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Non-Confidential Description - PSU No. 4256
"Combating Bacterial Infections by Killing Persister Cells"

Field of Invention/Keywords:

Biofilm infections, Bacterial resistance, Broad-spectrum antibiotics, Metabolic dormancy.

Inventors:

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Background

All pathogens produce a small subpopulation of dormant, metabolically inactive persister cells that are highly tolerant to traditional antibiotics, which target actively growing cells. Once an antibiotic concentration drops, surviving persisters re-establish the population, causing a relapsing chronic infection. Persisters are especially significant when the pathogen is shielded from the immune system by biofilms, or in sites where the immune components are limited; for instance within the nervous system, the stomach, or inside macrophages. It appears that tolerance of persisters plays a leading role in chronic infections, while resistance is the leading cause of recalcitrance to therapy in acute infections.

Invention Description

The researchers have discovered a FDA-approved chemotherapy agent, which passively diffuses into cells. A specific functional group of the compound is reduced spontaneously within the bacterial cytoplasm and kills persister cells by crosslinking DNA. The unexpected results showed the agent's broad-spectrum activity against growing, non-growing and persister cells in an animal model as well as in a wound model. When compared to ciprofloxacin, the agent was 2,300 fold more effective against exponentially-growing *E. coli* cells and 150,000-fold more effective against mid-stationary-phase cells in a buffered medium. In addition, the agent killed 100,000 fold more biofilm cells than ciprofloxacin. The disparity was mirrored even when in an anaerobic environment. The researchers examinerd the viable but nonculturable state (VBNC) - a metabolic state closely related to persistence. The researchers found a 7-fold increase in VBNC mortality compared to ciprofloxacin, while also eradicating the culturable population. The lethality extended to Gram-native and Gram-positive pathogens.

Status of the Invention

The subject invention identified a novel mode of action to kill persister cells. The FDA-approved agent offers a well-characterized structure that may be further modified to create downstream composition-of-matter patent rights. Examples are chronic infections of implanted medical devices such as catheters and artificial joints, urinary tract infections, middle ear infections and fatal lung disease such as cystic fibrosis and tuberculosis. The invention has applications as a therapeutic to treat the seventeen million new biofilm infections every year in the USA, which leads to 550,000 fatalities.

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