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Editorial

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Bismuth thiols as anti-biofilm agents

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Editorial

Bismuth thiols (BTs) are antimicrobial agents with great potential to prevent and treat biofilms. The active ingredient in BTs is bismuth- a popular, over-the-counter, antimicrobial agent (e.g., Pepto-Bismol®), which exhibits anti-biofilm properties, likely by inhibiting exopolysaccharides (EPS)- the biofilm matrix in most bacteria.[1] Bismuth appears to interfere with iron transport/metabolism,[2] which is essential for ATP production and, in turn, EPS synthesis.

The other halves of BT's are thiols-small, sulfhydryl-containing, organic molecules. Natural thiols include methionine, cysteine and ∝-lipoic acid, which interact with iron, zinc and other metal-cofactors for enzyme function, immune surveillance, detoxification, and protein structure. Medically, thiols are employed as chelating agents and antidotes for heavy metal poisoning.[3] However, only lipophilic thiols potentiate bismuth antimicrobial activity, some by several orders of magnitude. Lipophilic thiols not only solubilize bismuth, but also allow it to traverse biological membranes to help reach its target.[4] BTs likely interfere with iron transport and redox enzymes involved in EPS expression, via thiol exchange.[5]

The combination of bismuth and thiol (preferably dithiol) produces a potent, broad-spectrum antimicrobial agent with diverse properties, depending on the thiol employed. The simplest and most potent BT is bismuth ethanedithiol (BisEDT). However, each thiol has unique biological properties: whether bacteriostatic or bactericidal; acidic or alkaline; hydrophilic or hydrophobic; and anti-bacterial, anti-fungal,[6] or even anti-viral activity. Rather than a single drug, BTs are a versatile family of agents.

BTs show potent antimicrobial activity against a wide range of bacteria.[7] At sub-inhibitory concentrations (≤1µg/mL), BTs prevent biofilm formation in methicillin-resistant *Staphylococcus aureus* (MRSA)[8] and *Pseudomonas aeruginosa*.[9-11] Subinhibitory BTs inhibited EPS production in *Klebsiella pneumoniae* by over 90%, which drastically increased uptake and killing by white blood cells.[12] In animal models, BT-coated grafts inserted subcutaneously into rats, then contaminated with MRSA, disallowed build-up of bacteria on graft surfaces.[13] BTs significantly decreased adherence of several bacterial pathogens on the surface of stents.[14] Intratracheal administration in rats with liposomal BT-tobramycin reduced pulmonary *P. aeruginosa* infection significantly.[15] When administrated locally to infected open fracture wounds, BTs prevented *S. aureus* biofilm formation, disrupted preexisting biofilm and sensitized bacteria to antibiotic treatment and immune defenses.[16] Several antibiotics were potentiated in combination with sub-MIC BTs,[17] even against highly-resistant *Burkholderia* strains.[18]

BisEDT is now poised to begin Phase 2 clinical studies. It has been granted FDA Qualified Infectious Disease Product (QIDP) status for treatment of serious, life- or limb- threatening infections associated with orthopedic implants and chronic wounds. New antimicrobial/anti-biofilm therapies for serious lung infections and for biodefense are underway.

By virtue of enhancing antibiotics, reducing virulence, and fostering immune defenses at low, nontoxic concentrations- without inducing bacterial resistance-BTs may address many unmet needs in medicine. BTs are expected to safely and effectively treat antibiotic-resistant infections, including those from MRSA, VRE, resistant Gram-negative bacteria, TB, bioterrorism agents, and many other bacteria. They also hold promise as environmentally responsible solutions to the problem of biofouling in industrial processes.[19,20]

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Conflicts of interest

Author declares that there is no conflict of interest.

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