



Ph.D. DISSERTATION DEFENSE

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Title: Peptoid-Loaded Microgel-Modified Self-Defensive Antimicrobial Surfaces

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ABSTRACT

Biomedical device-associated infections are challenging to resolve because colonizing bacteria develop into antimicrobial-resistant biofilms. Our approach to preventing device-associated infections thus centers on preventing the initial adhesion by using a self-defensive surface modification that can be applied to the surface of an existing biomedical device such as a hip prosthesis, a pacemaker, or a heart valve. The procedure first involves the electrostatic deposition of polyanionic microgels onto a surface. Cationic antimicrobials can then be loaded by complexation within the interior of the microgels, and, under appropriate conditions, the antimicrobial remains sequestered within the microgels until contacted by a bacterium. At that point, the cationic antimicrobial can be transferred from the microgel to the bacterium and the bacterium is killed. This thesis explores self-defensive behavior using a novel class of antimicrobials based on peptoids. These are peptide mimics where the R group is appended to the Nitrogen rather than to the alpha-Carbon in an amino acid. We experimentally studied their complexation behavior with polyacrylic acid (PAA) microgels synthesized by membrane emulsification. In contrast to an FDA-approved antibiotic like colistin, we found that the TM1 peptoid remains sequestered in PAA microgels for several weeks in buffer with pH = 7.4 and $[Na^+] = 0.14$ M. To assess the self-defensive antibacterial activity of modified surfaces, we developed an *in-vitro* operating room (OR) contamination model to mimic the deposition of airborne bacteria onto an implant surface during surgery at contamination levels of only a few hundred CFU. We found that Ti rods modified by peptoid-loaded PAA microgels very effectively resisted colonization by *S. epidermidis* and Methicillin-Sensitive *S. aureus* (MSSA). Moreover, the modified Ti surface displayed excellent cytocompatibility in morphological and metabolic activity assays. Experiments using a series of different peptoids that self-assemble into structures ranging from monomeric oligopeptoids to tetrameric bundles indicate that supramolecular structure plays a key role in achieving stable sequestration under the physiological conditions needed for self-defensive behavior.