Polymer-Based Therapy for Mitigation of Pathogens

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Continuous population growth and microbial resistance engenders a demand for sustainable disease management. Conventional strategy to combat pathogens employs high doses of antibiotics, which results in the development of antibiotic resistance in common pathogens and therefore treatment failure. Here we demonstrate an application of macromolecular therapy for mitigation of diseases without onset of resistance.

IBM's answer to the current dearth of antimicrobial drugs is the development of therapeutic polymers with broad spectrum antimicrobial properties. These operate through selective, yet non-specific interactions and demonstrate the ability to overcome pathogenic resistance. They will serve as non-toxic, stable, easily accessible, and affordable mimics to highly efficacious antimicrobial peptides, which suffer from proteolytic instability, high cytotoxicity, and high manufacturing cost.

Antimicrobial polymers contain cationic moieties, which allow for electrostatic docking to a negatively-charged bacterial cell wall and hydrophobic portions, which integrate, destabilize, and lyse it. The range of polymers shows low minimum inhibitory concentrations (MIC) in *acinetobacter baumannii* and *mycobacterium tuberculosis*. Compared with the drug, imipenem, which saw an increase in MIC toward *acinetobacter baumannii* over 30 passages *in vitro*, polymeric therapy shows no increase in MIC, indicating resistance mitigation.

Antiviral drug development also faces rapidly mutating viruses. A broad spectrum antiviral polymer developed at IBM is coated with sugar molecules, which can complex with viral surface proteins regardless of mutations. Additionally, they can complex with immune cell receptors to compete with viruses and neutralize already infected cells via inhibition of replication. This polymer has been tested against Dengue, Chikungunya, Enterovirus, Influenza, Ebola, Marburg, and Herpes. It has an EC50 value of 0.012 mg/L against A/H3N2 flu virus, high selectivity (EC50/IC50 > 83,000), high LD50 (463 mg/kg) in mice, no *in vivo* toxicity to the liver and kidneys or hemolysis at 1200 mg/L, and no resistance development after 5 passages against enterovirus (EV 71) and dengue (DENV-2). Ultimately, this class of polymer has been designed for use as a vaccine or to mitigate symptoms of viral infection.

Ongoing work encompasses the development of polymers, which contain cationic moieties in addition to generators of reactive oxygen and nitrogen species. These polymers are designed to broadly target multiple types of pathogens at once.

We hope that these macromolecular therapies compliment their small-molecule counterparts and mitigate rapidly mutating pathogens.

Additionally, antimicrobial polymers are sure to emerge within the defense community. As an aid to help treat wounded soldiers on the battlefield and as a preventative measure against biological weapons, these polymers will serve a critical role.