Repurposing Bismuth-Based Drugs to Overcome Antibiotic Resistance in *Pseudomonas aeruginosa*

The rise of antibiotic-resistant *Pseudomonas aeruginosa* (P. aeruginosa) infections presents a significant global healthcare challenge. Conventional antibiotic therapies are hindered by the bacterium's robust resistance mechanisms, including efflux pumps, biofilm formation, and restricted membrane permeability. This study explores the potential of bismuth-based drugs, such as bismuth subsalicylate (BSS), to sensitize *P. aeruginosa* to a range of antibiotics through a novel mechanism targeting bacterial iron homeostasis.

Bismuth compounds disrupt the iron acquisition system of *P. aeruginosa* by binding to siderophores and interfering with iron–sulfur cluster enzymes critical for cellular respiration. This leads to the inhibition of the electron transport chain, dissipation of the proton motive force, and impairment of multidrug efflux pumps. Consequently, intracellular antibiotic accumulation increases, enhancing the efficacy of antibiotics across diverse classes, including tetracyclines, macrolides, and quinolones. Notably, the combinatory therapy demonstrated strong bactericidal effects, reducing bacterial load by up to 8-log units in *ex vivo* models and improving survival rates in murine acute pneumonia models.

Importantly, the use of bismuth-antibiotic combinations was found to prevent the evolution of high-level antibiotic resistance during prolonged exposure. Safety evaluations confirmed low cytotoxicity and no significant adverse effects following pulmonary delivery in mice. These findings underscore the translational potential of bismuth-based drugs as effective adjuvants for treating multidrug-resistant *P. aeruginosa* infections.

This study highlights a promising and cost-effective strategy to extend the utility of existing antibiotics, addressing the critical need for innovative solutions to combat antimicrobial resistance.

Reference: https://www.nature.com/articles/s41564-024-01807-6

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