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Title: Design of Antimicrobial Macromolecules

Antimicrobials, including antibiotics, antivirals, and antifungals, are effective lifesaving therapeutics against pathogenic microorganisms. As the clinical pipeline of new antimicrobials runs dry, the emergence of resistance (bacterial and viral) against existing medicines poses a serious threat to public health. There is thus an urgent need for innovative, rationally designed molecular platforms that can be rapidly developed to combat resistant strains. In the first part of this talk, I will describe our research effort toward creating a synthetic sequence-defined macromolecular prodrug that actively targets a pathogen of interest (*Pseudomonas aerugionsa*) and releases a tailored sequence-defined antibacterial agent only in the presence of virulence factors emitted by the pathogen. This mechanism of action, similar to that used in the field of antibody-drug conjugates, should decrease the toxicity profile of the antibacterial agent while maintaining its potency. In the second half of this talk, I will discuss the design of a fusion inhibitory dimeric lipopeptide with potent activity against the SARS-CoV-2 virus. Viral infection of target cells occurs via the coordinated action of binding and fusion proteins. Peptides derived from the heptad repeat region of the viral fusion protein can interfere with the structural transition of the fusion protein, thus inhibiting infection at the entry stage. In a collaborative effort with the Porotto and Moscona research groups, our team collectively developed a lipopeptide inhibitory ligand that self-assembles into serum stable nanoparticles with potent antiviral activity. Self-assembly of the amphipathic lipopeptides enhances their biodistribution and half-life and contributes to enhanced *in vivo* efficacy. Proposed anchoring of the dimeric lipopeptide in the host cell membrane, interactions with the viral proteins, and retention in the lungs prevented direct-contact transmission in ferrets.