Title: **Innovation in Sepsis: Can Antimicrobial Peptides Offer a New Therapeutic Approach?**

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Background: OMN6 is a clinical stage, bioengineered antimicrobial peptide (AMP) inspired by the native peptide Cecropin A. Acting rapidly through membrane disruption that triggers ATP depletion and loss of vital solutes, OMN6 demonstrates potent activity against multi-drug-resistant (MDR) Gram-negative bacteria associated with serious hospital-acquired infections such as hospital/ventilator-associated bacterial pneumonia (HABP/VABP) and bloodstream infections (BSI). Previous studies in bacteremia confirmed the bactericidal effect of OMN6. Interestingly, recent studies have demonstrated that OMN6 is also able to rescue mice in a lethal sepsis model, suggesting; a possible sequestration mechanism that may have significant therapeutic implications.

Methods: Peptide-LPS binding was analyzed via displacement assay, spatial structure determined by circular dichroism (CD), and immunomodulatory activity screened through *in-vitro* assays including enzyme-linked immunosorbent assay (ELISA) and Griess reagent analysis. *In-vivo* efficacy was evaluated in a lipopolysaccharide (LPS)-induced sepsis murine model. Mice received intraperitoneal (IP) injection of *E.coli* LPS. One-hour post-LPS challenge, animals were administered with four intravenous (IV) doses of OMN6 or saline at hourly intervals and a survival was assessed.

Results: OMN6 demonstrates high-affinity binding to LPS, a ubiquitous structural component of the Gram-negative bacterial outer membrane. Importantly, this is the binding that induces the conformational shift into the alpha-helical active conformation of the peptide when targeting bacteria. In this recent research, we demonstrate this active conformation facilitates LPS sequestration and allows OMN6 to attenuated macrophage-mediated inflammatory responses, reducing nitric oxide production and positively modulating cytokine expression. These LPS-neutralizing properties translated to *in vivo* efficacy, with OMN6 providing protection in a murine model of LPS-induced sepsis.

Conclusions: Omnix Medical's findings demonstrate that OMN6 not only neutralizes LPS with high affinity but also converts this activity into meaningful *in vivo* protection, highlighting its promise as a therapeutic candidate for sever hospital-acquired infections, **aiming to position OMN6 as a future first-line treatment in MDR Gram-negative sever and life-threatening infections.**