Molecular Dynamics Simulation of Novel Klebsiella pneumoniae Treatment Disrupting the Outer Membrane

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Klebsiella pneumoniae exhibits among the highest rates of antibiotic resistance and is currently the main cause of carbapenem resistant infections, yet there are no clinically effective treatments available for many who contract the Gram-negative bacterium. Artilysins, proteins each composed of an endolysin and a lipopolysaccharide (LPS) degrading peptide fused together, are a possible alternative to antibiotics for Gram-negative bacterial infections. In an earlier phase of this project, an Artilysin to target K. pneumoniae was designed and a model was created of its endolysin portion. In the current stage of this project, a computational model of the rest of the Artilysin is created, validated, and used to demonstrate stability in water at body temperature. Because fusing domains can bring about unforeseen changes to protein behavior, molecular dynamics is used to provide insight to mechanisms at the molecular level. However, with accuracy, size, and simulation time comes an increasingly expensive computational cost. To evaluate the efficacy of the designed Artilysin before investing a large amount of resources, the Artilysin is simulated above a model of an outer membrane resembling that of K. pneumoniae for 2 microseconds at body temperature. This is compared against two controls, one with the endolysin above the outer membrane and the other with only the outer membrane. Compared to the endolysin, the Artilysin is shown to disrupt membrane density deeper into the bilayer. Further investigation reveals changes in specific bonds in the LPS backbone and carbon tails that accompany the density changes.

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