Abstract Submitted
for the CUWIP22 Meeting of
The American Physical Society

Antimicrobial peptides derived from the SPLUNC1 protein perturb bacterial and eukaryotic lipid model membranes TANVI JAKKAMPUDI, Carnegie Mellon University, QIAO LIN, University of Pittsburgh, FRANK HEINRICH, AISHWARYA VIJAI, WEIHENG QIN, ANN KANG, JESPAR CHEN, SAHELI MITRA, Carnegie Mellon University, ROBERT ERNST, University of Maryland, PETER DI, University of Pittsburgh, STEPHANIE TRISTRAM-NAGLE, Carnegie Mellon University — SPLUNC1 is a host defense protein found in the human respiratory. Five novel antimicrobial peptides (AMPs) were rationally designed from SPLUNC1 with different lengths, charges, hydrophobicities (H) and hydrophobic moments (μH). The goal of this study was to compare the biological activities of these AMPs by means of testing against paired clinical isolates of the Gram-negative (G(-)) bacteria. In addition, mechanistic studies were carried out to study interactions between the AMPs and bacterial lipid model membranes utilizing x-ray diffuse scattering (XDS), circular dichroism (CD) and neutron reflectivity (NR). One of the SPLUNC1-derived AMPs, A4-112, displayed superior antibacterial activity and the lowest toxicity to mammalian cells at low peptide concentration. CD indicated A4-112 has the highest α-helical content and the lowest μH/H ratio. NR and XDS revealed A4-112 is located primarily in the headgroup region in a G(-) model membrane with only a shallow hydrocarbon penetration. XDS revealed that A4-112's mechanism of bacterial killing could involve domain formation with leakage of ions and water along the domain walls. A4-198, with the same amino acid composition but minimal μH, displayed the least helicity but with almost no bacterial killing activity, suggesting that helicity and effectiveness are correlated in these AMPs.

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Date submitted: 11 Jan 2022 Electronic form version 1.4