Applications of Acyldepsipeptide (ADEP) Fragments in Antibacterial Therapy (Case 2275)

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Technology description

Brief Description:
Acyldepsipeptide (ADEP) antibiotics hold promise as antibacterial drugs in this time of drug resistance and the urgent need for more therapeutic options. ADEPs are molecules that act by binding to and activating the activity of ClpP peptidase – no antibacterial agents on the market today have this mechanism of action.
It has been demonstrated that ADEPs have efficacy in mouse models of infection against pervasive bacterial pathogens such as Staphylococcus aureus, Streptococcus pneumoniae, and Enterococcus faecalis. While the ADEPs have potential as antibacterial drugs, they have two known liabilities. First, the chemical synthesis of ADEPs requires multiple chemical steps. Syntheses with multiple steps are expensive due to increased reagent costs and the purifications of products after each step. Second, some strains of bacteria, like Mycobacterium tuberculosis, are not susceptible to ADEPs because they have membrane-bound efflux pumps that mediate resistance. In order for ADEPs to be effective in the treatment of infections caused by bacteria with efflux pumps, strategies to circumvent the efflux pump mechanism need to be developed. The Brown technology offered here is proving to be an effective and promising strategy.
The novel technology uses fragments of the ADEP structure in two compelling and beneficial ways: as either antibacterial agents directly or as critical competitors of the efflux pumps. Notably, ADEP fragments are much easier to prepare than the full structures. In direct toxicity, the side chain of ADEPs is necessary and sufficient for their antibacterial activity. Indeed, the ADEP side chain is toxic to bacteria like Bacillus mycoides and Bacillus subtilis (relatives of the anthrax-causing bacterium Bacillus anthracis) and Mycobacterium tuberculosis. The efficacy of the ADEP side chain against M. tuberculosis is not only toxic, but is also not recognized by (evades) the efflux pump. 技术优势

Advantages

In the competitive scenario, particular analogs of the ADEP side chain that do not have direct antibacterial activity can instead act as potentiators of ADEP activity against bacteria that have resistance-conferring efflux pumps; the ADEP fragments are recognized by the efflux pumps and compete in the presence ADEPs.

ADEP fragments may provide a unique and highly efficacious strategy as a potent antibacterial against challenging microbes with or without efflux pumps.

Institution

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