

Promising New Antibiotics Effective Against Infections Resistant To And Tolerant Of Current Treatments

St Jude Children's Research Hospital

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For over 100 years, antibiotics have been used to fight bacterial infection and disease. However, bacteria are increasingly developing resistance to front line antibiotics, and new therapies are needed to treat these bacterial strains. Dr. Richard Lee, Ph.D., a member of the St. Jude Department of Chemical Biology and Therapeutics, is developing two new classes of compounds to be effective in treating strains that are no longer effectively treated with current therapies. One compound is an adaptation of an old antibiotic- Spectinomycin, which is modified using structure based drug design. The other compound is designed to treat chronic infections and biofilms caused by persister cells that have become tolerant of existing antibiotics. Both compound classes are described below:

Treating resistant bacteria

Dr. Lee's laboratory designed a promising new class of antibiotics, called aminomethyl spectinomycins, which follows his work on Spectinomycin analogs for treating tuberculosis. In this case a new series of spectinomycin analogs has been developed for treating a broad spectrum of respiratory tract infections including *S. pneumoniae*, the most common pathogenic bacteria associated with this type of infection. The aminomethyl spectinomycins are active against drug resistant strains. In collaboration with Dr. Jason Rosch in the Infectious Diseases department, the robust efficacy of this compound series has been demonstrated at low compound dosing levels, further validating this series. These compounds have been licensed by Microbiotix, a privately-held, clinical stage biopharmaceutical company engaged in the discovery and development of novel small molecule anti-infectives.

"This study demonstrates how classic antibiotics derived from natural products can be redesigned to create semi-synthetic compounds to overcome drug resistance." - Richard Lee, Ph.D.

Treating tolerant bacteria

Dr. Lee and his collaborators developed another set of compounds designed to treat bacteria, fungi and parasites that develop multidrug tolerance by becoming dormant.

“ *Small subpopulations of tolerant microbial cells are called persister cells, because they can survive the antimicrobial treatments that kill their genetically identical siblings.*”

When persister cells are left behind, they become a reservoir from which an infection can recur. Examples of chronic infections include endocarditis, urinary tract infections, gingivitis, middle ear infections, fatal lung disease (cystic fibrosis) and infections produced by biofilms.

These infections are often associated with implanted medical devices, such as catheters and artificial joints. Multidrug tolerant infections account for more than 60% of all microbial infections, are hard to treat and subject to infection relapse. Traditional antibiotics kill active cells via inhibition; however, this new set of compounds acts to kill dormant cells. They could be used to treat infections caused by biofilms; and other infections caused by chronic bacteria persister cells. These compounds have been licensed to Arietis, a Boston-based biotechnology company, focused on the discovery and development of novel antimicrobial agents.

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