Bismuth-based drugs sensitize *Pseudomonas aeruginosa* to multiple antibiotics by disrupting iron homeostasis

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Presenter : Wan Jing Chen **Date/Time** : 2025/4/10 16:20-17:10

Commentator : Po Lin Chen Ph.D. **Location** : Room 601, Med College Building

Background :

Pseudomonas aeruginosa is a typical opportunistic pathogen that causes severe infections in vulnerable patients. Due to it's biofilm forming ability and muti-drug efflux pump, *P.aeruginosa* can adapt to environment and develop antibiotic resistance, leading to recurret infection . Repurposing existing drugs to enhance antibiotics efficacy is a promising strategy to combat antibiotics resistance. Bismuth compounds are currently used to treat peptic ulcers caused by *Helicobacter pylori*. Previous reports indicate that the combination of bismuth drug and antibiotics is effective to against *H. pylori*, including resistant strains. Recent studies have also showed that bismuth compounds can inhibit metallo-β-lactamases and tetracycline inactivation enzyme, suggesting that the combination of bismuth drug and antibiotics may help overcome antibiotics resistance in bacteria.

Objective :

To elucidate the potential of bismuth drug in combination with various antibiotics to against *P. aeruginosa*.

Results :

The authors combined bismuth subsalicylate (BSS) with 30 antibiotics to against World Health Organization priority pathogen. BSS exhibited great synergy with all antibiotics classes against *P. aeruginosa* (PAO1). They found that BSS downregulated genes associated with iron acquisition system and reduced pyoverdine production. Further analysis revealed that bismuth directly interacted with siderophores and promoted Fur protein, which repressed siderophore synthesis, bind to its target. These data indicate that bismuth disrupts iron homeostasis by interacting with siderophore and Fur. Additionally, BSS inhibited iron-sulfur-containing enzymes, reducing electron transport chain (ETC) activity and dissipating proton motive force. This suppressed efflux pumps and led to intracellular accumulation of antibiotics. The combination of bismuth drug and antibiotics showed potent antibacterial efficacy and significantly improved the survival rate of mice in mouse lung infection model.

Conclusion :

Bismuth drugs decreased intracellular iron and ETC by targeting iron uptake system, leading to inhibition of ATP generation and multidrug efflux pump. This resulted in increased intracellular antibiotic accumulation and enhanced *Pseudomonas aeruginosa* susceptibility to antibiotic treatment.

Reference :

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