Docket #: S17-243

Strategy for more effective antibiotics- conjugation to a molecular transporter

Researchers at Stanford have developed a strategy to improve the efficacy of antibiotics by conjugating the antibiotic to a guanidinium-rich molecular transporter (GR-MoTr). The overuse of antibiotics has led to increasing development of antibiotic-resistant bacteria, including “superbugs”, with more than 2 million people infected in the U.S. per year. To further complicate matters, new antibiotic development has lagged. Thus, there is a major need for new therapeutics against bacterial infections, especially for those that can overcome antibiotic-resistance and eradicate chronic infections. To help meet this need, the inventors took advantage of their molecular transporter technology (see Stanford Docket S15-370). Here, they have conjugated the molecular transporter to the conventional antibiotic, vancomycin. The molecular transporter helps keep vancomycin associated with the cell enabling it to outperform conventional vancomycin. The conjugate is effective in eradicating vancomycin-resistant bacteria, slow-growing biofilms, stationary and persister cells, and is capable of reducing the intracellular bacterial load in infected mammalian skin cells. This technology provides the means to effectively treat multi-drug resistant and biofilm-associated bacteria linked to recurrent and chronic infections.

Stage of research

The inventors have shown that the vancomycin-GR-MoTr conjugate outperforms conventional vancomycin (often by orders of magnitude) in persister cell and biofilm assays, and demonstrates a faster bactericidal mode of action, tighter membrane association and intracellular accumulation. Further, the conjugate reduced biofilm loads *in vivo*, while exhibiting no acute toxicity or damage to skin cells.

Applications

- Antibiotic to treat bacterial infections, including:
  - Biofilms
  - Stationary and persister cells
  - Multidrug-resistant bacteria
  - Intracellular bacteria
- Research tool

Advantages

- Solves an unmet need- can be used to treat biofilm-associated, antibiotic-resistant, and/or intracellular bacterial infection
- Rapid and potent bactericidal activity
- Significantly increased efficacy as compared to conventional vancomycin against slow-growing bacterial populations
- Excellent therapeutic index
- Enhances antimicrobial penetration into mammalian cells
- Conjugate retains activity of conventional vancomycin in treating exponentially-growing planktonic bacteria
- Strategy may be extended to other antibiotics- enables development of novel derivatives of FDA-approved antimicrobial agents

Publications

- Alexandra Antonoplis, Xiaoyu Zang, Melanie A. Huttner, Kelvin Chong, Yu B. Lee, Julia Y. Co, Manuel Amieva, Kimberly Kline, Paul A. Wender, and Lynette Cegelski, "A dual function antibiotic-transporter conjugate exhibits superior activity in sterilizing MRSA biofilms and killing persister cells," *J. Am. Chem. Soc.,* (2018).
- Nathan Collins, "Stanford chemists develop a new way to treat potentially deadly antibiotic-resistant infections," Stanford News (2018).
- Nathan Collins, "Deadly bacteria are no match for this new antibiotic treatment plan," Stanford Engineering (Nov. 8, 2018).

Patents

- Published Application: WO2019165051
- Published Application: 20240016945
- Issued: 12,194,105 (USA)

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