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Abstract

Deciphering the therapeutic code of cationic peptides to overcome bacterial resistance to traditional antibiotics: the tryptophan impact

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Abstract:

Infections associated with multidrug-resistant (MDR) bacteria constitute an imminent health crisis (WHO, 2014). Antimicrobial peptides (AMPs) are essential components of the innate immunity of most multicellular organisms with the potential to overcome bacterial resistance mechanisms to traditional antibiotics. The contextual activity of AMPs constitutes a major challenge to their development for systemic administration, particularly for hospitalized patients requiring intravenous therapy. To address these challenges, we have developed a rational framework for de novo-designed helical AMPs to titrate the structure-function relationships under different physiologically-relevant conditions. Our lead Trp-rich peptides from multiple libraries remained active against most MDR clinical isolates from the Center for Disease Control and Prevention. In resistance selection assays under antimicrobial selective pressure, S. aureus developed resistance to cell wall inhibitor antibiotics in contrast to our select lead AMPs with no emergence of resistance phenotypes. These peptides interact with negatively charged lipids on the bacterial surface prior to rapid disruption of the membranes. More importantly, systemic in vivo efficacy was demonstrated in an otherwise lethal bacterial sepsis model in mice with 100% survival. Lessons learned from these systematic structure-function and pre-clinical studies indicate the need for continuously enhancing the cationic amphipathic structure using our iterative rational framework for increased therapeutic index and safety to overcome resistance by incessantly evolving bacterial pathogens.

Biography:

I moved to the U.S.A from Haiti, my native country. After earning a bachelor's degree at City College of the City University of New York (Anthropology and Biochemistry double major), I remained in attendance for graduate studies in Biochemistry for another four years. I then transferred to the Medical Scientist Training Program (MD, PhD) at the University of Pittsburgh, completed in 2008.As Assistant professor, I seek to develop a

novel class of antibiotics,inspired by naturally occurring antimicrobial peptides,as a logical progression from my graduate and postdoctoral training. My laboratory is supported by an R01 from NIGMS to elucidate the mechanisms of the therapeutic efficacy of engineered AMPs in sepsis treatment.

Recent Publications:

1. Berthony Deslouches, et al, Mass Balance Study of the Engineered Cationic Antimicrobial Peptide, WLBU2, Following a Single Intravenous Dose of 14C-WLBU2 in Mice, 2020
2. Berthony Deslouches, et al Direct antimicrobial activity of cationic amphipathic peptide WLBU2 against Staphylococcus aureus biofilms is enhanced in physiologic buffered saline, 2020
3. Berthony Deslouches, et at, Engineered Cationic Antimicrobial Peptides (eCAPs) to Combat Multidrug-Resistant Bacteria, 2020
4. Berthony Deslouches et al,, Enhanced therapeutic index of an antimicrobial peptide in mice by increasing safety and activity against multidrug-resistant bacteria, 2020
5. Berthony Deslouches, et al, Synergistic Biophysical Techniques Reveal Structural Mechanisms of Engineered Cationic Antimicrobial Peptides in Lipid Model Membranes, 2020

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