to play a crucial role in bacterial defenses against antibiotics. The team utilized a multi-pronged approach combining computational, structural, and biochemical methodologies to screen, select, and validate small-molecule compounds that specifically target bacterial CSE (bCSE). Three promising compounds, designated NL1, NL2, and NL3, inhibited the activity of bCSE at low nanomolar concentrations. High-resolution x-ray structures demonstrated that the inhibitors act allosterically, binding to a region distinct from the bCSE catalytic site, and importantly, do not affect human CSE, suggesting a low potential for off-target effects. These inhibitors were tested *in vivo* using murine models of infection, where they were found to significantly enhance the efficacy of various bactericidal antibiotics, reduce the population of persister cells, and inhibit biofilm formation. These findings highlight the novel approach of these inhibitors in combating antibiotic resistance and enhancing the efficacy of existing antibiotics.

Background

Antibiotic resistance is a growing public health concern, with predictions that antibiotic-resistant pathogens will cause 10 million deaths per year by 2050. Existing antibiotics often fail to effectively treat infections due to the presence of biofilm-encased and persister bacteria, which exhibit high levels of tolerance. The development of drugs that can potentiate existing antibiotics, while also reducing bacterial tolerance, is urgently needed. The production of H_2S by bacteria, a process primarily mediated by the enzyme CSE, has been found to be a critical part of bacterial defense mechanisms against antibiotics. The inhibitors developed by the Nudler Lab disrupt this defense mechanism, thereby enhancing the action of antibiotics and offering a much-needed therapeutic for antibiotic-resistant infections.

Development Stage

The innovators have conducted considerable pre-clinical validation of 3 small molecule inhibitors of bCSE and are looking for a commercial partner to proceed to clinical development for antibiotic-resistant bacterial infections.

Technology ID

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Category

Life Sciences/Biochemicals & Small Molecules
Life Sciences/Therapeutics/Antibacter

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Application

- Potentiation of existing antibiotics against a broad spectrum of bacterial infections
- Reduction in time course of antibiotic treatment
- Reduction of bacterial tolerance, including in biofilm-associated and persister bacteria
- Treatment of gram-positive and gram-negative clinically significant bacterial pathogens

Advantages

- **Broad-spectrum enhancement:** Potentiates multiple classes of bactericidal antibiotics against both gram-positive and -negative pathogens
- **Tolerance reduction:** Reduces the number of persister bacteria and disrupts biofilm formation
- **Highly specific:** Allosteric inhibitors target bacterial CSE without affecting human CSE
- **Rapid:** Targeting of the H2S-producing system does not require de novo protein synthesis, offering a rapid effect even under conditions of translational shutdown imposed by antibiotics
- **Potent and reversible:** The identified compounds have mid- to low-nanomolar potency and act via reversible mechanisms

Intellectual Property

NYU has filed a pending U.S. nonprovisional patent application covering the bCSE inhibitors.

References

1. Shatalin K, Nuthanakanti A, Kaushik A, et al. , https://pubmed.ncbi.nlm.nih.gov/34112687/