Intrapolymeric Catalysis of Nitric Oxide Release via a Metal-Organic Framework for Potent Antimicrobial Materials

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Statement of Purpose: Contamination of medical devices such as urinary catheters and blood-contacting devices constitutes up to 75% of the urinary and bloodstream-related nosocomial infections reported annually. To combat medical device-related infection and failure, nitric oxide (NO)-releasing materials have been developed in recent years to evolve NO gas at the polymer-solution interface that elicits antimicrobial responses and disperses biofilms. Small molecule NO donors, such as *S*-nitroso-*N*-acetylpenicillamine (SNAP), are readily integrated into polyurethane elastomers to fabricate catheters and medical devices with NO release capabilities. Despite the potential of this technology to prevent nosocomial infection, it has seen limited clinical translation due to the inability to sustain and modulate NO flux profiles from the materials. Metal-organic frameworks (MOFs) are a well-characterized platform for catalyzing the decomposition of some NO donor compounds, including SNAP, enabling a novel means to generate NO even from the low levels of donor compounds endogenously present in the body. In this study, we developed novel metal-organic polyurethane composites based on multilayer scaffolding of SNAP with the Cu-based MOF $H_3[(Cu_4Cl)_3(BTTri)_8\text{-}(H_2O)_{12}]\cdot 72H_2O$ (CuBTTri). These materials afforded tunable NO release properties, enabling potent antimicrobial action without cytotoxic effects characteristic of other strategies.

Methods: Both CuBTTri and SNAP were readily synthesized based on previously reported methods. Polycarbonate urethane resins with 20 *wt%* polydimethylsiloxane were used in the formulation of composites. Base layers of the resin with 10 *wt%* SNAP were solvent casted then dip-coated with a topcoat containing variable weight percent CuBTTri. Finally, composites were sealed with a coat of resin to reduce leaching. The SNAP+CuBTTri films were characterized for several mechanical and chemical properties, including tensile strength, NO release, SNAP/Cu leaching, and storage stability. The materials were further evaluated in *in vitro* models of cellular compatibility with human fibroblast and endothelial cells, as well as for antimicrobial action against clinically relevant *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA).

Results: The combination SNAP+CuBTTri composites were shown to have tunable NO release kinetics contingent on the weight percent CuBTTri incorporated (**Figure 1**). CuBTTri drastically increased the average NO surface flux over 4 h, leading up to a 1200% increase over baseline levels with just SNAP. This tunable release threshold was mirrored by no significant difference in SNAP/Cu leaching, implicating improved NO release kinetics could be obtained without introducing any additional leachates into the physiological environment.

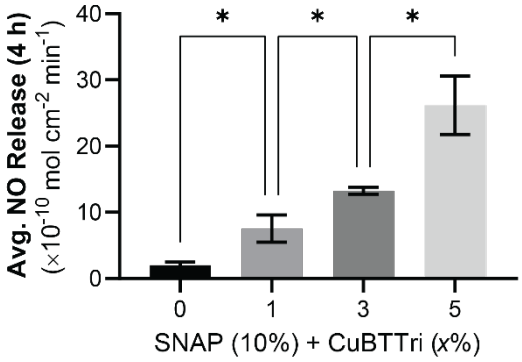

Figure 1: Average NO release from composites after 4 h incubation at physiological conditions. *(P<0.05)

Further biological evaluation of the composites in 24-h bacterial adhesion studies demonstrated the ability for the SNAP(10%)+CuBTTri(3%) films to exhibit up to a 2.75-log reduction in adherent bacteria (**Figure 2**), with similar trends observed for planktonic bacterial growth. Finally, cytotoxicity evaluation of the composites in 24-h leachate growth models demonstrated greater than >80% cellular viability, supporting the biocompatibility of the scaffold and suitability for further *in vivo* studies. These studies demonstrate the efficacy of merging MOFs with NO donors in polymers to enhance device longevity with great potential for future preclinical evaluation.

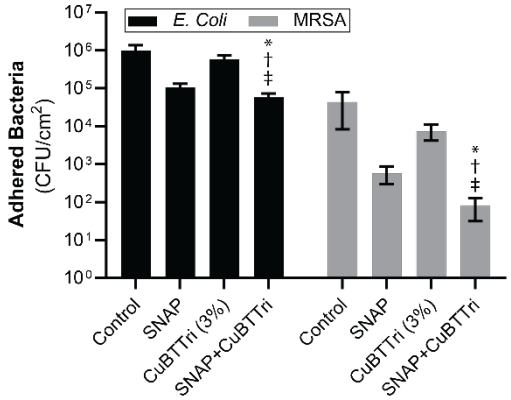

Figure 2: 24-h bacterial adhesion assay of SNAP(10%) +CuBTTri(3%) films. Statistical significance (P<0.05) indicated against *control, †SNAP, and ‡ CuBTTri for each strain.